

Mutation

MUTATION

Mutation is defined as a change in the nucleotide sequence of DNA

Different types of mutation are

- 1. Point mutation**
- 2. Frame shift mutation**

1.POINT MUTATION

Point mutation are single base alterations

Point mutation may be

a) Transitions

b) Transversions

Transition :- Change of a Purine to the other Purine or change of a Pyrimidine to another Pyrimidine

Eg: $A \rightarrow G$, $G \rightarrow A$, $T \rightarrow C$ or $C \rightarrow T$

Transversion: If a Purine base is replaced by a Pyrimidine or Pyrimidine for a Purine called **Transversion**.

Eg: $A \rightarrow T$, $G \rightarrow C$, $C \rightarrow G$

EFFECT OF *POINT MUTATION*

- 1. Silent mutation
- 2. Missense mutation
- 3. Non sense mutation

1. Silent mutation

- No effect of mutation due to degeneracy of genetic code
- There is more likely if the altered base is the 3rd one in codon.
- Due to wobbling, translation codon is least sensitive to a change in 3rd position
- Eg: UUU ,UUC - Phe

2. Mis-sense Effect

- The alteration in the nucleotide may result in incorporation of a different amino acid.
- The mistaken amino acid is known as a **mis-sense**.

Depending on its location in specific protein **mis-sense** may be :-

- **Acceptable**
- **Partially acceptable**
- **Unacceptable**

Acceptable Mis-sense- Hb Sydney

A transition at 2nd position results in replacement of **Val β_{67} to Ala β_{67} .**

Beta chain	Codon	Amino acid	Protein
Normal	GUU 	67 Val	Hb A
Altered	GCU	67 Ala	Hb Sydney

No clinical symptoms, but an altered electrophoretic mobility.

Partially acceptable Mis-sense- HbS

Partial abnormal function

A transversion at the 2nd position of codon results in replacement of β_6 Glu to β_6 Val.

Beta chain	Codon	Amino acid	Protein
Normal	GAG ↓	6 Glu	Hb Normal
Altered	G <u>U</u> G	6 Val	HbS

A polar amino acid is replaced by a nonpolar amino acid. This produces a **sticky patch** on the surface of the molecule causing **sickling**. No effect on Oxygen carrying capacity of Hb.

Unacceptable Mis-sense- HbM

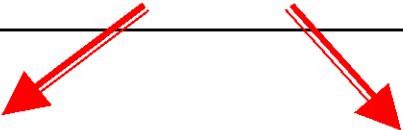
No function due to altered structure

Alpha chain	Amino acid	Protein
Normal	His ₅₈	Hb Normal
Altered	Tyr ₅₈	HbM-Boston

Histidine is replaced by **tyrosine residue** in heme pocket. Fe^{2+} is **oxidized to Fe^{3+}** . Met Hb **cannot carry O_2** . Hence mutation is **unacceptable**

3.Nonsense Mutation

A Tyrosine codon is mutated to a stop codon causing premature termination of polypeptide chain.

Codon	Amino acid	Protein
UAC	Tyrosine	Normal
 UAA or UAG Stop codons	Stop protein synthesis	Non functional protein

- Sometimes a terminator codon may be mutated to a coding one .
- This causes elongation of protein to produce “run on polypeptide”
- Eg: Hb constant spring

2. Frame shift Mutation

- Deletion or Insertion of one or more bases cause **frame shift mutation**.
- A shift in the reading frame of the codon results from the point where **a base is deleted or inserted**.
- Translating machinery **fails to recognise the change**.

Normal mRNA - AUG CAA UCA UUA GCA UUU

1 2 3 4 5 6

If C in the 3rd codon is missing then it is

Read as - AUG CAA UAU UAG CAU and so on

1 2 3 4 5

• Since there is **no punctuation** in the reading frame, the alteration in the frame results in **garbled translation /Totally irrelevant translation.**

This results in synthesis of abnormal protein

Hemoglobinopathies provide excellent examples of frame shift mutation

Eg- **Hb Wayne** – An abnormal Hb formed due to frame shift mutation

Frame shift mutations can result in **Thalassemias & Premature Polypeptide chain termination**

Mutagens

- Mutagen is a physical or chemical agent that can increase DNA damage or cell proliferation of an organism , increasing the rate of mutation.
Eg:- X-ray, gamma ray, UV rays, acridine orange
- Mutagens are likely to be carcinogens;not always necessarily so.
- Not all mutations are caused by mutagens
- Some are spontaneous mutations caused due to hydrolysis, errors in replication, DNA repair and recombination

Ames test

- Ames test is a widely employed method that uses bacteria to test whether a given chemical can cause mutations in the DNA of the test organism
- A positive test indicates that the chemical is mutagenic and hence carcinogenic
- This test is commonly used by pharmaceutical industry to test carcinogenic effect of drugs and chemicals
- Salmonella typhimurium bacteria is used in this test

- This bacteria will grow only in histidine medium
- Chemical to be tested is mixed with this bacteria and is allowed to grow in a medium devoid of histidine
- All bacteria will die except those that are mutated to synthesise histidine (Reverse mutation)
- No: of bacterial colonies will be proportional to the quantity of mutagen

◊ *Thank you*

