L.9 Gene mutations

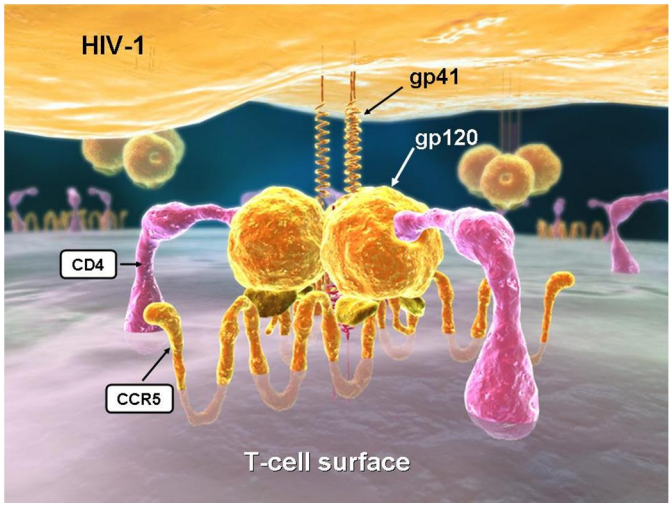
Is a change in the nucleotide sequence of a gene, mutation generally showed up as altered phenotype due to change in genotype.

In fact, cells do make mistake s during replication ,and changes in the genetic message do occur, though only rarely .Typically, a particular gene is alteration in only one out of million gametes. One category of mutational changes affects the message itself, producing alterations in the sequence of DNA nucleotides.

Mutation can be classified into three types according to their effects:

1-Beneficial mutation:

This type of mutation produces a new genotype whose phenotype may be better adapted to the environment. For example: a mutation protects against HIV infection about 1% of general population is homozygous for the recessive allele that encodes a cell surface protein called CCR5.To infect an immune system cell ,HIV must bind CCR5 and another protein. Because the mutation prevents CCR5 from moving from cytoplasm to surface, HIV cannot bind. Heterozygous are partially protected against HIV infection .



2-Neutral mutation:

Any changes in gene sequence caused changes in the structure of proteins that changes either unaffected or affected on the phenotype but tin both conditions do not

can confer any advantage or disadvantage to the organism .Such as red hair do not confer advantage or disadvantage to human .

3- Harmful mutation:

Many mutations are harmful because changes in the amino acids sequence of protein. Even minor ones can affect its function in a negative way for example:

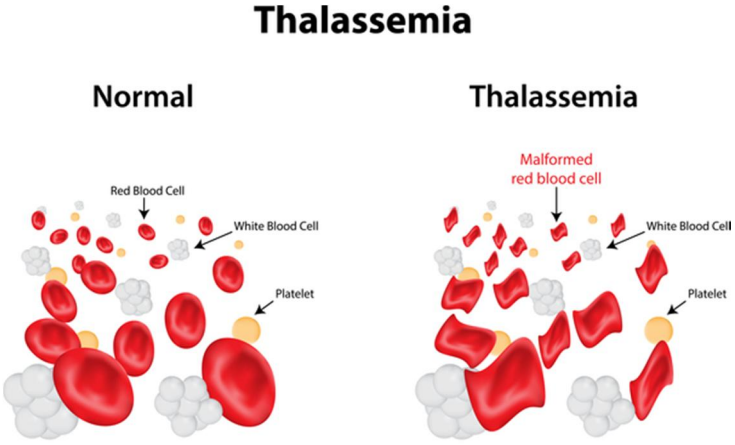
Thalassemia (Cooly's), Mediterranean anemia

Is a heredity anemia in which the synthesis of globin polypeptide chains are reduced or absent.

There are two types of **Thalassemia**:

1- **Alpha thalassemia**: is caused by a deletion of one or both copies of α-gene from one chromosome. That caused reduced synthesis or no synthesis of alpha polypeptide .

2- **Beta thalassemia**, which affect the synthesis of beta chains. It caused by mutation at the junction between an intron and an exon interferes with normal mRNA splicing events, resulting in very low levels of functional mRNA and , in turn, low levels of beta globin cause an excess of alpha globin polypeptides, which form hemoglobin molecules. Without both chains ,not enough Hb are assembled to effectively deliver O2 to tissues, the fatigue and bone pain arise during the 1st year of life as the child depletes fetal Hb , and adult B-globin genes are not transcribed and translated into Hb. Both conditions are inherited as autosomal recessive traits.



On the other hand there are 3 types of a mutation according to the chemical changes:

1- Base substitution (point mutation):

In which one nucleotide is replaced by another some of the point mutation arise due to spontaneous errors that occur during DNA replication, others are the result of damage to the DNA caused by mutagens (radiation, chemical). Point mutation either **transition**: the purine replaces a purine (A to G or G to A) or pyrmidine replaces a pyrmidine (C to T or T to C). Or **transversion** if a purine replaces a pyrmidine or verse versa (A or G to T or C). There are many types of point mutation:

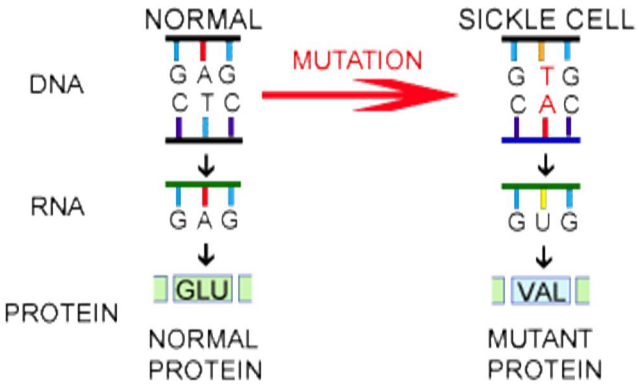
A- Silent mutation:

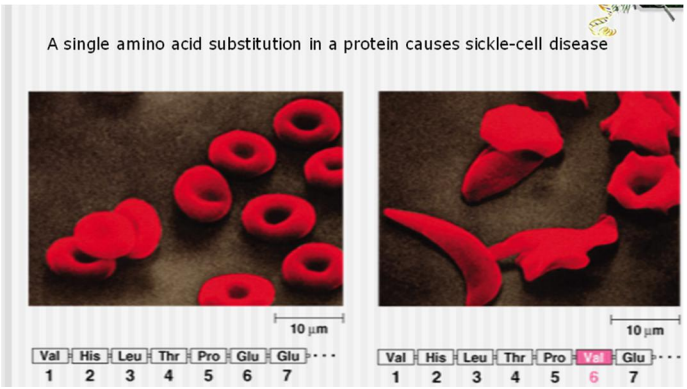
There is no noticeable effect because both of those codons cods for the same amino acid. ex. if UAC is changed to UAU (both of those codons cods for the tyrosine) .

Type of Change	Mutation in the DNA	Example
None	None	5′–A–T–G–A–C–C–G–A–C–C–C–G–A–A–A–G–G–G–A–C–C–3′* Met – Thr – Asp – Pro – Lys – Gly – Thr –
Silent	Base substitution	5′–A–T–G–A–C–C–G–A–C–C–C–**C**–A–A–A–G–G–G–A–C–C–3′ Met – Thr – Asp – Pro – Lys – Gly – Thr –

B- Missense mutation:

The changes of single nucleotide, that causes the substitution of one amino acid for another in a protein. This substitution may or may not affect the function of the gene product. For example: In the gene coding for beta globin, a single nucleotide substitution in codon 6 from GAG (glu.) to GUG (val.) result in sickle cell anemia .





C- Sense mutation:

Produce longer than normal proteins by changing a stop codon into one that code for amino acids .

D- Nonsense mutation:

Change codons that specify amino acids into one of the three stop codons(UAA,UAG,UGA).This leads to the formation of shortened polypeptide chains .For example blood clotting disorder changes one GAA coding for glutamic acid to UAA stop codon (cause the blood do not clotting during surgery or injury) .

E- Splice site mutation:

A point mutation can greatly affect a gene's product if it alters a site where introns are normally removed from mRNA. This is called a splice site mutation it can changes

the phenotype if an intron is translated into amino acids ,or if an exon is skipped instead of being translated, shortening the protein. For example: In cystic fibrosis, a split site mutation alters an intron site so that it is not removed. The encoded protein is too bulky to move to its normal position in the plasma membrane, where it should enable salt to exit the cell. As a result, chloride (a component of salt) accumulates in cells and water move in , drying and thickening the mucus outside.

2-Base deletion:

Which involve elimination one or more bases in a gene. Deletion range from a single DNA nucleotide to thousands of bases to larger pieces of chromosomes .For example: many cases in male infertility are caused by tiny deletions in Y-chromosome.

3- Base insertion:

Which involve addition of one or more bases in a gene .For example: In Gaucher disease, an inserted single DNA base prevents production of an enzyme that normally breaks down glycolipids in lysosomes .The resulting buildup of glycolipid enlarges the liver and spleen and causes easily fractured bones and neurological impairment.

The deletion and insertion of also called frame-shift mutation can be a completely non function protein because the sequence of codons completely altered.