Genetic, Plant breeding, evolution and boistatistics

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Chromosomal Aberrations

- The somatic (2n) and gametic (n) chromosome numbers of a species ordinarily remain constant.
- This is due to the extremely precise mitotic and meiotic cell division.
- Somatic cells of a diploid species contain two copies of each chromosome, which are called homologous chromosome.
- Their gametes, therefore contain only one copy of each chromosome, that is they contain one chromosome complement or genome.
- Each chromosome of a genome contains a definite numbers and kinds of genes, which are arranged in a definite sequence.

Chromosomal Aberrations

- Sometime due to mutation or spontaneous (without any known causal factors), variation in chromosomal number or structure do arise in nature. - Chromosomal aberrations.
- Chromosomal aberration may be grouped into two broad classes:

  1. Structural and 2. Numerical

Structural Chromosomal Aberrations

- Chromosome structure variations result from chromosome breakage.
- Broken chromosomes tend to re-join; if there is more than one break, rejoining occurs at random and not necessarily with the correct ends.
- The result is structural changes in the chromosomes.
- Chromosome breakage is caused by X-rays, various chemicals, and can also occur spontaneously.

- There are **four** common type of structural aberrations:
    1. Deletion or Deficiency
    2. Duplication or Repeat
    3. Inversion, and
    4. Translocation.

- Consider a normal chromosome with genes in alphabetical order: a b c d e f g h i

1. Deletion: part of the chromosome has been removed: a b c g h i

2. Dupliction: part of the chromosome is duplicated:

a b c d e f d e f g h i

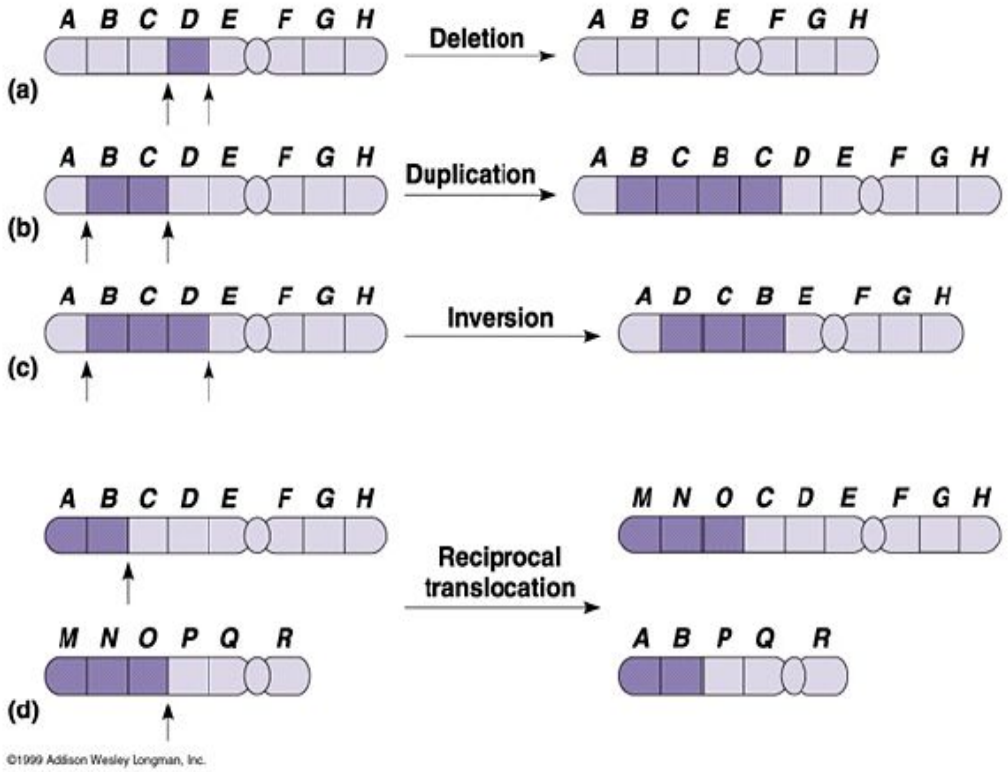
3. Inversion: part of the chromosome has been re-inserted in reverse order: a b c f e d g h i

ring: the ends of the chromosome are joined together to make a ring

4. translocation: parts of two non-homologous chromosomes are joined:

If one normal chromosome is a b c d e f g h i and the other chromosome is u v w x y z,

then a translocation between them would be a b c d e f x y z and u v w g h i.


A B C D E F G H
Deletion
A B C E F G H
(a)
A B C D E F G H
Duplication
A B C B C D E F G H
(b)
A B C D E F G H
Inversion
A D C B E F G H
(c)
A B C D E F G H
M N O P Q R
Reciprocal translocation
M N O C D E F G H
A B P Q R
(d)
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Deletion or deficiency

Loss of a chromosome segment is known as deletion or deficiency

It can be terminal deletion or interstitial or intercalary deletion.

A single break near the end of the chromosome would be expected to result in **terminal deficiency**.

If two breaks occur, a section may be deleted and an **intercalary deficiency** created.

Terminal deficiencies might seem less complicated.

But majority of deficiencies detected are intercalary type within the chromosome.

Deletion was the first structural aberration detected by Bridges in 1917 from his genetic studies on X chromosome of Drosophila.

- Deletion generally produce striking **genetic and physiological effects.**
- When homozygous, most deletions are lethal, because most genes are necessary for life and a homozygous deletion would have zero copies of some genes.
- When heterozygous, the genes on the normal homologue are **hemizygous**: there is only 1 copy of those genes.
- Crossing over is absent in deleted region of a chromosome since this region is present in only one copy in deletion heterozygotes.
- In Drosophila, several deficiencies induced the mutants like Blond, Pale, Beaded, Carved, Notch, Minute etc.

Deletion in Prokaryotes:

Deletions are found in prokaryotes as well, e.g., E.coli, T4 phage and Lambda phage.

In E.coli, deletions of up to 1 % of the bacterial chromosome are known.

In lambda phage, however 20% of the genome may be missing in some of the deletions.

Deletion in Human:

Chromosome deletions are usually lethal even as heterozygotes, resulting in zygotic loss, stillbirths, or infant death.

Sometimes, infants with small chromosome deficiencies however, survive long enough to permit the abnormal phenotype they express.

Cri-du-chat (Cat cry syndrome):

The name of the syndrome came from a catlike mewing cry from small weak infants with the disorder.

Other characteristics are microcephaly (small head), broad face and saddle nose, physical and mental retardation.

Cri-du-chat patients die in infancy or early childhood.

The chromosome deficiency is in the short arm of **chromosome 5** .

Myelocytic leukemia

Another human disorder that is associated with a chromosome abnormality is chronic myelocytic leukemia.

A deletion of **chromosome 22** was described by P.C.Nowell and Hungerford and was called **"Philadelphia" (Ph')** chromosome after the city in which the discovery was made.

Duplication

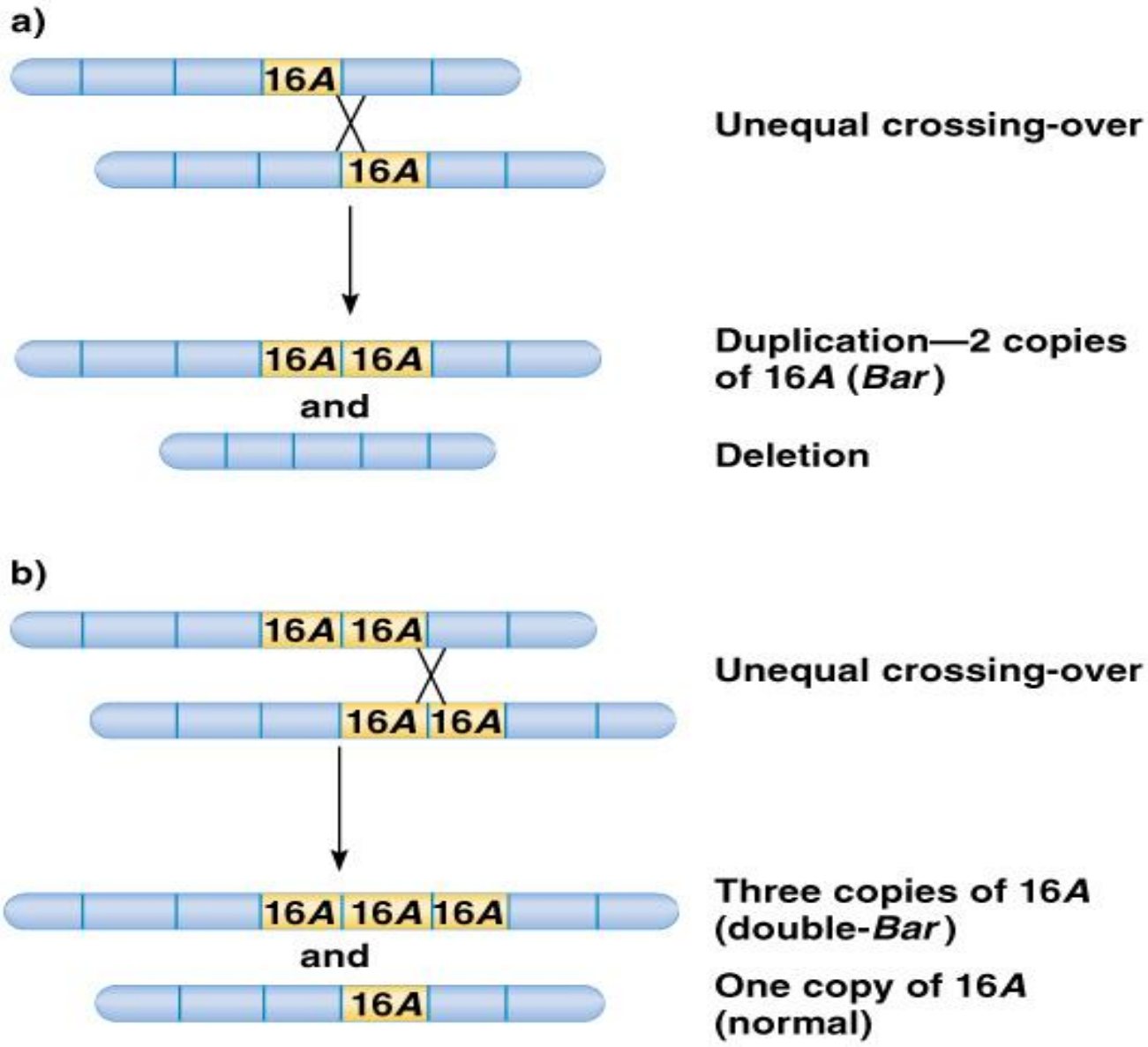
The presence of an additional chromosome segment, as compared to that normally present in a nucleus is known as Duplication.

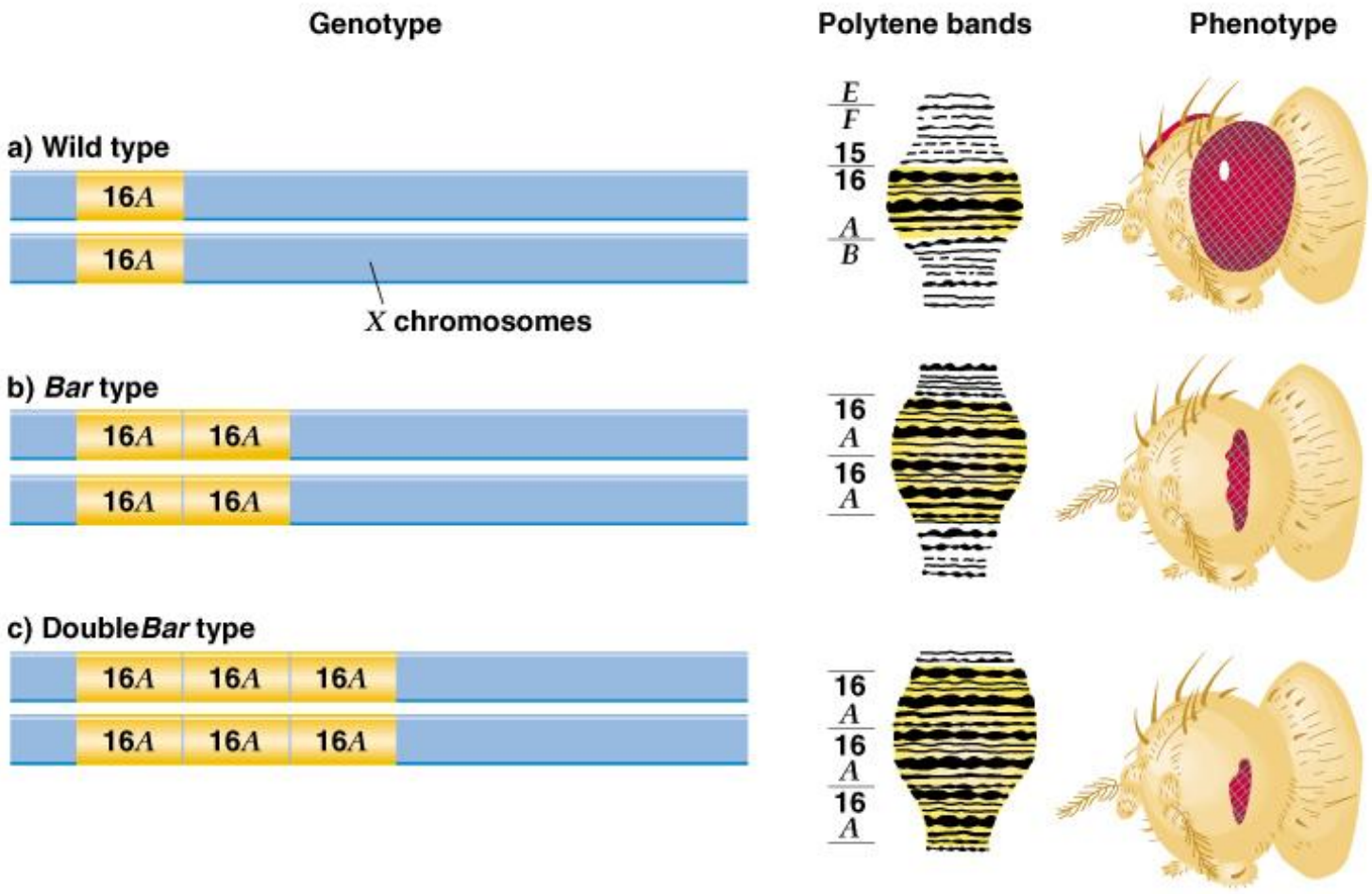
- In a diploid organism, presence of a chromosome segment in more than two copies per nucleus is called duplication.
- Four types of duplication:
    1. Tandem duplication
    2. Reverse tandem duplication
    3. Displaced duplication
    4. Translocation duplication

- The extra chromosome segment may be located immediately after the normal segment in precisely the same orientation forms the **tandem**
- When the gene sequence in the extra segment of a tandem in the reverse order i.e, inverted , it is known as **reverse tandem duplication**
- In some cases, the extra segment may be located in the same chromosome but away from the normal segment – termed as **displaced duplication**
- The additional chromosome segment is located in a non-homologous chromosome is **translocation duplication**.

Origin

- Origin of duplication involves chromosome breakage and reunion of chromosome segment with its homologous chromosome.
- As a result, one of the two homologous involved in the production of a duplication ends up with a deficiency, while the other has a duplication for the concerned segment.
- Another phenomenon, known as unequal crossing over, also leads to exactly the same consequences for small chromosome segments.
- For e.g., duplication of the band **16A of X** chromosome of Drosophila produces Bar eye.
- This duplication is believed to originate due to unequal crossing over between the two normal X chromosomes of female.

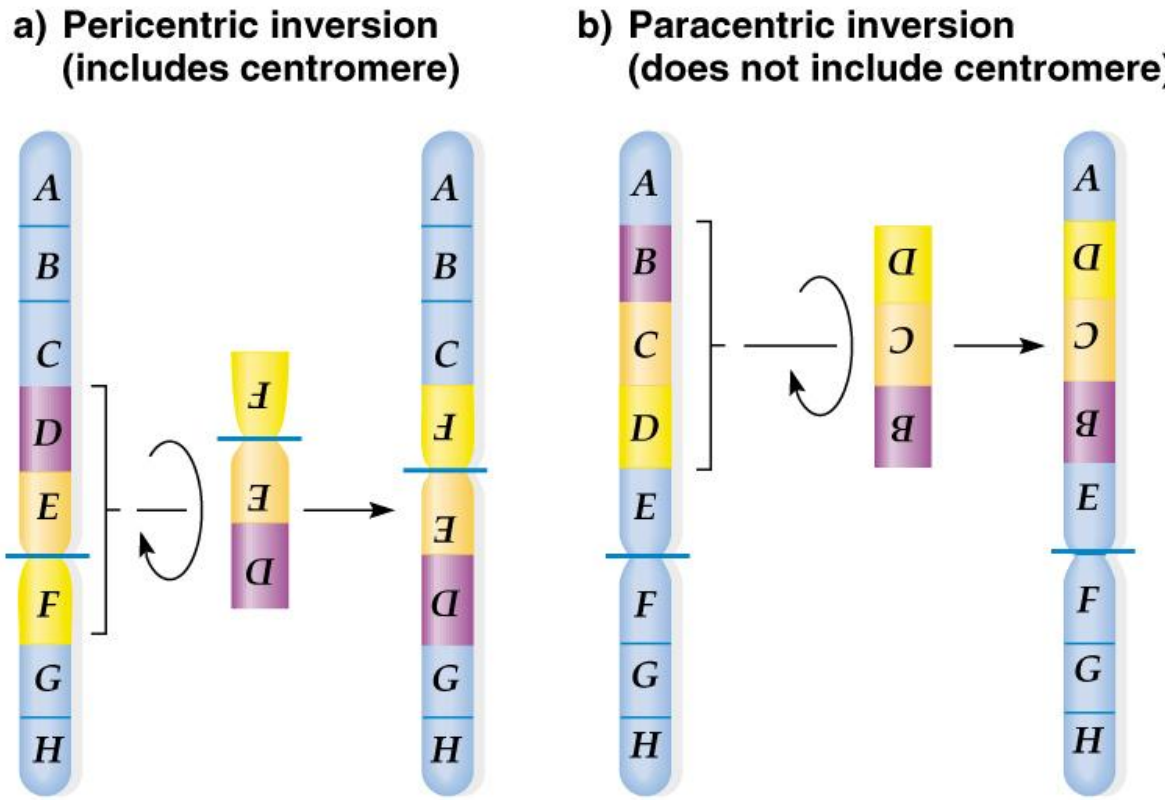

a)
16A
16A
Unequal crossing-over
16A 16A
and
Duplication—2 copies of 16A (Bar)
Deletion
b)
16A 16A
16A 16A
Unequal crossing-over
16A 16A 16A
and
Three copies of 16A (double-Bar)
16A
One copy of 16A (normal)



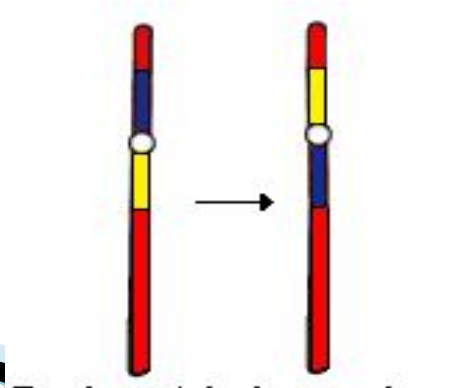
Inversion

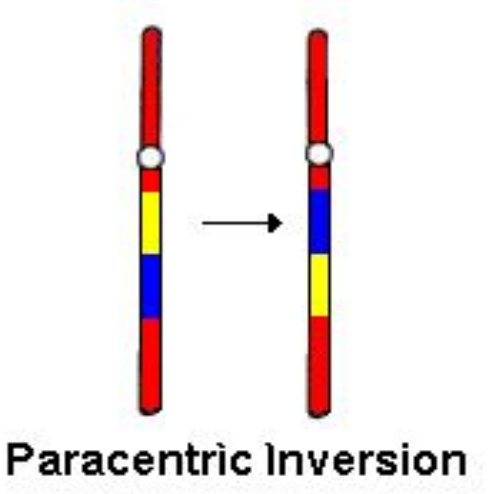
- When a segment of chromosome is oriented in the reverse direction, such segment said to be inverted and the phenomenon is termed as inversion.
- The existence of inversion was first detected by **Strutevant** and **Plunkett** in 1926.
- Inversion occur when parts of chromosomes become detached , turn through 180^0 and are reinserted in such a way that the genes are in reversed order.
- For example, a certain segment may be broken in two places, and the breaks may be in close proximity because of chance loop in the chromosome.
- When they rejoin, the wrong ends may become connected.
- The part on one side of the loop connects with broken end different from the one with which it was formerly connected.
- This leaves the other two broken ends to become attached.
- The part within the loop thus becomes turned around or inverted.

- Inversion may be classified into two types:
  - **Pericentric** - include the centromere
  - **Paracentric** - do not include the centromere



- An inversion consists of two breaks in one chromosome.
- The area between the breaks is inverted (turned around), and then reinserted and the breaks then unite to the rest of the chromosome.
- If the inverted area includes the centromere it is called a pericentric inversion.
- If it does not, it is called a paracentric inversion.





Inversions in natural populations

- In natural populations, pericentric inversions are much less frequent than paracentric inversions.
- In many sp, however, pericentric inversions are relatively common, e.g., in some grasshoppers.
- Paracentric inversions appear to be very frequent in natural populations of *Drosophila*.

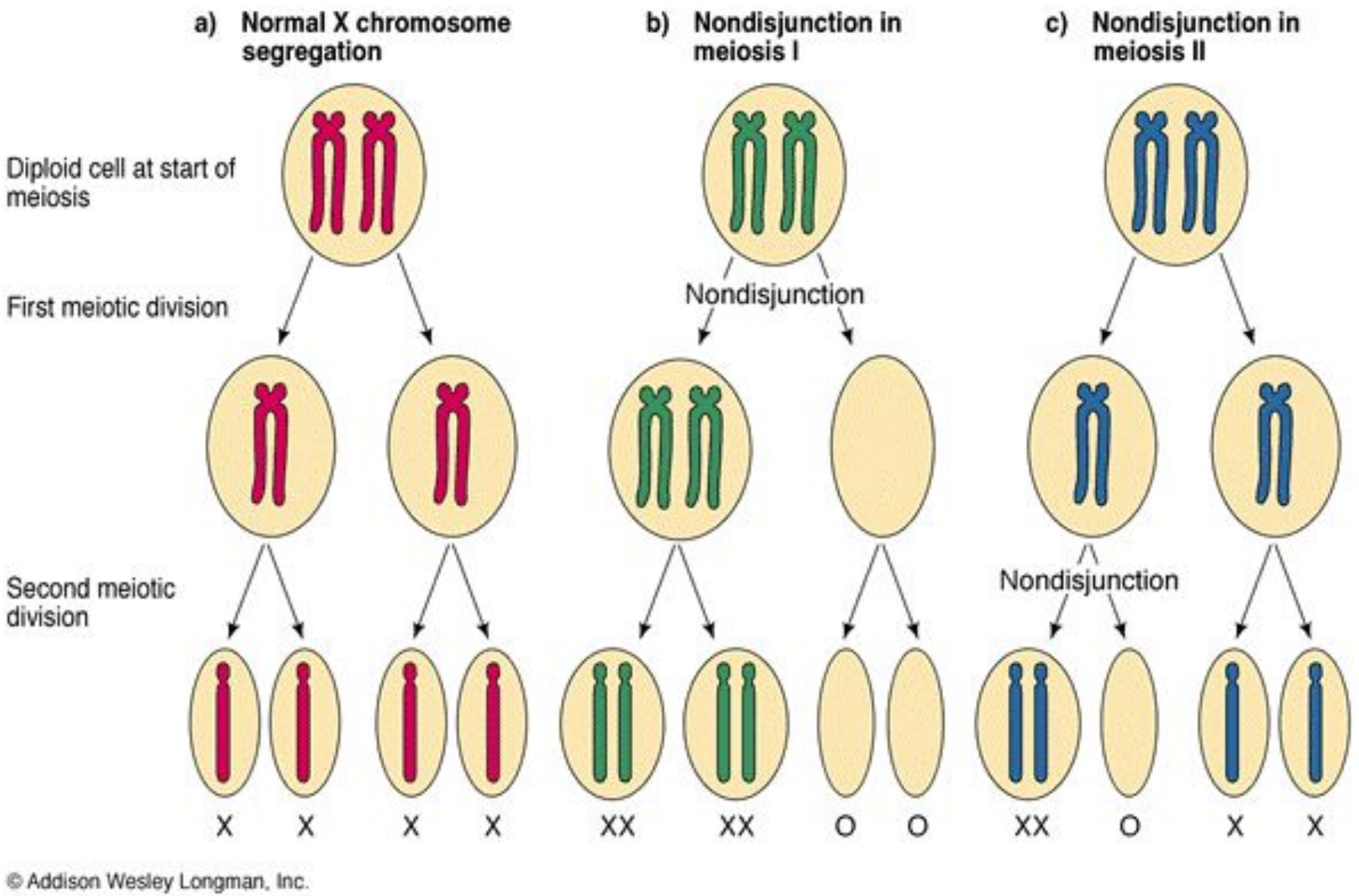
Translocation

- Integration of a chromosome segment into a nonhomologous chromosome is known as **translocation**.
- Three types:
    1. simple translocation
    2. shift
    3. reciprocal translocation.

- **Simple translocation**: In this case, terminal segment of a chromosome is integrated at one end of a non-homologous region. Simple translocations are rather rare.
- **Shift**: In shift, an intercalary segment of a chromosome is integrated within a non-homologous chromosome. Such translocations are known in the populations of *Drosophila*, *Neurospora* etc.
- **Reciprocal translocation**: It is produced when two non-homologous chromosomes exchange segments – i.e., segments reciprocally transferred.
- Translocation of this type is most common

Non-Disjunction

- Generally during gametogenesis the homologous chromosomes of each pair separate out (disjunction) and are equally distributed in the daughter cells.
- But sometime there is an unequal distribution of chromosomes in the daughter cells.
- The failure of separation of homologous chromosome is called **non-disjunction**.
- This can occur either during **mitosis** or **meiosis** or **embryogenesis**.



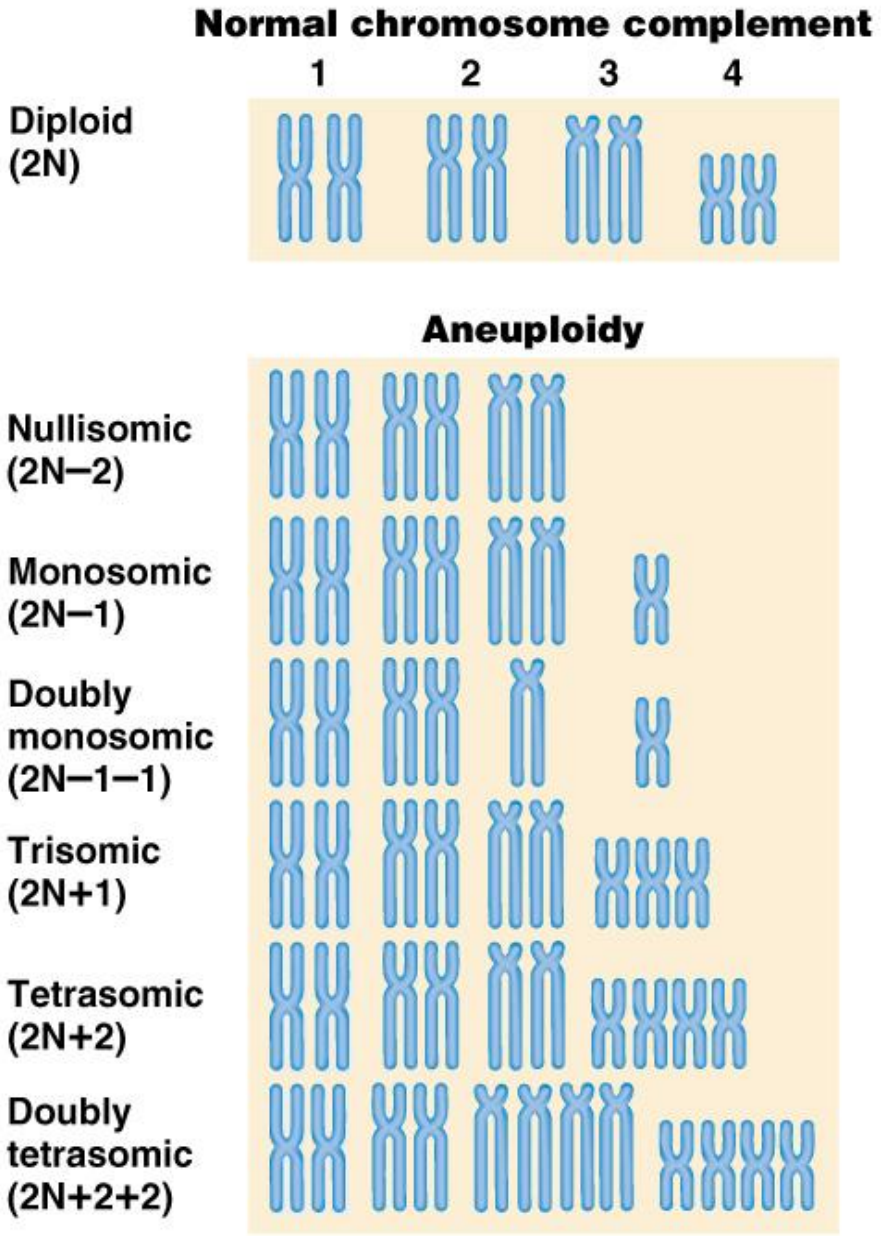
- **Mitotic non-disjunction**: The failure of separation of homologous chromosomes during mitosis is called mitotic non-disjunction.
- It occurs after fertilization.
- May happen during first or second cleavage.
- Here, one blastomere will receive 45 chromosomes, while other will receive 47.
- **Meiotic non-disjunction**: The failure of separation of homologous chromosomes during meiosis is called mitotic non-disjunction
- Occurs during gametogensis
- Here, one type contain 22 chromosome, while other will be 24.

Variation in chromosome number

- Organism with one complete set of chromosomes is said to be euploid (applies to haploid and diploid organisms).
- Aneuploidy - variation in the number of individual chromosomes (but not the total number of sets of chromosomes).
- The discovery of aneuploidy dates back to 1916 when Bridges discovered XO male and XXY female ***Drosophila***, which had 7 and 9 chromosomes respectively, instead of normal 8.

More about Aneuploidy

- **Nullisomy** - loss of one homologous chromosom pair. (e.g., Oat)
- **Monosomy** – loss of a single chromosome (Maize).
- **Trisomy** - one extra chromosome. (Datura)
- **Tetrasomy** - one extra chromosome pair.



Uses of Aneuploidy

- They have been used to determine the phenotypic effect of loss or gain of different chromosome
- Used to produce **chromosome substitution** lines. Such lines yield information on the effects of different chromosomes of a variety in the same genetic background.
- They are also used to produce **alien addition** and **alien substitution lines**. These are useful in gene transfer from one species to another.
- Aneuploidy permits the location of a gene as well as of a linkage group onto a specific chromosome.

Trisomy in Humans

Down Syndrome

- The best known and most common chromosome related syndrome.
- Formerly known as "Mongolism"
- 1866, when a physician named **John Langdon Down** published an essay in England in which he described a set of children with common features who were distinct from other children with mental retardation he referred to as "Mongoloids."
- One child in every 800-1000 births has Down syndrome
- 250,000 in US has Down syndrome.
- The cost and maintaining Down syndrome case in US is estimated at $ 1 billion per year.

- Patients having Down syndrome will Short in stature (four feet tall) and had an epicanthal fold, broad short skulls, wild nostrils, large tongue, stubby hands
- Some babies may have short necks, small hands, and short fingers.
- They are characterized as low in mentality.
- Down syndrome results if the extra chromosome is number 21.

Amniocentesis for Detecting Aneuploidy

- Chromosomal abnormalities are sufficiently well understood to permit genetic counseling.
- A fetus may be checked in early stages of development by karyotyping the cultured cells obtained by a process called **amniocentesis**.
- A sample of fluid will taken from mother and fetal cells are cultured and after a period of two to three weeks, chromosomes in dividing cells can be stained and observed.
- If three No.21 chromosomes are present, Down syndrome confirmed.

- The risk for mothers less than 25 years of age to have the trisomy is about 1 in 1500 births.
- At 40 years of age, 1 in 100 births
- At 45 years 1 in 40 births.

Other Syndromes

Chromosome Nomenclature: 47, +13

Chromosome formula: 2n+1

Clinical Syndrome: Trisomy-13

Estimated Frequency Birth: 1/20,000

Main Phenotypic Characteristics:

Mental deficiency and deafness, minor muscle seizures, cleft lip, cardiac anomalies

Other Syndromes

Chromosome Nomenclature: 47, +18

Chromosome formula: 2n+1

Clinical Syndrome: Trisomy-18

Estimated Frequency Birth: 1/8,000

Main Phenotypic Characteristics:

Multiple congenital malformation of many organs, malformed ears, small mouth and nose with general elfin appearance.

90% die in the first 6 months.

Other Syndromes

Chromosome Nomenclature: 45, X

Chromosome formula: 2n - 1

Clinical Syndrome: Turner

Estimated Frequency Birth: 1/2,500 female

Main Phenotypic Characteristics:

Female with retarded sexual development, usually sterile, short stature, webbing of skin in neck region, cardiovascular abnormalities, hearing impairment.

MUTATION

- A mutation is the permanent alteration of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal DNA or other genetic elements.

- Mutations result from errors during DNA replication or other types of damage to DNA

CHROMOSOMAL MUTATION

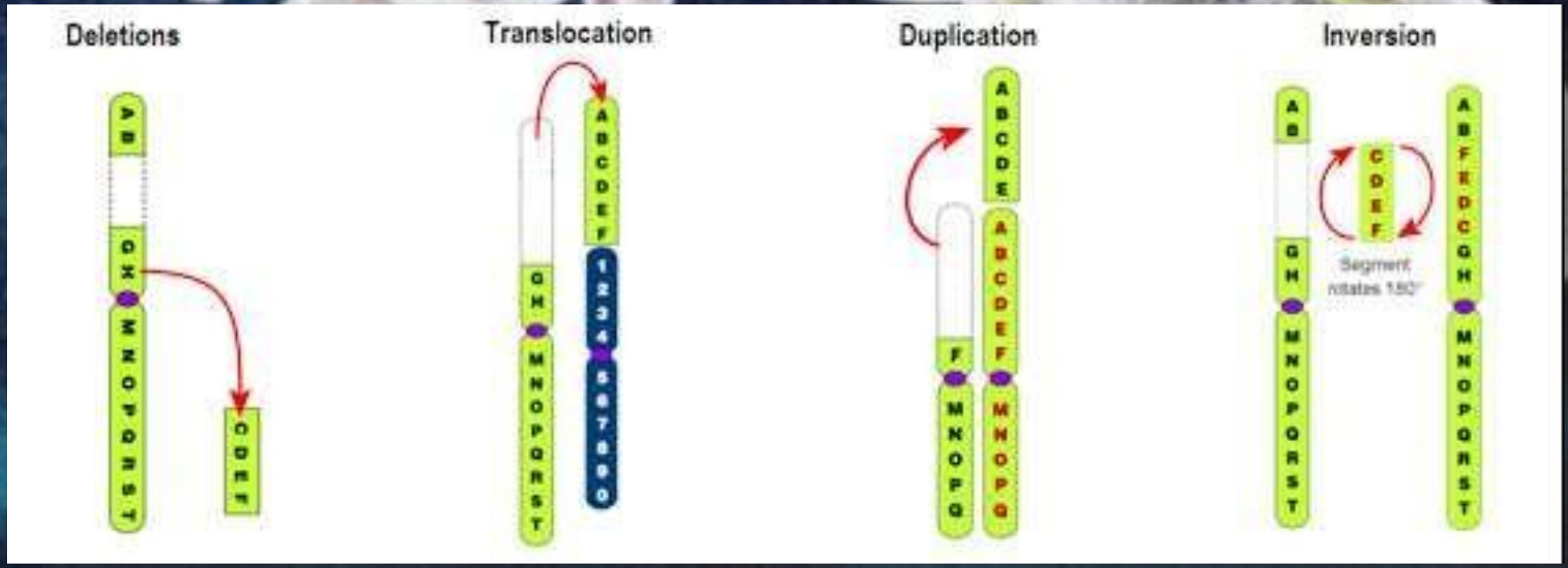
i. DELETION
ii. DUPLICATION
iii. INVERSION
iv. TRANSLOCATION

GENE MUTATION

i. **POINT MUTATION**
   - SILENT
   - MISSENSE
   - NONSENSE

ii. **FRAMESHIFT MUTATION** INSERTION
   - DELETION

CHROMOSOMAL MUTATIO



CHROMOSOMAL MUTATION

A chromosome aberration, or mutation is a missing, extra, or Irregular portion of chromosomal DNA. It can be from an atypical number of chromosomes or a structural abnormality in one or more chromosomes.

There are many types of chromosome anomalies. They can be organized into two basic groups, numerical and structural anomalies.

i. Numerical disorders

This is called aneuploidy (an abnormal number of chromosomes), and occurs when an individual either is missing a chromosome from a pair (monosomy) or has more than two chromosomes of a pair (trisomy, tetrasomy etc.). In humans, an example of a condition caused by a numerical anomaly is Down Syndrome, also known as

DOWN SYNDROME

Q. WHAT IS DOWN SYNDROME ?

Down syndrome is a chromosomal disorder caused by an error in cell division that results in an extra 21st chromosome. The condition leads to impairments in both cognitive ability and physical growth.

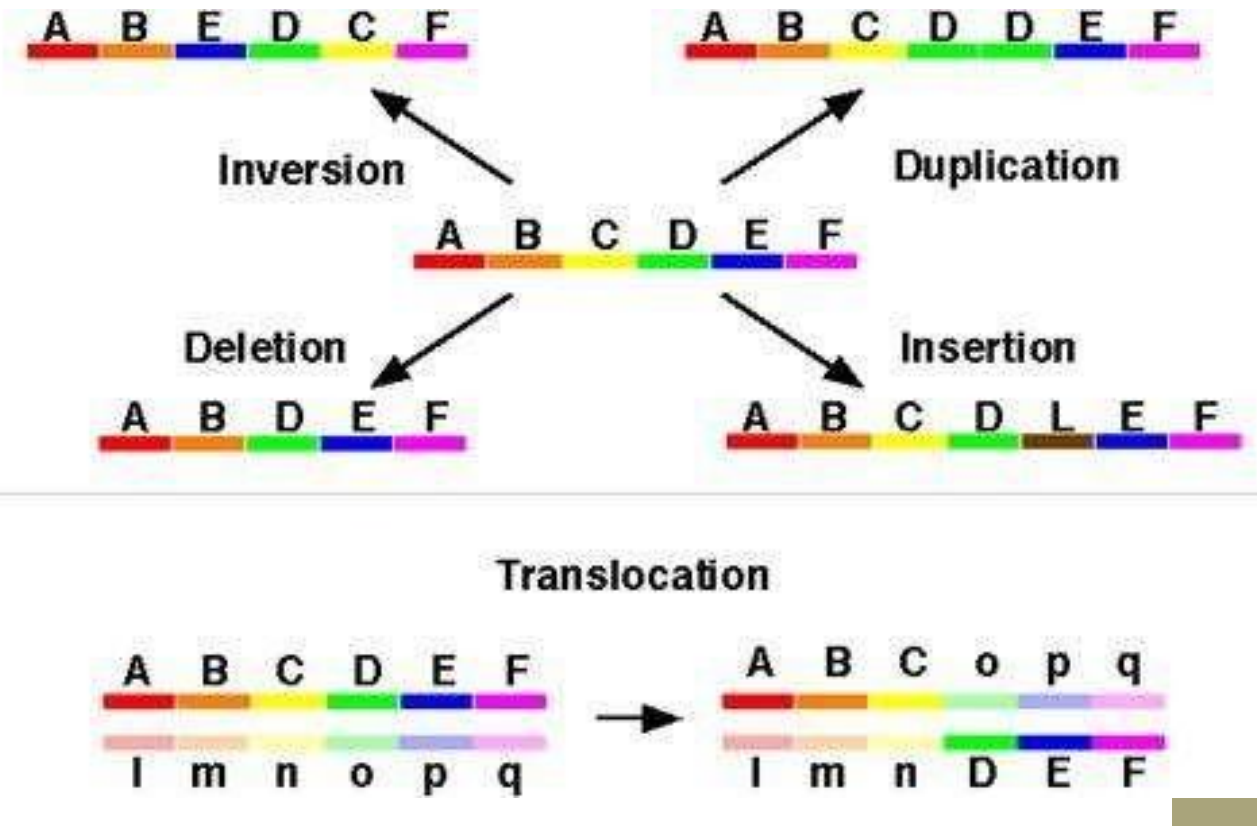
Q .HOW DO YOU HAVE A BABY WITH DOWN SYNDROME ?

Down syndrome is typically caused by what is called nondisjunction. Nondisjunction happens when a pair of chromosomes fails to separate egg (or sperm) formation. When that egg unites with a norm sperm to form an embryo, the embryo ends up with three copies of chromosome 21 instead of the normal two.

ii. Structural abnormalities

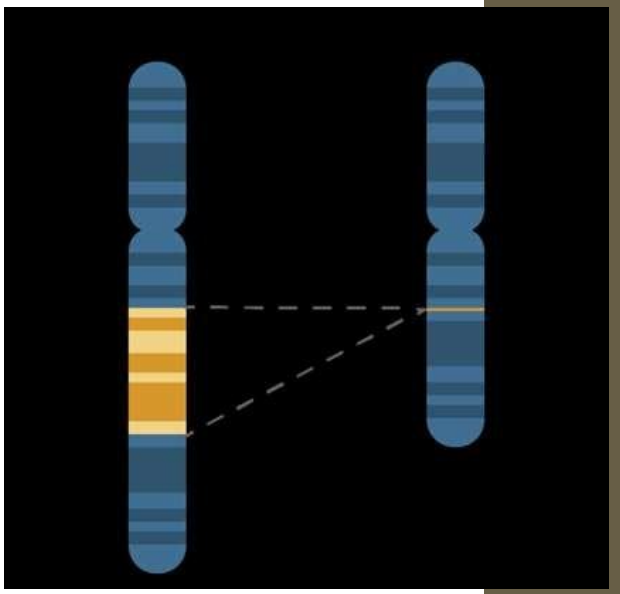
When the chromosome's structure is altered, this can take several forms:

1. DELETION
2. DUPLICATION
3. INVERSION
4. TRANSLOCATION

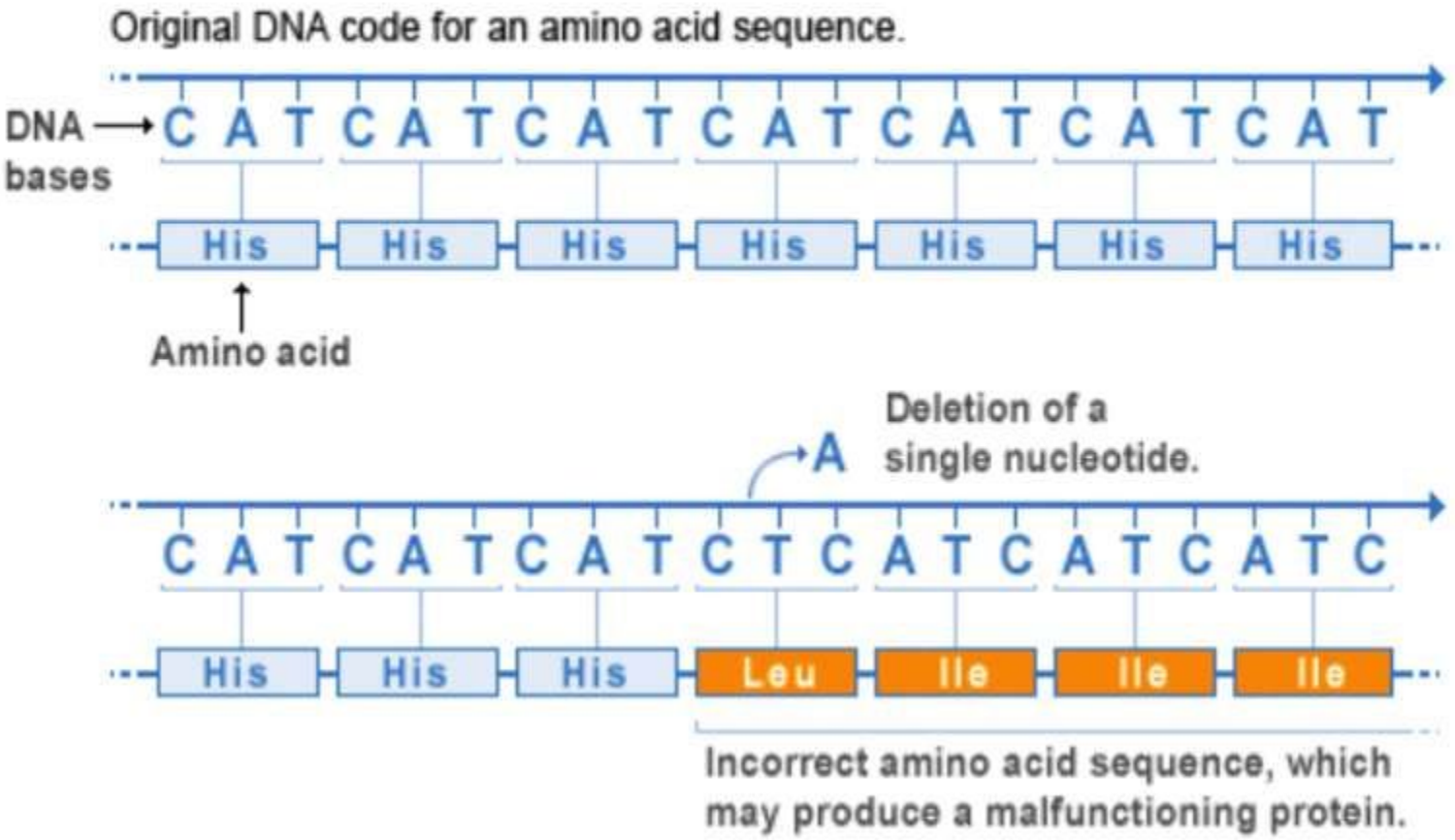


DELETION

- Deletion occurs when nucleotides are left out of gene.
- They also usually cause a shift in reading frame that will ultimately truncate the protein.
- Deletions can be caused by errors in chromosomal crossover during meiosis, which causes several serious



Deletion mutation



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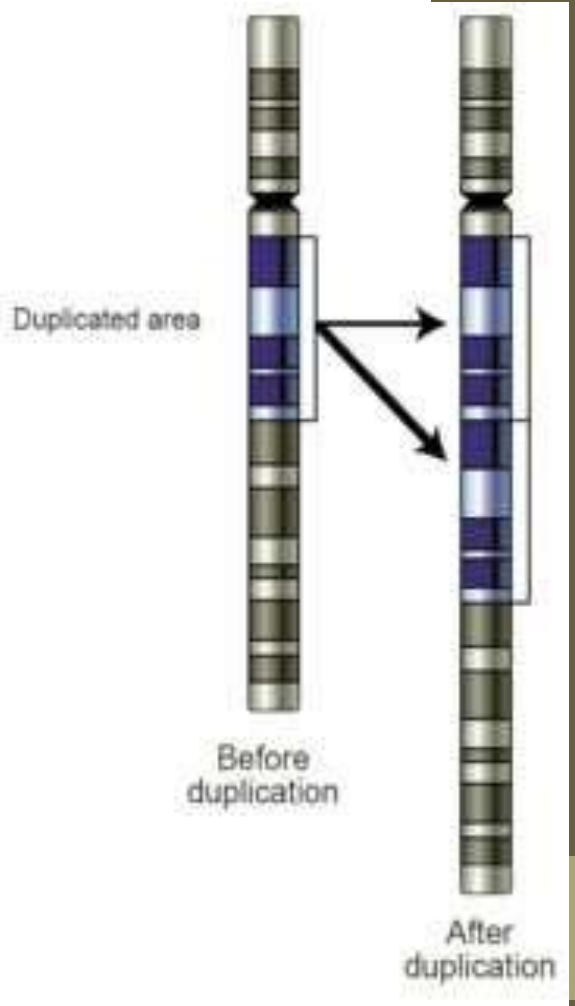
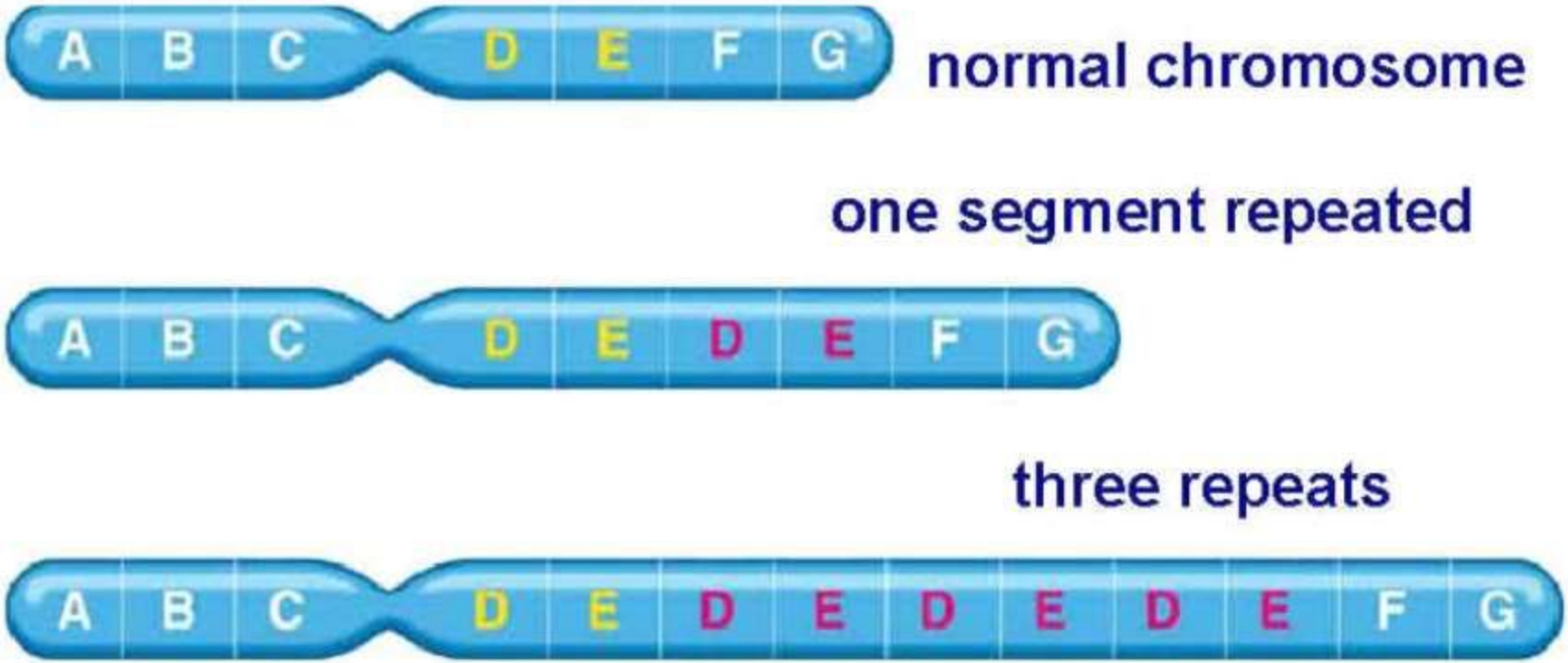
DUPLICATION

- A portion of the chromosome is duplicated, resulting in extra genetic material

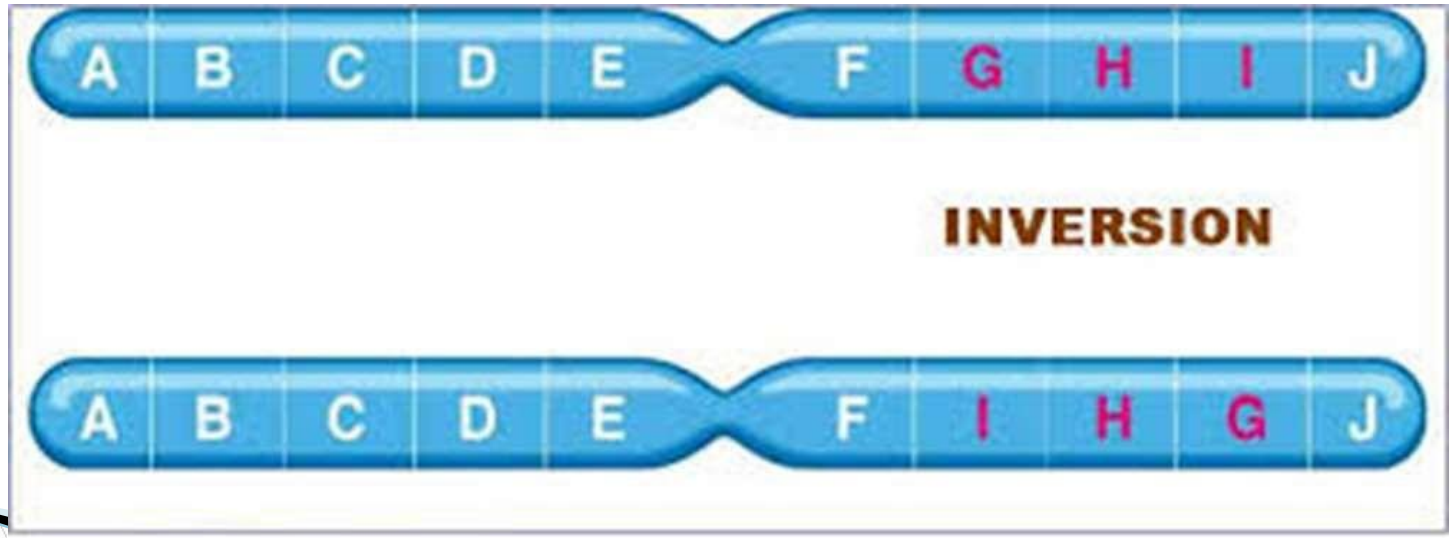
- Duplications arise from an event termed unequal crossing-over that occurs during meiosis between misaligned homologous chromosomes.




A B C D E F G
normal chromosome
one segment repeated
A B C D E D E F G
three repeats
A B C D E D E D E D E F G

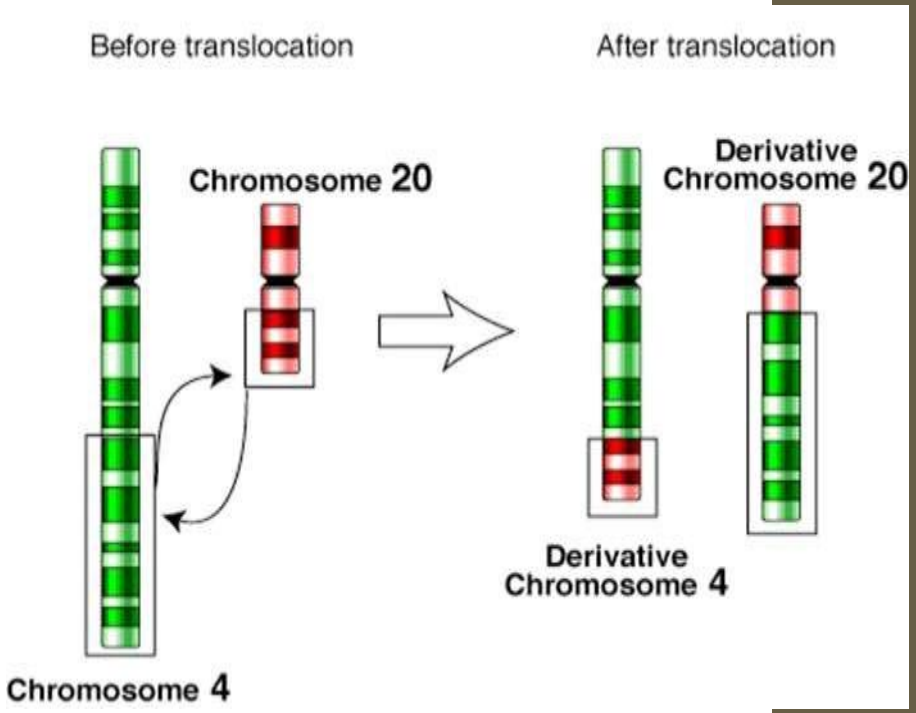
INVERSION

- A portion of the chromosome has broken off, turned upside down, and reattached, therefore the genetic material is inverted.

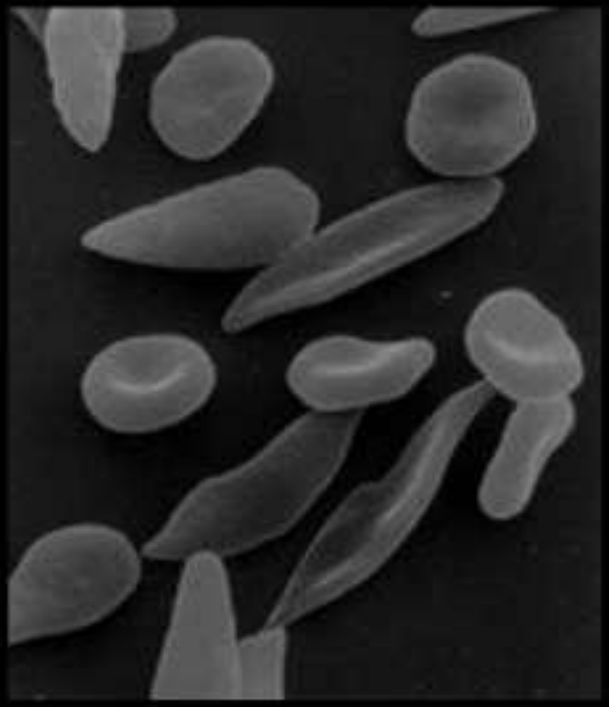


TRANSLOCATION

- **Chromosome translocation is caused by rearrangement of parts between nonhomologous chromosomes.**



Gene Mutations



Sickle Shaped Red Blood Cells

GENE MUTATION

A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people.

Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

POINT MUTATION

A point mutation is a type of mutation that causes a single nucleotide base substitution, insertion, or deletion of the genetic material, DNA or RNA.

Causes of point mutations

- Point mutation is a random SNP (single-nucleotide polymorphism) mutation in the DNA.
- A single point mutation can change the whole DNA sequence.
- Point mutations may arise from spontaneous mutations that occur during DNA

Functional categorization

Nonsense mutation:

Code for a stop, which can truncate the protein. A nonsense mutation converts an amino acid codon into a termination codon. This causes the protein to be shortened because of the stop codon interrupting its normal code.

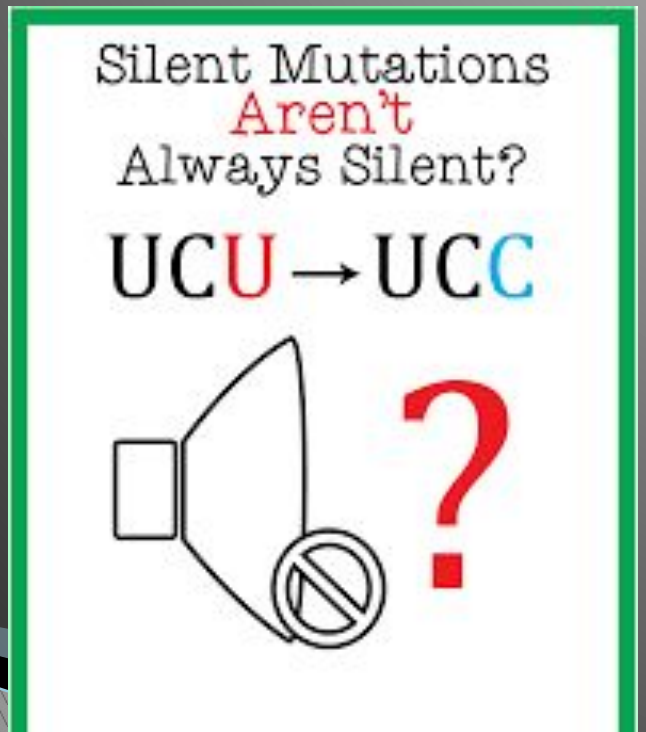
Missense mutation:

It is a point mutation in which a single nucleotide change results in a codon that codes for a different amino acid.

It is a type of nonsynonymous substitution

Silent mutations:

Code for the same amino acid. A silent mutation has no effect on the functioning of the protein. A single nucleotide can change, but the new codon specifies the same amino acid, resulting in an unmutated protein. This type of change is called synonymous change, since the old and new codon code for the same amino acid.



FRAMESHIFT MUTATION

A frameshift mutation (also called a framing error or a reading frame shift) is a genetic mutation caused by indels (insertions or deletions) of a number of nucleotides in a DNA sequence that is not divisible by three.

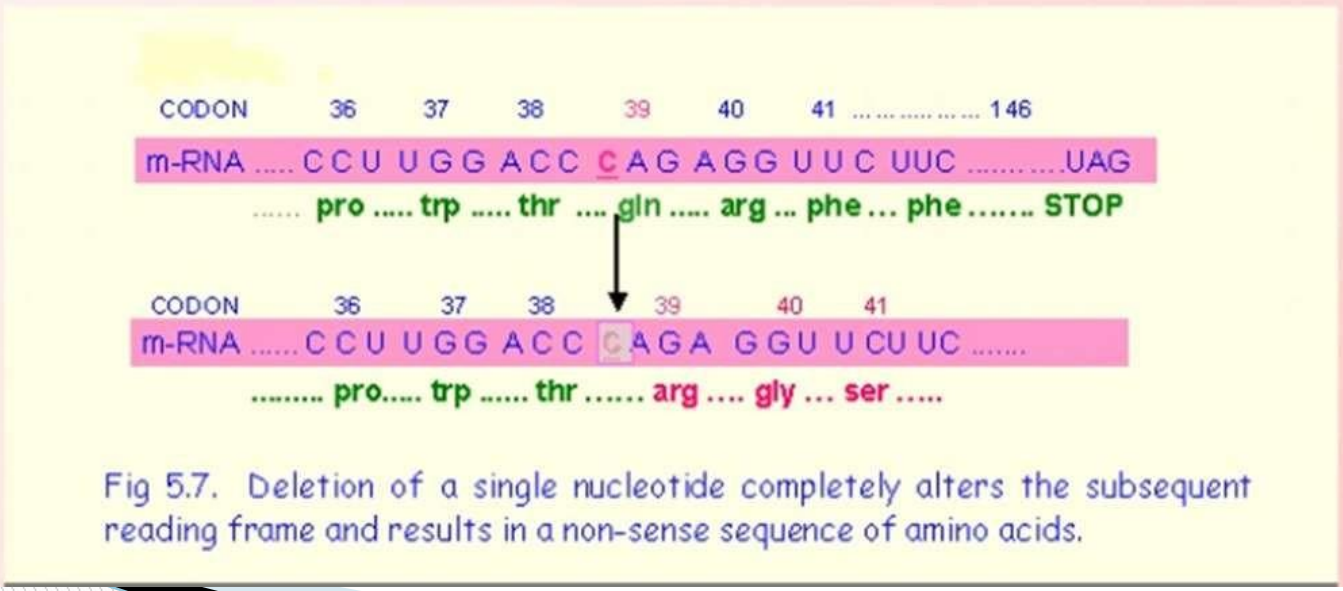


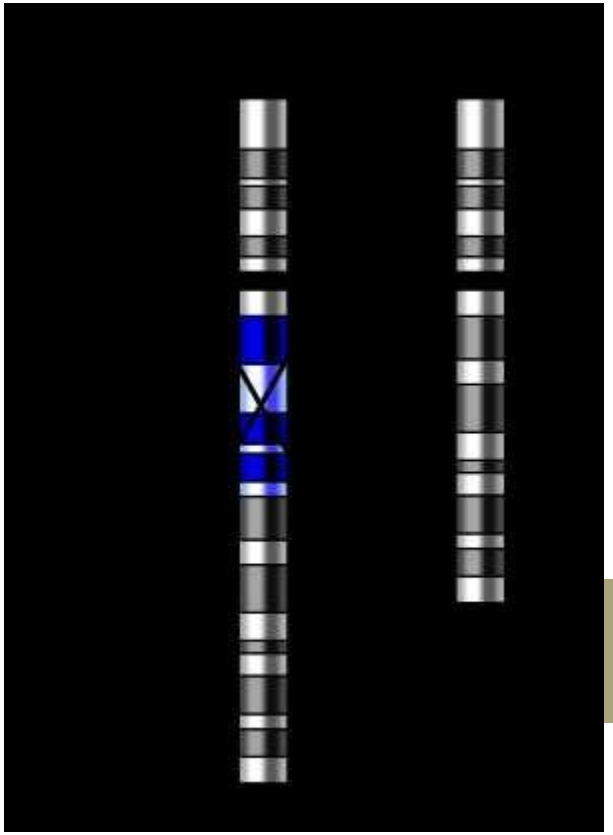
Fig 5.7. Deletion of a single nucleotide completely alters the subsequent reading frame and results in a non-sense sequence of amino acids.

DELETION MUTATION

Deletion mutation is a mutation in which a part of a chromosome or a sequence of DNA is lost during DNA replication.

Deletions can be caused by errors in chromosomal crossover during meiosis , which causes several serious genetic diseases. e.g. Williams syndrome.

Small deletions are less likely to be fatal; large deletions are usually fatal



INSERTION MUTATION

Insertion mutation is the addition of one or more nucleotide base pairs into a DNA sequence.

Insertions can be particularly hazardous if they occur in an exon, th ıe