7.5 Genetic Mutations

Figure 1 Cigarette labels clearly describe the negative consequences of smoking.

Over the years, legislation has forced cigarette manufacturers to print warnings on their packages about the dangers of smoking (**Figure 1**). What if the following warning was placed on a cigarette package: "Smokers with a particular mutation have a higher risk of developing cancer." If you were a smoker, would you be concerned that you might have this mutation? Would you get tested for it or stop smoking? If you knew about any mutation in your genome, would you alter your lifestyle choices?

Genetic mutations are changes in the DNA sequence, caused by various mechanisms. For example, synthetic chemicals, radiation, incorrect replication, and random mutations can change the structure and function of the genome. Mutations caused by smoking increase the risk of various forms of cancer. A region on human chromosome 15 is known to play a part in an individual's susceptibility to developing lung cancer. If mutated, this region increases a smoker's risk of lung cancer by 30 to 80 %, depending on whether the smoker has one or two copies of the 15q24 susceptibility locus. A susceptibility locus is a region on a given chromosome where mutations that affect one or more genes are more likely to be present, based on statistical evidence.

The word "mutation" has developed a negative connotation. However, it is important to remember that mutations have given rise to the variety of life that we see today. The current inhabitants of Earth are a result of many mutations over time—the products of natural selection. In this section, you will look at the different types of mutations and learn how these mutations affect the functions of genes and the synthesis of proteins.

point mutation a change in a single nucleotide within a gene

substitution the replacement of one base pair in a DNA sequence by another base pair

insertion the addition of a base pair (small-scale mutation) or larger coding region (large-scale mutation) to a DNA sequence

deletion the removal of a base pair (small-scale mutation) or larger coding region (large-scale mutation) from a DNA sequence

inversion two adjacent bases trading places (small-scale mutation) or the reversal of a sequence of DNA (large-scale mutation)

single nucleotide polymorphism (SNP) a difference in the DNA between individuals caused by point mutations

missense mutation a mutation that changes a single amino acid in the coding sequence

nonsense mutation a mutation that results in a premature stop codon

silent mutation a mutation that does not alter the resulting sequence of amino acids

frameshift mutation a shift in the reading frame resulting in multiple missense and/or nonsense effects

Small-Scale Mutations

Small-scale mutations include mutations of an individual base pair, called **point mutations**, and of small groups of base pairs. There are several different types of point mutations, including

- the **substitution** of one base for another
- the **insertion** or **deletion** of a single base pair
- the **inversion** of two adjoining base pairs

Small-scale mutations of a small group of base pairs are categorized similarly: the substitution, insertion, or deletion of the group.

As a result of a point mutation, either a substitution or a deletion mutation, individuals with β-thalassemia cannot synthesize β-globin. Part of normal hemoglobin, β-globin is 146 amino acids in length. The mutated gene codes for a stop codon in the position of codon 39. Because β-globin is absent, individuals with β-thalassemia have small erythrocytes that rupture easily. These people often require blood transfusions.

The differences in the DNA of individuals within a population that are caused by point mutations are referred to as **single nucleotide polymorphisms** or **SNPs** (pronounced "snips"; *poly* means "many" and *morphisms* means "alternative forms"). In other words, population X may have 120 known SNPs in allele Y. Because SNPs are particularly common and variable in non-coding parts of the genome, they are sometimes used in forensics and paternity testing.

The effects of small-scale mutations can range from being positive, through having no effect, to being severe. Functionally, small-scale mutations can be categorized into four groups: missense mutations, nonsense mutations, silent mutations, and frameshift mutations. These are described in **Figure 2** (next page).

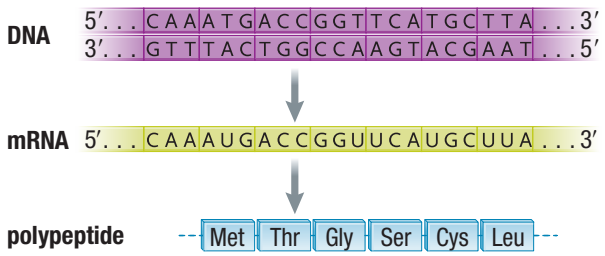
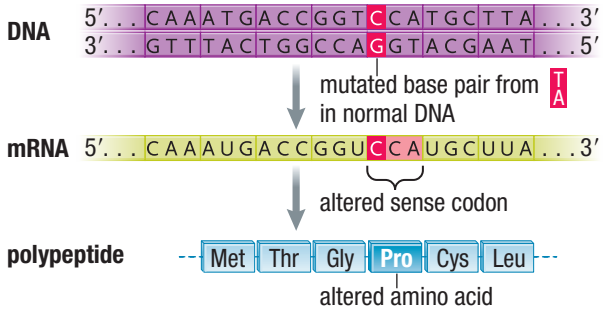
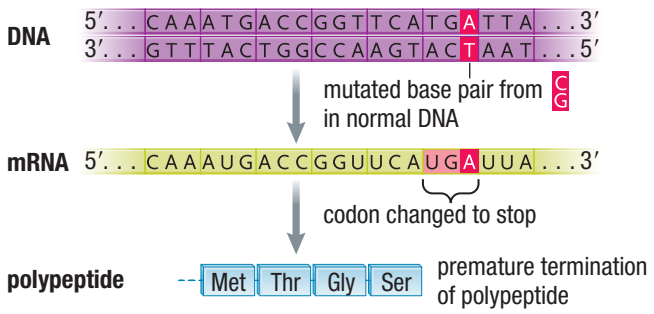
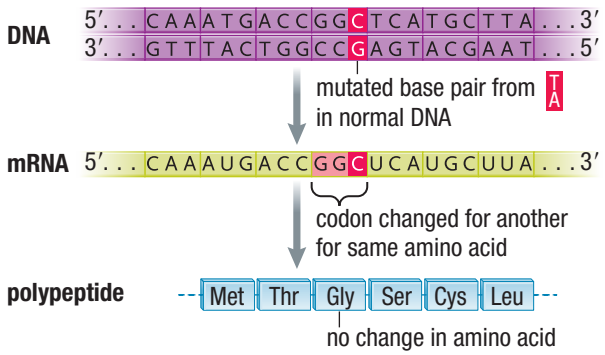
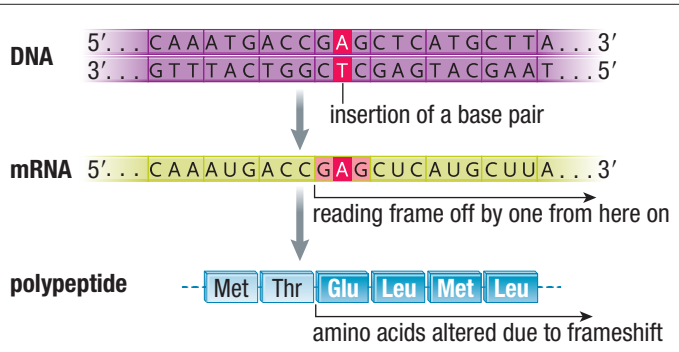
Mutation and description	Illustration
No mutation: This is the normal condition.	
A **missense mutation** occurs when a change of a single base pair or group of base pairs results in the code for a different amino acid. The protein that is synthesized will have a different sequence and structure, and it may be non-functional or function differently. A missense mutation can be beneficial if it creates a new, desirable effect.	
A **nonsense mutation** occurs when the change of a single base pair or group of base pairs results in a premature stop code in the gene. The polypeptide is cut short and, most likely, will be unable to function.	
A **silent mutation** occurs when the change in one or more base pairs does not affect the functioning of the gene. The mutated DNA sequence codes for the same amino acid as the non-mutated sequence, and the resulting protein is not altered.	
A **frameshift mutation** occurs when one or more nucleotides are inserted into or deleted from a DNA sequence, causing the reading frame of codons to shift in one direction or the other. This results in multiple missense and/or nonsense effects. The frameshift mutation "shifts" the reading frame by one or more steps, and every amino acid coded for after this mutation is affected. Any deletion or insertion of base pairs in multiples of three does not cause frameshifts because the reading frame is unaltered. Tay-Sachs disease is a result of the insertion of four base pairs.	

Figure 2 Types of mutations in a DNA sequence and how they affect the mRNA and protein sequences

Large-Scale Mutations

Large-scale mutations can involve multiple nucleotides, entire genes, or whole regions of chromosomes. Like point mutations, large-scale mutations can have various effects on the organization of a genome and the functioning of the organism. Amplification, also known as gene duplication, occurs when a gene or group of genes is copied to multiple regions of chromosomes. This duplication leads to a larger number of copies of the gene or group of genes, which compounds its effects. An important biological implication of amplification is the creation of opportunities for new genes with new functions to evolve. The original gene function is retained by one gene, but the copies are subjected to further mutations, which may be selected for by nature.

In large-scale deletions, entire coding regions of DNA are removed. Unless multiple copies of a gene are available, this large loss of genetic material may negatively affect the functioning of a cell. Dystrophin is a protein that is an important component of skeletal muscle. Deletion of all or part of the dystrophin gene results in Duchenne muscular dystrophy. Individuals with this mutation usually die in their early 20s due to weak respiratory muscle. If a small part of this gene is deleted, Becker muscular dystrophy results. Individuals with Becker muscular dystrophy have weak muscles but live an almost normal life.

translocation the movement of entire genes or sequences of DNA from one chromosome to another

Chromosomal **translocation** occurs when entire genes or groups of genes are moved from one chromosome to another. Translocation between two non-homologous chromosomes usually occurs when portions of each chromosome break off and exchange places. If a DNA coding sequence is translocated adjacent to another coding sequence, this can result in an entirely new gene and a completely novel polypeptide chain. Certain sequences of DNA, called transposable elements, move freely about the genome. If transposable elements are inserted near an existing gene sequence, they can enhance, disrupt, or otherwise modify the expression of the gene.

Inversion occurs when a portion of a DNA molecule, often containing one or many genes, reverses its direction in the genome. This does not directly result in the loss of genetic material. However, if the break occurs in the middle of a coding sequence, the gene may be compromised.

A trinucleotide is a triplet of nucleotides. An example of a trinucleotide repeat is CAG CAG CAG CAG. Trinucleotide repeats are normal in the genome. Sometimes a mutation occurs, and these repeats become unstable and expand uncontrollably. This mutation, known as trinucleotide repeat expansion, increases in the number of repeats from one generation to the next. Huntington's disease arises from a trinucleotide repeat.

Causes of Genetic Mutations

spontaneous mutation a mutation that is caused by an error in DNA replication

induced mutation a mutation that is caused by an environmental agent

mutagen an environmental agent that directly alters the DNA within a cell

Mutations can be grouped into two categories: spontaneous mutations and induced mutations. **Spontaneous mutations** arise from inaccurate DNA replication. Recall that genomes use a comprehensive quality control system to ensure that DNA is replicated as accurately as possible. However, there is still the possibility of errors during replication. **Induced mutations** are caused by an environmental agent, known as a **mutagen**, that directly alters the DNA within a cell. A mutagen can enter the cell nucleus and directly access the genome. Two of the most common forms of mutagens are chemicals and radiation (**Figure 3**, next page). Both spontaneous and induced mutations can take the form of either small-scale or large-scale mutations. Every subsequent round of cell division can compound the effects of a mutation. WEB LINK

Chemical Mutagens

A chemical mutagen is any chemical agent that can enter the cell nucleus and chemically alter the structure of the DNA. Carbon monoxide, found in exhaust fumes and tobacco smoke, acts as a mutagen and is linked to various forms of cancer. Some chemical mutagens, such as nitrous acid, can modify individual nucleotides so that the nucleotides resemble other base pairs. This type of mutation confuses the replication machinery and results in inaccurate copying.

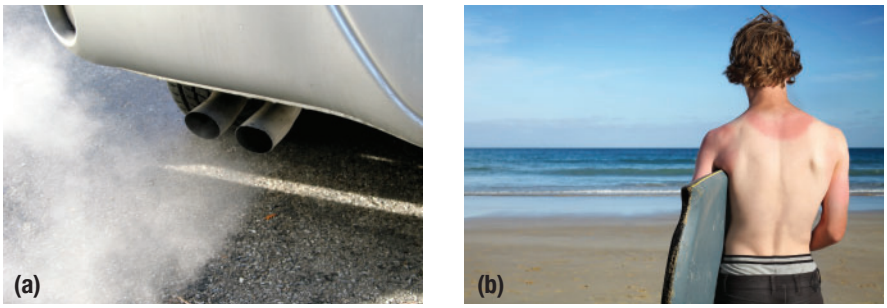


Figure 3 (a) Chemical (exhaust fumes) and (b) radiation (UV rays) mutagens can damage a cell's DNA.

Other chemical mutagens cause mutations by mimicking a DNA nucleotide. For example, individual nucleotides that have bonded with benzene molecules can be added to a replicating DNA strand. This chemical change can alter the shape of the DNA and negatively affect replication. Another example is ethidium bromide, which is used widely in biotechnology research and is similar in structure to a nitrogenous base. It can insert itself between the strands of the double helix and alter the structure of the molecule (**Figure 4**). This may lead to inaccuracies in replication and damage future generations of cells.

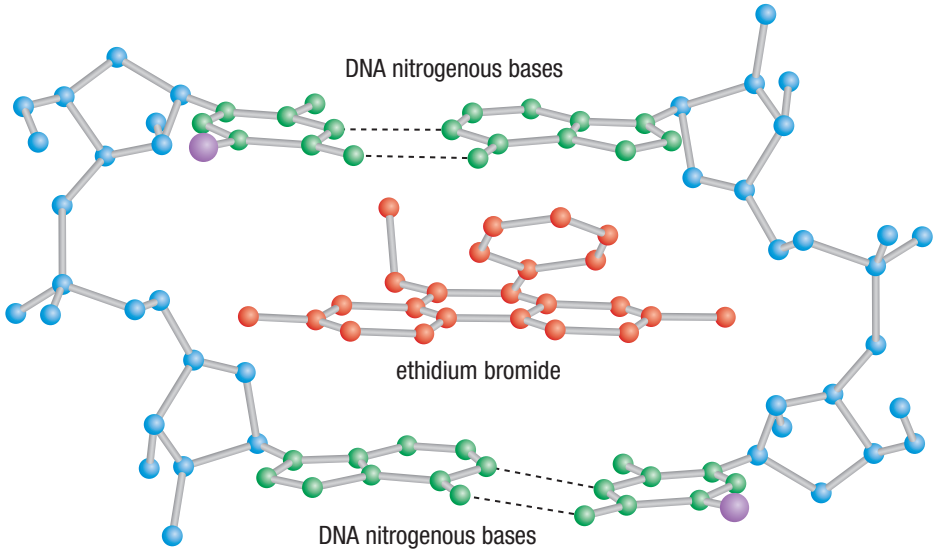


Figure 4 The structure of ethidium bromide is similar to the structure of a nitrogenous base. As a result, it has the ability to insert itself into a DNA molecule.

Radiation

Electromagnetic radiation can also cause mutations. Lower energy radiation, such as ultraviolet B radiation, can cause bonds to form between adjacent nucelotides along a DNA strand (a phenomenon known as non-homologous end joining). The bonds form a kink in the backbone of the DNA strand and complicate replication and transcription. This form of radiation-induced mutation can lead to certain types of skin cancer.

Higher-energy radiation, known as ionizing radiation, can strip molecules of electrons and break bonds within the DNA molecule, causing the rearrangement or deletion of large portions of chromosomes. Prolonged exposure to X-rays has been linked to the development of certain types of tumours. (This is why you wear a lead vest when getting dental X-rays.) Some of the highest-energy radiation comes from gamma rays and radioactive decay products of nuclear material. Children of residents near the former nuclear reactor at Chernobyl have suffered from various birth defects, and the 2011 tsunami-induced nuclear meltdowns in Japan have raised ongoing public health concerns. WEB LINK

Research This

Can Mutations Lead to a Longer Life?

Skills: Researching, Analyzing, Communicating

SKILLS HANDBOOK A4.1

An organism that researchers frequently use to study lifespan is *Caenorhabditis elegans*, a microscopic roundworm that usually lives for two to three weeks. Researchers have discovered that *C. elegans* with a specific single-gene mutation called *daf-2* live twice as long as those that lack the mutation. This suggests that a single gene could dramatically regulate an organism's lifespan.

1. Using reputable sources, research *Caenorhabditis elegans*. Use your findings to answer the following questions.

A. Why is *C. elegans* an ideal organism to use for studying aging? T/I

B. How does the *daf-2* gene work, and how does this lead to life extension? T/I

C. What types of genes does the *daf-2* gene control when it is turned on? What types of genes does it control when it is turned off? K/U T/I

D. Describe an example of a different advantageous mutation in an organism. T/I A

E. Other examples of positive mutations are nylonase in bacteria and HIV immunity in people of European descent. Research how nylonase can be used to treat wastewater or how a mutation in the CCR5-delta 32 gene blocks the entry of the HIV virus. Present your findings in a written or electronic format of your choice. C A

WEB LINK

Mutations: Positive or Negative?

Despite the damaging effects of mutations, it is important to remember that mutations are ultimately responsible for the variety of individuals and species of organisms. A mutation that is truly harmful is only harmful to the individual. It does not cause immediate harm to the group or the species. A negative mutation renders the individual less fit than other members of its group and will be selected against by nature.

A beneficial mutation, however, is advantageous to the individual. The individual experiences greater survival and reproductive success, and passes the beneficial mutation on to future generations. The majority of mutations, however, are neutral. For example, silent mutations have no effect on an organism. Also, because most of our DNA (90 %) is non-coding, changes in the non-coding regions are almost always neutral and unnoticed. This is more likely to be true in eukaryotes, which usually have a lot of non-coding DNA, and less likely to be true in prokaryotes. Prokaryote DNA is mostly coding sequences, so a mutation is much more likely to be harmful than neutral or positive.

A mutation is only beneficial or negative in a given time and situation. What may seem like a negative trait may become useful under different circumstances. For example, the mutation that causes lactose tolerance in humans had no useful benefit until we began to domesticate large mammals and drink their milk. The mutation that causes sickle-cell anemia—a potentially lethal blood disease—also gives a heightened resistance to malaria.

Recently, researchers have discovered that a mutation in the gene filaggrin increases the risk of having a peanut allergy. In fact, one in five peanut allergy sufferers possesses the mutation. In our current environment, we view the peanut allergy as a disadvantage. However, the key point is not to consider mutations as inherently good or bad, but simply as a change that can lead to the evolution of life.

Investigation 7.5.1

Mutations: Cause for Concern? (p. 355)

Point mutations can have numerous effects on the sequences of amino acids that are produced. In this investigation, you will examine how single point mutations change the resulting amino acid sequence coded for by a given gene.

7.5 Review

Summary

- A mutation is a change in the sequence of DNA. A point mutation is specific to one base pair. Substitution involves the replacement of one base pair with another base pair. Other mutations involve the insertion or deletion of a nucleotide or the inversion of two adjoining base pairs.
- A small-scale mutation can be a silent mutation (which has no effect on the resulting amino acid sequence), a missense mutation (which changes a single amino acid in the sequence), a nonsense mutation (which results in a misplaced stop codon and prematurely ends translation), or a frameshift mutation (which causes the reading frame to shift in one direction or the other).
- Large-scale mutations include translocations (the movement of entire sequences of genes between chromosomes) and inversions (the reversal in the orientation of a gene in a chromosome.)
- Mutations can either arise spontaneously or be induced by mutagens. Mutagens include radiation and certain chemicals.
- Mutations have given rise to the diversity of life and are determined to be beneficial or harmful by natural selection.

Questions

1. Define the following terms:
   (a) mutation
   (b) frameshift mutation
   (c) point mutation
   (d) nonsense mutation
   (e) missense mutation K/U
2. The normal form of a gene contains the nucleotide sequence 3′-ATACCCGCCTTTTCGTACTTCCTAG-5′. What type of mutation is each of the following, and what effect will this mutation have on the structure of the protein encoded in the gene? K/U
   (a) Three extra adenine nitrogenous base pairs are inserted in positions 10, 11, and 12.
   (b) The third nucleotide is changed from an adenine to a thymine nucleotide.
   (c) The thymine nucleotide in position 10 is removed.
3. What is a duplication, and what evolutionary significance might it have? K/U A
4. Which of the following amino acid changes can result from a single base-pair substitution? Explain your reasoning. K/U
   (a) Phe→Leu (c) Ser→Arg
   (b) Ile→Thr (d) Asp→Gly
5. During the translation of a molecule of mRNA, the process is stopped prematurely. What type of mutation has occurred? What type of codon has been read by the ribosome? K/U
6. How can a mutation that is deemed negative to an individual when it first arises later become beneficial to individuals and the species as a whole? T/I
7. How does the information in this section relate to what you learned about cancer in Section 7.4? A
8. Which types of mutations might be neutral in their effect on an organism? A
9. Huntington's disease is a result of a trinucleotide repeat expansion. Using the Internet or other sources, research answers to the following questions. T/I
   (a) What is the trinucleotide repeat sequence in Huntington's?
   (b) How many repeats are required for the probable onset of Huntington's?
   (c) Why do the repeats cause Huntington's?
10. Smokers with the susceptibility locus on chromosome 15 increase their chance of developing lung cancer by 30 to 80 %. Using the Internet or other sources, research answers to the following questions. T/I
    (a) What is a susceptibility locus?
    (b) Should we be given the option of being tested for the presence of known susceptibility loci? Why or why not?
    (c) Does the lack of a susceptibility locus justify a person's decision to engage in health-damaging behaviour such as smoking? Why or why not?

WEB LINK