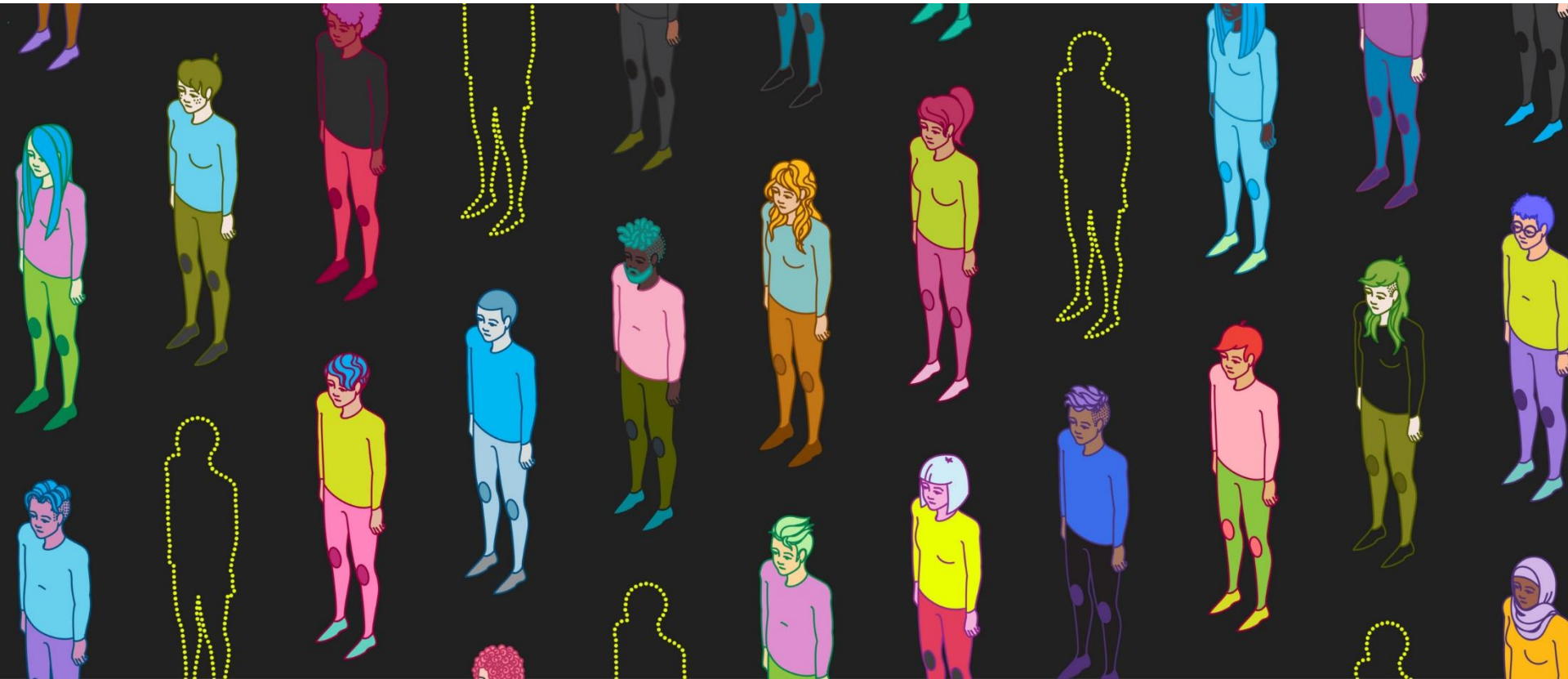
Mutations

Assoc. Prof. Bengi ÇINAR KUL

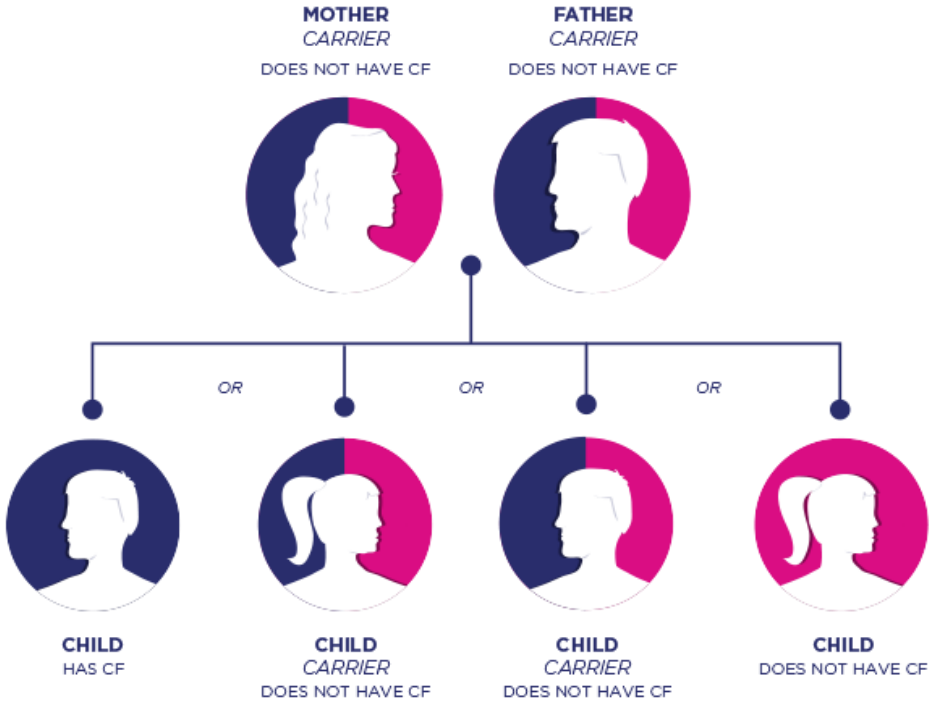


What is the common feature…

mutation

- We have the same eye and hair color as many of our family members. The same thing can happen with diseases—they can be passed down from one family member to another. The way this happens is through genes, the genetic information that you get directly from your parents.

In most cases, diseases or other problems do not have one single cause. They come from a combination of your genes, your choices, and your environment.



- Mutation is a permanent change in the DNA sequence that makes up a gene.
- Mutations range in size from one DNA base to a whole chromosome change.

Gene mutations **occur in two ways**:

- they can be inherited from a parent (hereditary mutations or germline mutations) or
- acquired during a person's lifetime and occur in the DNA of individual cells (acquired or sporadic mutations).

Mutations can be grouped according to

- their sizes,
- phenotypic effects,
- the cause of occurrence
- the type of cell in which they occur.

Mutations by size

- **Microscopic (**macro mutations**, chromosomal abnormalities**) –it varies from 2000 kb to larger

- **Submicroscopic** (micro mutations, **gene** mutations)

  - **a single base** or

  - mutations that are too small not to be evaluated at the microscope level

Chromosome abnormalities

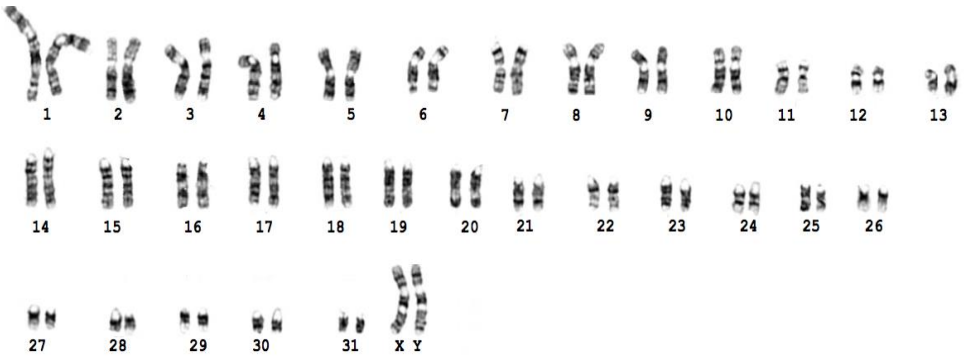
- There are usually two sets of haploid chromosomes in diploid organisms, but in some cases they can change for reasons such as changes in chromosome number, fragment deletion, addition or repetition, interchromosomal fragmentation.
- Changes are visible in a light microsope
- Chromosomal abnormalities are identified in approximately 0.6% of liveborn infants
- More than 50% miscarriages in the first trimester of pregnancy may be due to chromosomal changes

Types of chromosomal abnormalities:

- **Numerical abnormalities**: - poliploidy: triploidy, tetraploidy - aneuploidy: trisomy, monosomy

- **Structural**: translocation, deletion, inversion, duplication, ring, marker

The Cytogenetics field particularly works on chromosomal aberrations by using Karyotyping.



I.Numerical chromosomal abnormalities:

- **Poliploidy** - occurs when there are more than two paired (homologous) **sets of chromosomes** (triploidy, tetraploidy, etc.).

Triploidy – 3n
(if it is human 69,XXX 69,XXY 69,XYY)

- Triploidy - is a rare lethal chromosome abnormality caused by the presence of an extra set of chromosomes
- The most usual cause is two sperm fertilizing a single oocyte (dispermy)
- Sometimes the cause is a diploid gamete
- The condition is not compatible with life

Tetraploidy – 4n (if it is human 92,XXXX 92,XXYY)

- is caused by the presence of two extra sets of chromosomes
- is extremely rare, lethal condition
- it is usually due to failure to complete the first zygotic division

I.Numerical chromosomal abnormalities:

Aneuploidy - **one chromosome is extra (trisomy) or one is lost (monosomy)**. They can occur within autosomal and sex chromosomes

- Trisomy - is an abnormality in which there are **three copies of a particular chromosome** (e.g. 47,XX,+21)
- Monosomy – occurs when there is **only one of a pair** of chromosomes (e.g. 45,X)

Aneuploidy cells arise through two main mechanisms:

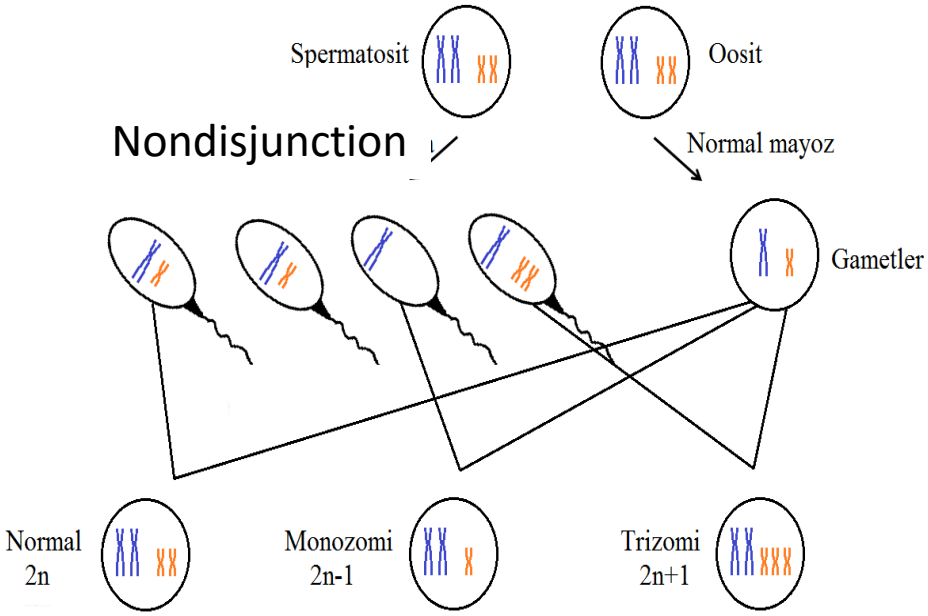
- Nondisjunction – failure of chromosome pairs to separate properly during cell division or failure of sister chromatids to disjoin (trisomy or monosomy)
- Anaphase lag – delayed movement of chromosome during anaphase (monosomy)

Nullisomy 2n-2

Monosomy 2n-1

Trisomy 2n+1

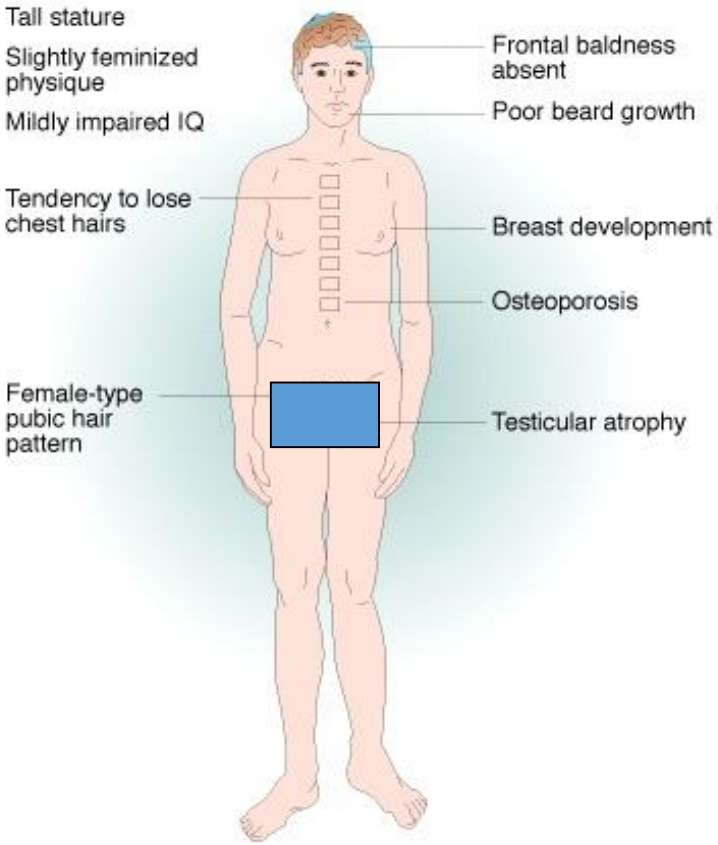
Tetrasomy 2n+2



Aneuplidies of sex chromosomes

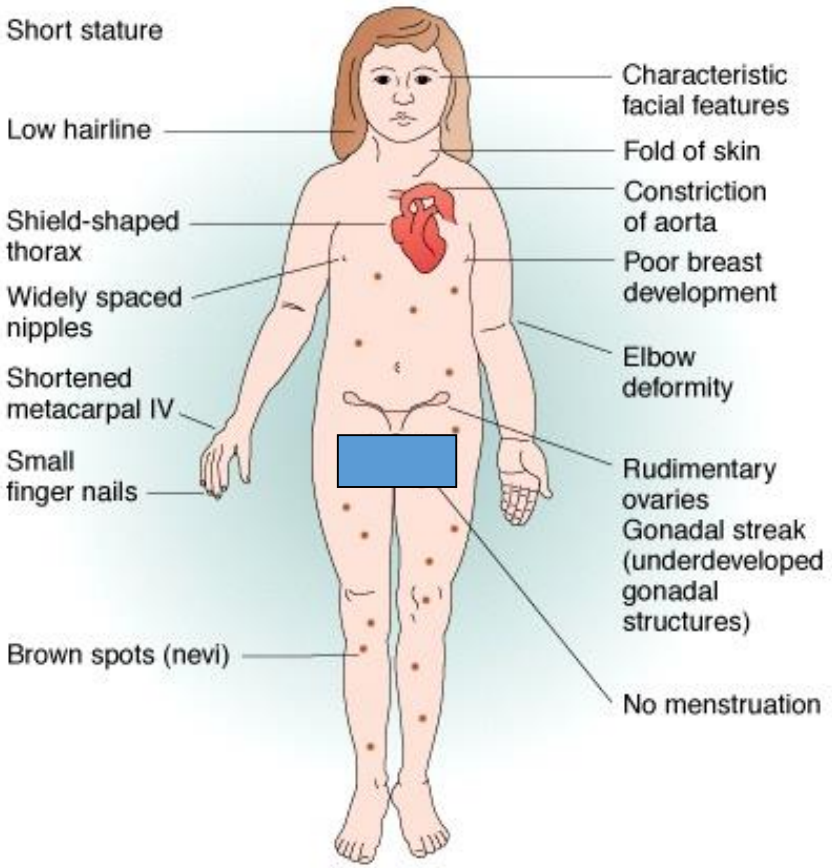
Klinefelter syndrome, 47,XXY

- Children: learning disabilities, delayed speech and language development
- The older child or adolescent may be discovered during an endocrine evaluation for delayed or incomplete pubertal development, gynecomastia, and small testes.
- Adults are often evaluated for infertility or breast malignancy



45,X – Turner syndrome

- Short stature - broad chest - low hairline - low-set eares - webbed neck Girls with Turner syndrome typically experience gonadal dysfunction (non-working ovaries), which results in amenorrhea(absence of menstrua cycle) and sterility –
- Mental development is normal



II.Structural chromosomal abnormalities

Structural chromosomal abnormalities result from breakage and incorrect rejoining of chromosomal segments.
Structural rearrangements are defined as balanced if the complete chromosomal set is still present, and unbalanced if information is additional or missing.

Balanced: if there is no gain or loss of chromosomal material

- Translocations
- Inversions

Unbalanced: – if there is gain or loss of chromosomal material

- Duplication
- Deletion
- Insertion
- Ring chromosome

Balanced Structural rearrangements

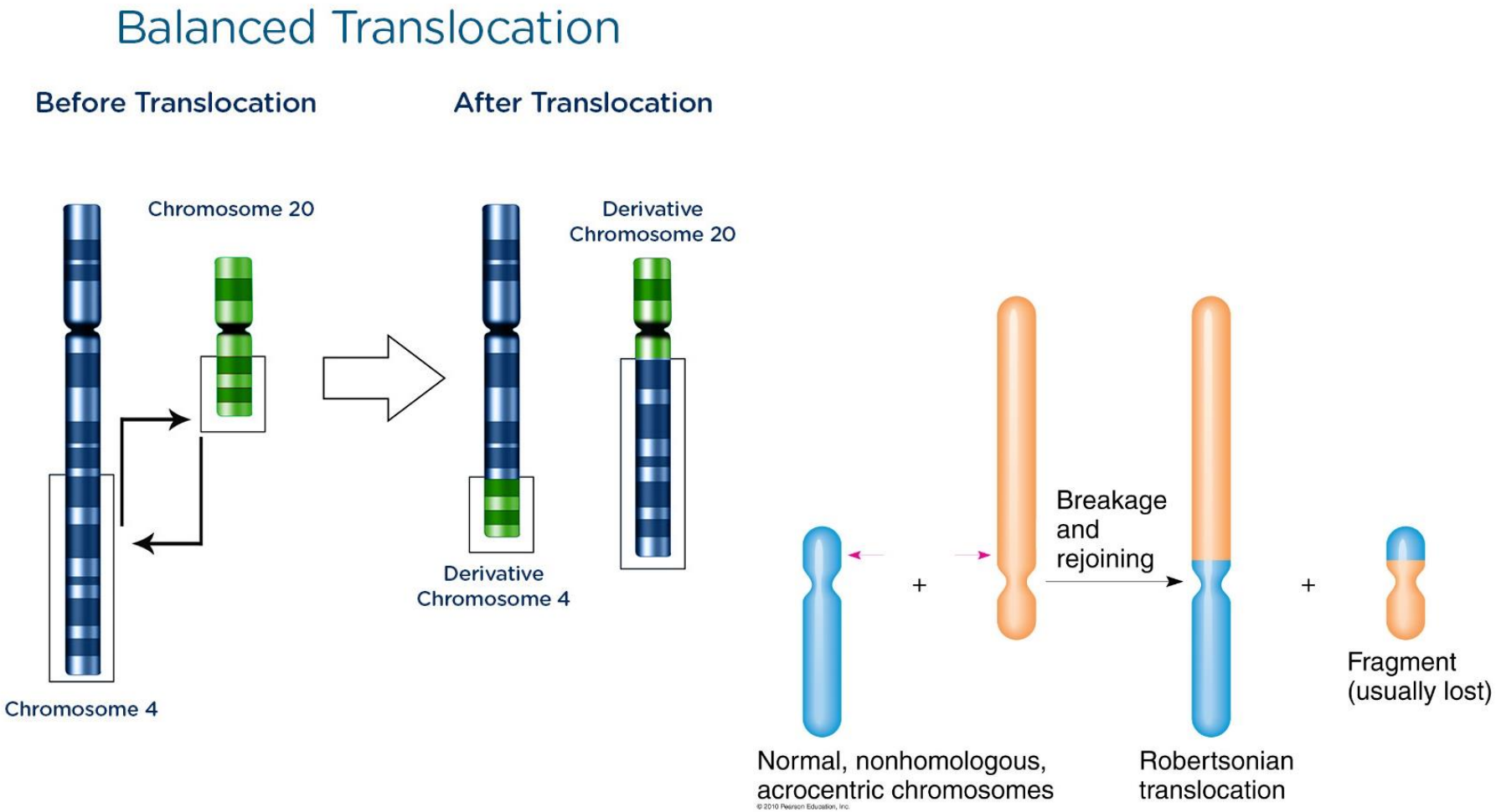
Reciprocal Translocation : A type of chromosome rearrangement involving the exchange of chromosome segments between two chromosomes that do not belong to the same pair of chromosomes.

- Carriers of balanced reciprocal translocation are healthy persons but can produce gametes with unbalanced chromosomal material

For example: Robertsonian translocation

- A type of chromosome rearrangement involving the exchange between the proximal short arms of the acrocentric chromosomes: 13, 14, 15, 21 and 22.
- The most common Robertsonian translocation is between chromosomes 13 and 14
- Carriers are asymptomatic but often produce unbalanced gametes that can result in miscarriage (monosomic or trisomic zygote).

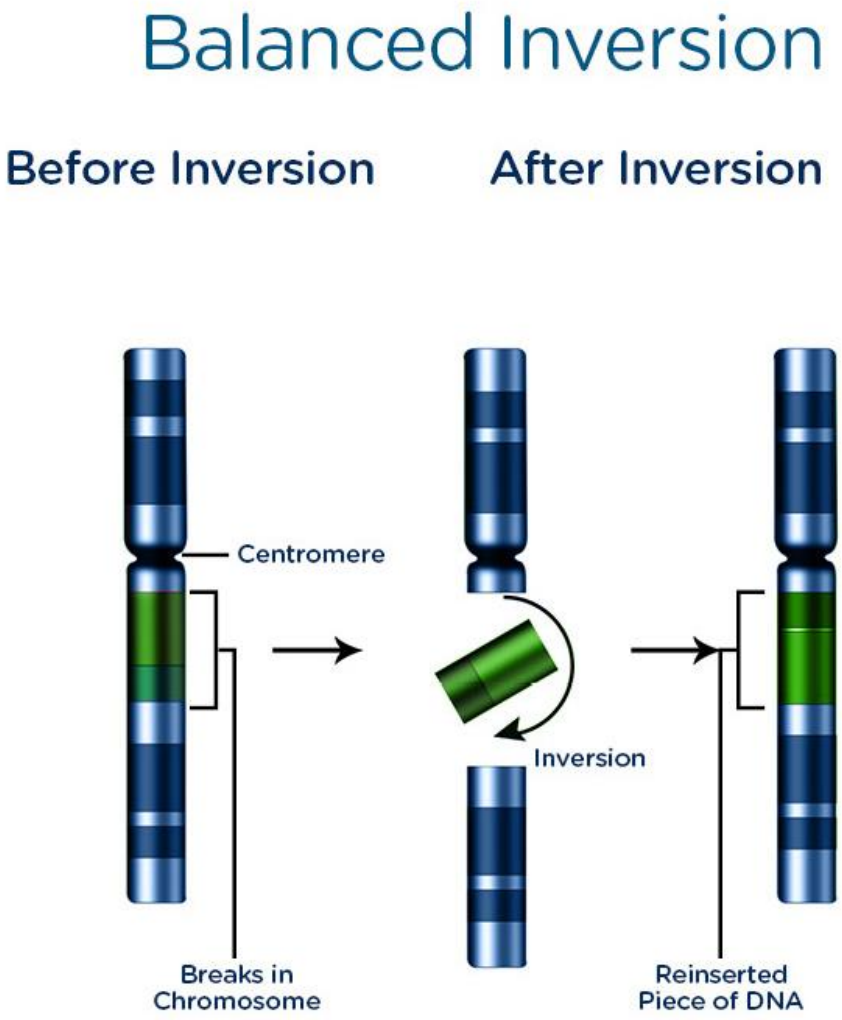
Balanced Structural rearrangements



A Robertsonian translocation results when the long arms of two acrocentric chromosomes fuse at the centromere and the two short arms are lost.

Balanced Structural rearrangements

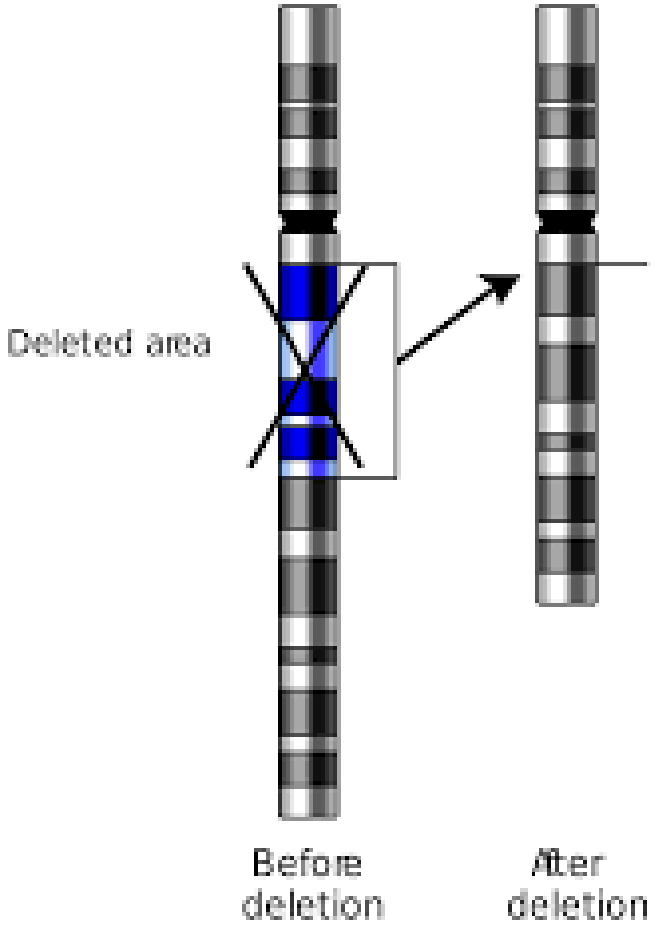
- **Inversion:** Inversion occurs when the segment between two breakpoints is inverted before rejoining the breaks



Unbalanced Structural rearrangements

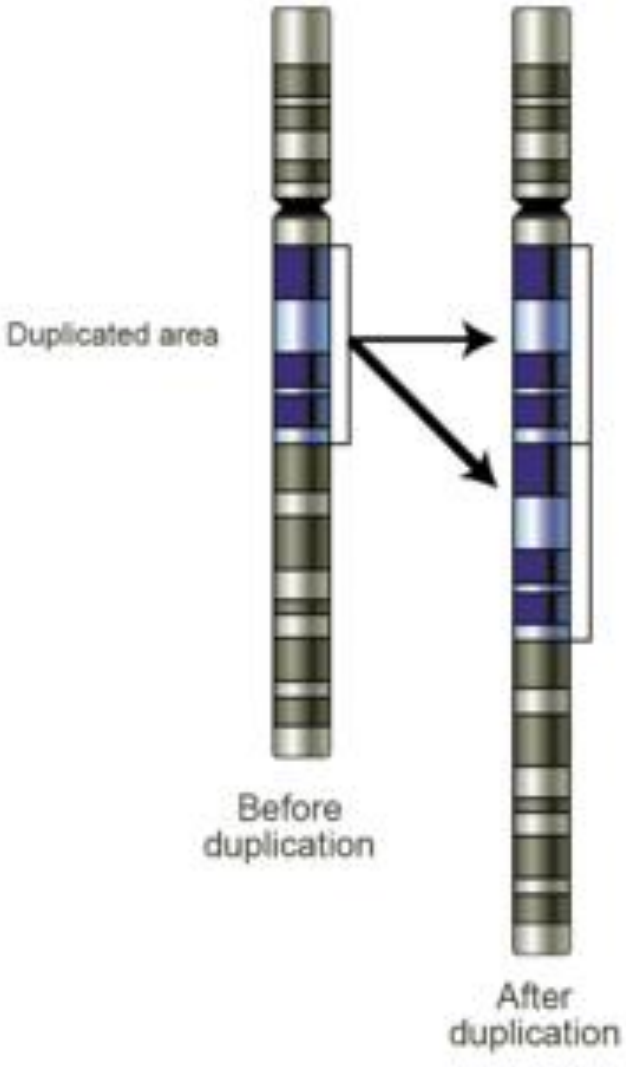
(if there is gain or loss of chromosomal material)

- Deletion - loss of a segment of the chromosome



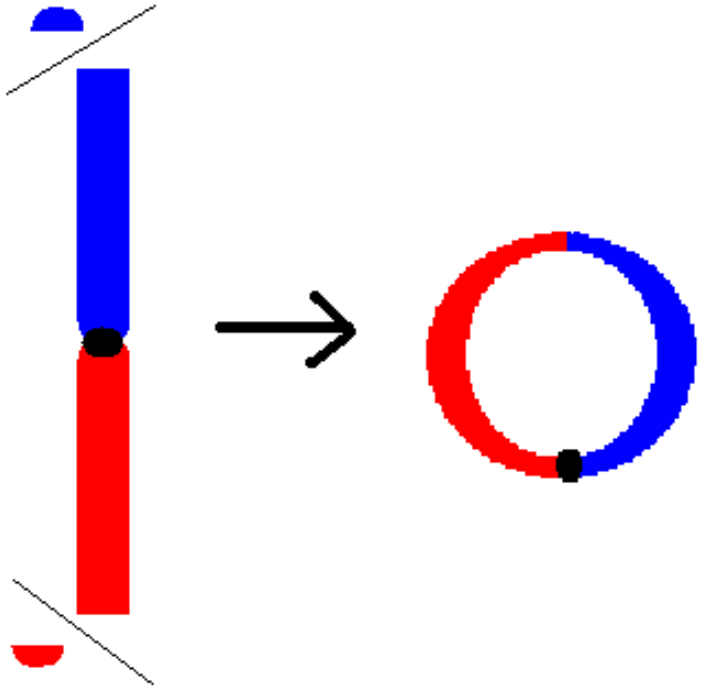
Unbalanced Structural rearrangements

- Duplication occurs when a segment of the chromosome is repeated, once or several times.



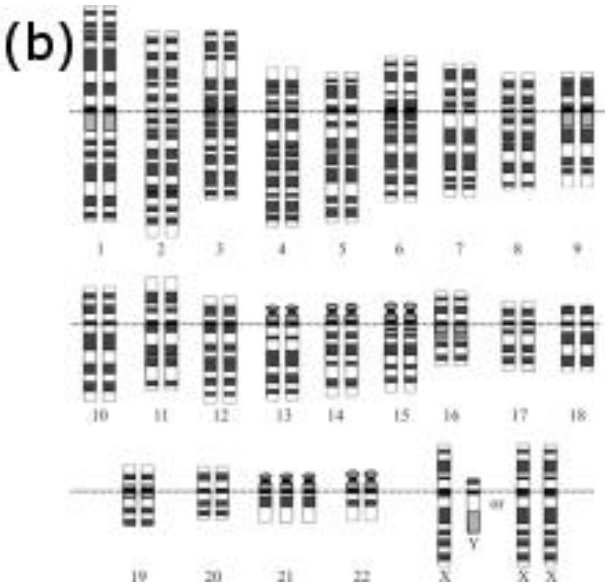
Unbalanced Structural rearrangements

- Ring chromosome: Two ends of the segment between breakpoints are joined to form a circular structure.

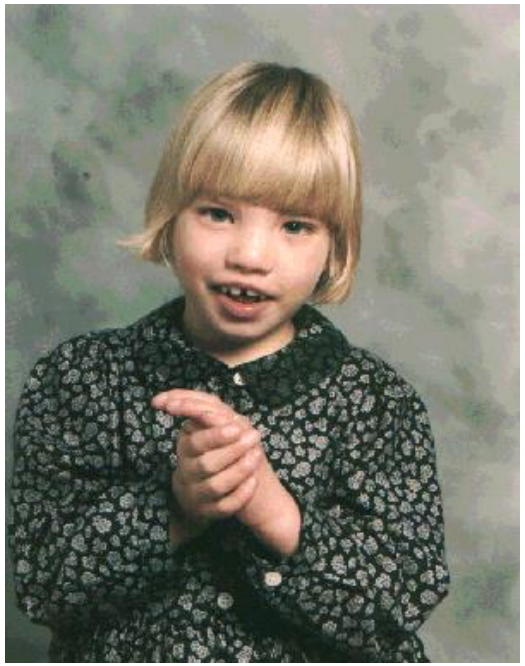


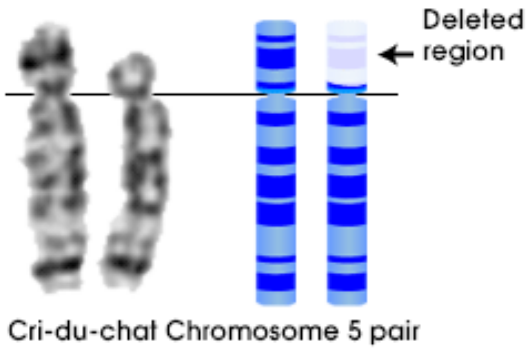
What kind of abnormalities?

- Down sendromu



- Cri-du-chat sendromu





Mutations can be grouped according to

- their size,
- the cause of occurrence
- the type of cell in which they occur,
- phenotypic effects.

the cause of occurrence

- A mutation occurs when a DNA gene is damaged or changed in such a way as to alter the genetic message carried by that gene.

- **spontaneous:** Caused by replication mistakes

- **induced**: Induced by exposure to a variety of mutagenes

Mutations can be grouped according to

- their size,
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- the type of cell in which they occur,
- phenotypic effects.

the type of cell in which they occur

- **Somatic cells** - the mutation is not passed along to the next generation Cancer tumours are a unique class of somatic mutations.
- **Germinal cells** - germ cells give rise to gametes, some gametes will carry the mutation and it will be passed on to the next generation.

Typically germinal mutations are not expressed in the individual containing the mutation.

Remember…

Mutations by size

- Microscopic (macro mutations, chromosomal abnormalities) –it varies from 2000 kb to larger

- **Submicroscopic (micro mutations, gene mutations)**

  - a single base or

  - mutations that are too small not to be evaluated at the microscope level

Gene mutations
(Submicroscopic, micro mutations)

Base pair substitution mutations in a nucleotide is observed as conversion to another nucleotide.

- transition - exchange purin-purin or pirymidyn-pirymidin
- transversion - exchange purin-pyrimidin

Example:

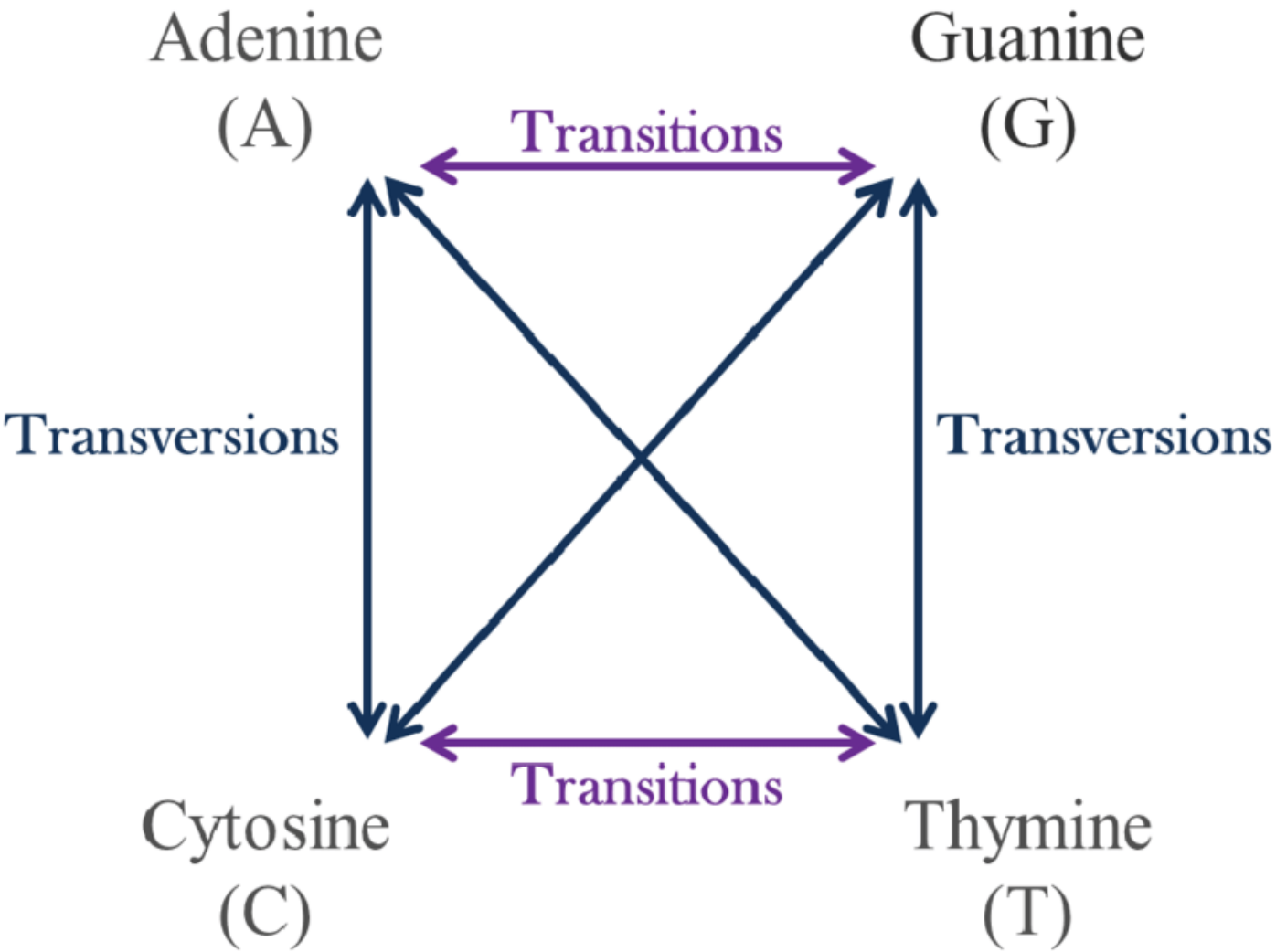
Substitution in FGFR3 (Fibroblast Growth Factor Receptor 3) gene, Achondroplasia,

Autosomal dominant disorder

- long, narrow trunk - short extremities, particularly in

the proximal (rhizomelic) segments

- a large head with frontal bossing
- hypoplasia of the midface
- trident configuration of the hands

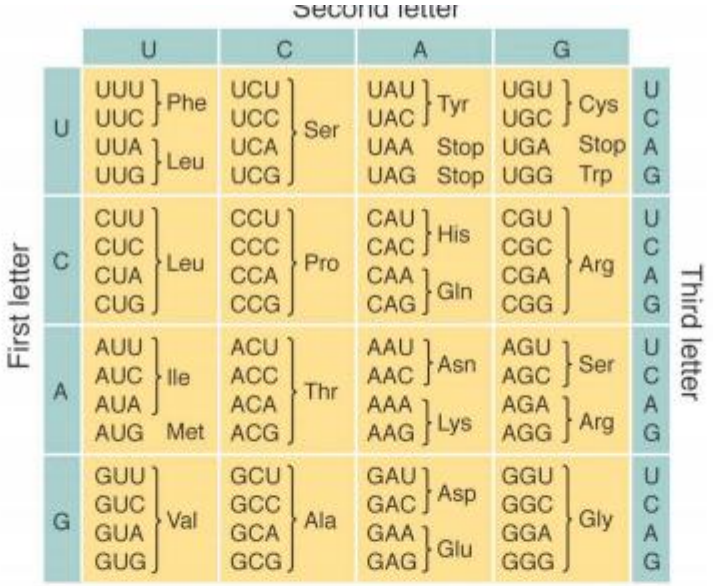

Adenine
(A)
Guanine
(G)
Transitions
Transversions
Transversions
Transitions
Cytosine
(C)
Thymine
(T)

missense mutations – replace one amino acid with another in gene product. These are nonsynonymous substitutions occur in coding region and changes the triplet codon for different amino acid

nonsense mutations – replace an amino acid codon with a stop codon. Point mutation, which converts the normal codon to UAA, UGA, UAG, creating a premature STOP codon is called.

synonymous (silent) mutations do not change the sequence of the gene product. Causes a codon change but does not result in an altered amino acid because of the degenaracy of the genetic code.

frameshift mutation - Insertion or deletion of a small number of nucleotides (different than multiplication of three) into a coding region, which alter the reading frame of translation from that point.



Wild-type mRNA 5' GCU GGA GCA CCA GGA CAA GAU GGA 3'

Wild-type polypeptide N Ala Gly Ala Pro Gly Gln Asp Gly C

Silent mutation GCU GGA GCC CCA GGA CAA GAU GGA

Ala Gly Ala Pro Gly Gln Asp Gly

Missense mutation GCU GGA GCA CCA AGA CAA GAU GGA

Ala Gly Ala Pro Arg Gln Asp Gly

Nonsense mutation GCU GGA GCA CCA GGA UAA GAU GGA

Ala Gly Ala Pro Gly Stop

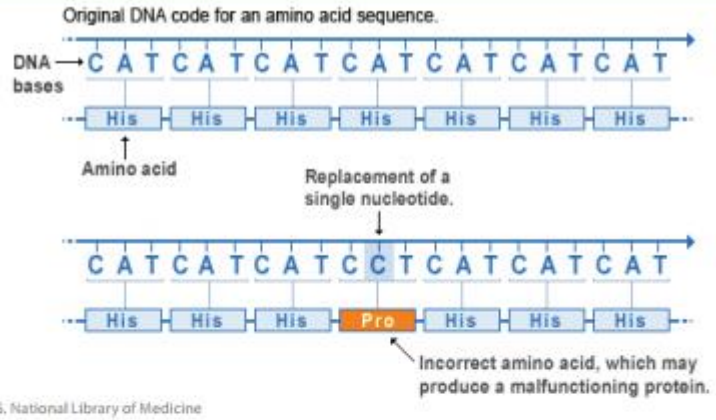
Note: these are all *substitutions*

Frameshift mutation GCU GGA GCC ACC AGG ACA AGA UGG A

Ala Gly Ala Thr Arg Thr Arg Trp

This one is an *insertion*

MISSENSE MUTATION



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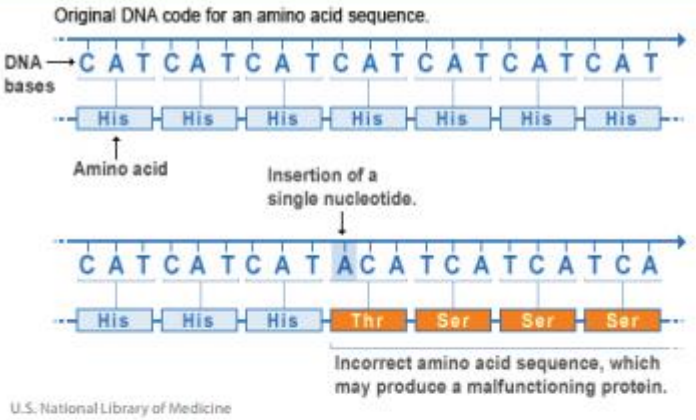
This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.

INSERTION



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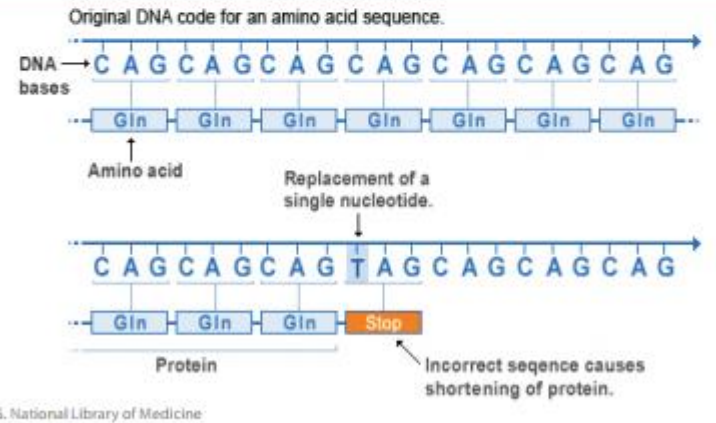
An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.

NONSENSE MUTATION



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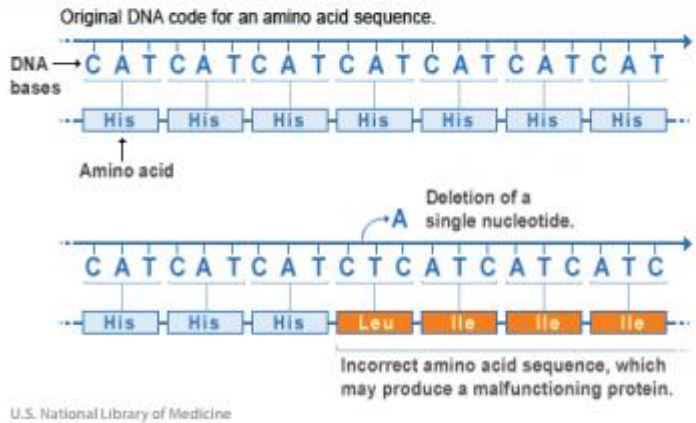
A nonsense mutation is also a change in one DNA base pair. Instead of sub stituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.

DELETION



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A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).

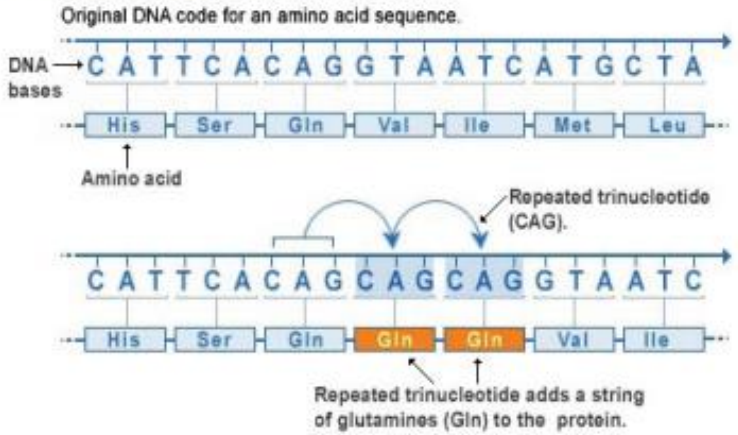
Dynamic mutations

- Dynamic mutation is caused by the expansion of trinucleotide repeats within the genome
- Trinucleotide repeat units lies within or adjacent to a disease-associated gene, there is a tendency for the tract to become progressively larger by expansion at meiosis, it becomes «unstable» by reaching a certain treshold size.
- Anticipation – the tendency for the severity of a condition in successive generations
- **Huntington's disease- example of dynamic mutation**

HD is a rare neuredegenerative disorder of the central nervous system characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia.

CAG repeats expansion in IT15 gene - which adds a string of glutamines (Gln) to the encoded protein called huntingtin

REPEAT EXPANSION



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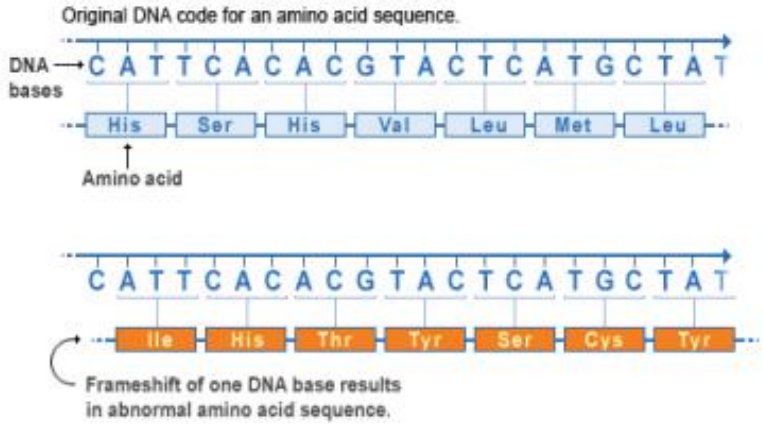
Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

FRAMESHIFT MUTATION



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This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.

- Fragile X syndrome is an example for repeat extension

Michael Phelps

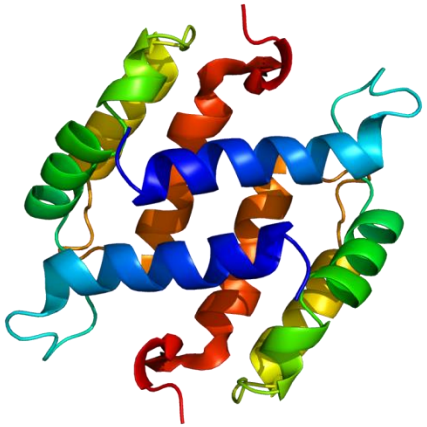
FXS: Common Physical Features

- Elongated face & Broad forehead
- Large, prominent ears
- High arched palate
- Prominent jaw, Dental crowding
- Macro-orchidism (post-pubertal)
- Strabismus (squint)
- Murmur, Mitral valve prolapse, cardiomegaly, dilation of aorta
- Hypotonia & joint laxity
- Flat feet, Hollow chest, Scoliosis

According to phenotypic effects

Loss of function mutations: *Such mutations cause protein to be partially (hypomorph) or totally (amorph) loss of function.*

Gain of Function mutations: *Due to such mutations, the gene product acquires a new, hypermorphic function.*



- **Lethal Types of mutations** seen in genes with vital functions.

In a mutation that is associated with a functional protein, if the mutant protein unable to tolerate the lack of expression, this situation is resulted in the death of the organism and the mutation is termed "LETHAL" mutation.

Lavender foal syndrome

Genetic variation

- All individuals are 99.9 percent the same genetically. The differences in the sequence of DNA among individuals, or genetic variation, explain some of the differences among people such as physical traits and higher or lower risk for certain diseases.
- Mutations and polymorphisms are forms of genetic variation. While mutations are generally associated with disease and are relatively rare, polymorphisms are more frequent and their clinical significance is not as straightforward. Single nucleotide polymorphisms (SNPs, pronounced “snips”) are DNA sequence variations that occur when a single nucleotide is altered. SNPs occur every 100 to 300 bases along the 3 billion-base human genome. A single individual may carry millions of SNPs.

- Although some genetic variations may cause or modify disease risk, other changes may result in no increased risk or a neutral presentation. For example, genetic variants in a single gene account for the different blood types: A, B, AB, and O. Understanding the clinical significance of genetic variation is a complicated process because of our limited knowledge of which genes are involved in a disease or condition and the multiple gene-gene and gene-behavior-environment interactions likely to be involved in complex, chronic diseases. New technologies are enabling faster and more accurate detection of genetic variants in hundreds or thousands of genes in a single process.