MUTATIONS: TYPES AND CAUSES

Azerbaijan Medical University

Department: Medical biology and genetics

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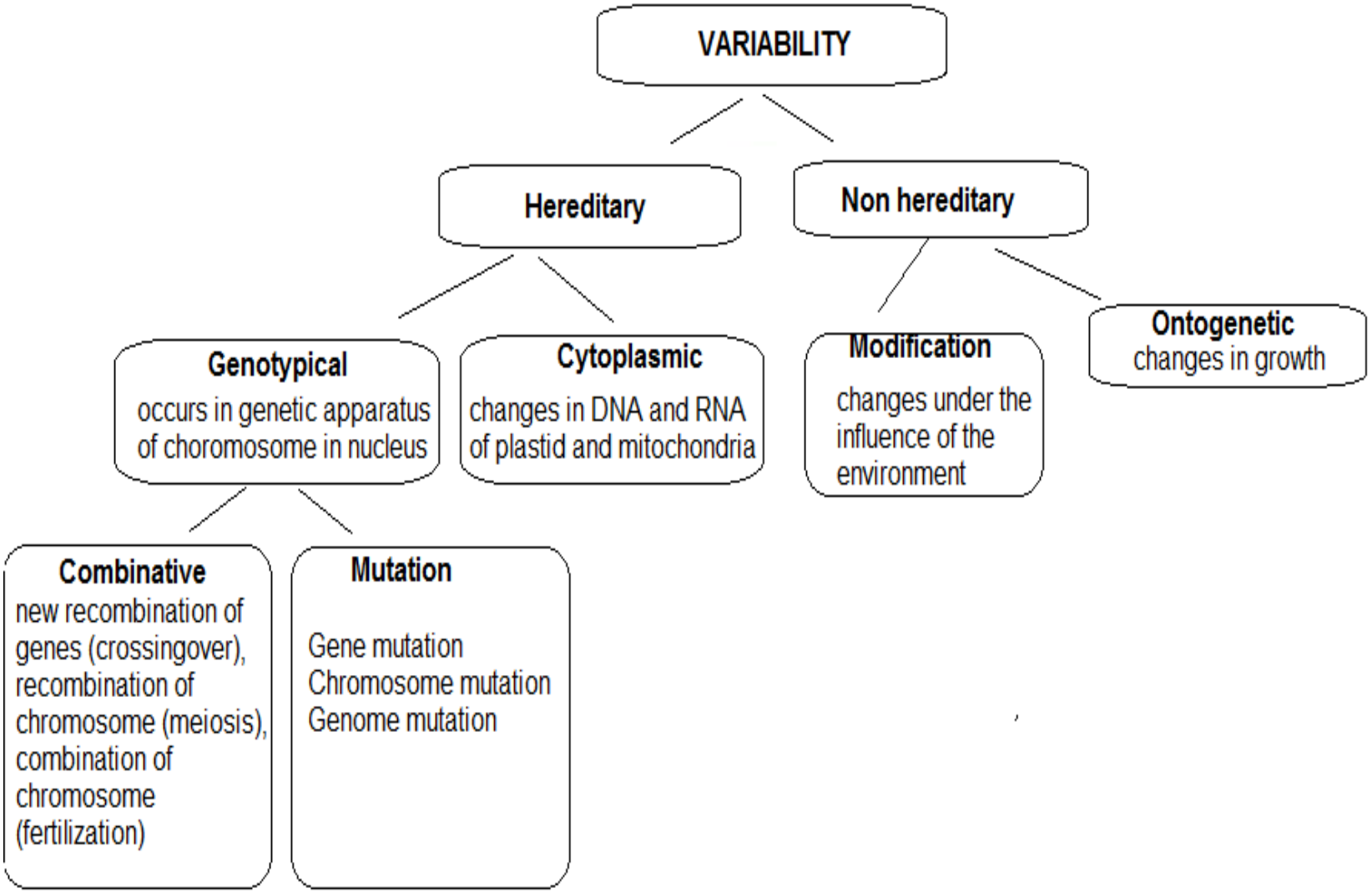
Lecture plan:

1. General characteristics of mutations
2. Classification of mutations
3. Gene mutations
4. Chromosome mutations
5. Genome mutations
6. Polyploidy in humans
7. Epimutation

Variability



Mutation

- The theory of mutations is one of the foundations of genetics. Its main provisions were developed by the Dutch scientist Hugo de Fries in the early XX century.

Mutation

- Mutation is the alteration in DNA sequences that result in changes in the structure of a gene.
- Causes of mutations:

1. May be caused an error during DNA replication (especially during meiosis);
2. May be caused by exposure to radiation or carcinogens;
3. May be caused an error during forms of DNA repair;
4. May be result of inversion, insertion or deletion of segments of DNA).

Classification of mutations

1. **Mutations at the place of their occurrence:**

Generative - arising in sex cells.

Somatic - arising in somatic cells.

2. **Mutations by adaptive value:**

Useful - increasing the viability of individuals.

Harmful:

Lethal - causing the death of individuals;

Semi-lethal - reducing the viability of an individual

Neutral - not affecting the viability of individuals.

3. **Mutations by the nature of the manifestation:**

Dominant, which can make the owners of these mutations non-viable and cause their death in the early stages of ontogenesis;

Recessive mutations are not manifested in heterozygotes, therefore, they persist for a long time in the population and form a reserve of hereditary variability.

Classification of mutations

4. **Mutations according to the degree of phenotypic manifestation:**

Large - clearly visible mutations that strongly change the phenotype;

Small - mutations that practically do not give a phenotypic manifestation.

5. **Mutations for changing the state of a gene:**

Straight lines - the transition of the gene from the wild type to a new state;

Reverse is the transition of a gene from a mutant state to a wild type.

6. **Mutations by the nature of their appearance:**

Spontaneous - mutations that occur naturally under the influence of environmental factors;

Induced - mutations artificially caused by mutagenic factors.

Classification of mutations

7. **Mutations by the nature of the change in genotype:**

Gene - mutations expressed in changes in the structure of individual sections of DNA;

Chromosome - mutations characterized by a change in the structure of individual chromosomes;

Genome - mutations characterized by a change in the number of chromosomes

8. **Mutations at the place of their manifestation:**

Nuclear:

Chromosomal

Point-to-point - A gene mutation that represents a replacement (as a result of a transition or transversion), insertion or loss of one nucleotide.

Genome

Cytoplasmic - mutations associated with mutations of non-nuclear genes found in mitochondrial DNA and DNA of plastids - chloroplasts.

Classification of mutations

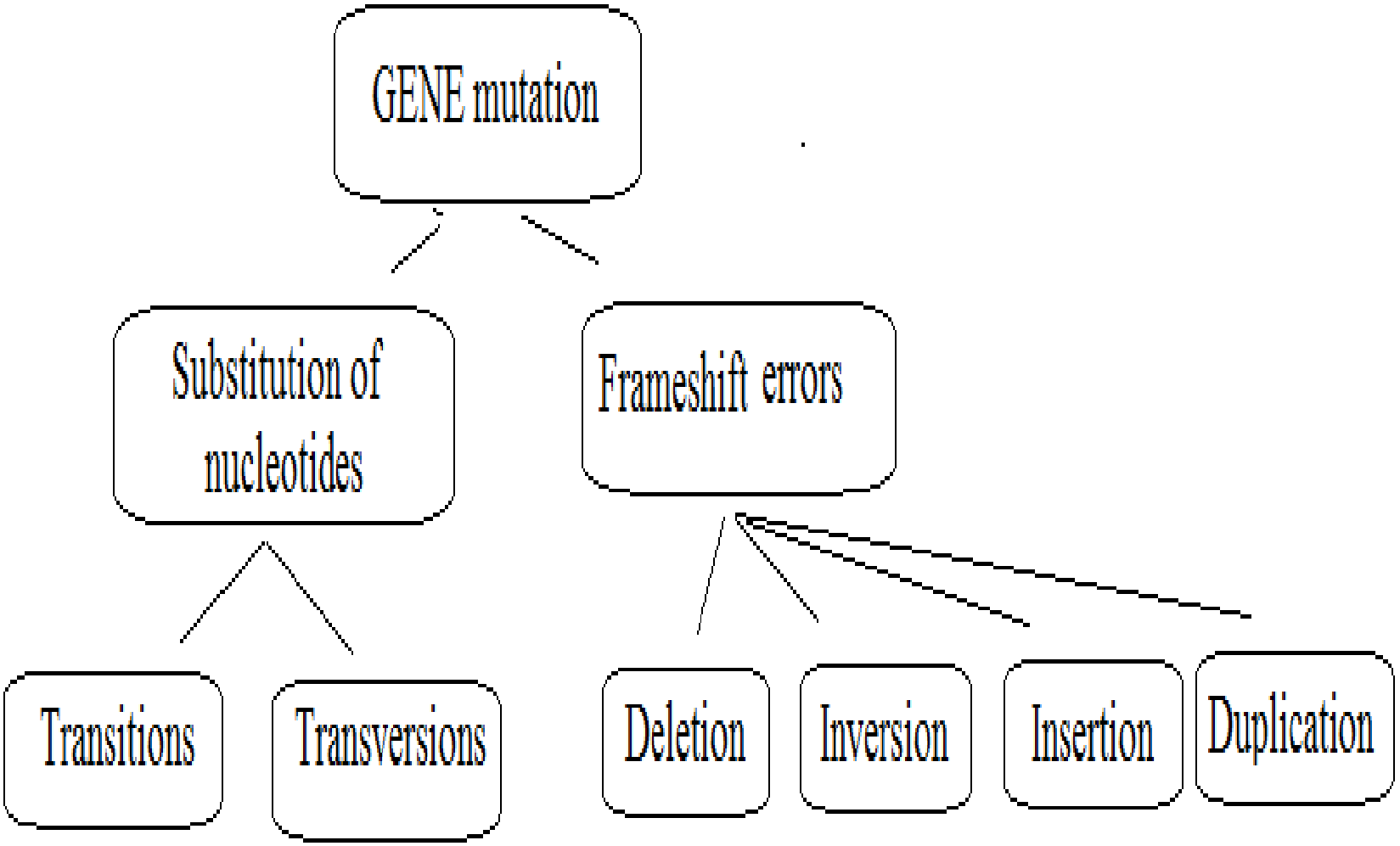
- In the modern educational literature, a more formal classification is used, based on the nature of changes in the structure of individual genes, chromosomes, and the genome as a whole. According to this classification, the following types of mutations are distinguished:

  - Gene;

  - Chromosome;

  - Genome.

Gene mutation



Gene mutation

- **Gene mutation** is alteration in the DNA sequence that makes up a gene (if only a single nucleotide is affected, they are called **point mutations**).
- Gene mutations include:

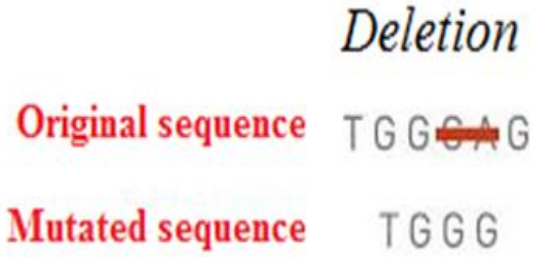
Insertions add one or more nucleotides into the DNA.

Gene mutation

- Duplication is duplication of a DNA segment from one nucleotide to whole genes.

Gene mutation

- **Deletions** remove one or more nucleotides from the DNA.



- **Substitution** mutations, often caused by chemicals or malfunction of DNA replication, exchange a single nucleotide for another. These changes are classified as transitions or transversions.

Gene mutation

TRANSITION

PURINE → PURINE

$A \rightarrow G$

$G \rightarrow A$

PYRIMIDINE → PYRIMIDINE

$C \rightarrow T$

$T \rightarrow C$

TRANSVERSION

PURINE → PYRIMIDINE

$A \rightarrow T;\ A \rightarrow C$

$G \rightarrow T;\ G \rightarrow C$

PYRIMIDINE → PURINE

$T \rightarrow A;\ T \rightarrow G$

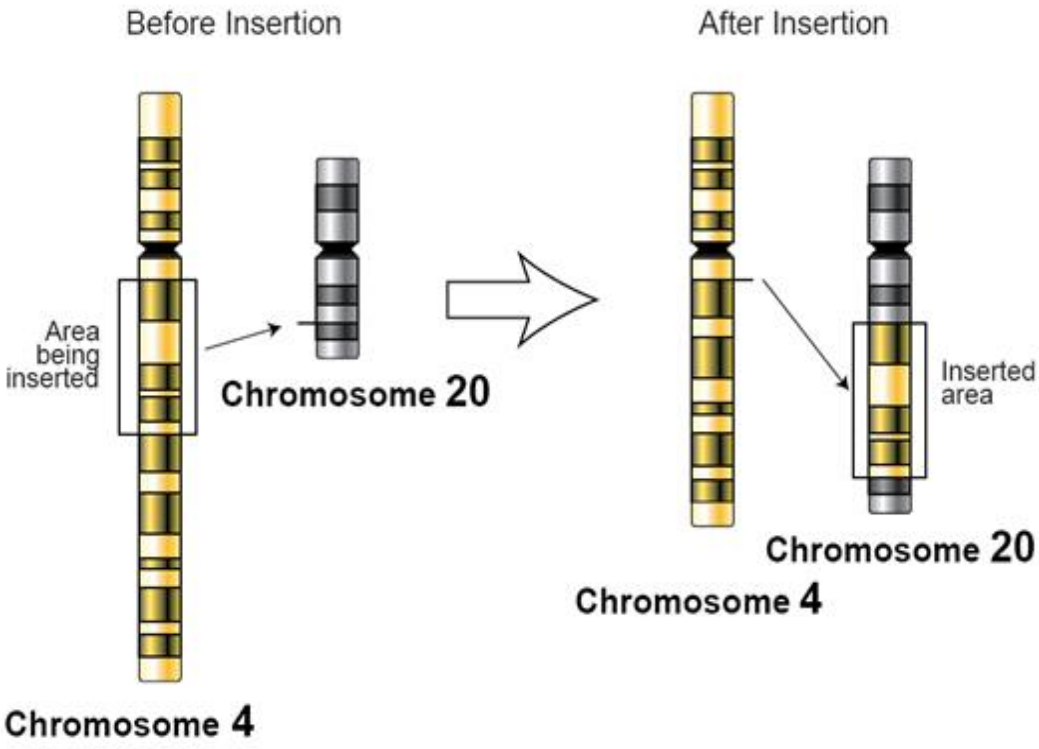
$C \rightarrow A;\ C \rightarrow G$

Gene mutation

- **Inversion** occurs due to the rotation of the DNA region 180° within a one gene.

Gene mutation

- **Insertion** is a genetic mutation in which another DNA sequence is inserted into the DNA sequence. The minimum size of such an insert is one nucleotide.



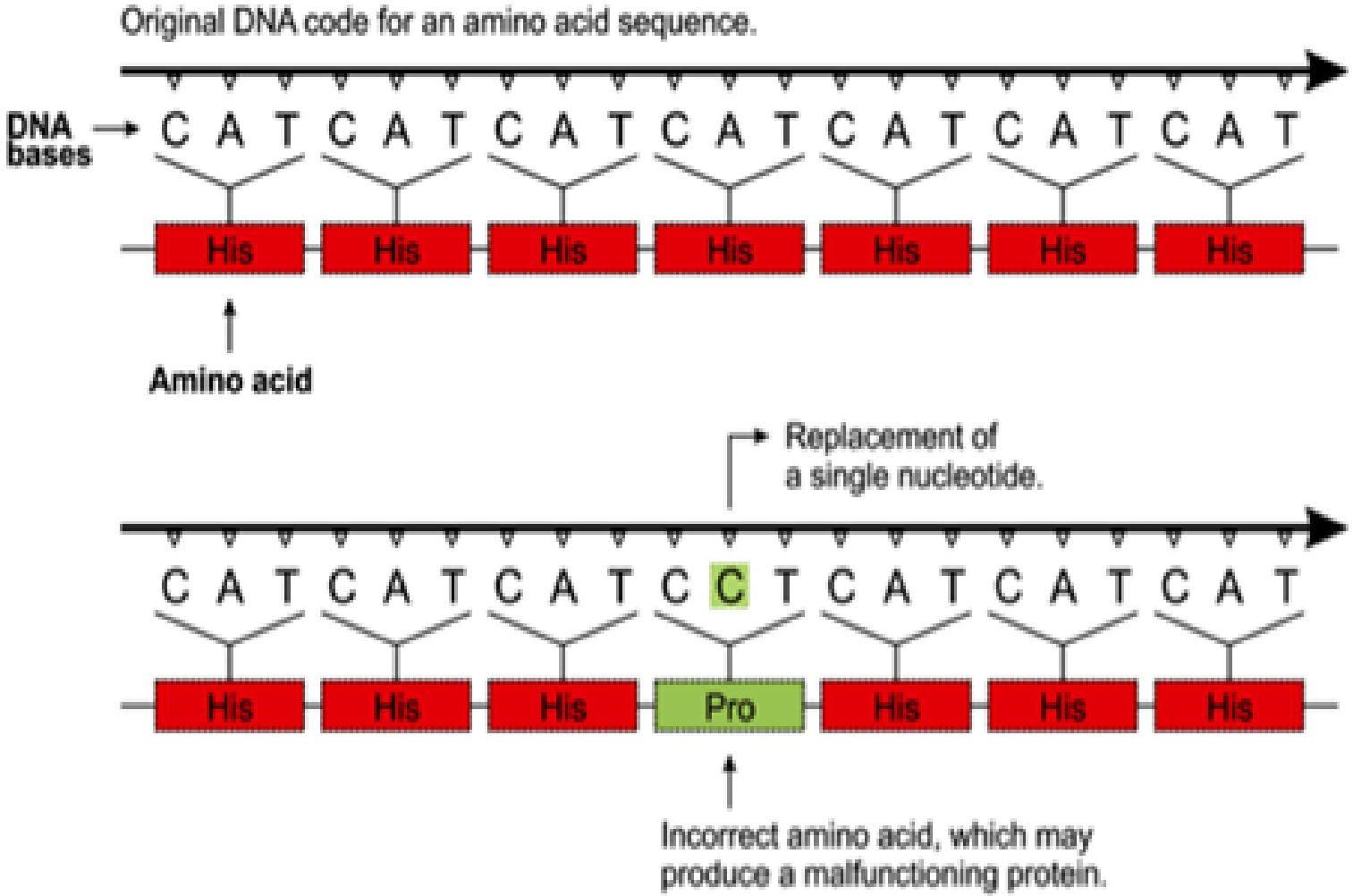
Gene mutation

- Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:
- **Missense mutation:** a missense mutation is a point mutation in which a single nucleotide change results in a codon that codes for a different amino acid.

- In a conservative missense mutation, an amino acid change. However, the properties of the amino acid remain the same (e.g., hydrophobic, hydrophilic, etc.). For example, hemoglobin hikari can bind oxygen in the same way as regular hemoglobin.

- Non-conservative missense mutation, result in an amino acid change that has different properties than the wild type. The protein may lose its function, which can result in a disease in the organism. For example, Hemoglobin S also binds oxygen, but not as effective as regular hemoglobin.

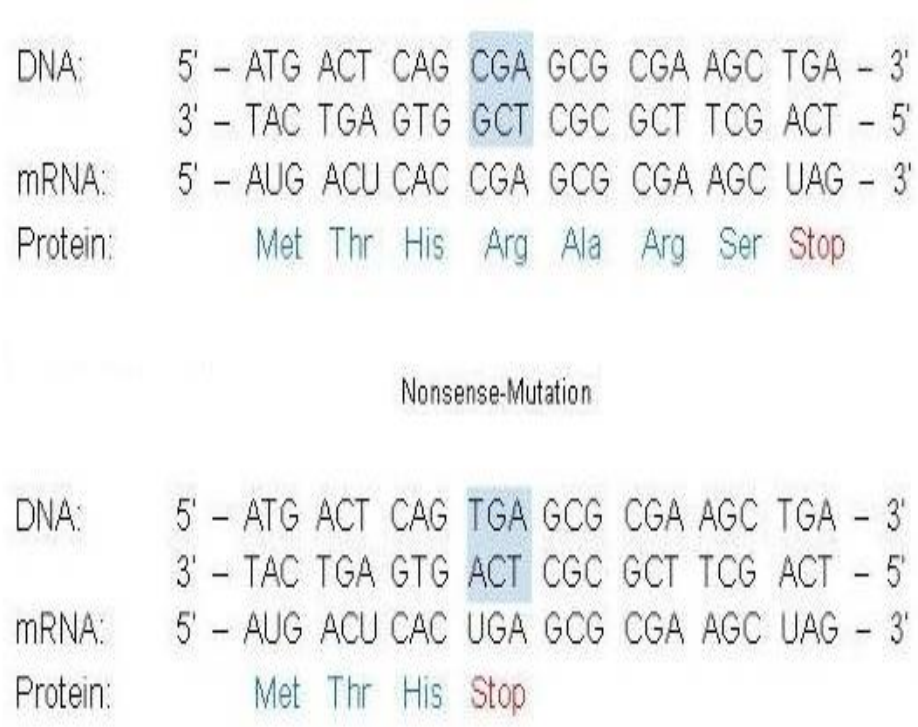
Missense mutation



Gene mutation

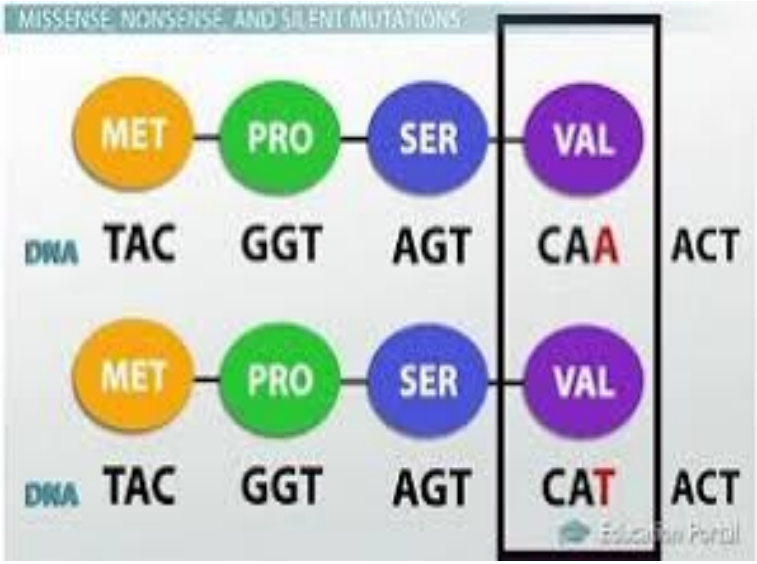
- **A nonsense mutation** is a genetic mutation in a DNA sequence that leads to the appearance of a stop codon (UAA, UAG, UGA), resulting in premature termination of the synthesis of the desired protein.
- Diseases caused by nonsense mutations:

- Cystic fibrosis (caused by mutations in the regulatory transmembrane protein gene);
- Duchene myodystrophy (mutation in the gene that encodes the dystrophin protein)
- Beta thalassemia (β-globin)

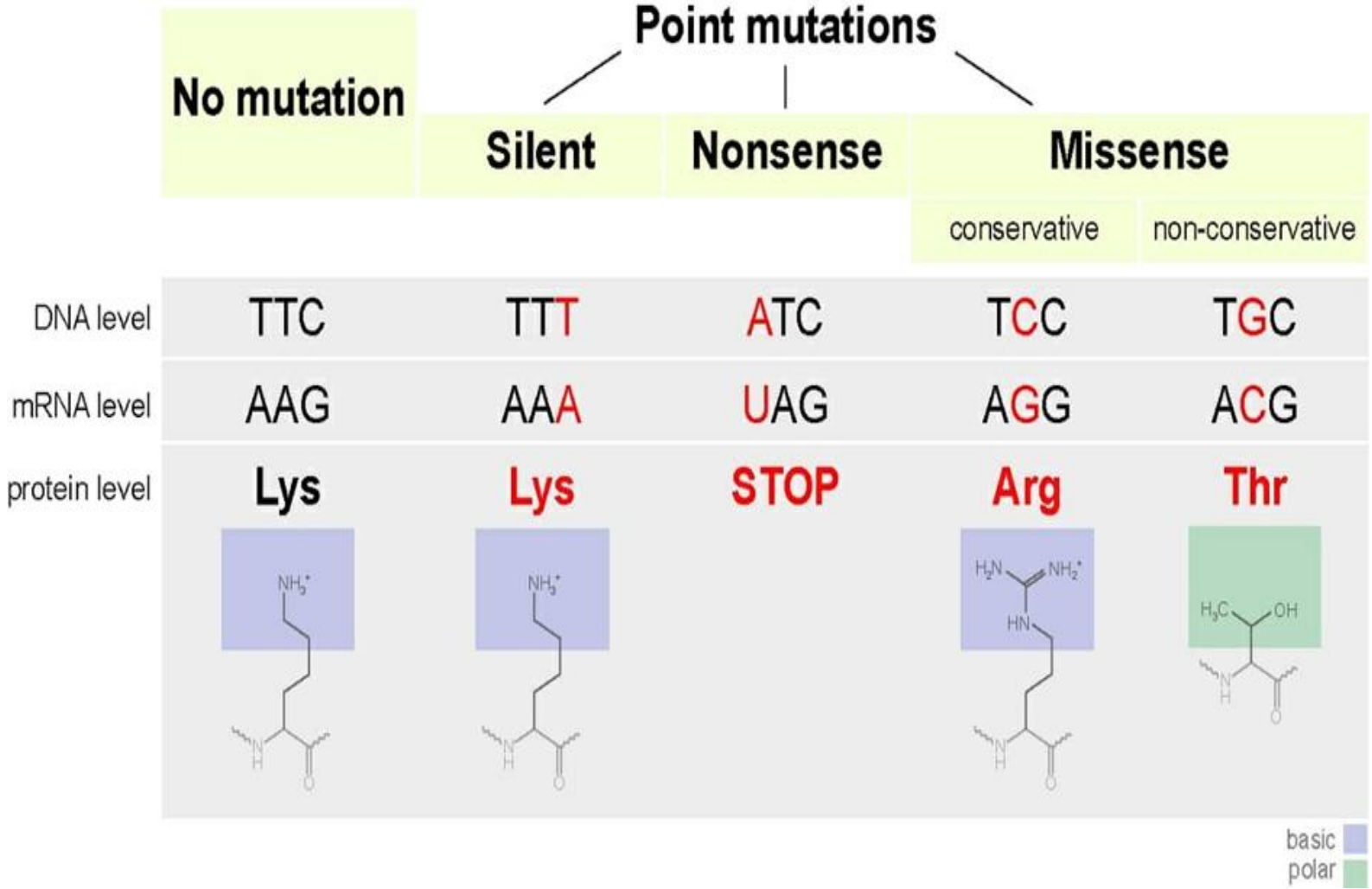


Gene mutation

- **Silent mutations** are mutations in DNA that do not have an observable effect on the organism's phenotype. They are a specific type of neutral mutation. For example, the amino acid valine is encoded by triplets - **CAA, CAG, CAC** and **CAT**. In these triplets in the 3rd position, the replacement of nucleotides (A, G, C, T) does not change the meaning of the codon.



Gene mutation

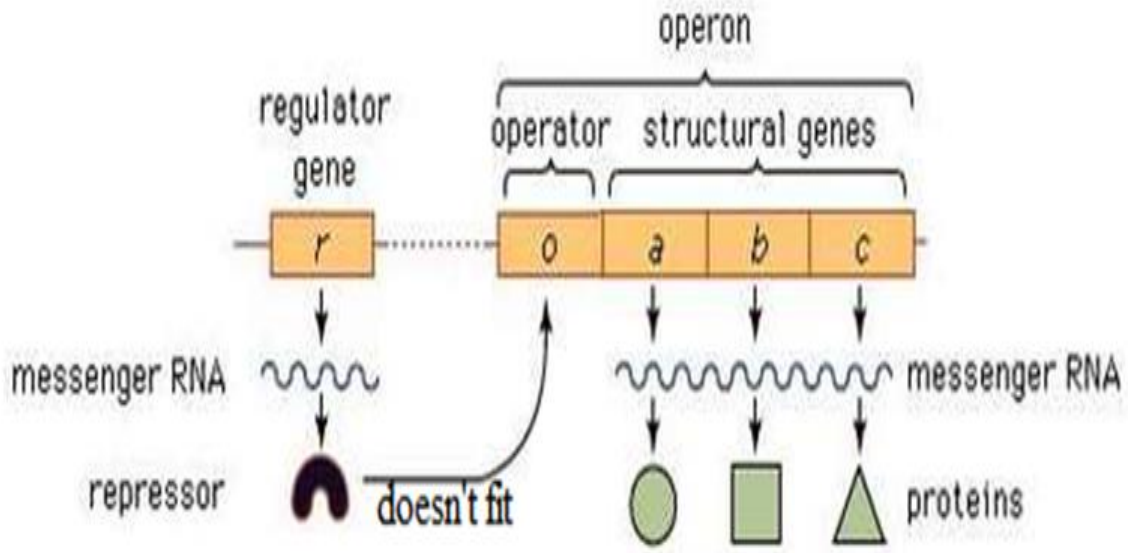


Gene mutation

- **Regulatory mutation** - changes in the 5'- or 3'- transcribed but on untranslated regions of the gene. Such a mutation disrupts gene expression.
- Mutations in the regulatory gene or operator gene:

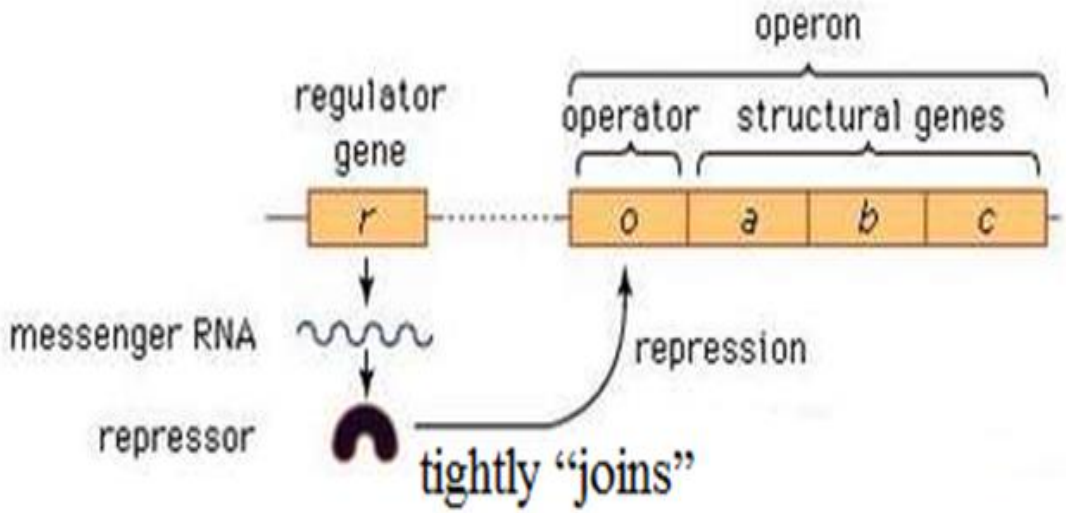
Gene mutation

1) The repressor protein "does not fit" to the operator gene ("the key does not enter the keyhole") - structural genes work constantly (proteins are synthesized all the time).



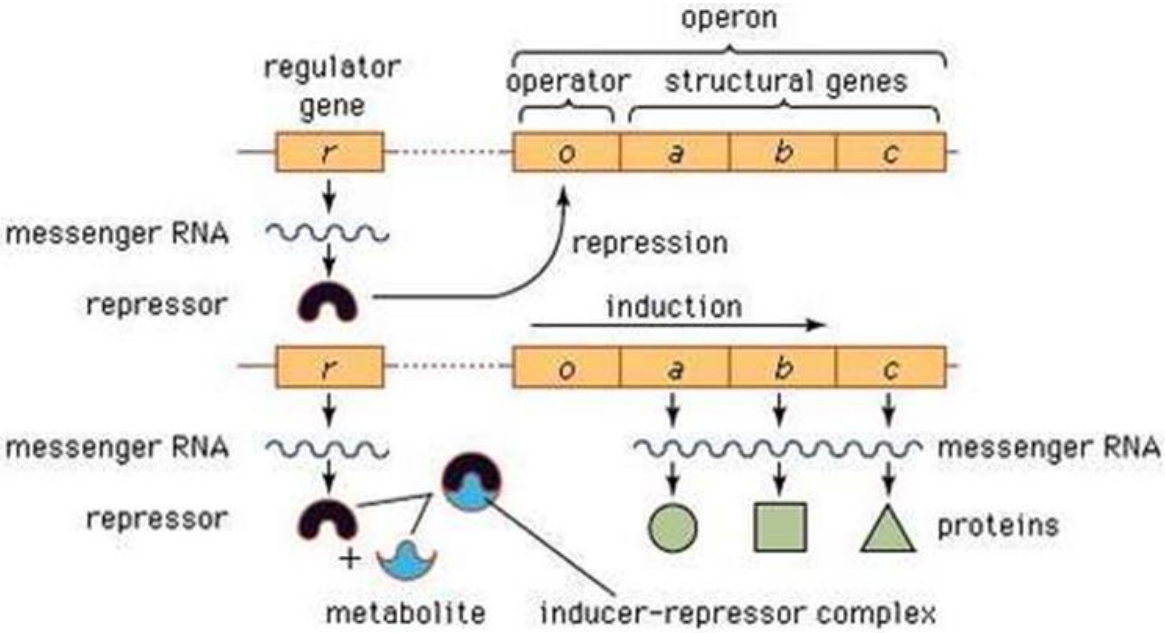
Gene mutation

2) The repressor protein tightly "joins" to the operator gene and is not removed by the inducer ("the key does not come out of the keyhole") - structural genes do not work constantly, and the proteins encoded in this transcript are not synthesized.



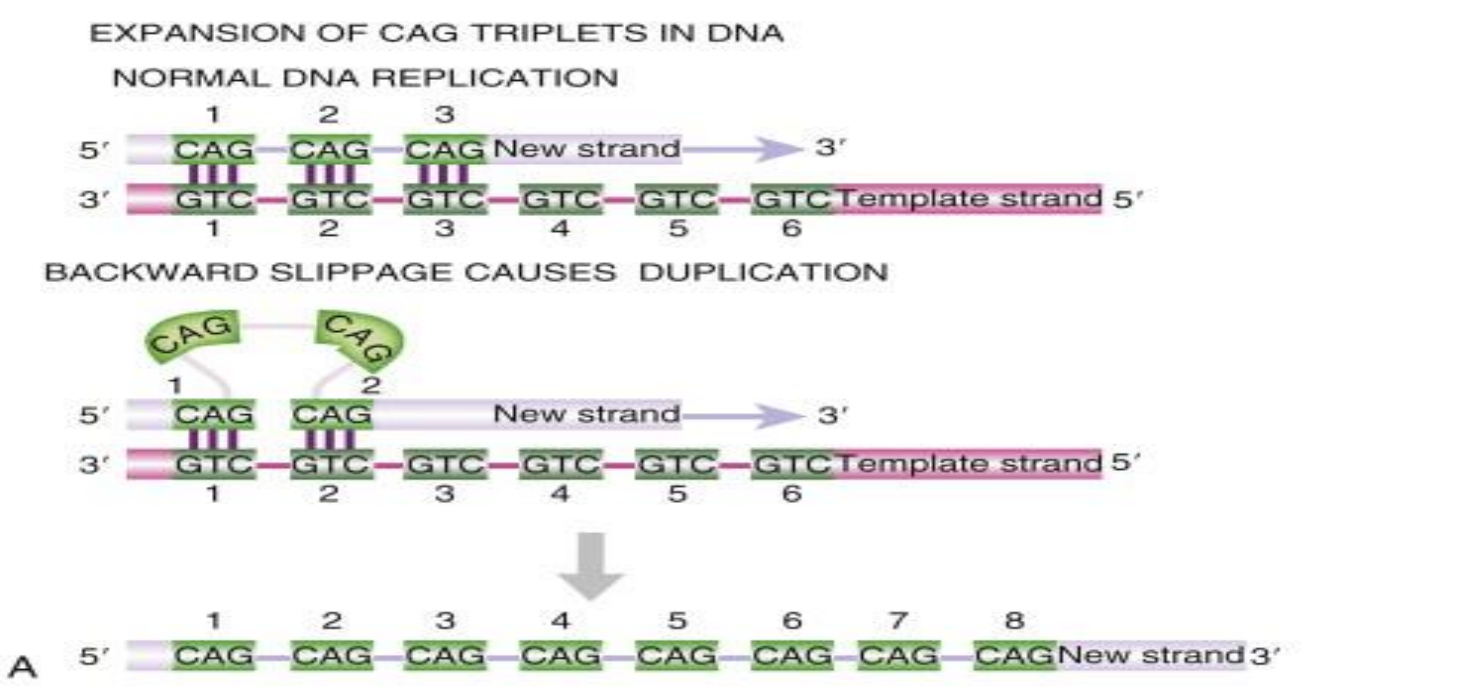
Gene mutation

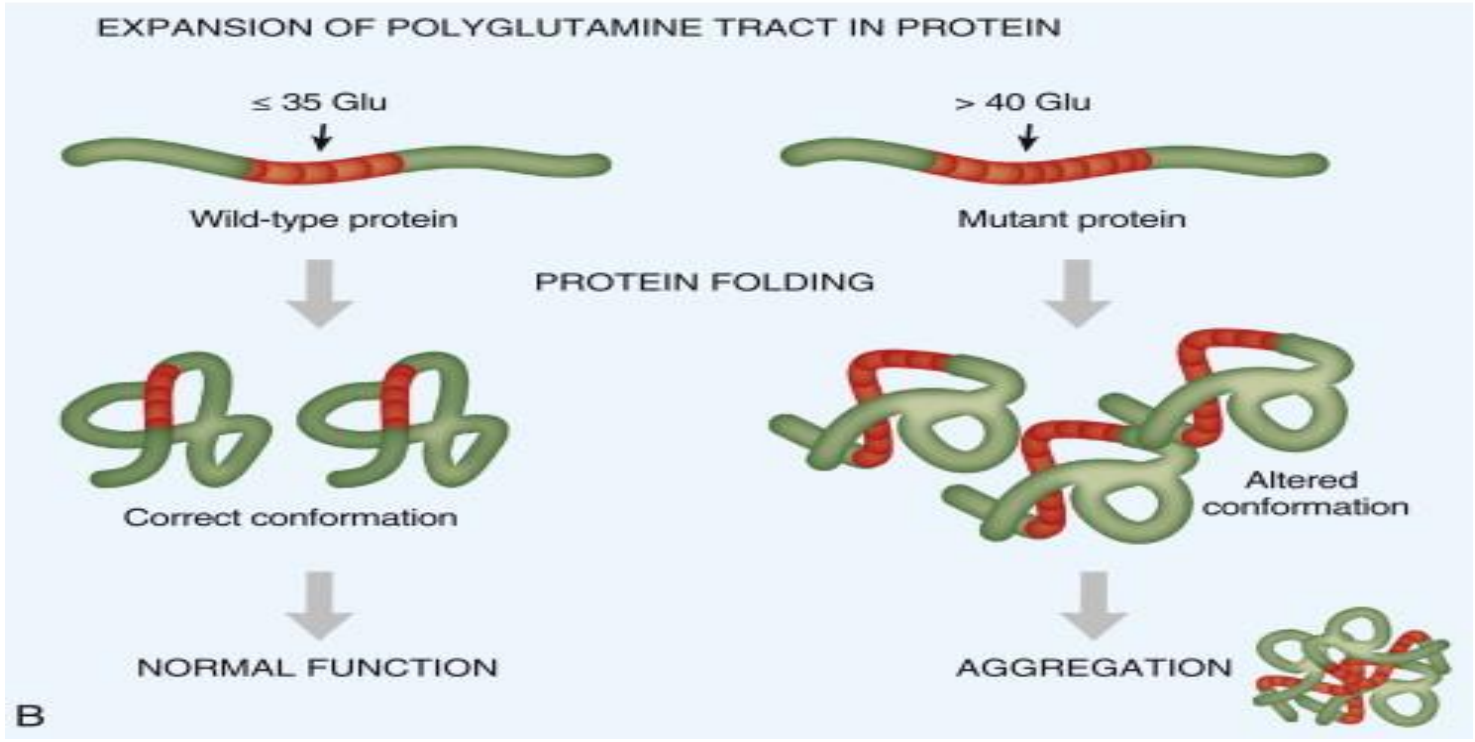
3) Violation of the alternation of repression and induction - in the absence of an inducer, a specific protein is synthesized, and if it present, protein is not synthesized.



Gene mutation

- **Dynamic mutations, or trinucleotide repeat expansion** are due to an increase in the number of trinucleotide repeats in functionally significant parts of the gene. Such mutations can lead to inhibition or blockade of transcription, the acquisition by protein molecules of properties that violate their normal metabolism.


EXPANSION OF CAG TRIPLETS IN DNA
NORMAL DNA REPLICATION
1 2 3
5′ CAG CAG CAG New strand 3′
3′ GTC GTC GTC GTC GTC GTC Template strand 5′
1 2 3 4 5 6
BACKWARD SLIPPAGE CAUSES DUPLICATION
CAG CAG
1 2
5′ CAG CAG New strand 3′
3′ GTC GTC GTC GTC GTC GTC Template strand 5′
1 2 3 4 5 6
1 2 3 4 5 6 7 8
5′ CAG CAG CAG CAG CAG CAG CAG CAG New strand 3′
A


EXPANSION OF POLYGLUTAMINE TRACT IN PROTEIN
≤ 35 Glu
> 40 Glu
Wild-type protein
Mutant protein
PROTEIN FOLDING
Correct conformation
Altered conformation
NORMAL FUNCTION
AGGREGATION
B

Gene mutation

- A **behaviour mutation** is a genetic mutation that alters genes that control the way in which an organism behaves, causing their behavioural patterns to change.
- Behaviour mutations have important implications on the nature of the evolution of animal behaviour. They can help us understand how different forms of behaviour evolve, especially behaviour which can seem strange or out of place.

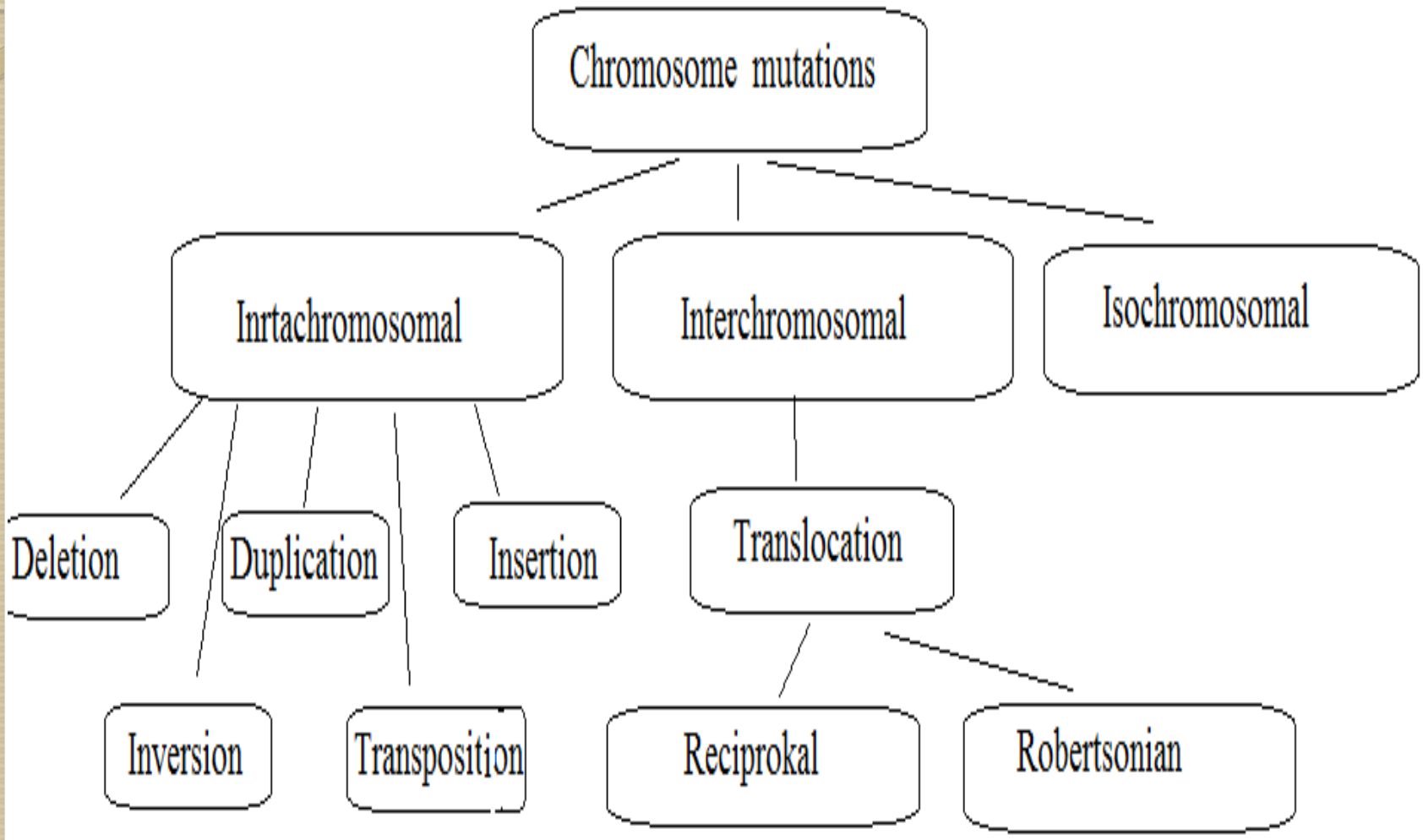
Behaviour mutation

- Aggression is a survival trait that can be favoured by natural selection in nearly any species.
- Neurotransmitters, dophamine and serotonin in particular, play an important role in the regulation of aggressive behaviours. Many studies are focused on genes that change the way neurotransmitters interact with receptors within the organism. For example, when individuals suffer from a mutation that causes them to have low levels of serotonin, there is an observed increase in impulsivity and depression.

Chromosome mutations

- Chromosome mutations, or chromosomal aberrations, are a type of mutation that changes in the structure of a chromosome.
- Unlike a gene mutation which alters a single gene or larger segment of DNA on a chromosome, chromosome mutations change and impact the entire chromosome.
- The main reason for the occurrence of chromosomal rearrangements is the breaks of both strands of the DNA helix within a few base pairs.

Chromosome mutations



Chromosome mutations

Chromosomal aberrations can be intrachromosomal, interchromosomal, and isochromosomal.

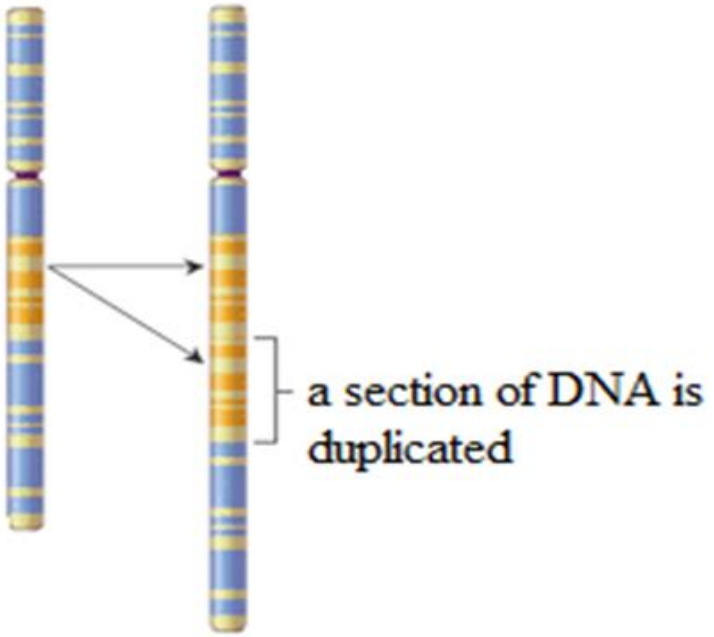
- **Intrachromosomal** include rearrangements within the same chromosome.
- **Interchromosomal** rearrangements occur between non-homologous chromosomes.

Intrachromosomal aberrations

- **Deletions**: a portion of the chromosome is missing or deleted: can cause a violation of embryogenesis and the formation of multiple developmental anomalies.
- When the telomeres of both arms of the chromosome are deleted, a closure of the remaining structure into the ring — ring chromosomes — is often observed.

Intrachromosomal aberrations

- **Duplications**: a portion of the chromosome is duplicated, resulting in extra genetic material.

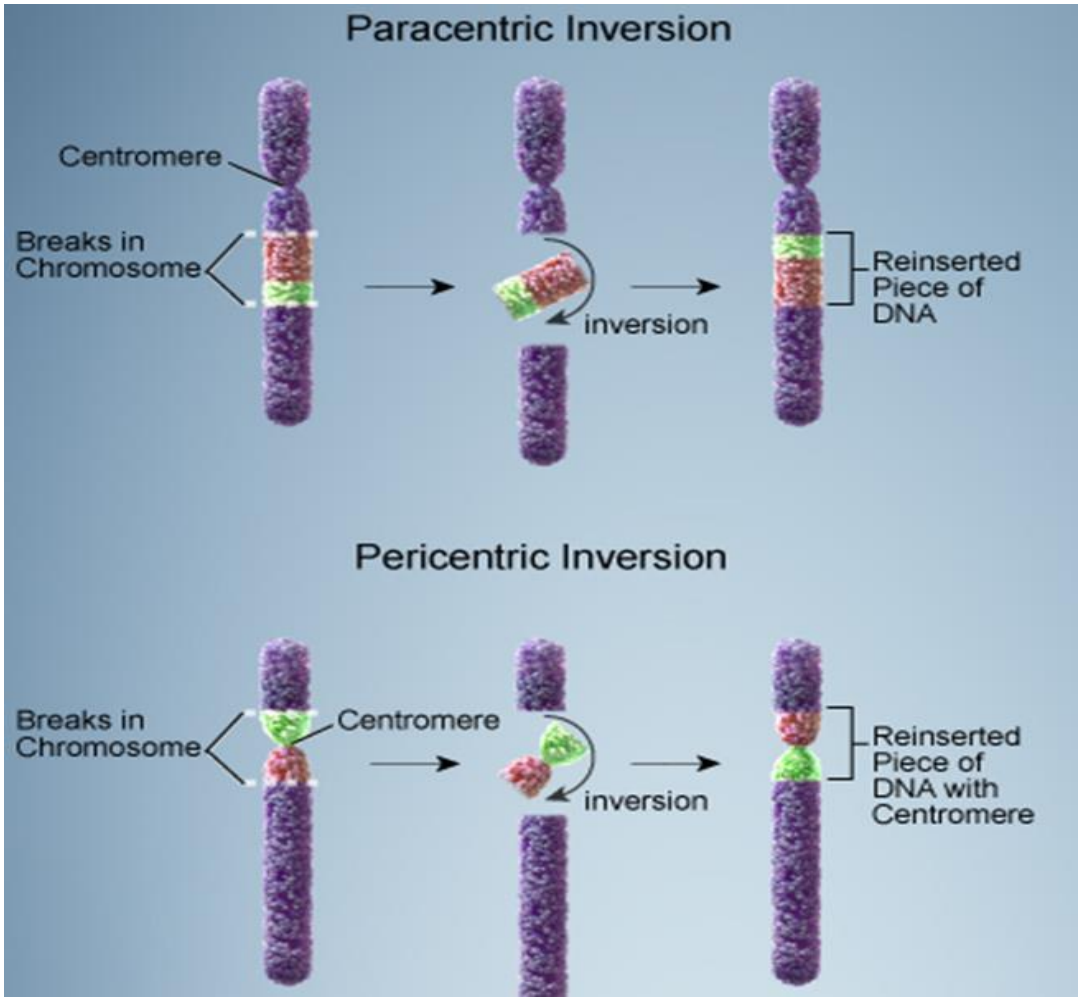


Chromosome mutations

- **Inversion** is a chromosome rearrangement in which a single chromosome undergoes breakage and rearrangement within itself.
- There are 2 types of inversion: Paracentric and Pericentric inversions.

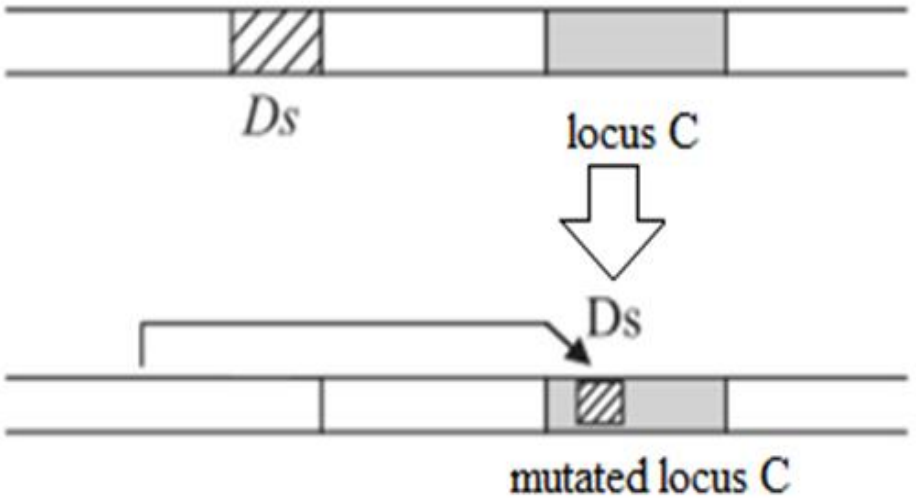
Intrachromosomal aberrations

- Paracentric inversions do not include the centromere and both breaks occur in one arm of the chromosome.
- Pericentric inversions include the centromere and there are break points in each arm.



Intrachromosomal aberrations

- **Transposition** - attachment of a fragment to its own chromosome, but in a different place.

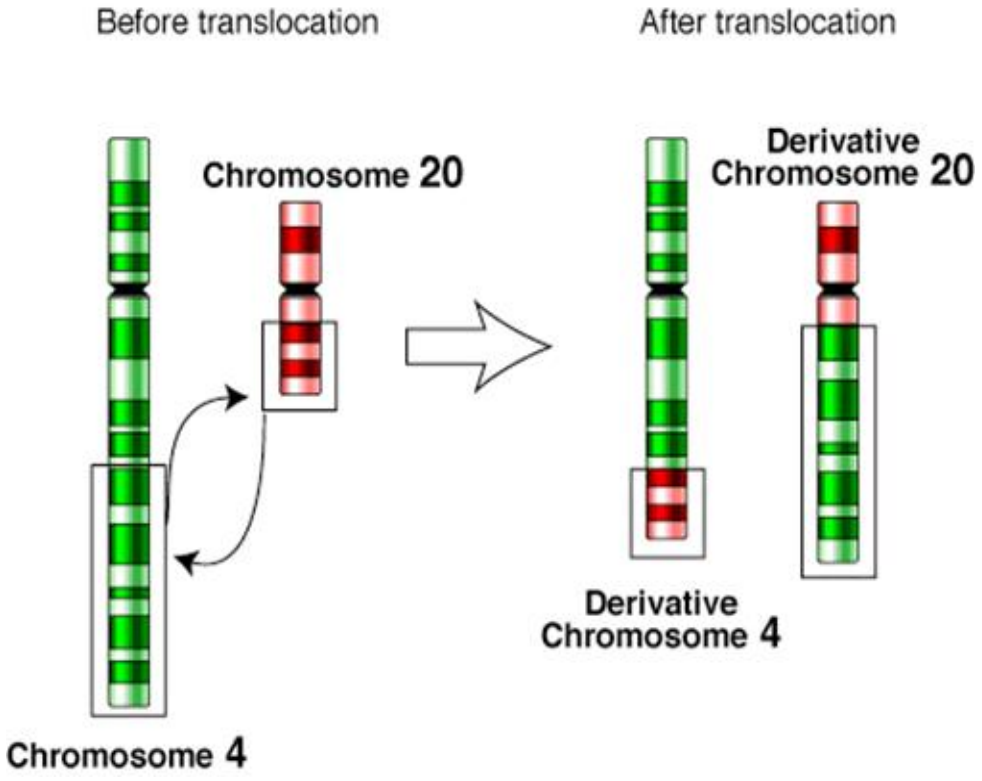


Interchromosomal aberrations

- **Interchromosomal aberrations** occur between non-homologous chromosomes.
- **Translocations**: A portion of one chromosome is transferred to another chromosome.
- There are three main types of translocations: Reciprocal, insertion and Robertson.

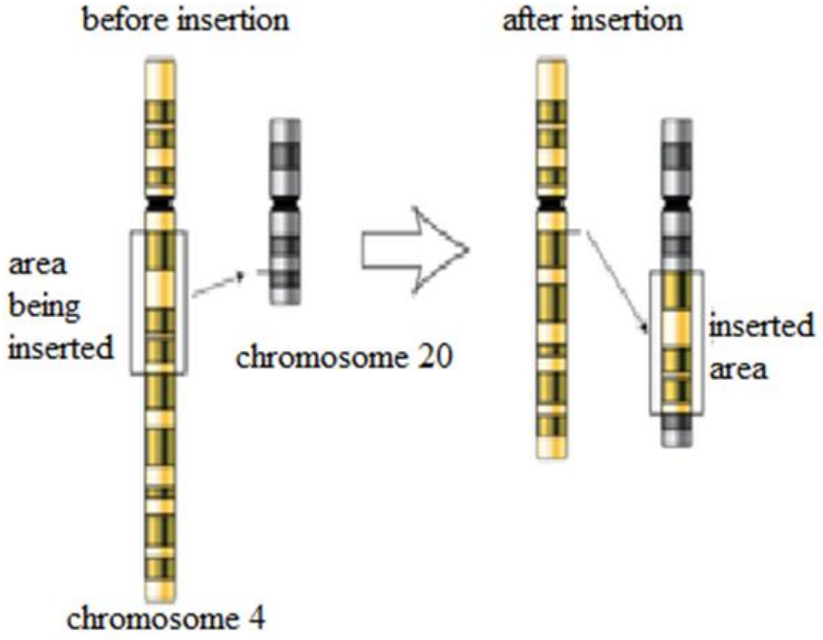
Interchromosomal aberrations

- Reciprocal translocation: segments from two different chromosomes have been exchanged.



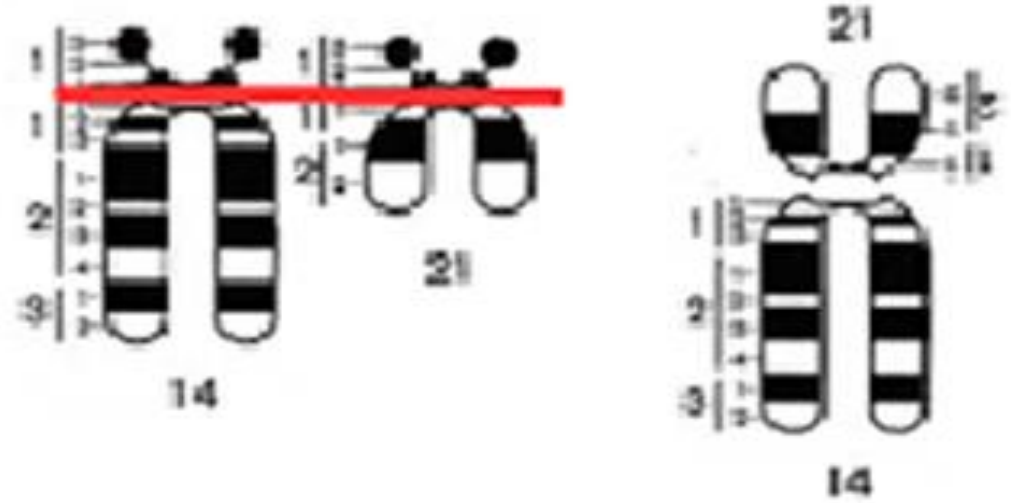
Interchromosomal aberrations

- Insertions is the addition of one or more nucleotide base pairs from one chromosome into a DNA sequence of another chromosome.



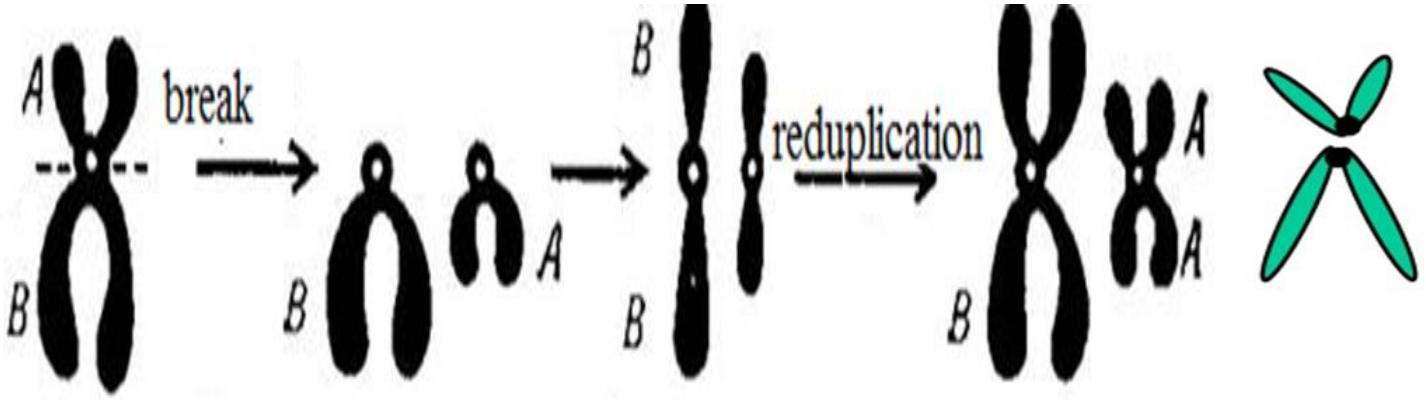
Interchromosomal abberations

- Robertson translocation when two acrocentric chromosomes are connected by their centromere regions with the loss of short shoulders.



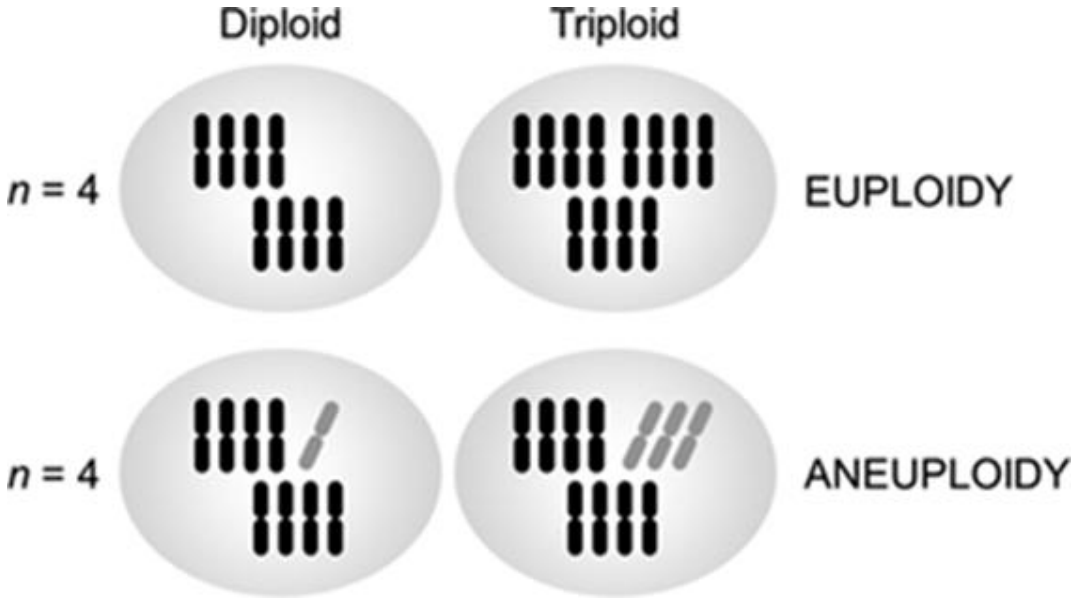
Isochromosomal aberrations

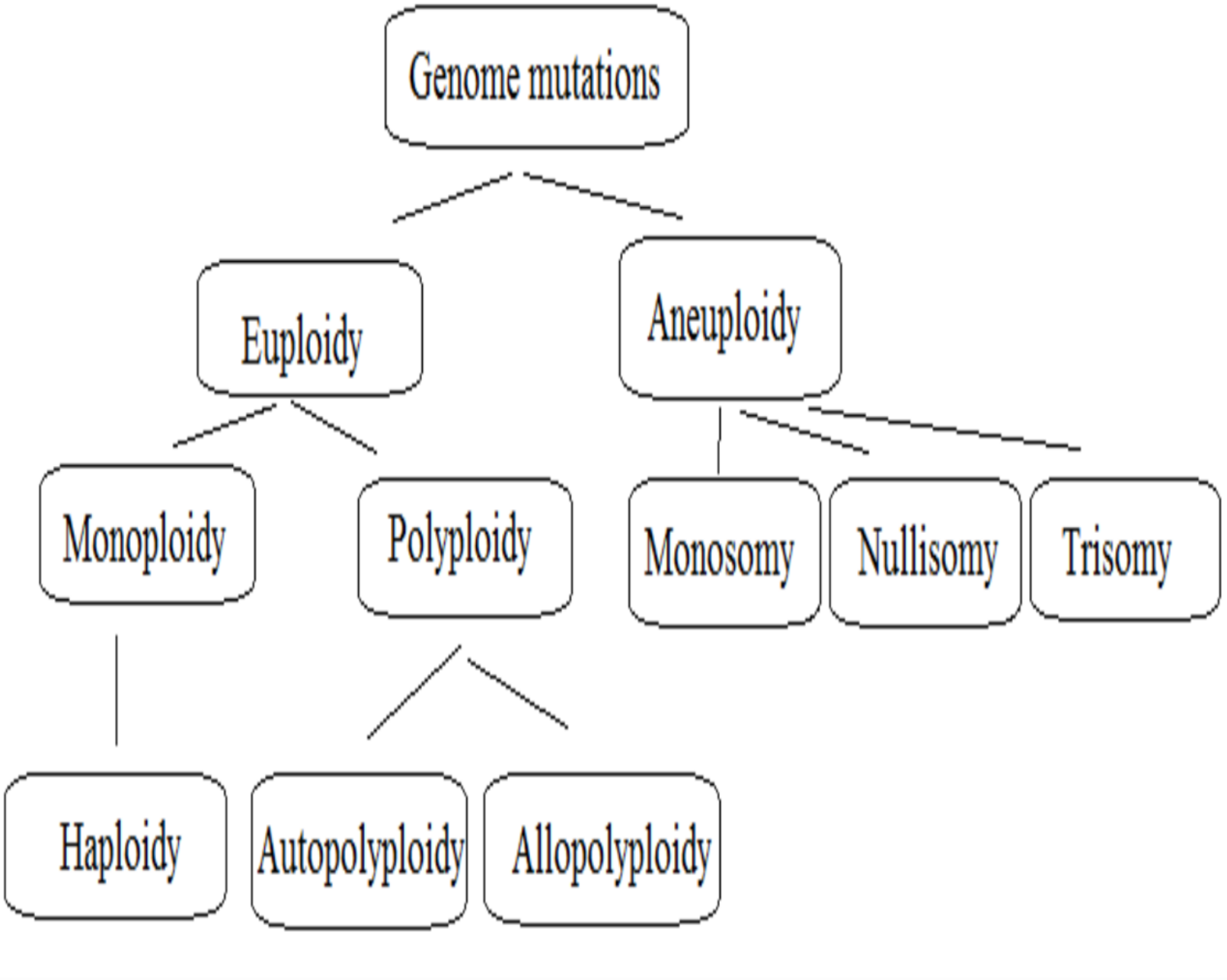
- Isochromosomal aberrations is a structural abnormality in which the arms of the chromosome are mirror images of each other. The chromosome consists of two copies of either the long (q) arm or the short (p) arm because isochromosome formation is equivalent to a simultaneous duplication and deletion of genetic material.



Genome mutations

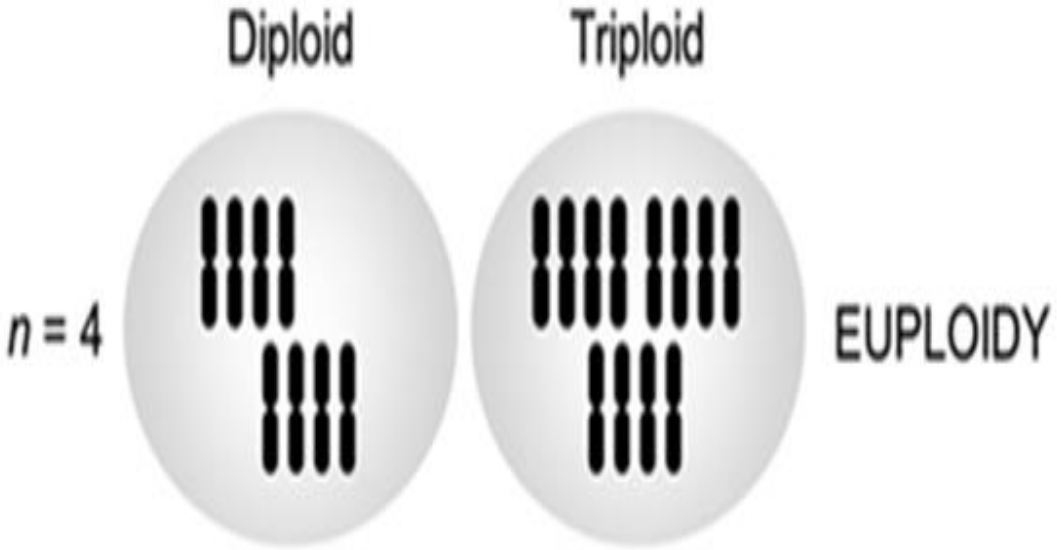
- **Genome mutations** are changes in the number of chromosomes.
- Genome mutation is greater or smaller number of chromosome (aneuploidy), or one or more than one complete set of chromosomes (euploidy).




Genome mutations
Euploidy
Aneuploidy
Monoploidy
Polyploidy
Monosomy
Nullisomy
Trisomy
Haploidy
Autopolyploidy
Allopolyploidy

Genome mutations

- Euploidy is the presence of chromosome number which is the multiple of the basic chromosome set. An organism with the basic chromosome number 7, may have euploids with chromosome number 7, 14, 21, 28, 35, 42.



Genome mutations

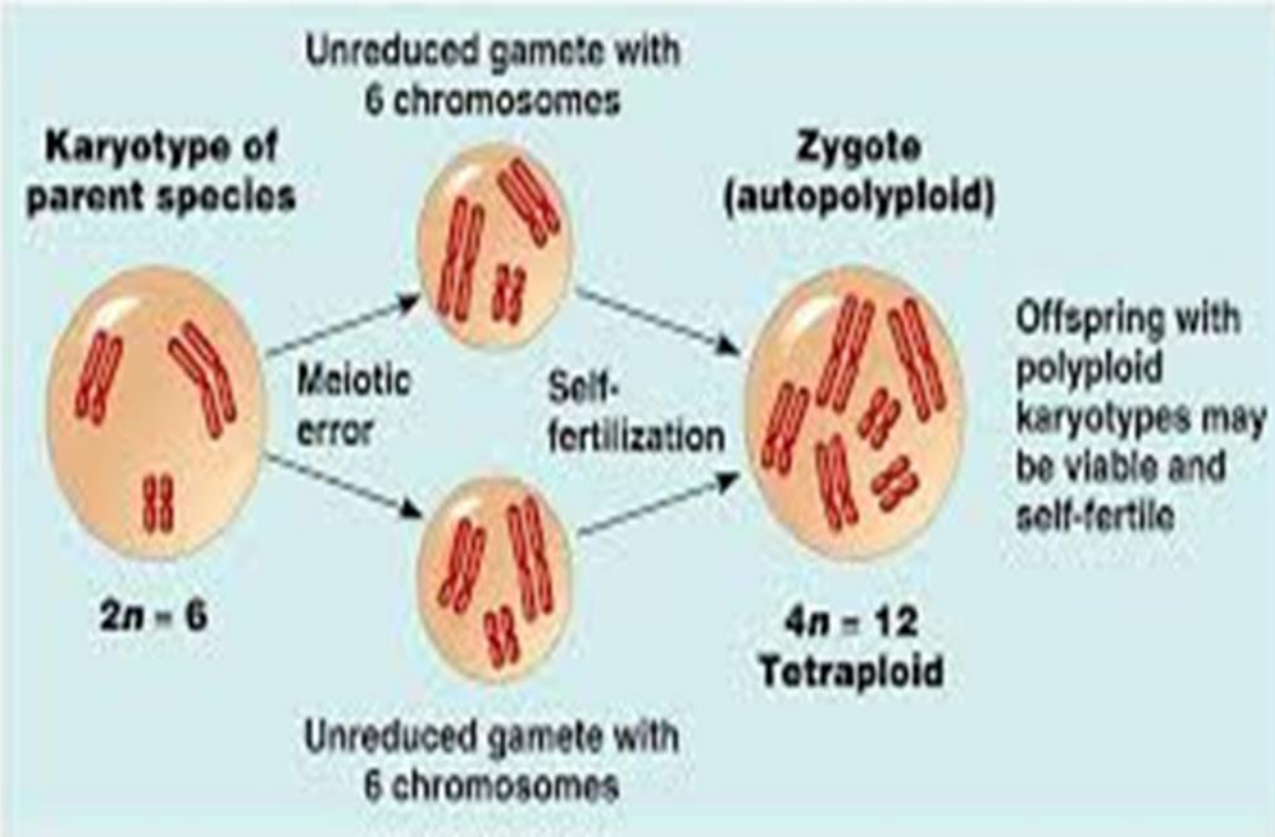
- **Monoploidy** is state of having a single set of chromosomes and is represented by 1n.
- Haploidy is a mutation in the form of a decrease in the entire set of chromosomes to a haploid set. It is found mainly in plants. For mammals and human is a lethal.

Genome mutations

- **Polyploidy** is the condition in which a normally diploid cell or organism having one or more additional sets of chromosomes.
- Polyploidy arises as the result of total nondisjunction of chromosomes during mitosis or meiosis.

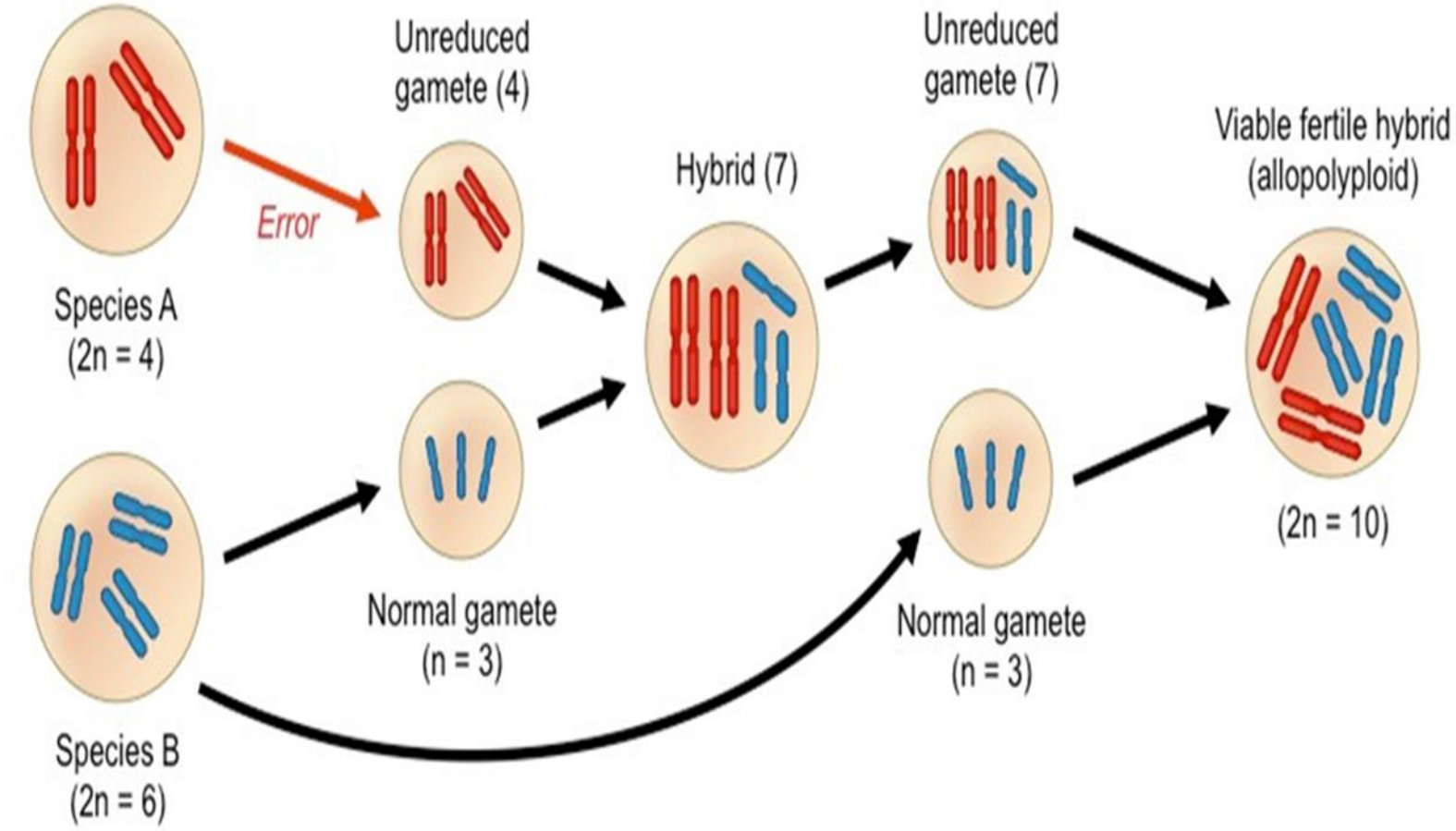
Genome mutations

- *Autopolyploidy* is an increase in the number of haploid sets of chromosomes of the same species. This type of mutation is quite widely spread among plants.



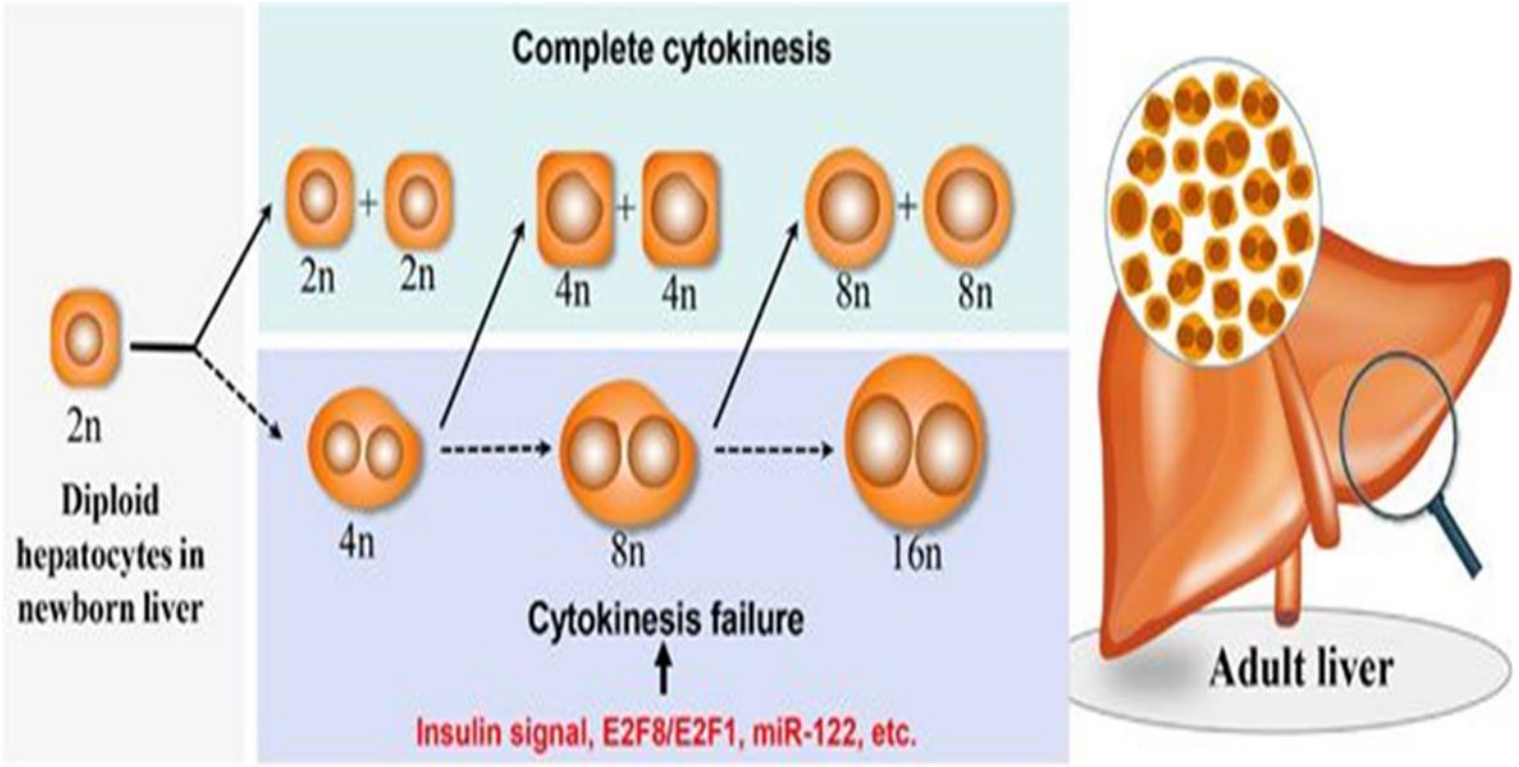
Genome mutations

- Allopolyploidy is a doubling of the set of chromosomes in distant hybrids. For example, if a hybrid has two different AB genomes, then the polyploidy genome will be AABB. Interspecific hybrids are often sterile.



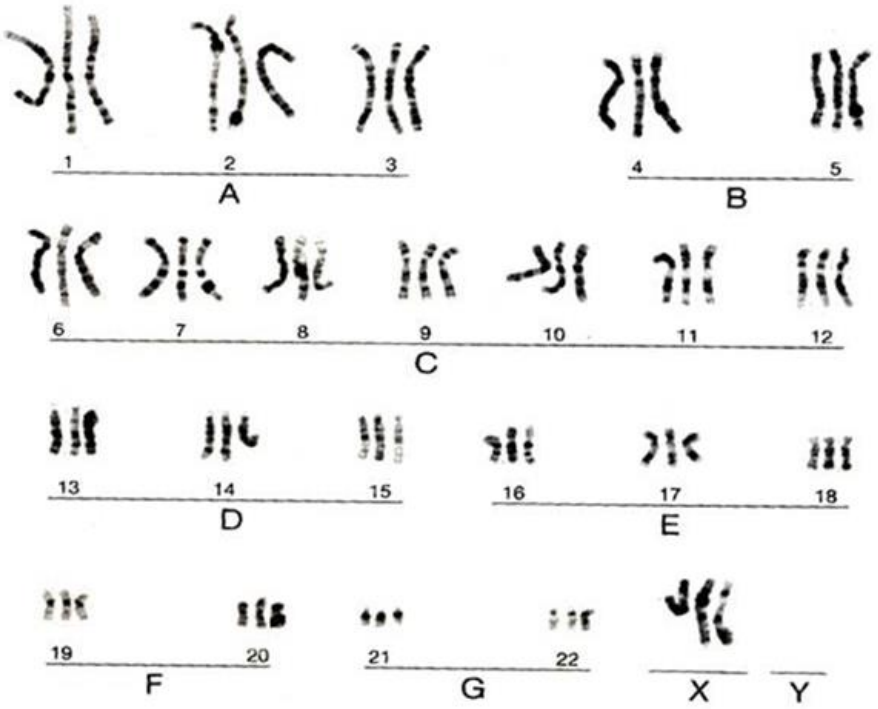
Genome mutations

- **Polyploidy in human**. True polyploidy rarely occurs in humans, although polyploid cells occur in highly differentiated tissue, such as liver parenchyma, heart muscle, placenta and in bone marrow (endomitosis).



Genome mutations

- Polyploidy occurs in humans in the form of triploidy, with 69 chromosomes (sometimes called 69,XXX), and tetraploidy with 92 chromosomes (sometimes called 92,XXXX).

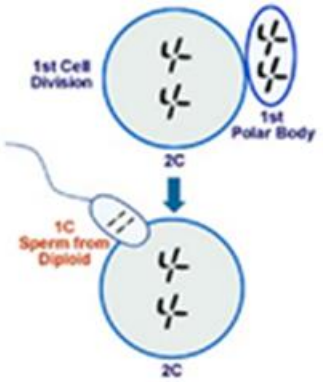


Causes of triploidy

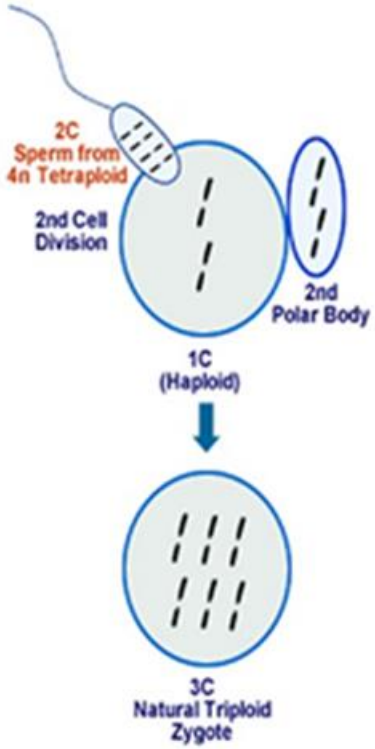
- Triploidy may be the result of either digyny (the extra haploid set is from the mother) or diandry (the extra haploid set is from the father).
- Diandry is mostly caused:

1. by the fertilization of an egg by two sperms;
2. by the fertilization of an egg by a sperm that has an extra set of chromosomes

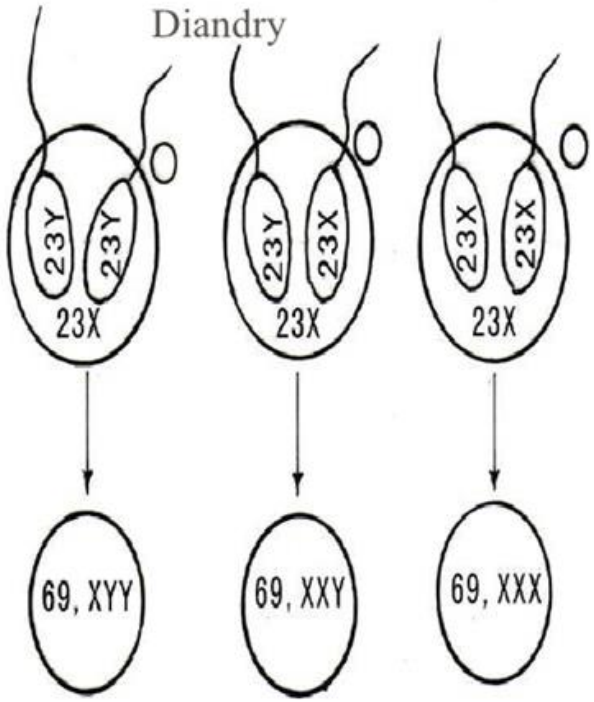
Diandry


1st Cell Division
1st Polar Body
2C
1C Sperm from Diploid
2C

A

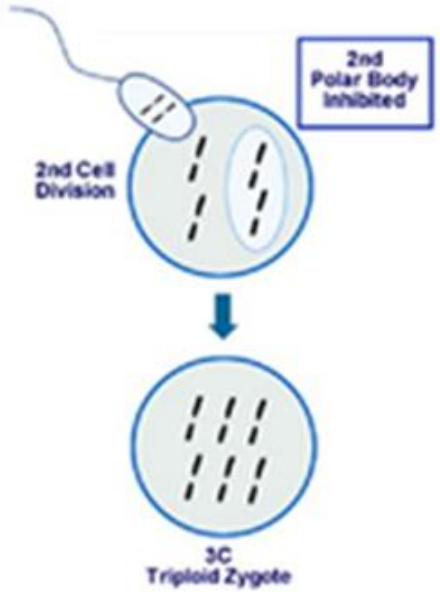

2C Sperm from 4n Tetraploid
2nd Cell Division
2nd Polar Body
1C (Haploid)
3C Natural Triploid Zygote

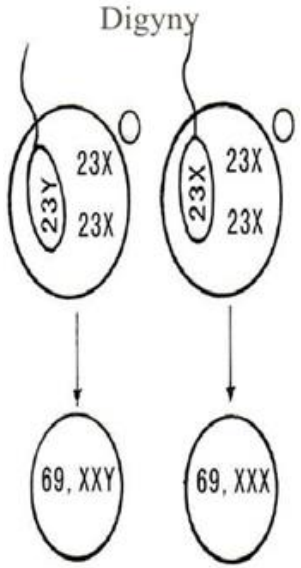
B

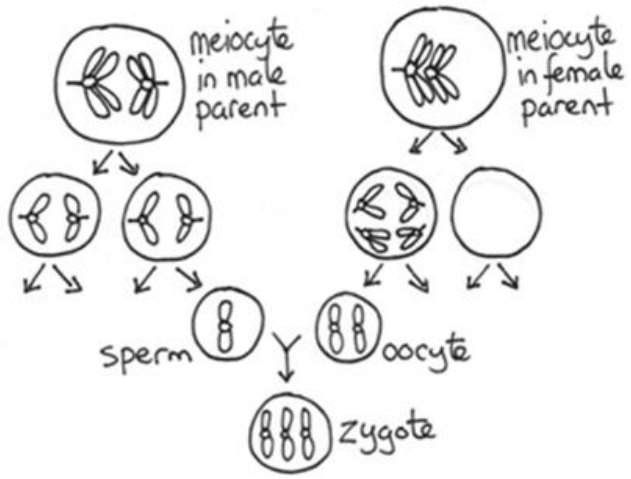

Diandry
23Y
23Y
23X
23Y
23X
23X
23X
23X
23X
69, XYY
69, XXY
69, XXX

Digyny

- Digyny is most commonly caused by either failure of one meiotic division during oogenesis leading to a diploid oocyte or failure to extrude one polar body from the oocyte.

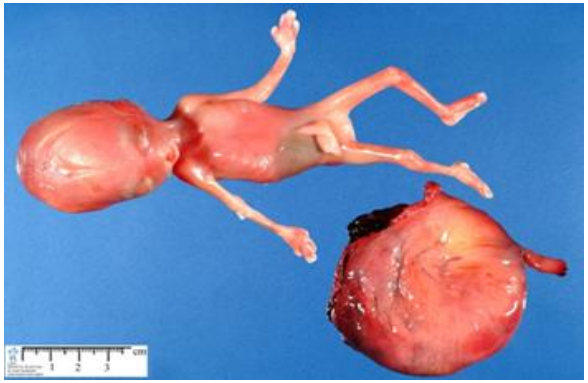


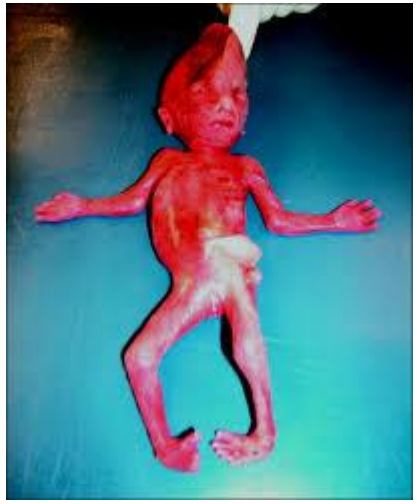




Genome mutations

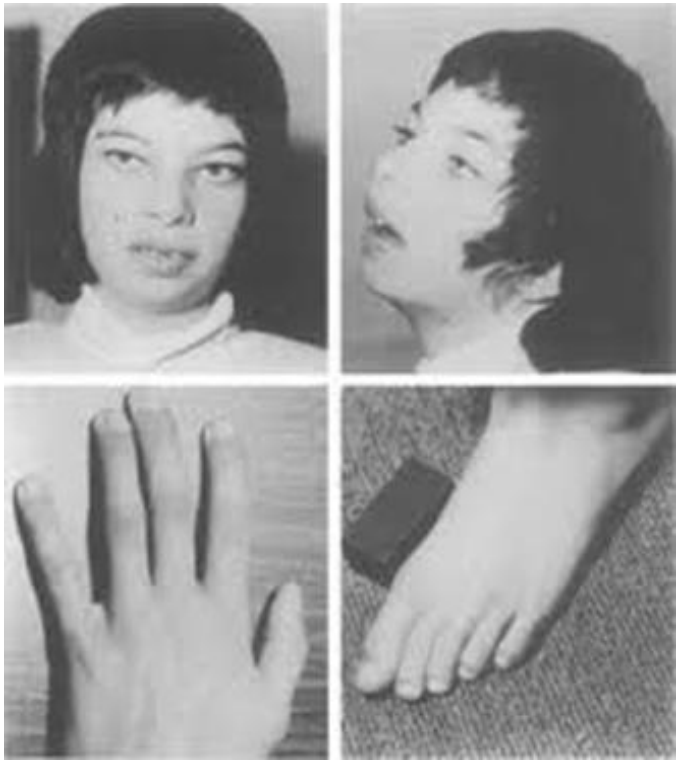
- The vast majority of triploid conceptions end as a miscarriage; those that do survive to term typically die shortly after birth. Many organ systems are affected by triploidy, but the central nervous system and skeleton are the most severely affected.
- In some cases, survival past birth may be extended if there is *mixoploidy* with both a diploid and a triploid cell population present.





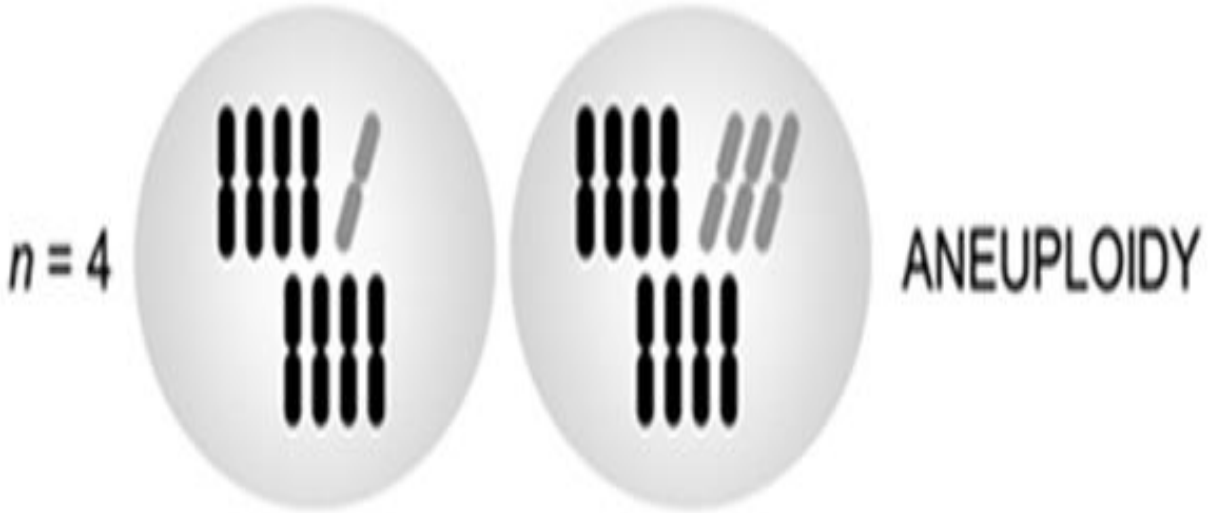
Genome mutations

- Mixoploidy (diploid/tetraploid (2n/4n)) in surviving females:



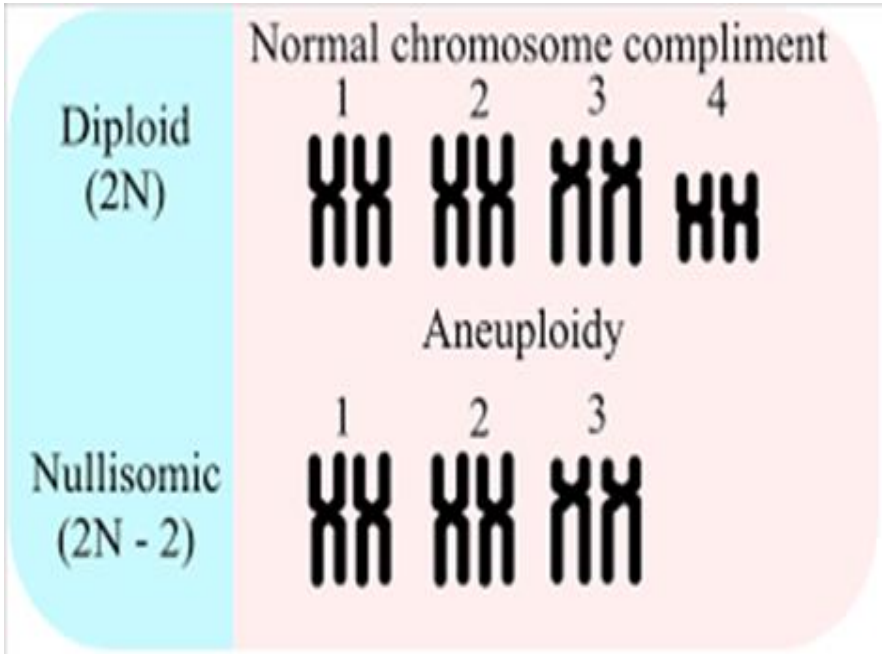
Genome mutations

- **Aneuploidy** is a condition when in cell one or more chromosomes (not an entire set) are missing, or are present in excess.



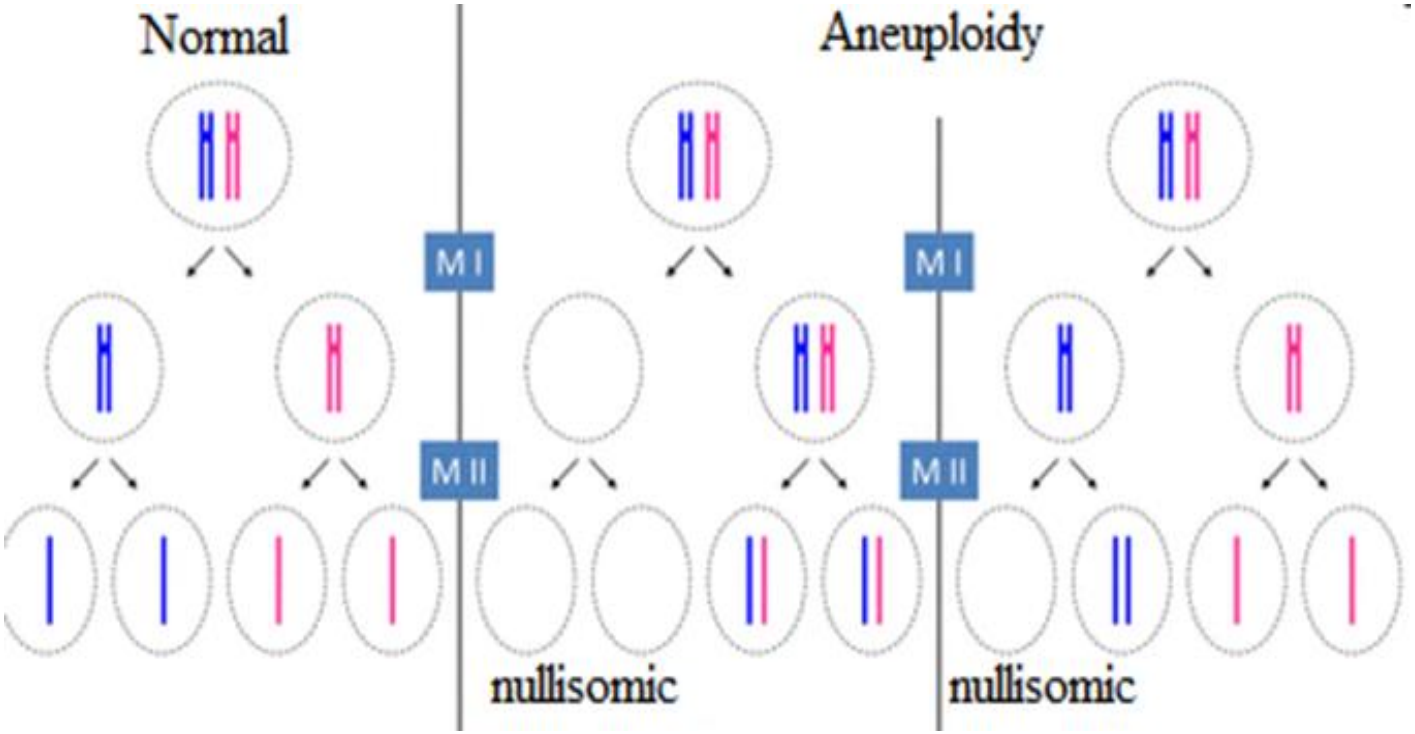
Genome mutations

- **Nullisomic** is a genetic condition involving the lack of both the normal chromosomal pairs for a species (2n-2). Humans with this condition will not survive.



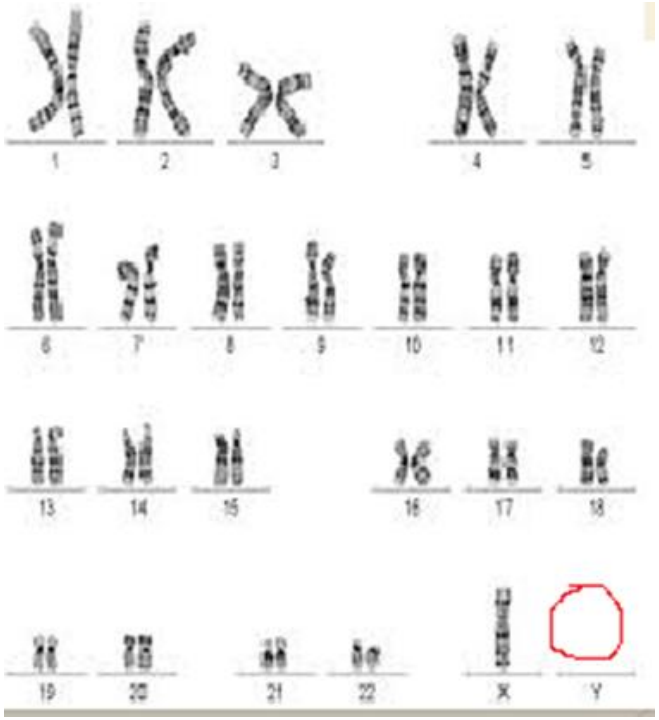
Genome mutations

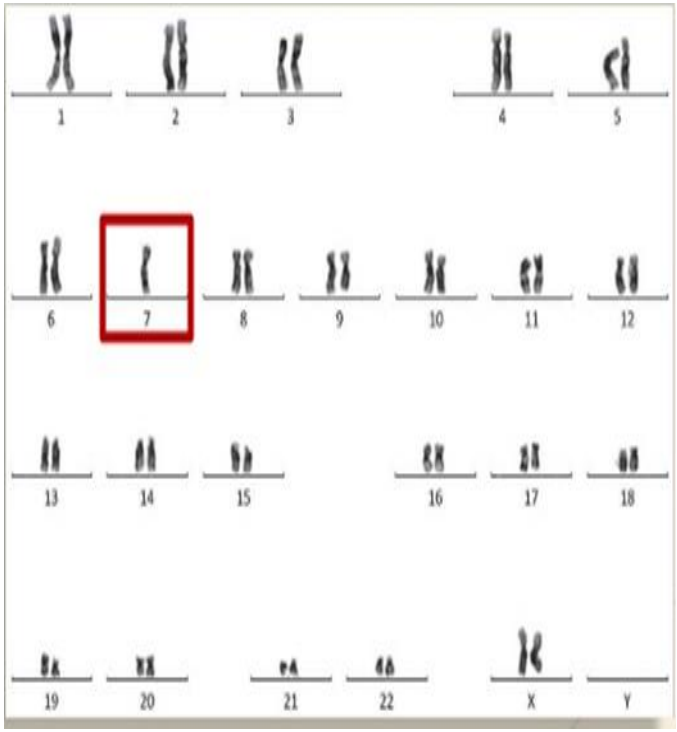
- *Nullisomy* is caused by nondisjunction during meiosis. Due to the lack of genetic information, the nullisomic gametes are rendered unviable for fertilization.



Genome mutations

- *Monosomy* is a form of aneuploidy with the presence of only one chromosome from a pair.

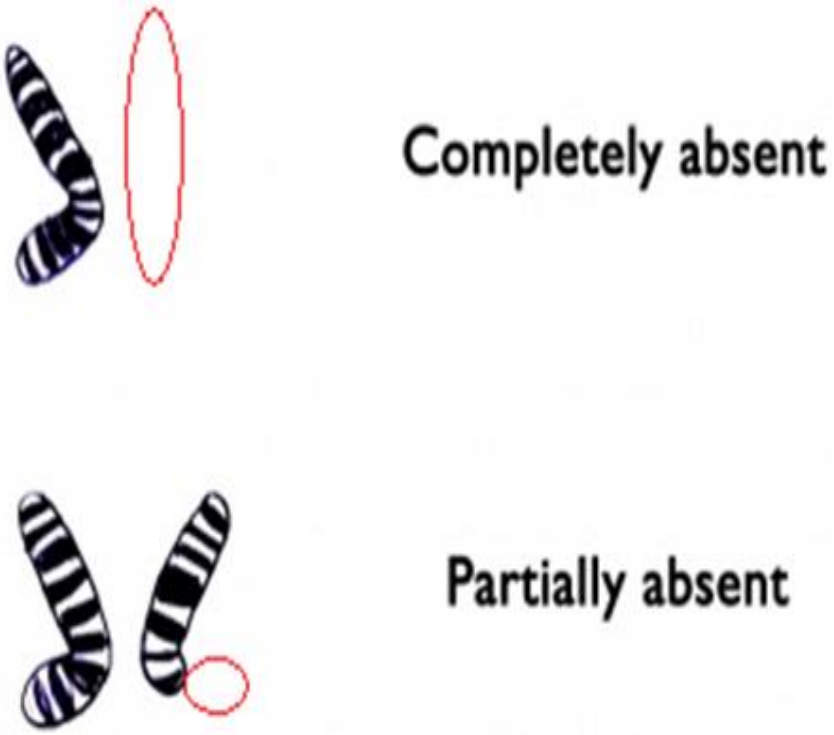




Genome mutations

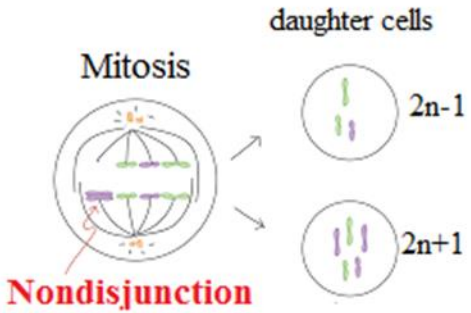
Partial monosomy occurs when a portion of one chromosome in a pair is missing.

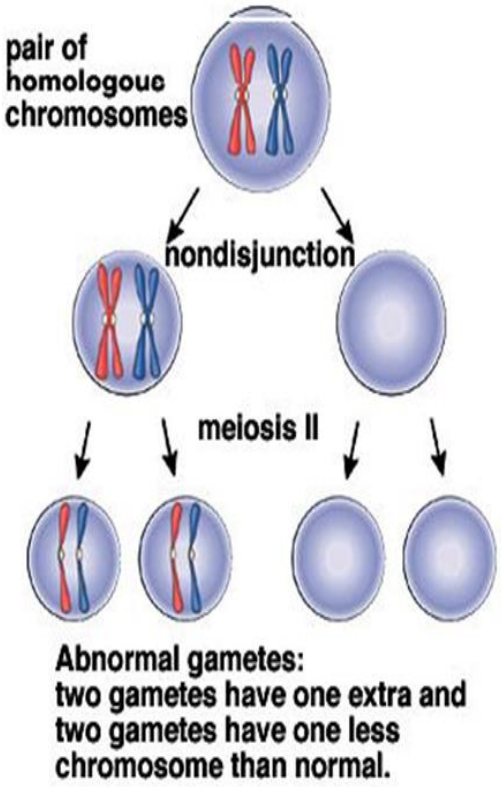
The causes of monosomy are not related to hereditary factors. Violations occur when exposed to adverse factors. Radiation, certain medications, chemicals, an unfavourable environmental situation, harmful working conditions, etc. can affect sex cells.

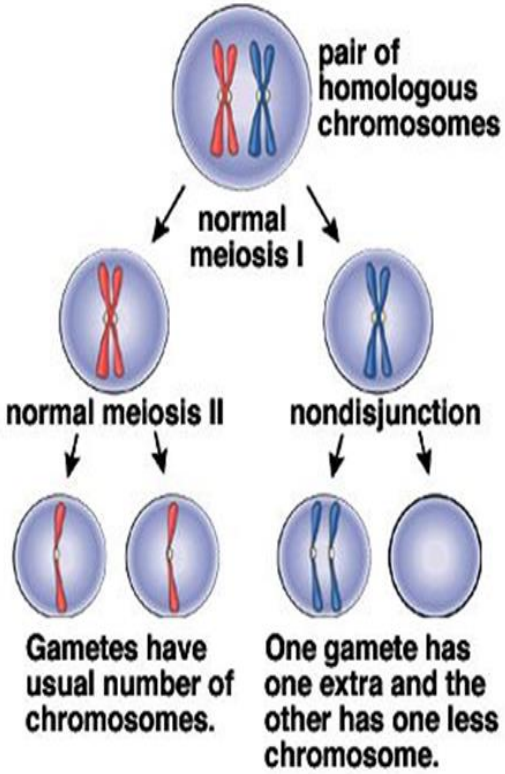


Genome mutations

- Monosomy can occur at various stages of cell division (mitosis or meiosis).



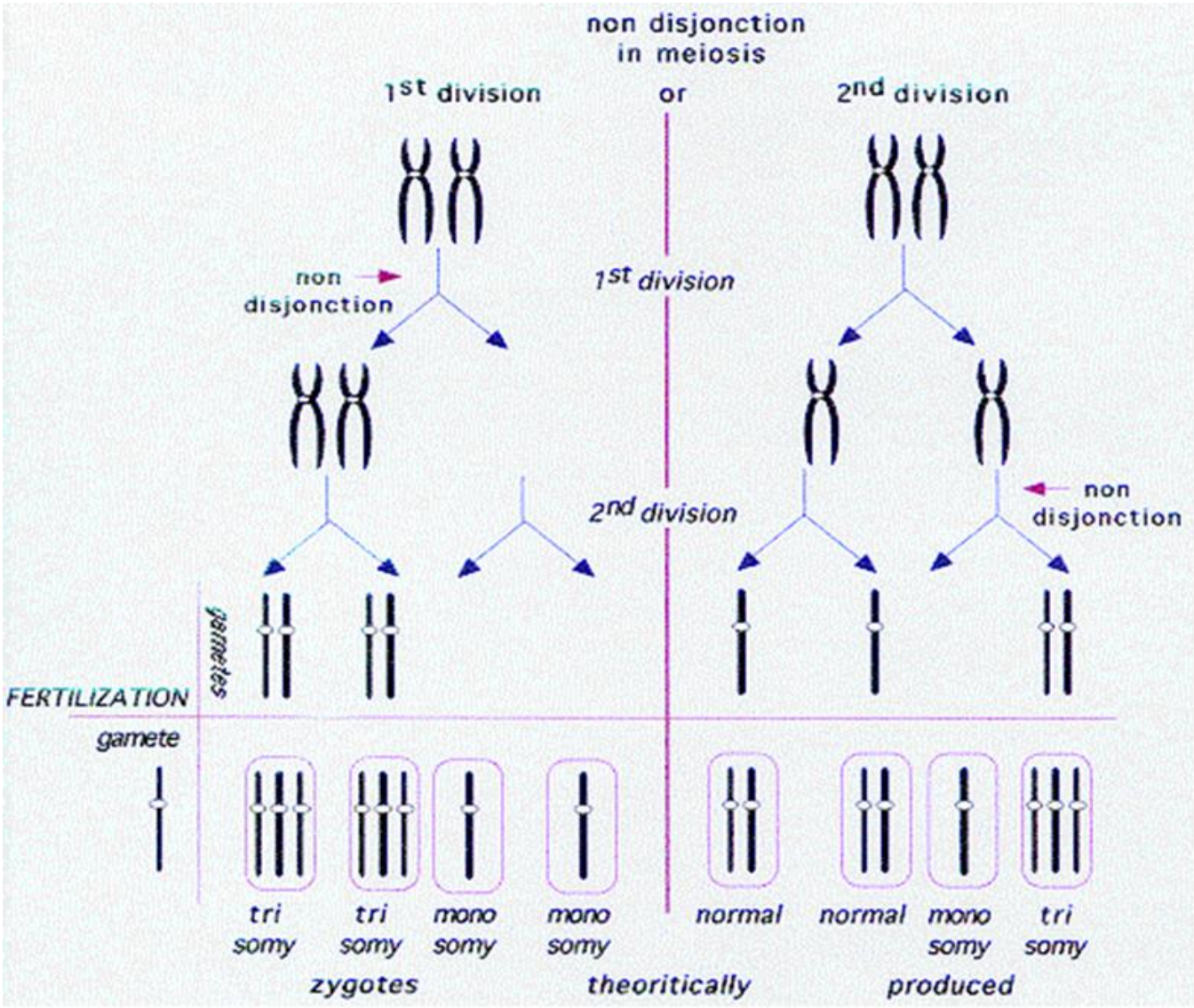




Genome mutations

- *Trisomy* is the presence of an extra chromosome in a human karyotype(2n+1, etc.). The causes of trisomy are mistakes in the separation of homologous chromosomes.
- “Complete trisomy", also called "primary trisomy", means that an entire extra chromosome has been copied.
- “Incomplete trisomy" means that there is an extra copy of part of a chromosome.

Genome mutations



Cytoplasmic mutation

- Cytoplasmic mutations are changes in non-nuclear genes.
- Mutations in the organelle genome are usually represented by point mutations and deletions.
- The main carriers of extranuclear genetic information in the cells of higher eukaryotes are chloroplasts and mitochondria.
- In chloroplasts, the phenotypic manifestation of mutations is expressed by a violation of photosynthesis, a change in sensitivity to temperature and resistance to antibiotics.

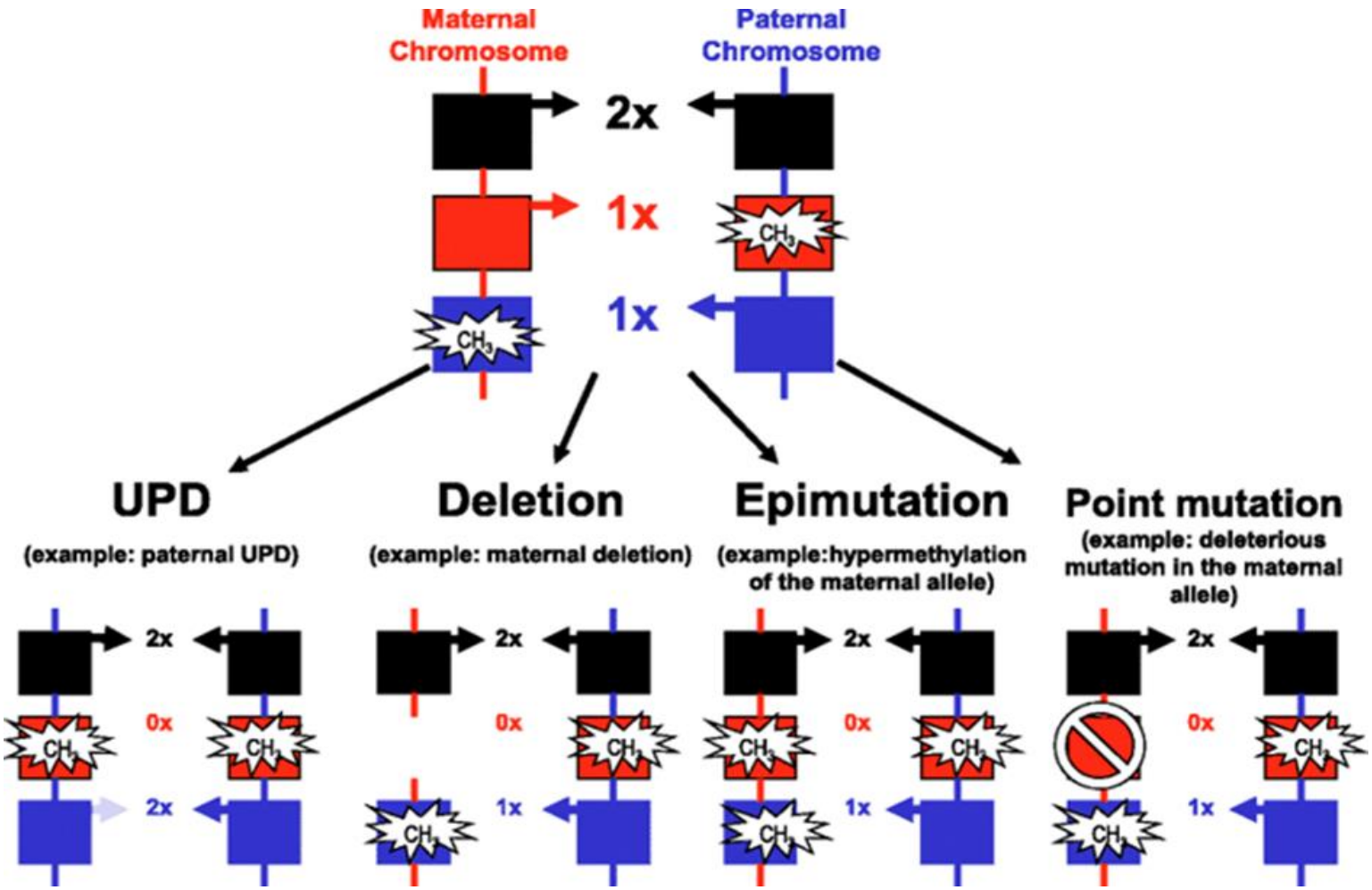
Cytoplasmic mutation

- The phenotypic manifestation of mtDNA mutations largely depends on the level of ATP consumption by one or another tissue. Since the nervous and muscle systems are the most energy-dependent, such mutations are most often manifested in the form of various neuropathies and myopathies.

Epimutation

- **Epigenetics** is the study of heritable phenotype changes that do not involve alterations in the DNA sequence.
- **Epimutations** occur in the body when chemical groups called methyl groups are added to or removed from DNA. These changes may occur with age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals. They can affect a person's risk of disease and may be passed from parent to child.

Epimutation



The four molecular mechanisms of IDs, resulting in a disturbed expression of imprinted genes.


THANK YOU
FOR YOUR
ATTENTION