- *Disorders related to mutations in single genes with large effects.* These mutations cause the disease or predispose to the disease and with some exceptions, like hemoglobinopathies, are typically not present in normal population. Such mutations and their associated disorders are highly penetrant, meaning that the presence of the mutation is associated with the disease in a large proportion of individuals. Because these diseases are caused by single gene mutations, they usually follow the classic Mendelian pattern of inheritance and are also referred to as Mendelian disorders. A few important exceptions to this rule are noted later.

  Study of single genes and mutations with large effects has been extremely informative in medicine since a great deal of what is known about several physiologic pathways (e.g., cholesterol transport, chloride secretion) has been learned from analysis of single gene disorders. Although informative, these disorders are generally rare unless they are maintained in a population by strong selective forces (e.g., sickle cell anemia in areas where malaria is endemic, Chapter 14).
- *Chromosomal disorders*. These arise from structural or numerical alteration in the autosomes and sex chromosomes. Like monogenic disease they are uncommon but associated with high penetrance.
- *Complex multigenic disorders*. These are far more common than diseases in the previous two categories. They are caused by interactions between multiple variant forms of genes and environmental factors. Such variations in genes are common within the population and are also called *polymorphisms*. Each such variant gene confers a small increase in disease risk, and no single susceptibility gene is necessary or sufficient to produce the disease. It is only when several such polymorphisms are present in an individual that disease occurs, hence the term *multigenic* or *polygenic*. Thus, unlike mutant genes with large effects that are highly penetrant and give rise to Mendelian disorders, each polymorphism has a small effect and is of low penetrance. Since environmental interactions are important in the pathogenesis of these diseases, they are also called multifactorial disorders. In this category are some of the most common diseases that afflict humans, including atherosclerosis, diabetes mellitus, hypertension, and autoimmune diseases. Even normal traits such as height and weight are governed by polymorphisms in several genes.

The following discussion describes mutations that affect single genes, which underlie Mendelian disorders, followed by transmission patterns and selected samples of single gene disorders.

Mutations

A *mutation* is defined as a permanent change in the DNA. Mutations that affect germ cells are transmitted to the progeny and can give rise to inherited diseases. Mutations that arise in somatic cells understandably do not cause hereditary diseases but are important in the genesis of cancers and some congenital malformations.

General principles relating to the effects of gene mutations follow.

- ***Point mutations within coding sequences.*** A point mutation is a change in which a single base is substituted with a different base. It may alter the code in a triplet of bases and lead to the replacement of one amino acid by another in the gene product. Because these mutations alter the meaning of the sequence of the encoded protein, they are often termed *missense mutations*. If the substituted amino acid is biochemically similar to the original, typically it causes little change in the function of the protein and the mutation is called a "conservative" missense mutation. On the other hand, a "nonconservative" missense mutation replaces the normal amino acid with a biochemically different one. An excellent example of this type is the sickle mutation affecting the β-globin chain of hemoglobin (Chapter 14). Here the nucleotide triplet CTC (or GAG in mRNA), which encodes glutamic acid, is changed to CAC (or GUG in mRNA), which encodes valine. This single amino acid substitution alters the physicochemical properties of hemoglobin, giving rise to sickle cell anemia. Besides producing an amino acid substitution, a point mutation may change an amino acid codon to a chain terminator, or *stop codon (nonsense mutation)*. Taking again the example of β-globin, a point mutation affecting the codon for glutamine (CAG) creates a stop codon (UAG) if U is substituted for C (Fig. 5-1). This change leads to premature termination of β-globin gene translation, and the short peptide that is produced is rapidly degraded. The resulting deficiency of β-globin chains can give rise to a severe form of anemia called β^0-thalassemia (Chapter 14).
- ***Mutations within noncoding sequences.*** Deleterious effects may also result from mutations that do not involve the exons. Recall that transcription of DNA is initiated and regulated by promoter and enhancer sequences (Chapter 1). Point mutations or deletions involving these regulatory sequences may interfere with binding of transcription factors and thus lead to a marked reduction in or total lack of transcription. Such is the case in certain forms of hereditary anemias called thalassemias (Chapter 14). In addition, point mutations within introns may lead to defective splicing of intervening sequences. This, in turn, interferes with normal processing of the initial mRNA transcripts and results in a failure to form mature mRNA. Therefore, translation cannot take place, and the gene product is not synthesized.

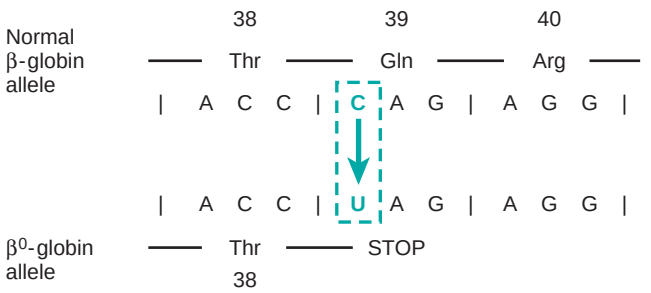

Figure 5-1 Nonsense mutation leading to premature chain termination. Partial mRNA sequence of the β-globin chain of hemoglobin showing codons for amino acids 38 to 40. A point mutation (C → U) in codon 39 changes a glutamine (Gln) codon to a stop codon, and hence protein synthesis stops at amino acid 38.