Notes

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Molecular Basis of Mutation

Mutations at the molecular level, should mean permanent alterations in sequences of nucleotides (bases) in the nucleic acid, which forms the genetic material. The alterations in the base sequences may be of the following types: 1) deletion of bases 2) insertion of bases 3) inversion of a sequence 4) substitution of a base pair.

Deletions, insertions and inversions include those changes in the base sequences which involve breakage and reunion of DNA segments. However, substitution of a base pair may take place during replication of DNA without any breakage of DNA.

These base pair substitutions can be of two types, transitions and transversions. In Transitions, purine is replaced by another purine base (i.e., A by G or G by A) and a pyrimidine is replaced by another pyrimidine. (i.e., T by C or C by T). Transitions are most common types of mutations.

Base-pair substitutions involving the replacement of a purine with a pyrimidine and vice versa are called transversions. A ------ C ; T ------ G

There are three substitutions—one transition and two transversions—possible for every base pair. A total of four different transitions and eight different transversions are possible.

Tautomerism

Real spontaneous mutations arise from **tautomerism.** Transistions can be produced by tautomeric shift.

Watson and Crick pointed out that the structures of the bases in DNA are not static. Hydrogen atoms can move from one position in a purine or pyrimidine to another position—for example, from an amino group to a ring nitrogen. Such chemical fluctuations are called tautomeric shifts. Although tautomeric shifts are rare, they may be of considerable importance in DNA metabolism because some alter the pairing potential of the bases.

The ability of a molecule to exist in more than one chemical form is called tautomerism. All the DNA bases (adenine, guanine, cytosine and thymine) have unusual tautomeric forms which are however rare in occurrence.

The nucleotide structures that are the common, are more stable forms, in which adenine always pairs with thymine and guanine always pairs with cytosine. The more stable keto forms of thymine and guanine and the amino forms of adenine and cytosine may infrequently undergo tautomeric shifts to less stable enol and imino forms, respectively.

The bases would be expected to exist in their less stable tautomeric forms for only short periods of time. However, if a base existed in the rare form at the moment that it was being replicated or being incorporated into a nascent DNA chain, a mutation would result.

When the bases are present in their rare imino or enol states, they can form adenine-cytosine and guanine-thymine base pairs. The net effect of such an event, and the subsequent replication required to segregate the mismatched base pair, is an A:T to G:C or a G:C to A:T base-pair substitution.

Mutations resulting from tautomeric shifts in the bases of DNA involve the replacement of a purine in one strand of DNA with the other purine and the replacement of a pyrimidine in the complementary strand with the other pyrimidine (transitions).

Watson and Crick (1955) have hypothesized that the occurrence of bases in tautomeric forms possibly provides a mechanism for mutation during DNA replication. If in an old strand of DNA, adenine is in tautomeric condition, it will pair with normal cytosine in the new complementary strand during DNA replication. This may result in a new DNA molecule containing exceptional base pair. The tautomeric shift is not stable and in the next replication tautomeric adenine is supposed to return to its normal state and then it will pair with thymine. The cytosine added to complementary strand would then pair with guanine. Thus 2 kinds of DNA molecules are formed; some with normal base sequence and some with changed base sequence. The 2 kinds

of DNA molecules formed by transition will eventually be separated into different cells which may result in a recognisable mutation.

Frameshift mutations

Frameshift mutation: a type of gene mutation in which the addition or deletion of one or more nucleotides causes a shift in the reading frame of the codons in the mRNA, which may lead to the alteration in the amino acid sequence at protein translation.

In a nucleic acid (e.g. DNA), the nucleotides may be "*read*" in groups of non-overlapping, consecutive triplets referred to altogether as a reading frame. During translation, triplets (or codons) in a reading frame are translated into specific amino acids (or a codon signal). Thus, if a mutation, for example, an insertion or a deletion of the nucleotide, occurs, this could result in the alteration of the reading frame. It completely changes the amino acid sequence. Such mutations are known as frameshift mutation.

The *addition or deletion of the nucleotides in the multiples of* three, however, *will not alter the reading frame*. Thus, the protein in such cases would likely have either an extra or missing amino acid.

Usually, frameshift mutations occur as caused by a mutational error during DNA repair or replication. They can also occur by exposure to acridine dyes, which are capable of inducing frameshift mutations.

The resultant codons after frameshift mutations can be of three types:

1. Sense codons: these are codons that are read in the same manner as before frameshift mutation.
2. Missense codons: these are the codons that result in an incorrect amino acid or a different amino acid formation.
3. Non-sense codons**:** these are the codons for which there is no corresponding tRNA, resulting in the truncation of the translation process.

Hence, frameshift mutations result in an abnormal or defective protein product containing an improper sequence of amino acids. Depending upon the location of the mutation, such proteins may be wholly new or non-usable. Frameshift mutation can also result in the stop codon. This occurrence of the *premature stop codon* on mRNA will terminate the translation process, thereby, resulting in a short-length polypeptide.