LASHLEY’S ESSENTIALS of Clinical Genetics in Nursing Practice
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Dr. Kasper has published more than 110 research papers, book chapters, reviews, and editorials in highly respected nursing and scientific journals. She was the founding editor of Biological Research for Nursing and is the current editor of the Annual Review of Nursing Research. She was a co-author of the ground-breaking book, In Search of Nursing Science, used in many nursing programs as a philosophy of science text. Her research has included funding from the National Institutes of Health (NIH), the National Aeronautics and Space Administration (NASA), and the Department of Veterans Affairs as the principal investigator on 10 grants. Additionally, she has received funding for 11 studies from foundations and universities, and has participated as a co-investigator on 14 additional interdisciplinary grants ranging from clinical genomics in nursing practice to genotoxic changes arising from embedded military-relevant heavy metals.

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.
Felissa R. Lashley, PhD, RN, FABMGG, is former dean and professor at the College of Nursing at Rutgers, The State University of New Jersey. Prior to that, she was a dean and professor at the Southern Illinois University—Edwardsville and a clinical professor of pediatrics at the School of Medicine, Southern Illinois University—Springfield. She is the first nurse to be certified as a PhD medical geneticist by the American Board of Medical Genetics, and is a founding fellow of the American College of Medical Genetics. She began her practice of genetic evaluation and counseling in 1973.
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.
Editor's Note

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
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
Preface

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
Tonya A. Schneidereith
Felissa R. Lashley

REFERENCE

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 (Mjoseth, 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
I: The Basics

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.

REFERENCES


BIBLIOGRAPHY


CHAPTER 4

Inheritance Patterns in Human Phenotypes and Types of Genetic Disorders

Timothy M. Dwyer, Rivka L. Glaser, and Tracey M. Mason

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
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>
<thead>
<tr>
<th>TABLE 4.1 Major Characteristics of Autosomal Recessive Inheritance and Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>► Gene is located on autosome.</td>
</tr>
<tr>
<td>► Two copies of the mutant gene are needed for phenotypic manifestations.</td>
</tr>
<tr>
<td>► Males and females are affected in equal numbers on average.</td>
</tr>
<tr>
<td>► No sex difference in clinical manifestations is usual.</td>
</tr>
<tr>
<td>► Family history is usually negative, especially for vertical transmission (in more than one generation).</td>
</tr>
<tr>
<td>► Other affected individuals in the family in the same generation (horizontal transmission) may be seen.</td>
</tr>
<tr>
<td>► Consanguinity or relatedness is more often present than in other types of inherited conditions.</td>
</tr>
<tr>
<td>► Fresh gene mutations are rare.</td>
</tr>
<tr>
<td>► Age of disease onset is usually early—newborn, infancy, or early childhood.</td>
</tr>
<tr>
<td>► Exert the greatest negative effect on reproductive fitness.</td>
</tr>
</tbody>
</table>
### TABLE 4.2 Selected Genetic Disorders Showing Autosomal Recessive Inheritance

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Occurrence</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinism (tyrosinase negative)</td>
<td>1:15,000 to 1:40,000 1:85–1:650 (Native Americans)</td>
<td>Tyrosinase negative disorder resulting in melanin lacking in skin, hair, and eyes; nystagmus; photophobia; susceptibility to neoplasia, strabismus, and impaired vision</td>
</tr>
<tr>
<td>Argininosuccinic aciduria (ASA)</td>
<td>1:60,000 to 1:70,000</td>
<td>Urea cycle disorder; hyperammonemia, mild mental retardation; vomiting; seizures; coma; abnormal hair shaft</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1:2,000 to 1:2,500 (Caucasians) 1:16,000 (American Blacks)</td>
<td>Ion channel function disruption resulting in pancreatic insufficiency and malabsorption; abnormal exocrine glands; chronic pulmonary disease (see Chapter 9)</td>
</tr>
<tr>
<td>Ellis–van Creveld syndrome (EvC)</td>
<td>Rare, except among eastern Pennsylvania Amish</td>
<td>Multiple mutations in the EVC gene result in short-limbed dwarfism; polydactyly; congenital heart disease; nail anomalies, natal teeth, cleft palate</td>
</tr>
<tr>
<td>Glycogen storage disease Ia (von Gierke disease)</td>
<td>1:200,000</td>
<td>Glucose-6-phosphatase deficiency; bruising; hypoglycemia; enlarged liver; hyperlipidemia; lactic acidosis, hyperuricemia; neutropenia; hypertension; short stature</td>
</tr>
<tr>
<td>Glycogen storage disease II (Pompe disease)</td>
<td>3:100,000 to 4.5:100,000</td>
<td>Mutation in GAA 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</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1:3,000 (Caucasians)</td>
<td>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)</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Occurrence</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocystinuria</td>
<td>1:40,000 to 1:140,000</td>
<td>Cystathionine β-synthase deficiency causing mental retardation; tall build with skeletal defects; optical abnormalities; neurologic problems; risk for myocardial infarction</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>1:40,000 (1:75) Habbanite Jews of Israel</td>
<td>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</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>1:400 to 1:600 (American Blacks)</td>
<td>Hemoglobinopathy with chronic hemolytic anemia; growth retardation; susceptibility to infection, painful vascular crises, leg ulcers, dactylitis (see Chapter 9)</td>
</tr>
<tr>
<td>Tay–Sachs disease</td>
<td>1:3,600 (Ashkenazi Jews) 1:360,000 others</td>
<td>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)</td>
</tr>
<tr>
<td>Usher syndromes</td>
<td>Rare</td>
<td>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</td>
</tr>
<tr>
<td>Xeroderma pigmentosa</td>
<td>1:60,000 to 1:100,000</td>
<td>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</td>
</tr>
</tbody>
</table>
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
pregnancies. Unless nonpenetration 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 nonpenetration 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.

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

![FIGURE 4.2. Mechanisms of autosomal dominant inheritance with one pair of chromosomes and one pair of genes.](image-url)
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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Occurrence</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
<td>1:10,000 to 1:12,000</td>
<td>Mutation in the <em>FGFR3</em> gene involved in development of bone and brain tissue. Short-limbed dwarfism; large head; narrowing of spinal canal</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>1:250 to 1:1,250</td>
<td>Mutations in <em>PKD1</em> or <em>PKD2</em> 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)</td>
</tr>
<tr>
<td>Aniridia</td>
<td>1:100,000 to 1:200,000</td>
<td>Mutation in the <em>PAX6</em> 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</td>
</tr>
<tr>
<td>Facioscapulohumeral muscular dystrophy 1A</td>
<td>1:100,000 to 5:100,000</td>
<td>Hypomethylation of the <em>FSHD1</em> 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</td>
</tr>
<tr>
<td>Familial hypercholesterolemia (type IIa)</td>
<td>1:200 to 1:500</td>
<td>Mutation of the <em>LDLR</em> gene causing low-density lipoprotein (LDL) receptor mutation. Symptoms are elevated LDL, xanthomas, arcus lipoides corneae, and coronary artery disease (see Chapter 10)</td>
</tr>
<tr>
<td>Hereditary spherocytosis</td>
<td>1:2,000 to 1:5,000</td>
<td>Mutation in <em>ANK1</em> gene causing a red blood cell membrane defect leading to abnormal spherical shape, impaired survival, and hemolytic anemia due to cell rupture</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>1:18,000 to 1:25,000 (United States), 1:333,000 (Japan)</td>
<td>Progressive neurologic disease caused by CAG trinucleotide repeat expansion of the <em>HTT</em> 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)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Occurrence</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail–patella syndrome</td>
<td>1:50,000</td>
<td>Mutation of the <em>LMX1B</em> 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</td>
</tr>
<tr>
<td>Neurofibromatosis 1</td>
<td>1:3,000 to 1:3,300</td>
<td>Mutation in the <em>NF1</em> gene involved in skin pigmentation. Café-au-lait spots, neurofibromas, and malignant progression are common; complications include hypertension; variable expression</td>
</tr>
<tr>
<td>Osteogenesis imperfecta type I</td>
<td>1:30,000</td>
<td>Mutation in <em>COL1A1</em> 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)</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>1:100 to 1:300</td>
<td>Extra (supernumerary) digit on hands or feet</td>
</tr>
<tr>
<td>Tuberous sclerosis-1 (TSC1)</td>
<td>About 1:10,000</td>
<td>Mutation in the <em>TSC1</em> 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</td>
</tr>
<tr>
<td>van der Woude syndrome</td>
<td>1:80,000 to 1:100,000</td>
<td>Mutation of the <em>IRF6</em> gene involved in transcription factor development. Cleft lip and/or palate with lower lip pits, missing premolars</td>
</tr>
<tr>
<td>von Willebrand disease</td>
<td>1:1,000 to 30:1,000</td>
<td>Deficiency or defect in plasma platelet protein called von Willebrand factor, leading to prolonged bleeding time; bruising; bleeding from mucous membranes (nosebleeds)</td>
</tr>
</tbody>
</table>
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 craniosenosis, 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.

**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](image-url)

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

---

**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
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

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**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.
### TABLE 4.6 Selected Genetic Disorders Showing X-Linked Recessive Inheritance

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

(continued)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Occurrence</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter syndrome (MPSII)</td>
<td>1:100,000 male births</td>
<td>Mucopolysaccharide storage disorder resulting from mutation in the <strong>IDS</strong> 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)</td>
</tr>
<tr>
<td>Lesch–Nyhan syndrome</td>
<td>Rare</td>
<td>Deficiency of purine metabolism enzyme due to mutation in the <strong>HPRT</strong> gene; hyperuricemia, spasticity, athetosis, self-mutilation, developmental delay (see Chapter 9)</td>
</tr>
<tr>
<td>Menkes syndrome</td>
<td>1:200,000 male births</td>
<td>Mutation in the <strong>ATP7A</strong> gene, causing defective copper transport; short stature; seizures; spasticity; hypothermia; kinky, sparse hair (pili torti); intellectual disability</td>
</tr>
<tr>
<td>X-linked ichthyosis</td>
<td>1:5,000 to 1:6,000</td>
<td>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</td>
</tr>
</tbody>
</table>
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
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 \textit{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 (homoplasy) or in some (heteroplasy). 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 4.7 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.
### TABLE 4.8 Selected Genetic Disorders Showing X-Linked Dominant Inheritance

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns–Sayre syndrome</td>
<td>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</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>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</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>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.</td>
</tr>
<tr>
<td>Mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)</td>
<td>Usually begins with migraine-like headache, seizures, dementia, nausea and vomiting, and stroke-like episodes leading to neurologic deficits, aphasia, hemianopia</td>
</tr>
<tr>
<td>Myoclonic epilepsy with ragged red fibers (MERFF)</td>
<td>Presents in childhood or young adulthood with myoclonic epilepsy, ataxia, and other signs and symptoms such as dementia, optic atrophy, and deafness</td>
</tr>
</tbody>
</table>
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
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>
<thead>
<tr>
<th>Disorder</th>
<th>Triplet Repeat</th>
<th>Unaffected Individuals</th>
<th>Premutation</th>
<th>Affected Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentatorubral-pallidoluysian atrophy (DRPLA)</td>
<td>CAG 6 to 35</td>
<td></td>
<td>49 to 88</td>
<td></td>
</tr>
<tr>
<td>Huntington disease (Chapter 10)</td>
<td>CAG 10 to 26</td>
<td>27 to 41</td>
<td>36 to 121</td>
<td></td>
</tr>
<tr>
<td>Spinobulbar muscular atrophy</td>
<td>CAG 9 to 36</td>
<td></td>
<td>38 to 62</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 1</td>
<td>CAG 6 to 44</td>
<td></td>
<td>39 to 81</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 2</td>
<td>CAG 14 to 31</td>
<td>31 to 36</td>
<td>36 to 64</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 3 or Machado–Joseph disease</td>
<td>CAG 12 to 43</td>
<td></td>
<td>56 to 86</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 6</td>
<td>CAG 4 to 18</td>
<td></td>
<td>21 to 33</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 7</td>
<td>CAG 4 to 19</td>
<td>30 to 36</td>
<td>37 to 306</td>
<td></td>
</tr>
<tr>
<td>Fragile X syndrome (Chapter 9)</td>
<td>CCG 6 to 53</td>
<td>53 to 200</td>
<td>200 to 2,000</td>
<td></td>
</tr>
<tr>
<td>Fragile XE mental retardation</td>
<td>GCC 6 to 35</td>
<td></td>
<td>&gt;200</td>
<td></td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>GAA 7 to 34</td>
<td></td>
<td>&gt;100</td>
<td></td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>CTG 5 to 37</td>
<td>38 to 49</td>
<td>50 to 1,000</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 8</td>
<td>CTG 16 to 37</td>
<td></td>
<td>110 to 250</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 12</td>
<td>CAG 7 to 28</td>
<td></td>
<td>66 to 78</td>
<td></td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Change</th>
<th>Description</th>
<th>Example of Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosomy</td>
<td>1 chromosome is missing.</td>
<td>Turner syndrome. Cells in females contain 45 chromosomes with 1 X chromosome rather than 2.</td>
</tr>
<tr>
<td>Trisomy</td>
<td>1 extra chromosome is present.</td>
<td>Trisomy 21 (Down syndrome). Cells contain 47 chromosomes.</td>
</tr>
<tr>
<td>Tetrasomy</td>
<td>2 extra chromosomes are present.</td>
<td>Cells contain 48 chromosomes. Not compatible with life.</td>
</tr>
<tr>
<td>Triploidy</td>
<td>1 extra chromosome set of haploid genome is present.</td>
<td>Cells contain 69 chromosomes. Not compatible with life.</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td>2 extra chromosome sets of haploid genome are present.</td>
<td>Cells contain 92 chromosomes. Not compatible with life.</td>
</tr>
</tbody>
</table>
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-

### TABLE 4.13 Major Changes in Chromosome Structure

<table>
<thead>
<tr>
<th>Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion (del)</td>
<td>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</td>
</tr>
<tr>
<td>Duplication (dup)</td>
<td>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</td>
</tr>
<tr>
<td>Inversion (inv)</td>
<td>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</td>
</tr>
<tr>
<td>Ring chromosome (r)</td>
<td>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</td>
</tr>
<tr>
<td>Translocations (t)</td>
<td>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</td>
</tr>
</tbody>
</table>
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,
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

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

*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.*
I: The Basics

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

**FIGURE 4.8.** Incidence of giving birth to a baby with Down syndrome, by age of the mother.
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.](image)

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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](image-url)

**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.
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.
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
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
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
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.

**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.
4: Inheritance Patterns in Human Phenotypes and Types of Genetic Disorders

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.
I: The Basics

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

(continued)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description of Major Features</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muenke syndrome</td>
<td>Craniosynostosis, some mild abnormalities of hands and feet</td>
<td>AD</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple endocrine neoplasia, type 2A</td>
<td>Thyroid cancer (medullary thyroid carcinoma), adrenal tumors (pheochromocytomas), hyperparathyroidism</td>
<td>AD</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia, type 2B</td>
<td>Thyroid cancer (medullary thyroid carcinoma); adrenal tumors (pheochromocytomas); tumors on the eyelids, lips, and tongue</td>
<td>AD</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>Short stature, heart defects, enlarged distance between the eyes, small jaw, webbed neck</td>
<td>AD</td>
</tr>
<tr>
<td>Oculodentodigital dysplasia</td>
<td>Digital anomalies such as incurved fifth finger (camptodactyly) or syndactyly; tooth enamel hypoplasia, other dental abnormalities; microphthalmos, glaucoma possible</td>
<td>AD</td>
</tr>
<tr>
<td>Pfeiffer syndrome</td>
<td>Craniosynostosis, wide thumbs and big toes, short fingers and toes, fusion of some digits</td>
<td>AD</td>
</tr>
<tr>
<td>Waardenburg syndrome 1</td>
<td>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</td>
<td>AD</td>
</tr>
<tr>
<td>Progeria</td>
<td>Thin skin; alopecia; growth deficiency; atherosclerosis; appearance of premature aging</td>
<td>AD, AR(?)</td>
</tr>
</tbody>
</table>

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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