Chapter 1

Introduction

CHAPTER OBJECTIVES

✓ Review molecular genetics and associated terminology.
✓ Review Mendelian genetic principles.
✓ Define mutation and give examples of different types of mutations.
✓ Describe different inheritance patterns.

The goal of this chapter is not to go into exhaustive genetic detail, but to familiarize the reader with basic genetic concepts (e.g., meiosis and mitosis, haploid versus diploid) by providing a basic overview of molecular genetics, simple inheritance patterns, chromosomal aberrations, and mutations. For more detailed information or to refresh your memory, the reader is referred to any one of a number of comprehensive genetics textbooks. The following texts are all recommended:

- Hartl DL, Jones EW. *Genetics: Analysis of Genes and Genomes,* 6th ed. Sudbury, MA: Jones and Bartlett; 2005.
- Jameson JL, Kopp P. Principles of Human Genetics. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (Eds.), Harrison's *Principles of Internal Medicine,* 17th ed. New York: McGraw-Hill Medical; 2008.
- Jorde LB, Carey JC, Bamshad MJ, White RL. *Medical Genetics,* 3rd ed. St. Louis, MO: Mosby; 2006.
- Mange EJ, Mange AP. *Basic Human Genetics.* Sunderland, MA: Sinauer Associates; 1994.
- Singer M, Berg P. *Genes and Genomes: A Changing Perspective.* Mill Valley, CA: University Science Books; 1991.

Basic Genetics

Genetics is the study of biologically inherited traits determined by elements of heredity that are transmitted from parents to offspring in reproduction. These inherited elements are called **genes**. Recent advances in the field of **genomics** have led to development of methods that can determine the complete **deoxyribonucleic acid (DNA)** sequence of an organism. Genomics is the latest advance in the study of the chemical nature of genes and the ways that genes function to affect certain traits.

The work of Gregor Mendel, a monk and part-time biologist, with garden peas is regarded as the beginning of what would become the science of genetics. Mendel is credited with showing the existence of genes as well as illuminating the rules governing their

transmission from generation to generation. The study of genetics through the analysis of offspring from matings is sometimes referred to as classical genetics.

The billions of nucleotides in the nucleus of a cell are organized linearly along the DNA double helix in functional units called genes. Each of the 20,000 to 25,000 human genes is accompanied by various regulatory elements that control when that gene is active in producing **messenger ribonucleic acid (mRNA)** by the process of **transcription**. In most situations, mRNA is transported from the nucleus to the cytoplasm, where its genetic information is used in the manufacture of proteins (a process called **translation**), which perform the functions that ultimately determine phenotype. For example, proteins serve as enzymes that facilitate metabolism and cell synthesis; as DNA binding elements that regulate transcription of other genes; as structural elements of cells and the extracellular matrix; and as receptor molecules for intracellular and intercellular communication. DNA also encodes many small RNA molecules that serve functions that are not yet fully understood, including regulating gene transcription and interfering with the translational capacity of some mRNAs.

Chromosomes are the means by which the genes are transmitted from generation to generation. Each chromosome is a complex of protein and nucleic acid in which an unbroken double helix of DNA is tightly wound (**Figure 1-1**). Genes are found along the length of chromosomes. A variety of highly complicated and integrated processes occur within

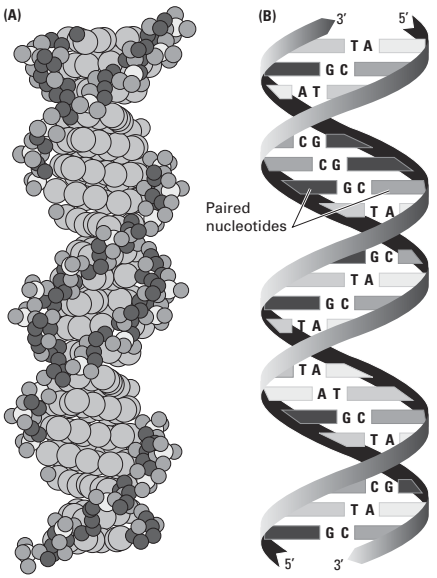

Figure 1-1 Molecular structure of a DNA double helix. (A) A space-filling model in which each atom is depicted as a sphere. (B) A diagram highlighting the helical backbones on the outside of the molecule and stacked A-T and G-C pairs inside.

the chromosome, including DNA replication, recombination, and transcription. In the nucleus of each of their somatic cells, humans normally have 46 chromosomes, which are arranged in 23 pairs. One of these pairs, consisting of the **sex chromosomes** X and Y, determines the sex of the individual; females have the pair XX and males have the pair XY. The remaining 22 pairs of chromosomes are called **autosomes**. In addition to these nuclear chromosomes, each mitochondrion (an organelle found in varying numbers in the cytoplasm of all cells) contains multiple copies of a small chromosome. This **mitochondrial chromosome** encodes a few of the proteins for oxidative metabolism and all of the **transfer ribonucleic acids (tRNA)** used in translation of proteins within this organelle. Mitochondrial chromosomes are inherited almost entirely from the cytoplasm of the fertilized ovum and, therefore, are maternal in origin.

The exact location of a gene on a chromosome is known as its **locus**, and the array of loci constitutes the human gene map. Currently, researchers have identified the chromosomal sites of more than 11,000 genes (i.e., those for which normal or abnormal function has been identified).

Homologous copies of a gene are termed **alleles**. In comparing alleles, it must be specified at which level of analysis the comparison is being made. For example, if alleles are truly identical, their coding sequences and the number of copies do not vary, so the individual is **homozygous** at that specific locus. However, if the DNA is analyzed using either restriction enzyme examination or nucleotide sequencing, then, despite having the same functional identity, the alleles would be viewed as different and the individual would be **heterozygous** for that locus. Heterozygosity based on differences in the protein products of alleles has been detectable for decades and represents the first hard evidence proving the high degree of human biologic variability. In the past decade, analysis of DNA sequences has shown genetic variability to be much more common, with differences in nucleotide sequence between individuals occurring about once every 1200 nucleotides.

Mutation

A **mutation** is defined as a change in DNA that may adversely affect the host. A heterozygous allele frequently results when different alleles are inherited from the egg and the sperm, but it may also occur as a consequence of spontaneous alteration in nucleotide sequence that results in a mutation. A **germinal mutation** occurs during formation of an egg or a sperm. If the change occurs after conception, it is termed a **somatic mutation**. The role of somatic mutation is now increasingly recognized as a key factor in the etiology of human disease.

The most dramatic type of mutation is an alteration in the number or physical structure of chromosomes, a phenomenon called a **chromosomal aberration**. Not all aberrations cause problems in the affected individual, but some that do not may lead to problems in their offspring. Approximately 1 in every 200 live-born infants has a chromosomal aberration that is detected because of some effect on phenotype. The frequency of this finding increases markedly the earlier in fetal life that the chromosomes are exam-

ined. By the end of the first trimester of gestation, most fetuses with abnormal numbers of chromosomes have been lost through spontaneous abortion.

For example, during the reduction division of meiosis that leads to production of mature ova and sperm, failure of chromosome pairs to separate in the dividing cell (**nondisjunction**) causes the embryo to have too many or too few chromosomes. When this type of error occurs, it is called **aneuploidy**, and either more or fewer than 46 chromosomes are present. Three types of aneuploidy may occur: (1) **monosomy**, in which only one member of a pair of chromosomes is present; (2) **trisomy**, in which three chromosomes are present instead of two; and (3) **polysomy**, in which one chromosome is represented four or more times.

During **translocation** or **inversion**, there is a rearrangement of chromosome arms. This effect is considered a mutation even if breakage and reunion do not disrupt any coding sequence (**Figures 1-2 and 1-3**). In an inversion, a chromosomal region becomes

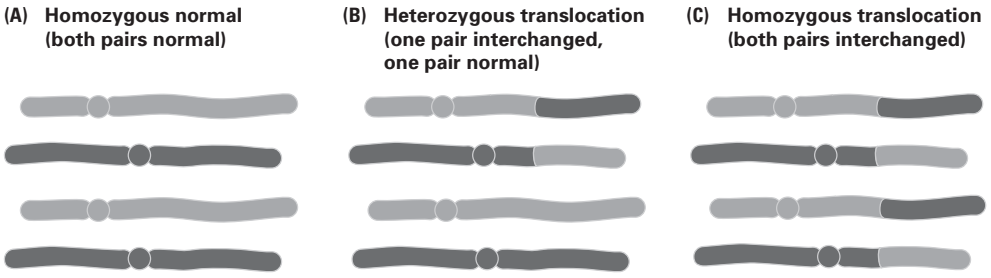

Figure 1-2 (A) Two pairs of nonhomologous chromosomes in a diploid organism. (B) Heterozygous reciprocal translocation in which two nonhomologous chromosomes (the two at the top) have interchanged terminal segments. (C) Homozygous reciprocal translocation.

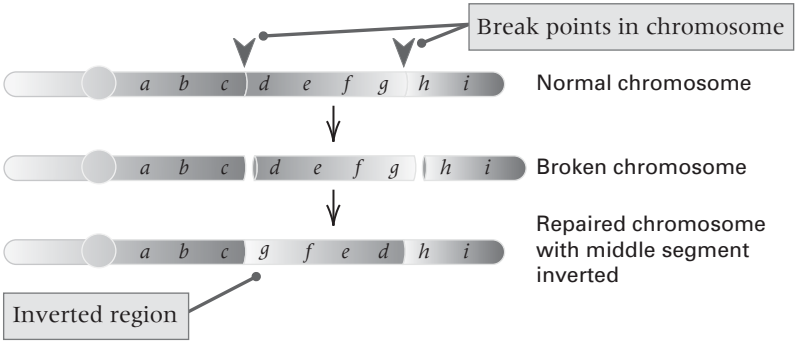

Figure 1-3 Origin of an inversion by reversal of the region between two chromosomal break points.

reoriented 180 degrees out of the ordinary phase. In each case, the same genetic material is present, but appears in a different order. Consequently, the phenotypic effect of gross chromosomal mutations can range from profound (as in aneuploidy) to innocuous.

Less obvious, but still detectable cytologically, are **deletions** of part of a chromosome. These mutations almost always alter phenotype, because a number of genes are lost. However, a deletion may involve only a single nucleotide, whereas 1 to 2 million nucleotides (1 to 2 megabases) must be lost before the defect can be visualized by the most sensitive cytogenetic methods. More sensitive molecular biology techniques are needed to detect smaller losses.

Changes in one nucleotide can alter which amino acid is encoded. For example, if the amino acid is present in a critical region of the protein, normal protein function might be severely disrupted (e.g., sickle cell disease; see Chapter 9). In contrast, some other amino acid substitutions have no detectable effect on function, such that the phenotype is unaltered by the mutation. Also, within the genetic code, two or more different three-nucleotide sequences called **codons** may encode the same amino acids (**degenerate**), such that nucleotide substitution does not necessarily alter the amino acid sequence of the protein. Three specific codons signal termination of translation, so a nucleotide substitution that generates one of the stop codons prematurely usually causes a **truncated protein**, which is frequently abnormal.

Nondisjunction Syndromes

Mutations may occur spontaneously or may be induced by radiation, medication, viral infections, or other environmental factors. Both advanced maternal and paternal age are associated with different types of mutations. In women, meiosis is completed only when an egg ovulates, and chromosomal nondisjunction is increasingly common as the egg becomes older. An example is trisomy 21, also known as **Down syndrome**. The risk that an aneuploid egg will result increases exponentially and becomes a major clinical concern for women older than their early 30s who wish to conceive a child (**Figure 1-4**). In men, mutations affecting nucleotide sequences are more subtle and increase with age. Offspring of men older than 40 years of age are at an increased risk for having primarily **autosomal dominant** Mendelian conditions.

Down syndrome is one of the most common trisomies, with approximately 1 of every 800 babies born in the United States being affected by this condition, which includes a combination of birth defects. Affected individuals have some degree of mental retardation, characteristic facial features, and, often, heart defects and other health problems. They are typically short with round, moonlike faces (**Figure 1-5**). Their tongues protrude forward, forcing their mouths open, and their eyes slant upward at the corners. The severity of these problems varies greatly among affected individuals.

Some of the health problems associated with Down syndrome are shown in **Table 1-1**. Fortunately, most are treatable. Thus life expectancy for persons with trisomy 21 is now approximately 55 years. The degree of mental retardation varies from mild to severe.

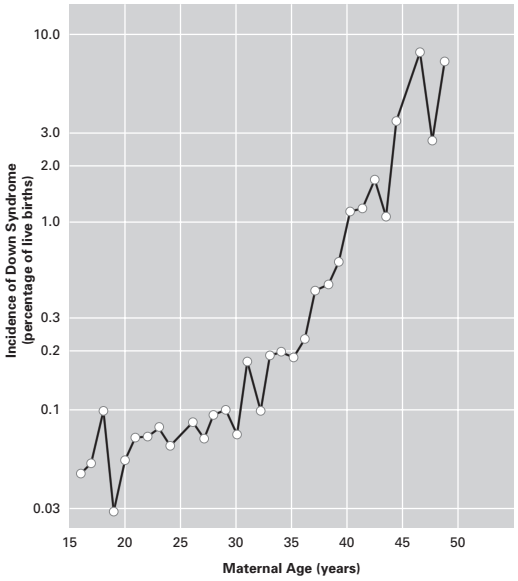

Figure 1-4 Frequency of Down syndrome (number of cases per 100 live births) related to age of mother. The graph is based on 438 Down syndrome births (among 330,859 total births) in Sweden in the period 1968 to 1970.
Source: Data from Hook EB, Lindsjö A. *American Journal of Human Genetics*. 30:19; 1978.

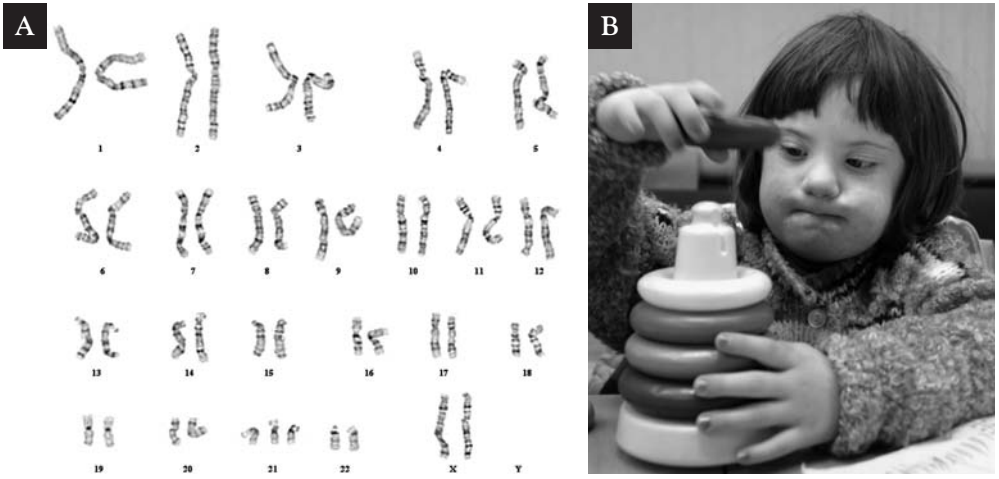

Figure 1-5A, B Down syndrome. (A) Karyotype of Down syndrome girl with trisomy of chromosome 21. (B) Distinguishing characteristics of Down syndrome.
Source: (A) Courtesy of Viola Freeman, Associate Professor, Faculty of Health Sciences, Dept. of Pathology and Molecular Medicine, McMaster University. (B) PhotoCreate/ShutterStock, Inc.

Table 1-1 **Health Problems Associated with Down Syndrome**

Problem	Specifics	Recommendation
Heart defects	Almost half of babies have heart defects.	Babies should be examined by a pediatric cardiologist and have an echocardiogram in the first 2 months of life.
Intestinal defects	Approximately 12% of babies are born with intestinal malformations that require surgery.	
Vision problems	Crossed eyes, near- or far-sightedness, and cataracts.	Babies should have a pediatric ophthalmologist exam within the first 6 months of life and have regular vision exams.
Hearing loss	Approximately 75% of children have some hearing loss. It may be due to fluid in the middle ear (which may be temporary), a nerve, or both.	Babies should be screened for hearing loss at birth or by 3 months of age as well as have regular exams.
Infections	Children tend to have many colds and ear infections as well as bronchitis and pneumonia.	Children should receive all the standard childhood immunizations.
Memory loss	Affected individuals more likely than unaffected individuals to develop Alzheimer's disease at an earlier age.	

Source: Adapted from Down syndrome. Pregnancy & Newborn Health Education Center. March of Dimes Web site. http://www.marchofdimes.com/pnhec/4439_1214.asp. Accessed January 16, 2010.

Because severe mental retardation is less likely, many affected individuals are able to go to school and participate in special work programs.

The American College of Obstetricians and Gynecologists recommends that all pregnant women be offered a screening test for Down syndrome, regardless of the woman's age. Screening may consist of a maternal blood test done in the first trimester (at 11 to 13 weeks of pregnancy), along with a special ultrasound examination of the back of the baby's neck (called nuchal translucency), or a maternal blood test done in the second trimester (at 15 to 20 weeks of pregnancy). These tests help to identify pregnancies that are at higher-than-average risk of Down syndrome, but cannot diagnose Down syndrome or other birth defects.

Women who have an abnormal screening test result are offered a diagnostic test, such as **amniocentesis** or **chorionic villus sampling** (CVS), that will either confirm or dis-

prove the presence of Down syndrome in the fetus. Amniocentesis involves the removal and examination of a small sample of the amniotic fluid that surrounds the fetus. Chorionic villus sampling involves taking a tiny tissue sample from outside the sac where the fetus develops (chorionic villi) and is done earlier in pregnancy (usually between 10 and 12 weeks) than amniocentesis (usually 15 to 20 weeks). Both procedures pose a small risk of miscarriage, with CVS having a slightly higher risk than amniocentesis. These tests are highly accurate at diagnosing or ruling out Down syndrome.

Nondisjunction of the sex chromosomes can lead to a variety of nonlethal genetic disorders. One of the most common occurs when an ovum with an extra X chromosome is fertilized by a sperm with a Y chromosome. This process results in an XXY genotype, known as **Klinefelter syndrome**. Klinefelter syndrome occurs in approximately 1 out of every 700 to 1000 newborn males. Even though these individuals are males, their masculinization is incomplete. Their external genitalia and testes are unusually small, and approximately 50% of these individuals develop breasts. Spermatogenesis is abnormal, and affected males are generally sterile. Klinefelter syndrome is the most common chromosomal disorder associated with male hypogonadism and infertility.

Another disorder associated with nondisjunction of sex chromosomes is **Turner syndrome**. This monosomy syndrome results when an ovum lacking the X chromosome is fertilized by a sperm that contains an X chromosome. It may also occur when a genetically normal ovum is fertilized by a sperm lacking an X or Y chromosome. The result is an offspring with 22 pairs of autosomes and a single, unmatched X chromosome (XO).

Turner syndrome occurs in only 1 out of every 10,000 female births, as the XO embryo is more likely to be spontaneously aborted. These individuals look like females and are characteristically short with wide chests and a prominent fold of skin on their necks. Because their ovaries fail to develop at puberty, they are sterile and have low levels of estrogen and small breasts. Mental retardation is not associated with this disorder, so individuals lead fairly normal lives.

Genes in Individuals

Most human characteristics and common diseases are **polygenic**, whereas many of the disordered phenotypes thought of as "genetic" are **monogenic** but still influenced by other loci in a person's genome. Phenotypes due to alterations at a single gene are frequently referred to as **Mendelian**, after Gregor Mendel, the monk/biologist who studied the reproducibility and recurrence of variation in garden peas. Mendel showed that some traits were **dominant** relative to other traits; he called the latter traits **recessive**. Dominant traits require only one copy of a "factor" to be expressed, regardless of what the other copy is, whereas recessive traits require two copies before expression occurs. We now recognize that the Mendelian factors are genes, and the alternative copies of the gene are alleles. For example, if *B* is the common (normal) allele and *b* is the mutant allele at a locus, then the phenotype is dominant whether the genotype is *BB* or *Bb*. Conversely, the phenotype is recessive when the genotype is *bb*.

Inheritance Patterns

As described earlier, phenotypes due to alterations at a single gene are characterized as Mendelian and monogenic human diseases are frequently referred to as Mendelian disorders. The mode of inheritance for a given phenotypic trait or disease is determined by **pedigree analysis**. All affected and unaffected individuals in the family are recorded in a pedigree using standard symbols (**Figure 1-6**). The principles of allelic segregation, and the transmission of alleles from parents to children, are illustrated in **Figure 1-7**. One

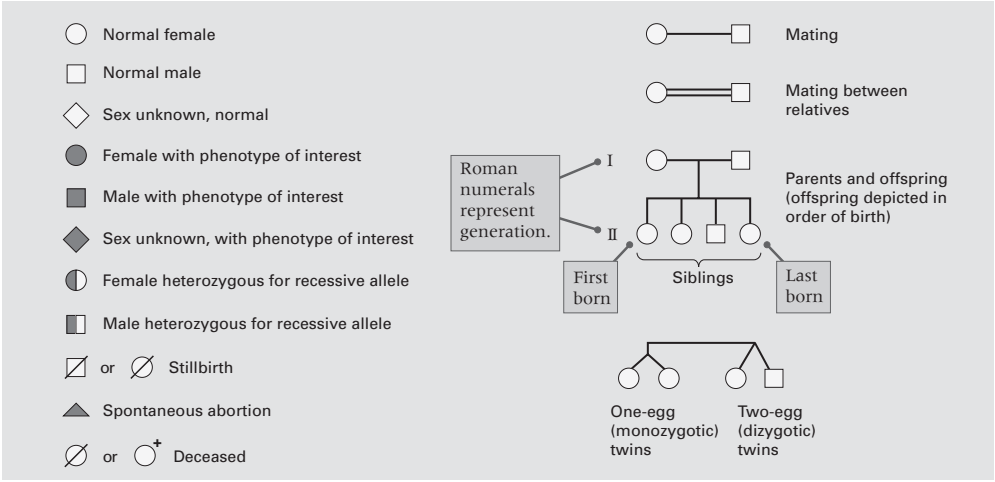

Figure 1-6 Conventional symbols used in depicting human pedigrees.
Source: Bennett R, French K, Resta R, Doyle D. Standardized Human Pedigree Nomenclature: Update and Assessment of the Recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling*. 17:424–433;2008. ©National Society of Genetic Counselors, Inc. 2008.

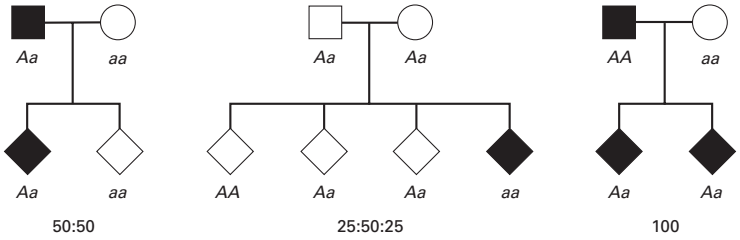

Figure 1-7 Segregation of genotypes in the offspring of parents with one dominant (*A*) and one recessive (*a*) allele. The distribution of the parental alleles to their offspring depends on the combination present in the parents. Filled symbols = affected individuals.
Source: Reproduced from Fauci AS, Kasper DL, Braunwald E, Hauser SI, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine*, 17th ed; 2008. http:www.accessmedicine.com.

dominant (*A*) allele and one recessive (*a*) allele can display any of three Mendelian modes of inheritance: autosomal dominant, autosomal recessive, or chromosome X-linked. Approximately 65% of human monogenic disorders are autosomal dominant, 25% are autosomal recessive, and 5% are X-linked. Genetic testing is now available for many of these disorders and plays an increasingly important role in clinical medicine.

Autosomal Dominant Inheritance

Autosomal dominant disorders are relevant because mutations in a single allele are sufficient to cause the disease (**Figure 1-8**). In contrast to recessive disorders, in which disease pathogenesis is relatively straightforward because there is loss of gene function, dominant disorders can be caused by various disease mechanisms, many of which are unique to the function of the genetic pathway involved.

Autosomal Recessive Inheritance

In the case of recessive disorders, mutated alleles result in a complete or partial loss of function. An example pedigree of autosomal recessive inheritance is shown in **Figure 1-9**. Recessive disorders frequently involve enzymes in metabolic pathways, receptors, or proteins in signaling cascades. The affected individual can be of either sex and either a homozygote or compound heterozygote for a single-gene defect. Fortunately, autosomal recessive diseases are, for the most part, rare and often occur in the context of parental

CHARACTERISTICS OF AUTOSOMAL DOMINANT INHERITANCE

- A vertical pattern is observed in the pedigree, with multiple generations being affected.
- Heterozygotes for the mutant allele show an abnormal phenotype.
- Males and females are affected with equal frequency and severity.
- Only one parent must be affected for an offspring to be at risk for developing the phenotype.
- When an affected person mates with an unaffected one, each offspring has a 50% chance of inheriting the affected phenotype. This is true regardless of the sex of the affected parent—specifically, male-to-male transmission occurs.
- The frequency of sporadic cases is positively associated with the severity of the phenotype. Autosomal dominant phenotypes are often age dependent, less severe than autosomal recessive phenotypes, and associated with malformations or other physical features.

Source: Reproduced from Pyeritz RE. Medical Genetics. In Tierney L, et al. *Current Medical Diagnosis & Treatment*, 42nd ed. 2003.

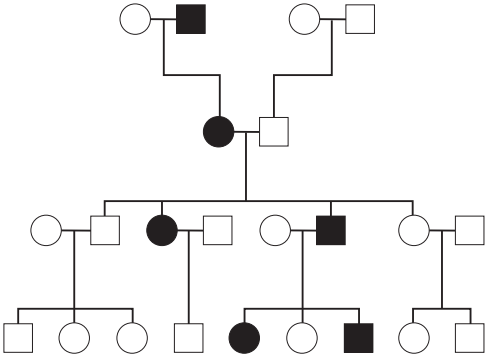

Figure 1-8 A pedigree illustrating autosomal dominant inheritance. Square symbols indicate males and circles indicate females; open symbols indicate that the person is phenotypically unaffected, and filled symbols indicate that the phenotype is present to some extent.
Source: Reproduced from Tierney L, et al. *Current Medical Diagnosis & Treatment*, 42nd ed; 2003. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

consanguinity. The relatively high frequency of certain recessive disorders, such as sickle cell anemia (see Chapter 9), cystic fibrosis (see Chapter 11), and thalassemia (see Chapter 9), is partially explained by a selective biologic advantage for the heterozygous state. Heterozygous carriers of a defective allele are usually clinically normal, but they may display subtle differences in phenotype that become apparent only with more precise testing or in the context of certain environmental influences (i.e., sickle cell disease; see Chapter 9).

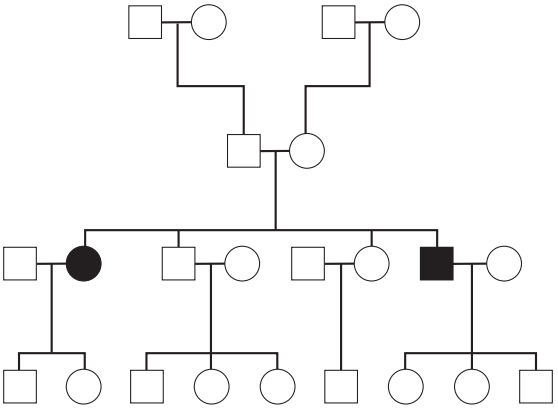

Figure 1-9 A pedigree illustrating autosomal recessive inheritance.
Source: Reproduced from Tierney L, et al. *Current Medical Diagnosis & Treatment*, 42nd ed; 2003. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Autosomal recessive phenotypes are often associated with deficient activity of enzymes and are thus termed **inborn errors of metabolism**. Such disorders include phenylketonuria, Tay-Sachs disease, and the various glycogen storage diseases. They tend to be more severe, less variable, and less age dependent than dominant conditions. When an autosomal recessive condition is quite rare, the chance that the parents of affected offspring are consanguineous for the phenotype is increased. As a result, the prevalence of rare recessive conditions is high among inbred groups such as the Old Order Amish and Ashkenazi Jews.

CHARACTERISTICS OF AUTOSOMAL RECESSIVE INHERITANCE

- A horizontal pattern is noted in the pedigree, with a single generation being affected.
- Males and females are affected with equal frequency and severity.
- Inheritance is from both parents, each of whom is a heterozygote (carrier) and each of whom is usually clinically unaffected by his or her carrier status.
- Each offspring of two carriers has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither mutant allele. Thus two-thirds of all clinically unaffected offspring are carriers of the autosomal recessive phenotype.
- In matings between individuals, each with the same recessive phenotype, all offspring will be affected.
- Affected individuals who mate with unaffected individuals who are not carriers have only unaffected offspring.
- The rarer the recessive phenotype, the more likely it is that the parents are consanguineous (related).

Source: Reproduced from Pyeritz RE. Medical Genetics. In Tierney L, et al. *Current Medical Diagnosis & Treatment*, 42nd ed. 2003.

X-Linked Inheritance

Because males have only one X chromosome, a daughter will always inherit her father's X chromosome in addition to one of her mother's two X chromosomes (**Figure 1-10**). Conversely, a son inherits the Y chromosome from his father and one maternal X chromosome, so the risk of developing disease due to a mutant X-chromosomal gene differs in the two sexes. Due to the presence of one X chromosome, males are said to be **hemizygous** for the mutant allele on that chromosome. Therefore, they are more likely to develop the mutant phenotype, regardless of whether the mutation is dominant or recessive. A female with two X chromosomes may be either heterozygous or homozygous for the mutant allele, which may be dominant or recessive. Therefore, the terms "X-linked dominant" and "X-linked recessive" are applicable to expression of the mutant phenotype only in women.

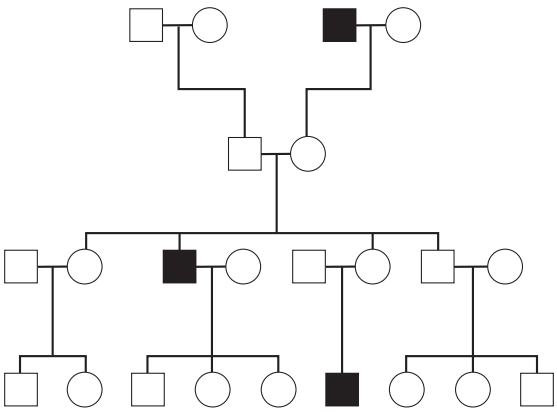

Figure 1-10 A pedigree illustrating X-linked inheritance.
Source: Reproduced from Tierney L, et al. *Current Medical Diagnosis & Treatment*, 42nd ed; 2003. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

CHARACTERISTICS OF X-LINKED INHERITANCE

- There is no male-to-male transmission of the phenotype.
- Unaffected males do not transmit the phenotype.
- All daughters of an affected male are heterozygous carriers.
- Males are usually more severely affected than females.
- Whether a heterozygous female is counted as affected—and whether the phenotype is called "recessive" or "dominant"—often depends on the sensitivity of the assay or examination.
- Some mothers of affected males will not themselves be heterozygotes (i.e., they will be homozygous normal) but will have a germinal mutation. The proportion of heterozygous (carrier) mothers is negatively associated with the severity of the condition.
- Heterozygous women transmit the mutant gene to 50% of their sons, who are affected, and to 50% of their daughters, who are heterozygotes.
- If an affected male mates with a heterozygous female, 50% of the male offspring will be affected, giving the false impression of male-to-male transmission. Among the female offspring of such matings, 50% will be affected as severely as the average hemizygous male; in small pedigrees, this pattern may simulate autosomal dominant inheritance.

Source: Reproduced from Pyeritz RE. Medical Genetics. In Tierney L, et al. *Current Medical Diagnosis & Treatment*, 42nd ed. 2003.

The characteristics of X-linked inheritance depend on phenotypic severity. For some disorders, affected males do not survive to reproduce. In such cases, approximately two-thirds of affected males have a carrier mother; in the remaining third, the disorder arises by new germinal mutation in an X chromosome of the mother. When the disorder is nearly always manifested in heterozygous females (X-linked dominant inheritance), females tend to be affected approximately twice as often as males; on average, an affected female transmits the phenotype to 50% of her sons and 50% of her daughters.

The Y chromosome has a relatively small number of genes. One gene, the sex-region determining Y factor (*SRY*), encodes the testis-determining factor that is crucial for normal male development. Normally there is infrequent exchange of sequences on the Y chromosome with the X chromosome.

Mitochondrial Inheritance

As described earlier, transmission of genes encoded by DNA contained in the nuclear chromosomes follows the principles of Mendelian inheritance. In addition, each mitochondrion contains several copies of a small circular chromosome that encodes tRNA, **ribosomal RNA (rRNA)**, and proteins that are involved in oxidative phosphorylation and ATP generation. The mitochondrial genome does not recombine and is inherited through the maternal line because sperm does not contribute significant cytoplasmic

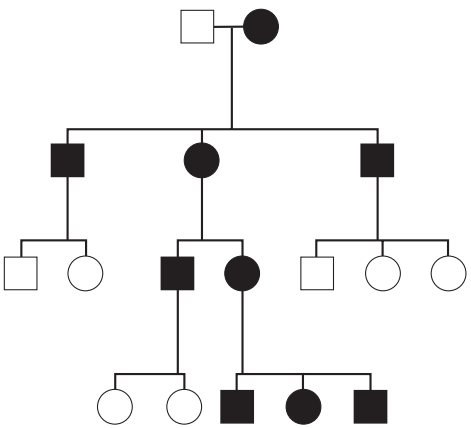

Figure 1-11 Mitochondrial ("maternal") inheritance. A mitochondrial genetic mutation, indicated by darkened symbols, is passed by the female (circle) to all of her offspring, including males (squares). Among the subsequent offspring, the males do not transmit the mutation, but the females continue to transmit the mutation to all of their offspring because mitochondria are passed through ova, not sperm.

Source: Reproduced from Pyeritz RE. Chapter e2: Basic Genetics. McPhee SJ, Papadakis MA, Tierney LM, Jr. *Current Medical Diagnosis & Treatment,* 48th ed; 2009. http:www.accessmedicine.com/content.aspx?aID=774551.

components to the zygote. Mutations in the genes encoded by the mitochondrial chromosome cause a variety of diseases that affect (in particular) organs highly dependent on oxidative metabolism, such as the retina, brain, kidneys, and heart. An affected woman can pass the defective mitochondrial chromosome to all of her offspring, whereas an affected man has little risk of passing his mutation to a child (**Figure 1-11**).

Human Genome Project

Genomics is the study of all the genes in a person as well as the interactions of these genes with one another and with the individual's environment. All people are 99.9% identical in genetic makeup, but differences in the remaining 0.1% offer important clues about health and disease. The goals of the Human Genome Project were to determine the complete sequence of the 3 billion DNA subunits (bases), identify all human genes, and make that information accessible for further biological study. The project was completed in 2003 and identified approximately 25,000 genes in human DNA.

GENOMIC SEQUENCING HIGHLIGHTS

- The human genome contains 3.2 billion chemical nucleotide bases (A, C, T, and G).
- The average gene consists of 3000 bases, but sizes vary greatly. The largest known human gene is dystrophin, which has 2.4 million base pairs.
- Functions are unknown for more than 50% of discovered genes.
- The human genome sequence is almost exactly (99.9%) the same in all people.
- Approximately 2% of the genome encodes instructions for the synthesis of proteins.
- Repeat sequences that do not code for proteins make up at least 50% of the human genome.
- Repeat sequences are thought to have no direct functions, but they shed light on chromosome structure and dynamics. Over time, these repeats reshape the genome by rearranging it, thereby creating entirely new genes or modifying and reshuffling existing genes.
- The human genome has a much greater portion (50%) of repeat sequences than the mustard weed (11%), the worm (7%), and the fly (3%).
- More than 40% of the predicted human proteins share similarity with fruit-fly or worm proteins.
- Genes appear to be concentrated in random areas along the genome, with vast expanses of noncoding DNA occurring between these areas.

Continued

- Chromosome 1 (the largest human chromosome) has the most genes (3168), and the Y chromosome has the fewest (344).
- Particular gene sequences have been associated with numerous diseases and disorders, including breast cancer, muscle disease, deafness, and blindness.
- Scientists have identified millions of locations where single-base DNA differences occur in humans. This information promises to revolutionize the processes of finding DNA sequences associated with such common diseases as cardiovascular disease, diabetes, arthritis, and cancers.

Source: U.S. Department of Energy Genome Programs, Insights from the Human DNA Sequence. Available at http://www.ornl.gov/sci/techresources/Human_Genome/publicat/primer2001/4.shtml. Accessed August 13, 2010.

The completion of the Human Genome Project has inspired much excitement regarding the many potential applications using this information: (1) improved disease diagnosis, (2) ability to detect genetic predispositions to disease, (3) development of drugs based on molecular information, (4) use of gene therapy and control systems as drugs, and (5) creation of "custom drugs" based on individual genetic profiles. In addition, the creation of more detailed genome maps has helped researchers seeking genes associated with dozens of genetic conditions, including myotonic dystrophy, fragile X syndrome, neurofibromatosis types 1 and 2, inherited colon cancer, Alzheimer's disease, and familial breast cancer. Even though the concept of using this genetic information to treat and/or cure many diseases is very exciting, many challenges must be overcome before viable and safe treatments are available for human diseases.

Chapter Summary

- Genetics is the study of biologically inherited traits determined by genes that are transmitted from parents to offspring during the course of reproduction.
- Chromosomes are how the genes are transmitted from generation to generation.
- The human genome is estimated to contain 20,000 to 25,000 genes. A germinal mutation occurs during formation of an egg or a sperm, but if change occurs after conception it is termed a somatic mutation.
- Advanced maternal and paternal age are associated with different types of mutations.
- Phenotypes due to alterations at a single gene are characterized as Mendelian, and monogenic human diseases are frequently referred to as Mendelian disorders.
- Genomics is the study of all the genes in a person as well as the interactions of these genes with one another and with an individual's environment.

Key Terms

Allele: any of the alternative forms of a given gene.

Amniocentesis: a prenatal test in which a small sample of the amniotic fluid surrounding the fetus is removed and examined.

Aneuploidy: a condition in which extra or fewer copies of particular genes or chromosomal regions are present compared with the wild type.

Autosomal dominant: a pattern of inheritance in which an affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal chromosomes. Individuals with autosomal dominant diseases have a 50:50 chance of passing the mutant gene—and, therefore, the disorder—on to each of their children.

Autosomes: all chromosomes other than the sex chromosomes.

Chorionic villus sampling (CVS): a prenatal test that involves taking a tiny tissue sample from outside the sac where the fetus develops. It is performed between 10 and 12 weeks after a now-pregnant woman's last menstrual period.

Chromosomal aberration: alteration in the number or physical structure of chromosomes.

Chromosome: a DNA molecule that contains genes in linear order to which numerous proteins are bound.

Codon: a sequence of three adjacent nucleotides in an mRNA molecule, specifying either an amino acid or a stop signal in protein synthesis.

Consanguinity: degree of relationship between persons who descend from a common ancestor.

Degenerate: a feature of the genetic code in which an amino acid corresponds to more than one codon.

Deletion: loss of chromosomal material.

Deoxyribonucleic acid (DNA): a macromolecule usually composed of two polynucleotide chains in a double helix that is the carrier of genetic information in all cells.

Dominant: refers to an allele whose presence in a heterozygous genotype results in a phenotype characteristic of the allele.

Down syndrome: a chromosomal dysgenesis syndrome consisting of a variable constellation of abnormalities caused by triplication or translocation of chromosome 21. Affected individuals have some degree of mental retardation, characteristic facial features, and, often, heart defects and other health problems.

Gene: a region of DNA containing genetic information, which is usually transcribed into an RNA molecule that is processed and either functions directly or is translated into a polypeptide chain; the hereditary unit.

Genomics: systematic study of an organism's genome using large-scale DNA sequencing, gene-expression analysis, or computational methods.

Germinal mutation: a mutation that takes place in a reproductive cell.

Hemizygous: describes an individual who has only one member of a chromosome pair or chromosome segment rather than the usual two; refers in particular to X-linked genes in males who under usual circumstances have only one X chromosome.

Heterozygous: carrying dissimilar alleles of one or more genes; not homozygous.
Homozygous: having the same allele of a gene in homologous chromosomes.
Inborn errors of metabolism: a genetically determined biochemical disorder, usually in the form of an enzyme defect that produces a metabolic block.
Inversion: a structural aberration in a chromosome in which the order of several genes is reversed from the normal order.
Klinefelter syndrome: a disorder that occurs when an ovum with an extra X chromosome is fertilized by a sperm with a Y chromosome. This results in an XXY genotype male who is sterile.
Locus: the site or position of a particular gene on a chromosome.
Mendelian genetics: the mechanism of inheritance in which the statistical relations between the distribution of traits in successive generations result from three factors: (1) particulate hereditary determinants (genes), (2) random union of gametes, and (3) segregation of unchanged hereditary determinants in the reproductive cells.
Messenger ribonucleic acid (mRNA): an RNA molecule that is transcribed from a DNA sequence and translated into the amino acid sequence of a polypeptide.
Mitochondrial chromosome: a small circular chromosome found in each mitochondrion that encodes tRNA, rRNA, and proteins that are involved in oxidative phosphorylation and ATP generation.
Monogenic: of, relating to, or controlled by a single gene, especially by either of an allelic pair.
Monosomy: a condition in an otherwise diploid organism in which one member of a pair of chromosomes is missing.
Mutation: heritable alteration in a gene or chromosome; also, the process by which such an alteration happens.
Nondisjunction: failure of chromosomes to separate (disjoin) and move to opposite poles of the division spindle; the result is loss or gain of a chromosome.
Pedigree analysis: a diagram representing the familial relationships among relatives.
Polygenic: genetic disorder resulting from the combined action of alleles of more than one gene.
Polysomy: condition of a diploid cell or organism that has three or more copies of a particular chromosome.
Recessive: refers to an allele, or the corresponding phenotypic trait, that is expressed only in homozygotes.
Ribosomal RNA (rRNA): a type of RNA molecule that is a component of the ribosomal subunits.
Sex chromosome: a chromosome, such as the human X or Y, that plays a role in the determination of sex.
Somatic mutation: a mutation arising in a somatic cell.
Transcription: the process by which the information contained in a template strand of DNA is copied into a single-stranded RNA molecule of complementary base sequence.
Transfer ribonucleic acids (tRNA): a small RNA molecule that translates a codon into an amino acid in protein synthesis; it has a three-base sequence, called the anticodon,

complementary to a specific codon in mRNA, and a site to which a specific amino acid is bound.

Translation: the process by which the amino acid sequence of a polypeptide is synthesized on a ribosome according to the nucleotide sequence of an mRNA molecule.

Translocation: a mutation results from an exchange of parts of two chromosomes.

Trisomy: a disorder in which a normally diploid organism has an extra copy of one of the chromosomes.

Truncated protein: a protein that does not achieve its full length or its proper form, and thus is missing some of the amino acid residues that are present in a normal protein. A truncated protein generally cannot perform the function for which it was intended because its structure is incapable of doing so.

Turner syndrome: a monosomy syndrome that results when an ovum lacking the X chromosome is fertilized by a sperm that contains an X chromosome. It may also occur when a genetically normal ovum is fertilized by a sperm lacking an X or Y chromosome. The result is an offspring with 22 pairs of autosomes and a single, unmatched X chromosome.

Chapter Review Questions

1. The _____ encodes a few of the proteins for oxidative metabolism and all of the _____ used in translation of proteins within this organelle.
2. A change in DNA that could adversely affect the host that occurs after conception is termed a _____.
3. The three types of aneuploidy are _____, _____, and _____.
4. Autosomal recessive phenotypes are often associated with deficient activity of enzymes and, therefore, are termed _____.
5. Due to the presence of one X chromosome, males are said to be _____ for the mutant allele on that chromosome.

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