CHAPTER 2 Genetic Disease

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Mechanisms of cellular and tissue dysfunction in genetic diseases are as varied as the organs they affect. To some extent, these mechanisms are similar to those that occur in non-heritable disorders. For example, a fracture resulting from decreased bone density in osteoporosis heals in much the same way as one caused by a defective collagen gene in osteogenesis imperfecta, and the response to coronary atherosclerosis in most individuals does not depend on whether they have inherited a defective low-density lipoprotein (LDL) receptor. Thus, the pathophysiologic principles that distinguish genetic disease focus not so much on the affected organ system as on the mechanisms of genetic and genomic changes, inheritance, and molecular pathways from genotype to phenotype.

This chapter begins with a discussion of the terminology used to describe inherited conditions, the prevalence of genetic disease, and some major principles and considerations in medical genetics. Important terms and key words used throughout the chapter are defined in Table 2–1.

Next, a group of disorders caused by pathogenic variants (formerly termed "mutations") in collagen genes is discussed (ie, **osteogenesis imperfecta).** Although osteogenesis imperfecta is often considered a single entity, different pathogenic variants and different genes subject to alteration lead to a wide spectrum of clinical phenotypes. The different types of osteogenesis imperfecta exhibit typical patterns of autosomal dominant or autosomal recessive inheritance and are, therefore, examples of so-called **mendelian conditions.** To show how environmental factors can influence the relationship between genotype and phenotype, another mendelian condition, **phenylketonuria,** is discussed. This serves as a paradigm for newborn screening programs and for treatment of genetic disease. Several genetic conditions have been found to depend not only on the gene being inherited but also on the phenotype or the sex of the parent. As an example of a condition that exhibits non-autosomal inheritance, **fragile X–associated mental retardation syndrome** is discussed. This syndrome not only is the most common inherited cause of mental retardation but also illustrates how different types of pathogenic variants can explain the perplexing phenomenon of **genetic anticipation,** in which the severity of a mendelian syndrome appears to progress with every generation of inheritance. Another group of disorders that depend on the phenotype and sex of the parent consists of those that affect the mitochondrial genome. As examples, **Leber hereditary optic neuropathy (LHON)** and **myoclonic epilepsy with ragged red fibers (MERRF)** are considered. These illustrate the principles of mitochondrial inheritance and its pathophysiology. **Aneuploidy** is discussed as one of the most common causes of human genetic disorders that does not affect DNA structure but instead alters the normal chromosome content per cell. The example that is considered, **Down syndrome,** has had a major impact on reproductive medicine and reproductive decision making and serves to illustrate general principles that apply to many aneuploid conditions. Finally, this chapter considers how genome sequences and sequencing are improving our understanding of pathophysiology for many diseases. With the completion of the annotation of the human genome and technological advances that allow individual genomes to be sequenced rapidly and inexpensively, prospects are at hand to identify genetic components of any human phenotype and to provide medical care that is truly personalized.

UNIQUE PATHOPHYSIOLOGIC ASPECTS OF GENETIC DISEASES

Although the phenotypes of genetic diseases are diverse, their causes are not. The primary cause of any genetic disease is a change in the sequence or cellular content of DNA that ultimately deranges gene expression. Most genetic diseases are caused by an alteration in DNA sequence that alters the synthesis

of a single gene product. However, some genetic diseases are caused by (1) structural rearrangements that result in deletion or duplication of a group of closely linked genes or (2) abnormalities during mitosis or meiosis that result in an abnormal number of chromosomes per cell.

TABLE 2-1

Glossary of terms and keywords.

Term	Definition
Acrocentric	Refers to the terminal location of the centromere on chromosomes 13, 14, 15, 21, and 22.
Allelic heterogeneity	The situation in which multiple alleles at a single locus can produce one or more disease phenotypes.
Amorphic	Refers to pathogenic variants that cause a complete loss of function for the respective gene and therefore yield the same phenotype as a complete gene deletion.
Aneuploidy	A general term used to denote any unbalanced chromosome complement.
Antimorphic	Refers to pathogenic variants that, when present in heterozygous form opposite a nonmutant allele, will result in a phenotype similar to homozygosity for loss-of-function alleles.
Ascertainment bias	The situation in which Individuals or families in a genetic study are not representative of the general population because of the way in which they are identified.
Autosomal	Located on chromosomes 1–22 rather than X or Y.
CpG Island	A segment of DNA that contains a relatively high density of 5'-CG-3' dinucleotides. Such segments are frequently unmethylated and located close to ubiquitously expressed genes.
Dictyotene	The end of prophase during female meiosis I in which fetal oocytes are arrested prior to ovulation.
Dominant	A pattern of inheritance or mechanism of gene action in which the effects of a variant allele can be observed in the presence of a nonmutant allele.
Dominant negative	A type of pathophysiologic mechanism that occurs when a mutant allele interferes with the normal function of the nonmutant gene product.
Dosage compensation	Mechanism by which a difference in gene dosage between two cells Is equalized. For XX cells in mammals, decreased expression from one of the two X chromosomes results in a concentration of gene product similar to an XY cell.
End-product	A pathologic mechanism in which absence or reduction in the

Term	Definition
deficiency	product of a particular enzymatic reaction leads to disease.
Epigenetic	Refers to a phenotypic effect that is heritable, through somatic cell division and/or across organismal generations, but that does not depend on variation In DNA sequence. Instead, epigenetic Inheritance Is associated with alterations in chromatin structure such as DNA methylation or histone modification that can be transmitted during cell division.
Expressivity	The extent to which a variant genotype affects phenotype, including the tissues that are affected, and the severity of those effects.
Fitness	The effect of a variant allele on an individual's ability to produce offspring.
Founder effect	One of several possible explanations for an unexpectedly high frequency of a deleterious gene in a population. If the population was founded by a small ancestral group, It may have, by chance, contained a large number of carriers for the deleterious gene.
Gamete	The egg or sperm cell that represents a potential reproductive contribution to the next generation. Gametes have undergone meiosis and so contain half the normal number of chromosomes found in zygotic cells.
Gene dosage	The principle that the amount of product expressed for a particular gene is proportionate to the number of gene copies present per cell.
Genetic anticipation	A clinical phenomenon in which the phenotype observed in Individuals carrying a deleterious gene appears more severe in successive generations. Possible explanations Include ascertainment bias or a multistep mutational mechanism such as expansion of triplet repeats.
Haplotype	A set of closely linked DNA sequence variants on a single chromosome.
Hemizygous	A term referring to the presence of only one allele at a locus, either because the other allele is deleted or because it is normally not present; eg, X-linked genes in males.
Heterochromatin	One of two alternative forms of chromosomal material (the other is euchromatin) In which chromosomal DNA is highly condensed and, usually, devoid of genes that are actively transcribed.

Term	Definition
Heteroplasmy	The mixture of abnormal and normal mitochondrial DNA molecules in a single cell.

(continued)

TABLE 2–1 **Glossary of terms and keywords (continued)**

Term	Definition
Heterozygote advantage	One way to explain an unexpectedly high frequency of a recessively inherited pathogenic variant in a particular population. During recent evolution, carriers (ie, heterozygotes) are postulated to have had a higher fitness than homozygous wild-type individuals.
Heterozygous	Having two alleles at the same locus that are different.
Homozygous	Having two alleles at the same locus that are the same.
Hypermorphic	Refers to a variant that has an effect similar to increasing the number of normal gene copies per cell.
Hypomorphic	Refers to a variant that reduces but does not eliminate the activity of a particular gene product.
Imprinting	Most commonly, the process whereby expression of a gene depends on whether it was inherited from the mother or the father.
Linkage disequilibrium	A condition in which certain combinations of closely linked alleles, or haplotypes, are present in a population at frequencies not predicted by their individual allele frequencies.
Locus heterogeneity	A situation in which pathogenic variants of different genes produce similar or identical phenotypes. Also referred to as genetic heterogeneity.
Mendelian	A form of inheritance that obeys the "laws" or principles of heredity postulated by Gregor Mendel, ie, segregation, independent assortment and dominance; clinically, these are commonly expressed as autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive.
Monosomy	A reduction in zygotic cells from two to one in the number of copies for a particular chromosomal segment or chromosome.
Mosaicism	A situation in which a genetic alteration is present in some but not all of the cells of a single individual. In germline or gonadal mosaicism, the alteration is present in germ cells but not somatic cells. In somatic mosaicism, the genetic alteration is present in some but not all of the somatic cells (and is generally not present in the germ cells).
Neomorphic	Refers to a variant that imparts a novel function to its gene product and consequently results in a phenotype distinct from an alteration in gene dosage.

Term	Definition
Nondisjunction	Failure of two homologous chromosomes to separate, or disjoin, at metaphase of meiosis I, or the failure of two sister chromatids to disjoin at metaphase of meiosis II or mitosis.
Penetrance	In a single individual of a variant genotype, penetrance refers to whether the variant genotype can be inferred based on defined phenotypic criteria. In a population, reduced penetrance refers to the rate at which individuals of a variant genotype cannot be recognized according to specific phenotypic criteria.
Phenotypic heterogeneity	The situation that occurs when pathogenic variants of a single gene produce multiple different phenotypes.
Postzygotic	A mutational event that occurs after fertilization and that commonly gives rise to mosaicism.
Premutation	A genetic change that does not result in a phenotype itself but has a high probability of developing a second alteration–a fully pathogenic variant/full mutation–that does cause a phenotype.
Primordial germ cell	The group of cells set aside early in development that go on to give rise to gametes.
Recessive	A pattern of inheritance or mechanism of gene action in which a particular mutant allele harboring a pathogenic variant causes a phenotype only in the absence of a normal allele. Thus, for autosomal conditions, the variant or disease phenotype is manifest when two copies of the allele harboring a pathogenic variant are present. For X-linked conditions, the variant or disease phenotype is manifest in cells, tissues, or individuals in which the normal allele Is either inactivated (a heterozygous female) or not present (a hemizygous male).
Robertsonian translocation	A type of translocation In which two acrocentric chromosomes are fused together with a single functional centromere. A carrier of a robertsonian translocation with 45 chromosomes has a normal amount of chromosomal material and is said to be euploid.
SNP	Single nucleotide polymorphism–one of the most common types of genetic variation. There are approximately 1 million common SNPs in the human genome (those that exist at a frequency >1 %), and billions of rare single-nucleotide variants (at a frequency >0.001%). Most do not affect protein structure, but the common SNPs may serve as valuable markers for determining the effect of genetic variation on complex and common diseases and disorders such as diabetes, heart disease, hypertension, and obesity.

Term	Definition
Structural variant	A deletion, insertion, or more complex rearrangement, usually caused by recombination between repetitive elements. Also referred to as "copy number variant" (CNV) and the most common type of genomic variation. Most structural variants involve deletions or insertions that are relatively small (<10 kb) and do not cause any clinical phenotype. Larger structural variants (>100 kb) are increasingly likely to have clinical effects.

(continued)

TABLE 2-1 **Glossary of terms and keywords. (continued)**

Term	Definition
Substrate accumulation	A pathogenetic mechanism in which deficiency of a particular enzyme causes disease because the substrate of that enzyme accumulates in tissue or blood.
Triplet repeat	A three-nucleotide sequence that is tandemly repeated many times; ie, $(XYZ)_n$. Alterations in length of such simple types of repeats (dinucleotide and tetranucleotide as well) occur much more frequently than most other kinds of pathogenic variants; in addition, alteration in the length of trinucleotide repeats is the molecular basis for several heritable disorders.
Trisomy	An abnormal situation in which there are three, instead of two, copies of a chromosomal segment or chromosome per cell.
Variant	A genetic sequence alteration. A variant can be classified further using modifiers such as "pathogenic,""likely pathogenic, "uncertain significance,""likely benign," and "benign." Use of this nomenclature has replaced the previously used terms "polymorphism" and "mutation."

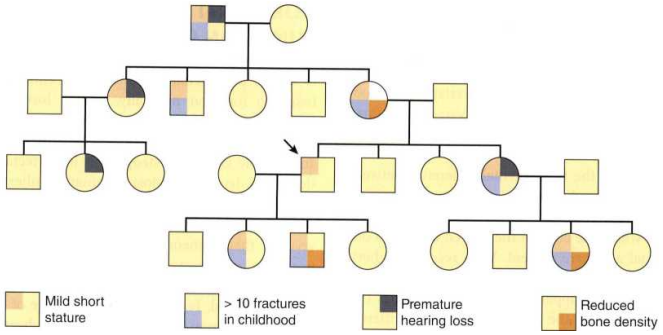
In most genetic diseases, every cell in an affected individual carries the mutated gene or genes as a consequence of its inheritance via a mutant egg or sperm cell **(gamete).** However, mutation of the gametic cell may have arisen during its development, in which case somatic cells of the parent do not carry the variant, and the affected individual is said to have a "de novo variant." In addition, some variants may arise during early embryogenesis, in which case tissues of the affected individual contain a mixture, or **mosaic,** of abnormal and normal cells. Depending on the time of embryogenesis and cell type in which a new variant arises, an individual may carry the alteration in some but not all of their germ cells **(germline mosaicism),** some but not all of their somatic cells **(somatic mosaicism),** or both.

It is helpful to begin with a brief review of terms that are commonly used in discussing genetic disease with patients and their families. Although genes were recognized and studied long before the structure of DNA was known, it has become common to regard a **gene** as a short stretch of DNA, usually but not always <100,000 base pairs (bp) in length, that encodes a product (usually protein) responsible for a function within the cell. DNA length is typically measured in base pairs, kilobase pairs (kb), or megabase pairs (Mb); chromosomes vary in length from about 46 Mb to 245 Mb. The **locus** is where a particular gene lies on its chromosome. A gene's DNA sequence nearly always has slight differences when compared across many unrelated individuals within a population. These variant versions of a gene are referred to as different **alleles** of that gene. A genetic variant arises via a biochemical event such as a nucleotide change, deletion, or insertion that has produced a new allele. The historic terms "polymorphism" and "mutation" are rarely used in current scientific and clinic discourse. A "polymorphism" was defined as a benign variant when it exhibited a population frequency greater than 1% in DNA sequence and did not contribute to disease manifestation. A "mutation" was defined as a pathogenic change in DNA sequence that did contribute to disease manifestation. The term "variant" is now the recommended term to define a change in DNA sequence from the population norm and is used with the following modifiers: "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign." Many changes in the DNA sequence of a gene, such as those within introns or at

the third "wobble" position of codons for particular amino acids, do not affect the structure or expression of the gene product; therefore, although all variants result in a biochemical or molecular biologic phenotype (ie, a change in DNA), only some of them result in a clinically abnormal phenotype.

At the molecular level, variant sequences are usually detected through laboratory evaluation (DNA sequencing) and are referred to as a single nucleotide variant (SNV) if a single base pair change has occurred. At the clinical level, variant alleles are recognized by their effect on a phenotype such as human leukocyte antigen (HLA) type or hair color. Two copies or alleles of each autosomal gene (ie, genes on chromosomes 1–22) are present per cell. Individuals carrying identical copies are **homozygous,** whereas individuals whose two copies differ from each other are **heterozygous.** These terms–"homozygous" and "heterozygous"–can apply to the DNA sequence, the protein product, or the clinical phenotype. In other words, an individual may be heterozygous for a single nucleotide polymorphism (SNP) that does not alter the protein product, heterozygous for a deletion that causes a genetic disease, or heterozygous for a DNA sequence alteration that causes a change in protein structure but does not cause disease.

This discussion helps to illustrate the use of the word **phenotype,** which refers simply to any characteristic that can be measured, with the type of measurement depending on the characteristic. Hair color and height are phenotypes readily apparent to a casual observer that are not obviously associated with disease; diabetes and coronary artery disease are disease phenotypes that typically require clinical investigation to be recognized; and restriction fragment length polymorphisms (RFLPs), simple sequence length polymorphisms (SSLPs), and SNPs are molecular biologic phenotypes that can be detected only with a laboratory test.



[Caption start]

FIGURE 2-1 Penetrance and expressivity in type I osteogenesis imperfecta. In this schematic pedigree of the autosomal dominant condition of type I osteogenesis imperfecta, nearly all affected individuals exhibit different phenotypic features that vary in severity (variable expressivity). As is shown, type i osteogenesis imperfecta is fully penetrant, because every individual who transmits the pathogenic variant is phenotypically affected to some degree. However, if mild short stature in the individual indicated with the arrow had been considered to be a normal variant, then the condition would have been nonpenetrant in this individual. Thus, in this example, judgments about penetrance or nonpenetrance depend on the criteria for normal and abnormal stature.

[Caption end]

PENETRANCE & EXPRESSIVITY

One of the most important principles of human genetics is that two individuals with the same mutated gene may have different phenotypes. For example, in the genetic condition of type I osteogenesis imperfecta, pedigrees may occur in which there are both a phenotypically affected grandparent and an affected grandchild even though the obligate carrier parent of the grandchild with the identical genetic variant is asymptomatic (Figure 2–1). Given a set of defined criteria, phenotypic expression of the condition in individuals known to carry the pathogenic variant gene is described as **penetrance.** In other words, if 7 of 10 individuals older than 40 with the type I osteogenesis imperfecta mutation have an abnormal bone density scan, the condition is said to be 70% penetrant by that criterion. Penetrance may vary both with age and according to the set of criteria being used; for example, type I osteogenesis imperfecta may be 90% penetrant at age 40 when the conclusion is based on a bone density scan in conjunction with laboratory tests for abnormal collagen synthesis. **Reduced penetrance,** or **age-dependent penetrance,** is a common feature of dominantly inherited conditions (see below) that often have a relatively high **fitness** (the extent to which individuals carrying an altered allele produce offspring relative to individuals who carry a normal allele); Huntington disease and polycystic kidney disease are examples of disorders with low **fitness.** Genetic conditions that result in a high degree of embryonic lethality have low **fitness.**

The same altered gene giving rise to a spectrum of different phenotypes is referred to as **variable expressivity.** For example, blue scleras and short stature may be the only manifestations of type I osteogenesis imperfecta in a particular individual, whereas a sibling who carries the identical mutation may be confined to a wheelchair as a result of multiple fractures and deformities. The pathogenic variant is penetrant in both individuals, but its expression is variable. Both reduced penetrance and variable expressivity may occur in individuals who carry the same altered allele; therefore, phenotypic differences between these individuals must be due to the effects of other "modifier" genes, to environmental interactions, or to chance.

MECHANISMS OF MUTATION & INHERITANCE PATTERNS

Genetic variants can be characterized both by their molecular nature–nucleotide deletion, insertion, substitution–and by their effects on gene activity (ie, no effect [neutral or silent], complete loss of function [amorphic variant], partial loss of function [hypomorphic variant], gain of function [hypermorphic variant], or acquisition of a new property [neomorphic

variant]). Geneticists who study experimental organisms frequently use specific deletions to ensure that an altered allele causes a loss of function, but human geneticists rely on biochemical or cell culture studies to assess both losses and gains of function. Amorphic and hypomorphic variants are probably the most frequent types of pathogenic variant in human genetic disease because there are many ways to interfere with a proteins function.

For autosomal genes, the fundamental difference between dominant and recessive inheritance is that, with dominant inheritance, the disease state or phenotypic trait being measured is apparent when one copy of the altered allele and one copy of the normal allele are present. With recessive inheritance, two copies of the altered allele must be present for the disease state or trait to be apparent. However, for genes that lie on the X chromosome, the situation is slightly different because females have two X chromosomes and males have only one. X-linked dominant inheritance occurs when one copy of an abnormal gene causes the disease phenotype (in males and females); X-linked recessive inheritance occurs when two copies of an abnormal gene cause the disease phenotype (in females). Because most pathogenic variants are amorphic or hypomorphic, however, one copy of an X-linked abnormal allele in males is not "balanced" with a normal allele, as it would be in females; therefore, in X-linked recessive inheritance, one copy of an abnormal allele is sufficient to produce a disease phenotype in males, a situation referred to as **hemizygosity.**

RECESSIVE INHERITANCE & LOSS-OF-FUNCTION PATHOGENIC VARIANTS

Most recessive pathogenic variants are due to loss of function of the gene product, which can occur from a variety of causes, including failure of the gene to be transcribed or translated and failure of the translated gene product to function correctly. There are two general principles to keep in mind when considering loss-of-function variants. First, because expression from the normal allele usually does not change (ie, there is no **dosage compensation),** gene expression in a heterozygous carrier of a loss-of-function allele is reduced to 50% of normal. Second, for most biochemical pathways, a 50% reduction in enzyme concentration is not sufficient to produce a disease state. Thus, most diseases resulting from enzyme deficiencies such as phenylketonuria (Table 2–2) are inherited in a recessive fashion.

DOMINANT INHERITANCE & LOSS-OF-FUNCTION PATHOGENIC VARIANTS

If 50% of a particular product is not enough for the cell or tissue to function normally, then a loss-of-function variant in this gene produces a dominantly inherited phenotype. Such pathogenic variants often occur in structural proteins; an example is type I osteogenesis imperfecta, which is considered in detail later. Most dominantly inherited phenotypes are actually **semidominant,** which means that an individual who carries two copies of the abnormal allele is affected more severely than someone who carries one abnormal and one normal copy. However, for most dominantly inherited conditions, individuals homozygous for two pathogenic variants are rarely observed. For example, inheritance of achondroplasia, the most common genetic cause of very short stature, is usually described as autosomal dominant. However, rare matings between two affected individuals have a 25% probability of producing offspring with two copies of the abnormal gene. This results in homozygous achondroplasia, a condition that is very severe and usually fatal in the perinatal period; thus, achondroplasia exhibits semidominant inheritance. Huntington disease, a dominantly inherited neurologic disease, is the only known human condition in which the homozygous abnormal phenotype is identical to the heterozygous abnormal phenotype (sometimes referred to as a "true dominant").

DOMINANT NEGATIVE GENE ACTION

A special kind of pathophysiologic mechanism, referred to as dominant negative, occurs frequently in human genetic diseases that involve proteins that form oligomeric or polymeric complexes. In these disorders, the abnormal allele gives rise to a structurally abnormal protein that interferes with the function of the normal allele. Note that any molecular lesion (ie, deletion, nonsense, missense, or splicing) can produce a loss-of-function allele. However, only molecular lesions that yield a protein product (ie, splicing, missense, or nonsense variants) can result in a dominant negative allele. Type II osteogenesis imperfecta, described later, is an example of a dominant negative pathogenic variant.

Although the terms "dominant" and "recessive" are occasionally used to describe specific pathogenic variants, a DNA sequence alteration itself cannot, strictly speaking, be dominant or recessive. The terms are instead appropriate to the effect of a pathogenic variant on a particular trait. Therefore, in characterizing a particular pathogenic variant as "recessive," one is referring to the effect of the variant on the trait being studied.

MUTATION RATE & THE PREVALENCE OF GENETIC DISEASE

At the level of DNA sequence, nucleotide variants (substitutions, small insertions, or small deletions) in humans occur at a rate of approximately 2×10^{-8} per nucleotide per human generation, or 150 new variants per diploid genome. However, only about 5% of the human genome is protein coding, so most new variants have no effect. Still, with approximately 23,000

genes in the human genome and an estimated deleterious "per locus" mutation rate of 10^{-5} per generation, the chance of a new deleterious variant occurring in any one individual is about 20%. Furthermore, assuming 10 billion new births in the last millennium, every gene in the human genome has probably been mutated (in a deleterious manner) about 100,000 different times. However, from a clinical perspective, only about 6000 single-gene disorders have been recognized to cause a human disease. In considering possible explanations for this disparity, it seems likely that deleterious variants of many single genes are lethal very early in development and thus not clinically apparent, whereas deleterious variants in other genes do not cause an easily recognizable phenotype. The overall frequency of disease attributable to defects in single genes (ie, mendelian disorders) is approximately 1% of the general population.

TABLE 2-2 **Phenotype, inheritance, and prevalence of selected genetic disorders.**

Disorder	**Phenotype**	**Genetic Mechanism**	**Incidence**
Down syndrome	Intellectual disability and growth deficiencies, dysmorphic features, internal organ anomalies	Chromosomal imbalance; caused by trisomy 21	≈1:700; increased risk with advanced maternal age
Fragile X–associated mental retardation syndrome	Intellectual disability, characteristic facial features, large testes	X-linked; progressive expansion of unstable DNA causes failure to express gene encoding RNA-binding protein	≈1:1500 males; can be manifested in females; multistep mechanism
Sickle cell anemia	Recurrent painful crises, increased susceptibility to infections	Autosomal recessive; caused by a single missense mutation in beta-globin	≈1:400 blacks
Cystic fibrosis	Recurrent pulmonary infections, exocrine pancreatic insufficiency,	Autosomal recessive; caused by multiple loss-of-function mutations in a chloride	1:2000 whites; very rare in Asians

Disorder	Phenotype	Genetic Mechanism	Incidence
	infertility	channel	
Leber hereditary optic neuropathy	Acute or subacute blindness, occasional myopathy or neurodegeneration	Pathogenic variant of electron transport chain encoded by mtDNA	≈1:50,000–1:10,000
Myoclonic epilepsy with ragged red fibers	Uncontrolled periodic jerking, muscle weakness	Pathogenic variant of mitochondrial tRNA in mtDNA	≈1:100,000–1:50,000
Neurofibromatosis	Multiple café-au-lait spots, neurofibromas, increased tumor susceptibility	Autosomal dominant; caused by multiple loss-of-function variants in a signaling molecule	≈1:3000; =50% are new mutations
Duchenne muscular dystrophy	Muscular weakness and degeneration	X-linked recessive; caused by multiple loss-of-function variants in muscle protein	≈1:3000 males; =33% are new mutations
Osteogenesis imperfecta	Increased susceptibility to fractures, connective tissue fragility, blue scleras	Phenotypically and genetically heterogeneous	≈1:10,000
Phenylketonuria	Intellectual disability and growth deficiencies	Autosomal recessive; caused by multiple loss-of-function variants in phenylalanine hydroxylase	≈1:10,000

Table 2-2 lists the major symptoms and signs (phenotypes), genetic mechanisms, and prevalence of the diseases considered in this chapter as well as of several others. The most common conditions, such as neurofibromatosis, cystic fibrosis, and fragile X–associated mental retardation syndrome, will be encountered at some time by most health care professionals regardless of their field of interest. Other conditions, such as Huntington disease and adenosine deaminase deficiency, although of academic and pathophysiologic interest, are not likely to be seen by most practitioners.

Many common conditions such as atherosclerosis and breast cancer, while in a minority of cases are caused by a single-gene disorder, usually do not show strictly mendelian inheritance patterns but have some genetic component evident from familial aggregation or twin studies. These conditions are usually described as **multifactorial,** which means that the effects of one or more mutated genes and environmental differences all contribute to the likelihood that a given individual will manifest the phenotype.