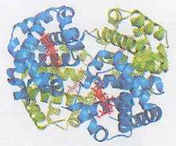
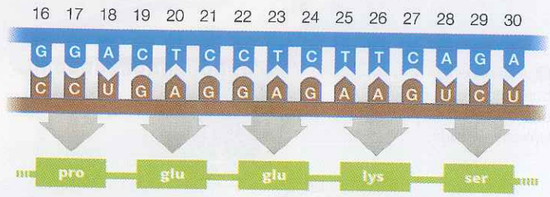
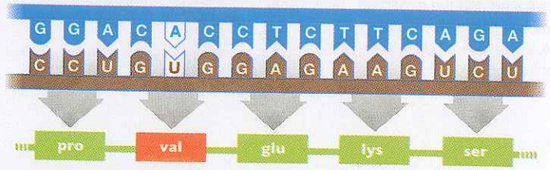
9.6 Mutated Genes and Their Protein Products



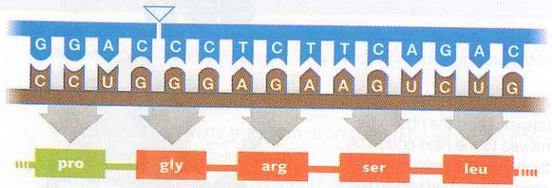
A Hemoglobin, an oxygen-binding protein in red blood cells. This protein consists of four polypeptides: two alpha globins (blue) and two beta globins (green). Each globin has a pocket that cradles a heme (red). Oxygen molecules bind to the iron atom at the center of each heme.



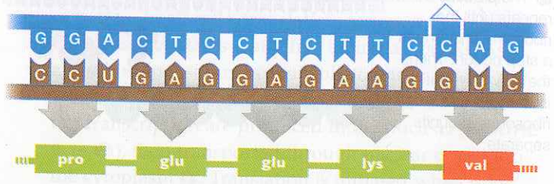
B Part of the DNA (blue), mRNA (brown), and amino acid sequence of human beta globin. Numbers indicate nucleotide position in the mRNA.



C A base-pair substitution replaces a thymine with an adenine. When the altered mRNA is translated, valine replaces glutamic acid as the sixth amino acid. Hemoglobin with this form of beta globin is called HbS, or sickle hemoglobin.



D A base-pair deletion shifts the reading frame for the rest of the mRNA, so a completely different protein product forms. The mutation shown results in a defective beta globin. The outcome is beta thalassemia, a genetic disorder in which a person has an abnormally low amount of hemoglobin.



E An insertion of one nucleotide causes the reading frame for the rest of the mRNA to shift. The protein translated from this mRNA is too short and does not assemble correctly into hemoglobin molecules. As in **D**, the outcome is beta thalassemia.

FIGURE 9.13 ▶**Animated** Examples of mutations.

✔ If the nucleotide sequence of a gene changes, it may result in an altered gene product, with harmful effects.

Mutations, remember, are permanent changes in the DNA sequence of a chromosome (Section 8.6). A mutation in which one nucleotide and its partner are replaced by a different base pair is called a **base-pair substitution**. Other mutations involve the loss of one or more base pairs (a **deletion**) or the addition of extra base pairs (an **insertion**).

Mutations are relatively uncommon events in a normal cell. Consider that the chromosomes in a diploid human cell collectively consist of about 6.5 billion nucleotides, any of which may become mutated each time that cell divides. On average, about 175 nucleotides do change during DNA replication. However, only about 3 percent of the cell's DNA encodes protein products, so there is a low probability that any of those mutations will be in a protein-coding region.

When a mutation does occur in a protein-coding region, the redundancy of the genetic code offers the cell a margin of safety. For example, a mutation that changes a CCU codon to CCC may have no further effect, because both of these codons specify proline. Other mutations may change an amino acid in a protein, or result in a premature stop codon that shortens it.

Mutations that alter a protein can have drastic effects on an organism. Consider the effects of such mutations on hemoglobin, an oxygen-transporting protein in your red blood cells (Section 3.2). Hemoglobin's structure allows it to bind and release oxygen. In adult humans, a hemoglobin molecule consists of four polypeptides called globins: two alpha globins and two beta globins (**FIGURE 9.13A**). Each globin folds around a heme, a cofactor with an iron atom at its center (Section 5.6). Oxygen molecules bind to hemoglobin at those iron atoms.

Mutations in the genes for alpha or beta globin cause a condition called anemia, in which a person's blood is deficient in red blood cells or in hemoglobin. Both outcomes limit the blood's ability to carry oxygen, and the resulting symptoms can range from mild to life-threatening.

Sickle-cell anemia, a type of anemia that is most common in people of African ancestry, arises because of a base-pair substitution in the beta globin gene. The substitution causes the body to produce a version of beta globin in which the sixth amino acid is valine instead of glutamic acid (**FIGURE 9.13B,C**). Hemoglobin assembled with this altered beta globin chain is called sickle hemoglobin, or HbS.

U… charg… base-… …mutation, a tiny patch of the beta globin polypeptide that is normally hydrophilic becomes hydrophobic. This change slightly alters hemoglobin behavior. Under certain conditions, HbS molecules stick together and form large, rodlike clumps. Red blood cells that contain the clumps become distorted into a crescent (sickle) shape (**FIGURE 9.14**). Sickled cells clog tiny blood vessels, thus disrupting blood circulation throughout the body. Over time, repeated episodes of sickling can damage organs and eventually cause death.

A different type of anemia, beta thalassemia, is caused by the deletion of the twentieth nucleotide in the coding region of the beta globin gene (**FIGURE 9.13D**). Like many other deletions, this one causes the reading frame of the mRNA codons to shift. A frameshift usually has drastic consequences because it garbles the genetic message, just as incorrectly grouping a series of letters garbles the meaning of a sentence:

The fat cat ate the sad rat
T hef atc ata tet hes adr at

The frameshift caused by the beta globin deletion results in a polypeptide that differs drastically from normal beta globin in amino acid sequence and in length. This outcome is the source of the anemia. Beta thalassemia can also be caused by insertion mutations, which, like deletions, often result in frameshifts (**FIGURE 9.13E**).

Not all mutations that affect protein structure disrupt codons for amino acids. DNA also contains special nucleotide sequences that influence the expression of nearby genes (we return to this topic in the next chapter). A promoter is one example; an intron–exon splice site is another. Consider a mutation that causes the hairless appearance of sphynx cats (**FIGURE 9.15**). In this case, a base-pair substitution disrupts an intron–exon splice site in a gene for keratin, a fibrous protein (Section 3.6). The intron is not correctly removed during post-transcriptional processing. The altered protein translated from the resulting mRNA cannot properly assemble into filaments that make up hair. Cats with this mutation still make hair, but it falls out before it gets very long.

base-pair substitution Type of mutation in which a single base pair changes.
deletion Mutation in which one or more nucleotides are lost.
insertion Mutation in which one or more nucleotides become inserted into DNA.

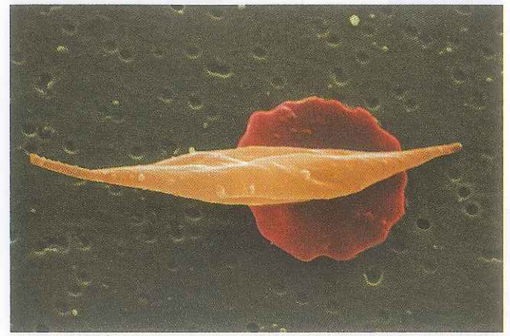


FIGURE 9.14 ▶**Animated** A sickled red blood cell compared with a normal one. A single base-pair substitution gives rise to an abnormal beta globin chain that, when assembled in hemoglobin molecules, forms HbS. The sixth amino acid in these abnormal beta globin chains is valine, not glutamic acid. In the body, the difference causes HbS molecules to form rod-shaped clumps that distort normally round blood cells (red) into the sickle shape (tan) characteristic of sickle-cell anemia. Sickled cells clog small blood vessels.

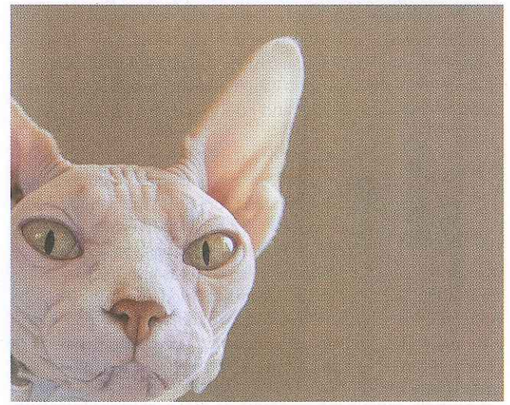


FIGURE 9.15 The hairless appearance of a sphynx cat arises from a single base-pair mutation in a gene for keratin, a fibrous protein that makes up hair. The altered keratin that results from the mutation does not assemble correctly into filaments. Sphynx cats are not truly hairless; they produce hair, but it is easily dislodged.

TAKE-HOME MESSAGE 9.6

What happens after a gene becomes mutated?

✔ Mutations that result in an altered protein can have drastic consequences.

✔ A base-pair substitution may change an amino acid in a protein, or it may introduce a premature stop codon.

✔ Frameshifts that occur after an insertion or deletion can change an mRNA's codon reading frame, thus garbling its protein-building instructions.