

Lashley's

ESSENTIALS OF
CLINICAL GENETICS
IN NURSING
PRACTICE

Second Edition

Christine E. Kasper
Tonya A. Schneidereith
Felissa R. Lashley

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LASHLEY'S ESSENTIALS
of
Clinical Genetics
in Nursing Practice

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Dr. Kasper has been inducted as a fellow of the American Academy of Nursing and the American College of Sports Medicine. In 2015, she received the distinctive honor of becoming an inductee of the Sigma Theta Tau International Nurse Researcher Hall of Fame.

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Among her national and international presentations, Dr. Schneidereith has published in the *Annual Review of Nursing Research*, *Experimental Hematology*, and *Human Molecular Genetics*. She also serves as a reviewer for the *Journal of Nursing Education* and *Nursing Education Perspectives*.

Additionally, Dr. Schneidereith maintains a clinical practice as a pediatric nurse practitioner, with over two decades of experience in pediatric acute and primary care.

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Editors

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To my parents, David and Betty Andrade, who developed and fostered my passion for learning. To my wonderful husband, Scott, and my children, Sam and Lauren, without whom this would not be possible.

—TAS

To my earliest mentor in science, my father, John M. Kasper, and to my first professional mentor, Luther Christman, PhD, RN, FAAN, who made it all possible. And to my family: Ray, and my talented daughters, Alexandra and Gabrielle, for their constant encouragement and support.

—CEK

To my very special children (Peter, Heather, and Neal) and grandchildren (Ben, Hannah, Jacob, Grace, and Lydia). You make everything brighter.

—FRL

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EDITOR'S NOTE

It is hard to believe that my interest in genetics began more than 50 years ago, when I chose genetics, as opposed to a less demanding course, as a needed free elective at Adelphi University. At the same time, one of my nursing instructors noted that I was “too interested in the unusual.” In the 1960s, it was at New York University, influenced by Dr. Martha Rogers and Inga Thornblad, where I really discovered that I was a critical thinker and that even as a woman and a mother, the sky was the limit. Yet, it was not until I began my doctoral work in the Department of Biological Sciences at Illinois State University, when I had to repeat a genetics course because of all the changes that had occurred since my undergraduate course, that I saw the potential that genetics held for people's health and how necessary that knowledge would be for the health professions.

So I set my sights in that direction, switching my major to genetics, specifically human and medical genetics, with a minor in biochemistry. That was in 1970. I especially am grateful for the shared knowledge and professionalism of two of the genetics faculty there, Dr. Herman Brockman and Dr. William (Bill) Daniel, who were wonderful role models of scholarship and decency.

And if the potential was visible then, surely all of the applications available now were only a dream. Over my career, however, understanding human genetic variation interacting with the environment, along with its implications, has led to exciting applications not only in health and illness, but also in fields such as forensics and law. Genetics and genomics have truly permeated all aspects of our lives, and even young schoolchildren are conversant in the terminology and concepts, if not the societal implications.

It hardly needs to be said that the increasing importance of genetics and genomics translates to all fields of nursing, as well. By now, I hope that nurses are truly “thinking genetically” and looking at their clients with a “genetic eye.” To do otherwise would be a failure to practice nursing in the way that it should be practiced by the professional nurse.

I am now happily retired from active practice and am lucky enough to be able to spend my time doing the things I love most, especially spending time with family and friends. Throughout my past genetic evaluation and counseling practice, I met so many wonderful people affected by genetic variation. I am grateful for the lessons I learned from them.

I have had wonderful friends and colleagues in and out of nursing, and there is not space to mention all of them; however, two long-time nursing friends and colleagues deserve special mention: Dr. Jerry D. Durham and Dr. Wendy M. Nehring.

I marvel at how thoroughly genetics is now integrated into our culture and society. Being in the genetics field has always been an honor for me and my contributions have been a labor of love.

And how many more amazing things in genetics there are to come ... the excitement has just begun.

Felissa R. Lashley
Overland Park, Kansas

PREFACE

The practice of clinical genetics and genomics has infiltrated nearly every area of health care. Currently there are over 3,000 genetic and genomic tests available to health care providers to query a wide range of diagnostic and pharmacogenetic needs, such as individual patient heredity and metabolic responses to drug treatment. Today's nurses not only participate in pedigree construction and risk identification, but are increasingly responsible for referral to genomic medical services. The formal academic process of bringing genetics into nursing began in 2000 and has since resulted in the 2009 publication of the American Nurses Association (ANA) Consensus Panel on Genetic/Genomic Nursing Competencies. These establish genomics as a core competency for all registered nurses (RNs), regardless of academic preparation, clinical role, or practice specialty. The endorsement of these guidelines by most professional nursing organizations leads to the hope that soon the study of genetics in the undergraduate curriculum will be as ubiquitous and required as anatomy and physiology are today.

Being able to assess clients and families with a “genetic eye” has become critical for all nurses. Advances from genetic and genomic research have influenced all areas of health care and all periods of the life cycle. Genetic factors are responsible in some way for both indirect and direct disease causation; for variation that determines predisposition, susceptibility, and resistance to disease; and for response to treatment. When we look into the future, we can see that the application of genetic knowledge, including genetic screening and personalized drug therapy, will have a direct influence on health care.

Nurses must be able to “think genetically” to help individuals and families, in all practice areas, that are affected in some way by genetic disease or are contemplating genetic testing. Each person's state of health and risk for developing diseases may be based on genetic variation. This includes not only diseases thought of as genetic but also more common disorders such as cancer and heart disease.

Becoming competent in the use of genetic content begins in undergraduate and generic nursing education programs. It was with this in mind that *Lashley's Essentials of Clinical Genetics in Nursing Practice* was originally written. Given the rapid progress of genetic and genomic science, the original work has been revised and extensively updated as *Lashley's Essentials of Clinical Genetics in Nursing Practice, Second Edition*. Part I of the book discusses the place of genetics in health care and the health care trends related to genetics. This is followed by a review of basic and molecular biology, a discussion of human variation and diversity, and gene action and types of inheritance. The topics of prevention of genetic disease, genetic testing, and treatment are presented, including aspects of genetic counseling. Part II applies these principles to areas of clinical nursing practice. Specific application of genetics and genomics in regard to pharmacology, history taking and physical assessment, maternal–child nursing, adult health and illness and medical–surgical nursing, psychiatric mental health nursing, policies, and social and ethical issues are

all discussed. The broad concepts are presented in a nursing context with selected disease examples and case examples. Many key concepts, questions, and examples from Dr. Lashley's practice appear liberally throughout this new edition. **Qualified instructors may obtain access to ancillary materials, including PowerPoints and a test bank, by contacting textbook@springerpub.com.**

Within this book, the term *normal* is used as it is by most geneticists—to mean free from the disorder or condition in question. Genetic terminology does not generally use apostrophes (e.g., Down syndrome instead of Down's syndrome), and this pattern has been followed.

The writing of this book in a manner that allows students to understand and apply genetics is an important step toward early educational preparation. Thinking inclusively about genetics in all types of disease conditions will help nurses preserve the optimum function and health of patients. All nurses, as health care providers and as citizens, are charged with understanding advances in genetics and the resultant implications on health care and social decisions. In the words of Florence Nightingale (1859), “[T]he knowledge of nursing...of how to put the constitution in such a state as that it will have no disease, or that it can recover from disease, takes a higher place. It is recognized as the knowledge which everyone ought to have.” For today's nurses, this is genetics.

*Christine E. Kasper
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PART I

The Basics

CHAPTER 1

Genomics in Health Care

Tonya A. Schneidereith and Christine E. Kasper

Since the inception and completion of the Human Genome Project (HGP), the field of genetics has experienced unimaginable growth. The identification of approximately 30,000 human genes, coupled with advancements in molecular techniques, has created an opportunity to delve deep into every part of the human life span. No longer confined to the sciences and health care, discussions on genetics and the role of genes in disease are part of everyday conversation. From television and mainstream media to the grocery store and genetically modified foods, society is deluged with genetic information. The chromosomal locations for known diseases can now be found with the click of a mouse, making information accessible for everyone.

HUMAN GENOME PROJECT

Much of the detailed information now known about human genetics evolved from the HGP. Started in 1990, the HGP was a collaborative research program coordinated through the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) and the Department of Energy (DOE). David Smith directed the program at the DOE, and James Watson and Francis Collins were the first and second directors at NIH, respectively. Although the primary focus of research included gene sequencing and mapping of the human genome, a major contribution of the HGP was the development of large-scale molecular technologies. These contributions, along with the development of computer technologies to handle the enormous amount of sequencing data, have allowed for the continued, rapid advancements in all areas of genetic research.

In April 2003, the full sequence of the human genome was published in *Nature*. The complexity of the genome highlighted the discovery that only 1% to 2% of bases encode proteins, meaning that the role of 98% of human DNA is unknown. The total number of identified genes that code for proteins is approximately 30,000, fewer than what was originally expected. Some of the other unexpected findings included “the more complex architecture of human proteins compared to their homologs in worms and flies, the profoundly important lessons that could be learned from the human repeat sequences, and the discovery of apparent horizontal transfer from bacterial species” (Collins, 2001, p. 643).

The HGP also led to the establishment of the ethical, legal, and social implications (ELSI) programs of genetic research. The ELSI programs fund research in four main categories: genomics research; genomic health care; broader societal issues; and legal, regulatory, and public policy. To date, the major impact from ELSI research includes policies related to the conduct of genomics research, mostly involving informed consent. The future role of the ELSI program includes frequent reassessment of research priorities due to this constantly emerging science and protection of researcher autonomy and independence in a field filled with policy implications.

INCREASING GENETIC LITERACY

Educators have recognized the importance of an informed public that is able to understand genetic risk and predisposition. Historically, aspects of genetics were taught in middle/high school and primarily included the basics of Mendelian inheritance. None of the complexities involved in disease were taught, leading students to believe that genetics followed only the primary inheritance patterns. The American Society for Human Genetics recognized these limitations and suggested a curriculum for K-12 education, increasingly focused on improving genetic literacy.

In today's health care, there is an expectation that providers are capable of understanding and translating findings from genetic screening and testing into language that is easily understood. This requires incorporation and comprehension of genetic content in both undergraduate and graduate education that is commensurate with the rapidly expanding gains toward understanding genetic risk and predisposition.

Knowledge and Competencies

Many of the challenges and applications of new genetic information are still unknown, but health professionals in all areas of practice will encounter clients with disorders that have either a known genetic etiology or genetic component. Preparation of the provider will aid in recognition of the role of genomics in many conditions and the application of gene-based diagnostic tests and therapies. This includes a breadth of genetic and genomic knowledge regarding testing and assessment of risk, as well as the ability to interpret results and provide education and counseling.

However, staying current with genetic and genomic knowledge is, in itself, a seemingly insurmountable challenge for educators. A study of over 7,700 practicing nurses revealed knowledge deficits in genetics and genomics, while more than 50% of the group identified genetics in their curriculum (Calzone, Jenkins, Culp, Caskey, & Badzek, 2014). This suggests an inadequacy in genetic curricula and inappropriate academic preparation for both students and educators. Making academic preparation a priority is essential for future nurses.

The NHGRI and the National Cancer Institute (NCI) collaborated on a series of articles to help nurse educators focus on genetics and genomics (Mjoseh, 2012). Additionally, in 2006, an esteemed consensus panel comprising nurses from national organizations (NHGRI, American Nurses Association [ANA], Centers for Disease Control and Prevention [CDC], Health Resources and Services Administration

[HRSA], American Nurses Credentialing Center [ANCC], Sigma Theta Tau International, etc.), universities, and nurses' associations (Society of Pediatric Nurses, National Association of Hispanic Nurses, National Alaska Native American Indian Nurses Association, etc.) established essential competencies and curriculum guidelines. These guidelines were updated to include outcome indicators in the second edition, published in 2009 as the *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators* (Jenkins, 2008). This document identifies essential competencies including:

- ▶ Professional responsibilities
 - Demonstrating understanding of genetics as applied to health prevention and screening
 - Ability to obtain three-generation family health history and construct a pedigree
 - Critically analyzing history for risk factors
- ▶ Applying/integrating genetic and genomic knowledge
- ▶ Identification of those who may benefit from genetic services
- ▶ Referral activities
- ▶ Provision of education, care, and support

Although the importance of these competencies is irrefutable, their implementation in nursing education is still inadequate. The *Essentials*, along with integration of genetics in core science courses, provide the very basic components to best prepare future nurses to provide safe, cost-effective care that will improve health outcomes.

NURSING ROLES IN A GENOMIC ERA

Traditionally, nurses were expected to interview clients, obtain an accurate history over three generations, and identify risk based on pedigree. However, the information gained from the HGP has added layers of complexity, including the idea of relatedness. As previously determined through a three-generation pedigree, inheritance and risk were measured through identity by descent (IBD). However, IBD does not account for molecular variability, including meiotic recombination, thereby making it an imprecise way to establish inheritance risk. The availability of molecular testing and analysis of genome-wide single-nucleotide polymorphism (SNP) data allows for more accurate diagnosis, limiting the value of the traditional pedigree. Will nurses forego the pedigree for whole-genome analysis (WGA)? Does this mean that teaching the art of eliciting a pedigree has become obsolete? Regardless, nurses should be prepared to explain and interpret correctly the purpose, implications, and results of genetic tests.

The role of the nurse will vary depending on the disorder, the needs of the client and family, and the nurse's expertise, role, education, and job description. Nurses will treat adults with genetic diseases of childhood who present with common

health problems and people with traditional adult-onset disorders, such as hemochromatosis and Huntington disease. Technological advances have increased life expectancy for many chronic diseases, including sickle cell disease and cystic fibrosis. This will lead to greater knowledge of the effects of illness across the life span. Different mutational changes within a gene may produce different phenotypic outcomes with varying responses to treatment and prognosis. Persons with specific genotypic mutations already are known to have preferential responses to certain medications or therapeutic approaches. Large-scale genome-wide association studies (GWAS) are shedding insight into the role of SNPs in complex diseases such as cancer, chronic obstructive pulmonary disease, diabetes mellitus, and heart disease. Additionally, access to whole-genome sequencing may be available within the next decade, making the idea of personalized medicine in diagnosis and treatment of disease a real possibility.

Consideration of the family unit is important for nurses. Identification of a genetic disorder in one member can allow others in the family to receive appropriate preventive measures, detection, and diagnosis or treatment and to choose reproductive and life options concordant with their personal beliefs. Also, there is a toll on the community and society. Although mortality from infectious disease and malnutrition has declined in the United States, the proportion due to disorders with a genetic component has increased, assuming a greater relative importance. Furthermore, nurses must be aware of potential increases in health disparities, especially among the poor and disadvantaged from various ethnic backgrounds, as the demand for genetic services continues to grow.

Nurses are in an ideal position to apply principles of health promotion, maintenance, and disease prevention. Coupling an understanding of cultural differences, technical skills, family dynamics, growth and development, and other professional skills with the person and family unit threatened by a genetic disorder, nurses can ensure an appropriate outcome.

For those interested in learning more about genetics, the International Society of Nurses in Genetics (ISONG; www.isong.org) offers various certifications for nurses related to genetics, depending on their education and experience. Additional certifications are available through the American Board of Medical Genetics.

SUMMARY

Nurses are uniquely positioned to assess, treat, and educate individuals and their families on the presence, absence, or future possibility of disease. As members of the profession, it is the responsibility of the nurse to remain up to date on testing and therapies related to genetics and disease.

To paraphrase Francis Collins, the payoff of the HGP for health care professionals is a better ability to diagnose, treat, and prevent disease. Understanding the role of genetics and genomics throughout the life span, increasing genetic literacy, and applying new technologies in diagnosis and treatment is a great place to start.

KEY POINTS

- ▶ Health care and society are increasingly influenced by genetics and genomics.
- ▶ Many genetic disorders that appear to follow Mendelian patterns of inheritance and were ascribed to a single mutant gene are now known to be more complex than formerly thought.
- ▶ The influence of genetic testing for screening and diagnosis has a greater weight now than once prior to the HGP.
- ▶ Genetic disorders may appear in any phase of the life span.
- ▶ Nurses will encounter clients/patients with genetically influenced disorders in every area of clinical nursing practice.
- ▶ Nurses play many roles in caring for persons and families affected by genetically influenced disorders.
- ▶ Nurses, as well as educators, should have basic genetic and genomic knowledge, competencies, and literacy.
- ▶ Personalized medicine may be a reality within the next decade.

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CHAPTER 2

Basic Concepts in Molecular Biology

Wendy L. Kimber

This chapter introduces the fundamental concepts in molecular biology that underlie the principles of genetics and inheritance. It begins with a discussion of the way that genetic material is organized into genes and chromosomes and the mechanisms by which these are transmitted to the next generation. This is followed by an explanation of the molecular nature of genes and the processes of DNA replication and gene expression. The flow of information from DNA to RNA to protein is described along with the consequences of mutations on this system. Finally, a brief survey of current genetic technologies is presented, including the burgeoning field of genomics. This chapter provides the foundational concepts on which subsequent chapters are built.

CHROMOSOMES

The term *chromosome* is derived from the Greek words for color (*chroma*) and body (*soma*) as chromosomes were first observed as colored threads inside the nucleus of stained cells by scientists in the 1800s. These thread-like structures are present in the nucleus of all cells and are the basic units of heredity that are passed from parents to their offspring.

Chromosomes are composed of a single molecule (double strand) of DNA, which is wrapped around histone proteins (Figure 2.1). The association of DNA with histone proteins is known as *chromatin*. Chromosomes exist in the cell in one of two forms, condensed (closed) or relaxed (open). For most of the time, the DNA in chromosomes is only loosely wound around histone proteins so that the genes on the chromosomes are accessible to the transcriptional machinery of the cell. In this form, chromosomes exist as long slender threads that are not visible under a light microscope. Only when a cell is getting ready to divide does the DNA become compacted to take on the characteristic shape and form of a chromosome.

Before a cell divides it makes a duplicate copy of each chromosome; both chromosome copies remain temporarily stuck together, with each individual chromosome referred to as a *chromatid* (Figure 2.2). During cell division the DNA of both chromatids are wound tightly around histone proteins so that it forms a short tight bundle.

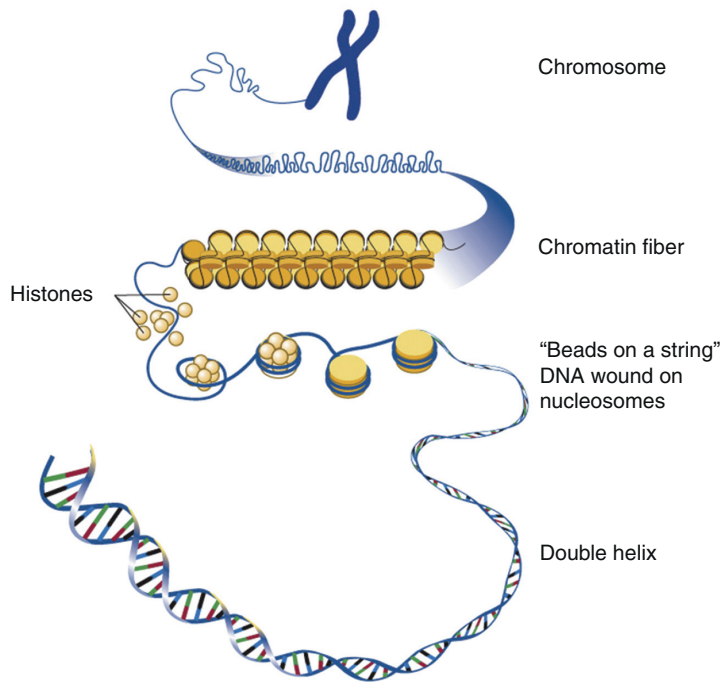


FIGURE 2.1. The association of DNA and histone proteins to form chromatin.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85280>

This makes it easier for the cell to move the chromosomes around the cell, and is analogous to taking multiple lengths of yarn and winding them up into individual balls for ease of handling. In this condensed form, chromosomes are visible under the light microscope, and each individual chromosome can be identified on the basis of its size and the pattern of bands created when the chromosomes are stained with Giemsa (G banding). During the time that chromosomes are in this condensed form, the DNA is so tightly wound around the histones that transcription cannot take place. For this reason, as soon as nuclear division is complete, the chromosomes rapidly decondense so that the DNA is accessible once more and can be used by the cell to direct the production of proteins.

In the condensed state, certain features of a chromosome become visible. A constriction in the chromosome identifies the chromosome *centromere*, which holds the two chromatids together. During nuclear division (*mitosis* or *meiosis*), spindle fibers attach to specialized regions of the centromere known as *kinetochores* to move the chromosomes around the cell. The ends of each chromosome are called *telomeres*, which are made up of short DNA sequences that are repeated over many times and do not code for proteins. Telomeres have a protective function for the chromosome, and shortening of telomeres has been linked to aging and cancer.

Humans have 23 pairs of different chromosomes in a *somatic* (nonsex) cell, with one of each pair being inherited from each parent. Twenty-two of these chromosome pairs do not play a role in sex determination and are referred to as *autosomes*. The

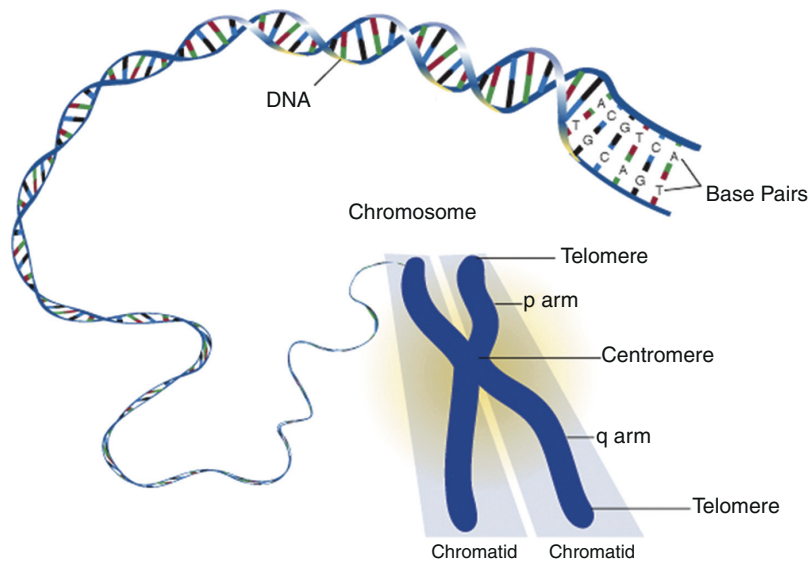


FIGURE 2.2. The structure of a duplicated chromosome.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85281>

remaining pair are called the *sex chromosomes* or X and Y chromosomes, because these determine the sex of an individual. In humans, sex is determined by the presence or absence of the Y sex chromosome, with females having two X chromosomes and males having one X and one Y chromosome. In the absence of a Y chromosome, embryonic development proceeds along the default female pathway. In the presence of a Y chromosome, development is switched to that of male by a transcription factor that is encoded by the *sex-determining region Y (SRY)* gene, which is found only on the Y chromosome. Because somatic cells contain two copies of each chromosome type, they are referred to being *diploid*, and their chromosome number is denoted as $2n$. *Gametes*, which are cells specialized for fertilization (sperm and oocytes), have only one of each chromosome and are said to be *haploid* and are given the n designation. The fusion of haploid male and female gametes during fertilization restores the diploid number of chromosomes (46) to the zygote, with one maternally derived chromosome and one paternally derived chromosome for each pair.

CELL DIVISION

Cell Cycle

Cells preparing to divide progress through a series of phases, which collectively are known as the *cell cycle* (Figure 2.3). The cell cycle could be considered the “life cycle” of the cell; however, only cells that have been given “permission” to divide complete the cell cycle, and nondividing cells remain in the first phase of the cell cycle indefinitely, which is referred to as the resting phase or G_0 .

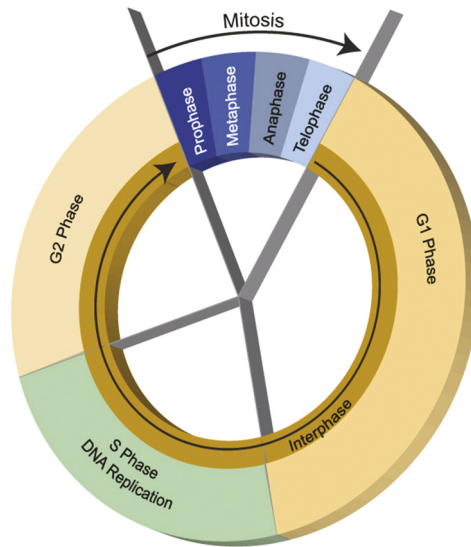


FIGURE 2.3. The four phases of the cell cycle.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85276>

The first phase of the cell cycle, called the *gap 1* (G_1) phase, occurs immediately following cell division. When the parental cell divides in half to create two daughter cells, these are initially half the size of the parental cell with only half the number of organelles. The first task for this newly created cell is to increase its size and synthesize additional organelles. Therefore, the G_1 phase is considered to be a period of growth. Once a cell has reached its full size and capacity it does not automatically proceed to cell division. There are strict controls on which cells are allowed to divide, and division is only permitted if there is a need for more cells for the purposes of growth, repair, or regeneration. Therefore, there are a host of *cell cycle controls* that prevent a cell from leaving G_1 and proceeding with division. These are enforced by proteins, such as *cyclins*, that enforce *cell cycle checkpoints*, the maintenance of G_1 state, and prevent cells from leaving G_1 and progressing through the cell cycle. Mutation of one or more of these genes results in loss of cell cycle control, and cells progress through the cell cycle and divide in an uncontrolled way, leading to cancer. The *mitotic index* is a measurement of cell proliferation that measures the ratio of mitotic (dividing) cells to nondividing cells within a population. An elevated mitotic index can be indicative of the presence of cancerous cells that have lost cell cycle control.

When cell division is required, a chemical signal will be received by the cell, which leads to the removal of G_1 checkpoint controls, and the cell then enters the second phase of the cell cycle, the *S phase*. During this phase of the cell cycle, *DNA synthesis* occurs, and all of the chromosomes are replicated, leading to a doubling of the DNA content of a cell. There is no checkpoint at the end of the S phase; rather, cells proceed directly into the *gap 2* (G_2) phase, which is another period of growth. During the G_2 phase, the cell prepares for nuclear and cell division, by synthesizing the proteins that will be required to drive this process. The gap phases of the

cell cycle (G_1 and G_2) were named by early researchers studying the cell cycle by observing visible changes under the microscope. In contrast to S and M phases, the processes taking place during G_1 and G_2 do not create any visible changes in cellular morphology, leading scientists to name them “gap” phases to reflect what they incorrectly thought of as periods of inactivity in the cell.

At the end of the G_2 phase there is another cell cycle checkpoint, and cells can only progress to the next phase of the cell cycle when their DNA has been checked and found to be undamaged. If any DNA damage is found, it must be repaired before cells can proceed any further. Cells that pass the G_2 checkpoint proceed into the *M phase*, which is where *nuclear division* and eventually *cytokinesis* (cell division) takes place. The G_1 , S, and G_2 phases are known collectively as *interphase*, to reflect that these are the phases leading up to nuclear and cell division.

The ploidy status, which is the number of sets of chromosomes of a cell, is determined by the method of *nuclear division* that is used to create the two nuclei during the M phase of the cell cycle, as a precursor to cytokinesis. Nuclear division occurs during the M phase of the cell cycle by one of two methods, mitosis or meiosis, depending on the function of the cell.

Mitosis

Somatic cells do not participate in reproduction and are therefore diploid, having two copies of each chromosome, referred to as *homologous chromosomes*. During the S phase of the cell cycle, a somatic cell makes a copy of all of its chromosomes; this double complement of chromosomes must become organized into two separate nuclei, each containing a complete set of chromosomes, before cell division can occur. Somatic cells achieve this through the process of mitosis, a method of nuclear division which, in humans, separates a set of 46 chromosomes into each of two nuclei. Mitosis is followed by cell division to generate two diploid daughter cells that have maintained the chromosome number of 46. This method of nuclear division is used by all dividing cells except gametes, for the purpose of growth, regeneration, and repair, and generates daughter cells that are genetically identical to the original parental cell. Organisms that reproduce asexually also divide by mitosis, leading to offspring that are identical, genetic clones of the parent.

Mitosis begins with all of the chromosomes being in their duplicated state, having been replicated during the S phase. Both of the chromosome duplicates, known as *sister chromatids*, remain fastened together at the centromere. The goal of mitosis is to pull apart these chromosome copies and move them into separate nuclei. Mitosis is divided into five stages, the first of which is *prophase* (Figure 2.4). During this phase, the chromosomes condense to become shorter and thicker in preparation for being moved around the cell. At the beginning of prophase, stained chromosomes are barely visible as thin threads; however, by the end of prophase the chromosomes have condensed to such an extent that they are then visible as the shapes that we commonly associate with chromosomes. The end of prophase is marked by the disappearance of the nuclear membrane to allow access of the spindle fibers to each chromosome. *Metaphase* is the most characteristic stage of mitosis, as this is the phase where spindle fibers move the chromosomes so that they are lined up

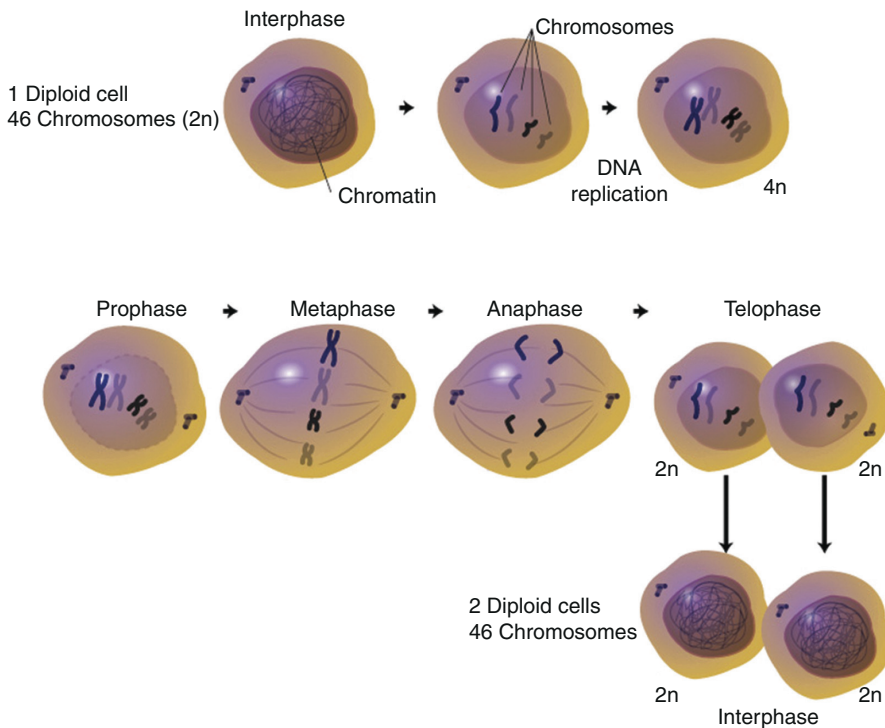


FIGURE 2.4. The four phases of mitosis, which achieves nuclear division in somatic cells.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85204>

along the center of the cell (*metaphase plate*). This stage of the cell cycle is used for preparing *karyotypes* (images of individual chromosomes for the purpose of identifying abnormalities in chromosome number or structure). When preparing cells for karyotyping, they are treated with a chemical inhibitor, which prevents the cells from leaving metaphase. This ensures that the chromosomes are in their most condensed state and therefore most highly visible under a light microscope. Before the cell proceeds to the next phase of mitosis, a cell cycle checkpoint is encountered, which ensures that all spindle fibers are attached to the chromosome centromeres. This is very important because errors at this point could lead to incorrect separation of duplicated chromosomes (*nondisjunction*), leading to conditions of *aneuploidy* (abnormal chromosome number). (For a more detailed description of aneuploidy, see Chapter 4.) Once this cell checkpoint has been verified, cells enter *anaphase*, which is when the spindle fibers abruptly shorten, pulling duplicated chromosomes apart and toward opposite poles of the cell. When adequate separation of the chromosome pairs has been achieved, the nuclear membranes quickly re-form around each complete set of chromosomes in the last phase of mitosis known as *telophase*. At this stage the chromosomes rapidly decondense, allowing access to the DNA for the resumption of transcription. For a very brief period, the cell has two nuclei; however, as soon as telophase is complete, the cell quickly divides its cell contents in half to form two cells. At this point, the cell cycle is complete and each newly created daughter cell enters the G_1 phase.

Meiosis

Gametes, which are cells specialized for reproduction (sperm and eggs), do not use mitosis for nuclear division because a haploid nucleus must be generated during cell division. In order to generate two haploid nuclei with only one of each chromosome type, the nucleus must divide using meiosis. Meiosis is a form of nuclear division that includes two rounds, resulting in the formation of four haploid cells. The first nuclear division, *meiosis I*, separates each pair of homologous chromosomes to generate two haploid nuclei, and for this reason is referred to as a *reductive division*. Although the first round of meiosis has generated two haploid nuclei, each chromosome is still in the duplicated state with the two sister chromatids connected at the centromere. The second round of meiotic nuclear division, *meiosis II*, is similar to mitosis in that it functions to separate duplicated sister chromatids, creating haploid nuclei, each with a set of unduplicated chromosomes; this is an *equational division*. Both meiosis “I” and “II” are divided into the same four stages of prophase, metaphase, anaphase, and telophase as mitosis (Figure 2.5). A phase is

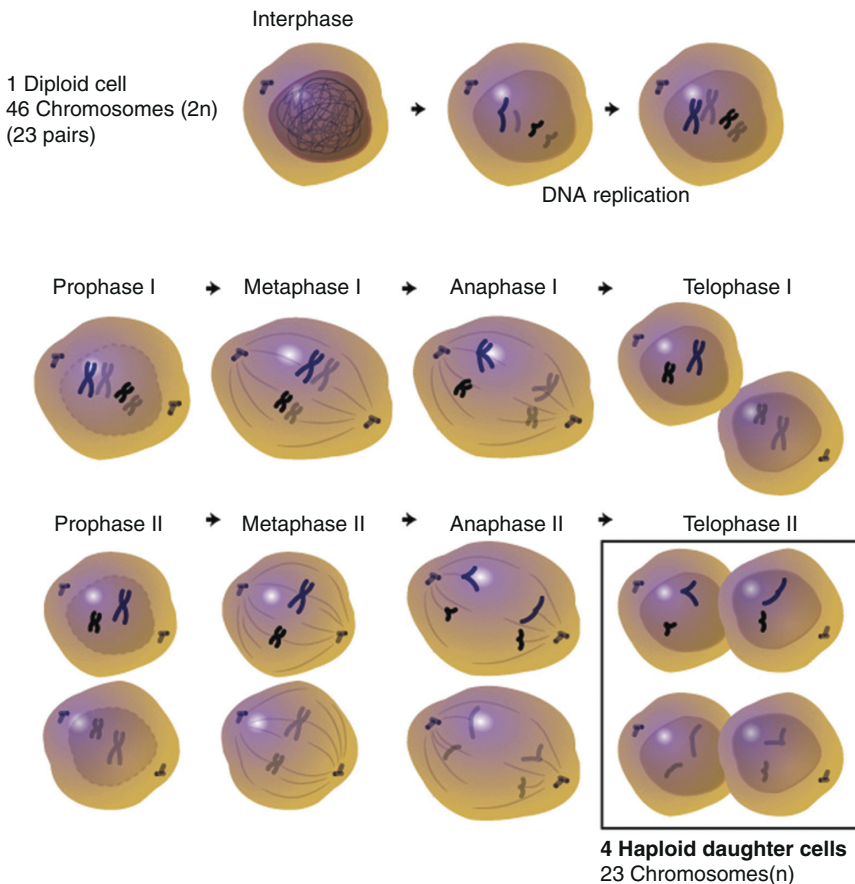


FIGURE 2.5. The four phases of meiosis, which create haploid nuclei during nuclear division of germ cells.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&rid=85196>

TABLE 2.1 A Comparison of Mitosis and Meiosis

| Mitosis | Meiosis |
|--|---|
| Used for growth, repair, or regeneration | Used for gamete formation |
| Occurs in somatic cells | Occurs in germ cells in testes and ovary to form gametes |
| Involves one round of cell division | Involves two rounds of cell division |
| Results in two diploid daughter cells | Results in four haploid daughter cells |
| Daughter cell chromosome number is the same as parent cell (2n, diploid) | Daughter cell chromosome number is half of parent cell (n, haploid) |
| Daughter cells are normally genetically identical | Daughter cells are genetically unique |

identified as being from meiosis I or II by the use of the Roman numeral I or II. For example, metaphase I indicates that this is metaphase from meiosis I and metaphase II indicates metaphase of meiosis II; the absence of a number indicates that this is a phase of mitosis (e.g., metaphase). A comparison of mitosis and meiosis is shown in Table 2.1.

Meiosis begins, like mitosis, when the chromosomes are in their duplicated state. In *prophase I*, the chromosomes begin to condense and become visible as thin threads, as in prophase of mitosis. However, during prophase I, a process unique to meiosis occurs in which homologous chromosomes find each other and pair up in a zipper-like process known as *synapsis*. The synapsed chromosome pair is known as a *bivalent*, although it actually represents four chromosome copies and is sometimes referred to as a *tetrad*. Once the chromosomes are paired up, the chromosomes continue to condense, becoming visibly shorter and thicker, as well as more closely associated with each other due to the formation of the *synaptonemal complex* between the chromosomes; this protein complex is thought to mediate synapsis. During this period when the chromosomes are so intimately associated, chromatids on opposite chromosomes (referred to as nonsister chromatids) swap segments in the process of *crossing over* (Figure 2.6). In humans, crossovers occur on average at two points on each chromosome during meiosis, and the frequency and location of crossing over have been used to map genes (Box 2.1). A physical connection occurs between chromosomes during crossing over and is called a *chiasma* (plural *chiasmata*) because it resembles the Greek letter chi (χ). Crossing over is a significant genetic event as it is an important source of genetic variation during sexual reproduction, leading to new combinations of alleles on chromosomes. Prophase I, like prophase of mitosis, ends with the breakdown of the nuclear membrane and the attachment of the spindle fibers to the centromeres of each tetrad.

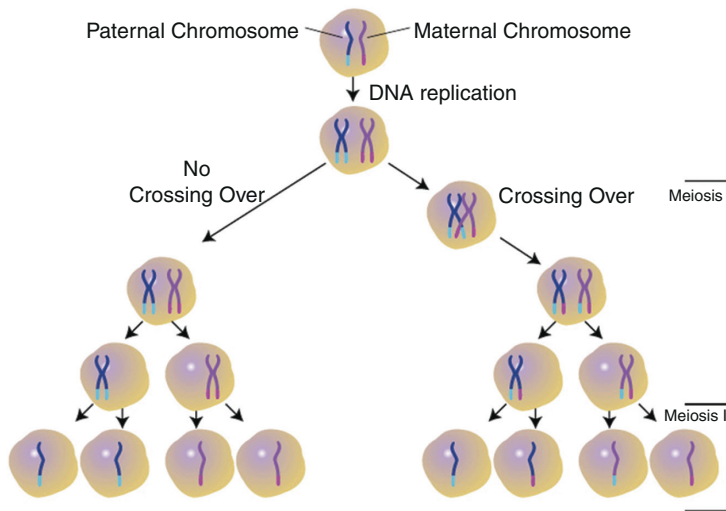


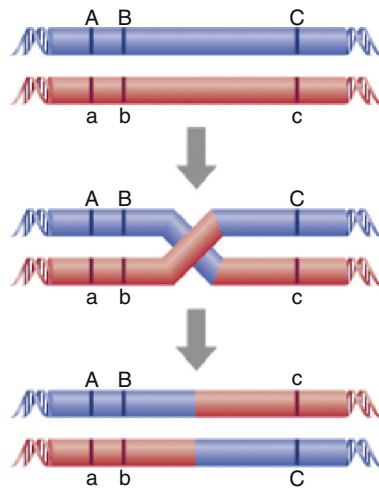
FIGURE 2.6. Crossing over during prophase I of meiosis creates new combinations of alleles on chromosomes.

Source: http://www.genome.gov/Glossary/resources/crossing_over.pdf

BOX 2.1

Linkage Analysis and Gene Mapping

Crossing over between chromosomes results in shuffling of genetic information between chromosomes, and is an important source of genetic variation. Crossing over occurs randomly along the length of a chromosome, and creates new combinations of alleles. If two alleles of different genes are located closely together, the chances of them being separated by crossovers are much smaller than if they were located more further apart. By measuring how frequently two alleles are separated through *recombination* (crossing over) it is possible to get an estimate of their relative distance. This approach has been used to map the position of genes on chromosomes and is referred to as *linkage analysis*. The distance between genes on the same chromosome is commonly expressed in terms of map units or centimorgans (after the geneticist Thomas Morgan), and genes located 50 or fewer map units apart are said to be *linked* as their alleles are usually inherited together.



Source: <http://www.genome.gov/Glossary/index.cfm?id=115>

Metaphase I of meiosis is characterized by the unique way that the chromosomes are lined up along the metaphase plate. In metaphase of mitosis and meiosis II, chromosomes are lined up along the middle of the cell in a single file; however, in metaphase I of meiosis I, the chromosomes remain paired up in a tetrad, and are lined up in two rows of chromosomes along the metaphase plate. The way that the tetrads are aligned on the metaphase plate is random with respect to the maternal chromosome and paternal chromosomes. This introduces another source of genetic variation, as a random mix of maternal and paternal homologous chromosomes will segregate to different nuclei with only one chromosome of each pair existing in a given gamete. It is a matter of chance as to whether, for example, a chromosome number 1, which was originally from the mother, and a chromosome number 2, which was originally from the father, end up in the same gamete or not, or whether, by chance, all maternally derived chromosomes end up in the same gamete, a concept that is described by Mendel's *Law of Independent Assortment*.

The phases of *anaphase I* and *telophase I* are very similar to mitosis; however, in this case anaphase is identified by the shortening of spindle fibers to pull apart the tetrads and move duplicated chromosomes consisting of two sister chromatids to opposite poles, in contrast to anaphase of mitosis where single chromatids are separated. In telophase I, the nuclear membrane quickly re-forms around each duplicated chromosome and the cell immediately begins to divide. The end result is two haploid cells with only one of each chromosome type.

Cells completing meiosis I go immediately into meiosis II as there is no need for DNA replication to occur. Although the cells are now haploid, each chromosome is still in the duplicated state and the sister chromatids need to be separated from each other. The stages of meiosis II follow more closely those of mitosis, and differs only in that the cell is now haploid. During prophase II, the chromosomes shorten and thicken, the nuclear membrane disappears, and the spindle fibers attach to the centromeres. *Metaphase II* is characterized by the alignment of a haploid number of chromosomes along the metaphase plate. In human cells, this means that there will only be 23 chromosomes aligned on the metaphase plate. The sister chromatids are separated during *anaphase II* and the nuclear membrane re-forms around each set of chromosomes during *telophase II*. Cytokinesis completes the process, with the end result being the generation of four haploid cells.

Gametogenesis

Diploid germ cells divide using meiosis to produce haploid gametes. In males, this process is called *spermatogenesis* and begins with the division of diploid *spermatogonia* in the seminiferous tubules of the testes. In humans, spermatogenesis begins at puberty and continues throughout the lifetime of the male, with cells moving continuously through all of the stages of meiosis. In contrast, the process of female gamete formation, *oogenesis*, is discontinuous, with cells arrested at two points in this process. Oogenesis takes place in the *oogonial* cells in the ovary during the first 6 months of embryonic development. Meiosis is not completed at this time and instead is arrested at the prophase stage of meiosis I in primary oocytes, which remain in this state indefinitely. At the onset of puberty in human females, one oocyte per month is released from the ovary during ovulation. Ovulation triggers the completion of

meiosis I in an oocyte, which then goes on to complete meiosis I and enter meiosis II. This cell becomes arrested for the second time at metaphase II of meiosis II. The oocyte remains arrested at this stage unless it encounters sperm and fertilization occurs. Sperm entry during fertilization stimulates the oocyte to complete meiosis II, prior to fusion of the pronuclei containing the maternal and paternal chromosomes.

Cell division during spermatogenesis is symmetrical, with meiosis I generating two equally sized cells, which each divide by meiosis II to generate a total of four equally sized spermatids. In contrast, cell division during oogenesis is asymmetric, with each cell division generating one cell that contains the majority of the cell contents and a much smaller cell, called a *polar body*, containing a nucleus and very little cytoplasm. The end result of oogenesis is the creation of one large ovum containing a large amount of cytoplasm and cellular contents, as well as three small polar bodies that do not participate in reproduction. During the process of sperm maturation, *spermiogenesis*, spermatids actively eliminate most of the cytoplasm from the cell. Therefore, at fertilization, the ovum contributes most of the cellular contents including mitochondria, and sperm contributes the haploid male pronuclei. The inheritance of mitochondria from the mother is an interesting genetic phenomenon because mitochondria also contain DNA. Mitochondria are the sites of energy production in the cell, and have a genome of 16,500 base pairs of DNA containing 37 genes. It is now known that some genetic disorders result from mutations in mitochondrial DNA, which are discussed further in Chapter 4.

CHROMOSOMES AND INHERITANCE

Genes are arranged in a linear fashion along a chromosome, and are always found at the same position on the same chromosome, with this position being referred to as its *locus* (plural: *loci*). There is one copy of each gene at a given locus; however, somatic cells are diploid, having two of each chromosome: one maternal and one paternal in origin. Therefore, there are two copies of each gene per cell: one gene copy inherited from the mother and one from the father. The exceptions are the X and Y chromosomes of the male. The Y chromosome has a much lower number of genes than the X chromosome, with around 50 genes compared to the approximately 800 genes on the X chromosome. In addition, some genes are unique to the Y chromosome, such as *SRY*, and function in male development. For this reason, a gene on the X chromosome often does not have a corresponding copy on the Y chromosome.

A single gene contains the information for making a specific polypeptide and is the hereditary determinant of a trait. Different versions of the same gene often exist, usually differing by one or a few base pairs, which produce the same protein but with slightly differing activities. Different versions of the same gene are called *alleles*, and lead to variations in a given trait. For any given gene, if both alleles are identical, an individual is said to be *homozygous*. If an individual has two different alleles (versions) of the same gene, he or she is said to be *heterozygous* for that gene. The term *genotype* is used to describe the genetic makeup of a person when discussing combinations of specific gene alleles, and *phenotype* refers to an observable trait that is a result of a genotype. A trait or characteristic is considered *dominant* if the trait

encoded by the allele is apparent when one copy of the allele is paired with a different allele of the same gene. A trait is considered to be *recessive* when the phenotype for that allele is seen only in individuals with two copies (homozygous) of that allele. In males, only one recessive allele is needed to express a recessive phenotype if the gene is located on the X chromosome with no corresponding allele on the Y chromosome. These traits are called *X-linked recessive traits*. Genes on the X chromosome of the male are often referred to as *hemizygous*, when a second allele on the Y chromosome is absent. In order to avoid a double dosage of X-linked gene products in females, a process known as *X-inactivation* silences gene expression from one of the X chromosomes in each somatic cell. A situation of *codominance* occurs when both alleles are expressed, as in the case of the AB blood group. A summary of these genetic terms is presented in Box 2.2.

To explain patterns of inheritance more simply, geneticists often use capital letters to represent alleles for dominant traits and lowercase letters to represent recessive ones. Thus, a person who is heterozygous for a given allele pair can be represented as Aa, one who is homozygous for two dominant alleles as AA, and one who is homozygous for two recessive alleles as aa. For autosomal recessive traits, the homozygote (AA) and the heterozygote (Aa) may be indistinguishable on the basis of phenotypic appearance, but they may be distinguishable biochemically because they may make different amounts or types of a gene product. This information can often be used in carrier screening for recessive disorders to determine genetic risk and for genetic counseling. When geneticists discuss a particular gene pair or disorder, normality is usually assumed for the rest of the person's genome, and the term *normal* is often used unless stated otherwise.

BOX 2.2

Common Genetic Terms

| <i>Term</i> | <i>Definition</i> |
|--------------|---|
| Alleles | Alternative forms of the same gene at a given locus |
| Codominant | When traits encoded by both alleles of a heterozygote are expressed (observed) in an individual |
| Dominant | A trait encoded by one allele that is expressed even when other alleles of that gene are present |
| Genotype | Combination of alleles for a specific gene |
| Hemizygous | Having only one copy of a particular gene |
| Heterozygous | Having two different alleles of the same gene |
| Homozygous | Having two identical alleles for a given gene |
| Phenotype | Observable expression of a specific trait or characteristic |
| Recessive | A trait that is apparent or expressed only when two recessive alleles are present or if one copy is missing |

Standards for both gene and chromosome nomenclature are set by international committees. To describe known genes at a specific locus, genes are designated by uppercase Latin letters, sometimes in combinations with Arabic numbers, and they are italicized or underlined. Alleles of genes are preceded by an asterisk. Some genes have many possible alleles. This can lead to slightly different variants of the same basic gene product. For any given gene, any individual would have only two alleles present in somatic cells—one on each corresponding chromosome. Thus, in referring to the gene for the ABO blood groups, *ABO**A**, *ABO**O**, and *ABO**B** are examples of the formal ways for identifying the different alleles at the ABO locus. As an example, a genotype for different alleles of the adenosine deaminase gene may be written as *ADA**1**/*ADA**2** or *ADA**1**/*ADA**2** to depict the two alleles that are present. Further shorthand is used to describe more precisely mutations and allelic variants. These describe the position of the mutation, sometimes by codon or by the site. For example, a cystic fibrosis mutation, deletion of amino acid number 508, phenylalanine, is written as PHE508DEL or AF508.

GENES AND DNA

Genes are the basic units of heredity. A *gene* can be defined as a segment of DNA that encodes the amino acid sequence of a polypeptide. A *polypeptide* is a chain of amino acids connected to one another; one or more polypeptides make up a *protein*. There are about 20,000 to 25,000 genes in a person's *genome* (total genetic complement or makeup). The vast majority of genes are located in the cell nucleus, but there are also 37 genes in the mitochondrial genome of cells, which are mostly concerned with *adenosine triphosphate* (ATP) or energy production.

Not all of the DNA within a cell encodes proteins, and less than 5% of the DNA in the genome corresponds to the coding sequence of proteins. The large amount of noncoding DNA was once referred to as “junk” DNA; however, there is now a growing body of evidence that many regulatory elements are located within these noncoding regions, which control gene expression and can contribute to the disease state.

The Structure of DNA

DNA is a nucleic acid that comprises subunits called *nucleotides*. All nucleotides have the same three components: a nitrogenous base, a five-carbon sugar, and a phosphate group. In DNA there are four different nucleotides, which differ only in the nitrogenous base component. The nucleotides *adenine* (A) and *guanine* (G) are double-ring purine bases, and *cytosine* (C) and *thymine* (T) are single ring pyrimidine bases. The five carbons in the DNA sugar molecule are numbered from right to left, starting with the carbon atom closest to the oxygen atom. This carbon is designated as the 1' carbon, the second carbon the 2' carbon, and so on. In DNA, the five-carbon sugar is a deoxyribose sugar that is differentiated from ribose sugars by the presence of a hydrogen (H) functional group on the 2' carbon.

Nucleotides are joined together by a condensation reaction that links the hydroxyl (OH) group of the 3' carbon atom of one nucleotide to the phosphate group of the 5' carbon of another nucleotide via a *phosphodiester bond*. Many nucleotides are joined together in this fashion to make a strand of DNA. The 5' carbon of the first nucleotide

in the strand is said to be “free” because it does not participate in a phosphodiester bond and so the designation of 5' is used to denote the beginning of a strand of DNA. Likewise, the 3' carbon on the last nucleotide of a strand of DNA is free and the designation of 3' is used to denote the last nucleotide on a strand of DNA. A molecule of DNA consists of two strands of DNA that are held together by hydrogen bonding between the nitrogenous bases. The strands run in opposite directions (*antiparallel*) with the 5' end of one DNA strand pairing with the 3' end of another strand. The pairing between the nitrogen bases on opposite strands is very specific, with guanine always forming three hydrogen bonds with a cytosine (G:C) and adenine forming two hydrogen bonds with thymine (A:T); this is referred to as *complementary base pairing* (Figure 2.7). The two strands of DNA take on the secondary structure of a *double helix*. This may be visualized as a flexible ladder in which the sides are the phosphate and sugar groups, and the rungs of the ladder are the bases from each strand that form hydrogen bonds with the complementary bases on the opposite strand. This flexible ladder is then twisted into the double helix of the DNA molecule.

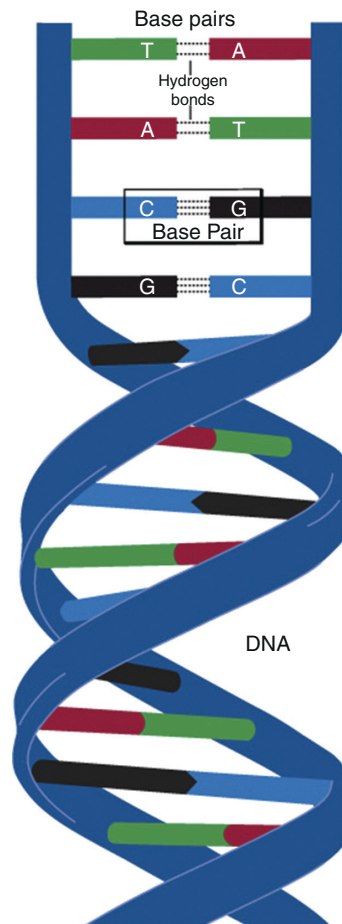


FIGURE 2.7. The double helical structure of a molecule of DNA.

Source: http://www.genome.gov/Glossary/resources/base_pair.pdf

DNA Replication

When a cell divides, both daughter cells must receive a complete set of chromosomes. Therefore, before meiosis or mitosis and cell division can occur, a cell must synthesize an entire new copy of its DNA. This occurs during the S phase of the cell cycle (Figure 2.3). Due to the specificity of nucleotide base pairing, each existing strand of DNA can serve as the template for the synthesis of a new strand of DNA.

In order for the DNA to be replicated, the double-stranded DNA must unwind or relax to separate the individual strands. This is achieved by the action of a *helicase* enzyme. Once the strands are separated, another enzyme, *DNA polymerase*, synthesizes a new strand of DNA by lining up nucleotides on the existing strand according to the base pairing rules (adenine pairing with thymine and guanine with cytosine; Figure 2.8). DNA replication is said to be *semiconservation* because at the completion of DNA synthesis, two double-stranded molecules of DNA are created, each consisting of one original strand and one newly synthesized strand of DNA.

It is important that DNA replication is highly accurate; otherwise, mutations would frequently occur. After replication is complete, a type of “proofreading” for mutations occurs, and repair takes place if needed. Despite several repair mechanisms, sometimes errors persist and the mutations that are created are passed down to the daughter cells.

The Structure of RNA

Within a cell there is a second type of nucleic acid, RNA, which plays an important role in gene expression. Like DNA, RNA is made up of nucleotide subunits containing a five-carbon sugar, a nitrogenous base, and a phosphate group. The difference between a DNA nucleotide and an RNA nucleotide is that in RNA the carbon sugar is a ribose sugar with a hydroxyl (OH) group on the 2' carbon atom. All but one of the nitrogenous bases found in DNA are also found in RNA, with the exception of thymine. A strand of DNA contains adenine, thymine, cytosine, and guanine

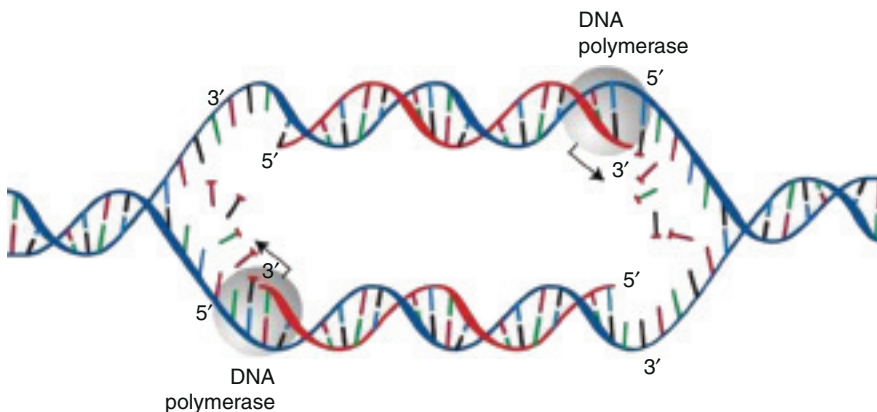


FIGURE 2.8. Synthesis of DNA by DNA polymerase using existing strands of DNA as templates.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85151>

bases, whereas RNA contains adenine, guanine, cytosine, and then *uracil* in place of thymine.

As in DNA, RNA nucleotides are joined together via phosphodiester bonds between the 5' and 3' carbon atoms by a condensation reaction; however, RNA synthesis occurs from just a single strand of DNA and generates a single-stranded product. Strands of RNA do not form a double helix, although a single strand of RNA may fold back on itself to form a hairpin structure.

GENE EXPRESSION

A gene is a stretch of DNA nucleotides that encodes the information for making a specific protein, a concept that is described by the *one gene–one polypeptide hypothesis*. The order of nucleotides in a gene corresponds to the order of amino acids in a polypeptide. The process by which information encoded by DNA is used to synthesize a protein is referred to as *gene expression*, which is a multistep process that takes place in multiple locations within the cell.

Genes are located on chromosomes within the cell's nucleus, and do not leave the nucleus under normal conditions. However, the protein-making machinery of the cell, the *ribosome*, is located in the cytoplasm or on the rough endoplasmic reticulum outside of the nucleus. The information for making a protein must be conveyed to the ribosomes, and this is achieved by making an RNA copy of the DNA sequence. The RNA copy of a gene, called *messenger RNA (mRNA)*, leaves the nucleus and travels to the ribosomes to be used as the template for protein synthesis. The process of copying the information in a gene into RNA is called *transcription* and the process of reading the mRNA to make a protein is *translation*. Therefore, the flow of genetic information within the cell is from DNA to RNA to protein, which is commonly referred to as the *central dogma of molecular biology* (Figure 2.9). The central dogma applies to all cells and organisms with a few exceptions such as retroviruses. The genome of retroviruses takes the form of RNA instead of DNA, and when a retrovirus infects a cell, it transcribes its own RNA into DNA through the activity of a unique enzyme, *reverse transcriptase*. The retroviral DNA is then transcribed back into RNA, which is then translated by the host cell to produce retroviral proteins.

Transcription

In order for the information in a gene to be copied into RNA, the double helix must first be unwound. Unlike DNA replication, only a short stretch of DNA corresponding to the gene being expressed needs to be copied, and so the DNA double helix is unwound only in that local region. Once unwound, one of the strands of DNA, the *template* or *sense strand*, is used as a template for the synthesis of an RNA copy known as a *transcript*. The enzyme *RNA polymerase* assembles RNA nucleotides on the sense strand following the base pairing rules; however, in the case of RNA there is no thymine, and adenine pairs, instead, with uracil (Figure 2.10). The end product of transcription is a single-stranded RNA copy of a gene.



FIGURE 2.9. The flow of genetic information in a cell.

In eukaryotes, the RNA produced by transcription, known as the *primary transcript*, undergoes modification before leaving the nucleus. One of these modifications is the removal of intronic sequences. *Introns* are DNA sequences within a gene that do not code for amino acids in the final gene product. In eukaryotes, the protein coding sequences of genes are called *exons* and are frequently interrupted with one or more noncoding intron sequences. It is estimated that 94% of genes in the human genome are interrupted with intronic sequences. These noncoding sequences are initially incorporated into the primary transcript during transcription but are removed by the process of *RNA splicing*, which cuts out the introns and rejoins the exons together forming an mRNA product that is considerably smaller than the DNA sequence from which it was transcribed (Figure 2.11). It used to be thought that introns were “junk” DNA or just DNA “fillers” but there is a growing body of evidence that introns contain important regulatory elements. The mRNA transcript is processed further by the addition of a 5' cap structure that protects the mRNA transcript, facilitates RNA splicing, and promotes translation efficiency; in addition, a run of multiple adenosine monophosphates on the 3' end of the primary transcript is used to generate a *poly (A) tail*. The poly (A) tail protects the RNA from degradation by nucleases and is also important for nuclear transport and translation of the RNA. Once fully processed, the RNA is referred to as the *mature mRNA transcript*, which leaves the nucleus to be translated by the ribosome.

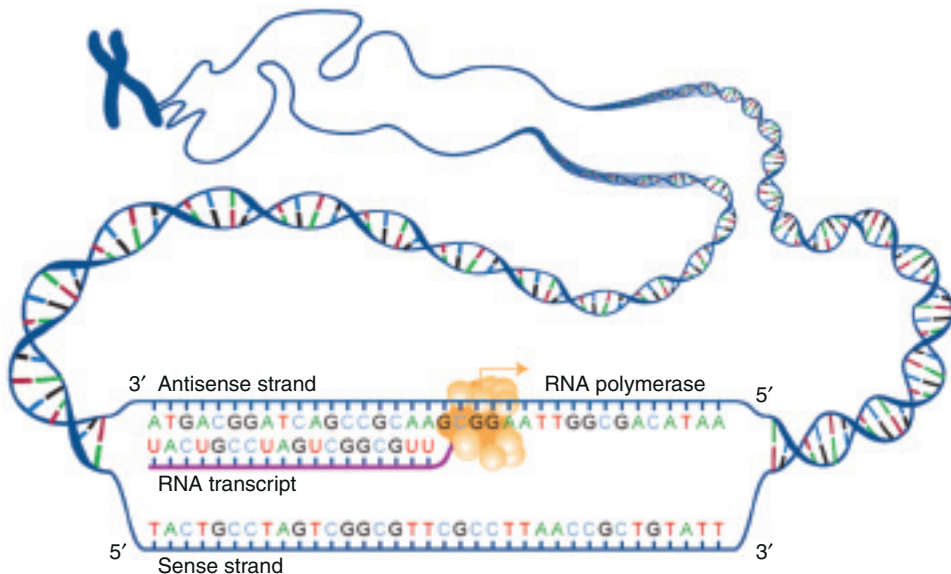


FIGURE 2.10. Transcription of the DNA sequence of a gene into RNA by RNA polymerase.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85249>

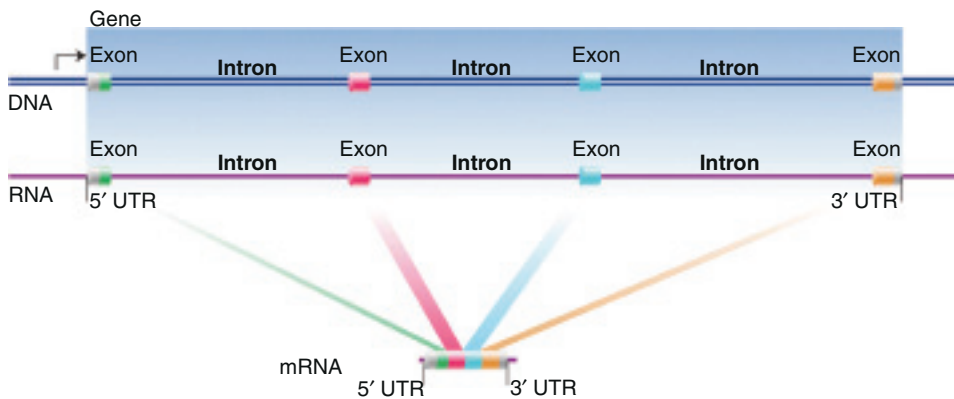


FIGURE 2.11. The relationship between the nucleotide sequences in the DNA of a gene, the primary RNA transcript, and the resulting mature mRNA transcript.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&rid=85163>

THE GENETIC CODE

The position or sequence of the nucleotide bases in DNA ultimately determines the identity and position of the amino acids in the resulting polypeptide chain, and is referred to as the *genetic code*. The genetic information in a gene is copied into RNA, and three nucleotides in the mRNA correspond to one amino acid in the resulting polypeptide, with each set of three nucleotides referred to as a *codon*. There is some redundancy in the genetic code as there are 20 different amino acids encoded by a total of 61 codons, with multiple codons encoding the same amino acid. In addition, there are three codons that do not code for an amino acid, called *stop codons*; these act like punctuation marks indicating to the ribosome to stop translation whenever these codons are encountered. Furthermore, the codon AUG encodes a methionine amino acid and is always found at the beginning of an mRNA sequence. The genetic code of all mRNA sequences has been determined and is shown in Figure 2.12. One of the most remarkable features of the genetic code is that it is universal, with all organisms, almost without exception, using the same codons for the same amino acids. This phenomenon led to the development of the field of *genetic engineering*, which exploits this property by transferring genes between species to produce novel proteins. An important example of this is the production of recombinant human insulin in the bacteria *Escherichia coli*. By transferring the human insulin gene into bacteria, scientists are able to produce large quantities of high-purity human insulin from bacterial cultures, a process which was one of the first successes of the now highly lucrative biotechnology industry.

The genetic code is nonoverlapping, and the mRNA sequence CACUUUAGA is read as codons CAC UUU AGA, which can be translated using the genetic code table (Figure 2.12) to the amino acids histidine, phenylalanine, and arginine, respectively. A shorthand way of referring to a specific amino acid is to use either a specified group of three letters or a single letter to denote a specific amino acid. In this system, for example, histidine may be referred to as His or H, arginine as Arg or R, and phenylalanine as Phe or F.

| 1st position | 2nd position | | | | 3rd position | |
|--------------|--------------------------|--------------------------|----------------------------|---------------------------|------------------|--|
| | U | C | A | G | | |
| U | Phe Phe Leu Leu | Ser Ser Ser Ser | Tyr Tyr stop stop | Cys Cys stop Trp | U C A G | Ala: Alanine Arg: Arginine Asn: Asparagine Asp: Aspartic acid Cys: Cysteine |
| C | Leu Leu Leu Leu | Pro Pro Pro Pro | His His Gln Gln | Arg Arg Arg Arg | U C A G | Gln: Glutamine Glu: Glutamic acid Gly: Glycine His: Histidine Ile: Isoleucine |
| A | Ile Ile Ile Met | Thr Thr Thr Thr | Asn Asn Lys Lys | Ser Ser Arg Arg | U C A G | Leu: Leucine Lys: Lysine Met: Methionine Phe: Phenylalanine Pro: Proline Ser: Serine Thr: Threonine Trp: Tryptophan Tyr: Tyrosine Val: Valine |
| G | Val Val Val Val | Ala Ala Ala Ala | Asp Asp Glu Glu | Gly Gly Gly Gly | U C A G | |

Amino Acids

FIGURE 2.12. The genetic code table showing the amino acids encoded by codons in mRNA.

Adapted from <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85173>

There are three major classes of RNA involved in protein synthesis: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). The RNA that receives information from DNA and serves as a template for protein synthesis is mRNA. Ribosomal RNA is one of the structural components of ribosomes—the RNA–protein molecule that is the site of protein synthesis. Transfer RNA serves as a molecular “adaptor” that acts as an intermediary between the codon on the mRNA and its corresponding amino acid. Transfer RNA molecules are cloverleaf-shaped, with two functionally important areas. One end of the tRNA structure is the *anticodon*, a three-nucleotide region that recognizes and binds with the complementary codon on mRNA. At the opposite end of the cloverleaf is a region that binds the amino acid encoded by the complement of the anticodon. Each tRNA can only bind a single amino acid that corresponds to the mRNA codon bound by the tRNA codon (Figure 2.13). The relationship between nucleotide sequences in DNA, mRNA codons, the anticodon in tRNA, and the translation into an amino acid is shown in Figure 2.14.

Translation

Translation is the last major stage in the flow of information from DNA to protein, and describes the mechanism by which the information in mRNA is used to assemble amino acids to synthesize a polypeptide.

Following transcription and RNA processing, the mature mRNA leaves the nucleus and enters the cytoplasm, where it binds to a ribosome. Ribosomes are large protein and RNA complexes that are responsible for synthesizing cellular polypeptides. They exist as two subunits, the small (40S) and large (60S) subunits in eukaryotic cells. During the *initiation phase* of translation, the small ribosomal

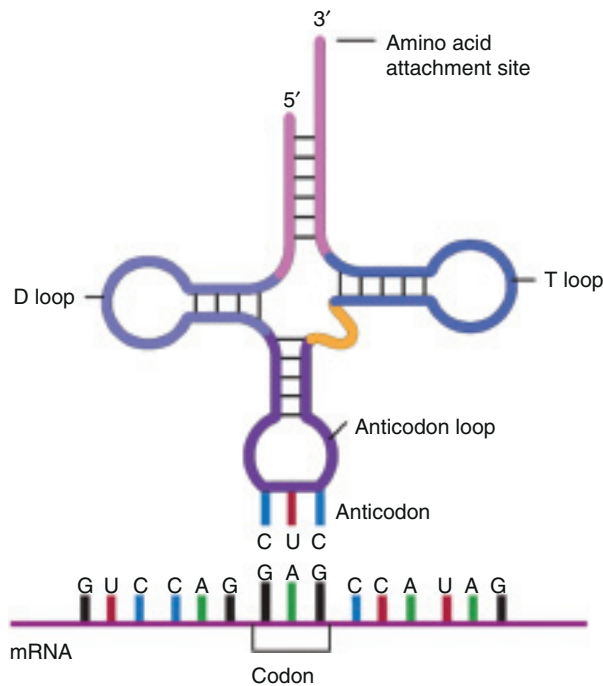


FIGURE 2.13. The structure of tRNA and its interaction with a codon on mRNA.
 Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85264>

subunit binds to the incoming mRNA just upstream of the AUG start site. An initiator tRNA carrying a modified methionine amino acid binds to the AUG start site and the large ribosomal subunit then attaches, “sandwiching” the mRNA between the two ribosomal subunits. In the *elongation phase* of translation, the mRNA passes through the ribosome, and tRNA molecules carrying the amino acids specified by the mRNA codons enter the ribosome and bind to the corresponding mRNA codon (Figure 2.15). As the tRNAs line up bound to the mRNA codons, polypeptide bonds are formed between the adjacent amino acids that they carry. Once an amino acid is added to the growing polypeptide chain, the tRNA releases the amino acid and exits the ribosome. Therefore, as RNA is pulled through the ribosome,

| | | | |
|-------------------|---------------------|-----|----------------|
| DNA template | 3'...AAA | TGA | CTG...5' |
| mRNA | 5'...UUU | ACU | GAC...3' |
| tRNA anticodon | 3'...AAA | UGA | CUG...5' |
| Polypeptide chain | NH ₂ ... | phe | thr asp...COOH |

FIGURE 2.14. Relationship among the nucleotide base sequence of DNA, mRNA, tRNA, and amino acids in the resulting polypeptide. A, adenine; asp, aspartic acid; C, cytosine; phe, phenylalanine; T, thymine; thr, threonine; U, uracil.

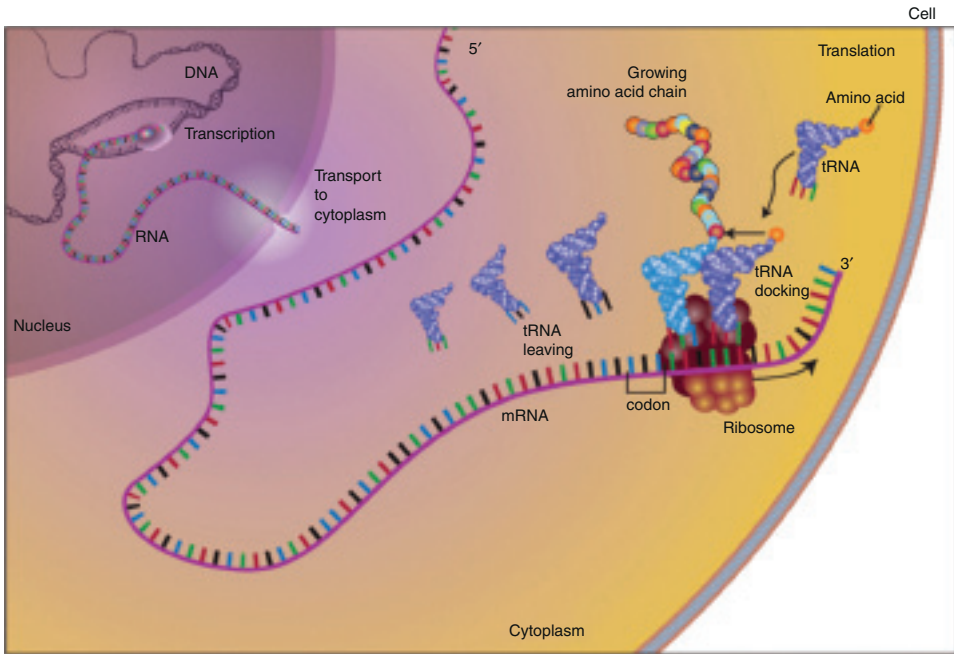


FIGURE 2.15. Translation of mRNA by a ribosome. Transfer RNA molecules (shown in blue) bind to the mRNA codons, bringing with them the appropriate amino acids.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&rid=85252>

a polypeptide chain is synthesized due to delivery of the amino acids by tRNAs. When a termination codon is encountered, such as UAA, UAG, or UGA, translation is terminated by the entry of release factors into the ribosome, which causes the ribosomal subunits to disassociate from each other and fall off the mRNA, releasing the newly synthesized polypeptide.

After release, most polypeptides undergo some form of *post-translational modification* to generate a mature, fully functional protein. These modifications include folding of the polypeptide chain to generate secondary or tertiary structures or combination with other polypeptides (quaternary structure). Biochemical groups such as phosphates, carbohydrates, or lipids may be added to the protein, and in some cases enzymatic removal of a number of amino acids needs to take place in order to activate the protein, as in the case of insulin.

GENE ACTION AND EXPRESSION

Although the same genes are present in every somatic cell of a given individual, they are not all being actively transcribed and translated (expressed) in all cells at the same time. Genes are selectively expressed depending on whether there is a need for that particular gene product. For example, the genes that determine the various chains that make up the hemoglobin molecule are present in brain cells, but hemoglobin is not produced because the hemoglobin genes are not expressed. Some genes, known

as *housekeeping genes*, are expressed in virtually all cells all of the time because these genes produce proteins that mediate essential cellular processes common to all cells, such as ATP synthesis.

MUTATIONS

A mutation is defined as a change in a DNA sequence. These changes commonly arise due to errors in DNA replication during cell division, infection by viruses, exposure to chemicals called *mutagens*, or exposure to ionizing radiation. Mutations can arise *de novo* (spontaneously) or they may be inherited. A mutation that occurs in a somatic cell affects only the descendants of that mutant somatic cell and is not inherited. If a mutation occurs early in the division of the zygote, it is present in a larger number of cells than if it appears later in development. If a mutation occurred before zygotic division into twins, both twins would harbor the mutation; however, if it occurred after zygotic twin division, the twins would have different versions of the gene or chromosome. When a mutation occurs in the germline, the mutation will be transmitted to all the cells of the offspring, both germ and somatic, and is inherited.

Mutations can involve changes in large amounts of genetic material (macro), as in the case of chromosomal abnormalities, or they may involve very tiny amounts (micro), such as the alteration of one or just a few DNA bases (Figure 2.16). Micromutations can involve the deletion, insertion, or substitution of one or a few DNA bases. Macromutations affect large regions of chromosomes, which may be deleted, duplicated, inverted, substituted, or translocated. The word *mutation* has a negative connotation; however, mutations can be detrimental, neutral, or beneficial. Mutations only affect a phenotype when the resulting protein functions abnormally; in fact, mutations are an important source of genetic variation.

Chromosome mutations are macromutations that delete, add, or rearrange large portions of one or more chromosomes. In most cases, chromosome mutations arise due to breaks in the chromosomes, which can occur spontaneously or as a result of chemical damage. The chromosome ends rejoin with other broken ends; however, if this occurs between different chromosomes or even different portions of the same chromosome, it can lead to changes in the chromosome structure. Deletions occur when chromosomes are broken in more than one place and a portion of the chromosome is lost when the ends rejoin. An inversion occurs when two broken ends on the same chromosomes rejoin with the intervening segment being rotated 180 degrees. No chromosomal material is lost in this case; however, the breakpoints may span genes, which become disrupted. When broken ends rejoin with ends on different chromosomes, portions of chromosomal material are relocated to other chromosomes. Sometimes a portion from one chromosome gets moved to another, as in chromosomal substitution mutations, and in other cases chromosomes may swap segments, as in translocations. A duplication is a chromosomal mutation that does not usually occur through rejoining of chromosomal ends, but rather through mistakes in meiosis. If chromosomes do not equally swap segments during crossing over of meiosis, it is possible for one chromosome to end up with two copies of a

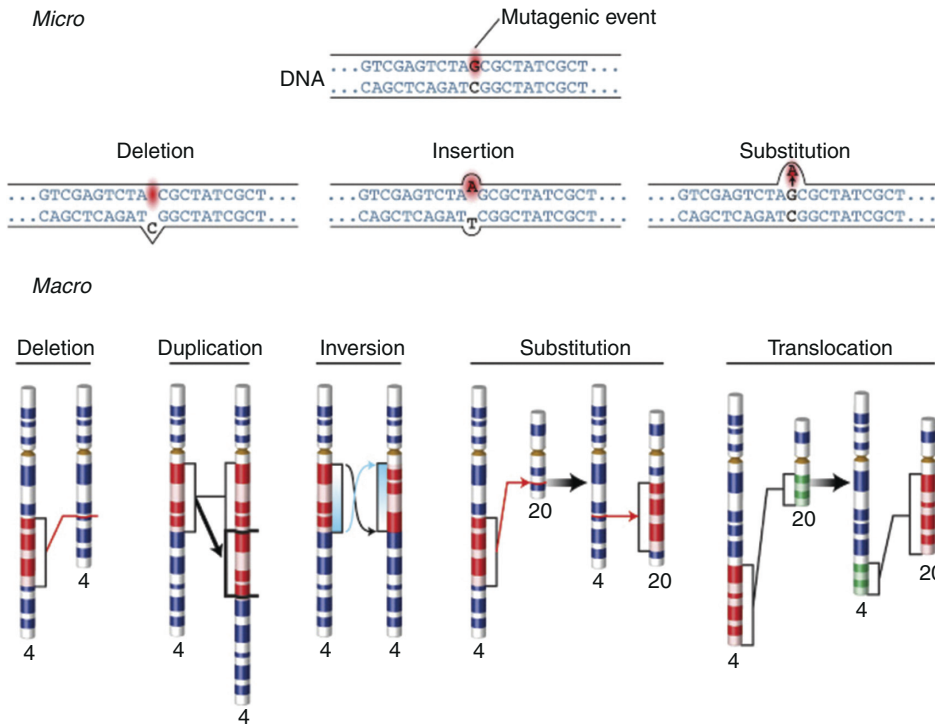


FIGURE 2.16. The spectrum of micro- and macromutations.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85206>

chromosomal segment and the other chromosome to lack the same region. Alternatively, duplications may occur due to mistakes in chromosome replication prior to meiosis.

Micromutations usually affect a single gene, with changes in the DNA sequence resulting in changes in the amino acid composition of the resulting protein. One of the most common types of micromutations is *point mutations*, sometimes referred to as base substitutions. These are changes in a single nucleotide of a gene. There are four categories of point mutations based on their effect on amino acid sequence:

1. *Missense mutations* are single nucleotide changes that change a codon so that it encodes a different amino acid (Figure 2.17).
2. *Silent mutations* are changes in DNA sequence that do not result in a change in amino acid sequence. This is possible because multiple codons encode the same amino acid, and these codons usually vary by the nucleotide in the third position of the codon. If a point mutation changes a codon to one that encodes the same amino acid, there is a change in genotype that is not accompanied by a change in phenotype.
3. *Nonsense mutations* arise when a change in one of the nucleotides of a codon changes the sequence to that of a stop codon. This results in premature termination of protein synthesis and produces a shortened protein (Figure 2.17).

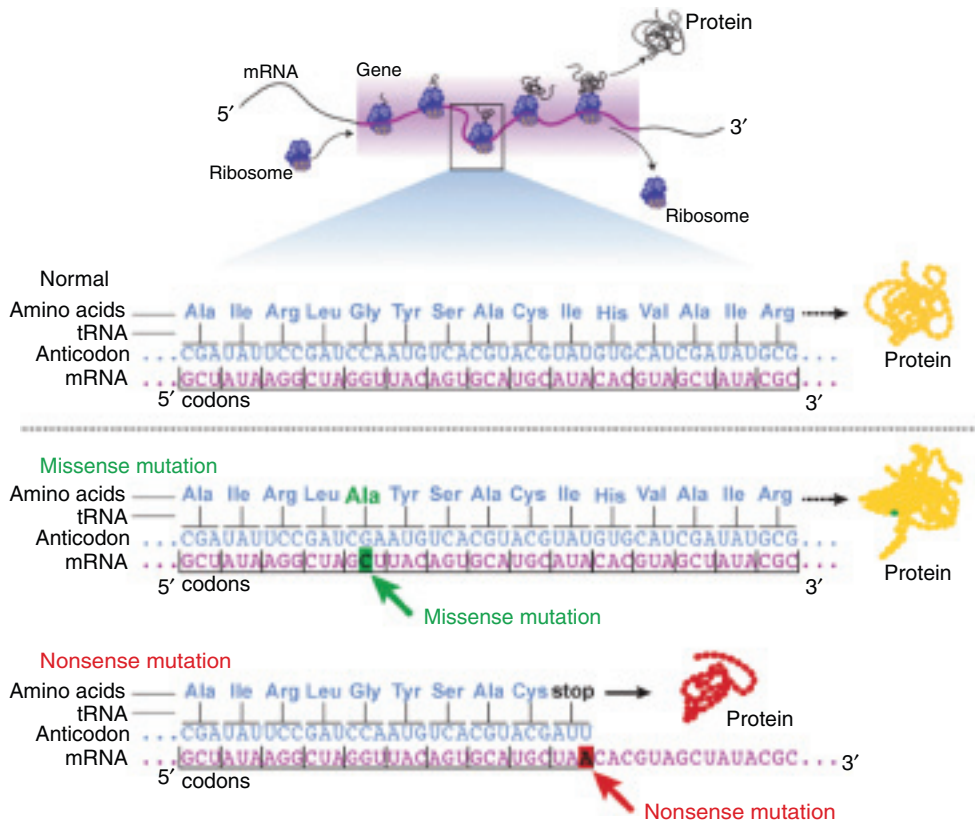


FIGURE 2.17. The effect of missense and nonsense mutations on the amino acid sequence of a polypeptide.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85225>

4. **Frameshift mutations** occur due to the insertion or deletion of a single nucleotide. This has a devastating effect on the resulting amino acid sequence as it throws off the reading frame, which is the group of three nucleotides that make up the codons in the mRNA. All of the codons downstream of where the frameshift mutation occurs are altered and now encode different amino acids, which completely changes the composition of the resulting protein. For this reason, frameshift mutations have a greater effect when they occur toward the 5' end of a gene than when they occur at the 3' end (Figure 2.18).

Alteration of the gene product may have different consequences, including the following:

- ▶ It may be clinically apparent in either the heterozygous or homozygous state.
- ▶ It might not be apparent unless the individual is exposed to a particular extrinsic agent or a different environment (as in exposure to general anesthetics in persons with malignant hyperthermia, as discussed in Chapter 6).
- ▶ It may be noticed only when individuals are being screened for variation in a population survey.

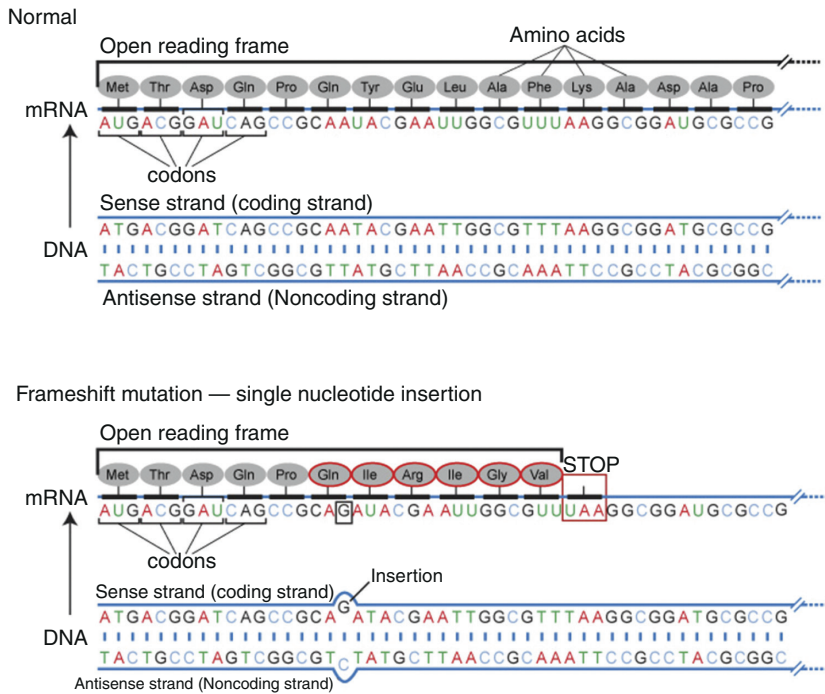


FIGURE 2.18. The effect of a frameshift mutation on the amino acid sequence of a polypeptide.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85168>

- It may be noticed only when a specific variation is being looked for (as in specific screening detection programs among populations for sickle cell trait or when specific genetic diagnostic testing among individual family members is done).

Sometimes mutations are described in terms of function. A *loss-of-function mutation* is said to occur when it results in defective, absent, or deficient protein. Mutations that result in a completely nonfunctional protein are called *null mutations*. Some mutations enhance the function of the resulting protein, often by increasing the quantity of the protein or conferring a new function on the protein, and are referred to as *gain-of-function mutations*. Mutant alleles may also code for a protein that interferes with the protein expressed by the nonmutated allele, often by binding to it and preventing it from carrying out its normal function. These are *dominant negative* mutations, and often are more deleterious to the cell than a null mutation where no functional protein is produced from a mutant allele.

Some DNA changes affect gene expression without alteration of the DNA sequence. Such alterations are referred to as *epigenetic modifications*, and the field of *epigenetics* studies the effect of these modifications on gene expression. There are three major epigenetic mechanisms: (a) addition or removal of methyl groups to histone proteins; (b) reversible methylation of DNA; and (c) regulation of gene expression by short noncoding RNA molecules called microRNAs. All of these modifications are heritable and affect gene expression.

MOLECULAR TECHNIQUES AND TOOLS FOR DETECTION AND DIAGNOSIS OF GENETIC DISEASES

Genomics

In 2001, the sequence of the human genome was published and marked the beginning of a revolution in the way that genetic information is analyzed. This venture, known as the *Human Genome Project*, was a combined effort between a publicly funded international collaboration and a privately funded venture. At a cost of around \$1 billion, it took 13 years to complete and spurred huge advances in DNA technology (National Human Genome Research Institute, 2014). These advances in our ability to analyze the genetic code have created a new approach to genetic analysis, known as “omics.”

Advances in our ability to sequence and analyze whole genomes (*whole-genome sequencing*) have progressed at a rapid pace led by next-generation sequencing technologies utilizing state-of-the-art fluorescent imaging techniques. It is now possible to sequence an entire genome in 2 to 3 days at a cost of around \$5,000 (Wetterstrand, 2014). Intense effort is under way to reduce this cost further, and a prize of \$10 million has been offered to any research group that is able to sequence the genome of 100 people in 10 days with high reliability, for a cost of just \$10,000 per genome. The goal is to eventually reduce the cost of DNA sequencing to a level of around \$1,000 so that it would be feasible to sequence the genome of an individual and include this information as part of his or her medical record. This *personalized genome* could then be scanned for the presence of genetic sequences that would directly impact health, particularly those that would indicate predispositions to preventable disorders.

The widespread availability of human whole-genome sequences has led to the development of many different fields of genomics research that use this information in different ways (Table 2.2). The *HapMap* project is a database of common genetic variants (*haplotypes*) in the human genome. By collecting and comparing genetic variations in different populations, it has been possible to identify disease genes and genetic factors contributing to complex traits. This type of approach is known as a *genome-wide association study* (GWAS), and has for the most part replaced genetic linkage studies. Individuals can vary in their response to certain medications depending on the gene variants that they carry, and the field of *pharmacogenomics* studies how different genetic variations affect a patient's response to medications. The era of *genomic medicine* is fast approaching when an individual's genetic information will be used for both diagnostic and therapeutic purposes as part of his or her clinical care.

Human genetic disorders can arise not only through changes in DNA sequence, but also through changes in levels or timing of gene expression. The field of *transcriptomics* analyzes gene expression of cells or tissues on a global level, thus creating an *expression profile*. This enables scientists to identify normal gene expression patterns, and detect changes from this norm that arise during disease development. Development of the technique of *DNA microarray analysis* has facilitated the comparison of gene expression profiles and allows the detection and analysis of thousands of genes simultaneously. A microarray consists of a solid surface such as a glass slide or silicon wafer on which single-stranded DNA molecules for thousands

TABLE 2.2. Definition of Fields of “Omics” Research

| “Omics” | Definition |
|------------------|---|
| Epigenomics | The study of the effect of epigenetic changes on gene expression |
| Genomics | The study of all of an individual’s genes (genome) including their interaction with other genes and the environment |
| Metagenomics | The study of genomes from a mixed population such as environmental samples |
| Pharmacogenomics | The study of how variations in a gene’s sequence affect responses to medication |
| Proteomics | The analysis of all of the proteins of a cell, tissue, or organism |
| Toxicogenomics | The analysis of the effects of toxic chemicals on gene and protein activity |
| Transcriptomics | Also known as <i>expression profiling</i> , and refers to the analysis of all mRNA transcripts in a population of cells or tissue |

Note: The suffix “-ome” is derived from the Greek word for *all* or *every*, and was originally used in the word *genome* to describe all of the DNA of an individual, including all of its genes.

of genes are spotted and immobilized (Figure 2.19). A single microarray slide can hold the entire human genome, and each gene is identified by its location coordinates. Tissue or cell samples to be compared are processed by extracting mRNA from each sample and labeling the mRNA with a fluorescent tag. The fluorescently labeled sample is then applied to a microarray slide and incubated to allow hybridization (binding) to the immobilized target DNA. The fluorescent signal is measured from each sample and compared so that differences in gene expression can be determined, and gene expression profiles can be developed for each sample. This technique has been very useful in classifying different types of cancers based on their expression profile; this information can then be used to design treatment strategies targeted to each specific type of cancer. For more information on microarray analysis, see National Human Genome Research Institute (2011).

The field of *epigenomics* studies the effect of epigenetic modifications on gene expression. Epigenetic changes are reversible modifications of a cell’s histones or DNA that alter gene expression without changing the DNA sequence. Techniques to identify these modifications, such as *chromatin immunoprecipitation* or *DNA methylation assays*, are used in conjunction with microarray analysis to determine the effect of these epigenetic modifications on resulting gene expression profiles. *Toxicogenomics*, likewise, uses a combination of genomic technologies to identify and characterize the effects of toxic chemicals on DNA structure and gene expression (www.ctdbase.org).

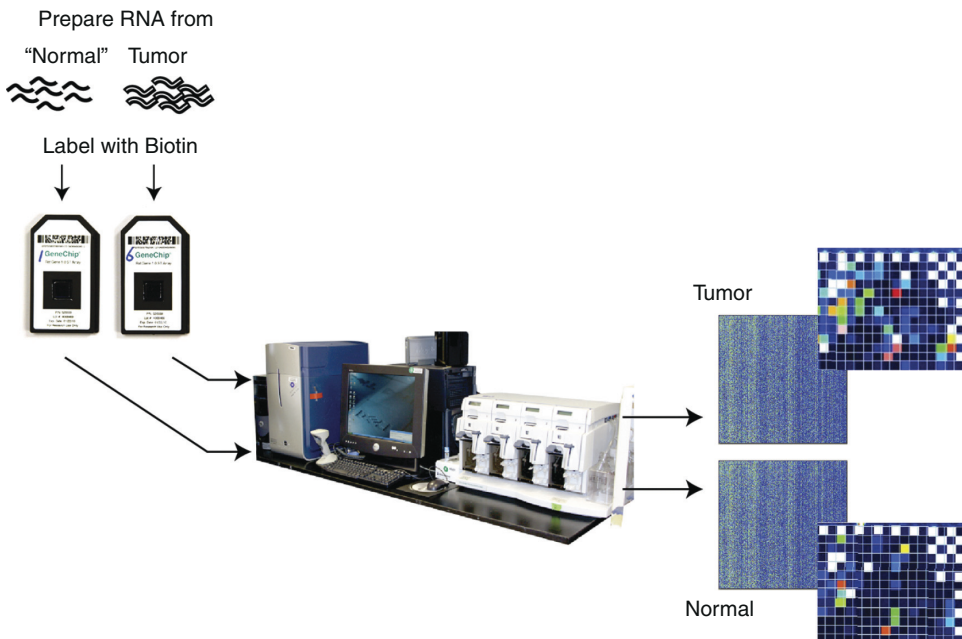


FIGURE 2.19. Workflow diagram of microarray analysis. RNA is extracted from the samples to be compared and is labeled with a fluorescent dye. (In this example, the RNA is labeled with biotin, which is then bound by antibiotin antibodies carrying a fluorescent tag.) The labeled RNA is applied to the slide and the amount of bound fluorescence is read by a microarray scanner. Computer software compares the intensity of the fluorescence for each gene in both samples and uses this to determine relative expression levels for each gene.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85200>

The study of *proteomics*, which is the large-scale characterization of the entire protein complement of a cell or organism, gives a broader picture of protein modifications and mechanisms involved in protein function, and allows the study of entire complex systems. This is important because transcriptome analysis has limitations as mRNA is not always translated into protein. Furthermore, there are many protein modifications that take place post-translationally, which can affect protein function; therefore, analysis at the protein level yields the most comprehensive picture of gene expression within a cell or tissue.

Metagenomics is an approach that sequences DNA from entire communities of microbes present in an environmental sample in order to identify all of the microbial members of that community. This is a powerful technique for analysis of microbial populations as many microbes cannot be cultivated by conventional laboratory techniques and therefore cannot be identified. This technique allows identification of microbes directly from the environmental sample and is being used to characterize all of the microorganisms in both healthy and diseased humans as part of the *Human Biome Project*.

Polymerase Chain Reaction

Another technique that has had a far-reaching impact in the medical field is the *polymerase chain reaction (PCR)*. This technique is powerful because it can specifically

amplify a chosen DNA segment rapidly and exponentially from a very small starting sample.

The PCR process mimics the method of DNA replication used by a cell. Heat is used to denature (unwind) the DNA of the sample to be amplified (template), which is then cooled to a temperature that permits two short pieces of DNA, approximately 18 to 20 base pairs, called *primers* to hybridize (bind) to complementary sequences on the template (sample) DNA (Figure 2.20). The sequences of these primers have been selected so that the primers contain sequences that are complementary to regions flanking the stretch of DNA to be amplified. The temperature of the reaction is then raised to that at which a heat stable form of DNA polymerase, called *Taq polymerase*, is active, which then binds to the primers and synthesizes a new strand of DNA using the base pairing rules and the existing strand as a template. The temperature of the reaction is then raised again to 95°C, which causes the DNA to denature once more. This is then repeated for around 30 cycles, and the result is exponential amplification of the template DNA with as much as 1 billion copies of target sequence produced in just a few hours.

The power of PCR lies in two of its properties. The first is that it can amplify DNA from extremely small starting samples such as a single nucleated cell. Thus, DNA can be obtained from scant sources such as a single hair, dried blood spots, saliva traces, or decayed DNA. This technique has revolutionized the field of forensics, where minute quantities of crime science DNA can be amplified to give unlimited faithful copies in sufficient quantities for meaningful analysis. In the medical field, PCR allows amplification of DNA from small samples such as single cells, which has facilitated techniques such as the genetic analysis of single cells from preimplantation embryos (Figure 2.20).

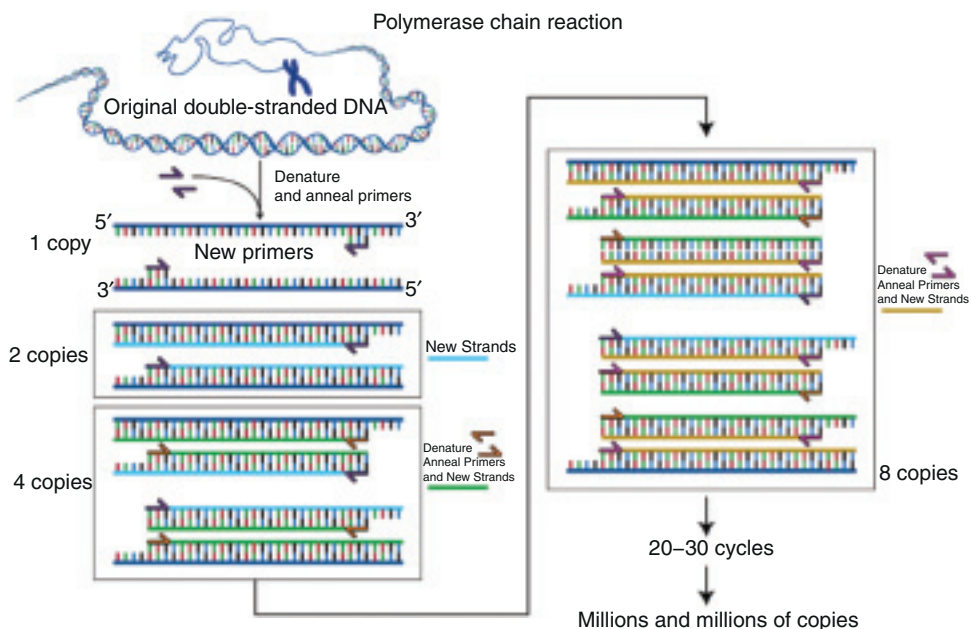


FIGURE 2.20. Amplification of DNA by the polymerase chain reaction.

Source: <http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85227>

In addition, the need for a relatively small starting sample has meant that samples can be collected in noninvasive ways such as cheek swabs. The second property of PCR that defines its usefulness is the specificity of the reaction. Amplification of the template will only occur if there is an exact match between the primer sequence and the template. Therefore, the presence of amplified DNA can be diagnostic for the presence of a specific DNA sequence. This property has been exploited for the detection of different genetic mutations, and also for the detection of infectious agents.

An additional application of PCR technology is the ability to generate a *genetic fingerprint*. The technique of *DNA profiling* uses PCR to amplify sections of the genome containing short sequences of DNA known as *short tandem repeats (STRs)* that are repeated many times in the genome. These DNA sequences do not encode proteins and are highly variable between individuals. Each STR can have as many as 20 different alleles (repeat lengths) with hundreds of different STRs being present in the genome. By analyzing just a small subset of the STRs, it is possible to uniquely identify an individual. This technique has revolutionized the field of forensic science, and because STRs are inherited, has found widespread application in the determination of paternity.

Other techniques for DNA analysis, such as the use of restriction enzymes that cut DNA at specific sequences for *restriction fragment length polymorphism (RFLP) analysis* or the identification of gene locations by *linkage mapping*, have mostly been superseded by DNA sequence analysis and PCR-based techniques. Although these techniques still have some limited applications, the ability to detect specific DNA sequences by PCR-based technology or by direct sequencing is usually much faster and more cost-effective.

KEY POINTS

- ▶ Genes are the basic units of heredity.
- ▶ Prior to cell division, replicated chromosomes are divided by mitosis in somatic cells, and by meiosis in germ cells.
- ▶ Mitosis gives rise to genetically identical diploid cells, whereas meiosis generates haploid cells that are genetically unique.
- ▶ Mutations create different alleles of a gene, which can cause variations in traits.
- ▶ A molecule of DNA consists of two strands of nucleotides held together by hydrogen bonds in a double helix conformation.
- ▶ DNA replication is semiconservative with an existing strand of DNA serving as the template for the synthesis of a new strand.
- ▶ The flow of genetic information within a cell is from DNA to RNA to protein.
- ▶ The DNA sequence of a gene is copied into mRNA during transcription.
- ▶ The codons on mRNA determine the sequence of amino acids in a polypeptide when translated by a ribosome.
- ▶ Changes in DNA sequence usually result in changes in the amino acid composition of the resulting polypeptide.

- ▶ The field of genomics allows direct analysis of DNA sequences and gene expression, and has had a great impact on the field of genetics.
- ▶ PCR is a powerful technique that allows the amplification of DNA from minute amounts with great specificity, and is the basis for many diagnostic tests.

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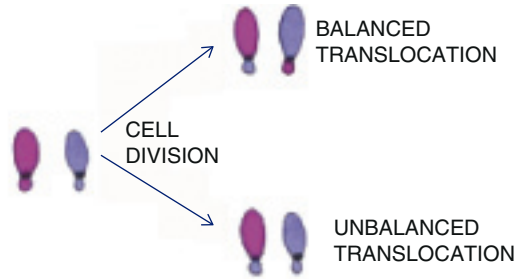
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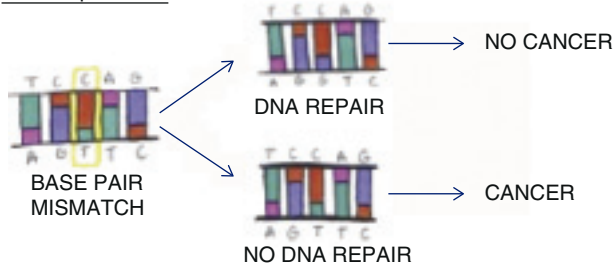
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Chromosomal Translocation

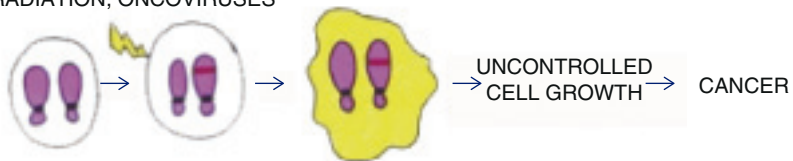


DNA Repair Gene



Oncogene

TOXINS, IONIZING RADIATION, ONCOVIRUSES



Tumor Suppressor Gene

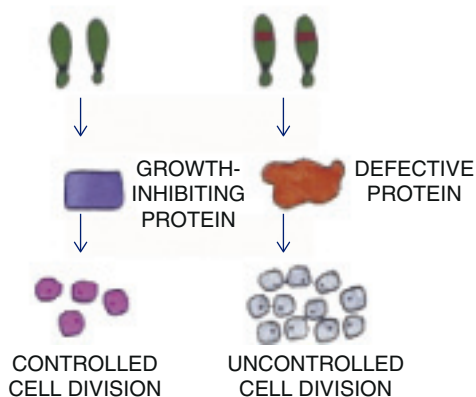


FIGURE 11.1. Genetic alterations in cancer.

CHAPTER 3

Human Diversity and Variation

Emma L. Kurnat-Thoma

WE ARE NOT ALL GENETICALLY IDENTICAL

CASE EXAMPLE 1

Ellen and Mary are next-door neighbors in Kansas City, Missouri. Both of them have had appointments with the same woman's health nurse practitioner for preconception counseling. Ellen, who is of Ashkenazi Jewish descent, has been asked to consider genetic testing to determine whether she might be a carrier for Tay–Sachs disease, as well as certain other conditions, but not β -thalassemia. Tay–Sachs disease is an autosomal recessive neurodegenerative disorder. Mary, who is of Greek descent, has been asked to consider genetic testing to determine whether she might be a carrier for β -thalassemia, but not Tay–Sachs disease. β -thalassemia is an autosomal recessive disorder resulting in deficient or absent synthesis of the β hemoglobin chains. After reading this chapter, you should be able to answer why the recommended testing was considered appropriate for each woman.

CASE EXAMPLE 2

Joan recently experienced a pulmonary embolism and must receive warfarin anticoagulation to prevent life-threatening clot formation. Genetic variation in two genes responsible for the metabolism of the drug accounts for up to 50% of patients' clinical response to warfarin. The nurse is reviewing a clinical test report for Joan that identifies her as having a *VKORC1*-1639 G>A single-nucleotide polymorphism (SNP) genotype AA, for which the Food and Drug Administration recommends a reduced warfarin starting dose. After reading this chapter, you will understand what this means and why SNP genotype should be considered before starting warfarin.

GENETIC INDIVIDUALITY

Each individual has a unique genetic constitution that makes him or her genetically and biochemically distinct from all other individuals (except for monozygous twins, triplets, and other identical multiples). No individuals, with the exceptions mentioned, have the exact same genotype or phenotype. Even identical twins can show *epigenetic* differences. Because a person's genetic constitution and environmental interactions are unique, each person has his or her own relative state of health and is not at equivalent risk for developing a given disease. A person's genetic makeup plays a pivotal role in the maintenance of homeostasis and in susceptibility and resistance to disease.

Most genes in humans are shared by all members of the human species. Differences have more to do with variation in frequency of certain alleles than in whether the gene is present or absent. The differing sequences (alleles) that result in genetic variation across individuals are called *polymorphisms* when they are maintained in a population with a frequency of at least 1%. Historically, genetic variation in humans was assessed by studying variation in proteins. For example, the ABO and Rh blood groups and the human leukocyte antigen (HLA) system are some of the best-known and classical examples of human genetic variation. Understanding genetic variation in these systems resulted in the ability to perform compatible blood product transfusions and tissue transplants between patients. Other classic examples of genetic variation include diseases characterized by microscopically observable alterations in chromosome number or shape (e.g., trisomies, monosomies, aneuploidies, translocations, and microdeletions).

Prior to the Human Genome Project, genetic variation in populations and/or families was evaluated by mapping genes to the chromosomes where they were located; once a gene was located on a chromosome, gene function was identified (e.g., how the cystic fibrosis gene was identified in 1989). Knowledge from recent federal and international scientific initiatives, such as the Human Genome Project (completed in 2003), the HapMap (Phase 3 completed in 2009), and the 1000 Genomes Project (Phase 3 completed in 2014), is fueling new understanding of human health.

Through advanced genotyping technologies that are also cost-effective, these initiatives have provided millions of newly identified sites of genetic variation, and are driving innovative approaches to detecting, diagnosing, and treating human disease. Knowledge of genetic variation in individuals and populations lays the foundations for understanding diagnostic genetic testing, performing forensic analysis in legal investigations, and determining variable risks/outcomes in disease development and therapeutic treatments Chapter 6, “The Application of Genomics to Pharmacology,” will review how individuals’ genetic differences can impact their responses to drugs.

VARIATIONS AND POLYMORPHISMS IN PROTEINS

Blood Group Systems

Immunogenetics is the study of the genetics of the immune system, and encompasses all the cells and mechanisms the body uses to determine “self” from “non-self” (e.g., to fight invading pathogens, foreign substances, etc.). The field came into being in 1900 when Dr. Karl Landsteiner first discovered that fatal hemolytic reactions after blood transfusions were caused by incompatible cell-surface antigens on red blood cells, known as the ABO blood group system. Presently, the ABO blood group system is one of 35 blood group systems, with hundreds of antigens recognized to be clinically significant in transfusion medicine (International Society of Blood Transfusions, 2014). However, the best characterized and most important are the ABO and Rhesus (Rh) systems. Compatibilities between the ABO and Rh blood group systems are crucial for successful blood transfusions and tissue graft transplantations. Incompatibilities in these systems between mothers and their developing fetuses can also have severe, even life-threatening consequences.

ABO System

The ABO system is the most clinically important blood group system. There are two major antigens found on the surface of red blood cells: A and B. These two antigens correspond to four blood group types: A (individual has the A antigen), B (individual has the B antigen), AB (individual has both the A and B antigens), and O (individual carries neither the A nor B antigen). In plasma, individuals with A antigen have anti-B antibodies, and individuals with B antigen have anti-A antibodies. The ABO locus is on chromosome 9; while A and B alleles are codominant, O is recessive. The A and B alleles code for glycosyltransferases, which are enzymes that add carbohydrate sugar precursors to form the A and B glycoprotein antigens. The O allele does not produce an enzyme. The A and B antigens are not confined to the red blood cell but are widely distributed throughout the body. There are various subtypes and polymorphisms of the A, B, and O alleles, and are beyond the scope of this chapter. The relationships between blood group phenotypes and genotypes are shown in Table 3.1, and examples of the inheritance of the ABO and Rh blood groups are illustrated in Figure 3.1. Persons with blood group O are universal blood transfusion donors, and are sometimes said to have a “null” phenotype. Persons with blood group AB are universal blood transfusion recipients because they have no antibodies in their plasma. Fre-

TABLE 3.1 ABO Blood Group System Relationships

| Blood Group (Phenotype) | Genotype(s) | Red Cell Antigen(s) | Antibodies in Plasma |
|-------------------------|-------------|---------------------|----------------------|
| A | AO, AA | A | Anti-B |
| B | BO, BB | B | Anti-A |
| AB | AB | A, B | None |
| O | OO | | Anti-A and Anti-B |

quency of the ABO blood group varies across ethnic and geographic groups and has been used in population genetics to study human diversity, migration, and selection. The ABO blood group has also been associated with various diseases. For example, the A antigen is linked to slightly increased risk of gastric cancer.

Rhesus (Rh) System

The Rh system is the second most clinically important blood group system because of its role in blood transfusion incompatibilities. It was not until 1940 that Dr. Landsteiner and Dr. Alexander Wiener discovered this system in experiments involving Rhesus monkeys. Since the initial discovery, this system has become complex with identification of over 40 known antigens encoded by two highly polymorphic genes. The most common is the D/d antigen. If D is present, this confirms a patient's "Rh-positive" status; conversely, if no D antigen is present the individual is "Rh-negative." Two other allele pairs, C/c and E/e, are also found on the Rh protein

ABO system*

| | | | | | | |
|---|----------------|---------|---------|---------|---------|---------|
| Parents | AO × BO | AB × OO | AA × BB | AA × BO | AB × BB | BB × OO |
| | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| Offspring genotype | AB, AO, BO, OO | AO, BO | AB | AB, AO | AB, BB | BO |
| Theoretical proportion for each pregnancy | ¼ ¼ ¼ ¼ | ½ ½ | all | ½ ½ | ½ ½ | all |
| Blood group phenotype | AB, A, B, O | A, B | AB | AB, A | AB, B | B |

Rh system

| | | | |
|---|---------|----------------|------------------------|
| Parents | Dd × dd | Dd × dd | Dd × Dd |
| Offspring | DD | Dd, dd | DD, Dd, dd |
| Theoretical proportion for each pregnancy | all | ½, ½ | ¼, ½, ¼ |
| Rh type | Rh (+) | Rh (+), Rh (-) | Rh (+), Rh (+), Rh (-) |

*Not all possible combinations are shown.

FIGURE 3.1. Selected examples of blood group gene transmission.

but are much less antigenic than D. The Rh antigen genes D/d, E/e, and C/c are very closely *linked* on chromosome 1 and are inherited as a *haplotype* (e.g., cDe, CDe, etc.). Figure 3.1 outlines this inheritance pattern. An Rh-negative (dd) woman and an Rh-positive man are more likely to have an Rh-positive child if the father is homozygous (DD) than if he is heterozygous (Dd). In the latter case, the chance that the child would be Rh-positive at each pregnancy is 50% as opposed to 100%. The frequency of Rh-positive, Rh-negative status varies widely based on ethnicity. Approximately 85% of Caucasians are Rh-positive, compared to 92% for African Americans and 99% for Asians.

The D Rh-antigen is highly immunogenic. Individuals without the D antigen produce anti-D antibodies if exposed, resulting in a hemolytic reaction. The significance of the Rh-system lies in its application to maternal–fetal Rh incompatibility. When the father is Rh-positive and the mother is Rh-negative, the Rh-positive fetus can receive maternal anti-Rh antibodies across the placenta in utero or during delivery and trigger hemolytic disease of the newborn (erythroblastosis fetalis). Hemolytic disease of the newborn is most often seen during the second or later pregnancies, after maternal sensitization to the D antigen develops. First pregnancies are often unaffected unless the mother experienced previous lost pregnancies that sensitized her immune system; later pregnancies can become progressively more severe as sensitization increases.

Rh incompatibility between a mother and fetus has a range of symptoms ranging from mild to fatal. In its mildest form, Rh incompatibility results in destruction of red blood cells, leading to jaundice in the newborn. At its most severe, infants may die in utero as a result of massive antibody-induced hemolytic anemia. Factors such as concurrent ABO incompatibility, volume of transplacental exposure, and extent of maternal immune response determine reaction severity. Consequently, determination of maternal Rh blood type is a standard requirement of prenatal care (The American College of Obstetricians and Gynecologists, 2013). For Rh-negative women, Rh immunoglobulin (i.e., RhoGAM) is administered at 28 weeks gestation and 72 hours after delivery to reduce the incidence of antenatal alloimmunization to about 0.1%. If the Rh of the father of the child is unknown and other conditions indicate the possibility of incompatibility (e.g., mother Rh [–], second pregnancy), Rh immunoglobulin should be administered.

Since the availability of Rh (D) immunoglobulin in 1968, the incidence of hemolytic disease of the newborn has markedly decreased. However, not all women who should be receiving Rh immunoglobulin are. Therefore, nurses need to be aware of events that can cause sensitization requiring Rh immunoglobulin administration, such as fetomaternal hemorrhage, spontaneous or induced abortion even in early pregnancy, any previous blood transfusion that was (or might have been) Rh incompatible, amniocentesis, chorionic villus sampling, fetal blood sampling, fetoscopy, abdominal trauma, and cesarean section.

The HLA System

A particular group of molecules located on the surfaces of most cells in the human body is known as the major histocompatibility complex (MHC; class I). MHC

molecules (class II) also present protein fragments to immune cells when detecting foreign substance(s), and triggers the body to mount an immune response. In humans, these MHC molecules are called human leukocyte antigens (HLAs). Major functions of the HLA system include acting as a marker of “self” and the presentation of antigens to T-helper cells. There is a large group of over 220 MHC genes located close together (within 4-Mb) on the short arm of chromosome 6, at 6p21.3. The MHC genes are categorized into three classes (I, II, and III) based on structure and function (World Health Organization Committee for HLA Nomenclature, 2014). The most clinically important antigen groups are the class I loci—*HLA-A*, *HLA-B*, *HLA-C*—and the class II loci—*HLA-DR*, *HLA-DP*, and *HLA-DQ* (Genetics Home Reference, 2009). Roles of others continue to emerge. The HLA system is the most polymorphic system known and expresses hundreds of different alleles. It provides tremendous human variability and ensures resistance to a wide variety of pathogens.

The major class I genes—*HLA-A*, *HLA-B*, and *HLA-C*—encode for antigens that are present on cell membranes of nucleated cells throughout the body. Class I antigens present antigenic peptide to cytotoxic-T (CD8+) cells and determine the response of natural killer cells. Class II locus antigens—*HLA-DQ*, *HLA-DP*, and *HLA-DR*—are primarily expressed on the surfaces of immunocompetent cells (e.g., B-lymphocytes, monocytes, endothelial cells, dendritic cells, activated T-lymphocytes, and macrophages) and present antigenic peptide to T-helper (CD4+) cells. The class III locus encodes numerous serum proteins and membrane receptors that are important for proper immune function, including complement components C2, Bf, C4A, C4B, as well as products unrelated to the immune system such as steroid 21-hydroxylase, the major heat shock protein, and tumor necrosis factors (TNFs).

Since letters are assigned to the HLA loci in the order of their discovery, they do not reflect their order on the chromosome. The HLA genes are tightly linked and are usually inherited together codominantly, with infrequent recombination (less than 1%) occurring. *Linkage disequilibrium* occurs when two or more of the alleles in the HLA system are inherited together in a haplotype more frequently than would be expected by chance. In European populations, *HLA-A1* and *HLA-B8* occur together with an observed frequency that far exceeds the expected frequency from random assortment of alleles during meiotic recombination. The frequency of individual HLA antigens varies according to different ethnic populations; for example, *HLA-A9* is present in 65% of Asian populations but only 17% of European Caucasian populations. *HLA-B8* is common in White populations and rare in Asians. There is also significant variation in the ethnic distribution of HLA haplotypes.

The largest single use for HLA typing is in tissue and organ transplantation, including blood products. In some institutions, typing of the *HLA-A*, *HLA-B*, and *HLA-C* loci is used to screen donors for platelet and leukocyte transfusions because of the problem of sensitivity for those persons already having such multiple transfusions.

HLA and Disease Associations

Intense interest in the HLA system was originally generated because of the realization of its role in successful tissue graft and organ transplantation. This interest expanded to include the relationship among HLA antigens, haplotypes, and the development

of certain diseases. It was recognized that individuals with specific HLA alleles and haplotypes were much more likely to develop certain diseases. Some of the strongest associations involve autoimmune diseases or disorders featuring an immunologic defect.

In genetics, scientists can study the expected frequency of disease prevalence in groups of patients with and without certain genotypes and/or haplotypes, and calculate an estimate for the strength of the association and a patient's risk for developing an illness. Relative risk refers to how much more frequently a specific disease develops in individuals carrying a specific HLA antigen, compared to the frequency of disease in individuals who do not carry it. It is important to remember that relative risk calculations produced from genetic association studies are estimates and not an absolute prediction of risk. Not all individuals with a particular HLA genotype may develop a certain illness despite the strong association. In addition to disease susceptibilities, genetic association studies can also identify protective genetic effects. For example HLA-B*53 is protective against severe malaria in West Africa.

Two of the most striking HLA-disease associations are between HLA-B27 and ankylosing spondylitis, an inflammatory joint disease often resulting in vertebral fusion, and of HLA-DQB1*0602 and narcolepsy, a primary sleep disorder characterized by excessive daytime sleepiness and disturbances of rapid eye movement (REM) sleep due to deficiency of the neuropeptide hypocretin. HLA-B27 is found in 90% to 95% of patients with idiopathic ankylosing spondylitis regardless of ethnic group. In populations without the disorder, HLA-B27 is found in 6% to 8% of European and North American Whites, 2% of Chinese and Black Americans, and 0.2% of Japanese populations. It is estimated that a male with the B27 antigen has a relative risk of developing the disorder that is 90 to 100 times greater than a male not possessing this antigen. The chance for a person who has HLA-B27 to develop ankylosing spondylitis is estimated at 5% to 20%. Thus, not all those with HLA-B27 develop ankylosing spondylitis, although some may have subtle symptoms that never develop into disease and are not detected. HLA-B27 is found in 75% of persons with Reiter disease, and up to 90% of persons who develop arthritis after enteric infection due to *Shigella*, *Salmonella*, and certain *Yersinia* species.

In narcolepsy, HLA DQB1*0602 is present in 90% to 100% of persons with narcolepsy and cataplexy (brief sudden episode of weakness in voluntary muscles triggered by emotions such as laughing or anger). In contrast, HLA DQB1*0602 is present in 12% to 38% of the general population. Hypocretin genes are located in the HLA vicinity, although how they interact is not known. There has also been an association between HIV-1 disease and various HLA genotypes. For example, both HLA-B27 and HLA-B57 have been associated with slow progression, while certain HLA-B35 alleles (HLA-B*3502, *3503, and *3504) have been associated with rapid progression.

VARIATIONS AND POLYMORPHISMS IN DNA

With the exception of identical multiples, humans resemble each other in 99.9% of their DNA. This means that out of the total 3 billion base pairs in the human genome, there are ~10 million polymorphisms that make us uniquely different from one

another. Thus, the remaining 0.1% difference creates a unique “fingerprint” among individuals and populations, and occurs within the coding (exonic) regions or non-coding (intronic) regions. Polymorphisms occur with a frequency of approximately 1:300 base pairs and are more frequent outside of gene coding areas. Polymorphisms may be single or multiple, and the more alternate alleles that exist in populations, the more useful they are for genetic and medical applications (see genetic testing in Chapter 5). Table 3.2 summarizes the most common types of human genetic variation. Genetic variation provides the basis of various DNA tests used for:

- ▶ Genetic testing for diagnosis of certain disease conditions
- ▶ Prenatal diagnosis of genetic disease
- ▶ Tissue typing for organ transplantation
- ▶ Distinguishing between similar-appearing diseases at the molecular level
- ▶ Determining carrier status for certain genetic disorders
- ▶ Determining the microbial etiology of a person’s infectious disease, and tracing variations in microbes to determine origins and patterns of spread
- ▶ Determining genetic parentage and other family relationships in clinical testing, criminal investigations, and legal disputes
- ▶ Individual identification in legal and forensic cases, including disasters and military personnel, and matching DNA in material at crime scenes or on victims with that of suspects on file in data banks
- ▶ Defining population structure and performing research studies elucidating the clinical impact of genetic sequence (functional studies)

TABLE 3.2. Selected DNA Variations

| Variation | Description |
|-----------|---|
| RFLPs | Single base pair changes in DNA sequence resulting in “cutting” at a recognition site for a restriction enzyme. This produces increased or decreased strand lengths for cut restriction fragments, and can be measured in laboratory analysis. Used in classic genetic mapping experiments. |
| SNPs | Single-nucleotide changes in DNA. Patterns of SNPs are being used to look at particular variation patterns across populations and ethnic groups. SNPs may or may not be associated with disease, and are used in laboratory research studies to elucidate a gene’s function (functional studies). SNP applications are fueling genomic health care, or <i>personalized medicine</i> . |
| STRs | Short nucleotide repeats of two to five base pairs that are repeated a few to several hundred times. Commonly used in forensic analyses. |
| VNTRs | Short DNA sequences from 10 to 100 base pairs that are repeated in tandem order a varying number of times. Used in forensic analyses. |

Restriction Fragment Length Polymorphisms (RFLPs)

An early method of detecting DNA polymorphisms used bacterial *restriction enzymes* (restriction endonucleases) to recognize short, specific nucleotide sequences and make a “cut” in the DNA strand (Nussbaum, McInnes, & Willard, 2004). During RFLP laboratory analysis, the presence or absence of polymorphisms (can also be deletions or insertions) determines if “cuts” are made. When a particular polymorphism sequence is present and a “cut” occurs, one long strand of DNA is cut into shorter fragments (i.e., a 1.3 kb segment becomes 1.1 kb and 200 bp). The variable lengths of these restriction fragments can be separated and sorted by gel electrophoresis, transferred to a radioactive-isotope-labeled probe, and visualized by x-ray. RFLP analysis was the method used to identify polymorphisms instrumental in mapping the genes for cystic fibrosis and Huntington disease. While RFLP analysis was essential to early genetics medical care and research, it is not used frequently today. The enzyme can only detect two possible alleles (presence or absence of polymorphism) at the restriction site sequence, so the amount of genetic diversity that can be detected is limited. Since high-throughput genotyping has become so cost-effective in the past decade, SNPs are more plentiful, informative, relevant, and appropriate for use with genomic technologies.

Minisatellite and Microsatellite Polymorphisms— Variable Number of Tandem Repeats (VNTRs) and Short Tandem Repeats (STRs)

Another class of polymorphism similar to RFLPs allowing for detection of greater human diversity is *minisatellites* and *microsatellites* (Nussbaum, McInnes, & Willard, 2004). Minisatellites and microsatellites are distinct areas of the genome where the same DNA sequence repeats over and over. The terms are often used interchangeably to denote VNTRs and STRs. Minisatellites (VNTRs) are characterized by longer repeating DNA segments (i.e., 10 to 100 bp) while microsatellites (STRs) are characterized by shorter repeating DNA segments (i.e., 2, 3, 4, 5 bp). The number of repeats occurring within minisatellite and microsatellite regions of the genome can vary between individuals and is a significant type of human variation.

VNTRs are a type of polymorphism detected between two restriction sites. Individuals can have as few as 2 to 3 copies of repeating 10 to 100 bp DNA sequence in a minisatellite region, while others could have more than 20 copies. VNTRs are detected by a process similar to that described in the RFLP section above. A restriction enzyme digest is performed, and cut fragments are separated by gel electrophoresis, transferred to a radioactive-isotope-labeled probe, and visualized by x-ray. VNTRs are characterized by many alleles, as the number of repeats across individuals at specific sites in the genome varies greatly.

Occurring in even greater frequency than VNTRs, STRs are also a type of polymorphism, but cannot be detected between two restriction sites. The *polymerase chain reaction (PCR)* laboratory technique is used to amplify large quantities of a specific segment of DNA that contain STRs. Individuals can have as many as several

hundred repeats of 2, 3, 4, or 5bp sequence copies (i.e., TAC, TAC, TAC, etc.). STRs occur widely throughout the genome and are extremely useful for gene mapping.

Both VNTRs and STRs are used for forensic applications including criminal investigations, genetic parenthood testing, and identification of deceased individuals following disasters and military conflicts. Since DNA is present in all tissues, it can be isolated and accurately amplified with PCR from most samples (e.g., tissue, blood, saliva, hair, semen, etc.), even if the sample is very small or has been stored for several years. Because VNTRs and STRs have so many alleles, a combination of several loci can be used to generate a highly specific DNA profile for an individual. Since two persons could have the same DNA profile at one locus, multiple sets of specific and highly variable regions are used to decrease the probability that a randomly selected person in the population has the exact same genotype; for example, estimated random match probability that two individuals have the exact same number of allelic repeats for all loci in a Federal Bureau of Investigation (FBI) standardized panel (Combined DNA Index System—CODIS) of 13 STRs approaches 1 in 100 trillion (Federal Bureau of Investigation, 2014; Hill, 2012). The greater the number of VNTRs or STR loci that are used in conducting forensic analyses, the greater the odds are that the match is not coincidental, but more time and expense is involved. Typically the 13 CODIS markers suffice for most general forensic matching applications, but more can be used. The uniqueness of the DNA profile is often referred to as a form of “fingerprinting” and serves as a powerful tool in criminal investigations. Given sound sample collection techniques and carefully calibrated laboratory conditions, DNA evidence using VNTRs and STRs provides solid proof of innocence, guilt, or personal identity.

Single-Nucleotide Polymorphisms (SNPs)

Completion of the Human Genome and HapMap projects provided a detailed map of the human genome and the extent of human genetic variation from single-nucleotide polymorphisms (pronounced “snips”). SNPs are genetic polymorphisms involving the variation of a single base pair at a given loci among individuals in a population. The difference between SNPs and RFLPs is that more than two options for SNPs are possible—SNPs can have any range of C, T, A, G, or deletion, at a given loci—versus the specific presence/absence of a singular difference for RFLP. In the following example, the third patient has a C-to-T base pair polymorphism in the second position. In medical, research, and clinical literature, this C-to-T SNP substitution could be indicated in several ways: C/T, C → T, or C > T.

Patient 1 sequence: TCCAGT

Patient 2 sequence: TCCAGT

Patient 3 sequence: TTCAGT

Patient 4 sequence: TCCAGT

There are different types of SNPs, and they can be located in exons and introns. SNPs in exons are categorized as being *synonymous* or *nonsynonymous*. Synonymous

SNPs are single-nucleotide alleles that *do not* result in an amino acid change. Nonsynonymous SNPs are single-nucleotide alleles that *do* result in a different amino acid being incorporated into a protein. Thus, the most clinically relevant SNPs are those occurring in exons of genes that produce amino acid changes—the nonsynonymous category. SNPs in critical locations of an exon can exert functional effects on protein translation just like mutations do. Nonsynonymous SNPs mirror the categories of genetic mutations discussed in Chapter 2 and include the following types: missense (a SNP results in an amino acid substitution); nonsense (a SNP results in an amino acid being switched for a stop codon, causing a shortened protein); and frameshift (a SNP is a single base indel that throws the reading frame off for all downstream amino acids). While it seems counterintuitive for intronic sequence variants to have an impact on protein coding, this can be the case for intronic SNPs near splice sites or in gene flanking regions that regulate transcription (the 5' or 3' untranslated regions). SNPs that are near a gene, or within several thousand base pairs, can still have an impact on protein assembly. SNPs in introns at a great distance from any gene are called genomic or extragenic. Effects of extragenic SNPs may impact the regulation of gene expression or other DNA functions such as replication.

SNPs have multiple ways of being identified, and significant inconsistency exists in SNP documentation for clinical applications and scientific research (Human Genome Variation Society, 2014). Thus, patient genetic test reports containing SNP results can include any combination of the content discussed in this paragraph. The Human Genome Variation Society (HGVS) provides some general SNP nomenclature guidelines, the most important of which include either (a) the use of a reference sequence number to denote a SNP's genomic position (i.e., rs9621049) or (b) a gene coding position (c.1043C>T). There is significant debate in the field for which approach to use. Typically, SNPs are given an established reference sequence number (rs#) in dbSNP, a federal database (www.ncbi.nlm.nih.gov/SNP) that catalogs millions of formally registered SNPs. Knowing the SNP rs# or coding position is very useful because a clinician can go to dbSNP, enter this information, and obtain the gene name, position in the gene where the SNP is located, and what category of SNP it is. Different letters before a gene coding position are used to describe the type of reference sequence being used: “c” for a coding DNA sequence (e.g., c.1043C > T); “g” for a genomic sequence (e.g., g.15259C > T); “p” for a protein sequence (e.g., p.Ser348Phe); “r” for an RNA sequence (e.g., r.76a > u); or “m” for a mitochondrial sequence (e.g., m.8993T > C). SNP insertions or deletions are indicated by the shortened abbreviations “del” (e.g., c.205delC) or “ins” (e.g., c.103insT). Readers are referred to the HGVS (www.hgvs.org/content/guidelines) for additional details beyond the content summarized here. Box 3.1 provides an example of SNP naming and its clinical application.

As high-throughput technologies have drastically reduced DNA sequencing costs in the past 10 years, use of SNPs in health care applications exploded. Currently, SNPs are driving *personalized medicine*—an emerging health care specialty that uses an individual's genetic profile to make decisions about disease prevention, diagnosis, and treatment. Similar to how knowledge of the ABO and Rh proteins transformed transfusion medicine safety and treatments, knowledge of SNPs and gene sequences are being harnessed to understand patients' individual disease presentations, drug

BOX 3.1**SNP Nomenclature—Key to Understanding a Patient's SNP Genotype in Clinical Settings**

Since the completion of the Human Genome and HapMap Projects, the knowledge of genetic sequence and SNP polymorphism sequence is changing health care. Understanding information about human genetic variation and interpreting a patient's gene mutation report or SNP test result can be challenging if a clinician does not understand the nomenclature.

Clinical Example: SNP Name Variations for VKORC1 rs9923231

The vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) gene encodes a protein essential for blood clotting. The Food and Drug Administration currently recommends adjusted dosing for the anticoagulant warfarin (Coumadin) that takes *VKORC1* SNP genotype (and others) into account (see Chapter 6 for a more detailed discussion). *VKORC1* SNP rs9923231 is a G>A SNP located on the short arm of chromosome 16 (16p11.2) in the promoter region of the gene. This SNP alters efficacy of *VKORC1* transcription; the activity of the G allele performs 44% more effectively than the A allele. These functional differences in gene expression lead to fewer copies of the *VKORC1* protein (which is a rate limiting enzyme in the vitamin K cycle), and accounts for 15%–30% of the clinical variability in a patient's warfarin response. Individuals with the AA genotype need reduced anticoagulant dosing because they are at highest risk for warfarin-related adverse events such as life-threatening bleeding.

There are several names used in clinical reporting and in medical literature for this SNP:

- ▶ **rs9923231**. Reference sequence number
- ▶ **G3673A**. G-to-A SNP at gene position 3673
- ▶ **c.-1639 G > A**. G-to-A SNP in coding position –1639 (the negative sign indicates promoter, before the start of coding)
- ▶ **upstream –1639 G > A**. G-to-A SNP, upstream of coding start site at position –1639

It should be noted that because this SNP is located in a promoter, it does not code for an amino acid switch. This is why there are no protein names in addition to the gene and coding names. SNPs that exert protein coding effects are also named by their amino acid changes, similar to mutations (see Chapter 2). A SNP causing a serine to proline amino acid switch at coding position 235 would be called Ser235Pro or S235P.

Clinical Translation: Where to Find Further Information to Understand SNPs

If, during your clinical practice, you become confused by a patient's sequence or mutation report, try the following:

1. Identify the SNP by entering the rs# or coding sequence information into dbSNP.
2. Identify whether it is a coding or noncoding exonic SNP, or intronic SNP near important areas of the gene. Note the gene name if you do not already know it.
3. Go to the Online Mendelian Inheritance in Man website (www.ncbi.nlm.nih.gov/omim) and enter the gene name. Read the brief gene summary and interpret implications of the patient's SNP in the context of normal gene function and clinical phenotype.
4. *Optional.* Verify SNP allele frequency for ethnic populations of interest (see hapmap.ncbi.nlm.nih.gov). Under "Project Data," select an option including Phase 3 data. Insert rs number into search box to locate the SNP of interest. Under "Details," scroll the mouse over or select the blue/red icon for genotyped SNP allele frequency data. Allele frequencies will be shown for ethnic subpopulations including: Caucasian (CEPH = Utah), African (Southwest United States, Kenya, or Nigeria), Chinese (Denver or Beijing), Japanese, Mexican (Los Angeles), Gujarati Indian, and others.
5. *Optional.* Verify relevant pharmacogenetic implications for the SNP (see www.pharmgkb.org).

responses (see Chapter 6), and other phenotypes of interest. Although each person's SNP pattern is unique (except for monozygotic multiples), most SNPs are not responsible for causing disease. But SNPs can be located near a gene associated with a disease of interest, similar to the previous HLA disease association examples in this chapter. SNPs can also contribute to disease development if the person carries a higher risk SNP allele and is exposed to a particular environment or toxin (e.g., higher risk genotype plus smoking). Recent research in this field uses genomic sequence generated by the Human Genome Project to correlate SNPs in linkage disequilibrium with diseases, drug responses, environmental exposures, and clinical phenotypes. Greater understanding of genetic contributions to multifactorial diseases (e.g., diabetes mellitus, cancer, addictions, depression) is leading to the development of novel therapies, identification of target genes responsible for diseases, and quantification of disease risks, given specific lifestyle choices (e.g., nutrition, smoking, alcohol use, etc.).

Mitochondrial DNA Variants

Mitochondria are the complex energy-producing "power plants" of cells in the body. While much smaller than the human nuclear genome, mitochondria have their own genomes, which contain just over 16,000 nucleotides and 37 genes. However each mitochondrion has on average five full mitochondrial genomes and most cells can

have over 1,000 mitochondria. Thus, mutations and polymorphic variants may not produce an effect if there are only several variations in a single cell's mitochondria for the same individual. Variation from mutations and polymorphisms in a single cell of an individual's mitochondrial genome is known as *heteroplasmy*, and occurs in 90% to 100% of individuals. Disease occurrence is dependent on the proportion of normal mitochondrial DNA to mitochondrial DNA with variants and mutations in the cells of various tissue types (tissues with higher energy requirements are usually the most affected). Cellular mitosis in dividing cells/tissues can affect this proportion. Research continues to elucidate the role of mitochondrial polymorphic variation in disease development. Recent findings differentiate benign and harmful heteroplasmy, and identify mechanisms used by the body (albeit inefficient) to reduce harmful ones. Research is ongoing to link mitochondrial polymorphism heteroplasmy to diseases of mitochondrial malfunction. Chapter 4 reviews mitochondrial diseases and their inheritance in more detail.

MAINTENANCE OF VARIATION AND POLYMORPHISM IN POPULATIONS

Rare, inherited, single gene biochemical disorders are extreme examples of the spectrum of genetic diversity or variation. This is because all genetic variations begin with mutation. But once multiple alleles occur for a given locus with a frequency in a population of individuals greater than 1%, they are classified as genetic polymorphisms. Genetic variations that are too rare to meet the criteria for a polymorphism in the general human population may assume higher frequencies within particular population groups. Population groups that have shared a common ancestry may be isolated from the general population for cultural, social, religious, economic, political, linguistic, or geographic reasons. Members of a particular population group often pick mates or intermarry within that same group. This results in the occurrence of specific rare alleles in the population group's gene pool (the collection of genes in a particular population), as compared to the general population. Examples of such groups include Finns, Icelanders, Pacific Islanders, and Ashkenazi (Eastern European) Jews. Knowing whether a patient belongs to a particular population group can help a clinician to understand if additional screening, prenatal consultation, diagnostic workup, or specific health prevention measures are needed. Genetic diseases known to be present in higher frequencies of certain population groups are shown in Table 3.3. The presence of these rare alleles and disorders in higher frequency in some population groups is not "good" or "bad." Many evolved because in the heterozygous or carrier state, they offered some type of protection (selective advantage), or because of founder effects and population "bottlenecks," as described later in this chapter. As members of specific racial and ethnic groups intermarry, intermate, and become less isolated, there will be fewer definable genetic disorders occurring with greater frequency within given population groups.

Population geneticists are interested in why certain variations and polymorphisms occur in populations. They use mathematic formulas to determine mutation rates and to measure the effects of migration. One of the fundamental principles

TABLE 3.3 Distribution of Selected Genetic Traits and Disorders by Population or Ethnic Group

| Ethnic or Population Group | Genetic or Multifactorial Disorder Present in Relatively High Frequency |
|----------------------------|---|
| Aland Islander | Ocular albinism (Forsius–Eriksson type) |
| Amish | Limb-girdle muscular dystrophy (Adams, Allen counties, Ohio) Ellis–van Creveld (Lancaster County, Pennsylvania) Pyruvate kinase deficiency (Mifflin, Ohio) |
| Armenian | Familial Mediterranean fever |
| Black (African) | Sickle cell disease Hemoglobin C disease Hereditary persistence of hemoglobin F glucose-6-phosphate dehydrogenase (G6PD) deficiency, African type Lactase deficiency, adult β -thalassemia |
| Burmese | Hemoglobin E disease |
| Chinese | G6PD deficiency, Chinese type Lactase deficiency, adult |
| Costa Rican | Malignant osteopetrosis |
| Finnish | Congenital nephrosis Generalized amyloidosis syndrome, V Retinoschisis Aspartylglucosaminuria Diastrophic dwarfism |
| French Canadian (Quebec) | Mucopolysaccharidosis, type IV A (Morquio syndrome) |
| Gypsy (Czech) | Congenital glaucoma |
| Hopi Indians | Tyrosinase positive albinism |
| Icelander | Phenylketonuria (PKU) |
| Inuit | Congenital adrenal hyperplasia Pseudocholinesterase deficiency Methemoglobinemia |

(continued)

TABLE 3.3 Distribution of Selected Genetic Traits and Disorders by Population or Ethnic Group (continued)

| Ethnic or Population Group | Genetic or Multifactorial Disorder Present in Relatively High Frequency |
|---|--|
| Irish | PKU Neural tube defects |
| Japanese | Acatlasemia Cleft lip or palate Oguchi disease |
| Jewish | |
| Ashkenazi | Tay–Sachs disease (juvenile) Niemann–Pick disease (juvenile) Gaucher disease (adult type) Dubin–Johnson syndrome Familial dysautonomia Bloom syndrome Torsion dystonia Factor XI (plasma thromboplastin antecedent) deficiency |
| Sephardic | Familial Mediterranean fever Ataxia–telangiectasia (Morocco) Cystinuria (Libya) Glycogen storage disease III (Morocco) |
| Lapp (North Scandinavian) | Developmental hip dysplasia |
| Lebanese | Dyggve–Melchior–Clausen syndrome |
| Mediterranean (Italians, Greeks) | G6PD deficiency, Mediterranean type β -thalassemia Familial Mediterranean fever |
| Middle East Northern European Caucasian | Dubin–Johnson syndrome (Iranian and Moroccan Jews in Israel) Werdnig–Hoffmann disease (Karaite Jews) G6PD deficiency, Mediterranean type PKU (Yemenite Jews) Metachromatic leukodystrophy (Habbanite Jews, Saudi Arabia) Cystic fibrosis PKU |
| Nova Scotia Acadian | Niemann–Pick disease, type D |

(continued)

TABLE 3.3 Distribution of Selected Genetic Traits and Disorders by Population or Ethnic Group (continued)

| Ethnic or Population Group | Genetic or Multifactorial Disorder Present in Relatively High Frequency |
|---------------------------------------|---|
| Polynesian | Clubfoot |
| Polish | PKU |
| Portuguese | Familial transthyretin (TTR) amyloidosis, type I Machado–Joseph disease |
| Scandinavian (Norwegian, Swede, Dane) | Cholestasis–lymphedema (Norwegians) Sjögren–Larsson syndrome (Swedes) Krabbe disease PKU |
| Scottish | PKU Cystic fibrosis |
| Slovakian | Alkaptonuria |
| Zuni Indian | Tyrosinase positive albinism |

in population genetics is the Hardy–Weinberg principle, which is useful for population health inferences and practical applications in genetic counseling. Briefly, it holds that population gene frequencies and population genotype frequencies remain constant across generations if mating is random, and the effects of mutation, selection, immigration, and emigration are not present. The Hardy–Weinberg equation is $p^2 + 2pq + q^2 = 1.0$ and can provide an estimate of disease prevalence in a population, or provide estimates of heterozygous carriers for rare autosomal recessive diseases (Jorde, Carey, & Bamshad, 2009). Table 3.4 identifies how the Hardy–Weinberg equation terms are applied to the classic Punnett Square.

TABLE 3.4 Punnett Square Illustrating Hardy–Weinberg Principle

| | Allele A p = Gene frequency | Allele B q = Gene frequency |
|---|---|---|
| Allele A p = Gene frequency | AA Genotype p^2 | AB Genotype pq |
| Allele B q = Gene frequency | AB Genotype pq | BB Genotype q^2 |

TABLE 3.5 Expected Versus Observed Frequencies for Hardy–Weinberg Evaluation

| Expected Frequency per Hardy–Weinberg Law | Observed Frequency in Sample |
|---|------------------------------|
| $AA = p^2 = 0.547 \times 0.547 = 0.299$, or 2,990 individuals | 2,900 |
| $AB = 2pq = 2 \times 0.547 \times 0.453 = 0.496$, or 4,960 individuals | 5,140 |
| $BB = q^2 = 0.453 \times 0.453 = 0.205$, or 2,050 individuals | 1,960 |

This section outlines an example of how to tell whether a sample population is in Hardy–Weinberg equilibrium. Let us say, we obtain a sample of 10,000 individuals from a town’s population and the allele frequencies for a disease-causing gene locus are counted. There are two alleles, A and B, yielding the following genotype frequencies for the sample: 2,900 individuals have AA genotype (2,900/10,000 = 0.290 or 29%); 5,140 individuals have AB genotype (5,140/10,000 = 0.5140 or 51.4%); and 1,960 individuals have BB genotype (1,960/10,000 = 0.196 or 19.6%). The sum of the sample’s population genotype frequencies equals 1.0 = 0.29 + 0.514 + 0.196. We next derive the sample population’s allele frequencies:

- ▶ Frequency of allele A = $0.290 + 0.5 \times 0.514 = 0.547$
- ▶ Frequency of allele B = $1 - 0.547 = 0.453$

We have now calculated all the allele and genotype frequencies from our town’s sample population. Finally, we must calculate the *expected* genotype frequencies under the principle of Hardy–Weinberg law using the $p^2 + 2pq + q^2 = 1.0$ formula. To obtain the number of expected individuals, we multiply each genotype frequency by the total number of the sample population (i.e., $0.299 \times 10,000$) and compare to what was observed (Table 3.5).

If the expected and observed values do not match, our town’s population is not in Hardy–Weinberg equilibrium. It is common for disequilibrium to be present, as the assumptions of the principle are fairly stringent. Reasons for disequilibrium are often explored further by population geneticists but can be difficult to identify exactly. Allele frequencies in populations can change because of effects including: mutation, selection, migration, fitness, random genetic drift, nonrandom mating, and linkage to a favorable or an unfavorable gene (the so-called hitchhiker effect). Collectively over time, these influences comprise the basic mechanisms of genetic evolution. Common factors that impact allele frequencies in population groups are highlighted in Table 3.6.

Selection and Selective Advantage

Some alleles can be eliminated from the gene pool in the homozygous recessive state, while simultaneously maintaining a higher heterozygous frequency than could be observed by mutation alone. This suggests that their presence confers some type of selective advantage to the heterozygote over the homozygote. A common

TABLE 3.6 Factors That Alter Allele Frequencies in Populations

| Factor | Definition |
|------------------------|--|
| Fitness | The ability of a person to reach reproductive age and pass on his or her genes to the next generation (Orr, 2009). An example is individuals who are homozygous for the gene for juvenile Niemann–Pick disease, an autosomal recessive disorder characterized by severe neurological effects and delays, and childhood death. These genotypes have a low degree of fitness because they are not transmittable to the next generation. |
| Founder effect | A genetic mutation observed in higher frequency due to the presence of the mutation in a single ancestor or a small number of ancestors; for example, when a small group from a large population migrates to another locale and one or more members of the founding group possess a variant allele that is rare in the original population. That variant allele now assumes a greater proportion. Porphyria variegata is an example (Chapter 6). |
| Linkage | Refers to genes or DNA sequences on the same chromosome that are in close proximity. They are so closely associated with one another that their alleles do not independently assort (Mendelian inheritance) during meiosis. |
| Migration | Also called gene flow, it is movement of migrants across populations and mating with members of a new/different population. Different allelic frequencies from the original (migrant) population are introduced, resulting in altered allele frequencies for future generations. |
| Mutation | A change in DNA sequence that can occur in germ or somatic cells. Usually used to connote harmful effects, but this is not necessarily so. |
| Population bottlenecks | Events that drastically decrease the size of a population. |
| Random genetic drift | When gene and allele frequencies change over time, from one generation to the next, as a result of random chance. |
| Segregation distortion | Also called meiotic drive, it is when a gene produces distorted segregation (non-Mendelian) ratios for a particular genetic locus. |
| Selection | Nonrandom reproduction of certain alleles or genotypes in a population. The evolution forces resulting in these patterns can be positive (advantageous) or negative (deleterious). |

example is sickle cell disease, for which research evidence indicates that sickle cell heterozygotes (SA) in endemic malarial areas of Africa are less severely affected by *Plasmodium falciparum* (a type of malarial parasite) than are the normal homozygote (AA) or sickle cell disease homozygote (SS). A positive correlation between the endemic malarial areas in Africa and the distribution of the hemoglobin (Hb) S gene is observed. The same correlation appears for the Hb C allele (West Africa) and the Hb E allele (Southeast Asia) for β -thalassemia in the formerly endemic malarial areas in parts of Italy and Greece, and for one type of glucose-6-phosphate dehydrogenase (G6PD) deficiency in Mediterranean populations. However, heterozygotes do not retain this advantage once their environment changes to a malaria-free area (i.e., to the United States). The frequency of the sickle cell allele in Blacks of African descent is decreasing in the United States, as would be expected once the heterozygous advantage is removed.

OTHER EXAMPLES OF HUMAN GENETIC VARIATION

Similar interactions between certain genes and the environment also exist for other traits. In mammals, lactase activity is highest in the newborn and then declines; by adulthood, the recessive allele for lactase is switched off in most adults, but in some there remains a hereditary persistence of lactase. This may have conferred a selective advantage on societies that had cow's milk available for food. Individuals lacking lactase activity experience gastrointestinal symptoms (including flatulence, abdominal pain, and diarrhea) following exposure to small and moderate amounts of lactose in dairy products. Data indicates that native population groups in Northern Europe, Africa, and Southwest Asia have a high frequency of hereditary persistence of lactase activity, while Southeast Asia, Arabia, Thailand, and Native American groups (among others) do not. These patterns are linked to societies with milk production traditions dating back up to 9,000 years. Persistent lactase activity benefited nomadic groups in particular, where consumption of milk during dry seasons or within desert conditions provided valuable nutrition (Hollox & Swallow, 2002). In the United States, persons with low lactase activity adjust to their changed environment by consuming less lactose or taking supplements to minimize symptoms.

Another trait demonstrating these concepts is taste sensitivity, which is influenced by genetics. For humans to perceive the sensation of taste, taste buds on the tongue, palate mucosa, and throat collect saliva that interacts with ingested food. Impulses are transmitted to the brain by cranial nerves, and are translated into familiar sensations—taste. There are nontasters, regular tasters, and supertasters; supertasters have ~1,100 taste buds per square centimeter compared to nontasters' ~11 taste buds per square centimeter. Research correlates supertasters' ability to perceive "bitterness" of the chemical compound 6-*n*-propylthiouracil to dietary taste preferences. It is hypothesized that supertaster individuals, who are easily able to detect subtle bitter tastes, can more readily avoid toxic environmental substances. This includes specific plant toxins that could be fatal (e.g., the biological warfare agent ricin that is found

in the bean of the Castor tree). Studies have identified that supertasters are more likely to find the taste of cigarettes bitter, and are less likely to smoke. Additional examples of genetic mutations and variations conferring selective advantages are highlighted in Table 3.7.

TABLE 3.7 Examples of Disease Susceptibility and Resistance Conferred by Genetic Variants

| Genes/Variants | Comments |
|--|--|
| ABO blood group O | Higher susceptibility to cholera |
| <i>CCR5</i> $\Delta 32$ homozygotes | Highly resistant to HIV infection |
| Cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) mutation | Results in cystic fibrosis and in defects in clearing <i>Pseudomonas aeruginosa</i> from respiratory tract |
| Duffy blood group negative | Resistance to <i>Plasmodium vivax</i> malaria |
| Fucosyltransferase (<i>FUT2</i>) mutation, nonsecretors | Susceptibility to recurrent urinary tract infections |
| Galactose-1 phosphate-uridylyltransferase (<i>GALT</i>) mutation | Susceptibility to neonatal Gram-negative bacterial sepsis |
| <i>HLA-DRB1</i> *1101 | Associated with resistance to persistent hepatitis C infections in some European populations |
| <i>HLA-DRB1</i> *1302 | Associated with resistance to persistent hepatitis B infections in West African populations |
| <i>HLA-DQB1</i> *0501 | Susceptibility to <i>Onchocerca volvulus</i> infection (river blindness) |
| Human prion protein gene (<i>PRPN</i>) homozygous at position 129 | Greater susceptibility to Creutzfeldt–Jakob disease |
| Interleukin 12 receptor, β -1 (<i>IL12Rb1</i>) | Homozygous mutations associated with both <i>Salmonella</i> and <i>Mycobacterium</i> infections |
| Microsomal epoxide hydrolase deficiency | Associated with chronic hepatitis C liver disease severity and hepatocellular carcinoma risk |
| <i>NRAMP1</i> variants | Associated with tuberculosis susceptibility |
| Plasminogen activator inhibitor-1 4G/4G genotype | Associated with poor outcomes in meningococcal sepsis |

KEY POINTS

- ▶ Humans are remarkably alike. They are similar in 99.9% of their genes.
- ▶ Genetic variation was first detected in important proteins, such as the ABO and Rh blood group systems, and the HLA system.
- ▶ SNPs are important polymorphisms in humans and are fueling personalized medicine.
- ▶ Knowledge about human genetic variation has important forensic applications.
- ▶ Population genetics provides information about the maintenance of certain variations and polymorphisms in specific groups.
- ▶ The Hardy–Weinberg principle is important in assessing and estimating population characteristics, disease prevalence, and the number of heterozygous carriers in populations.
- ▶ Human variation is important in susceptibility and resistance to genetic and complex diseases.

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CHAPTER 4

Inheritance Patterns in Human Phenotypes and Types of Genetic Disorders

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Genetic conditions can be inherited in various ways. Typical Mendelian patterns of inheritance include autosomal recessive (AR), autosomal dominant (AD), X-linked recessive (XR), X-linked dominant (XD), and Y-linked inheritance. Although Mendelian patterns of inheritance tend to be well known, it is important to note that disorders inherited in this way are rare, compared with complex or multifactorial traits and disorders. In the first section of this chapter, we discuss typical Mendelian patterns of inheritance, in addition to non-Mendelian mechanisms of inheritance such as mitochondrial inheritance, uniparental disomy (UPD), genomic imprinting, gonadal mosaicism, and unstable or expanding triplet repeat mutations. The second section of the chapter is devoted to the different classifications of genetic disorders. Factors affecting the expression of the phenotype are discussed as well.

INHERITANCE PATTERNS OF HUMAN PHENOTYPES

AR Inheritance

In AR inheritance, the mutant gene is located on an autosome rather than on a sex chromosome. Therefore, males and females are affected in equal proportions. The affected person usually inherits one copy of the same mutant gene from each heterozygous (Aa), or carrier, parent, and is thus homozygous (aa) at that locus, having two copies of the mutant gene. Parents who have had a child with an AR disease are sometimes referred to as “obligate heterozygotes,” meaning that each must have one copy of the mutant gene, even if no test for detection exists. Occasionally, a rare recessive disorder is manifested in a person when only one parent is a carrier. This can result in one of two ways:

- ▶ Because of a small deletion of the chromosome segment involving the normal gene, thus allowing expression of the mutant gene on the other chromosome of the pair
- ▶ Because the person inherits two copies of the same chromosome from the parent with the mutant gene (UPD)

Normal gene function is dominant to the altered function of the mutant recessive gene; therefore, the heterozygote usually shows no obvious phenotypic manifestations but, depending on the disorder, the heterozygote may show biochemical differences that form the basis for heterozygote detection by biochemical testing. DNA testing is now commonly used where possible, due to the prevalence of enzyme defects and deficiencies.

In clinical practice, most situations involving AR inheritance come to attention in a variety of ways, as listed in Box 4.1. Therefore, such individuals may have different immediate and long-range needs, ranging from genetic testing and carrier detection to genetic counseling to prenatal diagnosis. The nurse should refer such individuals to a professional providing these services.

If a couple has had a child with an AR disorder, the rest of the family history for the genetic disease may be completely negative, due in part to the trend to smaller family size and in part because two copies of a rare mutant gene are needed in order for one to be affected. If there are other affected individuals, they are usually members of the same generation. If the parents of the affected child are related to each other by blood (consanguinity), this suggests, but does not prove, AR inheritance. The more common the disorder is in the general population, the less relevant is the presence of consanguinity.

The mechanics of transmission of autosomal recessively inherited genes are shown in Figure 4.1. The most common situation is when both parents are heterozygotes (carriers). The theoretical risks for their offspring, regardless of sex, are to be:

- ▶ Affected with the disorder (aa), 25%
- ▶ Carriers like their parents (Aa), 50%
- ▶ Normal, without inheriting the mutant gene (AA), 25%

BOX 4.1

Clinical Practice Situations Involving Autosomal Recessive Inheritance

- ▶ Recent birth of an affected infant
- ▶ Recent diagnosis, usually of an affected child
- ▶ Couples who have been identified as carriers of a specific disorder (e.g., Tay–Sachs disease) and are contemplating marriage or children
- ▶ One member of a couple has a sibling or cousin known to have a genetic disorder and is concerned that he or she may be a carrier
- ▶ Both members of a couple belong to a population group in which a specific genetic disorder is frequent (e.g., thalassemia in Mediterranean people)
- ▶ A couple is contemplating pregnancy after an earlier birth of an affected child, who may be either living or deceased

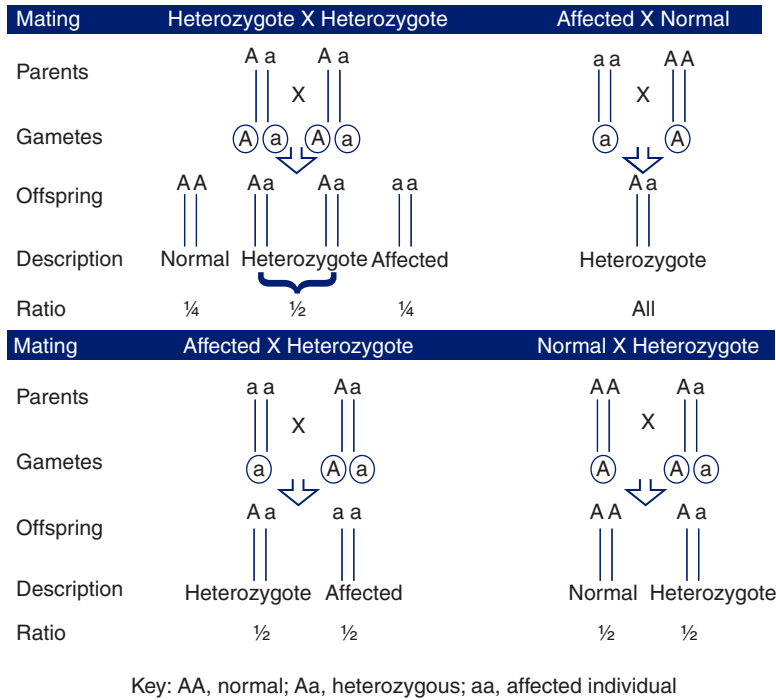


FIGURE 4.1. Mechanisms of autosomal recessive inheritance with one pair of chromosomes and one pair of genes.

Of the phenotypically normal offspring (AA and Aa), two thirds will be carriers. These risks hold true for each pregnancy. Because chance has no memory, each pregnancy is, in essence, a throw of the genetic dice; in other words, the outcome of the past pregnancy has no effect on a future one. These theoretical risks hold true with large numbers of families. Within an individual family at risk with two carrier parents, the actual number of affected children can, by chance, range from none who are affected to all who are affected. This does not change their risks for another pregnancy from those described previously. This is a point that clients often need clarified and reinforced. Nurses should therefore be able to understand it and explain it. If two carriers have had three unaffected children in three sequential pregnancies, it does not mean that their next child will be affected: Each prior event has no bearing on the outcome of the next pregnancy in AR inheritance.

In general, most AR disorders tend to have an earlier, more severe onset than do diseases from other inheritance modes. Many are so severe that they are incompatible with a normal life span, and many affected individuals do not reach reproductive age. Due to recent advances in diagnosis and treatment of certain AR diseases, such as sickle cell anemia and cystic fibrosis, individuals who would have otherwise died in childhood are now reaching young adulthood and having their own children, creating obligatory transmission of the mutant gene to all of their offspring. If the affected person mates with someone who does not carry the same mutant gene, then all of his or her children, regardless of sex, will be carriers, but none will be affected (see Figure 4.1).

If the affected person mates with someone who is a carrier for the same recessive gene, then there is a 50% risk of having an affected child and a 50% risk of having a child who is a heterozygous carrier, regardless of sex, for each pregnancy. This risk is most likely to materialize for a disorder such as cystic fibrosis in which the frequency of carriers in the White population is about 5%, or for sickle cell disease in which the frequency of carriers in the American Black population is 7% to 9%. If the mother is the one who has the genetic disease in question, there may be effects on a fetus that result from an altered maternal environment, as occurs in phenylketonuria (PKU). The salient characteristics of AR inheritance are summarized in Table 4.1. Examples of different genetic disorders inherited in this manner are presented in Table 4.2, with many of these disorders explained in greater detail in Chapters 8, 9, 10, and 12.

Consanguinity and AR Inheritance

Concern about consanguinity relates mostly to marriage between blood relatives. Although most individuals would be distantly related to their mate if one went back far enough in time, only relationships closer than first cousins are usually genetically important. Each individual carries from 5 to 10 harmful recessive genes that are not usually apparent. Individually, each of these is extremely rare (except for a few, like cystic fibrosis), so that the likelihood of selecting a mate with the same harmful recessive genes is remote. This chance becomes less remote if the two individuals are related to each other by blood or are from the same ethnic group or population isolate. The consequence of consanguineous mating results from the possible bringing together of two identical recessive alleles that are inherited by descent from a common ancestor, thus bringing out deleterious genes in the homozygous (aa) state. The resulting homozygous phenotypes that are deleterious are more obvious than those that are neutral or favorable. This effect may also operate for single-nucleotide

TABLE 4.1 Major Characteristics of Autosomal Recessive Inheritance and Disorders

- ▶ Gene is located on autosome.
- ▶ Two copies of the mutant gene are needed for phenotypic manifestations.
- ▶ Males and females are affected in equal numbers on average.
- ▶ No sex difference in clinical manifestations is usual.
- ▶ Family history is usually negative, especially for vertical transmission (in more than one generation).
- ▶ Other affected individuals in the family in the same generation (horizontal transmission) may be seen.
- ▶ Consanguinity or relatedness is more often present than in other types of inherited conditions.
- ▶ Fresh gene mutations are rare.
- ▶ Age of disease onset is usually early—newborn, infancy, or early childhood.
- ▶ Exert the greatest negative effect on reproductive fitness.

TABLE 4.2 Selected Genetic Disorders Showing Autosomal Recessive Inheritance

| Disorder | Occurrence | Brief Description |
|--|---|---|
| Albinism (tyrosinase negative) | 1:15,000 to 1:40,000 1:85–1:650 (Native Americans) | Tyrosinase negative disorder resulting in melanin lacking in skin, hair, and eyes; nystagmus; photophobia; susceptibility to neoplasia, strabismus, and impaired vision |
| Argininosuccinic aciduria (ASA) | 1:60,000 to 1:70,000 | Urea cycle disorder; hyperammonemia, mild mental retardation; vomiting; seizures; coma; abnormal hair shaft |
| Cystic fibrosis | 1:2,000 to 1:2,500 (Caucasians) 1:16,000 (American Blacks) | Ion channel function disruption resulting in pancreatic insufficiency and malabsorption; abnormal exocrine glands; chronic pulmonary disease (see Chapter 9) |
| Ellis–van Creveld syndrome (EvC) | Rare, except among eastern Pennsylvania Amish | Multiple mutations in the <i>EVC</i> gene result in short-limbed dwarfism; polydactyly; congenital heart disease; nail anomalies, natal teeth, cleft palate |
| Glycogen storage disease Ia (von Gierke disease) | 1:200,000 | Glucose-6-phosphatase deficiency; bruising; hypoglycemia; enlarged liver; hyperlipidemia; lactic acidosis, hyperuricemia; neutropenia; hypertension; short stature |
| Glycogen storage disease II (Pompe disease) | 3:100,000 to 4.5:100,000 | Mutation in <i>GAA</i> gene resulting in acid maltase deficiency. Infant, juvenile, and adult forms exist. In infant form, cardiac enlargement, cardiomyopathy, hypotonia, respiratory insufficiency, developmental delay, macroglossia, death from cardiorespiratory failure by about 2 years of age |
| Hemochromatosis | 1:3,000 (Caucasians) | Several types exist, each with its own specific mutation. Excessive iron storage and tissue damage can result in cirrhosis, diabetes, pancreatitis, and other diseases; abnormal skin pigmentation seen (see Chapter 10) |

(continued)

TABLE 4.2 Selected Genetic Disorders Showing Autosomal Recessive Inheritance (continued)

| Disorder | Occurrence | Brief Description |
|---|--|---|
| Homocystinuria | 1:40,000 to 1:140,000 | Cystathionine β -synthase deficiency causing mental retardation; tall build with skeletal defects; optical abnormalities; neurologic problems; risk for myocardial infarction |
| Metachromatic leukodystrophy | 1:40,000 (1:75) Habbanite Jews of Israel | Arylsulfatase A deficiency leading to disintegration of myelin and accumulation of lipids in white matter of brain; psychomotor degeneration; hypotonia; adult, juvenile, and infantile forms |
| Sickle cell disease | 1:400 to 1:600 (American Blacks) | Hemoglobinopathy with chronic hemolytic anemia; growth retardation; susceptibility to infection, painful vascular crises, leg ulcers, dactylitis (see Chapter 9) |
| Tay–Sachs disease | 1:3,600 (Ashkenazi Jews) 1:360,000 others | Hexosaminidase A deficiency causing progressive mental and motor retardation with onset at about 6 months; poor muscle tone; deafness; blindness; convulsions; decerebrate rigidity; death usual by 3 to 5 years of age (see Chapters 9 and 10) |
| Usher syndromes | Rare | Several types exist, with mutations in multiple genes. Manifests as a group of syndromes characterized by congenital sensorineural deafness, visual loss due to retinitis pigmentosa, vestibular ataxia, occasionally mental retardation, speech problems; several subtypes |
| Xeroderma pigmentosa (complementation groups A–G) | 1:60,000 to 1:100,000 | Mutations in genes responsible for DNA repair; sun sensitivity, freckling, atrophic skin lesions, skin cancer develops; photophobia and keratitis; death usually by adulthood. Some types have central nervous system involvement |

variations in genes. Effects that determine one trait are more evident than those contributing to a complex trait, such as body size or intelligence.

Many cultures and groups have actively encouraged consanguineous marriages. These have included the ancient Egyptians, Incas, royalty, and many modern societies, such as Japan, various Hindu groups in India, Muslim groups (especially in the eastern Mediterranean), and groups in which arranged marriages are an accepted custom. The frequency of consanguineous marriages depends on social custom, religious customs and laws, socioeconomic concerns, family ties and traditions, the degree of geographic isolation of a village, and the degree of isolation of a specific group within a community. It is estimated that in parts of Asia and Africa, consanguineous marriages account for about 20% to 50% of all marriages. Other groups oppose it. In South Korea, it is frowned upon to marry someone with the same family name, and same-clan marriages are barred. Every 10 years or so there is an amnesty period during which such marriages can occur. Among certain followers of the Koran, there are taboos against marriage between a boy and a girl who were breastfed by the same woman more than a certain number of times during the first two years of life. Thus, consanguinity may be perceived differently among different cultures.

AD Inheritance

As in AR inheritance, the mutant gene is on an autosome, so males and females are equally affected. Only one copy of the dominant gene is necessary for the detrimental effects to be evident; the affected individual is heterozygous, and there is no carrier status. It is believed that in most AD disorders, homozygous individuals who have inherited two genes for an AD disorder are so severely affected that they die in utero or in infancy. An example of an exception is familial hypercholesterolemia (see Chapter 10) in which the homozygote survives but shows the very early onset of severe effects. In contrast to AR inheritance, structural protein defects, rather than those involving enzymes, are common. AD disorders are usually less life-threatening than AR ones, although they may have more evident physical malformations.

A later age of onset of symptoms and signs is frequent and may not become evident until adulthood. In practice, persons usually seek counseling or experience events that come to clinical attention for reasons shown in Box 4.2.

BOX 4.2

Usual Clinical Practice Situations Involving Autosomal Dominant (AD) Inheritance

- ▶ The person or his or her mate is affected with a particular AD disorder.
- ▶ Someone in their family (often a parent, aunt or uncle, or sibling) has an AD disorder.
- ▶ They have had a previous child with an AD disorder.

The recognition of an AD disorder in a child may indicate the presence of that disorder in one of the parents as well. However, there are exceptions. When the parents appear normal, several possibilities exist:

- ▶ The gene can be present but nonpenetrant (discussed further in the section “Penetrance”).
- ▶ The gene expression may be minimal and may not have been detected by the practitioner.
- ▶ The disorder can be caused by a new mutation.
- ▶ The child is not the natural offspring of both parents.

The following case example demonstrates the extreme importance of careful examination of both parents in the detection of an AD disorder.

CASE EXAMPLE

A child was brought for counseling with full-blown Waardenburg syndrome (deafness, heterochromic irises, partial albinism, and broad facial appearance); however, no evidence of the disorder was at first seen in either parent. This case occurred before subgrouping of this syndrome was known. If the disorder was caused by a new mutation, then the risk for those parents to have this syndrome appear in another child would be negligible. If, however, one of the parents had the syndrome, then the risk for recurrence in another child would be 50%. It turned out that the only manifestation that the mildly affected mother had was a white forelock of hair, which she usually dyed. Thus, simply looking at the couple would not have revealed the situation. This is an example of variable expression (discussed in further detail in Chapter 5) in which the parent was only mildly affected but the child had severe manifestations. Such cases represent a challenge to the practitioner. In this case, the counselor, knowing the full constellation of the syndrome, specifically asked the mother if anyone in the family had premature white hair. If the mother had not been directly asked, she may not have volunteered this information because

- ▶ the relevance of it was not recognized by the client
- ▶ of guilty feelings when only one parent transmits a disorder
- ▶ of fear of stigmatization or being blamed for transmission of the disorder
- ▶ of other reasons

The mechanisms of transmission of AD traits are shown in Figure 4.2. In matings in which one partner is affected and one is normal, the risk for their child to inherit the gene, and therefore the disorder too (except in disorders with less than 100% penetrance), is 50%, regardless of sex. The chance for a normal child is also 50%. This holds true for each individual pregnancy regardless of the outcomes of prior

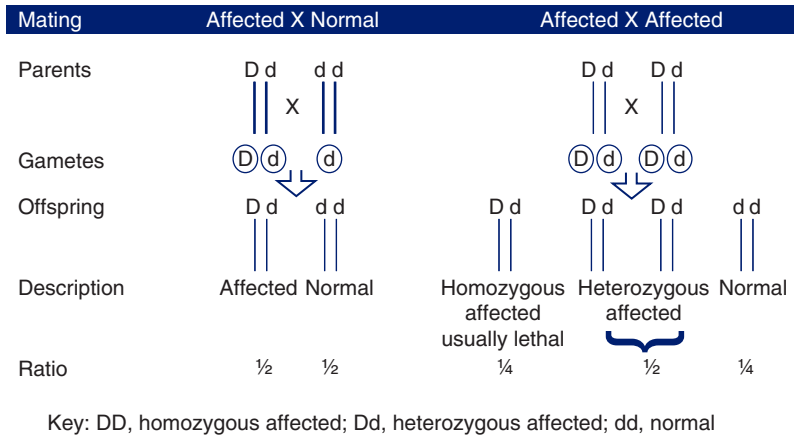


FIGURE 4.2. Mechanisms of autosomal dominant inheritance with one pair of chromosomes and one pair of genes.

pregnancies. Unless nonpenetrance has occurred, those truly unaffected individuals run no greater risk than the general population of having an affected child or grandchild of their own. Risk calculations that include the possibility of nonpenetrance can be made by the geneticist. If a woman were an affected heterozygote for a rare AD disorder with 60% penetrance and she was planning a family with a normal man, the risk for each child to both inherit the mutant gene and manifest the disorder is as follows: the risk to inherit the mutant gene from each parent (50% from the mother and the population mutation rate from the father, which in this case is disregarded because of rarity) multiplied by the penetrance (60%) or ($0.5 \times 0.6 = 0.3$). Therefore, the risk for the child to inherit the gene is 50% and to both inherit the gene and manifest the disorder is 30%.

If two individuals affected with the same AD disorder have children, as is frequently seen in some conditions such as achondroplasia (a type of dwarfism), then for each pregnancy, the chance is 25% for having a child who is an affected homozygote, 50% for having an affected heterozygote like the parents, and 25% for having a normal child without a mutant gene (see Figure 4.2). The homozygote is usually so severely affected that the condition is lethal in utero.

In many AD disorders, the primary defect is still unknown, so that diagnosis of the individual who is known to be at risk for having the disorder before symptoms become clinically evident or prenatal diagnosis for their offspring may not be possible, although gene mapping and DNA technology are making this situation less common. In disorders in which the onset is characteristically late and diagnosis is not available, individuals with a family history of such a disorder have difficulty in making reproductive and life plans because they may not know whether they have inherited the mutant gene. Some choose alternate reproductive options such as artificial insemination, in vitro fertilization, embryo transfer and implantation, or adoption rather than run a possible 50–50 risk, but others

become aware of the hereditary nature of the disease only after they have had children. Some choose to “take a chance.” Nurses should encourage individuals to talk with their partners about the options, and, if possible, both should also talk with a counselor to clarify their feelings and options. Such supportive counseling may need to be ongoing.

A summary of the major characteristics of AD inheritance is given in Table 4.3. Examples of disorders inherited in an AD manner are shown in Table 4.4.

New Mutation

If no other cases exist in a family and neither parent can be found to have any subclinical signs of the disorder, it may be caused by a new mutation. Such a case is often called *de novo* or *sporadic*. The affected person with the new mutation can transmit the disorder to his or her offspring in the same manner as an affected individual with an affected parent. When truly unaffected parents have had a child with a genetic disease caused by a new mutation, the risk of having another child with the same disorder is no greater than for that of the general population (except in rare cases of gonadal mosaicism, explained in the section “Gonadal (Germline) Mosaicism”). New mutations are most frequently seen immediately in the dominantly inherited syndromes, because only one mutant gene is necessary to produce a phenotypic effect. When a recessive single gene disorder appears in a person and both parents are not heterozygous, this should prompt cytogenetic analysis of the affected individual because a microdeletion of chromosomal material that includes the normal gene may be present that allows expression of a single recessive mutant gene without the countering effect of the normal gene that is missing. The more

TABLE 4.3 Major Characteristics of Autosomal Dominant Inheritance and Disorders

- ▶ Gene is on autosome.
- ▶ One copy of the mutant gene is needed for phenotypic effects.
- ▶ Males and females are affected in equal numbers on average.
- ▶ No sex difference in clinical manifestations.
- ▶ Vertical family history through several generations may be seen.
- ▶ There is wide variability in expression.
- ▶ Penetrance may be incomplete (gene can appear to skip a generation).
- ▶ Increased paternal age effect may be seen.
- ▶ Fresh gene mutation is frequent.
- ▶ Later age of onset is frequent.
- ▶ Male-to-male transmission is possible.
- ▶ Normal offspring of an affected person will have normal children and grandchildren.
- ▶ Exerts least negative effect on reproductive fitness.
- ▶ Structural protein defect is often involved.
- ▶ In general, disorder tends to be less severe than the recessive disorders.

TABLE 4.4 Selected Genetic Disorders Showing Autosomal Dominant Inheritance

| Disorder | Occurrence | Brief Description |
|---|---|--|
| Achondroplasia | 1:10,000 to 1:12,000 | Mutation in the <i>FGFR3</i> gene involved in development of bone and brain tissue. Short-limbed dwarfism; large head; narrowing of spinal canal |
| Adult polycystic kidney disease | 1:250 to 1:1,250 | Mutations in <i>PKD1</i> or <i>PKD2</i> genes resulting in enlarged kidneys, hematuria, proteinuria, renal cysts, abdominal mass; eventual renal failure; may be associated (adult) with hypertension, hepatic cysts, diverticula; aneurism resulting in cerebral hemorrhage may occur; cystic kidneys seen on x-ray films (see also Chapter 10) |
| Aniridia | 1:100,000 to 1:200,000 | Mutation in the <i>PAX6</i> gene involved in early eye development. Absence of the iris of the eye to varying degrees; vision impaired; glaucoma may develop; may be associated with other abnormalities in different syndromes |
| Facioscapulohumeral muscular dystrophy 1A | 1:100,000 to 5:100,000 | Hypomethylation of the <i>FSHD1</i> gene resulting in facial weakness; atrophy in facial, upper limb, shoulder girdle, and pelvic girdle muscles; speech may become indistinct; much variability in progression and age of onset |
| Familial hypercholesterolemia (type IIa) | 1:200 to 1:500 | Mutation of the <i>LDLR</i> gene causing low-density lipoprotein (LDL) receptor mutation. Symptoms are elevated LDL, xanthomas, arcus lipoides corneae, and coronary artery disease (see Chapter 10) |
| Hereditary spherocytosis | 1:2,000 to 1:5,000 | Mutation in <i>ANK1</i> gene causing a red blood cell membrane defect leading to abnormal spherical shape, impaired survival, and hemolytic anemia due to cell rupture |
| Huntington disease | 1:18,000 to 1:25,000 (United States), 1:333,000 (Japan) | Progressive neurologic disease caused by CAG trinucleotide repeat expansion of the <i>HTT</i> gene; involuntary muscle movements with jerkiness, gait changes, lack of coordination, mental deterioration with memory loss, speech problems, personality changes, confusion, and decreased mental capacity; usually begins in mid-adulthood (see Chapter 10) |

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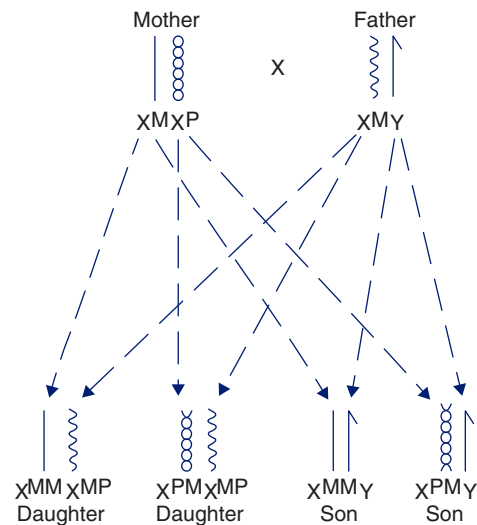
TABLE 4.4 Selected Genetic Disorders Showing Autosomal Dominant Inheritance (*continued*)

| Disorder | Occurrence | Brief Description |
|--------------------------------|--|--|
| Nail–patella syndrome | 1:50,000 | Mutation of the <i>LMX1B</i> gene causing nail abnormalities, hypoplasia or absent patella, and iliac horns; elbow dysplasia; renal lesions and disease; iris and other eye abnormalities; glaucoma; gastrointestinal problems |
| Neurofibromatosis 1 | 1:3,000 to 1:3,300 | Mutation in the <i>NF1</i> gene involved in skin pigmentation. Café-au-lait spots, neurofibromas, and malignant progression are common; complications include hypertension; variable expression |
| Osteogenesis imperfecta type I | 1:30,000 | Mutation in <i>COL1A1</i> gene responsible for collagen assembly. Blue-gray sclera; fragile bones with multiple fractures; mitral valve prolapse; short stature in some cases; progressive hearing loss in some cases; wormian bones of the cranium (see Chapter 9) |
| Polydactyly | 1:100 to 1:300 (Blacks), 1:630 to 1:3,300 (Caucasians) | Extra (supernumerary) digit on hands or feet |
| Tuberous sclerosis-1 (TSC1) | About 1:10,000 | Mutation in the <i>TSC1</i> gene controlling cell growth and size. White ash-leaf-shaped macules and shagreen patches of the skin; facial angiofibromas; erythemic nodular rash in butterfly pattern on face and other skin lesions; seizures; intellectual delay; learning and behavior disorders; may develop retinal pathology and rhabdomyoma of the heart |
| van der Woude syndrome | 1:80,000 to 1:100,000 | Mutation of the <i>IRF6</i> gene involved in transcription factor development. Cleft lip and/or palate with lower lip pits, missing premolars |
| von Willebrand disease | 1:1,000 to 30:1,000 | Deficiency or defect in plasma platelet protein called von Willebrand factor, leading to prolonged bleeding time; bruising; bleeding from mucous membranes (nosebleeds) |

incapacitating the disorder is, the more likely it is for a large percentage to be due to new mutations because the affected person is less likely to reproduce. Disorders in which a high proportion of cases are caused by new mutations include Apert syndrome (an AD disorder with craniostenosis, shallow ocular orbits, and syndactyly) and achondroplasia (a type of disproportionate dwarfism).

X-Linked Inheritance

In both dominant and recessive X-linked disorders, the mutant gene is located on the X chromosome. Males have only one X chromosome. There is no counterpart for its genes. In males, therefore, any gene located on the X chromosome is expressed when present in one copy regardless of whether it is dominant or recessive in females. Males cannot be carriers; they will show the effects of the gene in question and are said to be *hemizygous*. A female receives one X chromosome from each of her parents for a normal sex constitution of XX. A male receives his single X chromosome from his mother and his Y chromosome from his father for a normal sex constitution of XY. Whether it is the X chromosome that a woman gets from her father or the X she gets from her mother that is passed to her sons and daughters is random. Figure 4.3 illustrates X and Y chromosome transmission.



Key

X^M = maternally derived X

X^P = paternally derived X

X^{MM} = X derived from maternal grandmother and mother

X^{PM} = X derived from maternal grandfather and mother

X^{MP} = X derived from paternal grandmother and father

FIGURE 4.3. Transmission of the X and Y chromosomes.

X-Linked Recessive

The most common pattern of XR transmission is that in which the female partner is a heterozygous carrier for the mutant gene (see Figure 4.4). If her partner is normal, then for each pregnancy, the couple runs a 25% chance for the offspring to be one of the following:

- ▶ A female carrier like the mother
- ▶ A normal female without the mutant gene
- ▶ A normal male without the mutant gene
- ▶ A male who is affected with the disease in question

Thus, the risk for a male offspring to be affected is 50%. As in the other types of single gene inheritance, the outcome of one pregnancy does not influence the others; these odds remain the same. The carrier female usually shows no obvious clinical manifestations of the mutant gene unless X inactivation is skewed (discussed later in this chapter). In such an instance, she may be a *manifesting heterozygote*. For example, if the mutant gene was for Duchenne muscular dystrophy, a carrier female might

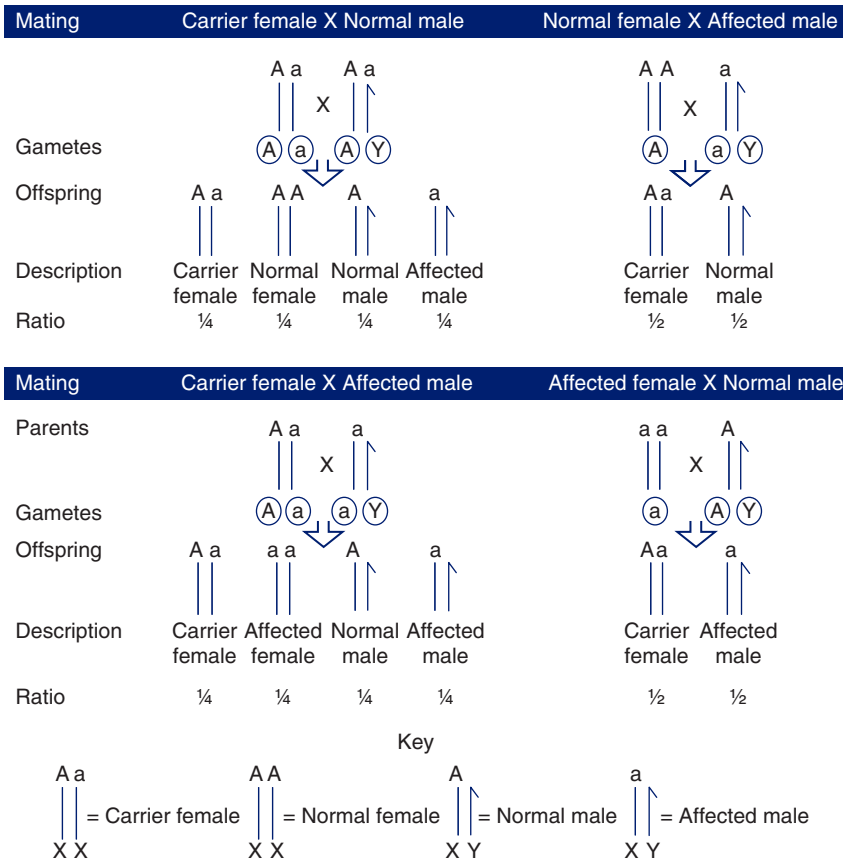


FIGURE 4.4. Mechanisms of X-linked recessive inheritance with one pair of chromosomes and one pair of genes.

BOX 4.3**Usual Clinical Practice Situations Involving X-Linked Recessive (XR) Inheritance**

- ▶ Before marriage or before planning children when they have a male family member such as an uncle or brother who has a known XR disorder
- ▶ After the birth of an affected child
- ▶ Mother is known heterozygote for XR disorder

demonstrate muscle weakness, enlarged calves, and moderately elevated serum creatine kinase levels. If the mutant gene were for hemophilia A, she might demonstrate prolonged bleeding times. Females with X chromosome abnormalities, even submicroscopic deletions, may also manifest XR disorders if the normal gene on the counterpart chromosome was deleted. Such individuals should have cytogenetic analysis. In practice, individuals at risk for XR disorders usually seek genetic counseling for the reasons shown in Box 4.3.

Because better treatment has increased the life span for many XR disorders such as hemophilia, affected males are now reproducing. If the female is normal in such a mating, all of their female children will be carriers and all the males will be normal; stated otherwise, the theoretical risk for each pregnancy is that there is a 50% chance that the offspring will be carrier females and a 50% chance that they will be normal males. If the male is affected and the female is a carrier for the same disorder, as may occur in the very common XR disorders such as glucose-6-phosphate dehydrogenase (G6PD) deficiency and color blindness, then with each pregnancy, there will be a theoretical risk of 25% for the birth of each of the following offspring: an affected female, a carrier female, a normal male, or an affected male (see Figure 4.4). A much rarer mating is that of an affected female and normal male in which, with each pregnancy, there is a 50% chance that the child will be a female carrier and a 50% chance that the child will be an affected male.

In the past, little could be accomplished in the way of prenatal detection for XR disorders except to determine the sex of the fetus. For the more common types of matings, this often resulted in the loss of normal, as well as affected, male offspring due to termination of those pregnancies in which the fetus was a male. It is now possible to provide more accurate prenatal diagnosis for many of the XR disorders by using molecular technology, so the nurse should be sure to refer such couples to a genetic counselor for the latest information and not rely on older printed material. A summary of the characteristics of XR disorders is given in Table 4.5, and examples of these disorders are listed in Table 4.6.

X-Linked Dominant

This type is less frequently seen than the other modes of inheritance discussed. Because the mutant gene is dominant, only one copy is necessary for its effects to be manifested phenotypically. Both males and females can be affected, and both can

TABLE 4.5 Major Characteristics of X-Linked Recessive Inheritance and Disorders

- ▶ Mutant gene is on the X chromosome.
- ▶ One copy of the mutant gene is needed for phenotypic effect in males (hemizygous).
- ▶ All daughters of affected males will be carriers if the mother is normal.
- ▶ All sons of affected males will be normal if the mother is normal.
- ▶ Males are more frequently affected than females.
- ▶ Some result from spontaneous gene mutations.
- ▶ There is no male-to-male transmission.
- ▶ Transmission is often through heterozygous (carrier) females.
- ▶ Two copies of the mutant gene are usually needed for phenotypic effect in females.
- ▶ Unequal X inactivation can lead to “manifesting heterozygote” in female carriers.

transmit the gene. Because of the gene’s location on the X chromosome, there are several differences between this type of inheritance and AD inheritance:

- ▶ An affected male (except in cases of new mutation) has an affected mother because males inherit their X chromosome from their mother, not their father.
- ▶ Male-to-male transmission is not seen because males transmit their X chromosome only to their daughters, not to their sons. Thus, an affected male would transmit the disorder to all of his daughters and none of his sons.
- ▶ There may be an excess of female offspring in the family tree or pedigree, as some XD genes are lethal in the male.
- ▶ Some affected females may be less severely affected than males because of X inactivation.

Affected females are more likely to transmit the gene to their offspring because the gene is less severe in females due to X inactivation. If her mate is not affected, the theoretical risk for each pregnancy to her offspring is a 25% chance for each of the following:

- ▶ An affected female
- ▶ An affected male
- ▶ A normal female
- ▶ A normal male

Put a different way, there is a 50% chance that the offspring of each pregnancy will be affected without considering the sex of the offspring.

The gene is often lethal in males because males have no normal gene counterpart. Therefore, the mating of an affected male and normal female is uncommon. For each pregnancy, there is a 50% risk for an affected female and a 50% risk for a normal male. Thus, all female children would be affected, although severity might differ, and

TABLE 4.6 Selected Genetic Disorders Showing X-Linked Recessive Inheritance

| Disorder | Occurrence | Brief Description |
|---|---|---|
| Color blindness (deutan) | 8:100 Caucasian males 4:100 to 5:100 Caucasian females 2:100 to 4:100 Black males | Normal visual acuity; defective color vision with green series defect |
| Duchenne muscular dystrophy | 1:3,000 to 1:5,000 male births | Mutation in the <i>DMD</i> gene causing muscle weakness with progression; eventual respiratory insufficiency and death (see Chapter 9) |
| Fabry disease (diffuse angiokeratoma) | 1:40,000 males | Mutation in the <i>GLA</i> gene, which is involved in production of α -galactosidase A; lipid storage disorder; onset in adolescence to adulthood; renal disease; ocular disease; angina, pain attacks, autonomic dysfunction, angiokeratoma |
| Glucose-6-phosphate dehydrogenase (G6PD) deficiency | 1:10 Black American males 1:50 Black American females | Enzyme deficiency due to mutation in the <i>G6PD</i> gene with subtypes shows effects in red blood cell; usually asymptomatic unless under stress or exposed to certain drugs or infection that trigger hemolysis (see Chapter 6) |
| Hemophilia A | 1:2,500 to 1:4,000 male births | Coagulation disorder due to deficiency of factor VIII protein; severity varies with factor VIII levels; in severe cases, spontaneous bleeding occurs in deep tissue such as joints (see Chapter 9) |
| Hemophilia B (Christmas disease) | 1:4,000 to 1:7,000 male births | Coagulation disorder caused by deficiency of factor IX protein; similar to hemophilia A |

(continued)

TABLE 4.6 Selected Genetic Disorders Showing X-Linked Recessive Inheritance (*continued*)

| Disorder | Occurrence | Brief Description |
|-------------------------|-----------------------|---|
| Hunter syndrome (MPSII) | 1:100,000 male births | Mucopolysaccharide storage disorder resulting from mutation in the <i>IDS</i> gene with iduronate 2-sulfatase deficiency; intellectual disability usual; hepatomegaly; splenomegaly; decline in cardiac function; coarse facial appearance; dwarfing; stiff joints; hearing loss; mild and severe forms (see Chapter 9) |
| Lesch–Nyhan syndrome | Rare | Deficiency of purine metabolism enzyme due to mutation in the <i>HPRT</i> gene; hyperuricemia, spasticity, athetosis, self-mutilation, developmental delay (see Chapter 9) |
| Menkes syndrome | 1:200,000 male births | Mutation in the <i>ATP7A</i> gene, causing defective copper transport; short stature; seizures; spasticity; hypothermia; kinky, sparse hair (pili torti); intellectual disability |
| X-linked ichthyosis | 1:5,000 to 1:6,000 | Steroid sulfatase deficiency resulting in symptoms usual by 3 months; may be born with sheets of scales (collodion babies); dry scaling skin, often appears as if unwashed; developmental delay; bone changes; vascular complications; corneal opacities |

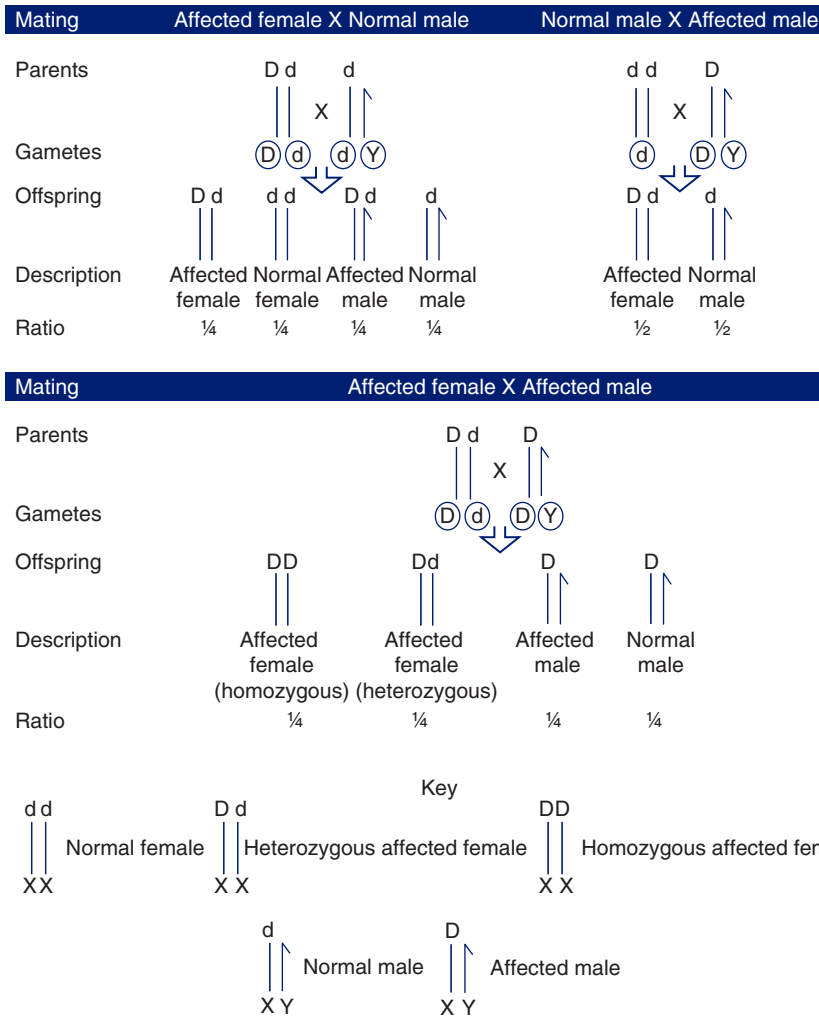


FIGURE 4.5. Mechanisms of X-linked dominant inheritance with one pair of chromosomes and one pair of genes.

all male children would be normal (see Figure 4.5). In such cases, prenatal determination of fetal sex would be all that is necessary in order to allow the parents to make reproductive choices.

The very unlikely event of two affected individuals mating would result in a 25% risk of each of the following: (a) a homozygous affected female (probably lethal in utero), (b) a heterozygous female, (c) an affected male, and (d) a normal male. The fragile X syndrome is considered to be inherited in an XD fashion with incomplete penetrance. The features of XD inheritance are summarized in Table 4.7, and a list of some disorders inherited in this way is given in Table 4.8.

Y-Linked (Holandric)

Few genes are known to be located on the Y chromosome, and so this type of inheritance has little clinical significance. Most Y-linked genes have to do with male sex

TABLE 4.7 Major Characteristics of X-Linked Dominant Inheritance and Disorders

- ▶ Mutant gene is located on X chromosome.
- ▶ One copy of the mutant gene is needed for phenotype manifestation.
- ▶ X inactivation modifies the gene effect in females.
- ▶ Often lethal in males, and so may see transmission only in the female line.
- ▶ Affected families usually show excess of female offspring (2:1).
- ▶ Affected male transmits gene to all of his daughters and to none of his sons.
- ▶ Affected males have affected mothers (unless new mutation).
- ▶ There is no male-to-male transmission.
- ▶ There is no carrier state.
- ▶ Disorders are relatively uncommon.

determination. Y-linked genes manifest their effect with one copy and show male-to-male transmission exclusively. All sons of an affected male would eventually develop the trait, although the age at which they do so varies. None of the affected male's daughters would inherit the trait. It can be hard to distinguish Y-linked inheritance from AD disorders that are male sex limited. Some genes on the Y chromosome are for determining height, male sex determination such as the *SRY* gene for the testis-determining factor, tooth enamel and size, hairy ears, and a zinc finger protein.

Mitochondrial Inheritance

Mitochondria are cellular organelles that use oxygen in the process of energy production. They have their own genome, consisting of a single circular chromosome containing 37 genes. Many of these genes encode subunits of enzyme complexes of the respiratory chain and oxidative phosphorylation (OXPHOS) system, while other subunits are encoded by nuclear genes. Each mitochondrion can contain multiple copies of the mitochondrial genome. In addition, in a given cell, there can be hundreds to thousands of mitochondria, depending upon the energy needs of a particular cell type. Cells with high energy demands such as nerve and muscle have many more mitochondria present than others. A mitochondrial DNA (mtDNA) mutation can be present in all mtDNA copies (homoplasmy) or in some (heteroplasmy). The percentage of mtDNA mutations necessary to cause dysfunction is believed to vary depending on the type of tissue affected and even among cells in the same tissue. A mutation may be present in the mtDNA somewhere in the cell, but the disease will not be evident until the mutation is present in a sufficient number of the mitochondria. Mutations in nuclear genes that encode subunits of enzymes used in cellular respiration will ultimately affect mitochondrial function. Most nuclear gene defects resulting in mitochondrial disorders are associated with abnormalities of OXPHOS. For example, Friedreich ataxia, a progressive neurodegenerative disease, is now known to be the result of the mutation of a nuclear-encoded mitochondrial protein known as frataxin that functions in some way to affect iron homeostasis in mitochondria and respiratory chain deficiency.

TABLE 4.8 Selected Genetic Disorders Showing X-Linked Dominant Inheritance

| Disorder | Occurrence | Brief Description |
|--|--|---|
| Albright osteodystrophy | Rare | Pseudohypoparathyroidism causing many endocrine problems; short stature; delayed dentition; brachydactyly; hereditary hypocalcemia; muscular atrophy; mineralization of skeleton; round facial features; possible intellectual disability; hypertension |
| Focal dermal hypoplasia | Very rare, exact unknown | Atrophy; linear pigmentation; papillomas of skin on lips, axilla, and umbilicus; alopecia, digital anomalies; hypoplastic teeth; structural renal and gastrointestinal abnormalities; ocular anomalies (coloboma, microphthalmia) |
| Incontinentia pigmenti | Very rare | Irregular swirling pigmentation of skin (whorled look), progressing to other skin lesions; dental anomalies; alopecia; intellectual disability common; seizures; uveitis; retinal abnormalities |
| Ornithine transcarbamylase (OTC) deficiency | 1:80,000 in Japan; very rare elsewhere | Inborn error in urea cycle metabolism; failure to thrive; hyperammonemia; vomiting; headache; confusion; rigidity; lethargy; seizures; coma; many males die in neonatal period |
| Orofaciodigital syndrome type I | 1:50,000 | Cleft palate, tongue, jaw, and/or lip; facial hypoplasia; intellectual disability; syndactyly; polydactyly; short digits; polycystic kidneys with renal failure |
| X-linked hypophosphatemia or vitamin D resistant | 1:25,000 | Disorder of renal tubular phosphate reabsorption; bowed legs; growth deficiency rickets with short stature; possible hearing loss |

Mitochondrial diseases can result from:

- ▶ Mutations in the mtDNA
- ▶ Defects in nuclear DNA that affect mitochondrial function such as defects of the Krebs cycle (these are becoming better understood and defined)
- ▶ Defects in communication between mtDNA and nuclear DNA
- ▶ Nonhereditary defects of mtDNA such as those resulting from zidovudine (an antiretroviral drug)

Mitochondrial diseases due to mutations in nuclear DNA are inherited in a Mendelian manner, whereas mitochondrial diseases due to mtDNA mutations are inherited matrilineally. Mitochondria are virtually always transmitted from the mother to all of her offspring. Although mitochondria are present in the sperm, they do not enter the egg upon fertilization, except in very rare cases. Maternal transmission may be ascertained by family history. During the division of cells containing both mutant and normal mtDNAs, individual cells can accumulate varying proportions of each. A mother with a homoplasmic mtDNA mutation can transmit only that mutant mtDNA to her offspring, while a mother with varying levels of mutated mtDNA may not always transmit mutated mtDNA, depending on the percentage of mutated mtDNA present. However, above a certain level, it is likely that all children will receive some mutated mtDNA. Susceptibility of specific tissue types to impaired mitochondrial function as a result of an mtDNA mutation, the proportion of mutated mtDNA in a given cell or tissue type, and the severity of the specific mutation determine the phenotype. This may explain why some disorders show a childhood form with early onset, rapid progression, and multiple organ effects, while others lead to an adult form with late onset, slower progression, and effects mainly confined to the nervous and muscular systems.

Diseases due to mtDNA mutations often involve tissues dependent on large amounts of adenosine triphosphate (ATP), such as the skeletal and heart muscles, central nervous system, kidney, liver, pancreas, and retina; sensorineural hearing loss is frequent. Some symptoms that might alert the clinician to consider mitochondrial disorders are ataxia, weakness, seizures, respiratory insufficiency, failure to thrive, ophthalmoplegia, retinopathy, stroke-like episodes, short stature, episodic vomiting, and sensorineural hearing loss. For example, the 1555A > G mitochondrial mutation results in susceptibility to deafness after taking aminoglycosides. Testing is available for this mutation, which then has a very practical application in that another antibiotic can be used in treatment. Phenotypic manifestation is wide-ranging, and some patients exhibit isolated deafness or diabetes. Symptoms may show wide clinical variability among patients and even within a family, and may worsen after exercise. In adults, exercise intolerance and generalized fatigue may be early indications. Laboratory results include abnormalities in serum lactate or pyruvate after exercise and ragged red fibers seen on muscle biopsy in certain disorders such as myoclonic epilepsy with ragged red fibers (MERFF). Selected mitochondrial diseases are shown in Table 4.9.

TABLE 4.9 Selected Mitochondrial Diseases

| Condition | Comment |
|---|--|
| Kearns–Sayre syndrome | Large mtDNA deletion leading to impaired oxidative phosphorylation. Onset usual in later childhood or adolescence; manifestations include progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects such as heart block |
| Leigh syndrome | Typical onset in infancy usually before 6 months; developmental delay, failure to thrive, poor sucking, vomiting, anorexia, irritability, seizures; if presents in childhood, may see ataxia, dysarthria, cognitive decline, respiratory disturbances, and ocular manifestations such as nystagmus or gaze palsy |
| Leber hereditary optic neuropathy (LHON) | Typical onset in early adulthood; may present with sudden painless central visual loss, headache on onset, cardiac conduction defects, and dystonia; may be incomplete penetrance and male bias in expression; pediatric-onset form. |
| Mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) | Usually begins with migraine-like headache, seizures, dementia, nausea and vomiting, and stroke-like episodes leading to neurologic deficits, aphasia, hemianopia |
| Myoclonic epilepsy with ragged red fibers (MERFF) | Presents in childhood or young adulthood with myoclonic epilepsy, ataxia, and other signs and symptoms such as dementia, optic atrophy, and deafness |

TABLE 4.10 Major Characteristics of Mitochondrial Inheritance and Disorders

- ▶ Mutant gene is located in the mitochondrial DNA.
- ▶ Each mitochondrion contains multiple DNA molecules.
- ▶ Cells contain multiple mitochondria.
- ▶ Normal and mutant mitochondrial DNA for the same trait can be in the same cell (heteroplasmy).
- ▶ Inheritance is through the maternal line.
- ▶ Males and females are affected in equal numbers on average.
- ▶ Variability in clinical expression is common.
- ▶ There is no transmission from a father to his children.
- ▶ Disorders are relatively uncommon.

Accumulating damage to mtDNA in somatic tissues over time appears important in aging and in the development of Parkinson disease. External influences are known to have effects, some of which are reversible. For example, zidovudine, which is used in the treatment of HIV infection, can inhibit mtDNA replication and cause mtDNA depletion, resulting in mitochondrial myopathy, which is usually reversible when it is discontinued.

Like mutations in nuclear DNA, those in mtDNA may be sporadic or inherited. Because mtDNA mutations are inherited through the female, a mother would potentially transmit the mutation to all of her offspring, while an affected father would not transmit it to any of his offspring. Some disorders due to mitochondrial mutation include Leber hereditary optic neuropathy, Leigh syndrome, mitochondrial myopathy with encephalopathy, lactic acidosis and stroke-like episodes (MELAS syndrome), and MERRF. Mutations in certain nuclear genes may predispose to mtDNA aberrations and thus result in mitochondrial disorders. Characteristics of mitochondrial inheritance are summarized in Table 4.10. Empirical recurrence risk figures for true mitochondrial diseases are about 3% for siblings and 6% for offspring, but in some families, in which a mother is known to have a point mutation for a mitochondrial disorder or more than one child has been affected, the risk is estimated at 1 in 2. These figures should be interpreted cautiously. As researchers learn more about these disorders, more precise information will become available.

NONTRADITIONAL INHERITANCE

A number of assumptions underlie the basic tenets of patterns of inheritance, such as equal expression of genes from both parents. While these assumptions are correct in the majority of instances, there are exceptions that have been elucidated relatively recently. These include UPD, genomic imprinting and differential gene expression, gonadal mosaicism, and unstable mutations involving expanding repeats that often include the phenomenon of anticipation.

Uniparental Disomy

In the normal course of events, a child inherits one of each pair of genes and chromosomes from the mother and one from the father. In UPD, both chromosomal homologs are inherited from the same parent instead of inheriting one copy of each chromosome pair from the mother and the father (e.g., two paternal chromosome 9 homologs and no maternal chromosome 9 homologs). The child has a normal total number of chromosomes. This is illustrated in Figure 4.6. UPD may apply to all or part of a chromosome. If all the genes involved are normal, then this may occur without being recognized, although sometimes growth restriction and other effects may result. However, if a mutant allele for an AR disorder was present on one parental chromosome and this is the one inherited, then it now will be present in two copies and be manifested. UPD was first recognized in a person who had inherited two maternal copies of chromosome 7 and came to attention with cystic fibrosis, short stature, and growth hormone deficiency. Uniparental maternal disomy for chromosome 7 may be responsible for up to 10% of cases of Silver–Russell syndrome (growth restriction, asymmetric limbs, small triangular faces), as well as some cases of intrauterine growth restriction.

Genomic Imprinting

Another nontraditional inheritance mechanism is genomic imprinting, also called *parental imprinting* and *genetic imprinting*. Normally, one of an identical pair of alleles from one parent is expressed in the same way as the other of the pair from the other parent. In imprinting, the alleles of a given pair of genes are not expressed in an

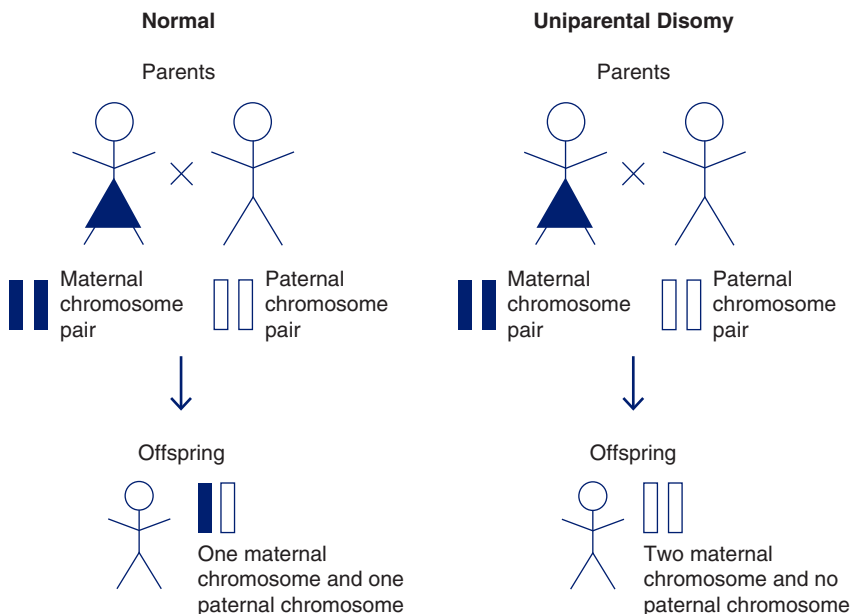


FIGURE 4.6. Illustration of uniparental disomy.

equivalent manner depending on the parent of origin. A gene is said to be maternally imprinted if the allele derived from the mother is the one that is silenced, turned off, repressed, or inactivated, and paternally imprinted if it is the allele contributed by the father that is turned off or inactivated. Thus, certain genes may be expressed from either the maternal or paternal chromosome, depending on imprinting. Methylation (see Chapter 2) is involved in imprinting, which is thought to occur before fertilization and confers transcriptional silencing for that gene. Imprinting is transmitted stably through mitosis in somatic cells and is reversible on passage through the opposite parental germline. Genomic imprinting may be suspected when:

- ▶ A given genetic disorder is always expressed when transmitted by only the male or only the female parent
- ▶ The sex of persons affected by the disorder in a pedigree will be approximately equal and not show a differentiation
- ▶ A disorder is present in one monozygous twin but not the other

Clinically, UPD and imprinting have been predominantly recognized in disorders of growth and behavior. The best-known examples of differential gene expression, due to parent-of-origin effects of UPD and imprinting, are Prader–Willi and Angelman syndromes. Prader–Willi syndrome (PWS) is a disorder that includes uncontrolled overeating, early obesity, hypotonia, hypopigmentation, small hands and feet, and intellectual disability ranging in degree (see Chapter 9). Angelman syndrome (AS) is marked by severe intellectual disability, inappropriate laughter, decreased pigmentation, speech impairments, ataxia and jerky arm movements, and seizures. In both disorders, UPD and imprinting errors involving genes on the long arm of chromosome 15 can be a cause. Beckwith–Wiedemann syndrome (an overgrowth disorder with macroglossia, omphalocele, and/or hypoglycemia) is associated with uniparental paternal disomy for the short arm of chromosome 11p, and imprinting abnormalities including insulin-like growth factor 2 (IGF2).

Gonadal (Germline) Mosaicism

Gonadal or germline mosaicism occurs when one parent has a mutant allele that results from mutation in the gonads, which occurs after fertilization, resulting in mosaicism. Clinical manifestations in that parent may not be seen because the mutation occurs in the cells of the developing gonad in either the male or the female and is present in few, if any, somatic cells. Thus, some germ cells may be normal, and others may carry the specific mutation. Gonadal mosaicism may occur in both AD and X-linked inheritance. One example is the case in which a clinically normal father had two children with osteogenesis imperfecta, an AD disorder, by two different women. The children both had the same point mutation in type I collagen, and it could be detected in their hair root bulbs, lymphocytes, and sperm. In this case, gonadal mosaicism was detected in the father. It has also occurred in the apparent sporadic occurrence of a male with X-linked Duchenne muscular dystrophy in which the apparent noncarrier mother may have had gonadal mosaicism. Gonadal mosaicism is important because if it is present, there is a risk of a second affected child following a first affected child who is thought to have a sporadic or new mutation. Genetic

counseling and evaluation for apparent new or sporadic mutations should take the possibility of gonadal mosaicism into account.

Unstable Repeat Expansions

Present throughout the human genome are short, repeated segments, usually in tandem, that contribute to polymorphism and thus are useful as markers. The most common repeats associated with disease to date are repeated units of three nucleotides that are arrayed contiguously and known as triplet repeats or trinucleotide repeats (e.g., CGG or CAG). Usually, in unaffected individuals, there are fewer than 20 to 40 of any given repeat. However, these repeats are prone to expanding during meiosis. When these nucleotides become unstable and expand or lengthen, they may cause disease. To date, there are 14 different trinucleotide repeat disorders. The number of repeats necessary to cause disease differs with each disease, and in some disorders, an intermediate number of repeats is associated with a premutation status (Table 4.11).

As the genes with the trinucleotide repeats are passed from generation to generation, the number of repeats often increases. In a pedigree, this increase in repeat numbers correlates with both the severity and the age of onset of the disease. The greater the number of repeats, the more severe the disorder and the earlier the age of onset. Anticipation is said to occur when the severity of a genetic disease increases with each generation, or the age at which the disorder manifests itself becomes earlier and earlier with each vertical generation. Anticipation is generally seen in AD disorders.

Types of Genetic Disorders

The term *genetic disorder* or *genetic disease* refers to diseases or disorders that result from deleterious or harmful changes in a person's genetic material. There are a variety of ways that genetic disorders can be classified:

- ▶ *Single gene disorders*—usually single gene disorders resulting from harmful alterations occurring in DNA in the nucleus or mitochondria
- ▶ *Chromosomal abnormalities*—due to quantitative or qualitative changes in chromosomes
- ▶ *Multifactorial disorders*—usually resulting from the interaction of mutations in multiple genes and environmental factors
- ▶ *Environmental*—due to exposure to a mutagenic agent; known as *teratogenic exposures* when the fetus is affected (discussed in more detail in Chapter 11)

SINGLE GENE INHERITED BIOCHEMICAL DISORDERS

The group of single gene errors, often called *inherited biochemical disorders*, includes a subgroup known as inborn errors of metabolism. Most inherited biochemical disorders are single gene defects, or Mendelian defects, and are caused by a heritable

TABLE 4.11 Triplet Repeat Disorders

| Disorder | Triplet Repeat | Number of Repeats | | |
|---|----------------|------------------------|-------------|----------------------|
| | | Unaffected Individuals | Premutation | Affected Individuals |
| Dentatorubral-pallidoluysian atrophy (DRPLA) | CAG | 6 to 35 | | 49 to 88 |
| Huntington disease (Chapter 10) | CAG | 10 to 26 | 27 to 41 | 36 to 121 |
| Spinobulbar muscular atrophy | CAG | 9 to 36 | | 38 to 62 |
| Spinocerebellar ataxia type 1 | CAG | 6 to 44 | | 39 to 81 |
| Spinocerebellar ataxia type 2 | CAG | 14 to 31 | 31 to 36 | 36 to 64 |
| Spinocerebellar ataxia type 3 or Machado–Joseph disease | CAG | 12 to 43 | | 56 to 86 |
| Spinocerebellar ataxia type 6 | CAG | 4 to 18 | | 21 to 33 |
| Spinocerebellar ataxia type 7 | CAG | 4 to 19 | 30 to 36 | 37 to 306 |
| Fragile X syndrome (Chapter 9) | CCG | 6 to 53 | 53 to 200 | 200 to 2,000 |
| Fragile XE mental retardation | GCC | 6 to 35 | | >200 |
| Friedreich ataxia | GAA | 7 to 34 | | >100 |
| Myotonic dystrophy | CTG | 5 to 37 | 38 to 49 | 50 to 1,000 |
| Spinocerebellar ataxia type 8 | CTG | 16 to 37 | | 110 to 250 |
| Spinocerebellar ataxia type 12 | CAG | 7 to 28 | | 66 to 78 |

permanent change (mutation) occurring in the DNA, usually resulting in alteration of the gene product. Gene products are usually polypeptide chains composed of amino acid sequences that form an entire molecule or subunit of such entities as structural proteins, membrane receptors, transport proteins, hormones, immunoglobulins, regulatory proteins, coagulation factors, and enzymes. Thus, gene mutation results in defective, absent, or deficient function of these products (often known as *loss-of-function* mutations), or, in some cases, no discernable phenotypic effect. Mutations not showing a phenotypic effect are called *null mutations*. Mutations that result in new protein products with altered function are often called *gain-of-function* mutations. Mutations may also code for a protein that interferes with a normal one, sometimes by binding to it, resulting in what is known as a *dominant negative* mutation. The consequences of altered function depend on:

- ▶ The type of defect
- ▶ The molecule affected
- ▶ The usual metabolic reactions it participates in
- ▶ Its usual sites of action
- ▶ How much (if any) residual activity remains
- ▶ Its interactions including those with other gene variants, the body milieu, external factors
- ▶ The degree of adaptation that is possible

Some proteins and enzymes are widely distributed in body cells, whereas others are confined to one type (e.g., hemoglobin is expressed only in red blood cells).

No official nomenclature currently exists for the inherited biochemical errors. Thus, great variation is seen in schemes used for classification and description. Such schemes may be based on mode of inheritance (e.g., AR—citrullinemia), the chief organ system affected (e.g., nervous system—Huntington disease), the biochemical pathway affected (e.g., urea cycle—argininemia), the general type of substance metabolized (e.g., amino acid—PKU), the specific cell type or tissue affected (e.g., red blood cell—adenylate kinase deficiency), the specific substance metabolized (e.g., branched chain amino acid—maple syrup urine disease), on a functional basis (e.g., active transport disorder—cystinuria), or by gene location (nuclear or mitochondrial).

Difficulties arise with any of these methods because, in some disorders, the basic defect is unknown; several organ systems can be involved (e.g., Holt–Oram syndrome, comprising limb and heart defects), or more than one type of inheritance has been identified for a disorder (e.g., retinitis pigmentosa), and so considerable overlap exists. For example, Tay–Sachs disease could be classified as a lysosomal storage disease, a neurologic disease, or an AR disorder. Relatively common, such disorders include sickle cell anemia, cystic fibrosis, neurofibromatosis, and hemophilia A. These are discussed in detail in Chapter 9; examples of such disorders that typically are manifested in adulthood such as Huntington disease are discussed in Chapter 10.

CHROMOSOMAL ABNORMALITIES

The basic structure of chromosomes and their transmission have been discussed in Chapter 2. In this chapter, various abnormalities are discussed. Certain changes in chromosome number or structure can result in various disorders. An alteration in the number of chromosomes is called *aneuploidy*. Because most of these tend to become evident at birth or in childhood, these disorders are discussed in Chapter 8. In contrast to single gene defects, chromosomal abnormalities usually involve multiple genes and result in congenital anomalies, developmental and intellectual disabilities, and behavioral difficulties. The majority of spontaneous abortions or miscarriages (about 50%–60%) are the result of chromosomal abnormalities, particularly if they occur early. Numerical changes in chromosomes are summarized in Table 4.12. Structural changes in chromosomes are summarized in Table 4.13 and illustrated in Figure 4.7.

Large surveys of consecutive newborns have allowed the incidence of chromosome aberrations present at birth to be well established at 0.5% to 0.6%, although prenatal diagnosis and selective termination of pregnancy have had an impact on decreasing this. Autosomal trisomies account for about 25% of all chromosomal abnormalities seen in live births (Nussbaum, McInnes, & Willard, 2007) while sex chromosome abnormalities account for about 35%, and structural rearrangements for about 40% of all chromosomal abnormalities. These figures represent only a small fraction of chromosomally abnormal conceptions. Nature exercises considerable selection, as only a small percentage of these abnormal conceptions survive to term. Between

TABLE 4.12 Changes in Chromosome Number (Aneuploidy)

| Change | Description | Example of Condition |
|-------------|--|---|
| Monosomy | 1 chromosome is missing. | Turner syndrome. Cells in females contain 45 chromosomes with 1 X chromosome rather than 2. |
| Trisomy | 1 extra chromosome is present. | Trisomy 21 (Down syndrome). Cells contain 47 chromosomes. |
| Tetrasomy | 2 extra chromosomes are present. | Cells contain 48 chromosomes. Not compatible with life. |
| Triploidy | 1 extra chromosome set of haploid genome is present. | Cells contain 69 chromosomes. Not compatible with life. |
| Tetraploidy | 2 extra chromosome sets of haploid genome are present. | Cells contain 92 chromosomes. Not compatible with life. |

TABLE 4.13 Major Changes in Chromosome Structure

| Change | Description |
|---------------------|---|
| Deletion (del) | Part of a chromosome is missing with the accompanying DNA. Can occur at the end (terminal) or in the middle (interstitial) of a chromosome. Example: del 5p, cri-du-chat syndrome |
| Duplication (dup) | Part of a chromosome is duplicated along with the accompanying DNA so that an extra piece of chromosomal material is present. Example: duplication of 17p11.2 resulting in Charcot–Marie–Tooth syndrome |
| Inversion (inv) | Alterations in which a portion of the chromosome is rearranged. This portion is rotation 180° from its normal orientation. Two breaks occur on the chromosomes, one on either side of the inverted piece of DNA, in order for the inversion to occur. Pericentric inversions involve the centromere, whereas paracentric inversions do not |
| Ring chromosome (r) | Rare chromosomal abnormality formed when a segment at each end of one chromosome is lost and the p and q arms fuse to form a circular structure. Example: Ring chromosome 14 is associated with psychomotor delay, mental retardation, and dysmorphic craniofacial features |
| Translocations (t) | Transfer of a chromosome segment to a nonhomologous chromosome after breakage has occurred. In reciprocal translocations, two chromosomes exchange pieces. Balanced reciprocal translocations usually do not cause problems since no genetic information is gained or lost. A Robertsonian translocation usually involves the fusion of the long arms of two acrocentric chromosomes. The p arms from the two acrocentric chromosomes are lost. A person with a Robertsonian translocation would have 45 chromosomes and typically not show a phenotype. Down syndrome may result from a Robertsonian translocation between chromosomes 14 and 21. These individuals have a normal chromosome 14, two normal chromosomes 21, and a translocation chromosome consisting of the second chromosome 14 and an extra chromosome 21 |

10% and 20% of all recognized conceptions end in spontaneous abortions. Studies of the products of spontaneous abortion have indicated that, overall, between 50% and 60% have detectable chromosomal abnormalities. Approximately 95% to 99% of all Turner syndrome embryos are spontaneously aborted, as are about 95% of those with trisomy 18 and 65% to 75% of those with trisomy 21. These data support the concept of therapeutic nonintervention in cases of imminent spontaneous abor-

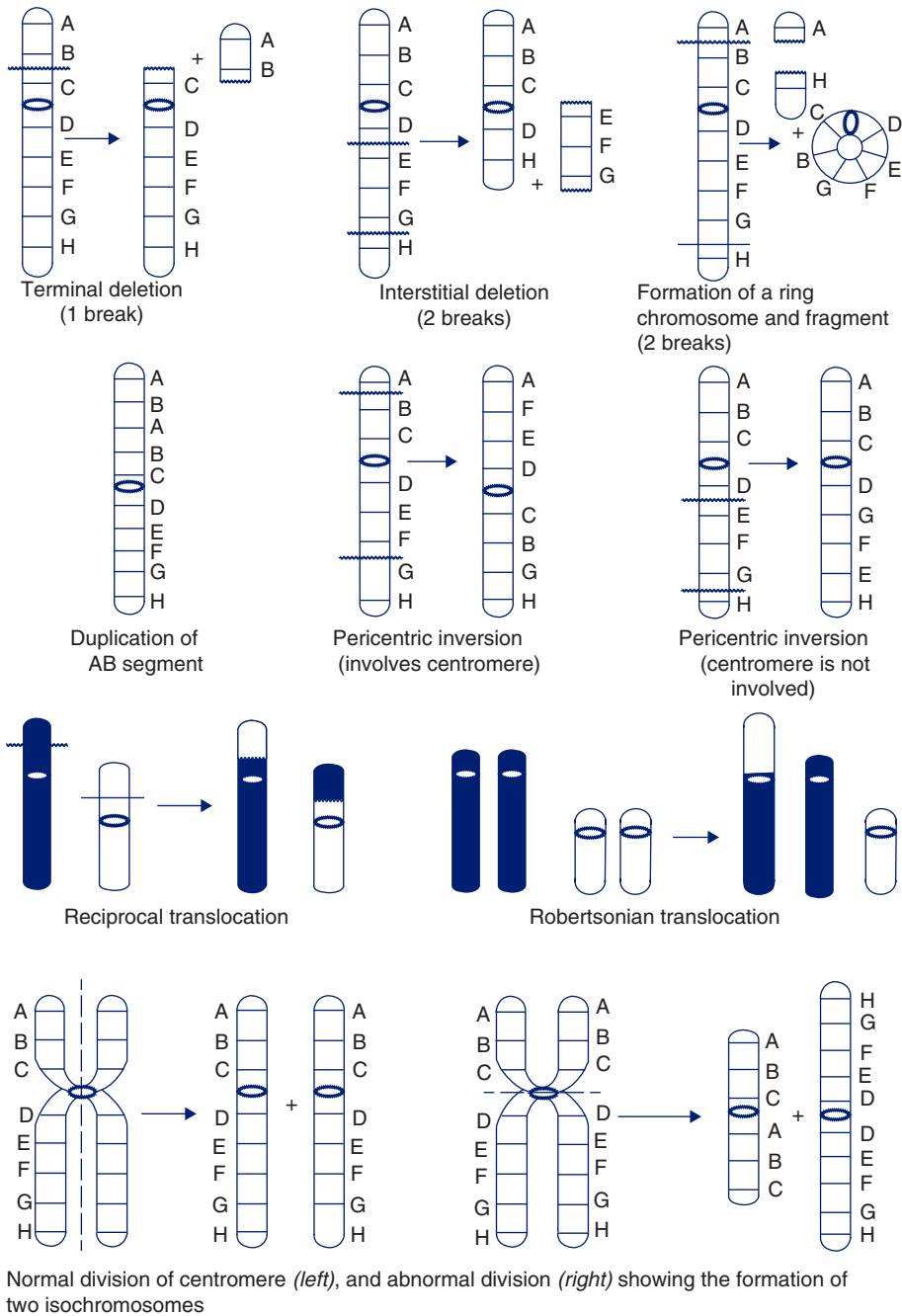


FIGURE 4.7. Diagrammatic representations of alterations in chromosome structure.

tion. Chromosomal abnormalities account for 6% to 12% of stillbirths and perinatal deaths, respectively; about 7% of deaths between 28 days and 1 year of age; and slightly over 7% of later infant deaths. The different incidence figures reported from study to study reflect the variety in gestational ages included, population differences,

TABLE 4.14 Incidences of Selected Chromosomal Abnormalities in Live-Born Infants

| Abnormality | Incidence in Live Births |
|--|----------------------------|
| Autosomal trisomies | |
| Trisomy 21 (Down syndrome) | 1:650 to 1:1,000 |
| Trisomy 13 (Patau syndrome) | 1:4,000 to 1:10,000 |
| Trisomy 18 (Edwards syndrome) | 1:3,500 to 1:7,500 |
| Sex chromosome disorders | |
| 45,X (Turner syndrome) | 1:2,500 to 1:8,000 females |
| 47,XXX (triple X) | 1:850 to 1:1,250 females |
| 47,XXY (Klinefelter syndrome) | 1:500 to 1:1,000 males |
| 47,XYY (Jacobs syndrome) | 1:840 to 1:1,000 males |
| Structural abnormalities | |
| Rearrangements (e.g., translocations, deletions) | ~1:440 live births |

Note: Based on statistics from surveys in different populations and not age adjusted. Data prior to use of prenatal diagnosis and selective termination of pregnancies became widespread.

differences in chromosome preparation techniques, and different rates of culture failure, particularly in tissue obtained from autopsy material. Extrapolating from available data, it appears that chromosome abnormalities are present in 10% to 20% of all recognized conceptions. This may eventually be higher, as techniques for determining cytogenetic causes improve. More than 1,000 chromosome abnormalities have been described in live births. The incidence of specific chromosome abnormalities found in live-born infants is summarized in Table 4.14.

FACTORS IN NUMERICAL CHROMOSOME ERRORS

A number of influences and mechanisms may be associated with numerical chromosome errors. Below, some of the most important, including maternal age and meiotic and mitotic nondisjunction, are discussed.

Parental Age

The increased risk for having a child with trisomy 21 (Down syndrome), or any trisomy, with advancing maternal age has long been known. This effect begins to

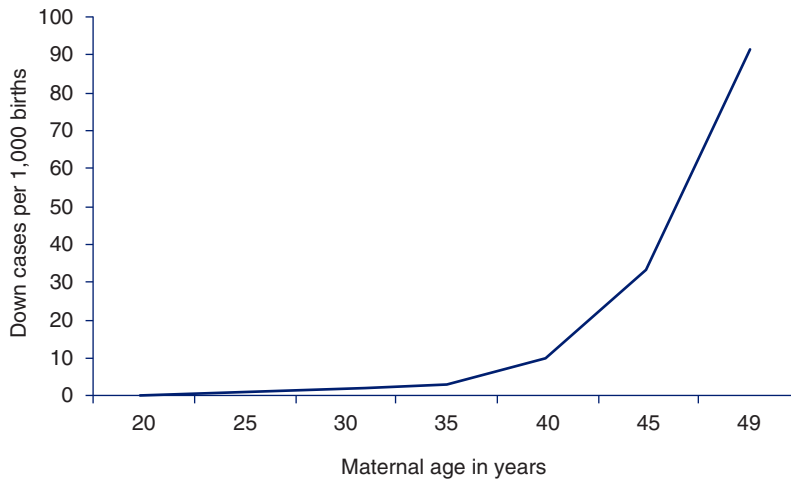


FIGURE 4.8. Incidence of giving birth to a baby with Down syndrome, by age of the mother.

assume more importance at about age 35; for this reason, women who get pregnant after the age of 35 are said to be of advanced maternal age (AMA). AMA is one of the indications for amniocentesis. Prenatal screening and diagnosis with selective pregnancy termination has had a considerable impact in reducing the number of live-born children with Down syndrome and other trisomies. Without accounting for prenatal diagnosis and selective pregnancy termination, the overall incidence of Down syndrome is about 1 in 800 live births, regardless of maternal age. The traditional, widely used risk figures for giving birth to a child with Down syndrome at any given age are illustrated in Figure 4.8.

These figures do not include conceptions that are not live-born, or the risk of other trisomies (e.g., trisomy 13; trisomy 18; 47,XXX; 47,XXY). Thus, the risk for bearing a child with any of these trisomies may be as much as twice the age-specific risk for trisomy 21. Nurses should recognize the implications of these data for health teaching. Chromosomally speaking, women should be encouraged to plan to complete their families before the age of 45 to prevent Downs and before the age of 35 to prevent the other trisomy and sex chromosome defects; women who plan to become, or are already, pregnant by that age should be referred for genetic counseling and prenatal genetic testing such as amniocentesis.

Nondisjunction and Mosaicism

There are two types of cell division: mitosis and meiosis. In normal mitosis (somatic cell division for growth and repair), each daughter cell ends up with the same chromosome complement as the parent. During oogenesis and spermatogenesis, meiosis (reduction division of $2N$ germ cells) normally results in gametes with the haploid (N) chromosome number. Nondisjunction, or improper separation of chromosomes, can occur in anaphase 1 or 2 of meiosis or in anaphase of mitosis, resulting in aneuploidy cells.

If nondisjunction occurs in meiosis, the chromosomes fail to separate and migrate properly into the daughter cells, so that both chromosomes of a pair end up in the

same daughter cell, leading to some gametes with $24 (N + 1)$ chromosomes and some with $22 (N - 1)$ chromosomes. When such gametes are fertilized by a normal gamete, trisomic or monosomic zygotes result, such as in trisomy 21 or in Turner syndrome ($45,X$), respectively. Offspring resulting from such fertilization generally have a single abnormal cell line. If nondisjunction occurs in the first meiotic division, only abnormal gametes result; if it occurs in the second division, half of the gametes will be normal. Nondisjunction during meiosis is shown in Figure 4.9.

The basis for the association of increased maternal age with the increased risk of bearing a child with a trisomy has been thought to be caused by nondisjunction during oogenesis. The process of oogenesis is halted at birth in females. All of the eggs are arrested in prophase of meiosis I, when the homologous chromosomes are paired up. Oogenesis restarts in the one egg per month that is ovulated. Therefore, many eggs can be arrested in prophase of meiosis I for decades. The longer the arrest, the harder it is for chromosomal separation to occur properly. Many trisomies are caused by nondisjunction in meiosis I. The precise molecular mechanism for nondisjunction remains to be found (Oliver et al, 2008; Subramanian & Bickel, 2008). For most trisomies, there is no association with advanced paternal age. However, there is some data that suggests that advanced paternal age may play a role in trisomy 21 and Klinefelter syndrome ($47,XXY$; Toriello & Meck, 2008).

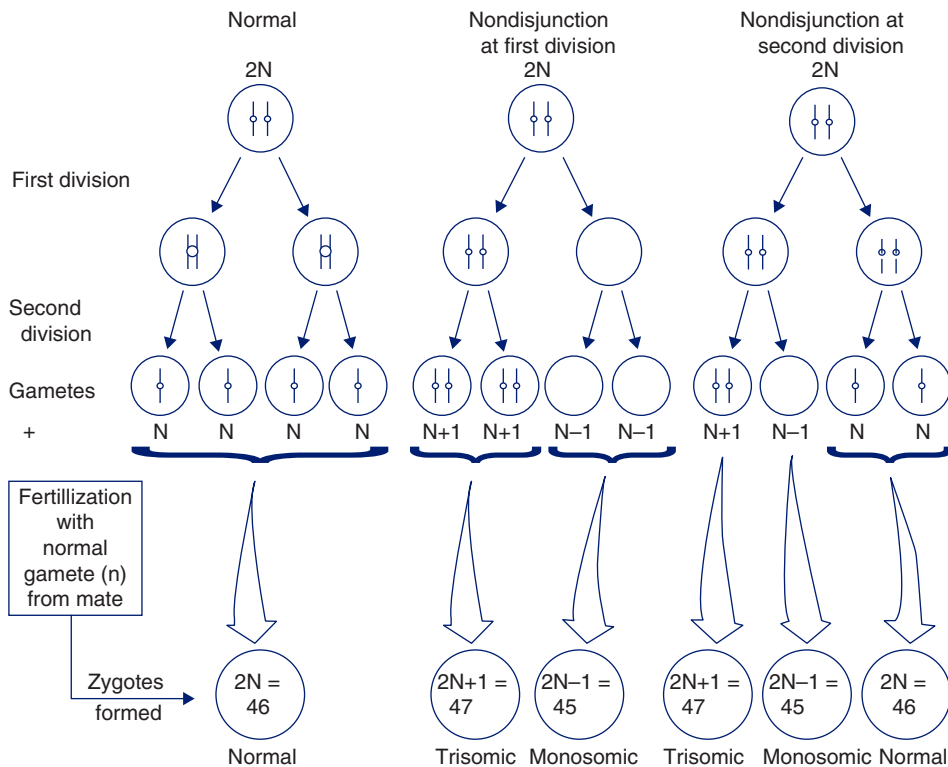


FIGURE 4.9. Mechanisms and consequences of meiotic nondisjunction at oogenesis and spermatogenesis.

Aneuploidy can also be caused by anaphase lag in either meiosis or mitosis, in which a chromosome (in meiosis) or chromatid (in mitosis) lags behind and eventually is degraded. As a result, one daughter cell will be euploid and the other daughter cell will be monosomic. The occurrence of either nondisjunction or anaphase lag during mitosis results in mosaicism in somatic cells. An individual who is mosaic possesses two or more cell populations, each with a different chromosome constitution that (in contrast to a chimera) arises from a single zygote during somatic cell development. The number of cells that will have an abnormal chromosome makeup will depend on how early in the division of the zygote the error occurs. The earlier it occurs, the higher the percentage of abnormal cells there will be. The results of abnormal division in mitosis leading to mosaicism are shown in Figure 4.10. Chromosome

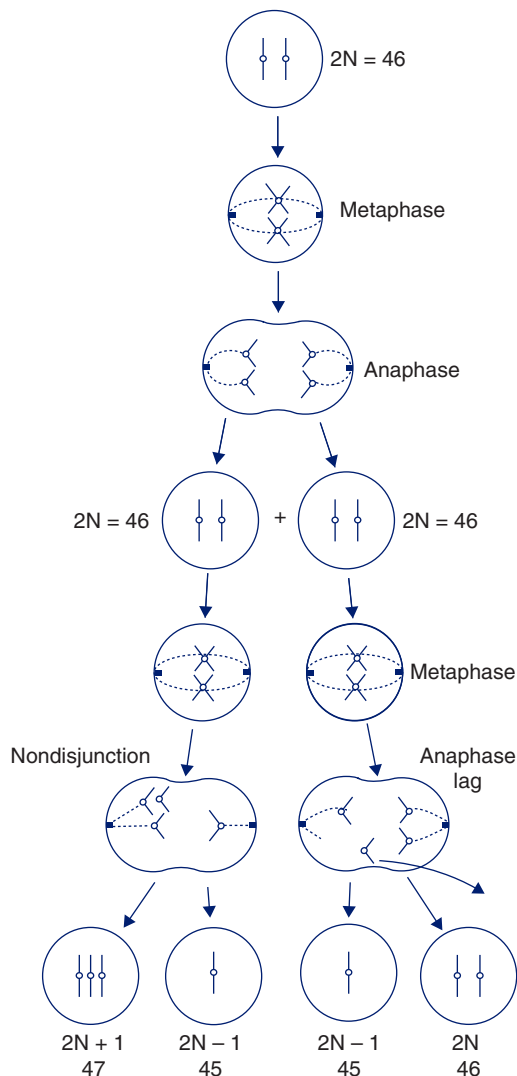


FIGURE 4.10. Mitotic division: (top) normal; (bottom) nondisjunction and anaphase lag producing mosaicism with three types of cell lines—(45/46/47).

abnormalities resulting from errors in mitosis are seen only in descendants of the initial cell with the error. Mosaicism is a common finding in chromosomal syndromes, and the degree to which a person is clinically affected depends on the percentage of cells with the abnormal chromosome makeup (Figure 4.10). Some persons with mild mosaicism show few or no phenotypic changes. Chromosome analysis of too few cells can miss mosaic persons with a small percentage of abnormal cells.

MULTIFACTORIAL DISORDERS

Some disorders, often including a variety of congenital malformations, do not follow a single gene inheritance pattern and are not known to be due to a chromosomal abnormality. They result from mutations in more than one gene combined with environmental factors. Some relatively common birth defects, such as neural tube defects, cleft lip, cleft palate, and some congenital heart defects, are inherited in this manner. Some common or complex disorders, such as cancer, diabetes mellitus, and heart disease, fall in this category and are discussed in Chapter 10.

Multifactorial Inheritance

Multifactorial refers to the interaction of several genes (often with additive effects) with environmental factors. Some have used the terms *multifactorial* and *polygenic* synonymously, but the latter does not imply any environmental component. Many morphologic features and developmental processes are believed to be under multifactorial control, with minor differences determining variability in the characteristic they determine. The spectrum ranges from different degrees of normal to abnormal outcomes.

Some of the more common congenital anomalies that are inherited in a multifactorial manner are listed in Table 9.1. One must, however, be careful to exclude specific identifiable causes before counseling on this basis. One way to accomplish this is to always seek diagnosis in an infant with congenital anomalies, especially if they are multiple. This includes chromosome analysis that should include high-resolution studies, detailed histories, a complete physical examination, and possibly DNA analysis.

An example of a normal trait inherited in a multifactorial manner is stature, in which ultimate height may be constrained within a range by genetic factors, but environmental factors (especially nutrition) play an important role in the final achievement of the genetic potential. This has been demonstrated in studies of immigrant families coming to the United States in which the height of the first generation of offspring is above the mean height of the first generation of the offspring of siblings who remained behind.

Mathematical calculations of additive multiple gene effects show a normal bell curve distribution within the population. To arrive at the concept of the presence or absence of a birth defect, one needs only to postulate a threshold beyond which the abnormal trait is manifested (Figure 4.11). In the case of some types of hypertension, the bell curve may represent the distribution of blood pressure in the general population, with the upper end of the continuous distribution representing hypertension, the exact threshold depending on the definition of “hypertension” used.

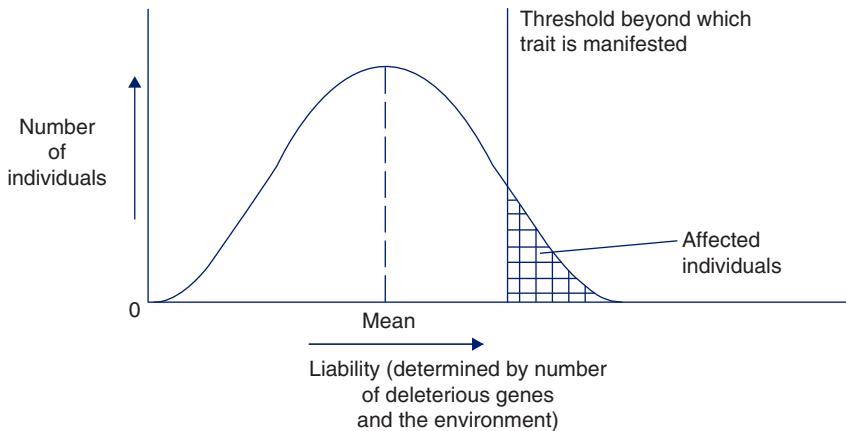


FIGURE 4.11. Distribution of individuals in a population according to liability for a specific multifactorial trait.

When each parent has several unfavorable alleles with minor effects that never encounter an unfavorable environment, they themselves may fall below the threshold. But when one of their children by chance inherits a genetic constitution with a large number of these unfavorable alleles from each parent and also encounters some environmental insult that someone without that particular genetic susceptibility could handle, a malformation results. Because relatives share a certain number of their genes in common, depending on their degree of relationship, they are at greater risk for the same defect than are others in the general population.

A theoretical example to help conceptualize the process is given in Figure 4.12. Consider 5 gene pairs with 10 possible alleles per person that are responsible for the determination of a certain developmental process. In our example, each parent has 4 abnormal alleles out of the 10. Theoretically, the way the example is composed, their offspring could inherit from 0 to 8 of the abnormal alleles. Two offspring are shown in Figure 4.12 (top). People in the general population might have from 0 to 10 abnormal alleles and be distributed in the bell curve as shown in Figure 4.12 (bottom). Perhaps, this hypothetical developmental process can function without apparent problems to result in a normal organ or part as long as a certain minimal normal number is retained or, conversely, until 8 unfavorable alleles are present. Then liability is too great, the threshold is passed, and a defect is manifested.

An analogy (although not an exact one) often used to explain this type of inheritance to the lay-person is to ask the person to imagine two glasses of water, each of which is three fourths full. These represent the unfavorable genes of the parents, whereas the airspace represents the favorable genes for the trait. They are below the threshold, which is the rim of the glass. When the water is poured into a glass (representing the child) that has an ice cube in it (representing unfavorable environmental factors), the water overflows, thus exceeding the threshold (Figure 4.13). It must be emphasized that this is what occurred with this pregnancy and that the genetic factors may be combined differently next time, and the unfavorable environmental factors may not be present. The actual recurrence risk figures for their specific trait should be presented along with this.

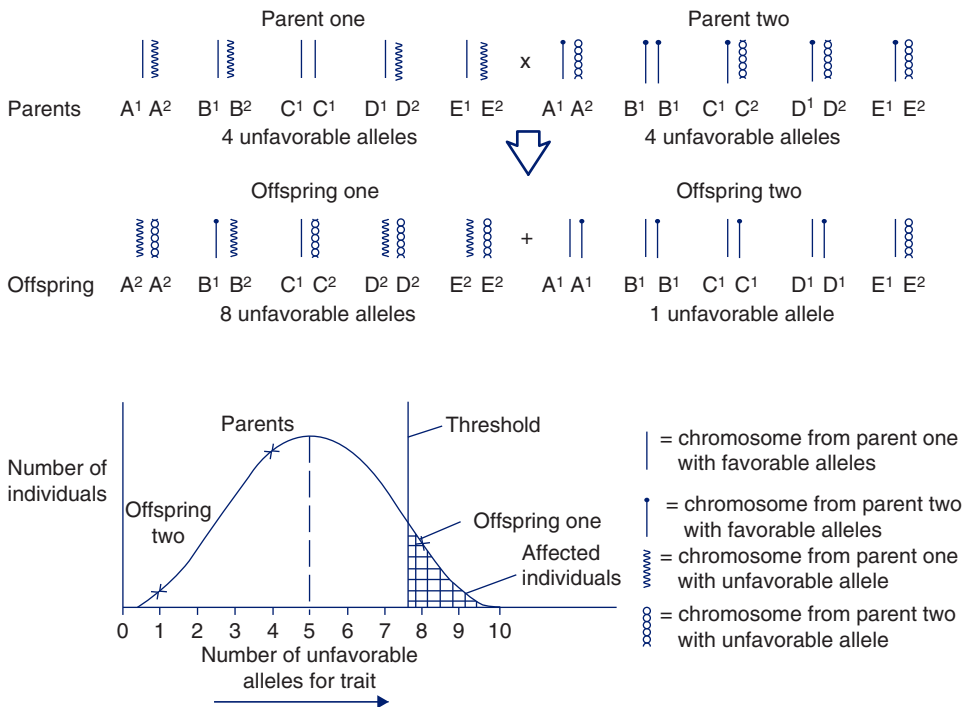


FIGURE 4.12. (Top) Theoretical example of transmission of unfavorable alleles from normal parents demonstrating chance assortment of normal and unfavorable alleles in two possible combinations in offspring. (Bottom) Position of parents and offspring from the example above is shown for a specific theoretical multifactorial trait.

The characteristics of multifactorial inheritance are summarized in Table 4.15. For the most part, only empirical (observed) recurrence risk figures are available for use in counseling. In contrast to the single gene disorders, in which the recurrence risk for subsequent pregnancies remains the same regardless of the number of affected offspring, in multifactorial inheritance, the risk increases with the number of affected individuals. For example, for some types of congenital heart disease, if one child is affected, the risk to the next is 2% to 4%, and if two siblings are affected (or one parent and one sibling), this rises to 8%. The risk for recurrence after one affected child is higher if the population incidence is higher. For example, neural tube defects are especially prevalent in Northern Ireland. Thus, the risk for a child with a neural tube defect is higher for one affected child born in Northern Ireland than it is for one born in the United States.

For defects in which one sex is affected more frequently than others, the risk to the relatives is greater when the defect occurs in the less frequently affected sex. This is because it is assumed that the threshold is higher for that sex and that it takes a greater number of unfavorable factors to exceed it (see Figure 4.14). The biological basis for the sex difference seen has not yet been identified.

The extent of the severity of the disease also influences the recurrence risk estimates. The more severely the child is affected, the more unfavorable factors are presumed to be operating and the higher will be the risk for recurrence. Another

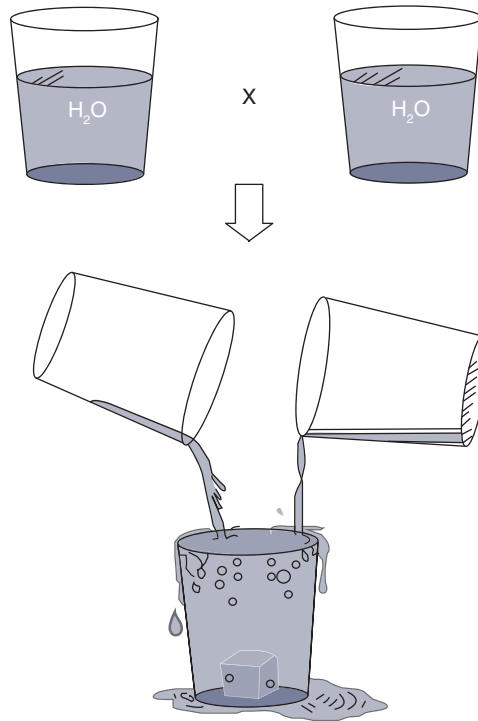


FIGURE 4.13. Water glass analogy for explaining multifactorial inheritance. In the top illustration, the water represents the parents' unfavorable alleles. The rim of the glass is the threshold. In the bottom illustration, the child inherits a large number of unfavorable alleles, plus unfavorable environmental factors (represented by the ice cube), and therefore “overflows” the threshold and manifests the anomaly.

characteristic is that the frequency of the defect in first-degree relatives (parents, siblings, offspring) is approximately equal to the square root of the frequency in the general population. Thus, if the population frequency for a specific defect was 1:10,000, it would be 1:100 among first-degree relatives. In addition, there is a sharp drop in the frequency of affected persons between first- and second-degree relatives and less between second- and third-degree relatives (Figure 4.14). For example, for cleft lip, the expected risks for first-, second (aunts, uncles, nephews, nieces)-, and third-degree (first cousins) relatives are, respectively, 40, 7, and 3 times that of the 1:1,000 incidence in the general population.

Risks for relatives less closely related are essentially the same as for the rest of the population.

The usual risk for recurrence of a multifactorial defect after one affected child is often cited as between 2% and 6%. However, those figures do not take into consideration all of the factors above, and thus, it is not as accurate as it should be. Each family should be individually evaluated and counseled.

ENVIRONMENTAL DISORDERS

Certain substances in the environment are capable of causing damage and mutation, resulting in effects on genetic material and resultant disease. The developing embryo

TABLE 4.15 Major Characteristics of Multifactorial Inheritance Assuming a Threshold

- ▶ The genetic component is assumed to be polygenic, quantitative, and additive in nature.
- ▶ The more severe the defect in the proband (index patient), the greater the recurrence risk in first-degree relatives.
- ▶ When the person with a congenital anomaly is of the less commonly affected sex, the greater the recurrence risk is in first-degree relatives.
- ▶ The more affected individuals in a family there are, the greater the recurrence risk is for additional members.
- ▶ The frequency of the defect in first-degree relatives is approximately equal to the square root of the frequency in the general population.
- ▶ There is a sharp drop in the frequency of affected persons between first- and second-degree relatives and a less sharp one between second- and third-degree relatives.
- ▶ The consanguinity rate is often higher in affected families than in the general population.
- ▶ The risk for recurrence is higher if consanguinity is present.
- ▶ The risk for an affected parent to have an affected child is similar to the risk for unaffected parents with one affected child to have another affected child.
- ▶ If concordance for the defect in monozygotic twins is more than four times higher than that in dizygotic twins, the defect is likely to be multifactorial.

and fetus can be exposed to teratogens during pregnancy, especially in the first trimester, resulting in birth defects. A *teratogen* is an agent that acts on the embryo or fetus, prenatally altering morphology or function, or both. Teratogens can include infectious agents such as the rubella virus, alcohol, certain drugs and medications such as valproic acid used as an anticonvulsant, and chemicals such as lead and mercury. These influences will be discussed in more detail in Chapter 11.

FACTORS AFFECTING THE EXPRESSION OF THE PHENOTYPE

Because genes operate within an integrated body system, their expression can be affected by internal and external variables. The most important of these variables are discussed next.

Penetrance

In the case of a mutant gene, individuals either have it or they do not. *Penetrance* refers to the percentage of persons known to possess a certain mutant gene who actually show the trait. Incomplete or nonpenetrance occurs when a person is known to have a specific genotype and shows no phenotypic manifestations of that genotype. As an example, if in a specific family a person's parent and offspring both had tuberous sclerosis, the person would be assumed to have the mutation even if

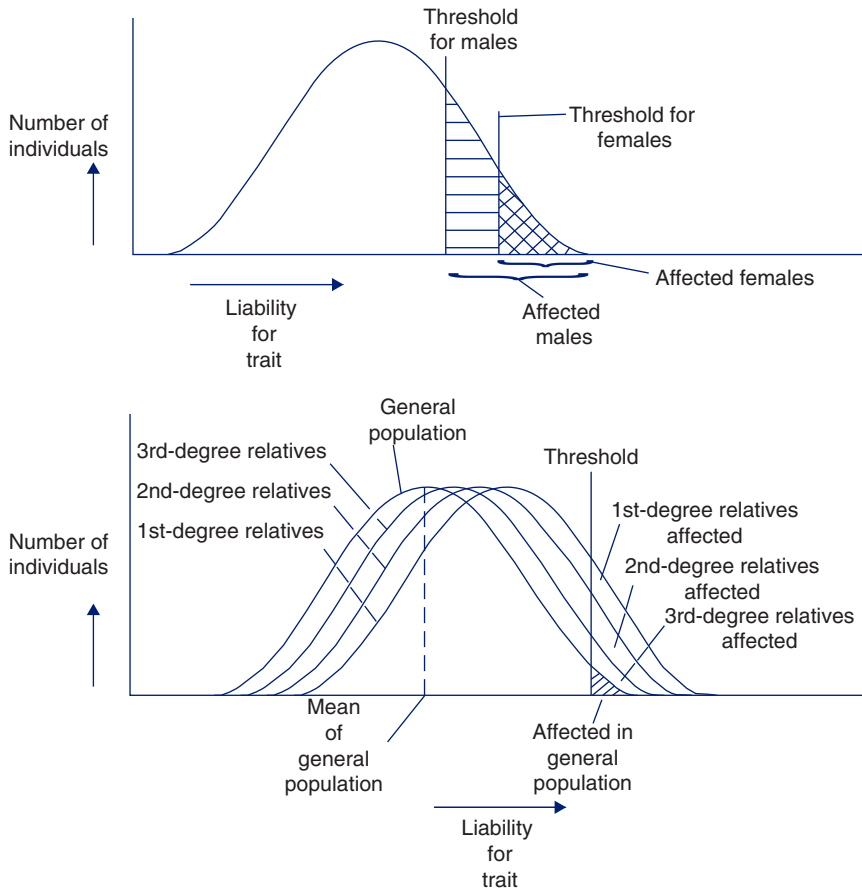


FIGURE 4.14. (Top) Distribution of the population for an anomaly such as pyloric stenosis that is more frequent in males than females. Note the difference in the position of the thresholds. The threshold for males is lower than that for females. (Bottom) Differences in the distribution of liability for a multifactorial trait are due to the degree of relatedness after birth of an affected infant.

he or she was clinically unaffected. Incomplete penetrance is a frequent finding in AD disorders. Estimates of penetrance have been calculated for certain AD genes so that they can be used in calculating risks for genetic counseling. For example, the penetrance for otosclerosis is 40%; it is nearly 100% for achondroplasia (a type of autosomal dominantly inherited dwarfism; see Chapter 9). One of the effects of incomplete penetrance is that the phenotype skips a generation, similar to what is observed in AR inheritance. This characteristic can be responsible for errors in genetic counseling if care is not exercised, although the use of molecular diagnostic techniques allows greater precision. The risk for a person to manifest a specific disorder is equal to the risk for inheriting the mutant allele multiplied by the penetrance.

Variable Expressivity or Expression

Variable expressivity, in contrast to penetrance, occurs when an individual has the allele in question and is clinically affected, but the severity of the phenotype varies.

As a simple example, in the case of polydactyly, the extra digit present may be full size or just a finger tag. Such variation may occur within a single family and may be caused by the influence of other factors on the major defective gene. It is most obvious in AD disorders. Careful examination or testing is necessary before deciding that someone is free of the manifestations of a genetic disorder. The extent of severity of a disorder in one family member is not related to its severity in another. This means that the offspring of a parent who is mildly affected, with only minor manifestations of a disorder, could be severely, moderately, or mildly affected. The severity cannot be predicted reliably by the gene's expression in another family member.

Heterogeneity, Allelism, and Phenocopies

The same or similar phenotype may result from:

- ▶ *Allelism*—different mutant alleles at the same locus
- ▶ *Genetic heterogeneity*—mutant alleles at different loci all result in the same phenotype
- ▶ *Phenocopies*—disorders arising from nonheritable environmental factors that closely resemble inherited disorders

Allelism

Various mutation types within a gene may lead to the same phenotype. However, depending upon the type of mutation, a difference in severity or prognosis of the disorder can be seen. For example, one would expect splicing errors and frameshift mutations to have a more severe effect on the protein, and therefore the phenotype, than a silent base substitution. This can result in different clinical pictures although the same enzyme is affected, as seen in the different forms of mucopolysaccharidosis type I (Hurler, Hurler–Scheie, and Scheie syndromes). All three syndromes result from mutations in the gene encoding the enzyme α -L-iduronidase; however, the age of onset and severity differ. The clinical course of Scheie syndrome has a later onset and is different from and milder than Hurler syndrome (see Chapters 7 and 9).

Some allelic disorders show different forms and degrees of severity at various points in the life cycle. Such disorders may show an acute, severe, progressive infantile form; a subacute juvenile form; and a milder chronic adult form. This may be because a less severe enzyme alteration may allow the person to function adequately for years unless he or she encounters a stressor such as infection, or even aging, or when a substance that has been accumulating finally reaches a toxic level. Notable examples of such disorders include Tay–Sachs disease (see Chapters 9 and 10), Niemann–Pick disease (see Chapter 9), citrullinemia (a urea cycle disorder due to deficiency of argininosuccinate synthase), and Gaucher disease (see Chapter 10).

Genetic Heterogeneity

In some disorders that show genetic heterogeneity, several genes, when mutated, can all result in the same phenotype. In order to determine if two individuals with the same phenotype have mutations in the same gene, complementation testing can be done. If two people with albinism (a condition lacking pigment) with the same

mutation at the same gene locus have children, all of them also will be albino, but if the mutations are in genes at different loci, then none of their children will be affected (except possibly by a rare mutation).

Yet other genetic disorders may show the same phenotype, but exhibit different modes of inheritance. On close examination or detailed molecular analysis, they may actually be a similar group of disorders. Examples are Ehlers–Danlos syndrome (a group of connective tissue disorders) and Charcot–Marie–Tooth disease (a group of peripheral nervous system disorders) that can show AD, AR, or X-linked inheritance. It is important to determine the correct inheritance pattern within a given family in order to provide accurate genetic counseling.

Phenocopies

Sometimes disorders resulting from environmental factors mimic those caused by single gene mutations. These are called *phenocopies*. An example is thalidomide, a teratogenic drug, in which the limb defects that result closely resemble those of Roberts syndrome or pseudothalidomide (SC) syndrome, which are inherited in an AR manner. While Roberts syndrome is heritable, phenocopies are not.

Age of Onset

In many of the inherited genetic disorders, the mutant gene itself is present from fertilization onward, yet the appearance of its effects may not be seen immediately but can occur at different times in the life span (see Chapter 1). Such appearance may be caused or influenced by any of the factors discussed in this section or by factors in the external environment. A correct diagnosis, which is important not only for treatment of the individual but also for genetic counseling, prenatal diagnosis, and life and reproductive planning for both the family and the affected person, is complicated by the fact that the same disorder may show different clinical pictures at different ages.

One of the most notorious diseases for late age of onset is Huntington disease, an AD disorder. Less than 10% of affected individuals show any symptoms before age 30. By age 40, about 50% of those who will become affected have developed the disease; by age 50, 75%; by age 60, 95%; and by age 70, almost 100%. It was not too long ago that there was no available method to distinguish individuals with the mutant allele from those with the normal allele. Individuals with a family history of Huntington disease used to have no way of knowing whether they had inherited the mutant gene until symptoms occurred. By the time it was known if a parent in fact had Huntington disease, the children may already have had their own children. This situation is often true as a prototype for other late-onset inherited disorders such as AD polycystic kidney disease, which is discussed in more detail in Chapter 10.

Genetic and Environmental Background

Genes function against the background of other genes and the internal and external environment. A simple example of environmental influence is seen in classical PKU, an AR disorder, in which individuals cannot metabolize phenylalanine. Despite being homozygous for mutations in phenylalanine hydroxylase (*PAH*) gene,

individuals may be phenotypically normal if they restrict their dietary intake of phenylalanine. He or she still has the gene mutations, and can pass them along to their offspring, but the environment has been manipulated so that the substrate is limited and toxic products do not build up. For this reason, PKU is one of the genetic disorders screened for at birth. If detected at birth, the appropriate diet will result in a normal phenotype. Other environmental factors that can influence the phenotype of various genetic conditions may include maternal nutrition, infection, noise, drugs, radiation, temperature, and amniotic fluid characteristics. Furthermore, the ways in which all proteins function together in cells, tissues and organs, and differential gene expression also influence ultimate functioning.

A mutant gene may interact differently with different genetic constitutions or within different tissue types. This helps to explain the varying degree of clinical severity seen in individuals with the same genetic disorder. An example of modifying genes is the milder disease seen in persons homozygous for the sickle cell gene who also have hereditary persistence of fetal hemoglobin. The chromosomal sex of an individual is another way in which the genetic background can regulate the internal environment through hormonal and other changes, and in turn influence the expression of genes in varying degrees. Thus, although mutation in one gene may be the major determinant, mutations at one or more other loci may be necessary for either pathogenesis or influencing severity.

Epistasis

One way in which the genetic background can affect gene action is illustrated by *epistasis*. Epistasis is the masking of the effect of one set of genes by a different set of genes at another locus. As an example, if an individual is homozygous for alleles for albinism, then any alleles at another locus for brown hair would not be expressed and the person would have white hair. Thus, one can say that the albinism genes are epistatic to the genes for hair pigment.

X Chromosome Inactivation (the Lyon Hypothesis or Principle)

A difference in gene dosage between males and females may be expected because males have only one X chromosome, whereas females have two X chromosomes. However, normal females and males have been shown to have equivalent amounts of enzymes coded by X-linked genes, such as *G6PD*, hypoxanthine-guanine-phosphoribosyltransferase (*HPRT*; deficiency resulting in Lesch–Nyhan syndrome), clotting factor VIII (deficiency resulting in hemophilia A; see Chapter 9), and others. Mary Lyon, in 1961, hypothesized that in female somatic cells, only one X is active, thus “compensating” for any male and female gene dosage difference. Although there are some deviations from it, the basic tenets of the now well-accepted Lyon hypothesis are as follows:

- ▶ In any female somatic cell, only one of the two Xs is active. In persons with several Xs (e.g., XXY males), all but one X are inactivated.
- ▶ X chromosome inactivation occurs early in embryonic development, probably at the early blastocyst stage.

- ▶ The inactive X (or Xs) can be seen in interphase nuclei as sex chromatin, heterochromatin, or the Barr body.
- ▶ In any given cell, it is generally random whether the maternal or paternal X chromosome is inactivated.
- ▶ Once it occurs, all descendants of the original cell will have the same X chromosome inactivated.
- ▶ Inactivation is irreversible (except perhaps in the oocyte).

Because X inactivation is generally a random occurrence in the population at large, there is a 50-50 chance as to whether the maternal or paternal X is inactivated. But any given individual may have ratios that deviate. Occasionally, the percentage of cells that have the X with the normal gene turned off is very high. This leads to a skewed population in which there is a preponderance of active, mutant-X bearing cells. This explains why hemophilia can clinically manifest itself in a female known to be a heterozygous carrier, although this can also result from chromosomal microdeletions of the normal gene. It also explains why traditional methods of carrier detection are difficult for XR disorders, as the possible range for enzyme activity values can vary greatly, depending on the genetic constitution of the X chromosome inactivated.

Nonrandom or skewed X inactivation can also result from (a) chance, (b) imprinting, (c) monozygotic twinning with unequal distribution of the X with the mutant gene, (d) cytogenetic abnormalities, (e) gene expression differences, (f) clonal selection in which there is nonrandom inactivation of the X chromosome with the mutant allele, (g) preferential selection that is either positive or negative for the X chromosome with the abnormal gene, and (h) a specific gene mutation affecting X inactivation. Methylation (discussed in Chapter 2) maintains the X inactivation.

Sex-Limited Traits

Some traits are expressed in either males or females, yet are controlled by autosomal genes. As such, these autosomal genes can be transmitted from either parent, but the phenotype still only appears in one sex. This sex-specific pattern of expression is usually seen in gender-specific secondary sexual characteristics, such as milk production or testes development.

Sex-Influenced Traits

Sex-influenced traits are expressed in males and females, but in different ways. These traits, like sex-limited traits, are also controlled by autosomal genes. However, unlike with sex-limited traits, these traits are seen in structures present in both sexes (e.g., hair cells). For example, both males and females can have the phenotype of hair loss. Male pattern baldness is an AD trait, requiring only one copy of the gene, whereas in females it appears to be recessive and expressed only when two copies are present. These differences in expression of the phenotype in males and females may be due to hormonal influences such as androgen levels.

Parental Age Effect

Parental age plays a role in the frequency and development of some genetic mutations in offspring. AMA (discussed earlier in this chapter) is associated with an increased risk of chromosomal abnormalities, like trisomies, in offspring. Advanced paternal age, while less known than AMA, is associated with an increased risk of base substitutions in offspring. There is a subset of nine “paternal age effect” (PAE) disorders, which are caused by spontaneous dominant gain-of-function mutations (Goriely & Wilkie, 2012). Interestingly, mutations in these disorders are all paternal in origin. To date, no maternally derived mutations have been identified in these PAE disorders. All nine disorders have a strong PAE, where fathers of affected children are older than fathers in the general population by at least 2 years, if not more. Disorders that have an association with advanced paternal age, including the nine PAE disorders, are shown in Table 4.16.

TABLE 4.16 Genetic Disorders Associated With Increased Paternal Age

| Disorder | Description of Major Features | Mechanism |
|---------------------------------|---|-----------|
| Achondroplasia | Short-limbed type of dwarfism with large head (see Chapter 9) | AD |
| Acrodysostosis | Intellectual disability, short limbs with deformities, especially in arms and hands; growth deficiency; small head, nose, and maxilla | AD |
| Apert syndrome | Craniofacial deformities such as craniosynostosis; skeletal deformities, especially “sock” feet and syndactyly | AD |
| Basal cell nevus syndrome | Nevi that become malignant; rib and spine anomalies; variable degree of intellectual disability; eye abnormalities | AD |
| Costello syndrome | Developmental delays, arrhythmias, hyperflexible joints, short stature | AD |
| Crouzon craniofacial dysostosis | Hypoplasia and abnormalities of skull and face; craniosynostosis, premature suture closure; shallow eye orbits | AD |
| Marfan syndrome | Elongated thin extremities; cardiovascular complications, especially of aorta; ocular anomalies, especially of lens | AD |

(continued)

TABLE 4.16 Genetic Disorders Associated With Increased Paternal Age (continued)

| Disorder | Description of Major Features | Mechanism |
|---------------------------------------|--|-----------|
| Muenke syndrome Noonan syndrome | Craniosynostosis, some mild abnormalities of hands and feet | AD |
| Multiple endocrine neoplasia, type 2A | Thyroid cancer (medullary thyroid carcinoma), adrenal tumors (pheochromocytomas), hyperparathyroidism | AD |
| Multiple endocrine neoplasia, type 2B | Thyroid cancer (medullary thyroid carcinoma); adrenal tumors (pheochromocytomas); tumors on the eyelids, lips, and tongue | AD |
| Noonan syndrome | Short stature, heart defects, enlarged distance between the eyes, small jaw, webbed neck | AD |
| Oculodentodigital dysplasia | Digital anomalies such as incurved fifth finger (camptodactyly) or syndactyly; tooth enamel hypoplasia, other dental abnormalities; microphthalmos, glaucoma possible | AD |
| Pfeiffer syndrome | Craniosynostosis, wide thumbs and big toes, short fingers and toes, fusion of some digits | AD |
| Waardenburg syndrome 1 | Bilateral perception deafness; pigment disturbances of hair and eyes (e.g., white lock of hair and uniform light-colored irises or heterochromic irises); lateral displacement of inner canthus of eye; may have other anomalies | AD |
| Progeria | Thin skin; alopecia; growth deficiency; atherosclerosis; appearance of premature aging | AD, AR(?) |

AD, autosomal dominant; AR, autosomal recessive.

The risk for sporadic AD single gene mutations is four to five times greater for fathers aged 45 years and older than for fathers 20 to 25 years old. Most sperm banks will not accept donations of sperm from older men for artificial insemination and other assisted reproductive techniques for this reason. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of

the Society for Assisted Reproductive Technology (2013) give detailed guidelines for sperm donation, including that “the donor should be of legal age, and ideally, less than 40 years of age” (p. 49).

SUMMARY

Knowledge of mechanisms of gene inheritance continues to expand. Complexities of epigenetic and other mechanisms that influence the regulation of gene expression and the influence of the modifying effects of other genes in the genome as well as environmental factors add to knowledge and understanding.

QUESTIONS FOR DISCUSSION

- ▶ Since normal males and females have one X and two X chromosomes, respectively, why don't these females have greater quantities of some of the gene products produced by genes on the X chromosome?
- ▶ A family who has received genetic counseling for an AR disorder for their affected child tells the nurse, “We are so relieved. There is a one in four chance for this to happen again. We can plan for three more children without worrying!” What would be some things for the nurse to think about? What would be appropriate responses from the nurse, and why?

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CHAPTER 5

Prevention, Genetic Testing, and Treatment of Genetic Disease

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In regard to genetic disorders, prevention is the ideal goal. If total prevention is not possible, the effects of morbidity and mortality, as well as the burden on the family and community, may be reduced. There are various ways of achieving this but, to date, prevention is not always possible. Treatment is also a way to prevent some of the morbidity and mortality engendered by genetic disease. This chapter reviews prevention, including genetic counseling. Genetic testing for diagnosis as opposed to screening is discussed, followed by treatment of genetic disease.

PREVENTION

Methods of prevention begin with education of the public and health care professionals and identification of those at risk, and are listed as follows:

- ▶ Education of the public and professionals at the appropriate educational level while considering and respecting cultural, social, and religious practices
- ▶ Family history over at least three generations and preparation of pedigree as part of risk assessment, including geographic origins of the family
- ▶ Identification of those at risk because of genetic constitution through history, screening, or targeted testing
- ▶ Follow-up with genetic counseling
- ▶ Research
- ▶ Access to and delivery of health care services, both preventive and therapeutic; includes cancer surveillance and preventive activities in those at risk for familial cancers as discussed in Chapter 10
- ▶ Identification and avoidance of environmental hazards
- ▶ Preconception counseling, discussed in detail in Chapter 8, including stabilization of any maternal diseases, avoiding agents harmful to the fetus, vaccinations, folic acid supplementation, adequate nutrition, and discussion of potential risks based on ethnic origin

- ▶ Newborn screening
- ▶ Carrier screening
- ▶ Predictive screening
- ▶ Genetic testing
- ▶ Prenatal detection and screening
- ▶ Prenatal diagnosis
- ▶ Identification of alternative reproductive options
- ▶ Selective pregnancy termination

Major preventive measures include genetic testing and screening followed by genetic counseling (discussed in the following subsection). An area of prevention includes surveillance and prophylaxis after diagnosis with, for example, a mutant gene that confers susceptibility to cancer. Examples include *BRCA1* and *BRCA2* mutations that confer a susceptibility to breast cancer (discussed in Chapter 11) and the *APC* gene mutation conferring susceptibility to colon cancer. In the breast cancer examples, if the person possesses the gene mutation that indicates he or she has increased susceptibility, he or she can embark on a program of surveillance.

Genetic Counseling

In response to increased demand for genetic counseling and the realization that little was known about the best ways to offer such services, a committee of the National Society of Genetic Counselors developed the definition shown in Box 5.1. Genetic counseling is provided primarily for single gene conditions. The advent of genomic testing for complex conditions has led to an expansion of traditional genetic counseling to a new “genomic counseling” to include whole-exome sequencing (WES) and whole-genome sequencing (WGS).

Genetic services are often offered by a team of professionals that may include any of the following as core individuals: physician, geneticist, genetic counselor, genetic associate, nurse, nurse practitioner, social worker, psychologist, or pastoral counselor. Any persons with the referral indications given in Chapter 7 are candidates

BOX 5.1

Definition of Genetic Counseling

Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. This process integrates the following: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources, and research; counseling to promote informed choices and adaptation to the risk or condition (Resta et al., 2006).

for genetic counseling referral. Those persons most commonly referred for genetic counseling are the following:

- ▶ Persons or couples who have had a child with a birth defect or known genetic disorder
- ▶ Persons or couples who are known to be heterozygous carriers of a specific genetic disease
- ▶ Persons affected by a trait or disorder known or suspected to be inherited
- ▶ Persons who have a known or suspected inherited disorder in the family and are contemplating marriage or starting a family
- ▶ Persons who are experiencing reproductive problems such as infertility, multiple miscarriages, or stillbirths or are considering artificial reproductive techniques
- ▶ Persons who are contemplating marriage to a relative
- ▶ Children entering the adoption process
- ▶ Members of ethnic groups with a high frequency of specific known genetic disorders to detect carrier status
- ▶ Those with possible exposure to toxic agents, illnesses, or mutagens during pregnancy
- ▶ Those with possible exposure to toxic agents or mutagens during military service or employment
- ▶ Women 35 years of age and older who are considering prenatal diagnosis
- ▶ Persons seeking risk assessment prior to genetic testing or interpretation of genetic tests for certain complex disorders, such as cancer or heart disease

The person who is seeking genetic counseling may be called the *counselee* or *consultand*. The term *proband* or *propositus* refers to the index case or to the person who first brought the family to the attention of the geneticist, for example, the affected child. In practice, the actual counselee may be more than one person—for example, mother, father, and child. Genetic counseling is also offered in conjunction with testing and screening programs and for those considering adoption or various reproductive technologies. About 90% of those who should be so referred are not. Indications that nurses can use as guides for referral are given in Chapter 7. If a formal referral is initiated, the counselees should bring all relevant records, family data, and even photographs with them or send this material before their first appointment. The genetic counselor should be notified of the referral by phone, letter, or secure electronic means. The nurse or the referring professional should also check with the counselee to see that follow-through has occurred.

Some clients are very self-directed and motivated to seek counseling. Others may be there because “the doctor told me I should come.” Elements of the Health Belief Model are relevant here in that the client must perceive that a serious situation exists, there is some personal vulnerability, and the benefits derived from the indicated action will outweigh the barriers or risks. Other factors, such as denial and guilt, are also operative.

Because many emotions are involved in a genetic disorder, it is not always helpful to provide genetic counseling immediately after the birth of an affected child or the unexpected diagnosis of a genetic disease in an adult. These events can precipitate a family crisis. Genetic disease is often perceived as permanent and untreatable. Shock followed by denial often is the first part of the coping process. When counselees are seen in this phase, which may be present 3 to 6 months after the crisis, they do not know what they want to know, and they may not hear what is said to them. Anxiety and anger follow, and this may be directed outward as hostility or inward as guilt. At this point, the counselee may be ready to intellectually understand and adjust only on an intellectual level. Depression occurs next, and if the counselee can achieve behavioral adjustment, successful accommodation can occur. Obviously, counselees may cycle between phases. Covert anger and avoidance behavior may lead to clients' canceling, not keeping, or arriving late for their appointments. Those who do not understand the basis for this behavior may demonstrate annoyance and hostility toward the client, which will act to negate efforts to establish a good client–counselor relationship.

An initial early interview can be used to assess the degree of negative feelings and to use intervention techniques or provide support services for ongoing counseling if it appears indicated. Usually a family history can be obtained and may provide the clients with the feeling that they are taking some positive action. Documentation of findings should be shared with the individual and family as appropriate. A second appointment is then scheduled.

Components of Genetic Counseling

As the setting, the professionals providing services, and the reasons for seeking counseling vary, so too does the counseling process. Nevertheless, all genetic counseling has some common elements. The usual components of the genetic counseling process are shown in Table 5.1. Their application and sequence also vary because the geneticist does not always know what additional information is needed until after the assessment process, the interview, and the histories are completed (e.g., chromosome analysis may need to be done, past records obtained, an illness in another family member confirmed). Usually there is more than one session anticipated, with information gathered and a relationship established first, and plans made to collect other needed data on which to formulate diagnoses or recurrence risks.

It is imperative to establish a baseline level of understanding that each counselee brings to the discussion. At the most basic level, focusing on whether or not the distinction between a somatic mutation and a germline mutation can be made by the counselee will provide clarity between nonheritable versus heritable diseases. For example, in the practice of oncology, genetic changes are common in cancer cells. These malignant cells often exhibit aneuploidy as well as translocations that are found only within the tumor cells. Genetic errors that arise from specific cell lines are somatic mutations. In contrast, if aneuploidy or mutation occurs during meiosis, then genetic changes will be present in every cell. Meiosis is the process of cell division in reproductive cells (i.e., eggs and sperm). An example of a germline mutation is trisomy 21 or Klinefelter syndrome. Somatic mutations are not a part

TABLE 5.1 Components of Genetic Counseling

- ▶ Initial interview
- ▶ Family history, pedigree preparation and analysis, other histories
- ▶ Assessment of counselee (e.g., physical examination)
- ▶ Considering potential diagnoses
- ▶ Confirmatory or supplementary tests or procedures such as:
 - Chromosome analysis
 - Biochemical tests
 - Molecular DNA testing or analysis
 - X-ray films
 - Biopsy
 - Linkage analysis
 - Developmental testing
 - Dermatoglyphics
 - Electromyography
 - Prenatal diagnosis
 - Immunological tests
 - Whole-exome sequencing
 - Whole-genome sequencing
- ▶ Establishment of an accurate diagnosis
- ▶ Literature search and review
- ▶ Use of resources and registries on the web
- ▶ Consultation with other experts
- ▶ Compiling of information and determination of recurrence risk
- ▶ Communication of the results and risks to the counselee and family if appropriate
- ▶ Communication of incidental findings from array-based testing or genomic sequencing
- ▶ Discussion of natural history, current treatment options, and anticipatory guidance if relevant
- ▶ Discussion of options
- ▶ Review and questions
- ▶ Assessment of understanding and clarification
- ▶ Referrals—for example, prenatal diagnosis and specialists
- ▶ Support of decisions made by counselee
- ▶ Follow-up
- ▶ Evaluation

Note: Order may vary depending on the reason for the initial referral. Psychosocial support should be provided throughout the process. All explanations should be culturally appropriate for counselees and appropriate to their educational level.

of the reproductive cells and therefore cannot be transmitted to offspring, whereas germline mutations may be transmitted.

Obtaining a History and Preparing a Pedigree

Recently there has been increased attention in the health care community regarding the importance of the family history over three generations. Most information

regarding the taking of the history is discussed in Chapter 7. There are, however, some points that should be considered here. The taking of the family history also gives the counselor a chance to observe family interactions, and it can provide clues for effective approaches when discussing risks and options. It is very helpful to have both members of a couple present when the history is taken because one person rarely has the precise information necessary about both sides of the family or, if they have attempted to gather it beforehand, they may not have asked the relevant questions indicated by the suspected genetic disorder (e.g., in neurofibromatosis 1 in the family, it may be helpful to know if axillary freckling is present in any relatives who cannot be personally examined). If all agree, it may be helpful to have an older relative present for part of the information gathering because that person may have detailed information about the family. Taking the history is time consuming because one cannot just ask a general question such as: "Does anyone in your family have a birth defect, intellectual disability, or genetic disease?" The concepts of disease, disability, and retardation may be culturally defined. Many counselees do not know what constitutes a genetic disease, and they may not equate "slowness" with intellectual disability. Thus, questions must be specifically tailored for the individuals, at their level of understanding, and within their sociocultural context. The history taking must result in the preparation of a pedigree, which may be helpful in determining the mode of transmission operating in a given family, even in the absence of a definite diagnosis that will allow a basis for counseling (see Chapter 7).

Anyone who has done such a history is aware of some of the problems and pitfalls that may be encountered. An issue for one couple who came for counseling was whether the disorder, which had incomplete penetrance, was a sporadic event or was caused by an autosomal dominant gene in that family. "I was told that Aunt Mary had something wrong with her. She was never allowed to marry, and they mostly kept her in her room." This could or could not be relevant to the situation at hand and needed to be further explored and documented. Sometimes this is difficult because people are reluctant to talk about defects and intellectual disability in their families. In recent times, families are less likely to be colocated with their extended families and may not be aware of the health status or history of family members. Difficulty in obtaining complete histories may also be impossible where the family migrated to new countries prior to the advent of modern communications and lost contact with the family of origin.

Often additional family information needs to be obtained and sent to the counselor. Some families do not wish to let other members know that they are seeking counseling, and this greatly complicates obtaining accurate information. A negative family history can have several meanings. If a couple has come for counseling, it is important to talk to the mother alone at some point in the interview. In such privacy, it is possible to ascertain, for example, situations involving the possibility of nonpaternity of the present mate, of sperm donation, or of adoption that has not yet been revealed to the child who may be accompanying his or her parents. Thus, a negative family history may mean that this mutation is sporadic or new or may be due to other reasons (see Chapter 7 for a complete list), including failure of the interviewer to ask the critical questions or conduct a thorough assessment or the withholding of information by the client.

Another sensitive area is that of consanguinity. By asking the names of all the relatives in the family history, the counselor can inquire further about those with the same last name on both sides of the family. Another way to ascertain this is by determining where both families have lived at various points in time, what their ethnic origin is, and what other countries the family originated from. Occasionally couples who did not realize they were related discover that they indeed have a common ancestor. A counselee whose child had Ellis–van Creveld syndrome (dwarfism with polydactyly and heart disease, which is common in the Pennsylvania Dutch) turned out to be married to a cousin. Both had Pennsylvania Dutch ancestors. The counselor can also lead into the subject by asking if there is any chance at all that the two partners are related. I have had several genetic counseling clients who were contemplating cousin marriages. Myths abound about such matings, particularly those between first cousins. One client reported that he had been told by a health professional that all of their children would be “crazy or retarded.” In fact, the risks are associated with the chance of bringing together the same recessive gene possessed by each one of them in their offspring. If no known genetic disease exists in the family and the persons do not belong to an ethnic group with a genetic disease that is above the usual population frequency, then the risk for homozygosity at a gene locus is 1/16 for first cousins. In the absence of a positive family history and under good economic conditions, empirical risk estimates for a genetic disease, malformation, or early mortality among the offspring of first cousin marriages are about 3% to 4% over the general population risk. For first cousins once removed and second cousins, the observed risk is about 1% to 1.5% over that of the general population. An uncle–niece mating would carry about a 10% risk. Individuals may be related to one another in more than one way. However, there can be risk when persistent intermarriage within isolated populations occurs over time. This is also known as inbreeding and can result in homozygosity, leading to a decreased biological fitness of a population or inbreeding depression. One prominent example is the persistent intermarriage of the Spanish Habsburg dynasty (1516–1700) who frequently over 300 years married close relatives. Another example is found in the population of the Faroe Islands in the North Atlantic Sea between Norway and Iceland. Because of the isolation, residents have been intermarrying for centuries, creating a highly endogamous population resulting in a high incidence of a number of genetically transmitted diseases. Ashkenazi Jews have also historically been an endogamous population due to geographic and cultural isolation and have an increased risk of certain genetic diseases such as Tay–Sachs.

Confusion about exact familial relationships is common to many people. Accurate risk estimates cannot be made unless the correct relationship is known, and so it may be up to the nurse to clarify it. For example, “first cousins once removed” refers to the relationship between the grandchild of one sibling and the child of another sibling, whereas “second cousins” refers to the relationship between the grandchildren of two siblings.

Incest in the legal sense refers to mating between related individuals who cannot be legally married; in the genetic sense, it refers to mating between persons more closely related by blood than double first cousins (those who have both sets of grandparents in common). All states prohibit parent–child, grandparent–grandchild,

and brother–sister marriages, and the vast majority prohibits uncle–niece and aunt–nephew marriages. The most frequent form of genetic incest is father–daughter, followed by brother–sister. The degree of genetic risk for an infant born of an incestuous mating between first-degree relatives is an important concern to adoption agencies and prospective adoptive parents. The risk is approximately one third for serious abnormality or early death, with an added risk of intellectual disability. Most abnormalities become evident within the first year of life, and a reasonable suggestion is that the finalization of adoption wait until this time. It is suggested that there is a thorough collection of family, genetic, and medical history for children entering the adoption process.

Deaths of siblings or stillbirths should be pursued. A parent may initially say that a child died of heart disease and not think it relevant to mention that the child had Holt–Oram syndrome. It is particularly important, especially in the case of parents who have had a child with a visible malformation, that in concluding the history of the pregnancy, the counselor raise issues that the couple may otherwise leave unspoken but not necessarily unthought, such as, “Many times, parents who have had a baby with anencephaly feel that some event in their pregnancy [like a long car trip taken against advice] caused or contributed to it.” It is important to get them to verbalize any feelings on this issue so that they can be dealt with. The clients may feel that they are being punished for an indiscretion or sin that is real or imagined. They may, aloud or silently, ask, “Why me? What did I do to be punished like this?” In many cultures (e.g., Italian and other Mediterranean, some African, Middle Eastern, Caribbean, and Latin), there may be the belief that the malformation was the result of a curse or of the “evil eye” (*el mal ojo*). Thus, the counselor must adjust the tone and content of the counseling toward the cultural group of the counselee. It is also important to know how the culture views not only the occurrence of a genetic condition but also beliefs about healing and the body. Who are the authority figures in the culture? How can they be included in facilitating adjustment? What is the decision-making power of the individual and couple, or are there others who will have a major influence? What are the concepts of privacy and stigma or shame in this culture? The occurrence of a genetic disorder can also be used to accentuate family difficulties that may have been latently present before the event, such as, “I told you not to marry her; her family is no good.” The history taking can be concluded by asking, “Is there anything else you think I should know about you or your family or that you would like to tell me?” It is not infrequent that even after a long initial counseling session, a counselee has telephoned to supply information that he or she “forgot” to tell me and that turns out to be quite relevant.

Establishing a Diagnosis

The family history is a first step in the establishment of a diagnosis if it has not been made before the client seeks genetic counseling. Diagnoses should be confirmed where possible. When no diagnosis has been established, then one of the roles of the geneticist is to recommend appropriate testing in order that one can be made. This may include chromosome analysis, molecular testing, or biochemical testing that is appropriate to the possible disorder, symptomatology, or ethnic group of the counselee; x-ray films; skin or muscle biopsy; electromyography; or others.

If genomic association studies are conducted, it is possible that these methods may produce findings of likely medical significance unrelated to the primary indication for testing. The American College of Medical Genetics and Genomics has published recommendations about reporting incidental findings in the exons of certain genes and has published a list of “Actionable, Pathogenic Incidental Findings.” Carrier status should be established if it is relevant and possible. If the syndrome is unknown, then referral to specialists or the National Institutes of Health (NIH) Undiagnosed Diseases Program may be indicated. Ideally, photographs, laboratory records, histories, physical examination data, and genomic array data should be recorded in an electronic medical records system to facilitate the comprehensive analysis and storage of large amounts of data, as well as the ability to share the data with other involved clinicians. Sometimes the establishment of a diagnosis is not possible. The affected person may be deceased, and essential information or autopsy results were not obtained, all testing and examination results are inconclusive, or a syndrome may not have been previously identified. This indicates why the nurse needs to be sufficiently alert to obtain pictures, specialized measurements, and tissue specimens in cases of spontaneous abortions and stillbirths.

The genetic counselor should know his or her limitations in diagnosis and be able to provide referral to get answers. For example, the client’s eyes may need examination by an expert in ophthalmology. The affected persons should be carefully examined if feasible. Family members who are at a risk for the disorder should be meticulously examined, especially when they are asymptomatic, in order to detect minimal signs of disease. An example is the case of a 30-year-old man who was at risk for facioscapulohumeral muscular dystrophy 1A (an autosomal dominant disorder with muscle weakness and retinal anomalies) and showed no obvious symptoms of muscle dysfunction. But when a neurologist examined him, he was found to have a “forme fruste” or minimal manifestation of the disorder, a finding that considerably changed the risk for his transmitting the gene. This diagnosis can be confirmed by targeted genetic testing of a characteristic 4q35 deletion, which is more than 90% specific for the disease.

Sometimes despite the best of efforts and for a variety of reasons, no diagnosis can be established. In one case a woman in her mid-20s was contemplating having children. She had a 22-year-old brother who had a muscle disorder, and she sought counseling to determine the risk of one of her children having the disorder. Her brother’s diagnosis had been made years before, when all muscle weaknesses of that variety were lumped into a single category and named accordingly. In more recent years, they had been found to be heterogeneous and transmitted by different modes of inheritance. Her brother was severely physically incapacitated but unaffected as far as intelligence was concerned; he had graduated from college. The counselor suggested that he be rediagnosed in order to accurately determine her risk, as the family history was unhelpful in this regard. The counselee felt very strongly that she did not want him to know she was concerned about a child of hers having the disorder, but after all the years she had watched him grow and develop, she felt that she could not assume this responsibility with her own child. She therefore refused any communication with him in regard to diagnosis by herself, another family member, a physician, or the counselor. Previously, the only

options at that time would have been to review with her the risks for the two types of inheritance then known to be involved and refer her for some psychological counseling in the hope that she might modify her feelings. Currently, array-based genetic testing of the prospective parents for the known markers of the various degenerative muscle disorders could be conducted to determine the possibility of genetic transmission.

Sometimes when a precise diagnosis cannot be made, the history and pedigree clearly reveals the mode of inheritance operating in that particular family, and counseling can proceed on that basis. Searches of the literature may be valuable in locating case reports with similar features and contacting the author or in locating experts who are using new techniques for rare disorders. If sequencing or array studies have been conducted, these can readily be uploaded and compared against large genetic databases such as Online Mendelian Inheritance in Man (OMIM), which is a freely available comprehensive, authoritative compendium of human genes and genetic phenotypes.

Inaccurate diagnosis can result from failure to recognize mild expression of a disorder. In another situation, young adults who learned that their institutionalized sibling had tuberous sclerosis complex (TSC) and that this could be inherited sought counseling. Examination included using a Woods lamp (ultraviolet light) to look at the skin for white, leaf-shaped macules and expert ophthalmological evaluation. Neither sibling had intellectual disability or seizures, which are often part of the disorder. One was ultimately found to have characteristic skin lesions and therefore was presumed affected following confirmation with CT or MRI of the brain. Counseling could proceed on the basis of the risk of transmitting this autosomal dominant disorder and the unpredictability of its severity in any children he might have. Sometimes the counselee may deliberately conceal stigmata of a disorder. In Chapter 4, a woman with Waardenburg syndrome type 1 who had only the white forelock of hair was described. When speaking to the counselor privately, she revealed that she dyed her hair to conceal it. However, she did not want the counselor to tell her husband (this was a second marriage) that she in fact had the gene that was present in its full-blown form in her child, because she felt that she could not handle the guilt or blame she believed would be forthcoming.

Another type of diagnostic problem is exemplified by the case of a couple who was referred to a counselor for infertility. A chromosome analysis was done that revealed that the wife had a male karyotype of 46,XY. She had testicular feminization syndrome, also known as complete androgen insensitivity syndrome. It is important to emphasize that she was not a male in nongenetic ways. She was raised as a female, believed she was a female, and looked phenotypically like a female, but she could not conceive. She was married to a normal man. Prior to the 1990s counselors believed that the counselor should not give them a specific diagnosis, but just tell them generally that there is a chromosome problem causing the infertility and recommend adoption. Currently it is the recommended practice to disclose the genotype at the time of diagnosis, starting when the affected girl is at least of adolescent age. If the affected individual is an infant or child, it is generally left to the decision of the parents in consultation with psychologists when to disclose the condition.

Determining and Communicating Recurrence Risks and Discussing the Disorder

After the initial visit there may be a considerable lapse of time during which all of the information is assembled. If the counselee is not aware that this is a usual occurrence, there may be considerable concern generated, so this information should be included at the conclusion of the initial visit. When the process of information gathering is completed, the geneticist must use all of the information collected to determine the risk of recurrence of a disorder for a child of the counselee, or for the counselees themselves, to be either a carrier or to develop the disorder in question. When planning the process of sharing the acquired information with the counselee, the geneticist takes into account the educational level and the ethnic, socioeconomic, and cultural background of the couple. Many counselees are reluctant to acknowledge that they do not understand the counselor, and so they may come away from the session with misinformation and confusion. Therefore, the counselor must take care to explain things in simple terms and repeat the content in different ways. The use of pictures, videotapes, computer programs, audiotapes, charts, photographs, and diagrams is helpful. Providing the counselees with information to take home with them or links to online sources is also helpful. In some Native American cultures, storytelling is an appropriate way to communicate the information. Asking the clients to repeat the information in their own words as the session proceeds may also assess understanding. Clients can also be asked to discuss the meaning of this information to them so that misconceptions can be addressed. Most counselees already have formed an idea about recurrence risks before genetic counseling, which is usually higher than the real risks. Some counselors also form ideas about risks in which they arbitrarily label those above 10% as high and below 10% as low. This pre-interpretation of material in order to present material simply is unacceptable.

Recurrence risks can be presented in different ways. The meaning of probability or odds can sometimes be clarified by the use of special color-coded dice appropriate to the mode of inheritance. Coin flipping is another method used. Risks can be phrased in more than one way, and the manner of their presentation is important. For example, one can say, "For each pregnancy, there is a one in four chance that the infant will have Hurler disease," or, "For each pregnancy, there is a three in four chance that the baby will *not* have Hurler disease." In the Mendelian disorders, it is important to clarify that this risk is true for each pregnancy—that "chance has no memory"—and so although they may have one affected child already, this does not influence the outcome of future pregnancies (aside from the possibility of gonadal mosaicism). In any case, the counselee must process the information relative to the risk of recurrence and make it personally meaningful, as each views it in terms of his or her own life experience. The meaning of a high risk of having male children with a genetic disease may be different to a Mexican American couple, because of a higher cultural value placed on a male infant, than to one of different ethnic origin. For some Bedouin populations, among whom about 60% of marriages are consanguineous, childbearing has a very high value. Women attain a higher status when they become mothers. Therefore, for example, some families prefer to take a 25% risk of a child affected with an autosomal recessive disorder and have the child die soon after birth rather than not have children, or practice selective pregnancy termination.

Sometimes the counselee's perception of the risk is quite different from that of the counselor's. Some see a risk of 50% for an affected child as "having a chance to break even" and do not view it as high. Others find a 2% risk unacceptable. Risks are also seen in the light of what they are for. Some can accept a high risk for a child to be born with a cleft lip, whereas for others, even a minimal risk of intellectual disability cannot be borne. Sometimes the counselor can be surprised by the client's response. A couple who both have achondroplasia were told their chances of conceiving a child of normal stature was only one in four. This was good news to them, as they believed they would have difficulty in adjusting to raising a child of normal stature. In an opposite example, a woman who had two children with celiac disease was given a risk of 10% for the next pregnancy to be similarly affected. This estimate was too low for her because she believed that the adjustment of the whole family to a gluten-free diet would be compromised by the birth of a normal child. Sometimes it is difficult for the counselor to remain neutral when parents with a genetic disorder choose to have a child who has a high risk for having the same disorder; however, most believe that genetic counselors need to support their clients in their decisions or refer them to someone who can. Risk figures may also be looked at by the clients in terms of what else is going on in their lives. For example, women who are undocumented immigrants, in an abusive relationship, struggling with poverty, living in dangerous or unsanitary conditions, and other issues may not regard genetic risks for a pregnancy as a pressing life issue regardless of the extent of that risk.

Along with risk figures, the natural history and impact of the disorder in question should be discussed, as the burden may not be appreciated or else it may be exaggerated. Then options appropriate to the individual counselee's problem can be discussed. These include prenatal diagnosis, a treatment plan, and other reproductive options. Alternatives such as "taking a chance," adoption, sterilization, sperm and egg donation, in vitro fertilization (IVF), pre-implantation diagnosis, and selective embryo transfer can be presented if they are relevant. Newer options such as three-person IVF may also be considered in rare cases. Although the couple should make the ultimate decision for options, the counselor may encourage them to think over the possibilities for a period of time if time is not a critical factor in their situation. In some cultures, the counselees may need to consult the entire family or certain respected members such as elders. Then the counselor should support their decision and help to make arrangements to facilitate that decision regardless of the personal opinion of the counselor. If that is not possible, they should be sure that another staff member meets with the clients to do that. If the family has sought genetic services because of the need to ascertain what the problem is in a family member, then decision making centers around the need to plan for the resources necessary for coping. To do this, they must have some ideas of what types of problems and what degree of disability and deterioration may be realistically expected, what treatments and resources are available, what living adjustments need to be made, and what kinds of ultimate outcomes are possible.

What is considered a disability varies from culture to culture. Arrangements may be made with persons who have made various types of decisions in this regard. In the case of deciding on reproductive alternatives, it may be useful to have them meet with parents of a child with the disorder in question, and perhaps with both parents

who have chosen pregnancy termination and those who have not. Long-term help with coping may be provided by the same genetic group during the counseling sessions or referrals, and the coordinator for comprehensive ongoing care may make arrangements. The counselees may need to have their self-worth affirmed and perhaps mourn the loss of their “normal” child if they have not already done so.

In the case of some disorders, it is desirable to notify extended family members that they are at risk for a detrimental gene, chromosomal aberration, or an adverse outcome because of their possible condition. The counselee’s permission for this and for a release of information should be obtained, preferably before any testing or counseling. This issue is discussed further in Chapter 13. The siblings of an affected person may need to be tested or examined, and the extent of this could depend on their age. If a couple is seeking counseling after birth of an affected infant, it may be appropriate to inform the parents that genetic counseling would be important in the future for other family members, such as other children in the family at the appropriate age. In Japanese and some other cultures, privacy may be quite valued.

After risks and options have been discussed, understanding can be assessed. Counselees should be able to tell the counselor in their own words what they understand about the disorder, how it was caused, what the risk is for recurrence, and what kinds of options are available and should be considered. Counselees should always be asked if there is anything else they want to know or if there are any other questions they have. Clients should always be supported in the decisions that they reach.

The traditional approach to genetic counseling was nondirective. The use of a directive approach without modifiers may reflect traditional paternalistic or maternalistic views of counseling. An approach reflecting an omnipotent or a one-sided relationship can be accentuated by the sometimes intimidating physical setting of a hospital or clinic, particularly if the genetic counseling is taking place in the context of a clinical trial. The use of a nondirective approach implies that both decision making and chosen courses of action become primarily the responsibility of the counselees, and not the counselor. This allows the counselee to maintain autonomy and control and to play an active role in decision making. It also provides some feelings of security for the counselor by relieving him or her of any decision-making burden. Another reason for using a value-neutral, nondirective approach in genetic counseling is that the counselor often does not know the client well or does not have an ongoing relationship with the client because the counselor is usually not the regular health caregiver. Therefore, the counselor may not be aware of the counselee’s resources, coping abilities, family and financial circumstances, or values or belief systems or understand the impact of the genetic problem at hand on this particular counselee. The counselees possess some information that is not necessarily shared with the counselor but contributes to his or her ultimate decision.

The nondirective approach contrasts with traditional medical practice. Therefore, some counselees expect to be told what to do as one counseling outcome, and they are confused when expected to make their own decisions. Clients may expect that the counselor should give expert advice because of his or her professional skills and knowledge. They may expect that as part of duty fulfillment and “getting their money’s worth.” Can any counselor be value neutral? For example, does an offer for

prenatal diagnosis imply a recommendation to accept that offer or a tacit recommendation to terminate an abnormal pregnancy? Does respect for a client's decisions and autonomy ever conflict with the principle of avoiding harm?

Probably few genetic counselors can always use a completely directive or nondirective approach. For one thing, it can be almost impossible for counselors not to communicate some of their own feelings and opinions by nonverbal cues or voice tones. Probably most genetic counselors today believe that their role lies chiefly in the clarification of issues and options once the material necessary has been presented in a way that clients can understand. When counselees have reached a decision, every effort should be made to facilitate and support that decision.

Follow-Up

After counseling is completed, a postcounseling follow-up letter should be sent to the counselee and the referring professional, reiterating the essential information covered in the counseling session. Information and findings should be saved to the electronic health record when possible with access provided to the counselees. This gives them something tangible to refer to when needed. A follow-up phone call is used to see if there are any additional questions. A home visit can be arranged through the community health nurse or genetic clinic nurse to assess coping, identify problems, and answer questions.

The Nurse in the Genetic Counseling Process

Nurses may play a variety of roles in genetic counseling that reflect their preparation, area of practice, primary functions, and setting. These roles will involve collaboration with other disciplines. One of the prime ways in which the nurse who is not involved in the offering of direct genetic services can help is by recognizing and referring clients and families in need of such services to the appropriate professionals. If the nurse is not sure about appropriate professionals, he or she should find out from another knowledgeable person. It may be a reasonable standard of practice to know which patients to refer to genetic specialists or counselors. Whether genetic counseling has been offered to hospitalized patients and their families for whom it would be appropriate can be noted on the chart and discharge summary, along with the results. Nurses also need to assess clients' understanding of any treatments to be carried out, such as for prophylactic penicillin in children with sickle cell anemia to prevent infection, and help the clients plan how they will implement the therapy, especially over the long term.

In addition to providing direct counseling or education, nurses may assist clients or families with genetic or potential genetic problems in many other ways:

- ▶ Become familiar with terminology and concepts used in genetics
- ▶ Become involved with public education about genetic disorders and their prevention
- ▶ Be competent in the construction of a basic genetic pedigree
- ▶ Help increase public awareness of availability of genetic services
- ▶ After providing a referral or information about genetic counseling, follow up on the action that was taken

- ▶ May tell clients what they can expect from a genetic counseling session
- ▶ May accompany clients to the session if, for example, the nurse has a close professional relationship with them, and all parties involved agree
- ▶ Identify the meaning of the genetic problem involved for this client and family
- ▶ Clarify misinterpretations and misunderstandings, including information about presymptomatic or cancer risk assessment
- ▶ Reinforce the information given by the genetic counselor or geneticist
- ▶ Help in alleviating any family guilt
- ▶ Encourage the family or client to voice fears about issues such as acceptance, stigmatization, dependency, and uncertainties
- ▶ Assess the coping mechanisms of the client or family and build on strengths
- ▶ Be able to explain meanings of results of commonly used genetic tests in the practice area of the nurse
- ▶ Help in identifying and getting external support from the family's friends, agencies, financial aid sources, equipment resources, and others
- ▶ Help the family identify ways to cope with the reactions of family, relatives, friends, and others
- ▶ Refer the client or family to community resources, schools, parent groups, and other supportive groups
- ▶ Act as a liaison between the client or family and the resources and sources they will need
- ▶ Notify genetic counselors or geneticists immediately if the family shows significant misunderstanding or misinterpretation so that they can contact the family to provide further clarification
- ▶ Assess the client and family's ability to carry out the treatment plan or long-range goals
- ▶ Be sensitive to common potential problems such as strains within the relationship and problems arising with siblings
- ▶ Help the individual or family to reaffirm self-worth and value
- ▶ Refer the family for further psychotherapeutic counseling if it appears necessary
- ▶ Assist the family in decision making by clarifying and identifying viable options
- ▶ Clarify the options related to reproductive planning, and assist clients in obtaining necessary information
- ▶ Be alert for crises in parenting if it is the child who has a genetic disorder
- ▶ If none exists in the area, establish and lead a group of parents facing similar issues
- ▶ Support the client or family's decisions

- ▶ Maintain contact and follow-up
- ▶ Apprise the counselor of any special information about the counselee (e.g., cultural beliefs of the community) that may assist him or her
- ▶ Assist in placing the genetic counseling information in the client's cultural context
- ▶ Act as an advocate for the family

Social, Legal, and Ethical Issues in Genetic Counseling

Some of the issues in this area overlap with those concerning genetic screening, pre-natal diagnosis, and others because counseling is a component of other programs. These include the issues of privacy; confidentiality; disclosure; sharing results with others, including family members, spouse, and outside persons such as insurance companies or employers; whether the counselor has a major responsibility to the counselee, others, or society; access to information; handling sensitive information such as uncovering misattributed parenthood; and duty to recontact. These ethical issues are discussed in Chapter 13.

GENETIC AND GENOMIC TESTING

Although genetic screening and testing have elements in common, there are also differences. *Genetic testing* tends to be diagnostic, while *genetic screening* is the first level of detection. Genetic screening may be offered or conducted within the context of general or targeted population screening programs or be offered to specific at-risk individuals and families, but the term *genetic testing* commonly refers to the use of specific tests for individuals who are believed to be at increased risk for a specific genetic condition because of their family history or symptom manifestations. The Task Force on Genetic Testing has defined a genetic test as “the analysis of human DNA, RNA, chromosomes, proteins and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes” (Holtzman & Watson, 1997, Chapter 1). This can be a very inclusive definition; others look toward a narrower one. They subdivide predictive testing performed in apparently healthy people into presymptomatic tests (for someone who has the mutant gene usually resulting in disease but is asymptomatic) and predispositional tests (for someone who has a gene mutation that may confer susceptibility for a given disease). The Centers for Disease Control and Prevention maintains a repository of guidelines, policies, and recommendations related to genetic and genomic testing.

Genetic testing includes laboratory assays and other tests performed on blood, urine, fibroblasts, amniotic fluid or cells, chorionic villi, hair bulbs, squamous cells from the buccal mucosa, or other tissue samples. These include DNA sequencing; gene expression assays; biochemical tests for enzymes, hormones, and the like; chromosome analysis and karyotyping; immunological testing; and protein array analysis. Genetic screening involves testing of populations or groups that is independent of a positive family history or symptom manifestations and includes some predictive

genetic testing. Screening may include population-based programs that are commonly sponsored by hospitals, health centers, community groups, or governmental agencies such as heterozygote (carrier) and newborn screening, those aimed at all pregnant women for detection of fetal anomalies such as maternal serum screening for replace with greek alpha: α -fetoprotein and other markers, or those conducted in the context of a specific industry or workplace for predictive screening. The NIH National Center for Biotechnology Information (NCBI) maintains the “GTR: Genetic Testing Registry” where one can find the correct genetic test for a disease along with laboratories that are certified to perform the specific genetic test. The American College of Medical Genetic and Genomics incidental findings gene set is also listed there.

The concept of testing is aimed at individuals or families for specific reasons such as family history that may include carrier, presymptomatic, or predictive testing for traditional genetic disorders or for diseases such as certain breast cancers that may be called *cascade screening* when offered to extended family members. Genetic tests in the context of screening or testing related to disease or susceptibility may be done for:

- ▶ Confirmatory diagnosis of a present disease state
- ▶ Determining carrier status
- ▶ Detecting disease susceptibility
- ▶ Detecting abnormalities in the fetus
- ▶ Predicting diseases in usually asymptomatic persons that may include late-onset or adult disorders

Information that should be provided by the health care provider to the client considering genetic testing is given in Box 5.2.

Detecting and Diagnosing Chromosome Changes and Disorders

Many advances have been made in the performance of chromosome studies to identify changes. Detecting chromosome changes allows for:

- ▶ Diagnosis of chromosome disorders
- ▶ Determining the parental origin in some chromosome errors
- ▶ Prenatal diagnosis
- ▶ Relating specific chromosome changes to diagnosis, treatment, and prognosis in certain conditions, such as in a type of leukemia

There are various ways of performing chromosome analysis. The sample for such studies from the person or persons of interest may be white blood cells, epithelial cells from the buccal mucosa, hair bulbs, skin fibroblasts, amniotic cells, or other tissue. Red blood cells are not used because they do not have a nucleus. A variety of staining methods can be used, depending on the information needed from the chromosome analysis. Each chromosome has its own individual unique banding pattern

BOX 5.2**Information for the Client Considering Genetic Testing**

- ▶ The reason that testing is appropriate for this person or family
- ▶ What is being tested for
- ▶ What estimation of risk and for surveillance can be done without genetic testing
- ▶ What the procedure being considered entails, including description, cost, length of time, and where it is to be done
- ▶ What can and cannot be tested. If relevant, this should include the information that, while some mutations will be looked for and detected, other rare ones might not be, and that negative results refer only to whatever was being tested and not to every genetic disorder. If one is testing for cystic fibrosis, the most common mutations in that population group will be looked for, but not every very rare mutation will be tested for. Usually within the context of an affected family, however, if a specific mutation has already been identified in a blood relative, it will be specifically looked for when another family member is undergoing genetic testing
- ▶ What both positive and negative results mean, including that negative results do not necessarily translate to a zero risk and that a positive test may result in fear and anxiety, whereas negative results can also have emotional and relationship impact
- ▶ The accuracy, validity, and reliability of the test including the likelihood of false-negative or false-positive results and the suitability of this test for the information the client is seeking
- ▶ The possibility that testing will not yield additional risk information
- ▶ The length of time between the procedure and when the results are obtained
- ▶ How the results will be communicated to the client
- ▶ What will be analyzed
- ▶ Whether the actual test result will be revealed. For example, in Huntington disease, in some cases there may be some correlation between the number of CAG repeats and the predicted age of onset but there is a gray area, so some centers do not disclose the actual number although such disclosure is generally recommended
- ▶ What happens to the sample used for testing—who owns it, what uses are possible
- ▶ A discussion of the possible risks of life and health insurance coverage or employment discrimination after testing results are done, although there may be benefits such as if a person is free of a certain mutation, better insurance rates or coverage might result
- ▶ The level of confidentiality of results and what this means (who can know or find out the results). Risks of psychological distress and negative impact on not only the individual but also the family, including stigmatization and altered self-image

(continued)

BOX 5.2**Information for the Client Considering Genetic Testing (*continued*)**

- ▶ Risk of passing on the mutation in the disorder being tested for to offspring and the meaning of the risks
- ▶ What disclosure the client might consider for other family members and those he or she will tell (if anyone) about the test results. What obligation the health provider might feel to inform other family members
- ▶ Provision for referral for periodic surveillance, further testing, lifestyle changes, or treatment after testing if needed
- ▶ What these mean in the context of both positive and negative tests. As in other genetic testing, a negative test can have several meanings: that the individual is truly free of the disease, that the result is false negative due to laboratory error, or that the person possesses alternate alleles other than what could be or what was tested for

The Genetic Counseling Definition Task Force of the National Society of Genetic Counselors (NSGC) developed the following definition of genetic counseling that was approved by the NSGC Board of Directors: Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. This process integrates the following: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources, and research; counseling to promote informed choices and adaptation to the risk or condition. The definition was approved after a peer review process with input from the NSGC membership, genetic professional organizations, the NSGC legal counsel, and leaders of several national genetic advocacy groups.

Source: Resta et al. (2006).

and therefore can be identified with certainty. In the United States, the most frequent routine banding method used is Giemsa (G) banding, which produces light and dark bands on each chromosome in a unique manner. Other more specialized techniques are available for specific purposes.

Another technique is fluorescent in situ hybridization (FISH), a variation of in situ hybridization techniques using fluorescent dyes instead of labeled isotopes. Basically, a standard cytogenetic preparation is treated to remove excess RNA and protein, a fluorescent-labeled single-stranded DNA probe is hybridized to these denatured chromosomes if there is a complementary sequence, and a signal results at the site of hybridization that can be visualized using fluorescence contrast microscopy. FISH is used to detect aneuploidy (this has made it useful for rapid screening of uncultured amniotic fluid cells in only 24–48 hours), the origin of marker chromosomes, microdeletions, small translocations, and other small aberrations, and can be used prenatally to detect fetal cells in maternal serum.

Describing and Interpreting the Karyotype

Karyotypes are arranged in a standardized way according to international agreement: first, on the basis of chromosome size from the largest to smallest, and second, according to the location of the centromere (the constricted portion of the chromosome). The only exception is that chromosome 22 is longer than chromosome 21, but it was agreed to retain this order and nomenclature because chromosome 21 was already too well associated with Down syndrome to make such a change realistic. Chromosomes are classified according to the position of the centromere as follows: metacentric (the centromere is in the center of the chromosome), submetacentric (the centromere is slightly off center, resulting in one longer and one shorter arm), acrocentric (the centromere is very near one end of the chromosome with one very short and one very long arm), and telocentric (the centromere is at one end, but this is not seen in humans). In 1960, cytogeneticists at the first international conference on nomenclature designated the groups and the chromosome pairs belonging to each group (see Figure 5.1A and B).

To facilitate communication and prevent confusion, a kind of shorthand system for describing the chromosome constitution of a karyotype was devised. Because these symbols are in international usage to describe the chromosome constitution of an individual, nurses should be able to interpret the meaning of at least the most commonly used symbols. These are illustrated in Table 5.2, and their use is explained below. For some conditions, both simple and complex symbolism may be used according to the audience to which the communication is geared or to the necessity of clarifying a precise point. For more details, the reader is referred to *ISCN 2005* (Shaffer & Tommerup, 2005), which is the accepted standard.

Through laboratory procedures, and depending on what tissue sample is used, in the most common analysis, chromosomes can be visualized in a spread under the microscope, analyzed, photographed, and arranged in a karyotype. A karyotype is the arrangement of chromosomes by size, from largest to smallest, and morphology, according to the location of the centromere by an international classification system. Each chromosome with its bands can thus be identified. A chromosome spread is shown in Figure 5.2. It is conventional to place the sex chromosomes together at the bottom of the karyotype, as shown in the karyotype of a normal male (Figure 5.2).

Rules and Examples for Interpreting and Describing Karyotypes

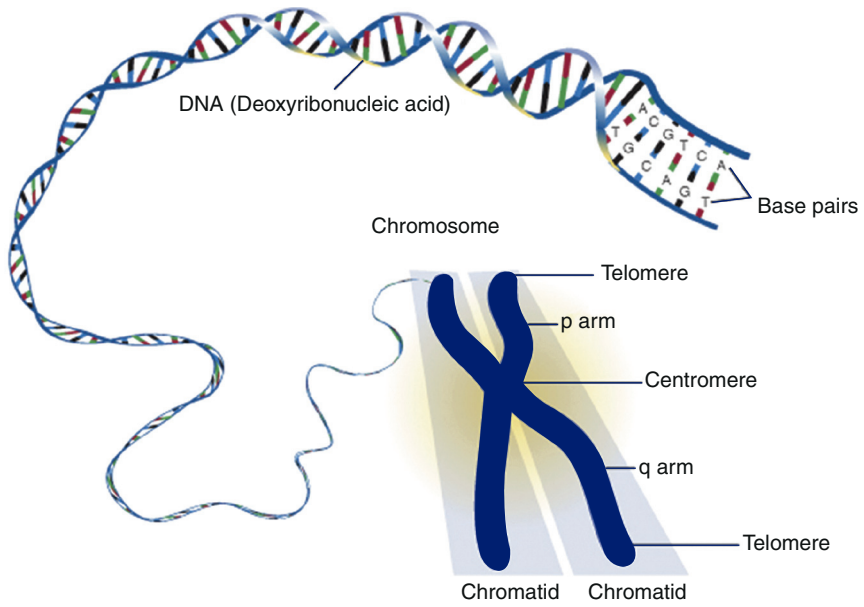
Both general rules and examples of the use of karyotypes are as follows:

1. The total number of chromosomes present is always given first, followed by the designation of the sex chromosome complement. Thus, the normal female is designated as 46,XX and the normal male as 46,XY.

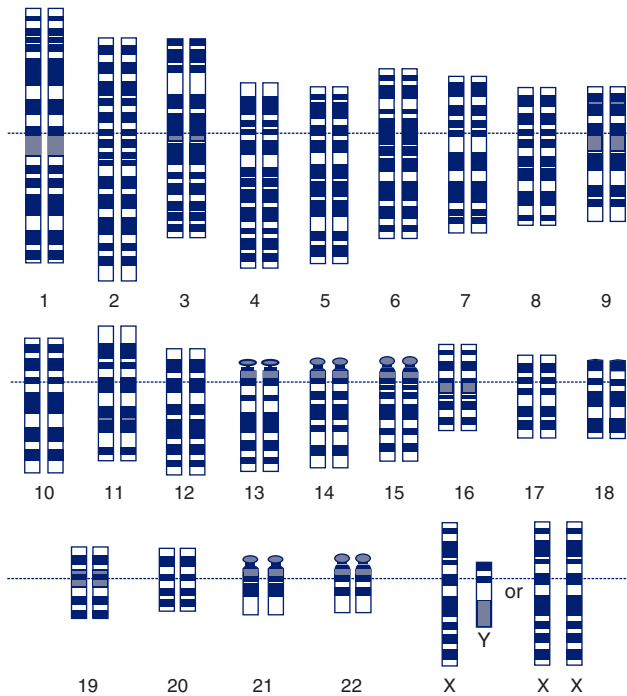
Example 1: A triploid cell—69,XXY

Example 2: A tetraploid cell—92,XXYY

2. After the sex chromosome designation, it is customary to indicate chromosomes that are missing (–), extra (+), or structurally altered. The short arm of the chromosome is designated as p and the long arm as q. If (+) or (–) is placed before the chromosome number, this indicates extra or missing whole chromosomes (e.g., +21 or –4). A (+) or (–) placed after the arm designation



(A)



(B)

FIGURE 5.1. (A) Diagram of chromosome structure. (B) Chromosome ideogram of complete female chromosome.

TABLE 5.2 Symbols and Nomenclature Used to Describe Karyotypes

| Symbol | Karyotype | Symbol | Karyotype |
|---------------------------------|--|--------------------------|--|
| A–G | Chromosome group | Dup | Duplication |
| 1–22 | Autosome numbers | E | Exchange |
| X,Y | Sex chromosome | F | Fragment |
| Diagonal (/) | Separates cell lines in describing mosaicism | G | Gap |
| | | H | Secondary constriction or negatively staining region |
| Plus sign (+) or minus sign (-) | Placed immediately before the autosome number indicates that the chromosome is extra or missing; placed immediately after the arm, structural or other designation indicates an increase or decrease in length | i | Isochromosome |
| | | inv | Inversion |
| | | inv ins | Inverted insertion |
| | | inv (p–q+) or inv (p+q–) | Pericentric inversion |
| (?) | Questionable identification of chromosome or structure | mar | Marker chromosome, unknown origin |
| | | mat | Maternal origin |
| (*) | Chromosome or structure explained in text or footnote | mn | Modal number |
| | | mos | Mosaic |
| : | Break—no reunion, as in terminal deletion | p | Short arm or chromosome (pter: end of short arm) |
| :: | Break and join | pat | Paternal origin |
| → | from–to | prx | Proximal |

(continued)

TABLE 5.2 Symbols and Nomenclature Used to Describe Karyotypes (continued)

| Symbol | Karyotype | Symbol | Karyotype |
|---------|-------------------------------------|---|--|
| () | Used to enclose altered chromosomes | q | Long arm of chromosome (qter: end of long arm) |
| Ace | Acentric | r | Ring chromosome |
| cen | Centromere | s | Satellite |
| chi | Chimera | sce | Sister chromatid exchange |
| cs | Chromosome | t | Translocation |
| del | Deletion | rcp | Reciprocal translocation |
| der | Derivative chromosome | rob | Robertsonian translocation |
| dic | Dicentric | ter | Terminal or end |
| dis | Distal | | |
| | | | |
| Group A | Chromosomes 1 to 3 | Large metacentrics | |
| Group B | Chromosomes 4 to 5 | Large submetacentrics | |
| Group C | Chromosomes 6 to 12, the X | Medium-sized metacentrics and submetacentrics | |
| Group D | Chromosomes 13 to 15 | Medium and large acrocentrics with satellites | |
| Group E | Chromosomes 16 to 18 | Relatively short metacentrics or submetacentrics | |
| Group F | Chromosomes 19 to 20 | Short metacentrics | |
| Group G | Chromosomes 21 to 22, the Y | Small acrocentrics with satellites except for the Y | |

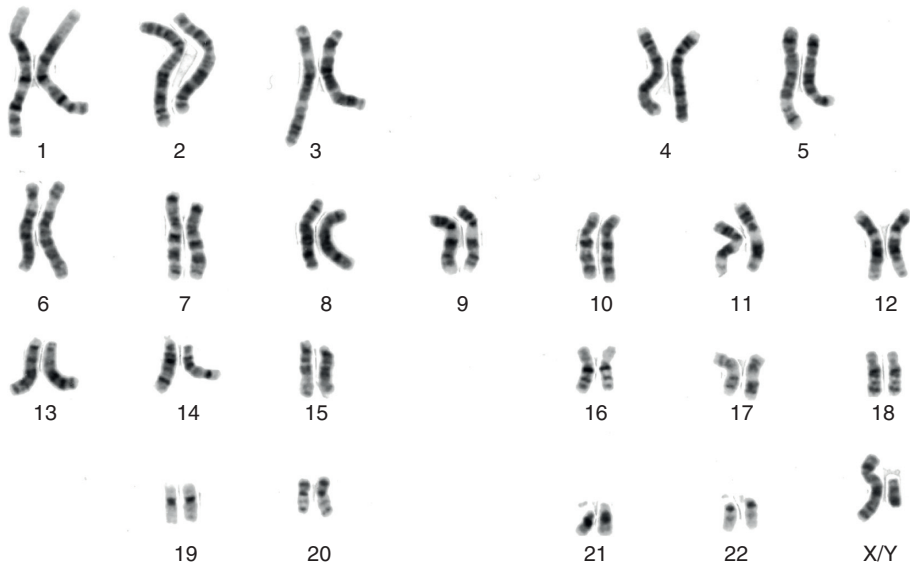


FIGURE 5.2. Giemsa banded chromosome spread.

indicates a change in that arm length (e.g., p- is a decrease in the length of the short arm; q+ is an increase in the length of the long arm).

Example 3: Trisomy 13 (Patau syndrome) in a female—47,XX+13

Example 4: Cri-du-chat or deletion of part of the short arm of chromosome 5 in a male—46,XY,5p-

Example 5: A male with an extra chromosome 15, which has an abnormally large long arm—47,XY,+15q+

Example 6: A male with 46 chromosomes that include a ring chromosome 9—46,XY,r(9)

Example 7: A balanced translocation between the long arms of chromosomes 13 and 14 in a male may be written as 45,XY,t(13q14q). This person has 45 chromosomes including one chromosome 13, one chromosome 14, and one translocation chromosome composed of chromosomes 13 and 14 instead of the usual two of each.

3. Different cell lines in the same individual are separated by a slash.

Example 8: A male who is mosaic for trisomy 21—46,XY/47,XY,+21 or mos 46,XY/47,XY,+21

Example 9: A female mosaic who has three cell lines—45,X/46,XX/47,XXX or mos 45,X/46,XX/47,XXX

4. If one wishes to indicate a specific point on a chromosome, this is done by giving, in the following order: the number of the chromosome, the chromosome arm (q or p), the region number, the band number, and, in some cases, if a

band is subdivided, a sub-band. If sub-bands are subdivided further, there may be an additional digit but no period (see Figure 5.2). An example of both a short and detailed way to indicate the same terminal deletion of chromosome 3 in a male with 46 chromosomes is as follows:

Example 10: 46,XY,del(3)(q22) or 46,XY,del(3)(pter→q22:). The single colon indicates a break in the long arm of chromosome 3 with deletion of the rest of the segment, and the retention in the cell of all of the short arm of chromosome 3 and the portion of the long arm between the centromere and region 2, band 2.

Example 11: For three sub-bands in the short arm of chromosome 1, one would write 1p31.1, 1p31.2, 1p31.3 (sub-band 1p31.1 is closest or proximal to the centromere and 1p31.3 is distal). An example of further subdivision of sub-band 1p31.2 would be 1p31.21, 1p31.22, and so on.

5. Sometimes shorthand forms are used in nontechnical literature.

Example 12: Cri-du-chat can be referred to as 5p– without any other designation, and a translocation between chromosomes 8 and 22 is written as t(8;22) with no further designation. A semicolon is used to separate the chromosomes involved in the translocation.

New methods of banding have made it possible to detect abnormalities such as microdeletions or small insertions, additions, and those rearrangements that do not alter the size of the chromosome; detect normal variants (polymorphisms) that occur within the population; and identify fragments of chromosomes to determine their origin. High-resolution banding of prophase and prometaphase chromosomes allows a greater number of bands to be identified than the usual number (850 as opposed to 300, 400, or 550).

Reasons for Chromosome Studies

Chromosome studies may be needed at any age depending on the indication. Reasons to recommend prenatal chromosome diagnosis are discussed in Chapter 8. Current indications for other age groups are summarized in Table 5.3. Some of these reasons are discussed in more detail next. Although the nurse may or may not be responsible for directly ordering chromosome studies, he or she should be able to identify individuals who may benefit from such studies and refer them to the geneticist or recommend such a course of action to the physician.

Some indications are most likely to be noticed at certain ages (e.g., dysmorphic features should be noticed and accounted for before adulthood), but they should not be ignored if present later in life, as sometimes individuals slip through the cracks. General reasons for undertaking chromosome study common to all indications listed are for genetic counseling of the individual and/or family members, reproductive planning, prenatal diagnosis, initiation of early treatment if needed, and realistic life planning including anticipatory guidance and goal setting for the affected individual and family. In addition, specific reasons are added where salient.

TABLE 5.3 Current Indications for Chromosome Analysis in Different Phases of the Life Span

| | Antenatal | Newborn/Infant | Child | Adolescent | Adult |
|---|-----------|----------------|-------|------------|-------|
| Two or more dysmorphic features or anomalies | | X | X | † | † |
| Intellectual disability | | X | X | † | † |
| Infertility or premature menopause | | | | | X |
| History of two or more spontaneous abortions or stillbirths | | | | | X |
| Neonatal death | | X | | | |
| Stillbirth or spontaneous abortion | X | | | | |
| Confirmation of a suspected syndrome | X | X | X | X | X |
| Ambiguous genitalia | | X | X | X | † |
| Inguinal masses/hernia in female | | X | X | | |
| Failure to thrive | | X | | | |
| Short stature (especially female) | | | X | X | † |
| Low birth weight (small for date) | | X | | | |
| Developmental delay | | X | X | | |

(continued)

| | | | | | |
|--|---|---|---|---|---|
| Amenorrhea (female) | | | | X | |
| Failure to develop secondary sex characteristics | | | | X | † |
| Structural chromosome error in family member | | | X | X | X |
| Small genitalia (males) | | | | X | † |
| Cancer (varies with type) | | X | X | X | X |
| Hydatidiform mole | X | X | | | |
| Gynecomastia (male) | | | | X | |
| Cryptorchidism (male) | | | X | † | |
| Lymphedema (female) | X | | | | |
| Unexplained appearance of an autosomal or X-linked recessive disorder (female) | | X | X | X | X |

†, if not previously investigated and explained.

X, primary indication.

Note: Prenatal indications are discussed in Chapter 8.

Suspicion of a Known Syndrome or Presence of a Known Chromosome Variant in Family Member, Parent, or Sibling

No one anomaly is exclusive to any one chromosome syndrome, and many abnormalities such as growth retardation and intellectual disability are common to most of the chromosomal syndromes. Therefore, even a suspected classic chromosome disorder such as Down syndrome must always be confirmed by chromosome diagnosis. The same disorder can arise from different chromosomal mechanisms (an example is translocation Down syndrome as opposed to trisomy 21) or from non-genetic mechanisms. It is important to distinguish among these in order to provide accurate genetic counseling and opportunity for prenatal diagnosis. For these same reasons, parents who have had a previous child or family member with an error or persons who have a family member with a chromosome error should have chromosome analysis for the reasons just given.

Unexpected Appearance of an Autosomal Recessive Disorder or an X-Linked Recessive Disorder in a Female

The unexpected appearance of an autosomal recessive disorder in cases in which both parents are not carriers suggests the possibility of a chromosomal explanation. Sometimes these disorders appear because the affected individual has one mutant gene for the recessive disorder and a microdeletion involving the normal copy of that gene on another chromosome. Thus, one copy of the mutant gene is expressed and seen in the phenotype. The same can happen in an X-linked recessive disorder in which there is a small deletion of the chromosome section with the normal gene, allowing the carrier female to express the disorder because the mutant gene has, in effect, no opposition. Another explanation may be uniparental disomy. In this case, both chromosomal homologs are inherited from the same parent instead of inheriting one copy of each chromosome pair from the mother and the father (e.g., two maternal chromosome 7 homologs, and no paternal chromosome 7). This is further explained in Chapter 4.

It should be noted here that the Human Genome Project (HGP) has provided the ultimate chromosome map. The HGP data provides a map of the chromosomes at the level of each single gene. The position of each gene is matched to a specific band at high resolution. The NCBI provides an interactive map between cytogenetic and sequence data by use of the “Graphic Chromosome Map Viewer” (National Center for Biotechnology Information, 2014).

Ambiguous Genitalia

Most ambiguous genitalia are detected at birth or in early infancy. Traditionally, it has been considered a medical emergency because the sex in which to raise the child is seen as needing to be determined as quickly and early as possible and because of psychological reasons for the parents and family. However, the clinical decisions surrounding this most complex of anatomic and ethical situations deserves considerable caution and consultation. Genetic and endocrine studies are required that will need the assistance of a pediatric endocrinologist, radiologist, and urologist. Full and prompt disclosure needs to be made to the parents and histories will include the

parents as well as the extended family. It is important to inform the parents that this condition is a normal human variation of intersex that is rare but not unheard of. It should be noted that many cases of intersex go undetected immediately after birth. Current research indicates that sex assignment should be based upon the nature of the diagnosis, nervous system, and genetics. This respects the neurologic involvement in adult sexuality, which is influenced by genetic and endocrine events, which will present after puberty.

In general, the following guidelines have been suggested (Diamond, 2011):

- ▶ Rear as male:
 - XY individuals with androgen insensitivity syndrome (AIS; grades 1–3)
 - XX individuals with congenital adrenal hyperplasia (CAH) with extensively fused labia and a penile clitoris
 - XY individuals with hypospadias
 - Persons with Klinefelter syndrome
 - XY individuals with micropenis
 - XY individuals with 5- α or 17- β reductase deficiency
- ▶ Rear as female:
 - XY individuals with AIS (grades 4–7)
 - XX individuals with CAH with hypertrophied clitoris
 - XX individuals with gonadal dysgenesis
 - XY individuals with gonadal dysgenesis
 - Persons with Turner syndrome

Two or More Dymorphic Features or Anomalies

Because it is unusual for two defects to occur in the same person, small abnormalities may go undiagnosed if chromosome analysis is not undertaken. This analysis is needed to differentiate a defect related to a chromosome abnormality from one caused by intrauterine infection, teratogen exposure, a single gene disorder, or another cause for counseling and prognostic purposes. One cannot conclude that such anomalies are isolated defects unless a chromosome error is excluded as one possibility.

Spontaneous Abortion, Stillbirth, or Neonatal Death

In cases of spontaneous abortion, stillbirth, or neonatal death, material should be obtained for chromosome study as quickly as possible. This should be done whether or not external malformations are visible. The rate of failure for tissue culture is higher than usual in these situations, so several samples from different tissues should be obtained since there will not be an opportunity for a second specimen. A specific protocol should be developed for the medical unit, inpatient or outpatient, with all equipment available. Photographs of the head, face, body, and especially of any unusual features should also be obtained; physical measurements, a detailed written

description of the physical findings, and a complete pathologist's report are essential. Often radiology also needs to be done; if there is doubt, then it should be carried out. An inadequate study at this time leads to the inability of the genetic counselor to discuss the couple's chance for a future affected child or another stillbirth or spontaneous abortion.

Infertility or Premature Menopause

Although chromosome disorders do not account for the majority of infertile couples, it has been determined that 10% to 15% have a chromosome anomaly present in one member, ranging from an undiscovered sex chromosome disorder to chromosome rearrangements such as balanced translocations.

History of Two or More Spontaneous Abortions, Stillbirths, or Neonatal Deaths

The incidence of chromosome abnormalities in these was discussed earlier. About 10% of couples with recurrent abortion have a chromosome anomaly in one member. Among couples who have recurrent abortions plus a previous stillborn infant, the incidence of chromosome abnormalities has been estimated at 15% to 25%. The risk of another spontaneous abortion is about 25% after one, and greater if the couple has no live-born offspring. The risk is also greater if the embryo had a normal chromosome complement. About 2% to 3% of normal couples have two spontaneous abortions by chance alone.

Hernia or Inguinal Mass in the Female

It is possible that this may represent a Y-bearing gonad or testis as in testicular feminization syndrome. The phenotype is female, but the chromosome constitution is male. Some believe the mass should be removed to prevent the common sequelae of neoplastic development, whereas others prefer to leave it in place until after puberty.

Hydatidiform Mole

Pregnancies resulting in hydatidiform moles (no fetus, placental tissue present) may be of normal or abnormal chromosome constitutions such as triploidy. Those with diploid chromosome constitutions have a risk for malignant transformation into choriocarcinomas. There is a recurrence risk of about 1% following a molar pregnancy.

Failure to Develop Secondary Sexual Characteristics

Some genetic anomalies include the failure to develop secondary sexual characteristics such as amenorrhea (females), proportional short stature (females), gynecomastia (males), lymphedema or webbed neck (female infant), cryptorchidism (males), and small genitalia (males). These findings are very common in a variety of chromosome abnormalities, particularly of the sex chromosomes; therefore, they should be explored as soon as possible for optimal management (e.g., maximum height attainment in Turner syndrome) and in order to provide genetic counseling, treatment, and life planning.

Cancer

More than 90% of persons with chronic myeloid leukemia have a characteristic translocation [t{9;22}] in their bone marrow. Other cancers also show distinct cytogenetic abnormalities. Such studies are useful for diagnosis, treatment choice, and prognosis.

Intellectual Disability, Failure to Thrive, Developmental Delay, and Low Birth Weight

These are found with such great frequency in so many of the chromosome disorders that they are an indication for chromosome analysis. An individual feature such as developmental delay is not itself diagnostic, but the reason needs to be determined.

Presymptomatic and Predictive Testing

In presymptomatic or predictive testing, the person is tested for the mutant gene for the disease itself—for example, in the case of Huntington disease (HD) or familial monogenic Alzheimer disease—or for susceptibility to disease—such as in the case of *BRCA1* mutations and susceptibility to ovarian and breast cancer (discussed in Chapter 10). Various other disorders in this category could be screened or tested for, including hemochromatosis, familial hypercholesterolemia (both homozygous and heterozygous), neuroblastoma, and autosomal dominant polycystic kidney disease. Because of the availability of testing asymptomatic persons for mutations that can detect if they have certain gene mutations that might predispose them to the development of cancers, genetic testing is becoming more commonplace after risk assessment. This aspect is covered in detail in Chapter 10 under the discussion of cancer.

HD is an autosomal dominant incurable degenerative disorder most frequently manifesting itself in middle to late adulthood. It is caused by expansion of CAG repeats in the HD gene. Its symptoms are discussed in Chapter 10. Direct presymptomatic diagnosis is possible through ascertaining the number of the CAG repeat length. Since HD is not currently treatable, the benefits of testing relate to life and reproductive planning as well as psychological parameters.

CASE EXAMPLE

Huntington disease (HD), an autosomal dominant disorder, usually becomes clinically evident in adulthood; it is progressive and eventually fatal. A woman, Brandi, age 22, comes to the clinic because she believes that her paternal grandmother died of HD. She provided care for this grandmother until she was no longer able to do so and the grandmother was transferred to a skilled nursing facility. Brandi is about to be married, and before she does so, she is considering whether she would want natural children if she carries the mutant gene for HD. Her father, who is 40 years old, does not want to know whether he has the mutant gene. One consideration would be to have verification of the diagnosis in her grandmother if possible. What other issues are there to consider in this case example?

A variety of studies have looked at why people decided to have testing or not. Some of the most frequent reasons for choosing testing are “wanting to know” and for planning, putting affairs in order, and decision making. Reasons for choosing not to be tested were because of the potential psychological burden of a positive test and fear of not being able to cope, because the risk to their children would increase, lack of treatment, potential loss of or increased cost for health and life insurance, no plan to have more children, cost of testing, not being able to “undo” the knowledge, and others. Some of those who were not found to have the gene experienced survival guilt and emotional numbness and had difficulty coping with the impact on the family. Many had lived for years struggling with the fear of developing HD, and the adjustment to the fact that these emotional struggles were unnecessary was difficult. Others believed they were ostracized by family members who had the HD gene. Partners of those who did not have HD were uniformly relieved. Some who have found that they have the HD gene have experienced hopelessness, depression, and suicide ideation. Others have not reported long-term significant problems. Reported adverse effects have been fewer than anticipated. Many feel that HD testing should be available only to those who have reached the age of majority in whatever country they reside; others do not.

Another issue has to do with whether to reveal the actual CAG length. This result is being increasingly requested because the longer repeat length in the abnormal area may be related to the age of onset prediction. To not reveal it is paternalistic and may not be consistent with the right to know. Discrimination has occurred in those who have been shown to have the HD gene. In one case, it was reported that a person was denied entrance to medical school on the basis that the educational efforts would be “wasted.” This points to the importance of guaranteeing confidential results and of legislating nondiscrimination for genetic susceptibility or actual disease. Anonymous testing has been suggested for HD and other conditions similar to that done in HIV testing and has been done in a limited way. Preserving anonymity, however, may limit support and counseling. When a pregnant woman requests prenatal diagnosis for her fetus for HD if the father is at risk, providing this information to her, depending on the outcome and her actions, may reveal the gene status of her partner, resulting in violation of his right not to know.

Genetic Testing and Screening of Children and Adolescents

Should children or adolescents be tested for susceptibility to genetic disease, presence of the genes for late-onset diseases, or carrier status? The issue of genetic testing and screening of children and adolescents has been an area of great controversy; however, genetic testing and screening of minors are now routine. Currently, approximately 4 million newborns in the United States are screened for sets of genetic disorders chosen by their state of residence. The goal of these screens is to find rare metabolic, hematologic, and endocrine disorders for which there may be early treatment or intervention with a goal of the reduction of morbidity and mortality.

Pediatric genetic testing after infancy is less routine. Diagnostic testing may be conducted when the child presents with physical and behavioral symptoms, which

may indicate a genetic syndrome. Predictive testing may be conducted if there is a family history for a genetic disorder and if early treatment may impact mortality and morbidity. Some reasons for such testing include:

- ▶ The institution of preventive measures or therapy that can treat or ameliorate the severity or influence the natural history of the disease in question. A direct, timely medical benefit or evidence-based risk-reduction program is the most compelling reason for testing
- ▶ Sparing the child the unpleasantness and trauma of continued testing for disorders such as familial cancer when the child may not possess the gene in question
- ▶ Knowledge for the parents in terms of their own financial and reproductive planning, given the future outlook for their existing children
- ▶ The elimination of the uncertainty of knowing whether they possess a gene for a serious disorder such as HD or adult polycystic kidney disease
- ▶ The psychological benefit of a negative test—the chance for parents to adjust to a diagnosis and plan ways to disclose and cope with the news at the appropriate time for their child
- ▶ The opportunity for life planning based on this information, including choices related to education, career, lifestyle, and reproductive decisions. For example, a child at risk for retinitis pigmentosa could choose a career that does not require visual acuity or a child with familial hypertrophic cardiomyopathy could receive early drug therapy for arrhythmia prevention

Some reasons given for not performing such testing include:

- ▶ The child may not be able to understand the ramifications of testing such as future insurability risks and possible effects on education and employability
- ▶ The child may not be able to give informed consent or even assent, thus taking away the child's right to decide
- ▶ The potential psychological consequences of learning that one has a genetic disorder or is a carrier, such as lowered self-esteem, changes in family dynamics and in parent–child bonding, and loss of confidentiality of the child's condition since the parents will know the status
- ▶ Stigmatization and labeling
- ▶ The potential negative psychological consequences of learning that one does not have a disorder and developing “survivor guilt” or feeling alienated from an affected sibling or family member

Several legal principles are important to the issue, including the scope and limits of parental authority, the “mature minor rule,” emancipated minor status, and recognition of the age of 7 years to assent to participate in human subject research. Competence to make decisions includes the ability to understand and communicate, to reason and deliberate, and to develop and sustain moral values, as well as the child's developmental level. The Working Party of the Clinical Genetics Society

(1994) believes that predictive genetic testing in children is appropriate when onset occurs in childhood or if there are medical interventions such as diet, medication, or surveillance for complications that can be offered; it does not believe such testing should be undertaken in a healthy child for an adult-onset disorder if there are no useful medical interventions that can be offered. In regard to genetic testing for cancer susceptibility (see Chapter 10), the American Society of Clinical Oncology (2003) recommended that when cancer develops during childhood and there are evidence-based risk-reduction strategies, the scope of parental authority includes deciding for the child participation or nonparticipation in such testing, and that if there is not an increased risk of childhood cancer that testing be delayed until the person is of an age to make an informed decision. It is also important to note that children may have limited options to refuse if they wish to do so.

Decisions of both children and adolescents and their parents are also influenced by personal experiences with the illness being tested for. The provider needs to be able to discuss issues with families and help them to consider the risks and benefits in a nonadversarial, reasoned manner. As part of this, the capacity of the child to understand and make decisions should be considered, and not based solely on age. While parents are generally considered to act in the best interests of their children, many believe that the provider should be the advocate for the child's best interest and that if the provider believes that it is not in the best interest of the child, the provider is not obligated to perform testing. Others believe that the decision rests with the family. The joint statement by the American Society of Human Genetics Board of Directors and the American College of Medical Genetics Board of Directors (1995) states that "a request by a competent adolescent for the results of a genetic test should be given priority over parents' requests to conceal information" (p. 1234). The Task Force on Genetic Testing stated that "Genetic testing of children for adult onset diseases should not be undertaken unless direct medical benefit will accrue to the child and this benefit would be lost by waiting until the child has reached adulthood" (Holtzman & Watson, 1997, Chapter 1). In general, there is support for testing children in childhood when they are symptomatic, when a genetic disorder generally appears in childhood, and presymptomatically when there is a benefit to preventive treatment. Testing children for the carrier status is even more complex. Commercial testing companies often do not ascertain the age of a person submitting a sample for testing through mail.

Ethical, Social, and Legal Issues

A variety of ethical issues including risks and benefits arise when considering genetic testing. Risks and benefits along with issues relating to testing in pregnancy are discussed in Chapter 8. Direct-to-consumer (DTC) companies currently offer a wide range of genetic and genomic assays, such as assessment of risk of monogenic and complex multifactorial conditions, paternity testing, and carrier testing. These tests do permit increased control by the patient; however, there are some considerations as to whether there is the possibility of potential harm. In 2014, the Food and Drug Administration (FDA) decided to bring DTC genetic testing under its regulatory authority as a medical device. It is certain that the controversy will continue as consumers desire some control of this process in spite of the FDA rulings. Ethical issues that overlap screening and testing are discussed in Chapters 8, 10, and 13.

THERAPEUTIC STRATEGIES EMPLOYED IN GENETIC DISORDERS

Although various types of therapeutic management are available, such management approaches depend on:

- ▶ The nature of the defect
- ▶ How well it is understood at the genetic and biochemical levels
- ▶ The practical feasibility of correction

In some conditions, certain management is tailored to the specific genotype. The client being treated may be the fetus, the infant, the child, or the adult. Treatment methods used in genetic disorders may involve surgical, cognitive/behavioral, pharmacologic, dietary, environmental avoidance, transfusion, plasma exchange, enzyme, behavioral, cell, or gene therapy (see Table 5.4). Some have been developed on the basis of knowledge of the defect in the gene and its product, whereas others are empirical or are aimed at controlling or mediating signs and symptoms without cure. Different rationales thus underlie the previously described methods (see Table 5.5). They are basically aimed at:

- ▶ Limiting the intake of a substrate or its precursor
- ▶ Depleting the accumulation or promoting the excretion of a substrate, precursor, or product
- ▶ Directly or indirectly replacing or stimulating production of the enzyme, or gene product
- ▶ Replacing, repairing, or reprogramming the gene itself

For example, diet therapy may be based on the principle of limiting the amount of a specific substrate that cannot be adequately metabolized by the appropriate enzyme, as in phenylketonuria (PKU), or it might be aimed at providing a product needed in order to circumvent a metabolic pathway, as in the provision of uridine in orotic aciduria. Gene product replacement might involve the administration of the product directly (e.g., insulin in type 1 diabetes mellitus) or indirectly by means of bone marrow transplantation (e.g., in severe combined immunodeficiency [SCID] caused by adenosine deaminase deficiency [ADA]). Toxic substances can be removed by chelation with drugs, plasmapheresis, or surgical bypass procedures. The administration of pharmacologic doses of vitamins supplies the needed cofactor for holoenzyme function in certain vitamin-responsive disorders.

For some disorders, multiple combinations of therapies are necessary. In Refsum disease (an autosomal recessive disorder with retinitis pigmentosa, ataxia, peripheral neuropathy, and accumulation of phytanic acid), for example, dietary restriction of phytanic acid and plasmapheresis at weekly intervals is usual. Correction of birth defects such as craniofacial anomalies or limb anomalies usually involves multiple phases of surgical treatment at various stages of the development of the individual, along with the use of prosthetic devices and a long rehabilitation. Such interventions require a skilled treatment group that is prepared to deal not only with the physical correction by surgery, but with the nursing, psychological, speech, hearing,

TABLE 5.4 Treatment Methods Used in Selected Genetic Disorders

| Method | Examples |
|---------------|--|
| Surgical | <p>Reconstructive surgery in cleft lip and palate; portacaval shunt in glycogen storage diseases I and III to limit deposition of glycogen</p> <p>Liver transplant to provide missing enzymes in Wilson disease and hereditary tyrosinemia by replacing defective tissue</p> <p>Bone marrow transplant to supply missing enzyme in severe combined immunodeficiency caused by adenosine deaminase deficiency. Stem cell transplant in β-thalassemia</p> <p>Correct defect in congenital heart disease</p> |
| Pharmacologic | <p>Danazol (an androgen) in angioedema to prevent acute attacks</p> <p>Tigason (synthetic retinoid) in Darier disease (autosomal dominant skin disorder)</p> <p>Growth hormone in pituitary dwarfism</p> <p>Insulin in type 1 diabetes mellitus</p> <p>Zinc in acrodermatitis enteropathica (an autosomal recessive disorder) to ameliorate zinc deficiency and bring clinical improvement</p> <p>Clofibrate in hyperlipoproteinemia III to decrease blood lipids</p> |
| Dietary | <p>Limitation of phenylalanine in PKU for substrate restriction</p> <p>Limitation of lactose and galactose in galactosemia for substrate restriction and prevention of accumulation</p> <p>Administering uridine in orotic aciduria to inhibit the first enzyme in the metabolic pathway and decrease orotic acid</p> |

(continued)

| | |
|-------------------------|--|
| Environmental avoidance | Avoiding mechanical stress to prevent fractures in osteogenesis imperfecta Avoiding halothane and related anesthetics in malignant hyperthermia Not eating fava (broad) bean in G6PD deficiency to prevent hemolytic anemia Avoiding sulfonamides in unstable hemoglobins to prevent hemolysis Avoiding alcohol consumption in acute intermittent porphyria Avoiding ultraviolet light in xeroderma pigmentosa to minimize skin lesions |
| Transfusion | Administration of factor VIII in hemophilia A as a replacement for the lacking circulating serum protein |
| Behavioral | Infant stimulation program to maximize potential in Down syndrome and other syndromes that include developmental delay |
| Plasmapheresis | In Refsum disease to remove high blood levels of phytanic acid due to defective metabolism |
| Enzyme | By administering cofactor such as biotin to allow increased propionyl-CoA carboxylase activity in propionic acidemia. Intravenous administration of α -galactosidase A in Fabry disease |
| Gene | Direct gene transfer of β -hemoglobin gene copies into bone marrow cells of patients with β -thalassemia Use of recombinant DNA to produce insulin Use of ribozymes to inactivate expression of mutant gene |
| Preventive | Genetic counseling Genetic testing and screening Prenatal detection and diagnosis Newborn screening |

CoA, coenzyme A; G6PD, glucose-6-phosphate dehydrogenase; PKU, phenylketonuria.

TABLE 5.5 Selected Approaches to Treatment of Genetic Disorders

| Approach | Examples |
|---|---|
| <i>Restricting or eliminating intake of substrate or precursor</i> | |
| Diet therapy | Restricting intake of the branched chain amino acids in MSUD, or phenylalanine in PKU, to prevent the accumulation of these substances and subsequent consequences |
| Environmental avoidance | Nonuse of barbiturates in hepatic porphyrias |
| <i>Depleting the accumulation or promoting the excretion of a substrate, precursor, or unwanted product</i> | |
| Chelation | Using D-penicillamine as a chelating agent to deplete copper in Wilson disease Using deferoxamine as a chelating agent to promote excretion of ferritin secondary to iron overload in β -thalassemia |
| Surgical bypass | Surgical bypass procedures such as portacaval shunt in glycogen storage diseases I and III, and ileal jejunal bypass in hyperlipoproteinemia IIa to decrease cholesterol absorption from the gut |
| Enhanced excretion | Enhancing excretion of bile salts to reduce serum cholesterol by giving cholestyramine in familial hypercholesterolemia Promoting waste nitrogen excretion by giving arginine as a dietary supplement in patients with argininosuccinate synthetase deficiency |
| Plasmapheresis (mechanical) | Plasmapheresis in Refsum disease for elimination of phytanic acid |
| Metabolic inhibition | Clofibrate in hyperlipoproteinemia III to inhibit glyceride and decrease blood lipid levels |

(continued)

| <i>Replacing or stimulating production of enzyme, gene product, or gene</i> | |
|---|--|
| Enzyme induction | Use of phenobarbital in Gilbert and Crigler–Najjar syndromes results in increased glucuronyl transferase |
| Cofactor administration (in vitamin-responsive forms) | Thiamine (B ₁) administration in pyruvic acidemia for pyruvate decarboxylase; in MSUD for branched chain ketoacid decarboxylase Ascorbate administration in Ehlers–Danlos syndrome VI for collagen lysyl hydroxylase Pyridoxine (B ₆) in gyrate atrophy for ornithine ketoacid aminotransferase; in homocystinuria for cystathionine synthetase; in infantile convulsions caused by glutamic acid decarboxylase Biotin in propionic acidemia for propionyl-CoA carboxylase; in mixed carboxylase synthetase Cobalamin (B ₁₂) for methylmalonic aciduria from adenosylcobalamin synthesis and methylmalonic CoA mutase Folate for homocystinuria caused by methylenetetrahydrofolate reductase |
| Enzyme administration (surgical and nonsurgical approaches) | Organ and tissue transplantation as in the kidney for Fabry disease and cystinosis; islet cell transplantation for diabetes; liver for hereditary tyrosinemia; fibroblasts in mucopolysaccharide disorders Transfusion of placental glucocerebrosidase in Gaucher disease (experimental) Intravenous infusion of α -galactosidase A in Fabry disease Oral pancreatic enzyme supplementation in cystic fibrosis |
| Direct administration of gene product | Factor VIII in classic hemophilia Cortisol in congenital adrenogenital syndrome Thyroxine in congenital hypothyroidism |
| Direct gene transfer | Factor IX in hemophilia B (experimental) |
| <i>Blocking production of a protein</i> | |
| Antisense oligonucleotide | Blocks translation of mRNA into protein; for example, in blocking conversion of angiotensinogen to angiotensin to control hypertension (experimental) |

CoA, coenzyme A; mRNA, messenger RNA; MSUD, maple syrup urine disease; PKU, phenylketonuria.

and rehabilitative measures needed to achieve optimum results. Thus, therapeutic approaches may range from a one-time surgical correction of a birth defect to a long-term special diet, to an infant stimulation program to improve maximum potential, to experimental gene replacement. This chapter concentrates on therapeutic modalities that are unique to, or especially important in, genetic disorders, and those requiring understanding and manipulation of the genetic problem at a biochemical level or at the level of the gene itself.

Diet Manipulation

One of the most common therapeutic modalities likely to be encountered by the nurse is diet manipulation. Diet manipulation may be used to restrict or eliminate a specific substrate from the diet in order to prevent buildup of the substrate itself, its product in a specific metabolic pathway, or a metabolic by-product. Such diet manipulations have been applied to several inherited biochemical disorders. Because of the rarity and complexity of these disorders, specialized and expert team management is required and may be available only in specialized centers. After therapy is initiated, continued management can be accomplished in the person's home community. Often the community health or school nurse becomes the link between the family and a host of other professionals involved in the care. Because PKU is the most frequent among these, this will be discussed in detail as a prototype; others are briefly discussed. Principles that nurses can apply generally to patients on these long-term substrate-restricted diets are given later.

Nursing Pointers

- ▶ Parents, and the child when old enough, need to understand the relationship of the basic defect in the disorder to the dietary restrictions. This should be explained in simple terms, and all information should be culturally congruent at a level the client can understand. The shock accompanying initial diagnosis may result in the nonretention of factual material that is presented at such a time, and so the information should be repeated again later.
- ▶ Parents should be told orally and also in written form the equipment that is necessary to have in the home to implement the diet and where it can be obtained. Some centers provide all necessary equipment.
- ▶ Parents must understand the dietary prescription and be able to use it with common household measurements. The importance of accurate measurement should be stressed.
- ▶ The dietary prescription should be given in written form and gone over verbally. All information should be in easily understood terms.
- ▶ Parents should be able to plan a sample day's diet from a given dietary prescription. The nurse can ask to have them do this while visiting the home.
- ▶ The meaning of the specific disorder in the family's cultural context should be determined and used in teaching and long-range planning.

- ▶ Consider ways for the dietary implementation and maintenance in the context of different cultural, ethnic, religious, and social eating patterns, so that they can be applied to families in appropriate ways.
- ▶ Help may be needed for the mother to get used to the time-consuming routine of a special diet. The nurse may be able to help her organize a schedule.
- ▶ Financial needs should be recognized. Some states provide free formula, food, or financial assistance for metabolic disorders.
- ▶ Stress the importance of reading labels in all commercial foods or requesting such ingredient lists from commercial manufacturers if they are not listed on the label.
- ▶ Parents should understand the importance of not running out of special necessary foods or formula. They should have an emergency stockpile at all times.
- ▶ Essential products and formulas should be taken with the family on trips and vacations.
- ▶ Parents should know what to do in the case of illness, refusal to eat prescribed foods, failure to stay on the prescribed diet, or appetite fluctuations. These should be in written form and verbally reviewed.
- ▶ Parents should have a telephone number to call in which a response is always available whenever they have specific diet-related questions.
- ▶ When possible, parents should be encouraged to use foods that are acceptable in the special diet for all family members, provided that a dietary imbalance would not result (e.g., everyone could have fruit ices for dessert instead of just the child with galactosemia, where lactose is restricted, while others eat ice cream).
- ▶ Neighbors, friends, relatives, babysitters, and teachers should have a clear explanation of foods that the child can and cannot have. If the child is likely to have a snack at a particular friend's house, specially prepared or acceptable snacks could be kept there. For example, all can enjoy home-baked cookies from a recipe that is low in phenylalanine.
- ▶ Open communication and involvement of school officials and teachers so that the child is treated as one that is normal, healthy, and on a special diet is essential. The nurse may help initiate contacts or give a program to teachers to alleviate their concerns.
- ▶ Parents may be helped to plan the diet by using some foods from the school lunch menu if it is possible to minimize differences.
- ▶ Involving the child in his or her own food choices from approved foods can be done by the age of 3 years or when developmentally appropriate for that child.
- ▶ Parent groups are useful for support and sharing coping measures.

Intrauterine and Fetal Therapy

The widespread use of prenatal detection and diagnosis has allowed the early identification of fetuses with biochemical errors and congenital defects. Prenatal diagnosis of genetic disease in the fetus now expands the list of choices for the pregnancy:

- ▶ Selective termination of the pregnancy
- ▶ Choice of a different mode of delivery (e.g., cesarean section in a fetus with osteogenesis imperfecta)
- ▶ Altering the geographic site of delivery for highly specialized management
- ▶ Specific prevention of premature labor
- ▶ Induced preterm delivery for the earliest possible correction or to prevent further damage (e.g., amniotic band syndrome)
- ▶ Preparation for immediate postnatal treatment at the normal delivery time
- ▶ Direct fetal therapy such as placement of a shunt in the fetus for correction of obstructive hydrocephalus
- ▶ Fetal surgery involving direct fetal exposure
- ▶ Indirect fetal therapy or intrauterine treatment, for example, in the case of administration of intravenous and oral digoxin to the mother for intrauterine treatment of fetal paroxysmal tachycardia as well as direct injection to the fetus

These procedures have had various degrees of success and risk. Experimental techniques such as in utero surgery to correct certain craniofacial anomalies have been suggested. In utero hematopoietic stem cell transplantation has been accomplished in a few cases and may be particularly useful for immunodeficiency disorders such as X-linked agammaglobulinemia, hemoglobinopathies such as β -thalassemia, and inborn errors of metabolism such as Gaucher disease.

Experience with many of the specific modalities used in intrauterine therapy has been limited due to the rarity of many of the individual disorders, technical difficulties, and the hazards that may be involved. For example, in fetal surgery, some of the possible undesirable outcomes are hemorrhage, infection, spontaneous abortion, premature labor, serious injury or death to the fetus or mother, the possibility of the need for future cesarean section due to the hysterotomy necessary for surgery, unsuccessful surgery, successful surgery but an unsuccessful outcome, the presence of other undetected defects in the fetus, and untoward effects from the anesthesia used.

As opportunities for fetal therapy grow, ethical and moral dilemmas are becoming more apparent. In addition to implications from the risks noted, others include divergent societal views of the fetus, conflicts between the rights and desires of the parents and of the fetus, the weighing of risks and benefits between the mother and the fetus, the lack of information on the chances for successful outcomes, the fact that the mother becomes a patient with the fetus and may possibly be an unwilling participant in fetal therapy, whether the right of a treatable defective fetus is the same as the right of a fetus with an untreatable defect, whether a fetus can be

considered truly a patient, and the interests of the researchers in advancing expertise and knowledge. Dilemmas are increased when twins are present and one is normal and the other has a defect. Nurses should make sure that as much information is available to parents involved in such a decision as is available, help to clarify choices, make sure that the information presented is in terms that they understand, provide an environment that is free from coercion and pressure, and support whatever decision the couple makes. There are concerns by some that fetal treatment can become too aggressive when alternative methods are available. For example, how much advantage is attained by fetal bone marrow transplant as opposed to performing this procedure after birth?

Gene Product Replacement

The replacement of the normal gene product may be accomplished in several ways—by simply administering the missing substance (e.g., thyroxin for hypothyroidism or factor VIII for classical hemophilia or pancreatic supplementation below 10,000 units of lipase/kg in cystic fibrosis) on a periodic basis, manipulating the defective enzyme by cofactor or coenzyme therapy, organ or tissue transplantation, or directly replacing the deficient or defective enzyme. Several years ago, it appeared that enzyme replacement therapy would be relatively simple in those disorders in which the enzyme defect was identified at the molecular level. In practice, the administration of enzymes in conventional ways was not effective. A major reason was that most enzymes are not normally circulating serum components like factor VIII (a blood-clotting factor deficient in hemophilia A). They need to gain access to cell interiors in specific organs and then reach specific organelles. The enzyme must get there without being destroyed, and it needs an appropriate delivery system. For example, in lysosomal storage diseases, the cells' normal delivery system must be used to get the enzyme into the lysosome by allowing the enzyme with its carrier to bind to the cell surface receptors as a macromolecule and allowing normal pinocytosis to occur.

Cofactor and Coenzyme Therapy

As discussed in Chapter 9, many enzymes are holoenzymes, that is, they are composed of an apoenzyme (protein part) plus a cofactor or coenzyme (prosthetic part) that is needed for function. Cofactors are frequently vitamins or metal ions. Many inherited biochemical disorders have both vitamin-responsive and -nonresponsive subtypes. The replacement of a missing or defective cofactor or supplying it in megadoses allows the formation of a functional holoenzyme or allows binding when large amounts of cofactor are available. In this way, they regulate the activity and amounts of apoenzyme. At least 25 vitamin-responsive inherited biochemical disorders are known. Fetal vitamin therapy for certain vitamin-responsive disorders has been accomplished, and the potential exists for the possibility of this approach with the others. Giving vitamins in high doses has been found in some cases to activate other pathways unintentionally with accompanying ill effects, and this must be watched for during therapy.

Recombinant DNA

Briefly, the process of creating recombinant DNA for use in the manufacture of certain proteins, enzymes, and hormones is as follows. So-called foreign DNA from a higher biologic organism or human is cut into specific sections containing the normal-functioning gene of interest by a type of enzyme called restriction endonucleases and is purified. These enzymes are also used to remove a segment from the DNA of a vector or carrier. Vectors most commonly used are bacteriophages (bacterial viruses) or plasmids (a type of bacterial DNA). The foreign DNA and the DNA from the vector are allowed to unite, thus forming a recombinant DNA molecule that is inserted into a host bacterial cell. This bacterium, with its own DNA plus that of the vector with the foreign DNA, multiplies, making identical copies of the foreign DNA inserted and its product—the protein or enzyme—desired. This process is called *cloning* and is being used commercially to produce human insulin, growth hormone, interferon factor VIII, and other substances in large quantities. This has led to the wider use of substances that were formerly limited in production and now are available, as well as removed the necessity of extraction from pooled blood, thus making safer (free of infectious organisms such as hepatitis or HIV) products available. Another use of restriction endonucleases is in the creation of gene “probes” for diagnosis as discussed in Chapter 2.

Gene Therapy

Gene therapy is the most direct approach to the treatment of genetic diseases. If it is successful, it eliminates the need for all of the other therapeutic modalities previously described. It has long been known that genetic material has been transferred nonpurposefully from one organism or species to another, as in the case of viruses that invade human tissue and become integrated into the cellular DNA. Gene therapy usually consists of inserting a new gene into somatic or germline cells but may also refer to repair or reprogramming of a gene. The optimal gene therapy would be the replacement of the abnormal gene with a normal copy in the proper location of that gene in every cell with the appropriate expression. The new gene must not only be delivered but also expressed correctly over time. Among current interests in gene therapy is the understanding of gene regulation and tissue-specific gene expression control that can be manipulated to correct the defect. Gene therapy can be used in several ways:

- ▶ Replacing a missing function as in the case of an absent or deficient gene product that usually occurs in autosomal recessive biochemical disorders
- ▶ Enhancing or activating normal functioning
- ▶ Providing a new function such as resistance to a disease such as influenza
- ▶ Interfering with an undesired or aberrant function such as in the case of an abnormal gene product formed in an autosomal dominant disorder

Gene therapy could be used to treat both genetic diseases and common diseases such as cancer and heart disease, and also as a prevention strategy. The idea of using germ cells for correction of a genetic defect has aroused ethical concerns about

whether it is appropriate to alter the human genome for future generations and the effect on those future generations. It is also technically difficult, but it is appealing in that it ideally would correct the genetic defect in all cells and all descendants. Now germline gene therapy is not actively being pursued in humans. Somatic cell gene therapy corrects the defect only in the person treated, not his or her descendants.

The first human gene therapy trial was the insertion of a functional gene into somatic cells (T-lymphocytes) to correct the defect in ADA, a type of SCID disorder, and the return of these cells by infusion to the affected children. This was not permanent, and infusions every 1 to 2 months were needed initially, followed by 3 to 6 months. Newer approaches involve the insertion of normal ADA genes into bone marrow stem cells. Other examples of conditions in which clinical trials of gene therapy have been done is the introduction of the gene for the low-density lipoprotein (LDL) receptor into the liver cells of patients with familial hypercholesterolemia, and the *CFTR* gene into lung and airway cells in cystic fibrosis patients. Gene therapy trials received a setback when an 18-year-old male with ornithine transcarbamylase deficiency who was receiving intravenous infusion of the normal gene via a weakened adenovirus vector developed multiple organ failure and died. After this, the FDA and others instituted stricter regulation. In late 2002, the development of leukemia in some children enrolled in a French gene therapy trial using retroviral vectors to insert genes into stem cells for X-linked SCID disease led to a temporary halt in 2003 of these types of trials by the FDA. Currently, gene therapy research has resumed for life-threatening illnesses, such as SCID. The field of study is rapidly expanding with new target drugs; however, most of the new drugs remain in clinical trial research.

Somatic cell gene therapy could involve gene insertion not only into the infant, child, or adult but also prenatally. The times for this would be in the zygote before and after fusion of pronuclei (this could be done by the microinjection of DNA into the male pronucleus of the fertilized ovum), in the preimplantation embryo, perhaps in conjunction with embryo transfer, or postimplantation into the embryo or the fetus at an early age of development before damage from the mutant gene has occurred. Newborn gene therapy also appears promising because of the infant's small size and for other reasons; ADA has been treated in this way. In some neurologic genetic diseases, damage is detectable by the third month or earlier. In one case, in utero stem cell transplantation of bone marrow from the father to the male fetus was accomplished to prevent the X-linked type of SCID disease. Several infusions were necessary using ultrasound-guided intraperitoneal injection, and at 5 months of age, the boy appeared well. The Patent and Trademark Office has allowed patents for gene therapy techniques.

Gene-based therapies have been tested for diseases such as cancer and heart disease. In cancer, one approach has been to alter cells to produce substances that alter the host response to cancer cells. In heart disease, angiogenic factors can be delivered into ischemic heart muscle. In HIV, it has been suggested that introducing drug resistance genes into normal bone marrow cells would allow more aggressive chemotherapy. Genetically engineered islet cells have been transplanted in type 1 diabetes.

Epigenetic Therapies

Epigenetics refers to changes in gene expression not coded for in DNA. Various genetic disorders are due to inappropriate gene silencing or expression. These may occur through such mechanisms as DNA methylation and modifications in chromosomal histones and are discussed in Chapter 2. Unlike genetic alterations, which are near impossible to reverse, epigenetic changes are potentially reversible. Thus, it follows that epigenetic therapeutic approaches would be developed. For example, DNA methyltransferase inhibitors or histone deacetylase (HDAC) inhibitors, such as 5-azacytidine, are being examined for their ability to reactivate genes that have been silenced. Applications include certain cancers such as myeloid dysplastic syndrome and certain hemoglobinopathies.

KEY POINTS

- ▶ What are some of the ways in which genetic testing and screening differ?
- ▶ Discuss elements to include in programs to prevent genetic disease.
- ▶ What are some advantages and disadvantages of nondirective genetic counseling? Should genetic counseling be more directive? Why or why not?
- ▶ What are some causes for concern with germline gene therapy?

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PART II

The Integration of Genetics Into Nursing Curricula

CHAPTER 6

The Application of Genomics to Pharmacology

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CASE EXAMPLE

A 21-year-old male student was brought to the hospital with a fractured leg. He was more worried about anesthesia than about his leg. When taking the family history, it was noted that 10 of his relatives had died after having general anesthesia. This chapter will explain why.

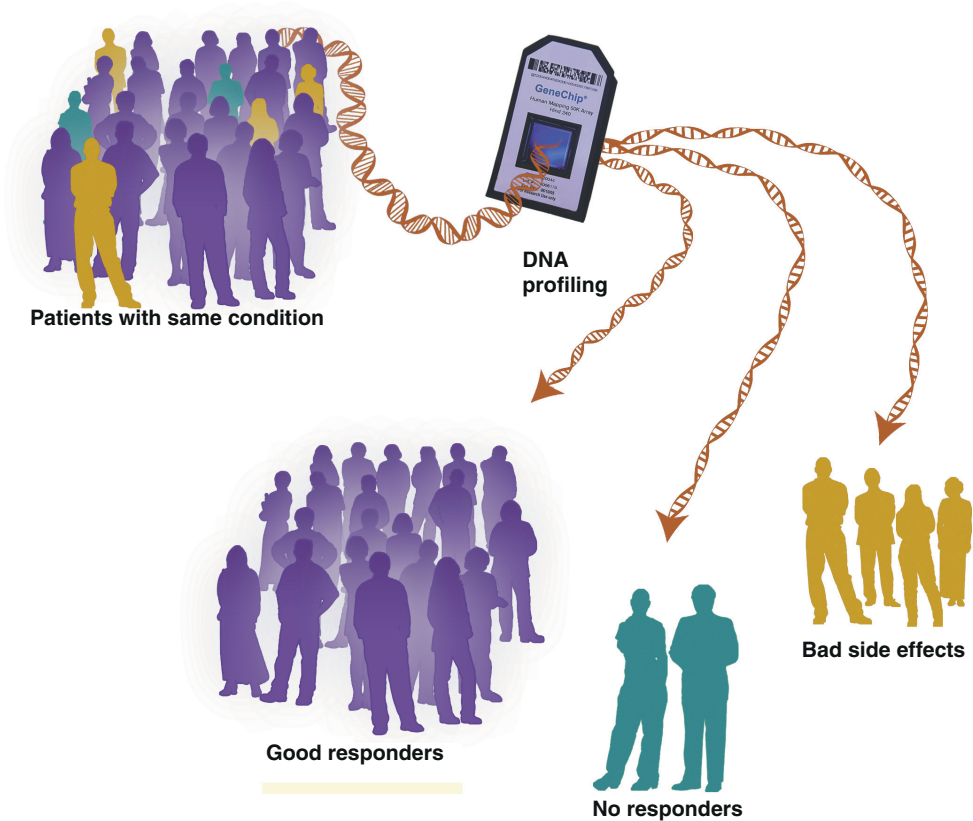
Differences in how individuals respond to drugs can be due to genetic or nongenetic factors. Certain individuals may require different doses of the same drug in order to achieve maximum effectiveness, others may not respond at all to certain drugs, and different adverse reactions may be manifested. Much of this variability is thought to be genetic, and some families may be at greater risk for adverse events than the population at large. The well-known and recently discovered polymorphisms in the genes coding for enzymes affecting drug metabolism, transport, disposition, excretion, and drug receptors affect large numbers of persons worldwide. Their clinical significance depends on a variety of factors, which are not directly genetic (e.g., age, weight, general health, liver function) as well as the therapeutic index of the drug. However, a person's genetic predisposition can influence any stage of the drug-handling process, as listed in Box 6.1.

Pharmacogenetics is the study of variable drug response and drug adverse events as a result of a person's heritable genetic differences. *Pharmacogenomics* is a more recent term, and is the study of how drugs impact the total genome and interact with its expression output. This includes how drugs act on and with gene variations, protein expression, and other biology network applications such as the human *microbiome* (the microbial genomes of bacteria, bacteriophage, fungi, protozoa, and viruses that live inside and on the human body). Pharmacogenetics and pharmacogenomics are often used interchangeably to denote drug therapies tailored to an individual's DNA, but they really mean distinctly different things. Figure 6.1 provides an overview of pharmacogenomics in today's health care setting.

BOX 6.1

Selected Stages in Drug Handling Influenced by Genetics

| | |
|----------------------------------|---|
| Absorption | Membrane transport |
| Distribution | Tissue sensitivity |
| Protein binding | Tissue storage |
| Metabolism | Elimination |
| Attachment to membrane receptors | Activation of special responses (e.g., immune response) |



Pharmacogenomics in the clinic. Health professionals take blood samples from patients with the same condition. DNA is purified from the blood and placed on a profiling chip. The chip tests for gene variants that affect response to a drug used to treat the condition. Depending on which genetic variants they have, patients may have a good response, no response, or bad side effects. The drug is given only to people who are likely to have a good response.

FIGURE 6.1. Clinical Premise of Pharmacogenetics and Pharmacogenomics.

Source: National Human Genome Research Institute (2014).

Genetic variation in drug metabolism and handling can be quantitative or qualitative. For example, mutant genes may produce enzyme variants with high, intermediate, low, or absent activity. The degree and type of variation in an individual's response may not be apparent if there is no important, easily detected consequence. Someone who has even a low level of activity for a given enzyme may have enough functioning product to cope normally unless some unusual stressor such as infection or trauma is encountered. Therefore, this person may be unaware of the impairment.

Information about response variation is particularly important in drugs with a narrow therapeutic margin, or therapeutic index. This means there is little difference between toxic and therapeutic doses; a classic example is the widely prescribed anticoagulant warfarin (Coumadin). Thankfully, many drugs have a wide enough margin of safety so that even with individual-response variation, effectiveness and safety are not dangerously compromised. However, practitioners must recognize that just as there can be variable responses in patients due to their age differences, persons from diverse racial and ethnic groups may respond differently to medications because of their genetic differences. Drug developers are increasingly using genetic and genomic knowledge to tailor disease treatment approaches.

Inherited drug receptor mutations can also cause functional changes with health implications, such as an individual's opiate receptor variability and their risk for drug dependence. Other drug receptor variants can result in resistance to vasopressin, estrogen, insulin, and the steroid hormones. Current research studies differences in the metabolism of alcohol and illicit drugs to generate new information about the genetics and biology of drug dependence and addiction.

Variations can be relatively common in certain populations—such as the case with *polymorphisms*, or they may be relatively rare. Some pharmacologically significant variations include:

- ▶ The widespread common polymorphisms in enzymes involved in the metabolism and processing of many different drugs, such as within the cytochrome P450 system
- ▶ A singular feature of a person's genetic disorder such as in the porphyrias
- ▶ A rare abnormality, such as in butyrylcholinesterase variation

In this chapter, both pharmacogenetic disorders and common polymorphisms leading to altered response to drugs are discussed, as are pharmacogenomic applications and the ethical problems engendered.

COMMON GENE MUTATIONS AND VARIATIONS AFFECTING DRUG METABOLISM

There are a number of genetic mutations and common polymorphisms that affect the way drugs are metabolized. A relatively common human enzyme genetic condition, glucose-6-phosphate dehydrogenase (G6PD) deficiency, is discussed in the following text. Also included in this chapter are polymorphisms in the drug-metabolizing enzymes such as cytochrome P-450 superfamily; acetylator variation; and

thiopurine-S-methyltransferase polymorphisms. Common variations that affect drug metabolism and handling in clinical practice are shown in Table 6.1.

TABLE 6.1 Examples of Gene Polymorphisms Affecting Drug Activity and Response

| Gene | Polymorphism Comments |
|----------------|--|
| <i>TPMT</i> | Thiopurine S-methyltransferase catalyzes S-methylation of sulfhydryl compounds, including the anticancer drugs 6-mercaptopurine, 6-thioguanine, and azathioprine. SNP rs1800460 (<i>TPMT*3B</i>): CC genotype with decreased toxicity risks with thiopurine drugs and purine analogs; TT genotype with increased toxicity risks. <i>TPMT</i> testing is recommended before starting therapy to better individualize dosing. |
| <i>MTHFR</i> | Methylenetetrahydrofolate reductase catalyzes conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for conversion of homocysteine to methionine. SNP rs1801133 (<i>C677T</i>): patients with AA genotype in leukemia or lymphoma who are treated with methotrexate are at increased risk and increased severity of oral mucositis. |
| <i>SLCO1B1</i> | Solute carrier organic anion transporter family member 1B1 transports eicosanoids, thyroid hormones, and conjugated steroids independent of sodium. Also mediates transport of prostaglandin E2 and estrone-3-sulfate, and facilitates efficient detoxification of bilirubin glucuronide in hepatocytes. SNP rs4149056: patients with C allele experience a significant increased myopathy risk when taking simvastatin. If patients with C allele do not achieve optimal LDL cholesterol-lowering efficacy with a lower dose (e.g., 20 mg), a different therapy should be selected. In 2013, the FDA added a product label warning to direct providers from initiating at the 80 mg simvastatin dose. |
| <i>VEGF</i> | Vascular endothelial growth factor induces angiogenesis in vascular endothelial cells. Therapeutic drugs inhibiting tumor angiogenesis have been developed as a new class of anticancer drugs. Metastatic breast cancer treatment outcomes varied according to polymorphism genotype for VEGF A allele of 1154G>A and VEGF A allele of 2578C > A. |
| <i>DPYD</i> | Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme for the catabolism of the pyrimidine bases uracil and thymine. Some variants (<i>DPYD*2A</i> , <i>*13</i> , and rs67376798) affect DPD activity related to 5-fluorouracil (5-FU) clearance, an anticancer drug resulting in increased risk for adverse effects (leukocytopenia, mouth sores, nausea, vomiting). Patients homozygous for <i>DPYD*2A</i> , <i>*13</i> , or rs67376798 may demonstrate complete DPD deficiency and 5-FU should be avoided. |

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic condition and is the most common enzyme abnormality known. G6PD deficiency was thought to have a protective effect against malaria, leading to its maintenance in the human population. It affects approximately 400 million people throughout the world, especially those of Mediterranean, African, Middle Eastern, Near Eastern, and Southeast Asian origin. Most persons with G6PD deficiency are not diagnosed due to mild or confounding clinical manifestations.

G6PD deficiency results from functional mutations or polymorphisms in the 18-kb G6PD gene located on the long arm of the X chromosome (Xq28); thus, males are *hemizygous*. Although there are more than 400 identified G6PD variants, not all are clinically significant. There are presently 187 known mutations in the G6PD gene that result in the disease phenotype, with 35 mutant polymorphic alleles. Disease severity is determined by the percentage of active G6PD enzyme present from the patient's specific G6PD mutation or variant. Various classifications exist and include:

- ▶ G6PD-A, which is most prevalent in Africa, the Americas, and West Indies with 10% to 60% of normal enzyme activity—class III in the World Health Organization (WHO) classification—and associated with mild or moderate hemolysis
- ▶ G6PD-Mediterranean, which is most prevalent in the Mediterranean, North Africa, and the Middle East with 0% to 10% of the normal enzyme activity usually associated with severe hemolysis—class II in the WHO classification

Approximately 10% to 15% of Black males in the United States have G6PD deficiency. In some areas of the Middle East, G6PD deficiency may be as high as 35% of males. Because of this high frequency, more homozygous females are found to be G6PD deficient than any other X-linked recessive disorder. Unlike males, whose red blood cells are all affected by a G6PD mutation, females who are heterozygous (one mutant allele, one normal allele) have two types of red blood cells: those that are normal and those that are G6PD deficient. Although the two types of red blood cell populations are usually about 50:50, X inactivation (see Chapter 4) can lead to unequal distribution. For example, females with more G6PD deficient cells (i.e., 30% normal, 70% deficient) are more susceptible to manifesting symptoms of the disease.

G6PD plays a key role in carbohydrate metabolism by producing ribose 5-phosphate and generating NADPH (see Glossary) in the hexose monophosphate pathway (also called pentose phosphate pathway). G6PD is found in all cells where it is needed to catalyze these reactions and maintain an adequate level of intracellular NADPH. For most cells, other metabolic pathways such as the citric acid cycle can provide the needed end products from this reaction.

In red blood cells, G6PD provides reductive capacity by producing NADPH—and is the only pathway available. While G6PD-deficient red blood cells can usually function well, their cell membrane integrity can become compromised in the presence of an oxidative challenge or stress, leading to accelerated destruction (hemolysis). Triggering stress events include:

- ▶ Oxidant- or peroxide-producing drugs
- ▶ Ketoacidosis
- ▶ Infections
- ▶ Exposure to naphthalene in mothballs
- ▶ Ingestion of the fava (broad) bean (favism)

Presenting signs and symptoms can include jaundice, fatigue, pallor, tachycardia, splenomegaly, and shortness of breath; the major clinical consequences requiring supportive treatment are:

- ▶ Neonatal jaundice (hyperbilirubinemia)
- ▶ Acute hemolysis, especially following exposure to certain oxidative drugs or fava beans
- ▶ Chronic hemolysis leading to chronic hemolytic anemia

Hemolysis typically begins within 24 to 72 hours of starting the oxidative drug, ingestion of fava beans (a common dietary component in the Mediterranean, Middle and Far East, and North Africa), or onset of acute infection (usually severe, such as typhoid fever, rickettsial infections, or viral hepatitis). Seasonal favism may be encountered after harvests, when fava beans are more plentiful. Classic clinical trajectories include (a) development of Heinz bodies in the red cells, (b) red blood cell destruction with resulting drop in hemoglobin, and (c) hemolytic anemia with dark urine, back and abdominal pain, and jaundice. Acute renal failure can often occur in G6PD-deficient persons with hepatitis or urinary tract infections. Chronic nonspherocytic hemolytic anemia accompanies certain G6PD variants and may be exacerbated by stress, infection, or drug intake. There may be a history of neonatal jaundice, as well as gallstones, splenomegaly, decreased stamina, weakness, iron overload, or progressive hepatic damage. Recovery from acute hemolytic anemia in G6PD deficiency requires removal of the offending stressor or agent. Clinical improvement usually takes place on its own but, if a clinical course is severe, red blood cell transfusion(s) and close observation or support of the patient's cardiorespiratory status are needed.

In people with G6PD-deficiency, hemolysis following the intake of the antimalarial drug primaquine was described in 1953. Since the original work, WHO has identified three classifications of drugs: (a) those that everyone with G6PD-deficiency should avoid; (b) those that G6PD-deficient persons of Mediterranean, Middle Eastern, and Asian origin should avoid; and (c) those that persons with the African (A-) variant should avoid. In some cases, use of a particular drug depends on the importance and dosage required. Other factors that influence response to these drugs include patient age, severity of the G6PD deficiency, hemoglobin level, factors relating to the red blood cell, presence of additional oxidative stresses such as infection, and other additional genetic differences.

Drugs and chemicals that cause adverse effects in persons with G6PD deficiency vary according to author. Selected major drugs to avoid are acetanilide, dimercaprol, dapsone, flutamide, methylene blue, nalidixic acid, naphthalene, niridazole, nitrites,

and nitrofurans including furazolidone, nitrofurantoin, nitrofurazone-pamaquine, pentaquine, phenazopyridine, phenylhydrazine, primaquine, sulfacetamide, sulfamethoxazole, sulfanilamide, sulfapyridine, toluidine blue, sulfone antimalarials, triazole, and trinitrotoluene. In addition to quinine water, mothballs and fava beans should be avoided.

Some researchers recommend screening all individuals in certain at-risk population groups before prescribing any of the previously listed drugs. Awareness of this deficiency has become important when prescribing drugs to treat HIV infection, such as the case for dapsone. In some instances, the need for the drug outweighs the risk of hemolytic anemia. Nursing implications are provided in Box 6.2.

Cytochrome P450 Polymorphisms (CYPs)

The hepatic cytochrome P450 (CYP) enzyme system comprises a group of related enzymes known as a superfamily (sharing common amino acid sequences within and across human, animal species). The P450 enzymes are responsible for oxidizing many chemicals and drugs. A separate gene codes for each, and more than 200 have been identified, some of which have multiple allelic forms. P450 enzymes are categorized into family and subfamily groups based on the percentage of sequence homology at the amino acid level, and are named according to the following system:

BOX 6.2

Nursing Implications Related to G6PD Deficiency

- ▶ Be aware of populations in which G6PD deficiency is known to be more common.
- ▶ Review the patient's prior drug exposure history and screen for previous adverse effects at the time of treatment.
- ▶ Inquire about any drug or dietary reactions in blood relatives, and consider whether further testing for G6PD deficiency is merited (e.g., if family members had need for hospitalization or blood transfusion to treat infections, dietary reactions, drug adverse events).
- ▶ Once an individual is known to have G6PD deficiency, educate the patient/family about triggers that can precipitate hemolytic anemia. Provide a list and review with the patient/family.
- ▶ Counsel the affected person on situations and triggers to avoid. Avoidance of the fava bean should be included, as well as discussion of breastfeeding risks if an infant is G6PD deficient. Mothers who take triggering drugs or who ingest fava beans may transmit these substances in their breast milk.
- ▶ Advise patients that family members may be at risk for the condition, and help facilitate referral for G6PD screening.
- ▶ Advise affected persons to wear some type of medical information identifying them as G6PD deficient and be sure their current health care provider is aware.

BOX 6.3**Forms and Functions of Selected Cytochrome P450 in Humans**

- ▶ **CYP1.** Drugs, steroid metabolism: 1A1, 1A2, 1B1
- ▶ **CYP2.** Drugs, vitamin, steroid metabolism: 2A6, 2A7, 2A13, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2F1, 2J2, and others
- ▶ **CYP3.** Drugs, steroid metabolism: 3A4, 3A5, 3A7
- ▶ **CYP4.** Fatty acid metabolism: 4A11, 4B1, 4F2, 4F3, 4F8
- ▶ **CYP5.** Thromboxane synthesis: CYP5A1
- ▶ **CYP7.** Bile acid synthesis: CYP7A1, CYP7B1
- ▶ **CYP8.** Prostacyclin and bile acids: 8A1, 8B1
- ▶ **CYP11.** Steroid hormone metabolism: 11A1, 11B1, 11B2
- ▶ **CYP17.** Steroid hormone synthesis: 17A1
- ▶ **CYP19.** Steroid hormone synthesis: 19A1
- ▶ **CYP21.** Steroid hormone synthesis: 21A2
- ▶ **CYP26.** Retinoic acid metabolism: 26A1, 26B1
- ▶ **CYP51.** Cholesterol biosynthesis: 51A1

CYP followed by a family number, a subfamily letter, and a number for the individual form (e.g., CYP4A11). Box 6.3 outlines some of the major human cytochrome P450 forms in humans.

While each CYP subfamily group has different numbers of genetic variants, clinically they fall into several functional categories: (a) ultrarapid, extensive activity (considered normal), (b) intermediate activity, and (c) low functional activity. Frequencies of these categories often vary in populations by ethnic ancestry. In general, poor metabolizers break down drugs more slowly, causing circulating blood levels of the drug to stay higher for longer periods of time, increasing the risk of toxicity. Poor metabolizers also need less frequent dosing to obtain optimum therapeutic effect without adverse reactions. Persons who are ultrarapid metabolizers, on the other hand, may need more frequent dosing, may not show expected therapeutic effectiveness, and may be classified as treatment failures. For some variants, genotyping is now available clinically in order to maximize drug effectiveness and prevent serious adverse reactions. Clinically important cytochrome P450 genetic variations are summarized in Table 6.2. Of particular interest to nurses is the inhibited metabolism of codeine in poor metabolizers of CYP2D6 who receive no analgesic effect from codeine. When a patient is not getting the expected pain relief from codeine, the reason may be genetic, and the nurse must help them find appropriate analgesic relief, not increase the dose of codeine or decide the patient is “faking.”

Acetylator Status and Drug Metabolism

The N-acetyltransferase (NAT) enzymes transfer acetyl groups to a substrate by using acetyl coenzyme A (CoA), and are responsible for varied functions such as regulation of circadian rhythm (melatonin, serotonin synthesis in response to light/dark cycles),

TABLE 6.2 Selected Cytochrome P450 Polymorphisms

| Polymorphism | Comments |
|----------------|---|
| <i>CYP2C9</i> | 58 confirmed genetic variations, many more sequence variants reported. Metabolizes ~20% of all prescribed medications. Especially important for drugs with narrow therapeutic indices, such as warfarin and phenytoin. In the case of the commonly prescribed anticoagulant warfarin, persons with the variants <i>CYP2C9</i> *2 and *3 have reduced clearance leading to reduced dose requirements. Standard dosages can cause toxicity, including severe bleeding complications. If these persons are given another <i>CYP2C9</i> inhibitor such as amiodarone (used to treat cardiac arrhythmias) concurrently, drug-drug interaction leads to serious bleeding or neurotoxicity due to diminished enzyme activity. |
| <i>CYP2C19</i> | More than 30 genetic variations. Most patients carry a <i>CYP2C19</i> *1, *2, or *17 allele. <i>CYP2C19</i> *17 allele results in enhanced gene transcription and increased metabolic activity. <i>CYP2C19</i> involved in hydroxylation of <i>S</i> -mephenytoin, an anticonvulsant, and metabolism of some proton pump inhibitors (i.e. omeprazole), antidepressants, clopidogrel, as well as proguanil; 14–30% of Asians and 2–6% of Whites are poor metabolizers. |
| <i>CYP2D6</i> | More than 100 genetic variations, substantial ethnic differences in allele frequencies. Metabolizes many antidepressants such as nortriptyline (Pamelor), clomipramine (Anafranil), desipramine (Norpramin); antipsychotics such as haloperidol; beta blockers such as timolol (Blockadren), metoprolol (Lopressor); encainide (Enkaid); flecainide (Tambocor); perhexiline; tamoxifen; oxycodone; phenacetin; and codeine. Poor metabolizers of the beta blockers need only a daily dose, whereas extensive hydroxylators need the same dose two or three times a day for effectiveness. Poor metabolizers show more intense and prolonged beta blockade if the dose is not adjusted, leading to side effects such as bradycardia. Those with ultrarapid metabolism may not show the expected therapeutic effectiveness, or demonstrate treatment failure due to low blood concentrations of the drug. |
| <i>CYP2B6</i> | More than 38 genetic variations. Metabolizes approximately 8% of current drugs. Specific genotype (G516T) found in 3% of Whites and 20% of Blacks. This genotype is associated with slow clearance of efavirenz, a nonnucleoside reverse-transcriptase inhibitor used in HIV therapy. Those with it have higher risk of toxicity and discontinuation, especially CNS difficulties. |

mood and behavior, and chromatin remodeling (histone acetyltransferase). While approximately 18 genes are thought to encode NATs, the ability to metabolize and eliminate certain drugs depends on acetylation in the liver by *NAT1* and *NAT2*. Both are known to have important roles in the detoxification of carcinogens and interaction with toxic environmental hazards, such as cigarette smoke. *NAT1* is expressed ubiquitously and *NAT2* is found primarily in the liver. Each has multiple alleles (28 for *NAT1*, 88 for *NAT2*), which are designated by an asterisk and allele number, for example, *NAT2*5B*.

While the importance of acetylator status was first recognized during therapy for tuberculosis with isoniazid (INH), drug efficacy and toxicity are currently linked to *NAT1* and *NAT2* function for a number of drugs. This includes the anti-infective drugs isoniazid (tuberculosis), dapsons, and sulfamethoxazole (*Pneumocystis* fungi); the cardiovascular medications hydralazine (antihypertensive) and procainamide (antiarrhythmic); caffeine; the anti-inflammatory, immunomodulating agent sulfasalazine (used to treat ulcerative colitis, Crohn disease, and arthritis); the monoamine oxidase inhibitor phenelzine (antidepressant); and the benzodiazepine nitrazepam (antianxiety, sedative).

Individuals can be categorized into the following three basic phenotype groups: slow or poor, rapid, and ultrarapid acetylators. Slow acetylators maintain higher serum levels of these drugs than do rapid acetylators. In general, slow acetylator individuals are more likely to experience greater therapeutic response, but are also at risk for higher incidence of side effects than rapid acetylators. *NAT2* slow acetylators may be at greater risk for the development of spontaneous systemic lupus erythematosus (SLE) after receiving the drugs hydralazine and procainamide. In North American and European populations, between 50% and 70% are slow acetylators, as are about 90% of some Mediterranean populations such as Egyptians and Moroccans. In eastern Pacific populations such as Chinese, Korean, Japanese, and Thai, about 10% to 30% are slow acetylators, as are about 4% of Alaskan Natives. There are also a number of studies that identify association of *NAT1* and *NAT2* genotype with risk of cancer development and cancer treatment resistance, but need confirmation to be conclusively established. Fast acetylators who eat meat may have a higher risk for colorectal cancer and slow acetylators may have a higher risk for bladder cancer when exposed to arylamines and cigarette smoke.

Thiopurine S-Methyltransferase (TPMT)

CASE EXAMPLE

Joseph is a 25-year-old diagnosed with inflammatory bowel disease. Consideration is being given to a course of azathioprine therapy. Before starting azathioprine, his blood TPMT levels were measured and found to be virtually absent. Genotyping determined that Joseph had a homozygous mutation at the TPMT locus. If azathioprine therapy was started, he would be at high risk for life-threatening severe adverse effects, especially myelosuppression. This is an example of predictive pharmacogenetics in clinical treatment.

Thiopurine S-methyltransferase (*TPMT*) is an enzyme that catalyzes the S-methylation of thiopurine drugs, a class of immunosuppressants that deactivate key processes in T-lymphocytes. There are three thiopurines used clinically: azathioprine, mercaptopurine, and thioguanine.

Azathioprine and mercaptopurine are used for nonmalignant immune system indications (e.g., systemic lupus erythematosus, inflammatory bowel disease, post-organ transplant immunosuppression, rheumatoid arthritis); mercaptopurine is used to treat lymphoid cancers; and thioguanine is used for myeloid leukemias. In the absence of functioning *TPMT*, thiopurine metabolism is shifted to an alternative pathway that forms toxic thioguanine nucleotide byproducts. Three polymorphisms account for more than 90% of *TPMT* inactivation, with approximately 1 in 178 to approximately 1 in 3,736 individuals inheriting two inactive *TPMT* alleles (any two of: *2, *3A, *3B, *3C, or 4). Absent *TPMT* activity causes profound myelosuppression when standard thiopurine dosing is administered. Approximately 3% to 14% of the population is heterozygous and demonstrates intermediate *TPMT* activity. The remaining 86% to 97% (approximately) of the population is homozygous wild type (normal), demonstrating high *TPMT* activity. There is also significant frequency variation in ethnic populations for low-activity *TPMT* allelic variants.

TPMT genetic variation presents a clinical challenge. Starting all patients at lower doses to ensure safety for a small number of deficient patients can result in disease progression for the majority, until doses are fully titrated. Thus, in 2011 and again in 2013, the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health's Pharmacogenomics Research Network recommended testing for *TPMT* activity or genotyping for allelic variants of the *TPMT* gene before beginning thiopurine therapy. Additionally, starting doses for thiopurine in nonmalignant conditions should include full doses for normal wild-type individuals, reduced doses (by 30%–70%) for heterozygotes, and substantially reduced or an alternative agent selected for homozygous deficient individuals. For malignancies, the CPIC also recommends high starting doses per the standards of anticancer treatment in clinical trial literature (e.g., 75 mg/m² of mercaptopurine) for wild-type individuals, lower-than-normal starting doses for heterozygotes, and at least a 10-fold reduction for homozygous deficient patients. During therapy, supplemental clinical tests assessing thioguanine nucleotide byproduct concentration can also be performed to monitor toxicity status.

LESS COMMON SINGLE GENE DISORDERS WITH PHARMACOGENETIC IMPLICATIONS

There are a variety of less common defects in single genes that are important in drug response and handling. Malignant hyperthermia (MH) and porphyria are described briefly in the following text because they are especially important in terms of impact or prevalence. Additionally, Table 6.3 outlines a selection of monogenic conditions, traits demonstrating altered responses to therapeutic drugs (e.g., metabolism, transport, uptake, etc.) that can result in drug toxicity, exaggerated drug responses, increased adverse effects, or treatment failure if an individual possesses one or both copies of the defective gene.

TABLE 6.3 Selected Disorders With Altered Response to Therapeutic Agents

| Condition or Disorder | Responsible Genes | Examples of Agents | Response or Effect |
|--|---|---|--|
| Acatlasia | <i>CAT</i> | Hydrogen peroxide | Tissue ulceration |
| Butyrylcholinesterase deficiency | <i>BCHE</i> | Succinylcholine | Apnea |
| C1 esterase inhibitor deficiency | <i>SERPING1</i> , <i>F12</i> | Oral contraceptives, hormone replacement therapy | Episodes of hereditary angioedema |
| Crigler–Najjar syndrome | <i>UGT1A1</i> | Salicylates, tetrahydrocortisone, menthol | Jaundice, drug toxicity |
| Dihydropyrimidine dehydrogenase deficiency | <i>DPYD</i> | 5-Fluouracil (5-FU) | Severe drug toxicity |
| Dubin–Johnson syndrome | <i>ABCC2</i> | Oral contraceptives | Jaundice |
| Familial dysautonomia | <i>IKBKAP</i> | Norepinephrine | Increased pressor response |
| Gilbert syndrome | <i>UGT1A1</i> | Oral contraceptives, alcohol, cholecystographic agents | Increased blood bilirubin, jaundice |
| Lesch–Nyhan syndrome | <i>HPRT1</i> | Allopurinol, 6-mercaptopurine azathioprine, azaguanine | Drug not metabolized to active form, resistance; formation of xanthine stones (allopurinol) |
| Osteogenesis imperfecta | <i>COL1A1</i> , <i>COL1A2</i> , <i>CRTAP</i> , <i>LEPRE1</i> | General anesthesia | Elevation of body temperature |
| PKU | <i>PAH</i> | Catecholamines | Increased pressor response |

Malignant Hyperthermia

Malignant hyperthermia (MH) is a potentially lethal, autosomal dominant inherited condition characterized by severe, and life-threatening, reactions to anesthetics. True incidence of the disorder is unknown since most MH individuals have no day-to-day symptoms. Predicted prevalence varies from 1 in 2,000 persons to 1 in 8,500 persons, with regional pockets of higher incidences from known gene mutations in north-central Wisconsin and some populations in North Carolina, Austria, France, and Quebec. The MH Association of the United States estimates the frequency of MH clinical episodes at 1:30,000 anesthetized pediatric and 1:100,000 anesthetized adult patients. The mortality rate formerly was 60% to 70%, but improved recognition and management of MH crisis events have significantly lowered it so that mortality from severe crisis is rare. In approximately 50% of MH cases, the mutation responsible is in the ryanodine receptor gene (*RYR1*), which provides instructions for making a large skeletal muscle calcium release channel. More than 300 *RYR1* variants have been identified; however, only 31 mutations have been confirmed in laboratory tests as functionally causing MH. Other loci are also implicated, including the gene encoding the $\alpha 1$ subunit of the voltage-gated dihydropyridine receptor. MH is also associated with several myopathies such as central core disease, myotonia congenita, Becker and Duchenne muscular dystrophy, and Evans myopathy. The model may be that of a major gene with the effect of modifying genes.

Inherited mutations confer susceptibility to an MH crisis when an individual is exposed to a volatile halogenated inhalational anesthetic (e.g., halothane, isoflurane, sevoflurane, enflurane, desflurane). Ether and cyclopropane are also triggers, but are not used today. MH can also occur after exposure to succinylcholine, a depolarizing neuromuscular blocking agent used before surgery. Under normal skeletal muscle conditions, an action potential is propagated to *RYR1* at the sarcoplasmic reticulum, which opens to allow release of calcium into the cytosol. Muscle contraction occurs as myofilaments are cross-linked, and terminates when calcium is taken back into the sarcoplasmic reticulum by an adenosine triphosphate (ATP)-dependent pump. In an MH crisis, the triggering anesthetic prolongs the opening of *RYR1* and an uncontrolled release of calcium causes ongoing muscle activation (muscle rigidity). With muscle

CASE EXAMPLE

The first recognized case of MH was published in 1960 by Denborough and Lovell, and is a classic case study. A 21-year-old male student with a fractured leg was brought to the hospital, where he turned out to be less concerned about the fracture than he was about having general anesthesia. Since 1922, 10 of his relatives had died as a direct consequence of having general anesthesia. Halothane was used to anesthetize the student, and an MH crisis occurred. His recovery, and the subsequent publication of the incident, led to awareness of the previously unrecognized problem.

cells on “constant activation,” oxygen consumption is drastically increased and leads to progressive hypoxia, lactic acidosis, hypercarbia, and hyperthermia. Calcium reuptake and sustained muscle activation depletes ATP stores, causing muscle rigidity and ultimately rhabdomyolysis (muscle breakdown) when cell membrane integrity fails. Potassium, creatine phosphokinase, and myoglobin are released into the circulation.

Early symptoms of MH include tachycardia, progressive muscle rigidity (especially in the masseters), tachypnea, hypercapnia, hypoxia, respiratory acidosis, and metabolic acidosis. If the offending trigger is not removed, symptoms progress to cardiac arrhythmias, rhabdomyolysis, a rapid rise in body temperature (42°C–44°C or 107.6°–111.2° F), the darkening of blood on the operative field, acute renal failure, hypotension, circulatory failure, and cardiac arrest. Myoglobinuria may appear 4 to 8 hours later. After the initial episode, there is a risk of acute recurrence hours later and of disseminated intravascular coagulation. Treatment includes removing the trigger agent and replacing it with an alternative anesthesia (opioids, sedatives, nondepolarizing neuromuscular blocking agents); administration of 100% oxygen via endotracheal tube; hyperventilation; administration of intravenous dantrolene (*RYRI* antagonist); and supporting the patient’s cardiovascular and metabolic needs.

Diagnostic testing for MH is recommended if a patient has a positive family history, experiences an MH crisis, and has nonspecific myopathy or an elevated serum creatine kinase. A traditional standard diagnostic MH test is the caffeine/halothane muscle contracture test (CHCT). Since the test requires 500 mg of fresh skeletal muscle tissue, is expensive, and is invasive, it is used only in certain circumstances. A favored approach is screening persons who had an MH episode for an *RYRI* mutation. If the DNA test identifies an *RYRI* mutation, first-degree relatives should also be tested. If no mutation is found, relatives may wish to have the CHCT test. If the CHCT test is negative, they are not MH susceptible. Unfortunately, both methods require specialized testing procedures and interpretation, so they are not suitable for population screening.

The person with MH usually appears well because the myopathy associated with it is subclinical until exposure to a volatile depolarizing anesthetic. Nevertheless, for some patients there may be mild ptosis, strabismus, muscle cramps, muscle weakness, recurrent dislocations, hernia, back problems such as kyphosis or scoliosis, short stature, unusual muscle bulk or other musculoskeletal complaints, or sometimes a cleft palate. A preponderance of heavily muscled young males have susceptibility to MH. Because the heart is a muscle, it may also be affected. Major stress, high environmental temperatures, strenuous exercise, or trauma may also induce MH in some cases. The combination of succinylcholine and the administration of halogenated inhalation anesthesia is especially provocative, although MH can occur after succinylcholine administration alone. Hyperkalemia, sudden general muscle rigidity, or isolated contraction of the jaw muscles can occur after succinylcholine administration, usually postinhalation induction. This presentation is frequent in children.

It is preferable to detect the MH-susceptible person before exposure to an inhalation anesthetic or succinylcholine so that, if possible, another type of agent can be used. Nurses and nurse anesthetists are in an ideal position to help minimize morbidity and mortality from MH. Nursing points are summarized in Box 6.4.

BOX 6.4**Nursing Pointers to Decrease MH Morbidity and Mortality**

- ▶ Before either surgical or obstetric anesthesia is given to any patient, a thorough personal and family history should be taken that includes the following questions: Have you ever had anesthesia? If so, what type? Have you ever had surgery? Was there any difficulty or problem with surgery or anesthesia? Dental surgery should be included, and specific complications such as fever, rigidity, dark urine, or any unexpected reactions should be questioned. The nurse should also ask about any musculoskeletal complaints or known muscular diseases in the family; any history of heat intolerance or fevers of unknown origin; or any unusual drug reaction (some MH patients have been reported to exhibit cramps or fever when taking alcohol, caffeine, or aspirin). The same questions should be asked of all family members, including any sudden or unexplained deaths. The nurse should review the patient's family history, going back two or three generations and including cousins. The presence of sudden death or fever while receiving anesthesia should be further investigated before the individual receives anesthesia. This information can also be collected before a student participates in strenuous school sports.
- ▶ Anesthesia for the MH-susceptible person can be planned before surgery. Planning may include prophylactic dantrolene administration, although this is somewhat controversial and can cause muscle weakness. Choice of anesthetic should exclude the use of triggering agents. Regional anesthesia is a safe choice for appropriate procedures. Special preparation of the anesthesia machine should be done to remove trace amounts of volatile agents. Alternative neuromuscular blockade agents such as pancuronium (Pavulon), atracurium (Tracrium), or mivacurium (Mivacron) should be used.
- ▶ A high index of suspicion should be maintained for an individual with any or all of the following characteristics, particularly young males with short stature, cryptorchidism, ptosis, low-set ears, lordosis, kyphosis, pes cavus, strabismus, weak serrati muscles, or lateral canthal angle dystopia (palpebral fissure slanting). Cases of MH have followed corrective surgery for strabismus.
- ▶ Abnormal electrocardiograms or unexplained cardiomyopathy in young patients may represent a person susceptible to MH and should be investigated.
- ▶ Any preoperative or preanesthetic physical examination should include a search for subclinical muscle weakness and the presence of any physical signs previously described, especially related to the muscular system.
- ▶ If succinylcholine (Anectine, Quelicin) is administered, the nurse or anesthesiologist should be alert for any abnormal reaction, such as failure to relax as expected, masseter stiffness, or muscle fasciculations that are greater than usual. Presence of an abnormal reaction should prompt consideration of postponing the surgical procedure pending further investigation and preparation. About half of children who develop this are later found to be MH susceptible.

(continued)

BOX 6.4**Nursing Pointers to Decrease MH Morbidity and Mortality**
(continued)

- ▶ During surgery, the temperature and pulse should be continually monitored. Unexplained tachycardia is often the first sign but may be preceded by a rising end-tidal CO₂ as shown by capnography. The development of any symptoms described earlier should mean the immediate institution of emergency procedures, anesthesia cessation, and the conclusion of surgery unless some other reason can account for a rapid rise in body temperature, such as excessive draping in a hot operating room (rare today).
- ▶ Any rapid rise in body temperature or myoglobinuria, as evidenced by dark red urine occurring in the first 24 hours after surgery, should be considered as possibly caused by MH and should be investigated further.
- ▶ Resuscitation equipment and drugs necessary for treating an MH crisis should be standard equipment in all operating rooms.
- ▶ Patients known to be susceptible to MH must be cautioned to avoid potent inhalation anesthetics such as those noted. None is considered completely safe. Depolarizing neuromuscular blockade agents such as succinylcholine and decamethonium should also be avoided.
- ▶ Information regarding MH should be put into written form for the susceptible person. One should be in professional language for his or her personal health care provider, and the other should be in the language that the patient and family can understand.
- ▶ Genetic counseling in MH includes discussion regarding the necessity for informing relatives of their potential risk and urging them to seek further evaluation. The written information mentioned above can be used for that purpose.
- ▶ Referral should be made to a support group such as the Malignant Hyperthermia Association of the United States.
- ▶ Patients who are susceptible to MH should be advised to wear medical alert identification with this information.

The Porphyrrias

The porphyrias are a group of inborn or acquired errors in the heme biosynthesis pathway leading to excessive porphyrins or their precursors. Porphyrins are the pigments that are present in hemoglobin, myoglobin, and cytochromes. Each type of porphyria is due to a specific enzyme defect in the heme biosynthetic pathway. Two major classifications are hepatic and erythropoietic (or erythroid). The more common hepatic group includes acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), ALA dehydratase deficiency porphyria (ADP, very rare), and porphyria cutanea tarda (PCT). The erythropoietic group includes erythropoietic protoporphyria (EPP), erythropoietic porphyria (EP), and X-linked

protoporphyrin (XLP). Others classify them as acute (characterized by acute attacks with neurological symptoms) and nonacute (characterized by photosensitivity), cutaneous or noncutaneous, or by type of inheritance; however, some of the porphyrias have overlapping features (e.g., some of the hepatic porphyrias have cutaneous lesions and erythropoietic symptoms). AIP, HCP, PCT, and VP are inherited in an autosomal dominant manner; EP and ADP are inherited in an autosomal recessive manner and XLP is X-linked. Symptoms vary according to porphyria type, and are shown in Table 6.4.

AIP is the most common genetic type, occurring in all races. It is an autosomal dominant disorder caused by deficiency of hydroxymethylbilane synthase. It is genetically heterogeneous with more than 375 mutations identified to date. It has an incidence of approximately 1 to 5 per 100,000 in the United States, but is more frequent in certain parts of Europe due to a founder effect. The prevalence of latent (presymptomatic) AIP is higher, and many cases never come to attention. Usually AIP is latent until puberty or early adulthood (with few cases presenting after menopause) and appears following an acute, life-threatening neurovisceral attack. These attacks may follow exposure to alcohol, certain drugs (including oral contraceptives), infection, fever, reduced caloric intake, or hormonal changes, especially menses and pregnancy. Clinical expression appears more frequent in females, perhaps because of contributing hormonal factors. In AIP, the most common symptoms during acute attacks are severe abdominal pain (which may be mistaken for acute surgical abdomen such as appendicitis), nausea, vomiting, constipation, abdominal distention with paralytic ileus, urinary retention, tachycardia, hypertension, neuropathy progressing to respiratory paralysis, convulsions, muscle weakness, sensory disturbances including the loss of pain and touch sensation, and mental symptoms including anxiety, insomnia, depression, disorientation, hallucinations, and paranoia. No skin manifestations are seen. Patients may become violent and are often treated with drugs such as narcotic analgesics that worsen the symptoms. The urine may become the color of port wine during an attack. Some cases of AIP present as respiratory failure. The acute attack can last several days to weeks and can become chronic at a low level. Early-onset chronic renal failure may occur, perhaps because of increased susceptibility to analgesic nephropathy, the effects of the porphyrins, or because of hypertension.

CASE EXAMPLE

Betty Brown was an 18-year-old college freshman admitted through the emergency department. She had been attending a fraternity party and had been drinking alcoholic beverages. She began having symptoms of nausea and vomiting and complained of abdominal pain. She was in the second day of her menstrual period. Betty had passed dark urine, which initially was attributed to either her menses or trauma. She was also confused and was agitated with visual hallucinations. Tachycardia, pallor, and sweating were present, and she was reported to have had one seizure. Among the considerations for diagnosis initially was acute psychosis. It was not until later the diagnosis of AIP was made. What are some of the teaching considerations for Betty Brown?

TABLE 6.4 Major Types of Porphyria

| Porphyria Type | Inheritance | Comments |
|------------------------------------|-------------------------|---|
| Acute intermittent porphyria (AIP) | AD | See text. |
| Erythropoietic porphyria | AR | Sometimes called congenital erythropoietic porphyria. Deficiency of uroporphyrinogen synthase (<i>UROS</i>). Age of onset varies, but usually cutaneous sensitivity begins in early infancy. Skin blisters on sun-exposed areas with thickened skin and hypertrichosis of face and extremities, hemolysis and hemolytic anemia, splenomegaly, reddish-brown discoloration of teeth. Can be milder adult form. >35 <i>UROS</i> mutations identified to date. |
| Hereditary coproporphyria (HCP) | AD | Hepatic type due to deficiency in coproporphyrinogen oxidase (<i>CPOX</i>). Abdominal pain; constipation prominent with acute attacks precipitated by certain drugs. May have cutaneous photosensitivity and psychiatric manifestations. >60 <i>CPOX</i> mutations identified to date. |
| Porphyria cutanea tarda (PCT) | AD, some cases acquired | The most common porphyria. Due to deficiency of uroporphyrinogen decarboxylase (<i>UROD</i>). May be sporadic or familial with an incidence of 1:10,000. Usually appears in adulthood but can appear earlier. Cutaneous findings are similar to VP. May show chronic liver disease. May be precipitated by alcohol, estrogens (including oral contraceptives), iron exposure, and polyhalogenated hydrocarbons. >105 <i>UROD</i> mutations identified to date. |
| Porphyria variegata (VP) | AD | Due to deficiency of protoporphyrinogen oxidase (<i>PPOX</i>). Particularly frequent among White South Africans, especially the Dutch Afrikaners at 1:300–400, and elsewhere is about 0.5:100,000. Acute neurovisceral attacks precipitated by essentially the same factors as AIP. Disease characteristics include adult-onset cutaneous blistering lesions (erosions, blisters, and bullae) of sun-exposed skin. Chronic findings include scarring, milia, skin thickening, areas of decreased or increased skin pigmentation, hypertrichosis. Effects are prominent on the face, ears, neck, and back of the hands. >165 <i>PPOX</i> mutations identified to date. |

After AIP is identified, a primary preventive effort is the avoidance of precipitating drugs, substances, and events. Drugs known to cause attacks in AIP include alcohol, antipyrine, barbiturates, carbamezepine, carbromal, chloramphenicol, chlorpropamide, danazol, dapsone, diphenylhydantoin, ergot preparations, estrogens, glutethimide, griseofulvin, halothane, meprobamate, methyldopa, novobiocin, oral contraceptives, phenylbutazone, phenytoin, progesterone, sulfonamides, theophylline, tolbutamide, and valproic acid. The nurse should question the prescription of these for a patient with known or suspected porphyria. Family members should be screened for the enzyme deficiency. Smoking, caloric restriction, and malnutrition may also precipitate attacks. Those with a deficiency should be warned to avoid triggering drugs and conditions, instructed on the association between their use and acute attacks, advised to wear a medical identification bracelet indicating that they have porphyria, and instructed to avoid alcohol ingestion, oral contraceptives, and low-calorie diets. If planning surgery, they need to review their preoperative preparations carefully with the surgeon and anesthetist, as both long periods of nothing by mouth (NPO) and certain drugs can be dangerous for porphyria patients.

Porphyria patients with skin manifestations should take care to avoid the sun and to use opaque sunscreens such as those with titanium dioxide. Topical antibiotics and beta carotene may also be useful. Patients may be seen in pre- or postoperative periods; during severe illness, infection, or fever; or during pregnancy. Support and encouragement are especially important in the care of these patients because the uniqueness of their symptoms may result in clinical mismanagement or misdiagnosis.

Genomic Approaches to Drug Therapy in Common Diseases

Genomic knowledge has contributed to improved understanding and treatment of multifactorial diseases, including cancer (diagnostics, individualized therapy, complications, metastasis) and heart disease. For cancer patients in particular, there is an added challenge in distinguishing the genetics of the individual from the genetics of the altered cancer cells (e.g., somatic vs. germline mutations) and treating patients based on the relevant mutation status. Greater understanding of diseases at the molecular level has yielded novel or tailored therapies for improved clinical management based on underlying pathogenetic mechanisms, an individual's susceptibility to certain drugs, or environmental influences known to modify a phenotype.

A classic case example of molecular medicine involves tyrosine kinase enzymes. Tyrosine kinases are enzymes involved with many cell functions, including cell signaling, cell growth and division. Tyrosine kinases are highly expressed in many solid tumors and correlate with disease progression, poor response to therapy, and poor survival rates. Several drugs act as inhibitors to tyrosine kinase signaling. The first tyrosine kinase inhibitor used in patients was imatinib (Gleevec) for treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML). In these cases, the *BCR-ABL* fusion oncogene [balanced translocation of (9;22) (q34;q11.2)] results in activated *BCR-ABL* tyrosine kinase, which is inhibited by imatinib. Imatinib is used for newly diagnosed Ph+ adults with CML and in pediatric patients experiencing recurring chronic disease after initial treatment.

Another example of targeted therapy in genomic medicine is the treatment of non-small cell lung cancers with epidermal growth factor receptor-activating mutations. In general, these mutations occur in patients without a previous smoking history, in females, and those of Asian heritage. *EGFR* activating mutations (e.g., exon 19 deletion; exon 21 Leu858Arg; and exon 18 Gly719X; X = termination codon, any amino acid) are sensitive to drug treatment with tyrosine kinase inhibitors (*EGFR*-TKIs) including erlotinib, afatinib (gefitinib discontinued in the United States in 2014), or the *EGFR* monoclonal antibody cetuximab. Approximately 10% of Western patients and 50% of Asian patients with nonsmall cell lung cancer have these mutations and experience an improved response rate and progression-free survival with *EGFR*-TKIs as first-line therapy. However, this benefit is not as marked for patients with wild-type tumors.

Asthma is a chronic complex and multifactorial condition with both genetic and environmental components affecting approximately 300 million globally. One of the primary treatments for bronchial asthma is inhaled beta agonist therapy (e.g., albuterol), which binds to β -2-adrenergic receptors in pulmonary smooth muscle to facilitate bronchodilation. The β -2-adrenergic receptor (*ADRB2*) gene is very small (2.6 kilobases) and has only one exon. However, *ADRB2* genetic variation has been shown to influence treatment response and is associated with disease severity (e.g., need for intubation and mechanical ventilation). The most frequent *ADRB2* gene polymorphism resulting in deleterious effects is the Arg16Gly (A>G; rs1042713) variant, which impacts the receptor's ligand binding site. Frequency of the Arg16 allele is approximately 39% to 42% in Caucasians and approximately 50% in African Americans. Homozygous (Arg16Arg) individuals are more susceptible to acute asthma exacerbations when using albuterol because of altered response to the drug.

Abacavir (Ziagen) is a nucleoside analog reverse transcriptase inhibitor used to treat HIV infection. It is associated with potentially fatal severe hypersensitivity reactions that occur in approximately 5% to 8% of patients. The strong association of the *HLA-B*5701* allele to severe adverse outcomes has led to recommended screening before prescribing abacavir to reduce risk of severe hypersensitivity.

Irinotecan (Camptosar) is a topoisomerase I inhibitor used to treat various types of solid tumors, but is used primarily in colorectal cancer. As a chemotherapy agent, irinotecan arrests cancer cell growth through inhibition of cell division. Neutropenia is a known adverse effect with fatal outcomes in approximately 7% of patients undergoing irinotecan treatment who present with fever. The enzyme uridine diphosphate (UDP) glucuronosyltransferase 1A1 (*UGT1A1*) catabolizes the active metabolite in irinotecan. More than 113 *UGT1A1* variant alleles have been described, in addition to several *UGT1A1* isoforms and *pseudogenes*. *UGT1A1* variants are denoted by the * symbol followed by a number. The *UGT1A1*28* variant allele (rs8175347) comprises seven thymine–adenine (TA) dinucleotide repeats in the *promoter*, as opposed to the six TA repeats for wild type (*UGT1A1*1*). The extra TA repeat results in decreased gene transcription by 70%, and lower functioning *UGT1A1* enzyme activity. *UGT1A1*28* homozygotes have significantly greater risk of developing grade 4 neutropenia when receiving the standard dose of irinotecan as compared to wild-type homozygous and heterozygous individuals. Several studies have shown that genotyping for the *28 allele

before irinotecan treatment is cost-effective in the treatment of colorectal cancer. *UGT1A1**28 occurs at high frequency in Caucasian (26%–31%) and African American (42%–56%) populations.

Warfarin (Coumadin) is an anticoagulant used in the prophylaxis and treatment of systemic thromboembolic disorders and complications (e.g., stroke, myocardial infarction, pulmonary embolism, etc.). Due to its narrow therapeutic index, warfarin presents many challenges to health care practitioners. These challenges include a need for routine phlebotomy to monitor patients' international normalized ratio (INR), difficulty in estimating required drug dose from physical criteria alone, and risk for serious bleeding events. Traditional dosing considerations include age, diet, gender, body weight, and use of other medications. From 2002 to 2005, clinical research identified that genetic variation in the cytochrome P450 *CYP2C9* enzyme and the vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) genes accounted for 35% to 50% of warfarin dosage variability differences in patients. A genetic test was developed and in 2010, the Food and Drug Administration (FDA) provided allelic dosing guidelines and issued a formal recommendation that health care providers perform *CYP2C9/VKORC1* genetic testing prior to prescribing warfarin for patients. Along with other dosing factors, these recommendations were incorporated into pharmacogenetic algorithms approved by the CPIC and should be used whenever possible (www.warfarindosing.org). A summary of the updated dosing information approved by the FDA used in these pharmacogenetic algorithms is given in Table 6.5. While genetic science is strong enough to warrant updated clinical guidelines for widespread implementation, acceptable *clinical utility* evidence remains elusive. For example, in 2009 the Centers for Medicare and Medicaid Services (CMS) concluded that, although warfarin genetic testing was predictive of INR, it did not impact bleeding outcomes and thrombotic sequelae much better than traditional clinical practices and was therefore not worth the

TABLE 6.5 Warfarin Dosing Guidelines for *CYP2C9* and *VKORC1* *

| Gene Variants | Warfarin Dosage in Milligrams per Day | | | | | |
|---------------|---------------------------------------|-------|-------|-------|-------|-------|
| <i>VKORC1</i> | <i>CYP2C9</i> | | | | | |
| -1639 G>A | *1/*1 | *1/*2 | *1/*3 | *2/*2 | *2/*3 | *3/*3 |
| GG | 5–7 | 5–7 | 3–4 | 3–4 | 3–4 | 0.5–2 |
| AG | 5–7 | 3–4 | 3–4 | 3–4 | 0.5–2 | 0.5–2 |
| AA | 3–4 | 3–4 | 0.5–2 | 0.5–2 | 0.5–2 | 0.5–2 |

*Updated warfarin (Coumadin) product label dosing for recommended daily doses (mg/day) to achieve therapeutic INR based on *VKORC1* and *CYP2C9* genotype, as approved by the U.S. Food and Drug Administration. *VKORC1* variant is rs9923231, and *CYP2C9* variants include: *1 = reference allele at all positions; *2 = C > T, rs1799853 (R144C); and *3 = A > C, at rs1057910 (I359L).

test cost (approximately \$300–\$500). CMS denied financial reimbursement for the *CYP2C9/VKORC1* genetic test but is willing to re-evaluate the issue if acceptable *clinical utility* and cost-effectiveness evidence can be demonstrated.

This chapter has described how genetic/genomic technologies and knowledge impact medication usage. As a result, FDA presently evaluates pharmacogenomic information in manufacturer drug labels, issues warnings about how individual variation can impact drug responses, and is a key contributor in the debate concerning pharmacogenomic clinical utility evidence. Table 6.6 includes some of the FDA-approved drugs that include pharmacogenomics information in their labeling to highlight these concepts. A comprehensive and updated list can be found at the FDA website.

TABLE 6.6 Selected FDA-Approved Drugs With Pharmacogenomic Label Information

| Drug | Therapeutic Area | Referenced Subgroup | Labeling Sections |
|----------------|-------------------|---|--|
| Abacavir | Infectious Dx | HLA-B*5701 allele carriers | Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information |
| Carvedilol | Cardiology | CYP2D6 Poor metabolizers | Drug Interactions, Clinical Pharmacology |
| Imatinib | Oncology | c-KIT D816V mutation negative | Indications and Usage, Dosage and Administration, Clinical Pharmacology |
| Metoclopramide | Gastroenterology | NADH cytochrome b5 reductase deficient | Precautions |
| Sodium nitrite | Antidotal Therapy | G6PD deficient | Warning and Precautions |
| Tamoxifen | Oncology | Factor V Leiden carriers, prothrombin mutation G20210A positive | Warnings |

ETHICAL, LEGAL, AND SOCIAL ISSUES RELATED TO PHARMACOGENOMICS

As the field of pharmacogenomics evolves, various ethical concerns are presented. This includes the need for patient confidentiality, the potential for misuse of genetic information (e.g., denial of insurance coverage, application of unfair insurance rates), and stigmatization within familial and community groups. In the era of pharmacogenomics, an individual's genotype could both identify a disease and the required pharmaceutical treatment to a number of parties involved in providing patient care (e.g., health care practitioners, support personnel, employers, health insurers, etc.). Consequently, the Genetic Information Nondiscrimination Act (GINA) was signed into law in May 2008, which prevents health insurance companies and employers from discriminating against individuals based on their genetic makeup. This includes using genetic information to make decisions on insurance eligibility, coverage, premiums, or underwriting (e.g., if a gene mutation or variant results in specific need for expensive medications, treatments).

SUMMARY

Pharmacogenetics and pharmacogenomics are rapidly changing sciences and their importance is increasingly recognized. Entire peer-reviewed research journals such as *Pharmacogenomics*, *American Journal of Pharmacogenomics*, *Pharmacogenomics Journal*, and *Current Pharmacogenomics* are devoted to exploring these fields. For the most part, persons taking drugs with broad therapeutic ranges and safety profiles do not show significant clinical consequences even if they are poor metabolizers. But for drugs with a narrow therapeutic index, such as many antidepressants, isoniazid, or warfarin, genetic polymorphisms become clinically important. In general, the usual effective drug dose given to any individual patient may be effective, ineffective, or even toxic depending on the patient's genetic makeup.

Eventually, the field of pharmacogenomics aims to determine which treatment should be used, given a patient's genetic profile and its specific disease features. This will allow drug therapy to be uniquely tailored to patient characteristics, yielding maximum effectiveness (e.g., determine the best dosage, withhold ineffective drugs, limit side effects). It is also hoped that with increased individualization, fewer medications will be needed and medication adherence can be enhanced.

Until scientific research can be fully translated into clinical care, there are clinical translation resources available to assist health care providers. The Pharmacogenomics Knowledgebase (PharmGKB), funded by the U.S. Department of Health and Human Services and supported by the National Institute of General Medical Sciences of the National Institutes of Health, curates and synthesizes current science on how genetic variation impacts drug responses. For example, there are searchable lists of well-known pharmacogenetic associations, clinical pharmacogenetic summaries, drug dosing guidelines, a general list of commercially available pharmacogenetic tests (noncomprehensive, not endorsed by federal government), and

pharmacogenetic drug label information. Most useful for clinicians, are the pharmacogenetic-based clinical drug dosing guidelines developed by the CPIC of the National Institutes of Health's Pharmacogenomics Research Network. Established in 2009, CPIC expert members use a consensus process to develop clinical guidelines for health care practitioners to translate genetic test information into actionable prescribing decisions. CPIC comprises more than 100 experts in the basic and clinical sciences from 58 institutions who review, grade, and synthesize pharmacogenetic science using standardized processes before developing a final clinical recommendation. CPIC results and guidelines are published in peer-reviewed journals and on the PharmGKB website; as of November 2014 there are 28 formal CPIC gene–drug dosing clinical guidelines. Additional approved expert consensus pharmacogenetic documents and guidelines from other organizations (e.g., other countries) are also curated with CPIC documents on the PharmGKB site.

To complement the PharmGKB site's drug dosing information, a useful resource is NCBI's Genetic Test Registry. This is a registry where submitters provide information to NCBI for 24,000 tests on 5,000 conditions and 3,600 genes. Clinicians can issue queries for genetic tests, medical conditions or phenotypes, genes, and labs.

A significant challenge in developing pharmacogenetic/pharmacogenomics clinical guidelines is synthesizing and reconciling numerous disparate gene–drug association reports. Not all studies use the same disease grading criteria, outcome measures, ethnic populations, or sample sizes. An important concern for expansion of pharmacogenetics and pharmacogenomics is that testing of new therapeutic agents must be replicated in sizeable populations comprising different ethnic backgrounds, since metabolism, effectiveness, and side effect data cannot be wholly transferred from one population to another. While polymorphisms and genetic variability concepts are being incorporated into drug development and efficacy trials, there is a long incubation period in acquiring this knowledge. Statistical significance in large study cohorts often translates to small effects for individual patients. Thus, researchers in these fields are faced with costly and lengthy initiatives when establishing widespread drug dosing recommendations based on pharmacogenetics and pharmacogenomics. This is the reason that, although there are thousands of gene/drug associations reported in the research literature, there are much fewer evidence-based clinical recommendation statements for widespread use. Because nurses observe that different individuals receiving the same dose of the same drug exhibit different responses and side effects, they are in an excellent position to contribute to and lead this type of research. Such studies will add to the knowledge of genetic diversity on metabolic functions that have both theoretical interest and clinical importance.

KEY POINTS AND QUESTIONS FOR DISCUSSION

- ▶ Genetic factors play important roles in response to medications.
- ▶ Genetic knowledge is being used to design drug therapy treatments based on specific molecular defects, and even on designing drugs specific to genotype.
- ▶ What is the difference between pharmacogenetics and pharmacogenomics?

- ▶ When should clinicians consider and incorporate pharmacogenetic and pharmacogenomic implications in their practice?
- ▶ What are the patient confidentiality considerations related to pharmacogenetics and pharmacogenomics?
- ▶ How can clinicians access pharmacogenetic and pharmacogenomics drug safety and dosing information to guide patient care?

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RESOURCES

Food and Drug Administration. <http://www.fda.gov/>

Gene Reviews. <http://www.ncbi.nlm.nih.gov/books/NBK11116/>

Genetics Home Reference. <http://ghr.nlm.nih.gov/>

National Human Genome Research Institute. <https://www.genome.gov/>

Online Mendelian Inheritance in Man. <http://omim.org/>

The Pharmacogenomics Knowledge Base (PharmGKB). <https://www.pharmgkb.org/>

CHAPTER 7

Assessing Patients With a Genetic “Eye”: Family History and Physical Assessment

Kendra L. Schaa

The initial recognition of the need for a genetics referral may arise when a nurse suspects a genetic contribution to disease because of personal or family medical history and/or findings from a physical assessment. For example, the nurse may notice very high low-density lipoprotein (LDL) cholesterol levels in a 34-year-old patient. Upon collection of a three-generation family history, the nurse discovers that the patient’s mother passed away in her early 40s from a heart attack. During physical examination, tendon xanthomas are noted in the patient (caused by cholesterol buildup). Discussion of these findings with the health care team leads to a diagnosis of familial hypercholesterolemia, the leading cause of inherited high cholesterol and an autosomal dominant genetic condition. This diagnosis has important implications for the care of other at-risk family members.

FAMILY HISTORY

Family history is a valuable and cost-effective tool that is often underutilized in clinical practice. Gathering an accurate three-generation family medical history can be critical to the identification of an individual and/or family member(s) at risk for a genetic contribution to disease and can be helpful in developing a personalized management and treatment plan for a patient. A family history can be collected through a face-to-face interview or over the telephone. Information provided by the patient is then used to draw a pedigree, a visual representation of the family medical history. It is important to recognize that gathering this information takes time and depends on the size and health of a patient’s family. However, once collected, family history can be easily updated during future clinic visits and used by the entire health care team to assess the patient’s risk for disease. My Family Health Portrait, an online tool from the Surgeon General, guides individuals in the collection and organization of personal and family health history (<https://familyhistory.hhs.gov>). This tool includes a printing feature to facilitate sharing this information during a

patient's health care visit. Several other tools are available for collecting family history and can be found on the following websites: the National Coalition for Health Professional Education in Genetics (www.nchpeg.org) and the American Medical Association (www.ama-assn.org).

Collecting Family History

Family history should span at least three generations of relatives, including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and cousins. Specific questions to ask while collecting family history depend on multiple factors, including the reason for the clinic visit, previously collected or observed personal or family medical history information, laboratory data or physical assessment, and a patient's answers to previous questions. Collecting personal and family history can be a sensitive subject and necessitates asking questions in a culturally and socially sensitive manner. It is beneficial to explain to the patient why collecting this information is important (i.e., it helps to inform a more comprehensive picture of the patient's health and facilitates the identification of risk factors).

The following is a list of essential information to collect as part of the personal and family history. This may require more than one visit to collect or may require that the patient speak with other family members to verify or collect missing information. When the patient is a child, each parent should ideally provide information about his or her respective side of the family.

Personal Medical History

- ▶ Age
- ▶ Medical diagnoses (current and previous; age at diagnosis)
- ▶ Medical conditions and age of onset, even if not formally diagnosed
- ▶ Medications (current and previous; adverse reactions)
- ▶ Allergies (e.g., food and medications)
- ▶ Occupation (current and previous—may indicate environmental exposures)
- ▶ Exposure to biological, chemical, or radiation hazards (at home, work, or during military service)
- ▶ Lifestyle practices that may affect health
- ▶ Substance use (including tobacco, alcohol, and recreational drugs—current and previous)

Family History

- ▶ Age of each family member (for deceased family members, record age and cause of death)
- ▶ Racial/ethnic background of both maternal and paternal lineages, including Jewish ancestry (many genetic disorders are more frequent among certain groups)

- ▶ Medical diagnoses (current and previous; age at diagnosis)
- ▶ Medical conditions and age of onset, even if not formally diagnosed (including developmental delay or learning disabilities)
- ▶ Similar or same symptoms, conditions, or diagnoses among family members
- ▶ Known health conditions that run in the family (e.g., depression and diabetes)
- ▶ Presence of birth defects or familial traits
- ▶ Known environmental exposures in childhood or adulthood
- ▶ Infertility, multiple miscarriages (i.e., three or more), stillbirths, or infant deaths
- ▶ Consanguineous relationships (e.g., first-cousin marriage)

More specific questions will depend on the responses received during the interview and/or observations from the physical examination. When possible, all information should be confirmed by medical records, laboratory data, photographs, autopsy reports, and other objective methods. Changes in personal/family medical history and lifestyle choices should be expected. Therefore, periodic updating of this information is critical, as it can impact a patient’s risk assessment.

Identifying relatives in a patient’s family with the same or similar diagnosis or medical condition does not necessarily mean that the patient will develop that condition. Similarly, obtaining a negative family history does not rule out an underlying genetic condition or genetic component to a patient’s disease. Furthermore, a negative family history does not necessarily suggest that other family members are not at increased risk to develop the disease. There are many reasons that can explain a negative family history and may warrant additional questions or testing, including:

- ▶ The disease is caused by a new (de novo) genetic mutation.
- ▶ The patient is not biologically related to other family members (e.g., adopted, conceived with a donor egg or sperm, nonpaternity).
- ▶ The disease is caused by autosomal recessive inheritance.
- ▶ The family size is very small and, therefore, not informative.
- ▶ The disease shows reduced penetrance.
- ▶ The disease shows variable expressivity and minor signs and symptoms in other family members are missed.
- ▶ A chromosome abnormality is present.
- ▶ Gonadal mosaicism is present (see Chapter 4).
- ▶ Uniparental disomy is present (see Chapter 4).
- ▶ The person providing the family history lacks complete knowledge of other family members’ health.
- ▶ The interviewer fails to ask critical questions.
- ▶ The patient deliberately withholds information.

Family history is discussed further in this chapter in the “Pedigrees” section.

Environmental and Occupational Histories

Many common genetic conditions result from complex interactions between genetic and environmental factors. These multifactorial conditions often cluster in families, given that family members share a fraction of their genes along with a similar environment. Therefore, it is critical to collect information about potential environmental exposures to help inform a patient's risk assessment. Health care professionals should become familiar about toxic environmental agents that are common in their specific geographic location. They should recognize that a number of environmental factors that cause adverse health outcomes disproportionately affect vulnerable and underserved populations. These populations are more likely to be exposed to higher levels of air pollution and more toxic indoor agents, such as lead and pesticides.

Environmental exposures can result from an individual's current or past occupations, residence location, volunteer activities (e.g., firefighting), recreational activities and hobbies, and, for children, anyplace where they spend a considerable amount of time (e.g., day care and a grandparent's home). Information to be obtained regarding the place of residence should include location, composition of the household, source of drinking water or food (especially in rural areas), the proximity of any factories, knowledge of any chemical spills or waste exposure, noticeable air pollution, type of insulation and heating, insecticide or pesticide exposure, and other data as relevant. Sometimes, the job itself can alert the practitioner to possibilities of toxic exposure; for example, military service can be associated with exposure to Agent Orange. Information should be gathered for both the patient and the other individuals living in the household. For example, the individual doing the laundry may be exposed to fibers on the clothing of the worker. Inquire about the kinds of materials that the person may be exposed to, such as radiation, chemicals, fumes, dust, fibers, tobacco, gas, temperature extremes, microorganisms, and vibrations. If the person is unsure about specific substances, it may be necessary to collect this information from the employer, depending on how critical the information is to the problem at hand. Patients should also be asked about contact with domestic animals (e.g., cats and dogs) and farm animals on the job or at home. Any affirmative answers about exposure should be followed up to determine the duration of exposure/employment, the frequency, and the last time the person was exposed.

Toxic environmental agents, including cigarette smoke exposure, are known to have a harmful effect on reproductive health across the life course. Patients with identified toxic exposures should be asked whether there is a history of infertility, miscarriages, stillbirths, or abnormalities in reproductive function (e.g., puberty and menopause). Those with children should be asked whether there is a history of birth defects, developmental or intellectual disabilities, or childhood cancer. If a specific health concern appears to be job or environmentally related, the patient should be asked if anyone at work or with exposure to the same environment (e.g., neighborhood) has had similar health problems (see Chapter 12).

If an environmental exposure is identified, educating the patient on the possible consequences of such exposure and methods to reduce exposure is critical. For

example, a pregnant woman who works at a pet boarding kennel can be advised on safe methods for disposing excreta and handling animals to minimize her own exposure without jeopardizing her employment.

Medication and Drug Use

It is helpful to ask the patient to bring a list of current medications to each clinical visit. Teaching and encouraging patients to keep an up-to-date list of medications will facilitate collection of this information. Patients should be asked about prescription drugs, over-the-counter medications, and home remedies. If the health care visit is after the birth of an affected child, document any medications taken a few months before pregnancy in both the male and female partner and during the pregnancy in the female. There are a number of drugs known to cause malformations in the fetus if taken during pregnancy, including many antiepileptic drugs and vitamin A analogues (e.g., Accutane). See Chapter 8 for more information on medications and drugs in pregnancy. Many individuals may overlook items that they do not consider to be drugs or medications. Therefore, asking broad questions about how a patient treats common ailments, such as headaches or stomachaches, may help to elicit this information. Use of recreational drugs, caffeine, alcohol, and tobacco should be explored in a sensitive manner. For any drug or medication taken, the dose, frequency of use, reason for use, duration, and approximate dates should be obtained.

The patient should be asked about any personal or family history of drug allergies, adverse drug reactions, or if she or he has received specific instructions to avoid certain medications or foods from a health care professional. In some cases, this information may suggest an underlying genetic variant in the patient that is affecting drug response and can often be confirmed by a pharmacogenetic test. A growing number of Food and Drug Administration (FDA) approved drugs have labeling that includes pharmacogenomic information, which can be used to optimize drug dosage and prevent adverse and life-threatening drug reactions in a patient or family member.

Reproductive History

There is some overlap between collecting the family history and collecting a complete reproductive history. All pregnancies, including miscarriages, abortions, stillbirths, infant deaths, and offspring, should be noted as part of the family history. Discussing pregnancy loss and infertility is particularly emotional for many individuals; therefore, it is important to acknowledge the sensitive nature of the information being requested. In the case of an affected infant or child, the following information should be obtained, if possible.

- ▶ Age of both parents at each pregnancy
- ▶ Exposure to radiation, medications, drugs, alcohol, and tobacco, including gestation during time of exposure
- ▶ Vaginal bleeding or discharge during the pregnancy
- ▶ Occurrence of any accidents, illnesses, fevers, rashes, or other health problems during pregnancy

- ▶ Medical history of chronic disease, infections, or sexually transmitted disease
- ▶ Toxic exposure from work, hobbies, or travel
- ▶ Medical treatments during pregnancy
- ▶ Nutrition and food habits, including pica
- ▶ Maternal weight gain
- ▶ Mode of delivery
- ▶ Presence of blood group incompatibilities (see Chapters 3 and 8)
- ▶ Gestational timing (i.e., preterm or term)
- ▶ Paternity for each pregnancy
- ▶ Information about fetal activity, uterine size, and details of labor and delivery (e.g., the amount of amniotic fluid present, length of labor, type of anesthetic and perinatal medications, if any)
- ▶ Apgar score, birth weight, and head circumference
- ▶ Postnatal growth and development
- ▶ Use of fertility medications or assisted reproductive technologies (ARTs)

One primary reason for collecting this information is to help inform whether a condition, such as intellectual disability, may have been caused by environmental factors or whether an underlying genetic cause is more likely. Keep in mind that it is always worth asking the patient whether there is any other relevant information worth sharing that might be important to the presenting issue. Confirmation of relevant data through records may be necessary for accuracy.

If the woman is currently pregnant, the date of the last menstrual period and the expected date of delivery should be obtained. Some clinics have developed a short questionnaire that is a screening tool for potential genetic risks to the pregnancy. These questionnaires are usually set up in a simple yes/no format and are best administered in the native language of the patient. When a patient answers affirmatively to any of the specific questions, the chart is flagged for a consultation with a geneticist or a genetic counselor. A genetics consultation may need to happen immediately, depending on how far along the woman is in her pregnancy, given that information discussed during such a consultation may influence the direction of the pregnancy. Information that can be ascertained on such screening tools, which typically warrants a genetics consultation, includes:

- ▶ Maternal age of 35 or older at time of delivery
- ▶ Specific ethnic groups with higher risk of known genetic diseases
- ▶ History of three or more miscarriages
- ▶ History of any stillbirths or infant deaths
- ▶ History of a child or family member with a birth defect or genetic disorder
- ▶ Known prenatal diagnosis or abnormal ultrasound findings

- ▶ Drug or alcohol use during pregnancy
- ▶ Maternal disease, such as a seizure disorder
- ▶ Personal or family history of blood disorders (e.g., abnormal clotting and sickle cell anemia)

Not infrequently, taking a reproductive history follows the birth of an affected child, recurrent pregnancy loss, or difficulty conceiving. Thus, retrospective information is likely to be influenced by feelings of guilt (real or imagined) as well as other emotions.

PEDIGREES

A pedigree is a graphic representation of the family history developed using a standard set of symbols described in Figures 7.1 through 7.3. Collecting and translating personal and family medical history into a pedigree makes it possible for the health care team to understand the patient from a holistic perspective and provides a permanent record of the genetic information in a family. Additional benefits of a pictorial representation of family history include:

- ▶ The visualization of relationships between affected individuals in the family
- ▶ The elucidation of the inheritance pattern of a disease or health problem in a family
- ▶ The identification of family members who may benefit from a genetics consultation
- ▶ Easier ability for other health care professionals to interpret family history and collect or update missing information
- ▶ The brief notation of other data relevant to effective counseling, such as family interactions

Computer software programs are available specifically for pedigree construction. Many printable templates exist as well and hand-drawn pedigrees are also acceptable. All methods require that the nurse not only understand the purpose of a pedigree but can successfully construct one from a family history. It is helpful to document the family names or initials on the pedigree, along with the date the pedigree was collected and the name of the individual recording the information.

Once the pedigree is drawn, characteristic findings of common inheritance patterns should be noted, including male-to-male transmission, maternal pattern of inheritance, ratio of affected males to affected females, or other features of the typical inheritance patterns as discussed in Chapter 4. In some cases, the mode of inheritance cannot be determined from the pedigree due to small family size, reduced penetrance or variable expressivity of the disease, lack of accurate information, presence of a new genetic mutation in the affected individual, or environmental/gene interactions.

































| | Male | Female | Gender Not Specified | Comments |
|---|--|--|--|--|
| 1. Individual |  b. 1925 |  30 y |  4 mo | Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol. |
| 2. Affected individual |  |  |  | Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected. |
| |  |  | | With ≥2 conditions, the individual's symbol can be partitioned accordingly, with each segment shaded with a different fill and defined in legend |
| 3. Multiple individuals, number known |  |  |  | Number of siblings written inside symbol. (Affected individuals should not be grouped). |
| 4. Multiple individuals, number unknown or unstated |  |  |  | "n" used in place of "?" |
| 5. Deceased individual |  d. 35 |  d. 4 mo |  d. 60's | Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+). |
| 6. Consultand |  |  | | Individual(s) seeking genetic counseling/testing. |
| 7. Proband |  P |  P | | An affected family member coming to medical attention independent of other family members. |
| 8. Stillbirth (SB) |  SB 28 wk |  SB 30 wk |  SB 34 wk | Include gestational age and karyotype, if known. |
| 9. Pregnancy (P) |  P LMP: 7/1/2007 47,XY,+21 |  P 20 wk 46,XX |  P | Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend. |
| Pregnancies Not Carried to Term | | Affected | Unaffected | |
| 10. Spontaneous abortion (SAB) | |  17 wks female cystic hygroma |  < 10 wks | If gestational age/gender known, write below symbol. Key/legend used to define shading. |
| 11. Termination of pregnancy (TOP) | |  18 wks 47,XY,+18 |  | Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency. |
| 12. Ectopic pregnancy (ECT) | | |  ECT | Write ECT below symbol. |

FIGURE 7.1. Common pedigree symbols.
Source: Bennett, French, Resta, and Doyle (2008).

DEVELOPMENTAL AND PHYSICAL ASSESSMENT

Information from the family history can suggest specific findings to look for during a physical assessment or in lab results. Clinical clues that suggest the need for further evaluation or testing depend on the individual's age. The appearance of certain features may be considered normal at a certain age but deviant at another. High cholesterol levels in an overweight 60-year-old may be unremarkable; however, high levels in a young adult may suggest the possibility of familial hypercholesterolemia and should be investigated. A newborn girl who has lymphedema may require a karyotype because of the possibility of Turner syndrome (see Chapter 9); however, the lymphedema rapidly disappears, and the next time of suspicion may be when menstruation and the development of secondary sex characteristics are delayed.

| | | | | | | | | | | |
|---|--|---|----------------------------|-------------|------------|--|--|--|--|---|
| 1. Definitions | | Comments | | | | | | | | |
| | | <p>If possible, male partner should be to left of female partner on relationship line.</p> <p>Siblings should be listed from left to right in birth order (oldest to youngest).</p> | | | | | | | | |
| 2. Relationship line (horizontal) | | | | | | | | | | |
| a. Relationships | | A break in a relationship line indicates the relationship no longer exists. Multiple previous partners do not need to be shown if they do not affect genetic assessment. | | | | | | | | |
| b. Consanguinity | | If degree of relationship is not obvious from pedigree, it should be stated (e.g., third cousins) above relationship line. | | | | | | | | |
| 3. Line of descent (vertical or diagonal) | | | | | | | | | | |
| a. Genetic | | Biologic parents shown. | | | | | | | | |
| – Multiple gestation | <table border="1"> <tr> <td>Monozygotic</td> <td>Dizygotic</td> <td>Unknown</td> <td>Trizygotic</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </table> | Monozygotic | Dizygotic | Unknown | Trizygotic | | | | | The horizontal line indicating monozygosity is placed between the individual's line and not between each symbol. An asterisk (*) can be used if zygoty is proven. |
| Monozygotic | Dizygotic | Unknown | Trizygotic | | | | | | | |
| | | | | | | | | | | |
| – Family history not available/known for individual | | | | | | | | | | |
| – No children by choice or reason unknown | | vasectomy or tubal | Indicate reason, if known. | | | | | | | |
| – Infertility | | azoospermia or endometriosis | Indicate reason, if known. | | | | | | | |
| b. Adoption | <table border="1"> <tr> <td>in</td> <td>out</td> <td>by relative</td> </tr> <tr> <td></td> <td></td> <td></td> </tr> </table> | in | out | by relative | | | | Brackets used for all adoptions. Adoptive and biological parents denoted by dashed and solid lines of descent, respectively. | | |
| in | out | by relative | | | | | | | | |
| | | | | | | | | | | |

FIGURE 7.2. Pedigree line definitions.

Source: Bennett, French, Resta, and Doyle (2008).

Likewise, Wilson disease (an autosomal recessive disorder of copper metabolism) should be considered in the child or adolescent who experiences acute liver failure. In an infant or child, certain odors are associated with specific biochemical abnormalities (see Chapter 9).

Physical examinations of children and adolescents can provide an opportunity for detection of disorders making their appearance around puberty and can provide a forum for preconception counseling for adolescent girls. Sexual development in relation to age may be assessed by use of the Tanner criteria. For girls or women with significant menorrhagia, screening is recommended for von Willebrand disease (a hereditary

| Instructions: | | |
|--|--|---|
| <ul style="list-style-type: none"> —D represents egg or sperm donor —S represents surrogate (gestational carrier) —If the woman is both the ovum donor and a surrogate, in the interest of genetic assessment, she will only be referred to as a donor (e.g., 4 and 5); the pregnancy symbol and its line of descent are positioned below the woman who is carrying the pregnancy —Available family history should be noted on the gamete donor and/or gestational carrier | | |
| Possible Reproductive Scenarios | | Comments |
| 1. Sperm donor | | Couple in which woman is carrying pregnancy using donor sperm. No relationship line is shown between the woman carrying the pregnancy and the sperm donor. |
| 2. Ovum donor | | Couple in which woman is carrying pregnancy using a donor egg and partner's sperm. The line of descent from the birth mother is solid because there is a biologic relationship that may affect the fetus (e.g., teratogens). |
| 3. Surrogate only | | Couple whose gametes are used to impregnate a woman (surrogate) who carries the pregnancy. The line of descent from the surrogate is solid because there is a biological relationship that may affect the fetus (e.g., teratogens). |
| 4. Surrogate ovum donor | | Couple in which male partner's sperm is used to inseminate (a) an unrelated woman or (b) a sister who is carrying the pregnancy for the couple. |
| 5. Planned adoption | | Couple contracts with a woman to carry a pregnancy using ovum of the woman carrying the pregnancy and donor sperm. |

FIGURE 7.3. Assisted reproductive technology symbols and definitions.

Source: Bennett, French, Resta, and Doyle (2008).

bleeding disorder characterized by deficiency of von Willebrand factor needed for optimum platelet adhesiveness). It is important to screen before initiation of oral contraceptive therapy, since this may mask diagnosis. Sometimes, physical examination takes place in a sports physical setting, where screening is rushed and there is pressure to approve a child for sports. It is important, however, to assess the child's personal and family medical history for heritable connective tissue disorders, such as Marfan syndrome (see Chapter 10), and for cardiomyopathies or other cardiac abnormalities.

Measurements

Measurements should be taken to determine whether a specific anomaly found during the physical examination is truly abnormal. Normal measurement charts are widely available for reference. The purpose of this section is to identify measures and observations that are of particular importance when making a diagnosis of a genetic syndrome.

The extent to which the nurse uses measurements depends on the area of practice. For the normal infant and child, standard measurements include height, weight, and head circumference. Other measurements, such as arm span, chest circumference, internipple distance, ear measurements, and craniofacial measures, should only be taken when indicated and by a trained clinician. Craniofacial examination is often evaluated by cephalometrics (three-dimensional craniofacial surface imaging from CT scans, MRI, and computer-driven techniques).

Any unusual physical findings should be compared to other family members to determine their relevance. The child's birth weight and maturity should always be considered when evaluating unusual results. The occurrence of two and, especially, three minor malformations in an otherwise healthy infant should alert the practitioner to search carefully for one or more major anomalies and consider chromosomal analysis (see Chapter 5). Keep in mind that major anomalies are not always visible (e.g., congenital heart defect).

Isolated measurements should be taken into consideration with other factors. One abnormal measurement should not cause immediate concern, but serial measurements should be kept so that growth velocity can be examined. When possible, sex and race/ethnic-specific growth charts should be used. If a growth disorder is present, determining the specific type is important for diagnosis, treatment, and genetic counseling. Failure to thrive (FTT) is a relatively common consultation in pediatric clinics. Failure to thrive may be organic (medical) or nonorganic (social and environmental). Determining the underlying cause of FTT is critical as it can be a feature of various inherited metabolic disorders that, in turn, may necessitate immediate, life-saving dietary restrictions. For all FTT cases, it is important to inquire about pregnancy history, feeding history, gastrointestinal symptoms, and food intolerance. Delayed or precocious puberty can be assessed through criteria for pubertal stage attainment. Hypogonadism and delayed puberty are frequent components of many genetic disorders and must be fully investigated. Other growth disorders should be noted. Macrosomia can be seen in the offspring of diabetic mothers. Truncal obesity, associated with hypotonia and FTT, is a feature of Prader–Willi syndrome (see Chapter 9).

Head circumference reflects brain development and should be measured over time. Given that brain growth completes around the age of 2, serial head circumference measurements should be obtained during each visit from infancy until 36 months. When measuring head circumference, a nonstretchable tape measure should be used. The child's head must be still. The tape should measure the greatest circumference, starting at the forehead between the eyebrows and hairline, then passing to the rear of the head over the occipital prominence and coming around to the forehead for the final measurement. The average head circumference is approximately 35 cm in a full-term infant but can range from 32 to 38 cm. There is approximately a 5-cm increase in the first 4 months of life and an increase of 5 cm more by the first year. Head size should always be evaluated within the context of other factors, including body size, weight, chest circumference, and parental head circumference. Variation in head size can be caused by familial characteristics and racial/ethnic group differences, as well as by other reasons. An unusually small (microcephaly) or large (macrocephaly) head

size warrants further investigation due to the association with genetic syndromes. Microcephaly is defined as approximately less than the second percentile. Conversely, macrocephaly is defined as approximately greater than the 98th percentile. Microcephaly can be caused by craniosynostosis, fetal alcohol syndrome, underlying structural abnormalities (diagnosed by MRI), congenital infection, metabolic disease, and chromosomal deletions/microdeletions. Macrocephaly is associated with hydrocephalus and other structural abnormalities of the brain, metabolic disease, overgrowth syndromes, Fragile X syndrome, and chromosomal abnormalities.

Appraisal and Assessment

When possible, unusual features discovered during the physical examination should be photographed for permanent documentation, to allow for interprofessional consultation and to permit later study and comparison. Photographs with the child's parents may be helpful in assessing familial contributions to facial features. Attention should be given to any parental concerns about delayed development or unusual behavior in an infant or child. For example, children with xeroderma pigmentosum (an autosomal recessive disorder with extreme sensitivity to sunlight that leads to malignancies) often cry on sun exposure, an event that occurs before any other signs and symptoms. Parents' recall of developmental milestones, except for walking, may not be reliable. Therefore, providing the parents with a book for recording important developmental milestones may be helpful. Developmental delay is a feature of many genetic conditions and an accurate assessment of the child's delay can be helpful in determining a list of differential diagnoses.

Clinical findings seen in some genetic conditions are organized by region of the body in Table 7.1. Note that this is not an all-inclusive list. Indications suggestive of specific conditions and those that necessitate a genetics evaluation are also given throughout the book and at the end of this chapter. The frequency of syndromes associated with blindness, deafness, failure to thrive, and developmental disability precludes discussion here but mandates full evaluation.

Head, Neck, and Face

Assessment of the head and face can be challenging, given the wide variation in normal measurements. Any suspected abnormality should warrant further investigation or consultation with a specialist. Mild asymmetry may be present in the newborn because of intrauterine factors and birth. In those with microcephaly, a tapering is noted from the forehead to the vertex. Premature closure of the cranial sutures (craniosynostosis) can result in an abnormal head shape. Delayed fontanel closure or a large fontanel can result from achondroplasia and other skeletal disorders, congenital hypothyroidism, Down syndrome, rickets, and increased intracranial pressure, among other conditions. A small fontanel or early fontanel closure can be related to craniosynostosis or abnormal brain development that may or may not result in microcephaly. Note that craniosynostosis is associated with a number of genetic syndromes, along with hyperthyroidism, hypophosphatasia, rickets, and hyperparathyroidism. A third fontanel located between the anterior and posterior

TABLE 7.1 Selected Clinical Anomalies and Associated Genetic Conditions

| Location and Anomaly | Genetic Condition or Syndrome |
|---------------------------|---|
| Head, Neck, Face | |
| Macroglossia | Beckwith–Wiedemann syndrome; Costello syndrome |
| Lower lip pits | Van der Woude syndrome |
| Smooth tongue | Familial dysautonomia |
| “Tongue thrusting” | Familial dysautonomia |
| Short philtrum | DiGeorge syndrome; Orofaciodigital syndrome |
| Smooth philtrum | Fetal alcohol syndrome |
| Long philtrum | Robinow syndrome; Williams syndrome |
| Micrognathia | Cornelia de Lange syndrome; Smith–Lemli–Opitz syndrome |
| Broad nasal bridge | Fetal hydantoin syndrome; Smith–Magenis syndrome |
| Low nasal bridge | Achondroplasia; Down syndrome; Noonan syndrome |
| Prominent nose | Rubinstein–Taybi syndrome |
| Malar hypoplasia | Bloom syndrome; Treacher Collins syndrome |
| Low-set ears | Rubinstein–Taybi syndrome |
| Frontal bossing | Achondroplasia; fetal valproate syndrome |
| Coarse facies | Mucopolysaccharidosis |
| Altered skin pigmentation | Peutz–Jeghers syndrome (perioral spots); tuberous sclerosis |
| Teeth | |
| Neonatal teeth | Sotos syndrome |
| Conical teeth | Hypohidrotic ectodermal dysplasia |
| Early loss of teeth | Hypophosphatasia |

(continued)

TABLE 7.1 Selected Clinical Anomalies and Associated Genetic Conditions (*continued*)

| Location and Anomaly | Genetic Condition or Syndrome |
|--|--|
| Late eruption of teeth | Apert syndrome; cleidocranial dysostosis |
| Hypodontia | Incontinentia pigmenti |
| Eyes and Ocular Region | |
| Nystagmus | Cardiofaciocutaneous syndrome |
| Cataract (infancy) | Galactosemia; other metabolic disorders |
| Cherry-red spot (macula) | Tay–Sachs disease; GM1 gangliosidosis |
| Blue sclera | Osteogenesis imperfecta types I and II |
| Aniridia | Wilms tumor |
| Glaucoma | Stickler syndrome |
| Lens dislocation | Marfan syndrome; Ehlers–Danlos syndrome |
| Hypertelorism | Retinoic acid embryopathy; chromosomal deletion syndromes |
| Hypotelorism | Trisomy 13 |
| Ptosis of eyelid | Aarskog syndrome; Kabuki syndrome |
| Up-slanted palpebral fissure | Down syndrome; Pfeiffer syndrome |
| Down-slanted palpebral fissure | Coffin–Lowry syndrome; Marfan syndrome |
| Short palpebral fissure | Fetal alcohol syndrome; DiGeorge syndrome (deletion 22q11.2) |
| Inner epicanthal folds | Down syndrome; Fragile X syndrome |
| Iris, unusual patterning or coloration | Wilson disease (Kayser–Fleischer ring); neurofibromatosis type 1 (Lisch nodules) |
| Iris coloboma | Cat-eye syndrome; CHARGE syndrome |
| Synophrys | Cornelia de Lange syndrome; Waardenburg syndrome |

(continued)

TABLE 7.1 Selected Clinical Anomalies and Associated Genetic Conditions (continued)

| Location and Anomaly | Genetic Condition or Syndrome |
|--------------------------------------|---|
| Limbs, Hands, Feet, and Trunk | |
| Arachnodactyly | Marfan syndrome; Stickler syndrome |
| Polydactyly | Trisomy 13; Pallister–Hall syndrome |
| Broad thumbs | Rubinstein–Taybi syndrome |
| Syndactyly | Amnion rupture sequence; oral–facial–digital syndrome |
| Joint hypermobility | Marfan syndrome; Ehlers–Danlos syndrome |
| Clenched hand | Trisomy 18 |
| Clinodactyly of fifth fingers | Down syndrome |
| Brachydactyly | Turner syndrome |
| Pectus excavatum | Marfan syndrome |
| Skin, Hair, and Nails | |
| Hirsutism | Cornelia de Lange syndrome; Hurler syndrome |
| Alopecia | Dubowitz syndrome |
| White forelock | Waardenburg syndrome type 1 |
| Low hairline | Turner syndrome |
| Xanthomas | Familial hypercholesterolemia |
| Café-au-lait spots | Neurofibromatosis type 1 |
| Photosensitivity | Bloom syndrome; xeroderma pigmentosum |
| Hyperelastic skin | Ehlers–Danlos syndrome classic type |
| Shagreen patch | Tuberous sclerosis |
| Marbled skin pigmentation | Incontinentia pigmenti |
| Thick skin | Hurler syndrome; Cardiofaciocutaneous syndrome |

(continued)

TABLE 7.1 Selected Clinical Anomalies and Associated Genetic Conditions (*continued*)

| Location and Anomaly | Genetic Condition or Syndrome |
|---------------------------|--|
| Telangiectasia | Ataxia–telangiectasia |
| Port-wine stain birthmark | Sturge–Weber syndrome |
| Single crease (simian) | Down syndrome; fetal alcohol syndrome |
| Blisters | Epidermolysis bullosa |
| Growth Disorders | |
| Early macrosomia | Beckwith–Wiedemann syndrome |
| Obesity | Prader–Willi syndrome; Turner syndrome |
| Genitalia | |
| Hypogonadism | Klinefelter syndrome; Down syndrome |
| Cryptorchidism | Aarskog syndrome; deletion syndromes |
| Macroorchidism | Fragile X syndrome |
| Ambiguous genitalia | Congenital adrenal hyperplasia, classical form |
| Bifid scrotum | Fryns syndrome |
| Labia majora hypoplasia | Prader–Willi syndrome |
| Micropenis | Klinefelter syndrome |
| Other | |
| Cat-like cry | Cri-du-chat syndrome (deletion 5p) |
| Omphalocele | Beckwith–Wiedemann syndrome |
| Photophobia | Ectodermal dysplasia |
| Seizures | Menkes syndrome; Angelman syndrome |
| Single umbilical artery | Chromosomal aneuploidies |

fontanel is found in 5% to 15% of normal infants, but is more common in infants with Down syndrome and hypothyroidism.

Characteristic facies have been described as components of specific genetic syndromes. For example, coarse facies are associated with many lysosomal storage disorders and may be present at birth or develop with time. A smooth philtrum, the vertical groove in the median portion of the upper lip, is associated with fetal alcohol syndrome. Cleft lip and palate may occur as single defects or as a part of a syndrome (see Chapter 9). A bifid uvula may be dismissed by the practitioner but is frequently associated with submucous cleft palate and Loeys–Dietz syndrome (a connective tissue disorder).

Careful examination of the teeth can provide clues to an underlying ectodermal dysplasia or other genetic conditions. Missing teeth or abnormally shaped teeth should be noted. Teeth anomalies are often associated with unusual hair, skin, and/or nails, given that all of these tissues share a common origin.

Eyes and Ocular Region

Congenital cataracts occur in approximately 3 to 6 per 10,000 births; nearly 50% of congenital cataracts are genetic. Cataracts can be isolated, inherited, or occur as part of a syndrome and, therefore, be associated with other malformations. Both unilateral and bilateral cataracts can be present. In general, unilateral cataracts are not typically inherited. Approximately one fifth of children born with bilateral cataracts will be registered blind. Cataracts are often the first abnormality noticed in congenital and acquired infections and in various metabolic disorders (e.g., galactosemia). Prompt referral to an ophthalmologist is essential if cataracts are suspected.

Like cataracts, corneal clouding can be a clue to an underlying genetic disorder. In childhood, clouding of the cornea is often associated with inherited metabolic conditions. In adults, corneal dystrophy can be a sign of Fabry disease or cystinosis. Various pigmentation abnormalities of the iris are often seen in Waardenburg syndrome type I, including irides of different color or brilliant blue irides. Brushfield spots are speckled white areas in the iris that occur in normal children, but are more common among those with Down syndrome. Lens dislocation is frequent in individuals affected with Marfan syndrome or homocystinuria.

Hypertelorism represents an increased interpupillary distance and is a frequent component of many genetic syndromes. This distance can also appear wide because of a low nasal bridge, telecanthus, or short palpebral fissures. The palpebral fissure length is the distance from the inner to the outer corner of the eye. Short palpebral fissures are common in individuals affected with fetal alcohol syndrome, among other genetic conditions. The slant of the palpebral fissure varies based on ethnic origin. However, up- and down-slanted palpebral fissures, in addition to other dysmorphic facial features, can point toward an underlying genetic syndrome. Inner epicanthal folds are often present in children with Down syndrome and Turner syndrome.

Ears

Much variation exists in the external ear; as previously suggested, photographs provide the best documentation if ear anomalies are suspected. Ears should be examined

for symmetry, position, and size. “Low-set ears” is a descriptor commonly used; however, ears can appear to be low-set because of other features, such as a short or extended neck, tilted ear, small chin, or high cranial vault, any of which can be present alone or in conjunction with another syndrome. Assessment of the position of the ear should ultimately be done by objective measurements, and a detailed investigation of craniofacial structures should follow.

Various degrees of malformation of the ear can occur and may be genetic or acquired. In some cases, ear malformations are associated with syndromes that include renal disease (e.g., branchio-oto-renal syndrome) and hearing loss (CHARGE syndrome) as primary components. For this reason, infants or children with a minor ear malformation may benefit from an audiogram and renal ultrasound scan. When collecting the family history of a patient suspected to have an ear anomaly, always inquire about hearing loss and renal problems in relatives. Note that hereditary hearing loss can be inherited in many different patterns, including mitochondrial, autosomal dominant, autosomal recessive, and X-linked recessive (see Chapter 4). The following list of red flags in the personal and family medical history may indicate an increased risk for hearing loss and warrant further investigation:

Genetic:

- ▶ Family history of congenital hearing loss or loss in early childhood (nearly 60% of hearing loss has an underlying genetic component)
- ▶ Presence of certain congenital anomalies, particularly ear malformations, eye abnormalities, renal disease, and head or neck malformations (goiter is a feature of Pendred syndrome)

Environmental:

- ▶ Maternal illness during pregnancy, particularly rubella or cytomegalovirus
- ▶ Pre-, peri-, and postnatal exposure to aminoglycosides (e.g., gentamicin)
- ▶ Perinatal asphyxia
- ▶ Hyperbilirubinemia (jaundice)
- ▶ Infection

Parents are the most likely to first suspect hearing loss and may report that their child fails to respond appropriately to sounds or has observable speech delays. Parental concerns about hearing loss should not be overlooked but investigated fully. Early detection of hearing loss can inform time-sensitive treatment options, including cochlear implantation and speech therapy. Many states now require screening for congenital hearing loss in their newborn screening programs.

Skin, Hair, and Nails

The skin, hair, nails, and teeth all arise from the ectoderm; therefore, careful examination of all these tissues is advised if any unusual finding is noted in one. As sweat glands are also derived from the ectoderm, it is important to inquire about abnormal

sweating in individuals with hair, skin, nail, or teeth abnormalities. Absent, reduced, and excessive sweating are features of various inherited ectodermal dysplasias.

Skin should be inspected for pigmentation, lesions, and texture. Always consider racial/ethnic background as well as sun exposure when examining the skin. Photosensitivity is a key feature of albinism, porphyrias (see Chapter 6), and xeroderma pigmentosum. A “butterfly rash,” or patch of reddened skin across the nose and cheeks that tends to occur following sun exposure, is associated with Bloom syndrome (an autosomal recessive disorder of chromosome instability leading to malignancy development; more common in people of Ashkenazi Jewish descent).

A dermal melanocytosis, commonly referred to as a Mongolian spot, is a blue or bluish-gray nevus that usually occurs on the back or buttocks. Although a Mongolian spot can persist into adulthood, it usually disappears in early childhood. The prevalence of Mongolian spots varies based on ethnic origin but is much more common among Blacks, Asians, and Hispanics. This birthmark is of particular importance since it can be mistaken as a sign of child abuse because it resembles a bruise.

Two common capillary vascular malformations are the salmon patch and port-wine stain. Salmon patches, as the name implies, are flat patches of pink or red skin that tend to be found on the eyelids, between the eyes, or on the back of the neck (referred to as a “stork bite”). These patches may fade with time, often within the first year of life. Port-wine stains are less common than salmon patches and range in color from faint pink to deep purple. They tend to occur on the face, and darken in color and change from a smooth texture to a cobblestone appearance with time. They may be associated with deeper hemangiomas, such as those of the nervous system seen in Sturge–Weber syndrome.

Light-colored spots, referred to as hypomelanotic macules or “ash leaf” spots, are common skin findings in individuals with tuberous sclerosis. In infants or those with very fair skin, these spots may only be visible with the use of a Wood’s lamp. Another skin finding associated with tuberous sclerosis is a shagreen patch, or skin that resembles the texture of an orange peel and is often found on the lower back.

Hair should be examined for color, texture (e.g., coarse and thin), position of hairline, and sparseness or broken ends. Unusual hair findings may represent pathology or familial, racial, or ethnic variation. Abnormal hair patterning can be caused by abnormal size or shape of the brain and upper facial area, as can be seen in individuals with varying degrees of microcephaly. Hair pigmentation may be altered in a variety of syndromes. A patch of white hair may indicate Waardenburg syndrome type I and should prompt a hearing test. Hirsutism is associated with ethnic and racial variation (occurring more commonly in Mediterranean, Middle Eastern, and South Asian ancestry), can be caused by excessive hormone levels (a feature of an inherited condition called congenital adrenal hyperplasia), or may be a feature of a genetic syndrome like Cornelia de Lange. Abnormalities of hair texture may also be present, such as the “steely” hair found in Menkes syndrome (an X-linked recessive disorder of copper metabolism with neurological impairment and seizures).

Fingernails and toenails should be examined for length, thickness, discoloration, and abnormal shape. Absent or abnormal fingernails are seen at birth in nearly all cases of nail–patella syndrome. Greatly thickened nails are a feature of pachyonychia congenita, a group of autosomal dominant disorders characterized primarily by nail dystrophy.

Limbs, Hands, Feet, Skeleton, and Trunk

Anomalies of the hands and feet may reflect an inherited familial trait, a sporadic malformation, or exist as part of a genetic syndrome. The anomalies described below may be isolated to the toes or fingers, present in both the hands and feet, and can be bilateral or unilateral in nature. Polydactyly is one of the more common single malformations and may represent a familial trait or an underlying genetic condition, such as Bardet–Biedl syndrome (characterized by vision loss, obesity, and polydactyl of the fingers or toes, among other features). Clinodactyly of the fifth finger is a feature of many syndromes, including Down syndrome. Syndactyly denotes webbing or fusing of the digits and is more common in Caucasian ancestry. Arachnodactyly is a common feature of Marfan syndrome and Stickler syndrome, among other genetic conditions. Specific to the hands, the fingertips can also provide clues when making a diagnosis. For example, unusual dermal ridge patterning is a feature of various chromosomal conditions, and prominent fingertip pads are commonly seen in Kabuki syndrome. Palmar crease variation, such as the single palmar crease, is more frequent in children with Down syndrome. In some cases, hand or feet positioning may help in making a diagnosis. Typical of this is the clenched hand and “rocker-bottom” feet seen prenatally and postnatally in babies with trisomy 18. Clubfoot is a relatively common birth defect, occurring in 1 in every 1,000 births, but is associated with an underlying genetic syndrome in about 20% of cases.

Limb anomalies are a common feature of teratogen exposure during pregnancy and may necessitate cardiac evaluation as congenital heart disease is seen in approximately 15% of those with limb reduction defects. Shortened limbs are a feature of many types of skeletal dysplasias and other genetic syndromes. Measurements, including upper to lower segment ratio and arm span, should always be recorded because a disproportionate body may not be apparent on physical examination alone.

The chest should be examined for abnormal shape and nipple anomalies, including supernumerary, widely spaced, hypoplastic, inverted, or absent nipples. Abnormalities in chest shape may point to pectus excavatum or pectus carinatum, which are major diagnostic criteria for Marfan syndrome (see Chapter 10).

A hairy patch or other abnormal skin finding in the lower back area may represent occult spina bifida, which may not be visible in a mild form in other family members. Abnormal curvature of the spine should be noted. Particularly in older children and adolescence, observation should be made for scoliosis. Scoliosis is a component of inherited connective tissue disorders, such as Marfan syndrome, and can also be caused by tumors, like those present in neurofibromatosis (see Chapter 9), or by neuromuscular diseases such as cerebral palsy. Although minor spinal curvature may not require treatment, surgery or bracing may be necessary for progressive and more severe curvature.

Neuromuscular System

The clinician should test the infant for the usual primitive reflexes. An increased startle reflex to noise is common in the infant with Tay–Sachs disease. Absent reflexes are often noted during the physical exam of a hypotonic infant (often referred to as a “floppy” infant). The most common neuromuscular cause of hypotonia is congenital

myotonic dystrophy, a triplet repeat (CTG) expansion disorder that often presents with respiratory difficulty. Hypotonia can also be associated with metabolic disorders, including Pompe disease and Zellweger syndrome. Hypotonia is generally classified as central (occurring in 60%–80% of cases) or peripheral (occurring in 15%–30% of cases). Peripheral hypotonia may initially present as poor feeding due to sucking and swallowing difficulties. Delays in achieving motor milestones, along with seizures, may be seen in central hypotonia. The floppy infant may assume the “frog” position when lying on the back and also demonstrate head lag. When assessing a hypotonic infant, take into account pregnancy history, including fetal movement, prematurity, labor and delivery, and presence of polyhydramnios (indicating poor fetal swallowing).

Delays in motor milestones, clumsiness, frequent falling, the inability to climb stairs, and unusual gaits such as waddling and toe walking are often seen in muscular dystrophies and ataxias, diseases that often include cardiac findings and necessitate a cardiac workup. Observing and documenting the child’s gait and muscle strength and any changes over time are critical to an accurate assessment. In adults, changes in gait, onset of tremors, and personality and cognitive degeneration are features of various genetic conditions, including Huntington disease and spinocerebellar ataxia. Such symptoms necessitate a referral to a specialist.

Seizures can be difficult to detect in neonates and may manifest as subtle jerking or limb twitching. Seizures in a dysmorphic infant or child are often associated with inborn errors of metabolism, where developmental delay and/or mental retardation can also be present.

Genitalia

The genitalia are a frequent site of congenital anomalies and are associated with many syndromes as well as metabolic conditions, such as Smith–Lemli–Opitz syndrome and Zellweger syndrome. These anomalies result from many etiologies, including drug exposure during pregnancy, biochemical defects, chromosomal abnormalities, and inadequate hormone production. At birth, ambiguous genitalia warrant immediate investigation in order to appropriately treat metabolic complications, if deemed necessary, and to determine gender assignment. Classic congenital adrenal hyperplasia is a common cause of ambiguous genitalia in females and steroid therapy should be initiated as soon as possible to optimize growth. It is important to assess whether other anomalies are also present in an infant with ambiguous genitalia, as such findings rule out congenital adrenal hyperplasias but suggest other syndromes.

SUSPECTING A GENETIC COMPONENT AND REFERRAL TO A GENETICIST

Development of the nurse’s mindset to “think genetically” has immense potential for identifying patients and family members affected with or at risk of a genetic condition. Consensus exists among many professional nursing organizations that nurses should practice genomics-based health care and are in a prime position to champion the integration of genetics into the health care system. As patient advocates, nurses

are essential in making sure patients are appropriately referred. When a genetic component to disease is suspected because of findings from personal or family medical history, including from a physical examination or developmental assessment, referral to a geneticist should be initiated.

How do you determine whether a referral to a geneticist is appropriate? There are a number of red flags in a personal and family history that indicate a genetic condition or an inherited susceptibility to a common disease (see Box 7.1). When reviewing the family history, the primary red flag for most common diseases (e.g., heart disease and cancer) is a large number of affected relatives with a close degree of relationship. This can indicate a genetic component to the disease and/or an environmental risk,

BOX 7.1

Red Flags Suggestive of a Genetic Component

- ▶ Ethnic predisposition to genetic conditions
- ▶ Personal or family history of a known or suspected genetic disease
- ▶ Two or more family members (first- or second-degree relatives) affected with the same or related condition
- ▶ Individual or first- or second-degree relative with earlier age of disease onset than is typically expected (age < 50–55 years), such as cancer, heart disease, stroke, or dementia (age < 60 years)
- ▶ Early sudden death in one or more family members (first- or second-degree relative) who seemed healthy
- ▶ Disease in the less often affected sex (e.g., female color blindness and male breast cancer)
- ▶ Disease in the absence of known risk factors
- ▶ Individual affected with more than one type of primary cancer
- ▶ Multifocal or bilateral occurrence of disease in paired organs (e.g., bilateral retinoblastoma is typically seen in individuals who have an inherited form of cancer)
- ▶ Individual or couple with unexplained infertility or recurrent pregnancy loss (i.e., three or more miscarriages)
- ▶ Single or multiple congenital anomalies
- ▶ Dysmorphic facial features or other abnormalities discovered upon physical examination
- ▶ Vision or hearing loss in an infant, child, or young adult
- ▶ Seizures in an infant or child
- ▶ Hypotonia in an infant or child
- ▶ Delayed development or failure to thrive in an infant or child
- ▶ Abnormalities in lab values in an otherwise healthy individual; extreme lab values for a typical clinical situation
- ▶ Unexpected drug or anesthesia reactions
- ▶ Consanguineous relationships

which may suggest an increased risk to family members. Keep in mind that a lack of family history does not rule out a genetic component to a disease.

CASE EXAMPLE

The nurse is examining Brian, age 3, and notices seven café-au-lait spots on his body. She asks Brian’s mother, Angela, if anyone else in the family has these skin findings. Angela tells the nurse that her husband does and that her husband’s brother has some “bumps all over his body.” What should the nurse think about and do? Are there other questions the nurse should ask?

KEY POINTS

- ▶ Collecting a three-generation family history is an important step in the evaluation of all patients.
- ▶ Obtaining a negative family history does not rule out an underlying genetic condition or genetic component to a patient’s disease.
- ▶ Family history should be considered in the context of findings from a patient’s developmental and/or physical assessment.
- ▶ Individuals with a personal or family medical history suggestive of an underlying genetic condition should be referred to a geneticist or genetic counselor for further evaluation.
- ▶ Nurses are in a key position to incorporate genetics into clinical practice.

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CHAPTER 8

Maternal–Child Nursing: Obstetrics

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Arguably, nurses working in the field of obstetrics must have a greater depth and breadth of genetic knowledge over any other subspecialty. Application of genetics can begin before pregnancy with assessment of risk and principles of prevention. During gestation, nurses should include education on the effects of teratogens, prenatal screening options, and prenatal diagnoses. After delivery, early recognition of genetic disorders (chromosomal, single gene errors of metabolism, congenital malformations) is important for immediate initiation of potentially life-saving therapies. Many of the diseases manifested in the pediatric period are discussed in Chapter 9.

PRECONCEPTION OR PREPREGNANCY COUNSELING

Preconception education is a critical component of health care for women of reproductive age. Today all women considering pregnancy should have the following areas addressed, including appropriate education and genetic referral (if needed):

Family history

- ▶ A three-generation family history should be obtained with identification of known, genetic diseases of family members. Following identification, carrier testing should be offered before pregnancy
- ▶ Discussion of potential risks based on ethnic origin. For example, if the couple is of Ashkenazi (Eastern European) Jewish, Cajun, or French-Canadian ancestry, carrier testing should be offered before pregnancy
- ▶ Discussion of testing available for known genetic disorders

Risk factors

- ▶ ABO blood type and Rh antigen status should be established
- ▶ Obtain completed past medical history including chronic disease (diabetes mellitus, maternal phenylketonuria [PKU], HIV status). Stabilization of any diseases such as diabetes mellitus should occur before pregnancy

- ▶ Discussion of any bleeding tendencies including menorrhagia, especially at menarche, which could prompt evaluation for von Willebrand disease, an inherited bleeding disorder. Testing for thrombophilias such as factor V Leiden if indicated
- ▶ Review of measures to prevent infection in pregnancy (e.g., toxoplasmosis from changing cat litter boxes)
- ▶ Avoid hot tubs

Diet

- ▶ Appropriate prenatal diet
- ▶ Appropriate folic acid and multivitamin supplementation

Immunization status

- ▶ Determination of rubella and varicella titers and vaccinations, if necessary

Medications

- ▶ Review of current medications and drug use, including alcohol, illicit drugs, and cigarettes
- ▶ Discussion of potential needs for medications in pregnancy (e.g., antiseizure medications for the patient with epilepsy)

The Centers for Disease Control and Prevention (CDC) recommend that all women of childbearing age consume 0.4 mg of folic acid daily to prevent neural tube defects (NTDs). If there is a history of a pregnancy with an NTD, the recommended dose increases to 4 mg daily beginning at least 1 month before becoming pregnant. Additionally, the male partner should be counseled to avoid environmental chemicals, cigarette smoking, certain drugs, radiation, and so on.

For those who seek prenatal counseling, identification of risk and appropriate treatments can result in a more favorable pregnancy outcome. For example, women with altered maternal metabolism such as diabetes mellitus or PKU can benefit from strict control and diet therapy before pregnancy. Understanding potential risk in someone who had a corrected congenital anomaly may help to reduce anxiety. For women with genetic disorders, such as Ehlers–Danlos disease (a group of connective tissue disorders), the effect of the disorder on the pregnancy should be considered. It is important for nurses to educate parents who may not be aware that relatively minor problems in themselves may mean that they are at increased risk for a more severe outcome in their children. An example of this is the case of a mother with spina bifida occulta who is at increased risk for a larger NTD in a child. In cases of disabilities arising from unknown or nongenetic causes, counseling can still be useful in terms of optimum pregnancy management in a setting best able to cope with any anticipated problems. Additionally, identification of likely hazards and prevention may decrease risk to the fetus. An example is the case of the potential for urinary tract infection. With avoidance of contributory factors and increased proactive measures (e.g., adequate fluid intake), the possibility of necessary treatment with medication is minimized.

Persons at risk of problems during pregnancy should consider:

- ▶ The likelihood of conception
- ▶ The effect of a pregnancy on the mother's health
- ▶ The effects of the maternal condition on the developing fetus
- ▶ The possibility of increased complications during the pregnancy
- ▶ The likelihood of having a child with a similar disorder

Then reproductive options, therapeutic options, and the possibility of prenatal diagnosis can be considered before embarking on the pregnancy. Prevention of genetic disorders is also discussed in Chapter 5.

PREGNANCY

Issues identified above in preconception counseling should be addressed as early as possible in pregnancy, especially if the mother has not participated in preconception counseling. This section discusses in more detail effects of teratogens on the fetus, prenatal screening, detection and diagnosis, and assisted reproductive technology (ART).

During the first prenatal visit, it is important to establish ABO blood type and RhD antigen status. RhD⁻ women with an RhD⁺ pregnancy are at 1.5 % risk of developing alloimmunization. However, treatment with RhoGAM (Rh₀D immune globulin) decreases that risk to 0.2%. It is recommended to nonsensitized women at 28 weeks gestation and again within 72 hours after delivery if the infant is RhD⁺. This should also be done after amniocentesis, abortion, and other procedures such as chorionic villus sampling (CVS) unless the biologic father is RhD⁻. (More information on this is in Chapter 3.)

Through personal and family history, women will be identified who should have carrier screening early in pregnancy for genetic disorders that occur more frequently in certain ethnic groups. This is important so that a full range of options, such as prenatal diagnosis, are available. In addition, the Committee on Genetics and the American College of Obstetricians and Gynecologists recommend that carrier screening for cystic fibrosis is offered to all pregnant women. Recent carrier frequencies from over 20,000 individuals were published, which corroborated and differed from published data. These results, as shown in Table 8.1, identify the 10 most commonly detected diseases alongside the number tested and previously published frequencies. With the blurring lines of self-reported ethnicity in the population, using ethnicity-based screening may be antiquated practice.

It is important to understand that screening tests are for the most frequent gene mutations in particular diseases; therefore, a negative screening test for either partner does not guarantee that the child will not be affected. For detailed information or complicated situations, the couple should be referred for genetic counseling. More information about genetic variation in population groups can be found in Chapter 3.

TABLE 8.1 Carrier Statistics Among ACOG- and ACMG-Targeted Populations

| Disease | Counsyl Frequency (1 in) | Counsyl 95% CI (1 in) | Literature Frequency (1 in) | # Tested | Screening? |
|---|--------------------------|-----------------------|-----------------------------|----------|------------|
| All populations ($N = 23,453$) | | | | | |
| α -1-antitrypsin deficiency | 13.1 | 12–14 | 11.5 | 15,484 | × |
| Cystic fibrosis | 27.8 | 26–30 | 31.7 | 23,369 | Y |
| DFNB1 | 42.6 | 39–47 | 42.8 | 15,799 | × |
| Spinal muscular atrophy | 57.1 | 52–63 | 54 | 23,127 | 1 |
| Familial Mediterranean fever | 64.2 | 57–73 | Unknown | 15,854 | × |
| Smith–Lemli–Opitz syndrome | 68.2 | 60–78 | 123 | 15,825 | × |
| Sickle cell disease/ β -thalassemia | 69.6 | 63–78 | 158 | 21,360 | × |
| Gaucher disease | 76.7 | 69–87 | 200 | 21,473 | × |
| Factor XI deficiency | 92.0 | 80–108 | Rare | 15,724 | × |
| Achromatopsia | 97.5 | 85–115 | 123 | 15,798 | × |
| Northwestern Europe ($N = 12,915$) | | | | | |
| α -1-antitrypsin deficiency | 10.2 | 10–11 | 11.4 | 8,570 | × |
| Cystic fibrosis | 22.9 | 21–25 | 28 | 12,870 | Y |
| DFNB1 | 46.0 | 40–54 | 33.2 | 8,735 | × |
| Spinal muscular atrophy | 49.9 | 45–57 | 47 | 12,730 | 1 |
| Smith–Lemli–Opitz syndrome | 50.3 | 44–59 | 123.9 | 8,750 | × |
| MCAD deficiency | 73.5 | 62–90 | 61.7 | 8,749 | × |

(continued)

TABLE 8.1 Carrier Statistics Among ACOG- and ACMG-Targeted Populations (continued)

| Disease | Counsel Frequency (1 in) | Counsel 95% CI (1 in) | Literature Frequency (1 in) | # Tested | Screening? |
|------------------------------------|--------------------------|-----------------------|---------------------------------|----------|------------|
| Hereditary fructose intolerance | 90.1 | 75–113 | 81.1 | 8,744 | × |
| Achromatopsia | 91.0 | 76–114 | 123 | 8,734 | × |
| Hereditary thymine-uraciluria | 96.4 | 80–122 | 33 | 8,680 | × |
| Familial Mediterranean fever | 99.5 | 82–126 | Unknown | 8,756 | × |
| Ashkenazi Jewish (N = 2,410) | | | | | |
| Factor XI deficiency | 12.6 | 11–15 | 8 | 1,501 | × |
| Familial Mediterranean fever | 13.2 | 11–16 | 10.5 | 1,513 | × |
| Gaucher disease | 16.8 | 14–20 | 17 | 2,384 | 1 |
| DFNB1 | 21.3 | 17–28 | 21 | 1,509 | × |
| Cystic fibrosis | 21.6 | 18–27 | 29 | 2,402 | Y |
| α -1-antitrypsin deficiency | 24.2 | 19–32 | 16 | 1,452 | × |
| Hexosaminidase A deficiency | 26.9 | 22–34 | 27.4 | 2,366 | Y |
| SCAD deficiency | 29.1 | 23–40 | Unknown | 1,511 | × |
| Familial dysautonomia | 41.8 | 33–57 | 31 | 2,385 | Y |
| CPT II deficiency | 43.2 | 33–65 | Rare/too few patients worldwide | 1,512 | × |
| Hispanic (N = 2,302) | | | | | |
| α -1-antitrypsin deficiency | 9.1 | 8–11 | 9.2 | 1,608 | × |

(continued)

TABLE 8.1 Carrier Statistics Among ACOG- and ACMG-Targeted Populations (continued)

| Disease | Counsel Frequency (1 in) | Counsel 95% CI (1 in) | Literature Frequency (1 in) | # Tested | Screening? |
|--|--------------------------|-----------------------|-----------------------------|----------|------------|
| Cystic fibrosis | 52.1 | 40–74 | 59 | 2,294 | Y |
| DFNB1 | 67.6 | 48–114 | 100 | 1,623 | × |
| Spinal muscular atrophy | 81.2 | 59–130 | 68 | 2,274 | 1 |
| Sickle cell disease/ β -thalassemia | 83.1 | 60–138 | 128 | 2,077 | × |
| Pompe disease | 134.7 | 85–326 | 100 | 1,616 | × |
| CDG-Ia | 135.4 | 86–328 | Unknown | 1,625 | × |
| Smith–Lemli–Opitz syndrome | 135.5 | 86–328 | No reliable data | 1,626 | × |
| Familial Mediterranean fever | 136.6 | 86–331 | Unknown | 1,639 | × |
| Phenylalanine hydroxylase deficiency | 162.8 | 99–462 | Unknown | 1,628 | × |
| African American (N = 1,193) | | | | | |
| Sickle cell disease/ β -thalassemia | 9.7 | 8–12 | 10 | 1,121 | 1 |
| α -1-antitrypsin deficiency | 29.2 | 21–50 | 37.3 | 672 | × |
| Cystic fibrosis | 74.2 | 50–149 | 84 | 1,188 | Y |
| Pompe disease | 112.5 | 61–800 | 59.7 | 675 | × |
| Spinal muscular atrophy | 117.8 | 72–334 | 72 | 1,178 | 1 |
| Galactosemia | 169.5 | 82– ∞ | 94 | 678 | × |
| Gaucher disease | 213.2 | 109–4,770 | 34.6 | 1,066 | × |
| DFNB1 | 226.0 | 99– ∞ | 25.3 | 678 | × |

(continued)

TABLE 8.1 Carrier Statistics Among ACOG- and ACMG-Targeted Populations (continued)

| Disease | Counsel Frequency (1 in) | Counsel 95% CI (1 in) | Literature Frequency (1 in) | # Tested | Screening? |
|---|--------------------------|-----------------------|-----------------------------|----------|------------|
| Hereditary fructose intolerance | 226.0 | 99–∞ | Unknown | 678 | × |
| Smith–Lemli–Opitz syndrome | 339.0 | 127–∞ | 137.8 | 678 | × |
| South Asia (N = 1,123) | | | | | |
| Achromatopsia | 23.5 | 18–35 | 123 | 798 | × |
| Sickle cell disease/ β -thalassemia | 30.1 | 23–45 | 25 | 1,055 | 1 |
| Cystic fibrosis | 40.1 | 29–64 | 118 | 1,122 | Y |
| Spinal muscular atrophy | 73.3 | 48–153 | 52 | 1,099 | 1 |
| Hereditary thymine-uraciluria | 99.8 | 58–371 | 33 | 798 | × |
| DFNB1 | 99.9 | 58–372 | 148 | 799 | × |
| Citrullinemia type 1 | 212.0 | 93–∞ | Unknown | 636 | × |
| MLC | 212.0 | 93–∞ | Unknown | 636 | × |
| Biotinidase deficiency | 266.3 | 116–∞ | 123 | 799 | × |
| Tyrosinemia type I | 266.3 | 116–∞ | 173 | 799 | × |
| Eastern Asia (N = 1,121) | | | | | |
| DFNB1 | 22.2 | 17–34 | 33–200 | 756 | × |
| Sickle cell disease/ β -thalassemia | 78.0 | 50–178 | 50 | 1,014 | 1 |
| Spinal muscular atrophy | 85.5 | 55–195 | 59 | 1,111 | 1 |
| Gaucher disease | 96.9 | 59–275 | Unknown | 969 | × |

(continued)

TABLE 8.1 Carrier Statistics Among ACOG- and ACMG-Targeted Populations (continued)

| Disease | Counsyl Frequency (1 in) | Counsyl 95% CI (1 in) | Literature Frequency (1 in) | # Tested | Screening? |
|---------------------------------------|--------------------------|-----------------------|---------------------------------|----------|------------|
| Achromatopsia | 189.0 | 91–∞ | 123 | 756 | × |
| Cystic fibrosis | 223.6 | 115–5011 | 242 | 1118 | Y |
| α-1-antitrypsin deficiency | 249.0 | 109–∞ | 450 | 747 | × |
| Pendred syndrome | 252.0 | 110–∞ | 51 | 756 | × |
| Pompe disease | 366.5 | 137–∞ | 112 | 733 | × |
| CPT II deficiency | 378.0 | 142–∞ | Rare/too few patients worldwide | 756 | × |
| Southern Europe (N = 1,063) | | | | | |
| α-1-antitrypsin deficiency | 17.0 | 13–24 | 13.1 | 715 | × |
| Cystic fibrosis | 35.3 | 26–55 | 28 | 1,059 | Y |
| DFNB1 | 37.2 | 26–67 | 33.2 | 745 | × |
| Spinal muscular atrophy | 40.3 | 29–66 | 47 | 1,049 | 1 |
| Sickle cell disease/ β-thalassemia | 52.4 | 36–97 | 50 | 996 | 1 |
| Familial Mediterranean fever | 74.5 | 46–211 | Unknown | 745 | × |
| Phenylalanine hydroxylase deficiency | 74.6 | 46–211 | 50.5 | 746 | × |
| Pompe disease | 81.9 | 49–260 | 100 | 737 | × |
| Smith–Lemli–Opitz syndrome | 82.9 | 49–263 | Unknown | 746 | × |
| Hereditary thymine-uraciluria | 105.1 | 59–495 | 33 | 736 | × |

(continued)

TABLE 8.1 Carrier Statistics Among ACOG- and ACMG-Targeted Populations (continued)

| Disease | Counsel Frequency (1 in) | Counsel 95% CI (1 in) | Literature Frequency (1 in) | # Tested | Screening? |
|---|--------------------------|-----------------------|--------------------------------------|----------|------------|
| Middle East (N = 512) | | | | | |
| Familial Mediterranean fever | 24.5 | 17–49 | Variable (1/10–1/20) | 392 | × |
| Sickle cell disease/ β -thalassemia | 5.1 | 31–165 | 30 (but variable) | 469 | × |
| Hereditary thymine-uraciluria | 54.9 | 31–256 | 33 | 384 | × |
| Achromatopsia | 55.1 | 31–257 | 123 | 386 | × |
| Cystic fibrosis | 63.1 | 37–234 | 91 | 505 | Y |
| Spinal muscular atrophy | 72.4 | 41–340 | 25 | 507 | 1 |
| DFNB1 | 77.6 | 40–1,627 | 83 | 388 | × |
| Inclusion body myopathy 2 | 96.5 | 47– ∞ | 15 (Iranian Jews), unknown in others | 386 | × |
| Hereditary fructose intolerance | 97.0 | 47– ∞ | Unknown | 388 | × |
| Smith–Lemli–Opitz syndrome | 129.3 | 57– ∞ | Rare | 388 | × |

Note: Confidence intervals computed as Wilson 95% score interval. Some listed diseases overlap in definition in terms of genetic variants.

Abbreviations: × = neither ACMG nor ACOG recommends offering screening to this population; 1 = either ACMG or ACOG recommends offering screening to this population; CDG-Ia = congenital disorder of glycosylation type Ia; CI = confidence interval; CPT II = carnitine palmitoyltransferase II; DFNB1 = *GJB2*-related DFNB 1 nonsyndromic hearing loss and deafness; MCAD = medium chain acyl-CoA dehydrogenase; MLC = megalencephalic leukoencephalopathy with subcortical cysts; SCAD = short chain acyl-CoA dehydrogenase; Y = both ACMG and ACOG recommend offering screening to this population.

Source: Lazarin et al. (2013).

BOX 8.1**Possible Consequences of a Teratogen**

| | |
|----------------------|--|
| No apparent effect | Prenatal or perinatal fetal death |
| Congenital anomalies | Altered fetal growth (e.g., growth retardation) |
| Carcinogenesis | Postnatal functional and behavioral deficits and aberrations |

THE VULNERABLE FETUS AND TERATOGENESIS

The term *teratogen* is often used to describe agents that interrupt the development of the fetus. The term *fetus* as used in this chapter also includes the embryo. In a given exposure during pregnancy, a teratogen can have any of the consequences shown in Box 8.1.

Complex and multifaceted maternal and fetal factors influence the consequences of drugs, radiation, and chemical and infectious agents to the developing fetus. As described in Table 8.2, drugs and chemicals can cause fetotoxic effects through direct fetal interaction and interference with maternal systems (e.g., circulatory, endocrine, excretory, appetite regulating). Table 8.3 identifies some of the problems involved in determining whether a specific substance is injurious to the fetus.

TABLE 8.2 Factors Influencing the Effects of Teratogens

- ▶ Access to and disposition within the fetus
 - Generally when the fetus is exposed to agents affecting the period from fertilization to implantation, the result is either death or regeneration.
 - During the period of organogenesis, the result is usually gross structural alterations. After organogenesis in the fetal period the result is usually related to alterations in cell size and number.
 - The central nervous system and external genitalia remain vulnerable through most of pregnancy.
- ▶ The age of the fetus at the time of exposure
- ▶ Level and duration of dosage or exposure
- ▶ Chemical, biologic, and physical properties of the agent (for microorganisms—type, virulence, and number)
- ▶ Maternal biochemical pathways and mechanisms for drug metabolism possibly altered by pregnancy.
- ▶ The degree of interference with maternal systems and the extent of modulation that occurs
- ▶ The genetic constitution of both mother and fetus
 - Dizygotic twins have been born with only one exhibiting anomalies typical of a drug effect.
- ▶ Agents often act differently in different species, and on individuals within the species (e.g., differences in genetic constitution, variability in metabolic pathways)
 - This applies to both the mother and fetus.
- ▶ Interactions with other agents and factors (e.g., environmental, nutritional, other drugs)

TABLE 8.3 Considerations Regarding Substances and Possibility of Fetal Injury

- ▶ Different outcomes may result from the gestational timing of fetal exposure.
 - This becomes a bigger problem when the exact date of pregnancy is not known.
- ▶ Drugs rarely produce only one type of defect.
- ▶ It takes time for long-term effects of substances to become evident.
 - For example, clear cell adenocarcinoma of the vagina appeared in the daughters of women who were treated with diethylstilbestrol (DES) during pregnancy.
- ▶ Bias in recall.
 - Mothers who give birth to infants with defects are more likely to recall adverse events such as illness and medications in their pregnancies than women who have infants without congenital anomalies.
- ▶ Effects may be subtle (e.g., behavioral alteration).
- ▶ Agents do not need to harm the mother in order to damage the fetus.
- ▶ Multiple drugs may interact.
- ▶ The disease process may be affected by mechanisms aside from the drug.
- ▶ Making associations and generalizations are difficult due to the following.
 - The number of pregnant women getting a certain drug or disease at the same time of gestation.
 - A slight increase in an anomaly that may not be statistically significant.
 - Differences in environment, drug indications, ethnic differences, and other external factors.
 - The complexity involved in detecting minor anomalies or delayed deficits.
 - One fetotoxic agent can have several different effects and many fetotoxic agents can show the same effect.
 - All of the interacting and modulating factors such as genotype of both mother and fetus, environmental chemicals, and nutrition may differ and cannot be controlled.

Drugs and Chemical Agents in Pregnancy

Several questions must be asked before recommending a drug for a pregnant woman, as shown in Box 8.2. To begin, the statement that a drug “has not been shown to be a human teratogen” does not mean that it is safe; it may never have been tested in the pregnant human female. As discussed previously, establishing drug safety is difficult due to the problems and factors influencing effects on the fetus (Table 8.3). In addition, when doing animal and laboratory studies, drug testing for safety may not use a species that is sensitive to the effects of the drug. Thalidomide appeared harmless in the species in which it was tested; however, it was extremely teratogenic in humans. Drugs tested in humans may be in specific population groups, from which generalizations should not be made, or have few or no pregnant women in the sample because of ethical concerns for safety. If the effect is one in which the increased incidence of defects is small and nonspecific, then the number of subjects in preliminary tests may not be sufficient to demonstrate the effect. Cost and time may limit the extent of testing due to the extreme pressure to get new drugs on the market quickly.

BOX 8.2**Questions to Consider Before Recommending a Drug in Pregnancy**

- ▶ Is pharmacologic intervention necessary for this condition?
- ▶ Are other effective alternative therapies available?
- ▶ Is the risk increased if no treatment is given?
- ▶ Is this specific drug the agent of choice for both the condition and the pregnancy?
- ▶ Does the risk of the disorder or its consequences outweigh the risk of the drug?
- ▶ Does the value of the drug to the mother for treatment of the disorder weigh favorably against any possible detrimental effects to the fetus?

The association of detrimental fetal effects with a specific drug is made by case reports, surveillance, and epidemiologic studies. The teratogenicity of thalidomide was discovered because of the sudden, increased incidence of a rare limb defect (phocomelia), coinciding with the widespread use of thalidomide in pregnant women. The numerous published case reports established a teratogenic association and subsequent withdrawal from the market. Thalidomide is available again, this time as an investigational drug particularly for erythema nodosum and aphthous ulcers.

After the birth of a child with a congenital defect, a retrospective analysis can help establish connections between the mother's illnesses and medications used during her pregnancy. Epidemiologic surveillance and reporting of congenital anomalies, especially the frequency of certain sentinel defects, is conducted by the CDC at several sites across the United States (www.cdc.gov/ncbddd/birthdefects/research.html). By using multiple sites, patterns or incidence that might reflect an environmental influence can be established.

Traditionally, prescription drugs were placed into five categories by the Food and Drug Administration (FDA) based on their pregnancy category (A, B, C, D, X). However, in 2014, the FDA released a new Pregnancy and Lactation Labeling Rule (PLLR) removing the pregnancy letter categories and instead using a new format to help health care providers counsel women to make informed decisions for themselves and their children. These categories are Pregnancy (including Labor and Delivery), Lactation (including Nursing Mothers), and Females and Males of Reproductive Potential. Effective June 2015, new prescription drugs will use the recent format while drugs approved after 2001 will be gradually phased in.

The Pregnancy category contains a risk summary, clinical considerations, and data for each prescribed drug used by women during pregnancy, labor, and delivery. Additionally, a pregnancy exposure registry will be required for all prescription drugs used in this category. The Lactation category includes information pertinent to the breastfeeding mother. This includes drug amounts in breast milk and drug effects on the nursing infant. Finally, the category for Females and Males of Reproductive

Potential provides information on the effects of the prescription drug on contraception, pregnancy testing, and infertility.

Certain fetotoxic drugs are discussed below, and others are presented in Table 8.4. Absence from the table does not imply safety, and some adverse fetal effects are not teratogenic. It is not possible to present an inclusive list here, and reports on the safety (or nonsafety) of drugs in pregnancy often conflict. Nevertheless, these drugs are best avoided when a less harmful, more efficacious one can be substituted. Selected drugs are discussed in more detail below.

TABLE 8.4 Selected Drugs Known or Suspected to Be Harmful or Teratogenic to the Fetus

| Drug | Reported Effects |
|-------------------------|---|
| Alcohol | See the text. |
| <i>Antibiotics</i> | |
| Aminoglycosides | Amikacin, gentamycin, kanamycin, tobramycin (see streptomycin). |
| Chloramphenicol | Effects in neonate from administration in second and third trimesters include Gray baby syndrome, hypothermia, failure to feed, collapse, and death. |
| Streptomycin | Ototoxic to fetal ear, eighth cranial nerve damage; other aminoglycosides may also cause this. |
| Tetracycline | Yellow/brown discoloration of tooth enamel, enamel hypoplasia, inhibits bone growth. |
| <i>Anticancer drugs</i> | |
| Alkylating agents | Chlorambucil has been associated with renal agenesis. Busulfan has been associated with growth retardation, cleft palate, microphthalmia, and increased incidence of multiple malformations; all apparently cause a risk of increased spontaneous abortion. |
| Aminopterin | Cranial dystosis, hydrocephalus, hypertelorism, micrognathia, limb and hand defects, multiple congenital malformations. |
| Antimetabolites | Cyclophosphamide has been associated with increased incidence of multiple malformations, especially skeletal defects and cleft palate. |
| Methotrexate | Increased incidence of miscellaneous congenital malformations, especially of the central nervous system and limbs. |

(continued)

TABLE 8.4 Selected Drugs Known or Suspected to Be Harmful or Teratogenic to the Fetus (continued)

| Drug | Reported Effects |
|-----------------------------|---|
| <i>Anticoagulants</i> | |
| Warfarin (Coumadin) | Fetal warfarin syndrome, facial abnormalities, nasal hypoplasia, respiratory difficulties, hypoplastic nails, microcephaly, hemorrhage, ophthalmic abnormalities, bone stippling, developmental delay. |
| <i>Anticonvulsants</i> | Also see text. |
| Phenytoin (Dilantin) | Fetal hydantoin syndrome, growth retardation, mental deficiency, dysmorphic feature, short nasal bridge, mild hypertelorism, cleft lip and palate, cardiac defects, transplacental carcinogenesis (neuroblastoma). |
| Trimethadione (Tridione) | Apparent syndrome of developmental delay, V-shaped eyebrows, low-set ears, high or cleft palate, irregular teeth, cardiac defects, growth retardation, speech difficulties, increased risk of spontaneous abortion. |
| Valproic acid | Spina bifida. |
| <i>Antimalarial</i> | |
| Chloroquine | Slight risk of chorioretinitis; may cause ototoxicity. |
| Quinine | Deafness, limb anomalies, visceral defects, visual problems, other multiple congenital anomalies. |
| <i>Antithyroid</i> | |
| Iodides and thiouracils | Depression of fetal thyroid, hypothyroidism, goiter. |
| Carbimazole | Scalp defects, dysmorphic facial features, other possible anomalies. |
| <i>Hormones</i> | |
| Adrenocorticoids | Intrauterine growth restriction; neonates may show adrenal suppression and possible increased susceptibility to infection; there are conflicting reports of increased incidence of cleft lip and palate. |
| Androgens | Masculinization of female fetus. |
| Clomiphene | Questionable increase in incidence of NTDs. |
| Diethylstilbestrol (DES) | Development of vaginal adenocarcinoma, usually in adolescence or young adulthood, reproductive tract structural alterations; in exposed males, testicular abnormalities, sperm, and semen abnormalities have been reported. |

(continued)

TABLE 8.4 Selected Drugs Known or Suspected to Be Harmful or Teratogenic to the Fetus (*continued*)

| Drug | Reported Effects |
|---|---|
| Oral contraceptives | Association of increased incidence of cardiac and limb defects, (progestogen/estrogen) VACTERL syndrome; conflicting research reports, may not be teratogenic. |
| <i>Psychotropics</i> | |
| Chlordiazepoxide (Librium) | Possible overall increased incidence of congenital malformations. |
| Diazepam (Valium) | Hypotonia, hypothermia, withdrawal symptoms at birth, increase in incidence of cleft lip and palate. |
| Haloperidol, trifluoperazine, prochlorperazine | Suspected of causing slight increase in incidence of limb defects in exposed fetuses; risk to fetus is weighed against benefit to mother. |
| Lithium | Increase in stillbirths, neonatal deaths; edema, hypothyroidism, goiter, hypotonia, cardiovascular anomalies such as Ebstein anomaly. Use another drug during pregnancy, if possible. |
| Meprobamate | Possible increase in cardiac defects or major malformations. |
| <i>Others</i> | |
| Aminoglutethimide (Cytadren) | Pseudohermaphroditism, increased incidence of fetal deaths, increased incidence of malformations. |
| Angiotensin-converting-enzyme inhibitors | Hypoplasia of skull, some skeletal anomalies, oligohydramnios, IUGR, patent ductus arteriosus (degree of risk uncertain). |
| Metronidazole (Flagyl) | Midline facial defects, cleft lip and palate, chromosome aberrations with long-term use; carcinogenic and mutagenic in nonhuman systems, debated in humans. |
| Misoprostol (a prostaglandin E ₁) | Moebius sequence. |
| Nonsteroidal inflammatory drugs Indomethacin (others may also have these effects) | Premature closure of ductus arteriosus, oligohydramnios. |
| Penicillamine | Connective tissue defects (e.g., cutis laxa). |
| Retinoids | See the text. |

(continued)

TABLE 8.4 Selected Drugs Known or Suspected to Be Harmful or Teratogenic to the Fetus (continued)

| Drug | Reported Effects |
|---------------|--|
| Salicylates | The use of aspirin has been associated with “postmaturity syndrome” and with a slight possible increase of hemorrhage, especially in premature infants, and possibly some anomalies (debated). |
| Sulfonylureas | Chlorpropamide and tolbutamide may be associated with increased congenital anomalies and increased fetal mortality (debated). |
| Thalidomide | Phocomelia and other limb defects, eye and ear malformations and abnormalities. |

Note: Not all exposed fetuses will show these effects. Absence from this table does not imply safety. See the text for discussion.

Diethylstilbestrol (DES)

DES, a proven teratogen, is a synthetic estrogen that was introduced in the 1940s. It was used extensively in pregnant women in the 1950s and 1960s to treat habitual abortion, bleeding, premature delivery, and toxemia. Many women (as many as 7% of all pregnant) took DES before the hazards to the fetus were identified. In 1971, the association was made between an epidemic in young women of clear cell adenocarcinoma (CCA) of the vagina and cervix and the maternal use of DES during pregnancy. Despite wide publicity in the lay press, the magnitude of the DES exposure problem is not completely known because many women did not know the precise medication they took or knew only the trade name and did not recognize that they had been exposed. It is estimated that there may have been about 4 million male (DES sons) and female (DES daughters) exposed offspring. The association between maternal DES use and delayed onset of CCA in the daughters has been well documented. Less widely recognized consequences in women include non-neoplastic alterations of the reproductive system, especially in the vagina, uterus (often T-shaped), or cervix, which may be seen in 25% to 35% of exposed women, and an increased incidence of spontaneous abortion, ectopic pregnancies, and prematurity. In exposed males (DES sons), sperm and semen abnormalities; testicular abnormalities, including benign cysts in the epididymis; and small and undescended testes have been reported as more prevalent than in controls, but no excess risk of cancer has been reported after long-term study. Some investigators report altered social behavior, but others disagree. DES daughters should not be given estrogen and should be advised to have continuing care. DES sons should see a urologist and be taught the technique and importance of self-examination of the testes.

More recently, animal studies have suggested that the effects of DES may transcend into the third generation. Mouse models have shown an increased susceptibility to tumor formation, suggesting that grandchildren of those who took DES may be at increased risk for cancer. These grandchildren, both males and females, should be closely monitored for reproductive tumors.

Anticonvulsants

The use of anticonvulsants for maternal seizures such as epilepsy during pregnancy needs to be carefully considered, balancing the risk of malformations with the risk of uncontrolled seizures to the fetus. Phenobarbital and phenytoin (Dilantin) are given together about three quarters of the time, so the individual effects of each drug have been hard to separate. Phenytoin and other hydantoins are associated with a risk of orofacial clefts, especially cleft lip and palate, and congenital heart disease of 5 to 10 times and 2 to 3 times that of the general population, respectively. In addition, a fetal hydantoin syndrome has been reported, which has many characteristic features of the head and neck (see Table 8.5). More recently, features were added to the phenotype of this “anticonvulsant face,” including a widened philtrum and small mouth.

Other antiepileptic medications, including carbamazepine, valproic acid, lamotrigine, and topiramate, have been associated with congenital malformations and delays. These include craniofacial defects, developmental delay, and lower IQ scores.

The consequences of these congenital defects must be weighed against the problems associated with prolonged, uncontrolled seizures. Risks have been estimated and appear to be about 10% for the full syndrome, and up to an additional 30% for part of the syndrome. If possible, monotherapy at the lowest possible effective dose is preferred, particularly in the first trimester, taking into consideration the stage of pregnancy most affected by the particular agent. Infants who were exposed to phenytoin during pregnancy may show vitamin K deficiency about 48 to 72 hours after birth. In these cases, vitamin K can be given to the mother during labor to prevent complications associated with hemorrhage.

Anticancer Drugs

Cancer during pregnancy is becoming more pervasive, with breast and hematological tumors among the most common forms. Chemotherapies administered during the first trimester often lead to congenital malformations; when given after the first trimester, surprisingly, many cytotoxic agents are not detrimental to the developing fetus. Anthracyclines (e.g., doxorubicin, daunorubicin, Epirubicin), potentially toxic to the heart, were shown in a European study to have no adverse effects on children exposed in utero. Additionally, these children were found to have no impairments to overall health.

Furthermore, pharmacokinetics are altered in the pregnant woman (beginning at about 4 weeks gestation) leading to a reduced plasma volume of chemotherapeutics. This, combined with the protective filtering of the placenta, may have clinical implications for providers prescribing chemotherapies.

TABLE 8.5 Harmful Effects of Selected Infectious Agents During Pregnancy

| Agent/Disease | Increased Reproductive Loss | Effects of Congenital Malformations | Prematurity or Growth Retardation |
|---|-----------------------------|-------------------------------------|-----------------------------------|
| Viral | | | |
| Coxsackie B | + | ?* | 0 |
| Cytomegalovirus | + | + | + |
| Chicken pox (varicella zoster) | 0 | + | + |
| Herpes simplex 1 and 2 | + | + | + |
| Mumps | + | ? | 0 |
| Parvovirus B19 | + | ? | + |
| Polio | + | 0 | + |
| Rubella | + | + | + |
| Rubeola (measles) | + | ? | + |
| Venezuelan equine encephalitis | + | + | 0 |
| Bacterial | | | |
| Syphilis (<i>Treponema pallidum</i>) | + | + | ? |
| Tuberculosis | + | 0 | + |
| Listeriosis (<i>Listeria monocytogenes</i>) | + | 0 | +? |
| Group B streptococcus infection | + | 0 | ? |
| <i>Chlamydia trachomatis</i> | + | 0 | + |
| <i>Neisseria gonorrhoeae</i> | 0 | 0 | + |
| Q fever | + | 0 | 0 |
| Parasitic | | | |
| Malaria (<i>Plasmodium</i> spp) | + | 0 | + |
| Toxoplasmosis (<i>Toxoplasma gondii</i>) | + | + | + |
| | + | 0 | ? |
| Chagas disease (<i>Trypanosoma cruzi</i>) | + | 0 | + |
| Fungal | | | |
| Valley fever (<i>Coccidioides immitis</i>) | | | |

+ = established; 0 = no present evidence; ? = possible, not established; *suspected of causing fetal cardiac anomalies.

If possible, therapy should be delayed until the second trimester, and combination therapy should be avoided, with the least toxic agent used. Males may wish to take advantage of sperm banking before beginning therapy, and women may wish to consider harvesting and saving ova.

Other Drugs

As new drugs come on the market, occasionally there is concern about their teratogenic potential. The vitamin A derivatives, including isotretinoin (Accutane) used in acne treatment, are known teratogens. These drugs are associated with an increase in spontaneous abortion, craniofacial malformations, heart defects, and central nervous system abnormalities. Frequently used in adolescent females, education regarding its teratogenicity is essential. Pregnancy should be avoided within 6 months of use.

Serotonin-reuptake inhibitors (SSRIs) have an associated increased risk of congenital malformations if taken during the first trimester of pregnancy. Additionally, if taken in the third trimester, there is an increased risk of infant withdrawal, prematurity, and persistent pulmonary hypertension of the newborn.

Nursing Pointers

- ▶ Educate all women of reproductive age about the potential teratogenic effects of medications.
- ▶ Encourage the client to tell her pharmacist, physician, nurse, and other health practitioners involved in her care that she is pregnant.
- ▶ Identify those most likely to be users of medications and drugs (including alcohol, caffeine, and cigarettes), and inform those who are considering pregnancy or who are already pregnant of the hazards.
- ▶ Teach women that over-the-counter products, including extra vitamins, herbals, and iron, are considered drugs.
- ▶ Integrate the above information into school health programs.
- ▶ Educate men about their role in conception and fetal health; advise waiting 90 days after certain medications before conceiving.
- ▶ Educate women regarding the dangers of self-medication in pregnancy.
- ▶ Provide education on nonpharmacologic measures to manage common conditions (e.g., relaxation techniques for tension).
- ▶ Involve the client in decision making regarding medications
- ▶ Instruct the client to keep an accurate list of all medications ingested during pregnancy, with the date, dose, length of time taken, and the reason.
- ▶ Maintain a record of all prescription or recommended drugs with the same information. This should be readily accessible for easy reference in the patient profile.
- ▶ If drug therapy is necessary, the lowest effective therapeutic dose of the least toxic agent should be used.
- ▶ The risks and benefits should always be considered, and doses should be individualized.
- ▶ Question any drug that appears contraindicated in pregnancy, as the practitioner prescribing it may not know that the patient is pregnant.

Alcohol in Pregnancy

The issues associated with alcohol in pregnancy and abnormal children were reported as far back as Ancient Greece, with scientific description of fetal alcohol spectrum disorders as early as the late 1800s. In 1980, the Surgeon General advised pregnant women not to drink alcoholic beverages and to be aware of alcohol content in other foods. A warning addressed to pregnant women is on alcohol containers and in stores selling alcohol that contains language such as, “According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects.”

Influences on Effects of Alcohol in Pregnancy. Factors such as genetic susceptibility, genetically determined differences in the metabolism of alcohol, the extent of fetal exposure, maternal nutritional status, and the dose of alcohol all play a role in fetal consequences. These include decreased birth rate, increases in spontaneous abortion rates, and stillbirths, as well as growth retardation, congenital anomalies, and functional deficits. Fetal alcohol syndrome (FAS) is the most severe form of the spectrum of effects that occur as a result of maternal consumption of alcohol in pregnancy. Additional contributors to fetal effects that can be found in conjunction with alcohol use may include the use of other drugs, cigarette smoking, and malnutrition.

Fetal Alcohol Spectrum Disorders (FASD). *Fetal alcohol spectrum disorders (FASD)* encompass alcohol-related effects, alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defects (ARBD), and the most clinically evident category, FAS, which is considered with and without confirmed maternal alcohol exposure. FASD is not considered a diagnostic term but is defined as an umbrella term for the other alcohol-related conditions. Alcohol consumption can affect reproduction and offspring:

- ▶ Before conception with lowered fertility
- ▶ Prenatally with an increased risk of spontaneous abortion and prematurity
- ▶ Perinatally and at birth with stillbirth, low birth weight, growth restriction, FAS, alcohol-related effects, ARBD, other anomalies
- ▶ Newborn and infant may have hyperactivity, fretfulness, failure to thrive, poor sucking and feeding, sleep disturbances, and behavioral and learning deficits, which may be part of FAS or ARND
- ▶ Childhood with hearing loss, vision impairment, ARND, behavioral and learning deficits, hyperactivity, sleep disturbances, and other
- ▶ Adolescence with behavioral and learning deficits, maladaptive behaviors, ARND

A variety of dysmorphic features and congenital anomalies have been associated with FAS. A dysmorphology scoring system is available along with cognitive and behavioral patterns to assist with diagnosis. Among the most frequent features found are microcephaly, growth deficiency, short palpebral fissures, smooth philtrum, and thin upper lip border. Cognitive and behavioral findings include emotional lability, motor dysfunction, poor attention span, deficient social interactions,

communication and speech problems, disorganization, and hyperactivity. Long-term studies of adolescents and adults with FAS found deficits in socialization, communication skills, attention deficits, and hyperactivity, and about half were mentally retarded. The facies were not as distinct, but microcephaly and shortness persisted.

The incidence of FAS is estimated at 0.5 per 1,000 live births overall but may be as high as 10 to 15 per 1,000 in some high-risk populations. Alcohol-related effects may be more frequently seen. These may be low estimates because diagnosis may not be made until later in life when functional deficits are more noticeable. FAS is many times higher among those of low socioeconomic status (SES) and is higher in some ethnic populations, but these data may be confounded because of SES. Various researchers have examined the outcomes from women who used alcohol in pregnancy. The results of studies vary because of different definitions of mild, moderate, and severe alcohol use; different alcohol content in different alcoholic beverages; and varying patterns of alcohol consumption, ranging from a regular daily amount, to periodic binges, to a combination of both. Nevertheless, it is estimated that the risk for any major or minor congenital anomaly in an alcohol-abusing pregnancy ranges from 38% to 71%, with an overall adverse pregnancy outcome average of 50%.

The toxicity of ethanol on the neurons through the agonistic effects on gamma aminobutyric acid (GABA) receptors is established. There are also known effects on specific receptors (glycine, NMDA, serotonin) and L-type calcium channels. However, the effects on the pregnant woman who ingests a minimal amount of alcohol either consistently or sporadically are less clear. Some researchers suggest that alcohol does not need to be totally avoided during pregnancy and that it may be more realistic for women to restrict their intake to one standard measure (1 oz equivalent of absolute alcohol) per day. They fear that unnecessary guilt may arise in mothers of children with birth defects who drank mildly during pregnancy. However, others disagree; presently, no minimum safe level for alcohol consumption in pregnancy has been established. Pregnant women should avoid drinking alcohol and be aware of the alcohol content in food and drugs.

Although there is a relationship between the dose of alcohol consumed, the time of pregnancy, and the severity of defects in the fetus, studies in animals and humans have determined that benefits are accrued if maternal consumption of alcohol ceases, even if this occurs after the first trimester. Thus, it is important to identify individuals who are still using alcohol at the first prenatal visit, or before conception at a contraceptive or annual gynecologic visit. In general, women want to have healthy babies, and this provides motivation even in the severe alcoholic. There is a decreased desire for alcohol during pregnancy, which may help to support nursing efforts to eliminate gestational intake of alcohol.

Nursing Pointers

- ▶ Be aware of referral information for women seeking help with alcohol consumption.
- ▶ Nurses working with women of reproductive age should familiarize themselves with common signs and symptoms of alcoholism including neglect,

family disruption, agitation, tremors, and laboratory signs (e.g., macrocytic anemia, liver function abnormalities).

- ▶ Encourage women identified as alcohol abusers to discontinue or decrease their intake before conception.
- ▶ Anticipate problems associated with chronic alcohol consumption, including abruptio placentae, precipitous delivery, tetanic contractions, or infection.
- ▶ At delivery, the infant exposed to alcohol perinatally may be at risk for altered glucose metabolism, withdrawal symptoms, respiratory problems, seizures, and tremors. The need for resuscitation is not uncommon.
- ▶ Consider the morphology associated with FASD when assessing newborns and infants.
- ▶ If FAS or alcohol-related effects are suspected in newborns, be alert for other defects.
- ▶ Infants with intrauterine growth retardation (IUGR) and an apparent cause (e.g., placental insufficiency) may also have undetected FAS. Therefore, all small-for-date infants should be closely followed for several years.
- ▶ Infants born with FASD typically have a poor suck. Therefore, those with failure to thrive are at increased risk for poor feeding and slowed development.
- ▶ Support and help for the mother should begin in the immediate postpartum period and reinforced on follow-up visits.
- ▶ Observe for problems associated with mother–infant bonding. Home follow-up should be arranged before the mother leaves the hospital.
- ▶ Consider enrolling the parents in parenting classes.
- ▶ Affected children and families should be referred to early intervention programs, counseling, family therapy, and appropriate language, speech, and learning services.
- ▶ Ongoing contact with a family who has had alcohol problems during pregnancy is necessary. Children who later manifest fretful behavior, hyperactivity, and abnormal sleep may be more prone to child abuse in an already unstable situation.
- ▶ School nurses may need to continue follow-up of the children, some of whom have learning deficits that manifest in the school years. These children often superficially appear to have a large vocabulary and may not be detected early.
- ▶ Include the rest of the family when making assessments and referrals.

Cocaine and Use of Other Social and Street Substances

The use of cocaine and crack cocaine has become epidemic; estimates are that 1% of the U.S. population has tried cocaine. Many women who use cocaine also use other street drugs such as marijuana or methamphetamines or alcohol and may also suffer from poor nutrition, stress, infections, and other confounding conditions, making

effects on the fetus difficult to isolate to one agent and difficult to evaluate. Multiple drug use may also be synergistic.

Street drug use is probably more dangerous to the homeless woman without prenatal care than to the middle-class woman. In general, cocaine use can result in IUGR, low birth weight, increased fetal loss, prematurity, obstetrical complications, microcephaly, urogenital and other congenital malformations, and neurologic and behavioral effects such as irritability, excitability, poor state regulation, and poor sleep. Later, poor feeding and poor visual and auditory tracking may occur. Prenatal exposure may also delay development of the prefrontal cortex. Cognitive and attentional process deficits as well as language delay and behavioral problems seem to persist.

Cigarette Smoking

Between 19% and 30% of pregnant women continue to smoke. Maternal cigarette smoking in pregnancy is related to detrimental effects. These include an increased spontaneous abortion rate, an increased perinatal mortality rate, an increased incidence of maternal complications such as placenta abruptio and placenta previa, decreased birth weight and size in later childhood, an increased incidence of preterm delivery, and lower Apgar scores at 1 and 5 minutes after birth. The last is a source of particular concern because low Apgar scores have been associated in other studies with developmental and neurologic disabilities in later life.

Ionizing Radiation

Radiation occurs naturally in the background such as cosmic radiation, and people on flights have some exposure depending on altitude and length of time. This is usually significant only for pregnant frequent flyers such as pilots and flight attendants. A frequent reason for seeking genetic counseling is radiation exposure during pregnancy. The consequences of the effects of low-dose radiation to the fetus are still undetermined. There is probably no threshold level that can be considered absolutely safe for radiation exposure. The type of radiation emitted, its affinity for certain tissues, and the actual dose absorbed by the fetus are factors to consider. The most sensitive stage for spontaneous abortion due to radiation is just before or after the time of the first menstrual period after becoming pregnant when neither pregnancy nor the loss may be realized. However, radiation may be detrimental to the fetus in any stage of pregnancy, including fetal death, malformation, tissue effects, or cancer, especially leukemia.

The major hazard associated with in utero radiation exposure is an increased risk of childhood cancer for the fetus, no matter which trimester in which it occurred. Doses less than 0.05 Gy (5 rads) typically have no cancerous effect on the embryo or fetus, while larger doses of radiation greater than 0.50 Gy (50 rads) may result in microcephaly, intellectual disability, microphthalmia, genital and skeletal malformations, retinal changes, and cataracts. The largest radiation accident occurred at the Chernobyl nuclear power plant in Ukraine on April 26, 1986. Some children exposed in utero were said to exhibit intellectual disability and behavioral effects. The Three Mile Island nuclear accident in Pennsylvania in 1979 has not led to a

significant increase in cancer deaths for area residents. The population exposed to the more recent Fukushima Daiichi nuclear accident in Japan in 2011 continues to be monitored for radiation effects.

It is obviously preferable to prevent inadvertent or unnecessary radiation exposure of pregnant women. Pregnant nurses and other female employees should not work with patients receiving radioisotopes.

Nursing Pointers

Nurses should educate women to:

- ▶ Limit radiation exposure to that which is clearly indicated, necessary, and for which information or treatment cannot be obtained any other way
- ▶ Use contraception and delay conception for several months after exposure to radiation to the lower abdomen or pelvis
- ▶ Ask exactly why an X-ray film is being ordered and how necessary it is
- ▶ Keep records of X-ray films so that unnecessary duplication does not occur
- ▶ Let a health professional know if there is a possibility of pregnancy before receiving radiation
- ▶ Be aware that pregnancy can mimic some gastrointestinal and genitourinary disorders

Nurses should:

- ▶ Inquire about the date of the last menstrual period, determine if pregnancy is possible, and communicate this information to the prescriber. If pregnancy is confirmed, determine the necessity and risk, and consider the possibility of delay. A pregnancy test may be done if there is considerable doubt.
- ▶ Effectively shield the gonads. Clients should be encouraged to request this because a recent study showed that in about one third of exposures, no shielding was used.
- ▶ Delay the procedure, if possible, until onset of next menstruation or within the 10 days following the first day of the last menstrual period, unless data are immediately needed due to illness of the woman.
- ▶ Always ask female patients in a nonjudgmental way if there is a possibility of pregnancy before the woman receives any radiation. It is particularly important to be nonjudgmental and appropriate in manner when asking this of an adolescent.
- ▶ Request the minimum number of radiographs in the smallest field, with the lowest duration and intensity of exposure.

Infectious Agents and Intrauterine Infections

The first recognized association between an infectious disease in the mother and congenital abnormalities in the newborn was made for syphilis in 1850. A definitive

cause-and-effect relationship between a virus and specific congenital malformations was first established by Sir Norman Gregg after a rubella epidemic in Australia in 1941 led to a significant excess of congenital cataracts and heart disease in infants whose mothers had contracted rubella in the first trimester. Fetal consequences of maternal infection may include:

- ▶ Embryonic or fetal death (if in the first few weeks, the embryo may resorb; otherwise, spontaneous abortion or stillbirth may occur)
- ▶ Premature or term delivery of a normal infant
- ▶ Premature or term delivery of an infant with IUGR/low birth weight, congenital infection, congenital anomalies, or persistent postnatal infection

Congenitally infected infants may show clinical or subclinical infection with or without immediate or long-term consequences. Fetal death may be due to either direct fetal invasion by the microorganism or to severe maternal damage (e.g., fever, toxins). The degree of damage to the fetus is not related to the severity of the maternal infection. Many infections with severe fetal consequences can occur in mothers with few or no signs of illness.

Nurses should identify the stage of fetal development related to onset of maternal infection as some may have been subclinical or very mild. The most important intra-uterine infections in the United States traditionally were syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex, known by the acronym STORCH. Since others such as HIV infection have become important, the acronym is not used as widely. Infection with some organisms is so rare in pregnancy that their effects are almost impossible to distinguish from chance events. Prevention of infection in pregnancy is an important consideration for nurses. Important diseases resulting in congenital anomalies in the fetus are individually discussed below, including rubella, toxoplasmosis, cytomegalovirus infection, and syphilis. Other information is found in Table 8.6.

Rubella

An epidemic of rubella resulted in the birth of more than 20,000 infants with congenital rubella syndrome in the United States in 1964. The development of a vaccine in 1966 led to a marked decrease in cases of congenital rubella syndrome in the United States, although rubella remains a worldwide problem.

The effects on the fetus are determined based on the timing of maternal exposure. The risk of fetal eye and cardiac malformations is greatest when infection occurs in the first 8 weeks of pregnancy, and the risk of deafness is greatest between 5 and 15 weeks of pregnancy. Data are insufficient for the consequences of infection acquired after the fourth to fifth month, but delayed development and hearing deficits have been described when infection occurred as late as the 31st week of pregnancy.

The frequency of specific clinical features of the rubella syndrome varies. Approximately one third of defects are missed in the neonatal period and become noticeable later in childhood. The classic features described in the early literature, such as cardiac malformations (especially patent ductus arteriosus and pulmonary stenosis), eye abnormalities (especially cataracts, retinopathy, microphthalmia,

TABLE 8.6 Maternal Infections Associated With Developmental Toxicity

| Infection | Effects | Prevalence of Effects After Infection | Sensitive Period | Comments |
|---|--|---|------------------|---|
| Cytomegalovirus (CMV; a DNA herpesvirus) | Jaundice, petechiae, thrombocytopenia, hepatosplenomegaly, growth restriction, nonimmune hydrops | 24% sensorineural hearing loss: 32% central nervous system (CNS) sequelae | First trimester | Primary infection: 5%–18% of children experience serious sequelae (especially, first half of pregnancy) |
| | Long term: developmental delay, seizures, sensorineural hearing loss | 2.5% sensorineural hearing loss: 15% CNS sequelae | Second trimester | Most common congenital infection Leading cause of sensorineural hearing loss 0.7%–4% primary CMV infection rate among pregnant women in the United States Risk of transmission to the fetus is 30%–40% |
| Varicella zoster virus (VZV; a DNA herpesvirus) | Spontaneous abortion, intrauterine fetal demise, hydrops, polyhydramnios | 0.4% | <13 weeks | Respiratory droplets |
| | Varicella embryopathy: limb hypoplasia, scars, malformed appendages, muscular atrophy, microcephaly, cortical atrophy, cataracts, chorioretinitis, microphthalmia, psychomotor retardation | 2% | 13–20 weeks | Neonatal VZV has 20%–30% mortality rate |

(continued)

| | | | | |
|------------------------------|---|-----|-------------|---|
| Rubella (an RNA virus) | Sensorineural hearing loss, growth retardation, miscarriage, stillbirth, heart defects, cataracts, glaucoma, retinitis, microcephaly, microphthalmia, intrauterine growth restriction, cerebral palsy, mental retardation | 67% | <12 weeks | Transmission by respiratory droplets |
| | | 35% | 13–16 weeks | Seen mostly in pregnancies in women born outside the United States Infection <12 weeks associated with greater severity of fetal effects Fetal defects rare with infection after 16 weeks |
| Parvovirus B19 (a DNA virus) | Fetal death, hydrops, spontaneous abortion | 19% | 1–12 weeks | Respiratory secretions |
| | | 15% | 13–20 weeks | Fetal infection in 33% of maternal infections |
| | | 6% | >20 weeks | Fetal death 11% with infection <20 weeks |

(continued)

TABLE 8.6 Maternal Infections Associated With Developmental Toxicity (continued)

| Infection | Effects | Prevalence of Effects After Infection | Sensitive Period | Comments |
|--|--|--|--------------------------------|--|
| Toxoplasmosis (a protozoan) | Mental retardation, chorioretinitis, periventricular calcifications, seizures, ventriculomegaly, hepatosplenomegaly, fever, ascites, rash | Congenital toxoplasmosis occurs in 1/8,000 pregnancies | All trimesters can be affected | Cat feces |
| | | Transmission rate | | Infected meat |
| | | 10%–15% | 1st trimester | Congenital toxoplasmosis is rare with chronic maternal infection |
| | | 25% | 2nd trimester | |
| | | 60% | 3rd trimester | |
| Syphilis (<i>Treponema pallidum</i> ; a spirochete) | Early congenital syphilis: hepatosplenomegaly, hydrops, intrauterine growth restriction, osteochondritis, jaundice, anemia, skin lesions, rhinitis, CNS involvement. Chorioretinitis | 8.8 cases/100,000 pregnancies | | |
| | Early latent syphilis: stillbirths, miscarriage, preterm delivery | Early latent: 20% prematurity, 10% stillbirths, 4% neonatal death, 40% congenital syphilis, 20% normal | | |

(continued)

| | | | | |
|---|--|--|-------------|--|
| Syphilis (<i>Treponema pallidum</i> ; a spirochete) | Late congenital syphilis: Hutchinson teeth, deafness, mental retardation, hydrocephalus, palsies, frontal bossing, saddle nose, saber shin, protuberant mandible | Late latent: 9% prematurity, 10% stillbirths, 1% neonatal death, 10% congenital syphilis, 70% normal | | |
| Listeria (a Gram-positive bacterium) | Late miscarriage, stillbirth, preterm delivery | 50% perinatal mortality 10% mortality among live-born infants | | Food borne: luncheon meats, soft cheeses, smoked seafood Flu-like symptoms Symptoms of food poisoning Septicemia, pneumonia, meningitis in the mother |
| Measles (an RNA virus) | Spontaneous abortion, preterm delivery | 20%–60% | | Respiratory droplets Pregnant women are 2 times more likely to be hospitalized, 3 times more likely to have pneumonia, 6 times more likely to die from complications than nonpregnant women No increased risk of malformations There has been an association of measles exposure at birth and Hodgkin disease in children |
| Herpes simplex virus (HSV; a DNA herpesvirus) | Skin vesicles, scarring, microcephaly, hydranencephaly, disseminated infection | 50%–60% mortality with disseminated infection | At delivery | Maternal fetal transmission during delivery |

(continued)

TABLE 8.6 Maternal Infections Associated With Developmental Toxicity (*continued*)

| Infection | Effects | Prevalence of Effects After Infection | Sensitive Period | Comments |
|---|---|---------------------------------------|------------------|---|
| Herpes simplex virus (HSV; a DNA herpesvirus) | Questionable intrauterine growth restriction with third trimester infection | 15% mortality with encephalitis | | Most often from primary infections rather than recurrences |
| | | Sequelae in 50% of survivors | | Fetal HSV infection in 1/200,000 deliveries Neonatal HSV in 1/3,500 deliveries Risk of neonatal HSV after primary infection 50%, after recurrent infection 0%–3% 70% of neonatal herpes is caused by HSV-2 |

Source: Običan and Scialli (2011).

and glaucoma), and permanent hearing loss (bilateral and unilateral), are still seen. To them, the following features of the expanded syndrome can be added: growth restriction, one manifestation of which is low birth weight for gestation; microcephaly; bone lesions and radiologic changes in long bones, often described as “celery stalk”; thrombocytopenia, petechiae, and purpura, which give the newborn a “blueberry muffin” appearance; jaundice; hepatosplenomegaly; pneumonitis; and encephalitis. Among the abnormalities often not detected in infancy are genitourinary anomalies, adrenal insufficiency, behavioral manifestations of minimal brain dysfunction, intellectual disability, autism, various thyroid disorders including hypothyroidism, and growth hormone deficiency. Hearing loss may not be evident until later childhood, after secondary learning and speech disabilities have accrued. These findings plus progressive panencephalitis seen in the second decade and diabetes mellitus, which develops in 10% to 20% of affected infants, may be caused by the persistence of virus in tissues. Approximately 30% of infants with congenital rubella syndrome die in the first 4 months. Because the risk of fetal damage is substantial, therapeutic termination of pregnancy should be discussed with any pregnant woman known to have contracted rubella during pregnancy, one with known exposure, or one to whom rubella vaccine was inadvertently administered during pregnancy.

Live vaccination is not recommended for the pregnant woman, but the CDC reports that women who were followed after receiving rubella immunizations in the first trimester delivered healthy infants.

Nursing Pointers

- ▶ Because there is no treatment for congenital rubella, all efforts must be directed at prevention. Women who are considering pregnancy should have serologic evaluation to determine whether rubella antibody is present.
- ▶ Susceptible women of childbearing age should be vaccinated only in the documented absence of pregnancy; instructions should include the necessity to use contraception and avoid pregnancy for at least three menstrual cycles after vaccination.
- ▶ Vaccination should be followed by serologic determination that appropriate antibody response has occurred.
- ▶ Vaccination as a routine part of childhood immunization programs should be supported and encouraged.
- ▶ Rubella titers and vaccination, if indicated, should be done for all female staff on obstetrics and newborn units or clinics, and in day care centers, schools, prisons, and facilities for the intellectually disabled.
- ▶ Seek confirmation of suspected exposure to rubella (e.g., examination of contact).
- ▶ Because infected infants shed virus through the nasopharynx and urine, they should be kept away from women in their childbearing years, isolated in the hospital, and kept apart from susceptible women in clinics and offices.

Toxoplasmosis

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. Adults may acquire the organism from the ingestion of raw or undercooked meat or by contamination of soil, litter, and food by the feces of infected cats. Acquired infection is usually found in children or young adults and can be detected by serum antibody screening. Overall, 20% to 30% of women of reproductive age in the United States have such serum antibodies, but this varies with geographic location, socioeconomic level, and cultural practices. The following are estimated rates of transmission to the fetus according to when the mother acquires toxoplasmosis: the first trimester, 10% to 15%; second trimester, 25%; and third trimester, 60%, with an overall risk of about 40%. Accurate transmission rates are difficult to determine because 70% of newborns later found to have congenital toxoplasmosis are asymptomatic at birth. The risk for severe manifestations is highest in the first trimester.

Congenital toxoplasmosis is almost always caused by acute primary infection in pregnancy (estimated at 0.2%–1.0%), which can be asymptomatic or consist of any of the following: mild fever, enlarged lymph glands, headache, or muscle aches—all of which may be easily dismissed or unappreciated. Thus, only those who became infected during pregnancy would be at risk for fetal complications or stillbirths. Antenatal testing would usually have to be done twice to determine this—once to detect negative individuals and again to see if seroconversion occurred. Drugs used in treatment are considered toxic with possible teratogenic effects, so therapeutic abortion is an option that should be discussed with patients who clearly have had seroconversion.

Congenital toxoplasmosis shows varying manifestations that may include chorioretinitis, cerebral calcification, hydrocephalus, microcephaly, convulsions, anemia, seizures, hepatosplenomegaly, anemia, rash, and intellectual disability. Late-manifesting sequelae include intellectual impairment, developmental delay, hearing loss, nystagmus, strabismus, and late-developing chorioretinitis resulting in blindness. Screening has been proposed for women before or during pregnancy and also for newborns. Prenatal diagnosis of fetal toxoplasmosis can be accomplished. Treatment has been attempted during pregnancy, and there is indication that it may be of benefit to the fetus without harm.

Other points that nurses should include in health teaching are to advise pregnant women to do the following:

- ▶ Eat only well-cooked meat (heated to 66°C; 151°F), or freeze all meat if they want to cook it less than well done.
- ▶ Avoid close contact with cats.
- ▶ If they have a cat in their home, someone else should change the cat's litter daily and dispose of feces in a sanitary manner. The cat should be fed only cooked, dry, or canned food; it should be kept away from wild rodents.
- ▶ Practice good hand washing before eating or handling food and after gardening or handling uncooked meat or touching pets.
- ▶ Do not eat raw eggs.

- ▶ Wash all raw fruits and vegetables carefully.
- ▶ Control flies and roaches, and limit their access to food.
- ▶ Use special precautions if their work involves animals in a lab or as a veterinarian.
- ▶ Cover children's sandboxes.

Cytomegalovirus

Cytomegalovirus (CMV) belongs to the same family as the herpes virus. Approximately 0.2% to 2.2%, with an average of 1%, of live-born infants have congenital CMV, but this varies considerably in different populations. It is said to be the most frequent cause of intrauterine infection in the United States, and is observed in about 1 in 150 infants. Intrauterine infection occurs usually because of primary maternal infection, but it can also result from reactivation of latent infection. The rate of transmission to the fetus after primary maternal infection in pregnancy can vary but is about 33%. Those at highest risk for primary CMV in pregnancy are young primiparas of the lower socioeconomic groups.

Health problems associated with CMV may not appear for 2 years after birth, with 80% of infants remaining symptom-free. Signs of CMV infection can include microcephaly, hepatosplenomegaly, jaundice, petechial rash, cerebral calcifications, motor disabilities, chorioretinitis, microphthalmia, hydrocephalus, and hernia. A small percentage has milder disease. Primary teeth may show characteristic enamel defects such as discoloration, opacity, and rapid wearing. Long-term sequelae can include sensorineural hearing loss, minimal brain dysfunction, intellectual disability, dental defects, motor defects, or poor school performance. Chorioretinitis may not be detected at birth but may be seen later. The magnitude of long-term insidious effects has only begun to be appreciated. Early detection helps children to achieve their maximum potential through early remedial efforts.

Nursing Pointers

- ▶ Asymptomatic infected newborns continue to shed virus through urine and saliva for up to 3 years after birth; therefore, they should be kept from direct contact with pregnant women, including the staff, when in the hospital, home, office, or clinic.
- ▶ Infants with suspected or proven disease should be closely monitored for delayed effects (including perceptual deficits and dental defects) and for appropriate medical, educational, and family support.
- ▶ Serologic testing should be done on the first prenatal visit in order to detect seroconverters, especially in high-risk groups.
- ▶ CMV should be suspected in women with mononucleosis-type symptoms.
- ▶ Documented maternal infection, especially in the first trimester, is a reason to discuss pregnancy termination with the client.

- ▶ Antibody determinations should be done in female employees. Those without antibodies who are planning pregnancy should not be assigned to obstetric or newborn units or seek employment in day care centers, schools, or congregate living facilities.
- ▶ If a blood transfusion is needed for a pregnant woman, use citrated blood that is more than 3 days old, if possible, because CMV can be transmitted in fresh whole blood.
- ▶ Emphasis should be placed on good hand washing for women throughout pregnancy, and especially after contact with potential infective sources.
- ▶ Care in handling blood and urine specimens is essential.
- ▶ Enforcement of good hand-washing techniques in hospitals, day care centers, and clinics is essential. Hospital personnel appear at increased risk for CMV, and full infection control measures may be warranted with known infected cases.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*. It is still a significant sexually transmitted disease (STD) in the United States with about 17,000 cases a year and over 300 cases of congenital syphilis per year. Infants with reactive tests or whose mother had untreated or inadequately treated syphilis are classified as not infected, confirmed case, or probable case. The major route of infection is through sexual contact, but it can also be transmitted through contaminated injection equipment, especially among drug users, or through direct nonsexual contact with infectious lesions. The infected pregnant woman can transmit syphilis to the fetus at any stage of her pregnancy and in any stage of the disease. Transmission occurs in 70% to 100% of cases; if the fetus is not treated, 25% die in utero.

The CDC recently revised criteria for congenital syphilis. Congenital syphilis can be manifested as *early* (before 2 years of age) or *late* (after 2 years of age), but overlap occurs. In early syphilis, the most common symptoms are rhinitis or “snuffles,” hepatosplenomegaly, generalized lymph node enlargement, jaundice, rash, and bone involvement including osteomyelitis. Often attention is first sought for affected infants because of rhinitis, persistent diaper rash, or failure to thrive. If not diagnosed or not treated completely, the manifestations of late congenital syphilis may be seen, including teeth changes (Hutchinson teeth, Moon or mulberry molars), eye lesions (keratitis, photophobia, uveitis, corneal scarring), deafness, bone changes (saddle nose, hard palate perforations, saber shins, impaired maxillary growth), neurologic involvement (paresis, convulsive disorders), and intellectual disability.

Nurses should be aware that all pregnant women should be tested for syphilis at their first prenatal visit because of the success in minimizing fetal damage when treated with penicillin. If a pregnant woman has a positive result, the underlying cause should be determined so that treatment can be instituted if necessary. Women at the greatest risk for developing syphilis should be retested later in pregnancy. Some factors associated with increased risk are women who are unmarried, very

young mothers, drug use in the woman or her partner, sexual promiscuity, contact with known syphilitics or those with STDs, history of past STDs including HIV, tattooed women, members of disadvantaged urban minority groups, and women who have unexplained lesions or rashes. Syphilis is disproportionately prevalent in the southeastern United States. A high index of suspicion is needed to consider syphilis in pregnant woman. Factors associated with risk at the time of delivery are premature delivery with no explanation, unexplained large placenta, hydrops fetalis, unexplained stillbirth, or no prenatal care. Further investigation and a blood test should be carried out in order to minimize severe fetal effects. The CDC recommends blood tests for pregnant women at the first prenatal visit and in the third trimester.

HIV

The number of women in the United States with HIV who are giving birth is increasing. Fortunately, perinatal (vertical) HIV infections are on the decline. Antiretroviral medications should be started on the first perinatal visit since HIV can be maternally transmitted to the fetus during pregnancy, delivery, and through breastfeeding. However, this should be done with caution as the teratogenic effects on the first trimester fetus are not completely understood. CD4 counts should be monitored every 3 to 6 months of the pregnancy. Additionally, viral load should be assessed more frequently in the pregnant woman to decrease the likelihood of vertical transmission. Throughout the pregnancy, the woman should be followed by both an obstetrician and infectious disease specialist.

Maternal Environment

The maternal environment and metabolism affects the developing fetus in many ways. Effects derive from interaction of maternal and fetal genotypes, as well as their interaction with internal and external environmental effects. The influence of maternal nutrition and risks of pregnancy and childbirth to adult women with genetic disorders such as Marfan syndrome (see Chapter 10) are beyond the scope of this book. Major genetically determined alterations, such as diabetes mellitus and maternal PKU, are discussed below.

Diabetes Mellitus

Ten percent of all pregnancies are complicated by diabetes. The incidence of major congenital anomalies in the offspring of diabetic women is three to four times that of controls. Maternal metabolic influences appear to be the primary determining factor. Although all major anomalies are increased, those of the cardiovascular system (especially a hypertrophic type of cardiomyopathy), kidneys, and skeletal system are most prominent, with caudal dysplasia or sacral agenesis present in 1%. Infants frequently have macrosomia; they are large for their gestational age but are physiologically immature, have increased total body fat, and have enlarged viscera. Nurses should anticipate that the infant of a diabetic mother frequently exhibits lethargy, hypotonia, polycythemia (hematocrits above 65%) leading to other complications, a poor sucking reflex, and metabolic imbalances such as hypocalcemia (present in up to 50%), hypomagnesemia (present in up to 38%),

hyperbilirubinemia, and hypoglycemia and plan accordingly. Careful observation is necessary because the neuromuscular system is often very excitable. Respiratory distress, often from hyaline membrane disease, is five to six times that found in normal newborns. Long-term effects include obesity (by 8 years of age, 50% of the weight of offspring were over the 90th percentile), cognitive impairment, and developmental delays. All these effects are more frequent with suboptimal control. Perinatal and maternal mortality are higher in diabetic women. Increase in hemoglobin A_{1C} is seen in poorly controlled diabetics and correlates with increased hyperglycemia. Increased congenital malformations are more likely in women with levels hemoglobin A_{1C} > 10%.

Nurses can help women of childbearing age consider the effects of diabetic health before diabetic-related pathology worsens. Additionally, folic acid for prevention of NTDs is recommended. Prenatal diagnosis should include ultrasound, amniocentesis, and α -fetoprotein levels. At delivery, fetal lung maturity should be determined, especially in the preterm infant. Additionally, measures to avoid shoulder dystocia in the macrosomic infant (> 4 kg) should be considered.

Most women are screened for gestational diabetes between 24 and 28 weeks. Nurses should also be aware of some risk factors associated with potential gestational diabetes:

- ▶ Family history of diabetes
- ▶ Previous infant with birth weight over 4 kg to 4.5 kg (8.8 lb.–9.9 lb.)
- ▶ Neonatal hypoglycemia or anomaly
- ▶ Previous or current polyhydramnios
- ▶ Unexplained perinatal death or recurrent spontaneous abortions
- ▶ Previous episode of latent diabetes
- ▶ Obesity (20 lb. above ideal weight)
- ▶ History of toxemia, pyelonephritis, recurrent urinary infections, glycosuria, or abnormal glucose tolerance test
- ▶ It is estimated that half of women who develop gestational diabetes become type 2 diabetics, so it is important to check glucose levels every 1 to 3 years

Maternal Phenylketonuria

Individuals with PKU, an autosomal recessive disorder, are unable to metabolize the amino acid phenylalanine (Phe). Therefore, those with PKU have restricted diets that are low in Phe. Increased levels of Phe are teratogenic, so it is important that women with PKU maintain Phe levels between 120 and 360 $\mu\text{mol/L}$ before conception and throughout pregnancy. Studies have shown intrauterine growth retardation in infants of mothers with Phe levels less than 120 $\mu\text{mol/L}$ or greater than 300 $\mu\text{mol/L}$, suggesting that levels that are too low may inhibit fetal growth.

Children born to mothers who are under metabolic control appear to have normal IQs. Those who are exposed to higher levels of Phe are subject to untoward fetal effects including intellectual disability, microcephaly, congenital heart disease, esophageal atresia, neurologic problems (convulsions and spasticity), and growth restriction. Maternal weight and nutrient intake need to be monitored.

The nurse should see that data regarding the outcome of maternal PKU are discussed with women known to be at risk, so that they may explore the options available. The nurse should then assist her in obtaining optimum dietary counseling with monitoring from a nutritionist experienced with maternal PKU and also help her to obtain products and recipes. Along with dietary restrictions, sapropterin, an enzyme cofactor, has been used successfully to decrease blood Phe levels in selected individuals. It is considered Category C (insufficient data to prove risk), so it should be used with caution.

Other Maternal Metabolic and Genetic Disorders

Improved detection and treatment in infancy and childhood has led to women with other biochemical disorders reaching adulthood and becoming pregnant. This is also true of women with disorders such as congenital heart disease, which can affect the fetus in an indirect biochemical sense, for example, through anoxia. Women with myotonic dystrophy (an autosomal dominant disorder with cataracts and muscle weakness) have increased rates of spontaneous abortions, stillbirths, and perinatal deaths, and polyhydramnios in such women may be correlated with an affected fetus. Women with acute intermittent porphyria (see Chapter 6) have exacerbations of disease in pregnancy and increased rates of prematurity and spontaneous abortion. It has been suggested that women such as those with maternal PKU use in vitro fertilization (IVF) and implantation of the pre-embryo in a surrogate mother for gestational carriage to term. Other problems experienced in pregnancy may not be directly connected to the biochemical milieu, but will not be discussed here. For example, women with Marfan syndrome (see Chapter 10) may experience stress on the already compromised cardiovascular system, and women with Ehlers–Danlos syndrome may have a higher incidence of hernias and delivery complications. Women with sickle cell anemia may deliver small-for-gestational-age infants and need to be watched for complications, and those with spina bifida can be at risk for premature labor.

Hyperthermia

Hyperthermia has been shown to be teratogenic in animals and may cause an increased risk of NTDs. Major sources of hyperthermia for pregnant women include fever, baths, saunas, and hot tubs. Data on fevers are confounded by effects of the microorganism such as a virus. For example, possible teratogenic effects of influenza and the common cold may be related to the accompanying fever. However, it is wise to prevent the effects of high fever in pregnancy by using a safe antipyretic, such as acetaminophen (Servey & Chang, 2014). Some advocate additional folic acid supplementation as well.

Other Environmental Exposures in Pregnancy

Evidence of environmental contamination by toxic chemicals often results from the observation of what appears to be a high frequency or clustering of birth defects, spontaneous abortions, or miscarriages, and may be observed by citizens or professionals. One of the first widespread examples was discovered in 1956 in the Minamata Bay area of Japan. Industrial waste from a fertilizer company containing methylmercury was discharged into the bay that was used for fishing. Many pregnant women either aborted or gave birth to infants with a congenital neurologic disorder resembling cerebral palsy, although the women did not appear sick themselves. Follow-up studies identified many with developmental deficits and mental deficiencies who were exposed in utero. In Iraq, grain treated with methylmercury as a fungicide was imported from Mexico. This grain was to be used for planting, but instead was used for bread by large numbers of individuals. The warning about toxicity was in Spanish and was not understood. Many of the infants subsequently born to women who ingested this bread showed a cerebral-palsy-like illness that included blindness and brain damage. In the United States, a family in New Mexico that ingested pork that had been fed grain contaminated by organic mercury used as a fungicide also became ill, and the pregnant mother gave birth to an infant with features of the disorder. In all these cases, some persons were more susceptible to the mercury; not all those who ate contaminated products evidenced toxicity. While the FDA has recognized the importance of ingesting fish for the beneficial fetal effects of omega 3 fatty acids, they recommend avoiding those fish with extraordinarily high levels of mercury (over 110 $\mu\text{g}/4$ ounces fish), including swordfish, tilefish, shark, and mackerel. The Environmental Protection Agency has gone further to recommend the safe amount of methyl mercury for pregnant women between 42 and 64 $\mu\text{g}/\text{week}$.

Toxic exposure to lead has occurred by means of environmental and workplace pollution and hobbies. A comparison of pregnancy outcomes was done in two Missouri cities: Rolla, which is in the lead mining belt, and Columbia, which is not. In Rolla there was a statistically higher rate of prematurity and molar pregnancies. It is believed that the fetus may be sensitive to lead but not manifest such sensitivity until early childhood in the form of impaired intelligence; subtle neurobehavioral changes; growth delay, including decreased height and weight; speech, language, or attention deficits; behavior abnormalities; and developmental deficits. Microcytic anemia may be seen. It can be difficult to sort out prenatal effects from environmental exposure in infancy and childhood. Recent studies have shown an inverse relationship between maternal blood lead levels and birth weight/preterm birth, even at lower lead levels. Additional considerations should not only include current sources of maternal lead, but also the mother's lifetime exposure. Since lead is stored in bone, the mother's previous exposures during childhood may become mobilized into the maternal circulation during pregnancy, exposing the fetus to increased levels of this metal.

In areas where the drinking water is high in lead, nurses can advise women planning pregnancy to have their water checked and use an alternate source, such as bottled water, for drinking if necessary. Additionally, household substances such as paint, dust in contaminated areas, or contamination through employment such as construction work can pose a risk to the worker and the family. It is important to

advocate safe environmental lead levels and to provide the necessary education and resources such as public health departments to make homes and communities safe from lead contamination. Good counseling prior to and during pregnancy can help the mother reduce lead exposure for herself and the fetus.

PRENATAL DETECTION AND DIAGNOSIS

The American College of Obstetrics and Gynecology recommends that all women, regardless of age, be offered prenatal screening. This can be through noninvasive tests such as using cell-free fetal DNA from maternal plasma or through invasive procedures such as amniocentesis or CVS. Detection techniques usually involve screening applied broadly to the pregnant population, while diagnostic techniques are targeted because of one or more specific reasons for increased risk. These methods include the techniques shown in Box 8.3. Ideally, preconception counseling can precede pregnancy, and therefore prenatal diagnosis, so that potential preventive steps such as rubella titer determination and vaccination before conception can be taken if necessary, and folic acid, other vitamin supplementation, and other preventive measures can be accomplished to reduce some risks.

In the years following the Human Genome Project, the field of genomic testing in perinatal medicine has grown exponentially. It is now possible to perform FISH analysis, microarray, and whole exome sequencing in addition to traditional karyotype and G-banding methods. This allows for more rapid detection of aneuploidies, chromosome aberrations and rearrangements, point mutations, and copy number alterations (Table 8.7). Cell-free fetal DNA analysis has improved since the late 1990s and is slowly becoming the standard for fetal aneuploidy screening for mothers at increased risk. It has shown remarkable sensitivity and specificity for trisomies 13, 18, and 21. However, there is still controversy as to whether to recommend invasive procedures following positive screening results. Most obstetricians still routinely offer the quad screen (maternal serum markers AFP, β -hCG, unconjugated estriol, and inhibin A) for trisomy 21.

BOX 8.3

Most Common Methods of Prenatal Detection and Diagnosis

- ▶ Maternal serum screening (detection)
- ▶ Ultrasonography (detection and diagnosis)
- ▶ Amniocentesis (diagnosis)
- ▶ Chorionic villus sampling (diagnosis)
- ▶ Embryofetoscopy (diagnosis)
- ▶ Fetal blood and tissue sampling (diagnosis)
- ▶ Pre-implantation diagnosis (diagnosis)
- ▶ The analysis of fetal cells and cell-free fetal DNA in maternal circulation (investigational)

TABLE 8.7 Testing Methodologies in Perinatal Diagnosis

| Method | Ploidy | Aneusomy | Balanced Chromosome Aberrations | Unbalanced Chromosome Rearrangements | Copy Number Alterations (Microdeletion/Duplication) | Point Mutations | Resolution | Molar Pregnancy | Uniparental Disomy, Homozygosity Detection | Sample for Testing | Viable Cells for Culturing |
|---------------------|--------|----------------|---------------------------------|--------------------------------------|---|-----------------|-------------------------------|-----------------|--|--------------------------|----------------------------|
| Karyotype | + | + | + | + | - | - | > 5–10 Mb | - | - | AF, CVS, FB, CB, PB | + |
| AneuVysion FISH | + | + ^a | - | - | - | - | Whole chromosome ^a | - | - | AF, CVS, FB, CB, PB FFPE | - |
| Locus-specific FISH | - | - | + | + ^b | + | - | 150–200 kb | - | - | AF, CVS, FB, CB, PB | -/+ |
| Array CGH | - | + | - | + | + | - | 10–100 kb | - | - | AF, CVS, FB, CB, PB FFPE | -/+ |
| CGH+SNP, SNP arrays | + | + | - | + | + | - | CNV 10–100 kb, ROH 5–10 Mb | + | + | AF, CVS, FB, CB, PB | -/+ |

(continued)

| | | | | | | | | | | | |
|-------------------|---|----------------|---|------------------|------------------|---|---|---|---|-------------------|-----|
| NIPT | - | + ^a | - | - ^{a,c} | - ^{a,c} | - | Whole chromosome ^a ~3–5 Mb ^a | - | - | MatSer | - |
| Sanger sequencing | - | - | - | + | + | + | 1 bp, single gene | - | - | Fetal DNA, CB, PB | -/+ |
| WES, WGS | - | - | - | + | + | + | 1 bp, multiple genes | - | - | Fetal DNA, CB, PB | -/+ |

AF, amniotic fluid; bp, base pair; CB, cord blood; CGH, comparative genomic hybridization; CVS, chorionic villus sampling; FB, fetal blood; FFPE, formalin-fixed paraffin-embedded tissue; FISH, fluorescence in situ hybridization; kb, kilobases (thousand base pairs); Mb, megabases (million base pairs); MatSer, maternal plasma serum; NIPT, noninvasive prenatal testing; PB, peripheral blood; ROH, regions of homozygosity; SNP arrays, array containing single nucleotide polymorphism probes; WES, whole-exome sequencing; WGS, whole-genome sequencing; -/+, might be necessary to obtain sufficient amount of fetal cells or DNA.

^a Limited to the selected chromosomes (13, 18, 21, X, and Y) or selected regions.

^b Balanced rearrangements can be detected by use of locus-specific probe on cultured metaphase cells.

^c Large rearrangements of chromosomes 13, 18, 21, or X might be revealed accidentally.

Source: Peters, Yatsenko, Surti, and Rajkovic (2015).

Additionally, with over 6,000 described Mendelian disorders, whole-exome sequencing has become a cost-effective way to diagnose diseases. This can be done either prenatally for genetic screening, or postnatally to pinpoint metabolic disorders, congenital syndromes, or neurologic disorders.

The American College of Obstetricians and Gynecologists recommend ultrasound as part of the first trimester screening. Ultrasonography may also be used for routine screening in the second trimester as well as for diagnosis at more sophisticated levels. Ultrasound is used for measurement of nuchal translucency (sometimes called NT screening test, the translucent or clear space in back of the fetal neck on ultrasound) in conjunction with the screening of a small sample of blood for maternal-serum-free β -human chorionic gonadotropin (β -hCG), and maternal-serum pregnancy-associated plasma protein (PAPP-A) to detect Down syndrome as early as possible in the pregnancy. Higher levels of β -hCG and lower levels of PAPP-A are associated with Down syndrome. The time for using this combination is 11 to 13 weeks gestation. At this time, some practitioners also look for the presence or absence of the nasal bone, and these data, along with maternal age, gestational age, and any chromosome abnormalities in any previous pregnancies, are entered into a computer program. This combination of markers is used to give a specific risk mainly for Down syndrome, trisomy 13, and trisomy 18. Other chromosome abnormalities found with increased NT measurements of more than 3 mm include Turner syndrome and triploidy, and some other birth defects such as certain abdominal wall defects and cardiac septal defects as well as some other genetic syndromes such as various skeletal dysplasias and Noonan syndrome. Suspicious findings should prompt further testing and counseling.

It must be remembered that this is a screening, not a diagnostic test. When all of these markers are used, the accuracy of the risk assessment for Down syndrome can be as high as 97% and is about 80% using NT alone. Those determined to be at increased risk may wish a diagnostic test such as CVS, which can be done early, or amniocentesis, done slightly later. Sometimes women who are at increased risk because of maternal age over 35 years who have a lower risk after this screening will decide not to have more invasive prenatal diagnostic testing, although they may wish to have targeted ultrasound and maternal serum testing for NTDs.

At 15 to 22 weeks (16 to 18 optimal) in the second trimester, the use of maternal serum screening for α -fetoprotein (MSAFP) and for other markers for detection of certain defects, particularly open NTDs, where AFP is elevated, and certain chromosome disorders, depending on the markers used, has become commonplace in pregnancy. It is important to stress, however, that this is a screening test, not a diagnostic test. Therefore, the finding of any abnormal results requires prompt diagnostic investigation. About 90% of infants with NTDs are born to mothers with no prior history or known high risk; therefore, they would not be predetermined to be at high risk and would not be referred for amniocentesis or targeted ultrasound. The severe burden of NTDs made this screening highly desirable. In maternal serum, typically these tests are called the multiple marker tests or screen, and include determination of AFP, β -hCG, and estriol. These are used in screening maternal serum for fetal aneuploidy, usually with at least one other indicator depending on trimester

such as PAPP-A or inhibin-A, often in conjunction with ultrasound determined fetal nuchal translucency measurements, and sometimes determination of the presence or absence of the nasal bone.

AFP is a glycoprotein, similar to albumin, that is first synthesized in the fetal yolk sac and later in the fetal liver. It can be detected in the amniotic fluid and the maternal serum. The AFP in amniotic fluid and maternal blood originates from the fetal cerebrospinal fluid, gastric fluid, meconium, bile, and urine. The outcome of AFP's variety of origins in the fetus means that elevation of AFP occurs not only with open NTDs, but also with other fetal anomalies, making AFP a nonspecific test. For example, in gastrointestinal anomalies such as esophageal atresia, normal clearance of AFP through fetal swallowing cannot occur. In renal disorders, such as congenital nephrosis, excess fetal serum AFP is excreted and thus is elevated in the amniotic fluid.

AFP is used as a specific test when both parents are known carriers of congenital nephrosis, especially of the type frequent in persons of Finnish extraction. In renal agenesis, AFP is very low or absent. In closed NTDs, the layer of skin or tissue present prevents AFP from leaking out through the fetal cerebrospinal fluid, and so AFP levels are not elevated. Thus, AFP cannot be used to detect the approximate 20% of spina bifidas and 94% of encephaloceles that are closed, while 90% to 100% of anencephaly is detected. The following major genetic conditions have been identified by elevated MSAFP levels during pregnancy:

- ▶ Open NTDs—spina bifida, anencephaly, and encephalocele
- ▶ Ventral wall defects—omphalocele (midline defect with herniation of abdominal organs into a membrane-covered sac), gastroschisis (extrusion of abdominal organs anteriorly with no covering membrane)
- ▶ Congenital nephrosis (Finnish type)
- ▶ Cystic hygroma (sometimes in association with Turner syndrome)
- ▶ Other fetal defects such as Turner syndrome, teratomas, hydrocele, certain congenital skin conditions, and esophageal and duodenal atresia

AFP in maternal blood rises during pregnancy until the 30th gestational week and then falls. The concentration of amniotic fluid AFP (AFAFP) is highest at the end of the first trimester. A number of variables influence how laboratory results are calculated. Some are patient characteristics such as maternal weight, race, gestational age, maternal diabetes mellitus, and population norms. Various formulas and tables have been developed to determine the probability of a given woman with particular findings and characteristics for having a fetus with an NTD that are also population adjusted for the population frequency of NTDs; combining these with the results from testing other serum values increases diagnostic accuracy.

While the chief reasons for elevated AFP levels (other than diseases) are errors in calculation of gestational age, low maternal weight, and African heritage, there can be other reasons for high MSAFP levels. Some of these relate to pregnancy outcome,

whereas others are population or biological in nature regarding interpretation when the MSAFP results are being evaluated. These include:

- ▶ Multiple pregnancy
- ▶ Prior amniocentesis or fetoscopy
- ▶ Fetal death
- ▶ Severe Rh incompatibility
- ▶ Threatened abortion
- ▶ Placental distress
- ▶ Levels in past pregnancies
- ▶ Bloody contamination

Some clinicians will repeat the MSAFP, while others believe that targeted ultrasound or amniocentesis is warranted immediately.

Waiting for serum screening results is difficult for families. Parents should be informed promptly of both normal and abnormal results. They should not be told to assume normality if they do not hear from the clinic or center. Those having abnormal results require sensitive and appropriate counseling and referral for appropriate prenatal diagnosis.

Clinicians should be sure that clients receive clear, nonbiased information about the meaning of the results of the prenatal screen, and that those with abnormal levels are promptly referred for ultrasonography and amniocentesis. Table 8.8 summarizes serum screening results for NTDs and chromosomal abnormalities.

TABLE 8.8 Association of Selected Maternal Serum Analytes and Selected Abnormality

| Analyte | NTDs | Abnormality | |
|-----------------------|--------|-------------|------------|
| | | Trisomy 21 | Trisomy 18 |
| Maternal serum AFP ** | ↑ | ↓ | ↓ |
| hCG | Normal | ↑ | ↓ |
| uE3 | Normal | ↓ | ↓ |
| PAPP-A | NA | ↓* | ↓ |
| Inhibin A** | NA | ↑ | NA |

* = first trimester. ** = second trimester.

When MSAFP levels are elevated, additional testing is indicated. Typically an ultrasound examination is performed that includes confirming gestational age and fetal viability, and ruling out multiple gestation if possible. If the gestational age used for the MSAFP interpretation was wrong, then a recalculation is done. If gestational age is correct, then targeted ultrasound is done to look for the malformations known to result in high MSAFP levels.

Identifying Candidates for Prenatal Diagnosis

Nurses should be able to identify individuals who are candidates for prenatal diagnosis, which is different from prenatal screening and detection suggested for all pregnancies. This information should include both maternal and paternal histories. It may be appropriate to identify candidates for prenatal diagnosis before the individual is pregnant and include that information in preconceptional counseling. This assessment may be accomplished by interview, questionnaire, and history.

Amniocentesis and CVS are the most common invasive diagnostic methods now used. Genetic indications for prenatal diagnosis are listed in Table 8.9. Various prenatal diagnostic procedures are listed in Table 8.10.

These indications identify individuals who will be at increased risk and thus form the basis for assessing which pregnant women are likely candidates for prenatal diagnosis. The most common reason for recommending prenatal diagnosis is advanced maternal age (AMA), 35 years or older. Interestingly, many women who are AMA are opting for noninvasive testing when no other risks are identified.

Individuals who belong to an ethnic group with an identified high frequency of a specific detectable inherited disorder should be asked about their carrier status. If they have not been asked, a first approach (depending on the stage of the pregnancy) may be to ascertain the carrier status of the father because, for some disorders, pregnancy makes accurate maternal determinations inaccurate. If he is a carrier, then amniocentesis may be appropriate and should be discussed. Both young and advanced paternal age can increase the risk of chromosome aberrations and other birth defects in the fetus. Advanced paternal age increases the risk of some dominant gene mutations (as discussed in Chapter 4) that are potentially detectable by ultrasound.

It is the standard of care to inform all pregnant women of the option of screening alone or as part of a multiple marker test, as described earlier, as well as for level I ultrasound. Many require informed consent whether the procedure is desired or not desired. If such diagnosis or expertise is not available in the area, it is the professional's responsibility to refer the client to a center that does provide the needed expertise or service, and assist in making arrangements for the service.

Client Information Before Prenatal Diagnosis

Before clients can make a decision of whether to have prenatal diagnosis, the nurse should be able to explain, clarify, and interpret the information at a level that the client can understand, one that is culturally sensitive, appropriate, and free from any coercion. This should be accomplished as early as possible in the pregnancy, so that the client can think about the options and discuss them again. Written reinforcement

TABLE 8.9 Some Current Genetic Indications for Prenatal Screening

| Indication | Possible Standard Prenatal Diagnostic Technique |
|---|--|
| Pregnancy at risk for chromosome aberration Maternal age of 35 years and above Previous child with chromosome abnormality or instability disorder Chromosomal abnormality in parent (mosaicism, translocation carrier, other aneuploidy) Previous stillbirth or perinatal death (cause unknown) History of infertility in either parent Habitual abortion history Previous child with malformations (no chromosomes analyzed) Intracytoplasmic sperm injection Abnormal serum levels of multiple markers | Amniocentesis, CVS Amniocentesis, CVS Amniocentesis, CVS Amniocentesis, CVS Amniocentesis, CVS Amniocentesis, CVS Amniocentesis, CVS, ultrasound Amniocentesis, CVS Amniocentesis, CVS, ultrasound |
| Pregnancy at risk for NTD High maternal serum level of AFP Previous child with NTD NTD in either parent or close relative | Amniocentesis, ultrasound Amniocentesis, ultrasound Amniocentesis, ultrasound |
| Pregnancy at risk for X-linked inherited disorders Mother a known carrier Close maternal male relative affected | Amniocentesis, CVS Amniocentesis, CVS |
| Pregnancy at risk for detectable inherited biochemical disorder Parents known carriers or affected Previous child born with known detectable biochemical disorder Close family member with a known inherited biochemical disorder | Amniocentesis, CVS Amniocentesis, CVS Amniocentesis, CVS |
| Other High degree of parental anxiety Significant exposure to radiation, infection, chemicals, or drugs Diabetes mellitus in mother Previous child with structural abnormality Family history of structural abnormality | Amniocentesis, CVS, ultrasound Amniocentesis, ultrasound, CVS Ultrasound amniocentesis Ultrasound amniocentesis, CVS Ultrasound amniocentesis, CVS |

NTD, neural tube defects; AFP, α -fetoprotein; CVS, chronic villus sampling. Ultrasound refers to targeted or extended ultrasound

TABLE 8.10 Selected Prenatal Diagnostic Procedures

| Name | Comments |
|---|---|
| Amniocentesis | A sample of amniotic fluid is withdrawn from amniotic sac after ultrasound guidance. Ideally done between 15th and 18th gestational week. See text. |
| Chorionic villus sampling | A sample of chorionic villi is obtained abdominally or cervically to test for chromosomal abnormalities and other genetic conditions at 10 to 12 weeks gestation. Fetal loss of 1% over baseline. |
| Early amniocentesis | Done at 12 to 14 weeks gestation. Have found increase in pregnancy loss and congenital foot deformities. No apparent advantage over CVS or amniocentesis. |
| Fetal blood sampling | Also known as percutaneous umbilical blood sampling (PUBS). Usually umbilical cord blood is sampled through an ultrasound-guided needle inserted in maternal abdomen. Used for diagnosis of genetic disorders that cannot be diagnosed any other way and rh disease; ascertain fetal blood chemistry such as acid–base balance. Fetal loss rates range from 2% to about 9%. |
| Fetal cells and fetal cell-free DNA circulating in maternal blood | Known that fetal cells and fetal DNA sequences are present in maternal circulation but in very small numbers. Once enriched and amplified, various technologies may be used to determine fetal sex and certain chromosomal abnormalities. |
| Pre-implantation diagnosis | Genetic analysis is carried out on embryos in the 4- to 8-cell stage, and unaffected embryos can be transferred to the uterus. Often done after assisted reproductive techniques such as in vitro fertilization. |
| Ultrasound | Used alone to detect fetal structural abnormalities between 18th and 20th week ideally. Sound waves are converted to images. Also used in conjunction with other procedures and tests such as for early detection of certain chromosome disorders using nuchal translucency and nasal bone, along with analysis of certain serum analytes. |

is an excellent way to supplement information. Information provided should include that shown in Box 8.4. An integral part of the nurse's goal for the client at this time should be to establish and build a supportive relationship for counseling during the rest of the pregnancy, especially after prenatal diagnosis.

BOX 8.4***Client Information to Include Before Prenatal Diagnosis***

- ▶ The reason prenatal diagnosis is considered appropriate for this woman or couple.
- ▶ What will be analyzed (e.g., chromosome and α -fetoprotein analysis are usually routinely done regardless of the primary reason for seeking amniocentesis; thus, unexpected results could occur).
- ▶ What information will be obtained (e.g., the couple should know that a search for chromosome abnormalities is broader than a search for only Down syndrome, even if that is the primary reason that the couple is interested in prenatal diagnosis).
- ▶ The risk of having an affected child in this pregnancy before prenatal diagnosis.
- ▶ What the procedure being considered entails, including description, cost, length of time, where it is to be done, and aftercare.
- ▶ What the risks of the procedure are—the magnitude and the kind.
- ▶ What can and cannot be detected—this should include the information that, while some disorders can be virtually excluded (e.g., chromosome disorders if an amniocentesis is being done), a completely normal infant cannot be ensured, both because of a slight risk of error and because no procedure can detect every possible defect.
- ▶ The length of time between the procedure and when the results are obtained.
- ▶ How the results will be communicated to them.
- ▶ That prenatal diagnosis can be done even if the couple does not wish to consider abortion as a viable alternative; if the results are negative, it may relieve anxiety; and if they are positive, they may change their minds, seek fetal therapy, plan for the delivery of the infant in an expert care center, or have time to think about alternative plans for care of the infant.
- ▶ In those now relatively uncommon cases where an X-linked recessively inherited disorder is in question and cannot be specifically assayed, they should understand that a specific test will not be done. The fetal sex will be determined and used for decision making.
- ▶ Unintended possible psychological consequences if a problem is detected.
- ▶ Potential unintended consequences such as pressure from insurance companies to not carry an affected child to term, or termination or diminution of benefits for the pregnancy, the child, and aftercare.

Amniocentesis

Amniocentesis preceded by ultrasound is still frequently used for prenatal diagnosis. With this frequently emerging diagnostic field, parents should see a geneticist who keeps abreast of current developments. All chromosome disorders are potentially

diagnosable, but as some may arise sporadically in women who are younger than 35 years of age, not all will be detected prenatally unless a fetal chromosome analysis is completed. Also, high-resolution karyotyping to visualize submicroscopic chromosome changes is not done routinely unless there is a prior reason for doing it. The risk of chromosome abnormalities at different maternal ages is discussed in Chapter 4. The determination of AFP levels and other parameters for NTDs is usually routine at the time of amniocentesis. Many inherited biochemical disorders can be diagnosed by specific biochemical assays or DNA assays, and the latter are used to detect hemoglobinopathies (e.g., sickle cell disease and the thalassemias). Thus, prenatal testing may be at the level of the mutant gene (DNA), chromosome, gene product (biochemical), or phenotype (morphology).

Amniocentesis refers to the withdrawal of a sample of amniotic fluid from the amniotic sac. It is usually performed at the 15th to 18th week of gestation, when the uterus has reached the pelvic brim, the amniotic fluid volume is adequate (150–250 mL), and enough fetal cells are present for analysis (see Figure 8.1). Fetal cells in the amniotic fluid come from the skin and mucous membranes of the respiratory, digestive, genital, and urinary tracts as well as the umbilical cord and amnion. This also allows analysis to be completed in time for the parents to terminate the pregnancy if they so choose. The procedure is usually done on an outpatient basis, paying careful attention to asepsis. Most practitioners recommend a dose of Rh immunoglobulin to all unsensitized Rh-negative women to prevent isoimmunization. With increased frequency of use, amniocentesis has become a safer procedure than it initially was. An accepted risk figure for fetal loss due to amniocentesis that is above the figure for losses in the same period of pregnancy has been given as 0.25% to 0.5%. An increased incidence of fetal loss and of other complications was associated with an increased number of needle insertions for sampling, uncertain placentation or anterior placentation, and the use of needles with gauges of 19 or larger.

Overall complications from amniocentesis are relatively infrequent. Questions as to whether infants of mothers having amniocentesis are more likely to develop respiratory problems and emphysema from chronic leakage of amniotic fluid, interfering with normal lung development, should be addressed, although this is estimated to occur in a very small percentage. Maternal complications can include vaginal bleeding, amniotic fluid leakage, infection, Rh sensitization, precipitation of labor, and perforation of the bladder or placenta. Fetal risks include spontaneous abortion, needle puncture injuries, and injury because of withdrawal of amniotic fluid such as amniotic band syndrome. It is not uncommon for the woman to have cramping, vaginal spotting, and amniotic fluid leakage as transient aftereffects.

After amniocentesis, the waiting period between the procedure and results can be 2 to 3 weeks, although rapid chromosome culture techniques can be used to provide results more quickly. This may be a time of anxiety and apprehension for the couple, particularly if they have had a previous birth with a genetic disorder. Indeed, amniocentesis has been referred to as a crisis situation in terms of the psychosocial stress and anxiety imposed on the normal stresses surrounding a pregnancy. Unresolved past problems, unconscious feelings of guilt and failure, and stresses within the family are exacerbated during this period, especially in families that have experienced

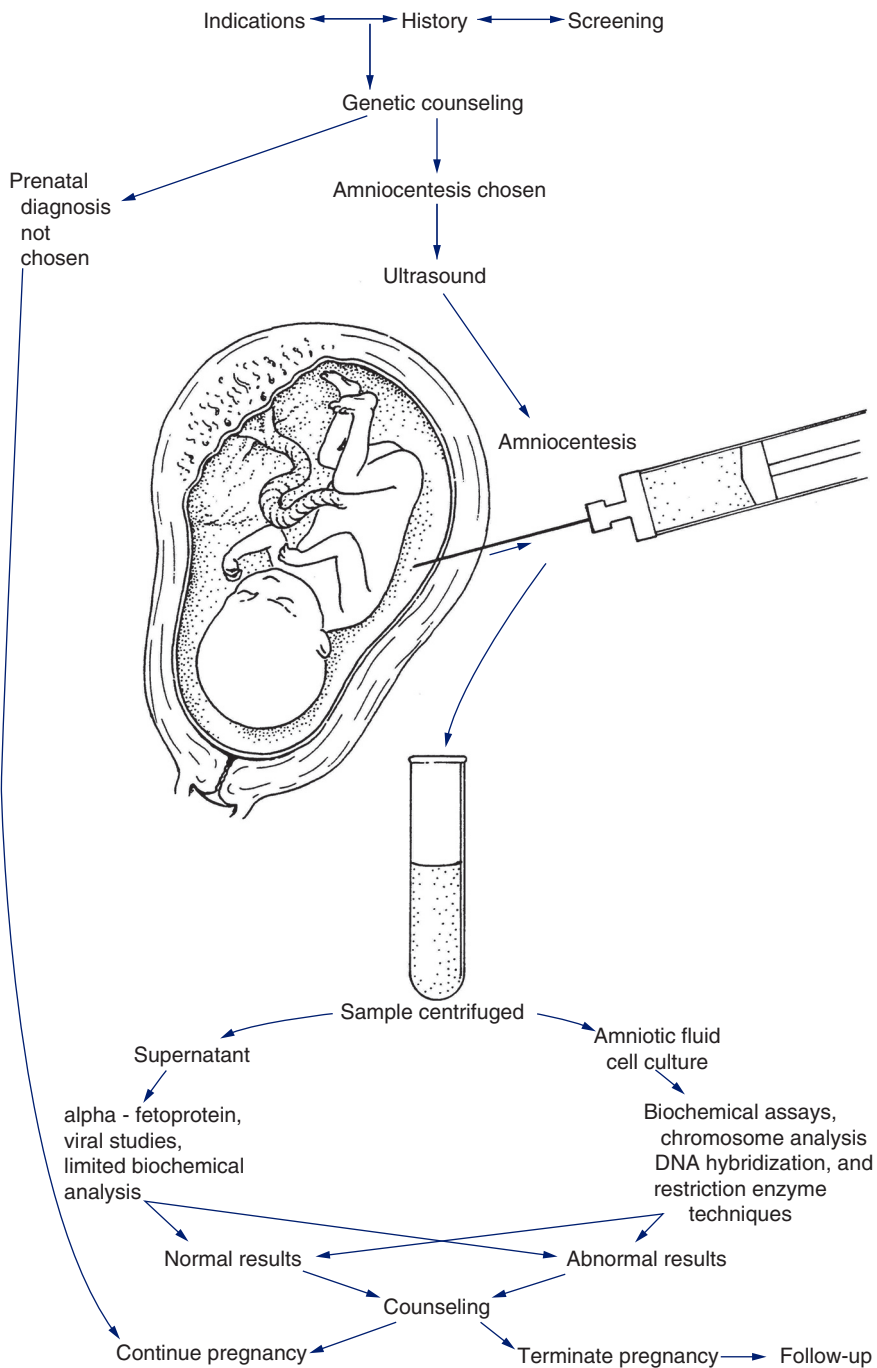


FIGURE 8.1. Amniocentesis: options and disposition of samples.

the birth of a child with a genetic disorder. Awareness of these aspects, the establishment of a good relationship with the family, and a clear, mutual understanding of the information prenatal diagnosis provides will be helpful during this period.

If abnormal findings result from the prenatal diagnosis, the couple has a limited time period in which to make a decision in regard to the continuation or termination of the pregnancy. They may need discussion and specialized counseling with experts on the disorder and with parents of children with the disorder, in addition to other supports. Giving the results to the family must be done sensitively and skillfully, and both members of the couple should be told in person by the practitioner in a private setting when there is time to discuss issues and options. For many couples who have had a child with an inherited genetic disorder and have a high risk for another child with the same disorder, the availability of prenatal diagnosis offers them the chance to have an unaffected child. Without it, 50% to 90% of couples who have a 25% to 50% risk of an affected child would not have attempted another pregnancy.

In a pluralistic society, it is important for the nurse and other professional practitioners to support the right of individual clients to make a decision that is compatible with their personal philosophy and lifestyle and to provide support for that decision. The World Health Organization (WHO) has stated that decisions following prenatal diagnosis should be made by the couple and that the responsibility of the health care worker is to provide the information in a manner that can be understood. While prenatal diagnosis is routine, both maternal and paternal feelings of depression after hearing that the fetus is affected may occur. Family disruption can also occur after the birth of an affected child. Thus, the nurse should be aware that ongoing counseling and contact are necessary after pregnancy termination and should make every effort to ensure access to such counseling for both partners. Studies of stress associated with amniocentesis indicate stress is greatest when waiting for results and, if the results are abnormal, when making a decision. Feelings may be similar to those waiting for the results of diagnosis following abnormal screening tests discussed later. If the pregnancy is terminated, then stress is great after the procedure, as well as just before it. Plans for nursing intervention should include support during these periods.

Chorionic Villus Sampling

Chorionic villus sampling (CVS) is typically done at 10 to 12 weeks gestation, but has been performed earlier. Usually CVS is done by the transcervical or transabdominal route. Early detection allows wider scope for in utero treatment or, if chosen, safer early pregnancy termination. Cytogenetic, enzymatic, and DNA studies can all be performed on chorionic villi, and the amount of material obtained makes this method preferable for DNA analysis. A disadvantage of CVS is that neither AFP testing nor any other assay needing amniotic fluid can be done on CVS specimens. Thus, women who have CVS should be referred for MSAFP screening at 15 to 20 weeks. Few effects immediately follow CVS except for vaginal bleeding. The major serious fetal sequelae from CVS are for transverse limb deficiencies or reduction defects. There appears to be a small risk of transverse limb deficiency that overall is 0.03% to 0.14% after CVS. The risk for spontaneous fetal loss from CVS is approximately 1.64% to 2.5%. This is lower using the transabdominal route. As with most of the other prenatal diagnostic procedures, CVS should be done in the context of an experienced center, practitioner, and program for best results. Usually chromosome

results from direct preparations are available as early as 24 to 36 hours, with cultures for confirmation in about 1 to 2 weeks.

Ultrasonography

Ultrasonography alone is the major method for detecting fetal malformations. Ultrasound consists of vibrations that are inaudible to the human ear. This high-frequency sound produces a mechanical pressure wave, causing vibration consisting of the contraction and expansion of the body tissues and fluids through which it passes. The waves are transmitted into the body through a transducer, and echoes at boundaries between adjacent tissues are reflected. These are converted into electrical signals and are amplified and processed so that they can be visually displayed on an oscilloscope and videotaped or photographed. Fluid-filled or surrounding structures are visualized especially well. The use of oil or gel on the abdominal wall is necessary to diminish the loss of waves. Ultrasound can be used in different ways or modes. In pregnancy, the frequencies used usually avoid known tissue effects from ultrasound that in some instances are the basis for its use, such as heat and tissue destruction. Ultrasound is noninvasive and nonionizing. Patient preparation is minimal.

Screening ultrasound in early pregnancy at 10 to 13 weeks is usually to accurately date the pregnancy by measures such as crown rump, examine the fetal anatomy, and measure fetal nuchal translucency (abnormal thickness at the posterior aspect of the neck of a fetus less than 13 weeks, after which it is called nuchal thickening, nuchal fold, or cystic hygroma). The absence of the fetal nasal bone may also be assessed since it is associated with Down syndrome. Alone, a nonvisualized nasal bone during the second trimester of pregnancy is said to identify 40% to 45% of Down syndrome pregnancies.

The prenatal uses of ultrasound may be either primary or adjunct. The placenta and internal and external fetal structures can be visualized. Ultrasound is used in conjunction with (a) amniocentesis, CVS, fetoscopy, and fetal blood and tissue sampling as a guide to increase safety and diagnostic accuracy and (b) abnormal AFP and/or serum screening test levels to rule out false positives and false negatives due to inaccurate gestational age assessment, fetal death, or multiple pregnancy or to define the abnormality present. Alone, ultrasound can be used for a number of reasons:

- ▶ Detecting certain fetal abnormalities in pregnancies identified as high risk. This can include such features as increased nuchal translucency or cystic hygroma, abnormal fetal bone length or absent fetal nasal bone, and certain other indicators that might be associated with fetuses with trisomy 21 and other aneuploidies.
- ▶ Monitoring fetal growth and fetal measurements such as crown-rump length and biparietal fetal head diameter.
- ▶ Determining the number of fetuses.
- ▶ Determining fetal presentation.
- ▶ Assessing gestational age.
- ▶ Ascertaining fetal hypoxemia.

- ▶ Ascertaining fetal environment, including amniotic fluid volume, assessment of the umbilical cord, blood flow, and evaluation of the placenta for anomalies or maturity.
- ▶ Detecting ectopic pregnancy.
- ▶ Assessing structural and functional integrity.
- ▶ Evaluating immediate fetal risk for optimum management and treatment.
- ▶ Assessing fetal viability.
- ▶ Detecting hydatidiform mole.

In addition, the extended or detailed examination and targeted imaging for fetal anomalies (TIFFA) are terms used for examination to detect fetal anomalies. Those who should be referred for targeted, detailed ultrasonography have these characteristics:

- ▶ Previous child or family history of detectable structural malformation or anomaly (including congenital heart defects)
- ▶ Those who are at other known high risk for detectable fetal anomaly such as:
 - Maternal condition predisposing to fetal anomaly
 - Drug/alcohol exposure in pregnancy
 - Maternal infection in pregnancy
- ▶ Abnormal pregnancy progression
- ▶ Abnormal maternal serum AFP or multiple serum screening results
- ▶ Abnormal AFP results on amniocentesis
- ▶ Intrauterine growth restriction
- ▶ Suspicious findings on routine ultrasound

The availability of high-resolution ultrasound machines incorporating both curvilinear and multifocal transducers allows for diagnostic interpretation in the hands of the skilled ultrasonographer. These can be translated into clinical outcomes. For example, if esophageal atresia is diagnosed, the esophageal pouch can be aspirated at birth and oral feedings avoided until repair is accomplished, thus preventing aspiration and pneumonia and decreasing morbidity. Moving structures such as the beating fetal heart (using Doppler), the placenta, and fetal movement can be observed, and four-chamber views of the heart allow for referral for fetal echocardiography and other procedures if needed. Sonographic screening effectiveness for detection of cardiac lesions varies with the type of defect. Advances in ultrasound imaging in three and four dimensions (real-time three-dimensional imaging) are beginning to be used in prenatal diagnosis.

Ethical, Social, and Legal Issues Associated With Prenatal Diagnosis

Some of the issues surrounding prenatal diagnosis relate to pregnancy termination after the results are available, because a second-trimester abortion is viewed by some

as both an ethical and a medical problem. The option of selective abortion allows meaningful reproductive alternatives to be presented to a couple at risk for a fetus with a known defect. The entire question of abortion is complex and fraught with emotion, which cannot be addressed here adequately, but will only be viewed in a limited way as it relates to prenatal diagnosis.

A professional nurse will have to recognize and separate personal beliefs from those of the clients in order to provide quality care. It is important that clients get accurate, clear, unbiased, comprehensible information, and then have support with whatever decision is made. Because 95% of amniocenteses have resulted in the detection of a normal fetus, the procedure may be very reassuring to couples at risk. In addition, some parents who would not consider pregnancy termination may change their minds if they discover a fetus with a poor prognosis or inevitable death. They may also arrange delivery at a site with specialized care. In some cultures, it may be preferable to accept what is given and have a child with a birth defect rather than no child.

Other issues include the right of the person to refuse to participate or to have a prenatal diagnostic procedure, disclosure, confidentiality, access to information, the right to privacy, ownership of the samples taken, and ambiguous finding (see Chapter 13). Other issues relate to access and how socioeconomic factors might influence the availability of prenatal diagnosis, especially for women who may not be defined as high-risk, thus creating conditions of health disparity.

Another situation for consideration is that in which the pregnancy is at risk for a relatively minor defect, such as cleft lip and palate. One must ask whether or not the practitioner can judge what a minor defect is to the couple concerned. Coping with necessary surgery and rehabilitation may be beyond the capacity of that particular couple's resources—financial, emotional, and physical. It may produce additional stresses to the rest of the family or to the marital relationship, of which the practitioner cannot be aware. A positive action that can be taken is to provide immediate (because the time element is so critical), expert counseling for the couple in order to try to elicit the true concerns and problems and help them arrive at a decision that is realistic for the couple, not the practitioner. A broader question is: Who decides normality? Should abortion be condoned or condemned for a defect such as an extra digit on the extremities?

Unexpected or ambiguous findings can result from prenatal diagnosis and can present dilemmas. The practitioner may or may not feel obligated to completely disclose such findings if there was an agreement before testing that limited what would be disclosed. For example, if a woman at risk for Down syndrome in the fetus was found to be carrying a fetus with a small chromosome inversion about which little is known, the practitioner may only wish to tell her that the fetus does not have Down syndrome, and not mention the inversion. However, this paternalistic approach is probably not legally or morally viable. Current knowledge and trends favor openness and honesty in informing the parents of such situations, combined with expert supportive counseling. The limitations of current knowledge should be made clear. Ambiguous findings may also arise after ultrasound screening that identify what are called fetal "soft" markers found on ultrasound such as choroid plexus cysts in the fetal brain or mild renal dilatation, which not too long ago was believed to be

associated with Down syndrome but is now known to be present in 1% to 2% of normal fetuses.

Other issues regarding prenatal diagnosis have more recently been discussed. For example, what are the issues for diseases that emerge in adulthood? What are the issues, concerns, and rights of parents to select pregnancy termination or life for a fetus for a disease such as Huntington disease or Alzheimer disease that will most likely not be symptomatic until that fetus is an adult? What about the risk for inherited, or susceptibility to, cancer? What is the meaning of the finding of a gene mutation such as *BRCA1* if found in the fetus? What will guide decisions when cancer development is not certain? These issues may not involve only disease states but issues of living such as life insurance, health benefit coverage, and stigmatization. An issue that has occurred in pre-implantation genetic diagnosis is that of late-onset genetic disorders such as Huntington disease in which parents wish to ensure that their offspring is disease-free but do not wish to know their own carrier status, and ask that a disease-free embryo be selected. Another application has been using pre-implantation genetic diagnosis for selection of an embryo based on HLA type to serve as a stem cell donor for a sibling in need of such treatment. Other issues also include the possibility of the finding of a future cure for a late-onset disease that is not now available. In the future, will selection of embryos after pre-implantation genetic diagnosis be only for disease, or will preferred traits eventually be sought, for example, taller stature or pleasing facial features if those could be determined, and should this be allowed?

A somewhat related situation is that in which prenatal diagnosis reveals that the mother is carrying a fetus with a disorder that will be extremely costly to society to treat and to educate and which she decides to carry to term. How will society regard such families in the future? Will society continue to assume financial responsibility? Should the values of the individual or of society prevail? If a woman has the right to choose to terminate a pregnancy, shouldn't she also have the right to choose not to terminate it? Can society morally deny services to a disabled child because of his or her parent's decision? All of these are complex fundamental issues that have to do with the rights of the individual and the good of society, freedom and equality, and the quality of and the right to life. Certainly simplistic, rigid methods cannot be used to solve them; a thoughtful, individualized approach should be taken. Professionals can help to emphasize the importance of the preservation of choice and to safeguard these choices in their practice.

ASSISTED REPRODUCTIVE TECHNIQUES

It was in July 1978 that the first “test tube” baby, Louise Joy Brown, was born in the United Kingdom using IVF; in 1992, the first birth using intracytoplasmic sperm injection occurred. It is now estimated that 1% of all births in the United States were conceived using ART. The use of ART, including IVF and embryo transfer, intracytoplasmic sperm injection (ICSI), and other approaches, has vastly benefited infertile couples but has created a variety of questions and ethical issues. Many experimental techniques are being used in order to find the most effective and safest approaches that minimize multiple pregnancies and unwanted side effects. In spite of these successes, questions have been raised that focus on the health and development

outcomes of children born after ART and of ethical issues that have emerged from this technology. Examining health and development of children born using ART are complicated by many issues, including parental infertility, parental age, parity, the cause of the infertility, whether hormonal or other therapy is used to maintain pregnancy, the maturity of sperm used, and delayed fertilization of the oocyte. In ICSI, most natural selection mechanisms are bypassed. ICSI has become commonly used in as many as 80% of all ART procedures. In regard to ICSI, in which a single spermatozoon is injected into the oocyte cytoplasm, lower birth weights have been observed. There is also an increase in multiple pregnancies, which are associated with additional complications. ICSI has been associated with a higher number of major birth defects than naturally conceived children, especially in regard to chromosomal defects, including those of the sex chromosomes. Those conceived using IVF had a greater number of cardiovascular and urogenital defects, particularly hypospadias.

A variety of social, legal, and ethical issues are engendered by ART. These include the creation of multiple embryos for ART and their potential selection for specific characteristics not related to a genetic disorder; the use of unused embryos who are under 14 days postconception and those between 14 and 18 days for research purposes; induction of twins; the use of eggs, sperm, or embryos for research when the donor has not given explicit consent; induction of twins through division of embryos; creation of embryos for research purposes; constructing embryonic cell lines from unused embryos; and selective reduction of multifetal pregnancies after ART. In some of these, issues of informed consent and the right to keep and store cells and tissues for later research and other purposes are of concern. Issues have also been created by mistakes during IVF that in one case involved transfer of embryos not selected for the procedure; in another, a White woman's eggs were fertilized by mixed sperm due to a poorly sterilized pipette. She gave birth to one Black and one White twin, so her partner was not the father of both her children. Such instances have raised questions involving parental rights and duties. Another issue has been the potential for ART children to seek their donor parent in much the same way people who are adopted have done, and issues of disclosure and confidentiality for gamete donors.

SCREENING GAMETE DONORS

Sperm donation for artificial insemination or IVF is a genetic reproductive option when both parents are known carriers of a deleterious autosomal recessive gene or the male is affected or at risk for carrying an autosomal dominant or X-linked mutant gene. Yet there is still misunderstanding and inappropriate use of the procedure, especially regarding screening of donors. The couple should always understand that a normal infant cannot be guaranteed, although with the advent of various prenatal diagnostic techniques such as pre-implantation genetic diagnosis, selection of embryos is improved. Every effort should be taken to exclude those ova and sperm donors at greater risk than the general population. Some possible indications for exclusion include:

- ▶ Presence of a single gene disorder, chromosome abnormality, or serious multifactorial disorder in the donor or close blood relative

- ▶ Rh or ABO blood group that might cause incompatibility between mother and fetus
- ▶ A male donor who is 40 years of age or older
- ▶ A female donor over 34 years of age
- ▶ Exposure to drugs, radiation, certain infectious diseases, or chemical mutagens
- ▶ Unexplained stillbirths, multiple miscarriages, or fetal deaths in their own children or close blood relative

NEWBORN SCREENING

Newborn screening is one of the great genetic public health success stories. Once PKU was associated with intellectual disability, which could be prevented with a low-Phe diet, a search began for a method to reliably detect PKU in newborns. Robert Guthrie developed such a test using blood taken from the neonate by heel stick with a few drops placed on filter paper and dried. Testing was based on a bacterial growth inhibition assay using the dried blood spot. This test became the prototype for screening virtually the entire newborn population.

In the early 1960s, newborn screening for PKU rapidly became part of state maternal–child health programs. Newer technology has identified additional mutations for genetic screening and provided ways to detect them. Thus, the number of disorders that can be detected in the newborn has vastly increased to nearly 60, but states vary as to which disorders are included in their newborn screening panels. Advocacy by parents has attracted popular press attention to this state variability. Articles in the popular press and electronic media have highlighted cases of adverse consequences of potentially detectable metabolic disease in newborns that were not detected because the state in which the parents resided did not include those conditions in their state screening programs, as well as stories in which an infant was identified through newborn screening with a rare disorder and treated.

CASE EXAMPLE

One example that provoked activism by parents was that of a 6-month-old South Dakota infant who developed a rotavirus infection with diarrhea and vomiting. He took Pedialyte and had little else but was not dehydrated. He was found dead in his crib the next morning, and sudden infant death syndrome was thought to be the cause; however, autopsy revealed fatty accumulation in the liver. These changes plus the history of reduced caloric intake led to further testing, which revealed that he had medium chain acyl-CoA dehydrogenase (MCAD) deficiency, described below. One of the reasons for including this disorder in routine newborn screening programs is that affected children and families can receive necessary preventive education and therapy and in many cases avert untoward incidents.

The major reason for universal newborn screening is to identify at-risk infants, provide early treatment, and prevent serious health consequences, especially severe intellectual disabilities. Infants with abnormal initial testing results usually have second screens and, depending on the results, further testing in order to confirm a diagnosis, but temporary treatment may be started in the interim if believed necessary. Many of the disorders detectable by newborn screening tests respond well to early treatment such as dietary restrictions.

Newborn screening must be concerned not only with screening and testing but with other components, such as:

- ▶ Education
- ▶ Recalls and short-term follow-up
- ▶ Genetic counseling
- ▶ Diagnosis
- ▶ Referral to specialists
- ▶ Management
- ▶ Treatment
- ▶ Nursing
- ▶ Social and psychological services, in the short and long terms
- ▶ Reproductive choices and life planning
- ▶ Assistance in other areas such as schools, setting standards, quality assurance, and evaluation, ideally functioning as a coordinated system

Newborn screening programs are managed by each state's public health department (see www.babysfirsttest.org/newborn-screening/states). States routinely screen newborns for a set of metabolic disorders by blood specimen or through other assessments of genetic or nongenetic causation such as congenital hearing loss, developmental hip dysplasia, HIV infection, and congenital toxoplasmosis. There have been a variety of standards and guidelines developed regarding criteria for inclusion of a disorder within screening programs, some specific to universal state newborn screening.

Some of the decision making of states has been based on the racial and ethnic population of those states and the most prevalent genetic disorders of those ethnic groups since certain disorders are known to be prevalent in certain ethnic groups and rare in others, with cost-effectiveness as a driving force. Some have suggested that some disorders do not need to be universally tested for but can be targeted by ethnic group, a practice that in our ethnically mixed society may be genetically as well as ethically unsound, although some states are piloting targeted newborn screening for certain disorders.

From time to time, states add disorders to mandated newborn screening programs, sometimes as a temporary pilot that may be:

- ▶ Universally applied
- ▶ Applied for specific selected populations deemed to be at greatest risk

- ▶ Included on a limited basis
- ▶ Performed only by request

The following genetic disorders are mandated for newborn screening in most states:

- ▶ PKU
- ▶ Congenital hypothyroidism
- ▶ Hemoglobinopathies such as sickle cell disease
- ▶ Galactosemia
- ▶ Tyrosinemia
- ▶ Maple syrup urine disease
- ▶ Biotinidase deficiency
- ▶ Congenital adrenal hyperplasia
- ▶ MCAD deficiency
- ▶ Cystic fibrosis
- ▶ Homocystinuria

States also mandate screening for other conditions such as congenital hearing loss, which may be genetic or nongenetic, congenital toxoplasmosis, and HIV infection. Other countries include conditions not currently mandated for inclusion in U.S. newborn screening programs and vice versa.

An issue is that some disorders can be detected at 1 or 2 days after birth, but others are not detectable until the newborn is 5 days or older. This time is usually after hospital discharge, meaning that responsibility for additional specimen collection from a primary health provider or public health clinic is needed. Thus, primary care practitioners, including nurses, are responsible for ascertaining that newborns referred to their practices have been screened and results have been returned. Often nurses are instrumental in ensuring that these initial and follow-up specimens are collected.

The Recommended Uniform Screening Panel (RUSP) from the U.S. Department of Health and Human Services has identified 57 conditions for inclusion in every state's newborn screen. The decision matrix for adding new conditions to the RUSP was revised in January 2013, making the process more consistent and transparent.

Disorders Included in Newborn Screening

Because nurses are likely to need information about disorders routinely screened for in newborns in order to assess the newborn intelligently, to communicate with and educate parents of newborns and infants, and to explain the need for further testing if an abnormal result is found, a brief synopsis of these are in Table 8.11. PKU is discussed in more detail below. The advent of mass newborn screening has shown that many of these disorders are more common than formerly believed. Infants dying from some inborn errors in the past were simply not diagnosed as having the disorder. Many were thought to have died of overwhelming sepsis, so the true disease

TABLE 8.11 Disorders Commonly Included in Newborn Screening Programs

| Disorder | Incidence | Number of States Requiring Inclusions | Description |
|--------------------------------|------------------------------------|---------------------------------------|--|
| Biotinidase deficiency | 1:60,000–1:137,000 | 40 | AR disorder. Various degrees of severity. Typically symptoms begin at 3–5 months but can be as early as 1 week or even present at 10–12 years of age. Clinical picture includes myoclonic seizures, hypotonia, feeding difficulties, fungal infections, vomiting, diarrhea, ketoacidosis, coma, alopecia, skin rash, ataxia, developmental delay, lethargy, respiratory, vision and hearing problems. In severe cases, one can see acute metabolic decompensation. Treatment consists of daily free biotin supplementation. |
| Congenital adrenal hyperplasia | Depends on type, 1:10,000–1:18,000 | 45 | AR inheritance for all types. 90% due to 21-hydroxylase deficiency; other types due to 11- β -hydroxylase deficiency and 17- α -hydroxylase deficiency. Several forms; some are mild, not appearing until adulthood. In the most common type, androgen hypersecretion results in masculinization of female fetuses and infants with ambiguous external genitalia, while in males premature pubic hair appears between 6 months and 2 years of age. Treatment is cortisol replacement therapy and correction of ambiguous genitalia. |
| Congenital hearing loss | 1–3:1,000 | 28 | Bilateral, profound congenital hearing loss can arise from a number of genetic causes with varying modes of transmission or infection such as cytomegalovirus. Connexin 26 gene mutations account for about 20% of childhood deafness. Early detection is important for optimal language development. |

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|---------------------------|--|----|--|
| Congenital hypothyroidism | 1:3,600–1:5,000 | 51 | Congenital thyroid deficiency results from transient (prematurity and maternal antithyroid medications) and nontransient causes including congenital deficiency of thyroid tissue, deficiency of thyrotropin-releasing hormone, thyroid-stimulating hormone (TSH) deficiency, impaired response to TSH secretion, and more. States vary in test used. If needed, therapy should begin no later than one month of age to prevent intellectual disability. Confirmatory diagnosis must be done as quickly as possible and treatment started immediately. Can be from genetic or nongenetic causes. Inheritance depends on type. |
| Cystic fibrosis | Varies with population—for example, 1:2,500 in Whites; 1:323,000 in Japanese | 33 | See Chapter 8 for clinical description. Screening for CF has been somewhat controversial because there are more than 1,000 mutations of the CFTR gene and because there is a question of the advantages offered by early detection. Currently it is believed that benefits can include reproductive planning, implementation of therapy that can maximize health, and nutrition. |
| Galactosemia | 1:40,000–1:60,000 | 51 | Defect in metabolism of galactose has several variants. The classic deficiency is in galactose 1-phosphate uridyltransferase. AR inheritance. Infant appears normal until feeding begins, and galactose and other metabolites accumulate. Signs/symptoms include vomiting, diarrhea, jaundice, failure to thrive, cataract development, hepatomegaly, hypoglycemia, and eventually intellectual disability. Susceptible to <i>Escherichia coli</i> infections. Often mistaken for milk allergy. In the older child and adult, may see delayed speech and language, learning disabilities, ataxia, tremor, and behavioral disorders. In females, ovarian failure, premature menopause, amenorrhea, and hypogonadism may be seen. Early elimination of lactose from the diet is essential. |
| Hemoglobinopathies | Depends on type | 51 | Can include Hb SS, Hb SC, Hb S/β-thalassemia. See Chapters 3 and 9. No direct newborn treatment. |

(continued)

TABLE 8.11 Disorders Commonly Included in Newborn Screening Programs (continued)

| Disorder | Incidence | Number of States Requiring Inclusions | Description |
|----------------------------------|---|---------------------------------------|--|
| Homocystinuria | 1:150,000– 1:200,000 | 41 | AR inheritance. Deficiency or impairment of cystathionine β -synthetase or methionine synthetase. Some are responsive to pyridoxine. More frequent in Ireland, England, and Australia; rare in Japan. Mild to moderate intellectual disability in about half. Clinical picture includes skeletal abnormalities such as kyphosis, scoliosis, pectus excavatum, tallness with excessively long limbs, osteoporosis, sparse and fragile hair; malar flush, spontaneous intravascular thromboses occur and in some cases lead to seizures. Dislocation of the lens occurs by 6 to 10 years of age. Often confused with Marfan disease. Treatment depends on cause but usually includes pyridoxine supplementation to responsive patients and dietary restrictions with betaine supplementation. |
| Maple syrup urine disease (MSUD) | 1:100,000 but 1:176 among Old Order Mennonites | 42 | AR inheritance. Several forms. Most due to deficiency of decarboxylase leading to elevations of the branched chain amino acids leucine, isoleucine, and valine. One type is vitamin responsive. In classic type, at 3–7 days, infant shows poor sucking, poor feeding, vomiting, lethargy, hypotonia, and a high-pitched frequent cry with eventual hypoglycemia, acidosis, convulsions, alternating flaccidity and hypertonicity, and eventual intellectual disability if not treated early. A characteristic odor of maple syrup may be noticed in urine, sweat, and ear cerumen as early as fifth day. Permanent intellectual disability can occur by 1 week of age. Treatment is a newborn emergency. Consists of diet restricted in the branched chain amino acids, which is maintained to some degree throughout life. |

(continued)

| | | | |
|--|--|----|---|
| Medium chain acyl-CoA dehydrogenase (MCAD) | 1: 6,500–1:20,000 | 41 | AR inheritance. Disorder of mitochondrial fatty acid oxidation deficiency metabolism affecting acellular energy. Multiple allelic variants but K3044E accounts for the majority. Common in Northern European ancestry. Usually presents with crisis when infant/child has prolonged fasting, often due to illness, between 3 months and 6 years of age, and is often mistaken as SIDS or Reye syndrome. The picture can include any of the following: hypoglycemia, vomiting, lethargy, encephalopathy, respiratory arrest, hepatomegaly, seizures, apnea, coma, and long-term developmental and behavioral disabilities. |
| PKU | See text | 51 | See text. |
| Tyrosinemia | 1:50,000–1:100,000 but 1:685 in one region in Quebec | 29 | AR inheritance. Several types including a type that improves with ascorbic acid intake. Type I results from deficiency of fumarylacetoacetate hydrolase. Can begin in first month of life in acute type with failure to thrive, lethargy, irritability, vomiting, edema, ascites, hypophosphatemia, hepatomegaly, cirrhosis, and renal tubular abnormalities. Urine may have boiled cabbage odor. Presentation can also be with liver failure. Treatment includes diet low in tyrosine and phenylalanine but progresses, and liver transplantation usually before 2 years of age is major treatment. |

incidence was not recognized. Some symptoms that should lead the nurse to consider recommending or referring the infant for screening test batteries for inherited biochemical disorders are discussed in Chapter 9. If the infant is diagnosed, siblings should be tested in case they have the disorder but have not manifested it, and they may benefit from treatment.

PKU

PKU was the first disorder to be included in mass newborn screening in the early 1960s. As described earlier in the section “Maternal Phenylketonuria,” amino acid Phe is essential for protein synthesis in humans. A complex reaction is involved in the hepatic conversion of Phe to tyrosine (see Figure 8.2), and blockage causes elevations collectively referred to as hyperphenylalaninemias.

It is now rare to see a child manifest the full spectrum of symptoms resulting from classic PKU because of screening programs and prompt treatment, but occasionally an affected infant is missed. Therefore, PKU should not be automatically ruled out in infants manifesting signs and symptoms associated with the disorder. Vomiting, eczema, and urine with a musty or mouse-like odor are usually the only early symptoms. Delay in achieving developmental milestones may be noticed after 6 months of Phe ingestion. Other symptoms that can occur are convulsions, increased muscle tone, agitated behavior, and delayed speech. A crossed-leg sitting position, tooth enamel hypoplasia, decalcification of the long bones, and a prominent maxilla are present. Pigment dilution occurs because of inhibition of tyrosinase by Phe accumulation in the metabolic pathway leading to melanin synthesis (see Figure 8.2). Thus, affected

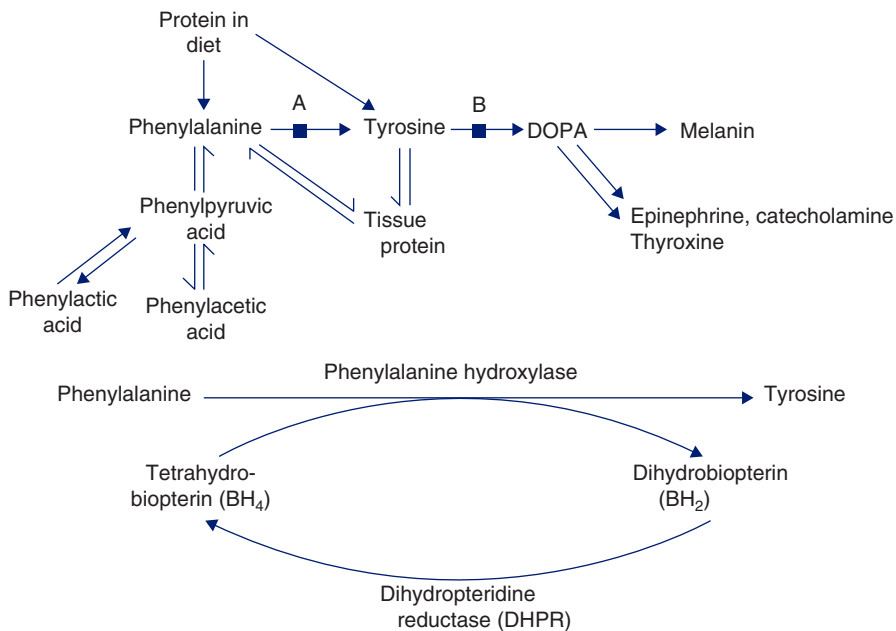


FIGURE 8.2. (Top) Abbreviated metabolism of phenylalanine and tyrosine. A = block in PKU (classical). B = block in albinism. (Bottom) Phenylalanine hydroxylating system (abbreviated). Some steps have been omitted for simplification.

untreated patients commonly have fair hair and blue eyes; in darkly pigmented families, the affected patient will be less pigmented than other family members.

It is very important to institute a Phe-restricted diet as soon as possible and before 1 month. Continuous lifelong treatment is essential; diet restriction should be sufficient to keep plasma Phe levels to normal ranges.

It has been suggested that all infants with persistent hyperphenylalaninemia and PKU be entered into a computerized registry for recontact in early adolescence in order to prevent the effects of maternal PKU on offspring. Questions of rights to privacy, confidentiality, and others must be balanced against the potential usefulness of such registry.

Infants found to have hyperphenylalaninemia on newborn screening may eventually be placed after diagnosis into one of several categories. The major ones are classic PKU; transient hyperphenylalaninemia without any further clinical significance; non-PKU hyperphenylalaninemia; and those with tetrabiopterin (BH₄) deficiency who need treatment for this.

Other Disorders

A large number of fatty acid oxidation defects, organic acidemias, aminoacidemias, and other disorders are detected within state newborn screening programs. Most of these disorders are individually rare, but when looked at collectively are said to have an incidence of 1 in 4,000 to 1 in 5,000. A number of other genetic and non-genetic disorders have been suggested for potential inclusion in newborn screening programs. Examples include diabetes mellitus type 1, hyperlipidemia, familial hypercholesterolemia, neuroblastoma, fragile X and other chromosomal disorders, α -1-antitrypsin deficiency, Duchenne muscular dystrophy, hemochromatosis, *BRCA1* and other gene mutations predisposing to cancer, Tay–Sachs disease, tuberous sclerosis, and Huntington disease. Instruction for nominating a condition for inclusion in the RUSP can be found here: www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/nominatecondition/index.html

CONCLUSIONS

Newborn screening is not without problems. Changes in obstetric practice have shortened the hospital stay of both mother and infant. Thus, specimens are usually obtained just before the infant leaves the hospital, which can be as early as 24 hours after birth, and screening tests for some disorders may not be accurate this early. If they are not performed then, however, the compliance rate may be substantially lower. Infants transferred from one hospital to another might be missed. Another criticism of mass newborn screening is the expense in screening low-risk infants for certain disorders. Is the expense justified if disease in any child can be prevented or treated? On the other hand, if one blood or urine specimen can be used for disease screening for many disorders, this reduces the expense, but such multiplex testing may compromise accuracy. In addition, screening for many disorders at a time when accuracy may not be optimal for all may later lead to their erroneously not being considered as diagnostic possibilities. However, after diagnosis is made and

treatment begins, vigilant monitoring is necessary to ensure not only optimal treatment, but also the exclusion of unnecessary treatment or misdiagnosis, which also can be hazardous. There is a relatively high false positive rate for newborn screening tests in general.

Effective newborn screening requires a coordinated, comprehensive, multidisciplinary, integrated system for delivery of care so that complex systems function effectively. This includes specimen collection; transport; tracking; laboratory analysis; data collection and analysis; locating and contacting families of infants with abnormal results on initial and subsequent screening for further evaluation and testing; and provision of follow-up services, including diagnosis, treatment, and long-term management that encompasses education, psychological, nursing, and social services, genetic counseling, medical nutrition therapy, and medical foods. To date, parents have been minimally aware that their newborn has been screened for genetic disorders. As awareness of newborn screening opportunities and issues grows, public and professional voices will influence how newborn screening occurs in the United States in the future.

SOCIAL AND ETHICAL ISSUES ASSOCIATED WITH SCREENING

A variety of social, ethical, and legal issues arise from conducting screening. Potential risks and benefits associated with screening are summarized in Table 8.12. Various social and ethical issues are discussed more fully in Chapter 13. Of particular significance in screening are the right to refuse to participate, informed consent, right to privacy and confidentiality of information, ownership of samples and future use, disclosure of incidental or unexpected findings, access to information, and alteration of familial relationships. Individual feelings that may be seen with genetic testing, such as the possibility of stigmatization and reduced self-worth, are also a potential consequence.

Although some newborn screening is compulsory, many states provide for exemption from screening of the newborn for genetic disorders if this is a violation of the parents' religious beliefs. This raises two interesting issues. The first is that parents are often not specifically asked to give informed consent for this type of screening, so they never have the opportunity to refuse their child's participation. They may either never find out that testing has been done or find out at the time of hospital discharge. The second point is whether the parents should have the right to deny the child the privilege of discovering whether he or she may have disorders such as PKU and hypothyroidism, which are amenable to early treatment, thus preventing retardation. How does the principle of causing no harm apply? Whose rights are most important in this instance? Should parental refusal be honored, or is it unjustifiable?

In other types of screening programs in which participation is purely voluntary, exercising the right to refuse to participate in screening should not result in the denial of any other services. Subtle coercion should also be avoided. This can inadvertently occur if screening is sponsored by a dominant social or religious institution in that culture or other perceived powerful group.

TABLE 8.12 Potential Risks and Benefits Associated With Screening

| | Type of Screening | | |
|--|-------------------|------------|------------|
| | Carrier | Newborn | Predictive |
| Potential risks | | | |
| Uncovering misattributed parenthood | X | X | X |
| Stigmatization | X | | X |
| Impaired self-concept | X | | X |
| Increased insurance rates or loss of benefits | X | | X |
| Loss of chosen marital partner | X | | X |
| Social and cultural consequences | X | X | X |
| Interference with parent–child bonding | | X | |
| Imposition of sick role | X | X | X |
| Anxiety associated with false-positive results | X | X | X |
| False feeling of security associated with false-negative results | X | X | X |
| Loss of the right not to know | X | | X |
| Overprotection of child | | X | X |
| Guilt feelings | X | X (parent) | X |
| Potential benefits | | | |
| Improved self-image if not a carrier or affected | X | | X |
| Recover potential productive member of society | | X | |
| Data collection for health planning | X | X | X |
| Allows reproductive planning options | X | X | X |

(continued)

TABLE 8.12 Potential Risks and Benefits Associated With Screening
(continued)

| | Type of Screening | | |
|---|-------------------|---------|------------|
| | Carrier | Newborn | Predictive |
| Initiation of early treatment | | X | X |
| Alter disease process | | X | X |
| Provide genetic counseling | X | X | X |
| Avoid costs associated with disease development | | X | |
| Extend services to other relatives | X | X | X |
| If negative, avoidance of later unpleasant, expensive tests | | | X |

It is wise for health professionals to thoroughly discuss and have a policy on what is to be done with unexpected findings before beginning testing or screening. Often a statement is included as part of informed consent as to what information will and will not be revealed. Incidental findings could also have an impact on stigmatization, insurance eligibility, and genetic discrimination issues.

One of the risks of screening is the discovery of misattributed parenthood, usually paternity. For example, if a screening program for sickle cell is undertaken in school screening and a child is discovered to have sickle cell trait, but neither putative parent has it, the chances are that one or both parents are not the natural parents of this child, barring a laboratory error. How is this situation to be handled? Does disclosure hold that such results must be shared? Can they be withheld? Can only the mother be informed of the result? The admonition to “do no harm” may be a guiding principle in making a decision. Again, incorporating a statement about policy into a pretesting or screening consent can be valuable.

Several types of problems can arise in this area. The first is to whom the results of testing or screening can be released. Ideally, only the person undergoing the screening should be given these results. In practice, testing or screening records may be kept and handled by a wide variety of nonprofessional personnel and volunteers. They may have access to other persons' identity for billing, insurance, and follow-up purposes. In small communities or neighborhoods, anonymity is not possible, and unintended stigmatization may result. In some screening programs, such as those for sickle cell, the actual sponsorship may be under the auspices of lay community groups. Patients can consent to disclosure of the findings of screening. This may be specified. For example, the person may wish to have results sent to his or her physician or to certain relatives,

which raises another issue. All records should be kept in such a way that the individual is not immediately identifiable. Therefore, a code number instead of names should be used. Special care must be taken when entering data in a central computer or data bank. Often these are accessible to individuals by means of telephone computer access.

Another type of a breach of confidentiality that can occur is by revealing statistical data that accidentally allow a person who has been tested to be identified. It is imperative that no individual can be identified in this way, even if it makes the research data presentation less detailed. Disclosure of information to unrelated third parties, such as insurance companies or employers, may have other consequences. These may include higher insurance rates, cancellation of insurance policies, or loss of job opportunities. Employers have long used various attributes in their selection process, and some now include genetic information.

Identification of a child with a genetic variant that has not been shown to have any definite correlation with clinical disease, the carrier state, or an actual genetic disorder itself can change the relationship between the child and his or her parents. In the newborn, disruption of parent–infant bonding can occur. Overprotectiveness can occur at any age, leading to impaired psychological development. Parents can experience guilt at having given this disorder to the child, whether or not there is any basis in fact for these feelings. A sick role may be imposed on the child. These issues may be particularly prominent in population testing or screening for disorders for which there is no present treatment such as Duchenne muscular dystrophy. The finding among siblings that one is a carrier and others are not can change their relationships with each other.

In the excitement of inducing participation in mass carrier screening or testing, it is easy to forget the risks that may occur. Impairment of self-image or self-worth is one such risk. Adolescents are particularly vulnerable because they are still searching for and developing their self-identity. Views of their peers are extremely important in this development. Thus, for example, the effect of identifying all Jewish students in a high-school population to volunteer for Tay–Sachs carrier testing can be extreme. First, they are identified as “different.” Second, many of those who are then identified as carriers have been shown to have an impaired self-concept.

Some researchers have attempted to justify this result by stating that many of the noncarriers had improved self-concepts. Because little long-term research has been done in this area, the long-term effects are not known. Nurses, with their understanding of growth and development, can assist in identifying these issues before screening begins. In a study of carrier testing for both Tay–Sachs disease and cystic fibrosis among Jewish high-school students in Australia, another question that arises is whether the identification of carrier status is important to this age group. What are the anticipated uses to which it will be put? These young people can, however, begin to identify themselves in new and less favorable terms such as, “I am a Tay–Sachs carrier.” In any school setting, it is difficult to prevent school officials from learning the results of the testing or screening. This should be considered in the planning phases of the program. Is it really the needs of the participants that are being met in the screening? Or is it the needs of the researchers? Once a person is identified as a carrier, regardless of age, there is no way to return to the pretesting or screening state of ignorance.

In a rural Greek population, an intensive educational effort and screening program were instituted for carriers of thalassemia in an effort to reduce the incidence. Carriers were identified, and the screeners left the village. When they returned several years later, they discovered that those individuals who were identified as carriers were virtually untouchable. Marriages could not be arranged for them as was the custom. The social status of their families was impaired, so that, in effect, all members were affected. It has been believed that education of an ethnic population as to the disorder will minimize stigmatization, but this might be a reflection of the culture of the health care provider, not the population being tested. It also emphasizes the importance of understanding the culture of the group in which screening is to be done before attempting to initiate a program. The participation of knowledgeable community individuals helps to minimize some of the negative aspects and alert the providers to potential cultural problems. Although the rationale for singling out ethnic groups for high-risk genetic screening centers on economic feasibility, the issue of discrimination can apply. Screening should be kept voluntary, and equal access for all to the screening should be allowed. Definition of groups on ethnic and racial lines may accrue both benefits and burdens for them. It was not long ago that arguments directed at improving the race through eugenics were popular in this country. The result of this thinking was the imposition of immigration restrictions, prohibitive marriage laws, sterilization acts, and the distraction from the real roots of labor and social problems. Between 1911 and 1930, about 30 states passed sterilization laws for a variety of conditions ranging from insanity to alcoholism to criminality. Thus, many fears are founded in history.

The misunderstanding of the health status of carriers, particularly in the case of sickle cell, has also led to unintended consequences. Loss of employment; loss of access to certain jobs, educational opportunities, and professions; discrimination for entry to the Air Force Academy; and increased insurance rates have been but a few. In addition, some who are identified as carriers may not themselves understand the meaning of that status.

THE FUTURE

The potential for various types of genetic screening is expanding. These will include population and targeted genetic screening for actual diseases, carrier state, predictive screening, and newborn screening, as well as prenatal applications. Advances in scientific understanding and in the technology to translate the findings into practice will continue to grow. Many social, ethical, legal, and cultural factors impinge on genetic screening. They must be carefully considered before enthusiasm and good intentions lead unwittingly to harmful effects on individuals and groups. In regard to newborn screening, as there will be an increased ability to identify and treat an expanding list of disorders, there will be increased consumer advocacy to make broader universal detection available in a timely and responsible manner. As awareness of these issues grows, public policy decisions will increasingly influence genetic screening in the future. Nurses, among other health professionals, will need to be aware of the trends and issues surrounding screening, be informed so that they can

educate and interpret information correctly for their clients in a culturally sensitive and educationally appropriate manner, understand the emotional and psychological impact of results and the potential impact on such issues as insurability and future life planning, and understand the need for a coordinated, comprehensive screening plan with appropriate follow-up of services.

KEY POINTS

- ▶ The preconception period and pregnancy are important points in time for preventing genetic disorders.
- ▶ Appropriate folic acid supplementation beginning prior to conception, if possible, and other preventive measures should be accomplished before pregnancy to minimize chances for untoward genetically related fetal outcomes.
- ▶ Prenatal screening and diagnosis have become relatively safe and have entered standard obstetric practice.
- ▶ Nurses should recognize couples who are candidates for prenatal screening and diagnosis.
- ▶ All candidates for prenatal screening and diagnosis should have certain information as discussed in this chapter.

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CHAPTER 9

Maternal–Child Nursing: Pediatrics

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The physical manifestations of genetic disorders are frequently identified first in infants and children, presenting as either obvious external malformations or more occultly as inborn errors of metabolism. Regardless of the type of genetic disorder diagnosed in a child, certain reactions often occur. A number of factors influence these reactions, including whether the disorder is visible, such as Down syndrome (DS), or hidden, such as congenital heart disease (CHD). Alterations in pediatric gene function frequently lead to chronic illness, affecting not only the child and parents, but siblings, grandparents, and extended family members. The ways in which the family is informed of the disorder, the supports provided, referrals made, and familial strengths influence short- and long-term coping. Genetic counseling is important for these families, including options relating to treatment, prenatal diagnosis, and reproductive options. Additional considerations for the family include anticipatory guidance, short- and long-term plans, coping with associated symptoms and conditions, insurance issues, resources, and school or work issues.

This chapter identifies the most common birth defects, chromosome disorders, and single gene disorders recognized in infancy and childhood.

BIRTH DEFECTS

The terms *birth defects* and *congenital anomalies* are essentially synonymous. Both are meant to convey a defect that is present at the time of delivery. Although sometimes obvious, the visual appearance does not always identify the etiology. For example, a cleft palate may be an isolated anomaly or part of a syndrome. It may be caused by a chromosomal aberration, a single gene disorder, an environmental insult, a combination of genetic and environmental factors, or unknown causes. Prenatal development is extremely complex, involving cell proliferation, differentiation, migration, programmed cell death, fusion between adjacent tissues, and effective chemical communication. The correct sequence and timing are crucial. Birth defects may be caused by any of the factors in Box 9.1.

BOX 9.1**Causes of Birth Defects**

- ▶ Chromosome disorders (e.g., trisomy 13)
- ▶ Single gene defects (e.g., Meckel syndrome)
- ▶ A combination of genetic and environmental factors (multifactorial; e.g., anencephaly)
- ▶ Physical constraints of the fetus in utero (e.g., torticollis)
- ▶ Infectious agents (e.g., rubella), drugs, or chemicals (e.g., thalidomide)
- ▶ Radiation exposure in utero (e.g., microcephaly)
- ▶ Maternal metabolic factors (e.g., diabetes mellitus)
- ▶ Other environmental causes (e.g., methylmercury exposure)
- ▶ Unknown causes

According to the Centers for Disease Control and Prevention, approximately 3% of babies born in the United States have a birth defect. Although there are a plethora of birth defects, this section expands on those believed to be of multifactorial causation.

Terminology

The nomenclature associated with birth defects varies. Terms like *malformations*, *anomalads*, and *complexes* have not been used with consistent meaning in the literature. Examples of definitions of the ones most likely encountered by the nurse are shown in Box 9.2. Other terms that describe various anomalies, such as *agenesis*, *aplasia*, *dysplasia*, and *hyperplasia*, are defined in the glossary at the end of this book.

Multifactorial Causation and Inheritance

The common congenital anomalies often have a familial basis, but they usually do not fit a Mendelian inheritance pattern or show an association with a chromosomal abnormality. Although exact causes remain unknown for the most part, it is believed that many of the common congenital malformations and isolated birth defects are inherited in a multifactorial manner, involving the interaction of several genes and the environment (see Table 9.1). The reasons for these are under investigation, including chromosomal deletions and duplications. An example is DiGeorge or velocardiofacial syndrome (VCFS), where microdeletions of chromosome 22q11.2 are associated with hypoplasia of the parathyroid gland, the thymus, and the cardiac outflow tracts. Even if a person had chromosomal or other testing that was negative years ago, it may be useful to repeat such testing in order to provide updated genetic counseling information.

BOX 9.2**Nomenclature Associated With Birth Defects**

- ▶ Association—Nonrandom occurrence together with a pattern of multiple anomalies, but that are not yet known to be a syndrome or sequence (e.g., VATER association—vertebral defects, anal atresia, tracheo-esophageal fistula with esophageal atresia, radial dysplasia, and renal defects).
- ▶ Disruption—The initial developmental process is normal, but a defective organ or part of an organ or tissue results from interference (usually external) with the process (e.g., limb defects resulting from thalidomide; amniotic band syndrome).
- ▶ Deformation—An abnormal form, shape, or position of a previously normal body part caused by mechanical forces (usually molding) on normal tissue (e.g., intrauterine restraint resulting in clubfoot).
- ▶ Malformation—A morphologic defect of an organ or part of an organ with poor tissue formation that results from an intrinsic abnormal developmental process (e.g., cleft lip).
- ▶ Syndrome—A recognized pattern of multiple anomalies presumed to have the same etiology (e.g., Down syndrome).
- ▶ Sequence—A pattern of multiple anomalies derived from a single prior anomaly; this replaces anomalous or complex (e.g., Robin sequence—micrognathia, large tongue, cleft palate).

Congenital Heart Disease

Approximately 35,000 babies are born in the United States each year with CHD. The defects can vary from simple to complex and may require extensive surgical repair. The etiology varies, with about 5% to 10% originating from chromosome or single gene mutation and 1% to 2% being of environmental origin. CHD may be due to:

- ▶ Teratogenic agents (e.g., lithium, alcohol, phenytoin, retinoic acid, valproic acid)
- ▶ Infection (congenital rubella)
- ▶ Maternal environment disturbances such as maternal phenylketonuria (PKU)
- ▶ Chromosomal origin (e.g., Turner syndrome, trisomy 21)
- ▶ Single gene disorder (e.g., Holt–Oram syndrome, an autosomal dominant disorder resulting from mutation of the *TBX5* gene that encodes a transcription factor and consists of upper limb skeletal defects and cardiac anomalies)
- ▶ Mitochondrial inheritance
- ▶ Multifactorial inheritance mechanisms
- ▶ Uncommon inheritance mechanisms, such as imprinting, germline mosaicism, or uniparental disomy

TABLE 9.1 The Occurrence and Sex Distribution of Selected Congenital Anomalies

| Congenital Anomaly | Incidence |
|--|----------------|
| Anencephaly | 1: 4,859 |
| Spina bifida | 1: 2,858 |
| Cleft lip with or without cleft palate | 1: 940 |
| Cleft palate alone | 1: 1,574 |
| Congenital heart disease | 8: 1,000 |
| Transposition of the great arteries | 1: 3,333 |
| Tetralogy of Fallot | 1: 2,518 |
| Atrioventricular septal defect | 1: 2,122 |
| Hypoplastic left heart syndrome | 1: 4,344 |
| Gastroschisis | 1: 2,229 |
| Hypospadias | 5: 1,000 males |

Source: www.cdc.gov

Children with CHD frequently have one or more extracardiac defects, ranging from 25% to 45%. Thus, all children known to have CHD should be carefully evaluated in order to detect other such anomalies. Some anomalies, such as cleft palate, are readily apparent, but others, such as those of the urinary tract, are more difficult to detect. The most frequent extracardiac defects associated with CHD are of the genitourinary tract, gastrointestinal tract, and musculoskeletal system. Nonimmune fetal hydrops (generalized edema and ascites in the fetus) is estimated to have a cardiac cause in as many as 25% of the cases. The most frequent congenital heart defects found in association with other anomalies include patent ductus arteriosus, atrial septal defects, atrioventricular septal defect, tetralogy of Fallot, coarctation of the aorta, ventricular septal defects, and malposition defects. About 10% of all CHDs are part of a syndrome (e.g., coarctation of the aorta and Turner syndrome). It is important to recognize these syndromes in order to provide accurate genetic counseling and management. Recurrence risk figures vary for the type of defect, as well as for other factors previously discussed. If the CHD is multifactorial, an overall risk to

a future sibling of an affected individual is 2% to 4%. This increases to 6% to 12% if a second sibling is affected.

An exciting advancement in CHD includes work by the Pediatric Cardiac Genomics Consortium. Sponsored by the National Heart, Lung, and Blood Institute (NHLBI), this translational research group is collecting data from multiple sites on the genetic causes of CHD. Through their “Bench to Bassinet” program, scientists are correlating data obtained from animal models with specific pediatric cardiac anomalies. To date, significant *de novo* mutations in genes involved in histone methylation have been identified, while the size of the estimated gene set involved in CHD is 401 genes.

Because of effective early interventions, many persons with CHD survive into adulthood. There are clinicians who specialize in adult CHD, and many may seek medical care accompanied by their parents into their 30s. A resource devoted to CHD can be found online (www.pted.org).

Developmental Dysplasia of the Hip (DDH)

Developmental dysplasia of the hip (DDH) is the most common orthopedic disorder in newborns. The interaction of genetic and environmental factors in DDH is striking. It is now thought of by most as a deformation rather than a true congenital malformation, with an incidence of about 1% of all live births, depending on the criteria used and the age of assessment. A full range of severity is possible, from a lax dislocatable hip to a dislocated hip that cannot be reduced. DDH is more common in firstborn children, in breech presentations, those with a positive family history, and is six times more common in females. Environmental factors present after birth may contribute to the development of DDH, including the use of a cradle board and swaddling. In Japan, the incidence of DDH decreased from 3.5% to 1.5% following a national effort to eliminate swaddling infants. Additional risk factors include the nature of the hip joint (e.g., a shallow-angled acetabulum is more susceptible to dislocation) or lax connective tissue from either heritable causes or hormones (e.g., inborn errors of estrogen or collagen metabolism, maternal estrogens, or hormones that may be given before delivery). Recently growth factor genes have been identified as susceptible to DDH, some of which include GDF5, TBX4, ASPN, IL-6, TGF- β 1, and PAPP2.

The nurse should carefully assess neonates and infants for clinical features of DDH by examining for shortening of the thigh with bunching up of tissue and skin fold accentuation, limitation of abduction, or other signs. The Ortolani or Barlow test may also be done. However, DDH may not be detected at birth, and surveillance should be maintained (Box 9.3). Ultrasound screening of the neonatal hip has become more common and has a specificity and sensitivity of over 90%. DDH is relatively easy to treat if diagnosed early, but if it is discovered after 1 year of age, more complex management is required and complete correction may not be possible. Nurses should be especially alert examining infants who are female, firstborn, and delivered in a breech position. Health teaching should include information about optimum positioning.

BOX 9.3**Common Presenting Signs and Symptoms of DDH**

- ▶ Limping
- ▶ Walking on tiptoe
- ▶ Unequal leg length
- ▶ Difficulty with crawling
- ▶ Delayed walking
- ▶ Noticeable short leg
- ▶ Asymmetric thigh creases
- ▶ Uneven shoe wear

Neural Tube Defects

Neural tube defects (NTDs) are congenital anomalies that affect the embryonic neural tube, the structure that ultimately develops into the brain and spinal cord. Many of these aberrations occur to the embryo during the first month of pregnancy, prior to a woman knowing that she is pregnant. The most common forms of NTDs include anencephaly, encephalocele, and spina bifida. Spina bifida can be further classified as spina bifida occulta, meningocele, or myelomeningocele, defined in Box 9.4.

A large proportion of NTDs can be detected prenatally by ultrasound and through measurement of α -fetoprotein (AFP) in maternal serum and amniotic fluid. Neural tube defects can be open or closed. In open NTDs, neural tissue is either exposed or covered with a thin transparent membrane. In closed NTDs, neural tissue is covered with skin or a thick, opaque membrane and therefore may not be detected by α -fetoprotein levels. Hydrocephalus may accompany spina bifida. Anencephaly and spina bifida are related etiologically and are generally discussed together. After having an

BOX 9.4**Major Neural Tube Defects**

- ▶ Anencephaly—the vault of the skull is absent, with a rudimentary brain
- ▶ Spina bifida, which includes:
 - Spina bifida occulta—one vertebra is not fused, and a tuft of hair may be present over the skin of the area.
 - Meningocele—meninges protrude or are herniated from the spinal canal, but the cord is in its usual position.
 - Myelomeningocele—the meninges and the spinal cord protrude from the defective vertebrae.
- ▶ Encephalocele—meninges and brain protrude through a gap in the skull, so part of the brain is outside the skull. This is less common than the others.

infant with either anencephaly or spina bifida, the recurrence risk is for either one, not just for the anomaly that was present in the affected infant.

A consistent observation has been that NTDs are more frequent in poorer socioeconomic groups and in conditions that result in poor diets, especially folic acid deficiency, but may also include deficiency in ascorbic acid and zinc. Although periconceptional intake of folic acid has decreased the frequency of NTDs, some studies have found a higher risk of NTDs in obese women that is independent of folic acid intake. Hyperthermia, such as that with sauna or hot tub use or maternal illness with fever, during early pregnancy has been shown to be capable of causing NTDs, especially anencephaly.

The vast majority of NTDs are attributable to genetic factors, including associations with folate-related genes and planar cell polarity genes. The *MTHFR* gene, located on the short arm of chromosome 1, is a folate-related gene that has shown a positive association with NTDs. A mutation in this gene leads to a form of methylenetetrahydrofolate reductase that is not as active at higher temperatures, possibly explaining why there is a relationship between NTDs and hyperthermia.

Surgical repair of NTDs can include the placement of a shunt, with the extent of surgery dependent on the severity of the defect. Long-term rehabilitation may be necessary, often requiring bowel and bladder training. In some centers, fetal surgery is performed to close myelomeningoceles, decrease shunting, and improve motor function.

In anencephaly, the infant's appearance is so shocking that often parents equate the severity of disease with the risk of recurrence. In fact, it falls into the same general range of other multifactorial disorders. Recurrence risks must always be adjusted to the population incidence, ethnic background, the number of affected relatives, and epidemiological factors when known. In general, however, the risk of recurrence in the United States for a Caucasian couple after having one affected infant and no other affected relatives is believed to be 3% to 4%. The risk for a woman with spina bifida to have an affected child is about 4%. There is some indication that there is an increased risk for NTDs among siblings of children who have other birth defects, such as cleft lip and palate.

The most important aspect of NTDs is prevention. It was discovered first that recurrence of NTDs could be prevented by periconceptional supplementation of folic acid and vitamins, followed by the expansion of this to prevent first occurrences as well. Recommendations are 0.4 mg (400 µg) of folic acid for all women of childbearing age. The American College of Medical Genetics also recommends that women with a previous history of NTDs take 4.0 mg of folic acid daily, optimally starting 3 months before conception.

Poor maternal nutrition in general may also contribute to NTD occurrence, as well as other birth defects including imperforate anus. Dietary counseling that is ongoing and periodically reinforced should be provided to females when reproductive age is reached.

Orofacial Clefts

The most common oral clefts are cleft lip, with or without cleft palate (CLP), and cleft palate alone (CP). Over 300 syndromes that include CLP or CP have been

recognized. Cleft uvula (1:80) and submucous cleft palates (1:1,000) are thought to represent incomplete forms of cleft palate.

Approximately 30% of orofacial clefts are accompanied by other congenital anomalies, including CHD, CHARGE syndrome, ectodermal dysplasia, and multiple forms of cancer. It is important that the infant with a cleft be fully evaluated to exclude other chromosomal disorders and single gene defects. Many genes related to syndromes associated with cleft lip and palate have been identified, while cleft lip and palate alone may be associated with noncoding, regulatory regions. More recently, studies investigating copy number variations (CNVs) suggest that the cumulative effect of changing the copy number of genes through duplications or deletions may result in abnormal phenotypes.

Environmental factors also appear to have a role. Preconceptional multivitamins including B₁₂ and folic acid supplementation have been reported to reduce the recurrence risk of orofacial clefts by as much as 50%. Cigarette smoking during pregnancy also appears to be a risk factor.

The appearance of a child with a cleft is shocking to the parent who is expecting a normal baby. They experience the same reactions most other parents experience for other birth defects, including guilt, anger, denial, and concern. Parents have also stated that an orofacial cleft was not an anomaly that could be hidden from others. Great sensitivity and skill are needed on the part of the entire professional staff immediately after the birth of the infant and throughout the hospital stay. Before leaving the hospital, contact should be arranged for the parents with the cleft palate team (who will ultimately be involved in the lengthy treatment) and also with one of the cleft palate parent groups for support and in-hospital visitation. Referral may be made to the local home health care or community health agency for a home visit by a nurse.

An immediate challenge is that of feeding the newborn with a cleft. It is important for the nursing staff to spend time helping the mother to feel comfortable feeding her infant because she will soon be assuming this responsibility alone. Infants with CLP or CP often cannot create adequate suction and may need a small plastic artificial palate or a different type of nipple. Breastfeeding may be possible, depending on the nature of the cleft. There are publications available to help the nurse advise the mother who wishes to do this, and mothers should not be discouraged. Infants should be held upright when fed to prevent choking and may need to be burped frequently, as they tend to swallow air. The infant may need 30 to 45 minutes or more to feed. Parents need to feel comfortable, the child needs nourishment, and both need to develop an emotional bond to one another. Many parent groups have individuals who come to the home with various successful “tricks” for feeding. The American Cleft Palate Educational Foundation can supply addresses of the local chapter.

It is not uncommon for genetic counseling to be sought by an adult with CLP or CP. The risk for an affected parent and one sibling is about 1 in 10. Often such adults have experienced emotional trauma in their own life, which they attribute to the anomaly, and they may require more in-depth counseling. Three-dimensional ultrasonography of the fetal face may help in prenatal detection.

The total habilitation of infants with oral clefts is complex, often requiring multiple surgical procedures and other therapies, and is generally agreed to be best

accomplished by a team. The early involvement of the family with such a team provides ongoing family support as well as other optimal therapy. Team members usually consist of professionals with specialties in pediatrics, plastic surgery, audiology, speech pathology, nursing, genetics, dentistry, orthodontia, otolaryngology, social service, and general surgery. Other specialists may include psychologists, nutritionists, and radiologists. Comprehensive, coordinated, and integrated multidisciplinary services are essential.

The current trend is to repair cleft lips as early as possible, almost always before 3 months of age. Many surgeons allow an infant to resume nursing 24 hours after cleft repair. Mothers can manually express breast milk for feeding during periods when the infant cannot nurse. A variety of procedures are used for CP closure, depending on the exact nature of the cleft and its extent.

During infancy and childhood, children with CLP have increased susceptibility to ear infections and frequently having hearing problems. Routine ear exams and testing should be done periodically and their importance explained to the parents. Hearing loss can also be responsible for speech distortion, and hypernasality is a frequent finding. There is a tendency for children with a cleft to develop speech later than usual, and therefore may need some language stimulation, which parents can provide in consultation with the speech pathologist. Parents should be told that hearing problems and discomfort may cause increased fussiness. Additionally, counseling assistance for the client and family may be beneficial due to the psychological sequelae and problems from the hearing and speech problems.

CHROMOSOME DISORDERS

Information about the structure and variation in chromosomes has been described in Chapters 2 and 4. Many fetuses with severe chromosomal abnormalities die prenatally or relatively soon after delivery, especially if the chromosomal defect is nonmosaic. Thus, only three trisomies (13, 18, and 21) are relatively common among live-born infants. Other trisomies and the monosomies are almost always mosaics, which include a normal cell line, with the assumption that enough normal cells are present to be compatible with life. A variety of structural changes of every chromosome have been reported, although each change is extremely rare. The only autosomal deletion defects that are relatively common (1:20,000 to 1:50,000) are cri-du-chat (5p⁻), DiGeorge/velocardiofacial syndrome (22q11.2⁻), and Wolf–Hirschhorn syndrome (4p16.3⁻).

The major autosomal abnormalities are:

- ▶ Trisomy 21 (DS)
- ▶ Trisomy 18 (Edwards syndrome)
- ▶ Trisomy 13 (Patau syndrome)
- ▶ Deletion 5p syndrome (cri-du-chat syndrome)
- ▶ 22q11.2 deletion syndrome
- ▶ Wolf–Hirschhorn syndrome (4p⁻)

Among the sex chromosome disorders, the overall incidence is about 1 in 300 live births. The most common are:

- ▶ Turner syndrome (45,X)
- ▶ Klinefelter syndrome (47,XXY)
- ▶ 47,XXX (triple X)
- ▶ 47,XYY males

In any of the trisomies, especially DS, the actual error can be caused by either the presence of an extra free chromosome or one that is translocated to another chromosome. In translocations, the chromosomal material of 47 chromosomes and three copies of those genes are present instead of the normal two copies, but the chromosome count is 46. This illustrates one reason that a full chromosome analysis is necessary.

The risks for recurrence are very different for translocations than free trisomies. For example, in DS, if one parent has 45 chromosomes and a translocation of chromosome 21 to chromosome 14, the gametes they produce can theoretically result in six possible combinations in a zygote, shown in Figure 9.1. In theory, the chance of each occurring is equal, and because three of the six outcomes result in nonviable offspring, the chances of a normal child, a balanced translocation carrier like the parent, or one with DS would each be one third. In practice, the distribution is observed to be different. If the female is the translocation carrier, then the actual observed risk is 10% to 15% for having a child with DS, whereas if the male is the carrier, it is 5% to 8%. The risk for having a normal-appearing child who, like the parent, is a translocation carrier is about 45% to 50%. In either case, the option of prenatal diagnosis should be explained to the parents. If both chromosomes 21 are involved in the translocation, 45,XX,t(21;21) or 45,XY,t(21;21), then only DS offspring can result since the monosomic alternative is nonviable. Therefore, the risk for parents with this type to have a child with DS is 100%. These parents should have genetic counseling that includes discussion of other reproductive options. Although more children with translocation DS are born to women under 30 years of age than over 30 years of age, assumptions of cause can never be made. Chromosome analysis *must be* done. The degree of mosaicism, if present, can also act to modify findings and prognosis. See Figure 9.2 for a karyotype illustrating the major autosomal and sex chromosome abnormalities.

Other than DS, those affected with severe autosomal anomalies die relatively soon after delivery or in the first year of life because multiple, severe, life-threatening problems are present. Some, particularly those who are less severely affected or are mosaic, do survive. Parents often have angry feelings toward professionals who may have told them that their child would not live beyond a certain age. Therefore, it is important to provide accurate information in a sensitive manner. One parent organization specifically for rare chromosome disorders is the Support Organization for Trisomy 18, 13 and Related Disorders (www.trisomy.org). DS is described in the following text. Information about the other autosomal chromosomal disorders is given in Table 9.2.

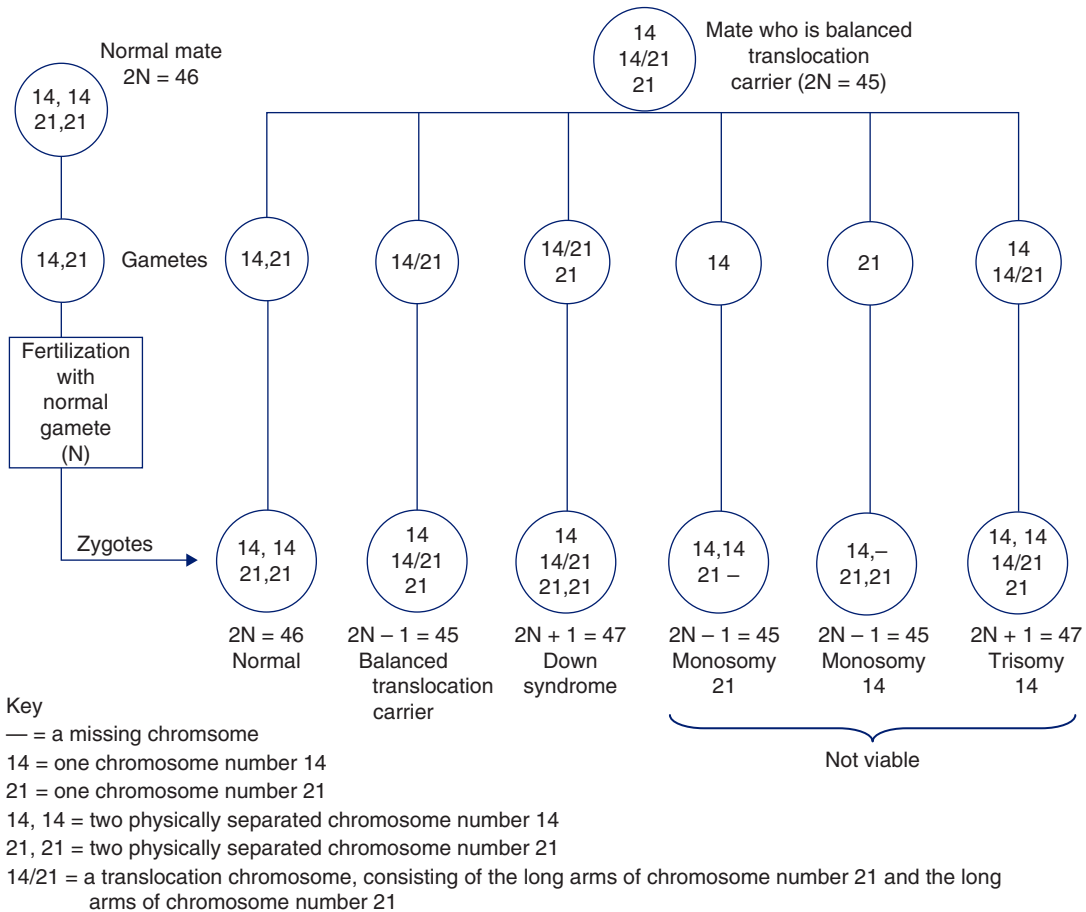


FIGURE 9.1. Possible reproductive outcomes of a 14/21 balanced translocation carrier.

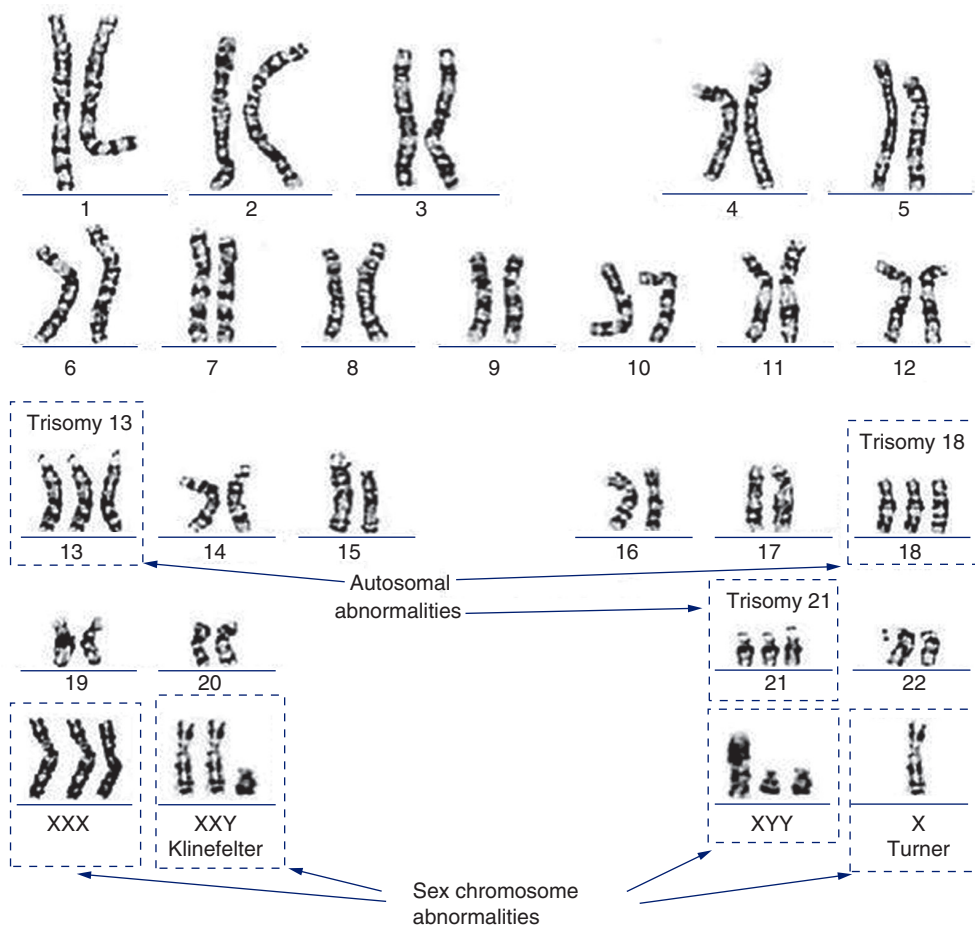


FIGURE 9.2. G-banded karyotype illustrating major chromosome aberrations in a composite.

Trisomy 21 (Down Syndrome)

Described by Dr. John Langdon Down in 1866, DS occurs in approximately 1 in 830 newborns. In 1959, Dr. Jerome Lejeune identified an extra chromosome 21 in three males with features associated with DS. This was the first chromosome abnormality associated with a specific chromosome.

There is no way, other than chromosome analysis, to tell if a free trisomy (about 95%), a translocation (about 5%), or mosaicism is present. About 90% of the time, the extra chromosome is of maternal origin. The area responsible for the phenotypic traits of DS has been identified as the Down syndrome critical region (DSCR), located on the long arm of Chromosome 21 at q22.1~21q22.3. Therefore, a complete trisomy is not necessary for typical clinical features (Figure 9.3) which can include:

- ▶ Hypotonia, the most frequent early finding (infants may be floppy)
- ▶ Dysmorphic features, many of which are seen in a percentage of normal people, including epicanthal folds, flat nasal bridge, upslanting palpebral fissures, and transverse palmar crease

TABLE 9.2 Most Frequently Recognized Autosomal Chromosome Disorders

| Chromosome Disorder | Incidence | Comments |
|--|-----------------------------|---|
| Trisomy 21 (Down syndrome) | | See text. |
| Trisomy 18 (Edwards syndrome) | 1: 5,000 live births | Second most common live-born autosomal trisomy. Have three copies of chromosome 18 as free trisomy or translocation. Approximately 5%–10% survive past 1 year of age. Clinical features include “rocker bottom” feet, mental disability, weak cry, poor sucking, failure to thrive, short sternum. |
| Trisomy 13 (Patau syndrome) | 1:16,000 live births | Results from three copies of chromosome 13, either free or as translocation. Severe external malformations include cleft lip and palate, polydactyly, microphthalmia, absence of eyes, hand, and nail deformities. Internal malformations include those of the heart, renal, and reproductive systems. Less than 10% survive beyond the first year of life. |
| Deletion 5p (cri-du-chat syndrome) | 1:20,000–50,000 live births | Deletion of all or part of the short arm of chromosome 5. Very early hear catlike, mewing cry, low birth weight with mental and growth retardation, microcephaly, hypotonia, round face, poorly formed ears, respiratory and feeding problems, expressive language delay, self-injurious behavior. Many survive into adulthood depending on degree of deletion. IQ usually below 30 but may function at higher level. |
| Deletion 4p (Wolf–Hirschhorn syndrome) | 1: 50,000 live births | Females more often affected. Deletion of certain region on the short arm of chromosome 4 (4p16.3), which may be submicroscopic. Includes microcephaly, intellectual disability, characteristic face with hypertelorism, wide nasal bridge, and congenital heart malformations. |
| 22q11.2 deletion syndrome (formerly known as DiGeorge syndrome, velocardiofacial syndrome, Opitz G/BBB syndrome) | 1 in 4,000 live births | Deletion in long arm of chromosome 22 (22q11.2). Typical clinical findings include conotruncal heart defects, cleft palate, learning, speech and language problems, hypotonia, T-cell abnormalities, thymus gland aplasia, or hypoplasia. At high risk for psychiatric disorders (schizophrenia, depression, and bipolar disorders) and attention deficit hyperactivity disorder. |

Source: National Library of Medicine (2015)



FIGURE 9.3. Typical phenotype of child with Down syndrome.
Source: Weijerman & de Winter, 2010

- ▶ Clinodactyly (incurved fifth finger)
- ▶ Wide spaces between first and second toes
- ▶ Short stature
- ▶ Short, broad neck
- ▶ Protruding tongue with high arched palate
- ▶ Brushfield spots of the eyes (light speckling of the edge of the iris)
- ▶ Intellectual disability, which may vary in degree
- ▶ Congenital heart defects, especially atrioventricular septal defects, ventricular septal defects, and tetralogy of Fallot, which occur in 40% to 60% of cases
- ▶ Elevated risk for transient myeloproliferative leukemia in the newborn period and acute lymphocytic leukemia (ALL) in childhood
- ▶ Gastrointestinal problems such as megacolon, celiac disease, and duodenal atresia
- ▶ Otitis media and hearing impairment
- ▶ Ocular problems such as nystagmus, strabismus, glaucoma, and cataracts
- ▶ Orthopedic problems such as scoliosis and hip dislocation
- ▶ Thyroid problems, especially hypothyroidism
- ▶ Hypogonadism in males and reduced fertility in females
- ▶ In adulthood, a pattern of aging and neuronal degeneration similar to that seen in Alzheimer disease

The karyotype of a patient with a trisomy 21 is shown in Figure 9.4. Whether due to a complete trisomy, translocation, or mosaicism, the severity of the disorder and the degree of developmental delay are not always as evident in the infant, making it hard for many parents to accept the diagnosis. It takes time to fully realize the impact of the diagnosis and for realistic decision making to occur. Support is essential, and it should be suggested to the parents that they enroll their baby in an early intervention program as part of the effort to maximize their child’s potential. Many persons with DS function at a higher social level than intellectual level.

Persons with DS require standard childhood care such as immunizations and growth monitoring with appropriate standards. However, the eyes and ears require special attention for problems such as strabismus, myopia, otitis media, and hearing loss. In addition, monitoring for heart disease, hematologic problems, orthopedic problems, gastrointestinal disorders, and abnormal thyroid function should also be part of standard care. Many individuals with DS are uniformly happy, friendly, and have good dispositions. However, others can be stubborn, mischievous, and poorly coordinated, and about 10% have serious emotional problems.

Males usually have hypogonadism and are infertile, whereas females can be fertile. Those with free trisomy have a 50% risk of having offspring with DS. At one time, involuntary sterilization of people with DS was almost routinely carried out in many institutions and is still part of the law in some states, although rarely invoked.

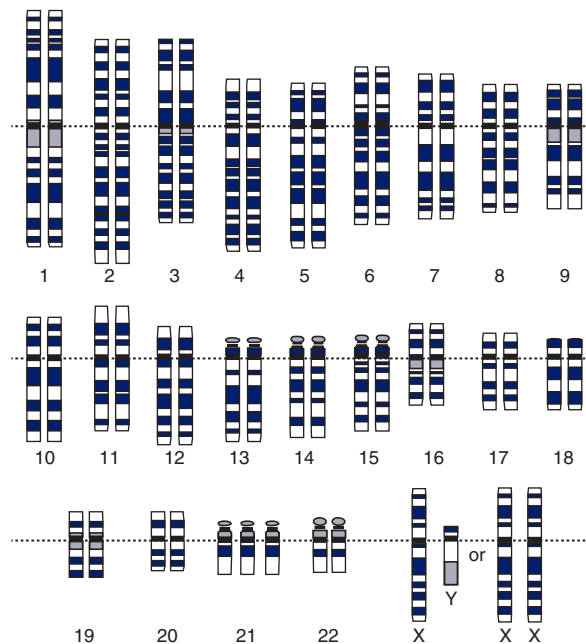


FIGURE 9.4. Trisomy 21 karyotype.
Source: Down Syndrome Karyotype, 2006.

It is important to provide developmentally appropriate sex education, including socially acceptable sexual behavior. Many parents need help recognizing the sexuality of their adolescent or young adult. Appropriate contraceptive information and care should also be provided. Adults with DS require care from clinicians who understand the syndrome and its manifestations and can provide sensitive, coordinated care.

With a current life expectancy of 60 years of age, health maintenance visits should include planning and discussion on transitioning to adulthood, appropriate school placements, vocational training, and health promotional programs for weight control. Additional considerations include education regarding increased possibilities of premature aging and development of early Alzheimer disease.

Families will require ongoing psychological support and counseling. Those with DS require ongoing medical treatment and, often, surgical procedures that may be difficult for both the affected person and the family. Detailed guidelines for health management have been developed by the American Academy of Pediatrics. Additionally, resources for families can be found on the National Down Syndrome Society website (www.ndss.org).

The Sex Chromosomes and Their Abnormalities

The human sex chromosomes are the X and the Y chromosome. Normal human females are 46,XX, and normal human males are 46,XY. Chromosome X contains over 1,400 genes, while chromosome Y contains over 200 genes (www.ncbi.nlm.nih.gov/books/NBK22266/#A295). As described in Chapter 4, daughters normally receive one X chromosome from the father and one from the mother. Sons normally receive an X chromosome from the mother and the Y chromosome from the father. In females, as discussed in Chapter 4, one of the two X chromosomes is inactivated within somatic cells, although a few genes apparently escape X inactivation.

Although nondisjunction gives rise to most of the sex chromosome abnormalities, neither 45,X nor 47,YYY is associated with increased parental age. The possible reproductive outcomes arising from meiotic nondisjunction at oogenesis and spermatogenesis are illustrated in Figure 9.5. First-division nondisjunction does not result in a normal karyotype, whereas second-division nondisjunction results in half-normal and half-abnormal gametes and offspring.

Considering all the sex chromosome aneuploidies together, the overall incidence is about 1 in 400 newborns. The most common sex chromosome variations are those in which there is an extra or missing X or Y chromosome, resulting in Turner syndrome (45,X), triple X (47,XXX), Klinefelter syndrome (47,XXY), or XYY (47,XYY). Those in which more X or Y chromosomes are added, such as tetrasomy or pentasomy X (48,XXXX; 49,XXXXX), are rare, and intellectual disability is common. For sex chromosome variations, the most common mosaic conditions are 46,XX/47,XXY; 45,X/46,XX; 46XX/47,XXX; and 46,XY/47,XYY.

In general, those with mosaic sex chromosome abnormalities tend to show milder signs, and the degree tends to be related to the percentage of abnormal cells. The

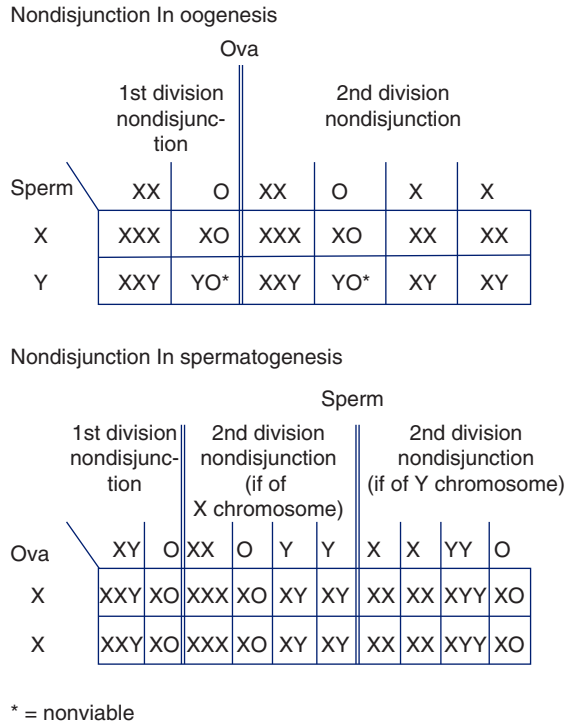


FIGURE 9.5. Possible reproductive outcomes after meiotic nondisjunction of sex chromosomes.

identification of persons with sex chromosome abnormalities often occurs at the following points in the life cycle (examples are given in parentheses):

- ▶ **Prenatally**—due to prenatal cytogenetic diagnosis (all types)
- ▶ **At birth**—confirmation of prenatal diagnosis (all variations), clinical suspicion (45,X), or through newborn chromosome screening (all types)
- ▶ **Childhood**—due to establishing the cause of short stature (45,X) or speech or language disabilities (47,XXY)
- ▶ **Adolescence**—due to delayed development or absence of secondary sex characteristics (45,X; 47,XXY), delayed menarche (45,X), or short stature (45,X)
- ▶ **Adulthood**—due to fertility or reproductive problems (45,X; 47,XXY)

Mildly affected individuals, especially some with 47,XYY, 47,XXY, and 47,XXX or mosaics, may go unrecognized. Sex chromosome variations appear more frequently after the use of intracytoplasmic sperm injection, a method of assisted reproductive technology.

The four major sex chromosome variations (45,X; 47,XXX; 47,XXY; 47,XYY) are summarized in Table 9.3, and Turner and Klinefelter syndromes are discussed in the following text. The major sex chromosome disorders or variations are illustrated by karyotype in Table 9.3.

TABLE 9.3 Sex Chromosome Variations

| Variation | Incidence | Comments |
|-------------------------------|--------------------------------|--|
| Turner syndrome (45,X) | 1: 2,500 live births | See text. |
| Triple X syndrome (47,XXX) | 1:1,000 live births | Phenotypic females who tend to be tall; have some learning disabilities, as well as delayed speech and language skills; may have some delay in walking, with clumsiness and poor coordination. |
| Klinefelter syndrome (47,XXY) | 1; 500–1,000 live births—males | See text. |
| 47,XYY syndrome | 1:1,000 live births | Phenotypic males who have above-average height and are hard to distinguish from other males. In the past, they had been called supermales, and in some cases were thought to be associated with criminal tendencies, but this is not the case. May have some delayed speech; learning difficulties, especially in reading; difficulties with fine motor coordination; Some behavioral difficulties may be related to low frustration threshold, immaturity, and impulsiveness, with childhood temper tantrums. |

Turner Syndrome (45,X)

This monosomy is usually written as 45,X. The complete absence of the X chromosome occurs in about 50% to 60%, with the rest having various combinations of partial deletion, isochromosome formation, and 45,X/46,XX mosaicism. In about 75% of the cases, individuals with Turner syndrome have the maternal X chromosome, while 25% have the paternal X chromosome, and there may be a relationship between decreased maternal age and a missing maternal X chromosome. Something under maternal control (e.g., rates of aneuploidy) may have a larger role once attributed to paternal loss of the chromosome.

Chromosome analysis is necessary not only for diagnostic confirmation but also because about 25% of mosaic individuals can menstruate. There is also an increased risk of malignancies such as dysgerminomas or gonadoblastomas in those with a XY cell line (5%–6%).

Phenotypically, short stature is the most consistent feature, with an average untreated height attainment of about 144 cm (4'6"). Final height in those with

Turner syndrome is influenced by other height-determining factors such as parental height and the extent of ovarian failure and cardiovascular status.

Prenatal detection is possible through chromosome analysis or sometimes through characteristics revealed on ultrasonography. Other cases are detected in later childhood because of the child's short stature, the lack of secondary sex characteristics at puberty, or the absence of menarche (about 90%). Some are not detected until adulthood, when they are noted to have amenorrhea or infertility. The external genitalia and vagina remain infantile without hormone therapy.

Common clinical features include:

- ▶ Short stature
- ▶ Cubitus valgus (an increased carrying angle of the arms so that the arms turn out at the elbow)
- ▶ Broad “shield” chest with widely spaced nipples
- ▶ Short neck
- ▶ Low hairline
- ▶ High narrow-arched palate
- ▶ Short fourth metacarpals
- ▶ Many pigmented nevi
- ▶ Hypoplastic nails
- ▶ Urinary tract anomalies (45%–80% have some malformation such as horseshoe kidney)
- ▶ Cardiovascular anomalies, which occur in 20% to 44% (most frequently occurring are bicuspid aortic valve anomalies, coarctation of the aorta, and mitral valve prolapse)
- ▶ Nondevelopment of secondary sex characteristics; amenorrhea
- ▶ Infantile external genitalia and vagina without treatment
- ▶ Infertility (affecting about 99%)
- ▶ Hypertension even without any accompanying cardiac or renal malformations
- ▶ Primary hypothyroidism as well as antithyroid antibodies and Hashimoto thyroiditis
- ▶ Other autoimmune phenomena, such as inflammatory bowel disease
- ▶ Recurrent otitis media and a progressive sensorineural hearing loss, which may occur and should be evaluated
- ▶ Ophthalmic disorders such as strabismus and ptosis
- ▶ Developmental dysplasia of the hip, scoliosis later in life, and degenerative arthritis in the older individual
- ▶ Though intelligence is normal, there are cognitive defects in spatial perception and orientation, resulting in difficulties telling left from right and reading maps

If untreated, the greatest problems reported by patients are short stature and the absence of secondary sex characteristics. Early diagnosis before cessation of bone growth permits the use of recombinant growth hormone (GH) therapy, often with oxandrolone, usually beginning at about age 9 or 10 years. This may be followed by ethinyl estradiol with or without progesterone to induce breast development, menstruation, and vaginal maturation. Growth velocity should be monitored with specific growth charts for Turner syndrome. It should be stressed that females with Turner syndrome have a feminine gender identity, so if reproduction is desired, referral should be made to specialists in this area. Family support groups and information are available through the Turner Syndrome Society of the United States (www.turnersyndrome.org).

Klinefelter Syndrome (47,XXY)

In Klinefelter syndrome (47,XXY), the origin of the extra X chromosome is maternal in about 50% of cases and paternal in 50% of cases. Klinefelter syndrome is underdiagnosed as most of the affected males are not identified until the absence of secondary sex characteristics is noted. These individuals may exhibit sparse body hair, gynecomastia, or small testes on physical exam. In adults, 47,XXY men may account for 14% of the cases of azoospermia; many are first diagnosed with evaluation for infertility. Some reports indicate an increase in the presence of minor congenital anomalies, especially clinodactyly. If multiple anomalies are present, these boys might be detected through chromosome analysis in infancy.

Penile size may be small (below the 50th percentile) in children, but is usually near normal in adolescence and adulthood alongside normal sexual functioning. Development of gynecomastia is more common and tends to persist in males with Klinefelter syndrome. An increased risk of breast cancer and various germ cell tumors has been noted in these individuals. Mammoplasty or prophylactic mastectomy may be recommended for patients with persistent gynecomastia.

Clinical features include:

- ▶ Tall stature, with increased leg length
- ▶ Overweight with female fat distribution and sometimes an incomplete masculine body build
- ▶ Decreased head circumference
- ▶ Intelligence in the low normal range, but impaired coordination may give the impression of slowness
- ▶ Speech and language delays, reading deficiencies, and poor spelling, plus difficulties in processing, retrieving, and storing information
- ▶ Delayed walking and clumsiness
- ▶ Personality impairment may exist in the form of passivity, unassertiveness, and shyness

Although the timing of testosterone therapy administration is not clearly established, testosterone replacement therapy can begin around the time of puberty to promote male phenotype development. Therefore, it is important to make adequate therapy available to such men so that problems related to appearance are minimized.

Some other nursing points should be stressed to the individual and family:

- ▶ Males with Klinefelter syndrome have a male gender identity. Normality should be emphasized.
- ▶ Sexual adequacy is not impaired. Most 47,XXY males marry, and some (usually mosaics) can reproduce. If they are infertile, reproductive options such as adoption or artificial insemination can be discussed.

INBORN ERRORS OF METABOLISM

Individually, inherited biochemical disorders are rare, but as a group, they impose a considerable burden on the patient, family, community, and society. The total reported incidence at birth varies from 1% to 2%, but accuracy is compromised by:

- ▶ The delayed appearance of mutant gene effects
- ▶ Failure to accurately diagnose certain inherited disorders, especially in newborns who die suddenly

Most geneticists use the term *inborn error of metabolism* to describe a subgroup of approximately 300 inherited biochemical disorders that comprises single gene mutations affecting known enzymes and metabolism. With a few exceptions, these are inherited in an autosomal recessive manner. Enzymes catalyze most reactions in metabolic pathways by acting on substrates in sequence. Some enzymes are conjugated (holoenzymes); that is, they consist of a protein core (apoenzyme) and a cofactor (inorganic compound such as a metal ion) or a coenzyme (organic component such as vitamin; see Figure 9.6, top). Interruption of any of the steps in forming a functional coenzyme can lead to a nonfunctional holoenzyme as well and result in disease (e.g., methylmalonic acidemia [MMA] can result from failure of coenzyme vitamin B₁₂ either to be absorbed or utilized). Replacement of the defective coenzyme effectively treats these disorders. Thus, metabolic dysfunction can occur because of alterations in the substrate, apoenzyme, cofactor, transport proteins, membrane receptors, or holoenzymes. A defect or deficiency of the needed substance at any stage of a metabolic reaction is referred to as a “block” and may be partial or total.

Consequences of Blocks in Metabolic Pathways

Specific consequences of a metabolic block depend on the pathway of which it is a part, but some general statements apply. A schematic representation of a hypothetical metabolic pathway is shown in Figure 9.6, bottom. From this diagram, it can be seen how a particular defect leads to various consequences or combination of consequences:

1. Lack of a functional transport carrier or membrane receptor protein means that a substance will not be able to get inside the cell (block 1) and will be excreted, lost, or accumulated in the wrong place, leading to ill effects. Subsequently, it is not available for participation in other reactions or pathways. For example, in cystinuria, the carrier responsible for transporting the amino

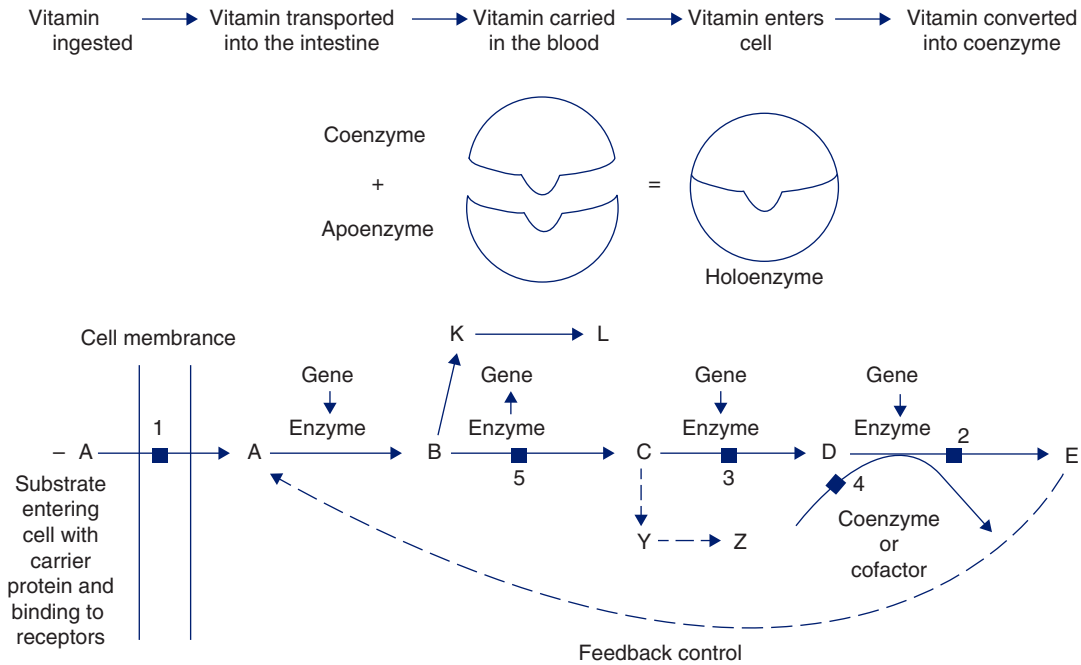


FIGURE 9.6. (Top) Relationship between vitamins, coenzymes, apoenzymes, and holoenzymes. (Bottom) Hypothetical metabolic pathway illustrating consequences of metabolic blocks A, B, C, D, K, L, Y, Z = substrates or precursors; ■ = block, E = product (see text for explanation).

acids cystine, lysine, ornithine, and arginine across the epithelial cell membrane in the renal tubules and in the intestinal wall is defective; excessive amounts are excreted, and renal calculi often occur. Hartnup disease is another example of a transport disorder. Familial hypercholesterolemia, a receptor disorder, is discussed in Chapter 10.

2. The substrate (D) immediately before the block (block 2 or 4) or a more distant precursor (A, B, or C) can accumulate. This substance may be toxic to the cell itself, interfere with other biochemical reactions, or give rise to systemic clinical manifestations. It may also be toxic because of the accumulation of the substrate or precursor itself (e.g., in Farber disease, ceramidase deficiency results in the accumulation of the lipid ceramide, causing joint swelling, stiff joints, psychomotor retardation, nodules, vomiting, hoarseness, and respiratory problems), or because such an accumulation (of substrate C) causes the opening of an alternate minor biochemical pathway (Y–Z), causing a product to be produced that normally is not, and it is this product that causes toxic signs and symptoms (e.g., in PKU, phenylpyruvic and phenylacetic acids are formed and excreted in the urine). In Figure 9.6, block 4 would prevent the availability of a needed cofactor.
3. The usual product (E) of the metabolic pathway either cannot be produced (blocks 1, 2, 3, 4, or 5) or is produced in inadequate amounts or defective form. Clinical effects can be seen due to its direct lack (e.g., lack of melanin in albinism caused by lack of tyrosinase); if it is needed as a substrate for a subsequent reaction, that reaction cannot occur, and the clinical manifestations may be somewhat removed from the original defect (e.g., lack of phenylalanine hydroxylase in classic PKU prevents the conversion of phenylalanine [Phe] to tyrosine to dopa, and so melanin synthesis is diminished and persons with PKU have lighter hair and skin than their siblings).
4. Excess available substrate from the defective pathway (block 5) may be channeled to another normal pathway (B–K–L), causing overproduction of its product. This too may affect other reactions.
5. The usual product from the affected metabolic pathway may be functioning in a negative feedback loop or another control mechanism (dotted lines from E to A), and thus, when not produced, fails to control production of some precursor in its own or another pathway (e.g., in congenital adrenal hyperplasia caused by the lack of 21-hydroxylase, cortisol production is decreased, so the hypothalamus responds by secreting more corticotropin-releasing factor, causing increased adrenocorticotrophic hormone [ACTH] by the anterior pituitary).

Clinical Manifestations of Inherited Biochemical Disorders in Newborns and Infants

In contrast to the chromosomal disorders and congenital malformations, most of the metabolic disorders show no gross anomalies at birth. Recognition of such disorders and their ultimate diagnosis is complicated by the fact that there are few precise

clinical manifestations that can be considered diagnostic. Many defects of the same enzyme are due to alleles that take different clinical forms and may show a rapidly progressive severe infantile picture, a less severe later juvenile onset, or a milder adult form.

Clinical manifestations in the newborn and infant that should lead to further evaluation are shown in Table 9.4. Developmental assessment and signs and symptoms present in older children are discussed in Chapter 7. Dietary history is particularly important, because infants with certain metabolic errors do not exhibit problems until poorly tolerated food is introduced. Some infants develop symptoms of intolerance when they are switched from breast milk to formula because of changes in the protein composition. It is important to emphasize that early identification of an inherited biochemical disorder can allow for early treatment and eligibility for government-funded programs, family studies, genetic counseling, reproductive decision making, life planning, and, in subsequent pregnancies, prenatal detection and even in utero treatment. Because few symptoms are pathognomonic of a disorder and can be used for diagnosis, most require biochemical or DNA testing for confirmation. Testing should be done for parents, and sometimes other family members, if appropriate.

Because the newborn can respond to such illness in only a limited variety of ways, any history of the death of a sibling in infancy, even if a diagnosis was established, should be an indication for heightened observation and an increased index of suspicion for the nurse working with newborns and infants. Often the initial presentation is nonspecific, such as lethargy, poor feeding, failure to thrive, vomiting, irritability, or tachypnea. The major types of presentation include those that lead to intoxication and often neurologic deterioration from accumulation of toxic compounds

CASE EXAMPLE

An extreme example of a missed metabolic disorder was the Stallings case. Patricia Stallings brought her 3-month-old son to an emergency room in St. Louis with symptoms that included vomiting and lethargy. When the laboratory reported finding ethylene glycol in his blood, suspicion of poisoning ensued, and the infant was placed in foster care. Another hospitalization for this infant occurred, and Stallings was accused of feeding him antifreeze. The infant died. She was tried for his murder and found guilty. By this time, she was pregnant again. When she had another son, a similar situation developed. Again, she was suspected of poisoning the second son. Alert geneticists read about the case and contacted legal counsel. This time the infant was diagnosed as having MMA, a rare autosomal recessive biochemical disorder. After many twists and turns, Stallings was vindicated in the death of her first son, who was determined to have died from MMA, and she was released. Some cases of sudden infant death syndrome (SIDS) are known to be from inborn errors of metabolism, and increasingly this is investigated as a cause of death in these circumstances.

TABLE 9.4 Some Clinical Manifestations of Inborn Metabolic Errors in Newborns and Early Infancy

| Sign/Symptom | Examples of Disorders |
|---|---|
| Overwhelming illness, may resemble sepsis | Propionate metabolism defects, MSUD, glycemia |
| Lethargy | Urea cycle disorders, galactosemia, MSUD, GM1 gangliosidosis, Gaucher disease, orotic aciduria, nonketotic hyperglycemia |
| Coma | Urea cycle disorders |
| Convulsions | PKU, Menkes disease, Krabbe disease, MSUD, urea cycle disorders, infantile hypophosphatasia |
| Exaggerated startle reflex | Tay–Sachs disease |
| Hypotonia | Urea cycle disorders, Tay–Sachs disease, Menkes disease, glycogen storage disease II, acid phosphatase deficiency |
| Poor feeding | Propionate metabolism defects, GM1 gangliosidosis, Menkes disease |
| Failure to thrive | Propionate metabolism defects, galactosemia, glycogen storage disease I, Gaucher disease, hypophosphatasia, glycogen storage disease II, Andersen disease, orotic aciduria, Menkes disease, severe combined immune deficiency |
| Eczema | PKU |
| “Sand” in diapers | Lesch–Nyhan syndrome |
| Candidiasis | Severe combined immune deficiency, propionate metabolism defects |
| Jaundice | Galactosemia, G6PD deficiency, α -1-antitrypsin deficiency, Crigler–Najjar syndrome, erythropoietic porphyria, hypothyroidism, pyruvate kinase deficiency |
| Vomiting | Urea cycle disorders, galactosemia, propionate metabolism defects, isovaleric acidemia, MSUD, PKU, fructosemia, Wolman disease, hypophosphatasia, Menkes disease, glycogen storage disease I |
| Cataract formation | Galactosemia, Hallermann–Streiff syndrome |

(continued)

TABLE 9.4 Some Clinical Manifestations of Inborn Metabolic Errors in Newborns and Early Infancy (continued)

| Sign/Symptom | Examples of Disorders |
|---|--|
| Acidosis | Propionate metabolism defect, MSUD, isovaleric acidemia, oxoprolinuria, glutaric aciduria, pyruvate dehydrogenase deficiency |
| Enlarged abdomen | Propionate metabolism defect, MSUD, isovaleric acidemia, oxoprolinuria, glutaric aciduria, pyruvate dehydrogenase deficiency |
| Diarrhea | Galactosemia, Wolman disease, severe combined immune deficiency |
| Hypoglycemia | Glycogen storage disease Ia, galactosemia, MSUD, propionate metabolism defects, isovaleric acidemia, galactosemia |
| <i>Characteristic odors (e.g., of urine, sweat)</i> | |
| Musty, mousy | PKU, tyrosinemia |
| Burnt sugar | MSUD |
| Cheese, “sweaty feet” | Isovaleric acidemia |
| Hops, dried celery | Oasthouse urine disease (methionine malabsorption) |

Note: Urea cycle disorders include N-acetylglutamate synthase (NAGS) deficiency, carbamoyl phosphate synthetase (CPS) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinate synthetase deficiency (citrullinemia I), citrin deficiency (citrullinemia II), argininosuccinate lyase deficiency (argininosuccinic aciduria), arginase deficiency (hyperargininemia), and ornithine translocase deficiency (HHH) syndrome. Propionate metabolism defects include methylmalonic acidemia, propionic acidemia, and multiple carboxylase deficiency. MSUD, maple syrup urine disease; PKU, phenylketonuria.

(organic acidemias), deficiency in energy production or utilization (presenting with hypoglycemia such as hyperinsulinism or fatty acid oxidation disorders), seizures (such as vitamin-responsive seizures of various types), jaundice or liver failure (such as fructose intolerance or tyrosinemia), and cardiac disorders or failure (suggesting mitochondrial fatty acid oxidation disorders).

Links for support groups and patient information on inherited metabolic diseases can be found online (www.simd.org/Links).

SELECTED GENETIC DISORDERS COMMONLY SEEN IN CHILDHOOD

This section is devoted to disorders following the inheritance patterns discussed in Chapter 4 that are important because of frequency or because they illustrate an important point. Some, such as Marfan disease, may be recognized in childhood, adolescence, or adulthood, and are discussed in Chapter 10.

HEMOGLOBIN AND ITS INHERITED VARIANTS

The major normal adult hemoglobin (Hb A₁) is a tetramer composed of two alpha and two beta globin polypeptide chains and the associated heme groups. The genes that code for α -like chains (zeta [ζ] and alpha [α]) are on chromosome 16, whereas the β -like genes, epsilon (ϵ), gamma (γ), β , and delta (δ), are all located on chromosome 11 as seen in Figure 9.7. During development, the embryo and fetus synthesize different Hb chains to meet evolving oxygenation needs (Table 9.5). Embryonic hemoglobin, ($\zeta_2\epsilon_2$) is the earliest synthesized and is typically found in embryos under 12 weeks. By 5 weeks of gestation, synthesis moves from the embryonic yolk sac to the fetal liver and spleen. This shift leads to an increased production of fetal hemoglobin (Hb F; $\alpha_2\gamma_2$). Major production of β chains coincides with the shift of hematopoiesis to the bone marrow, decreasing gamma chain synthesis and increasing assembly of Hb A. The shift does not reach its maximum rate until about 6 months after birth, when Hb F decreases to less than 2% (Table 9.6). Therefore, any disorder that causes insufficient β chain synthesis is not usually manifested clinically until the infant is 3 to 6 months of age. The minor adult hemoglobin (Hb A₂; $\alpha_2\delta_2$) also becomes assembled around birth.

More than 1,500 hemoglobin variants have been identified. There are two basic classes: those due to qualitative changes or structural changes, that is, an amino acid substitution or deletion in the globin part of the molecule as in Hb S or Hb C, and those resulting from quantitative changes, such as deficient globin synthesis as

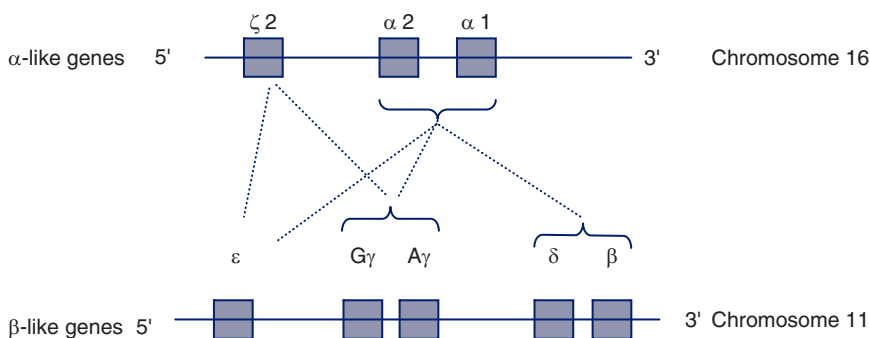


FIGURE 9.7. α -globin and β -globin gene clusters: Hemoglobin is synthesized from two α -globin genes and two β -globin genes. This figure shows how embryonic, fetal, and adult hemoglobins are paired.

Source: Schneidereith (2012).

TABLE 9.5 Hemoglobin Synthesis

| Type of Hemoglobin | Site of Synthesis | Time of Synthesis | Globin Chains |
|--------------------|------------------------|--|---|
| Embryonic | Yolk sac | Up to week 6 postconception | $\zeta_2\varepsilon_2$, $\zeta_2\gamma_2$, or $\alpha_2\varepsilon_2$ |
| Fetal (Hb F) | Fetal liver and spleen | Approximately 6 weeks postconception to 48 postnatal weeks; continues at low levels throughout adulthood | $\alpha_2\gamma_2$ |
| Adult (Hb A) | Bone marrow | Approximately 6 weeks postconception and throughout adulthood | $\alpha_2\beta_2$ |

in the thalassemias (see Table 9.7). This latter group also includes the hereditary persistence of fetal hemoglobin (HPFH), an abnormal continued production of high amounts of Hb F.

The substitution of one nucleotide base for another, resulting in a different amino acid in one of the chains, may change the charge of the Hb molecule and its electrophoretic mobility, or it may be silent. Changes can alter such qualities as oxygen

TABLE 9.6 Composition and Description of Normal Hemoglobin

| Chain Composition | Designation | Description | Percentage in Normal Adult |
|-------------------------|-------------------|-------------------------------|----------------------------|
| $\alpha_2\beta_2$ | Hb A | Major normal adult hemoglobin | 97–98.5 |
| $\alpha_2\delta_2$ | Hb A ₂ | Minor normal adult hemoglobin | 1.5–3 |
| $\alpha_2\gamma_2$ | Hb F ^a | Fetal hemoglobin | 1 |
| $\zeta_2\varepsilon_2$ | Gower I | Embryonic hemoglobin | 0 |
| $\alpha_2\varepsilon_2$ | Gower II | Embryonic hemoglobin | 0 |
| $\zeta_2\gamma_2$ | Portland Hb | Embryonic hemoglobin | 0 |

Note: Hb F exists in two forms: $\alpha_2\gamma_2^{136\text{ala}}$ = alanine at position 136 in the gamma chain and $\alpha_2\gamma_2^{136\text{gly}}$ = glycine at position 136 in the gamma chain.

TABLE 9.7 Examples of Selected Hemoglobin Variants

| Designation | Comment |
|--------------------|--|
| Hb S | Point mutation in which valine is substituted for glutamic acid at β chain position 6; reduced solubility of deoxy form |
| Hb C | Same as above but lysine is substituted for glutamic acid; trait (AC) found in 2%–3% of American Blacks |
| Hb D | Point mutation in which glutamine replaces glutamate at β chain position 121. More common in those of Mediterranean and Indian descent; low prevalence |
| Hb H | Tetramer of β chains formed; impaired oxygen transport (see text) |
| Hb M Boston | Tyrosine substituted for histidine at α chain position 58; cyanosis, methemoglobinemia (see text) |
| Hb Barts | Tetramer of β chains formed; impaired oxygen transport (see text) |
| Hb Chesapeake | Leucine substituted for arginine at α chain position 92; high oxygen affinity, polycythemia |
| Hb Constant Spring | Elongated α chain due to α chain termination mutation; has 31 extra amino acid residues, slow synthesis; may resemble α -thalassemia clinically |
| Hb Freiberg | Deletion of valine at β chain position 23; increased oxygen affinity; unstable Hb with mild hemolysis when exposed to sulfonamides |
| Hb Zurich | Arginine substituted for histidine at β chain position 63; mild hemolysis when exposed to sulfonamides, unstable Hb |

affinity, solubility, or stability, resulting in cyanosis or hemolytic anemia, but the majority show no manifestations unless a stressor is encountered, such as altered oxygenation, fever, or drug exposure (see Chapter 6).

Hemoglobin Variants and Sickle Cell Disease

The disorders of sickling include sickle cell anemia (SS), sickle cell trait (SA), or compound heterozygous states, including SC disease (Hb S and Hb C). Hb S results from the substitution of valine for glutamic acid at position 6 of the β chain (Glu-6Val), while Hb C results from the substitution of lysine for glutamic acid at the same position (Glu6Lys). The combination of these two alleles, or SC disease, results

in fewer vaso-occlusive crises and a longer life span than in sickle cell disease. Hb SC disease occurs overall in about 1 in 800 persons. One parent of a person with SC will have Hb S trait (SA), and one will have Hb C trait (AC). The incidence of Hb C trait in American Blacks is 2% to 3% and 17% to 28% in West Africans (see Chapter 3). Hb C disease is often asymptomatic despite mild to moderate hemolytic anemia, but abdominal and joint pain may occur with splenomegaly. The hemoglobin D (Glu121Gln) mutation is more common in those of Mediterranean and Indian descent while Hb E (Glu26Lys) is most common in people of Southeast Asian descent. The Hb E trait occurs in 15% to 30% of Southeast Asian immigrants to the United States, especially Cambodians and Laotians. It may also occur in American Blacks. Hb E disease is often asymptomatic except for mild anemia. Combinations of Hb E with thalassemias occur frequently in Southeast Asians, leading to more severe disease.

In sickle cell anemia, the basic defect is caused by the substitution of the amino acid valine for glutamic acid in the sixth position of the β chain of the hemoglobin molecule, forming sickle cell hemoglobin (Hb S) instead of the normal adult hemoglobin (Hb A). This changes the charge of the hemoglobin molecule, resulting in a different mobility detected on hemoglobin electrophoresis. When this occurs in only one of the two chains, the individual is said to have sickle cell trait (Hb AS). An individual who receives two of these recessive mutant genes has sickle cell disease (Hb SS). Approximately 7% to 9% of Black Americans have sickle cell trait. Individuals of Mediterranean ancestry (Greek, Italian, Arabic) also have a higher frequency of sickle cell than other population groups. It is believed that persons with Hb AS are generally asymptomatic, but may show some exercise intolerance, especially at high altitudes. It is important to screen for sickle cell trait so that carriers can be identified and counseled. Also, identification of this trait in pregnant women may help minimize risk for complications such as hematuria, urinary tract infections, and fetal distress at delivery.

Sickle cell anemia may be diagnosed as part of newborn screening programs or in childhood. Following diagnosis, parents should be encouraged to seek specialized care through comprehensive sickle cell centers. Additionally, families should be educated regarding signs of infection, jaundice, and fever, as well as other possible clinical manifestations and complications. These can include respiratory distress, overwhelming sepsis, painful sickle cell crises, splenic sequestration (abdominal distention with pallor and listlessness), dactylitis, leg sores, and ulcers. Other neurologic symptoms, such as paresis, might indicate a stroke.

Most complications associated with vaso-occlusive crises are decreased in individuals with higher amounts of Hb F. For infants, the normal production of Hb F is protective for approximately the first 6 months of life. Pharmacologic therapies, especially hydroxyurea (HU), have been shown to increase production of Hb F and decrease vaso-occlusive crises, but the *in vivo* responses are variable. Increasing Hb F continues to be an active area of research including investigation of the cGMP and cAMP pathways and a phase II clinical trial of HQK-1001, a short chain fatty acid. Additionally, new transcription factors involved in γ -globin gene repression have been identified and may be an exciting target for future therapies.

The American Academy of Pediatrics has published health supervision guidelines for sickle cell disease. Children should receive the usual recommended immunizations and usually start penicillin prophylaxis by 2 months of age. Hydration is important, and folic acid supplementation may be useful. For the adolescent, sports activities, pregnancy risks, and contraception should be evaluated. For example, females with SS may be at higher risk for thrombosis when using oral contraceptives and increased complications with pregnancy. The website of the Sickle Cell Disease Association of America provides information and links for patients and families regarding treatment and research (www.sicklecelldisease.org).

The Thalassemias

The Thalassemias are a group of disorders that result from deficient or absent production of α - or β -globin. This change in the rate of synthesis of one or more globin chains creates an imbalance as seen in Table 9.8. Those with a deficiency in the α chains have α -thalassemias, which are most prevalent in Southeast Asians, North Africans, and Blacks of African descent. The most severe α -thalassemia is Hb Barts hydrops fetalis, in which there is complete absence or inactivation of all four α genes, usually through deletion. This is often denoted as --/--. Infants with the disorder are usually stillborn or die in the neonatal period. Clinical features include generalized edema, hydrocephalus, cardiac defects, and urogenital defects.

TABLE 9.8 The Thalassemias

| Normal production Absent production | | | | |
|---|--|--------|----------------------------|-----------------|
| α -Thalassemia | α -Globin Chains $\alpha_2 \alpha_1$ | | β -Thalassemia | β -Globin |
| Normal | ■ ■ | ■ ■ | Normal | ■ ■ |
| Silent Carrier | ■ ■ | ■ □ | | |
| Trait | ■ □ | ■ □ | Trait/minor | ■ □ |
| Hb H | ■ □ | □ □ | | |
| Major (Hydrops fetalis) | □ □ | □ □ | Major (Cooley's anemia) | □ □ |

In Hb H disease, three of the four α genes are absent ($--/\alpha$). Some normal Hb is produced, but the unstable Hb H causes hemolytic anemia, splenomegaly, microcytosis, and impaired oxygen transport. In α -thalassemia trait, two of the four genes are absent ($--/\alpha\alpha$, called α^0 thalassemia, or $-\alpha/\alpha$, called α^+ thalassemia), and infants may have mild anemia with other hematologic findings. In silent gene carriers, one of the four genes is absent ($-\alpha/\alpha\alpha$), and there may be no signs except for slight microcytosis. It is important to recognize the disorder to avoid mistreatment for iron deficiency anemia and for accurate genetic counseling.

The β -thalassemias result from a reduced rate of synthesis of β -globin and are most prevalent in populations bordering the Mediterranean Sea, especially Italy, Greece, Cyprus, and the Middle East. In β -thalassemia, there may be a decreased synthesis of β chains (β^+) or no production (β^0). In the homozygous state, β -thalassemia is known as thalassemia major or Cooley's anemia. Although the clinical course can vary, typically symptoms are not noticed right after birth because of the presence of Hb F in the normal newborn. Manifestations do not occur until hemoglobin production switches to β -globin production. Hb F may persist as a compensatory mechanism, but it is not sufficient to prevent symptom development. Infants are pale and jaundiced, fail to thrive, have hepatosplenomegaly, and show prominent bones in the skull, spine, and face as the marrow hypertrophies. Long bone fractures and short stature are common findings. The hemolytic anemia results in frequent blood transfusions and subsequent iron overload. The iron deposition creates dysfunctional cardiac, hepatic, and endocrine systems. Lung disease may also occur. Various approaches, such as iron chelation with desferrioxamine, have been used to remove the iron burden brought about by transfusion.

Population screening is common in Mediterranean countries, such as Greece and Italy. When this blood is screened, the major findings of thalassemia include a mean cell volume (MCV) less than 72 to 75 fL and microcytic anemia.

Similar to sickle cell disease, HU is used as a treatment for β -thalassemia. Retrospective studies suggest a role for XmnI and BCL11A single-nucleotide polymorphisms (SNPs) in response to HU in β -thalassemia. Overall, however, many questions remain for how HU increases fetal hemoglobin production.

Over 3,000 allogeneic stem cell transplants have been performed worldwide with a 90% survival. However, there is still debate on best practices for patient selection, timing of transplant, and post-transplant antirejection medications, need for transfusion, and chelation therapy.

Nurses should be alert for β -thalassemia in persons of Mediterranean descent and for α -thalassemia in persons of Southeast Asian descent who present with apparent anemia. Another nursing implication of this disorder is the need to provide genetic counseling, including the option of prenatal diagnosis, to the parents who are heterozygotes for thalassemia.

Phenylketonuria and Hyperphenylalaninemia

Mutations in the phenylalanine hydroxylase gene (PAH; 12q22-q24.2) result in increased levels of the amino acid Phe. Phe is normally converted in the liver to tyrosine, but inhibition of the PAH enzyme leads to blockages collectively referred to

as hyperphenylalaninemias (see Chapter 8, Figure 8.2). Several defects in the steps of Phe metabolism or its cofactor can result in elevated Phe. The inheritance pattern is autosomal recessive with over 850 variants responsible for the spectrum of Phe-related disorders.

The traditional classifications for PKU have been changed to reflect two new categories. The forms that require treatment include classical PKU (Phe levels greater than 20 mg/dL), moderate PKU (15–20 mg/dL), and mild PKU (10–15 mg/dL). Mild hyperphenylalaninemia (HPA)-gray zone (6–10 mg/dL) is a category where there is debate about when to treat due to inconclusive data regarding effects on cognitive functioning. The category of mild HPA-NT (2–6 mg/dL) is generally considered acceptable and requires no treatment.

It is now rare to see a child manifest the full spectrum of symptoms resulting from classic PKU because of screening programs and prompt treatment, but occasionally an affected infant is missed. Therefore, PKU should not be automatically ruled out in infants manifesting signs and symptoms associated with the disorder. PKU is discussed in more detail in Chapter 8.

Lysosomal Storage Diseases

Lysosomal storage diseases are a group of about 50 genetic diseases that involve the accumulation of certain metabolites within the cell organelle known as the lysosome. This accumulation is due to defective lysosomal enzyme activity or a genetic defect in a receptor, activator protein, membrane protein, or transport molecule. The abnormal deposition and storage of the particular substance can affect the central nervous system or have other systemic manifestations. The individual disorders vary from the mucopolysaccharidoses (MPS) such as Hurler disease; to the sphingolipidoses, which include the gangliosidoses such as Sandhoff disease and Tay–Sachs disease; glycogen storage disorders, such as Pompe disease; as well as mucopolipidosis IV and Chédiak–Higashi syndrome.

Collectively the incidence is 1 in 7,000 to 8,000 live births. The majority are inherited in an autosomal recessive manner with the exception of Hunter disease and Fabry disease, which are X-linked recessive, and Danon disease (glycogen storage disease IIb), which is X-linked dominant. These disorders are generally progressive and may have variant forms that differ in age of onset (often with a severe form with infantile onset and less severe juvenile or adult forms, so that many patients first come to clinical attention as adults), clinical presentation, or disease course. Those who present as adults are often not diagnosed promptly. For example, a 38-year-old man with Niemann–Pick disease type C was misdiagnosed as having schizophrenia for 8 years, and a late adolescent male with Tay–Sachs disease was misdiagnosed with catatonic schizophrenia. Adult-onset Tay–Sachs disease can mimic Friedreich ataxia. Selected lysosomal storage disorders are summarized in Table 9.9. The mucopolysaccharide disorders and Tay–Sachs disease are discussed next as examples.

Mucopolysaccharide Disorders (Mucopolysaccharidoses)

The MPS are a group of lysosomal storage disorders (MPS I, II, III, IV, VI, VII, IX) that are characterized by the accumulation of glycosaminoglycans (GAG; originally called

TABLE 9.9 Characteristics of Selected Lysosomal Storage Diseases

| Disorder | Enzyme Deficiency | Selected Characteristics (Infantile Form Unless Noted) |
|---|--|---|
| Fabry disease (diffuse angiokeratoma) | α -galactosidase A | Onset in late childhood, adolescence, or adulthood; telangiectasia, pain attacks, autonomic dysfunction, angina, electrocardiogram changes, paresthesia, lymphedema, hypertension, renal failure; death by middle age usual |
| Farber disease | Ceramidase | Psychomotor deterioration, subcutaneous nodules, failure to thrive, swollen joints, intellectual disability, hepatosplenomegaly, hoarseness, death |
| Gaucher disease | β -glucosidase | See text |
| Generalized gangliosidosis | β -galactosidase | Hepatosplenomegaly, skeletal abnormalities with dwarfism, joint stiffness, intellectual disability, cerebral degeneration, decerebrate rigidity, death |
| Krabbe disease | Galactocerebrosidase β -galactosidase | Irritability, convulsions, mental and motor deterioration, deafness, blindness, death |
| Metachromatic leukodystrophy | Arylsulfatase A | Hypotonia, quadriplegia, blindness, mental deterioration, megacolon, death |
| Niemann–Pick disease type A | Sphingomyelinase | Has many subforms; seizures, coronary artery disease, hepatosplenomegaly, failure to thrive, hypotonia, intellectual disability, death |
| Refsum syndrome | Phytanic acid oxidase | Peripheral neuropathy, cerebellar ataxia, retinitis pigmentosa, ichthyosis, deafness, cardiac arrhythmias (child) |
| Sandhoff disease | Hexosaminidase A and B | Muscle weakness and wasting, mental and motor deterioration, cerebellar ataxia, blindness, cardiomegaly, hepatosplenomegaly |
| Tay–Sachs | Hexosaminidase A | See text |

mucopolysaccharides). GAGs are long chain complex carbohydrates which, when accumulated in the lysosomes, can lead to various somatic and neurologic sequelae. The pertinent GAGs include chondroitin sulfate (SO_4), heparan SO_4 , dermatan SO_4 , keratan SO_4 , and hyaluronic acid.

There are seven distinct classification groups, each with a pattern of deposition and urinary excretion of MPS that is valuable in diagnosis (see Table 9.10). These disorders are progressive and may show considerable variability in clinical severity.

The combined incidence of all the MPS disorders is 1 in 25,000 newborns. MPS I is usually classified into Hurler syndrome (most severe), Scheie (mild), and Hurler–Scheie, which is intermediate. It is believed that these are points on a continuous spectrum of severity. Hurler syndrome is one of the most frequently seen. Clinically, it is not usually detected until 6 to 12 months of age, although infants may have umbilical or inguinal hernias, macroglossia, and hepatosplenomegaly. Usually the syndrome does not develop fully until well into the second year. Cardiac disease is very common, and cardiomyopathy may result in early death. Most affected children do not live past 14 years of age. Enzyme replacement therapy using recombinant human α -L-iduronidase (Aldurazyme) has been used in treatment in mucopolysaccharidosis I, as has bone marrow transplantation and the combination of both. Support for families living with MPS can be found online (mpssociety.org/mps). The following case illustrates many typical features.

CASE EXAMPLE

A 22-month-old girl was referred to the genetic counseling center because of developmental delay and growth retardation. Examination revealed typical coarse facies, an enlarged tongue, kyphosis, hirsutism, and a protruding abdomen caused by an enlarged liver and spleen. Corneal clouding was noted. Her mother stated that the child had frequent colds and ear infections. The family history was negative; her 5-year-old brother was normal. Laboratory testing revealed findings characteristic of Hurler syndrome. The health care professional referred the family to genetic services. Included in the usual genetic counseling of the family based on the autosomal recessive inheritance was the information that prenatal diagnosis was available and could be used if another pregnancy was desired.

Tay–Sachs Disease

Tay–Sachs disease is the best known of the lysosomal storage diseases. It is classified as a GM_2 gangliosidosis due to mutation of the *HEXA* gene (15q24.1) encoding the α -subunit of hexosaminidase A (Hex A), a lysosomal enzyme composed of α and β polypeptides. At least 78 mutations in this gene have been identified.

In the classic infantile form, the infant appears well except for an exaggerated Moro (startle) reflex. At 4 to 6 months of age, onset of hypotonia, difficulty feeding, and apathy are typical. Motor weakness, developmental regression, and mental retardation follow. A cherry-red spot is observed on the fundus during an ophthalmic

TABLE 9.10 List of Mucopolysaccharidoses

| Type | Deficient Lysosomal Enzyme | Deposited GAGs | Incidence (numbers /100, 000 births) | Clinical Manifestations |
|------|---|----------------|--------------------------------------|--|
| I | α -L-iduronidase (IDUA) | HS, DS | IH: 0.8–1.3 | Coarse facies, short stature, dysostosis multiplex, joint stiffness, spinal cord compression, organomegaly, corneal clouding, hearing loss, cardiac/respiratory disease, and mental retardation if severe |
| | | | IH/S: 0.2–0.6 | |
| | | | IS: 0.1 | |
| II | Iduronate-2-sulfatase (I2S) | HS, DS | 0.2–1.4 males | Coarse facies, short stature, dysostosis multiplex, joint stiffness, spinal cord compression, organomegaly, diarrhea, retinal degeneration, cardiac/respiratory disease, pebbled skin, and mental retardation if severe; no corneal clouding |
| III | A: heparan N-sulfatase (sulfamidase; SGSH) | HS | A: 0.3–1.9 | Severe mental impairment, aggressive behavior, sleep disturbances, and dementia, accompanied by relatively mild somatic symptoms |
| | B: N-acetyl- α -glucosaminidase (NAGLU) | | B: 0.4–0.7 | |
| | C: acetyl-CoA: α -glucosaminide N-acetyltransferase (HGSNAT) | | C: 0.1–0.2 | |
| | D: N-acetylglucosamine 6-sulfatase (GNS) | | D: 0.1 | |

(continued)

| | | | | |
|-----|--|------------|---------------------|---|
| IV | A: N-acetylgalactosamine-6-sulfate sulfatase (GALNS) | A: KS, CS | A: 0.2–1.3 | Short stature, ligamentous laxity, joint hypermobility, dysostosis multiplex, odontoid hypoplasia, pectus carinatum, kyphoscoliosis, genu valgum, corneal clouding, hearing loss, and cardiac disease; no mental impairment |
| | B: β -galactosidase (GLB1) | B: KS | B: 0.1 | |
| VI | N-acetylgalactosamine-4-sulfatase | DS, CS | 0.3 | Coarse facies, short stature, dysostosis multiplex, joint stiffness, odontoid hypoplasia, kyphoscoliosis, genu valgum, organomegaly, and cardiac/respiratory disease; no mental impairment |
| | (arylsulfatase B; ASB) | | | |
| VII | β -glucuronidase (GUSB) | DS, HS, CS | 0.3 | Coarse facies, short stature, dysostosis multiplex, joint stiffness, spinal cord compression, odontoid hypoplasia, organomegaly, cardiac disease, corneal clouding, and mild mental impairment |
| IX | Hyaluronidase | Hyaluronan | Four cases reported | Short stature, polyarthropathy, periarticular soft tissue masses with painful swelling and acetabular erosion |

CS, chondroitin sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate.

Source: Noh and Lee (2014).

CASE EXAMPLE

The nurse in the well-baby clinic in the Williamsburg section of Brooklyn, New York, was talking to Ruth, the mother of a 7-month-infant girl, Sarah. Ruth is of Ashkenazi (Eastern European) Jewish descent. Ruth tells the nurse that she is concerned about Sarah because she had begun to sit up by herself but has seemed to lose this skill. In addition, she is having difficulty feeding Sarah. The nurse ascertains that Ruth and her husband, Stuart, had not undergone carrier screening for Tay–Sachs disease before or during pregnancy, and in reviewing the family pedigree and history, she notes that they are second cousins. The nurse during the physical examination sees a cherry-red spot on Sarah’s fundus during ophthalmic examination. At this point, referral is made for more intense evaluation. Sarah is ultimately found to have Tay–Sachs disease. What would the nurse think about in terms of testing for the parents and in terms of the implications for the immediate and extended families?

examination, and blindness occurs by 12 to 18 months. Neurologic deterioration follows. Seizures, decerebrate rigidity, and deafness occur, with an eventual vegetative state. The head enlarges about 50%, and hypothalamic involvement may cause precocious puberty. Death is inevitable and typically occurs by 2 to 4 years of age, although a few children have survived to 6 years. Tay–Sachs is most common in Ashkenazi Jews and in French Canadians from eastern Quebec. Both juvenile and adult forms have been described. Those with the juvenile form may develop symptoms between ages 1 and 9 years. The availability of carrier screening and its use among population subgroups has decreased the number of infants born with Tay–Sachs disease.

Duchenne and Becker Muscular Dystrophy

The muscular dystrophies are a group of inherited muscle disorders, termed *dystrophinopathies*. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are both X-linked recessive disorders that are allelic and result from different deletions in the dystrophin gene at Xp21.1. Mutation results in deficiency or defect of the functional gene protein product dystrophin. This cytoskeletal protein is located in the muscle membrane and is destabilized if dystrophin is deficient or altered, resulting in lack of structural integrity of the muscle membrane. DMD is the most common (1 in 3,000–5,000 male births) and most severe. Initial common symptoms appear in early childhood, usually insidiously. These include:

- ▶ Delayed walking
- ▶ Abnormal gait, which is described as a duck-like waddle
- ▶ Toe walking
- ▶ Difficulty in climbing steps
- ▶ Protruding abdomen

- ▶ Tendency to fall
- ▶ Gower sign (climbing up oneself by pressing on the thighs to get up from the floor)

About one third of these patients appear sporadically, with no previously affected relative. The diagnosis is often delayed unless there has been a previously affected child in the family.

Boys with DMD usually lose the ability to walk between 7 and 13 years of age and may become wheelchair dependent. It is important to keep them ambulatory as long as possible to prevent deformities and degeneration. Muscle weakness is progressive, with loss of function. The tendency for toe walking may lead to flexion contractures and forward hip tilt. Range of motion may help with these, but the child may benefit from braces. Death usually occurs in the second decade of life because of respiratory insufficiency and infection, progressing from trivial to severe. Death may be sudden and caused by myocardial insufficiency. Dilative cardiomyopathy leading to arrhythmias can occur and treatment with angiotensin-converting enzyme (ACE) inhibitors and β -blockers is often indicated. Congestive heart failure may occur. Boys with DMD are at increased risk for features of malignant hyperthermia when given anesthesia.

Once a child is diagnosed, female family members become concerned about their carrier status. Females with an affected son and another affected male relative are obligate heterozygotes, but where there is only one affected male relative, carrier status is more difficult to ascertain. Some carriers (about 10%) manifest mild symptoms such as pseudohypertrophy of the calves or muscle weakness. Carrier identification today is usually by DNA testing. DMD has been suggested as appropriate for newborn screening; although treatment is not available, further affected children in a family might be avoided. Corticosteroids have been used for some effects, but the main hope lies in gene therapy. Approaches for treating DMD with gene therapy have undergone tremendous growth and may go to clinical trials in the near future.

BMD usually shows the presence of muscle dystrophin, but it is abnormal in size and quantity. Onset usually occurs in adolescence and ambulation is usual until about the age of 16 years. Affected males often survive into the fourth decade or later. Symptoms are similar to DMD but milder, often with exercise-related muscle pain. Usually the affected man becomes wheelchair dependent. Dilated cardiomyopathy may occur, requiring heart transplantation. Carrier detection is possible.

Neurofibromatosis 1

First characterized in 1882 by von Recklinghausen, neurofibromatosis attracted attention because of publicity resulting from the movie and play *The Elephant Man* (although Joseph Merrick did not actually have neurofibromatosis). There are two major types:

- ▶ Neurofibromatosis type 1 (NF1), formerly called von Recklinghausen disease
- ▶ Neurofibromatosis type 2 (NF2), formerly called bilateral acoustic neurofibromatosis

NF1 has a prevalence of approximately 1 in 3,000 to 4,000 individuals, while the incidence of NF2 is 1 in 33,000. Both are autosomal dominant disorders with one of the highest new mutation rates known—about 50%. The *NF1* gene, identified in 1990, is located at chromosome 17q11.2 and codes for neurofibromin, a protein product involved in control of cell growth and differentiation with a tumor-suppressor function. Over 1,000 different mutations of NF1 have been identified, many of which lead to the production of an ineffective, truncated protein that does not stop normal cell division.

Despite widely variable clinical features and expression, diagnostic criteria have been established. For diagnosis, a person must have two or more of the following:

- ▶ Six or more café-au-lait spots (Figure 9.8) over 5 mm (0.5 cm) in prepuberty and over 15 mm (1.5 cm) in postpuberty (the normal population usually has 0–3). The café-au-lait spots are not usually seen at birth but develop around 1 year of age and may fade in older adults.
- ▶ Two or more neurofibromas (Figure 9.9) or one plexiform neurofibroma.
- ▶ Freckling in the axillary or inguinal regions.
- ▶ Optic glioma (tumor of the optic pathway).
- ▶ Two or more Lisch nodules (benign hamartomas of the iris).
- ▶ A distinctive bony lesion such as dysplasia of the sphenoid bone or thinning of the long bone cortex.
- ▶ A first-degree relative with NF1 by the previous criteria.

Other features may develop:

- ▶ Macrocephaly
- ▶ Short stature
- ▶ Spinal curvature (scoliosis or kyphosis)
- ▶ Hemihypertrophy
- ▶ Neural crest malignancies (e.g., pheochromocytoma)
- ▶ Hypertension
- ▶ Seizures
- ▶ Speech defects
- ▶ Learning disabilities, especially visual-spatial learning problems

Knowledge of possible manifestations forms the framework for diagnosis, treatment, and management. The severity of NF1 varies greatly. Even within a family, one patient may have only café-au-lait spots, or axillary freckling, whereas another has macrocephaly, multiple neurofibromas, severe spinal curvature, learning disabilities, and hemihypertrophy. It is important to differentiate neurofibromatosis from an individual with an isolated physical characteristic.

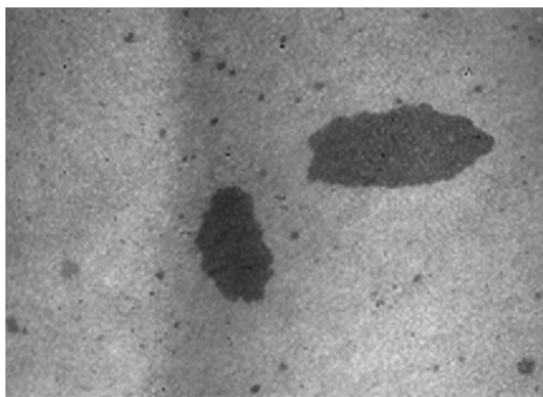


FIGURE 9.8. Café-au-lait macules in a patient with NF1.
Source: Jett and Friedman (2010).

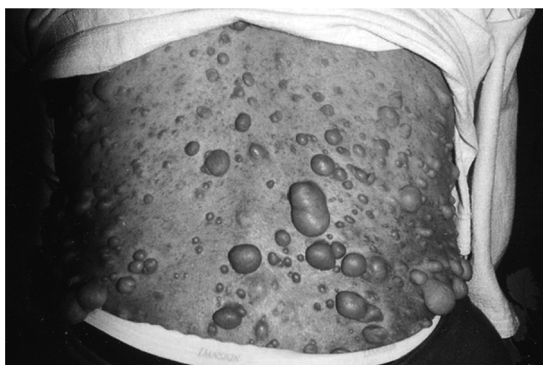


FIGURE 9.9. Numerous cutaneous neurofibromas of various sizes in an adult with NF1.
Source: Jett and Friedman (2010).

CASE EXAMPLE

One young woman sought genetic counseling regarding her 2-month-old son. Her father had NF1 and had multiple neurofibromas on his body. She had lost an eye to optic glioma and had macrocephaly, freckling, and hypertension. Interestingly, she did not regard herself as severely affected, believing that her father's manifestations would be harder to live with for her. Her son did show macrocephaly and one café-au-lait spot. Before all information was collected, she moved across the country, and was followed by a genetic counseling center there. It was later determined that her son was affected.

Nurses should be aware of the worsening of symptoms that occurs in puberty and pregnancy. Published recommendations for health supervision and anticipatory guidance of children with NF include:

- ▶ Frequent ophthalmological examination
- ▶ Evaluation of speech, neurodevelopmental progress, and learning needs
- ▶ Examination for neurologic pathology and changes in skin lesions

Support for families can be found online (www.nfnetwork.org).

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI), a group of autosomal dominant genetic disorders that typically affects bones, has an incidence of about 6 to 7 per 100,000 live births. There are eight recognized types that result from mutations in four genes: *COL1A1*, *COL1A2*, *CRTAP* and *LEPRE1*. Mutations in *COL1A1* and *COL1A2*, genes that encode proteins for the assembly of type 1 collagen, are responsible for 90% of OI. This collagen is needed for strength and structure of bones, skin, and connective tissue. Type 1 OI is due to an ineffective allele, leading to half the normal production of type 1 collagen.

OI is characterized by connective tissue and bone defects and include one or more of the following:

- ▶ Bone fragility and osteoporosis leading to fractures
- ▶ Blue sclerae
- ▶ Progressive bone deformities (including long bone curvature)
- ▶ Presenile hearing loss
- ▶ Dentinogenesis imperfecta (a dentin abnormality of the teeth showing opalescence and blue or brown discoloration)
- ▶ Wormian bones (additional intrasutural bones)

Other features include:

- ▶ Hernias
- ▶ Joint hyperlaxity
- ▶ Elevated body temperature of 1°F or 2°F
- ▶ Heat intolerance, which may include difficulties with anesthesia
- ▶ Varying degrees of short stature
- ▶ Triangular face
- ▶ Large “tam-o’shanter”-shaped skulls

Variability in clinical expression is common, and type I may be mild enough to be missed altogether. Some individuals may suffer hundreds of fractures in a lifetime, whereas others suffer only one or a few, and still others have little bone fragility; some have little height effect, others are two to three standard deviations below the

mean, and others are six or more deviations below the mean. Kyphosis and scoliosis are very common with age.

Although most OI is inherited in an autosomal dominant manner, there are rare mutations that are inherited in an autosomal recessive transmission (2%–5% of OI). Prenatal diagnosis is available and, in those choosing to continue an affected pregnancy, arrangements for delivery in a specialty hospital should be made to include cesarean section and minimal fetal trauma.

Children diagnosed in infancy present immediate problems and challenges to the new parents and the nursing staff. The simple act of lifting the child may cause bones to break. In diapering, the infant should never be lifted by the ankles but supported carefully in good alignment. The crib, and later the playpen, should be mesh and padded. All treatment tables should be padded. The infant can be most easily held or transported in an infant seat, on a padded piece of plywood, or on a pillow so that support is provided. Because of the ongoing body temperature elevation, light clothing should be used and water, or later juice, should be offered frequently. Infants with OI have the same need for physical contact and stimulation as other infants, but parents and others may be afraid to handle them because of fragility. The nurse should help the parents become secure handling the child and help promote bonding through stroking and touching. Those children with severe disease will have many hospitalizations. Nurses should listen to both the parents and the child, who are usually experts by early childhood on how movement can best be accomplished. Support for the family can be found at the Osteogenesis Imperfecta Foundation website (www.oif.org).

Before a diagnosis of OI is made, the parents of the infant who has sustained multiple fractures may be suspected of child abuse. Such an experience can be very traumatic. Radiologic confirmation of OI due to the fracture type and presence of wormian bones, a family history of OI or its signs and symptoms, the presence of dentinogenesis imperfecta or blue sclera (although normal infants may have this as well), and DNA testing will help to establish a true diagnosis. The potential for respiratory insufficiency due to instability of the ribs and infections is present. Coughing can result in rib fracture, and each fracture episode can increase deformity, further decreasing respiratory capabilities. Respiratory infections can be life-threatening in infants and children with severe disease, so prevention and prompt treatment are important to include when educating parents regarding the disease. Children may experience delayed developmental milestones, such as standing and walking, because of fear of fractures and pain.

Children with OI should be evaluated for appropriate intake of calcium and vitamin D. The most widely used pharmacologic therapy for OI includes bisphosphonates to improve bone mass. The decision to use this therapy depends upon the clinical severity of disease, not on bone density. Pamidronate may be used intravenously in severe forms and appears particularly useful when started early.

Pregnancy problems for the woman with OI may include respiratory problems, increased spontaneous fractures, increased awkwardness, and an increased susceptibility to hernias. Careful monitoring of the pregnancy is necessary, and cesarean section may be necessary due to the possibility of fractures in labor and delivery. Genetic counseling and prenatal diagnosis should be provided.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common semilethal genetic disease in Caucasians, with an incidence of about 1 in 2,500 live Caucasian births. It is especially frequent in certain ethnic groups, such as the Hutterites in Alberta, Canada, where the frequency is 1 in 313. It is less frequent in American Blacks and Asian populations.

It is transmitted in an autosomal recessive manner. The frequency of heterozygote carriers in White populations is about 1 in 25, in Ashkenazi Jews about 1 in 29, in Hispanics 1 in 48, in American Blacks 1 in 65, and in Asians about 1 in 150.

Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, located on chromosome 7q31.2, lead to the phenotype associated with CF. Although there are over 1,000 *CFTR* mutations identified in people with CF, the most common mutation (60%) is known as F508del, a deletion of 3 base pairs in exon 10 that causes a loss of Phe. The loss of this amino acid leads to a disruption of chloride channels and the inability of chloride and water to flow across cellular membranes. Found in the membrane of epithelial cells that line such structures as the pancreas, intestines, sweat ducts, vas deferens, and lungs, this protein is an important regulator of viscosity.

The correlations between genotype and phenotype are determined by functionality of the *CFTR*. Therefore, a person's specific mutation can be useful when counseling a family regarding the expected course of disease. There are six classifications of mutation, with class 1 displaying a severe phenotype, classes 2 through 5 with varying phenotypes, and class 6 with a truncated, highly unstable *CFTR* and an associated severe phenotype. Those who are most severe, with less than 1% of activity, usually have the full spectrum of involvement, including pancreatic exocrine deficiency, progressive pulmonary infection, and congenital absence of the vas deferens. Genetic testing is complicated because of the large number of *CFTR* mutations known, but most commercial laboratories test for the 70 most common mutations. About 1% of persons with CF do not demonstrate known gene mutations, and about 18% show only one mutated gene despite symptoms. Because of variability in pulmonary disease among those with the same *CFTR* genotype, researchers are actively investigating other influences, both genetic and environmental. Environmental factors that were postulated to influence variability of phenotype included *Pseudomonas aeruginosa*, *Burkholderia cepacia*, tobacco use, and nutrition. CF modifier genes have also been suggested.

Generally, a child will have the same mutation as the carrier parent, so prenatal testing for the parental mutations is often accurate. Diagnosis may still include sweat testing, but genotyping, tests of pancreatic function, and measurements using nasal potential difference are more common.

Various presenting manifestations may be seen in different age groups as shown in Table 9.11. Commonly, children present with a persistent cough, often with colonization, and perhaps loose, bulky stools and failure to thrive. There is extreme variability in the severity of clinical illness and in the system involved. About 50% are diagnosed before 1 year of age. Those with milder disease or less common manifestations may not be diagnosed until adolescence or adulthood and frequently have previously been misdiagnosed as having asthma, celiac disease, or chronic bronchitis.

TABLE 9.11 Various Presenting Signs and Symptoms of Cystic Fibrosis in Various Age Groups

| | |
|--------------------------------------|---------------------------------|
| <i>Newborn</i> | |
| Meconium ileus | Intestinal atresia |
| Meconium plug syndrome | “Salty” taste |
| <i>Infancy</i> | |
| Failure to thrive | Steatorrhea |
| “Salty” taste | Hypoproteinemia, anemia, edema |
| Rectal prolapse | Hypoprothrombinemia, hemorrhage |
| Heat prostration/dehydration | Rapid finger wrinkling in water |
| Frequent, bulky stools | Abdominal distention |
| <i>Childhood</i> | |
| Frequent, bulky, offensive stools | Heat prostration/dehydration |
| Chronic secretory otitis media | Inguinal hernia |
| Intussusception | Hydrocele |
| Biliary cirrhosis, jaundice | Type 1 diabetes mellitus |
| Rectal prolapse | |
| <i>Adolescent/Young Adult</i> | |
| Aspermia (males) | Chronic cough |
| Infertility | Bronchiectasis |
| Chronic cervicitis (females) | Glucose intolerance |
| Thick cervical mucus (females) | Type 1 diabetes mellitus |
| Cervical polyps (females) | Intestinal obstruction |
| Delayed secondary sexual development | Reactive airway disease, asthma |
| Poor growth/small for age | Acute pancreatitis |

(continued)

TABLE 9.11 Various Presenting Signs and Symptoms of Cystic Fibrosis in Various Age Groups (continued)

| | |
|--|--|
| All Ages | |
| Chronic cough | Sinusitis |
| Elevated sweat electrolytes | Clubbed fingers |
| Nasal polyps (especially below 16 years of age) | Recurrent pneumonia, bronchitis |
| Absence of vas deferens (males) | Bronchiectasis |
| Cor pulmonale | Sputum culture showing <i>Staphylococcus aureus</i> or <i>Pseudomonas aeruginosa</i> |
| Pancreatic insufficiency and malabsorption | Family history of similar symptoms, infant deaths, diarrhea |
| Presence of hard fecal masses in right lower quadrant of abdomen | |

Because aspermia is present in 95% to 98% of males with CF, infertility with azoospermia should lead the practitioner to include CF as a diagnostic possibility. Men seeking assisted reproduction by such techniques as intracytoplasmic sperm injection are now usually tested for CF status before the procedure is done; depending on results, further testing of their partner and counseling would be done. Females may have delayed puberty as well as decreased fertility.

Advances in CF care and experience at specialized centers have allowed survival with good life quality into the fourth decade. Gender differences still exist, with shorter life spans for women. Management is dependent on the severity of disease, age of diagnosis, and degree of involvement of body systems. It is aimed at controlling and preventing respiratory infections; maintaining nutrition; minimizing unpleasant gastrointestinal effects; preventing and treating complications; and providing support, teaching, and counseling to the client and the family. Treatment may include postural drainage with chest percussion; antimicrobial therapy; diet therapy, including determining a diet to result in stabilization of pulmonary function and optimal growth, paying attention to energy expenditure, pancreatic enzymes, and fat-soluble vitamins; anti-inflammatory therapy; use of bronchodilators and aerosolized substances such as rhDNase I (dornase alfa) and Pulmozyme (recombinant human DNase); and more drastic measures such as lung transplantation. Because use of high-dose pancreatic enzyme supplements can cause the complication of fibrosing colonopathy, it has been recommended that the daily dose should be below 10,000 units of lipase per kg. Gene therapy appears to hold great promise. Testing for status

as a CF carrier in couples planning pregnancy, in those with a family history of CF, partners of persons with CF, and as a part of prenatal screening programs has rapidly become a standard of care. CF is now one of the newborn core conditions included in the Recommended Uniform Screening Panel (RUSP).

Although there is no known impairment of sexual performance or desire, most males with CF are sterile, and decreased fertility may be present in females due to thick cervical mucus. Menstrual problems and vaginal yeast infections due to antibiotic therapy are common, and the client should be referred to a gynecologist experienced in the care of patients with CF. Both females and males should be encouraged to consider alternative reproductive plans and options such as contraception, sterilization, adoption, and artificial insemination. Preconception counseling and family planning information is important in adolescence, and genetic counseling may also need to be provided. Pregnancy in CF women may be complicated because of pulmonary function changes and the increased cardiac work load. Couples contemplating children should also be encouraged to consider the necessary increase in everyday work and activities.

Hemophilia

Hemophilia A (classical hemophilia) and hemophilia B (Christmas disease) are caused by deficiencies of coagulation factor VIII (antihemophilic factor) and coagulation factor IX, respectively. Their incidence is 1 in 4,400 to 1 in 7,500 male births. Hemophilia A results from a mutation on the *F8* gene located on Xq28, and hemophilia B results from mutations on the *F9* gene at Xq27; more than 2,100 mutations are known.

Both diseases are X-linked recessive and about one third result from a new mutation with no prior family history. In such isolated cases without prior positive family history, it is important to determine if the mother is a carrier. Females at risk can have a determination of relevant factor activity and those below the normal range confirm carrier status, but for those within the normal range, the possibility of a maternal carrier is not excluded. DNA testing may be useful in certain cases to detect carriers. Prenatal diagnosis for women who are known carriers has been accomplished.

The severity of clinical disease varies with the percentage of the factor present, ranging from those with a small factor and severe disease, to essentially normal coagulation efficiency at levels of 50% or higher. The availability of concentrated factor preparations such as cryoprecipitates, comprehensive care programs, and therapeutic and prophylactic home infusions has radically altered treatment, complications, and prognosis, allowing less disruption for the family. The use of recombinant factor VIII and factor IX concentrates for home infusion has minimized the fear previously associated with possible HIV infection. Desmopressin, an antidiuretic hormone analog, can be used to raise the factor VIII:C concentration in persons with mild hemophilia A. In addition to treatment, prophylaxis may be used several times a week through infusion to prevent bleeds.

A major complication associated with frequent infusions is the development of antibodies to the factor replacement. Known as inhibitors, these develop in 25% to

30% of individuals with hemophilia A and in 1% to 5% of individuals with hemophilia B, minimizing the desired response of factor replacement. Bypassing agents are available for prophylaxis; however, there is a subset of the population that does not respond to these agents or factor replacement. Immune tolerance induction (ITI) is a therapy where individuals are regularly exposed to prolonged doses of factor toward a goal of eradicating inhibition. This therapy has been successful in approximately 70% of those with hemophilia A and 30% of those with hemophilia B. While long-term information is not yet available, this approach may be an option for some, permitting a young child even with severe hemophilia to have a normal life with few or no bleeds and few restrictions.

The major problem in hemophilia is hemorrhage into the joints and muscles; if not stopped, it can result in prolonged bleeding, leading to deformities and immobilization. These often occur spontaneously without a recallable injury, but probably result from normal physiologic strains. The most common sites are ankles, knees, wrists, and elbows. In the past, parents of boys with hemophilia were concerned with spontaneous bleeds because it usually meant hospitalization. Additional concerns included the risk of loss of function, nerve damage, deformity, the wearing of various orthopedic appliances, long school absences, and high costs. Often parents were overprotective, but such spontaneous bleeds were not preventable until the advent of prophylaxis. Some boys notice a “bubbly” feeling at the site of the bleed before it is otherwise noticed.

Most infants with hemophilia develop symptoms in the first year of life, including subcutaneous hematomas, easy bruising, or increased bleeding at circumcision. Increased bleeding may also accompany intramuscular injections or mouth injury. Often the parents are suspected of child abuse. The type of bleeding is slow, steady, internal bleeding as opposed to gushing from superficial cuts. Referral should be made to a comprehensive hemophilia center for care and to hemophilia organizations such as the Hemophilia Federation of America (www.hemophiliafed.org).

Achondroplasia

Achondroplasia is the most common type of short-limbed dwarfism, occurring in 1 in 15,000 to 40,000 newborns. It is inherited in an autosomal dominant manner with complete penetrance, but in 80% of cases it is a new mutation for children from average-sized parents. Achondroplasia is from a mutation in the fibroblast growth factor receptor-3 (*FGFR3*) gene that causes changes in the transmembrane domain of the receptor and increased tyrosine kinase activity.

The typical phenotype includes shortened limbs, a large head with prominent forehead and mandible, a flattened area at the base of the nose, “trident” hands, and marked hypotonicity. Later, kyphosis and lordosis may develop. It is important to remember that there is no intellectual impairment. The mean height for females and males with achondroplasia is about 48 inches and 52 inches, respectively. The American Academy of Pediatrics has developed health supervision recommendations for persons with achondroplasia at various age ranges. Little People of America is devoted to supporting patients with short stature and their families (www.lpaonline.org).

The Fragile X Syndrome

Fragile X syndrome is the most common inherited cause of mental retardation, with a prevalence of 1 in 4,000 males and 1 in 7,000 females. The mutation resulting in fragile X syndrome results from an expansion of CGG trinucleotide repeats in the fragile X mental retardation (*FMRI*) gene located at Xq27.3. The *FMRI* gene encodes fragile X mental retardation protein (FMRP), which is involved in regulation of RNA metabolism and subsequent development of axons and dendrites. Normal persons generally have 5 to 50 stable repeats at that site, and these are stable when they are transmitted to the next generation. In some families, this repeat is unstable and expands with each generation. The expanded CGG repeats inhibit transcription of *FMRI* through methylation (explained in Chapters 2 and 4). Geneticists have distinguished four categories of these repeats, shown in Box 9.5.

The clinical signs are subtle and become more obvious in later childhood and adulthood, although the presence of mental retardation may prompt chromosome studies, leading to earlier diagnosis. Early indicators in infancy can include increased birth weight, macrocephaly, frontal bossing, and a large anterior fontanelle, but it is difficult to detect in early childhood. Later, males with the fragile X syndrome generally have one or more of the following:

- ▶ Macroorchidism (enlarged testes, which may not be seen until 8 or 9 years of age but are seen in 90% after puberty)
- ▶ Large, prominent jaw and forehead
- ▶ Large, low-set ears
- ▶ Large head circumference
- ▶ Hypotonia
- ▶ Flat feet
- ▶ Soft skin, which may become callused with self-inflicted bites
- ▶ High arched palate

BOX 9.5

CGG Repeat Size in the *FMRI* Gene

| CGG Repeat Size | Consequence |
|-----------------------|--|
| 6 to 50–54 | Normal |
| 45 to 55 | Gray zone or inconclusive, borderline; not a clear delineation |
| 55 to 200 repeats | Premutation |
| More than 200 repeats | Full mutation (can be hundreds to thousands of copies) |

- ▶ Aversion of gaze
- ▶ Strabismus
- ▶ Hyperextendable joints
- ▶ Mitral valve prolapse
- ▶ Hyperactivity
- ▶ Behavioral alterations such as autism, attentional deficits, sensitivity to sensations, hand flapping, mood lability, and tantrums
- ▶ Language and speech difficulties, including echolalia (repetition of words continuously at the end of the phrase) and talking inappropriately and incessantly about a single topic
- ▶ Intellectual disability to some degree in about 85%, with typical IQs of 20 to 70

Males who are premutation carriers are susceptible to the fragile X-associated tremor/ataxia syndrome (FXTAS), which develops in about 30% between 50 and 60 years of age (see Chapter 10). This syndrome is a neurodegenerative disorder with cerebral ataxia, dementia, parkinsonism, and peripheral neuropathies.

In females with the full mutation, approximately 50% to 67% have some intellectual disability, about one third have normal intelligence, and approximately one third are severely affected. Females with full fragile X often have learning difficulties and behavior problems that might suggest the diagnosis, such as attentional deficits, language problems, mathematical difficulty, excessive shyness, and social anxiety. Facial features are similar to those of males. Fragile X premutation carrier females have a median age of menopause that is 6 to 8 years earlier than other women, and about one fourth have ovarian failure before 40 years of age. They may be at increased risk for lower bone mineral density. In general, when a male with a premutation passes it to his daughters, they are unaffected, but their children are at risk. The premutation must pass through the female in order for it to expand to a full mutation with clinical expression. This expansion is believed to occur during early development of the embryo. When there are more than 200 repeats present, methylation occurs, and the *FMRI* gene is silenced.

Fragile X syndrome is an X-linked disease. Females may inherit a premutation from the father to become unaffected carriers. The father's premutation is not amplified during spermatogenesis. However, amplification of CGG repeats to greater than 200 frequently occurs during oogenesis, so the daughter's sons will inherit a full mutation. If the premutation is at the lower end of the range, there may be less of an increase in the size of the unstable sequence as it is passed through oogenesis. Thus, somatic features tend to be less noticeable in females than in males, but they can have full expression with characteristic features and profound mental retardation.

Molecular diagnosis is possible for diagnostic testing and prenatal diagnosis but has not been recommended for population screening at this time. Testing for fragile X syndrome should be considered for persons with intellectual disability, developmental delay, autism, a family history of fragile X, or undiagnosed intellectual

disability. Prenatal diagnosis is indicated if the mother is a carrier. All testing should be accompanied by appropriate counseling. Other cytogenetic fragile sites have been identified. Fragile X and other sites have been proposed for newborn screening programs but are debatable because no curative treatment is available. However, screening would provide benefits including anticipatory guidance and life planning for the individual and genetic counseling, prenatal diagnosis, and reproductive options for the family. New molecular targets have been identified that could influence the fragile X phenotype and may have a role in future therapies. Support for patients and families can be found on the Fragile X Foundation website (www.fragilex.org).

Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a complex genetic condition found in 1/15,000 to 1/30,000 individuals. Inheritance can occur through:

- ▶ Deletion of 15q11-q13 (approximately 70%)
- ▶ Maternal uniparental disomy (UPD; explained in Chapter 4) in which the child has inherited two copies of 15q11-q13 from the mother (approximately 25%)
- ▶ A methylation defect (explained in Chapter 4) in chromosome 15, inactivating this critical region (approximately 5%)

PWS is interesting because it can arise through more than one genetic inheritance mechanism. It is an example of the clinical consequences of a specific type of imprinting and also UPD.

Clinical features include:

- ▶ Hypotonia in infancy, which can lead to hypoventilation and respiratory infection
- ▶ Feeding problems and failure to thrive in infancy
- ▶ Delay of developmental milestones
- ▶ Characteristic facial features, including almond-shaped eyes, thin upper lip, downturned mouth, and mild strabismus
- ▶ Hypogonadism, and delayed or incomplete puberty
- ▶ In males, cryptorchidism, small testes, or hypoplastic scrotum
- ▶ In females, hypoplastic labia minora and clitoris
- ▶ Rapid weight gain between ages 1 and 6, with extreme food-seeking behavior and obesity

Minor criteria include:

- ▶ Small hands and feet
- ▶ Sleep disturbances such as apnea
- ▶ Small stature

- ▶ Hypopigmentation
- ▶ Narrow hands

The risk of recurrence depends on the genetic cause. PWS is challenging because of the extreme behavior manifestations and need for lifelong vigilance. GH has been used to successfully treat some children to improve growth and minimize obesity. Recently, prenatal indicators for PWS were suggested, including polyhydramnios with asymmetrical intrauterine growth. These findings may direct providers to rule out PWS with methylation testing in cell-free fetal DNA.

Primary Immunodeficiencies

The primary immunodeficiencies occur in 1 in 2,000 to 1 in 10,000 live births. They are commonly classified as shown in Table 9.12. Some of the primary immunodeficiencies have milder forms that become evident in later childhood rather than early. The following points should alert the nurse to consider the possibility of immune dysfunction or deficiency in an infant or child (although no one point is diagnostic by itself and may occur in other disorders as well):

- ▶ Increased susceptibility to infections, including increased frequency, severity, and duration.
- ▶ The development of complications, rare disease manifestations, or infections with organisms that are generally weak pathogens such as *Pneumocystis jirovecii* (formerly *carinii*).
- ▶ Frequent and severe upper respiratory infections in excess of the normal six to eight per year.
- ▶ Bronchitis, purulent otitis, tonsillitis, or sinusitis, eventually resulting in mastoiditis, draining ears, pneumonitis, bronchiectasis, or pneumonia.
- ▶ Osteomyelitis or meningitis.
- ▶ History of unusually severe childhood illnesses such as chickenpox.
- ▶ Distended abdomen.
- ▶ Chronic diarrhea, with *Giardia lamblia* often being isolated from the stool.
- ▶ Skin rashes such as eczema and lesions.
- ▶ Malabsorption and vomiting.
- ▶ Persistent *Candida* infections of mouth, anal area, or mucous membranes.
- ▶ A family history of early deaths or severe courses of infection or consanguinity.
- ▶ An altered response to immunization. A normal response to live-virus vaccines usually indicates a normal cellular immune system.
- ▶ Failure to thrive leading to growth retardation.
- ▶ Delay of developmental milestones.
- ▶ Paleness, listlessness, and irritability.

TABLE 9.12 Examples of Primary Immunodeficiencies

| Group | Disease Example | Comments |
|---|--|--|
| Defects in stem cell development with combined immunodeficiency of both the cellular and humoral components | Adenosine deaminase (ADA) deficiency | Results in both cellular and humoral deficiency with recurrent infections and skeletal dysplasia. Autosomal recessive (AR) inheritance. |
| T-cell defects leading to defective cellular immunity | Purine nucleoside phosphorylase deficiency | Abnormal T-cell function. Neurologic abnormalities and lymphoma development. Autosomal dominant (AD) inheritance. |
| B-cell defects leading to defective immunoglobulins and impaired humoral immunity | Bruton agammaglobulinemia | Agammaglobulinemia but intact cell-mediated immunity. Prone to bacterial infections and infection with <i>Giardia lamblia</i> . Tend to develop rheumatoid arthritis. X-linked recessive inheritance. |
| Complement component disorders | Hereditary angioedema, deficiency of the C1 esterase inhibitor | Episodic recurrent episodes of edema of the skin with facial swelling and swelling of the upper respiratory and intestinal tract. The latter causes severe abdominal pain, vomiting, and diarrhea. Laryngeal edema can result in death. Can be triggered by trauma, stress, or infection. AD inheritance. See Chapter 6. |
| Phagocytic functional defects | Chédiak–Higashi syndrome | Defective mobility and bactericidal activity in neutrophils leading to recurrent infections, partial oculocutaneous albinism, photophobia, and nystagmus. Malignant lymphoma and leukemia develop. AR inheritance. |

In humoral deficiencies, the Gram-positive bacteria are usually responsible for infection, whereas in cellular immune deficiencies, the Gram-negative bacteria, fungi, viruses, protozoa, and mycobacteria are found more often.

In addition to the general ones described, several of the known immunodeficiencies have distinctive features. For example, Job syndrome is known to occur most frequently in females with red hair, fair skin, hyperextendable joints, with eczema and recurrent cold staphylococcal abscesses occurring along with defects in neutrophil chemotaxis and high serum IgE levels.

Once the particular immunodeficiency is determined, genetic counseling services should be sought. Some types of deficiency are detectable through prenatal diagnosis. If the disease is detected in one sibling, the others should be screened in order to prevent complications that otherwise could be avoided. Siblings who are heterozygotes may have subtle immune system alterations and may benefit from genetic counseling and reproductive planning.

Therapy varies according to the disorder. For example, infusions of purified human immunoglobulin (IVIG) may be used for certain combined immunodeficiencies and for agammaglobulinemias. Because the mortality rate is very high for disorders such as severe combined immunodeficiency (SCID), bone marrow transplantation may be a viable alternative. One of the first trials of gene therapy was for adenosine deaminase (ADA) deficiency, and this promised hope for treatment in other conditions (see Chapter 5). However, gene therapy complications including leukemia and death have led to restrictions on who best to treat. One preventive measure is the widespread use of rubella vaccination to eliminate immunodeficiencies that develop secondary to in utero rubella infection. Additionally, newborn screening programs have led to early diagnosis and treatment for many of these complicated diseases.

KEY POINTS

- ▶ Many genetic disorders are identified in childhood.
- ▶ All members of a family including parents, siblings, and grandparents are affected by the birth of a child with a genetic disorder.
- ▶ A child with a genetic disorder requires multiple forms of assistance and support, including access to virtual support groups.
- ▶ Birth defects may result from various causes.
- ▶ Nurses should be familiar with the most common genetic disorders of childhood.
- ▶ The nurse should refer the family of a person with a birth defect or congenital anomaly for genetic evaluation and counseling.
- ▶ Provision of expert health care with continuity of care is especially important for children and families with a genetic disorder.
- ▶ Health care for children with genetic disorders must also include transition into adulthood.

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CHAPTER 10

Adult Health and Illness and Medical–Surgical Nursing

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Two major categories of genetic disorders are particularly important in adult health:

1. Single gene/inherited biochemical disorders, which may first be manifested in adulthood, such as Huntington disease (HD).
2. Common or complex diseases that generally result from the contribution of several genes and environmental factors. Some of these may coexist with rare single gene forms, such as cancer, which is discussed in Chapter 11.

In addition, other single gene mutation disorders can occur along a continuous spectrum of severity, including mild forms that become evident in adulthood. Increasingly, persons with genetic disorders that typically present in childhood, such as cystic fibrosis (CF) and congenital heart disease, are living into early and middle adulthood. This can present unique care challenges since many health care practitioners specializing in adult health may not have experience managing these disorders. Also, minimal knowledge may exist about the interaction of certain genetic conditions with the normal process of aging. The sex chromosome disorders such as Turner syndrome, Klinefelter syndrome, triple X syndrome, and XYY syndrome are often not diagnosed until adolescence or adulthood, but may be detected in childhood as outlined in Chapter 9.

In this chapter, some of the most commonly manifested genetically inherited disorders in adulthood are described: HD, autosomal dominant polycystic kidney disease, Marfan disease, Gaucher disease, and hemochromatosis, as well as adulthood effects of premutation carriers of fragile X syndrome. The common multifactorial conditions of cardiac disease, emphysema, diabetes mellitus (DM), and Alzheimer disease are also included.

SINGLE GENE INHERITED BIOCHEMICAL DISORDERS TYPICALLY MANIFESTING IN ADULTHOOD

Examples of inherited biochemical disorders due to mutation in a single gene are included here. In each case, the mutant gene is present at birth and could be detected at any time (including prenatally), but the usual signs and symptoms are not usually manifested until adulthood.

Huntington Disease

HD is a progressive, degenerative, incurable disease of the nervous system. It is inherited in an autosomal dominant manner. Described by George Huntington in 1872, HD was earlier known as “chorea.” It is believed that some of the women burned as witches in Salem, Massachusetts, in the 1690s had HD. For many years, the famous folk singer Woody Guthrie was erroneously believed to be an alcoholic rather than a person with HD. Symptoms usually do not appear until age 35 years or older. Before DNA testing, one could not be said to be absolutely free of the disorder until the age of 70 years.

HD occurs in 3 to 7 per 100,000 people of European descent and is less common in those of Asian (Chinese and Japanese) and African heritage. HD is caused from a mutation in the *HTT* gene, located on chromosome 4p16.3. The gene, which encodes for the huntingtin protein, belongs to a family of genes known as endogenous ligands. Although the exact function of huntingtin is unknown, it is believed to play a role in normal prenatal development of neurons in the brain.

The DNA contains a triplicate repeat of three nucleotides, CAG, normally occurring 10 to 35 times within the gene. In HD, this triplicate repeat is expanded from 36 to more than 120 repeats.

Individuals with 36 to 39 repeats may or may not develop signs and symptoms of HD, while those with 40 or more will become symptomatic. The problem with the elongated versions of the protein comes from the resultant fragments that accumulate in the neurons and interrupt normal neuronal function. The cerebellum, striatum, and cerebral cortex are affected, leading to symptoms of emotional lability and uncoordinated movements. It may begin with subtle behavioral changes such as forgetting, inattention, irritability, impaired judgment, poor concentration, hypochondriasis, personality changes, and carelessness about hygiene. Symptoms such as slurred speech or unsteady gait can lead to arrest for alcoholism (known patients should wear medical identification). Promiscuity or an increased sexual drive may occur, resulting in increased numbers of descendants at risk. Over a period of as much as 10 to 20 years, the patient progressively deteriorates, showing increased tremor. Eventually he or she becomes bedridden and develops swallowing difficulties, choking, and the loss of bladder and bowel control. These families are under great stress not only because of the condition of the family member, but also because of the possible and uncertain onset.

Presymptomatic or predictive testing for HD is available for affected families. The trinucleotide expansion typically increases with each generation, so many families

want this information early for planning and preparation. People with 27 to 35 repeats may be asymptomatic, but are at risk for having a child with the disease. Those with 40 to 50 CAG repeats have adult-onset disease, which appears in mid-adulthood while those with more than 60 repeats will develop a juvenile onset, presenting in childhood or adolescence. Family support can be found through the Huntington's Disease Society of America website (<http://hdsa.org/about-hdsa/support-groups/>).

Polycystic Kidney Disease

Autosomal dominant (adult) polycystic kidney disease (ADPKD) is the fourth leading cause of renal failure in adults. It is a systemic disorder that usually manifests in adulthood, although renal cysts may begin in the fetus. Its frequency is 1 in 1,000 people in the United States. The renal cysts increase in both size and number, damaging the structure and function of the kidney, but loss of function usually is not seen until the 30s or 40s. By age 50 years, about half of all patients develop renal failure, and about half have end-stage renal disease by 60 years of age.

Other symptoms and complications include pain, infection, and hypertension. Extrarenal manifestations include polycystic liver disease, intracranial aneurysms, and cardiac defects, which may manifest and affect women more severely than men. Hormonal influences such as pregnancy, birth control pills, and postmenopausal estrogen use are associated with more severe polycystic liver disease.

Approximately 85% of patients with ADPKD have mutations in *PKD1* (polycystic kidney disease-1 on chromosome 16p13.3) coding for polycystin-1, while mutation of *PKD2* (on chromosome 4q21-23) coding for polycystin-2 is milder and accounts for 10% to 15%. Although the exact functions of the proteins encoded by *PKD1* and *PKD2* are not completely understood, it is believed that they work together to promote normal kidney development and function. *PKD1* and *PKD2* belong to a family of genes called transient receptor potential cation channels (TRP), while *PKD2* also belongs to the EF-hand domain containing genes. There are over 1,200 known mutations of *PKD1* and over 200 of *PKD2* and those with truncating mutations appear to have more severe disease.

DNA testing for these mutations can be done presymptomatically or to confirm diagnosis in someone with symptoms. An advantage of presymptomatic testing in persons at risk for inheriting a mutated ADPKD gene is that they can practice good diet habits and keep their blood pressure under control. A positive genetic test for one or both of these mutations does not predict time of onset or severity of disease. A positive ultrasound in utero can be the first indicator of polycystic disease and subsequent genetic testing in other family members.

Recently, clinical trials are targeting medications that decrease levels of cyclic AMP as cAMP signaling is believed to have a role in the hyperproliferation of renal cells in ADPKD. Tolvaptan is a highly potent and selective receptor antagonist of arginine vasopressin V2 receptor that has shown tremendous success following a 3-year trial. However, it is not yet approved in the United States for treatment of ADPKD. Other therapies undergoing investigation include somatostatin (SST) analogs, bosutinib (an *SRC/ABL* inhibitor), and pravastatin.

Resources for patients and families can be found on the Polycystic Kidney Disease Foundation website (www.pkdcure.org).

Hemochromatosis

CASE EXAMPLE

Malcolm, age 50, has been complaining of vague symptoms such as fatigue, weakness, arthralgia, and weight loss, but these had not been investigated in depth previously. To these, he has added loss of libido and impotence and also is complaining of mild dyspnea. As part of the workup, serum ferritin levels were done and found to be elevated. Genotyping was then done, and Malcolm was diagnosed with hereditary hemochromatosis. Other family members were tested. One of his sisters does not have any *HFE* mutations, but the other has two mutated alleles, as Malcolm does. What can each sister be told about her risk to develop hereditary hemochromatosis? What considerations are there for their children? Malcolm is now on a phlebotomy regimen and can expect no further complications from other organ damage. What kind of education should be provided to Malcolm?

Hemochromatosis is an inborn error of iron metabolism, which causes increased iron stores and subsequent organ damage. It is the most common autosomal recessive disorder in Caucasians, with a homozygote frequency of 1 in 200 (Caucasians) to 1 in 400 (Bretons) and a carrier frequency of 10% in White populations. It is most frequent in those of Scottish, Irish, Swedish, and English descent.

The most commonly mutated gene in classic hereditary hemochromatosis, also known as hemochromatosis type 1, is *HFE*, located on chromosome 6 (6p21.3); it has over 20 known disease-causing mutations. Most North Americans (85%) have a mutational change known as C282Y (accounts for over 90% of cases), which substitutes tyrosine for cysteine at position 282 of the *HFE* protein, in contrast to others who have H63D mutations in the same gene.

However, not all persons with the mutated gene show symptoms. This finding raises the possibility that modifier loci contribute to the disease phenotype. It has been suggested that the mutations in the *HFE* gene modulate the uptake of transferrin-bound iron by intestinal crypt cells that program absorptive capacity of enterocytes that are derived from these cells in the mucosa of the small intestine responsible for the final step in digestion and micronutrient absorption.

Laboratory tests include elevated iron saturation of serum transferrin (fasting) of 45% to 50% or higher in females and 60% or higher in males, as well as serum ferritin in which values over 200 ng/mL in premenopausal females and above 300 ng/mL in males and postmenopausal females are very suggestive. Confirmation of the genetic status is often by genotyping for the two major *HFE* gene mutations.

Most individuals are not symptomatic before the age of 40. Men may show more serious disease than women, probably because of the physiological loss of iron due to menstruation and pregnancy in women. Iron is deposited in the liver, joints, heart,

pancreas, and endocrine glands. Initial symptoms are somewhat vague, including lethargy, weakness, and abdominal and/or joint pain. Later, loss of libido, dyspnea, cardiac complaints, liver disease, DM, arthritis, skin pigmentation, and hypogonadism and infertility may be seen.

The prevalence of DM in those with hemochromatosis is 13% to 23% and is related to the destruction of pancreatic islet cells. Another frequently occurring comorbidity is musculoskeletal involvement, including symptoms of osteoarthritis, gout, and rheumatoid arthritis.

Liver biopsy is no longer the gold standard for diagnosis. Molecular genetic testing has surpassed liver biopsy, except in cases where genetic testing cannot confirm diagnosis.

Hemochromatosis has been suggested for population screening because of the potential for prevention of damage. While there is a high population frequency, gene mutations do not always cause disease. Population screening raises questions about the best time for testing and other issues such as penetrance and actual disease development.

Lifelong therapeutic phlebotomy is an effective treatment for hemochromatosis. Approximately 500 mL of blood is removed, usually weekly initially and then every 3 to 4 months, depending on iron levels and tolerance. If early treatment is not initiated, cirrhosis, liver failure, liver cancer, portal hypertension, carbohydrate intolerance, and diabetes may occur, as may cardiomegaly, dysfunction, and arthropathy. It has been suggested that hemochromatosis is so common because it once conferred some type of selective advantage. For example, heterozygous women might have a reproductive advantage because of less likelihood of iron deficiency anemia, and for both men and women, survival in times of starvation might have been enhanced.

Vitamin C supplementation can increase iron overload, as can supplemental iron. In addition, persons with hemochromatosis are susceptible to infection with *Vibrio vulnificus*, a bacterium present in raw oysters that thrives in iron-rich blood and organs; deaths have occurred from ingestion. Some teaching pointers include those shown in Box 10.1.

Resources for patients and families can be found on the Iron Disorders Institute website (www.irondisorders.org/hemochromatosis).

Marfan Syndrome

Marfan syndrome is an autosomal dominant disorder that is extremely pleiotropic (multiple phenotypic effects from a single gene). It is a connective tissue disorder caused by mutations in the fibrillin gene, *FBNI*, on chromosome 15q21.1. *FBNI* encodes fibrillin-1, a glycoprotein in the extracellular matrix, which combines with other molecules to form the microfibrils used for strength and flexibility of connective tissue. Additionally, microfibrils are used to store and release transforming growth factor- β (TGF- β), a critical growth factor.

Over 1,300 mutations of *FBNI* have been identified with Marfan syndrome. Most of the mutations cause a change in a single amino acid of the protein, ultimately leading to decreased formation of microfibrils and activation of increased levels of

BOX 10.1**Nursing Pointers in Hemochromatosis**

- ▶ Maintain a high index of suspicion for those with vague signs and symptoms typical of hemochromatosis, especially in the most at-risk ethnic and age groups.
- ▶ Stress treatment adherence as this is a chronic condition.
- ▶ Do not use iron supplements unless directed by a health care practitioner.
- ▶ Read labels of foods as well as vitamin supplements to avoid excess iron intake.
- ▶ Vitamin C supplementation should be limited.
- ▶ Avoid eating raw oysters.
- ▶ Limit alcohol consumption.
- ▶ Educate family members regarding availability of biochemical and genetic testing.
- ▶ Consider referral for genetic counseling.

TGF- β . This causes decreased stability of connective tissues and overgrowth. It has also been found that mutations in genes encoding TGF- β receptors can result in individuals with symptoms similar to Marfan syndrome.

Diagnosis is sometimes difficult due to the variable clinical expression. Some persons with Marfan syndrome are detected in childhood or adolescence, often because of height. Others remain undetected until adulthood. Marfan syndrome is believed present in about 1 in 5,000 persons but may be more frequent and underrecognized; 15% to 30% represent new mutations, meaning that others in the family do not have this mutant gene, and may be due to paternal age.

Among the characteristic features are skeletal findings including tall stature compared to normal family members, ectopia lentis (dislocated lens), strabismus, and other ocular findings; aortic dilatation, dissecting aneurysms of the aorta, mitral valve prolapse, and other cardiovascular manifestations; pectus excavatum (hollow chest) or pectus carinatum (pigeon chest), reduced upper- to lower-segment ratio, arm span that may be greater than the height, scoliosis, joint hypermobility, and arachnodactyly (long, spider-like hands and long thumbs). Other features are a narrow, highly arched palate with crowding of the teeth and extreme overbite. Marfan syndrome is the major reason for aortic dilatation and aortic aneurysms in persons under 40 years of age.

Because of their tall stature, it is not unusual for persons with Marfan syndrome to be athletes. Isaiah Austin, a Baylor University basketball star who at age 20 was 7 foot, 1 inch tall, was given a career-ending diagnosis of Marfan syndrome. Thus, it is important that school nurses and practitioners ensure adequate sports physicals and, if Marfan syndrome is suspected, make a referral for a full diagnostic examination including echocardiography, a slit lamp examination by an ophthalmologist, and others, depending on the symptoms.

Most morbidity and mortality for individuals with Marfan syndrome is due to aortic dissections and rupture. Therefore, treatment is aimed at decreasing heart rate and blood pressure through the use of β -blockers, including propranolol or atenolol. Treatment with invasive surgery is most often indicated when the diameter of the aortic root is greater than 50 mm.

Activity needs modulation, and pregnancy poses increased risks needing close supervision depending on the person's cardiac status. Population screening in this group for both carrier status and disease is possible, but accurate genetic counseling that includes prognosis can be difficult because of variability in expression. Information for individuals and families can be found on the Marfan Foundation website (www.marfan.org/about/marfan).

Gaucher Disease

Gaucher disease is a lysosomal storage disorder caused by deficiency of β -glucocerebrosidase, the enzyme required to reduce glucocerebroside (GLC) to glucose and ceramide (a fat molecule). The disease occurs in three forms: type 1, the visceral form that is usually chronic, often first appearing in adulthood; type 2, an acute neurologic form often appearing in infancy; and type 3, a subacute neurologic type often appearing first in childhood.

The disease is autosomal recessive and affects 1 in 50,000 to 100,000 people, with an increased frequency in those of Ashkenazi Jewish heritage of one in 500 to 1,000. The mutation of the *GBA* gene on chromosome 1q21 leads to an altered, nonfunctional form of β -glucocerebrosidase, with subsequent increases of GLC in macrophages and damage to organs and tissues. Detection of carriers and prenatal diagnosis is possible.

In contrast to many of the other disorders in this category, the adult form is the most prevalent, accounting for about 80% of cases. Multiple alleles may cause mutations in the *GBA* gene, with five mutations responsible for about 97% of the disease alleles among Ashkenazi Jews. A particular mutation, 1448C, occurs as a polymorphism in northern Sweden, leading to type 3 disease. Another specific mutation, 1226G, leads to mild type 1 disease in homozygotes; such individuals often are undetected unless revealed in the course of family or population studies. A rare perinatal-lethal type has been described, and is often associated with hydrops fetalis.

In adult type 1, which is non-neuronopathic, Gaucher cells with accumulated GLC infiltrate the spleen, liver, and bones. Patients may first experience nonspecific symptoms such as fatigue, easy bruising, and enlarged abdomen with hepatosplenomegaly. Hepatopulmonary syndrome is a known complication of this disease. Eventually bone fractures, infarctions and necrosis, pain, thrombocytopenia, anemia, and infection occur. The pain may be nonspecific and migratory, with episodes lasting 1 to 3 days. In addition, this disease is associated with peripheral insulin resistance with known effects on insulin receptor functioning. Ocular manifestations include “white spots” in the corneal epithelium, anterior chamber angle, ciliary body, and pupil margin.

The age of onset is variable, ranging from birth to 80 years but commonly first presents in adulthood. Some may be asymptomatic entirely, and others may not develop disease manifestations until in their 50s, in which case all of their children

will already have inherited one mutant gene. This finding may be related to as yet unknown epigenetic moderators that affect post-translational processing of the *GBA* gene and have not been correlated to genotype. Consequently, the issue of population screening is unsupported due to the inability to predict disease onset or severity.

Historically, the diagnosis was made from chemical analysis of a 24-hour urine collection. “Magnetic resonance imaging (MRI) is a sensitive method for detecting bone involvement” (OMIM, 2013). Detection of low activity of β -glucocerebrosidase is the gold standard for diagnosis. Genetic testing for *GBA* mutations has limited utility because a positive test result can be expected to identify asymptomatic homozygotes as well as individuals along a continuum of phenotype characteristics that depend on the specific types of mutations on both alleles, as well as other factors.

Clinical trials for treatments of Gaucher disease include enzyme replacement therapy (ERT; enzymes to replace defective β -glucocerebrosidase) and substrate reduction therapy (SRT; reduces the amount of influx of GLC into the lysosome). Other treatment options include partial splenectomy to manage thrombocytopenia, control anemia, and reduce bone involvement postsurgery, as well as bone marrow transplantation with stem cells.

Support for individuals and families can be found on the website for the National Gaucher Foundation (www.gaucherdisease.org).

Fragile X Premutation Carriers

Fragile X syndrome is a disorder due to expansion of trinucleotide repeats in the *FMRI* gene located on the Xq27.3 (Chapters 4 and 9). The *FMRI* gene is responsible for making the fragile X mental retardation protein (FMRP), which facilitates communication between nerve cells in the brain. The DNA of this gene normally contains 5 to 40 repeats of three nucleotides, CGG. Mutations of the gene lead to an expansion in the number of the trinucleotide repeats that are greater than normal, but fewer than those with fragile X syndrome. These individuals are known as premutation carriers.

Males and females who are premutation carriers may exhibit 55 to 200 CGG repeats and can manifest with fragile X-associated tremor/ataxia syndrome (FXTAS) or fragile X-associated primary ovarian insufficiency (FXPOI). Symptoms of FXTAS consist of parkinsonism, intention tremors, cerebellar ataxia, autonomic dysfunction, peripheral neuropathy, and weakness in the legs and cognitive decline, plus short-term memory loss and executive function deficits. FXPOI is the leading heritable form of ovarian failure and infertility, with symptoms including irregular or absent menstrual periods and elevated levels of FSH before 40 years of age.

The premutation affects 1 in 250 females and 1 in 800 men. It is believed that about one third or more of all male carriers will develop FXTAS over time and approximately 20% of women will develop FXPOI. Progression of FXTAS is variable, so those who manifest ataxia and intention tremor should be screened for the *FMRI* gene mutation, even in the absence of a positive family history. Additional environmental and intrinsic determinants for who will develop effects of premutation have yet to be determined.

For men who carry the mutation, all their daughters will carry the premutation. Almost all the daughters of premutation mothers will be fragile X mutation carriers. These daughters have a 50% chance of having a child who carries a fragile X premutation. Whether a child will have a full mutation depends on the size of the repeat carried by the mother. Approximately 33% to 50% of females with a full mutation show clinical symptoms of fragile X syndrome.

Other Disorders Manifesting in Adulthood

Many of the single gene disorders have forms that first appear in adulthood. In these cases, with severe infantile forms and moderate juvenile forms, the adult forms tend to be milder. An example is the case of a 38-year-old man who was misdiagnosed with schizophrenia for 8 years but actually had Niemann–Pick disease type C, an autosomal recessive neurometabolic disorder associated with chorea, ataxia, seizures, and other signs most common in childhood.

Mitochondrial Disorders Manifesting in Adulthood

Mitochondrial DNA contains 37 genes, many of which are essential to the production of adenosine triphosphate (ATP), transfer RNA, and ribosomal RNA, and are similarly subject to mutation. Mitochondrial DNA deletions occur *de novo*, thus often affecting only one family member. The majority of mitochondrial conditions present at a rate of 1 in 10,000 births and most manifest in childhood. Some cases of early stroke (below 50 years of age) are mitochondrial disorders that have stroke as a feature, such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), which can present in childhood, adolescence, or adulthood. Persons with Leber hereditary optic neuropathy (LHON), another mitochondrial disorder, typically present in their 20s or 30s with sudden and painless central visual loss and central scotoma. Other symptoms may include headache at onset, cardiac conduction defects, and dystonia with lesions in the basal ganglia. A type of epilepsy called myoclonic epilepsy with ragged red fibers (MERRF) is associated with multiple mtDNA point mutations with the most frequent being 8344A>G change in the transfer RNA for the lysine protein. This condition has variable age of onset and clinical features.

COMMON/COMPLEX DISEASES OF ADULTHOOD

The common (complex) diseases have long been observed to “run in families.” The genetic contribution to the common or complex diseases is of particular interest to medical geneticists because of the potential for early identification of susceptible individuals followed by targeted interventions that might prevent the disease, prevent or ameliorate complications, or allow initiation of early treatment. In general, the common diseases refer to disorders that are frequent in the population and that are not, in large part, attributable to single gene mutations. A subset of most of the common diseases may be due to single gene mutations, especially cases with an early age of onset, but for most of them, causation appears due to multiple gene mutations

and environmental influences (multifactorial inheritance is described in Chapter 4). These may include coronary artery disease, cerebrovascular disease, DM, cancer, and emphysema.

The genetic contribution of adult diseases could be one or two major genes in combination with minor ones; several minor ones with additive effects; several genes, some with protective effects; or other inherited or acquired epigenetic combinations. Environment could be internal or external and includes dietary components, exposure to infectious agents, biochemical toxins, level of exercise, temperature extremes, sunlight exposure, radiation, and the molecular milieu of cells. There may be many susceptibility factors for a given condition and these may vary in different populations. Susceptibility does not necessarily mean disease development, so some persons with multiple gene mutations or epigenetic biochemical alterations may develop the condition, while others may not.

In some instances, forms of a multifactorial common disorder may be inherited as a single gene mutation or Mendelian disorder. These tend to have an earlier age of onset with a decreased frequency in normal, young individuals. An example is a subtype of type 2 DM known as maturity-onset diabetes of the young (MODY).

A major problem that plagued early investigations of the genetic component in common disorders is variation in the disease phenotype. A variety of methods have been used to look for genetic components in common disorders, including complex trait genome-wide association studies (GWAS), used to sort out gene–gene and gene–environment interactions that could impact disease susceptibility. To understand disease-causing mechanisms, molecular pathway analysis regarding novel gene–gene interactions and certain environmental exposures are under investigation to uncover disease risk loci. Below, the known genetic components of common diseases are described, including heart disease, Alzheimer disease, emphysema, and DM.

Cardiac Disease

Cardiac disease is the leading cause of death in most industrialized countries. In some cases, a single gene mutation results in direct heart disease either alone (e.g., long QT syndrome, discussed in the section “Arrhythmias”), or as part of other genetic syndromes (e.g., Marfan syndrome, discussed previously). For these Mendelian mutations, genetic testing using a single *chip* for specific inherited mutations involved in heart disease is available. While some rare gene mutations result in heart disease, most cases involve minute effects of many gene-to-gene and gene-to-environment interactions; in other words, changes to the epigenome that are biochemical and acquired.

The use of GWAS has identified dozens of novel gene variants called single-nucleotide polymorphisms (SNPs). More than 50 gene variants for coronary artery disease (CAD) have been identified. However, combinations of gene variants still explain only a small fraction of heritable genetic factors with a typical odds ratio of 1.3% or lower. This limits the predictive value of genetic testing and adds a layer of complexity still quite foreign to most clinicians. Many of the identified loci are mapped to genes associated with lipid traits that affect lipid metabolism and inflammation. These gene variants provide new targets for potential new biotherapies for CAD prevention.

It is possible for gene mutations to have indirect cardiac effects. For example, gene mutations may affect conditions that contribute to cardiac risk factors such as obesity, DM, and hypertension. Genes may also influence response to therapy for cardiovascular disease. Early heart disease is more likely to have a stronger genetic component than heart disease that develops in middle age or later and may be due to mutations in single genes. Besides congenital heart disease (discussed in Chapter 9), the major categories of heart disease that are caused by or are heavily influenced by genetics are the diseases due to:

- ▶ Hyperlipidemia and atherosclerosis
- ▶ Cardiomyopathies
- ▶ Disorders of rhythm

Disorders of Lipid Metabolism

The risks of diseases associated with lipid metabolism involve both dietary intake and genetic influences. Genetically determined defects and deficiencies of lipoprotein components, alone or in combination, and their transport and metabolism are known to affect the risk of developing CAD. Both established and emerging cardiovascular risk factors are known, including small, dense low-density lipoprotein (LDL) levels, metabolic syndrome, and homocysteine levels.

Numerous conditions have been identified as risk factors for coronary artery disease. The major ones include elevated total or low-density lipoprotein cholesterol (LDL-C); decreased high-density lipoprotein cholesterol (HDL-C); family history of myocardial infarction (MI) or sudden death in male or female parents or siblings before 55 years and 65 years, respectively; male gender aged 45 or above; female gender aged 55 or above; DM; obesity; cigarette smoking; and hypertension. Other factors that affect lipoproteins include high-fat diets, stress, sedentary lifestyle, liver disease, renal disease, certain medications, and excessive alcohol intake. The association between hyperlipidemia, the process of atherosclerosis, and CAD is generally accepted. Some characteristics have been noted assessing genetic susceptibility to CAD that would then allow clinicians to stratify individuals and in some cases families into population or average-, familial or moderate-, and heritable or high-risk categories. Based on the risk category, early detection and prevention approaches could be designed. Genetic susceptibility characteristics are shown in Box 10.2.

Categories of single gene disorders causing hyperlipidemias and subsequent CAD include defects in the genes that produce apolipoproteins (*APO*). For example, *APOB* deficiency leads to an excessively short protein that impacts a variety of lipid events in the bloodstream, liver, and intestines with mutations such as: receptor defects (e.g., LDL receptor disorder leading to familial hypercholesterolemia), enzyme defects (e.g., lipoprotein lipase deficiency), and defects in transfer proteins (e.g., cholesteryl ester transfer protein deficiency).

Aside from those with single gene defects, hyperlipidemia is not a single disorder; it exists as various types, each with its own causes, manifestations, and profiles. In the general population, plasma lipid levels are modulated by the interaction of environmental factors within the boundaries set by genetic determinants. Environmental factors such as diet act on the person with a single gene disorder affecting

BOX 10.2**Genetic Influences on Cardiovascular Disease Risk**

- ▶ Early onset of CAD (below 55 years of age for men and below 65 years of age for women)
- ▶ Involvement of multiple vessels with atherosclerosis
- ▶ Angiographic severity
- ▶ Two or more close relatives with CAD
- ▶ Female relatives with CAD
- ▶ Presence of multiple CAD risk factors in affected family members such as diabetes, hypertension, stroke, high cholesterol, insulin resistance, or the prothrombin G20210A mutation increasing susceptibility to thrombosis formation
- ▶ Presence of related disorders (such as diabetes or hypertension) in close relatives
- ▶ Established risk factors in family members with CAD such as hypertension or smoking
- ▶ Sudden death in the family, including unexplained accidental death (drowning or car accidents)
- ▶ History of preeclampsia during pregnancy

lipoprotein, gene–gene interactions, and thus the degree of gene expression. Blood lipid levels are a continuous curve in the general population and are influenced by age and sex.

Because of their solubility properties, dietary lipids such as cholesterol and triglycerides are transported in the blood mainly in the form of complex macromolecules called lipoproteins. These molecules often consist of a core of nonpolar lipids, a surface layer of polar lipids, and apoproteins (APO-I). Each class of lipoprotein contains triglycerides (esters of glycerol and long chain fatty acids), cholesteryl esters (esters of cholesterol and long chain fatty acids), free cholesterol, apoproteins, and phospholipids combined in different proportions. Each component in the system has some control, as do other factors such as hormones, cholesterol intake, and metabolic alterations. The components, enzymes, and cell surface receptors are involved in the regulation of lipid levels. In another example, an inherited MTTP gene mutation affects absorption of dietary fats, cholesterol, and fat-soluble vitamins. The signs and symptoms of abetalipoprotein or malabsorption can appear in the first few months of life, later in childhood, or in adults in their 30s and 40s.

Familial Hypercholesterolemia (FH)

FH is an autosomal dominant (AD) disorder due to mutations in several genes including *LDLR*, *APOB*, and *PCSK9*. These mutations cause disposition of atherosclerotic plaque and early age onset coronary heart disease, most commonly manifested as angina or MI. Because it is an autosomal dominant disorder, both heterozygotes and

homozygotes are affected. Penetrance for FH is nearly 90% with heterozygote *LDLR* pathogenic variants.

In the United States, the prevalence of heterozygotes and homozygotes is 1 in 500 and 1 in 1 million, respectively, making it a very common genetic disorder. Among survivors of MIs, the frequency of heterozygotes has been estimated at 1 in 20. The result of the gene mutation is reduced or defective LDL receptors, depending on which mutant allele is present. This results in the decreased ability or inability of LDL-C to bind to its cell surface receptors. LDL-C therefore cannot enter the cell for degradation, accumulates in the plasma, and is deposited in abnormal sites such as the arteries (causing atheromas and atherosclerosis), the soft tissue of the eyelids, the cornea (arcus corneae), the tendons, elbows, ankles, and knees. Tendon xanthomas (fatty deposits resembling bumps) of the dorsum of the hand and Achilles tendon may be very painful and are characteristic. They do not usually manifest in the heterozygote before 20 years of age. The finding of such xanthomas on physical examination should alert the practitioner to the need for increased testing. In heterozygotes, LDL-C levels are about 3 times normal; in the homozygote, they may be 6 to 10 times normal.

The heterozygote is exposed to the effects of premature and accelerated atherosclerosis even in early childhood. Whether to institute vigorous therapy at an early age is debatable because myelination of the central nervous system is not complete until about 6 years of age, and LDL-C is important in the delivery of lipids to the tissues. For male heterozygotes, the typical age of onset of coronary heart disease is 40 years of age; by 60 years, 85% will have had an MI as compared to 15% for males without the mutant gene. For females, the typical age of onset is 55 years of age, and by 60 years, 50% will have a MI as compared with a 10% risk in unaffected females. Both the heterozygote and homozygote may also have peripheral or cerebral vascular disease.

The homozygote is much more severely affected. By 4 years of age, most patients will have developed planar yellow-orange xanthomas at the knees, buttocks, elbows, and hands, especially between the thumb and the index finger, as well as tendon xanthomas and arcus corneae. MI, angina pectoris, and even sudden death usually occur in the homozygote between 5 and 20 years of age. MIs have been reported as early as 18 months. Few live past 30 years, and death may occur in childhood. The statins are a mainstay of therapy, but different LDL receptor mutation genotypes can result in varying responses to therapy. For both the heterozygote and homozygote, diet therapy alone will not lower lipid levels to the normal range, but may be used as adjunctive therapy. The most promising approach is gene therapy.

Genetic screening can be valuable for individuals at risk for the three known gene mutations described above, as 60% to 80% of the cases with this diagnosis are identified through molecular testing. Such screening is somewhat controversial, especially for infants and children. Targeted or cascade testing can be useful for at-risk families:

- ▶ To benefit from lifestyle modifications, closer monitoring, or more aggressive lipid-lowering therapy depending on the specific mutation
- ▶ To identify a family pattern of disease development (FH tends to have similar patterns within families), such as lipid levels and other parameters

BOX 10.3**Nursing Points Related to Genetic Influences on Hyperlipidemia and Coronary Disease**

- ▶ Assess young persons with hyperlipidemia and CAD, particularly those with MIs, for a genetic contribution to disease.
- ▶ Obtain a family history for lipid-related problems and sudden deaths of persons who have been diagnosed with coronary disease, especially if early onset.
- ▶ Be aware of those with the highest risk for cardiovascular disease based on assessment of genetic risk factors.
- ▶ Close blood relatives of persons having a coronary disorder at an early age should be referred for plasma lipid analysis and DNA analysis.
- ▶ Assess for signs and symptoms of hyperlipidemias, including xanthomas, abdominal pain of unexplained origin, and fatty food intolerance; make referrals as necessary.
- ▶ Acknowledge that some symptoms associated with hyperlipidemia (such as xanthomas and arcus corneae) can occur in individuals with normal lipid levels.
- ▶ Encourage the reduction of secondary risk factors in those with hyperlipidemia and their blood relatives, including cigarette smoking, sedentary lifestyle, obesity, excess alcohol consumption, stress, and high-carbohydrate diet.
- ▶ Utilize specific risk-reduction programs that are culturally sensitive and include individual motivational factors that include the degree of risk (average, moderate, or high) and lifestyle factors.
- ▶ Verify that contributing factors (e.g., oral contraceptives) or secondary disorders (e.g., diabetes mellitus) are controlled before initiating therapy for hyperlipidemia.
- ▶ Acknowledge hyperlipidemia is a chronic illness requiring long-term treatment.
- ▶ Periodically assess for patient compliance and help with adherence as needed.
- ▶ Assess the current food and alcohol intake and medication use.
- ▶ Recognize that dietary restrictions (low-cholesterol, low-fat) may not be enough to lower plasma lipid levels.
- ▶ Suggest cookbooks and food substitutes to assist with meal planning.

Nursing points related to genetic factors in hyperlipidemia and coronary disease are given in Box 10.3. Information for individuals and families can be found on the FH Foundation website (thefhfoundation.org).

Cardiomyopathies

Cardiomyopathies and channelopathies are diseases of the heart muscle that may be primary or secondary to other inherited disorders such as glycogen storage disease II.

There are five major classifications of cardiomyopathy phenotype: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), left ventricular noncompaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC). The channelopathies include long QT syndrome (LQTS), short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and familial atrial fibrillation. The cardiomyopathies are believed to be responsible for about 2% of sudden deaths. These cardiac conditions are marked by heterogeneity of genotype variants and their phenotypic presentation. Clinical genetic testing for these conditions is available commercially and can be useful for diagnosis and treatment decisions. See Table 10.1 for a list of important genes involved in cardiomyopathy. Support for individuals and families can be found on the website for the Cardiomyopathy Association (www.cardiomyopathy.org).

Hypertrophic Cardiomyopathy. The prevalence of HCM in the general population is about 1 in 500, with an autosomal dominant mode of transmission. Genetic heterogeneity is prevalent. The pattern of phenotypic expression may be influenced by other modifying genes and environmental factors. HCM results from genes that encode cardiac sarcomere proteins that are essential for heart muscle contraction. Two myosin genes account for 40% of this condition (*MYH7* and *MYBPC3*). However, there are 16 genes associated with HCM. For patients diagnosed with HCM, clinicians should consider genetic testing so that other family members can benefit from early diagnosis. In families with known HCM, clinical surveillance may need to be continued throughout adulthood.

HCM is characterized by left ventricular hypertrophy. It has been the most common cause of sudden death in children and adolescents, especially in athletes. Sometimes the initial presentation is sudden death without previously recognizable symptoms. For others, there can be varying degrees of clinical severity, including a slow, relatively benign course. The most common initial complaints in the 50% who present with symptoms are chest pain, dyspnea, mild exercise intolerance, and syncope. Atrial fibrillation may develop in about 10% to 25%. In those without symptoms, detection usually occurs during a routine physical exam such as for a school athletic physical or electrocardiogram (ECG). Further exploration such as a transthoracic echo Doppler examination and studies to detect ventricular function is necessary in those with a suggestive family history. Outcomes vary and include sudden death, heart failure with congestive features, and atrial fibrillation. Treatment depends on manifestations. Both surgical and nonsurgical approaches are used for septal reduction. An automatic implantable cardioverter defibrillator may be needed to prevent sudden death. Molecular techniques can be used for gene testing and will identify about 60% to 70% of those with HCM. Presymptomatic testing is possible. If a family member has been diagnosed with HCM as a result of sudden death, screening of children or adolescents may be warranted so that preventive measures may be taken. The nurse should be alert to this when taking family histories. In families with multiple affected members, adolescents, even if symptom-free, may be advised to avoid strenuous athletics.

TABLE 10.1 List of Important Genes Involved in Cardiomyopathy

| Gene | Chromosomal Location | Major Phenotype |
|----------------------------|----------------------|---------------------|
| Sarcomere | | |
| <i>MYH7</i> | 14q11.2 | HCM, RCM, DCM, LVNC |
| <i>MYBPC3</i> | 11p11.2 | HCM, DCM |
| <i>TNNT2</i> | 1q32.1 | HCM, RCM, DCM, LVNC |
| <i>MYH6</i> | 14q11.2 | HCM, DCM |
| Desmosome | | |
| <i>DSP</i> | 6p24.3 | ARVC |
| <i>PKP2</i> | 12p11.21 | ARVC |
| <i>DSG2</i> | 18q12.1 | ARVC |
| <i>DSC2</i> | 18q21.1 | ARVC |
| Cytoskeleton, Z-disc, etc. | | |
| <i>ACTN2</i> | 1q43 | HCM, DCM |
| <i>LDB3</i> | 10q23.2 | HCM, DCM, LVNC |
| <i>TTN</i> | 2q31.2 | DCM |
| <i>DMD</i> | | DCM |
| <i>MYPN</i> | 19q21.3 | HCM, DCM, RCM |
| <i>VCL</i> | 19q22.2 | HCM, DCM, LVNC |
| Syndromic | | |
| <i>TAZ</i> | Xq28 | DCM, LVNC |
| <i>ALMS1</i> | 2p13.1 | |
| <i>PTPN11</i> | 12q24.13 | HCM |
| <i>RAF1</i> | 3p25.2 | HCM, DCM |

(continued)

TABLE 10.1 List of Important Genes Involved in Cardiomyopathy (continued)

| Gene | Chromosomal Location | Major Phenotype |
|---------------|----------------------|-----------------|
| Others | | |
| <i>LMNA</i> | 1q22 | DCM, LVNC |
| <i>RYR2</i> | 1q43 | ARVC |
| <i>ABCC9</i> | 12p12.1 | DCM |
| <i>SCN5A</i> | 3p22.2 | DCM |
| <i>TMEM43</i> | 3p25.1 | ARVC |

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction cardiomyopathy; RCM, restrictive cardiomyopathy.
Source: Tariq and Ware (2014).

Dilated Cardiomyopathy. DCM, which occurs with a prevalence of 36.5 per 100,000, is a chronic heart muscle condition characterized by dilatation and impaired contractility of the left or both ventricles. It may result from genetic causes or from viral, toxic, or metabolic agents, alcohol use, immune dysfunction, or idiopathic causes. Men are more frequently affected. There is usually a long period in which the person has no symptoms and the disorder remains unrecognized. The typical age of onset is 20 to 50 years. The most frequent presentation is end-stage heart failure manifested by exercise intolerance, exertional dyspnea, and chest pain. Sometimes the enlarged heart or ECG abnormalities are detected during a routine examination. Conduction abnormalities may be frequent. Nearly 30% of relatives of persons with DCM have ECG abnormalities. Ventricular dilatation may lead to impaired systolic contraction, congestive heart failure, and sudden death. The heart is increased in weight. Mendelian inheritance is seen in about 25% of cases. Inheritance is most commonly autosomal dominant, but autosomal recessive, mitochondrial mutation, and X-linked recessive inheritance have been described.

More than 30 genes have been linked to familial DCM, most in those encoding proteins to make cardiomyocytes. One gene, *TTN*, is responsible for the production of titin, used to create structure in sarcomeres of muscle cells (including cardiomyocytes). The truncated version of this protein is responsible for 20% of DCM. Some other gene mutations have been identified, including those in cardiac actin (15q14), desmin (2q35), and 8-sarcoglycan genes (5q33-34), and loci have been linked to the AD form, including *CMD1D* (chromosome 1q32), *CMD1G* (2q31), and *CMD1B* (9q13-22), as well as locations on other chromosomes. In some cases,

DCM is associated with other features such as sensorineural hearing loss (6q23-24). DCM frequently accompanies both Duchenne and Becker muscular dystrophy (see Chapter 9). The Heart Failure Society of America has published guidelines for genetic testing for patients with DCM (<http://www.hfsa.org/hfsa-wp/content/uploads/2015/04/HFSA-2010-HF-Guidelines-Section-17.pdf>).

Treatment includes weight control, restricted sodium intake, angiotensin-converting enzyme (ACE) inhibitors, digitalis, diuretics, anticoagulants, β -blockers, and other medications, depending on symptoms and need. Currently, DCM is the major indication for heart transplant.

Arrhythmias. Primary disorders of the cardiac electrical system resulting from genetic abnormalities include primary rhythm disturbances. Certain gene variations may also increase the risk of arrhythmias resulting from treatment with certain medications and are thus significant for treatment choices. The actual prevalence of dysrhythmias due to genetic causes is underestimated.

The best-described arrhythmia is LQTS, a cardiac arrhythmia showing a prolonged QT interval on ECG. LQTS consists of recurrent syncope with abnormal myocardial repolarization and sudden death, usually from ventricular arrhythmias. Occasionally, an affected person presents with seizures. It has both autosomal dominant (Romano–Ward syndrome) and autosomal recessive (Jervell and Lange-Nielsen syndrome) inheritance patterns.

The Romano–Ward syndrome occurs in approximately 1 in 7,000 individuals and is the most common form of inherited LQTS. Mutations in five genes (*KCNE1*, *KCNE2*, *KCNH2*, *KCNQ1*, and *SCN5A*) alter the structure or function of ion channels, leading to abnormal electrical conduction through the heart muscle.

The autosomal recessive form of LQTS is known as the Jervell and Lange-Nielsen syndrome. Worldwide, it is an uncommon disease, affecting 1.6 to 6 per million people; however there is a higher prevalence in Denmark of 1 in 200,000. The prognosis for Jervell and Lange-Nielsen syndrome is poor, with an estimated mortality rate of 93% by the age of 40 years. About 90% of this syndrome is caused by mutations in the *KCNE1* gene, located on 21q22.12. The alterations of this protein inhibit movement of potassium through cardiac cells and cells of the inner ear. This leads to altered cardiac conduction and profound hearing loss. Additionally, mutations in the *KCNQ1* genes (11p15.5) can also cause LQTS. These proteins interact with proteins from *KCNE1* genes to form potassium channels and are associated with congenital sensory deafness as well. LQTS has been reported in up to 1% of children with congenital deafness, so children who have congenital deafness should be screened for LQTS.

Unexplained cases of near-drowning have revealed families with inherited LQTS, and women with hereditary LQTS are at risk for untoward cardiac events in the postpartum period, which may be prevented prophylactically by using β -adrenergic blockers.

Most individuals with LQTS can be treated with β -blockers, but they are not effective in those with Jervell and Lange-Nielsen syndrome. Implantable cardioverter defibrillators (ICDs) have been used in combination with β -blocker therapy or in those with a history of MI. Information for patients and families can be found on the website Sudden Arrhythmia Death Syndromes (www.sads.org).

Other Conditions

Other conditions with a genetic component may also result in heart disease. For example, there is a cardiac form of hereditary transthyretin amyloidosis that causes a build-up of amyloid proteins in cardiac tissue. There are over 100 mutations in the *TTR* gene on chromosome 18q12.1, which affect production of transthyretin, altering its ability to transport vitamin A and thyroxine. This condition is particularly common among Black populations, affecting 3% to 3.9% of African Americans and 5% of people in West Africa. This same population possesses the *TTR* mutation that replaces the amino acid valine with isoleucine at position 122 in the transthyretin protein. Symptoms, including arrhythmias and cardiomegaly, vary widely and can present between 20 and 70 years of age.

Alterations in the renin–angiotensin system may be related to heart disease. A particular genotype of the angiotensin I converting enzyme gene (*ACE*; 17q23.3), DD, has been associated with a susceptibility to MI, CAD, and stroke, probably because of aberrant blood pressure regulation. The use of ACE inhibitors may be useful in prevention.

Aging and Alzheimer Disease

With the rapid increase of the elderly population, 85 years and older, the study of aging has intensified. The influence of genetics on biologic aging can affect length of life or longevity, patterns of aging, the aging process, and maximum life span. The search for specific aging genes has resulted in interest in disorders with a known genetic basis that have some of the characteristics of aging. These include conditions such as Down syndrome (discussed in Chapter 9) and rarer genetic syndromes such as progeria, Werner syndrome, and Cockayne syndrome.

Various dementias are not necessarily a consequence of aging. Dementias, however, may accompany aging. One of these, Alzheimer disease (AD), is the fourth leading cause of death in the United States and the most common form of dementia (50%–70%). It affects 2.4 to 4.5 million Americans.

The lifetime risk of developing AD ranges between 10% and 15% in the general population. AD is characterized by dementia involving personality changes; memory loss; deterioration of cognitive functions such as language, as well as poor judgment, motor skills, perception, and attention with neuronal cell loss; and deposition of increased amounts of amyloid plaques and neurofibrillary tangles in the cerebral cortex. There may also be associated symptoms such as depression, emotional outbursts, agitation, withdrawal, gait disorders, seizures, incontinence, and sexual disorders.

Cases of AD may be early-onset (before 65 years of age) or late. The early-onset form is least common, accounting for approximately 5% of cases, and is inherited in an autosomal dominant pattern. Most early-onset disease is caused by mutations in one of three genes: amyloid β precursor protein (*APP*; 21q21.3), presenilin 1 (*PSEN1*; 14q24.3), or presenilin 2 (*PSEN2*; 1q42.13). When any of these genes are mutated, increased build-up of amyloid β protein creates plaque in brain cells, characteristic of AD. Because of the mutations associated with chromosome 21, individuals with Down syndrome are at an increased risk of developing AD.

Most cases of AD are of the late-onset form and do not involve the genes in early-onset disease. GWAS have identified a short list of genes associated with late stage AD: *BINI*, *CLU*, *PICALM*, and *CRI*; however, the Alzheimer Disease & Frontotemporal Dementia Mutation Database maintains an up-to-date list of all reported mutations (www.molgen.ua.ac.be/ADMutations). An additional genetic mechanism for this form of the disease is associated with the apolipoprotein E (*APOE*) gene on chromosome 19q13.2; it has at least seven allelic forms, $\epsilon 1$ through $\epsilon 7$. To date, three allelic variants are known to be associated with AD. One specific form, the *APOE4* gene variant, is the most important predictive risk factor for AD; however, 50% of individuals with AD do not have an $\epsilon 4$ allele. Presence of the $\epsilon 2$ allele may have a protective effect by lowering the risk and increasing the age of onset. These findings have implications for genetic testing, drug treatment, and preventive drug compounds that might mimic the action of *APOE* $\epsilon 2$.

Genetic testing for the *APOE* genotype can be used for confirmatory diagnosis of a person who shows symptoms of dementia or for those who are asymptomatic and at risk (predictive or presymptomatic testing). The issue of clinical testing for the *APOE* genotype has provoked various cautionary statements regarding genetic testing of *APOE* alleles for predictive screening in asymptomatic persons because the *APOE* $\epsilon 4$ allele is also found in persons without AD. A major issue with susceptibility testing for late-onset AD disease is the associated uncertainty of the meaning of the results. However, first-degree relatives have a lifetime risk of 20% to 25%, which is 2.5 times higher than background population risk.

Most drug treatment for AD is focused on decreasing the amyloid cascade, including amyloid β proteins. So far, these have yielded disappointing results, but identifying other molecular targets may provide additional avenues for drug development.

Resources for patients and families can be found on the Alzheimer's Foundation of America website (www.alzfdn.org/?gclid=CPLA386mmcMCFZYjgQodRHkAlg).

Emphysema and Alpha-1-Antitrypsin Deficiency

CASE EXAMPLE

Harold, a 27-year-old man of Swedish ancestry, has come to the clinic with a complaint of dyspnea on exertion, along with a chronic but mild cough. He smokes cigarettes occasionally and recently started volunteering as a firefighter. Family history reveals one sister who died in early childhood of "liver disease." After various tests, results identify expiratory airflow limitation; notably, the forced expiratory volume in 1 second (FEV_1) is 33% of the predicted value. This, combined with the history, provides a rationale for α -1-antitrypsin deficiency testing. Harold is found to have a ZZ allelic variation in the *SERPINA1* gene, known to be associated with a respiratory disease. Refer to this case as you read below, and think about future life planning for Harold.

Emphysema or chronic obstructive pulmonary disease (COPD) may be due to genetic or nongenetic factors. One of the most well-described risk factors associated

BOX 10.4**Pi Nomenclature**

- ▶ Pi^*M , Pi^*S , Pi^*Z , etc. for alleles at the Pi locus
- ▶ Pi^*MM , Pi^*MS , etc. or simply $PiMM$ or $PiMS$ or MM , MS for phenotypes
- ▶ Pi^*M/Pi^*S , Pi^*M/Pi^*Z , etc. or Pi^*MS or Pi^*MZ for genotypes

with COPD is α -1-antitrypsin (AAT) deficiency. AAT is synthesized in the liver and is rapidly released into the plasma under the direction of a gene known as *SERPINA1*, located on chromosome 14q32.1 (previously identified as the Pi locus). The small molecular size of AAT allows it to leave the plasma and enter other body tissues and fluids easily, where it is widely distributed. When proteolytic enzymes such as elastase are released from cells after tissue injury, AAT inhibits their activity and protects organs such as the liver and lungs. The main function of AAT in the lungs is to protect lung tissue from inflammation. Approximately 10% of infants with AAT will develop liver disease.

The Pi (protease inhibitor) system of naming AAT mutation alleles demonstrates genetic variability with more than 100 alleles coding for different molecular variants. According to standardized nomenclature, the designations in Box 10.4 are commonly used, although some use PI instead of Pi .

AAT variants may be classified as normal, deficient, null, or dysfunctional. The most common normal allele is Pi^*M . The most common normal phenotype is $PiMM$ and is associated with a 100% serum level of AAT. There are subtype variants of M , such as $M1$, $M2$, $M3$, and others, which differ in amino acid sequence but appear to function normally, and there are other normal non- M variants.

There are two important deficient variant alleles: Pi^*Z and Pi^*S . These may be present in the heterozygous state ($PiMS$, $PiMZ$, $PiSZ$) or the homozygous state ($PiSS$ or $PiZZ$). Thus, there are varying degrees of AAT deficiency with variable presentations. The Pi^*Z allele is the one most commonly associated with clinically significant effects of deficient serum AAT levels.

AAT deficiency occurs in 1 in 1,600 to 1 in 2,000 live births in White North American and Northern European populations and less frequently in Southern European and other populations. It is particularly frequent in Sweden, where it is included in newborn screening programs. It is estimated that $PiZZ$ is present in 1 in 40,000 to 1 in 100,000 Blacks and was originally thought to be infrequent in Asian populations. More recent epidemiological studies among various geographic and ethnic groups in 58 countries indicate that there are at least 3.4 million persons with deficiency alleles ($PiSS$, $PiSZ$, $PiZZ$) and 116 million carriers ($PiMS$ and $PiMZ$) worldwide. In the United States, an estimated 100,000 people have the $PiZZ$ genotype, while all racial subgroups appear to be affected by AAT deficiency.

The inheritance mechanism is autosomal recessive with codominant expression of each gene (two traits coexist) affecting the quantity and activity of the enzyme. Clinical expression of AAT deficiency commonly occurs bimodally in relation to age: in infancy or childhood manifested by symptoms of liver disease or in early adulthood

manifested by pulmonary symptoms and, more rarely, liver disease. Clinical expression also depends on the genotype, the degree of AAT deficiency, and modulating factors such as cigarette smoke exposure. The most information is known about *PiZZ*. It has been estimated that of all infants born with *PiZZ*, 80% will eventually develop emphysema, 10% will suffer from childhood cirrhosis, and the rest will show no overt clinical disease.

Emphysema caused by AAT deficiency usually involves the basal regions of the lung. Onset is early, often beginning in the late 20s or early 30s. Before age 40, 39% to 60% of *PiZZ* individuals develop COPD, as do 85% to 90% by 50 years of age. Even in clinically asymptomatic individuals, abnormalities in lung function can be detected early. The first symptom is usually dyspnea on exertion, followed by cough and recurrent pulmonary infections with severe expiratory airflow limitation and typical findings associated with emphysema. By adulthood, it is possible for a *PiZZ* individual to have both liver abnormalities and COPD. The detrimental effects of smoking in the *PiZZ* individual have been firmly established. The onset of COPD occurs approximately 15 years earlier in *PiZZ* individuals who smoke, decreasing life expectancy. Smoking also leads to an early, permanent loss of tolerance for exercise. Gender may have an undefined protective role, as adult *PiZZ* females who are nonsmokers are the least likely to develop pulmonary disease, while adult *PiZZ* males who smoke are the most likely. Other disorders such as panniculitis, a rare inflammation of subcutaneous fat, with firm red bumps and necrosis, as well as some autoimmune disorders, may be seen.

For those with severe damage from emphysema, lung transplant may be an option. For less severe circumstances, therapy is directed at symptom management of emphysema or liver disease. Augmentation therapy of twice monthly intravenous infusions of exogenous AAT (Prolastin) has minimal side effects, but can cost \$60,000 to \$150,000 per year. Use of recombinant AAT preparations is also possible and avoids risks of plasma-derived product. Gene therapy aimed at the lung or liver to correct AAT deficiency may be a future option. Administering AAT by inhalation of aerosolized AAT is considered experimental, but may have future application.

The nurse should consider the possibility of AAT deficiency in adults and children with COPD and liver disease. All individuals with neonatal jaundice or childhood liver disease should undergo *Pi* genotyping to determine their AAT status. Box 10.5 includes important topics for patient and family education.

The occupational health nurse should consider the stigma that may result from pre-employment screening for AAT-deficient individuals. Although current employees may benefit from placement in a position that is lower risk and inclusion of health-promoting measures as previously described, job discrimination can also result. This may potentially limit the advancement of a person who is AAT-deficient. It may even result in loss of job due to the potential of developing emphysema and other associated conditions. Predicting the clinical course for heterozygous individuals is not possible and, at the present time, widespread general population screening has not been recommended.

In some AAT-deficient individuals, liver disease may not be detected until late childhood or adolescence, when patients present with abdominal distention caused

BOX 10.5**Nursing Points for AAT Deficiency**

- ▶ Consider testing for AAT deficiency in someone diagnosed with COPD.
- ▶ Emphasize the danger of second-hand smoke for the individual with COPD and those living in the same household.
- ▶ Emphasize avoidance of agents toxic to the liver, including medications and alcohol.
- ▶ Emphasize avoidance of respiratory irritants at home and on the job.
- ▶ Educate females on the dangers of oral contraceptives and provide information on alternative contraceptive measures.
- ▶ Educate on the signs and symptoms of respiratory infection and need for early treatment.
- ▶ Encourage vaccination for pneumococcal infections and other respiratory pathogens as indicated.
- ▶ Promote cardiovascular fitness through physical activity.
- ▶ Assess the AAT-deficient individual for symptoms of COPD, liver disease, and glomerulonephritis.
- ▶ Maintain good nutritional health to promote immunocompetence.
- ▶ Provide career guidance for jobs with low environmental irritants (grain, cotton, and other fibers, coal dust, wood dust [as in sawmills], hair sprays), or to any noxious chemical irritants or hepatotoxins.
- ▶ Provide recommendations for a residence that is low in pollution and other environmental irritants.

by hepatosplenomegaly or portal hypertension and esophageal variceal hemorrhage. Some latent hepatic dysfunction in middle-aged and older adults has been linked to AAT deficiency. The older adult may present with hepatitis, cryptogenic cirrhosis, and/or hepatocellular carcinoma. Patients in older age groups with liver disease should be tested for AAT deficiency. Patients over 40 years of age with AAT deficiency should have periodic liver function assessment.

Support for patients and families can be found on the COPD foundation website (www.copdfoundation.org).

Diabetes (Type 1, MODY, Type 2)

In the United States, approximately 29 million individuals have diabetes: about 90% to 95% of these cases have diabetes mellitus type II (DM II). Estimates indicate that over 8 million of those with diabetes are currently undiagnosed. DM II is more common among Blacks, Latino, Native American, and Asian/Pacific Islander populations in the United States than among Caucasians, with the highest rates among Native American populations and non-Hispanic Blacks. DM II has previously been described as “adult-onset,” with the majority of new diagnoses among people

between ages 40 and 60 years (1.7 million new cases in 2012). However, numbers of new diagnoses of DM II are increasing in individuals younger than 20 years, mostly among minority populations.

DM is not a single disease. DM is an important cause of morbidity, mortality, and health care costs; individuals with diabetes have a death rate 1.5 times higher than those without the diagnosis. Additionally, DM results in complications such as cardiovascular disease, hypertension, blindness, kidney disease, and nerve damage. Hypertension and hyperlipidemia have been documented among 71% and 65% of adults with diabetes, respectively. Heart attack (1.8 times higher), cardiovascular death (1.7 times higher), and stroke (1.5 times higher) occur among American adults diagnosed with diabetes compared with the general population. Diabetic retinopathy and microvascular damage caused by diabetes can lead to vision changes and eventual vision loss in more than 25% of adults with diabetes. Diabetic patients account for about 60% of nontraumatic lower limb amputations.

DM is more frequent in certain ethnic and racial groups. The highest known prevalence is in the Pima Native Americans in Arizona (35%–50%) and the Nauruans (a Pacific Island group). In such populations, DM II may result from a single major gene rather than multiple ones. Among the U.S. population at age 65 years, the prevalence is 33% in Hispanics, 25% in Blacks, and 17% in Whites.

Evidence for genetic contribution to DM comes from twin studies, sibling studies, migration studies, population studies, genetic and molecular techniques such as linkage analysis, DNA techniques including mapping and genome scans, the identification of genetic markers and variations, and the association with certain HLA types (see Chapter 3). The propensity to develop diabetes-related complications such as nephropathy, cardiovascular disease, neuropathy, and retinopathy is also believed to have a genetic component.

Although genetic disorders that have impaired glucose metabolism as a component are comparatively rare when considering all known causes of diabetes, they are important because they underscore the fact that known gene mutations at different sites can all result in the same end point. This is true regardless of the pathogenetic mechanism involved—whether it is insulin deficiency due to pancreatic degeneration or to hyperglycemia resulting from production of an abnormal proinsulin molecule. There are more than 60 genetic disorders that have glucose intolerance, diabetes, or hyperglycemia as components, with a variety of inheritance patterns. These include such diverse disorders as Williams syndrome (a rare autosomal recessive disorder characterized by elfin facies, intellectual disability, and insulin-resistant diabetes), Mendenhall syndrome (an autosomal recessive disorder characterized by insulin-resistant diabetes), pineal hyperplasia (skin problems, hirsutism, and phallic enlargement), disorders affecting the pancreas such as CF or hemochromatosis, as well as disorders of the adrenal and pituitary glands. Many drugs and chemicals are also known to promote glucose intolerance and frank diabetes. The extent of their ability to cause damage may be influenced by the genotype (genetic makeup) of the person exposed to the agent, as well as to external factors.

The two major types, type 1 (DM I; formerly called insulin-dependent diabetes mellitus, or IDDM) and type 2 (formerly called noninsulin-dependent diabetes mellitus, or NIDDM) are quite different in genetic and clinical aspects.

Type 1 Diabetes

Type 1 diabetes (DM I) is considered a progressive, autoimmune disorder, where T-cells destroy insulin-producing cells of the pancreas. Exogenous insulin is necessary for control of glucose metabolism. DM I usually has an onset before the age of 40 years (considered before 30 by some), with a peak between 5 and 15 years of age, and often another less-defined peak at age 20 to 35 years. It was formerly referred to as juvenile diabetes, although now it is evident that about half of the cases are recognized above 20 years of age. Obesity is rarely present. DM I occurs at a rate of 10 to 20 per 100,000 people per year in the United States.

DM I is considered to be multifactorial in that both genetic and environmental factors are necessary for expression (see Chapter 4). The genetic component is generally considered to be polygenic, in which many genes each contribute a susceptibility effect. Data from twin studies show a concordance rate (or occurrence in both members of a twin pair) of 50% in monozygotic twins by age 40, with rates in dizygotic twins and siblings at about 5% to 6%. To date, several chromosomal areas have a well-established association with DM I. These are the HLA genes, which are the major histocompatibility complex (MHC) in humans (see Chapter 3) on chromosome 6p21.3 in the histocompatibility region. This genomic region is most strongly associated with other autoimmune diseases.

Within the HLA region, more than 90% of White persons diagnosed with DM I before the age of 18 years express the serologically determined HLA *DRB1*04-DQA1*03:01-B1*03:02* (DR4–DQ8) and *DRB1*03:01-DQA1*05:01-B1*02:01* (DR3–DQ2), with the highest risk being for those who are heterozygous for DR3 or DR4. But these antigens are also present in persons who do not develop it. Thus, possession of these antigens alone is not sufficient to cause DM I. Alleles distinguished by molecular tests suggest that combinations of *DQA1* and *DQB1* alleles, especially *DQA1*05:01-DQB1*02:01/DQA1*03:01-DQB1*03:02*, confer even higher susceptibility in all ethnic groups. Various combinations confer varying degrees of susceptibility in different ethnic and racial groups. Of particular interest is the finding that some combinations of HLA alleles appear to be protective to DM I, including *DRB1*15:01-DQA1*01:02-DQB1*06:02*, *DRB1*14:01-DQA1*01:01-DQB1*05:03*, and *DRB1*07:01-DQA1*02:01-DQB1*03:03*.

Recent epigenetic evidence involving DNA methylation has identified different methylation patterns in DM I discordant monozygotic twins (one with DM I/one without DM I). The different methylation patterns involve immune-response genes. Additionally, histone modifications from hyperglycemia can result in persistent inflammation and diabetic complications. Another epigenetic factor includes clusters of microRNA (miRNA) that are considered biomarkers of DM I due to the pathology controlled by these molecules.

The nature of the nongenetic or environmental contribution to DM I is believed to be most important in early childhood, and even in utero. Some of these putative

modifiers or triggers are the early introduction of artificial milk (cow's milk) and solid foods to infants under 3 months, viral infections (especially rubella, mumps, and Coxsackie virus), toxic exposures, maternal–fetal blood group incompatibility, and conditions that increase stress on the β cells such as a cold climate, puberty, pregnancy, and rapid growth or low vitamin D intake.

DM I is associated with other comorbidities including neuropathy, complications of pregnancy, hearing loss, depression, and erectile dysfunction. Although diabetes is sometimes recorded as a cause or underlying cause of death, it may be underreported in the general population.

Type 2 Diabetes (DM II)

DM II is a progressive disease that results from increased insulin resistance in body tissues and subsequent hyperglycemia. Over time, pancreatic cells may lose function and ability to secrete sufficient insulin, leading to a need for exogenous insulin supplementation. DM II was formerly referred to as adult-onset diabetes, as it usually begins after age 40 years, but an earlier age of onset is on the rise in the United States.

In contrast to DM I, DM II is predominantly a result of environmental and lifestyle interactions. It is well established that obesity and a sedentary lifestyle contribute to the development of DM II. Excess weight can cause insulin resistance, which later leads to failure of β cells to keep up with the increased insulin demand.

DM II is genetically heterogeneous with a risk for development of 40% if one parent is affected (lower if the father is diabetic) and 70% if both parents are affected. A few rare single gene defects that affect small subgroups of people with DM II have been identified such as the maturity-onset diabetes of the young (MODY), and defects in genes encoding glucokinase, insulin, the insulin receptor, and in the mitochondria. For the majority of affected persons, it is considered to be polygenic or multifactorial—caused by a number of genes and influenced by other factors such as epigenetic risk factors, obesity, and exercise. Some genes may be primary and others may be secondary—for example, those that predispose to obesity. In some cases, DM II susceptibility genes may be population specific such as with Native Americans.

Research has shown a strong association between the high mobility group AT-hook 1 gene (*HMGAI*) and DM II. This gene, located on chromosome 6p21, is an active biomarker for genetic studies. Other research is investigating genes involved in β -cell insulin secretion and insulin resistance.

Support for individuals and families can be found on the website of the American Diabetes Association (www.diabetes.org).

Genetic Defects of Beta-Cell Function

This category includes the following:

- ▶ MODY (discussed in this section)
- ▶ Mitochondrial DNA mutations
- ▶ Others such as the inability to convert proinsulin to insulin or the production of mutant insulin molecules with impaired receptor binding. Each of these is inherited in an autosomal dominant (AD) pattern with relatively mild impaired glucose metabolism.

MODY consists of several types of autosomal dominant single gene conditions with high penetrance in which mild hyperglycemia develops at a young age (usually before age 25 years), in gestational diabetes (occurs in 50% gene mutation carriers), or in the situation of familial recurrence. It is considered by some to be a subtype of DM II that does not generally require insulin administration and some feel that the term *MODY* should not be used but rather highly penetrant *autosomal dominant DM II*.

There are several subtypes of MODY, but the one that occurs most in the United States is MODY-3, caused by mutations in the *HNF-1a* (hepatocyte nuclear factor) gene on chromosome 12q24.2. Clinical features include significant hyperglycemia, sensitivity to sulfonylureas, and development of end-organ complications. Genetic counseling differs for persons in this category, and it is important to have a correct diagnosis as misdiagnosis is not uncommon. The pedigree offers a clue with one family member diagnosed with diabetes before age 35. Carbohydrate metabolism with oral glucose tolerance testing (OGTT) is recommended rather than hemoglobin HbA_{1c} testing due to its greater sensitivity to carbohydrate metabolism. The depressed secretory response to carbohydrate metabolism indicates insulin production problems that could lead to DM II later in life. Early treatment should prevent progression to more severe hyperglycemia and insulin dependence. The gene mutations specifically related to diet susceptibility risks have not yet been identified.

Observation of persons with DM who had an affected parent revealed that they more frequently had affected mothers than affected fathers, and DM is frequently associated with certain mitochondrial diseases. This suggested that mtDNA mutations (see Chapter 4) might play a role in DM. The first identified association of a specific point mutation in the mtDNA (A3243G, an A to G mutation in mtDNA at position 3243) in the tRNA *LEU, UUR* gene with deafness and diabetes is known as maternally inherited diabetes and deafness (MIDD). About 1% of diabetes is due to this mutation, which is highly penetrant (85%) and is neither DM I nor DM II. This mutation is only inherited from the maternal lineage as can be seen in a pedigree.

ISSUES IN ADULT HEALTH: GENETIC SCREENING AND GENETIC TESTING

Major public health initiatives involving genomics have increased in recent years, especially with carrier and workplace screening. This section will address these screening initiatives, the impact of environmental exposures on birth defects and genetic disorders, and exposures in the workplace.

Genetic Testing and Screening for Heterozygotes (Carriers)

Each person is a carrier for 5 to 10 recessive harmful genes for rare disorders. These are so rare that the likelihood of having a mate with these same genes is small. However, when there is homozygosity, genetic disease can occur in the offspring. Both carrier testing and carrier screening are available. Carrier *testing* is usually performed in a specialized setting on individuals already known to be at high risk due to family history, whereas *screening* usually can occur in many places and involves

those with no family history. For example, CF screening is possible, but at present there are more than 1,000 mutations of the *CFTR* gene that can result in CF. This makes widespread population testing difficult, particularly in some ethnic groups, but mutation panels that identify a high percentage of carriers are available. CF has been recommended for screening of the pregnant population and newborns. Within families, genetic testing can be much more accurate when directed at the most common mutation in that family, especially in non-White populations.

For nonaffected individuals, carrier screening for detection of known genes provides the opportunity for genetic counseling, life and reproductive decision making, and prenatal diagnosis. The prevention of genetic disease for a known carrier can be achieved through various reproductive options, including adoption, or reproductive options such as gamete (sperm or egg) donation, in vitro fertilization, or preimplantation genetic testing. If the fetus is affected, pregnancy termination can be considered. These choices are illustrated in Figure 10.1 and can be discussed with the individuals involved in the genetic counseling that accompanies the carrier detection program.

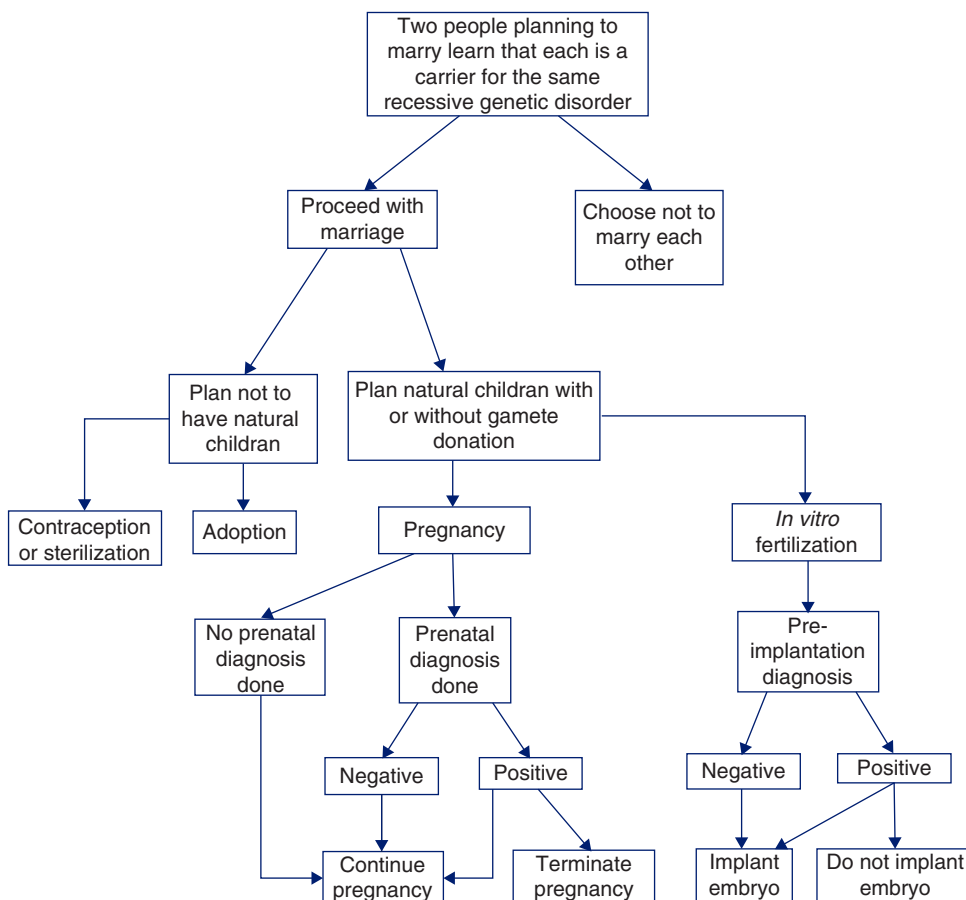


FIGURE 10.1. Flow chart for decision making in premarital carrier screening.

Screening is not yet possible for many recessively inherited genetic disorders due to poor reliability of testing measures, lack of simple or acceptable techniques for screening, or expense resulting. Carrier screening for Tay–Sachs, CF, β -thalassemia, and others have been performed in some high schools. There have been concerns regarding consequences of making decisions for early testing including altered self-image, stigmatization, retention and understanding of information, impact, parental consent, the rebellion of adolescents, and effect on self-identity. On the other hand, many adolescents are sexually active, and proper genetic counseling following carrier screening can be important for some high-risk groups.

Tay–Sachs Disease: A Prototype

Tay–Sachs disease is considered a prototype for carrier screening. An infant born with this disease, in which GM₂ gangliosides accumulate in cells of the nervous system, appears normal until about 6 months of age. Subsequently, progressive mental and physical deterioration occurs, and death is inevitable (usually by 4 years of age). The basic defect is a lack of the enzyme hexosaminidase A (Hex A), which can result from a number of different mutations in the *HEXA* gene. The following characteristics made this disorder very amenable to heterozygote screening programs:

- ▶ There is a detectable reduction in Hex A activity in Tay–Sachs carriers.
- ▶ DNA analysis is also possible.
- ▶ A simple, inexpensive test is available for detection of carriers.
- ▶ Prenatal diagnosis is available.
- ▶ The mutant gene is concentrated in a specific population group: Jews of Eastern European (Ashkenazi) ancestry, particularly from one area of Poland and Lithuania.
- ▶ The carrier rate in Ashkenazi Jews is approximately 1 in 27 to 30 individuals, defining a high-risk population group.
- ▶ The natural course of the disease is progressive, inevitable, and fatal, making it a severe physical, emotional, and financial burden.
- ▶ The lack of cure has made the option of terminating an affected pregnancy a less controversial option than it might have been otherwise.

Members of the Jewish religion who practice the traditional orthodox Jewish code do not believe in sterilization, abortion, or artificial insemination. Abortion can be permitted in specific cases with permission of rabbinical authorities. Conservative and reformed Judaism take more liberal views. All three groups identify the benefits of premarital Tay–Sachs disease screening. In some traditional Jewish communities, Tay–Sachs screening is considered when marital matchmaking is performed by professional matchmakers. A special program begun in Israel, the Chevra Dor Yeshorim Program, was designed to avoid Tay–Sachs disease in Hasidic Jews who oppose abortion and contraception. In this program, when a woman or man turns 18 or 20 years of age, respectively, his or her blood is anonymously tested for Tay–Sachs and the number recorded in a registry. When a couple is about to be

matched, the matchmaker or a couple can query the registry. If both are carriers, they are told that another match will be arranged.

Additionally, large-scale screening for Tay–Sachs disease was developed in Jewish communities in Baltimore and Washington, DC, and spread to other communities, allowing researchers to study various aspects of the program. This program became a model for others and provided lessons regarding the most effective ways of recruiting participants (word of mouth and media), the importance of educating stakeholders (the rabbi provided information about Tay–Sachs screening availability to new members), and community education (understanding risk).

Screening for Other Genetic Diseases

A number of selected genetic diseases have been proposed for inclusion in population screening programs of various types, including those with recessive inheritance and those with pharmacogenomic implications. These include factor V Leiden mutations, prothrombin 20210A mutation, methyl-enetetrahydrofolate reductase mutation C677T, polymorphism of the angiotensin I-converting enzyme, hereditary hemochromatosis, and the A1555G mutation in the mitochondrial genome associated with aminoglycoside ototoxicity.

Factor V is part of the coagulation cascade that eventually forms clots. The factor V Leiden mutation is present in about 2% to 15% of the general population, is most common in Caucasians, and occurs less frequently in African Americans (1.2%) and Asian populations. It leads to a prevalent form of hereditary thrombophilia, which has a synergistic effect with certain environmental factors (contraceptive drugs) and other genes (prothrombin 21210A mutation). Factor V Leiden heterozygotes have a 10% risk for venous thrombosis, while it may be up to 80% for homozygotes. It is considered a risk factor for venous thromboembolism in pregnancy and should be assessed in those with a family history and past history of thrombosis. It can also cause spontaneous abortion and placental abruption. Considerations should be given to screening women at risk for factor V Leiden mutations before prescribing oral contraceptives.

ECOGENETICS AND PUBLIC HEALTH GENOMICS

Ecogenetics can be defined as individual variation in response to agents in the environment causing genotoxic and other effects. Because of genetic variance, people will react differently to the environment, including exposure to chemicals, food, and drug intake, and exposure to infectious agents. (Aspects of individual susceptibility and response are discussed in Chapters 3 and 6.) With knowledge, the affected individual can avoid a noxious substance. Examples include avoiding ingestion of fava beans in those with G6PD deficiency, and avoiding barbiturates in those with acute intermittent porphyria.

In the case of food additives, the picture is more complex. Food additives such as dyes and preservatives may modify the metabolism of chemicals. Examples include monosodium glutamate (Chinese restaurant syndrome) and foods containing nitrates and tyramine. Tartrazine (FD&C yellow no. 5), a color additive to food, drink, and pharmaceuticals, can induce asthma, urticaria, rhinitis, or angioedema.

The Food and Drug Administration (FDA) estimates that 50,000 to 100,000 individuals in the United States are intolerant to tartrazine. About 15% of those who are intolerant to aspirin are also affected by tartrazine. Recent labeling requirements have made products containing tartrazine easier to identify.

Such concerns are not limited to foods. As an example, a child who used an insect repellent containing N,N-diethyltoluamide (DEET) developed a Reye-like syndrome and died. She was heterozygous for ornithine carbamoyltransferase deficiency (a urea cycle enzyme disorder), which caused her to have a lower level of this enzyme. These decreased levels apparently did not allow her to metabolically process the chemicals in the repellent properly. Yet most people use the product without apparent effect, and it is particularly effective in repelling mosquitoes, some of which may carry diseases such as the West Nile virus.

PROBLEMS IN ASSOCIATING EFFECTS WITH ENVIRONMENTAL AGENTS

There are many difficulties associating a particular agent with an adverse outcome, as shown in Box 10.6. Other difficulties related to teratogenic agents are discussed in Chapter 8.

BOX 10.6

Difficulties Associating Environmental Agents With Adverse Outcomes

- ▶ A particular agent may induce a specific genetic change that is phenotypically varied.
- ▶ Individual genetic differences can alter susceptibility and resistance.
- ▶ Effects can be indirect. For example, a chemical can alter the metabolism of other substances.
- ▶ Chemicals in the environment are rarely present alone; rather, they are in mixture and can then interact with other substances.
- ▶ Exposure of both males and females can result in germ cell mutations, adverse reproductive outcomes, and increased risk to subsequent generations.
- ▶ Identifying the role of an environmental agent with birth defects can be difficult if that anomaly is rare or if it occurs within a small population.
- ▶ Lack of knowledge regarding synergistic and additive effects.
- ▶ Knowledge of genotype prior to exposure is often unavailable.
- ▶ Retroactive substance identification is difficult as individuals may not be aware of exposure.
- ▶ Those who know they were exposed to a toxic agent may not know what it was.
- ▶ Influence of personal habits such as smoking on outcome.

(continued)

BOX 10.6**Difficulties Associating Environmental Agents With Adverse Outcomes (continued)**

- ▶ There may be no available confirmatory records of either the exposure or the genotoxic outcome.
- ▶ Unless individuals have a common care provider, making an association between common exposures to an agent is difficult. For example, if several workers are exposed to one chemical and all of them developed a certain type of cancer but were seen by practitioners in towns many miles apart, the connection might be missed.
- ▶ There is a dependence on memory recall or incomplete or vague data.
- ▶ The duration, dosage, and concentration of the agent to which they were exposed may be unknown.
- ▶ Vital information may be withheld due to embarrassment, poor recall, and fear of job loss, altered self-image, or lack of knowledge regarding effects on members in the household.
- ▶ Political and economic pressure from private industry, health departments, the military, and the government because of fear of litigation, expediency, or perceived necessity for the use of a substance.
- ▶ Testing systems are insensitive.
- ▶ High costs and time may inhibit long-term testing.
- ▶ Extrapolating test results from animal studies to humans is difficult.
- ▶ Increased length of time between exposure and adverse effects can minimize likelihood of establishing relevant relationships.
- ▶ Information related to compliant use of protective measures may not be available.
- ▶ Companies may be reluctant to inform workers and others of all substances used in processing due to risk for releasing “trade secrets.”

HAZARDOUS EXPOSURES IN THE ENVIRONMENT AND WORKPLACE

Hazardous exposures to genotoxic agents can occur through the release of substances into the environment or exposure in the workplace. In fact, much of the information about the effects of toxic substances in humans has been obtained through unintentional exposure. Usually exposure is either low dose over a prolonged period of time or a short-term intense exposure, such as in accidental exposure. There may be overlap in exposures between the workplace and environment, since those exposed to a toxic agent at work may also live near the workplace. Families of those working in certain industries are exposed to specific agents through contact with clothes and other articles of the worker. Sometimes hazardous workplaces, such as university chemistry laboratories, are less recognized.

Deleterious genetic effects can manifest through difficulties of reproduction in both males and females. This may be evidenced by impaired fertility (menstrual

irregularities, abnormal sperm), infertility, spontaneous abortion, fetal or perinatal death, stillbirth, intrauterine growth restriction, birth defects, or altered ratios of gendered offspring. These may be used as end points in monitoring exposure effects. Some agents believed to cause such effects are listed in Table 10.2 but there is still no general consensus. A discussion of selected agents follows.

TABLE 10.2 Selected Environmental Agents With Reported Genotoxic and Reproductive Effects in Humans

| Agents | Reported Effects* |
|--|--|
| Benzene | ↑ Chromosome aberrations including breaks; leukemia |
| Carbon disulfide | Sperm abnormalities, impotency, decreased libido (M); menstrual disorders, ↑ spontaneous abortions (F); ↑ prematurity |
| Chlordecone (Kepone) | ↓ Spermatogenesis; ↓ libido (M) |
| Chlorinated hydrocarbon pesticides | ↑ Blood dyscrasias; ↑ childhood neuroblastomas |
| Chloroprene | ↑ Spontaneous abortions in wives of male workers; ↑ chromosome aberrations, disturbances in spermatogenesis |
| Dibromochloropropane (DBCP) | Low or absent sperm; infertility (M) |
| Formaldehyde | ↑ Spontaneous abortions; ↓ birth weight in offspring |
| Hexachlorophene | ↑ Birth defects |
| Polychlorinated biphenyl (PCBs) | ↓ Birth weight in offspring; specific congenital anomalies such as brown pigmentation, gum hyperplasia, skull anomalies; developmental delay |
| Nonionizing radiation | ↑ Perinatal death; ↑ congenital malformations; ↓ birth weight; ↑ congenital anomalies |
| Smelter emissions (mixed substances including arsenic, sulfur dioxide, cadmium, lead, mercury) | ↑ Spontaneous abortions; infertility (M); ↓ birth weight; ↑ congenital anomalies ↑ frequency of Wilms tumor in offspring |
| Vinyl chloride | ↑ Chromosome aberrations; ↑ spontaneous abortions in wives of workers; carcinogenesis, ↑ birth defects |
| High temperature exposure | ↓ spermatogenesis; ↑ birth defects |

*Research reports vary as some report these effects and others report negative findings.
 ↑, increased; ↓, decreased; M, male; F, female

Evidence of environmental contamination by toxic chemicals is often identified after a high frequency or clustering of birth defects, spontaneous abortions, or miscarriages, and may be observed by citizens or professionals. One of the first widespread examples was discovered in 1956 in the Minamata Bay area of Japan. Industrial waste from a fertilizer company containing methylmercury contaminated the fishing bay. In all these cases, some persons were more susceptible to the mercury, as not all those who ate contaminated products evidenced toxicity (discussed in Chapter 8).

In the United States, high levels of mercury (above 1 ppm) are present in certain fish, such as swordfish, shark, tilefish, whale, and mackerel. Pregnant women, nursing mothers, and young children should minimize ingestion of these fish. Another source of mercury is thimerosal, used as a preservative in vaccines. This use has engendered concerns that have been somewhat controversial. While some have believed that the use of thimerosal in vaccines was associated with the development of autism spectrum disorders, the published research findings do not resolve the issue. The World Health Organization has indicated that thimerosal use in vaccines is safe, but use in the United States has been virtually eliminated. Dental amalgam fillings are a source of inorganic mercury exposure, often through inhalation during preparation or removal. Cultural practices such as in religious ceremonies in some sects such as voodoo and Santaria may also expose segments of the population, as may the use of cosmetic creams that contain calomel.

Perhaps the most controversial and widely publicized episode of environmental exposure to hazardous wastes was in the Love Canal neighborhood of Niagara Falls, New York. In the 1940s, chemical companies filled an abandoned canal with toxic wastes, including chlorinated hydrocarbons, amounting to more than 21,000 tons of more than 200 different chemicals. In 1953, Hooker Chemical and Plastics Company sold the property to the Niagara Falls Board of Education for \$1. Hooker maintains that the board was told the site was not suitable for a school, and the deed apparently contains a clause indicating the presence of the waste with provisions that no claims could be filed. In the late 1950s, about 100 homes were built along the banks of the dirt-covered canal, with a school built in the center. Residents noticed chemicals migrating through the topsoil, children falling in the soil received chemical burns, and there were odors and seepage in basements. Eventually the anger and fears of the residents became largely directed at the state health department because the chemical companies were major employers in the area and the state was not perceived as taking adequate action. Differences also existed within the scientific community as to the handling, analysis, and interpretation of data. For example, data on spontaneous abortions and birth defects could be analyzed by simple proximity to the canal center or by those homes designated as “wet” (those that were on former streambeds from the canal) versus “dry” homes. A study that was about 15 years old was chosen as the control group for comparing the frequency of spontaneous abortions. This study had a preselected population and bias because it was done on a group of women with previous problem pregnancies. Debate also centered on the methods and results of chromosome studies, including the lack of a contemporary control group. Also controversial was the method of interpretation of data related to

cancer development in the Love Canal area. Love Canal has now been deemed safe for occupancy by some, and new homes have been sold in that area.

Toxic exposure to lead has occurred by means of environmental pollution through air contaminated water, and agricultural soil, from substances such as lead-based paint in older homes, as well as through the workplace, as people in many occupations are exposed to lead. Exposures from hobbies may also occur. This is discussed in Chapter 8 with maternal–child health.

The largest radiation accident occurred at the Chernobyl nuclear power plant in Ukraine on April 26, 1986. The most contaminated areas were Ukraine, Belarus, and the Russian Federation, but other areas of Europe were also exposed. At least 5 million people were exposed to ionizing radiation as a result. One of the major outcomes was the increase in childhood thyroid cancer. There was also an increased likelihood of leukemia development (2.6 times) in children exposed during early pregnancy in Greece. Some children exposed in utero were said to exhibit mental retardation and behavioral effects. Excesses were observed of unstable chromosome-type aberrations, but not chromatid-type aberrations.

There are more than 100,000 waste sites in the United States. Therefore, nurses should be prepared to deal with the types of issues identified by the Love Canal incident. These include inadequate communication among professionals and between professionals and residents, misconceptions about research results, inadequate attention to the needs and fears of the residents, poor preparation and planning for research on the impact of waste, and the political issues and legal liabilities that affected the entire investigation. Other exposures may occur in communities involved in wastewater disposal or chlorination of drinking water, which suggests that other by-products such as trihalomethanes and trichloroethylene may be associated with birth defects and adverse pregnancy outcomes.

The nurse who is involved with potential or actual hazardous exposures can participate in the prevention of such hazards and the protection of the client as both a citizen and a professional. Some ways involve consideration of the following questions:

- ▶ Which agents are of major concern in causing genetic damage or carcinogenesis?
- ▶ How can they be accurately identified before exposure occurs?
- ▶ What actions should be taken when a potential genotoxic agent is discovered?
- ▶ What are minimum safe levels of exposure?
- ▶ How can exposure be minimized?
- ▶ Are there protective devices and measures that can be taken? If so, what are they?
- ▶ Are they likely to result in nonadherence?
- ▶ Can individuals who are susceptible to damage by a specific agent because of their genetic constitution be identified? If so, how should this information be used? What weight should it have?
- ▶ Does it affect males and females the same way? If not, what special precautions must be taken?

- ▶ What information should be given to workers? Should all workers know their genetic profile in relation to toxic chemicals? How should this information be presented?
- ▶ How can their risks be explained to them in a noncoercive, realistic manner?

Some of these issues are addressed in the next section. It is important for the nurse to have the client's confidence so that effective protection can take place.

TESTING, SURVEILLANCE, AND GENETIC MONITORING

There are several approaches for the minimization of genetic hazards from agents used in the workplace and encountered in the environment. For example:

- ▶ Identifying agents with potential mutagenic, teratogenic, and carcinogenic effects before widespread human exposure occurs by the use of various types of assays and through the use of large toxicogenomic databases
- ▶ Devising appropriate regulations, controls, standardization, and guidelines for the use of such agents
- ▶ Monitoring the emission of toxic substances and the concentration and levels of toxic agents emitted into the atmosphere, water, food, and so on, of the environment and workplace
- ▶ Using protective practices and devices within the workplace
- ▶ Using pre-employment screening and testing
- ▶ Using ongoing periodic genetic monitoring of those believed to be exposed to toxic agents

New methods of monitoring and standardization are being developed using DNA and RNA microarray and profiling technology for detecting genetic variations and gene expression variations leading to risk assessment and monitoring.

WORKPLACE SCREENING AND TESTING

The use of genetic testing or screening before or during employment is controversial. Benefits include minimizing the deleterious effects of workplace agents through identification of those genetically predisposed, identification before employment in the particular industry, or before assignment to a new location where different potentially hazardous substances will be encountered. Only a small number of individuals who have genetically determined differences in susceptibility to environmental agents found in the workplace can be identified, but the potential is growing. In addition, the use of such testing to determine susceptibility to diseases such as colon or breast cancer or for the development of a late-onset disorder such as HD presents dilemmas. What is the potential for discrimination not only in terms of initial employment but also for promotion opportunities? Can a company refuse to hire a

qualified individual because testing shows that person will eventually develop HD? Can such discrimination extend to family genetic testing?

The workplace may also be a site for population screening for genetic disorders or carrier conditions. For example, such screening has been conducted for hemochromatosis. However, while the usual standards for genetic screening must be met in such programs, maintaining privacy and confidentiality and protecting workers from any adverse effects of employment are extremely important. There may be some justification determining susceptibility to agents used at the employment site. Such identification diminishes health hazards, can prevent severe reactions or disease, and allows early diagnosis and ongoing monitoring for the identified individual. However, an approach that may “blame the victim” and decrease the responsibility of the industry to control hazardous environmental conditions can be problematic. The Occupational Safety and Health Administration (OSHA) medical surveillance requirements and National Institute for Occupational Safety and Health (NIOSH) bulletins required “genetic factors” to be included in the personal, family, and occupational history before assignment to certain chemicals. Some U.S. companies use or plan to use routine genetic screening and monitoring along with tests for genetic susceptibility.

Some of the known genetic diseases affected by exposures include:

- ▶ Persons with G6PD deficiency (discussed in Chapter 6) may experience hemolysis on exposure to certain chemicals such as aniline, acetanilide, benzene, carbon tetrachloride, chloroprene, lead, nitrites, and toluidine.
- ▶ Exposure to respiratory irritants and cigarette smoke aggravates respiratory disease in persons with α -1-antitrypsin deficiency.
- ▶ Hypersensitivity on immunologic skin tests can detect sensitivity to organic isocyanates and indicate which individuals are most likely to exhibit an asthma-like syndrome or a delayed hypersensitivity response when exposed.
- ▶ Persons who are slow acetylators of N-acetyltransferase (see Chapter 6), which inactivates chemical arylamines such as naphthylamine, benzidine, and others, may have higher risks of bladder cancer when exposed to these agents.
- ▶ Persons with the low-activity form of the enzyme paraoxonase, which inactivates the pesticide parathion, may be predisposed to developing poisoning at low levels of exposure, either as spray pilots, mixers, field hands, or from general environmental exposure. An interesting example followed the release of sarin, a nerve gas, in Tokyo in 1995. It is believed that those who died were more vulnerable than others because their paraoxonase activity was such that they did not convert the sarin to a less toxic chemical rapidly enough.
- ▶ Those with reduced capacity to metabolize carbon disulfide may develop sensitivities such as polyneuritis.

Regardless of the type of screening, the interpretation of results must be clear. An example of recent widespread misunderstanding was the restriction of persons with sickle cell trait from becoming pilots in the U.S. Air Force because of the inaccurate belief that high altitudes could not be tolerated. Genetic testing or screening should not be used to discriminate. However, only relatively few states have laws

prohibiting employer discrimination on the basis of genetic testing. A suit filed in California alleged that Black employees had been tested for the sickle cell gene mutation without their consent. The suit was dismissed on grounds that this did not constitute employee privacy intrusion. Although the Equal Employment Opportunity Commission states that under the Americans with Disabilities Act compliance manual employers cannot discriminate on genetic information, the extent of protection is debated.

In a case of genetic testing of employees in the workplace, a legal challenge filed in 2001 stated that the Burlington Northern Railway Company was requiring those who claimed work-related carpal tunnel syndrome to undergo DNA testing for a genetic predisposition to this disorder, specifically deletion of the peripheral myelin protein-22 gene. This deletion can result in hereditary neuropathy with a liability to pressure palsies that can result in carpal tunnel syndrome. It was reported that at least one person was not told that blood samples requested were for genetic testing, and that one person who refused was threatened termination if he did not comply. The company agreed to stop such testing. On the other hand, employers might be expected to protect their employees from hazards in the workplace by use of genetic testing. For example, the Dow Chemical Company was sued by the widow of a worker who died from leukemia. She claimed that cytogenetic testing of her husband might have detected early indications of leukemia due to the workplace exposure to benzene. It is expected that the use of genetic testing in the workplace will grow and that the issues engendered by such use must be sufficiently addressed before growth occurs.

Protective Devices and Practices

Concern about the effect of certain chemical and physical agents on fertile women has been a source of some controversy. Regulations have been devised in regard to substances to which the pregnant worker cannot be exposed. In some cases, concern has also been directed to the employment of fertile women in certain industries or for work with certain agents. This is because the agent in question may not be universally recognized as having mutagenic or teratogenic effects and exposure may not be regulated. The women may choose to work in such areas because of pay advantages and therefore assume risk, or they may even choose sterilization because they fear job loss if they become pregnant. Some companies have offered comparable pay at other jobs for fertile or pregnant women when the substance is known to be fetotoxic. Others have instead immorally, and in some circumstances illegally, withheld raises or promotion unless women chose to be sterilized in order to stay at certain jobs with risky exposures. This issue is fraught with complexities about sex and job discrimination and legal compensation. In the United States, the decision to continue employment is ultimately at the discretion of the pregnant woman.

Substances can be mutagenic or affect the fetus through the male directly or indirectly, such as secondary exposure through contaminated clothing and other items. Physical protective measures such as respirators and protective clothing may be used to minimize exposure to employees who handle some known toxic

substances. In these instances, compliance may be an important factor because of the severe discomfort associated with such protection or because of failure to associate danger with substances that are odorless, colorless, and tasteless with no immediately apparent effect. Some employers consider employees responsible for their own protection in their adherence to safety regulations and in relation to personal habits such as cigarette smoking or alcohol consumption, which may increase their risk of carcinogenesis.

SURVEILLANCE

Surveillance for genetic effects of chemical agents may be done in the workplace or in the general environment. For example, monitoring the rates of spontaneous abortions, general or specific birth defects, and an increased incidence of specific cancers can be used to try to detect a change that may be attributed to a specific agent that has been previously undetected. This may be done among specific workers and their spouses or in specific geographic areas. There can be difficulties in this effort, however:

- ▶ There can be many different etiologies for these outcomes.
- ▶ The exposed populations are too small to readily establish statistical significance.
- ▶ The effects seen are apparent only years or decades after the event. As one can imagine, how easy would it be to connect a case of neuroblastoma in a child with his father's employment working with chlorinated hydrocarbon pesticides 4 years previously?

Various studies have looked at the parental occupations of children born with birth defects. Nurses, like workers in any other industry where toxic agents are used, should be aware of specific hazards and take advantage of protective measures. Some states are now acquiring detailed occupational data on birth certificates, but some view this as an invasion of privacy. When taking an occupational or recreational history, the nurse should be sensitive to potential exposures commonly found among certain occupations. Some of these are listed in Table 10.3. Questions pertinent to the histories are discussed in Chapter 7.

Chemical and physical agents in our environment constantly bombard us at home, at work, at school, and at leisure. Various genes are involved in the metabolism of such chemicals and in mechanisms of repair in response to them. Understanding has increased regarding the role that genes play in the manifestation of effects from both short-term and long-term exposures, but there is still not a uniform consensus on the best ways to assess damage or interpret results. A funding initiative from the National Institute of Environmental Health Sciences began in 2006, named Disease Investigation Through Specialized Clinically Oriented Ventures in Environmental Research (DISCOVER), to examine the relationship between genes and childhood environmental exposures (prenatal through 21 years) to determine disease risk.

TABLE 10.3 Selected Occupations With Exposures to Toxic Agents

| Occupation | Possible Exposures |
|---------------------------------|--|
| Barber, hairdresser, beautician | Aerosol propellants, hair dye, acetone, ethyl alcohol, benzyl alcohol, halogenated hydrocarbons, hair spray resins |
| Dentist, dental technicians | Mercury, nitrogen dioxide, anesthetics, x-rays, vibration |
| Farmer | Mercury, arsenic, lead, nitrogen dioxide, silica, pesticides, fertilizers |
| Dry cleaner | Benzene, contaminated clothing, trichloroethylene, naphtha |
| Nurse | Anesthetic gases, chemotherapies, alcohol, ethylene oxide, carcinogenic agents, radiation, infectious agents, nitrogen dioxide |
| Photographer | Mercury, bromides, iodides, silver nitrate, caustic agents, iron salts, lead |
| Printer | Inks, antimony, lead, noise, vibration, benzene, methylene chloride |
| Textile industry | Cotton dust, synthetic fiber dust, formaldehyde, benzene, toluene, chloroprene, styrene, carbon disulfide, heat |

KEY POINTS

- ▶ There are differences between genetic testing and genetic screening.
- ▶ Consider the chemicals that pose risks to individuals with certain genotypes and whether those products should be removed from market and/or include warning labels.
- ▶ Identify the current public policies that address environmental health.
- ▶ Consider the pros and cons of conducting screening for genetic conditions in the workplace.

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CHAPTER 11

The Genetic Basis of Cancer

Gwen Anderson, Jennifer Francis, and Caitlyn Cornell

Cancers arise from a wide variety of etiologies. The incidence of most cancers increases significantly with age, which can be attributed, in part, to the accumulation of genetic alterations triggered by environmental exposures that collectively predispose a cell to inappropriate division, regulation, and function. It is important to understand that most cancers are multifactorial, and genetic insults contribute to a progressive compilation of events whereby somatic cell changes develop into an uncontrolled cancer growth. Amid these changes, the cells that develop into cancer have evolved over many divisions that can take years to progress and manifest into an unregulated, undifferentiated mass of tumor cells.

Cancers all share a common link through the entwinement of environmental, genetic, genomic, and epigenetic alterations that characterize unregulated cell growth and neoplastic transformation. With the mapping of the human genome in 2003 and the advent of next-generation sequencing technology, researchers and clinicians have a new understanding of cancer genetic expression profiles, molecular pathways that are potential targets for selective biotherapies, and cancer-specific tissue biomarkers that can be used for early diagnosis and surveillance of treatment effectiveness. In this chapter, genetics refers to the inherited germline gene mutations and chromosomal rearrangements that lead to cancer. Epigenetics refers to alterations in genes and chromosomes that can be inherited or acquired from the environment.

For the purpose of understanding the genomic etiology of cancer, an overview of four types of cancer genomic mechanisms is provided: hereditary, chromosomal, epigenetic biochemical modifications, and sporadic mutations. First, each type of mechanism is described followed by the genetic etiologies of specific pediatric and adult cancers. The genomic mechanisms for cancers are identified in a pediatric table and an adult table. The commonly occurring cancers in the United States have been selected to illustrate each of the genomic mechanisms in cancer.

GENOMIC MECHANISMS IN CANCER: AN OVERVIEW

Hereditary cancers involve specific genetic changes, passed from parent to child, which predispose an individual to cancer. Genetic testing can show how inherited single gene mutations and chromosomal rearrangements contribute to carcinogenesis. However,

only 5% to 10% of all cancers can be attributed to a hereditary gene mutation. The fact that cancers recur in families is well documented in large population-based studies. By examining the family medical histories and degree of shared DNA among biological relatives, factors that predict risk and calculate statistical population risk of cancer occurrence and recurrence in families are identified. The vast majority of genetic alterations are spontaneously acquired during an individual's lifetime. These initiate oncogenesis through the disruption of DNA repair mechanisms, silencing tumor suppressor genes and promoting oncogenes and oncoviruses that lead down a multistep pathway to cancer mutagenesis and tumor growth. Epigenetic mechanisms involve a chemical structure, the epigenome, which surrounds the DNA and further influences gene translation and expression in somatic cells.

Inherited Mutations

Some cancers arise due to an inherited predisposition, such as occurs in single gene mutations characteristic of inherited cancer syndromes. This type of cancer susceptibility begins as a genetic alteration in parental gametes (sperm and ova) and is then incorporated into the zygote during fertilization. Since an individual develops from a single-celled zygote, every somatic cell in the body, and the germ cells, will carry this germline mutation. Transmission of the mutation in the offspring's germ cells is how a heritable predisposition to cancer is passed from one generation to the next; mutations arising in somatic cells are not involved in fertilization and, thus, are not passed on to the next generation. Note that it is the genetic alteration that increases risk for cancer that is inherited and not the cancer itself. In addition, the gene mutation is located in every cell of the body, not just in the cancer tissue or organ of interest.

Due to the number of roles that different gene products play within the body's complex pathways, genes that have been identified in heritable cancers are frequently implicated in more than one cancer or condition. It is also important to understand that a single cancer can emerge from very distinct, separate pathways, and thus, different genes can contribute to the development of the same cancer through different mechanisms.

Hallmarks of inherited cancer syndromes include early age of onset, development of multiple cancers within a single individual, bilateral tumors in paired organs, cancer in the gender less frequently affected (such as breast cancer in males), and presentation of the same cancer or clusters of different types of cancers among biological relatives. Examples include hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndromes I (HNPCC) and II, and familial adenomatous polyposis (FAP), as will be discussed in this chapter.

Inheritance of cancer-implicated genes does not imply obligate carcinogenesis, but it does increase one's risk above that of the general population. People who have a gene mutation may never develop cancer, while other gene mutation carriers in the same family do develop the disease at an early age. The specific gene mutation variant and the pattern of inheritance are highly influential; the presence of one damaged allele may be sufficient (dominant) to exert an effect in one case, whereas both alleles (recessive) may be needed in another. Cancer predispositions associated with germline mutations can be transmitted as autosomal dominant, recessive, X-linked,

or through maternal mitochondrial DNA, with the majority being autosomal dominant. Autosomal dominant transmissions pose a 50% risk of passing the mutation to each offspring. Lifestyle and environmental factors also play a contributing role; the vast majority of these syndromes, accounting for 5% to 10% of all cancers, require additional, acquired genetic insults in order for a predisposition to turn into active cancer. However, inherited predispositions still entail relatively high rates of penetrance. Early age of disease onset is a hallmark of inherited cancer gene mutations because people with heritable predispositions are already one step (or more) closer to acquiring the number of genetic insults needed to initiate carcinogenesis.

Chromosomal Rearrangements

With cancer development and progression in somatic cells and tissues, aberrations in chromosome structure and number are prevalent in many cancers and can contribute to increased susceptibility to cancer initiation at an early age as well as later in life. There are three basic types of chromosomal alterations that effect cancer etiology. One is an alteration in the copy number of chromosomes inside the nucleus of the cell. Abnormal numbers of chromosomes is termed aneuploid or amplification of chromosomal material. Copy number variation can lead to multiple oncogene copies or even the loss of important tumor suppressor genes. For example, inheritance of an extra chromosome increases the risk of cancer in people with Down syndrome.

Another mechanism is a translocation of one or more segments on one or more chromosomes to a new position on the same or a different chromosome. This type of chromosomal instability often results from errors during cell division in germline and somatic cells. Translocations can be balanced, where no additions or deletions take place and the same genomic material is retained inside the cell. Repositioning DNA within the genome may occur by the breakage of one or more chromosome segments and the subsequent incorrect reattachment to the same or a different chromosome. In one type of translocation, a coding region from one gene may be placed next to the promoter region of another gene. For example, translocation of a proto-oncogene to a particularly active promoter may incite hyperactivity and result in uncontrolled growth. This is the case in Burkitt lymphoma involving the movement of the *MYC* proto-oncogene on chromosomes 8 to the immunoglobulin heavy chain (IG) promoter on chromosome 14. Similarly, a translocation can be unbalanced, resulting in a loss or gain of genome material. In this instance, a translocation may cause the loss of an important tumor suppressor gene.

In another example, the translocation of two genes can produce a novel gene product through gene fusion, where two genes become one novel gene with a different structure and function. One example of this is with chronic myelogenous leukemia (*CML*) where two genes, *BCR* and *ABL*, fuse to become one new gene with aberrant properties. *CML* involves the side-by-side placement of two different gene coding regions, resulting in the production of a fusion gene with a novel *BCR-ABL* protein that activates growth pathways within the cell. Chromosomal translocations are one of many contributors to cancer through instigating oncogene activation or suppressing important protective mechanisms such as tumor suppression or DNA repair.

It is important to remember that these same chromosomal aberrations take place inside somatic cells as neoplastic transformations take hold and progress. As cancer progresses, cells exhibit a higher frequency of both types of chromosomal aberrations (copy number variation and translocations) that further degrade the normal genomic structure and function of molecular pathways inside the cell. Structural instability of chromosomes leads to further impairments in the cell's ability to repair DNA or recover from the slippery slope of tumorigenesis. Four types of genetic alterations disrupt cell differentiation and function: DNA repair, oncogenes, chromosomal translocations, and tumor suppressor genes (Figure 11.1)

Epigenetic Biochemical Modifications

In 1942, biologist Conrad Waddington defined *epigenetics* as “the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being”. In modern times, the epigenome is known as a second inherited biological code that sits on the DNA genome and serves as a chemical modifier inside the chromatin structure of chromosomes. Epigenetic inheritance refers to cellular information that is inherited during cell division but is not encoded in the DNA sequence of the genome. The epigenome is a complex assortment of proteins and chemical modifications that are associated with DNA, control its transcription, and influence which genes are expressed and in which cells.

There is an abundance of research evidence, which indicates that epigenome chemical modifications are both inherited and acquired in response to environmental exposures, especially early in life. Epigenetic alterations affect the process of gene to protein expression, thus metabolic functioning within the cytoplasm of the cell. Alterations in gene regulation can disrupt cellular homeostasis during transcription, translation, or post-translation processes to effect gene signaling pathways, gene expression, and protein expression, thus affecting cellular functioning.

Acquired somatic cell epigenomic changes describe another genetic mechanism that leads to cancer development. There are numerous types of interrelated epigenetic biochemical modifications; four are well studied: DNA methylation, genomic imprinting, histone modification, and miRNA. DNA methylation regulates DNA expression and silencing of repeat elements in the genome. Histone modifications are important in transcriptional regulation and often associated with DNA methylation. Genomic imprinting is a parent of origin-specific allele where one parental allele is silenced. Characterized by global hypomethylation and hypermethylation, the aberrant molecular landscape of tumorigenesis consists of both inherited and acquired epigenetic abnormalities. The hypomethylation activates proto-oncogenes and increases genomic instability, while the hypermethylation silences genes. While oncogenes are activated through dominant mutations or overexpression of a gene, tumor suppressor genes become silenced. The epigenetic chemical tags effect chromatin and histone packaging that allows genes to be turned on or turned off. For example, in normal cells, CpG island promoters are generally not methylated and active. Similarly, the chromatin is open in a normally active tumor suppressor gene. During tumorigenesis, tumor suppressor gene CpG island promoters become methylated, resulting in the formation of silent chromatin structures, thus silencing

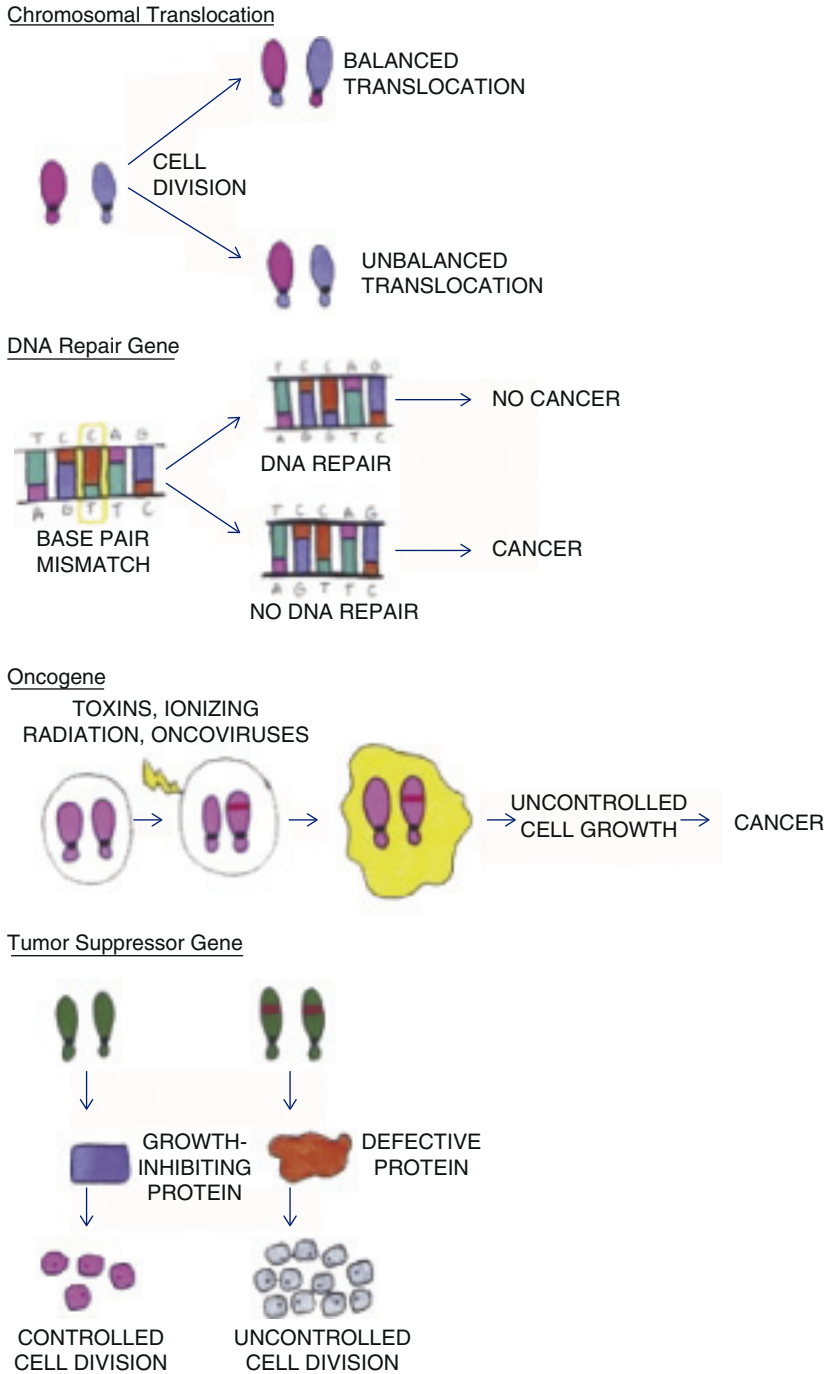


FIGURE 11.1. Genetic alterations in cancer. (See color insert.)

the promoter region. These biochemical tags, or marks on the genetic chromatin, influence whether or not a gene is expressed.

As the global exposure to chemical pollutants, ionizing radiation, and toxic metals is shown to increase cancer incidence, epigenetic cancer research is enhancing our knowledge of how “pathologic epigenetic changes are increasingly considered as alternatives to mutations and chromosomal alterations in disrupting gene function” (Hatzia Apostolou & Iliopoulos, 2011, p. 1682). Examples of epigenetic chemical modifications that initiate cancer by altering gene (protein) expression are those associated with cigarette smoking and toxic metals. These are included later in this chapter.

Sporadic Mutations

In contrast to inherited cancer syndromes, the term *sporadic cancer* is used to describe disease that happens *de novo*, or by chance. Although sporadic cancers are not linked to an identifiable, heritable cancer susceptibility gene, they nevertheless involve genetic and chromosomal alterations. This category comprises 90% to 95% of all cancers not attributable to gene mutations or chromosomal aberrations. Theoretically, a majority of these spontaneous cancers are related to epigenetic biochemical modifications. Cancer-inducing changes can result from spontaneous mutations involving environmental factors such as radiation, viruses, carcinogenic chemicals, toxic metal exposure, or even certain lifestyle factors. Sporadic cancers can occur at an early age of onset; however, for the majority of individuals without heritable risk factors, spontaneous or sporadic cancer risk increases as humans age. This is a direct reflection of cancer’s multistep progression of genetic insults.

GENOMIC MUTATIONS THAT DISRUPT CELL DIFFERENTIATION AND FUNCTION IN CANCER

Genomic mutations can occur in one or a combination of the four major genetic mechanisms described above. There are four types of classic germline and somatic cell genomic mutations that act at the molecular level to disrupt normal cell growth. Table 11.1 provides examples of each type of mutation and describes the genetic nature of each.

DNA Repair Genes

Certain categories of genes have been identified as important players in the development of cancer due to their functions in growth, inhibition, and repair. The protein products of DNA repair genes monitor and correct errors or damage to DNA from a variety of exogenous and endogenous insults that would otherwise have potentially harmful repercussions. When a mutation in this type of gene occurs, the cell loses its ability to repair damaged DNA sequences and cell division results in daughter cells that not only carry the mutation and DNA damage, but are more susceptible to further insult. Impaired DNA repair genes can be inherited as germline mutations, silenced through epigenetic mechanisms, or result from acquired somatic changes.

TABLE 11.1 Genomic Mutations That Disrupt Cell Differentiation and Function in Cancer

| Type of Alteration | Gene Mutations and/or Chromosomal Biomarkers | Cancer Diagnosis |
|--------------------------------|--|---|
| DNA Repair | <i>MSH2, MSH6, PMS2, MLH1</i> | Hereditary colon cancer |
| | <i>XPA, XPC</i> | Xeroderma pigmentosum, skin cancers |
| | <i>ATM</i> | Lymphoma, leukemia, breast cancer |
| | <i>MRE11</i> | Breast cancer |
| | <i>WRN</i> | Sarcoma, colorectal, skin, thyroid, pancreatic cancers |
| Chromosomal Alterations | Chromosomes 9 and 22 (<i>BCR</i> and <i>ABL</i> genes) | Chronic myeloid leukemia |
| | Chromosomes 8 and 14 (<i>MYC</i> and <i>IG</i> heavy chain genes) | Burkitt lymphoma |
| Oncogenes | <i>ERBB2 (HER-2)</i> | Breast cancer |
| | <i>MYC</i> | Lung cancer |
| | <i>RAS</i> | Pancreatic, colon, and lung cancers |
| | <i>EGFR</i> | Lung cancer |
| | <i>MITF</i> | Melanoma |
| | Mutant <i>B-Raf</i> | Melanoma |
| | Cyclin <i>E</i> | Liver cancer |
| | B-Catenin | Colon cancer |
| | <i>K-ras</i> ¹² | Pancreatic cancer |
| | <i>K-ras</i> ^{mut} | Pancreatic cancer |
| | Cyclin <i>D1</i> | Esophageal, colon, pancreatic, squamous, nasopharyngeal cancers |

(continued)

TABLE 11.1 Genomic Mutations That Disrupt Cell Differentiation and Function in Cancer (continued)

| Type of Alteration | Gene Mutations and/or Chromosomal Biomarkers | Cancer Diagnosis |
|------------------------|--|---|
| Tumor Suppressor Genes | <i>BRCA1, BRCA2</i> | Breast and ovarian cancer |
| | <i>RB1</i> | Retinoblastoma |
| | <i>WT1, WT2</i> | Wilms tumor |
| | <i>CDKN2A</i> | Melanoma |
| | <i>APC</i> | Colorectal cancer |
| | <i>VHL</i> | Kidney cancer |
| | <i>NF1, NF2</i> | Nerve tumors, brain cancer |
| | <i>TP53</i> | Has been identified in over half of human cancers |

Source: GeneReviews (2014).

There are a variety of DNA repair mechanisms, such as nucleotide excision repair, base excision repair, and mismatch repair. Overall, dysregulation of DNA repair predisposes a cell to genomic instability, which is a classic characteristic of cancer. An example of impaired DNA repair can be seen in xeroderma pigmentosum, which involves impairments of genes that are normally involved in the repair of ultraviolet-light-induced damage. Ineffective repair results in heightened sensitivity to sunlight and a predisposition for skin cancers.

Oncogenes

For more than 50 years, cancer initiation theories have centered on activation of oncogenes or inactivation of tumor suppressor genes. In humans, there are more than 40 proto-oncogenes, which are a class of genes that contribute to a variety of growth-control pathways, such as growth factors, signaling enzymes, transcription factors, or growth factor receptors. The normal growth-control pathway involves the binding of growth factors to receptor sites on the cell's membrane, which in turn trigger signaling enzymes to activate transcription factors within the nucleus. The transcription factors subsequently activate specific genes involved in cell growth and division.

There are a number of mechanisms by which proto-oncogenes, vital to the health and function of a cell, become harmful, cancer-promoting oncogenes. Conversion of proto-oncogenes to oncogenes occurs through:

- ▶ Point mutations, deletions, or insertions leading to a hyperactive gene product
- ▶ Point mutations, deletions, or insertions in the promoter region of a proto-oncogene leading to increased transcription
- ▶ Gene amplification events leading to extra chromosomal (aneuploidy) copies of a proto-oncogene
- ▶ Chromosomal translocations can relocate a proto-oncogene to a new chromosomal site, leading to higher-than-normal gene expression
- ▶ Chromosomal translocations that lead to a fusion between a proto-oncogene and a second gene, producing a fusion protein with oncogenic activity

Oncogene activation can result from either inherited predisposition or more commonly through acquired/environmental triggers, such as exposure to retroviruses or carcinogens. Oncogenes behave in a dominant fashion, which means only one abnormal allele is necessary for expression and subsequent deleterious effects. Whatever the mechanism for oncogene activation, the effect is growth promotion and the potential for cancer. Examples of oncogenes include the *HER2* gene implicated in aggressive breast cancer and the *MYC* gene associated with Burkett lymphoma and lung cancer.

Certain pathogens, such as viruses, can contribute through the insertion of viral RNA into a human cell. Infectious agents, mainly retroviruses, act as oncoviruses that contribute to a variety of malignancies (Table 11.2). Collectively, these account for up to 20% of cancers around the globe. Although bacteria have the ability to become oncogenic, not much is known about specific bacteria. Viruses and bacteria exert their oncogenicity by three common pathways:

- ▶ Inserting their genome into human DNA
- ▶ Hijacking the epigenome and tagging genes with biochemicals (miRNAs, DNA methylation, or histone modifications) that inhibit or silence tumor suppressor genes and promote transcription of oncogenes
- ▶ Infecting human cells and indirectly transforming the cell's progression toward cancer growth and oncogenic maintenance.

Tumor Suppressor Genes (Anti-Oncogenes)

Tumor suppressor genes represent an innate mechanism of cancer prevention. These genes regulate cell growth by limiting cell division, aiding in DNA repair, and inducing programmed cell death in cells that could otherwise cause harm. Both oncogenes and tumor suppressor genes contribute to cancer development, but a primary difference is the *inhibition* (or silencing) of tumor suppressor genes—as compared to the *expression* of oncogenes—that potentiates unregulated growth. When silenced, a tumor suppressor gene loses its ability to repair genetic insults, halt the continuation of damaged cell lines, and maintain growth within healthy boundaries.

Tumor suppressor genes can be silenced through chromosomal alterations such as translocations, inherited gene mutations, or by multiple acquired mutations as a consequence of environment and lifestyle influences. In contrast to oncogenes, tumor suppressor genes are recessive in nature; both alleles of the genes must be

TABLE 11.2 Oncogenic Pathogens

| Oncovirus* | Cancer Type |
|--|---|
| Human papillomavirus (HPV) | Cervical |
| Human polyomavirus (HPMV) | Mesotheliomas, brain tumors |
| Epstein–Barr virus (EBV) | Lymphoproliferative diseases and nasopharyngeal |
| Kaposi sarcoma herpesvirus | Kaposi sarcoma and primary effusion lymphomas |
| Hepatitis B and hepatitis C viruses | Hepatocellular |
| Human T-cell leukemia virus-1 (HTLV1) | T-cell leukemias |
| Oncopathogen** | Cancer Type |
| <i>Helicobacter pylori</i> | Gastric |
| <i>Chlamydia trachomatis</i> | Cervical |
| <i>Helicobacter</i> | Biliary tract |
| <i>Staphylococcus aureus</i> (i.e., chronic osteomyelitis) | Sinus tracts, skin ulcers, squamous cell |

Adapted from *Pagano et al. (2004) and **Chang and Parsonnet (2010).

abnormal for significant gene malfunction to occur. Since mutations from an inherited etiology already involve one abnormal copy, only one more insult is required to silence the gene. Compare this to cells without a hereditary cancer predisposition, which require two damaging events to knock out the function of the tumor suppressor gene. Well-known examples of tumor suppressor genes implicated in hereditary breast cancers include *BRCA1* and *BRCA2*.

GENOMICS OF CHILDHOOD CANCERS

Childhood cancers account for less than 1% of all cancers diagnosed each year. In 2015, about 10,450 children under the age of 15 will be diagnosed in the United States, with the rate of diagnosis increasing slightly each year over the past few decades. As technology and treatments become more advanced, over 80% of children with cancer now survive 5 years or more, which is an increase from only 60% in the 1970s. About 1,350 children younger than 15 years old are expected to die from cancer in 2014, making it second only to accidents as the leading cause of death in children.

TABLE 11.3 Childhood Cancer Statistics

| | |
|----------------------------------|-----------------------------------|
| Leukemia (ALL and AML) | 31% of childhood cancer diagnoses |
| Brain and central nervous system | 21% of childhood cancer diagnoses |
| Neuroblastoma | 7% of childhood cancer diagnoses |
| Wilms tumor | 5% of childhood cancer diagnoses |
| Hodgkin lymphoma | 4% of childhood cancer diagnoses |
| Non-Hodgkin lymphoma | 6% of childhood cancer diagnoses |
| Rhabdomyosarcoma | 3% of childhood cancer diagnoses |
| Retinoblastoma | 3% of childhood cancer diagnoses |
| Primary bone cancers | 4% of childhood cancer diagnoses |

Adapted from Ward et al. (2014).

In this section, the hereditary and acquired genetic mechanisms of the most common types of cancer in children are described (Table 11.3). In recent years, there has been tremendous effort by researchers to understand the molecular genetics of pediatric cancer through investigation of tumors or somatic cell genomic dysregulation at varying stages of cancer development. The two major types of cancer genetic mechanisms present in childhood cancers are inherited (gene mutations and chromosomal translocations) and acquired (epigenomic biochemical alterations and sporadic mutations, which show no identifiable patterns of familial inheritance). Childhood cancers do not appear to fit neatly into one category or the other, but instead are a combination of inherited and acquired, genetic and epigenetic mechanisms (Table 11.4). High-dose ionizing radiation and maternal pesticide use inter-uterine and early childhood exposure are the most commonly cited environmental risk factors.

LEUKEMIAS

Leukemia is the most commonly occurring childhood cancer, starting in early blood-forming cells (hematopoietic stem cells). Most often, leukemia is a cancer affecting the white blood cells; however, some leukemias can start in other blood cell types. Any cell from the bone marrow can become a leukemia cell, and once altered from a normal cell, a leukemia cell does not go through normal cell processes of maturation and apoptosis. Leukemia cells can reproduce quickly and survive, causing them to build up in the bone marrow. This crowding impedes the growth and development of normal cells so that, once leukemia leaves the bone marrow, it can travel to other organs in the body crowd normal cells and keep them from

TABLE 11.4 Genetic Mechanisms in Pediatric Cancers

| Type of Cancer | Type of Cancer Genetic Mechanism | Other Cancers or Diseases | Risk of Occurrence |
|----------------------------------|---|---|--|
| Acute lymphocytic leukemia (ALL) | Chromosomal translocation, gene fusion, and epigenetic or acquired genome mutation (radiation, chemicals) | Increase risk of ALL with Down syndrome, Klinefelter syndrome, Li–Fraumeni syndrome, neurofibromatosis, Fanconi anemia, ataxia–telangiectasia, Wiskott–Aldrich syndrome, and Bloom syndrome | Risk of leukemia is 32%, ALL is responsible for 75% of leukemias |
| Acute myelogenous leukemia (AML) | Chromosomal translocation, gene mutation | Down syndrome, rare cases develop after renal transplant or in HIV infection | Risk of leukemia is 32%, AML is responsible for about 24% of leukemias |
| Brain tumors | Single gene mutation, germline mutation | Turcot and Gorlin syndromes increase risk of medulloblastoma | 21% of childhood tumors |
| Neuroblastoma | Chromosomal gene fusion, germline mutations, or somatic mutations, unbalanced chromosomal translocation | None found (on American Cancer Society [ACS]) | 7% of all cancers in children |
| Wilms | Chromosomal translocation, germline and somatic mutations | Birth defects such as WAGR syndrome | 5% of all cancers in children |

(continued)

| | | | |
|------------------|---|--|-------------------------------|
| Lymphoma | Somatic mutation due to viral infection or epigenetic influences, chromosomal translocation | Congenital and acquired viral infections such as HIV, Epstein–Barr virus, or post-transplant immunodeficiency, congenital immunodeficiency syndromes like Wiskott–Aldrich syndrome, severe combined immunodeficiency (SCID) syndrome, ataxia–telangiectasia, common variable immunodeficiency, Bloom syndrome, and X-linked lymphoproliferative syndrome | 4% of all cancers in children |
| Rhabdomyosarcoma | Chromosomal translocation | Neuroblastomas | 3% of all cancers in children |
| Ewing sarcoma | Chromosomal translocation | None found* | 1% |
| Osteosarcoma | Hereditary single gene mutations | Increased <i>HER2</i> growth factor presence. Increased risk of developing osteosarcoma with Li–Fraumeni syndrome and retinoblastoma. | 3% childhood cancers |

*Askin tumor in the lung
Adapted from GeneReviews (2014).

developing normally. Leukemia may cause bone and joint pain, fatigue, weakness, pale skin, bleeding or bruising, fever, weight loss, and other symptoms.

Two main types of leukemia with childhood onset are acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML). There are also rare forms of leukemia including hybrid, mixed, or chronic. Chronic leukemia includes myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL), but these are very rare in children.

Acute Lymphocytic Leukemia (ALL)

ALL comprises approximately 75% of leukemias in children and teenagers, is slightly more common in White children, and most commonly occurs in early childhood between the ages of 2 and 4 years. While there are some genetic factors believed to increase the risk of childhood leukemia, most cases of leukemia are not linked to any known genetic cause. Several inherited disorders can increase the risk of developing childhood leukemia including Down syndrome (trisomy 21), Klinefelter syndrome, and Li–Fraumeni syndrome. Children with Down syndrome have a 2% to 3% increased risk of developing ALL or AML compared to the general population. Li–Fraumeni syndrome is a rare condition caused by an alteration in the *TP53* tumor suppressor gene and has an autosomal dominant pattern of inheritance where multiple individuals are affected with different types of cancers including leukemia, bone and soft tissue sarcoma, breast cancer, and others. Genetic disorders such as neurofibromatosis and Fanconi anemia carry an increased risk for developing leukemia. Children with inherited immune system problems such as ataxia–telangiectasia, Wiskott–Aldrich syndrome, and Bloom syndrome are at an increased risk.

Siblings of children with leukemia have a two to four times higher-than-normal risk of developing leukemia. Identical twins have a one in five chance of developing leukemia when the other twin is affected. There are currently no identified lifestyle risk factors for the development of leukemia, although some studies have suggested that maternal alcohol abuse during pregnancy elevates the risk of childhood leukemia. There are several environmental risk factors including radiation exposure, exposure to chemotherapy or certain other chemicals linked to higher risk of leukemia including cyclophosphamide, chlorambucil, etoposide, and teniposide. Chemical exposure is more strongly associated with an increased risk of AML compared to ALL. Some studies have shown a link between childhood leukemia and household pesticides, either during pregnancy or in early childhood; however, these studies need further confirmation.

Chromosomal translocation is a common genetic abnormality leading to leukemia. A translocation seen in almost all cases of childhood chronic myeloid leukemia (CML) and in 3% to 5% of ALL cases there is a translocation between chromosomes 9 and 22 (q34;q11), leading to what is known as a Philadelphia chromosome. This creates a fusion gene by moving the *ABL* proto-oncogene from chromosome 9 to the *BCR* gene on chromosome 22. In most cases of childhood *BCR–ABL*-positive ALL, the *BCR* breakpoints are distributed in an upstream breakpoint cluster region. In this location, the chimeric proteins from the fusion gene play a role in multiple signaling pathways, leading to leukemic transformation.

Epigenetic or acquired genome mutations tend to occur after conception, but can occur very early in development, even prior to birth. In some cases acquired

mutations can result from exposure to radiation or cancer-causing chemicals, but in a vast majority of cases the cause for leukemia development is unknown. A few studies have suggested that some childhood leukemias may result from inherited genes that may inhibit the process of cleansing the body of harmful chemicals, but further study is needed.

ACUTE MYELOGENOUS LEUKEMIA (AML)

AML occurs in boys and girls of all races and is generally distributed across the life span with a bimodal increase in frequency in the first 2 years of life and the teenage years. The vast majority of children (90%–95%) diagnosed with CML are Philadelphia-chromosome-positive, which entails a reciprocal translocation $t(9;22)(q34;q11)$ leading to the *BCR-ABL* fusion gene and protein mutation. The development of AML involves an arrest in the maturational process of granulocyte or monocyte precursors secondary to chromosomal translocations or accumulation of other molecular dysfunctions. There are several gene mutations identified in AML. *FLT3* mutations create tandem internal duplications and have a poor prognosis. *RAS* and tyrosine kinase receptor mutations such as in *ckit* occur in 25% of AML cases, with unclear prognostic significance. *GATA1* is a transcription factor receptor gene for the development of erythroid, megakaryocyte, eosinophil, and mast cells; it is a common gene mutation in patients with Down syndrome and megakaryocytic AML. Rare cases have been associated with Down syndrome, postrenal transplant, and in HIV infection.

BRAIN TUMORS

Brain and spinal cord tumors are the second most common cancers in children, making up 21% of childhood tumors, or one out of five childhood cancers diagnosed. Over 4,000 central nervous system tumors are diagnosed each year in children. Brain tumors in children and teenagers are more likely to start in the cerebellum and brain stem, but can occur in upper parts of the brain, albeit less commonly. Tumors can form in almost any type of tissue or cell in the brain or spinal cord, and some tumors even have a mixture of cell types. There are a number of primary brain tumors that occur in children. These include gliomas, primitive neuroectodermal tumors (PNETs), craniopharyngiomas, mixed glial and neuronal tumors, choroid plexus tumors, schwannomas, meningiomas, chordomas, germ cell tumors, neuroblastomas, lymphomas, pituitary tumors, and cancers that start elsewhere in the body but metastasize to the brain.

Glioma is a general term for a group of tumors that start in glial cells, and accounts for about half of all brain and spinal cord tumors in children. A number of tumors are considered gliomas, including glioblastoma, anaplastic astrocytoma, astrocytoma, oligodendroglioma, ependymoma, brain stem glioma, and optic glioma. Astrocytomas are tumors that start in astrocytes, and can spread throughout the brain and integrate with normal brain tissue, making removal by surgery difficult. Astrocytomas can also grow along cerebrospinal fluid pathways, but it is rare for them to spread outside the brain or spinal cord. Oligodendrogliomas are tumors that start in

oligodendrocytes, and while they tend to be slow growing, they can infiltrate normal brain tissue similarly to astrocytomas. Oligodendrogliomas rarely spread along cerebrospinal fluid pathways or outside the brain or spinal cord. Only about 1% of brain tumors are oligodendrogliomas. Ependymomas account for 5% of brain tumors in children and are tumors that start in ependymal cells that line the ventricles or central canal of the spinal cord. While these tumors may spread through cerebrospinal fluid pathways, they do not spread outside the brain or spinal cord. As ependymomas usually do not grow in normal brain tissue, removal can be achieved by surgery, providing these tumors have not significantly spread throughout the system.

PNETs are tumors that start in immature cells called neuroectodermal cells. These tumors account for one in five brain tumors in children. These tumors can have different names depending on where they initiate in the system, including medulloblastomas, pineoblastomas, and others. Medulloblastomas account for most PNETs in children, and are tumors that start in the cerebellum. These tumors can be treated and often have the best outcomes of PNETs that occur in other parts of the brain. PNETs that develop in the pineal gland are called pineoblastomas and are more difficult to treat than medulloblastomas. Other more rarely occurring PNETs include medulloepitheliomas, ependymoblastomas, and neuroblastomas that start in the brain or spinal cord.

In many cases, it is still unclear why individuals without inherited susceptibility develop central nervous system tumors. However, researchers hypothesize that inactivation of tumor suppressor genes may result in the development of childhood central nervous system tumors. Two genes have been identified: *TP53* gene alterations in some forms of glioma and the *PTEN* gene in glioblastoma multiforme. Currently, the most researched brain tumor is medulloblastoma as it is the most common brain tumor in children. The most common genetic abnormality occurring in medulloblastoma is loss of chromosome 17p, which is found in roughly 50% of cases. Medulloblastoma is also noted to occur more frequently in patients who have Turcot (APC gene mutation associated with colon cancer) or Gorlin (*PTCH1*, or patch-1 receptor gene mutation) syndrome. Germline mutations in the *PTC* gene and resulting basal cell carcinomas suggest that *PTC* functions as a tumor suppressor gene. One allele in *PTC* is occasionally mutated in medulloblastomas, suggesting the *PTC* pathway involves tumorigenesis.

Researchers have proposed several prognostic indicators of gliomas, including *TP53* mutation and expression, overexpression or amplification of *EGFR*, *CDKN2A* alteration and deletion, and *MDM2* amplifications. The *MDM2* gene has been noted to be key to maintaining cell proliferation and apoptosis. Loss of heterogeneity of chromosome 10q has been shown to lead to shorter survival in glioblastoma multiforme, and loss of heterogeneity of 1p and 19q may have a better prognosis.

NEUROBLASTOMA (CHROMOSOMAL GENE FUSIONS)

Neuroblastoma is a cancer that is initiated in very early forms of nerve cells in an embryo or fetus. It most commonly affects infants and young children, only rarely occurring in children over the age of 10 years. It is the most common cancer in infants, accounts for 7% of all cancers in children, and results in 10% to 15% of all

cancer deaths in children. There are about 700 new cases of neuroblastoma each year in the United States, with 90% of cases diagnosed by the age of 5. In two out of three cases, the disease has already metastasized to the lymph nodes or other parts of the body by the time of diagnosis.

These tumors start in the sympathetic nervous system, including nerve fibers, ganglia, and nerve-like cells that are found in the medulla of the adrenal glands. About one in three neuroblastomas start in the adrenal glands, one in four in the sympathetic nerve ganglia in the abdomen, and the remainder start in ganglia near the spine in the cervical, lumbar, or pelvic regions.

Neuroblastomas have a wide variety of behaviors, with some tumors growing and metastasizing quickly, while others grow slowly or even die off. Patients older than 1 year of age and with metastases have the poorest prognosis for treatment; these clinical features have been used to help guide specific therapies. Understanding and identifying genetic alterations in neuroblastoma are key to improving risk assessment and patient outcomes.

Characterized by gene fusion alterations, sarcomas are different from neuroblastomas, which are known for gene amplification, inactivation of tumor suppressor genes, and alterations in gene expression. Some patients inherit a genetic predisposition to neuroblastoma due to the development of germline mutations, where others develop sporadic disease that could be the result of either germline or somatic mutations. Most neuroblastomas are not caused by inherited DNA mutations. Only in rare cases does neuroblastoma seem to occur because of genetic alteration or an inherited mutation. Most inherited cases of neuroblastoma seem to occur from an inherited change in the *ALK* oncogene, or rarely in *PHOX2B*, a gene that normally helps nerve cells mature. Only 10% to 15% of noninherited neuroblastomas have changes in the *ALK* genes. For noninherited cases of neuroblastoma, the development of disease is a result of gene alteration that happens early in the child's development, oftentimes before birth, pointing to inherited epigenetic marks or biochemical tags. The genetic alterations are only found inside cancer cells, meaning that mutations are not passed on to later generations. Other inherited or epigenetic changes involved in neuroblastomas are not yet known.

Genetic alteration in some genes can affect how quickly a neuroblastoma is likely to grow. Neuroblastoma cells that have extra copies of the oncogene *MYCN*, located on chromosome 2p24, are indicative of a tumor that grows quickly and is difficult to treat. Approximately one fourth of neuroblastoma is associated with extra copies of *MYCN*, which contributes to rapid disease progression. *MYCN* has become a powerful predictor of outcome and is a factor in the decision of intensive therapy. In addition to unfavorable outcomes associated with extra copies of the oncogene *MYCN*, loss of heterozygosity of the short arm (q) of chromosome 1 is also associated with adverse outcomes, suggesting that the tumor suppressor gene may be located in this area. The gain of all or a section of chromosome 17 is the most common finding, although those gains associated with unbalanced translocation result in poor prognosis. Alternatively, the *NTRK*, a gene responsible for producing the TrkA protein, is generally more reactive in neuroblastoma cells and is more easily treated.

In infants, hyperdiploid tumors respond favorably to typical treatment, while diploid tumors require more intensive treatments. Older children with neuroblastoma are more likely to have changes to the *ATRX* tumor suppressor gene, which causes

tumors to grow more slowly and are more difficult to cure. Research is ongoing to better determine causes of neuroblastoma and additional contributing genetic alterations. At this time, there are no identified environmental causes of lifestyle-related factors that contribute to cancer development.

WILMS TUMOR

The most common cancer that occurs in the kidneys of children is the Wilms tumor. Most Wilms tumors only affect one kidney, having a unilateral development, but in 5% of children bilateral disease can occur. Most often there is only one tumor developing; however, in 5% to 10% of children with Wilms tumors there can be more than one tumor in the same kidney.

Wilms tumors account for about 5% of all cancers in children, and each year there are about 500 new cases diagnosed in the United States. These tumors tend to occur in young children, with the average age of diagnosis around 3 to 4 years of age. Most Wilms tumors do not have a clear cause and research has not yet discovered any strong links between the development of this tumor and environmental factors. However, some factors that confer risk for tumor development have been found, including young age, African American or Caucasian race, female gender, family history of Wilms tumor or cancer in general, and certain kinds of birth defects including WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation), Beckwith–Wiedemann syndrome, Denys–Drash syndrome, and several others.

While more than 95% of Wilms tumor cases are sporadic, there are cases due to a congenital anomaly or as part of a familial predisposition. Patients with congenital anomalies or a family history have an increased incidence of diagnosis at an earlier age and bilateral tumors, indicating a germline loss of tumor suppressor gene in these children. Studies of children with concurrent WAGR syndrome and Wilms tumor have demonstrated the key role of the 11p13 band in the development of Wilms tumor. Alterations or loss of *WT1* or *WT2* tumor suppressor genes, also located on chromosome 11, has demonstrated that these genes encode a transcription factor that is important to normal kidney development. However, mutations to *WT1* and *WT2* are detected in only a small number of Wilms tumor cases, indicating that there are other genes involved in the development of this disease. A small number of Wilms tumors display a change in the tumor suppressor gene *WTX*, located on the X chromosome, as well as the *CTNNB1* gene. Additional research has indicated that altered expression of genes located at 11p15, including *H19*, *IGF2*, and *Tp57*, in addition to others, are also involved in tumorigenesis. A large number of Wilms tumors also contain *p53* mutations, and loss of heterozygosity for 16q, 1p, and 22q which are indicative of poor outcomes.

Lymphoma

Lymphoma is a type of cancer that starts in immune system cells called lymphocytes. These cells grow in lymph nodes and other lymph tissues, like the tonsils. They also have an effect on the bone marrow and other organs, and symptoms can vary depending on the location of the cancer.

There are two main types of lymphoma: Hodgkin lymphoma (otherwise known as Hodgkin disease) and non-Hodgkin lymphoma (NHL). Both types occur in children and adults; however, NHL occurs at a higher rate in children (6% of childhood cancers) and is most likely to affect young children. Hodgkin lymphoma accounts for 4% of childhood cancers, and is most common in older teenagers, young adults, and in individuals over 55 years of age.

The most common types of NHL in children are different from those occurring in adults, and usually belong to three main types: lymphoblastic lymphoma, Burkitt lymphoma, and large cell lymphoma. Lymphoblastic lymphoma accounts for about 25% to 30% of NHL, and is most common in teenagers. Males are affected twice as often as females. This lymphoma starts in young lymphocyte cells called lymphoblasts and develops from either T cells or B cells. There are two main subtypes: anaplastic large cell lymphoma (ALCL) and diffuse large B-cell lymphoma. Relatively little is known of the epidemiology; however, immunodeficiency is associated with most cases of NHL that result from congenital and acquired viral infections, including HIV, Epstein–Barr virus (EBV), or post-transplant immunodeficiency. EBV infections are endemic around the world, but mostly in equatorial Africa, where 85% of children before the age of 3 years contract EBV infections. In addition, EBV is present in approximately 15% of Burkitt lymphoma cases seen in Europe and the United States.

RHABDOMYOSARCOMA

Rhabdomyosarcomas (RMSs), a family of separate and unique tumors that includes Ewing sarcoma, PNET, and neuroblastomas, can be viewed as similar soft tissue masses with undifferentiated small round cells. Making up about 3% of childhood cancers, RMS is the most common type of soft tissue sarcoma in children. RMS initiates in cells that normally develop into skeletal muscle tissue, commonly found in the head and neck, arm, leg, or pelvis. Common symptoms include pain or swelling at the tumor site.

There are two types of RMS: alveolar and embryonal. In RMS, the *PAX* and the *FOXO1* genes are translocated and create a fusion gene. Most alveolar rhabdomyosarcomas (ARMSs) appear to be the result of translocation errors, either $t(2;13)(q35;q14)$ or less commonly $t(1;13)(p36;q14)$. In this type of cancer, a small segment of chromosome 2, or more rarely a segment of chromosome 1, is attached to chromosome 13. This translocation results in a gene called *PAX3* (or *PAX7* if chromosome 1 is involved) placed immediately next to the *FOXO1* gene. The normal function of *PAX* genes is to promote cell growth during the development of embryonal tissue, but these genes are later turned off when embryonal growth is no longer necessary. The usual function of the *FOXO1* gene is to activate surrounding genes. Thus, the translocation error occurring in ARMS causes the *FOXO1* gene to activate the *PAX* genes that are inappropriately placed, resulting in tumor formation. Clinically, tumors expressing *PAX3-Fkhr* are associated with favorable features, and the prognosis for patients with these tumors is better than that of patients with *PAX3-Fkhr*-positive tumors.

Embryonal rhabdomyosarcoma (ERMS) is believed to develop differently than ARMS, with cells in these tumors losing a piece of chromosome 11 from maternal

DNA, replaced by a second copy of DNA from the paternal chromosome. This is believed to be the cause of the overreactivity of the *IGF2* gene on chromosome 11, which is a gene that codes for a protein that promotes cell growth. Recent research has uncovered that about one in four tumors generally considered by physicians to be ARMS lacks a fusion gene, the typical hallmark of many childhood cancers.

EWING SARCOMA

Approximately 1% of all childhood tumors are classified as Ewing tumors, a rare type of bone cancer. In North America, about 225 children are diagnosed each year, most of these occurring in teenage children but occasionally affecting younger children. Statistically, more males than females develop these tumors with higher incidence in Caucasians, including non-Hispanic and Hispanic ethnicities. This disease is rare among African Americans and other racial groups. Survival rates for Ewing sarcoma are affected by a number of factors, such as the child's age, tumor location, staging, and tumor responsiveness to treatment. The 5-year survival rate for patients with localized Ewing tumors is about 70%, but for patients with metastatic tumors, the 5-year survival rate is around 15% to 30%.

There are three main types of Ewing tumors, including Ewing sarcoma of bone, extrasosseous Ewing tumor (EOE), and peripheral primitive neuroectodermal tumor (PPNET). The Ewing sarcomas are the most commonly occurring tumors in this family, and the most common symptom observed is bone pain, generally radiating from the bones of the pelvis, chest wall, or the long leg bones. EOE tumors start in the soft tissues surrounding bones, but they closely resemble Ewing sarcomas. PPNETs are rare tumors and can start in bone or soft tissue. PPNETs share many features with Ewing sarcoma and EOE, and researchers have discovered that the cells that make up these three tumors have the same gene abnormalities and share similar protein abnormalities rarely present in other cancer types.

Current research in somatic tissue expression arrays indicates that certain chromosomal changes lead to Ewing tumors, and these changes are not inherited. Environmental and lifestyle-related causes of Ewing tumors are unknown at this time. Changes occur in the chromosome after birth, developing initially in a single cell. Most Ewing tumor cells have mutations that involve the *EWS* gene, which is located on chromosome 22. Translocation occurs between chromosomes 22 and 11, or more rarely between chromosomes 22 and 21, or chromosome 22 and another chromosome. Upwards of 90% of Ewing tumors are characterized by the *EWS-FLI1* fusion gene that is formed by the translocation of chromosomes 22 and 11, or the variant *EWS* fusion gene between chromosomes 22 and 21, or chromosomes 22 and 7. This translocation causes a piece of a chromosome to be placed immediately adjacent to the *EWS* gene on chromosome 22, causing the constant activation of the *EWS* gene. This leads to cell proliferation and the development of cancer. Recent researchers suggest that the breakpoint location between chromosomes 22 and 11 has prognostic significance, and the more common type of breakpoint (called type 1 by researchers) is associated with a more favorable outcome than type 2 breakpoints between chromosomes 22 and 21 or chromosomes 22 and 7.

OSTEOSARCOMA

Osteosarcoma, also called osteogenic sarcoma, is a type of cancer that starts in bone. Osteosarcoma is not a common cancer, accounting for only about 3% of childhood cancers, with about 400 new cases in the United States each year. Five-year survival rates for individuals with localized osteosarcoma are between 60% and 80%, with the higher percentage for those with surgical tumor resection. If osteosarcoma has metastasized, the 5-year survival rate is between 15% and 30%.

Similar to osteoblasts in normal bone, the cells that compose this form of cancer construct the bone matrix. However, the bone composition is not as strong as normal bones. Teenagers are the most commonly affected age group, but osteosarcomas can occur at any age. In children, osteosarcoma usually develops in areas of rapid bone growth, such as near the ends of long bones. Recent research has discovered that increased expression of the growth factor *HER2* is associated with a decreased response to chemotherapy treatments and poor outcome, providing researchers a prognostic marker and a potential therapeutic target.

While most osteosarcomas are not caused by inherited gene mutations, there are some syndromes that are linked with an increased risk for the development of osteosarcoma. Two of these conditions are the hereditary single gene mutation Li–Fraumeni syndrome and hereditary retinoblastoma. Li–Fraumeni syndrome is caused by germline mutations that deactivate the *TP53* tumor suppressor gene. These mutations greatly increase the risk of developing different forms of cancer. Additionally, germline changes in the retinoblastoma *RBI* tumor suppressor gene not only increase the risk of developing retinoblastoma, but for osteosarcoma as well.

In addition to hereditary susceptibility to osteosarcomas, accumulated gene alterations found in tumor tissues are acquired during an individual's lifetime. Loss of heterozygosity at gene loci 17p, 18q, 13q, and 3q is a frequent finding in tumor tissues, suggesting that tumor suppressor genes in these areas may be inactivated. One way these alterations can occur is through radiation therapy. While radiation therapy is extremely useful for treating some types of cancer, it can also incite cancer by damaging DNA. Individuals who receive radiation therapy are at greater risk for developing osteosarcoma at the treatment site. Other gene alterations have no clear reason for development, resulting either from random errors or as yet unidentified environmental causes.

GENOMIC MECHANISMS IN ADULT CANCERS

In 2014, the lifetime risk of developing cancer in the United States was one in three for women and less than one in two for men. Differences in risk are attributed to environmental exposure, lifestyle habits, and genetic susceptibility. Cancer susceptibility is increased when an individual inherits gene mutations or chromosomal alterations from either the paternal or maternal side of the family, or when a *de novo* (or spontaneous) mutation occurs in a fertilized egg (Table 11.5). In both of these cases, the genetic alteration and associated cancer risk are passed to future offspring.

TABLE 11.5 Genomic Mechanisms in Adult Cancers

| (a) Hereditary Genetic Mechanisms in Adult Cancers | | | | |
|--|--|--|---|---|
| Type of Cancer Genetic Mechanism | Type of Cancer | Other Cancers or Diseases | Gene Testing | Risk of Cancer |
| Autosomal dominant | Breast and ovarian cancer | Hereditary breast and ovarian cancer syndrome (HBOC) | <i>BRCA1</i> and <i>BRCA2</i> are tumor suppressor genes | 40%–80% for breast cancer 11%–40% for ovarian cancer 1%–10% for male breast cancer Up to 39% for prostate cancer 1%–7% for pancreatic cancer, and melanoma incomplete penetrance results in variable age of onset |
| Autosomal dominant | Hereditary nonpolyposis colorectal cancer (HNPCC) | Lynch syndrome I is associated with site-specific colonic cancer Lynch syndrome II is associated with extracolonic tumors Muir–Torre syndrome is a form of Lynch syndrome II associated with sebaceous skin tumors | <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , and <i>PMS2</i> , <i>TGFBR2</i> , and <i>MLH3</i> are mismatch repair genes | 4%–6% of colon cancers |
| Autosomal recessive | Familial adenomatous polyposis (FAP), attenuated FAP | Gardner syndrome, and Turcot syndrome Extracolonic manifestations are variably present and include: polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumors, desmoid tumors, and associated cancers | Adenomatous <i>Polyposis coli</i> (<i>APC</i>) gene | 70% of people have a family history of affected relatives By age 35 years, 95% of individuals with FAP have polyps; without colectomy, 100% of gene mutation carriers develop colorectal cancer (CRC) |

(continued)

| | | | | |
|---------------------|---|--|--|---|
| Autosomal recessive | MUTYH-associated polyposis (MAP) (Cruz-Correa et al., 2013) | Adenomas in both the upper and lower gastrointestinal tract; > 10 - < 100 polyps | <i>MuTYH</i> gene Two common mutations, c.536A>G (p.Tyr179Cys) in exon 7 and c.1187G>A (p.Gly396Asp) in exon 13, are missense variants carried by approximately 1%–2% of the general population | Increased lifetime risk of CRC (43% to almost 100% in the absence of timely surveillance) |
| Autosomal dominant | The <i>PTEN</i> hamartoma tumor syndrome (PHTS) | Cowden syndrome Bannayan–Riley–Ruvalcaba syndrome (BRRS), <i>PTEN</i> -related Proteus syndrome (PS), and Proteus-like syndrome Peutz–Jeghers syndrome (PJS) | <i>PTENS</i> gene <i>STK11 (LKB1)</i> gene reveals disease-causing mutations in 80%–94% of affected individuals; associated with gastrointestinal polyposis, mucocutaneous pigmentation, and cancer predisposition | The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The risk for endometrial cancer, although not well defined, may approach 28%. |

(continued)

TABLE 11.5 Genomic Mechanisms in Adult Cancers (continued)

(a) Hereditary Genetic Mechanisms in Adult Cancers

| Type of Cancer Genetic Mechanism | Type of Cancer | Other Cancers or Diseases | Gene Testing | Risk of Cancer |
|----------------------------------|--|--|---|--|
| Autosomal dominant | Li–Fraumeni syndrome (LFS) and Li–Fraumeni-like (LFL) syndrome | A rare cancer predisposition syndrome | <i>TP53</i> gene mutations (tumor suppressor gene) | Risk of developing soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumors, adrenocortical carcinoma (ACC), and leukemia |
| Autosomal dominant | Prostate cancer | Aggressiveness varies widely: Some tumors progress to invasive, potentially life-threatening disease; others stay latent for the remainder of an individual's lifetime | <i>CDH1</i> <i>CHEK2</i> <i>MSR1</i> <i>HPC1</i> , <i>HPC5</i> , and <i>HPC6</i> gene mutations <i>BRCA2</i> gene mutations <i>PTEN</i> gene mutations | Risk of prostate cancer increased in HBOC and Cowden syndrome |
| Autosomal dominant | Pancreatic | Multiple endocrine neoplasia type 1 | <i>MEN1</i> , <i>MEN2</i> genes | Parathyroid tumors are the main <i>MEN1</i> -associated tumors with hypercalcemia by age 50; pituitary tumors; gastroenteropancreatic (GEP) tract; carcinoid tumors; adrenocortical tumors |

(continued)

| | | | | |
|--------------------|---------------------|--|--|---|
| Autosomal dominant | Hereditary melanoma | Familial multiple mole and melanoma (FAMM) accounts for 20%–40% of hereditary melanoma cases | <i>p16</i> gene mutation (known as <i>CDKN2A</i>) is a tumor suppressor gene that inhibits cellular proliferation | 3%–15% of all malignant melanomas (MM) are familial cases |
|--------------------|---------------------|--|--|---|

(b) Chromosomal Genomic Mechanisms in Adult Cancers

| Type of Cancer Genetic Mechanism | Type of Cancer | Other Cancers or Diseases | Gene Testing | Risk of Cancer |
|----------------------------------|--|--|---|-------------------------|
| Chromosomal alteration | Leukemia Acute myelogenous leukemia (AML) | Myeloid/lymphoid Platelet disorder, pulmonary fibrosis, and bone marrow failure Myelodysplastic syndrome | Gene fusion of <i>MLL</i> gene to the <i>ENL</i> gene at 19p13.3 Gene fusion of <i>MLL</i> gene to the <i>ELL</i> gene <i>ALL1</i> gene translocation t(4;11)(q21;q23) and t(9;11)(p22;q23), respectively T(11;19)(q23;p13) translocation <i>TERT</i> gene mutation in sporadic acute myeloid leukemia | Age of onset in the 50s |

(continued)

TABLE 11.5 Genomic Mechanisms in Adult Cancers (*continued*)

| (c) Epigenetic Biochemical Modification in Adult Cancers | | | | |
|---|----------------|----------------------------|--|--|
| Type of Cancer Genetic Mechanism | Type of Cancer | Risk Factors | Epigenetic Mechanism/Somatic Cell Genetics | Cancer Risk |
| Epigenetics | Lung | Environmental and genetics | DNA hypermethylation <i>TP53</i> tumor suppressor hypermethylated; homeobox <i>HOXA</i> family of genes, specifically <i>HOXC9</i> and <i>HOXA1</i> ; <i>DDR1</i> ; <i>CDKN2A</i> and <i>RASSF1</i> | |
| Familial kinship pattern with increased risk in first-degree relatives by a factor of 2 and epigenetics | Bladder | Environmental and genetics | DNA hypermethylation Somatic oncogene mutations in <i>HRAS</i> , <i>KRAS2</i> , <i>RBI</i> , and <i>FGFR</i> (affecting epithelial cells) | Risk in first-degree and second-degree relatives ranges from 3% to 10% |

Source: GeneReviews (2014); OMIM (2014).

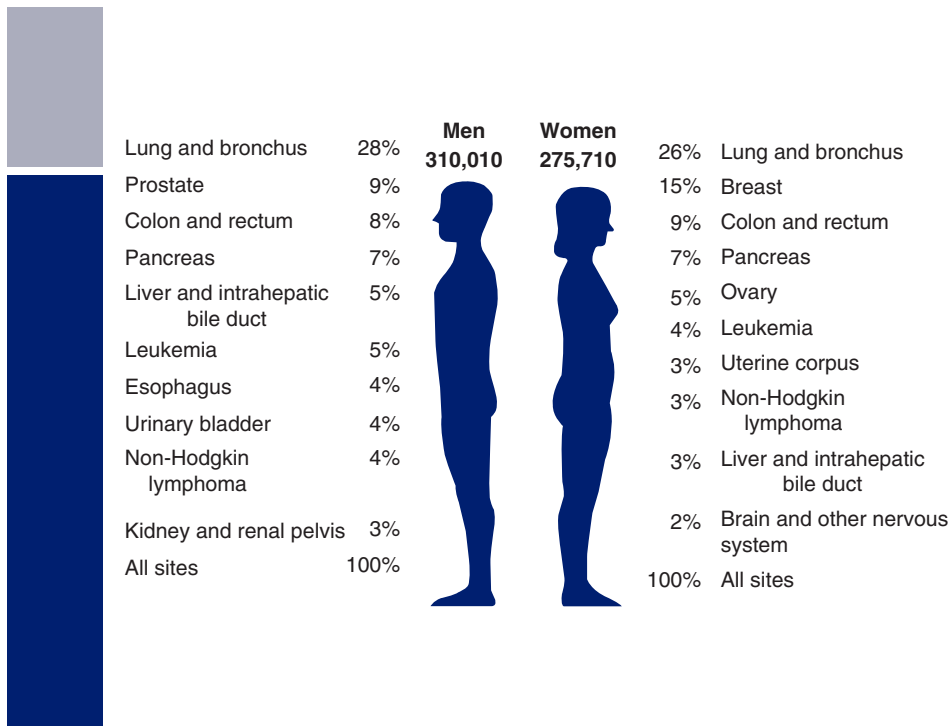


FIGURE 11.2. Estimated cancer deaths in the United States in 2015.

It is estimated that between 5% and 10% of cancers originate from inherited gene mutations or chromosomal alterations. On the other hand, 90% to 95% of cases are potentially preventable. The most common types of cancers in the United States are discussed to illustrate two hallmark genetic mechanisms that increase cancer risk: hereditary (aberrations in single gene mutations, chromosomal rearrangements), and epigenetic biochemical modifications (Figure 11.2).

HEREDITARY CANCER SYNDROMES IN ADULTS

Breast and Ovarian Cancer

More than 231,840 new cases of breast cancer are diagnosed each year in the United States, and about 1 million worldwide. It is the second leading cause of cancer in women after lung cancer, with about 10% of the total or 2,350 new cases in men. The lifetime risks in the general population for breast cancer and ovarian cancer occurring are about 12.3% and 1.4%, respectively. Breast cancer is one of the numerous cancers in which a hereditary component was postulated early in the study of hereditary cancers; its presence in biological relatives was cited as a risk factor, especially in first- and second-degree relatives such as a mother, sister, or aunt before the age of 50. Breast cancer may be associated with other syndromes associated with cancer, such as Li–Fraumeni, Cowden, Lynch syndromes and PTEN mutations

(Table 11.5a) or it can occur alone. *BRCA* gene mutations are present in 90% of families with both breast and ovarian cancer.

BRCA1 and *BRCA2* mutations are believed to be responsible for about 5% to 10% of all breast cancers in women and men, and about one third of all hereditary breast cancers. Additional cumulative gene mutations with lower degrees of penetrance may confer susceptibility to breast cancer; however, some of the genes involved in breast cancer development are still unknown. Birth prevalence of *BRCA1*, *BRCA2*, and *p53* mutations has been estimated at 1 in 476, 1 in 667, and 1 in 5,000, respectively.

Ovarian cancer is the fifth most common cancer in women and is the most common cause of death from gynecological malignancy. At least 90% of cases are sporadic; the rest are believed to be due to inherited susceptibility. Hereditary ovarian cancer is often associated with hereditary breast cancer. The ovarian cancers associated with *BRCA1* and *BRCA2* gene mutations are likely to be high-grade serous adenocarcinomas with occult lesions occurring in the fallopian tubes. These cancers have a higher incidence of *TP53* mutations and they tend to metastasize more frequently to the viscera while sporadic cancers tend to be confined to the peritoneum. Ovarian cancer may also occur with hereditary nonpolyposis colon cancer (HNPCC; discussed later in this chapter) or Cowden syndrome. Similar to breast cancer, some of the hereditary gene mutations resulting in susceptibility to familial risk of ovarian cancer are still unknown.

BRCA1* and *BRCA2

BRCA1 and *BRCA2* normally function as tumor suppressor genes. Germline mutations of *BRCA1* are primarily associated with breast and ovarian cancer. Both male and female carriers have elevated risks for colon cancer and males are at increased risk for prostate cancer. Thus, persons who carry these mutations are more likely to develop cancer. Individuals with these mutations may develop cancer at an earlier age or have more than one type of cancer, such as having both breast and ovarian cancer simultaneously. There are over 900 known *BRCA1* gene mutations, located on chromosome 17q12-21. Families generally carry the same mutation due to its passage down the family tree. Both *BRCA1* and *BRCA2* mutations are particularly prevalent in certain population groups, especially Ashkenazi Jewish women. Among women with ovarian cancer, the hereditary proportion may approach 50%. In *BRCA1* mutations, a particular alteration, 185delAG (deletion of an adenine and a guanine), is highly prevalent in affected Ashkenazi Jewish women, and is present in approximately 1% of the female Ashkenazi Jewish population. Another prevalent alteration is 5382insC (insertion of a cytosine).

BRCA2 is located on chromosome 13q12-13 and also encompasses an array of over 900 known mutations. A particular mutation of *BRCA2* (6174delT; deletion of a thymidine), present in 1 in 40 Ashkenazi Jews, is one of the three most common *BRCA1* or *BRCA2* mutations. In the Icelandic population, most familial breast and ovarian cancers are associated with *BRCA2*, rather than *BRCA1* mutations. A particular mutation, 999del5, excessively occurs in Icelanders. Research suggests that there may be an association between the location of a mutation and the degree of risk. Further studies will help to elucidate this information and make counseling more accurate as ethnic specific data are reported in large sample sizes by researchers.

So, what is the risk of developing various cancers in persons with mutations in *BRCA1* and *BRCA2*? For females carrying a mutated *BRCA1*, the lifetime risk of developing breast and ovarian cancer has been widely variable over the years due to differences in study populations. It is likely that these estimates will continue to evolve as new information is uncovered. This highlights the importance of consulting the most recent data available for the population of interest. Other genetic factors, some of which remain unknown, also appear to influence risk. Currently, the lifetime breast cancer risk for a woman with a *BRCA1* or *BRCA2* gene mutation has been estimated at 50% to 85%. More recent studies tend to be closer to the lower end of this range.

The risk of prostate cancer for male carriers of *BRCA1* or *BRCA2* mutations is increased fourfold over the general population, and the risk of colorectal cancer (CRC) is increased fourfold for both males and females. Men with *BRCA2* mutations have an estimated 6% risk of developing breast cancer. Men who inherit one or both of these gene mutations have a lifetime risk of 5% to 10% (*BRCA1*) and 1% to 2% (*BRCA2*). The lifetime ovarian cancer risk for a woman with a germline *BRCA1* mutation is approximately 16% to 44%. Women with *BRCA1* mutations have a 25% to 30% risk of developing breast cancer in the contralateral breast within 10 years of an earlier breast cancer diagnosis. For women with *BRCA2* mutations, the lifetime risk of ovarian cancer is estimated at 10% to 27%. At this time, genetic testing can be done for a selection of the known mutations; however, it is not available for all of the possible identified mutations (more than 2,000).

The *BRCA1* and *BRCA2* genes are inherited in an autosomal dominant manner. Thus, a daughter of a man or woman with a mutated gene has a 50% chance of inheriting that gene mutation. However, inheritance of the gene does not mean the person will definitely develop cancer; it simply increases one's risk. It is very difficult to predict which mutation carriers will develop cancer, and if so, which types of cancer. It is important to note that some women who have early breast cancer as well as a positive family history do not possess a *BRCA1* mutation, and some women who have this mutation fail to exhibit a strong family history. Developing cancer at a young age has been found to be an important predictor. However, other genetic and non-genetic risk factors play a role and should be accounted for in individual risk assessments. These include a young age at menarche, a body mass index above 35, high intake of dietary fat, alcohol consumption, and heavy, long-term smoking started at an age prior to the woman's first pregnancy. Thus, developing appropriate guidelines to offer population-based genetic screening and testing for *BRCA1* or *BRCA2* remains challenging. Prenatal genetic diagnosis is now available for susceptibility to certain cancers, including certain *BRCA1* and *BRCA2* mutations.

Prostate Cancer

The public health burden of prostate cancer is substantial. A total of 220,800 new cases and an associated 27,540 deaths are anticipated in the United States in 2015. Prostate cancer is the second leading cause of cancer death in men, exceeded only by lung cancer. The three most important risk factors for prostate cancer are age, ethnicity, and family history. Under the age of 40 years, prostate cancer is rare. Fifty-six percent of prostate cancer occurs in men over the age of 65, with a 2.8% added risk each additional year. The probability of being diagnosed with prostate cancer is 1 in

298 among men 49 years or younger; 1 in 43 among men aged 50 through 59 years; 1 in 16 among men aged 60 through 69 years; and 1 in 9 for men aged 70 years and older. The overall lifetime risk of developing prostate cancer is 1 in 7. Japanese men have a very low rate of this disease, while African American men living in the United States have a 60% higher incidence compared to White men.

Among men who have been diagnosed with prostate cancer, those with a family history of CRC, bladder cancer, or chronic lymphoid leukemia are at an increased risk of developing one of these as a second, primary cancer. A familial pattern can also be attributed to genetic mechanisms in other hereditary cancer syndromes and nongenetic factors such as use of endogenous hormones (androgens and estrogens), dietary risk factors (fat and red meat), a history of cigarette smoking, and poor access to health care. The relative risk for developing prostate cancer among family members with a history of the disease varies from 3.3 to 4.6, depending on the population specific data. Risk appears to be greater among brothers with prostate cancer compared to men with affected fathers. The incidence of multiple primary cancers increases in men diagnosed under the age of 50 years (Table 11.6).

Many types of epidemiologic studies (case control, cohort, twin, and family) strongly suggest that prostate cancer susceptibility genes exist in the population. A family history of prostate cancer increases one's risk for the disease. Prostate cancer risk is known to accompany some hereditary cancer syndromes such as Lynch syndrome and with mutations in the *PTEN* and *BRCA* genes. Inheriting a *BRCA1* gene mutation confers susceptibility to breast, pancreatic, testicular, and early-age-onset prostate cancers. Men with a family history of both breast and prostate cancer are known to have a higher risk.

TABLE 11.6 Relative Risk (RR) Related to Family History of Prostate Cancer

| Risk Group | RR for Prostate Cancer (95% CI) |
|--|---------------------------------|
| Brother(s) with prostate cancer diagnosed at any age | 3.14 (2.37–4.15) |
| Father with prostate cancer diagnosed at any age | 2.35 (2.02–2.72) |
| One affected FDR diagnosed at any age | 2.48 (2.25–2.74) |
| Affected FDRs diagnosed <65 years | 2.87 (2.21–3.74) |
| Affected FDRs diagnosed ≥65 years | 1.92 (1.49–2.47) |
| Second-degree relatives diagnosed at any age | 2.52 (0.99–6.46) |
| Two or more affected FDRs diagnosed at any age | 4.39 (2.61–7.39) |

Abbreviations: CI = confidence interval; FDR = first-degree relative.

Source: Kiciński, Vangronsveld, and Nawrot (2011).

In 1992, segregation analysis studies suggested that familial clustering of prostate cancer has a strong hereditary component for almost 50% of men diagnosed at the age of 55 or younger. Genetic studies have determined an autosomal dominant pattern of inheritance. Although the specific genetic mechanisms of prostate cancer are not completely understood, multiple candidate germline mutations have been implicated. Most recently, researchers have discovered that a rare but recurrent mutation variant located on chromosome 17q21-22 in a *HOXB13* (*G84E*) gene recurs in early-age-onset prostate cancer (under 50 years of age). This gene mutation affects a transcription factor that leads to disease development. Genetic researchers have begun to offer insight into the genetic basis of the disease, which may have clinical implications for families.

Colorectal Cancer (CRC)

CRC is the third most common cancer in the United States; in 2015, there were 93,090 cases of colon cancer and 39,610 cases of rectal cancer. CRC may be due to epigenetic or germline mutations that can lead to cancer development in varying degrees of frequency. The most common inherited CRCs are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome; see Table 11.5a).

FAP is a relatively rare, autosomal dominant condition caused by a germline mutation that leads to inactivation of the adenomatous polyposis coli (*APC*) gene located on chromosome 5q. *APC* is a tumor suppressor gene that functions as a regulatory gatekeeper for colorectal epithelial cells. When mutated, hundreds to thousands of colon tumors develop and can progress to malignancy. Penetrance is very high for this mutation at nearly 100%, and it accounts for approximately 1% of all colon cancers. A variety of other mutations may also occur in *APC*. A specific mutation, 11307K, has been found in about 6% of Ashkenazi Jews, thus indicating one group where targeted population screening would be useful. Multiple colon polyps are common and can be seen as early as 8 years of age, but typically present in late adolescence or young adulthood. Gardner syndrome is a variant of FAP that tends to have a wider spectrum of extraintestinal findings, such as desmoid and soft tissue tumors and osteomas. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a common extracolonic manifestation in FAP. Other manifestations include dental and skeletal anomalies, hepatoblastoma, adrenal carcinoma, and papillary thyroid cancer.

MUTYH genes normally involved in base pair excision repairs are now known to be involved in CRC. *MUTYH*-associated polyposis (MAP) is correlated with a *MUTYH* gene mutation that results in multiple, adenomatous polyps and colon cancer. Individuals with multiple (10–99) colon adenomas (MCA) have increased risk for CRC and are candidates for risk-reducing colectomy or frequent colonoscopy surveillance, particularly if genetic testing confirms a predisposition. Genetic testing is recommended before *APC* gene mutation testing or with a negative result. Inherited mutations in the *APC* and *MUTYH* genes predispose to 15% to 20% of MCA, and testing is particularly important for at-risk relatives once a gene mutation is identified in a family. Other relatively rare single gene disorders may be associated with CRC, as shown in Table 11.5a, but for most CRCs the etiology is unknown.

Researchers are investigating epigenetic influences on CRC including diet, the gut microbiome and disease risk due to infectious agents, and environmental exposure from foods that modify molecular pathways that impact epithelial cells involved in polyposis. The epigenetic mechanisms of DNA methylation and histone multiple colon adenomas modification are under investigation to elucidate the molecular pathways of micronutrients that may promote or inhibit colonic cancer formation and development.

Chromosome Changes and Genetic Influences in the Leukemias, Lymphomas, and Other Cancers

Specific, nonrandom chromosome changes have been reported in most of the leukemias and lymphomas. Chromosome changes may involve gain or loss of a whole or part of a chromosome, translocations, inversions, or other changes alone or in combination (Table 11.5a and 11.5b). In many cases, the genes associated with these chromosome changes and their expression profiles are now being elucidated. The major result of chromosome aberrations is usually oncogene activation, often because the gene for a T-cell receptor, antigen receptor gene, or immunoglobulin (Ig) is relocated near it or because a fusion gene is created that may encode and affect transcription factors. The fusion protein that is created appears to be particularly important in solid tumor development. These fusion proteins are considered tumor-specific antigens and may eventually be utilized as therapeutic targets.

Testing for chromosomal aberrations specific to leukemias and lymphoproliferative disorders can be used for the following:

- ▶ Diagnosis—for example, identifying a clonal chromosomal aberration in a myeloproliferative disorder such as polycythemia vera can be used to distinguish it from a non-neoplastic reactive proliferation
- ▶ Following the natural history of a disorder—for example, to predict blast crisis in chronic myelogenous leukemia (CML)
- ▶ Establishing a prognosis—for example, in AML, a chromosome 16 inversion or a t(8;21) translocation is associated with a relatively good prognosis, while a t(9;22) translocation appears to carry a poorer outcome
- ▶ Selecting and monitoring chemotherapy for efficacy and resistance—for example, in adult ALL, t(1;9) carries a poor prognosis; also in ALL, patients with t(15;17) are treated with retinoic acid while those with t(8;21) and inv16 are treated with high-dose cytarabine
- ▶ Predicting or establishing remission or exacerbation—early relapses can be detected with certain cytogenetic abnormalities, permitting prompt changes in therapies

More than 90% of patients with CML have a specific chromosome marker in bone marrow cells, known as the Philadelphia (Ph) chromosome. Ph represents a translocation of genetic material from chromosome 22 to chromosome 9, noted as t(9;22). The *BCR-ABL* fusion gene and its protein products increase tyrosine kinase

activity. The new gene relationship is detected even in CML without detectable cytogenetic rearrangement. The $t(9;22)$ is also seen in about 15% of cases of ALL, rarely in AML, and in about 5% of cases of acute nonlymphocytic leukemia (ANLL). Identification and understanding regarding this process in CML has led to the development of a pharmacological treatment, imatinib mesylate, which is a *BCR-ABL* tyrosine protein kinase inhibitor. In CLL, gene expression profiling revealed that expression of the *ZAP-70* gene distinguished (with 93% accuracy) those who had relatively stable disease from those with progressive disease that required early treatment.

Another example of a well-described chromosomal rearrangement is in Burkitt lymphoma, a B-cell malignancy. Three major translocations have been identified in this cancer; one, translocation $t(8;14)(q24;q32)$ predominates in 75% to 90% of cases. The $t(8;14)$ translocation involves the relocation of the *MYC* gene to the site of the gene for the heavy chain of Ig, resulting in oncogene activation.

EPIGENOME BIOCHEMICAL MODIFICATIONS IN CANCER ETIOLOGY

Inherited and acquired epigenetic modifications arise in somatic cells as a result of a variety of factors including:

- ▶ Viral (RNA) or bacterial (DNA) invasion of human DNA
- ▶ Toxic chemicals or radiation
- ▶ Lifestyle factors that increase risk, such as alcohol or tobacco use
- ▶ Physical inactivity or obesity
- ▶ Use of certain medications (such as exogenous hormones)
- ▶ A deficiency of protective dietary micronutrients normally involved in anti-inflammatory or antioxidative activities, molecular cell signaling, growth, cohesion, and apoptosis

All cancers involve epigenetic alterations that are either inherited through the germline or arise in somatic cells located within specific body tissues. In order to understand environmental exposure and the associated cancer disease risks in human populations, researchers are currently in pursuit of epigenetic clues regarding the interaction between genes and the environment. Discovery of epigenetic biochemical patterns associated with disease has provided hope for identifying biomarkers for early screening, diagnosis, and evaluating the effectiveness of cancer treatment.

Two types of cancers, namely lung and bladder cancer, are discussed in the following sections in order to illustrate the effects of toxic insults to the human epigenome. Occupational hazards have been identified as posing the greatest risk, especially in those who also smoke cigarettes. Emerging epigenetic studies have shown that the carcinogenic potential of some heavy metals induces epigenetic changes such as silencing of DNA repair and tumor suppressor genes via DNA methylation. Toxic metals known to be associated with carcinogenesis include

cadmium, chromium, lead, mercury, and arsenic, which can be present in natural and man-made materials.

Lung Cancer

Nonsmall cell lung cancer (NSCLC) accounts for approximately 70% of lung cancer diagnoses. In 2015, lung cancer in the United States was the leading cause of death among all cancers for both men and women, accounting for approximately 158,040 deaths in 2015. Early stage diagnosis increases the 1- to 5-year survival rate to 54%; however, most lung cancers are not symptomatic until late stages. Cigarette smoking is by far the most important risk factor. Quantity, as well as duration, of smoking imposes a measurable dose effect that correlates to risk. Occupational risks or environmental exposures include second-hand smoke, asbestos, and radon gas from the ground, certain metals (chromium, cadmium, and arsenic), some organic chemicals, radiation, and air pollution, such as diesel exhaust. Exposures are associated with specific occupations, most prominently chimney sweeping, rubber manufacturing, paving, roofing, and painting.

The two main forms of NSCLC, adenocarcinomas and squamous cell carcinomas, are associated with tobacco smoke. Unfortunately, smoking cessation reduces but does not eliminate the risk. Whenever possible, the tumor tissue from patients with NSCLC should be evaluated for an epithelial growth factor receptor (EGFR) and for anaplastic lymphoma kinase (AKL), which are observed in 15% and 4%, respectively. EGFR confers a favorable prognosis and strongly predicts sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib, and afatinib. In the case of positive testing for *AKL* fusion genes arising from a translocation, the patients are younger and nonsmokers. Oncogenic *RAS* mutations are known to alter cellular function by disrupting signaling pathways, leading to cell proliferation and inhibition of cell death within tumors.

In terms of epigenetic cancer research, investigators have identified several genes in NSCLC tissue that demonstrate DNA hypermethylation (Table 11.5c) in numerous tumor suppressor loci, with particular investigation of *CDKN2A* and *RASSF1* genes. Recently, panels of candidate genes have been assembled from genome-wide association studies in an attempt to determine the molecular profile of epigenetic alterations in lung cancer and to identify biomarkers of clinical utility.

DNA methylation of tumor suppressor genes is a normal process of transcription regulation but it remains largely unregulated in cancerous cells. Approximately one half of all genes contain regulatory CpG islands. In cancer tissue, clusters of CpG islands are hypermethylated and result in gene silencing. Hypermethylation of the CpG island regions are excellent targets as biomarkers for the developing lung cancer and for selecting targeted therapies.

Bladder Cancer

In 2015, 74,000 new cases of urinary bladder cancer are expected. This type of cancer affects men more frequently than women; the lifetime risk of developing this disease is 1 in 26 for men and 1 in 90 for women. Caucasians are twice as likely to be diagnosed

compared to African Americans. The average age of diagnosis is 73 years. In about 50% of cases, the initial diagnosis is noninvasive or in situ cancer, due to blood in the urine and pain and frequency of urination.

Cigarette smoking is known to be a key risk factor for bladder cancer and increases the risk by fourfold. Workers who are cigarette smokers and also exposed to occupational toxins over long periods of time are at the highest risk for bladder cancer. Over 40 types of occupations have been associated with increased risk of bladder cancer including:

- ▶ Automotive mechanics
- ▶ Plumbers (before 1960)
- ▶ Computer systems analysts
- ▶ Information clerks
- ▶ Horticulturalists
- ▶ Landscape workers (pesticides)
- ▶ Cleaning and building services workers
- ▶ Leather manufacturers
- ▶ Those working in electronic component services
- ▶ Transportation equipment manufacturers
- ▶ Textile (cotton and wool) industry workers
- ▶ Health services industry workers

According to cancer epidemiologists from the National Cancer Institute (NCI) using large population datasets from workers in northern New England, researchers determined that the evidence for increased risk for bladder cancer is compelling. Workers employed in metal and plastic precision machining that requires complex chemical mixtures in the metalworking fluids are at the highest risk. These individuals repeatedly handle petrochemical products such as oils (mineral oil and semisynthetic fluids) and water with organics and additives as they work with a variety of metals. These substances are known to contain bladder carcinogens.

SUMMARY

Even with rapid advances in genome technologies to investigate and identify the causative mechanisms involved in cancer, the single most important tool for understanding cancer risk in a family is to conduct a cancer risk assessment and to document a detailed, three-generation family medical history and draw a pedigree. This valuable tool is readily available to every nurse and reveals emerging patterns of genetic and environmental influences on cancer susceptibility and development. Selective examples of pediatric and adult cancers are described in detail to enable the nurse to understand hereditary and acquired genetic mechanisms in cancer that involve single gene mutations, chromosomal rearrangements, and epigenetic biochemical modifications.

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CHAPTER 12

Genetic Elements of Behavioral Disorders

Christine E. Kasper

The genetics of cognitive abilities, mental functioning, social attitudes, psychological interests, psychiatric disorders, learning disorders, behavior, addiction, mood, and personality traits have long been of interest to geneticists. This interest has been complicated by the complexity of brain function as well as the social, ethical, legal, and political implications of research in this area. Also complicating the study is the tendency for such conditions to be too broadly defined, thus perhaps diluting the gene associations. For example, it is more fruitful to look for a specific type of genetic variation connected with a more narrowly defined communication disorder such as expressive, mixed, phonologic, and so on, rather than the broadly used term. Genomic research into the various psychiatric and behavioral disorders has rapidly progressed and it is now evident that the precision of genomic findings does not clearly match standard behaviorally based systems such as the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. In reality, behavioral disorders are more akin to continuums of genetic, cognitive, behavioral, personality, and environmental factors rather than a one-gene–one-disease phenomenon. The recognition that clinical diagnostic categories do not correlate with the biology of behavioral and psychiatric illnesses represents a new and radical change in this field of study. To this end, the National Institute for Mental Health (NIMH) has developed a new framework based on genomic findings that should flexibly expand as new research clarifies the underlying biology of mental health illnesses. The Research Domain Criteria (RDoC) project of the NIMH seeks to “Develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures” (National Institute of Mental Health, 2015). RDoC uses cutting edge research approaches in genetics, neuroscience, and behavioral science to study the problems of mental illness, studied independently from the classification systems by which patients are currently grouped. While rapidly progressing, the RDoC remains at this time a framework of psychiatric classification to guide research rather than one for immediate clinical use. However, the classification of behavioral and psychiatric disorders into groups based on genetics and similar traits between groups points clearly to these disorders having similar biologic origins and manifesting as more of a continuum of disorder from fundamental behavioral components

rather than discrete clinical phenomena. RDoC also seeks to study the full range of variation, from normal to abnormal, as well as using genetics and brain imaging point to the biological measures that will help explain the heterogeneity of symptoms. It is anticipated that important translational and interdisciplinary work of this nature will soon transform clinical practice in the fields of behavior and psychiatric disorder by leading to precision diagnoses.

GENETICS AND MENTAL HEALTH

The observations that disorders affecting mental health and behaviors tend to run in families have been historically claimed as support for genetic contributions to illness. Biological families tend to share their genes, their cultural heritage, and their living environment, which includes similar exposure to pathogens, diet, stressors, toxins, dynamic family interactions, patterns of behavior, and other parameters. Given recent research and genomic studies by the NIMH at the National Institutes of Health, we now know that this is true for some psychopathology. Disorders known to be due to a single gene error (e.g., Lesch–Nyhan syndrome), uniparental disomy (e.g., Prader–Willi syndrome), or a chromosomal variation (e.g., Klinefelter syndrome) can have effects manifested in terms of behavior. There has been increasing recognition of patterns of behavior that accompany some genetic disorders, and the term *behavioral phenotype* has been applied to these. These can provide genetic leads to areas for further exploration of chromosome and gene areas that may be responsible for certain behaviors. Their external environment can modify many genetic disorders, so that behavioral effects may or may not be apparent (e.g., phenylketonuria when phenylalanine is restricted). In multifactorial disorders, a model for the interaction of genes and environment is already present. These environmental influences are important in conditions such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). In both PTSD and MDD, prolonged stress conditions influence epigenetic regulation of neuronal gene transcription and the methylation of genomic DNA near key stress-response genes, which may influence stress vulnerability and resilience.

As previously discussed, the initial establishment of the broad categories of classical schizophrenia and affective, bipolar, or manic depressive illness was largely based on descriptive symptoms. These categories have been further subdivided over time, but they still represent somewhat heterogeneous subtypes that may, as in diabetes mellitus, represent more than one disease and etiology with different inheritance mechanisms. Previously, varying differences in nomenclature and in what was included in “schizophrenia” over the years have made genetic study and interpretation difficult. The major evidence for the role of genetic factors in schizophrenia and the mood disorders (MDs) originally came from family studies, twin studies, adoption studies, and biochemical analyses. More recently, genetic modeling, linkage, whole-genome linkage and association studies, proteomic approaches, whole-network gene expression studies, and other molecular genetic techniques are being used to understand the genetic contribution. Most of these early studies and techniques suffered from methodological problems, but nearly all of them documented some type of genetic component. At this time, however, the exact nature of the genetic contribution to the major mental disorders remains incomplete; however, significant advancements

in research are rapidly pointing to the genetic and biologic underpinnings. Another way in which genetic contribution has been studied is by examining drug action and effects on psychiatric disorders and using that information to examine gene variations that might be relevant.

Nurses practicing in the mental health area are integral to documenting and supporting families and individuals with behavioral-related genetic issues. Counseling and therapy skills related to issues surrounding the diagnosis of a family member with a genetic disorder, whether it is a birth defect in an infant or another type of disorder in the adult, include feelings of shock, denial, stigma, guilt, depression, and anger. Genetic testing and treatment decisions, coping with the results, and deciding who and how to tell about the results are some of the psychological and interpersonal issues in which services may be needed.

Early-Onset Alzheimer Disease (EOFAD)

Early-onset Alzheimer disease (EOFAD) tends to cluster in families, often over several generations, and can be considered a familial disease; thus, it is inherited in an autosomal dominant manner. Mutations in one of three genes have been linked to some cases of EOFAD. Online Mendelian Inheritance in Man (OMIM) lists these genes as the amyloid precursor protein (*APP*) gene and two presenilin genes (*PSEN-1* and *PSEN-2*). Those carrying any of these rare mutations tend to develop EOFAD during their fourth and fifth decades. Currently, 5% of a total 5 million cases of Alzheimer disease is classified as EOFAD.

Late-Onset Alzheimer Disease

Late-onset Alzheimer disease is the predominant form of Alzheimer disease and its genetic inheritance is more complex. A number of genes have now been identified, which may contribute to the chances of developing late-onset Alzheimer disease. The symptoms of Alzheimer disease are dementia beginning with loss of memory and progressing in severity to incapacitation. Other symptoms include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Typically the clinical duration of the disease is 8 to 10 years.

The three forms of apolipoprotein E (*APOE*) gene, *APOE e2*, *APOE e3*, and *APOE e4*, have been found to have the greatest influence on the disease and are found on chromosome 19. Further genomic studies have found additional genes, which are linked to increased risk, called *CLU*, *PICALM*, *CRI*, *BIN1*, *ABCA7*, *MS4A*, *CD33*, *EPHA1*, and *CD2AP*. Variants in these genes are linked to different risks of Alzheimer disease; however, they have a much smaller effect on the disease than for *APOE*. Teams of researchers have joined together to form the International Genomics of Alzheimer's Project to conduct the largest genetics study of Alzheimer disease to date, and to provide further insights into the inheritance of the condition.

SCHIZOPHRENIA

According to the American Psychiatric Association's *DSM*, schizophrenia is a psychotic disorder that "lasts for at least 6 months, and includes 1 month of active

phase symptoms (i.e., two [or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms)” (Tandon et al., 2013). Subtypes include paranoid, disorganized, catatonic, undifferentiated, and residual. In addition, schizoaffective disorder is a disturbance in which symptoms of schizophrenia and an MD occur together. The worldwide prevalence is about 1%. Some estimate that schizophrenia has heritability at about 80%, but unequivocal single genes have not yet been identified.

The major issues in studies include whether pure schizophrenia has been analyzed or whether the clinical spectrum of schizophrenic disorders has been included. At least 40 family and twin studies have been conducted. The essence of these studies is the consistent finding that there is a higher prevalence of the respective illness among blood relatives. Those studies that have compared the concordance of monozygotic (MZ) twins for schizophrenia with that of dizygotic (DZ) twins have found in all cases that the concordance rate for MZ twins is higher than for DZ twins. Although the exact rates have varied from study to study, these findings provide support for a heritability component. Overall concordance rates have varied from 35% to 92% in MZ twins and from 7% to 26% for DZ twins, with an overall pooled rate of 45.6% for MZ and 13.7% for DZ. High concordance rates appear to be associated with severity of the illness. The age of the onset of illness shows greater association between twins than would be expected by chance. In both groups, twins who have lived apart generally show similar concordance rates to those who have been raised in the same environment.

General conclusions from adoption studies reveal that children born of schizophrenic parents developed schizophrenia at significantly higher rates than did adoptees born of normal parents. Biologic relatives of those adoptees who developed schizophrenia had higher rates of schizophrenia and suicide than did the adoptive relatives and the biologic and adoptive relatives of adoptees who did not become schizophrenic. Adoptees born of normal parents but raised by schizophrenic adoptive parents did not show an increase in schizophrenia. In order to rule out the intrauterine environment or early interaction with a schizophrenic mother, some researchers studied paternal half-siblings. These half-siblings had the same biologic schizophrenic father but a different biologic mother. The increased incidence of schizophrenia found was interpreted as ruling out early maternal influences.

More recent studies have looked at the candidate gene approach or linkage, often focusing on genes or markers having pharmacologic, immunological, and biochemical associations. Based on these, some of those explored have been the gene for catecholamine methyltransferase, which metabolizes the neurotransmitters dopamine, epinephrine, and norepinephrine, as well as both receptors and transmitters for these and for gamma aminobutyric acid (GABA), serotonin, and monoamine oxidase. Other promising candidate genes for susceptibility include neuregulin (*NRG1*), dysbindin (*DTNBP1*), *G72/G30* gene complex, *RGS4* (the regulator of G-protein signaling-4), proline dehydrogenase (*PRODH*) disrupted in schizophrenia 1 (*DISC1*), the gene encoding phosphodiesterase 48 (*PDE48*), and catechol-O-methyltransferase (*COMT*). Many of these are located in chromosomal areas that are linked to schizophrenia. Molecular and mapping techniques have been

used. Newer strategies such as microarray technology to examine gene expression appear promising. At present, the most promising information appears to be an association or linkage for schizophrenia with the following chromosomal sites: 1q21-22, 6p22-24, 6q21-22, 8p21, 10p11-15, 13q32, and 22q11-13. A subtype of schizophrenia, periodic catatonia, was also found to be associated with chromosome 15q14. In the case of chromosome 22, chromosomal microdeletions in chromosome 22q11.21-q11.23 may increase susceptibility. A known genetic syndrome, velocardiofacial syndrome (an autosomal recessive disorder with cardiac anomalies, learning disabilities, and cleft palate, also known as DiGeorge syndrome, discussed in Chapter 9), which is associated with small deletions in chromosome 22q11, includes about 10% who develop psychiatric disorders such as chronic paranoid schizophrenia. A candidate for a susceptibility gene on 22q12-13 is the A2a adenosine receptor, one of the receptors mediating central nervous system effects of adenosine, which showed linkage to schizophrenia in some persons.

Another area of investigation for etiology is unstable tandem repeat expansion (Chapter 4). In at least some cases, anticipation (the appearance of more severe disease progressively earlier in successive generations) and a parent-of-origin effect has been noticed in schizophrenia, giving credence to the possible involvement of unstable tandem repeat nucleotide expansion in etiology. A theory that has had a resurgence of interest is that of events that disrupt neurodevelopment, and thus result in schizophrenia, such as Rh incompatibility and severe nutritional deficiencies. Advanced paternal age has also been associated with a higher risk for adult schizophrenia, perhaps due to de novo paternal mutations. Despite evidence for some yet unknown genetic basis for schizophrenia, environmental disturbances appear to be needed for ultimate expression.

Bipolar disorder (BD) and schizophrenia have been recognized as the most heritable common psychiatric disorders. Due to the wide heterogeneity of these diagnostic groups, identification of genes causal for susceptibility has not been straightforward. In recent years, there has been significant progress in the identification of common genetic risk factors for both BD and schizophrenia. Each gene by itself has a small effect on risk; certain chromosomal copy number variants (CNVs) are rarer, but have a larger effect on risk. Genome-wide association studies (GWAS) of schizophrenia and BD have recently found evidence for association to specific risk loci, specifically for the zinc finger binding protein 804A (ZNF804A) locus in schizophrenia and for the calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C) and ankyrin 3, node of Ranvier (ANK3) loci in BD. The commonality of the ZNF804A and CACNA1C loci to influence risk for both disorders supports the hypothesis that schizophrenia and BD are not etiologically distinct. This is one of the early studies that points to common mechanisms between psychiatric disorders.

Common genetic changes have also been demonstrated between autism, *attention deficit hyperactivity disorder* (ADHD), BD, major depression, and schizophrenia. These five diseases were previously believed to be distinct. Significant illness-associated genetic variation was found, including variation in two genes that code for the cellular machinery regulating the flow of calcium into neurons: *CACNA1C* and *CACNB2*. *CACNA1C* is known to impact brain circuitry involved in emotion, thinking, attention, and memory, which are disrupted in psychiatric illness. The

identification of these common genes points to the possibility of a fundamental biologic mechanism in these disorders.

MOOD DISORDERS

The mood disorders (MDs, formerly described as affective disorders) may consist of depressive disorders, BDs, and MDs secondary to a general medical condition or substance induced. They may affect at least 1% of the population. In many of the classic family, twin, and adoptive studies, results were reported in terms of unipolar illness (UP) or bipolar illness (BP). It has been proposed that there may be three distinct BP subgroups defined by age of onset with an early, middle, and late (over age 50 years) onset that might vary etiologically. In BP patients, first-degree relatives had a higher incidence of affective illness than those of UP patients, but both were higher than in the general population. If the index patient has BP disease, the risks to relatives are higher than if the index patient has a UP disease state. Moreover, 80% to 90% of patients with BP disorders have a family history of an affective disorder, and 50% of UP patients have a family history of a UP disorder, with few having any BP disease. They believe that a family history of BP disorders is important in diagnosis of an individual with depression. There are more female relatives affected than male relatives. This may represent a sex-influenced gene or a sex-related liability threshold as seen in congenital hip disease. Twin studies over time reveal the potential of a hereditary component, and have been reported at about 70% for MZ twins and 20% for DZ twins. Concordance in MZ twins increases with the severity of the proband's illness.

Some adoption studies have been reported for the affective disorders. These basically found an excess of all psychopathology in the biologic parents of the MD adoptees as compared to their adoptive parents. This incidence has been reported as similar to that of the biologic parents of MD persons who were not adopted. The most important finding of the adoption studies is that the incidence of mental illness paralleled that of the biological relatives of the adoptee rather than the adoptive relatives.

Although biochemical and immunological studies have been investigated, linkage and molecular studies have been the most recent approaches. These have focused on susceptibility regions on chromosomes and on certain biochemical polymorphisms. The latter have included disturbances in dopaminergic and noradrenergic transmitter systems, serotonin 2A receptor (*HTR2A*) gene polymorphisms, GABA, and the glutaminergic pathways. Gene expression arrays offer new ways to look for associated differences in gene expression. Past reports of linkages in regard to chromosomes have been in conjunction with the X chromosome and chromosomes 11 and 21 but have been difficult to substantiate. An observed excess of females in MDs suggested X chromosome associations. Various studies have had contradictory findings, and a gene on the X chromosome may represent at least one susceptibility gene. The most significant linkage associations with chromosomal areas for BD currently are as follows: 4p15-16, 9p22, 10q11, 12q23, 13q32, 14q, 18p11.2, 18q12, 18q22, 21q22, and 22q11-12. Recent approaches to depression consider it as a complex

and multifactorial trait with newer ideas about the mechanisms behind it, which then suggest different candidate genes that could be investigated in a systematic way. The expansion of unstable tandem repeats has also been suggested as an etiology. In one family, Darier disease (an autosomal dominant skin disorder) has been shown to be associated with bipolar illness.

Major Depressive Disorder

Major depressive disorder (MDD), or unipolar depression, is a serious psychiatric condition that is estimated to affect at least 350 million diagnosed patients and their families in the world and is associated with significant disability, poor quality of life, psychosocial impairment, morbidity, and mortality. About 25% of diagnosed cases are under 19 years old. Currently, approximately 40% of those with MDD do not respond to psychopharmacologic therapy. In addition, relapse following a positive response to medication without remission is common. Only about 40% of medicated patients achieve remission. This is not surprising given the lack of understanding of the biologic mechanisms underlying MDD. Despite ongoing genetic analysis and identification of risk variants, the causes of MDD remain elusive. However, some progress has been made in determining the metabolism and response of individuals to certain psychotropic drugs. Specifically, cytochrome P450 and pharmacodynamic genes related specifically to the serotonin system are tested to determine the rate of drug metabolism. Clinical testing of these genes is now commercially available to aid in the selection of individual specific psychotropic drugs.

BEHAVIOR AND GENETICS

The field of behavioral genetics is complex and interesting. It is reasonable to suppose that there are genetic influences on parameters such as behavior as one considers the genetic influence on structural determination and patterning of anatomical configurations or of the regulation of neurotransmitters, for example. Many of the investigations have been carried out in animal models because of problems in studying human populations, which have been difficult because of the belief that finding a genetic component to a behavioral trait means that the trait is immutable. Rather, such traits can be molded and are indeed shaped by environmental influences. Often, understanding the genetics can lead to treatment advances. For example, persons with some types of dyslexia have responded to particular educational approaches that improve outcome. Distinct reading phenotypes may each be linked to different chromosomal regions. Mutation in the gene *FOXP2*, located on chromosome 7, which encodes a transcription factor, leads to a rare speech and language disorder. In addition, a duplication of a segment in the long arm of chromosome 7 (7q11.23) contains many genes but also corresponds to a deletion in the same region found in the Williams (also known as Williams–Beuren) syndrome, which is a neurodevelopmental disorder with short stature and strong expressive language skills in addition to other features. More often, multiple genes are believed to be involved, with environmental influences as well. Genome-wide scans have identified regions on chromosomes 2, 13, 16, and 19 that may influence speech and language disorders.

A recent finding in dyslexia is that about 17% had a deletion in a stretch of DNA in a gene known as Doublecortin Domain Containing 2 (*DCDC2*).

In one large family, a defect in the gene for monoamine oxidase A (MAOA) leading to deficiency resulted in an X-linked recessive mild mental retardation and a pattern of aggressive, impulsive, and violent behavior, including arson and exhibitionism. This disorder has been named Brunner syndrome. An animal model has also shown the association between deletion of the gene encoding MAOA and aggression in males. In animals, there are many examples of behavioral genetics. For example, ants can manipulate gene expression in developing juveniles so that some larvae that would have become docile workers are stimulated to become aggressive soldiers in response to a threat. A gene that controls social interactions has been found in mice. Dogs maintain specific behavioral traits within breeds. For example, a Border Collie will maintain eye contact with humans. If put at birth with a type of dog that does not, the Border Collie will continue this trait, and if another breed is put with Border Collies at birth, it will not develop the eye contact behavior. The eye contact behavior is an example of how a genetically determined trait may influence behavior. People will respond differently to those who look directly at them as opposed to those who avoid eye contact, thus resulting in different interactions and experiences that shape development.

Persons with certain genotypes might create high-stress environments, thus increasing the probability of mental illness. A polymorphism in the dopamine D4 receptor gene (*DRD4*) that is related to novelty seeking has been reported. There has been considerable opposition to the genetic study of some traits such as aggression, intelligence, criminality, personality, and sexual orientation. In one well-publicized incident, a conference on genes and criminality was postponed for a considerable time because of political issues. However, there has been a recent resurgence in the influence of genes in virtually every realm of behavior, including social attitudes, psychological interests, and even such traits as divorce (by virtue of biochemical and personality systems) and religiousness. A recent twin study found that the heritability of cognition in elderly twins was 62%. Other conditions such as alcoholism, panic disorder, and dyslexia appear to have substantial genetic components. Discussion of these is beyond the scope of this text, however. Although it seems likely that many traits have some type of genetic component, how heredity and environment build on each other in complex ways is not understood. Understanding some of these aspects will make a real contribution to how we approach public policy issues.

Autism Spectrum Disorder

Autism is a pervasive developmental disorder that usually has its onset before 3 years of age. It is characterized by impairments in reciprocal social interaction and communication as well as preferred repetitive, stereotyped behaviors. It may include developmental delay, dysmorphic features, and epilepsy. Autism is more frequent in males. Several closely related disorders such as Asperger syndrome and disintegrative disorder are said to comprise autism spectrum disorders (ASDs). Although there are no biological markers for diagnosis, there are known genetic causes of autism, which include cytogenetically visible chromosomal abnormalities (approximately

5%), CNVs (i.e., submicroscopic deletions and duplications; 10%–20%), and single gene disorders in which neurologic findings are associated with ASD (approximately 5). Although observations suggest genetic effects, genome-wide linkage and candidate gene studies have shown a number of potential sequence variations. Variations in copy number have also been shown. These include 16p11.2 deletion syndrome, which can occur *de novo* or be transmitted in an autosomal dominant manner. It should also be noted that 16p11.2 deletions are seen in schizophrenia, BD, seizures, ADHD, and dyslexia. Another variation is the 15q13.3 deletion syndrome, which has been associated with cognitive disability, epilepsy, and ASD.

It appears that multiple small defects and variants combine to increase ASD risk. These studies provide strong evidence that the genetic basis of ASD is highly heterogeneous with hundreds of genes capable of conferring various degrees of risk. It should be noted that many of these genes are also risk factors for related neurodevelopmental disorders. Not all of these genes have a clear causal mechanism in ASD, such as regulators of chromatin modification and global gene expression. Others control for synaptic proteins: SHANKs, neuroligins, neurexins, and fragile X mental-retardation-associated proteins.

ALCOHOLISM, SMOKING, AND ADDICTION

Not everyone who uses recreational drugs, including nicotine from smoking, meets criteria for substance abuse disorder. Thus, while variation in drug metabolism, neuronal physiology, and other biological factors is recognized as important, other factors in development and from the environment play a role. A complete discussion of these complex conditions is not possible here.

Alcoholism has been investigated in twin studies and in adoption studies, and these have provided evidence of a genetic component. Complex disorders are difficult to study, and in alcohol dependence, end points and definitions have varied. However, in substance use disorders, genes explain up to 60% of the clinical disease. For example, items such as tolerance, acute intoxication, withdrawal symptoms, amount of alcohol consumed, and episodic versus steady consumption may be defined differently. Chief areas of interest have been variations in the gene for the mitochondrial aldehyde dehydrogenase (*ADLH2*), which converts an intermediate product of ethanol metabolism, acetaldehyde, to acetic acid. A mutation known as *ALDH2*2/*2*, and to a certain extent, the heterozygote, *ALDH2*1/*2*, results in elevated blood levels of acetaldehyde after ingesting alcohol, leading to a flushing reaction. Few with this genotype become alcohol dependent. In another example, the gene encoding the enzyme alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde, and variations in its subunits also affect alcohol dependence risk in various ethnic groups. Another gene of interest has been the dopamine D2 receptor gene. A large long-term study, the Collaborative Study of the Genetics of Alcoholism, is being carried out.

Smoking behavior is thought to have both genetic and environmental components. Evidence for genetic components comes from twin studies and from variability in nicotine metabolism. Environmental and social influences are also known to be

important, especially in the initiation of smoking. The common variant rs13273442 in the *CHRNA3–CHRNA6* region is associated significantly with nicotine dependence. A group of enzymes (see Chapter 6) known as cytochrome P450 (*CYP*) metabolizes nicotine to cotinine. Variations in the gene (*CYP2D6*) allow people to be poor, extensive, or ultrarapid metabolizers. People who metabolize nicotine more slowly appear less likely to become dependent, while those who are ultrarapid metabolizers may smoke more heavily to maintain their blood nicotine levels. Thus, while people may begin smoking for various reasons, becoming dependent may be related in part to metabolism. Polymorphisms of dopamine receptor genes, as well as genes encoding the opioid, cannabinoid, and glutamine receptors, may influence dependence on various drugs. Many of these genes interact with each other, influencing effects, as well as with the environment.

NURSES AND RISK REDUCTION

Nurses in this field may also be involved in assisting clients to decrease the psychological distress in individuals and families that may be associated with genetic testing, prenatal diagnosis, genetic screening, cancer risk assessment, genetic diagnoses, life adjustments, and genetic counseling. Nurses may do this in a number of ways depending on their preparation, including enhancing coping skills, stress and anxiety reduction, and providing actual counseling. For any client at risk, nurses may be able to intervene by maximizing positive environmental factors by providing or helping clients to find a supportive atmosphere and by providing access to ongoing counseling or development programs. Techniques for the reduction of stress and promotion of positive family interactions may also help to ameliorate effects due to genetic factors.

SUMMARY

Behavioral genomics is an area of intense interest and renewed research now using molecular methodologies and complex data analysis made possible by technological advances such as the study of gene expression through microarrays. As discussed earlier in this chapter, it is believed that the contribution of single gene mutations to overall behavioral genetics is relatively rare, although such contributions illustrate that abnormal behaviors can result from these mutations. It is more widely believed that in the vast majority of cases, multiple genes contribute to behaviors and that these are influenced by both environmental factors and genes that may not appear to be directly connected with behaviors. However, when subgroups for psychiatric disorders such as BD are examined by subcategories like early age of onset, there may be a greater contribution of single mutant genes similar to that found in diabetes mellitus.

Genetic analysis of various behavioral phenotypes, including personality, learning disabilities, and psychiatric disorders, is still a sensitive research area because of ethical, social, and legal concerns. Various societal and ethical concerns include the introduction of behavioral genetics in the courts (“my genes made me do it”) and their use in education and school settings, as well as in respect to employment. For

example, a gene variation may be associated with predisposition to a trait such as assertiveness. An employer might want to hire salespeople with predisposition for such a trait. In another theoretical situation, an employer might not want to hire employees with predisposition to a trait such as poor impulse control. It is expected that this area will grow in the future.

The occurrence of mental changes as side effects in drug therapy with agents such as corticosteroids, reserpine, amphetamines, methyldopa, and others that occur in some patients receiving them may uncover further information about the etiology of mental disorders and also identify susceptible subgroups in the population.

KEY POINTS

- ▶ What would be the implications of genetic testing for behavioral and personality traits if such were available? Discuss in terms of both policy and health care issues.
- ▶ Should the results of genetic testing for behavioral and personality traits be made available to school principals, school nurses, and teachers if a child is found to be genetically predisposed to a trait such as shyness or hyperactivity?
- ▶ What are the implications of genetic enhancement of personality traits or intelligence?
- ▶ Would you support or oppose the use of such genetic enhancement? Why or why not?

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CHAPTER 13

Ethical and Policy Issues in Clinical Genetics and Genomics

Leila Jamal

Since the completion of the Human Genome Project, advances in genetics and genomics have made DNA tests available for thousands of diseases in an expanding range of clinical settings, including preconception and prenatal care, pediatrics, oncology, neurology, and cardiology. These developments have increased the likelihood that a clinician will need to navigate the ethical and social issues associated with these tests. A better understanding will help the nurse clinician anticipate these issues and optimize the utility of genetic testing for patients while minimizing the risks.

This chapter focuses on the topics of eugenics, informed consent, genetic discrimination, privacy and confidentiality, direct-to-consumer (DTC) genetic testing, predictive genetic testing in children, and managing incidental findings from genome-wide sequencing. While issues related to ethics in research, human cloning, and transgenic plants are widely debated, they are less central to the work of a nurse clinician and are thus considered to be outside the scope of this chapter.

THE HISTORY OF EUGENICS

Eugenics refers to the improvement of a species through genetic manipulation. Positive eugenics seeks to accomplish this by increasing the frequency of traits considered desirable through encouraging selective mating and reproduction of those possessing such traits (the “fit”). Negative eugenics seeks to reduce the frequency of traits considered undesirable by preventing the reproduction of those persons possessing such traits (the “unfit”). Although plant and animal breeders have long practiced eugenics to improve crops and livestock, formal programs in humans began in the latter part of the 19th century.

The attempt to improve the genetic quality of the human species by “better breeding” developed as a worldwide movement between 1900 and 1940. It was particularly prominent in the United States, Britain, and Germany; in those countries, it was based on the then-new science of Mendelian genetics. Eugenicists developed research programs to determine the degree to which traits such as Huntington’s chorea, blindness, deafness, mental retardation (feble-mindedness). In 1910, the

Eugenics Record Office was established in Cold Spring Harbor, New York, with a major goal of preservation of the “racial welfare” of the United States through propagation of those whom they considered fit and prevention of propagation of those they considered unfit. Those considered fit were healthy, intelligent, affluent, Protestant individuals, of the upper or upper-middle class, with high moral character, and Anglo-Saxon or Nordic extraction. The characteristics were generally those possessed by the eugenicists themselves.

Although many proponents of eugenics were sincere in their intent to strengthen the human race and alleviate suffering, the movement was also a refuge for racial supremacists who came to dominate it. Genetics was used in an attempt to biologically justify the perceived inferiority of Blacks, Jews, Irish, and Southern and Eastern Europeans. The activities and influence of the eugenicists ranged from sponsoring blue ribbon baby contests at county and state fairs to the implementation of sterilization practices and the Immigration Restriction Act of 1924 (the Johnson Act). The latter restricted immigration to 2% of the number of each nationality listed in the 1890 Census, a year that was well before the mass immigration of persons from Southern and Eastern Europe.

Compulsory sterilization was seen as a way to prevent the propagation of the “unfit,” a term that in its various interpretations included the mentally retarded (now called “persons with intellectual disabilities”), the insane, alcoholics, orphans, paupers, derelicts, epileptics, diseased and degenerate persons, and even chicken thieves. Campaigns for eugenics sterilization laws were launched, although some enthusiasts were already performing sterilizations in state institutions. In addition to the institutionalized mentally retarded, involuntary sterilization abuses extended to those who were African American or poor.

The misuse and misunderstanding of genetic knowledge coupled with an emerging doctrine of racial superiority led to the denouncement of the movement by many geneticists and citizens. By the 1930s, the visible abuse of genetics and eugenics for totalitarian aims and the flagrant disregard for human rights were so evident in Nazi Germany that not only did the movement lose momentum in the United States, but the discipline of human genetics itself was left with a tinge of stigma that permeates many genetic research programs even today.

INFORMED CONSENT

In a clinical context, it has long been recognized that there is an ethical duty to secure *informed consent* from a patient before he or she undergoes genetic testing. This norm emerged in response to the atrocities of the eugenics movement, which made clear the necessity to respect patient autonomy in decisions about how genetic testing was used. Informed consent is also important because the results of genetic testing may have social, economic, and psychological implications for a patient and the family. When a genetic test is ordered, these implications may not be obvious to a clinician, but could be very important to the patient.

Another crucial reason to obtain informed consent for genetic testing is that the outcomes of testing are often the function of a patient’s choice about how to respond

to test results. Genetic test results may have forceful implications for one's reproductive future, life expectancy, or medical management. To equip a patient with the means to understand and act upon a genetic test result in his or her best interest, a clinician needs to discuss the purpose, limitations, and possible outcomes with the patient before ordering a specific test. Ideally, this discussion should employ straightforward vocabulary that is comprehensible to the individual considering the testing. The informed consent discussion is especially important in situations where a genetic test could yield results that are uninformative, or could provide false reassurance about a future disease risk. Additionally, results with unclear significance may raise anxiety levels without a clear, future course of action.

ISSUES OF PRIVACY, CONFIDENTIALITY, AND DISCLOSURE

Before availing themselves of genetic testing, individuals should know who can gain access to their test results and what rules of confidentiality are in place. This is especially important because genetic test results may have health implications for the relatives of the individual tested. By discovering the genetic cause of a disorder and its pattern of transmission, and by examining the pedigree of the family, other relatives at risk may be identified. Sometimes the original patient undergoing testing will not wish to share the test results with relatives for any number of reasons, including fear of stigmatization, a desire not to be in contact with certain relatives, a belief that the relative will not want the information obtained, or feelings of guilt about a diagnosis.

Under most circumstances, a clinician's primary duty of confidentiality is to the patient. However, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983) has recommended that:

A professional's ethical duty of confidentiality to an immediate patient or client can be overridden only if several conditions are satisfied:

- ▶ Reasonable efforts to elicit voluntary consent to disclosure have failed.
- ▶ There is a high probability that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm.
- ▶ The harm that identifiable individuals would suffer would be serious.
- ▶ Appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed

Because of the complexity of breaching professional confidentiality, even in the context of the "duty to warn," it has been suggested that the clinician contemplating such an action seek review by "an appropriate third party," such as a hospital ethics committee.

Additionally, the American Society of Human Genetics (ASHG) points out that confidentiality should be applied to genetic information in the same manner as other medical information. The ASHG Statement (1998) includes "confidentiality is not absolute, and, in exceptional cases, ethical, legal, and statutory obligations

may permit health-care professionals to disclose otherwise confidential information.” Additionally, the statement outlines exceptional circumstances that permit disclosure:

Disclosure should be permissible where attempts to encourage disclosure on the part of the patient have failed; where the harm is likely to occur and is serious and foreseeable; where the at-risk relative(s) is identifiable; and where either the disease is preventable/treatable or medically accepted standards indicate that early monitoring will reduce the genetic risk. (p. 474)

Finally, the statement includes, “The harm that may result from failure to disclose should outweigh the harm that may result from disclosure” (p. 474).

Although case law is not clear, there have been lawsuits because of physician failure to warn family members about their possible risk of genetic disease.

OWNERSHIP AND FUTURE USE OF SAMPLES TAKEN FOR TESTING/SCREENING

When human tissues are acquired for genetic testing in both clinical and research contexts, these tissues (and the data derived from them) may be retained for research purposes. At present, if samples or data from an individual will be useful in future research, it is standard practice to seek broad informed consent to use these samples or data in research at the time of acquiring them. However, the long-term retention of tissue samples and related data is controversial, because future research uses of individual samples and data are not always foreseeable at the time of their collection. Furthermore, it is unclear who “owns” these samples and data, or what rights they have to decide how they are used. As a result, it is difficult to obtain truly “informed” consent from an individual to use their samples and data in research.

In the past, the anonymization or de-identification of tissues and genetic data were the most trusted strategies for mitigating risks to genetic research participants from loss of confidentiality. However, with the growth of electronic data sharing, it is no longer possible to guarantee that anonymized donations of samples and data will remain de-identified in large data repositories. Another issue is that, increasingly, research participants wish to know how their samples are being used in research, and at times they may feel entitled to receive individual research results from studies to which they have contributed, especially if these results are relevant to their health. For these reasons they may actually prefer keep their identities linked to tissue samples and the genetic data derived from them.

These issues remain highly contested policy topics. At present, they are being addressed in a variety of ways: (a) restrictions are being placed on how broadly researchers can share data, (b) researchers are being encouraged to be more transparent about the risk that tissue samples and genetic data may be re-identified, and (c) researchers are being encouraged to develop and articulate plans to return medically actionable research results to participants in their studies. However, universal rules adjudicating these issues have not been developed. How they are handled remains largely a matter of individual researcher discretion.

GENETIC DISCRIMINATION

One reason genetic information raises privacy concerns is because it may reveal information about an individual's risk of developing a disease in the future. One concern is that this information could be used to discriminate in decisions about employment or insurance coverage. To address this risk, the Genetic Information Nondiscrimination Act of 2008 (GINA) was signed into federal law in 2008.

GINA is a federal statute that prohibits employers and health insurance companies from using genetic tests or information to inform employment practices or health insurance coverage decisions. The statute defines “genetic test” as an analysis of DNA, RNA chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes. “Genetic information” is defined as information about any of the following:

- ▶ An individual's genetic tests
- ▶ Genetic tests of the individual's family members
- ▶ Genetic tests of any fetus or an individual or family member who is a pregnant woman and genetic tests of any embryo legally held by an individual or family member using assisted reproduction
- ▶ The manifestation of a disease or a disorder in family members
- ▶ Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education)

Importantly, GINA's protections have limited scope (McGuire & Majumder, 2009). The statute's definition of “genetic information” does not include information about the age or sex of any individual. The law does not prevent the use of genetic information for life insurance, long-term care insurance, or disability insurance coverage decisions. Neither does GINA prohibit a health insurer from determining eligibility or premium rates based on the manifestation of an existing genetic disorder in that individual. Finally, because of amended health insurance and employment laws, GINA does not apply to federal employees participating in the Federal Employee Health Benefits program, participants in the U.S. Military's Tricare program, and the Veterans Health Administration, or the Indian Health Service.

DIRECT-TO-CONSUMER GENOME TESTING AND GENOME TEST REGULATION

In 2007, commercial laboratories started offering genome testing products on a DTC basis. These services, such as 23andMe and Ancestry.com, provide information about human ancestry and inherited risks for a variety of complex traits by analyzing single-nucleotide polymorphisms (SNPs) scattered throughout the genome.

Since the introduction of these tests, critics have raised concern that the average person is ill-equipped to understand the implications of the results, most of which are nondiagnostic and may only indicate small changes in a person's disease

risk. A number of professional medical societies raised concerns about this testing, expressing worry that they introduced new privacy risks or that consumers would erroneously believe DTC test results were medically actionable and pursue inappropriate remedies. On the other hand, proponents of DTC tests argued that users were empowered with direct access to information in the context of helpful multimedia interfaces and opportunities to join research. Debates about the merits and disadvantages of DTC genomics are complicated by the fact that, in the United States, there are no consensus standards for evaluating the clinical validity and utility of genome testing. Indeed, the U.S. genetic testing industry is only loosely regulated by a patchwork of agencies without a coordinated framework. This means that most genetic tests (whether marketed to health care providers or directly to consumers) enter the market without independent analyses to verify the claims of their sellers.

There is some oversight at the Centers for Medicare and Medicaid Services (CMS) with regulation of clinical laboratories, but the standards predate many of the testing modalities used to analyze the human genome today. Moreover, CMS does not evaluate whether genome tests are clinically harmful or useful in the long run.

In 2014, the Food and Drug Administration (FDA) announced the intention to regulate genome testing through a combination of premarket evidence reviews and by requiring commercial labs to submit mandatory adverse event reports to the agency (Federal Register, n.d.). It remains to be seen whether this approach will facilitate transparency and uniform standards in the genetic testing industry without making it prohibitively difficult to introduce new tests into the market.

GENETIC TESTING IN MINORS

Most genetic testing performed beyond the newborn period is done in children with intellectual disability, autism spectrum disorders, or multiple congenital anomalies. However, predictive genetic testing may also be done in children who have a family history of a genetic condition. Given the rapid growth in the number of genetic tests available, it is reasonable to expect that there will be a broader range of opportunities to use genetic testing in minors in the future.

When genetic testing is used to diagnose a child with symptoms of a suspected genetic disorder, it does not differ significantly from other diagnostic procedures. The benefits of genetic testing in children include timely initiation of treatment or supportive care, identification of family members at risk, and initiation of disease surveillance if needed. The risks include psychological harms of test-related anxiety or depression, harms of social stigma or privacy violations, and harms of failing to understand a result. Because of these risks, there is only a weak rationale for using genetic testing in minors unless there is reason to believe a child will benefit from medical intervention during childhood as a direct result of having these tests.

The American Academy of Pediatrics (AAP) recommends that genetic testing should be permitted in minors at risk of *childhood-onset conditions*, provided that parental informed consent has been obtained for testing. Where possible, AAP recommends that the child undergoing testing should also provide voluntary assent to be tested. Testing children for *adult-onset conditions* is generally discouraged by

the AAP, because of the potential harms of testing and out of respect for a child's future right to decide whether to be tested. The AAP stresses that exceptions to these guidelines may be appropriate in cases where there has been extensive family counseling and informed consent for testing has been obtained from at least one parent. For example, in some cases, adolescents may seek predictive genetic testing without parental involvement because of a teenage pregnancy or anxiety about a family history of hereditary disease risk. In these situations, providers are advised to be cautious about providing testing to minors without the collaboration of their parents.

Another controversial issue concerns the acceptability of performing genetic testing of children as part of the adoption process. While prospective adoptive parents have an interest in learning whether a child they might adopt is at risk of developing special needs, there is also a risk that genetic testing may reveal stigmatizing diagnoses in some children, thereby lowering their future chances of permanent placement with a family. To address this difficult issue, the American College of Medical Genetics and Genomics (ACMG) and ASHG have issued a joint statement recommending that all genetic testing performed in children as part of the adoption process should be consistent with guidelines for genetic testing in other children, and that the medical benefit of the child should be the primary consideration motivating testing (American Society of Human Genetics Social Issues Committee and The American College of Medical Genetics Social, Ethical, and Legal Issues Committee, 2000).

INCIDENTAL FINDINGS

Since 2012, clinical genome and exome sequencing (CGES) have been available to diagnose rare disorders that are cumbersome to diagnose using other means. These genome-wide test methods query roughly 20,000 human genes at the same time. Estimates of the diagnostic yield of CGES range from 25% to as high as 40% in some practice settings (Biesecker & Green, 2014; Srivastava et al., 2014). This approach is primarily useful in patients whose clinical features are suggestive of a single gene disorder after single gene tests have failed to reveal a diagnosis, or when a single or multigene approach would be prohibitively slow or expensive.

The outcomes of CGES can vary. Sometimes, testing may reveal a single candidate gene believed to cause disease; other times it may reveal multiple candidate variants, each of which may have a different level of evidence to support its relationship to a patient's clinical features. One challenging issue that arises in the context of CGES is the estimated 1% to 3% chance that CGES will yield a result that has clinical significance for a patient and family but is not related to the original reason for testing (Biesecker & Green, 2014). This possibility of discovering so-called *incidental* or *secondary findings* is not unique to CGES or even genetic and genomic testing. However, the scope of CGES has drawn renewed attention to the issue of managing incidental findings as this testing has been deployed in an expanding range of clinical settings.

Because clinical labs performing CGES did not initially report incidental findings to clinicians using consistent rules, the ACMG convened a working group to issue recommendations about clinical laboratory reporting of incidental findings from

TABLE 13.1 ACMG Recommendations for Incidental Findings

1. Constitutional mutations found in the genes on the minimum list should be reported by the laboratory, regardless of the indication for which the clinical sequencing was ordered.
 - a. Additional genes may be analyzed for incidental (secondary) variants, as deemed appropriate by the laboratory.
 - b. Incidental (secondary) variants should be reported regardless of the age of the patient.
 - c. Incidental (secondary) variants should be reported for any clinical sequencing conducted on a constitutional (but not tumor) tissue. This includes the normal sample of a tumor-normal sequenced dyad and unaffected members of a family trio.
2. The Working Group recommends that laboratories seek and report only the types of variants within these genes that we have delineated.
 - a. For most genes, only variants that have been previously reported and are a recognized cause of the disorder or variants that are previously unreported but are of the type which is expected to cause the disorder, as defined by prior ACMG guidelines, should be reported.
 - b. For some genes, predicted loss of function variants are not relevant (e.g., COL3A1 and most hypertrophic cardiomyopathy genes).
 - c. For some genes (e.g., APOB), laboratories should only report variants for certain conditions.
3. It is the responsibility of the ordering clinician/team to provide comprehensive pre- and post-test counseling to the patient.
 - a. Clinicians should be familiar with the basic attributes and limitations of clinical sequencing.
 - b. Clinicians should alert patients to the possibility that clinical sequencing may generate incidental findings that could require further evaluation.
 - c. Given the complexity of genomic information, the clinical geneticist should be consulted at the appropriate time that may include ordering, interpreting, and communicating genomic testing.
4. These recommendations reflect limitations of current technology, and are therefore focused on disorders that are caused by point mutations and small insertions and deletions, not those primarily caused by structural variants, repeat expansions, or copy number variations.

The Working Group recommends that the ACMG, together with content experts and other professional organizations, refine and update this list at least annually.

Source: Green et al. (2013).

CGES in 2013 (see Table 13.1). The ACMG working group's statement encourages clinical laboratories performing diagnostic CGES to routinely seek and report any gene variants that seem likely to cause disease if they occur in any of 56 genes associated with diseases that are considered *actionable*, that is, for which there are management and treatment recommendations. The majority of these 56 genes are associated with cancer syndromes for which there are heightened screening recommendations or cardiac disorders that confer an increased risk of sudden death.

Opponents of the ACMG recommendations argue that they unacceptably override patient choice in decisions about what kinds of genetic testing to undergo. There is also controversy surrounding the definition of an “actionable” result. In response to several critiques, the ACMG amended its recommendations in 2014 to suggest that labs and clinicians provide patients with the choice to opt out of receiving incidental findings from CGES. They have also instituted a formal process through which the list of 56 genes will be reviewed and updated on an ongoing basis.

The issue of managing incidental findings rose to the forefront of policy discussions about genetics and genomics in 2013 and 2014 when CGES was introduced to the clinical realm. However, it is important to remember that other tests, like multigene panels and chromosomal microarray testing, could reveal incidental findings as well. In some cases, the incidental findings may not reveal a risk of disease, but instead may reveal information about the degree of relatedness between family members. Incidental findings of nonpaternity or parental consanguinity in a family may have bearing on the accuracy of clinical risk assessment for a patient and family. For this reason, when there is a risk that incidental information about a family’s degree of relatedness may be revealed by genetic testing, it is ideal for the clinician and patient to agree upon a plan for disclosing these results to family members at the time of ordering the test.

SUMMARY

While far from exhaustive, this chapter has discussed some dilemmas that arise in the use of clinical and DTC genomics and has identified key issues at stake in various settings. However, the pace of scientific change in clinical genomics is rapid, and regulatory oversight for the genetic testing industry is under evolution. Any clinician who orders genetic testing on a routine basis should stay abreast of new developments in the field by checking for updated professional society guidelines and conferring with clinical geneticists, genetic counselors, or clinical ethics consultation services about the particulars of specific cases.

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APPENDIX A

Resources for Professionals

American Board of Genetic Counseling
www.abgc.net

American Board of Medical Genetics
www.abmg.org

American College of Medical Genetics
www.acmg.net

American Society of Human Genetics
www.ashg.org

Association of Professors of Human and Medical Genetics
www.aphmg.org

Centers for Disease Control and Prevention, Office of Public Health Genomics
www.cdc.gov/genomics

GeneTests
www.genetests.org

Genetic Alliance
www.geneticalliance.org

Genetics Competency and Curricular Resources
www.genome.gov/27527634#al-2

Genetics Home Reference
<http://ghr.nlm.nih.gov>

Genetic Nursing Credentialing Commission
www.geneticnurse.org

Genetic Society of America
www.genetics-gsa.org

Genome Overview With Interactive Map
www.ncbi.nlm.nih.gov/genome/51

Human Genome Epidemiology Network
www.cdc.gov/genomics/hugenet/default.htm

International Society of Nurses in Genetics

www.isong.org

National Birth Defects Prevention Network

www.nbdpn.org

National Coalition for Health Professional Education in Genetics

www.nchpeg.org

National Human Genome Research Institute, National Institutes of Health

www.genome.gov

National Newborn Screening & Genetics Resource Center

<http://genes-r-us.uthscsa.edu>

National Organization of Rare Disorders (NORD)

www.rarediseases.org

National Society of Genetic Counselors

www.nsgc.org

Online Mendelian Inheritance in Man (OMIM), National Center for
Biotechnology Information

www.omim.org

Society for the Study of Inborn Errors of Metabolism

www.ssiem.org

APPENDIX B

Websites Providing Information, Products, and Services for Genetic Conditions

GROUPS PROVIDING GENETIC SUPPORT GROUP INFORMATION

Canadian Directory of Genetic Support Groups

http://www.lhsc.on.ca/Patients_Families_Visitors/Genetic_Support_Directory/

Canadian Organization for Rare Disorders

www.raredisorders.ca

Center for Jewish Genetics

www.jewishgenetics.org

Easter Seal Society National Headquarters

www.easterseals.com

European Organization for Rare Diseases

www.eurordis.org

Genetics Education Center at the University of Kansas Medical Center

www.kumc.edu/gec

Hereditary Disease Foundation

www.hdfoundation.org

March of Dimes Birth Defects Foundation

www.marchofdimes.org

Maternal and Child Health Bureau, Health Resources and Services Administration

<http://mchb.hrsa.gov/>

National Center on Birth Defects and Developmental Disabilities; Centers for Disease Control and Prevention

www.cdc.gov/ncbddd/index.html

Office of Rare Diseases National Institutes of Health

<http://rarediseases.info.nih.gov/>

GROUPS PROVIDING SUPPORT INFORMATION ON SPECIFIC GENETIC DISORDERS

Aarskog Syndrome

<http://rarediseases.org/rare-diseases/aarskog-syndrome/>

Achondroplasia—See Short Stature

Acid Maltase Deficiency—See Glycogen Storage Disorders; Liver Diseases; Muscular Dystrophy

Acoustic Neuroma—Also see Neurofibromatosis

Acoustic Neuroma Association

<http://anausa.org>

Adrenal Disorders—Also see Ambiguous Genitalia; Growth Problems

National Adrenal Diseases Foundation*

www.hormone.org/diseases-and-conditions/adrenal

*Includes adrenal insufficiency, congenital adrenal hyperplasia, Cushing syndrome, and adrenal hyperplasia

Adrenoleukodystrophy and Adrenomyeloneuropathy

United Leukodystrophy Foundation

<http://ulf.org/adrenoleukodystrophy>

Agammaglobulinemia—See Immune Disorders

Alagille Syndrome—Also see Liver Diseases

Alagille Syndrome Alliance

www.alagille.org

Albinism

National Organization for Albinism and Hypopigmentation

www.albinism.org/

Alcohol and Drug Abuse, Including Fetal Alcohol Syndrome

AI-Anon/Alateen

www.al-anon.alateen.org

Alcoholics Anonymous

www.aa.org

National Organization on Fetal Alcohol Syndrome

www.nofas.org/

SAMHSA's National Clearinghouse for Alcohol and Drug Information

www.samhsa.gov/

Alpha-1-Antitrypsin Deficiency—Also see Liver Diseases

Alpha-1 Association

www.alpha1portal.org/

ALS Association

www.alsa.org

Les Turner Amyotrophic Lateral Sclerosis Foundation, Ltd.
www.lesturnerals.org

Alzheimer Disease

Administration on Aging, Department of Health and Human Services
www.aoa.gov
 Alzheimer's Association
www.alz.org/
 Alzheimer's Disease Education and Referral Center
www.nia.nih.gov/alzheimers

Ambiguous Genitalia

Ambiguous Genitalia Support Network
www.isna.org/node/531
 Accord Alliance *
www.accordalliance.org/
 *Includes Disorders of Sex Development (DSD)

Amputees—Also see Disabilities, General

Amputee Coalition
www.amputee-coalition.org/support-groups-peer-support/support-group-network/

Amyotrophic Lateral Sclerosis—Also see Muscular Dystrophy

Anderson Disease—See Glycogen Storage Disorders

Angelman Syndrome
 Angelman Syndrome Foundation
www.angelman.org

Angioedema—See Hereditary Angioedema; Immune Disorders

Ankylosing Spondylitis—Also see Arthritis

Spondylitis Association of America*
www.spondylitis.org
 *Includes ankylosing spondylitis, Reiter syndrome, psoriatic arthritis, and arthritis associated with inflammatory bowel disease

Anophthalmia

International Children's Anophthalmia Network
www.anophthalmia.org/

Apert Syndrome—Also see Craniofacial Anomalies

www.apert.org/

Argininosuccinic Aciduria—See Organic Acidemias

Arnold–Chiari Syndrome—Also see Hydrocephalus

American Syringomyelia Alliance Project*
<http://asap.org/>
 *Includes syringomyelia and Chiari I and II

World Arnold-Chiari Malformation Association
<http://community.presenter.net/~wacma/>

Arrhythmias—Also see Heart Defects/Diseases
Sudden Arrhythmia Death Syndromes Foundation
www.sads.org/

Arthritis

Arthritis Foundation
www.arthritis.org/arthritis-facts/disease-center/juvenile-arthritis.php
www.arthritis.org
Arthritis Society (Canada)
www.arthritis.ca/
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
www.niams.nih.gov/

Arthrogryposis Multiplex Congenita—Also see Muscular Dystrophy
Arthrogryposis Multiplex Congenita Support, Inc.
www.amcsupport.org/

Ataxia—Also see Friedreich Ataxia; Muscular Dystrophy

National Ataxia Foundation*
www.ataxia.org

*Includes ataxia–telangiectasia, Charcot–Marie–Tooth disease, hereditary tremor, hereditary spastic paraplegia

Ataxia–Telangiectasia (Louis-Bar Disease)—Also see Ataxia; Tay–Sachs Disease
A-T Children’s Project
www.atcp.org

Autism

Autism Society of America
www.autism-society.org/
Autism Speaks
www.autismspeaks.org/

Barth Syndrome

Barth Syndrome Foundation
www.barthsyndrome.org

Batten Disease (Batten Vogt Syndrome)—Also see Tay–Sachs Disease
Batten’s Disease Support and Research Association
<http://bdsra.org/>

Beta-Glucuronidase Deficiency—See Mucopolysaccharide; Tay–Sachs Disease

Biedl–Bardet Syndrome—See Retinitis Pigmentosa.

Biliary Atresia—See Liver Diseases

Biotinidase Deficiency—See Metabolic Disorders

- Birth Defects, General—Also see Disabilities, General;
 Genetic Disorders, General
 Birth Defect Research for Children
www.birthdefects.org
 Center for Jewish Genetics
www.jewishgenetics.org
 Easter Seals
www.easterseals.com
 March of Dimes Birth Defects Foundation
www.marchofdimes.org
 National Center for Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention
www.cdc.gov/ncbddd/index.html
- Blindness—See Vision Impairment
- Bloom Syndrome
 Center for Jewish Genetics
www.jewishgenetics.org
- Bone Diseases—Also see Osteogenesis Imperfecta; Osteoporosis; Paget Disease;
 Osteoporosis and Related Bone Diseases National Resource Center, National Institutes of Health
www.niams.nih.gov/Health_Info/Bone/
- Breast Cancer—Also see Cancer
 National Breast Cancer Coalition
www.breastcancerdeadline2020.org/homepage.html
 Susan G. Komen Breast Cancer Foundation
ww5.komen.org/
- Breastfeeding
 La Leche League International
www.llli.org/
- Burke Syndrome—See Shwachman Syndrome
- Byler Disease—See Liver Diseases
- Canavan Disease—See Tay–Sachs Disease
- Cancer—Also see specific type
 American Cancer Society
www.cancer.org
 Candlelighters Childhood Cancer Foundation
www.candle.org/
 Cure Search for Children's Cancer
www.curesearch.org/
 Kidscope
www.kidscope.org/

National Cancer Institute, National Institutes of Health
www.cancer.gov/
Starlight Children's Foundation
www.starlight.org

Cardiac Arrhythmias/Diseases—See Heart Defects/Diseases

Carnitine Deficiency—Also see Muscular Dystrophy
Fatty Oxidation Disorders Family Support
www.fodsupport.org/index.htm

Cartilage Hair Hypoplasia—See Short Stature

Celiac Disease—See Gluten Intolerance

Central Core Disease—See Muscular Dystrophy

Cerebral Palsy
Easter Seals
www.easterseals.com/
UCP—United Cerebral Palsy
www.ucp.org/

Charcot–Marie–Tooth Disease—Also see Ataxia; Muscular Dystrophy
Charcot-Marie-Tooth Association
www.cmtausa.org/

CHARGE Syndrome
CHARGE Syndrome Foundation
www.chargesyndrome.org/

Chromosome Abnormalities—Also see specific disorder (e.g., Down, Klinefelter, Turner, Cri-du-Chat); Genetic Disorders, General; Mental Retardation/Mental Illness; Disabilities, General 11q Net (UK)

4p⁻ Support Group
www.4p-supportgroup.org
Chromosome 22 Central
www.c22c.org/
Chromosome Disorder Outreach*
www.chromodisorder.org/

*Includes chromosome deletions, chromosome duplications, translocations, and inversions

Chromosome 18 Registry and Research Society
www.chromosome18.org

Cri-du-Chat Syndrome Support Group

Five P Minus Society
www.fivepminus.org

Dup15q Alliance*
www.dup15q.org/

*Includes inverted duplication of chromosome 15, supernumerary marker chromosomes, duplication of chromosome 15, and chromosomal anomalies

Parents and Researchers Interested in Smith-Magenis Syndrome*

www.prisms.org/

*Also includes deletion 17p11.2

SOFT (UK)

www.soft.org.uk/

Support Organization for Trisomy (SOFT) 18, 13 and Related Disorders

<http://trisomy.org/>

Trisomy 9 International Parent Support

www.trisomy9.org/9tips.htm

Unique, Rare Chromosome Disorder Support Group

www.rarechromo.org/html/home.asp

Wolf Hirschhorn Support Group UK

www.whs4pminus.co.uk/

Cleft Lip/Palate—Also see Craniofacial Anomalies

Children's Craniofacial Association

www.ccakids.com

Cleft Palate Foundation

www.cleftline.org/

Smiles Craniofacial Support Group

www.cleft.org

Cockayne Syndrome

Share and Care Cockayne Syndrome Network

<http://cockaynesyndrome.org/>

Coffin–Lowry Syndrome

Coffin-Lowry Syndrome Foundation

<http://clsf.info/>

Colorectal Cancer—Also see Cancer

Fight Colorectal Cancer

<http://fightcolorectalcancer.org/>

Familial Gastrointestinal Registry (Canada)

www.zanecohencentre.com/fgicr

Communicative Disorders—Also see Hearing Impairment

National Center for Stuttering

www.stuttering.com/

Sertoma International

www.sertoma.org/

Trace Center (communication devices and research), University of Wisconsin

<http://trace.wisc.edu/projects/>

Congenital Adrenal Hyperplasia—See Adrenal Disorders; Ambiguous Genitalia; Growth Problems

Congenital Heart Disease—See Heart Defects/Diseases

Conjoined Twins

Conjoined Twins Support Group

<http://theezelltwins.weebly.com/conjoined-twins-support-group.html>

Cooley Anemia—See Thalassemia

Cornelia de Lange Syndrome

Cornelia de Lange Syndrome Foundation

www.cdlsusa.org/

Craniofacial Anomalies—Also see Cleft Lip/Palate

Children's Craniofacial Association

www.ccakids.com/

Craniofacial Foundation of America

www.erlangier.org/CraniofacialCenter

National Craniofacial Association

www.faces-cranio.org/

myFace (formerly the National Foundation for Facial Reconstruction)

<http://myface.org/>

Cri-du-Chat—Also see Chromosome Abnormalities

Five P Minus Society

www.fivepminus.org

Crohn Disease—Also see Inflammatory Bowel Disease

Crohn's and Colitis Foundation of America

www.ccfa.org/

Crohn's and Colitis Foundation of Canada

www.crohnsandcolitis.ca/site/c.dtJRL9NUJmL4H/b.9012407/k.BE24/Home.htm

National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health

www.niddk.nih.gov

Cutis Laxa—See Ehlers–Danlos Syndrome

Cystic Fibrosis

Cystic Fibrosis Foundation

www.cff.org

Cystic Fibrosis Trust England, United Kingdom

www.cysticfibrosis.org.uk/

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

www.niddk.nih.gov

Dandy–Walker Syndrome

Dandy-Walker Syndrome Alliance

www.dandy-walker.org/

Darier Disease—See Ichthyosis; Skin Disorders

de Lange syndrome—See Cornelia de Lange Syndrome

Deaf—See Hearing Impairment

Deaf-Blind—Also see Hearing Impairment; Usher Syndrome; Visual Impairment

American Association of the Deaf-Blind

www.aadb.org

National Center on Deaf-Blindness

<https://nationaldb.org/>

Death, Neonatal and Infant—Also see Sudden Infant Death Syndrome

A.M.E.N.D. (Aiding a Mother and Father Experiencing Neonatal Death)

www.amendgroup.com/

Center for Loss in Multiple Birth (CLIMB)

www.climb-support.org/

Compassionate Friends (TCF)

www.compassionatefriends.org/home.aspx

A Heartbreaking Choice

www.ahartbreakingchoice.com/

SHARE Pregnancy and Infant Loss Support

www.nationalshare.org/

Dental Care

National Foundation of Dentistry for the Handicapped

www.1800dentist.com/national-foundation-of-dentistry-for-handicapped/

Depression

Depression and Bipolar Support Alliance

www.dbsalliance.org/site/PageServer?pagename=peer_support_group_locator

National Institute of Mental Health, National Institutes of Health

www.nimh.nih.gov

Diabetes Mellitus

American Diabetes Association

www.diabetes.org

Canadian Diabetes Association

www.diabetes.ca/

Juvenile Diabetes Research Foundation International

www.jdrf.org

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

www.niddk.nih.gov

Diethylstilbestrol (DES)

DES Action, USA

www.desaction.org/

National Women's Health Network

www.nwhn.org/

National Women's Health Resource Center

www.healthywomen.org

DiGeorge Syndrome—Also see Chromosome Abnormalities; Immune Disorders

VCFS Educational Foundation*

<http://www.vcfsfa.org.au/pages/home.php>

*Includes DiGeorge syndrome, Shprintzen syndrome, velocardiofacial syndrome, and 22q11.2 deletions

Disabilities, General—Also see Mental Retardation

ADA & IT Technical Assistance Centers

www.adata.org

Association of University Centers on Disabilities

www.aucd.org/template/index.cfm

Council for Exceptional Children

www.cec.sped.org/

Exceptional Parent Magazine

www.eparent.com

Family Resource Center on Disabilities

www.frcd.org

Information Center for Individuals With Disabilities

www.disability.net

Maternal and Child Health Bureau, Health Resources and Services Administration

<http://mchb.hrsa.gov>

Medic Alert Foundation International

www.medicalert.org

Mobility International USA

www.miusa.org/

National Association of the Physically Handicapped

<http://naphnet.blogspot.com/p/what-naph-is.html>

National Center for Education in Maternal and Child Health

www.ncemch.org

National Clearinghouse on Disability and Exchange

www.miusa.org/ncde

National Council on Independent Living

www.ncil.org

National Easter Seal Society

www.easterseals.com

National Organization on Disability

www.nod.org

Parents Helping Parents*

www.php.com

*General disabilities, children with special needs, and tuberous sclerosis

Down Syndrome—Also see Chromosome Abnormalities

Association for Children With Down Syndrome

www.acds.org/

Canadian Down Syndrome Society

www.cdss.ca

Caring

www.caringinc.org/

Down Syndrome Research Foundation (Canada)

www.dsrf.org
 Down's Syndrome Association (UK)
www.downs-syndrome.org.uk/
 National Down Syndrome Congress
www.ndscenter.org/
 National Down Syndrome Society
www.ndss.org

Dubowitz Syndrome
 Dubowitz Syndrome Family Support Network
www.ric.edu/sherlockcenter/dsyndrome/

Dwarfism—See Short Stature

Dysautonomia (Riley–Day Syndrome)
 Center for Jewish Genetics
www.jewishgenetics.org/
 Dysautonomia Center
www.dysautonomia.nyumc.org/
 Dysautonomia Foundation
www.familialdysautonomia.org/

Dyslexia—See Learning Disabilities

Dystonia (Torsion Dystonia)
 Center for Jewish Genetics
www.jewishgenetics.org/
 Dystonia Medical Research Foundation
www.dystonia-foundation.org/

Ectodermal Dysplasia
 Ectodermal Dysplasia Society
www.ectodermaldysplasia.org/
 National Foundation for Ectodermal Dysplasias
www.nfed.org

Edwards Syndrome—See Chromosome Abnormalities; Trisomy 18/13

Ehlers–Danlos Syndrome
 Ehlers-Danlos National Foundation
www.ednf.org

Environmental Mutagens
 Centers for Disease Control and Prevention
www.cdc.gov
 Environmental Health Clearinghouse National Institute of Environmental Health
 Sciences
<http://tools.niehs.nih.gov/wetp/>
 National Library of Medicine
www.nlm.nih.gov/

Epidermolysis Bullosa

Dystrophic Epidermolysis Bullosa Research Association of America
www.debra.org

Epilepsy

Epilepsy Canada
www.epilepsy.ca
Epilepsy Foundation
www.epilepsy.org

Fabry Disease—See Tay–Sachs Disease

Fanconi Anemia

Fanconi Anemia Research Fund
www.fanconi.org

Farber Syndrome—See Tay–Sachs Disease

Fetal Alcohol Syndrome—See Alcohol and Drug Abuse

Fibrodysplasia

International Fibrodysplasia Ossificans Progressiva
www.ifopa.org

Fragile X Syndrome—Also see Chromosome Abnormalities

FRAXA Research Foundation
www.fraxa.org
National Fragile X Foundation
www.fragilex.org/

Freeman–Sheldon Syndrome

Freeman-Sheldon Parent Support Group*
www.fsrgroup.org/

*Includes whistling face syndrome and craniocarpotarsal dysplasia.

Friedreich Ataxia—See Ataxia; Muscular Dystrophy

Fucosidosis—See Tay–Sachs Disease

Galactosemia—Also see Liver Diseases

Parents of Galactosemic Children
<http://galactosemia.org/>

Gaucher Disease—Also see Tay–Sachs Disease

Center for Jewish Genetics
www.jewishgenetics.org/
National Gaucher Foundation
www.gaucherdisease.org/

Genetic Disorders, General—Also see Birth Defects, General; Disabilities, General

Canadian Organization for Rare Disorders
www.raredisorders.ca
Center for Jewish Genetics

www.jewishgenetics.org
 Genetic Alliance
www.geneticalliance.org
 Hereditary Disease Foundation
www.hdfoundation.org
 Maternal and Child Health Bureau, Health Resources and Services Administration
<http://mchb.hrsa.gov>
 Med Help International
www.medhelp.org
 National Health Information Center Department of Health and Human Services
www.health.gov/nhic/
 National Organization for Rare Disorders
www.rarediseases.org
 Office of Rare Diseases, National Institutes of Health
<http://rarediseases.info.nih.gov/>

Gluten Intolerance

Celiac Sprue Association USA (CSA/USA)
www.csaceliacs.org/
 Gluten Intolerance Group of North America (GIG)
www.gluten.net/

Glycogen Storage Disorders—See Liver Diseases

Association for Glycogen Storage Disease*
www.agsdus.org/

*Glycogen storage disease, acid maltase deficiency, Anderson disease, and amylopectinosis

Goldenhar Syndrome

Goldenhar Syndrome Support Network
www.goldenharsyndrome.org/

Granulomatous Disease—Also see Immune Disorders

Chronic Granulomatous Disease Society
www.cgdsociety.org/

Growth Problems—Also see Short Stature; Tall Stature; specific disorder

Human Growth Foundation (HGF)
www.hgfound.org

MAGIC Foundation*

www.magicfoundation.org/www

*Includes growth disorders, growth hormone deficiency, McCune–Albright syndrome, congenital adrenal hyperplasia, precocious puberty, growth retardation in Down syndrome

Handicapped—See Disabilities, General

Hearing Impairment

Alexander Graham Bell Association for the Deaf
<http://listeningandspokenlanguage.org/>

American Society for Deaf Children

www.deafchildren.org

Better Hearing Institute

www.betterhearing.org

Canadian Hearing Society

www.chs.ca/

Deafness Research Foundation

<http://hearinghealthfoundation.org/>

International Hearing Society

www.ihsinfo.org

Laurent Clerc Deaf Education Center

www.gallaudet.edu/clerc_center.html

National Association for the Deaf

www.nad.org

National Institute on Deafness and Other Communication Disorders Information,

National Institutes of Health

www.nidcd.nih.gov/health

Self Help for Hard of Hearing People

www.shhhaust.org/

Heart Defects/Diseases

American Heart Association

www.heart.org/

National Heart, Lung, and Blood Institute, National Institutes of Health

www.nhlbi.nih.gov

Sudden Arrhythmia Death Syndrome Foundation

www.sads.org

Hemangiomas—See Vascular Birthmarks and Malformations

Hemochromatosis—Also see Iron Overload Diseases

Canadian Hemochromatosis Society

www.toomuchiron.ca/

Hemochromatosis Foundation

www.hemochromatosis.org

Iron Disorders Institute

www.irondisorders.org/iron-overload

Hemophilia

National Hemophilia Foundation*

www.hemophilia.org/

*Includes von Willebrand disease and other clotting disorders

World Federation of Hemophilia

www.wfh.org/

Hereditary Angioedema—Also see Immune Disorders

U.S. Hereditary Angioedema Association

<http://www.haea.org>

- Hereditary Exostoses, Multiple
Multiple Hereditary Exostoses Family Support Group
www.mhereseearchfoundation.org/
- Hereditary Hemorrhagic Telangiectasia
Hereditary Hemorrhagic Telangiectasia Foundation International*
www.curehht.org
*Also includes Osler–Weber–Rendu syndrome
- Hermansky-Pudlak Syndrome—See Albinism
- Hirschsprung Disease
International Foundation for Functional Gastrointestinal Disorders
www.iffgd.org/
National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health
www.niddk.nih.gov
- Homocystinuria—See Metabolic Disorders
- Hunter Disease—See Mucopolysaccharide Disorders; Tay–Sachs Disease
- Huntington Disease
Hereditary Disease Foundation
www.hdfoundation.org
Huntington Society of Canada
www.huntingtonsociety.ca/
Huntington’s Disease Society of America
www.hdsa.org
- Hurler Disease—See Mucopolysaccharide Disorders; Tay–Sachs Disease
- Hydrocephalus—Also see Arnold–Chiari Syndrome
Association for Spina Bifida and Hydrocephalus
www.spinabifidaassociation.org/site/c.evKRI7OXIoJ8H/b.8028963/k.BE67/Home.htm
Hydrocephalus Association
www.hydroassoc.org/
National Hydrocephalus Foundation
<http://nhfonline.org/>
- Hypercholesterolemia—Also see Heart Defects/Diseases
Foundation of the National Lipid Association
www.lipidfoundation.org/
- I-cell Disease—See Mucopolysaccharide Disorders
- Ichthyosis—Also see Skin Disorders
Foundation for Ichthyosis and Related Skin Types (FIRST)*
www.firstskinfoundation.org/

*Includes skin disorders, ichthyosis, Darier disease, Sjögren–Larsson syndrome, erythrokeratodermas, peeling skin syndrome, acquired ichthyosis, bullous ichthyosis (epidermolytic hyperkeratosis), Chananin-Dorfman syndrome, CHILD syndrome (unilateral CIE), epidermal nevus syndrome, progressiva symmetrica, harlequin fetus, ichthyosis linearis circumflexa, ichthyosis vulgaris, keratitis-ichthyosis deafness syndrome, lamellar ichthyosis/congenital ichthyosiform erythroderma

Immune Disorders

Immune Deficiency Foundation

<http://primaryimmune.org/>

National Jewish Center for Immunology and Respiratory Medicine

www.nationaljewish.org/about/depts/medicine/allergy-immunology/

U.S. Hereditary Angioedema Association

www.haea.org/

Incest

Child Welfare Information Gateway

<http://childwelfare.gov>

Survivors of Incest Anonymous

www.siaawso.org

Incontinentia Pigmenti

Incontinentia Pigmenti International Foundation

www.ipif.org/

Infertility

International Council on Infertility Information Dissemination

www.inciid.org/

Resolve, The National Infertility Association

www.resolve.org/

Inflammatory Bowel Disease—Also see Crohn Disease

National Digestive Diseases Education Information Clearinghouse, National Institutes of Health

www.niddk.nih.gov

Iron Overload Diseases—Also see Hemochromatosis; Thalassemia

Iron Overload Diseases Association

www.irondisorders.org/iron-overload

Isovaleric Acidemia—See Organic Acidemias

Joubert Syndrome

Joubert Syndrome Foundation

www.jsrdf.org/

Kearns–Sayre—See Mitochondrial Diseases

Kidney Diseases

American Association of Kidney Patients

www.aakp.org/

- National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
www.niddk.nih.gov/
 National Kidney Foundation
www.kidney.org/
- Klinefelter Syndrome—Also see Chromosome Abnormalities
 Klinefelter Syndrome Association, UK
www.ksa-uk.net/
 Klinefelter Syndrome Support Group
<http://klinefeltersyndrome.org>
- Klippel–Trénaunay Syndrome
 Klippel-Trenaunay Support Group
<http://k-t.org/>
- Krabbe Disease—See Tay–Sachs Disease
- Kugelberg–Welander Disease—See Muscular Dystrophy
- Lactic Acidosis
 Congenital Lactic Acidosis Support Group
<http://rarediseases.org/rare-disease-information/rare-diseases/byID/1231/viewAbstract>
- Learning Disabilities
 American Dyslexia Association
<http://american-dyslexia-association.org/>
 Council for Learning Disabilities
www.council-for-learning-disabilities.org/
 Learning Disabilities Association of America
www.ldaamerica.org
 Learning Disabilities Association of Canada
www.ldac-acta.ca
 National Attention Deficit Disorder Association
www.add.org
- Leigh Disease—Also see Mitochondrial Disorders
 United Mitochondrial Disease Foundation
www.umdf.org/site/c.8qKOJ0MvF7LUG/b.8637485/k.8A22/Leighs_Disease.htm
- Leukemia—Also see Cancer
 Leukemia & Lymphoma Society
www.lls.org/
 Leukemia Research Foundation
www.leukemia-research.org/
- Leukodystrophy—See Adrenoleukodystrophy and Adrenomyeloneuropathy
 Lissencephaly
 National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov/disorders/lissencephaly/lissencephaly.htm

Liver Diseases

American Liver Foundation*

www.liverfoundation.org

*Also includes Alagille syndrome, alpha-1-antitrypsin deficiency, galactosemia, and Wilson disease

Long QT Syndrome

Sudden Arrhythmia Death Syndromes

Foundation

www.sads.org

Lowe Syndrome (Oculocerebrorenal Disease)

Lowe Syndrome Association

www.lowesyndrome.org

Lupus Erythematosus—Also see Arthritis

Lupus Foundation of America

www.lupus.org

Lymphangiomyomatosis

LAM Foundation

www.thelamfoundation.org/

Lymphedema

National Lymphedema Network

www.lymphnet.org

Lymphoma—Also see Cancer

Leukemia & Lymphoma Society

www.lls.org/

Macular Diseases—Also see Vision Impairment

Association for Macular Diseases

www.macula.org

Maffucci Disease—See Ollier Disease

Malignant Hyperthermia—Also see Muscular Dystrophy

Malignant Hyperthermia Association of the United States

www.mhaus.org

Mannosidosis—See Tay–Sachs Disease

Maple Syrup Urine Disease—Also see Metabolic Disorders

Maple Syrup Urine Disease Family Support Group

www.msud-support.org

Marfan Syndrome—Also see Tall Stature

National Marfan Foundation

www.marfan.org

Canadian Marfan Association

www.marfan.ca

- Marfan Association (United Kingdom)
www.marfan-association.org.uk
- Maroteaux–Lamy Disease—See Mucopolysaccharide Disorders; Tay–Sachs Disease
- McArdle Disease—See Muscular Dystrophy
- McCune–Albright Syndrome—See Growth Problems
- Medium Chain Acyl-Coenzyme A Dehydrogenase (MCAD) Deficiency—Also see Mitochondrial Diseases
 Fatty Oxidation Disorders (FOD) Family Support Group
www.fodsupport.org
- MELAS—See Mitochondrial Diseases
- Menkes Disease
 The Menkes Foundation
www.themenkesfoundation.org/
- Mental Retardation—Also see Disabilities, General; specific disorders
 American Association on Intellectual and Developmental Disabilities
<http://aaidd.org/>
 Arc of the United States
<http://thearc.org/>
- Mental Retardation/Mental Illness
 National Association for the Dually Diagnosed
<http://thenadd.org/>
- MERFF—See Mitochondrial Disorders
- Metabolic Disorders—Also see specific disorder
 Society for Inherited Metabolic Disorders*
www.simd.org/Index.asp
 *Includes biotinidase deficiency, methylenetetrahydrofolatereductase deficiency, phenylketonuria, maple syrup urine disease, propionic acidemia, galactosemia, and others
 Fatty Oxidation Disorders Family Support Group*
www.fodsupport.org
 *Includes medium chain acyl-CoA dehydrogenase deficiency, short chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl-CoA dehydrogenase deficiency, very long chain acyl-CoA dehydrogenase deficiency, electron transfer flavoprotein dehydrogenase deficiency, carnitine palmitoyl transferase I & II deficiency
- National Institute of Diabetes, Digestive & Kidney Diseases, National Institutes of Health
www.niddk.nih.gov
- National Urea Cycle Disorders Foundation
www.nucdf.org/
- Organic Acidemia Association

www.oaanews.org/index.htm
Oxalosis and Hyperoxaluria Foundation
www.ohf.org/
Purine Research Society
www.purineresearchsociety.org/

Metachromatic Leukodystrophy—See Tay–Sachs Disease

Methylenetetrahydrofolate Reductase Deficiency—See Metabolic Disorders

Methylmalonic Acidemia—See Organic Acidemias

Microphthalmia—See Anophthalmia

Miller Syndrome

Foundation for Nager & Miller Syndromes
www.fnms.net/

Miscarriages—See Death, Neonatal and Infant

Mitochondrial Diseases

United Mitochondrial Disease Foundation*
www.umdf.org/site/c.8qKOJ0MvF7LUG/b.7929671/k.BDF0/Home.htm

*Includes Leigh disease; Kearns–Sayre syndrome; Pearson marrow-pancreas syndrome; mitochondrial encephalomyopathy/lactic acidosis and stroke-like episodes; myoclonic epilepsy/ ragged red fibers; neurogenic weakness, ataxia, retinitis pigmentosa.

National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov/index.htm

Moebius Syndrome

Moebius Syndrome Foundation
www.moebiussyndrome.com/

Morquio Disease—See Tay–Sachs Disease

Mucopolidoses—Also see Tay–Sachs Disease

ML4 Foundation
www.ml4.org/
National MPS Society*
<http://mpssociety.org/>

*Includes mucopolysaccharidosis, mucopolidosis, Hunter syndrome, Hurler syndrome, Maroteaux–Lamy syndrome, Sanfilippo syndrome, and Scheie syndrome

Mucopolysaccharide Disorders—Also see Tay–Sachs Disease

National MPS Society
www.mpssociety.org

Multiple Births

International Twins Association
www.intltwins.org/index.php/en/
Mothers of Supertwins (MOST)

www.mostonline.org/
 Multiple Births Foundation (UK)
www.multiplebirths.org.uk/
 National Organization of Mothers of Twins Clubs
www.nomotc.org/
 Twins Clubs (UK)
www.twinsclub.co.uk/
 The Twins Foundation
www.twinsfoundation.com
 Twins and Multiple Births Association
www.tamba.org.uk/ttsappeal?tab=1

Multiple Sclerosis

International MS Support Foundation
www.msif.org/
 Multiple Sclerosis Society of Canada
beta.mssociety.ca/
 National Multiple Sclerosis Society
www.nationalmssociety.org/

Muscular Dystrophy

FacioScapuloHumeral Muscular Dystrophy Society*
www.fshsociety.org/
 *Includes muscular dystrophy, facioscapulohumeral muscular dystrophy,
 Landouzy–Dejerine facioscapulohumeral muscular dystrophy
 Cure SMA*

www.curesma.org/
 *Includes spinal muscular atrophy, Werdnig–Hoffmann disease, Oppenheim dis-
 ease, Kugelberg–Welander disease, Aran–Duchenne type

Muscular Dystrophy Association*

www.mda.org/
 *Includes many muscle diseases such as Becker, Duchenne, congenital, facioscapu-
 lohumeral, limb-girdle muscular dystrophy, myotonic dystrophy; amyotrophic
 lateral sclerosis; Werdnig–Hoffmann, Kugelberg–Welander, Charcot–Marie–
 Tooth diseases; Friedreich ataxia; myasthenia gravis; McArdle, Pompe, Cori
 diseases; phosphofructokinase deficiency; carnitine palmitoyltransferase defi-
 ciency; malignant hyperthermia; arthrogryposis; miscellaneous myopathies

Muscular Dystrophy Association of Canada

www.muscle.ca

Parent Project Muscular Dystrophy

www.parentprojectmd.org/site/PageServer?pagename=nws_index

Myasthenia Gravis—Also see Muscular Dystrophy

Myasthenia Gravis Foundation of America

www.myasthenia.org

Myelin Disorders

The Myelin Project*

www.myelin.org/

*Also includes hypomyelination, delayed myelination, dysmyelination, periventricular leukomyelasia, macroencephaly, microencephaly

Myelin Repair Foundation

www.myelinrepair.org/

Myoclonus

Dystonia Medical Research Foundation

<http://dystonia-foundation.org/>

European Parkinson's Disease Foundation

www.epda.eu.com/he/

Myotonia Congenita—See Muscular Dystrophy

Myotubular Myopathy

Centronuclear and Myotubular Myopathy (UK)

<http://centronuclear.org.uk/>

Myotubular Myopathy Resource Group*

www.mtmrg.org/

*Includes centronuclear myopathy

Nager Syndrome

Foundation for Nager and Miller Syndromes

www.fnms.net

Nail–Patella Syndrome

Nail-Patella Syndrome Worldwide

www.npsw.org

Narcolepsy

American Sleep Association

www.sleepassociation.org/

Narcolepsy Network

<http://narcolepsynetwork.org/>

National Institute of Neurological Disorders and Stroke, National Institutes of Health

www.ninds.nih.gov

National Sleep Foundation

www.sleepfoundation.org

Neural Tube Defects—See Hydrocephalus; Spina Bifida

Neurofibromatosis

Neurofibromatosis Network

www.nfnetwork.org/

Children's Tumor Foundation

www.ctf.org/

Neurological Disorders—Also see specific disorder

National Institute of Neurological Disorders and Stroke, National Institutes of Health

www.ninds.nih.gov

Nevoid Basal Cell Carcinoma Syndrome—Also see Cancer
 BCCNS Life Support Network
www.gorlinsyndrome.org/

Niemann–Pick Disease—Also see Tay–Sachs Disease
 Center for Jewish Genetics
www.jewishgenetics.org
 National Niemann-Pick Disease Foundation
www.nnpdf.org/

Noonan Syndrome
 Noonan Syndrome Foundation
www.teamnoonan.org/
 Noonan Syndrome Foundation
<http://www.teamnoonan.org/>

Ollier Disease
 Bone Tumor.Org
www.bonetumor.org/tumors-cartilage/olliers-syndrome

Oppenheim Disease—See Muscular Dystrophy

Organic Acidemias—Also see Metabolic Disorders
 Organic Acidemia Association*
www.oaanews.org/index.htm

*Includes organic aciduria, isovaleric acidemia, methylmalonic acidemia, propionic acidemia, acidemia, and errors of amino and fatty acid metabolism

Osler Weber Rendu Syndrome—See Hereditary Hemorrhagic Telangiectasia

Osteogenesis Imperfecta—Also see Bone Diseases
 Osteogenesis Imperfecta Foundation
www.oif.org

Osteoporosis
 National Osteoporosis Foundation
<http://nof.org/>
 Osteoporosis and Related Bone Diseases, National Research Center, National Institutes of Health
www.niams.nih.gov/Health_Info/Bone/

Ovarian Cancer—Also see Cancer
 Familial Ovarian Cancer Registry
<http://ovariancancer.com/>
 National Ovarian Cancer Coalition
www.ovarian.org/

Oxalosis—Also see Kidney Diseases
 Oxalosis and Hyperoxaluria Foundation*
www.ohf.org
 *Also includes primary hyperoxaluria (PH), hyperoxaluria, oxaluria, calcium-oxalate kidney stones

Paget Disease (of the Bone) Paget Foundation

www.paget.org/

Pallister–Hall Syndrome

NORD

www.rarediseases.org/rare-disease-information/rare-diseases/byID/1016/viewAbstract

Pallister–Killian Syndrome

PKS Kids

www.pkskids.net/

Parkinson Disease

American Parkinson Disease Association

www.apdaparkinson.org/

National Parkinson Foundation

www.parkinson.org/

Parkinson's Action Network

<http://parkinsonsaction.org/>

Parkinson's Disease Foundation

www.pdf.org

The Michael J. Fox Foundation for Parkinson's Research

www.michaeljfox.org/

Patau Syndrome—See Chromosome Abnormalities; Trisomy 18/13

Peutz–Jeghers Syndrome—See Polyposis

Phenylketonuria (PKU)—Also see Metabolic Disorders

Children's PKU Network (CPN)

www.pkunetwork.org/Childrens_PKU_Network/Home.html

National PKU Alliance

<http://npkua.org/aboutnpkua/memberorganizations.aspx>

Pierre Robin Syndrome—See Stickler Syndrome

Pigment Disorders—See specific disorder such as Albinism; Vitiligo

Polycystic Kidney Disease—Also see Kidney Diseases

National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health

www.niddk.nih.gov

Polycystic Kidney Research Foundation

www.pkdcure.org/

Polyposis

Familial Gastrointestinal Cancer Registry (Canada)

www.zanecohencentre.com/fgicr

FAP Support Group

www.fapgene.com/

Porphyria—Also see Iron Overload Diseases

American Porphyria Foundation

www.porphyrifoundation.com/

Prader–Willi Syndrome

Prader-Willi Syndrome Association (UK)

www.pwsa.co.uk/

Prader-Willi Syndrome Association (USA)

www.pwsausa.org

Progeria

Progeria Research Foundation*

www.progeriaresearch.org/

*Includes progeria, Cockayne syndrome, Werner syndrome

Propionic Acidemia—See Metabolic Disorders; Organic Acidemias

Prune Belly Syndrome

Prune Belly Syndrome Network*

<http://prunebelly.org/>

*Also includes Eagle Barrett syndrome

Pseudoxanthoma Elasticum

NORD

<http://rarediseases.org/rare-diseases/pseudoxanthoma-elasticum-pxe/>

PXE International (PXE)

www.pxe.org/

Rare Disorders—See Genetic Disorders, General

Recreation and Leisure

Blaze Sports

www.blazesports.org/

Canadian Wheelchair Basketball Association

<http://www.wheelchairbasketball.ca/>

Disabled Sports, USA

www.disabledsportsusa.org/

HSA International (Handicapped Scuba Association)

www.hsascuba.com/

PATH International

www.pathintl.org/

Special Olympics International

www.specialolympics.org/

Wheelchair Sports USA

www.wasusa.org/

Wilderness on Wheels

www.wildernessonwheels.org/

Refsum Disease—See Tay–Sachs Disease

Rehabilitation

National Rehabilitation Association

www.nationalrehab.org/

National Rehabilitation Information Center
www.naric.com/
Rehabilitation International
www.riglobal.org/

Reiter Syndrome—See Ankylosing Spondylitis; Arthritis

Renal Disorders—See Kidney Diseases; specific disease

Respite

ARCH National Respite Network
<http://archrespite.org/>

Retinitis Pigmentosa—Also see Visual Impairment

Foundation Fighting Blindness
www.blindness.org/
Laurence Moon Bardet Biedl Syndrome Network
<http://mlmorris.com/lmbbs/>
RP International
<http://rpinternational.org/>

Rett Syndrome

International Rett Syndrome Association
www.rettsyndrome.org/

Rubinstein–Taybi Syndrome

Rubinstein-Taybi Parent Group
<http://rubinstein-taybi.com/>

Russell–Silver Syndrome

Magic Foundation*
www.magicfoundation.org/www

*Also includes Silver syndrome, Russell syndrome, Silver–Russell syndrome

Sandhoff Disease—See Tay–Sachs Disease

Sanfilippo Disease—See Tay–Sachs Disease; Mucopolysaccharide Disorders

Scheie Disease—See Mucopolysaccharide Disorders

Scleroderma

Scleroderma Foundation
www.scleroderma.org/site/PageServer

Scoliosis

National Scoliosis Foundation
www.scoliosis.org
Scoliosis Research Society
www.srs.org/

Self-Help Clearinghouses

American Self-Help Group Clearinghouse
<https://rarediseases.org/organizations/american-self-help-group-clearinghouse/>

National Self-Help Clearinghouse
www.mhselfhelp.org/

Sexuality

Sexuality Information and Education Council of the United States
www.siecus.org/

Short Stature—Also see Growth Problems

Human Growth Foundation
www.hgfound.org
 Little People of America
www.lpaonline.org
 MAGIC Foundation for Children's Growth
www.magicfoundation.org

Shprintzen Syndrome—See Chromosome Abnormalities

Shwachman Syndrome

Shwachman-Diamond Syndrome International*
www.shwachman-diamond.org

*Also includes Shwachman–Diamond syndrome, Burke syndrome, Shwachman–Bodian syndrome

Shy–Drager Syndrome

The Multiple System Atrophy Coalition (formerly Shy-Drager Syndrome)
www.multiplesystematrophy.org/

Siblings

Sibling Support Project
www.siblingsupport.org/
 The Arc
www.thearc.org/siblings

Sickle Cell Disease

American Sickle Cell Anemia Association
<http://www.ascaa.org/>
 National Heart, Lung, and Blood Institute National Institutes of Health
www.nhlbi.nih.gov
 Sickle Cell Disease Association of America
www.sicklecelldisease.org

Silver–Russell Syndrome—See Russell–Silver Syndrome

Sjögren Syndrome

Sjögren's Syndrome Foundation
www.sjogrens.org/

Skeletal Dysplasias

Little People of America
www.lpaonline.org/regional-skeletal-dysplasia-clinics

Skeletal Dysplasia Group (UK)
www.skeletaldysplasiagroup.org.uk/

Skin Disorders—Also see specific disorder
Foundation for Ichthyosis and Related Skin Types
www.firstskinfoundation.org

Smith–Magenis Syndrome—See also Chromosome Abnormalities
Parents and Researchers Interested in Smith-Magenis Syndrome*
www.prisms.org
*Also includes deletion 17p11.2

Sotos Syndrome
Sotos Syndrome Support Association
<http://sotossyndrome.org/>
Sotos Syndrome Support Group of Canada
www.sssac.com

Spina Bifida
Hydrocephalus Association
www.hydroassoc.org/
SHINE
www.shinecharity.org.uk/
Spina Bifida Association of America
[www.spinabifidaassociation.org/site/c.evKRI7OXIoJ8H/b.8028963/k.BE67/](http://www.spinabifidaassociation.org/site/c.evKRI7OXIoJ8H/b.8028963/k.BE67/Home.htm)
Home.htm
Spina Bifida and Hydrocephalus Association of Canada
www.sbhac.ca

Spinal Muscular Atrophy
Families of Spinal Muscular Atrophy
www.fsma.org

Sprue—See Gluten Intolerance

Stickler Syndrome
Stickler Involved People*
www.sticklers.org/sip2/
*Includes Stickler syndrome, hereditary progressive arthro-ophthalmopathy,
Pierre Robin syndrome

Sturge–Weber Syndrome—Also see Vascular Birthmarks and Malformations
Sturge-Weber Foundation
www.sturge-weber.org/

Sudden Infant Death Syndrome—Also see Death, Neonatal and Infant
Centers for Disease Control and Prevention
www.cdc.gov/sids/
First Candle/SIDS Alliance
www.firstcandle.org/
SIDS Resources
www.sidsresources.org/

Syringomyelia

American Syringomyelia Alliance Project
<http://asap.org/>

Tall Stature—Also see Growth Problems

Tall Clubs International
www.tall.org/

Tangier Disease—See Tay–Sachs Disease

Tay–Sachs Disease

Center for Jewish Genetic Diseases
www.jewishgenetics.org
 National Tay–Sachs and Allied Diseases Association*
www.ntsad.org/

*Includes the following disorders: Batten, Canavan, Fabry, Farber, fucosidosis, Gaucher, Krabbe, Landing, mannosidosis, metachromatic leukodystrophy, mucopolysaccharidoses I–IV (sialidosis, I-cell disease, etc.), mucopolysaccharidoses (Hunter, Hurler, Scheie, Maroteaux–Lamy, Morquio, Sanfilippo, Sly or beta-glucuronidase deficiency), Niemann–Pick, Pompe, Refsum, Tangier, Tay–Sachs, Wolman disease, and others

Thalassemia—Also see Iron Overload Diseases

AHEPA–American Hellenic Educational Progressive Association*
<http://ahepa.org/ahepa/>

*Thalassemia minor, thalassemia major, thalassemia intermedia, beta-thalassemia, Cooley anemia
 Cooley's Anemia Foundation
www.thalassemia.org/

Thrombocytopenia Absent Radius (TAR) Syndrome

NORD
<http://rarediseases.org/rare-disease-information/rare-diseases/byID/657/viewAbstract>

Thyroid Disorders

American Thyroid Association
www.thyroid.org/
 AllThyroid.Org
www.allthyroid.org/
 Graves' Disease and Thyroid Foundation
www.gdatf.org/

Torsion Dystonia—See Dystonia

Tourette Syndrome

National Institute of Neurological Disorders and Stroke, National Institutes of Health
www.ninds.nih.gov
 National Tourette Syndrome Association
www.tsa-usa.org/

Travel

Handicapped Travel Club
www.handicappedtravelclub.com/
Mobility International
www.miusa.org/
Society for Accessible Travel and Hospitality
www.sath.org
Travelin' Talk
www.nchpad.org/

Treacher Collins Syndrome

Treacher Collins Foundation

Tremor, Familial

Coping With Essential Tremor
www.essentialtremor.org

Trisomy 9—See Chromosome Abnormalities

Trisomy 18/13—See also Chromosome Abnormalities

Chromosome 18 Registry and Research Society
www.chromosome18.org/
Support Organization for Trisomy (SOFT) 18, 13, and Related Disorders
www.trisomy.org

Tuberous Sclerosis

Tuberous Sclerosis Alliance
www.tsalliance.org

Turner Syndrome—Also see Chromosome Abnormalities; Short Stature

Turner's Syndrome Society of Canada
www.turnersyndrome.ca/
Turner Syndrome Society of the United States
www.turnersyndrome.org/
Turner Syndrome Foundation
www.turnersyndromefoundation.org/

Twins—See Multiple Births

Tyrosinemia—See Liver Diseases; Metabolic Disorders

Tyrosinosis—See Liver Diseases

Ulcerative Colitis—See Inflammatory Bowel Disease

Urea Cycle Disorders—Also see Metabolic Disorders; Organic Acidemias

National Urea Cycle Disorders Foundation
www.nucdf.org/

Usher Syndrome—See Deaf-Blind; Hearing Impairment; Retinitis Pigmentosa; Vision Impairment

Vascular Birthmarks and Malformations— Also see Sturge–Weber Syndrome; Von Hippel–Lindau Syndrome

Vascular Birthmarks Foundation*

www.birthmark.org/

*Includes vascular malformations, port wine stain, Klippel-Trénaunay syndrome, hereditary hemorrhagic telangiectasia, Sturge–Weber syndrome, arteriovenous malformations, Von Hippel–Lindau syndrome, lymphangiomas

VATER Syndrome and Association

VACTERL Association

<http://stfrancishealth.org/health-library.html?documentID=nord486>

Velo-Cardio Facial Syndrome

Velo-Cardio Facial Syndrome Educational Foundation

<http://www.vcfsfa.org.au/pages/home.php>

Vision Impairment—Also see Disabilities, General

American Council of the Blind

www.acb.org/

American Foundation for the Blind

www.afb.org

Association for Education and Rehabilitation of the Blind and Visually Impaired

<http://aerbvi.org/>

Blind Children's Center

www.blindchildrenscenter.org/

Braille Institute

www.brailleinstitute.org

Canadian National Institute for the Blind

www.cnib.ca

Carroll Center for the Blind

www.carroll.org

Center for the Partially Sighted

www.low-vision.org

Choice Magazine Listening

www.choicemagazinelistening.org/

Foundation Fighting Blindness

www.blindness.org/

Guide Dog Foundation for the Blind

www.guidedog.org

Guide Dogs for the Blind

<http://welcome.guidedogs.com/>

Guiding Eyes for the Blind

www.guidingeyes.org/

Leader Dogs for the Blind

www.leaderdog.org

Library of Congress: Persons With Disabilities

www.loc.gov/disabilityawareness/people/

Lighthouse International

<http://lighthouse.org/>

National Association for Parents of the Visually Impaired

www.afb.org/directory/profile/national-association-of-parents-of-children-with-visual-impairments-national-headquarters/12

National Braille Association

www.nationalbraille.org

National Federation of the Blind

www.nfb.org

Learning Ally (formerly Recording for the Blind and Dyslexic)

www.learningally.org/

The Seeing Eye

www.seeingeye.org/

Vision Council of America

www.thevisioncouncil.org/

Vitiligo

National Vitiligo Foundation

www.nvfi.org

Von Hippel–Lindau Syndrome—Also see Cancer; Sturge–Weber Syndrome; Vascular Birthmarks and Malformations

VHL Family Alliance

www.vhl.org

Von Willebrand Disease—See Hemophilia

Werdnig–Hoffman Disease—See Muscular Dystrophy

Werner Syndrome—See Progeria

Williams Syndrome

Williams Syndrome Association

www.williams-syndrome.org

Wilson Disease—Also see Liver Diseases

Wilson's Disease Association

www.wilsonsdisease.org

Wolf–Hirschhorn Disease—Also see Chromosome Abnormalities

4p-Support Group

<http://4p-supportgroup.org/>

Wolf Hirschhorn Support Group UK

www.whs4pminus.co.uk/

Wolman Disease—See Tay–Sachs Disease

Xeroderma Pigmentosum

Share and Care Cockayne Syndrome Network

<http://cockaynesyndrome.org/>

Xeroderma Pigmentosum Society

www.xps.org

GLOSSARY

All terms in this section refer to their application in humans and human genetics.

aberration—any abnormality of chromosome structure or number

acentric fragment—a chromosome piece without a centromere due to breakage

acrocentric chromosome—one in which the centromere is near the end of the chromosome

agenesis—imperfect development or absence of an organ or its failure to form

allele—any one of two or more alternate forms of a gene located at the same locus

allozymes—enzymes that differ in electrophoretic mobility because of different alleles at a gene locus

amelia—complete congenital absence of one or more limbs

amnion—the innermost membrane of the amniotic sac that surrounds the fetus

amplification—the production of extra copies of genes or a section of DNA

anencephaly—a neural tube defect with partial or complete absence of the cranial vault and a rudimentary brain

aneuploid—any chromosome number that is not an exact multiple of the haploid (N) set; thus, trisomy 18 with 47 chromosomes is an aneuploidy, but triploidy with 69 chromosomes is a polyploidy

anhidrosis—absence of sweating

aniridia—absence of the iris of the eye

anodontia—absence of teeth

anomaly—abnormal variation in form or structure

anotia—absence of pinna of the ear

anticipation—refers to the occurrence of a trait or disorder at an earlier age with each successive generation and/or the increased severity of a disorder with each successive generation

antimongoloid slant—downward slant of palpebral fissures of eye

aplasia—absence of or irregular structure of tissue or an organ

apoenzyme—the protein part of a complex (conjugated) holoenzyme

apoptosis—the normal cellular process of programmed cell death

arcus corneae—an opaque ring seen in the cornea that is caused by a deposit of cholesteryl esters

ascertainment—the process of finding individuals or families for inclusion in genetic studies

association—anomalies that occur together more often than would be expected by chance but have not yet been recognized as a syndrome

assortative mating—nonrandom mating practices based on choosing or rejecting mates with certain traits

atresia—absence or closure of a normal opening

autosome(al)—any chromosome that is not a sex chromosome (X or Y); in normal human somatic cells, there are 22 pairs (44) of autosomes and two sex chromosomes (XX or XY)

Barr body—sex chromatin found at the edge of the cell nucleus in normal females that represents the genetically inactive X chromosome

base pair—two nitrogenous bases bonded together; in DNA, adenine pairs with thymine and cytosine pairs with guanine

base sequence—the order of bases on a chromosome or DNA fragment

brachydactyly—abnormally shortened digits

Brushfield spots—speckled areas noted on the iris in a small percentage of normal individuals and a large percentage of persons with Down syndrome

camptodactyly—flexion contracture or curvature of finger(s), usually the fifth finger

candidate gene—one that may be the site of causation for a given disease

canthus—outer or inner corner of the eye where upper and lower lids meet

carrier—a person who is heterozygous, possessing two different alleles of a gene pair (e.g., Aa as opposed to aa or AA)

centromere—the primary constriction of a chromosome where the long and short arms meet

CHARGE association—the nonrandom association of coloboma, heart disease, atresia choanal, retarded growth, and/or nervous system anomalies, genital anomalies, and ear anomalies or deafness

chimera—an organism composed of two or more cell lines; the product of the fusion of embryos

chromatid—after replication of a chromosome, two subunits attached by the centromere can be seen; each is called a chromatid, and after separation each becomes a chromosome of a daughter cell

chromatin—the material of which chromosomes are composed; contains DNA, RNA, histones, and nonhistone proteins

chromosomal translocation—see *translocation*

chromosome—microscopic structures in the cell nucleus composed of chromatin that contain genetic information and are constant in number in a species; humans have 46 chromosomes, 22 autosome pairs, and 2 sex chromosomes

clinical utility—relevance, usefulness of an intervention after accounting for potential harms. The ability of a diagnostic genetic test to prevent adverse health outcomes (e.g., morbidity, mortality) through the selection of effective treatments informed by the test's results

clinodactyly—crooked finger that is curved inward sideways, usually the fifth digit

clone—a genetically identical cell population derived from a common ancestor; to clone an organism is to make a genetically identical copy of it

cloning DNA—manipulation to produce multiple copies of a single gene or groups of genetically identical cells from the same ancestor

codominance—the expression of each of a pair of alleles when present in the heterozygous state

codon—triplet bases in nucleic acids specifying placement of a specific amino acid in a polypeptide chain

coenzyme—an organic molecule that acts as a cofactor (e.g., vitamin B₁₂)

cofactor—the nonprotein component of a conjugated enzyme that is required for activity; it can be organic or inorganic; if organic, often called coenzyme

coloboma—defect in or absence of tissue, usually in the iris of the eye; usually seen as a gap

complementary DNA (cDNA)—DNA that is synthesized from an mRNA template; usually used as a probe in physical mapping

complementation—ability of cells with different gene mutations to crosscorrect in cell culture

complex trait—a trait that has a genetic component but does not follow Mendelian inheritance patterns; possibly involves two or more genes or gene–environment interaction

compound heterozygote—presence of two different mutations of a given gene, one on each allele on each chromosome

concordance—the presence of a certain trait in two individuals, usually twins

congenital—present at birth; a congenital trait may or may not be caused by genetic factors

consanguineous—related by descent from a common ancestor, usually in the preceding few generations; blood relatives

consultand—the person whose genotype is of primary importance to the genetic counseling problem at hand; in practice, often used synonymously with *counselee*

contiguous gene syndrome—name given to disorders arising from small chromosome deletions or duplications of adjacent but functionally unrelated genes

copy number variation—interindividual differences in the number of copies of a gene or segment of DNA, such as may occur through large duplications or deletions

crossing over—the physical event or exchange that gives rise to recombinant chromatids

crossovers—chromatid with genetic material from each homologous chromosome

deformation—anomaly resulting from mechanical forces causing constraint on the fetus

deletion—loss of all or part of a chromosome

diploid—the number of chromosomes normally present in somatic cells; in humans, this is 46, and is sometimes symbolized as 2N

discordance—when two members of a twin pair do not exhibit the same trait

dizygotic—twins originating from two different fertilized eggs; fraternal twins

DNA—the primary genetic material in humans consisting of nitrogenous bases, a sugar group, and phosphate combined into a double helix

DNA fingerprint—a person's unique pattern in regard to a selected section or total DNA

DNA hybridization—the process of the joining of two complementary DNA strands to form a double-stranded molecule

DNA probe—a selected fragment of DNA that is labeled, often with a radioactive isotope and, through molecular hybridization, is used to find very similar or complementary regions of DNA in a sample

DNA repair gene—a gene whose product functions in the repair of DNA

dominant—a trait is considered dominant if it is expressed when one copy of the gene determining it is present

dyshistogenesis—result from aberrant development of a specific tissue type

dysplasia—developmental abnormality of a tissue, for example, a nevus

empirical risk—one based on observed data, not theoretical models

epigenetics—heritable genetic control factors that turn genes on/off and are impacted by environmental exposures (age, diet, toxins, drugs, lifestyle). Epigenetic changes do not involve DNA sequence alterations and include DNA methylation, histone modifications, and RNA silencing

epigenome—heritable changes to the chemical structure surrounding DNA that influence gene expression without altering the DNA sequence

epistasis—the prevention of the expression of one gene by another gene at a different locus

eugenics—improvement of a species by genetic manipulations

euploidy—having a complete correct chromosome set

exome—the part of the genome that encodes proteins (not introns or noncoding DNA)

exons—structural gene sequences retained in messenger RNA and eventually translated into amino acids

expressivity—see *variable expressivity*

familial—the occurrence of more than one case of an anomaly in a family; a trait that appears with a higher frequency in close relatives than in the general population; it is not synonymous with *hereditary*

fitness—ability of a person with a certain genotype to reproduce and pass his or her genes to the next generation

flanking region—DNA on either side of a particular locus

forme fruste—minimal manifestation or mild form of a disorder

fusion gene—a hybrid gene resultant from the joining of two separate genes, such as may occur through a chromosomal translocation

gamete—mature reproductive cells containing the haploid number of chromosomes (sperm or ovum)

gastroschisis—a congenital abdominal wall defect characterized by antenatal evisceration of the intestine through a small opening

gene—the functional unit of heredity; a sequence of nucleotides along the DNA of a chromosome that codes for a functional product such as RNA or a polypeptide

gene amplification—see *amplification*

gene mapping—assignment of genes to specific sites on specific chromosomes

gene pool—all of the genes in a specific breeding population at a certain time

genetic code—nucleotide base sequence in DNA or RNA coding for specific amino acids

genetic constitution—a person's genetic makeup; refers to either one gene pair or all

genetic load—the recessive deleterious genes concealed in the heterozygous state within a population

genocopy—the production of the same phenotypic appearance by different genes

genome—the total genetic complement of an individual genotype—a person's genetic constitution at one locus or in total

genomic imprinting—differences in gene expression depending on whether the gene in question is inherited from the individual's mother or father

genomics—the study of the genome including gene sequencing, mapping, and function

genotype—the specific set of two inherited alleles

germline mutation—a heritable mutation present within a germ cell that is incorporated into every cell of the developing offspring

hallux—big toe

hamartoma—an overgrowth of tissue normally present but in abnormal proportion and distribution; it is not malignant

haploid—the number of chromosomes present in the gamete; in humans this is 23, and can be symbolized as N

haploinsufficiency—the condition wherein one copy of a specific gene is not enough for normal development or function if one copy of that gene has been inactivated or deleted

haplotype—a set of DNA variations or polymorphisms that tend to be inherited together; haplotype can refer to single SNPs or a combination of alleles on the same chromosome

hemizygous—the condition in which only one copy of a gene pair is normally present, and so its effect is expressed (e.g., the genes on the X chromosome of the male as there is no counterpart present)

heterogeneity—in genetic use, the production of the same phenotype by different genetic mutations; in clinical use, differences within the same disorder

heteromorphism—morphologic chromosome polymorphism or variant

heteroplasmy—presence of multiple mitochondrial DNA sequence in the same mitochondria of the same individual

heterozygous—state in which the two alleles of a gene pair are different (e.g., Aa as opposed to aa or M)

HLA complex—the major histocompatibility region on chromosome 6

holandric—a trait controlled by genes on the Y chromosome; Y-linked inheritance

holoenzyme—a conjugated or complex enzyme consisting of an apoenzyme and cofactor

homologous chromosomes—chromosomes that are members of the same pair and normally have the same number and arrangement of genes

homozygous—state in which both alleles of a given gene pair are identical (e.g., AA or aa as opposed to Aa)

hydrocephalus—abnormal accumulation of fluid in the cranium, usually in ventricles or subarachnoid space, leading to an enlarged head and pressure on the brain

hyperlipidemia—increased blood lipid levels

hyperlipoproteinemia—elevation of blood lipoproteins

hyperplasia—increased cell production in normal tissues or organs

hypertrichosis—excessive hair growth

immunogenetics—the study of genetics involved in the immune system

inborn errors of metabolism—inherited biochemical disorders caused by single gene mutations affecting enzymes involved in metabolic pathways

inherited cancer syndrome—a condition involving increased cancer susceptibility due to inherited germline mutations

introns—intervening gene sequences in messenger RNA that are “cut out” and are not translated into amino acids

inversion—a chromosome aberration in which a segment has become reversed due to breakage, 180 degrees rotation, and reunion

in vivo—in the living organism

in vitro—in the test tube or laboratory

ion channel—a protein tunnel that crosses the cell membrane and changes conformation as it opens and closes in response to various signals; ion channels exist for such ions as calcium, chloride, potassium, and sodium

isochromosome—chromosome composed of either two long or two short arms due to abnormal separation during division

karyotype—the arrangement of chromosome pairs by number according to centromere position and length

Kayser–Fleischer ring—pigmented brownish-gold ring resulting from copper deposition in the cornea and seen in Wilson disease

library—a collection of cloned DNA probes

linkage—the close association of genes or other DNA sequences on the same chromosome. The closer two genes or other DNA sequences are to one another, the greater the probability they will be inherited together

linkage disequilibrium—when specific combinations of alleles for two (or more) linked loci occur more frequently than expected by chance

locus—the location on a chromosome where a gene resides

Lyon hypothesis—in the normal female (46,XX), one of the two X chromosomes is randomly inactivated and appears in somatic cells as sex chromatin

macroglossia—an unusually large tongue

macrosomia—growth excess of prenatal onset associated with several genetic disorders and seen in infants of diabetic mothers

malformation—morphologic defect of an organ resulting from an intrinsically abnormal developmental process

meiosis—reduction division of diploid germ cells resulting in haploid gametes

meiotic drive—mechanism resulting in unequal, nonrandom, or preferential assortment of chromosomes into gametes during meiosis

meningocele—bulging of meninges without involvement of the spinal cord

metabolome—the complement of all metabolites in the genome

metacentric chromosome—one in which the centromere is in the center of the chromosome

methylation—attachment of a methyl group to cytosine in DNA

microbiome—the microbial genomes of bacteria, bacteriophage, fungi, protozoa, and viruses, that live inside and on the human body

microcephaly—small head circumference, usually defined as below the third percentile for age, height, and weight; associated with intellectual disability in most cases

micrognathia—undersized jaws, especially the mandible

microsatellites—areas of the human genome where a 2, 3, 4, or 5 bp DNA sequence occurs repeatedly. Used interchangeably with STRs

microstomia—unusually small mouth

microtia—unusually small external ear

minisatellites—areas of the human genome where a 10 to 100 bp DNA sequence occurs repeatedly; used interchangeably with VNTRs

minute—a very small chromosome fragment

missense mutation—one in which the nucleotide alteration results in the placement of a different amino acid in the polypeptide chain from the one originally specified

mitosis—somatic cell division that normally results in no change from the usual diploid number of chromosomes

monosomy—missing one of a chromosome pair in normally diploid cells ($2N - 1 = 45$); a person with Turner syndrome ($45,X$) has a chromosome number of 45 instead of 46 and is monosomic for the X chromosome

monozygotic—twins originating from one fertilized egg; identical twins

mosaic—presence in the same individual of two or more cell lines that differ in chromosome or gene number or structure but are derived from a single zygote

multifactorial—determined by the interaction of several genes with environmental factors

multiple alleles—the occurrence of more than two alternate forms of a gene that can occupy the same locus, although only one can be present on each chromosome at a time

multiplexing—using several pooled samples simultaneously in analysis

MURCS association—nonrandom association of Mullerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia

mutagen—any agent that causes mutation or increases the mutation rate above the usual background rate existing

mutation—change in DNA sequence; can be heritable or induced by exposure to environmental stimuli

myelomeningocele—spina bifida with cord and membranes protruding

NADPH—nicotinamide adenine dinucleotide phosphate; is an essential coenzyme in cellular biochemistry, for oxidoreductase reactions (oxidized = NAD^+ and reduced = NADPH)

next-generation sequencing—a technology that permits fast and inexpensive sequencing of large amounts of DNA and RNA

nondisjunction—the failure of two homologous chromosomes or of sister chromatids to separate in meiosis appropriately during cell division, resulting in abnormal chromosome numbers in gametes or cells

nonsynonymous—category of exonic SNP that produces an amino acid change in the gene's protein

nuchal translucency—a thickening of the fetal neck seen on ultrasound examination in the first trimester; called *cystic hygroma* and *nuchal fold* when seen in the later trimesters

nucleotide—a nucleic acid building block comprising a nitrogenous base, a five-carbon sugar, and a phosphate group

oligonucleotide—a short segment of nucleotides

omphalocele—congenital abdominal wall defect, commonly known as umbilical hernia

oncogene—a mutated proto-oncogene that promotes unregulated cell growth, division, and cancer development

oncovirus—an RNA virus that causes cancer

p—in cytogenetics, refers to the short arms of a chromosome; in population genetics, stands for the gene frequency of the dominant allele

PCR—polymerase chain reaction. A laboratory technique whereby, using primers (i.e., 20–30 bp) that are specific to a genomic sequence of interest, free nucleotides in solution, the enzyme DNA polymerase, and repeated cycles of heating and cooling, large quantities of a specific genomic DNA sequence can be produced

pedigree—a diagrammatic representation of the family history

penetrance—fraction of individuals known to carry the gene for a trait who manifest the condition; a trait with 90% penetrance will not be manifested by 10% of the persons possessing the gene

personalized medicine—emerging health care practice that uses an individual's genetic profile to guide decisions regarding disease prevention, diagnosis, and treatment

pharmacogenetics—study of the variability in a drug's response as a result of a person's inherited genetic variability

pharmacogenomics—study of how drugs impact the total genome and interact with its expression output

phenocopy—a phenotype that mimics one that is genetically determined but is actually due to nongenetic causes

phenotype—the physical presentation resulting from the interaction between genes and the environment

philtrum—vertical groove between upper lip and nose

phocomelia—a type of limb defect in which proximal parts of extremities are missing so that a hand might be directly attached to the shoulder or attached by a single irregular bone

pleiotropy—the production of multiple phenotype effects by a single gene

polydactyly—presence of extra (supernumerary) digits

polygenic—a phenotypic trait whose expression is controlled by several genes at different loci, each having an additive effect

polymerase chain reaction—a technique to amplify a sequence of DNA using primers, which flank the DNA of interest, and multiple cycles of replication using a DNA polymerase enzyme

polymorphism—a genetic variation with two or more alleles that is maintained in a population, so that the frequency of the most common allele is not above 0.99, and the frequency of the uncommon alleles is maintained at a frequency of at least 0.01

polypeptide—chain of amino acids formed during protein synthesis; may be a complete protein molecule or combined with other polypeptides to form one

polyploidy—a cell or individual having more than two haploid sets in an exact multiple; examples are triploidy and tetraploidy

proband—the index patient; the person who brings the family to the attention of the geneticist

probe—see *DNA probe*

promoter—DNA site where the enzyme RNA polymerase binds to initiate transcription

propositus—essentially the same as *proband*

proteome—the complete set of all proteins in the genome

proto-oncogene—a gene that normally functions in cell growth and division, but when mutated can become a cancer-promoting oncogene

pseudogene—a copy of a gene that typically lacks introns and essential DNA sequences necessary for function

q—in cytogenetics, refers to the long arms of a chromosome; in population genetics, stands for the gene frequency of the recessive allele

recessive—when the effect of a gene is expressed phenotypically only when two copies are present, as in the homozygous recessive state (aa)

recombinant DNA—hybrid produced by combining DNA pieces from different sources

recombination—reassortment of genes to form new nonparental types

relative risk—the risk (or odds) that an individual with a certain risk factor will develop a disease compared to an individual without the risk factor. In genetics, relative risk is assessed by evaluating patients with inherited variations (typically polymorphisms or haplotypes) in two groups: one with a disease of interest, and one without

restriction enzymes—enzymes that recognize a specific base sequence in DNA and cut the DNA everywhere that the sequence occurs

restriction fragment length polymorphism—variation in a restriction enzyme recognition site in the fragments of DNA that have been cut by a restriction enzyme

RFLP—restriction fragment length polymorphism. Used in linkage and gene association studies of traits and diseases

RNA—ribonucleic acid

sentinel phenotype—disorders followed to monitor populations for genetic damage as an early warning system; usually refers to sporadic disorders that follow an autosomal dominant mode of inheritance

sequence—a pattern of multiple anomalies derived from a single prior anomaly; order of nucleotide bases in DNA or RNA

sequencing—a method to determine the order of bases in DNA or RNA

sex chromatin—the inactive X chromosome

sex chromosome—the X or the Y chromosome

sex influenced—an autosomally inherited trait whose degree of phenotypic expression is controlled by the sex of the individual

sex limited—an autosomally inherited trait that is manifested only in one sex

shagreen patch—raised, thickened skin plaque commonly seen in tuberous sclerosis

short tandem repeats—see *STRs*

siblings—brothers and sisters from the same natural parents

single-nucleotide polymorphism—single-nucleotide polymorphisms (SNPs) are a type of polymorphism involving DNA variation of a single base pair at a specific loci in the genome

sister chromatids—identical chromatids of the same duplicated chromosome before cell division

somatic cell—any cell other than a germ cell

somatic mutation—an acquired, nonhereditary mutation that occurs in any body cell except for germ cells

spina bifida—neural tube defect of the spinal column through which the cord or the membranes can protrude

sporadic—an isolated occurrence of a trait in a family

sporadic cancer—cancer that arises from acquired factors and is not attributable to a heritable predisposition or risk

STRs—short tandem repeats. DNA sequence with multiple short sequences of 2, 3, 4, or 5 bp repeated over and over, up to several hundred times

structural gene—one that determines the amino acid sequence of the polypeptide chain

submetacentric chromosome—one in which the centromere is between the meta-centric and acrocentric position

syndactyly—webbing or fusion of adjacent fingers or toes

syndrome—recognizable pattern of multiple anomalies, presumed to have the same etiology

synonymous—category of exonic SNP that does not produce an amino acid change in the gene's protein

syntenic—genes on the same chromosome that are more than 50 map units apart

tandem repeats—multiple copies of the same base sequence in a segment of DNA

teratogen—an agent acting on the embryo or fetus prenatally, altering morphology or subsequent function; causes teratogenesis

teratogenesis—exogenous induction of structural, functional, or developmental abnormalities caused by agents acting during embryonic or fetal development

tetraploid—cell or person with four copies of each chromosome, having a chromosome number of $4N = 96$

TORCH—abbreviation for the following organisms: toxoplasmosis, rubella, cytomegalovirus, and herpes simplex

transcription—the process by which complementary mRNA is synthesized from a DNA template

transcriptome—the complete set of RNA in the genome

translation—the process whereby the amino acids in a given polypeptide are synthesized from the mRNA template

translocation—transfer of all or part of a chromosome to another chromosome

transposable element—segment of DNA that can move from place to place in the genome; a jumping gene

triploid—cell or person with three copies of each chromosome, having a chromosome number of $3N = 69$

trisomy—the presence of one extra chromosome in an otherwise diploid chromosome complement ($2N + 1 = 47$); the most common autosomal trisomy is trisomy 21, or Down syndrome

tumor suppressor gene—a gene that functions in maintaining cell growth and division within healthy boundaries, but when mutated or silenced, can promote cancer development

uniparental disomy—both chromosomal homologs are inherited from the same parent instead of inheriting one copy of each chromosome pair from the mother and the father

VACTERL association—the nonrandom finding of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies

variable expressivity—when the same genotype produces disease phenotypes of varying clinical severity

variable number of tandem repeats—see *VNTRs*

VATER association—a nonrandom association of vertebral defects, anal atresia, tracheo-esophageal fistula, and radial or renal anomalies

VNTRs—variable number of tandem repeats in a minisatellite region; short stretches of DNA sequence of 10 to 100 bp repeated over and over anywhere from 2 to 20 times

wild type—the form of a gene or characteristic usually found in nature and thus usually considered the “normal” one; usually the most common as well

X-linked—located on the X chromosome

Y-linked—located on the Y chromosome

zygote—the diploid ($2N$) cell formed by fusion of a haploid egg and a haploid sperm during fertilization that develops into the embryo

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