I SEMESTER

PAPER – Cell Biology and Genetics

UNIT - IV

TOPIC – Types of Mutations and Factors affecting DNA Damage

SOURCE – INTERNET

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4.2 Types of Mutations

Mutations are changes in the DNA sequence that can affect the structure and function of proteins, sometimes leading to diseases or altered cellular functions.

Types of Mutation :

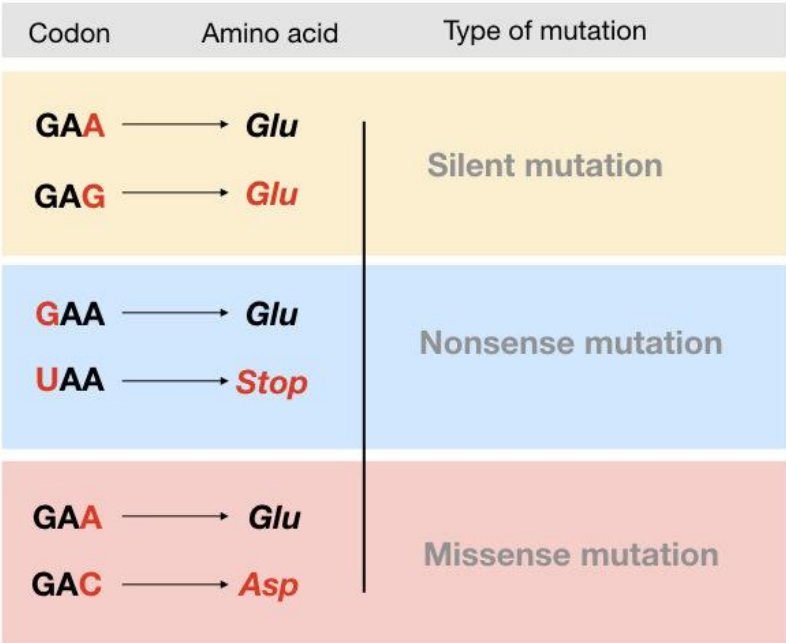
Point mutation changes a single nucleotide in a gene, whereas frameshift mutation involves insertion or deletion of nucleotides that shifts the reading frame of codons and usually alters all downstream amino acids. Both are gene (point) mutations but differ greatly in their effect on the protein produced.

Point mutation:

- A point mutation is a change in DNA or RNA in which one nucleotide base is added, deleted, or substituted at a single position in the sequence.
- The reading frame usually remains the same; only one codon (or at most a few) is directly affected.
- Point mutations can arise spontaneously during DNA replication or due to mutagens such as radiation or chemicals.

Types of point mutation

- Substitution: One base is replaced by another (e.g., A→T or G→C), which may be:
- **Silent Mutation:** A change in the nucleotide that does not alter the amino acid sequence of the protein. For example, changing a codon from GTA to GTT still codes for the same amino acid, valine, as shown below.
- **Missense Mutation:** A change in the nucleotide that results in a different amino acid being incorporated into the protein. This can affect protein function. For example, the mutation CCC (proline) to ACC (threonine) is a missense mutation.
- **Nonsense Mutation:** A change in the nucleotide that converts a codon into a stop codon, leading to premature termination of protein synthesis. This often produces a nonfunctional protein, particularly if it results in termination far upstream of the regular stop codon.
- Single-base insertion or deletion can also be described as point mutations, although when they change the reading frame they are called frameshift mutations.



Point mutation examples

- Sickle-cell anaemia: A single base substitution in the β-globin gene changes the codon GAG (glutamic acid) to GTG (valine) at the sixth position of the β-chain, producing abnormal haemoglobin (HbS).
- Example at codon level:
  - Normal DNA: GAA→GAA→ mRNA GAA → glutamic acid.
  - Mutated DNA: GTA→GTA→ mRNA GUA → valine (missense point mutation).

Frameshift mutation:

- A frameshift mutation is caused by insertion or deletion of one or more nucleotides in a coding region such that the total number of nucleotides added/removed is not a multiple of three.

- This shifts the reading frame so all codons downstream are regrouped into different triplets, usually changing every amino acid after the mutation and often introducing premature stop codons.

Frameshift mutation examples

- Generic codon example:
  - Normal mRNA: AUG-AAU-AAC-GCU → start–asparagine–asparagine–alanine.
  - Insertion of A after AUG: AUG-AAA-UAA-CGC-U… → start–lysine–stop–…; the frame shifts and an early stop codon appears, producing a very short, nonfunctional protein.

4.2 Factors affecting DNA Damage

DNA damage is a continuous process caused by a variety of internal biological events and external environmental exposures. It is estimated that a single human cell can experience between **1,000 and 1,000,000 lesions per day**.

These factors are generally categorized into two main groups: **endogenous** (internal) and **exogenous** (external).

1. Endogenous Factors (Internal)

These occur naturally within the cell as a byproduct of normal metabolic processes.

- **Oxidative Stress:** The most common source of damage. Reactive Oxygen Species (ROS), produced during mitochondrial respiration (energy production), attack DNA, causing base modifications like **8-oxo-guanine** and strand breaks.
- **Replication Errors:** Despite high fidelity, DNA polymerases can insert incorrect bases or skip sections during replication. If these mismatches aren't caught by proofreading, they become mutations.
- **Spontaneous Hydrolysis:** DNA is chemically unstable in an aqueous environment. This leads to the loss of bases (depurination/depyrimidination) or the conversion of one base to another (deamination, such as cytosine turning into uracil).
- **Metabolic Byproducts:** Compounds like formaldehyde or aldehydes from lipid peroxidation can form toxic DNA adducts or crosslinks.

2. Exogenous Factors (External)

These are environmental agents that directly or indirectly damage DNA structure.

- **Radiation:**
  - **Ultraviolet (UV) Light:** Causes pyrimidine dimers (covalent bonds between adjacent bases), which distort the DNA helix.
  - **Ionizing Radiation (X-rays, Gamma rays):** High-energy waves that cause the most lethal type of damage—**double-strand breaks (DSBs)**—and generate free radicals that further attack DNA.
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- **Chemical Agents:**
    - **Carcinogens:** Found in cigarette smoke (e.g., benzo[a]pyrene), automobile exhaust, and charred foods.
    - **Chemotherapy:** Certain drugs (e.g., cisplatin) work by intentionally damaging the DNA of rapidly dividing cancer cells.
    - **Toxins:** Natural fungal toxins like **Aflatoxins** (found in contaminated crops) form harmful DNA adducts.
- **Biological Agents:** Certain viruses (e.g., HPV, Herpesviridae) can cause strand breaks or inhibit the cell's natural repair proteins.