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Patterns of Single-Gene Inheritance

In Chapter 1, the three main categories of genetic disorders—single-gene, chromosomal, and complex—were named and briefly characterized. In the first section of this chapter, the typical patterns of transmission of single-gene disorders are discussed in further detail; the emphasis is on the molecular and genetic mechanisms by which mutations in genes result in recessive, dominant, and X-linked inheritance patterns. In the next section, we describe how gene imprinting and mosaicism can alter or obscure typical single-gene inheritance patterns.

Single-gene traits are often called **mendelian** because, like the characteristics of garden peas studied by Gregor Mendel, they occur on average in fixed proportions among the offspring of specific types of matings. The single-gene phenotypes known so far are listed in Victor A. McKusick's classic reference *Mendelian Inheritance in Man* (12th edition, 1998), which has been indispensable to medical geneticists for decades. The online version of *Mendelian Inheritance in Man* (OMIM) is continually updated and is available through the Internet. As of August 2003, OMIM lists nearly 11,000 genes, 5000 of which are clinically significant diseases inherited in a mendelian pattern. Approximately 1500 genes are known in which mutations have been found to cause over 2000 clinically significant disorders. Thus, of the approximately 30,000 human genes, about 5 percent have already been directly implicated in human genetic disease. The 5 percent figure is likely a great underestimate. The pace of new gene discovery is high, and it appears certain to accelerate because of international efforts dedicated to mapping and sequencing the entire human genome and the genes expressed in differentiated human tissues.

Single-gene disorders are primarily, but by no means exclusively, disorders of the pediatric age range; less than 10 percent manifest after puberty, and only 1 percent occur after the end of the reproductive period. Although individually rare, as a group they are responsible for a significant proportion of

childhood diseases and deaths. In a population study of more than 1 million live births, the incidence of serious single-gene disorders was estimated to be 0.36 percent; among hospitalized children, 6 to 8 percent are thought to have single-gene disorders.

TERMINOLOGY

Even though the principles of medical genetics are relatively easy to understand, the unfamiliar terminology may make the subject seem inaccessible at first. To help address the language problem, we review some terms and introduce others that have not been defined previously.

Inherited variation in the genome is the cornerstone of human and medical genetics. As introduced in Chapter 2, alternative variants of genetic information at a particular locus are called **alleles**. For many genes, there is a single prevailing version, present in the majority of individuals, which geneticists call the **wild-type** or normal allele. The other versions of the gene are **mutant** alleles that differ from the wild-type allele by **mutation**, a permanent change in the nucleotide sequence or arrangement of DNA. If there are at least two relatively common alleles at the locus in the population, the locus is said to exhibit **polymorphism** (literally "many forms"), as is discussed in detail in subsequent chapters. In addition to a normal allele or to common polymorphic alleles, loci may also have one or more rare, variant alleles; some of these rare alleles were originally identified because they cause genetic disease, whereas others are of no known significance to health.

The **genotype** of a person is the set of alleles that make up his or her genetic constitution, either collectively at all loci or, more typically, at a single locus. In contrast, the **phenotype** is the observable expression of a genotype as a morphological, clinical, biochemical, or molecular trait. A phenotype may, of course,