

# Human Genetics

## CHROMOSOME ANOMALIES

### Lecture Two

# Lecture Objectives:

**By the end of this lecture, the students should be able to:**

1. Describe and explain the events in mitosis & meiosis.
2. Define non-disjunction and describe its consequences on meiosis.
3. Classify chromosomal abnormalities: Numerical & structural
  - 3a Understand the common numerical autosomal disorders: trisomies 21, 13, 18.
  - 3b Understand the common numerical sex chromosome disorders: Turner`s & Klinefelter`s syndromes
  - 3c Recognize the main structural anomalies in chromosomes

# **1) Mitosis & Meiosis**

# Typical mitotic cell cycle

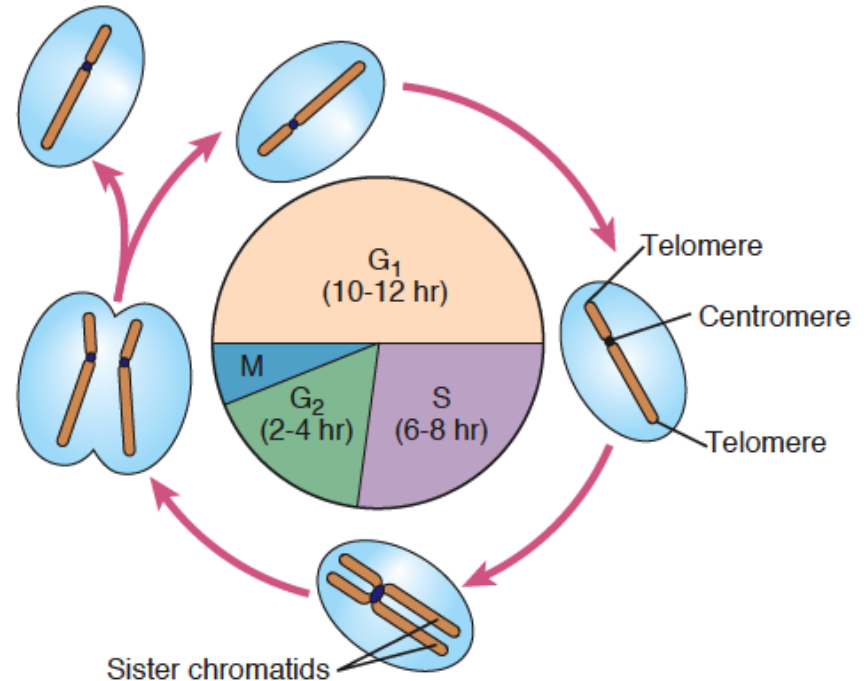
During G<sub>1</sub> = one diploid

S phase = duplication of each chromosome's DNA → Two sister chromatids

G<sub>2</sub> Phase = chromosomes begin to condense and become visible

**G<sub>1</sub>, S, and G<sub>2</sub> phases =** constitute interphase

Two daughter cells = equal genetic information



# Events of mitosis

## Prophase.

formation of mitotic Spindle & pair of centrosomes

## Prometaphase.

- Nuclear membrane dissolves
- Chromosomes to disperse & attach by kinetochores to mitotic spindle microtubules

## Metaphase.

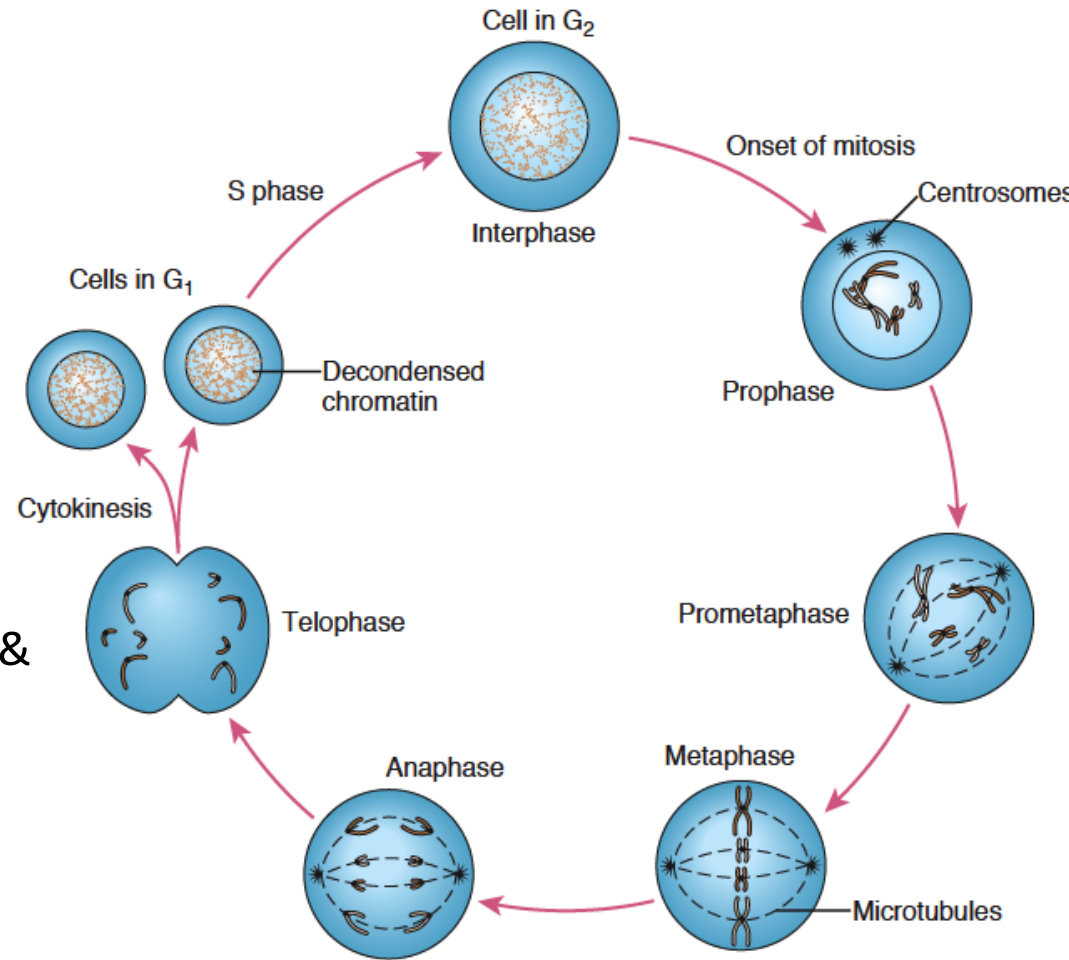
Chromosomes condensed & line up at the equatorial plane

## Anaphase.

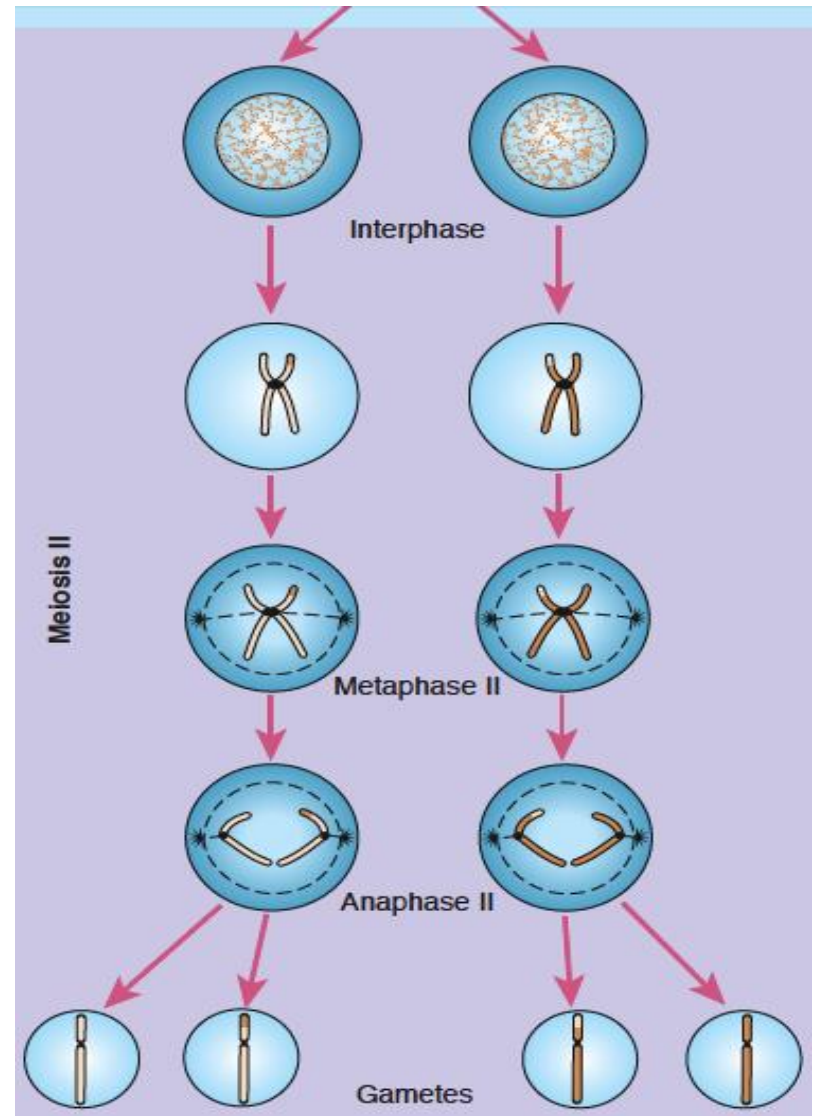
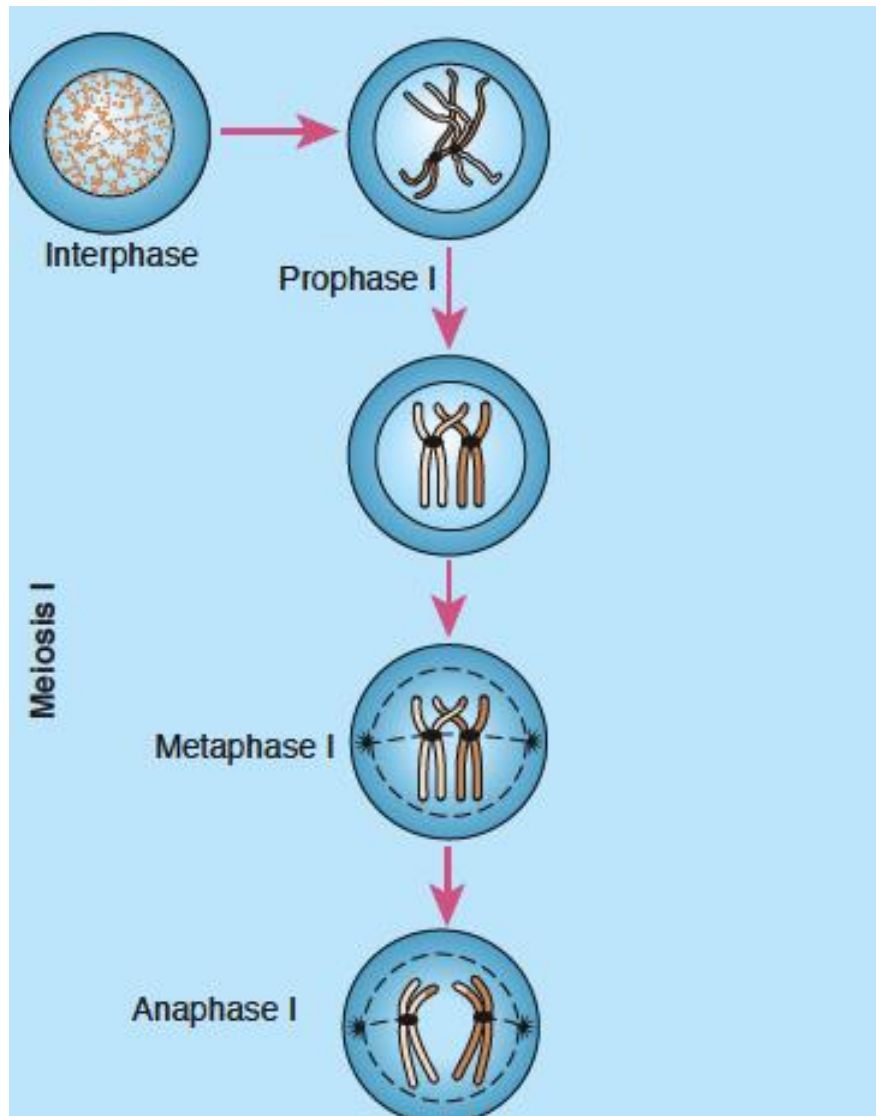
- Chromosomes separate at centromere &
- Sister chromatids of each chromosome become independent daughter chromosomes

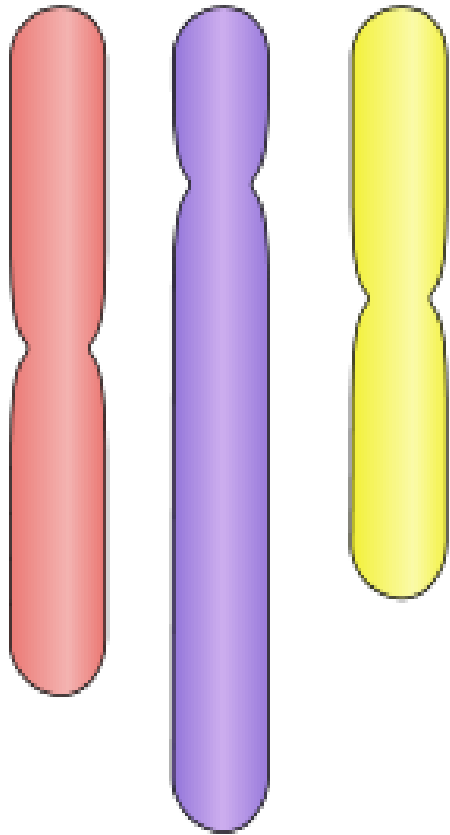
## Telophase.

- Chromosomes de-condense from their highly contracted state,
- Nuclear membrane re-form around each of the two daughter nuclei,
- resume their interphase

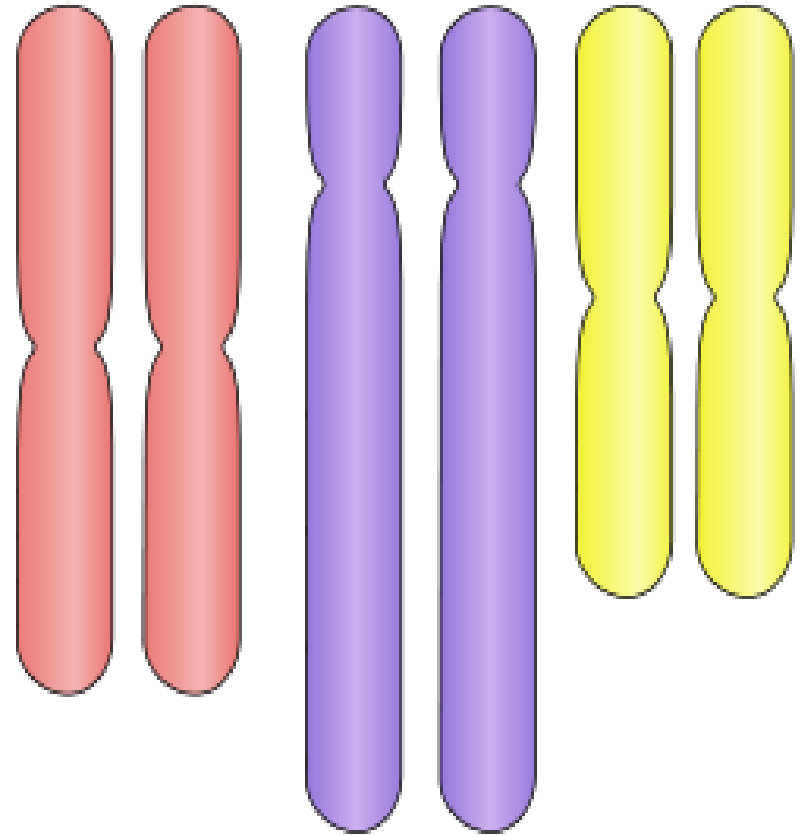


# Events of meiosis I & II



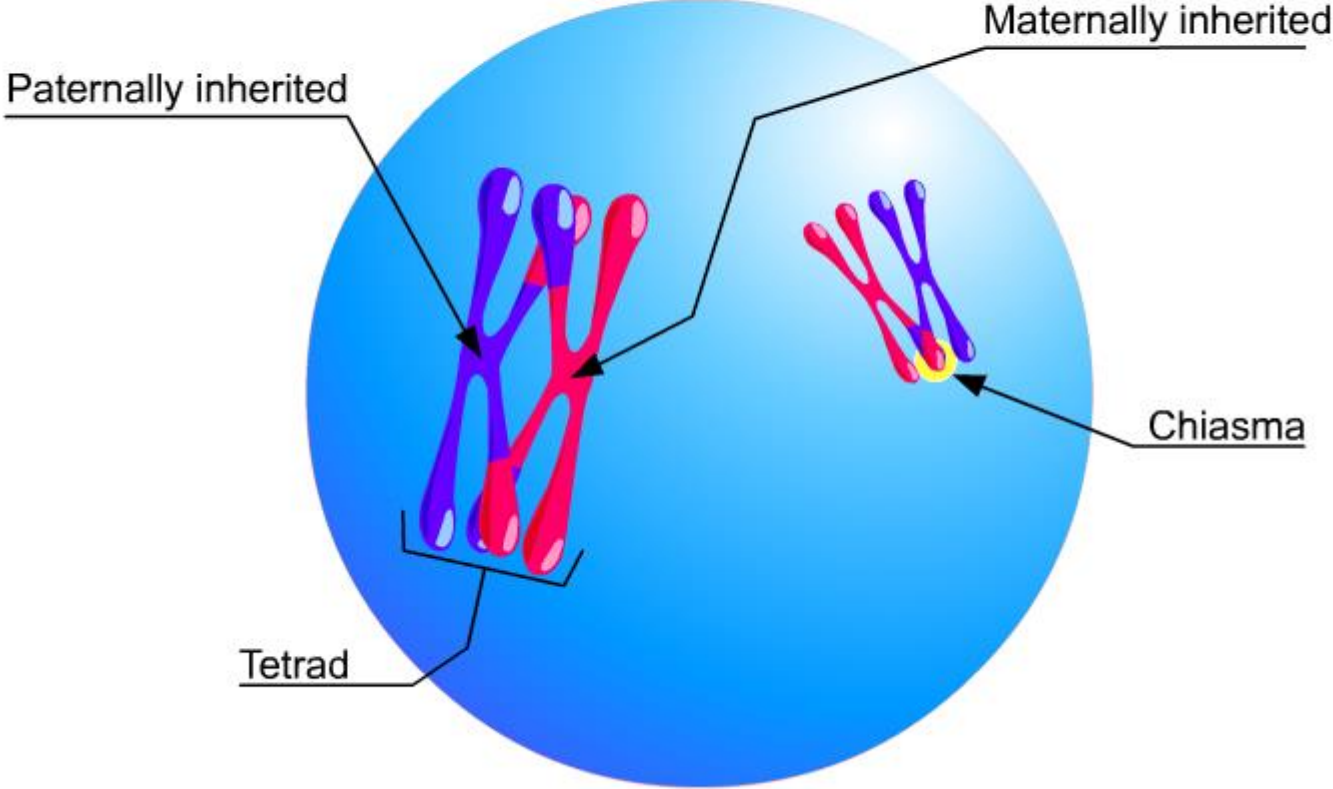


Haploid (N)



Diploid (2N)

# Meiosis I Prophase I





## **2-) Non-disjunction and its impact on meiosis**

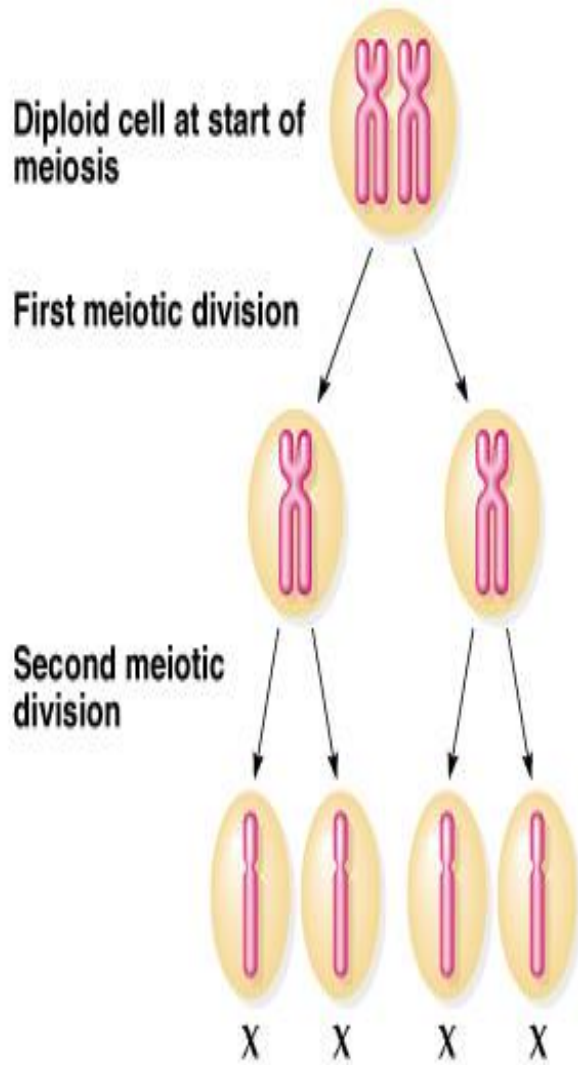
# Non-disjunction in Meiosis

- The failure of chromosomes to disjoin normally during meiosis phase 1 or phase 2.
- Two chromosome homologs migrate to the same daughter cell instead of disjoining normally and migrating to different daughter cells.
- The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)

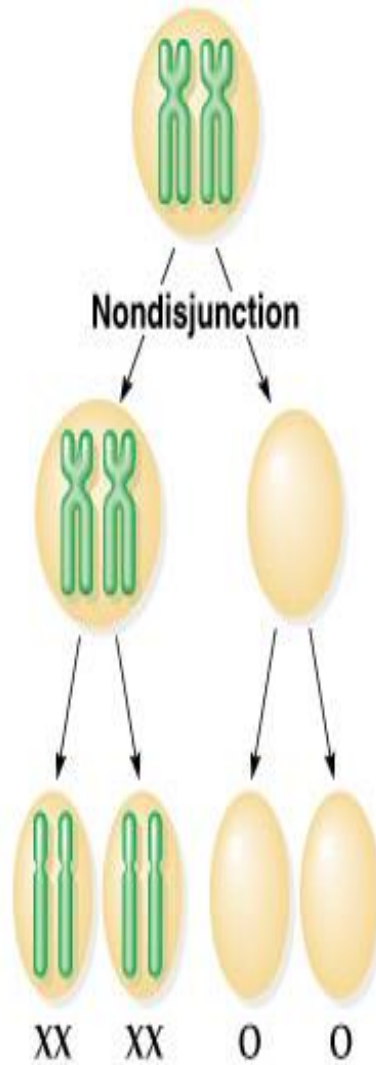
# Meiotic non-disjunction

- Can affect each pair of chromosomes
- is not a rare event
- Non disjunction in first meiotic division produces 4 unbalanced gametes.
- Non disjunction in second division produces 2 normal gametes & 2 unbalanced gametes:
  - Gamete with an extra autosome
  - Nullisomic gamete (missing one chromosome)

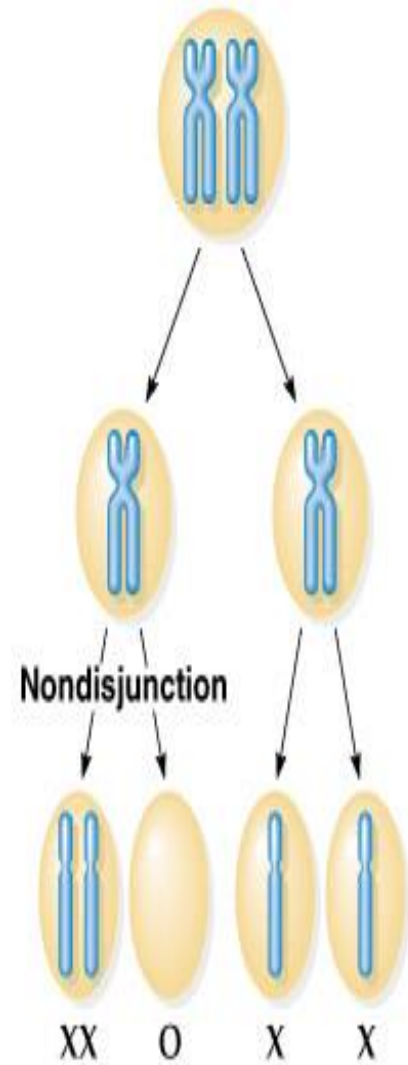
a) Normal X chromosome segregation

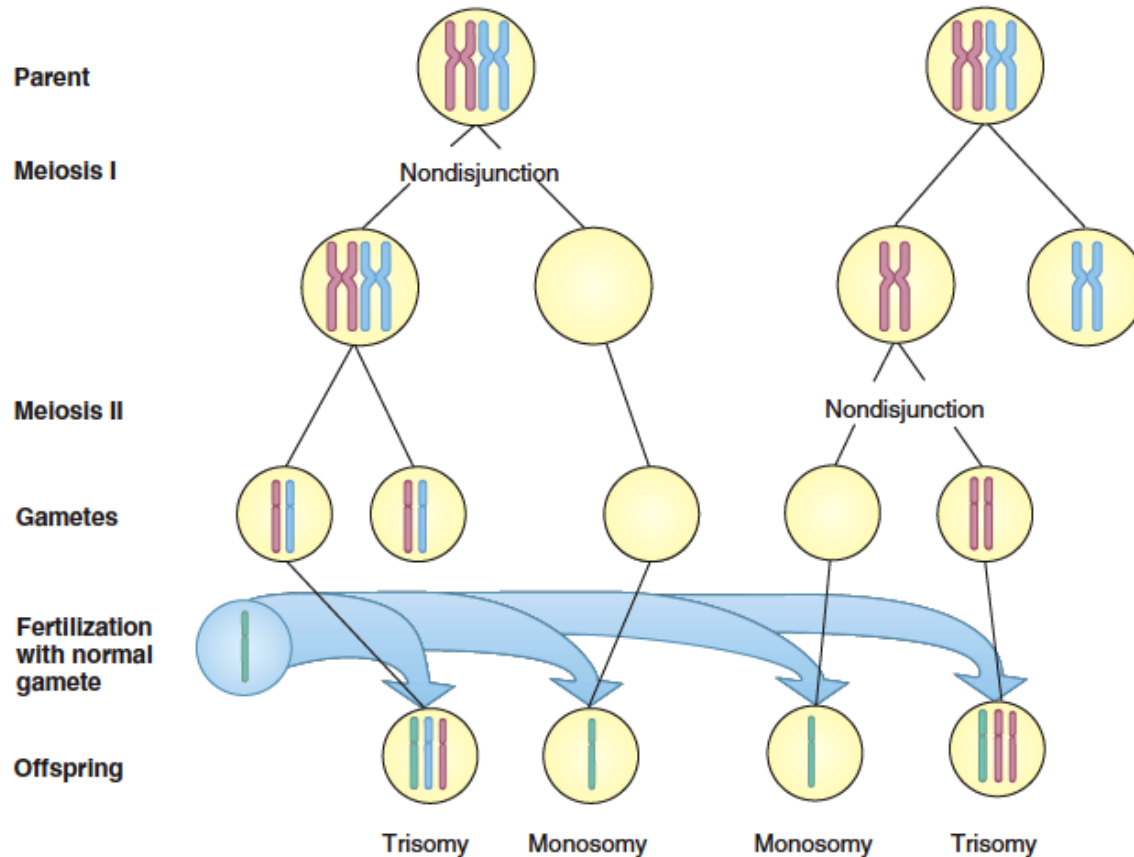


b) Nondisjunction in meiosis I



c) Nondisjunction in meiosis II





## In meiotic nondisjunction

- This product of fertilization with normal gamete would be monosomic and trisomic offspring (Aneuploidy)

# **3- Classifications of chromosomal abnormalities**

# CHROMOSOME ANOMALIES

## TYPES:

- *Numerical*

affect the number of complete haploid set ( $n$ ) of chromosomes

- *Structural*

Affect the structure and organization of genomic content of the chromosome

# **3a. NUMERICAL CHROMOSOMAL ANOMALIES**

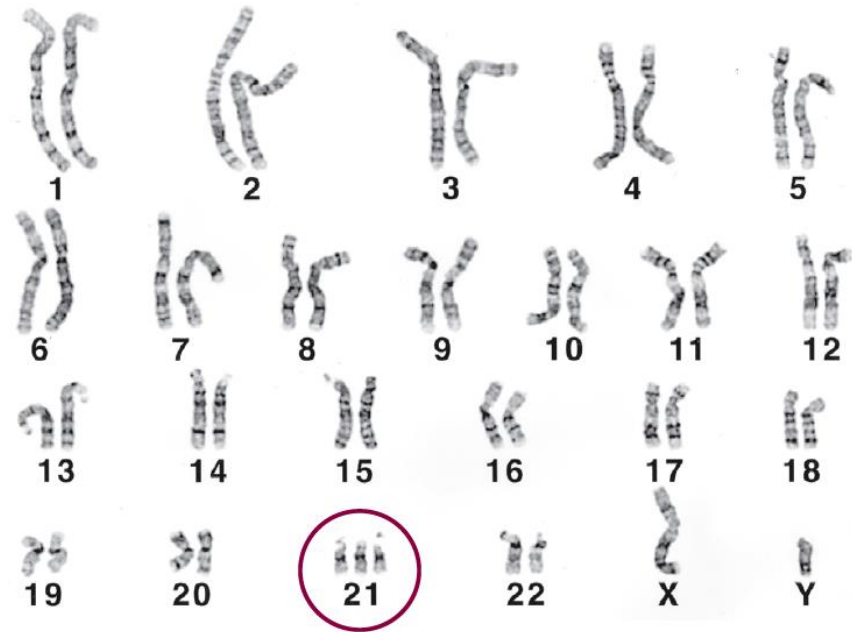
**Numerical anomalies in autosomes**



# Down syndrome, trisomy 21

**Karyotype: 47, XY, +21**

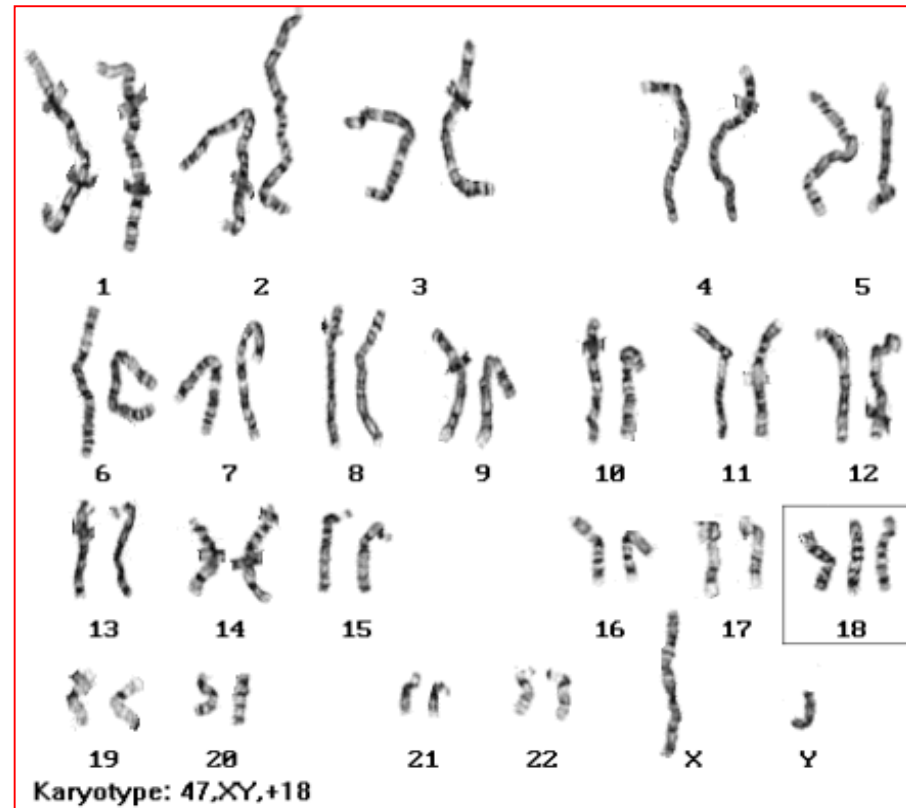
- Most cases arise from non disjunction in the first meiotic division
- The incidence of trisomy 21 rises sharply with increasing maternal age
- The father contributing the extra chromosome in 15% of cases
- The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50.



# Edward's syndrome, Trisomy 18

**Karyotype: 47, XY, +18**

- the second most common autosomal trisomy, after Down syndrome
- It occurs in around one in 6,000 live births
- Most babies die in the first year and many within the first month & has a very low rate of survival
- Common anomalies are heart abnormalities, kidney malformations, and other internal organ disorders



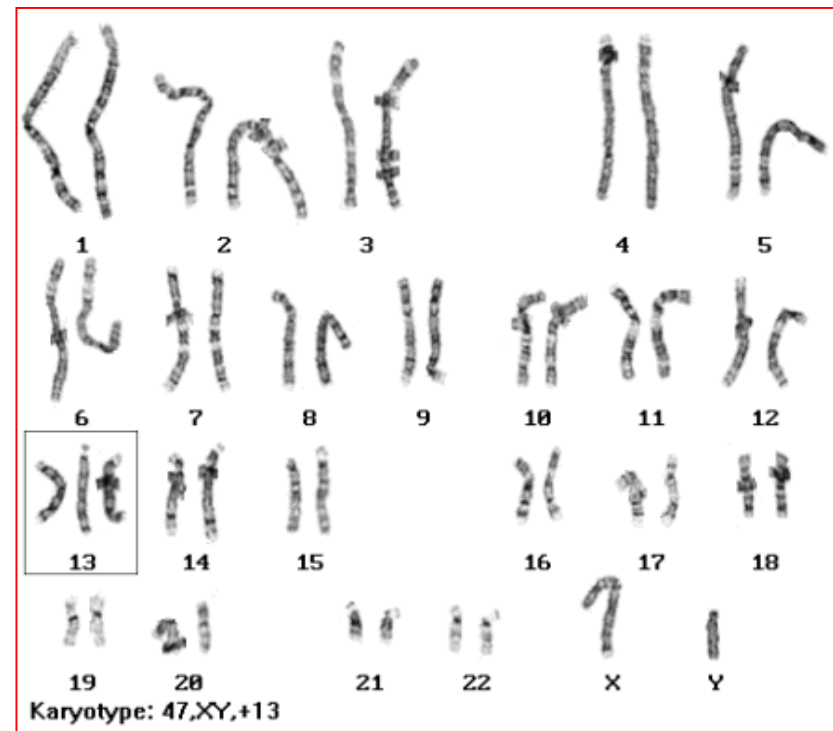
# Patau Syndrome, Trisomy 13

**Karyotype: 47, XY, +13**

- 50 % of these babies die within the first month and very few survive beyond the first year.

- There are multiple dysmorphic features.

Most cases, as in Patau syndrome, involve maternal non-disjunction.

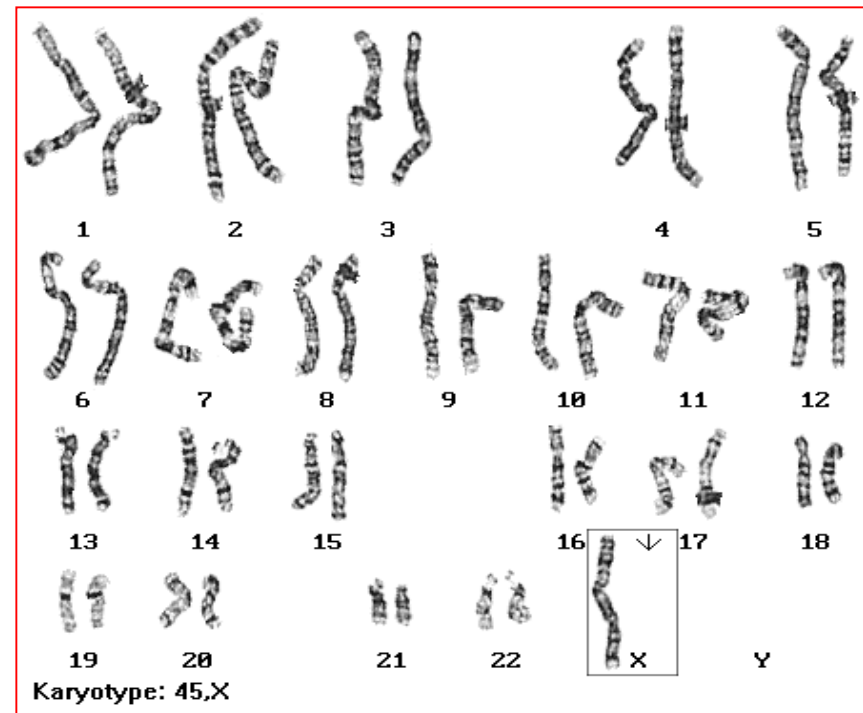


# **3b. NUMERICAL CHROMOSOMAL ANOMALIES**

Numerical anomalies in Sex  
chromosomes

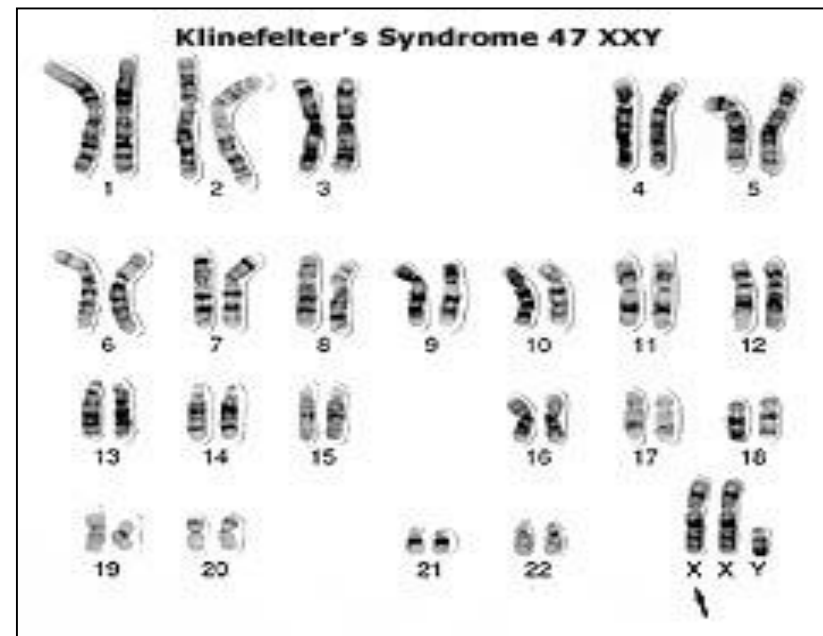
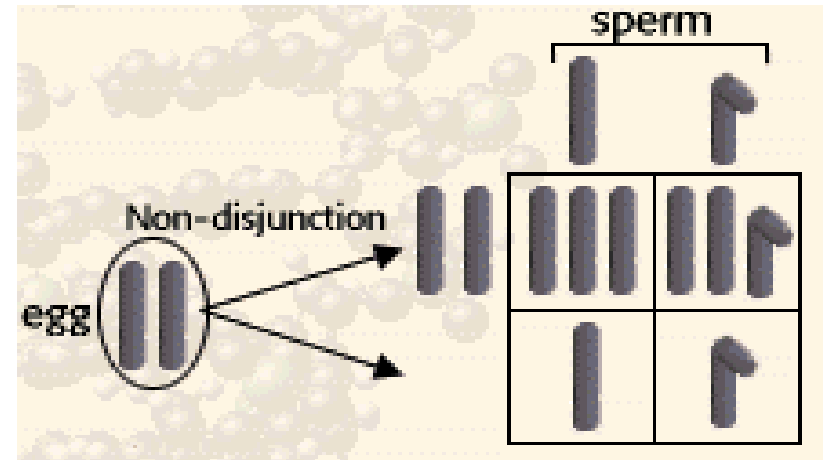
# Monosomy X (Turner's syndrome, 45,XO)

- Occurring in 1 in 4000 phenotypic females
- As a result of paternal meiotic nondisjunction
- The only viable monosomy in humans
- Characteristics:  
Webbed neck, Individuals are genetically female, not mature sexually, Sterile, Short stature, Boad chest, Low hairline, Streak ovaries, Normal intelligence, Normal life span



# Klinefelter Syndrome: 47,XXY males

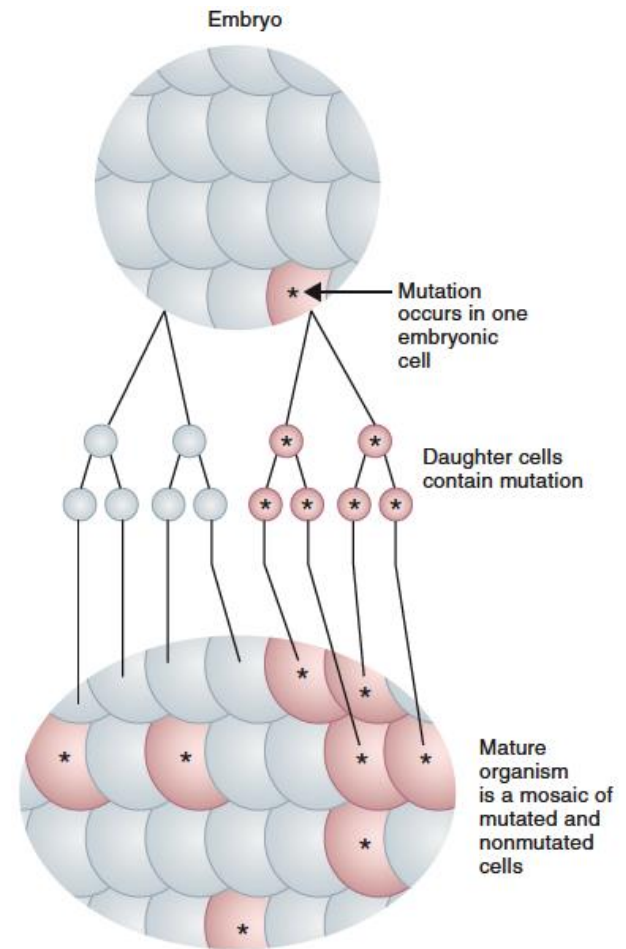
- 1/600 males
- Due to nondisjunction of X chromosomes during meiosis I in females
- Male sex organs; unusually small testes which fail to produce normal levels of testosterone → breast enlargement (gynaecomastia) and other feminine body characteristic
- Patients are taller and thinner than average and may have a slight reduction in IQ but generally they have normal intelligence
- No spermatogenesis → sterile



# MOSAICISM

The presence of more than one genetically distinct cell line in the body

A mosaic individual is made of 2 (or more) cell populations, coming from only 1 zygote



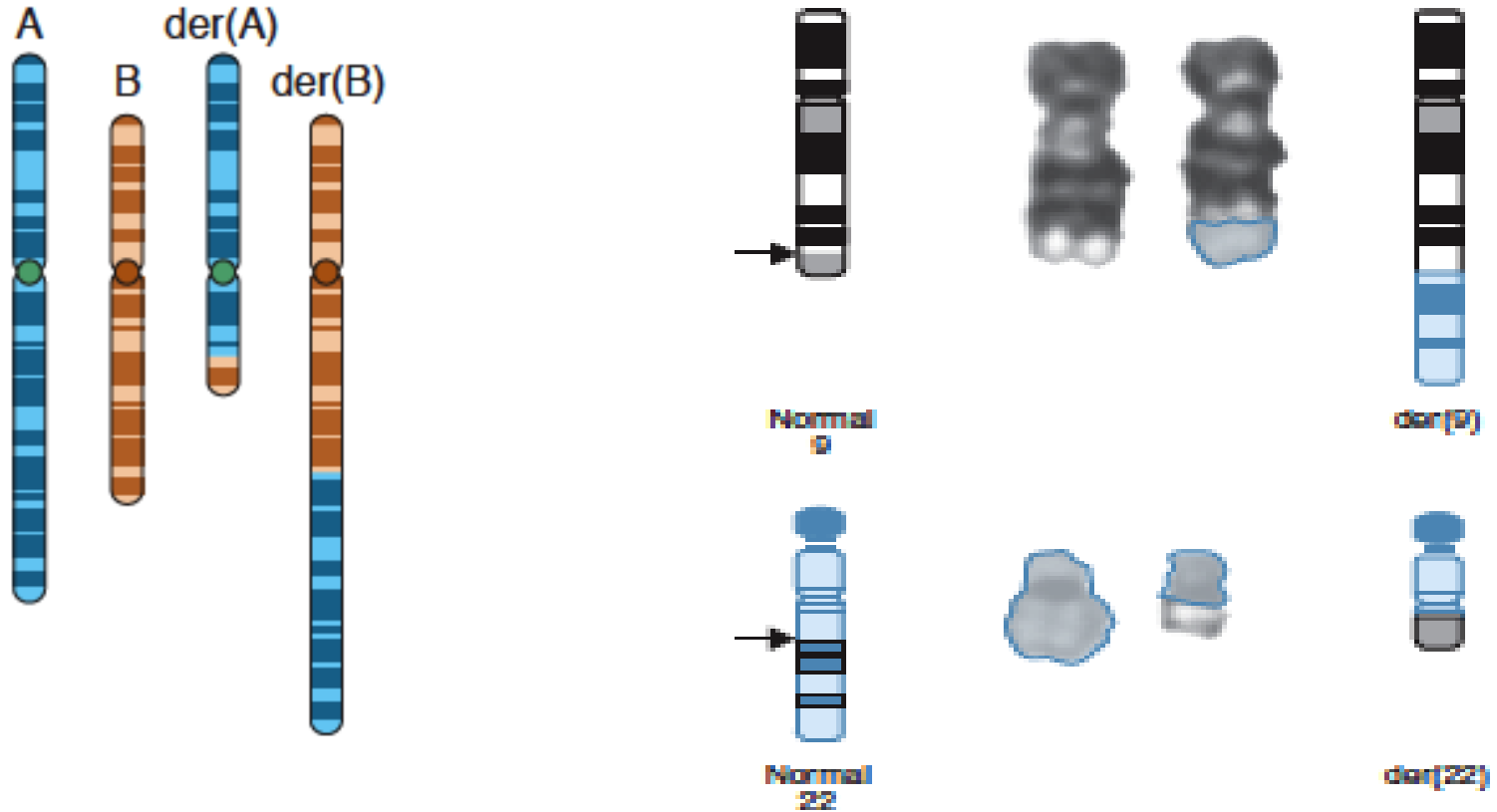
# MOSAICISM

- ❖ A mosaic individual is made of 2 (or more) cell populations, coming from only 1 zygote
- ❖ Is denoted by a slash between the various clones observed e.g. 46, XY / 47, XY, +21).
- ❖ Numerical mosaic anomaly is usually due to a mitotic non-disjunction
- ❖ A mosaic must not be confused with a chimeras.
- ❖ Chimerism is the presence in an individual of two or more genetically distinct cell lines derive from more than one zygote (e.g. 2 sperms fertilize 2 ova → 2 zygotes that fuse to form 1 embryo)



# **3c. STRUCTURAL CHROMOSOMAL ANOMALIES**

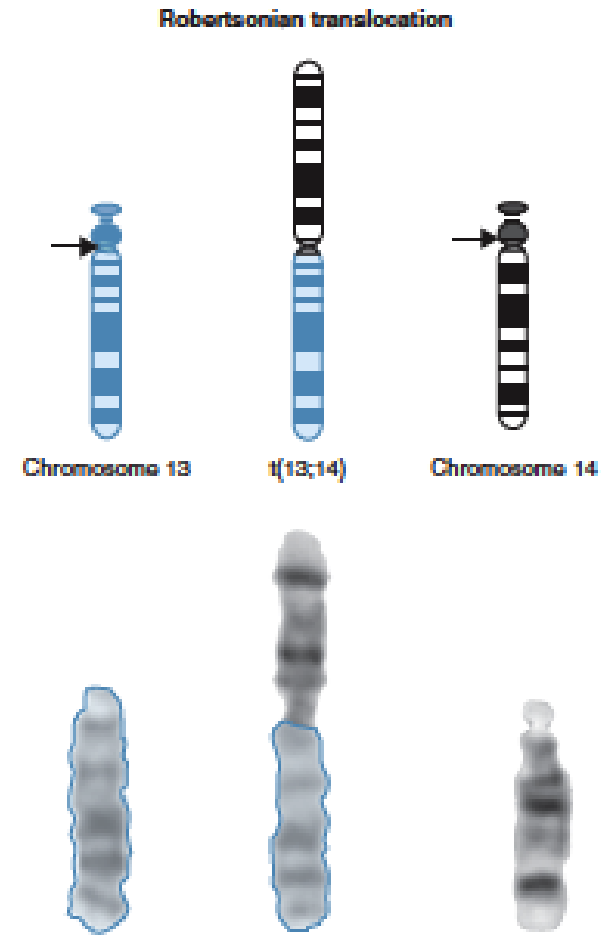
# Reciprocal translocation



- Reciprocal translocation between chromosome 22 and the long arm of chromosome 9 (the Philadelphia chromosome).
- The occurrence of this translocation in hematopoietic cells can produce chronic myelogenous leukemia (CML)

# Robertsonian translocation

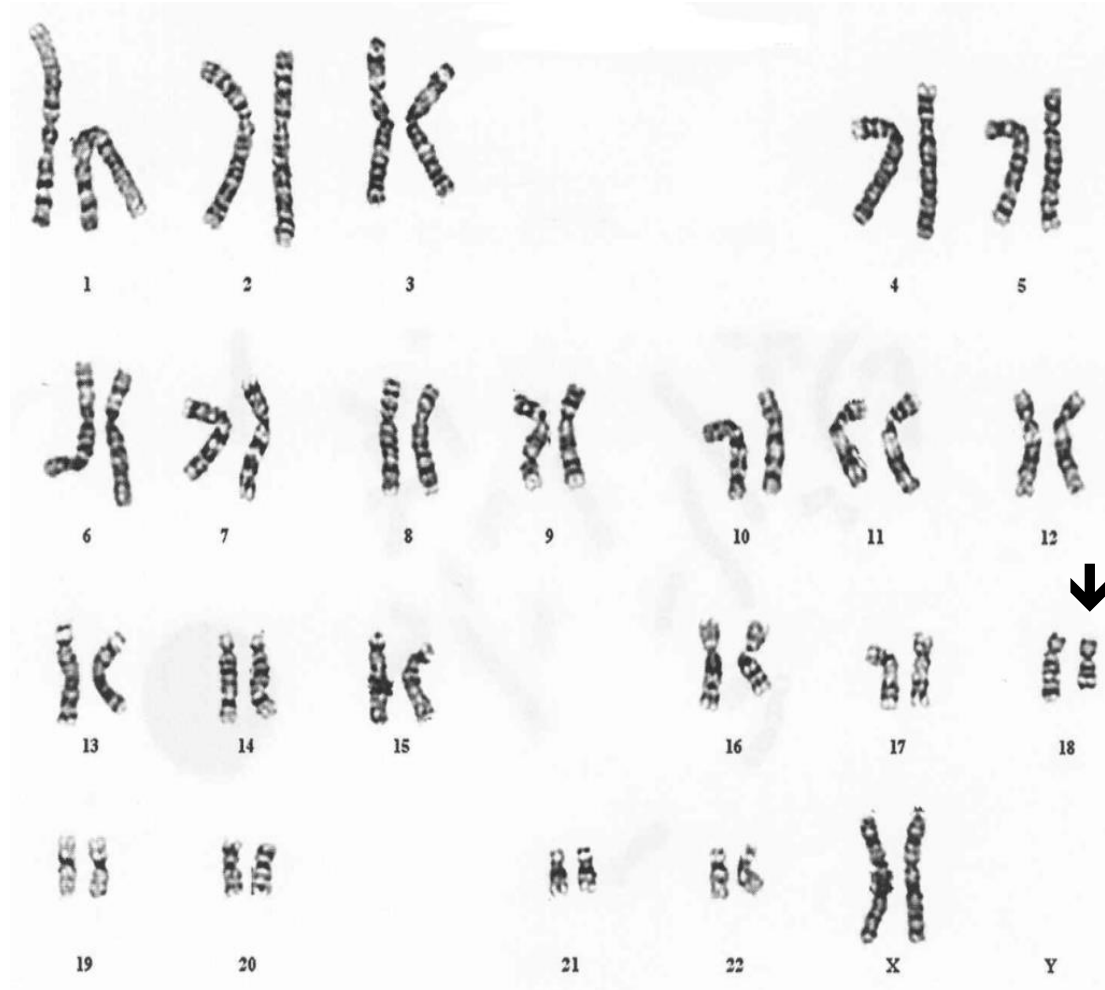
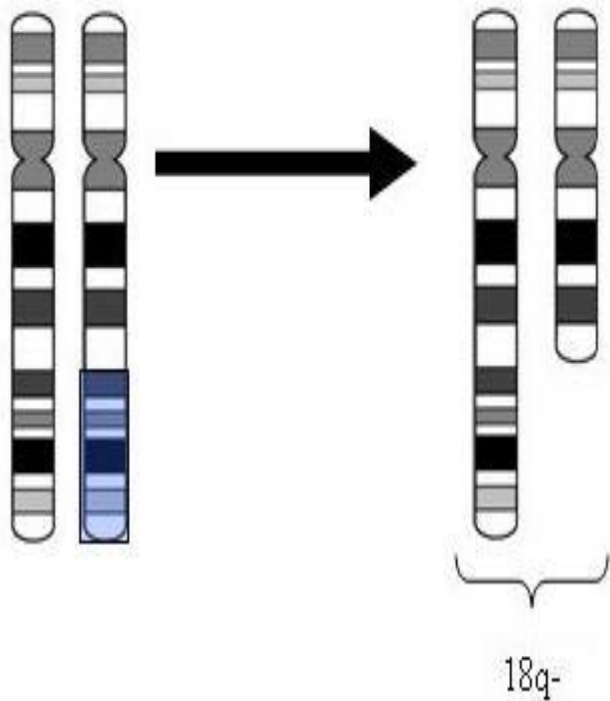
- Short arms of two non homologous chromosomes are lost and the long arms fuse at the centromere to form a single chromosome
- Confined to the acrocentric chromosomes(13, 14, 15, 21, and 22)
- Although carriers have only 45 chromosomes in each cell, they are phenotypically unaffected



# Deletion

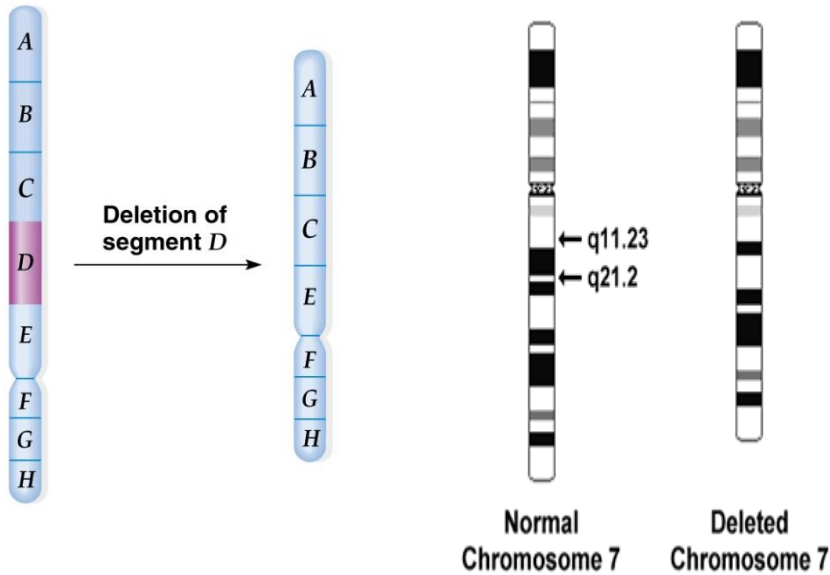
- ❖ - Loss of a segment from a chromosome, either terminal or interstitial
- ❖ Invariably, but not always, results in the loss of important genetic material
- ❖ Deletion is therefore an unbalanced rearrangement.
- ❖ Indicated in nomenclature **del**

# Terminal deletion

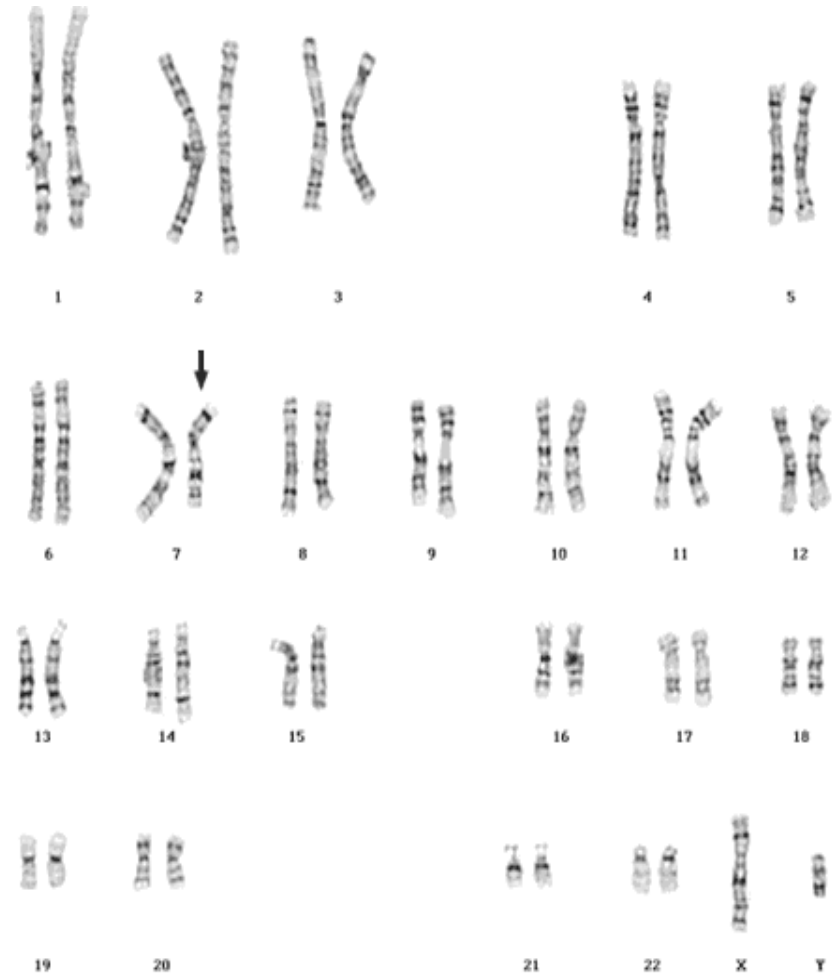


46,XX,del(18)(q21.3)

# Interstitial deletion



## Sample karyogram



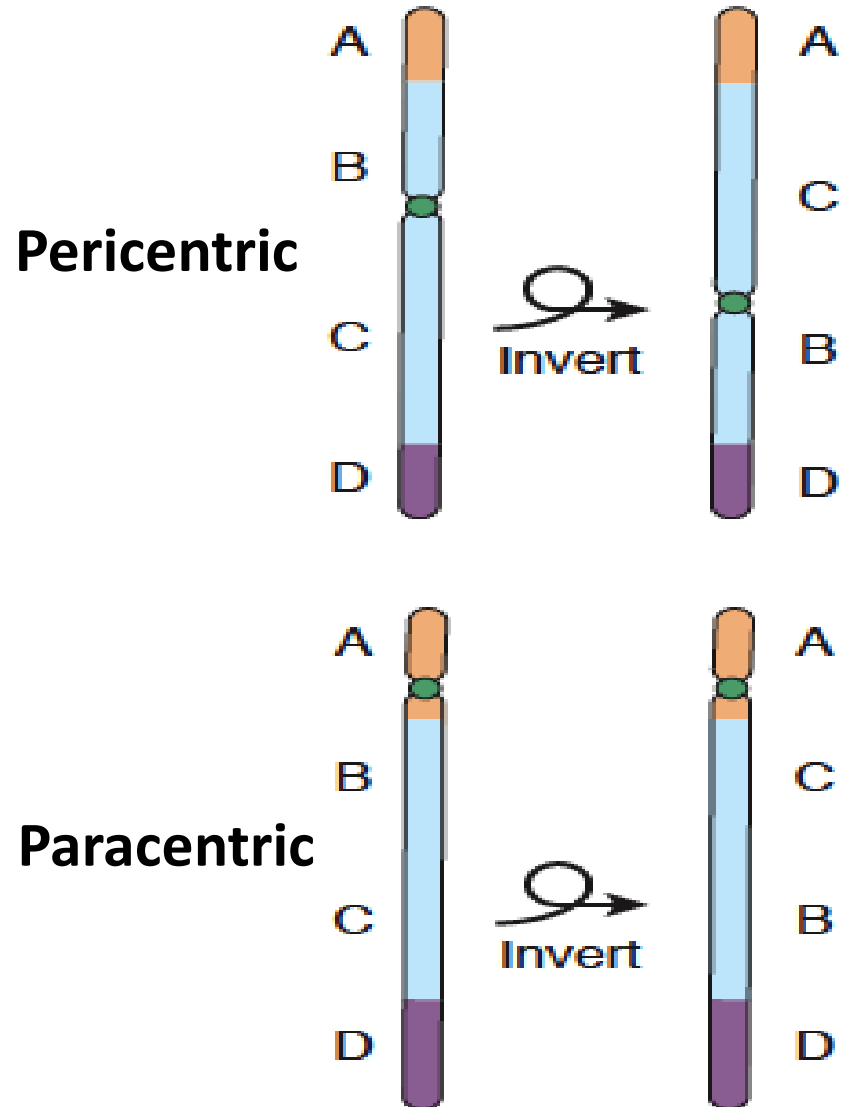
### karyotype description is as follows:

- 46: the total number of chromosomes.
- XY: the sex chromosomes (male).
- del(7): deletion in chromosome 7.
- (q11.23q21.2): breakpoints of the deleted segment.

46,XY,del(7)(q11.23q21.2)

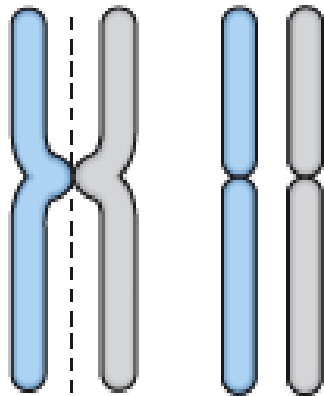
# Inversion

- Occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively.
  - Written in nomenclature as *inv.*
  - Only large inversions are normally detected.
- They are balance rearrangements that rarely cause problems in carriers

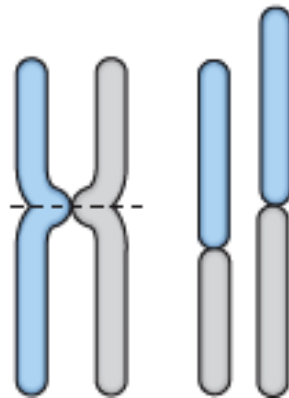


# Isochromosome

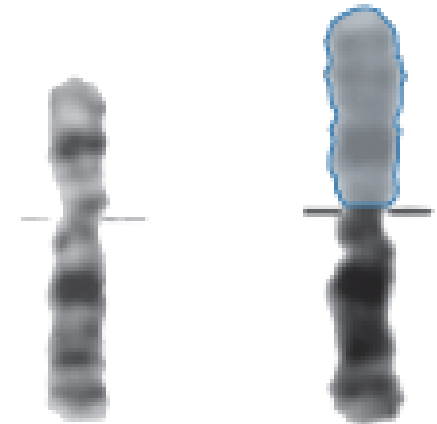
The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally



Normal



Isochromosome



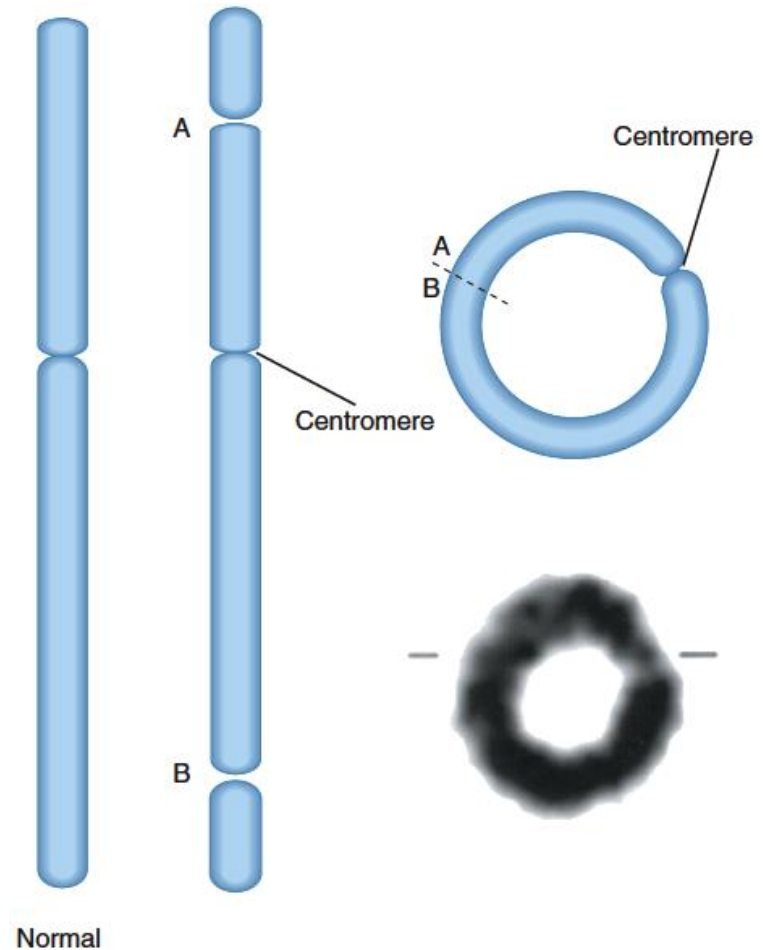
Normal

Isochromosome



# Ring formation (Ring chromosome)

- A break on each arm of a chromosome
- Two sticky ends
- Reunion of the ends as a ring loss of the 2 distal chromosomal fragments
- Ring chromosomes are often unstable in mitosis



# Take home message

- Chromosome abnormalities can be numerical or structural.
- Normal meiotic division result in four haploid gametes
- In trisomy, a single extra chromosome is present, usually as a result of non-disjunction in the 1<sup>st</sup> or 2<sup>nd</sup> meiotic division.
- Mosaicism arise from one zygote while Chimera from the fusion of two fertilized eggs
- Structural abnormalities include translocations (balanced or unbalanced), inversions, deletions, isochromosome & rings.