

v. Types of gene mutations

v. Types of gene mutations - base substitution, frameshift mutation, insertion, deletion, missense, nonsense, reverse, suppressor and lethal mutations; DNA damage and repair mechanisms

Types of Gene Mutations

General Concepts and Terminology

- A gene mutation is any heritable change in the nucleotide sequence of DNA.
- Mutations can occur spontaneously (e.g., due to DNA replication errors) or be induced by external factors (e.g., chemical mutagens, radiation).
- Mutations may affect a single base pair or large chromosomal segments and can have a wide range of phenotypic consequences—from no observable effect to lethality.

Base Substitution Mutations

Definition: A point mutation in which one nucleotide and its complementary partner on the opposite DNA strand are replaced by another pair of nucleotides.

1. Transition

- Purine \rightarrow Purine (A \leftrightarrow G) or Pyrimidine \rightarrow Pyrimidine (C \leftrightarrow T) substitution.
- Transitions are more common than transversions because of the structural similarity between purines or between pyrimidines.

2. Transversion

- \circ **Purine** → **Pyrimidine** (A or G \leftrightarrow C or T) or vice versa.
- o Transversions can cause more dramatic changes in DNA helix geometry and are generally less frequent.

Frameshift Mutations

Definition: Insertions or deletions (indels) of nucleotides not in multiples of three that shift the reading frame of the gene during translation.

• **Consequence**: All codons downstream of the mutation site are misread, typically resulting in a truncated or nonfunctional protein due to premature stop codons.

Insertions and Deletions

1. Insertion

- Addition of one or more nucleotides into the DNA sequence.
- If the number of nucleotides added is a multiple of three, the reading frame is preserved; otherwise, it is a frameshift.

2. Deletion

- $\circ\;$ Removal of one or more nucleotides from the DNA sequence.
- \circ Like insertions, if the number of deleted nucleotides is not a multiple of three, a frameshift mutation ensues.

Missense Mutations

Definition: A base substitution that alters a codon so that it encodes a different amino acid (e.g., GAG \rightarrow GTG, which changes Glu to Val).

• **Phenotypic Impact**: The effect on protein function depends on the biochemical properties of the original and substituted amino acids, as well as the location of the substitution within the protein.

Nonsense Mutations

Definition: A base substitution that converts a codon encoding an amino acid into a **stop codon** (UAA, UAG, UGA).

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• **Effect**: Truncated polypeptide that is often nonfunctional or rapidly degraded (nonsense-mediated decay in eukaryotes).

Reverse (Reversion) Mutations

Definition: Mutations that **revert** a mutated sequence back toward the wild-type sequence or phenotype.

1. True Reversion

• Restores the original codon to its exact wild-type sequence.

2. Equivalent Reversion (Second-site Reversion)

• Restores function or phenotype but not necessarily the original codon sequence (e.g., a different codon that codes for the same amino acid).

Suppressor Mutations

Definition: A mutation at a **second site** in the genome that **alleviates or compensates** for the effect of a primary mutation.

1. Intragenic Suppressor

• Occurs within the same gene but at a different codon (e.g., a frameshift insertion compensates for a frameshift deletion in an earlier codon).

2. Extragenic Suppressor

• Occurs in a different gene, often in tRNA genes where an altered anticodon can recognize a stop codon or a different codon, thus "suppressing" a nonsense or missense mutation in a separate gene.

Lethal Mutations

Definition: Mutations that cause death at some stage of an organism's development.

- **Mechanism**: Often disrupts essential genes (e.g., those required for DNA replication, chromosome segregation, metabolic pathways).
- Conditional Lethal: Some mutations are lethal under certain environmental conditions (e.g., temperaturesensitive mutations).

DNA Damage and Repair Mechanisms

Sources and Types of DNA Damage

DNA is constantly exposed to damaging agents:

- Spontaneous Errors: Replication misincorporation, deamination (e.g., C → U), depurination.
- Reactive Oxygen Species (ROS): Oxidative damage (e.g., 8-oxoguanine).
- Chemical Mutagens: Alkylating agents, base analogs, intercalating agents.
- Radiation: Ultraviolet (UV) light causing pyrimidine dimers; ionizing radiation causing double-strand breaks.

Key DNA Repair Pathways

1. Direct Reversal of Damage

- Photoreactivation: In bacteria and some eukaryotes, photolyase enzymes use visible light to break cyclobutane pyrimidine dimers (UV lesions).
- **Methyltransferase**: O^6-methylguanine DNA methyltransferase removes alkyl groups from guanine, restoring the base.

2. Base Excision Repair (BER)

- Function: Corrects single damaged bases (e.g., uracil in DNA, oxidized bases).
- Key Steps:
 - DNA Glycosylase recognizes and excises the damaged base, creating an AP (apurinic/apyrimidinic) site.

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- AP Endonuclease cleaves the backbone.
- **DNA Polymerase** (often Pol β in eukaryotes) inserts the correct nucleotide.
- **DNA Ligase** seals the nick.

3. Nucleotide Excision Repair (NER)

- Function: Removes bulky lesions like pyrimidine dimers and large chemical adducts.
- Key Steps:
 - **Damage Recognition**: Distorted helix recognized by specific protein complexes (e.g., UvrABC system in *E. coli*; XPC-HR23B in eukaryotes).
 - **Incision**: Endonucleases cut on both sides of the lesion (~12-30 nt region).
 - **Excision**: Damaged oligonucleotide is removed.
 - Repair Synthesis & Ligation: DNA polymerase fills in the gap; DNA ligase seals.

4. Mismatch Repair (MMR)

- Function: Fixes replication errors such as mispaired bases and small insertion-deletion loops that escape DNA polymerase proofreading.
- **Prokaryotes**: MutS-MutL-MutH system recognizes the mismatch, identifies the newly synthesized strand (often by its lack of methylation), excises, and resynthesizes.
- **Eukaryotes**: Analogous system (MSH and MLH protein families) without the methylation cue but using other strand-discrimination mechanisms (nicks in Okazaki fragments, replication factors).

5. Double-Strand Break (DSB) Repair

- Non-Homologous End Joining (NHEJ)
 - Process: Directly ligates the broken ends with minimal or no homology.
 - Advantage: Rapid repair mechanism when no sister chromatid is available.
 - Disadvantage: Error-prone; can lead to small insertions/deletions and is a major source of chromosomal translocations.
- Homologous Recombination (HR)
 - **Process**: Uses a sister chromatid or homologous chromosome as a template for error-free repair.
 - Advantage: High-fidelity mechanism (ideal during S/G2 phase of the cell cycle in eukaryotes).
 - **Key Players**: RAD51 in eukaryotes, RecA in prokaryotes.

6. Translesion DNA Synthesis (TLS)

- Function: Specialized, low-fidelity DNA polymerases bypass bulky or unrepaired lesions at the replication fork
- Trade-off: TLS prevents replication collapse but increases the risk of introducing mutations.

Regulation of DNA Repair and Cell Cycle

- **Checkpoint Control**: Damaged DNA can activate checkpoint kinases (e.g., ATM, ATR in eukaryotes) that halt the cell cycle, allowing time for repair.
- **p53 Pathway**: In eukaryotic cells, severe DNA damage can trigger apoptosis via p53-dependent or -independent mechanisms to prevent propagation of damaged genomes.

Clinical Implications

- Cancer Susceptibility: Defects in DNA repair genes (e.g., BRCA1/BRCA2 in homologous recombination; mismatch repair genes in Lynch syndrome) lead to higher mutation rates and tumorigenesis.
- **Therapeutic Targeting**: Some cancer treatments exploit defective repair pathways (e.g., PARP inhibitors in tumors with BRCA1/2 mutations) to selectively kill cancer cells.

Concluding Remarks

Gene mutations—ranging from single base substitutions to large insertions/deletions—are the raw material of evolution but can also underlie a vast array of genetic disorders. The fate of these mutations depends on the interplay between **DNA damage** (spontaneous or induced) and **DNA repair mechanisms** (e.g., BER, NER, MMR, DSB repair). Organisms have evolved a remarkable arsenal of repair pathways to safeguard genomic stability. Nonetheless, errors in replication and repair can produce pathogenic mutations or drive cancer development.

Understanding these processes at the molecular level not only illuminates fundamental biology but also guides medical

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diagnostics, **gene therapy approaches**, and the design of **targeted cancer treatments**, reflecting the profound translational importance of mutation and DNA repair research.

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