GENETIC DEFECTS IN THALASSEMIA

Gene deletions are the most common type of mutation encountered in \( \alpha \)-thalassemia. Gene deletions can involve the loss of an entire gene or gene cluster, resulting in the absence of production of the associated globin chain(s). A gene deletion can also be partial, which may abrogate chain production or produce globin chains of increased or decreased lengths.

Mutations of promoter sequences occur most often in thalassemias affecting the \( \beta \)-globin genes. Promoter sequences are regions of DNA, usually upstream of the gene, that function to regulate the transcription of the gene through interaction with DNA-binding proteins, particularly RNA polymerase. If the sequence is mutated, RNA polymerase may be unable to bind, thus preventing transcription. More often, the promoter mutation decreases the binding affinity of RNA polymerase, thus reducing transcription efficiency and, ultimately, the amount of protein produced.

Nonsense mutations are single nucleotide changes in a codon that alter the mRNA product. These mutations are also more common in \( \beta \)-thalassemias. If the nonsense mutation replaces a nucleotide with a different one, or if nucleotides are removed or added in multiples of three, the stop codon will be unaltered and the protein length will remain unchanged or be minimally affected. This type of mutation is referred to as an in-frame substitution. However, if nucleotides are added or subtracted in multiples other than three, the mutation is referred to as a frame shift mutation. In this case the nucleotide sequence, and thus the amino acid sequence of the protein, will be different downstream from the frame shift. This results in truncated or elongated proteins and altered protein survival and function.

Stop codon mutations commonly result from nonsense mutations and gene deletions. The generation of premature stop codons produces a shortened protein chain. Protein chains that are exceedingly short are recognized as abnormal by the cell and degraded. This process mimics gene deletion, because both result in the absence of protein product. If the protein length is similar to normal the protein may survive. Occasionally a nonsense mutation can occur at the natural stop codon, converting it to an amino acid message. In this case, transcription will continue past the natural termination point until a new stop codon is reached. This will result in an elongated protein product that can either be retained or degraded, depending on its length.

Mutations to splice sites within introns can cause a variety of alterations in gene transcription. Intron mutations can produce new splice sites or destroy the original splice sites. In either case, non-coding sequences (introns) are introduced into coding sequences (exons), thus creating new codons and the corresponding amino acids. In some cases the protein product may be unaltered, and in other cases the protein may be truncated or lengthened. Other mutations may result in the absence or reduction of mRNA.