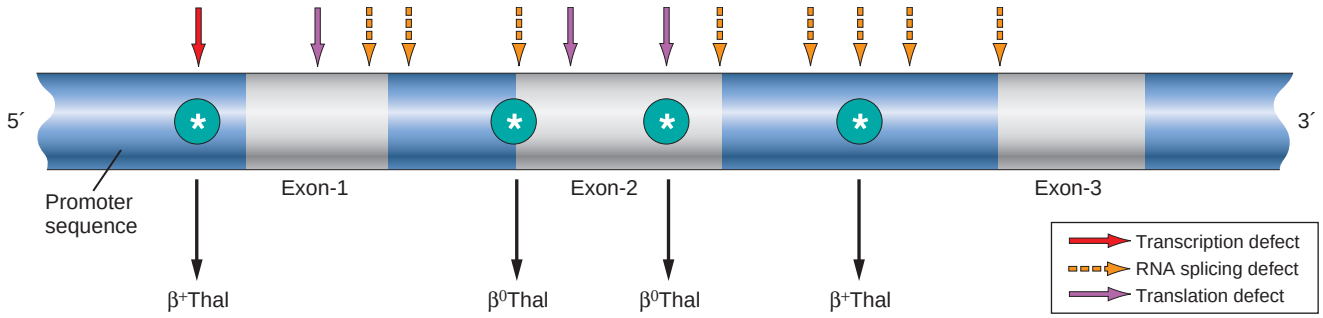

Figure 14-11 Distribution of β-globin gene mutations associated with β-thalassemia. Arrows denote sites where point mutations giving rise to β^0 or β^+ thalassemia have been identified.

introns, while a few are located within exons. Some of these mutations destroy the normal RNA splice junctions and completely prevent the production of normal β-globin mRNA, resulting in β^0-thalassemia. Others create an "ectopic" splice site within an intron. Because the flanking normal splice sites remain, both normal and abnormal splicing occurs and some normal β-globin mRNA is made, resulting in β^+-thalassemia.

- *Promoter region mutations.* These mutations reduce transcription by 75% to 80%. Some normal β-globin is synthesized; thus, these mutations are associated with β^+-thalassemia.
- *Chain terminator mutations.* These are the most common cause of β^0-thalassemia. Two subtypes of mutations fall into this category. The most common type creates a new stop codon within an exon; the other introduces small insertions or deletions that shift the mRNA reading frames (frameshift mutations; see Chapter 5). Both block translation and prevent the synthesis of any functional β-globin.

Impaired β-globin synthesis results in anemia by two mechanisms (Fig. 14-12). The deficit in HbA synthesis produces "underhemoglobinized" hypochromic, microcytic red cells with subnormal oxygen transport capacity. Even more important is the diminished survival of red cells and their precursors, which results from the imbalance in α- and β-globin synthesis. Unpaired α chains precipitate within red cell precursors, forming insoluble inclusions. These inclusions cause a variety of untoward effects, but membrane damage is the proximal cause of most red cell pathology. Many red cell precursors succumb to membrane damage and undergo apoptosis. In severe β-thalassemia, it is estimated that 70% to 85% of red cell precursors suffer this fate, which leads to *ineffective erythropoiesis*. Those red cells that are released from the marrow also contain inclusions and have membrane damage, leaving theme prone to splenic sequestration and *extravascular hemolysis*.

In severe β-thalassemia, ineffective erythropoiesis creates several additional problems. Erythropoietic drive in the setting of severe uncompensated anemia leads to massive erythroid hyperplasia in the marrow and extensive extramedullary hematopoiesis. The expanding mass of red cell precursors erodes the bony cortex, impairs bone growth, and produces skeletal abnormalities (described later). Extramedullary hematopoiesis involves the liver, spleen, and lymph nodes, and in extreme cases produces extraosseous masses in the thorax, abdomen, and pelvis. The metabolically active erythroid progenitors steal nutrients from other tissues that are already oxygen-starved, causing severe cachexia in untreated patients.

Another serious complication of ineffective erythropoiesis is excessive absorption of dietary iron. Ineffective erythropoiesis suppresses hepcidin, a critical negative regulator of iron absorption (see Iron Deficiency Anemia). Increased absorption of iron from the gut due to low hepcidin levels and the iron load of repeated blood transfusions inevitably lead to severe iron accumulation unless preventive steps are taken. Secondary injury to parenchymal organs, particularly the liver, often follows and sometimes induces *secondary hemochromatosis* (Chapter 18).

Clinical Syndromes. The relationships of clinical phenotypes to underlying genotypes are summarized in Table 14-3. Clinical classification of β-thalassemia is based on the severity of the anemia, which in turn depends on the genetic defect (β^+ or β^0) and the gene dosage (homozygous or heterozygous). In general, individuals with two β-thalassemia alleles (β^+/β^+,β^+/β^0, or β^0/β^0) have a severe, transfusion-dependent anemia called β-*thalassemia major.* Heterozygotes with one β-thalassemia gene and one normal gene (β^+/β or β^0/β) usually have a mild asymptomatic microcytic anemia. This condition is referred to as *β-thalassemia minor* or *β-thalassemia trait.* A third genetically heterogeneous variant of moderate severity is called β-*thalassemia intermedia.* This category includes milder variants of β^+/β^+ or β^+/β^0-thalassemia and unusual forms of heterozygous β-thalassemia. Some patients with β-thalassemia intermedia have two defective β-globin genes and an α-thalassemia gene defect, which improves the effectiveness of erythropoiesis and red cell survival by lessening the imbalance in α- and β-chain synthesis. In other rare but informative cases, individuals have a single β-globin defect and one or two extra copies of normal α-globin genes (stemming from a gene duplication event), which worsens the chain imbalance. These unusual forms of the disease serve to emphasize the cardinal role of unpaired α-globin chains in the pathology. The clinical and morphologic features of β-thalassemia intermedia are not described separately but can be surmised from the following discussions of β-thalassemia major and β-thalassemia minor.