An increase in dosage of a gene product may also result in disease, as illustrated by the duplication of the *DAX1* gene in dosage-sensitive sex reversal (Chap. 410). Mutation in a single allele can also result in loss of function due to a dominant-negative effect. In this case, the mutated allele interferes with the function of the normal gene product by one of several different mechanisms: (1) a mutant protein may interfere with the function of a multimeric protein complex, as illustrated by mutations in type 1 collagen (*COL1A1*, *COL1A2*) genes in osteogenesis imperfecta (Chap. 427); (2) a mutant protein may occupy binding sites on proteins or promoter response elements, as illustrated by thyroid hormone resistance, a disorder in which inactivated thyroid hormone receptor β binds to target genes and functions as an antagonist of normal receptors (Chap. 405); or (3) a mutant protein can be cytotoxic as in α_1 antitrypsin deficiency (Chap. 314) or autosomal dominant neurohypophyseal diabetes insipidus (Chap. 404), in which the abnormally folded proteins are trapped within the endoplasmic reticulum and ultimately cause cellular damage.

Genotype and Phnotype • ***ALLELES, GENOTYPES, AND HAPLOTYPES*** An observed trait is referred to as a *phenotype*; the genetic information defining the phenotype is called the *genotype*. Alternative forms of a gene or a genetic marker are referred to as *alleles*. Alleles may be polymorphic variants of nucleic acids that have no apparent effect on gene expression or function. In other instances, these variants may have subtle effects on gene expression, thereby conferring adaptive advantages associated with genetic diversity. On the other hand, allelic variants may reflect mutations that clearly alter the function of a gene product. The common Glu6Val (E6V) sickle cell mutation in the *β-globin* gene and the ΔF508 deletion of phenylalanine (F) in the *CFTR* gene are examples of allelic variants of these genes that result in disease. Because each individual has two copies of each chromosome (one inherited from the mother and one inherited from the father), he or she can have only two alleles at a given locus. However, there can be many different alleles in the population. The normal or common allele is usually referred to as *wild type*. When alleles at a given locus are identical, the individual is *homozygous*. Inheriting identical copies of a mutant allele occurs in many autosomal recessive disorders, particularly in circumstances of consanguinity or isolated populations. If the alleles are different on the maternal and the paternal copy of the gene, the individual is *heterozygous* at this locus (Fig. 82-10). If two different mutant alleles are inherited at a given locus, the individual is said to be a *compound heterozygote*. *Hemizygous* is used to describe males with a mutation in an X chromosomal gene or a female with a loss of one X chromosomal locus.

Genotypes describe the specific alleles at a particular locus. For example, there are three common alleles (E2, E3, E4) of the apolipoprotein E (*APOE*) gene. The genotype of an individual can therefore be described as *APOE3/4* or *APOE4/4* or any other variant. These designations indicate which alleles are present on the two chromosomes in the *APOE* gene at locus 19q13.2. In other cases, the genotype might be assigned arbitrary numbers (e.g., 1/2) or letters (e.g., B/b) to distinguish different alleles.

A *haplotype* refers to a group of alleles that are closely linked together at a genomic locus (Fig. 82-4). Haplotypes are useful for tracking the transmission of genomic segments within families and for detecting evidence of genetic recombination, if the crossover event occurs between the alleles (Fig. 82-6). As an example, various alleles at the histocompatibility locus antigen (HLA) on chromosome 6p are used to establish haplotypes associated with certain disease states. For example, 21-hydroxylase deficiency, complement deficiency, and hemochromatosis are each associated with specific HLA haplotypes. It is now recognized that these genes lie in close proximity to the HLA locus, which explains why HLA associations were identified even before the disease genes were cloned and localized. In other cases, specific HLA associations with diseases such as ankylosing spondylitis (HLA-B27) or type 1 diabetes mellitus (HLA-DR4) reflect the role of specific HLA allelic variants in susceptibility to these autoimmune diseases. The characterization of common SNP haplotypes in numerous populations from different parts of the world through the HapMap Project is providing a novel tool for association studies designed to detect genes involved in the pathogenesis of complex disorders (Table 82-1). The presence or absence of certain haplotypes may also become relevant for the customized choice of medical therapies (pharmacogenomics) or for preventive strategies.

Genotype-phenotype correlation describes the association of a specific mutation and the resulting phenotype. The phenotype may differ depending on the location or type of the mutation in some genes. For example, in von Hippel–Lindau disease, an autosomal dominant multisystem disease that can include renal cell carcinoma, hemangioblastomas, and pheochromocytomas, among others, the phenotype varies greatly and the identification of the specific mutation can be clinically useful in order to predict the phenotypic spectrum.

ALLELIC HETEROGENEITY *Allelic heterogeneity* refers to the fact that different mutations in the same genetic locus can cause an identical or similar phenotype. For example, many different mutations of the β-globin locus can cause β thalassemia (Table 82-3) (Fig. 82-9). In essence, allelic heterogeneity reflects the fact that many different mutations are capable of altering protein structure and function. For this reason, maps of inactivating mutations in genes usually show a near-random distribution. Exceptions include (1) a founder effect, in which a particular mutation that does not affect reproductive capacity can be traced to a single individual; (2) "hot spots" for mutations, in which the nature of the DNA sequence predisposes to a recurring mutation; and (3) localization of mutations to certain domains that are particularly critical for protein function. Allelic heterogeneity creates a practical problem for genetic testing because one must often examine the entire genetic locus for mutations, because these can differ in each patient. For example, there are currently 1963 reported mutations in the *CFTR* gene (Fig. 82-3). Mutational analysis may initially focus on a panel of mutations that are particularly frequent (often taking the ethnic background of the patient into account), but a negative result does not exclude the presence of a mutation elsewhere in the gene. One should also be aware that mutational analyses generally focus on the coding region of a gene without considering regulatory and intronic regions. Because disease-causing mutations may be located outside the coding regions, negative results need to be interpreted with caution. The advent of more comprehensive sequencing technologies greatly facilitates concomitant mutational analyses of several genes after targeted enrichment, or even mutational analysis of the whole exome or genome. However, comprehensive sequencing can result in significant diagnostic challenges because the detection of a sequence alteration alone is not always sufficient to establish that it has a causal role.

PHENOTYPIC HETEROGENEITY *Phenotypic heterogeneity* occurs when more than one phenotype is caused by allelic mutations (e.g., different mutations in the same gene) (Table 82-3). For example, laminopathies are monogenic multisystem disorders that result from mutations in the *LMNA* gene, which encodes the nuclear lamins A and C. Twelve autosomal dominant and four autosomal recessive disorders are caused by mutations in the *LMNA* gene. They include several forms of lipodystrophies, Emery-Dreifuss muscular dystrophy, progeria syndromes, a form of neuronal Charcot-Marie-Tooth disease (type 2B1), and a group of overlapping syndromes. Remarkably, hierarchical cluster analysis has revealed that the phenotypes vary depending on the position of the mutation (*genotype-phenotype correlation*). Similarly, identical mutations in the *FGFR2* gene can result in very distinct phenotypes: Crouzon's syndrome (craniofacial synostosis) or Pfeiffer's syndrome (acrocephalopolysyndactyly).

LOCUS OR NONALLELIC HETEROGENEITY AND PHENOCOPIES *Nonallelic or locus heterogeneity* refers to the situation in which a similar disease phenotype results from mutations at different genetic loci (Table 82-3). This often occurs when more than one gene product produces different subunits of an interacting complex or when different genes are involved in the same genetic cascade or physiologic pathway. For example, osteogenesis imperfecta can arise from mutations in two different procollagen genes (*COL1A1* or *COL1A2*) that are located on different chromosomes, and at least eight other genes (Chap. 427). The effects of inactivating mutations in these two genes are similar because the protein products comprise different subunits