

Gene Mutations

What you are made of and how your body functions begins with the instructions from your DNA. Your DNA carries the code from which all the proteins that give your body structure and help your body carry out life-maintaining processes are produced. Changes in DNA, or mutations, may result in diseases like sickle cell anemia. How do mutations occur and what causes them?

Causes of Mutations

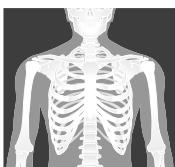
Mutations can be categorized as gene mutations or chromosomal mutations.

Gene mutations are changes in the DNA sequence of a single gene. Typically, gene mutations happen during DNA replication. DNA polymerase has a built-in proofreading function that repairs mutations, but a small number of replication errors do not get fixed. They build up over time, and can eventually affect how the cell works. Many studies suggest that mutations in somatic cells, coupled with a decrease in the body's self-repairing ability, may contribute to the process of aging.

Mutagens are agents in the environment that can change DNA or increase the frequency of mutation in organisms. Some mutagens occur naturally, such as ultraviolet (UV) rays in sunlight. Some chemicals have also been linked to mutations, such as those in food and cosmetics. Biological mutagens include bacteria and viruses.

 **Collaborate** When you get x-rays at the dentist, a lead vest is placed over your body. Write why you think this is necessary, and explain to a partner.

FIGURE 2: Mutagens can change DNA. The main types of mutagens include radiation, chemicals, and infectious agents.

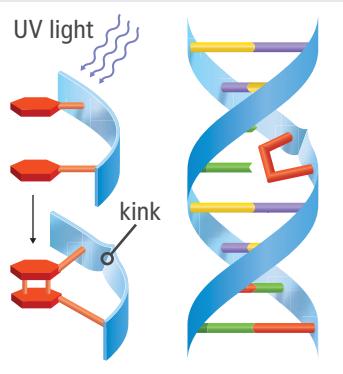
Radiation		Chemicals			Infectious Agents	
						
X-rays (medical uses)	UV (from sunlight)	Processed foods and preservatives	Cleaning products and cosmetics	Carcinogens (e.g., cigarettes)	Viruses (e.g., HPV)	Bacteria (e.g., H. pylori)

One example of a mutation caused by a mutagen is a thymine dimer. Recall that in DNA, adenine always pairs with thymine. UV light can cause neighboring thymine nucleotides to break their hydrogen bonds to adenine and bond together, forming a thymine dimer. The dimer causes the DNA to kink, which interferes with replication. Cells have a process for correcting these mutations. One enzyme removes the thymine dimer, another replaces the damaged section, and a third bonds the new segment in place. Sometimes, this process is not effective. When these mutations are not corrected in genes that regulate cell and tumor growth, they may result in cancer.



Explain Some cancer drugs take advantage of mutagenic properties. One type of drug wedges its way between nucleotides in DNA. Explain how the action of this drug would cause cancer cells to eventually lose their ability to function and reproduce.

FIGURE 3: Thymine Dimer



Point Mutations

A point mutation is a mutation in which one nucleotide is substituted for another. In other words, an incorrect nucleotide takes the place of the correct nucleotide. Very often, such a mistake is caught and fixed by DNA polymerase. If not, the substitution may permanently change an organism's DNA.



Cause and Effect

Let's examine some mutations and determine their effects on the sequence of amino acids. Remember that in protein synthesis, the DNA code is transcribed to make a strand of mRNA, which is then translated into a sequence of amino acids using codons. Some mutations affect the amino acid sequence, which can affect the structure and function of the resulting protein.

FIGURE 4: A codon chart shows which amino acids correspond to each possible combination of mRNA bases.

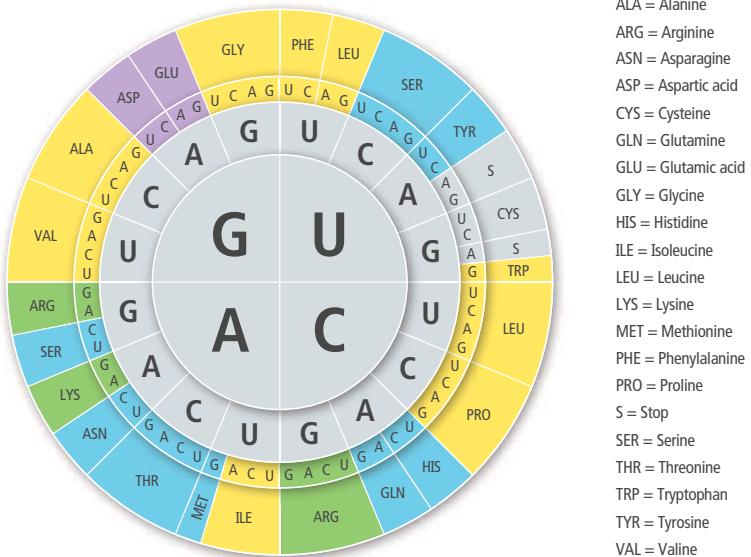


FIGURE 5: Normal and Mutated DNA Sequences

	Normal sequence	Mutation 1	Mutation 2	Mutation 3
DNA	CTC	CAC	ATC	CTT
mRNA	GAG	GUG	UAG	GAA



Analyze Use the chart in Figure 4 to analyze the DNA sequences in Figure 5.

- For each mRNA sequence, determine the corresponding amino acid.
- Which mutations changed the identity of the amino acid as compared to the normal sequence?
- If you had to create names for the three types of mutations you analyzed, what would they be?

Mutations that change a codon, but not the identity of an amino acid in a protein, do not affect the amino acid sequence of that protein. This type of mutation is sometimes called a “silent mutation” because it does not change the structure and function of the protein. However, there are times when the substitution of a base results in a change in a codon and consequently in a new amino acid. This is called a “missense” mutation. If a mutation results in a “stop” codon being formed, the protein will not be complete. This is called a “nonsense” mutation. In both types, the amino acid sequence has changed and the protein’s structure and function may be altered.

Sickle cell anemia is caused by a point mutation that alters the gene which codes for the hemoglobin protein in red blood cells. Hemoglobin is made of four subunits with each of the subunits containing iron. This arrangement allows red blood cells to be efficient in transporting oxygen molecules from the lungs to the cells because oxygen molecules bind to the iron atoms. In HbS alleles, glutamic acid is substituted by valine. The protein synthesized using the mutated gene as a template has a different structure than that of a typical hemoglobin protein.

Glutamic acid is a negatively-charged amino acid that is attracted to positively-charged amino acids. This interaction between amino acids helps the protein keep its shape. Unlike glutamic acid, valine is not attracted to positively-charged amino acids. So, instead of grouping together to form the structure in Figure 6, the hemoglobin subunits form long, rigid chains. This results in red blood cells that have a “sickle” shape.

FIGURE 6: Hemoglobin has four subunits, each with an iron atom to which oxygen molecules attach.

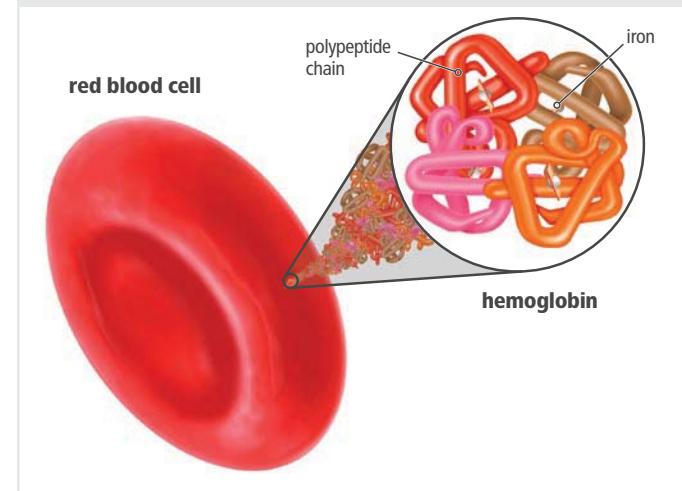
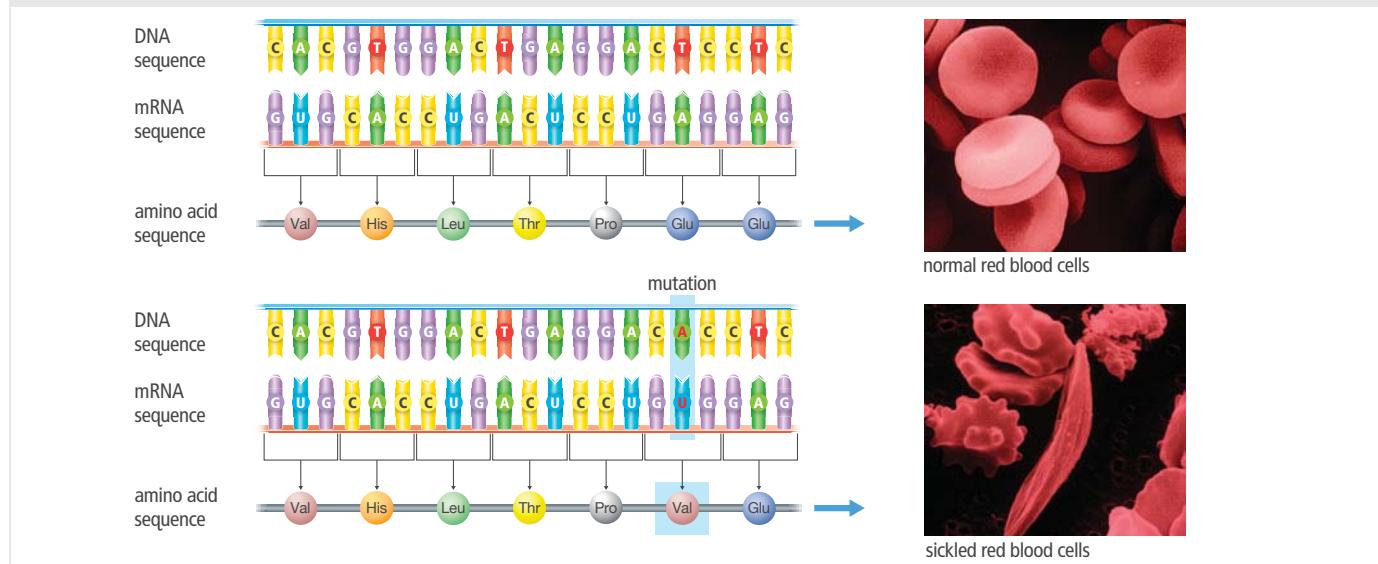


FIGURE 7: Sickle cell anemia results from a mutation that alters the structure of hemoglobin.



When sickle-shaped red blood cells stack on top of each other, they can clog blood vessels. This mutation causes anemia, and consequently fatigue and the other symptoms of sickle cell anemia. The cells do not get enough oxygen to produce the energy the body needs to properly maintain processes that keep the body healthy.



Model Draw a flow chart to illustrate how a change in a nucleotide in a DNA strand leads to symptoms experienced by those with sickle cell anemia.

Frameshift Mutations

A frameshift mutation involves the insertion or deletion of one or more nucleotides in the DNA sequence. This mutation changes the reading frame, or the arrangement of nucleotides into codons. To understand how a frameshift mutation affects an mRNA strand, imagine a short sentence of three-letter “codons”:

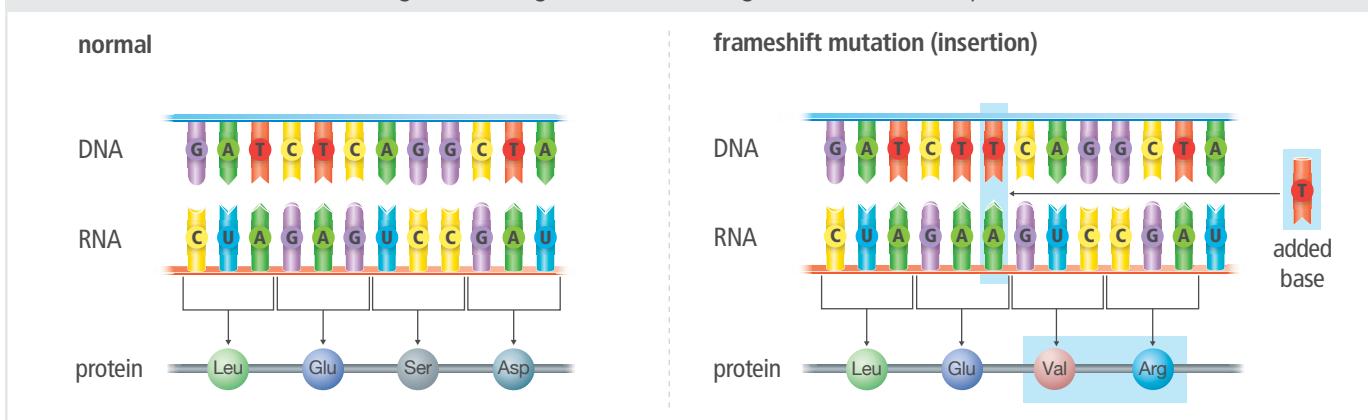
THE CAT ATE THE RAT

If the letter *E* is removed, or deleted, from the first “THE,” all the letters that follow shift to the left. The sentence now reads:

THC ATA TET HER AT...

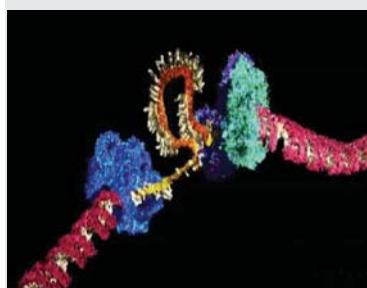
The sentence no longer makes sense. The same would be true if a nucleotide was added, or inserted, and all the letters shifted to the right, as shown in Figure 8.

FIGURE 8: Frameshift mutations change the reading frame, which changes the amino acid sequence after the mutation.



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FIGURE 9: Trinucleotide repeat expansions make a loop of duplicate nucleotides.



A nucleotide sequence loses its meaning when an insertion or deletion shifts all the codons by one nucleotide. This change throws off the reading frame, which results in codons that code for different amino acids.

Trinucleotide Repeat Expansions

Frameshift mutations may also occur in sections of DNA that consist of repeating nucleotides, such as CAG CAG CAG. These repeating segments are known as trinucleotide repeats because they involve three nucleotides. During replication, DNA polymerase may “slip” and make duplicate copies of the repeated sequence. This forms a “hairpin” loop of DNA that sticks out from its complementary strand. When this strand is replicated, the loop becomes part of the DNA, resulting in a longer double strand of DNA. This expansion continues as cells divide and DNA is replicated.



Analyze People with sickle cell anemia have two copies of the HbS allele. People with one copy are carriers and do not have the disease.

1. Is the sickle cell allele dominant or recessive? Explain how you know.
2. If two carriers have children, what is the probability of one of their children having the disease?