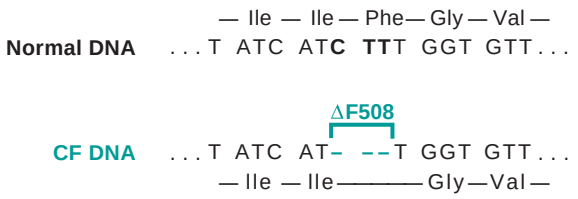

Figure 5-2 Three-base deletion in the common cystic fibrosis (CF) allele results in synthesis of a protein that lacks amino acid 508 (phenylalanine). Because the deletion is a multiple of three, this is not a frameshift mutation. (From Thompson MW, et al: Thompson and Thompson Genetics in Medicine, 5th ed. Philadelphia, WB Saunders, 1991, p 135.)

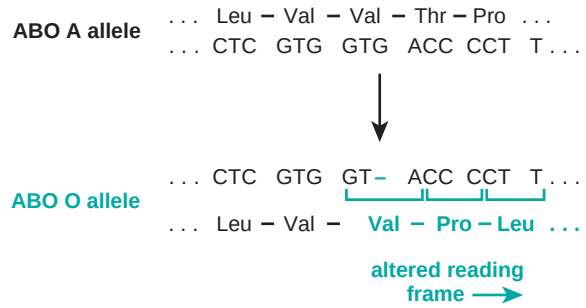

Figure 5-3 Single-base deletion at the ABO (glycosyltransferase) locus, leading to a frameshift mutation responsible for the O allele. (From Thompson MW, et al. Thompson and Thompson Genetics in Medicine, 5th ed. Philadelphia, WB Saunders, 1991, p 134.)

- ***Deletions and insertions.*** Small deletions or insertions involving the coding sequence can have two possible effects on the encoded protein. If the number of base pairs involved is three or a multiple of three, the reading frame will remain intact, and an abnormal protein lacking or gaining one or more amino acids will be synthesized (Fig. 5-2). If the number of affected coding bases is not a multiple of three, this will result in an alteration of the reading frame of the DNA strand, producing what is referred to as a frameshift mutation (Figs. 5-3 and 5-4). Typically, the result is the incorporation of a variable number of incorrect amino acids followed by truncation resulting from a premature stop codon.
- ***Trinucleotide-repeat mutations.*** Trinucleotide-repeat mutations belong to a special category of genetic anomaly. These mutations are characterized by amplification of a sequence of three nucleotides. Although the specific nucleotide sequence that undergoes amplification differs in various disorders, almost all affected sequences share the nucleotides guanine (G) and cytosine (C). For example, in fragile X syndrome, prototypical of this category of disorders, there are 250 to 4000 tandem repeats of the sequence CGG within a gene called *familial mental retardation 1 (FMR1).* In normal populations the number of repeats is small, averaging 29. Such expansions of the trinucleotide sequences prevent normal expression of the *FMR1* gene, thus giving rise to mental retardation. Another *distinguishing feature of trinucleotide-repeat mutations is that they are dynamic* (i.e., the degree of amplification increases during gametogenesis). These features, discussed in greater detail later, influence the pattern of inheritance and the phenotypic manifestations of the diseases caused by this class of mutation.

To summarize, mutations can interfere with gene expression at various levels. Transcription may be suppressed by gene deletions and point mutations involving promoter sequences. Abnormal mRNA processing may result from mutations affecting introns or splice junctions or both. Translation is affected if a nonsense mutation creates a stop codon (chain termination mutation) within an exon. Finally, some pathogenic point mutations may lead to expression of normal amounts of a dysfunctional protein.

Against this background, we now turn our attention to the three major categories of genetic disorders: (1) disorders related to mutant genes of large effect, (2) diseases with multifactorial inheritance, and (3) chromosomal disorders. To these three well-known categories must be added a heterogeneous group of *single-gene disorders with nonclassic patterns of inheritance.* This group includes disorders resulting from triplet-repeat mutations, those arising from mutations in mitochondrial DNA (mtDNA), and those in which the transmission is influenced by genomic imprinting or gonadal mosaicism. Diseases within this group are caused by mutations in single genes, but they do not follow the Mendelian pattern of inheritance. These are discussed later in this chapter.

It is beyond the scope of this book to review normal human genetics. Some fundamentals of DNA structure and regulation of gene expressions were described in Chapter 1. It is important here to clarify several commonly used terms—*hereditary*, *familial*, and *congenital.* Hereditary disorders, by definition, are derived from one's parents and are transmitted in the germ line through the generations and therefore are familial. The term *congenital* simply implies "born with." Some congenital diseases are not genetic; for example, congenital syphilis. Not all genetic diseases are congenital; individuals with Huntington disease, for example, begin to manifest their condition only after their 20s or 30s.

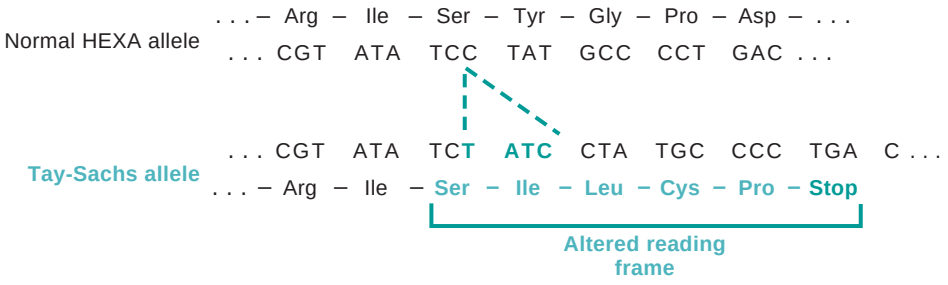

Figure 5-4 Four-base insertion in the hexosaminidase A gene, leading to a frameshift mutation. This mutation is the major cause of Tay-Sachs disease in Ashkenazi Jews. (From Nussbaum RL, et al: Thompson and Thompson Genetics in Medicine, 6th ed. Philadelphia, WB Saunders, 2001, p 212.)