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Paper: III, Group: B

Topic: Gene Mutation

Gene Mutation

A mutation, which may arise during replication and/or recombination, is a permanent change in the nucleotide sequence of DNA. Damaged DNA can be mutated either by substitution, deletion or insertion of base pairs.

Mutations, for the most part, are harmless except when they lead to cell death or tumor formation. Because of the lethal potential of DNA mutations cells have evolved mechanisms for repairing damaged DNA.

Germ line mutation:

A germ line mutation in the reproductive cells of an individual gives rise to a constitutional mutation in the offspring, that is, a mutation that is present in every cell.

A germ line mutation can be passed down through subsequent generations of organisms.

The distinction between germ line and somatic mutations is important in animals that have a dedicated germ line to produce reproductive cells

Somatic mutation:

A change in the genetic structure that is not inherited from a parent, and also not passed to offspring, is called a somatic mutation. Somatic mutations are not inherited by an organism's offspring because they do not affect the germ line.

However, they are passed down to all the progeny of a mutated cell within the same organism during mitosis.

These types of mutations are usually prompted by environmental causes, such as ultraviolet radiation or any exposure to certain harmful chemicals, and can cause diseases including cancer.

Types of Mutation:

1. **Point Mutation**
2. **Frame shift Mutation**

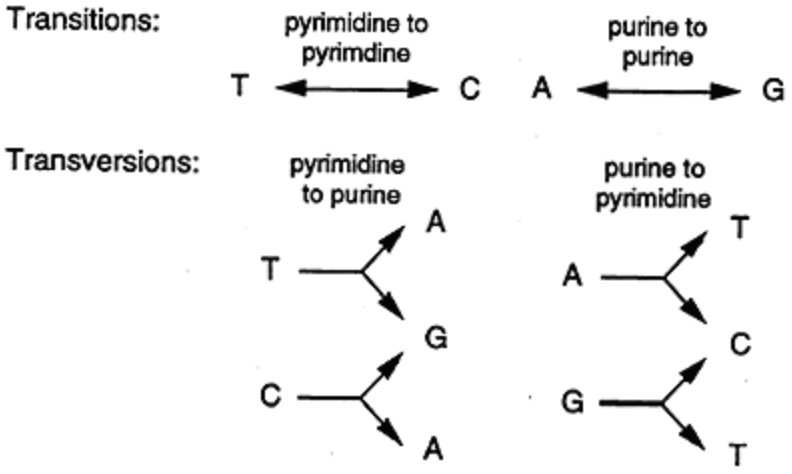
Point Mutation:

Occur due to base Substitution

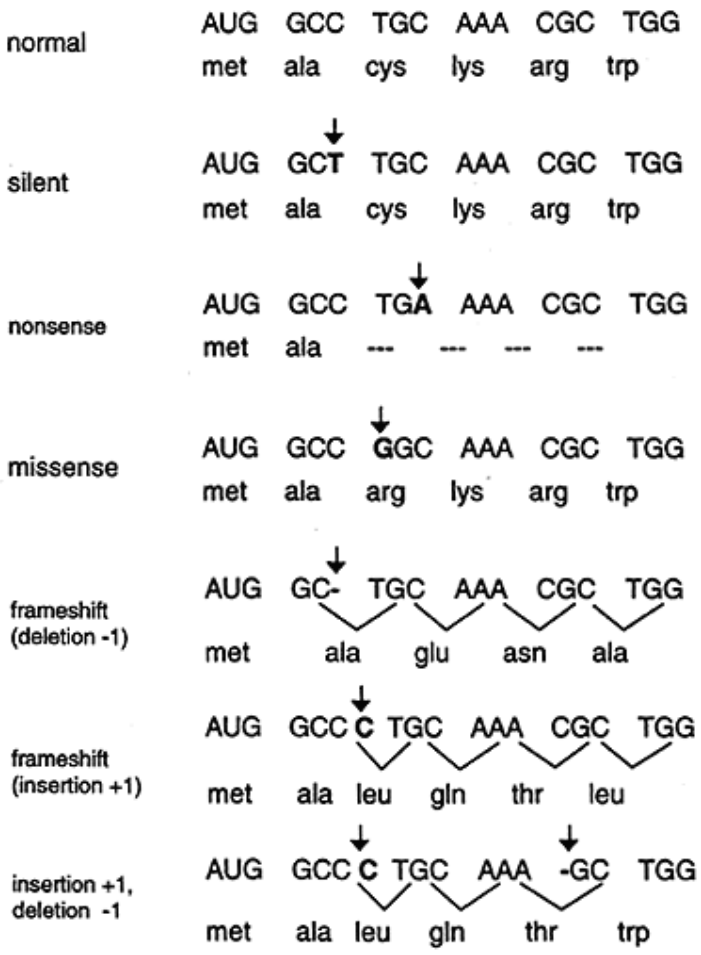
Single base substitutions are called point mutations; recall the point mutation Glu -----> Val which causes sickle-cell disease. Point mutations are the most common type of mutation and there are two types.

Transition: this occurs when a purine is substituted with another purine or when a pyrimidine is substituted with another pyrimidine.

Transversion: when a purine is substituted for a pyrimidine or a pyrimidine replaces a purine.



Point mutations that occur in DNA sequences encoding proteins are silent, missense or nonsense.



Silent:

If a base substitution occurs in the third position of the codon there is a good chance that a synonymous codon will be generated. Thus the amino acid sequence encoded by the gene is not changed and the mutation is said to be silent.

Missense:

When base substitution results in the generation of a codon that specifies a different amino acid and hence leads to a different polypeptide sequence.

Depending on the type of amino acid substitution the missense mutation is either conservative or nonconservative.

For example if the structure and properties of the substituted amino acid are very similar to the original amino acid the mutation is said to be conservative and will most likely have little effect on the resultant proteins structure / function.

If the substitution leads to an amino acid with very different structure and properties the mutation is nonconservative and will probably be deleterious (bad) for the resultant proteins structure / function (i.e**.,** the sickle cell point mutation).

Nonsense:

When a base substitution results in a stop codon ultimately truncating translation and most likely leading to a nonfunctional protein.

Frame shift Mutation:

A frame shift mutation is a mutation caused by insertion or deletion of a number of nucleotides that is not evenly divisible by three from a DNA sequence.

Due to the triplet nature of gene expression by codons, the insertion or deletion can disrupt the reading frame, or the grouping of the codons, resulting in a completely different translation from the original.

Deletions:

A deletion, resulting in a frameshift, results when one or more base pairs are lost from the DNA (see Figure above). If one or two bases are deleted the translational frame is altered resulting in a garbled message and nonfunctional product.

A deletion of three or more bases leaves the reading frame intact. A deletion of one or more codons results in a protein missing one or more amino acids. This may be deleterious or not.

Insertions:

The insertion of additional base pairs may lead to frameshifts depending on whether or not multiples of three base pairs are inserted. Combinations of insertions and deletions leading to a variety of outcomes are possible.

Cause of Mutation:

Errors in DNA Replication:

On very, rare occasions DNA polymerase will incorporate a noncomplementary base into the daughter strand. During the next round of replication the misincorporated base would lead to a mutation.

This, however, is very rare as the exonuclease functions as a proofreading mechanism recognizing mismatched base pairs and excising them.

Errors in DNA Recombination:

DNA often rearranges itself by a process called recombination which proceeds via a variety of mechanisms. Occasionally DNA is lost during replication leading to a mutation.

Chemical Damage to DNA:

Many chemical mutagens, some exogenous, some man-made, some environmental, are capable of damaging DNA. Many chemotherapeutic drugs and intercalating agent drugs function by damaging DNA.

Radiation:

Gamma rays, X-rays, even UV light can interact with compounds in the cell generating free radicals which cause chemical damage to DNA.