8.6: Mutations and Genetic Diseases

Learning Objectives

- Understand mutation, its causes, types, and effects, including genetic diseases and cancer.

What is mutation?

A **mutation** is any change in an organism's DNA nucleotide sequence. It may occur due to an error during DNA replication, exposure to mutagens, or a viral infection. A **mutagen** is a physical or chemical agent that can cause a permanent change in an organism's DNA. Physical mutagens include exposure to radioactivity, X-rays, UV light, etc. Chemical mutagens are chemical agents that react with and change the DNA, e.g., polycyclic aromatic hydrocarbons (PAH) found in smoke and barbecued foods. Some mutagens that may lead to cancer are called **carcinogens**. Mutations may be harmful, beneficial, or may have no effect. **Somatic mutations** in body cells affect daughter cells but are not passed on to the offspring. **Germline mutations** occur in eggs or sperm and are passed to the offspring. When a mutation alters proteins or enzymes severely, the cells may not survive, and the person may have a genetic disease.

Types of mutation

A mutation may be due to i) replacement, ii) deletion, or iii) insertion of one or more nucleotides, as illustrated in Figure 8.6.1. There are many types of mutations. One subclass of mutation, i.e., related with change in one nucleotide is described here to introduce the basic terminologies related with mutaions.

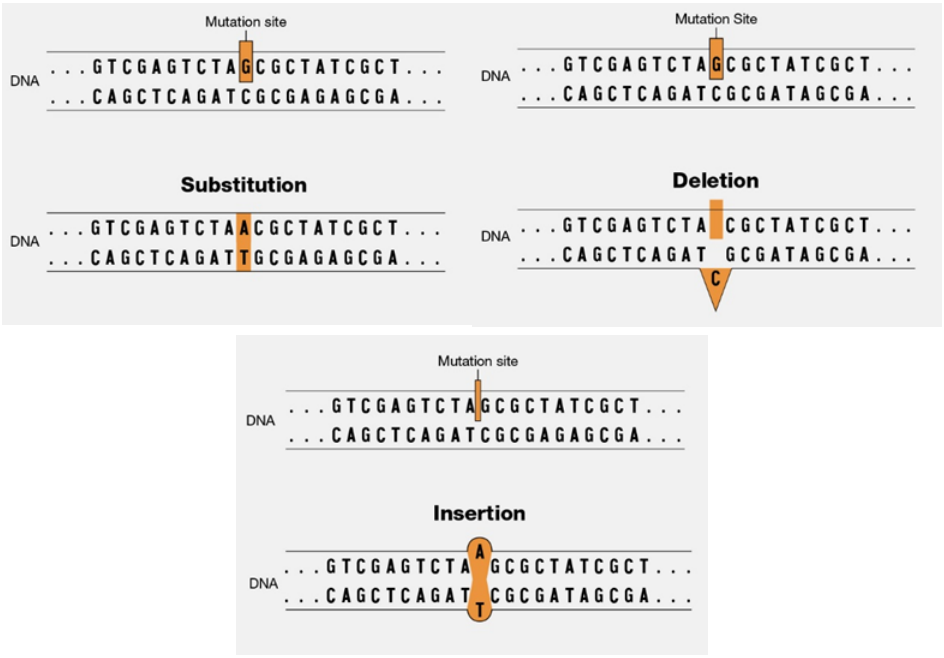

Figure 8.6.1: Illustration of three types of mutations, replacement or point mutation (left), deletion (middle), and insertion (right). (Copyright; National Human Genome Research Institute, Public domain)

Point mutation

Point mutation is the addition, deletion, or change (substitution) of one nucleotide with another. It changes the codon in which the nucleotide is located.

Substitution mutation

A replacement of one nucleotide with another in the DNA is substitution mutation. There are three sub-type of substitution mutations.

1. If the initial codon and the new codon represent the same amino acid, the mutation is called a **silent mutation**.
2. If a point mutation changes the codon to a different amino acid, it is called a **missense mutation**. If missense mutation replaces an amino acid with significantly different properties, it may cause disease. For example, sickle cell disease is caused by a point mutation of codon GAG for glutamic acid (acidic) to GTG for valine (nonpolar) in the hemoglobin gene. On the other hand, if the new amino acid is similar to the previous one, there may be little or no change rendered in the proteins. For example, a change from AAA for lysine to AGA for arginine may not affect the protein as both amino acids are basic amino acids.
3. If a point mutation changes the codon for an amino acid to a stop codon, it is called a **nonsense mutation**. It results in premature termination of protein synthesis rendering nonfunctional protein. For example, β-thalassemia is caused by a change from CAG for glutamine to UAG, i.e., stop signal. The missense and nonsense mutations are illustrated in Figure 8.6.2

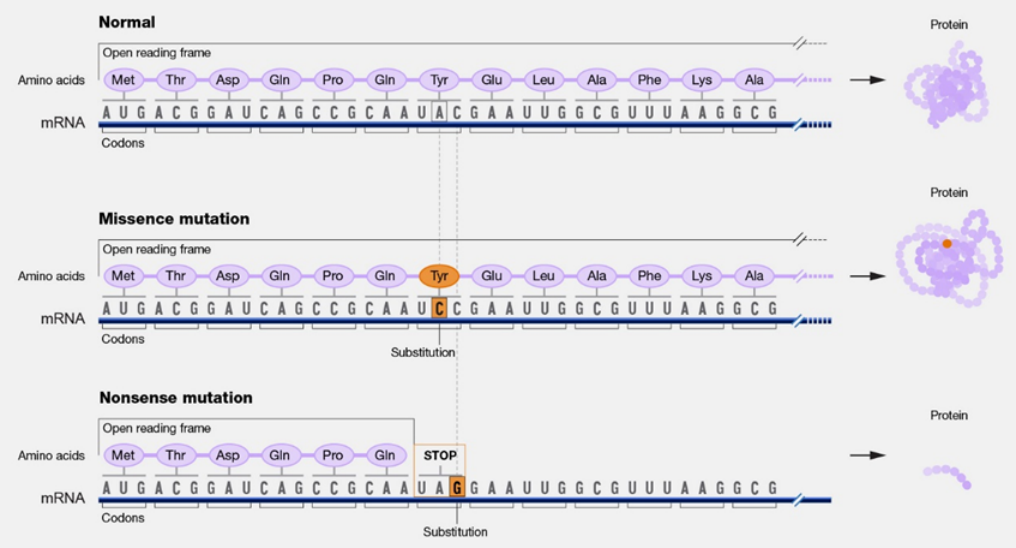

Figure 8.6.2: Misence and nonsense mutation illustrated. (Copyright; National Human Genome Research Institute, Public domain)

Deletion mutation

Deletion mutation is the loss of one or more nucleotides from a segment of DNA. Since the codon is three consecutive nucleotides, the loss of one nucleotide will not only change the codon from which the nucleotide is lost, but all the codons following it will be changed. Deletion mutation is related to a significant number of genetic diseases, e.g., two-thirds of cystic fibrosis cases are due to the loss of three nucleotides that results in the loss of amino acid phenylalanine in the protein involved, and cat cry syndrome is due to a partial chromosome deletion.

Insertion mutation

In insertion mutation, one or more nucleotides are inserted into the typical sequence of nucleotides in the DNA. So, the codon where insertion happens and all the codons following it are changed.

Effects of mutations

Some mutations do not cause a significant change in protein structures, allowing the protein to perform its function. Others may change an amino acid vital to the structure of the proteins with an amino acid of significantly different properties. It results in the proteins not being able to function correctly. For example, sickle cell disease is caused by replacing glutamic acid with a nonpolar valine that prevents the hemoglobin protein from working correctly. If the protein is an enzyme, it may no longer catalyze the reaction. In this situation, the reactants may accumulate and become poisonous, or the product may be vital for survival and not synthesized. For example, an enzyme required to metabolize galactose-1-phosphate is absent in galactosemia. It results in the accumulation of galactose-1-phosphate, which may cause cataracts and mental retardation.

Genetic disorder

Genetic disorders are health conditions caused by mutations in the genetic material. For example, phenylketonuria (PKU) results when DNA can not carry the correct codes for the synthesis of the enzyme phenylalanine hydroxylase that hydroxylates the phenyl ring of phenylalanine to convert it to tyrosine. When phenylalanine cumulates, other enzymes convert it to phenylpyruvate—

cumulation of phenylalanine and phenylpyruvate cause mental retardation. If diagnosed early on, a diet can be prescribed to the child that avoids foods containing phenylalanine. It can prevent the buildup of phenylpyruvate.

Similarly, if the enzyme that converts tyrosine to melanin is not functioning, melanin is not produced, causing albinism. Melanin is a pigment that gives color to skin and hair. People with albinism do not have skin, eye, or hair pigments. This disease also happens in animals. When a genetic disorder is inherited from one or both parents, it is called a **hereditary disease**. A few more genetic diseases are listed below.

- **Cystic fibrosis** results from a defective gene. It affects the lungs and digestive system. People with this disease can not digest food properly and have repeated lung infections.
- **Down syndrome** is a genetic disease in which peoples have cognitive impairment that may be mild or severe.
- **Hemochromatosis** is an inherited condition where the body absorbs and stores so much iron that it can lead to organ damage.
- **Haemophilia** is a genetic disorder in which blood does not clot properly. It makes bleeding challenging to control.
- **Huntington's disease** is a genetic disorder that affects the nervous system, and the effect worsens over time.
- **Tay-Sachs disease** is a genetic disorder that causes brain damage.
- **Duchenne muscular dystrophy** is a condition that causes gradual loss of muscle function.
- **Thalassemia** is a genetic disorder that causes less hemoglobin to be produced, making the blood cells small and pale.
- **Tourette syndrome** is a genetic disorder related to neurological problems. Peoples with this disorder make involuntary vocal sounds and movements. Relaxation and exercise may reduce the symptoms.

Cancer

Cancer is a disease in which some of the body's cells grow and multiply uncontrolled. Mutation in a cell may cause this uncontrolled division of cells. The uncontrolled division and growth of cells appear as a tumor, as illustrated in Figure 8.6.3. It is benign if the tumor remains limited in growth without harming the neighboring tissue. However, the tumor is cancer if it invades other issues and interferes with their normal functions.

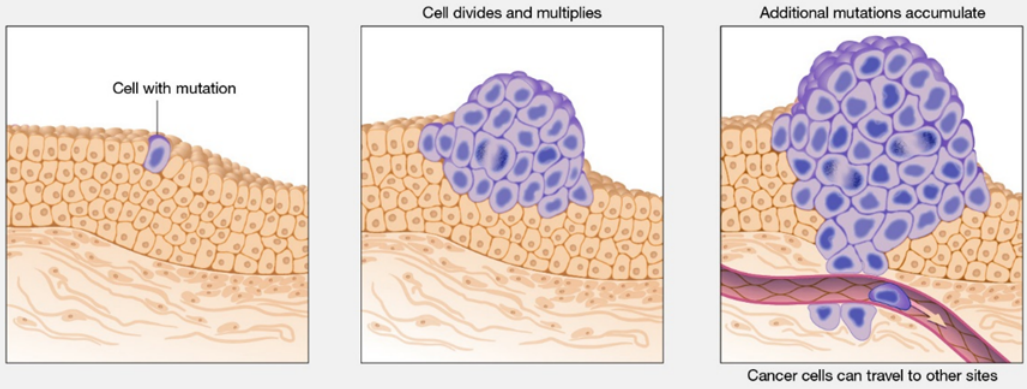

Figure 8.6.3: Illustration of tumor and cancer. (Copyright; National Human Genome Research Institute, Public domain)

The most common types of cancer are lung cancer, prostate cancer, breast cancer, colorectal cancer, stomach cancer, cervical cancer, and skin cancer. Melanoma and skin cancers account for about 40% of cancer cases. Cancer types common in children include acute lymphoblastic leukemia, brain tumors, and non-Hodgkin lymphoma.

The mutations causing cancers can result from errors during DNA replication or exposure to **carcinogens**, i.e., the substances or radiations that cause cancer. The **carcinogenic substances** include some compounds in tobacco smoke, automobile exhaust fumes, processed meat; asbestos; benzene; toxic metals like nickel, arsenic, beryllium, chromium, and cadmium and their compounds; nitrosamine; ethylene oxide, etc. About 22% of cancer-related deaths occur due to smoking. **Cancer-causing radiations** include radioactivity resulting in ionizing radiations, X-rays, and UV-radiations. About 15% of cancers are due to **cancer-causing viral infections** like HIV, hepatitis B, hepatitis C, Helicobacter pylori, Epstein-Bari virus, papillomavirus, etc. Sometimes inherited defects in genes are the cause of cancer. These factors cause or are at least partially involved in gene mutations that result in cancer.