Lecture 8.
Mutagenesis. Types of structural chromosomal abnormalities

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MUTAGENESIS AND MUTATIONS

Mutagenesis is a process by which the genetic information of an organism is changed, resulting in a mutation.

A ***mutation*** is defined as a heritable alteration or change in the genetic material. Mutations drive evolution but can also be pathogenic. Mutations can arise through exposure to mutagenic agents, but the vast majority occur spontaneously through errors in DNA replication and repair. Sequence variants with no obvious effect upon phenotype may be termed polymorphisms.

Somatic mutations may cause adult-onset disease such as cancer but cannot be transmitted to offspring. A mutation in gonadal tissue or a gamete can be transmitted to future generations unless it affects fertility or survival into adulthood. It is estimated that each individual carries up to six(!) lethal or semilethal recessive mutant alleles that in the homozygous state would have very serious effects. Harmful alleles of all kinds constitute the so-called *genetic load* of the population.

CLASSIFICATION OF MUTATIONS

Gene mutation (single base or point mutation)	Chromosome mutation	Genome mutation
✓ Substitution: • synonimous; • missense; • nonsense ✓ Insertion; ✓ Deletion; ✓ Amplification of trinucleotide repeats	✓ Translocation; ✓ Deletion; ✓ Inversion; ✓ Duplication; ✓ Insertion, etc	✓ Aneuploidy: • Monosomy; • Trisomy; ✓ Polyploidy

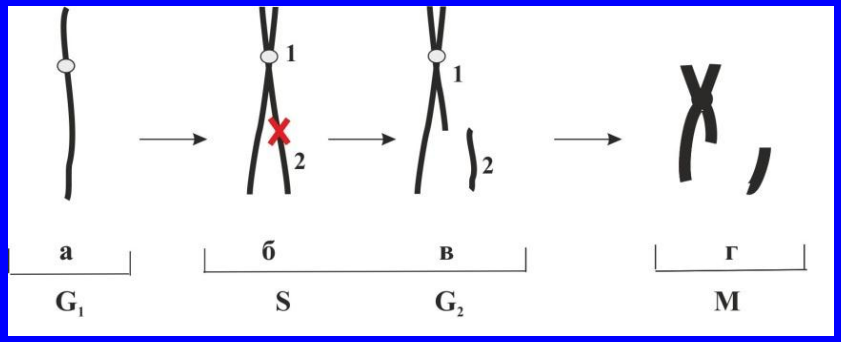
Box 3.1 Types of Chromosome Abnormality

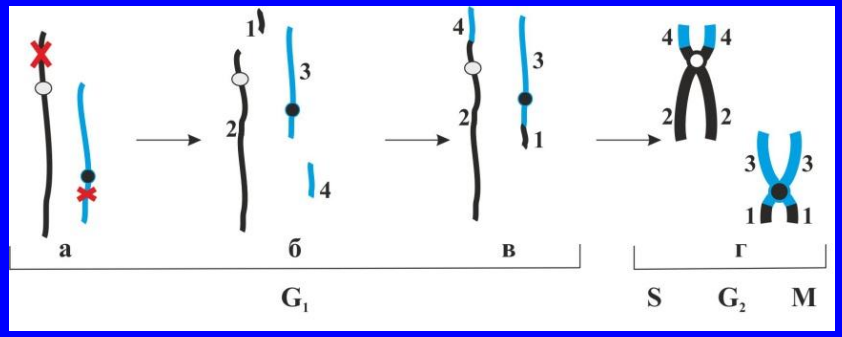
Numerical
Aneuploidy
Monosomy
Trisomy
Tetrasomy
Polyploidy
Triploidy
Tetraploidy
Structural
Translocations
Reciprocal
Robertsonian
Deletions
Insertions
Inversions
Paracentric
Pericentric
Rings
Isochromosomes
Different Cell Lines (Mixoploidy)
Mosaicism
Chimerism

Structural Abnormalities

Structural chromosome rearrangements result from chromosome breakage with subsequent reunion in a different configuration. They can be balanced or unbalanced. In ***balanced rearrangements*** the chromosome complement is complete, with no loss or gain of genetic material. Consequently, balanced rearrangements are generally harmless with the exception of rare cases in which one of the breakpoints damages an important functional gene. However, carriers of balanced rearrangements are often at risk of producing children with an unbalanced chromosomal complement.

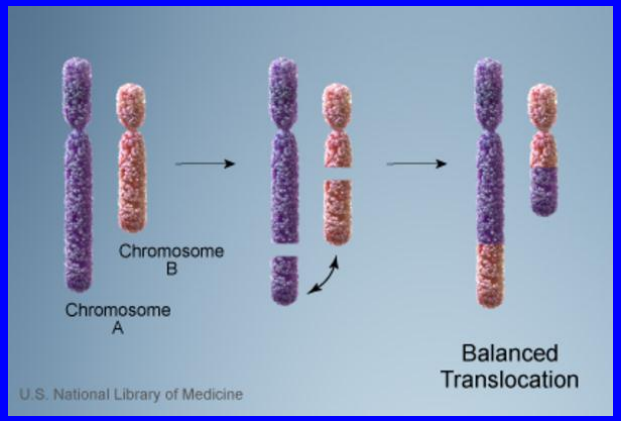
When a chromosome rearrangement is ***unbalanced*** the chromosomal complement contains an incorrect amount of chromosome material and the clinical effects are usually serious.

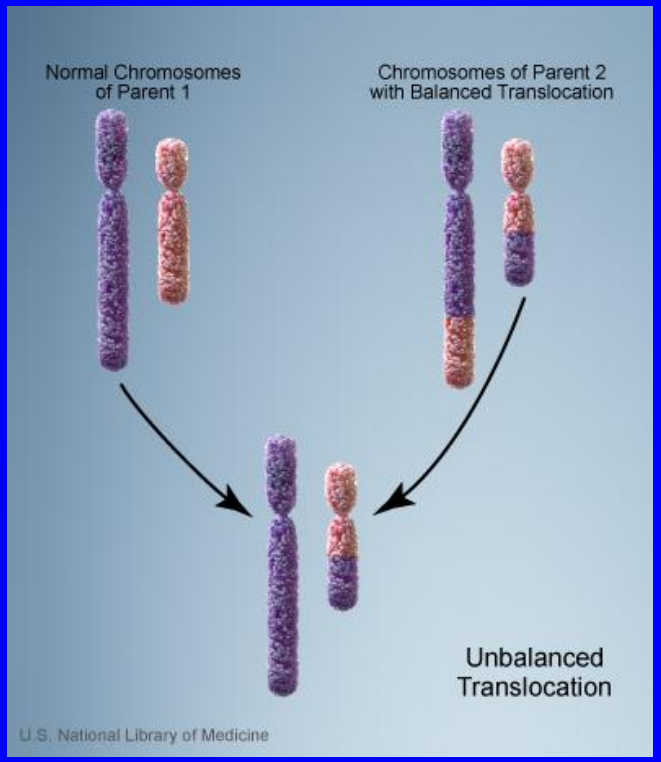


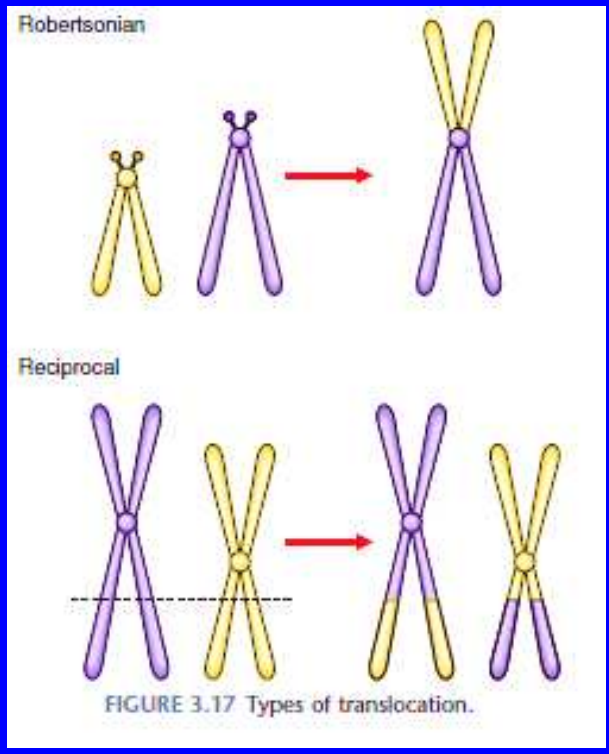


Translocations

A ***translocation*** (t) refers to the transfer of genetic material from one chromosome to another. A ***reciprocal translocation*** is formed when a break occurs in each of two chromosomes with the segments being exchanged to form two new derivative chromosomes. A ***Robertsonian translocation*** is a particular type of reciprocal translocation in which the breakpoints are located at, or close to, the centromeres of two acrocentric chromosomes.





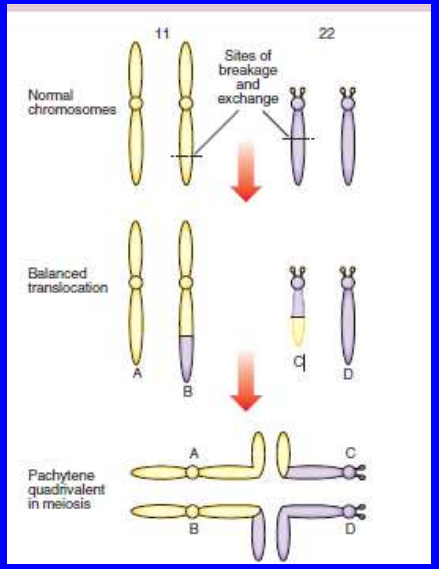


Translocations: Reciprocal translocation

A ***reciprocal translocation*** (rcp) involves breakage of at least two chromosomes with exchange of the fragments. The overall incidence of reciprocal translocations in the general population is approximately 1 in 500.

The importance of balanced reciprocal translocations lies in their behavior at meiosis, when they can segregate to generate significant chromosome imbalance. This can lead to early pregnancy loss or to the birth of an infant with multiple abnormalities. Problems arise at meiosis because the chromosomes involved in the translocation form a cluster (***pachytene quadrivalent***). The key point to note is that each chromosome aligns with homologous material in the quadrivalent.

When counseling a carrier of a balanced translocation it is necessary to consider the particular rearrangement to determine whether it could result in the birth of an abnormal baby. This risk is usually somewhere between 1% and 10%.



Translocations: Robertsonian Translocations

A ***Robertsonian translocation*** (rob) results from the breakage of two acrocentric chromosomes (numbers 13, 14, 15, 21, and 22) at or close to their centromeres, with subsequent fusion of their long (centric fusion). The short arms of each chromosome are lost, this being of no clinical importance as they contain genes only for ribosomal RNA, for which there are multiple copies on the various other acrocentric chromosomes. The total chromosome number is reduced to 45. Because there is no loss or gain of important genetic material, this is a functionally balanced rearrangement.

The overall incidence of Robertsonian translocations in the general population is approximately 1 in 1000, with by far the most common being fusion of the long arms of chromosomes 13 and 14 (13q14q).

Studies have shown that the female carrier of either a 13q21q or a 14q21q Robertsonian translocation runs a risk of approximately 10% for having a baby with Down syndrome, whereas for male carriers the risk is 1% to 3%. It is worth sparing a thought for the unfortunate carrier of a 21q21q Robertsonian translocation. All gametes will be either nullisomic or disomic for chromosome 21. Consequently, all pregnancies will end either in spontaneous miscarriage or in the birth of a child with Down syndrome.

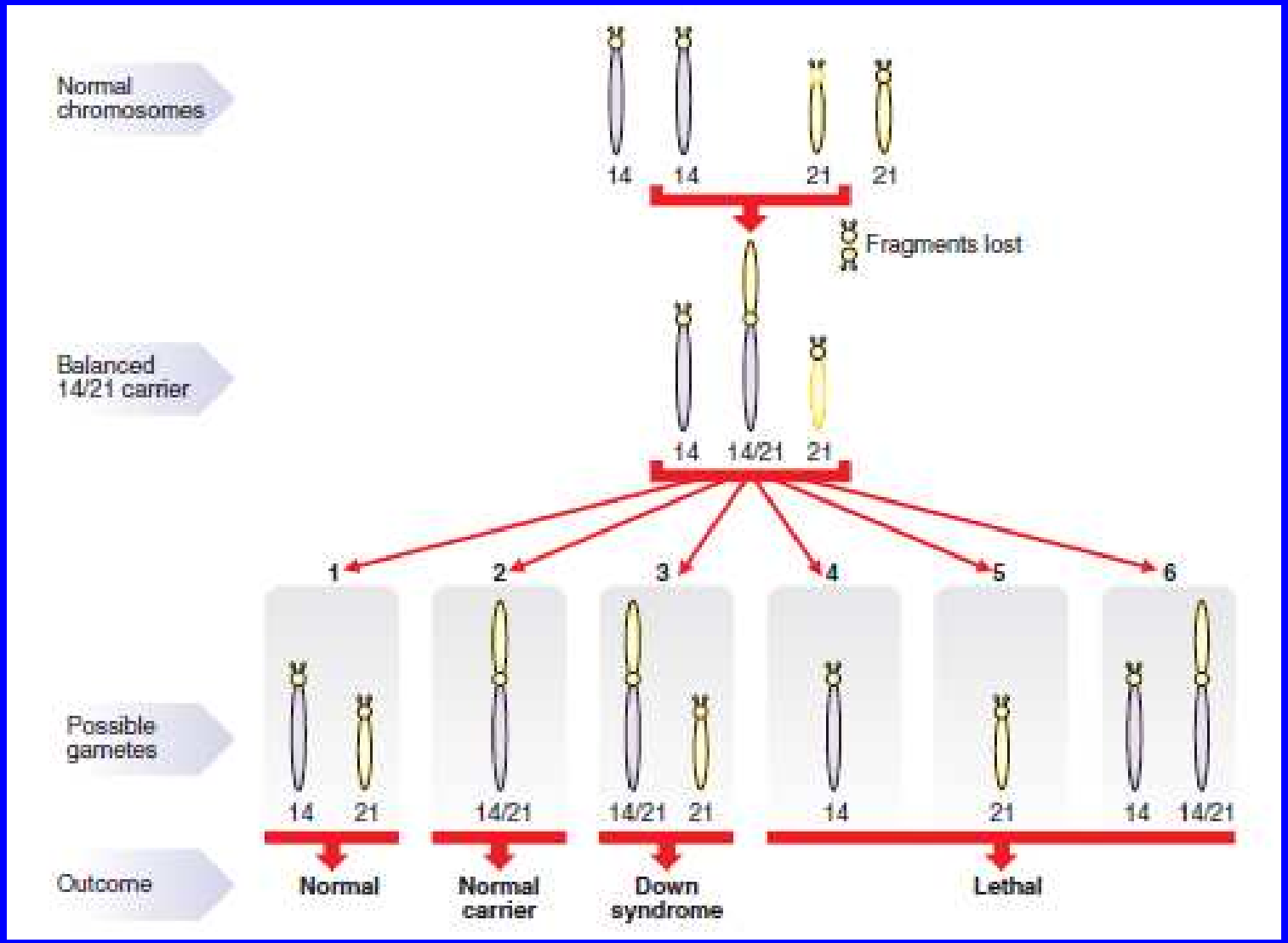
Translocations: Robertsonian Translocations

The importance of Robertsonian translocations lies in their behavior at meiosis. For example, a carrier of a 14q21q translocation can produce gametes with:

1. A normal chromosome complement (i.e., a normal 14 and a normal 21).
2. A balanced chromosome complement (i.e., a 14q21q translocation chromosome).
3. An unbalanced chromosome complement possessing both the translocation chromosome and a normal 21. This will result in the fertilized embryo having Down syndrome.
4. An unbalanced chromosome complement with a normal 14 and a missing 21.
5. An unbalanced chromosome complement with a normal 21 and a missing 14.
6. An unbalanced chromosome complement with the translocation chromosome and a normal 14 chromosome.

The last three combinations will result in zygotes with monosomy 21, monosomy 14, and trisomy 14, respectively. All of these combinations are incompatible with survival beyond early pregnancy.

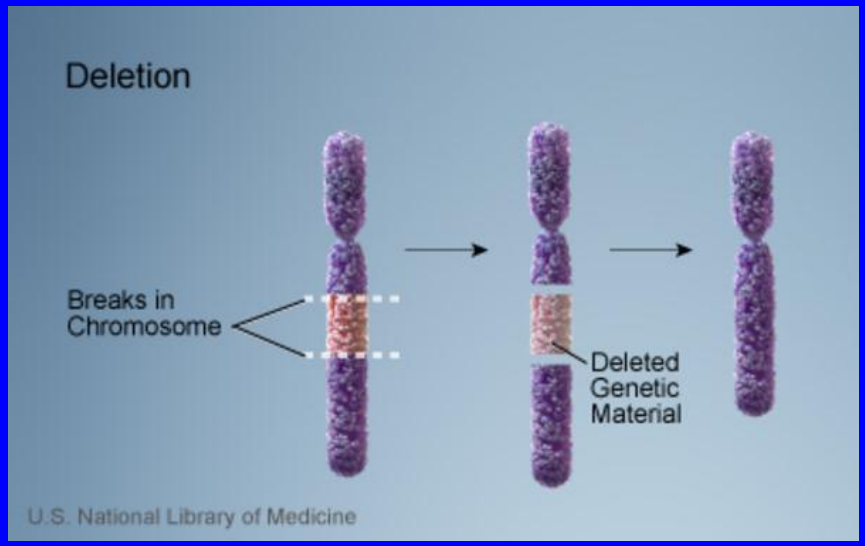
Translocations: Robertsonian Translocations



Deletions

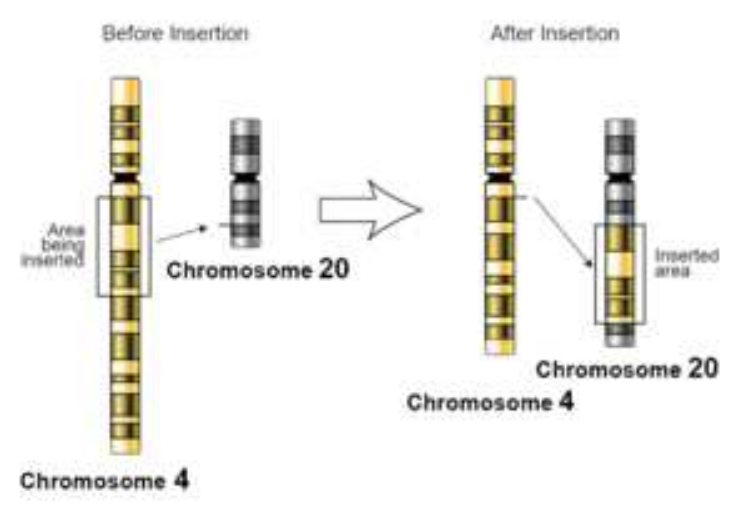
A ***deletion*** (del) involves loss of part of a chromosome and results in monosomy for that segment of the chromosome. A very large deletion is usually incompatible with survival to term, and as a general rule any deletion resulting in loss of more than 2% of the total haploid genome will have a lethal outcome.

Deletions are now recognized as existing at two levels. *A 'large' chromosomal deletion* can be visualized under the light microscope. Such deletion syndromes include Wolf-Hirschhorn and cri du chat, which involve loss of material from the short arms of chromosomes 4 and 5, respectively. *Submicroscopic microdeletions* were identified with the help of high-resolution prometaphase cytogenetics augmented by FISH studies and include Prader-Willi and Angelman syndromes



Insertions

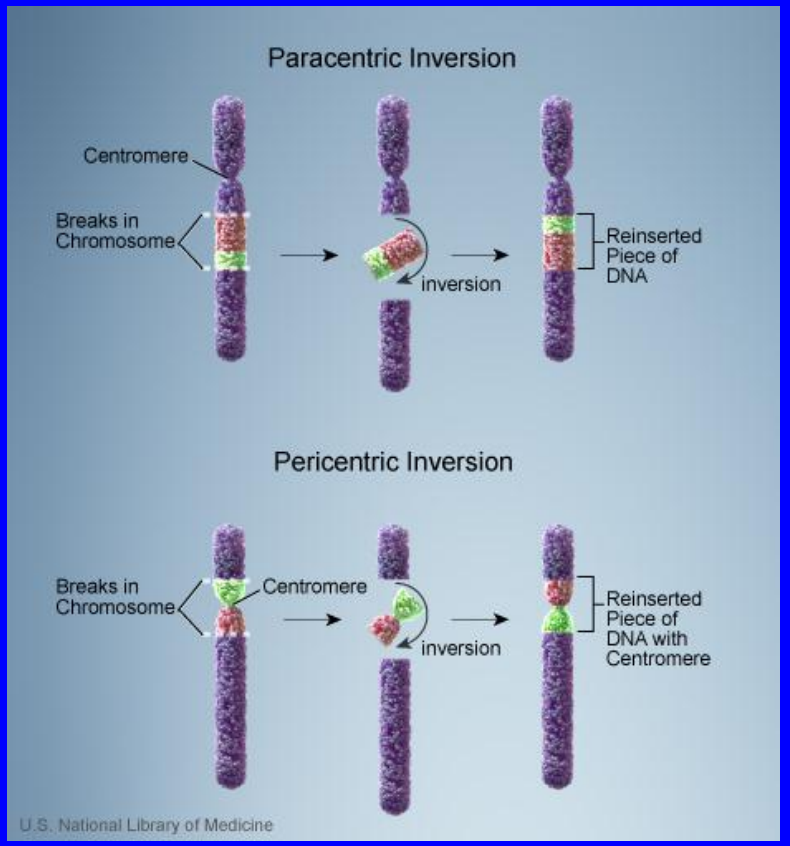
An ***insertion*** (ins) occurs when a segment of one chromosome becomes inserted into another chromosome. If the inserted material has moved from elsewhere in another chromosome then the karyotype is balanced. Otherwise an insertion causes an unbalanced chromosome complement. Carriers of a balanced deletion–insertion rearrangement are at a 50% risk of producing unbalanced gametes, as random chromosome segregation at meiosis will result in 50% of the gametes inheriting either the deletion or the insertion, but not both.



Inversions

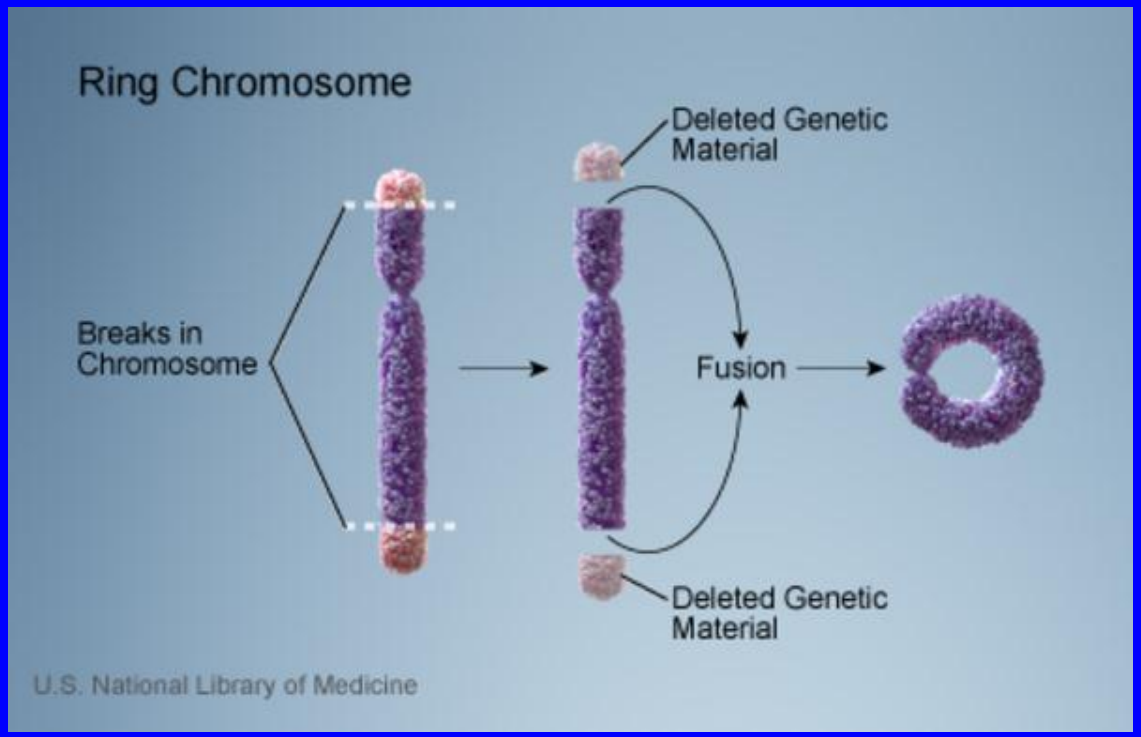
An ***inversion*** (inv) is a two-break rearrangement involving a single chromosome in which a segment is reversed in position (i.e., inverted). If the inversion segment involves the centromere it is termed a ***pericentric inversion***. If it involves only one arm of the chromosome it is known as a ***paracentric inversion***.

Inversions are balanced rearrangements that rarely cause problems in carriers unless one of the breakpoints has disrupted an important gene. A pericentric inversion involving chromosome number 9 occurs as a common structural variant or polymorphism, also known as a ***heteromorphism***, and is not thought to be of any functional importance. However, other inversions, although not causing any clinical problems in balanced carriers, can lead to significant chromosome imbalance in offspring, with important clinical consequences.



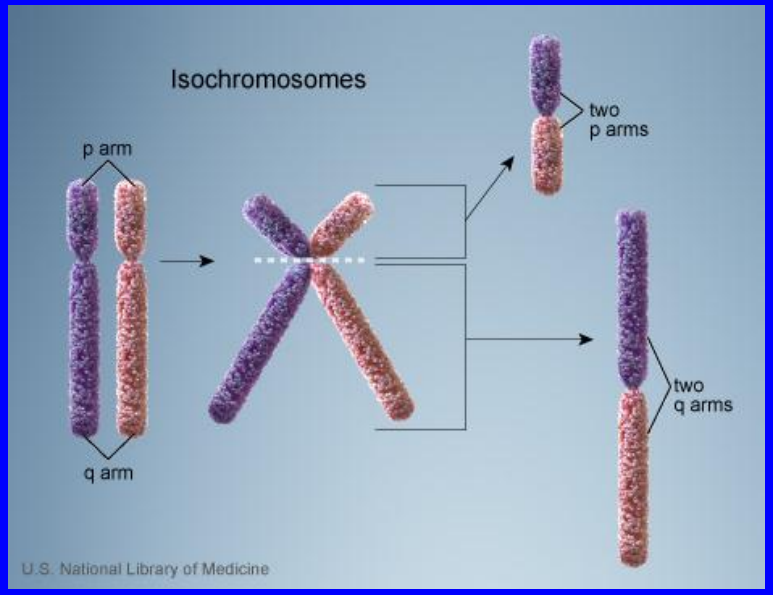
Ring chromosome

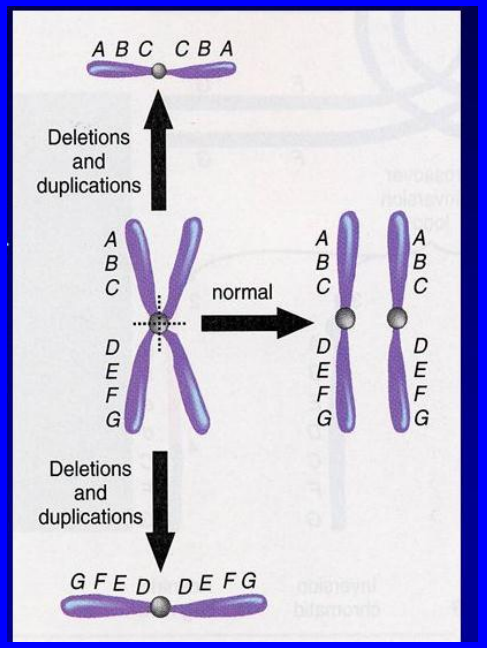
A ***ring chromosome*** (r) is formed when a break occurs on each arm of a chromosome leaving two 'sticky' ends on the central portion that reunite as a ring. The two distal chromosomal fragments are lost so that, if the involved chromosome is an autosome, the effects are usually serious. Ring chromosomes are often unstable in mitosis so that it is common to find a ring chromosome in only a proportion of cells. The other cells in the individual are usually monosomic because of the absence of the ring chromosome.



Isochromosome

An ***isochromosome*** (i) shows loss of one arm with duplication of the other. The most probable explanation for the formation of an isochromosome is that the centromere has divided transversely rather than longitudinally. Also may result from Misdivision of the centromere at mitosis or meiosis, through misrepair of chromatid breaks near the centromere, through crossing over in a small pericentric inversion The most commonly encountered isochromosome is that which consists of two long arms of the X chromosome. This accounts for up to 15% of all cases of Turner syndrome.





Thank you for attention!