Genetic Diseases
LEC. 3

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3. Diseases arising from chromosomal abnormalities (Cytogenetic disorders):

- Result from alterations in the number or structure of chromosomes and may affect autosomes or sex chromosomes.
- **1:200** newborn infants have some form of chromosomal abnormalities.
- **50%** of first trimester abortion is due to chromosomal abnormalities.

- Before discussion of chromosomal aberrations, it is appropriate to review karyotyping as the basic tool of the cytogeneticist.
- **Karyotype** is a paragraphic representation of a stained metaphase spread in which the chromosomes are arranged in order of decreasing length.
- A variety of techniques for staining chromosomes has been developed. With the widely used Giemsa stain (G banding) technique, each chromosome set can be seen to possess a **distinctive pattern of alternating light and dark bands of variable widths**

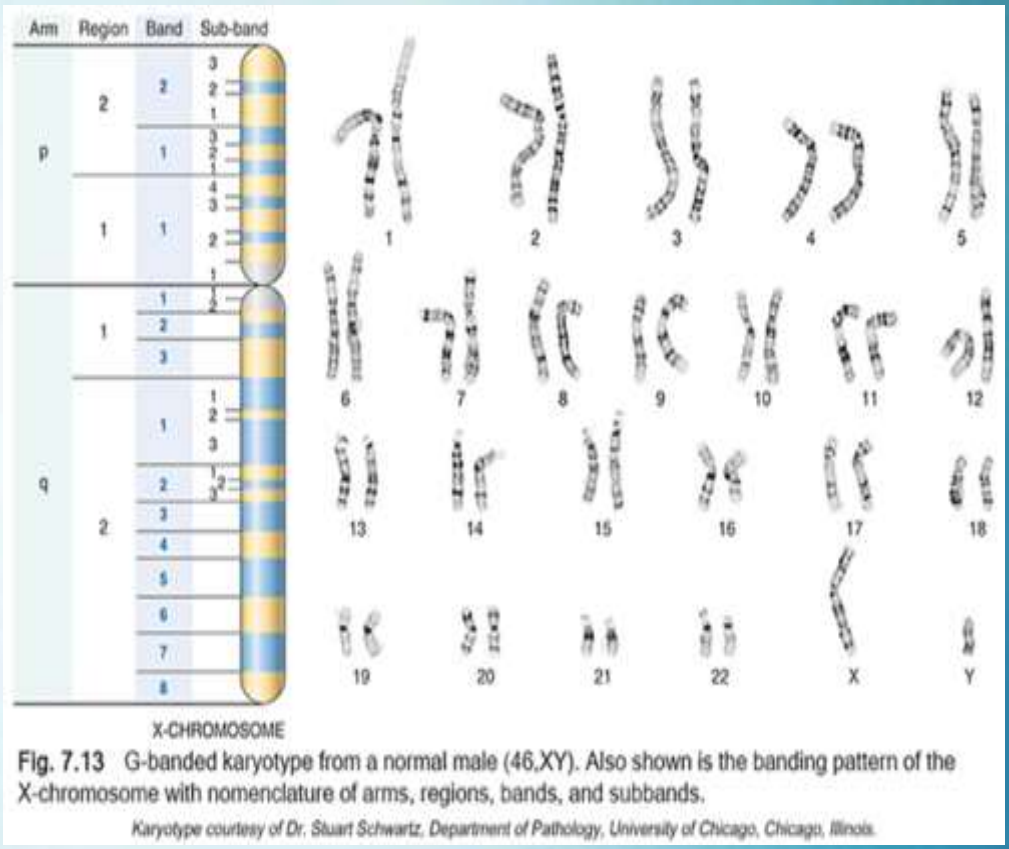


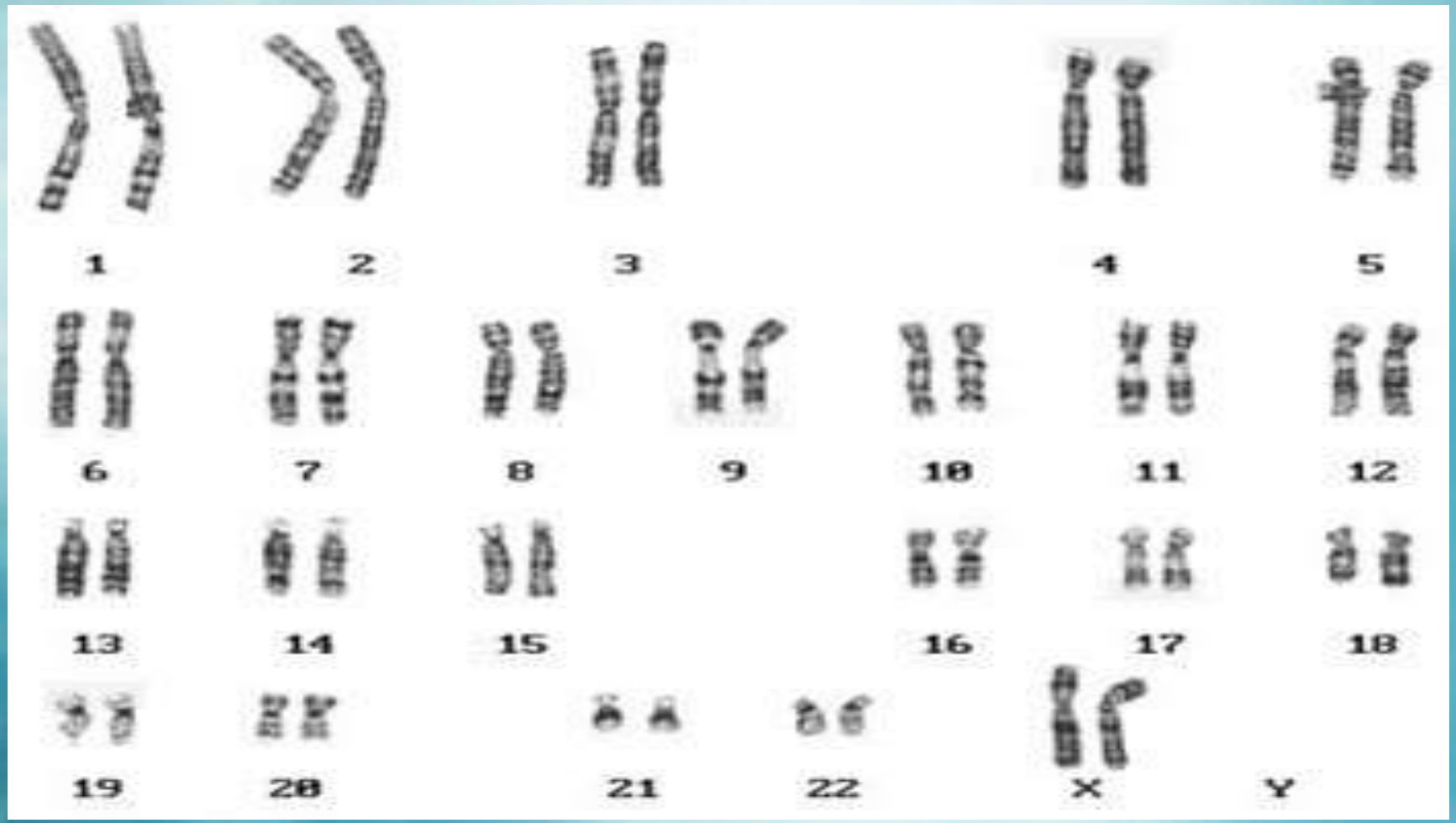
Fig. 7.13 G-banded karyotype from a normal male (46,XY). Also shown is the banding pattern of the X-chromosome with nomenclature of arms, regions, bands, and subbands.

Karyotype courtesy of Dr. Stuart Schwartz, Department of Pathology, University of Chicago, Chicago, Illinois.

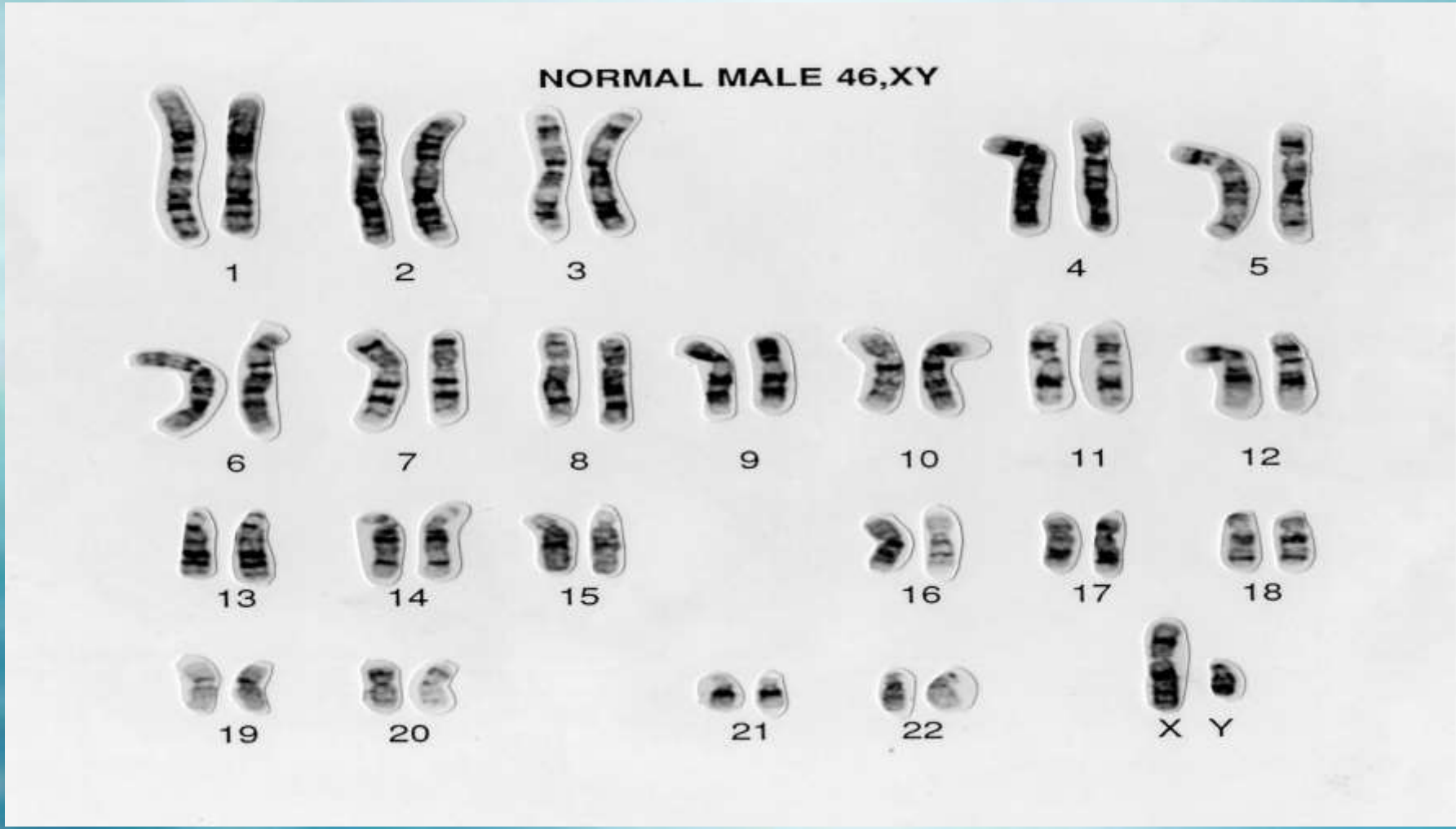
How to write a karyotype?

1. The number of chromosomes
2. The gender
3. Chromosomal disorders if present

Normal female karyotype
46 XX



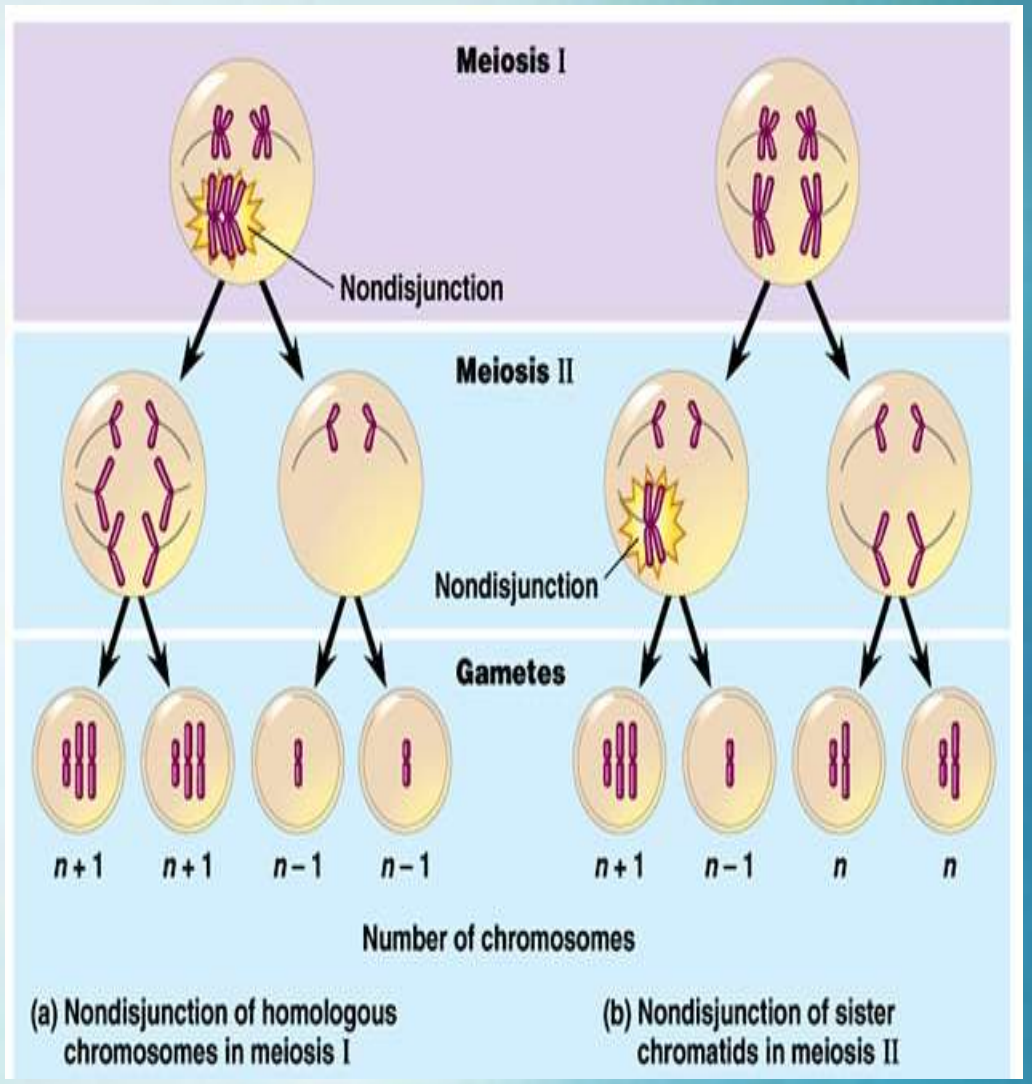
Normal male karyotype
46 XY



A. Numerical abnormalities:

- Are defined as a gain or loss of one or more chromosome(s) whether an autosome or a sex chromosome.
- The normal chromosome count is **46 (2n =46)**; an exact multiple of the **haploid number (n)** is called **euploid (normal state).**
- Chromosome numbers such as **3n and 4n** are called **polyploidy** (Incompatible with life); generally results in a spontaneous abortion.
- Any number that is not an exact multiple of the haploid (n) is **Aneuploidy (e.g. 47 or 45).**

- Most common cause of Aneuploidy is nondisjunction (attach) of either a pair of homologous chromosomes during meiosis I or failure of sister chromatids to separate during meiosis II.
- The resultant gamete will have either an extra chromosome (n+1) or one less chromosome (n-1).



- Fertilization of such gametes by normal gamete will result in two types of zygotes:
  - Trisomic with extra chromosome (2n+1) (e.g. Down's), or monosomic (2n-1) (e.g., Turner's).

- Monosomy involving an autosome is incompatible with life, whereas monosomy involving sex chromosomes & trisomy's of certain autosomes is compatible with life.

❖**Mosaicism**: term used to describe the presence of two or more populations of cells in the same individual (normal cells and monosomy or trisomy cells)

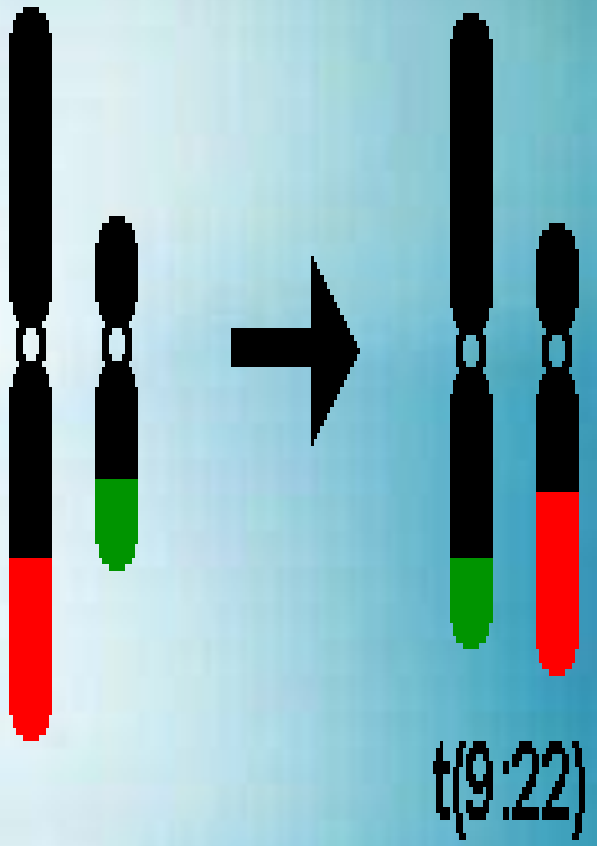
- Mosaicism affecting sex chromosomes is common while autosomal is much less frequent.
- Mosaicism is caused by an error in cell division very early in the development of the unborn baby
- **Examples of mosaicism include:**
- **Mosaic Down Syndrome**
- **Mosaic Klinefelter Syndrome**
- **Mosaic Turner Syndrome**

B. Structural abnormalities:

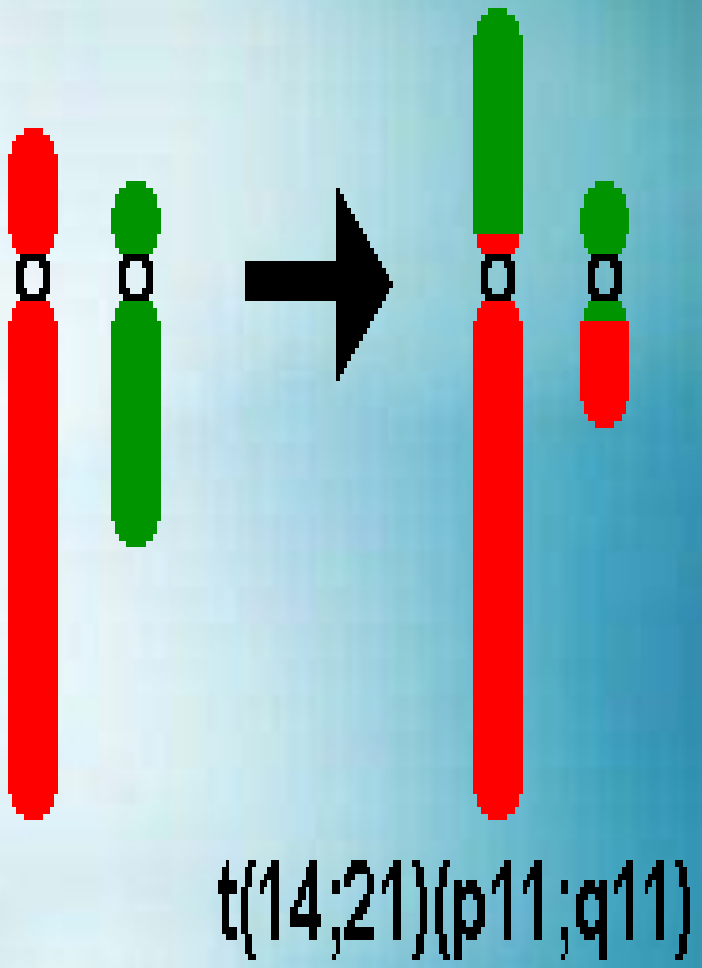
- In this case, the cell has a normal number of 46 chromosomes but they are morphologically or structurally abnormal.
- Structural abnormalities usually result from chromosomal breakage followed by loss or rearrangement of material.
- **They are of different types as follows:**

1- Translocation:

- Transfer of a part of one chromosome to another chromosome.
- The process is usually *Regular, balanced (reciprocal) translocation* when fragments are exchanged between two chromosomes

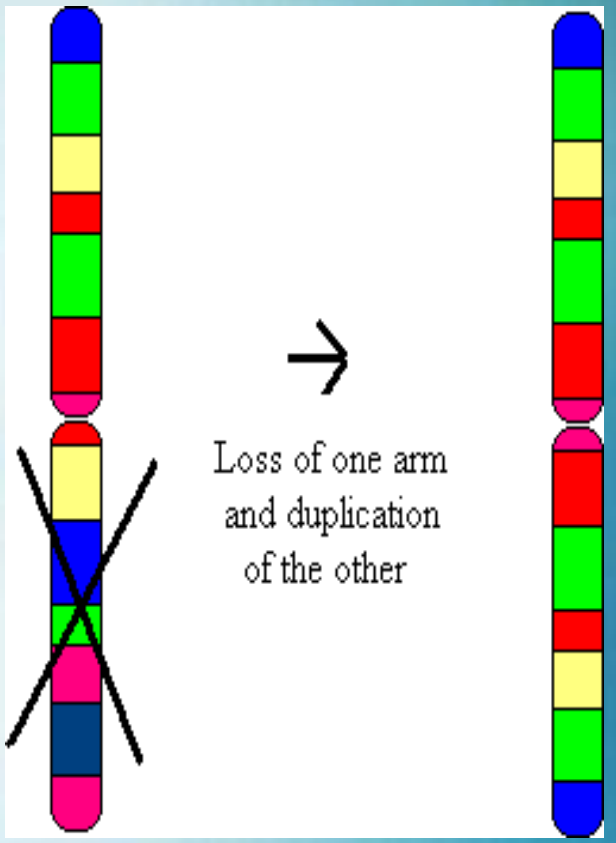


- A special pattern is called **centric fusion type or *Robertsonian translocation*** involving two acrocentric chromosomes (13, 14, 15, 21, and 22) typically the **breaks occur close to the centromere,** transfer of the segment lead to **one very large chromosome &one extremely small,** the **short segments are lost &the carrier has 45 chromosome,** such loss is compatible with life because the short arms of all acrocentric chromosomes carry highly redundant genes, but **difficulties arise during gametogenesis**, resulting in the formation of unbalanced gametes that could lead to abnormal offspring.



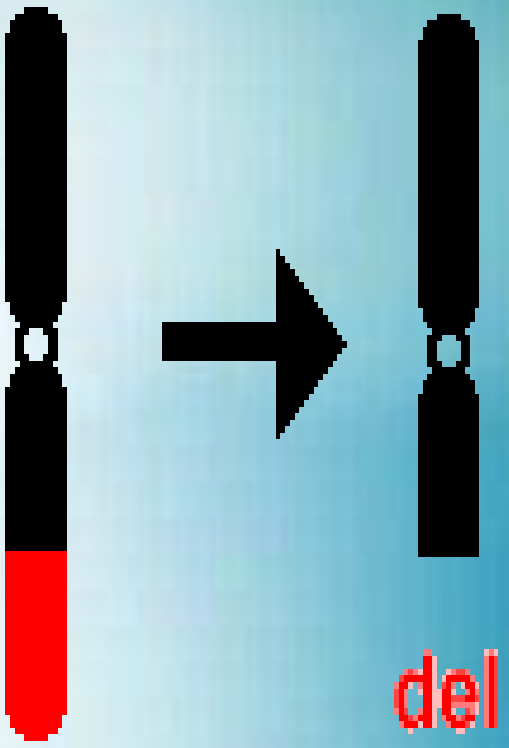
2- Isochromosomes:

- Result when the centromere divides horizontally rather than vertically.
- One of the two arms of the chromosome is then lost, and the remaining arm is duplicated, resulting in a chromosome with only two short arms or two long arms.



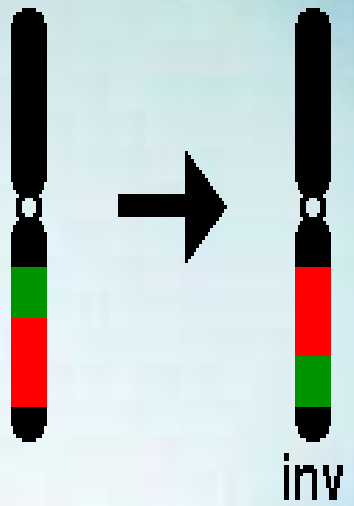
3- Deletion:

- Involve loss of a portion of a chromosome, **single break** may delete a terminal segment.
- **Two interstitial breaks** with reunion of the proximal &distal segment may result in loss of intermediate segment, the isolated fragment almost never survive.



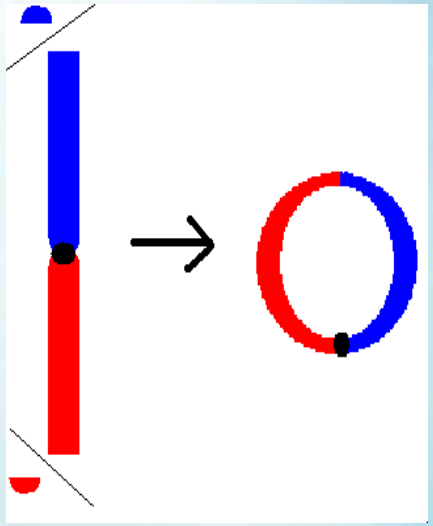
4- Inversion:

- Occur when there are **two interstitial breaks** in a chromosome &the segment **reunites** after a complete turnaround.
- Since there is no loss or gain of chromosomal material, **inversion carriers are normal.**



5- Ring chromosome:

- Is a variant of deletion, after loss of segments from **each end of the chromosome, the arms uniting to form ring.**



- **General Features of chromosomal disorders:**
- Associated with **absence, excess, or abnormal rearrangements** of chromosomes.
- Loss of genetic material produces more severe defects than does gain.
- Abnormalities of sex chromosomes generally tolerated better than those of autosomes.
- Sex chromosomal abnormalities are usually subtle and are not detected at birth.
- Most cases are due to de novo changes (i.e. parents are normal and recurrence in siblings is low).

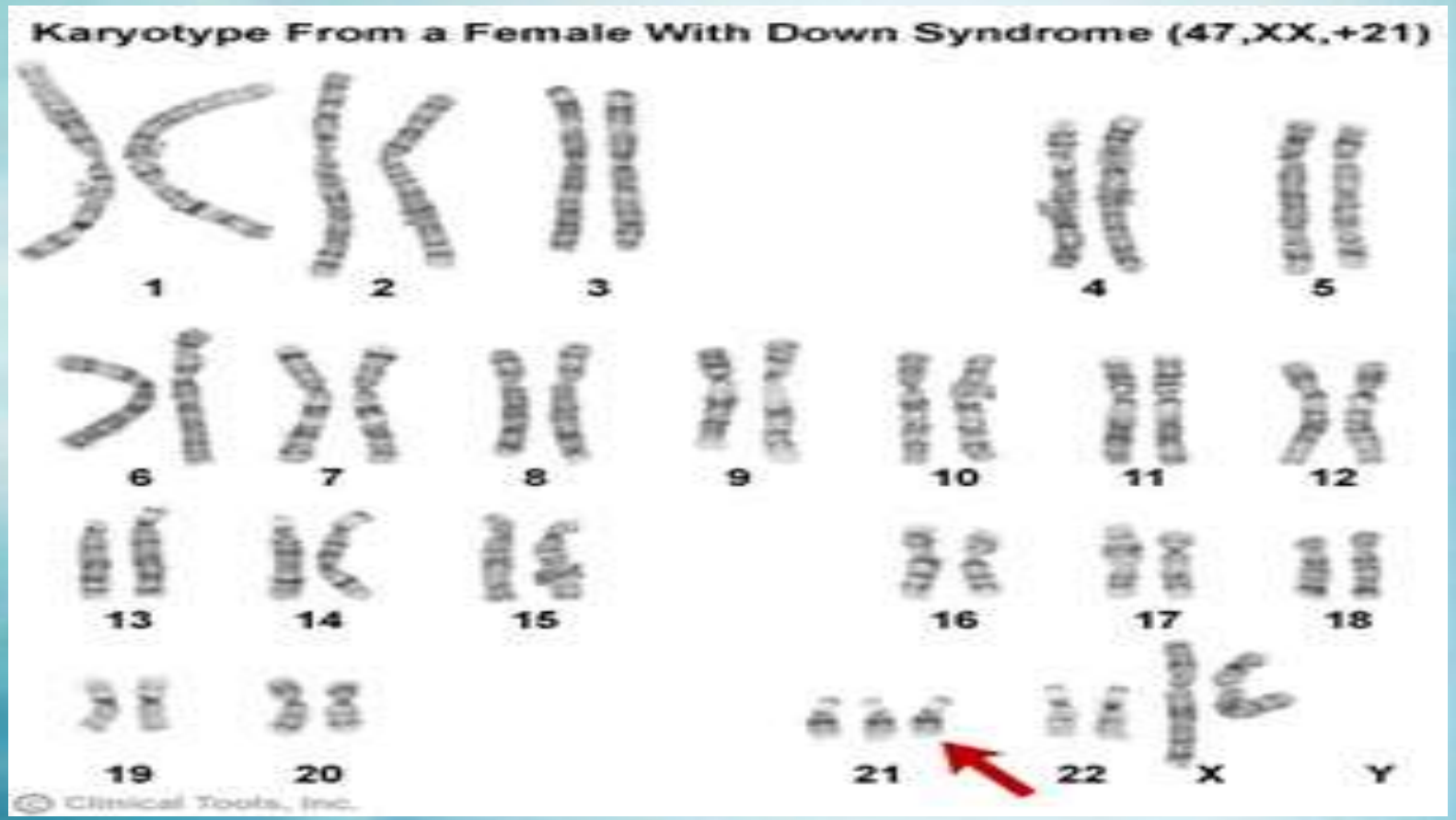
****de novo change:** An alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself.

Cytogenetic disorders involving autosomes: Trisomy mainly (21, 18, 13).

❖Trisomy 21 (Down syndrome):

- Is the most common chromosomal disorder.
- **About 95%** of affected persons have trisomy 21, so their chromosome count is 47.
- The most common cause is **meiotic non disjunction, with nondisjunction, a gamete (i.e., a sperm or egg cell) is produced with an extra copy of chromosome 21; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embyo now has 47 chromosomes, with three copies of chromosome 21;** the parents are normal but maternal age has a strong influence on the incidence of Down syndrome (in women more than 45years,1:25 birth).
- **In 4%,** the **extrachromosomal material** is present as a translocation of the long arm of chromosome 21 to chromosome 22 or 14.
- **1%** is mosaicism with **mixture of 46 &47 chromosome.**

Karyotype of Down syndrome



• Clinical features:

1- Mental retardation.

2- Epicanthic folds &flat facial profile.

3- Abundant neck skin.

4- Simian creases.

5- Congenital heart defects &
is the principle cause of death
in addition to serious infection.

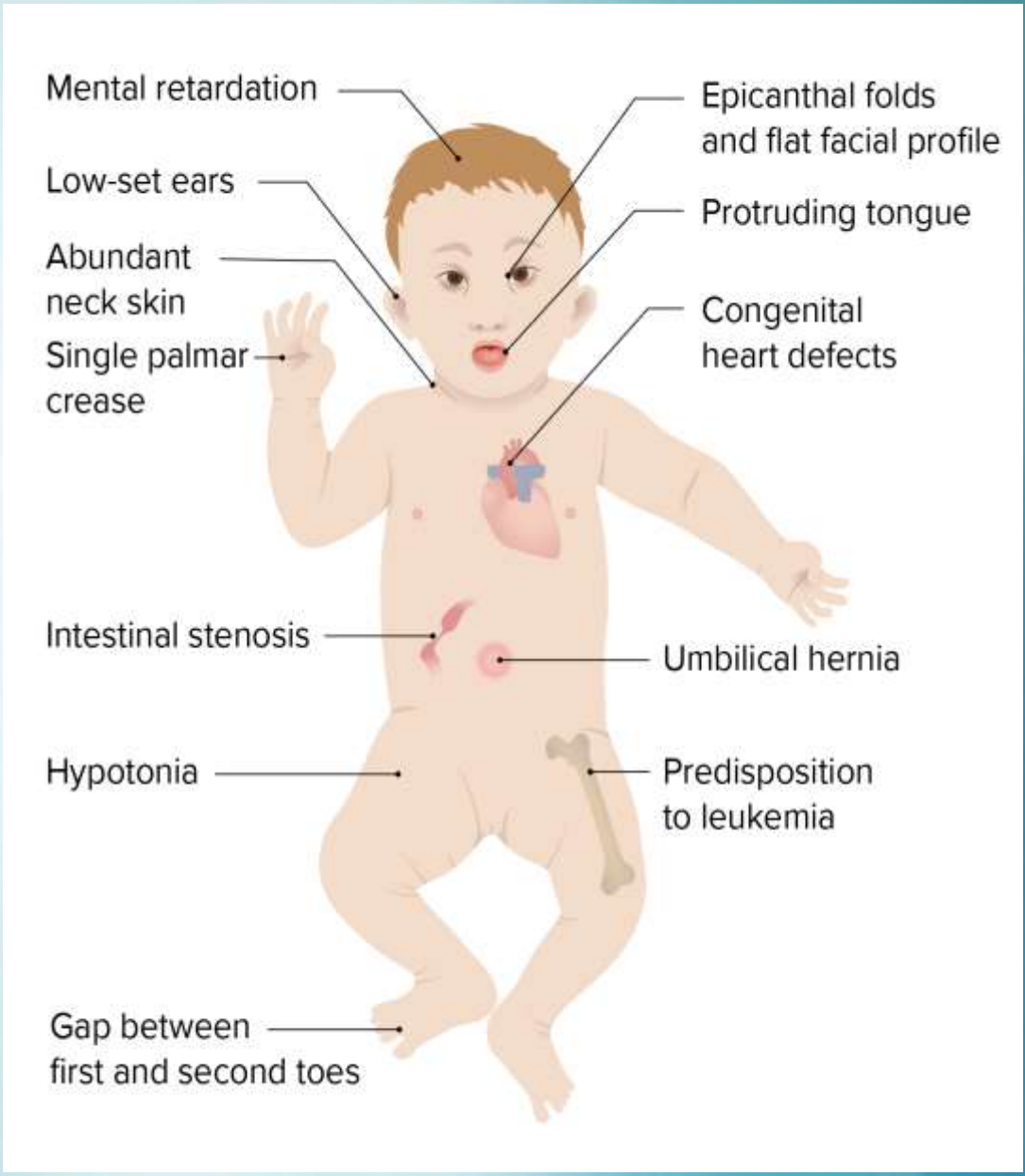
6- Umbilical hernia.

7- Intestinal stenosis.

8- Hypotonia.

9- Gab between first &second toe.

10- Predisposition to leukemia.



❖Trisomy 13 (Patau syndrome):

1- Microcephaly &mental retardation.

2- Microphthalmia.

3- Cleft lips &palate.

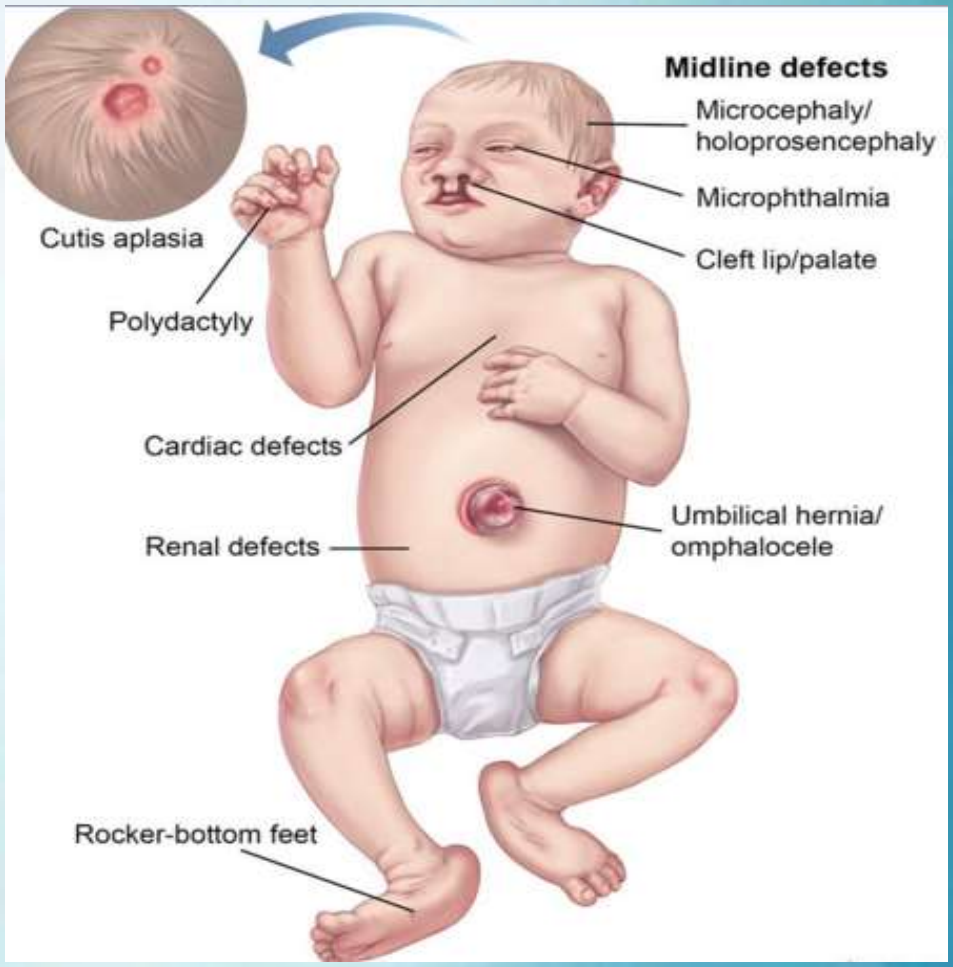
4- Cardiac defects.

5- Umbilical hernia.

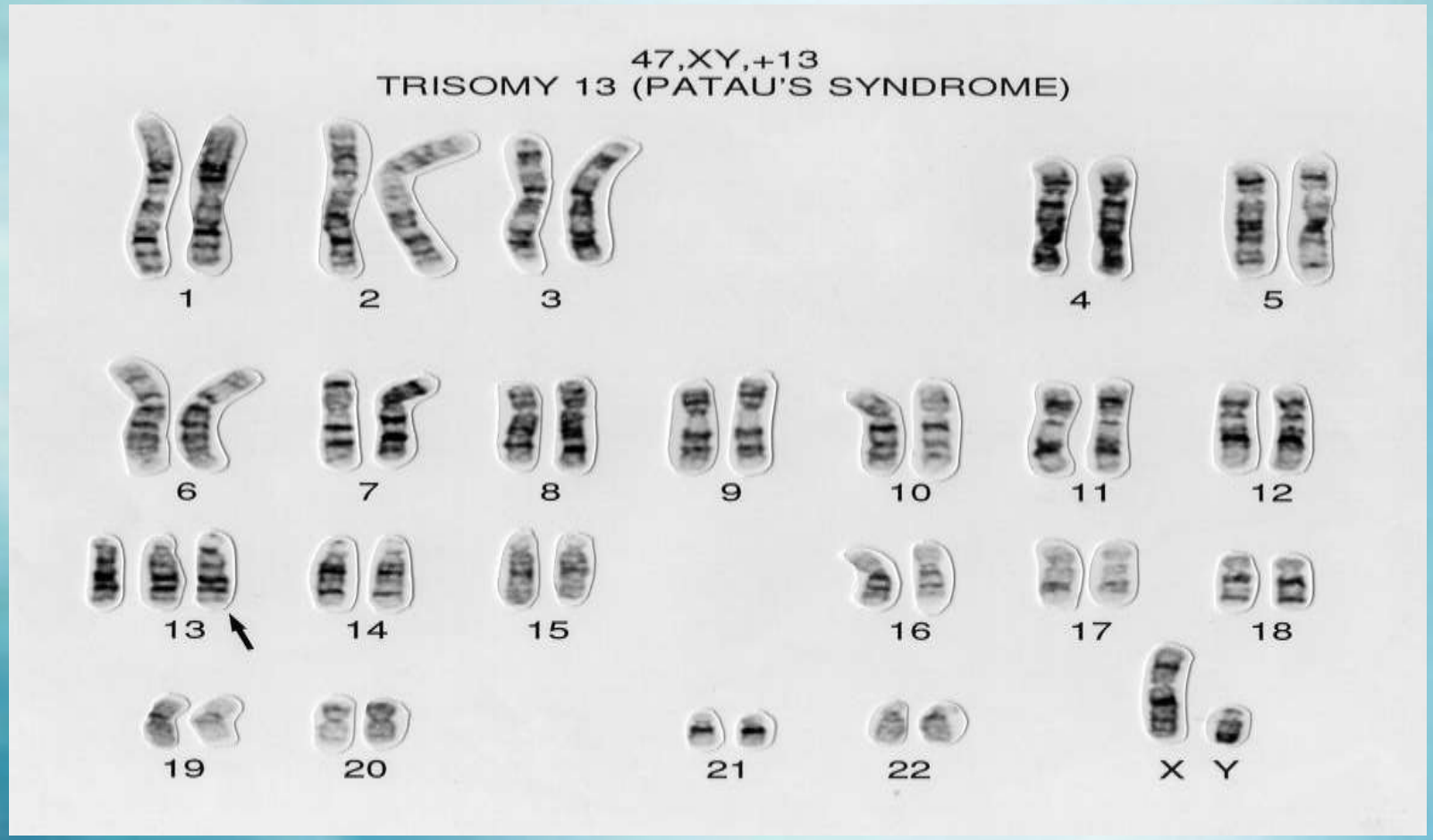
6- Renal defects.

7- Polydactyly.

8- Rocker-bottom feet.



Karyotype of Patau syndrome



Cytogenetic disorders involving sex chromosomes:

- Imbalances in sex chromosomes are more common than autosomal imbalances, because they are typically better tolerated duo to **two factors:**

(1) lyonization of X chromosomes (Lyon hypothesis) proposed that in females, only one X chromosome is genetically active. X inactivation occurs early in fetal life &called Barr body.

(2) The small amount of genetic information carried by the Y chromosome (Extra Y chromosome readily tolerated because the only information carried by it is related to male differentiation).

- Described briefly next are two disorders, **Klinefelter syndrome and Turner syndrome,** that result from abnormalities of sex chromosomes.

1- Klinefelter syndrome:

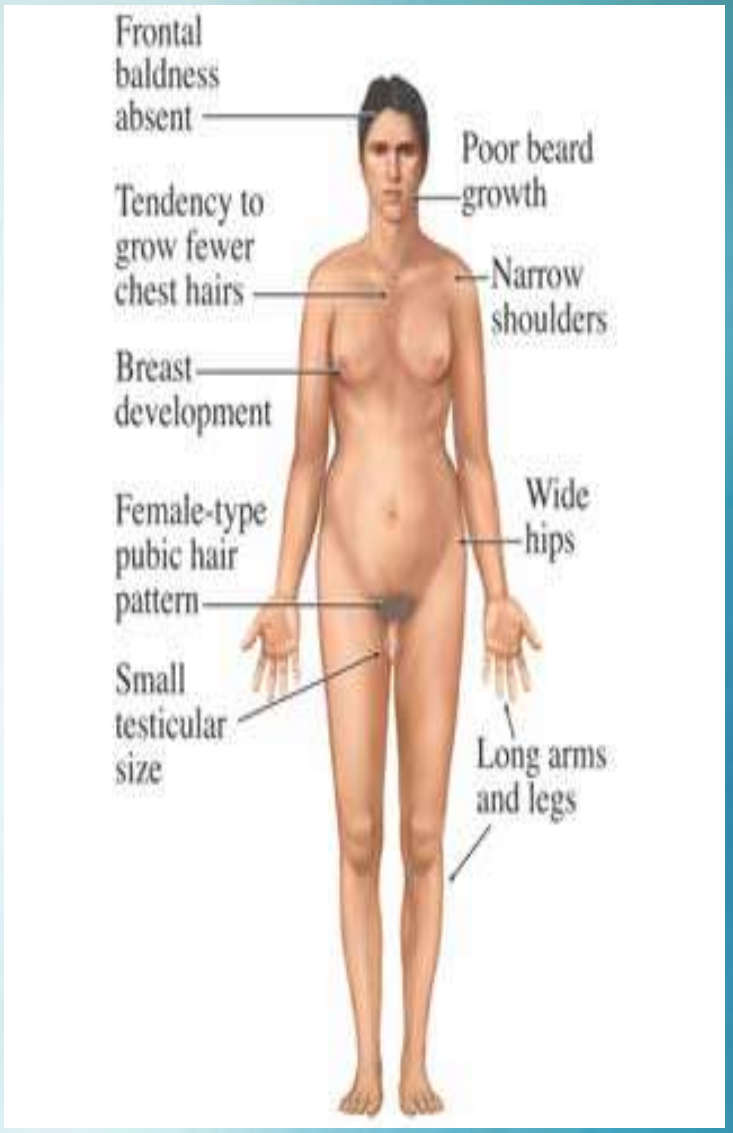
- Defined as a male hypogonadism that develops when there are at least two X chromosomes & one or more Y-chromosomes.
- **Karyotype:** most patients are 47,XXY in 80% and mosaic in 20%.
- **Causes:**

* Advanced maternal age.
* History of irradiation of either parent.

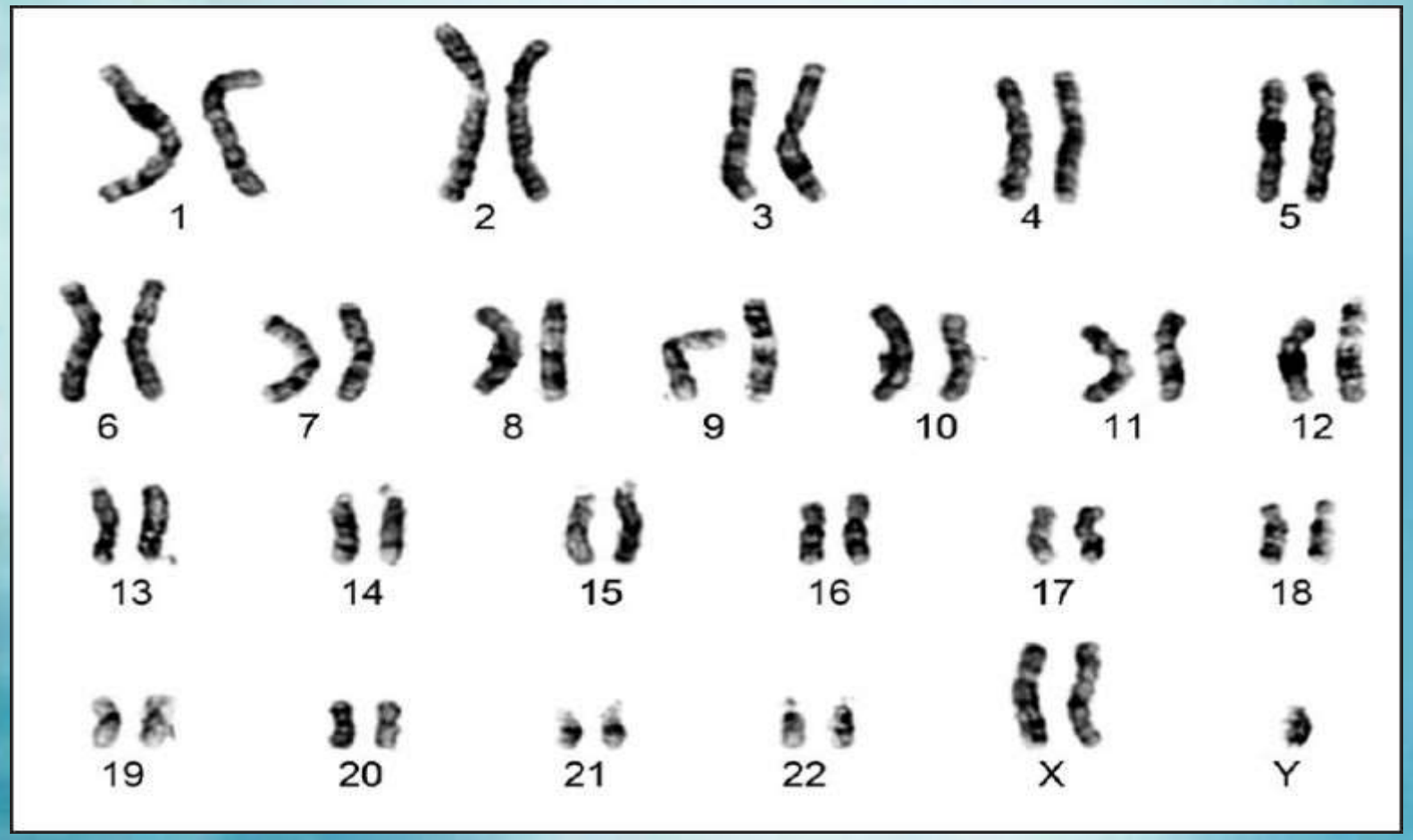
• Clinical features:

***Hypogonadism**

- Marked testicular atrophy (infertility)
- Gynecomastia
- Reduced facial &body hair (failure of male secondary sexual characteristics development)
- Increase length between the soles &pubic bones, **which creates the appearance of an elongated body.**
- Decrease serum testosterone level.
- Some with mental retardation.
- The principle clinical effect is sterility, only rare patient are fertile.
- **Histologically:**
- Hyalinization of tubules which appear as ghost like in contrast lydig cells are prominent.

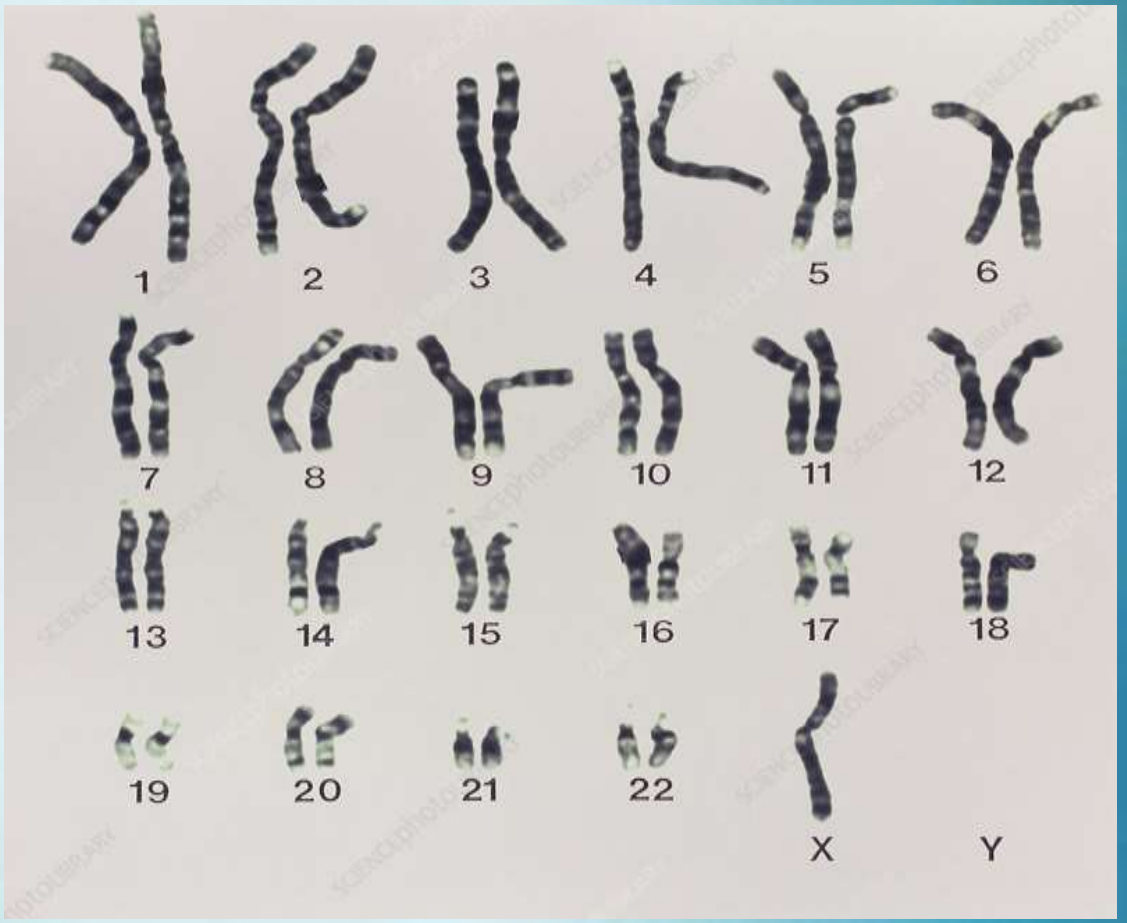


Karyotype of Klinefelter syndrome (47 XXY)



2- Turner syndrome:

- Characterized by hypogonadism in phenotypic female result from partial or complete monosomy of X chromosome
- **Karyotype: 45 XO .**



- **Clinical features:**

*Short stature.

* Low posterior hair line.

* Cubits valgus (increase in carrying angle of the arms).

* Shield like chest with widely spaced nipples

*High arched palate.

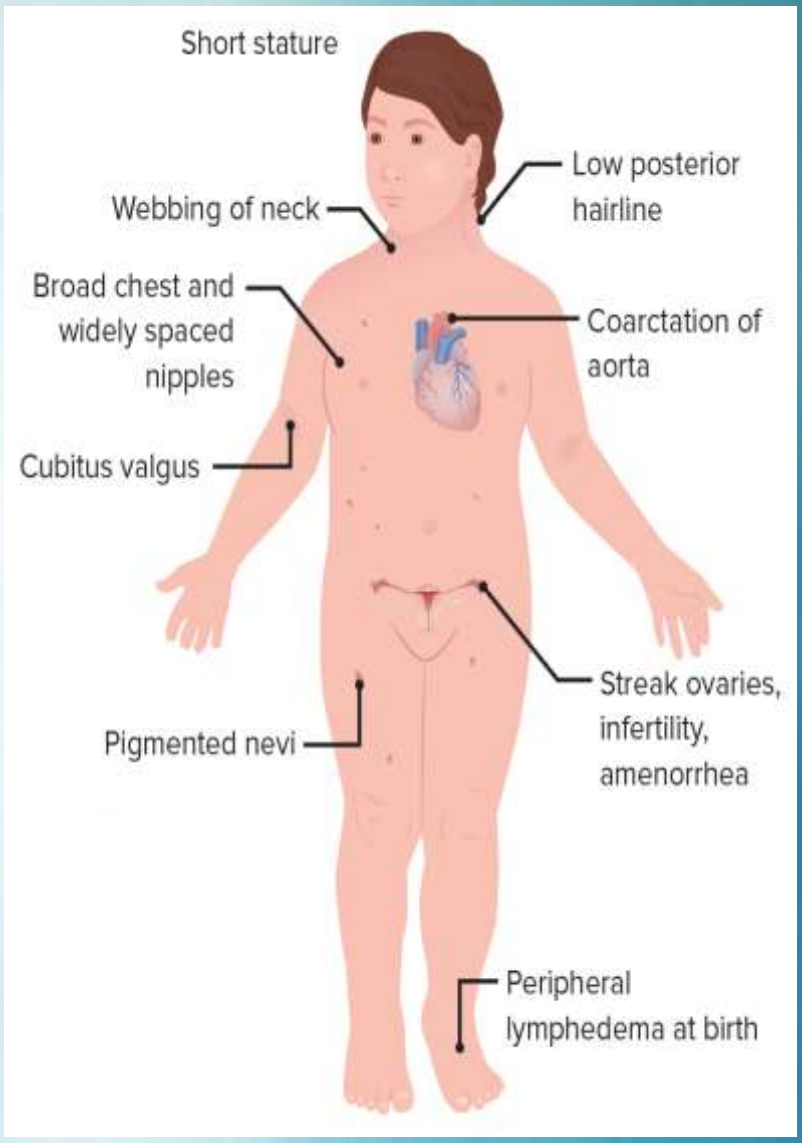
*Lymphedema of the hands &feet.

- Variety of congenital malformation e.g. horseshoe kidney, coarctation of aorta.
- Failure of development of secondary sexual characteristics.

*Genitalia remain infantile (little pubic hair)

* primary amenorrhea.

- Ovaries fibrosed which is devoid of follicles.
- Decrease ovarian estrogen level.




Thanks