Umm AL Qura University

MUTATIONS

Dr Neda M Bogari

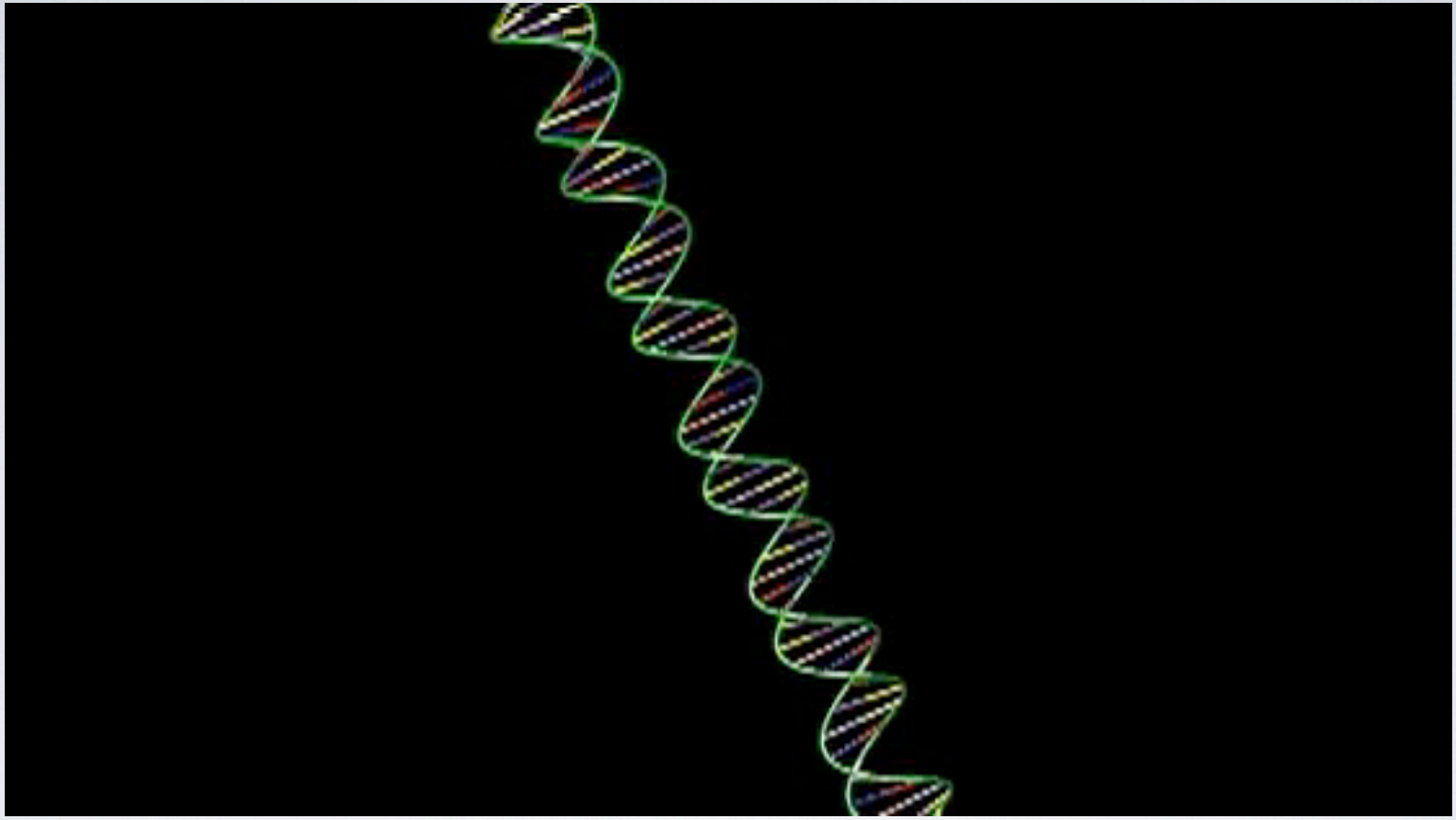
CONTACTS

- www.bogari.net
- http://web.me.com/bogari/bogari.net/

From DNA to Mutations

MUTATION

- Definition: Permanent change in nucleotide sequence.
- It can be at Chromosomal Or DNA levels.
- Chromosomal is Gross lesions & Accounts for less than 8%.
- DNA is Micro-lesions & Accounts for more than 92%)
- The cause of mutation could be through
  - Exposure to mutagenic agents
  - Errors through DNA replication and repair.



The cause of mutation

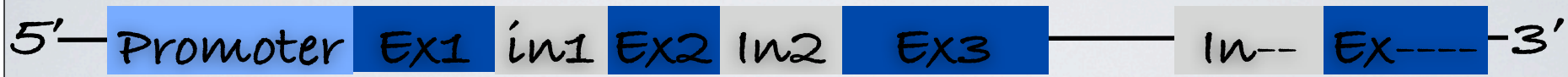
CHROMOSOMAL LEVEL MUTATION

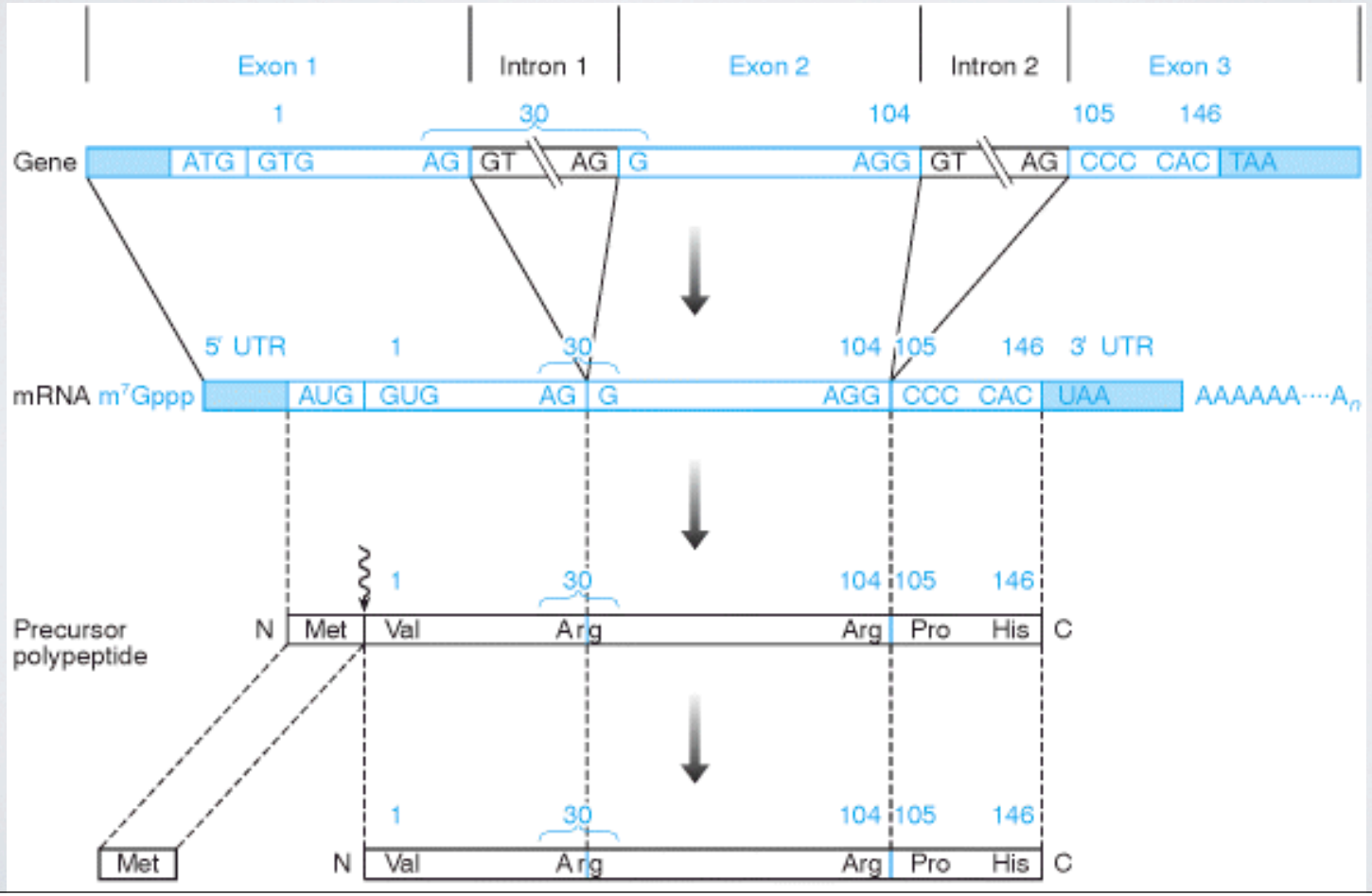
- **Numerical abnormalities:**
  - ★ **Aneuploidy**
    - Monosomy (45)
    - Trisomy (47)
    - Tetrasomy(48)
  - ★ **Polyploidy**
    - Triploidy (2♀+1♂)
    - Tetraploidy (2♀+2♂)
- **Structural abnormalities:**
  - Translocations
  - Deletions
  - Insertion
  - Inversions
  - Rings formation

MUTATION

- Mutation could be in somatic cells or germline cells.
  - A mutation arising in a somatic cell cannot be transmitted to offspring, whereas if it occurs in gonadal tissue or a gamete it can be transmitted to future generations.
- Mutations can occur either in non-coding or coding sequences
  - Mutation in the coding sequence is recognized as an inherited disorder or disease

THE GENE


5'
Promoter
Ex1
in1
Ex2
In2
Ex3
In--
Ex----
3'


Exon 1
Intron 1
Exon 2
Intron 2
Exon 3
Gene
ATG GTG AG GT AG G AGG GT AG CCC CAC TAA
5' UTR
mRNA m7Gppp
AUG GUG AG G AGG CCC CAC UAA AAAAAA····An
3' UTR
Precursor polypeptide
N Met Val Arg Arg Pro His C
Met
N Val Arg Arg Pro His C

POLYMORPHISM

- Polymorphism is change with no effect in the phenotype.

MUTATION & POLYMORPHISM

Mutation → Rare Genetic change(Less than 1%) Sever and alter the function of the protein or the Enzyme.

Polymorphism → is common variation (greater than 1%) no change in function or small effect and occur on average one every 200-1000 base Pairs.

TYPES OF MUTATIONS

- Mutations can be considered in two main classes according to how they are **transmitted from generation to another**.
- Fixed/Stable mutations: mutation which is transmitted unchanged (unaltered).
- Dynamic Or Unstable Mutations: This is new class of mutation which undergo alteration as they are transmitted in families.

FIXED/STABLE MUTATION

- Fixed/stable point mutations can be classified according to the specific molecular changes at the DNA level.
- These include single base pair
  - Substitutions,
  - Insertions,
  - Deletions, or
  - Duplications

FIXED/STABLE MUTATION: SUBSTITUTION

- Definition: substitution is the replacement of a single nucleotide by another.

- Two type of substitution:

  - **Transition**: If the substitution involves replacement by the same type of nucleotide

    - a pyrimidine for a pyrimidine (C for T or vice versa) or a purine for a purine (A for G or vice versa)

  - **Transversion**: Substitution of a pyrimidine by a purine or (vice versa)

FIXED/STABLE MUTATION: DELETION

- Definition: deletion involves the loss of one or more nucleotides.

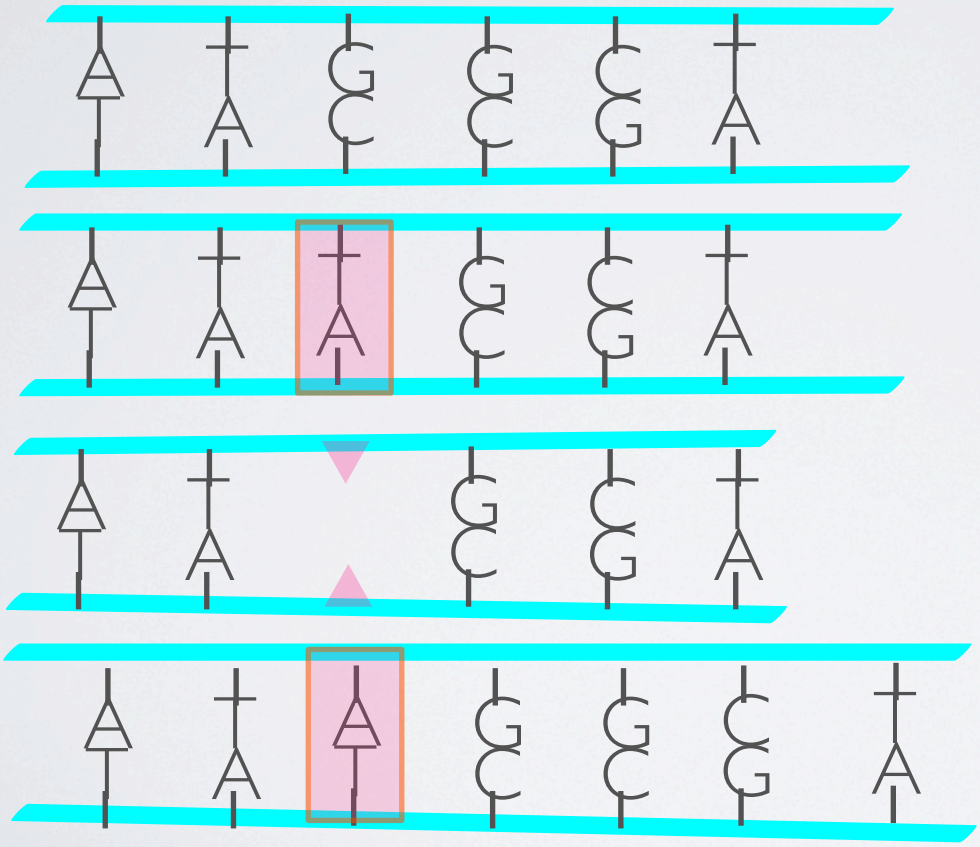
- If it occurs in coding sequences and involves one, two or more nucleotides which are not a multiple of three, it will disrupt the reading frame.

FIXED/STABLE MUTATION: INSERTION

- Definition: An insertion involves the addition of one or more nucleotides into a gene.

- If an insertion occurs in a coding sequence and involves one, two or more nucleotides which are not a multiple of three, it will disrupt the reading frame.

FIXED/STABLE MUTATION

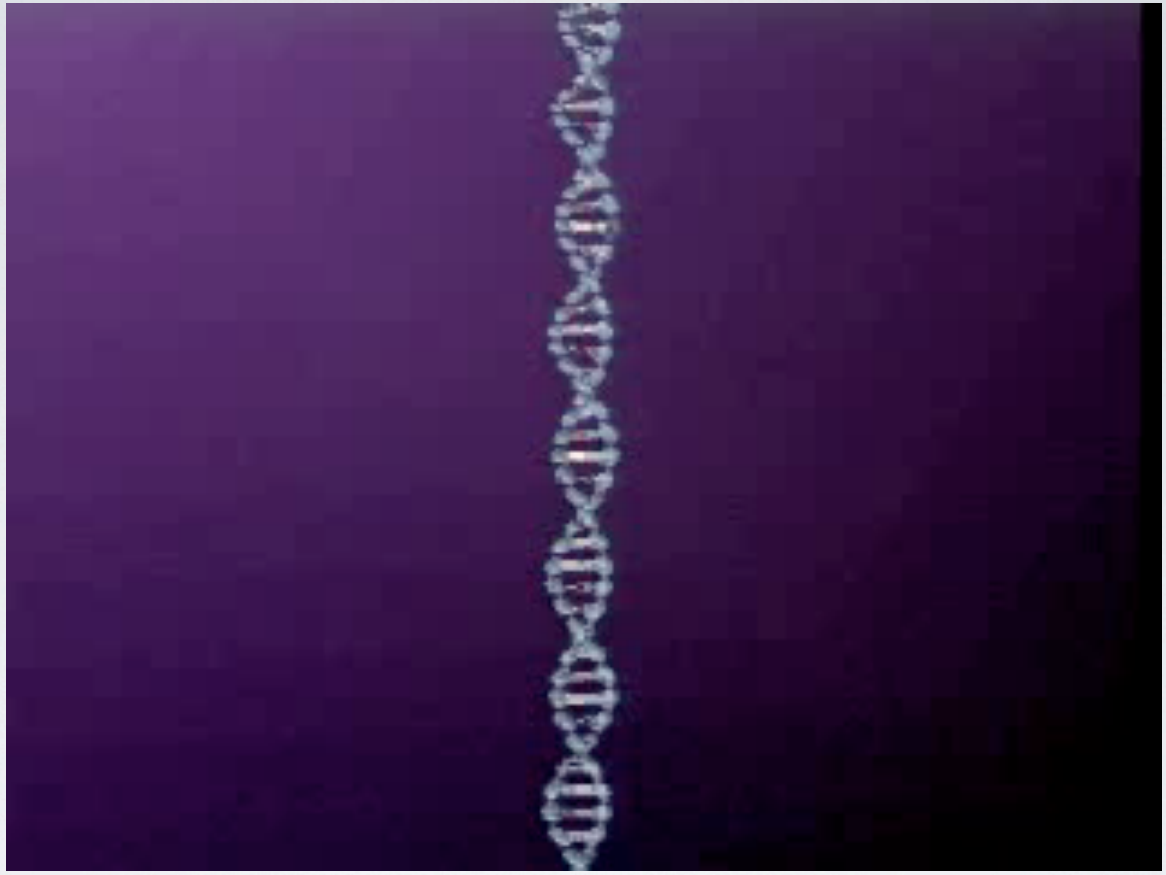


Wild-type

Substitution

Deletion

Insertion

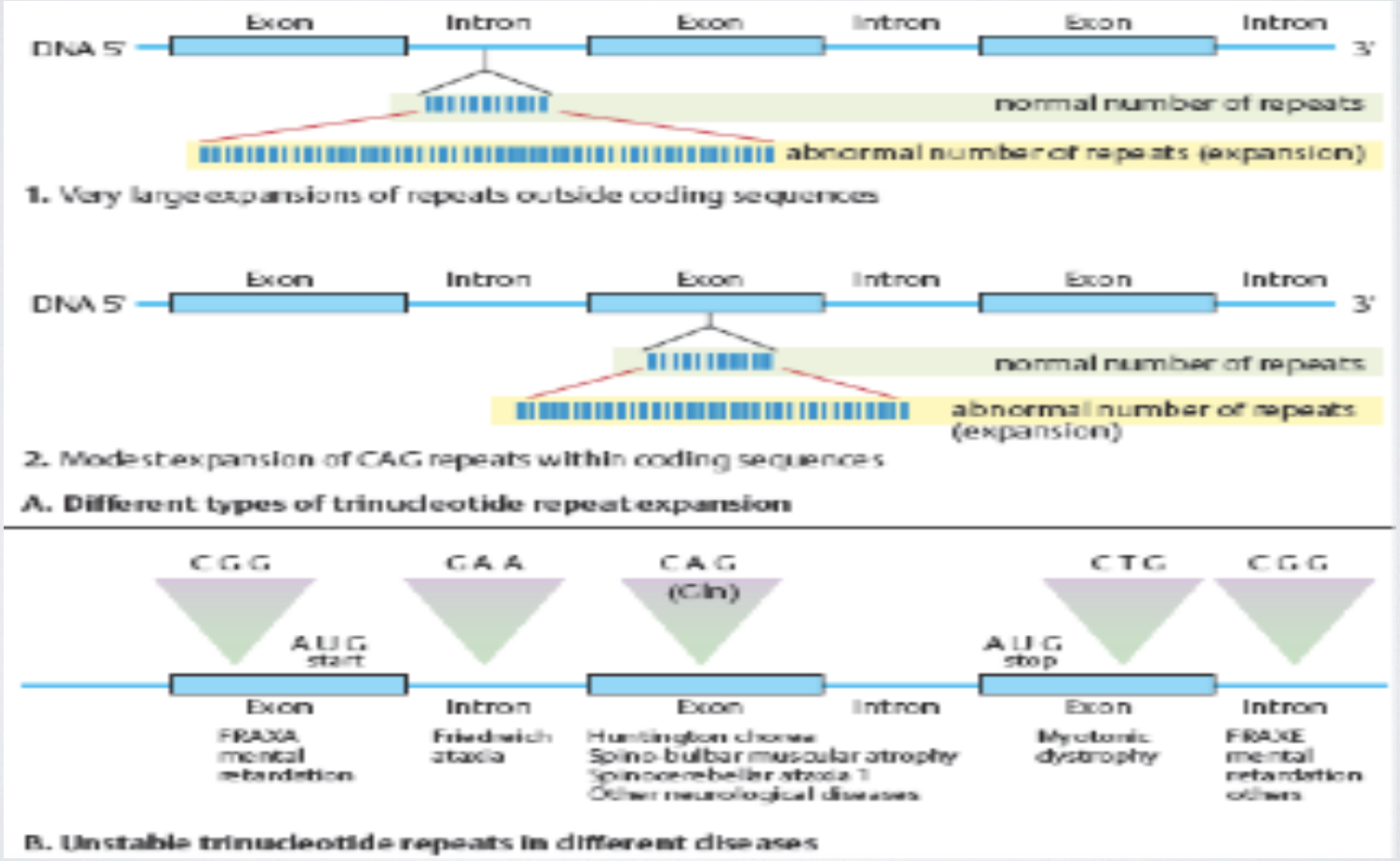


Fixed / stable point mutations

DYNAMIC/UNSTABLE MUTATION

- Unstable or dynamic mutations consist of triplet repeat sequences which, in affected persons, occur in increased copy number when compared to the general population.
- Triplet amplification or expansion has been identified as the mutational basis for a number of different single gene disorders.
- The mechanism by which amplification or expansion of the triplet repeat sequence occurs is not clear at present

DYNAMIC/UNSTABLE MUTATION



DISEASES ASSOCIATED WITH TRIPLET REPEAT EXPANSION

Disease	Repeat sequence	Repeat number	Mutation number	Repeat location
Huntington's disease (HD)	CAG	9-35	37-100	Coding
Mvotonic dystrophy (DM)	CTG	5-35	50-4000	3' UTR
Fragile X site A (FRAXA)	CGG	10-50	200-2000	5' UTR
Machado-Joseph disease (MJD,	CAG	12-36	67->79	Coding
Spino-oaebellar ataxia 6 (SCA6)	CAG	4-16	21-27	Coding
Spuio-ce ebellar ataxia 7 (SCAT)	CAG	7-35	37-200	Coding
Spmo-oaebellar ataxia 8 (SCA8)	CTG	16-37	100->500	UTR
I tatorubral-pallidoluysian atrophy (DRPLA)	CAG	7-23	49->75	Coding
Friedreich's ataxia (FA)	GAA	17-22	200-900	Intronic
Fragile X site E (FRAXE)	CCG	6-25	>200	Promoter
Fragile X site F (FRAXF)	GCC	6-29	>500	?
Fragile 16 site A (FRA16A)	CCG	16-49	1000-2000	?

UTR = untranslated region.

STRUCTURAL EFFECTS OF MUTATIONS ON THE PROTEIN

- Mutations can also be subdivided into two main groups according to the effect on the polypeptide sequence of the encoded protein, being either synonymous or non- synonymous

SYNONYMOUS/SILENT MUTATIONS

- If a mutation does not alter the polypeptide product of the gene, this is termed a synonymous or silent mutation.

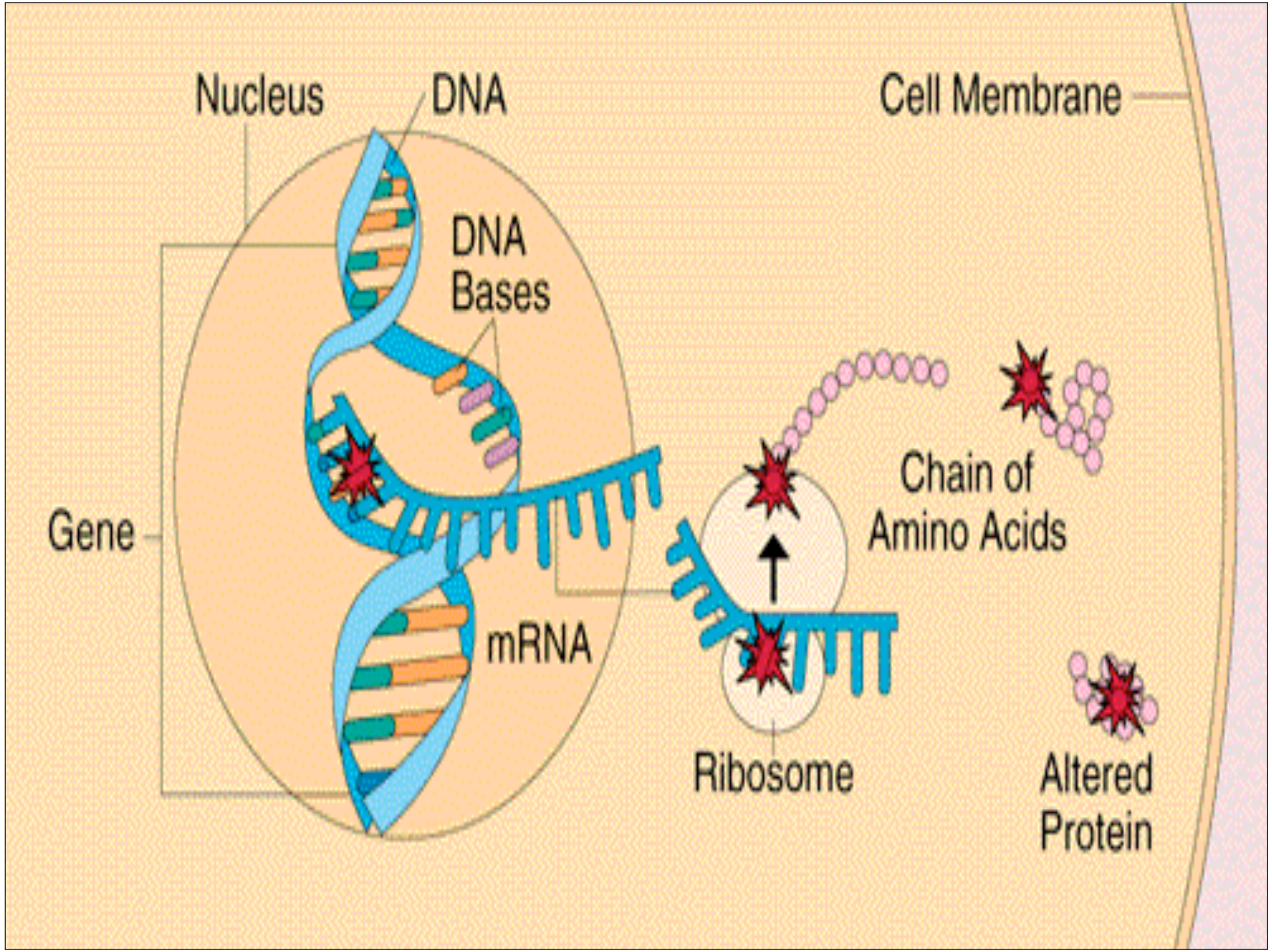
- A single base pair substitution, particularly if it occurs in the third position of a codon, will often result in another triplet which codes for the same amino acid with no alteration in the properties of the resulting protein.

NON-SYNONYMOUS MUTATIONS

- If a mutation leads to an **alteration** in the encoded polypeptide, it is known as a **non-synonymous mutation**.
- Alteration of the amino acid sequence of the protein product of a gene is likely to result in **abnormal function**.
- Non-synonymous mutations can occur in one of three main ways
  - Missense
  - Nonsense
  - Frameshift

SUBSTITUTION MUTATION

Mutation	Codon	Amino acids
Missense	GAG	Glu
	AAG	Lys
Nonsense	GAG	Glu
	UAG	Stop
silent	GAG	Glu
	GAA	Glu


Nucleus
DNA
Cell Membrane
DNA
Bases
Gene
mRNA
Chain of
Amino Acids
Ribosome
Altered
Protein

NON-SYNONYMOUS MUTATIONS :MISSENSE

- A single base pair substitution can result in coding for a different amino acid and the synthesis of an altered protein, a so-called missense mutation.
- Non-conservative substitution: If mutation coding for an amino acid which is chemically dissimilar such different charge of protein or structure of protein will be altered

NON-SYNONYMOUS MUTATIONS :MISSENSE

- Conservative substitution: If mutation coding for an amino acid which is chemically similar, have no functional effect.
- Non-conservative substitution will result in complete loss or gross reduction of biological activity of the resulting protein.

NON-SYNONYMOUS MUTATIONS :NONSENSE

- A substitution of base pair which leads to the generation of one of the stop codons will result in premature termination of translation of a peptide chain.
- Nonsense mutation result in reduce the biological activity of the protein

NON-SYNONYMOUS MUTATIONS :FRAMESHIFT

- If a mutation involves the insertion or deletion of nucleotides which are not a multiple of three, it will disrupt the reading frame and constitute what is known as a frameshift mutation
- The amino acid sequence resulting from such mutation is not the same sequence of the normal amino acid.
- This mutation may have an adverse effect in its protein function
- Most of these mutation result in premature stop codon

NON-SYNONYMOUS MUTATIONS :FRAMESHIFT

- A frameshift mutation causes the reading of codons to be different, so all codons after the mutation will code for different amino acids. Furthermore, the stop codon "UAA, UGA, or UAG" will not be read, or a stop codon could be created at an earlier or later site.
- The protein being created could be abnormally short, abnormally long, and/or contain the wrong amino acids. It will most likely not be functional.
- Frameshift mutations frequently result in severe genetic diseases such as Tay-Sachs disease.
- A frameshift mutation is responsible for some types of familial hypercholesterolemia .
- Frameshifting may also occur during protein translation, producing different proteins from overlapping open reading frames

FUNCTIONAL EFFECTS OF MUTATIONS ON THE PROTEIN

The mutations effect can appear either through loss- or gain-of-function.

LOSS-OF-FUNCTION MUTATION

- These mutations can result in either reduced activity or complete loss of the gene product.
- The complete loss of gene product can be the result of either reduced the activity or decreased the stability of the gene product (hypomorph or null allele or amorph).

LOSS-OF-FUNCTION MUTATION: HAPLOINSUFFICIENCY

- Loss-of-function mutations in the heterozygous state would be associated with half normal levels of the protein product (haploinsufficiency mutation).

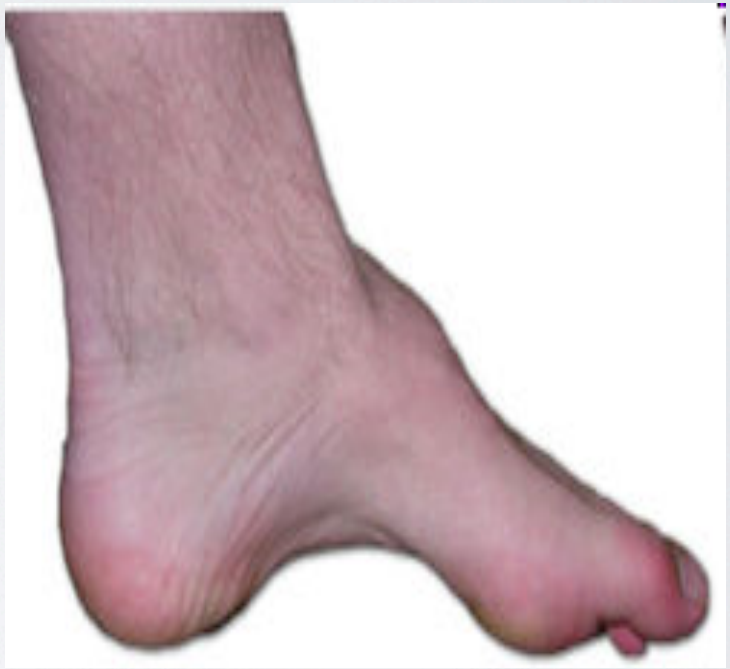
- **haploinsufficiency** occurs when a diploid organism only has a single functional copy of a gene (with the other copy inactivated by mutation) and the single functional copy of the gene does not produce enough of a gene product (typically a protein) to bring about a wild-type condition, leading to an abnormal or diseased state.

GAIN-OF-FUNCTION MUTATIONS

- Gain-of-function mutations result in either increased levels of gene expression or the development of a new function(s) of the gene product.
- Increased expression levels result of a point mutation or increased gene dosage are responsible for Charcot-Marie-tooth disease.

CHARCOT-MARIE-TOOTH DISEASE (CMT)

- **Charcot-Marie-Tooth disease** (**CMT**), known also as **Hereditary Motor and Sensory Neuropathy** (**HMSN**), **Hereditary Sensorimotor Neuropathy** (**HSMN**), or **Peroneal Muscular Atrophy**, is a heterogeneous inherited disorder of nerves (neuropathy) that is characterized by loss of muscle tissue and touch sensation in the feet and legs but also in the hands and arms in the advanced stages of disease.



- Presently permanent, this disease is one of the most common inherited neurological disorders, with 37 in 100,000 affected.

DOMINANT-NEGATIVE MUTATIONS

- A mutation whose gene product adversely affects the normal, wild-type gene product within the same cell
- Usually by dimerize (combining) with it. In cases of polymeric molecules, such as collagen, dominant negative mutations are often more harmful than mutations causing the production of no gene product (null mutations or null alleles).