

## CHROMOSOMAL ABNORMALITIES

*Chromosomal abnormalities* represent changes in chromosomes number (46 in human somatic cells) or their structural modifications. Thus, there are **genomic mutations** (that explains chromosomal number abnormalities), and **chromosomal aberrations** (that explain chromosomal structure abnormalities). Chromosomal disorders form a category of human genetic diseases, that are manifested by developmental and reproductive abnormalities, as well as playing an important role in the pathogenesis of malignancy.

Chromosomal abnormalities may be produced by:

- mitosis deregulating factors that produce DNA tears or affects replication
- chemical factors
- physical factors, as ionizing radiations
- biological factors as viruses
- mother advanced age increase offspring's aneuploidy risk
- one of the parents is carrier of equilibrate congenital abnormality (translocations, inversions)
- chromosomal rearrangements (unequal crossing-over, recombination's errors).

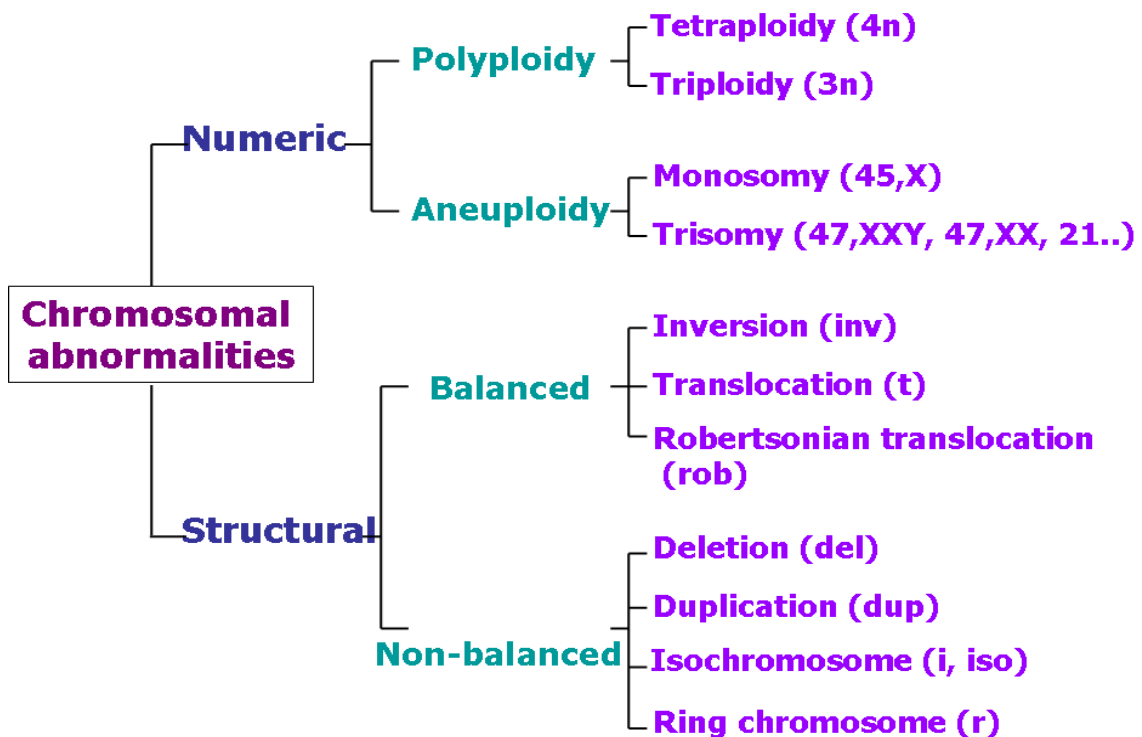


Fig.1. Classification of chromosomal abnormalities

## NUMERICAL ABNORMALITIES

**Numerical chromosomal abnormalities** include all the situations with total number of chromosome different than normal.

**Polyploidy** - the addition of complete haploid sets of chromosomes:

- $2n+n=3n$ , triploidy; examples: 69,XXX or 69,XXY or 69,XYY;
- $2n+2n=4n$ , tetraploidy; examples: 92,XXXX or 92,XXYY.

The triploidy may result during fecundation an abnormal gamete ( $2n$  =diploid) by normal one ( $n$ =haploid): diploid gamete is a result of II cite unseparation in parental meiosis (usually during ovogenesis , I polar corpuscle unexpulsion -digeny , and sometime during spermatogenesis –diandry ); fecundation errors : a ovule ( $n$ ) fecundation by two spermatozoids ( $2n$ )- dispermy .

The tetraploidy may result as a cleavage error during first zygote mitotic division , and chromosomal number duplication immediately after fecundation (endomitosis) , or 2 diploid gametes fecundation ( $2n+2n=4n$ ). The ploiploidies affects a wide genetic material amount and usually are unviable (abortion in I trimester term or dead new- borns).

**Aneuploidy** - the addition or loss of one, rarely, two chromosomes:

- $2n+1=47$ , trisomy
- $2n-1=45$ , monosomy.

Most trisomic embryos are lost early in pregnancy (the defects are so grave that the fetus cannot survive). Viability of embryos with trisomy depends on the type of the involved chromosome and the genetic content of this chromosome. As examples of viable trisomies could be trisomies 13, 18, 21, 8. All other trisomies that affect autosomes are lethal.

Trisomy for sex chromosomes has less pathological consequences on development and most fetuses survive up to birth.

Monosomy X is a single viable monosomy. All autosomal monosomies are lethal.

Most cases of aneuploidies are caused by chromosomal or chromatidian segregation errors in cells division called nondisjunctions. In these cases chromosomes number in daughter cells is unequal. This abnormalities can be produced in I,II meiosis, and mitosis. Sometimes nulisomic gametes, and then monosomic embryo can be produced as a result of chromosomes losses through anaphases late at equatorial plate level. The homogeny aneuploidies are the results of an normal gamete fecundation by an abnormal one produced by genetic material distribution errors in parental meiosis. The mosaic aneuploidies are

results of genetic material distribution errors in mitosis (usually sequent divisions of first embryonic levels).

**Aneuploidies** could be classified according to the following criteria:

a) type of the involved chromosome:

- autosomal - an autosome is extra/missing, ex: 47,XY, +21; 47,XX, +13; 47,XY, +18; 47,XX +8; 47,XY, +5 etc;
- gonosomal - a gonosome is extra/missing, ex:45,X; 47,XXX; 47,XXY; 47,XYY, 48,XXXY, 48,XXYY.

b) number of the affected cells:

- homogenous (abnormality presence in all body's cells) , ex: 47,XX, +13; 45,X; 47,XXX; 48,XXYY.
- mosaic ( normal and abnormal cells clones in the same body), ex: 45,X/46,XX,; 46,XY/\$\&,XY,+21.

c) structure abnormalities association or absence:

- free –without structural chromosomal abnormalities - ex: 47,XX, +13; 47,XY, +18; 47,XX +8.
- associated – the presence of some surplus chromosomes attached to other without normal diploid number modification, or false chromosome absence as a result of fusion with another one – ex: 46, XX, rob 21/21; 45,XY,rob13/13.

d) integrity of the affected chromosome:

- complete/total - an entire chromosome is extra/missing, ex:45,X; 47,XX, +13; 47,XXY;
- incomplete/partial – a part of chromosome is extra/missing, ex: 46,XXp-; 46,XXq-, 46,XY, i21q.

The effects and gravity of quantitative chromosomal abnormalities depend on :

- the abnormality type and genetic lack of balance proportion: the deficit has more grave results than the excess.
- gene contents and implicated chromosome activity –for ex., trisomy 1 is not viable , trisomy 21 is viable.

The type and number of affected cells- somatic cells affectation lead to individual phenotype modifications; sexual cells affectation lead to reproduction disorders.

## Table

### The major numerical abnormalities that survive to term

Syndrome	Abnormality	Incidence per 10 000 births	Lifespan (years)
Down	Trisomy 21	15	40
Edward's	Trisomy 18	3	<1
Patau's	Trisomy 13	2	<1
Turner's	Monosomy X	2 (female births)	30-40
Klinefelter's	XXY	10 (male births)	Normal
XXX	XXX	10 (female births)	Normal
XXY	XYY	10 (male births)	Normal

## STRUCTURAL CHROMOSOMAL ABNORMALITIES

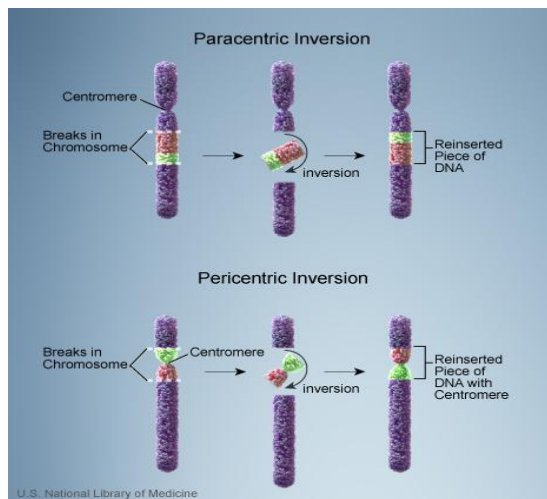
Structural chromosomal abnormalities are rearrangements of genetic material within or between chromosomes. Based on phenotypic effects, structure chromosomal abnormalities are divided in:

- Balanced rearrangements - usually do not lead to phenotypic abnormalities; all genetic information is present in the right amount, just in a different order or in the wrong location.
- Unbalanced rearrangements - there is a loss or gain of chromosome content, the phenotype of carrier is abnormal.

### Balanced abnormalities

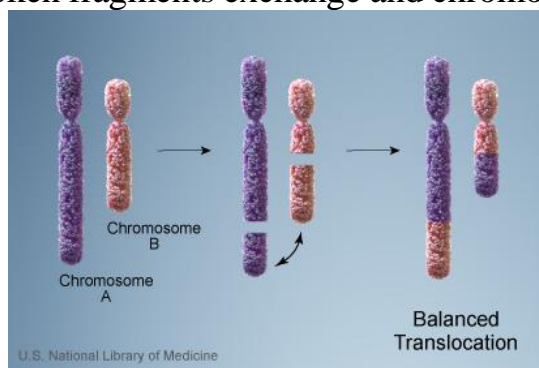
The inversion is a structure abnormality characterized by genes order modification in a chromosomal fragment. Producing mechanism consist in two points chromosome's tearing and 180 rotation of the intermediary fragment.

Inversions are of two types: *pericentric*: produced by two points tearing on different shoulders of the same chromosome, followed by a 180 rotation of intermediary fragment and fragments gathering; after this rotation chromosome's configuration is modified ; *paracentric* produced by two points tearing on the same shoulder, followed by a 180 rotation of the intermediary fragment and fragments gathering; after this rotation chromosome's configuration is not modified but just bends order.



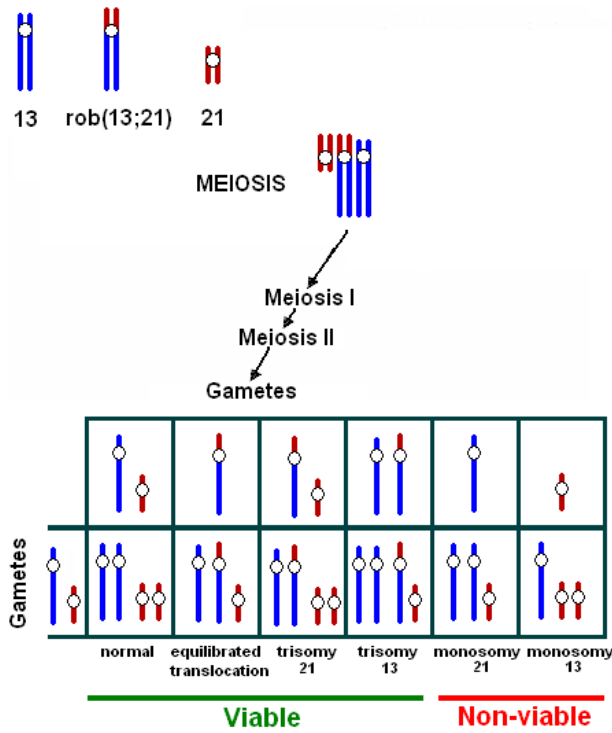
The translocations are structure abnormalities characterized by one or more fragments passing from one chromosome to another one, without phenotypic modifications. The translocations are of three types:

*balanced* (reciprocal) – produced by one tear in both chromosome, followed by broken fragments exchange and chromosomes joining.



*with insertions*- produced by two non-homologous chromosomes, one in a point and another one in two points on the same shoulder followed by second chromosomes intermediary fragment insertion in the first chromosome tearing point

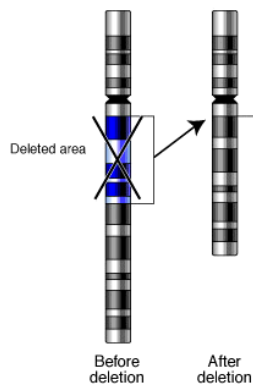
*Robertsonian translocations*- produced by two acrocentric chromosomes tearing at the centromer followed by long shoulders fusion (centric fusion) and short shoulders loss(they contains rRNA genes, and so its loss not determine phenotypic modification. This kind of abnormalities lead to chromosomes number decrease fro 46 to 45.



Balanced chromosomal abnormalities don't modify individual phenotype, because of chromosomal rearrangements that don't determine quantitative genetic material modifications. But a balanced translocation carrier, phenotypic normally, can produce abnormal gametes, because of conjugation errors and segregation errors of chromosomes implicated in replication.

### Non-balanced abnormalities

*The deletions* are structural abnormalities characterized by some chromosomal fragments loss.

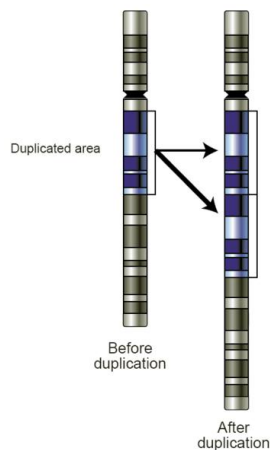


Abnormalities are of two types:  
*terminal* –produced by one point chromosomal tearing, followed by the terminal fragment loss.

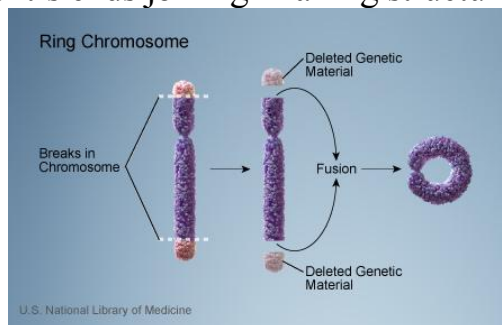
*interstitial-* produced by chromosomal tearing in two points of the same shoulder, followed by the intermediary fragment loss.

The deletions can be produced by other mechanism: unequal *crossing-over* between erroneous aligned homolog chromosomes, abnormal chromosomes segregation in parental meiosis when one of the parents presents a non- balanced abnormality. The deletion has as a effect a difference of homologue chromosomes length.

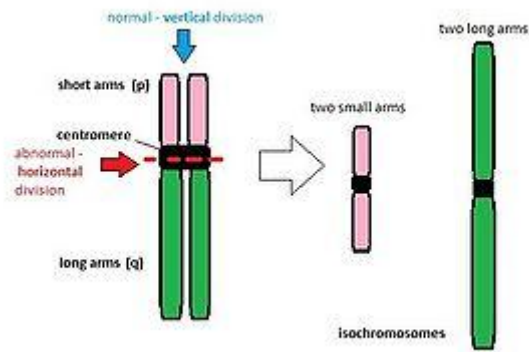
*The duplications* are structural abnormalities characterized by double example of the same chromosome's fragment. The abnormality can be produced by unequal crossing-over and abnormal segregation of the chromosomes with translocations.



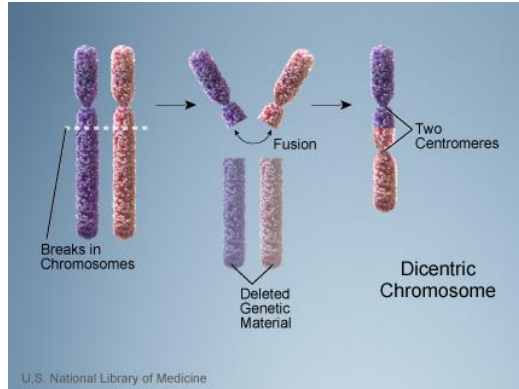
*Ring chromosomes* appeared after chromosomal tearing in two points of different shoulders, followed by terminal segment (acentric) loss and centric segment's ends joining in a ring structure.



*The isochromosomes* are abnormal chromosomes formed of two short shoulders or of two long shoulders. The producing mechanism is transversal cleavage of the centromere. The abnormality has as a effect a chromosome with the deletion of one of the shoulders and the duplication of another one.



*Dicentric chromosomes* are abnormal chromosomes with two centromeres in the same chromosome. Producing mechanism consists in two chromosomes tearing in a point for each other, followed by terminal fragments loss and the joining of the both chromosomes that has centromeres. Non-balanced chromosomal abnormalities determines a quantitative lack of piece of the genetic material (surplus or absence) that are phenotypic manifested as a number abnormality like (partial trisomy and partial monosomy). The trisomies and the monosomies of a chromosomes determine different abnormal traits in “*type and contratype*” like complete monosomy and trisomy of the same chromosome: trisomy 18 (Edwards sdr.) and partial trisomy determinate by 18q-; trisomy 13 (Patau sdr.) and partial monosomy determinate by r(13).





## ***CLINICAL FEATURES OF CHROMOSOME ANOMALIES***

Chromosome aneuploidies and unbalanced chromosome rearrangements are associated with well-defined clinical syndromes. A syndrome is a group of clinical features that are characteristic for a particular anomaly. Chromosome syndromes have been described for all chromosomes. Only a few of the commonest syndromes are outlined here.

### ***Trisomy 21 - Down's Syndrome***

Karyotype: 47,XX+21 or 47,XY+21

Frequency : 1 in 600 births

#### **Clinical features:**

- \* Mental retardation
- \* Hypotonia
- \* Flat occiput (brachycephaly)
- \* Round flat face
- \* Slanting palpebral fissure
- \* Broad nose
- \* Protruding tongue
- \* Short fingers (brachydactyly)
- \* Increased frequency of congenital heart disease

### ***Trisomy 18 - Edwards Syndrome***

Karyotype: 47,XX+18 or 47,XY+18

Frequency: 1 in 8,000 births; Predominance of females 4F:1M

#### **Clinical features:**

- \* Growth retardation
- \* Small mouth
- \* Micrognathia (small chin)
- \* Flat, pointed ears
- \* Short neck
- \* Clenched hands with overlapping fingers
- \* Rocker-bottom feet
- \* Cleft lip, congenital heart disease and diaphragmatic hernia are common.

### ***Trisomy 13 - Patau Syndrome***

Karyotype 47,XX+13 or 47,XY+13

Frequency of Trisomy 13: 1 in 10,000 births

#### **Clinical features:**

- \* Microphthalmia
- \* Cleft lip and palate (often bilateral)
- \* Polydactyly of hands and feet
- \* Microcephaly
- \* Scalp defect
- \* Early death

***5p monosomy (deletion) - Cri-du-chat syndrome***

Karyotype: 46,XX5p- or 46,XY5p-

Frequency : 1 in 50,000 births

**Clinical features:**

- \* characteristic cat-like cry (due to underdeveloped larynx)
- \* microcephaly
- \* round "moon-like" face
- \* micrognathia
- \* hypertelorism

***Klinefelter Syndrome - 47,XXY***

Frequency: 1 in 1,000 males (occurs only in males)

**Clinical features:**

- \* Testicular atrophy and azoospermia
- \* Gynaecomastia
- \* Usually tall stature

***Turner Syndrome - 45,X***

Frequency: 1 in 2,500 females (occurs only in females)

**Clinical features:**

- \* short stature
- \* lack of pubertal development
- \* amenorrhoea
- \* ovarian dysgenesis
- \* low posterior hair line
- \* webbed neck