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Chromosomal Abnormalities

Cytogenetics:

Is a field of genetics dealing with species or cell specific number of chromosomes, and their structure and characteristic segments, their functional roles, and all the differences - namely the chromosomal mutations - related to them.

Chromosome mutations are changes in the structure or in the number of chromosomes, and since they are relatively rare in this respect they differ from normally occurring common, harmless chromosome polymorphisms. Since both types of chromosome aberrations affecting many genes, and since the size of chromosomes or their affected segments are within the limits of microscopic resolution therefore they can be examined by light microscope, as opposed to gene mutations only be identified by molecular biological techniques. However, the application of modern hybridization based (FISH and CGH) techniques allow the identification of small structural changes (e.g. microdeletions or CNVs) previously unrecognized by light microscope.

Two aspects of the chromosomal abnormalities are regarded crucial: when and where they happen. While chromosome mutations may be formed during both mitosis and meiosis, those may occur in meiosis, lead to defective gamete formation, and to the birth of affected offspring. Thus their medical significance is greater than that of mitotic chromosome aberrations. From the point of mitotic chromosomal abnormalities it is also important when during development and in what kind of cell they are formed. Mutations occurred during the early cleavage divisions may have serious consequences for the entire organism, while aberrations occurred in a continuously proliferating cell type (e.g. epithelial cells) in adulthood may have negligible role. However, certain chromosomal mutations may have a role in the formation and subsequent rapid proliferation of tumor cells.

Two chromosomal regions have special importance in the formation of chromosome aberrations: the **centromeres** and the **telomeres**

Other classification of chromosomal abnormalities depends on fact which type of chromosome is affected – autosomes (down syndrome, digeorge syndrome) or sex chromosomes (klinefelter syndrome, turner syndrome).

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1- Structural chromosome aberrations

The prerequisite of structural chromosome aberrations is breakage of chromosome/s which can be spontaneous or induced. The classification of structural aberrations is based on the number and the location of breaks within chromosomes (Figure 3.1).

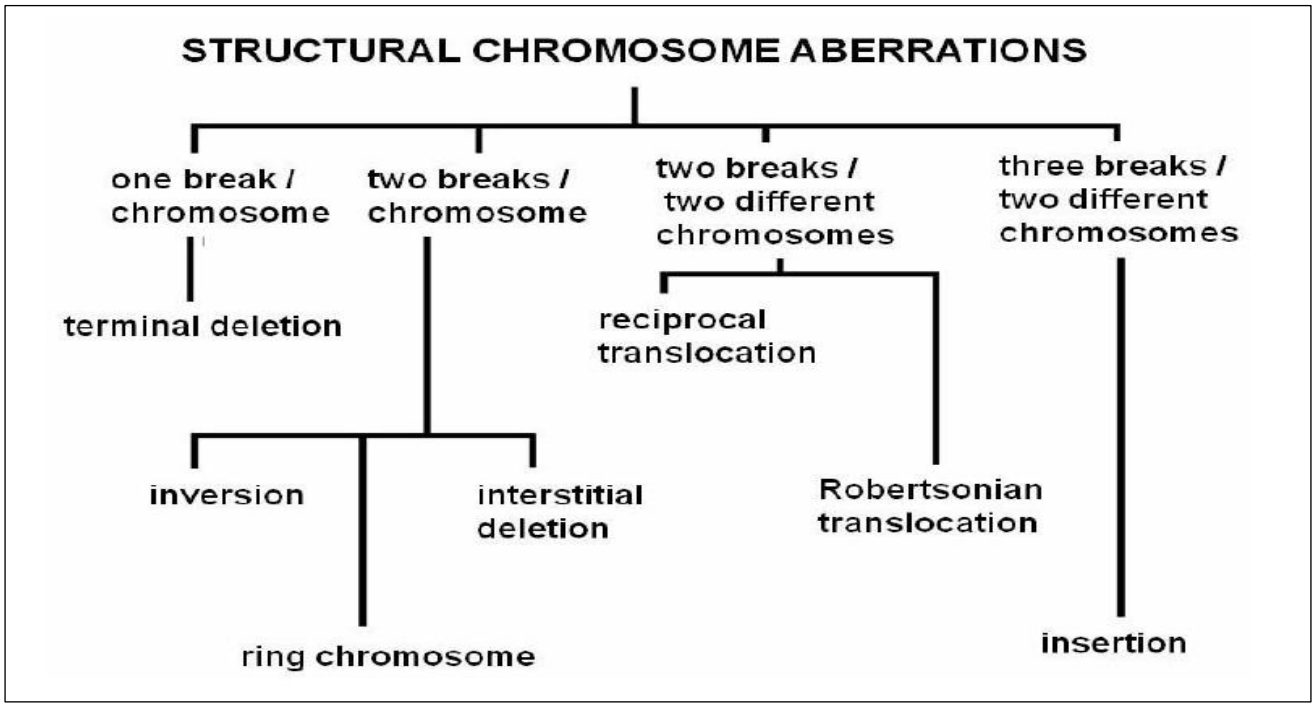

Figure 3.1: The classification of structural chromosome aberrations

1.1 Deletions:

If a chromosome is broken, and the broken piece lost, we are talking about deletion. Then the genetic information carried by the broken piece will be absent from the cell involved, whereupon the cell does not function normally or die. Since the deletions eliminate certain functions therefore certain proteins for example enzymes are not produced. By the help of deletions the location of the gene eliminated can be mapped - it was one of the earliest methods of gene mapping, the deletion mapping

If the break is close to the end of the chromosome, a terminal deletion is generated. In this case, in addition to other genes telomere is lost, too and this also contributes to the severity of symptoms, to early lethality. The best known example of a terminal deletion is the cat cry (cri du chat) syndrome: the short arm of chromosome 5 is deleted (5p-). The disease is named after the affected newborns characteristic mewing cry.

There are two breaks within one chromosome in the case of ***interstitial deletion***, and the intermediate piece is lost. Such lesions usually may cause severe physical and mental disabilities, spontaneous abortion, premature death depending on the chromosome involved. The best known interstitial deletion affects the long arm of chromosome 15: del15 (q11-13). This is one of the causes of Prader-Willi or Angelman syndrome. In the former case paternal deletion, in the latter one maternal deletion is found. Also interstitial, but small, so-called ***microdeletion***s are in background of Williams and DiGeorge syndromes (del7q11.23 and del22q11.2) as well (Figure 3.2).

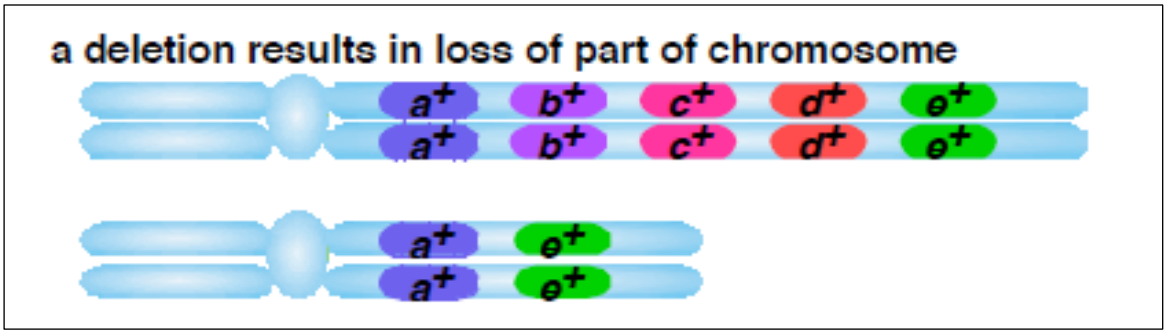

Figure 3.2: deletion of chromosome.

1.2 Duplications

During duplication a chromosomal segment is duplicated. It's either a replication error or due to meiotic unequal crossing over Example - Fragile X: the most common form of mental retardation. The X chromosome of some people is unusually fragile at one tip - seen "hanging by a thread" under a microscope. Most people have 29 "repeats" at this end of their X-chromosome, those with Fragile X have over 700 repeats due to duplications. Affects 1:1500 males, 1:2500 females. Like deletions, duplications are also used to identify the chromosomal location of a gene or group of genes, so to map a gene (Figure 3.2).

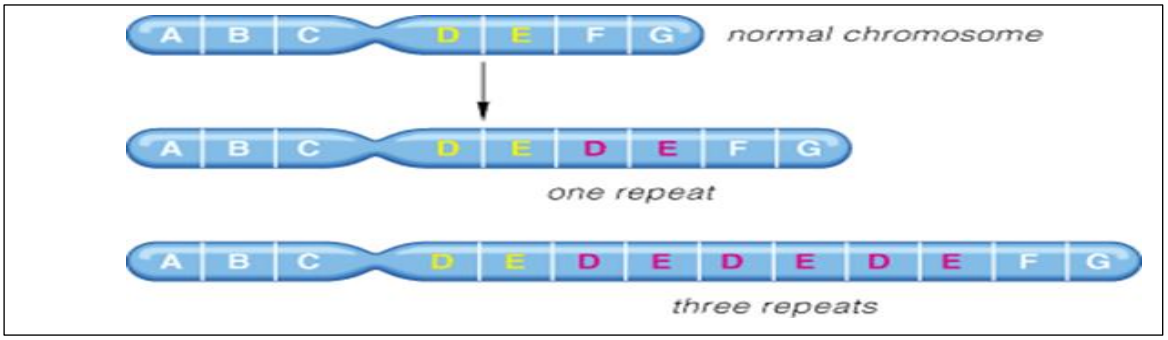

Figure 3.3: Duplication of chromosome.

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1.3 Translocations

During translocation, a part of one chromosome is transferred to another chromosome. It is very important whether the translocation is balanced or unbalanced. Balanced means that two chromosomes just exchange their parts but the number of chromosomes (46 chromosomes) as well as no loss of genetic material stays the same. Fortunately – typical place of break is near the centromere, usually only small arms of the acrocentric chromosomes are lost. There are no crucially important genes coded by these chromosomal segments. So, a carrier of such robertsonian translocation can normally survive this cytogenetic change. Unfortunately, problems occur during the fertilization with a gamete of a carrier of a balanced translocation. Carrier of the translocation may produce unbalanced zygotes, because the process s of homologous chromosomes pairing during meiosis is interrupted. This is very important because unbalanced gametes lead to abnormalities in offspring. The reason is that the offspring receives altered chromosome from the carrier which may lack several important genes. Therefore the only clinical symptom found in the carriers of balanced translocations may be the reproduction failure (Figure 3.4).

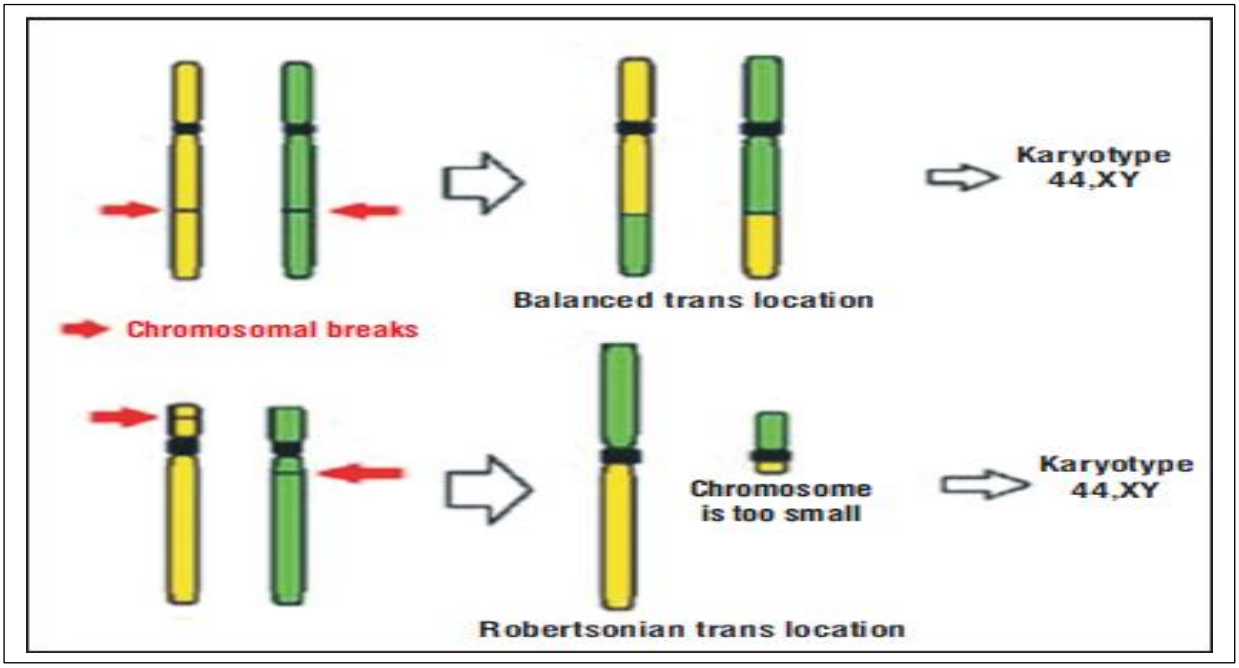

Figure 3.4: Translocation chromosome

Types of translocation :

A- Reciprocal – translocation between two chromosomes ("a segment" goes to "b chromosome" and "b segment" goes to "a chromosome")

B- B- Robertsonian – translocation (or fusion) of two acrocentric chromosomes.

The best example of reciprocal translocations leading to the formation of the ***Philadelphia chromosome (Ph1)***, is between 9 and 22 chromosomes, its cytogenetic abbreviation is t(9;22)(q34;11). This translocation occurs in ***chronic myeloid (CML)*** or ***acute lymphocytic leukemia (ALL)***. The breakpoint in chromosome 22 is in the BCR (breakpoint cluster region) gene, while the breakpoint of chromosome 9 affects in the ABL (Abelson murine leukemia) proto-oncogene. Since the ABL gene encodes a tyrosine kinase as the result of the translocation a BCR / ABL fusion protein is produced which not only has a greater molecular weight than the original enzyme, but also a higher activity. In fact, during this translocation the well-regulated promoter of ABL gene is lost, and the gene permanently overexpressed. Finally this leads to uncontrolled cell proliferation, i.e. the development of the tumor.

Another medically important example is the Burkitt's lymphoma caused mostly by Epstein-Barr virus. In this disease the c-myc proto-oncogene coded by chromosome 8 is translocated to chromosome 14 or 2 or 22. These two cases are examples of the relationship between translocations and proto-oncogenes, where the overexpression of a normal protein (Burkitt's lymphoma), or a fusion protein - although of normal function - regulation of independent production (CML) is responsible for tumor formation.

1.4.Inversions

For inversion are typical two breakages in the different part of the chromosome. The newly created segments then replace each other. Inversion was discovered in 1921. Although we still don´t know why inversion exists, we know that it is the most important mechanism of reorganizing of the genome.

There are 2 types of inversion:

A-Pericentric – the chromosome breakages are on both arms, that is on both sides of the centromere. The pericentric inversion of chromosome 9 is relatively common and found frequently in couples with recurrent abortions.

B- Paracentric – breakpoints are on the same arm of the chromosome, thus in the turn of the fragment the centromere is not involved more common type, it is less harmful for its carrier. Inversion suppresses the recombination process (Figure 3.5).

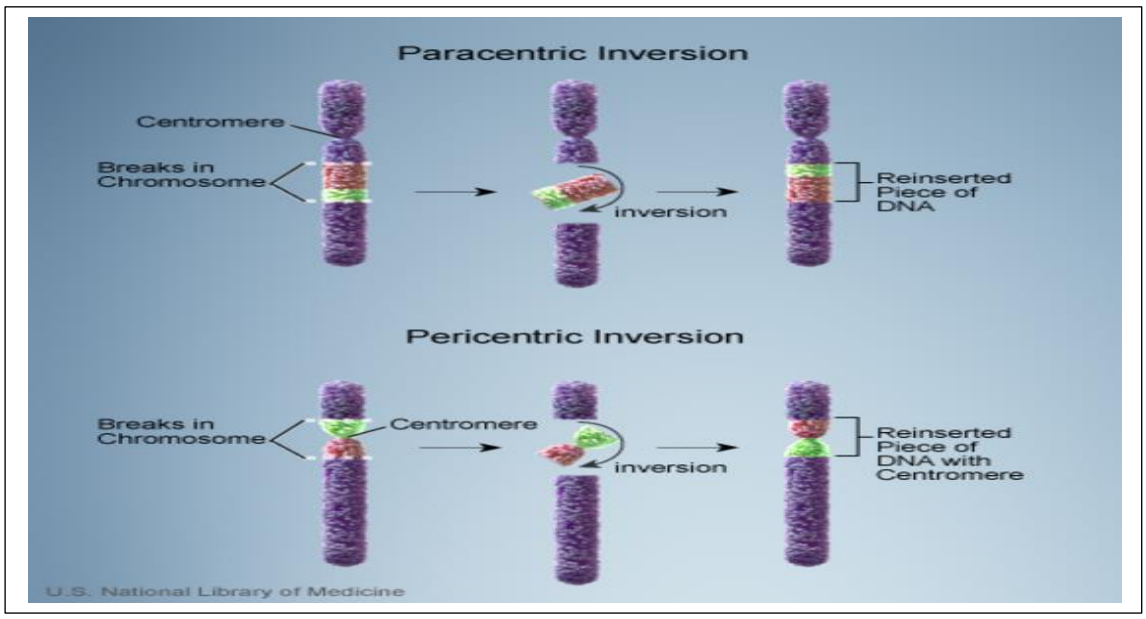

Figure 3.5: Pericentric and Paracentric inversion

1.5. Ring (ring) chromosome In this case, there are breaks on both arms of the chromosome - usually near the telomeres - then broken ends fold and a ring chromosome is formed. The fragments broken are lost during successive divisions.

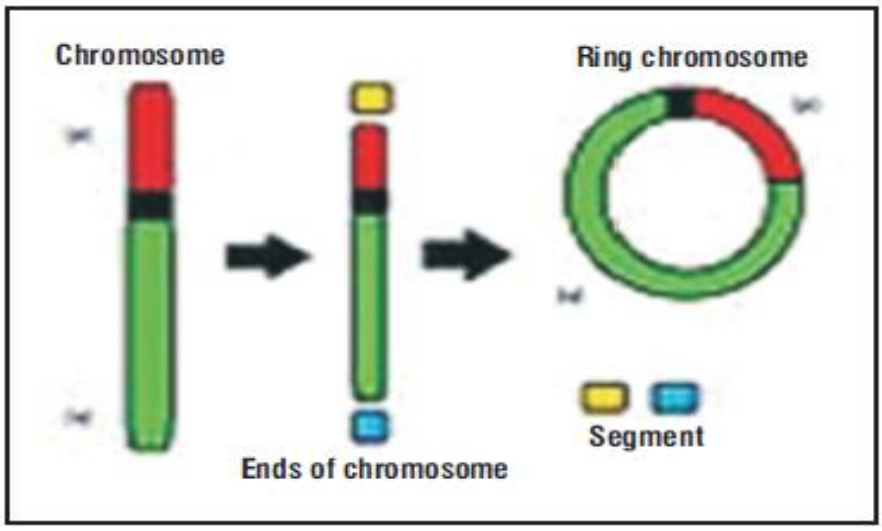

Figure 3.6: Ring chromosome

1.6. Isochromosome

Isochromosomes are created by the incorrect division of centromere. Normally centromere divides vertically. In this case it divides horizontally. The result is usually

the loss of one arm. It means that newly created chromosome has just two long arms or two short arms which are normally connected by centromere. It occurs relatively frequently in X chromosome. It is a huge problem during the fertilization. Because fetus then becomes trisomic for one arm and monosomic for the second arm. Thus aberrant chromosomes ultimately cells containing them are formed which contain either the short arm or the long arm specific information only on both arms and the information of the other arm is lost (Figure 3.7).

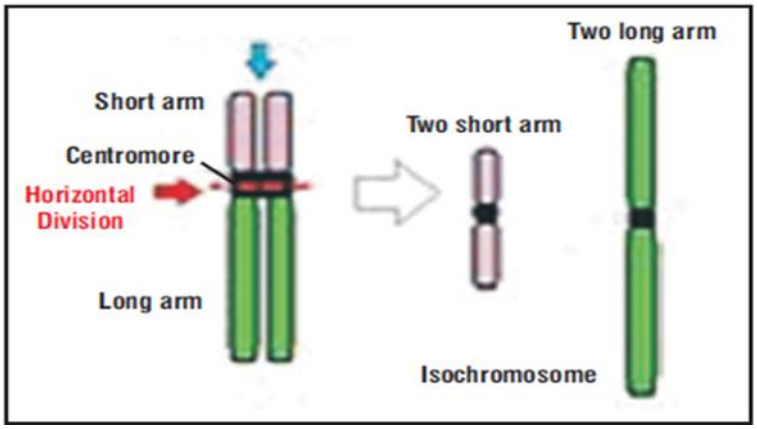

Figure 3.7: Isochromosome

1.7. Acentric fragment

More rarely broken fragment(s) without a centromere remain in the cytoplasm as small fragments. Due to the absence of centromere such pieces cannot migrate to cell poles and either a so called micronucleus is formed or they are during the subsequent cell divisions, and finally only the deleted chromosomes has retained within the cell. Since these acentric fragments are most commonly induced by some chromosome breakage causing mutagenic agents such as radiation, therefore they can be used for testing the mutagenic effects (micronucleus test).