# 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

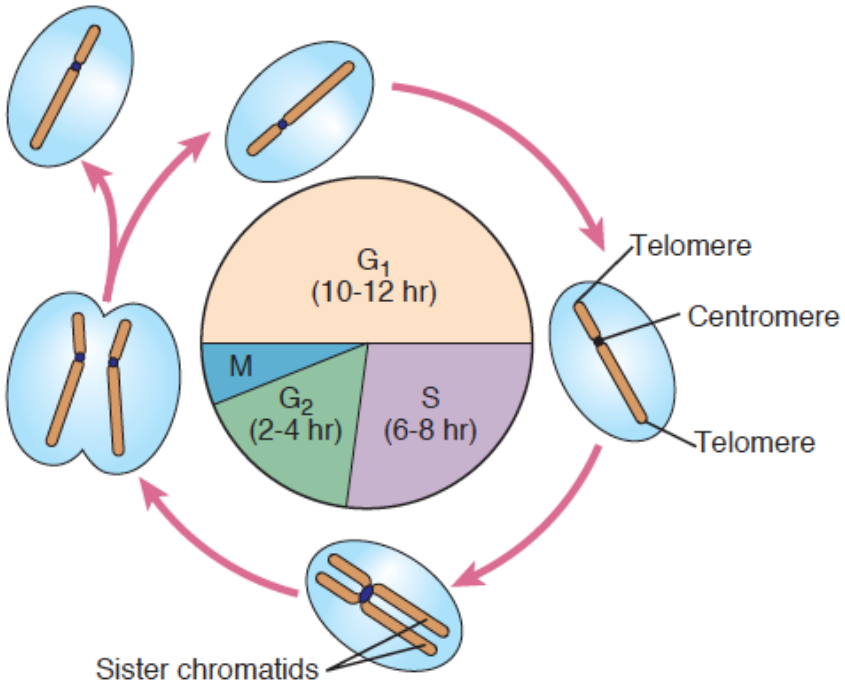
During G1 = one diploid

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

G2 Phase = chromosomes begin to condense and become visible

**G1, S, and G2 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.**

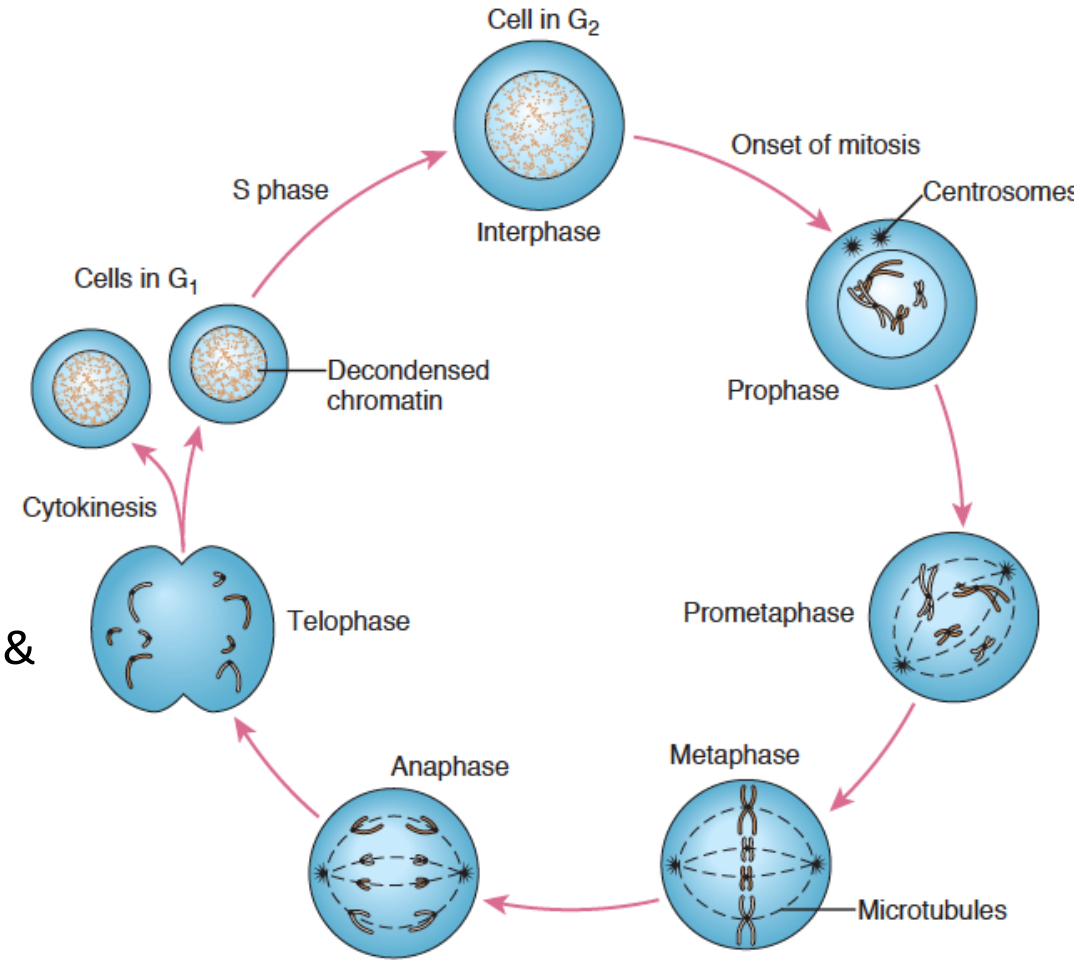
Chromosomes condensed & line up at the equatorial plane

**Anaphase.**

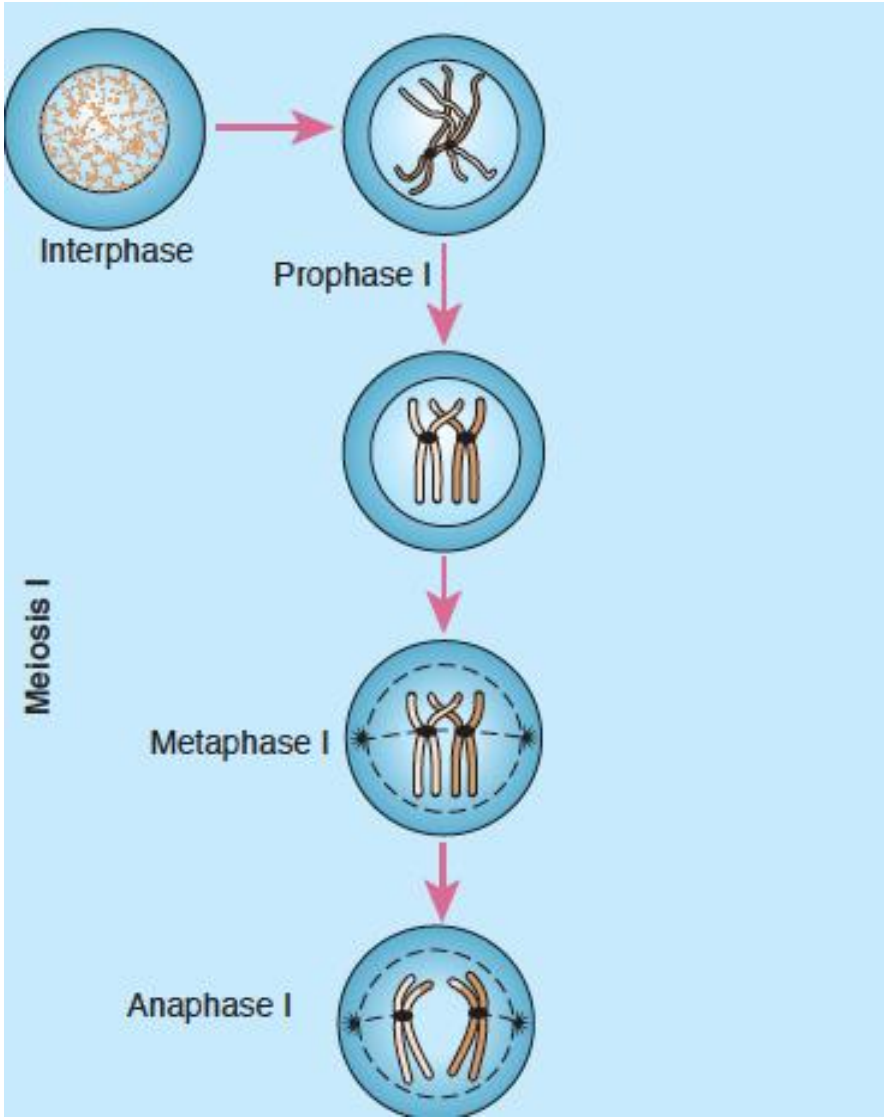
- Chromosomes separate at centromere &
- Sister chromatids of each chromosome become independent daughter chromosomes

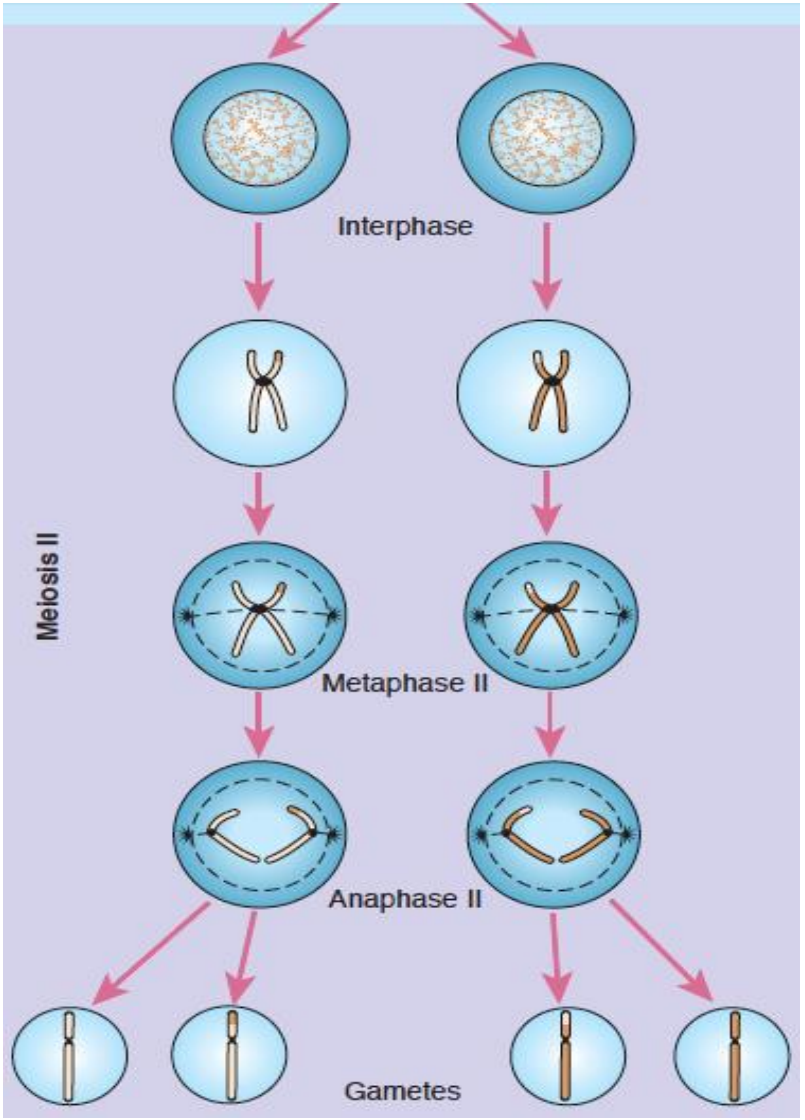
**Telophase.**

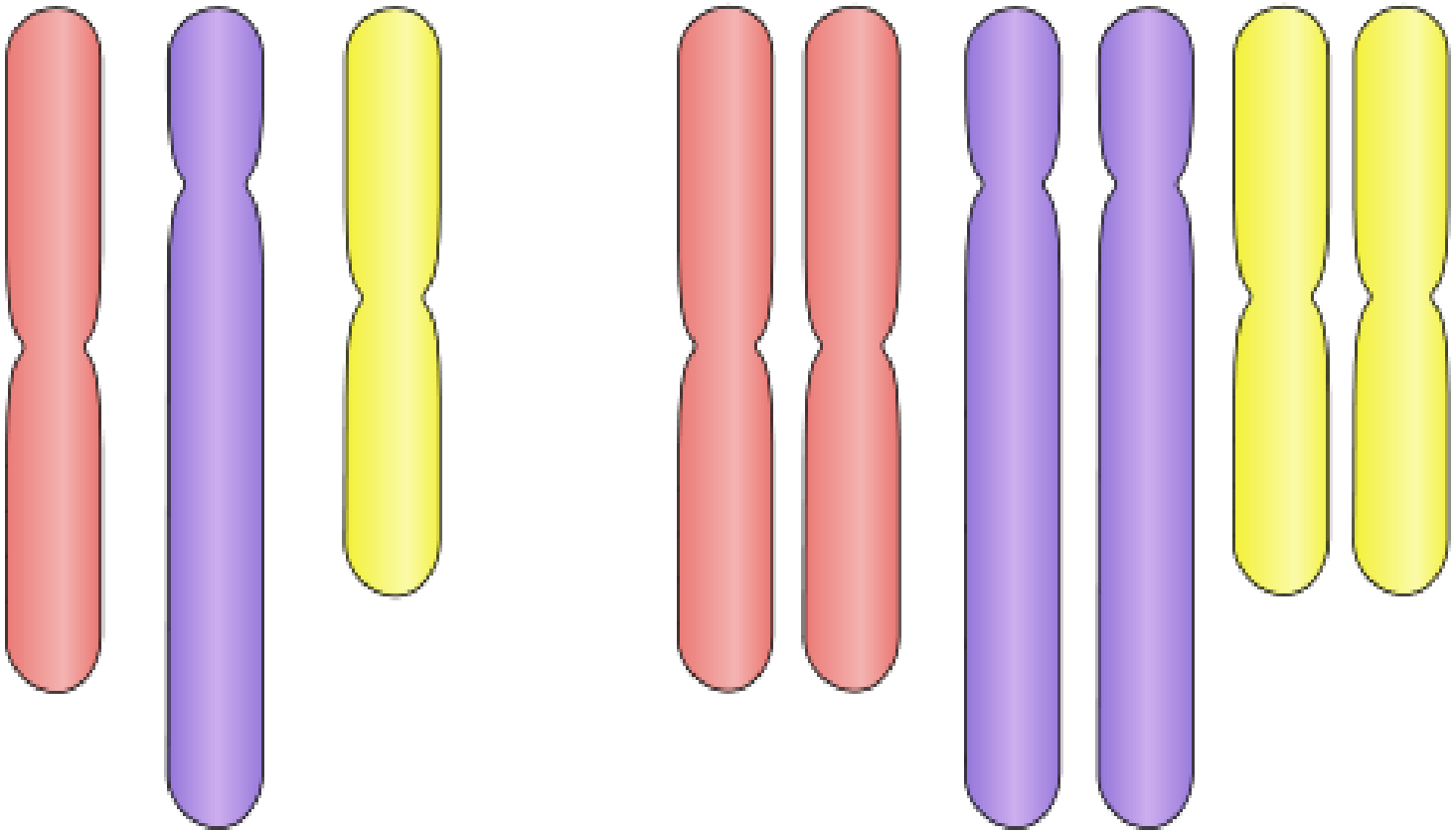
- Chromosomes de-condense from their highly contracted state,
- Nuclear membrane re-form around each of the two daughter nuclei,
- resume their interphase

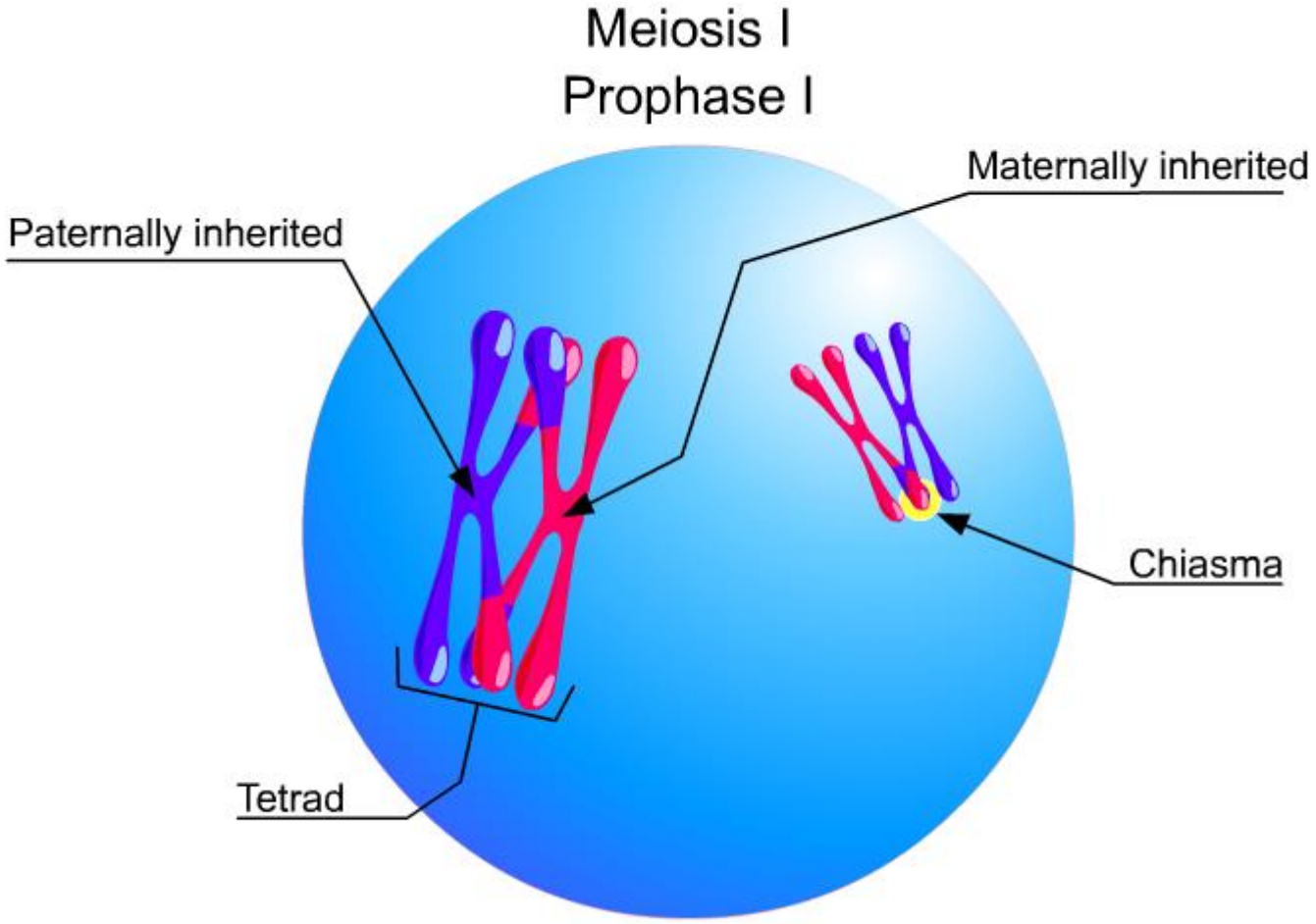


# Events of meiosis I & II




Haploid (N)
Diploid (2N)


Meiosis I
Prophase I
Maternally inherited
Paternally inherited
Chiasma
Tetrad

# 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.

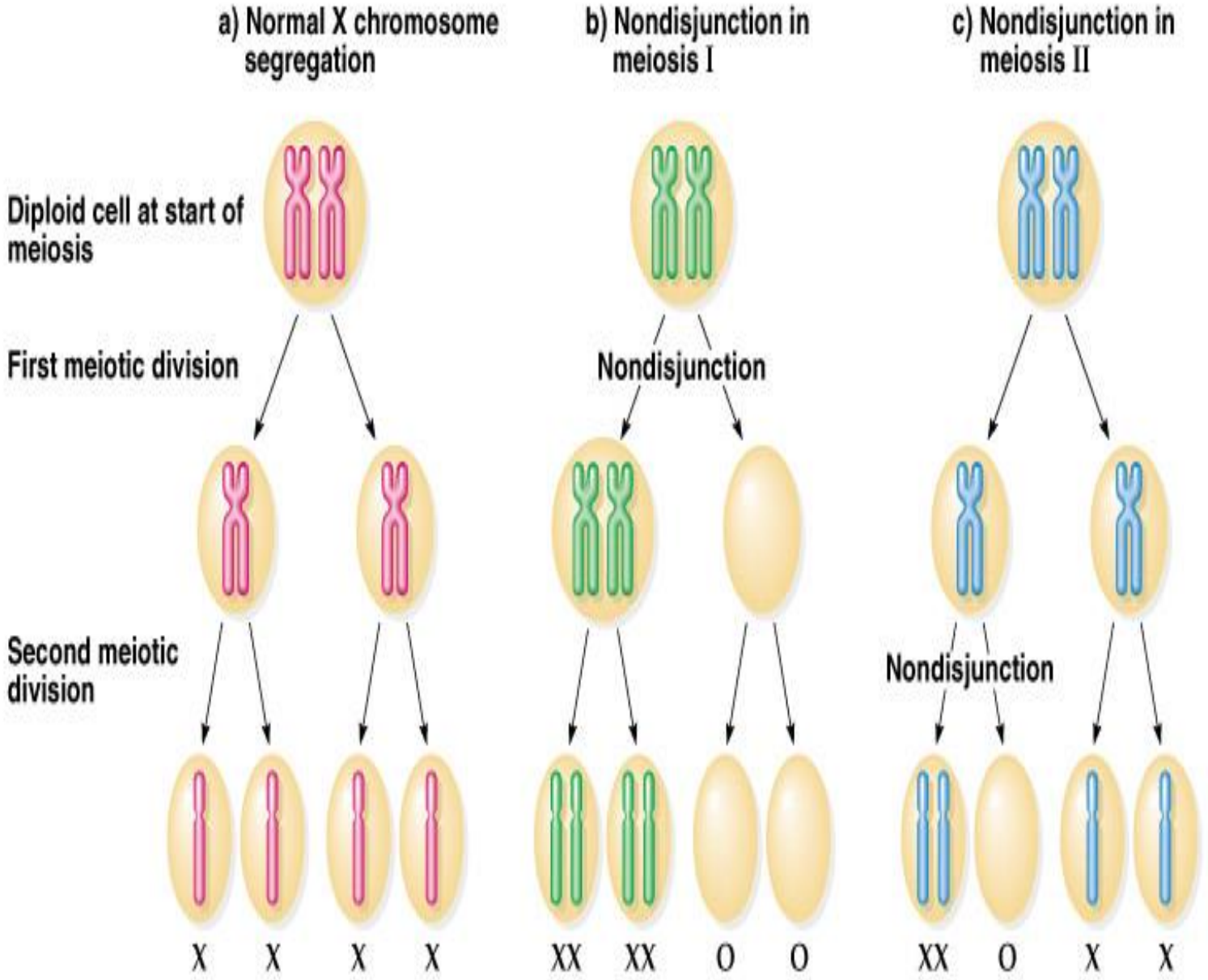
- The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)

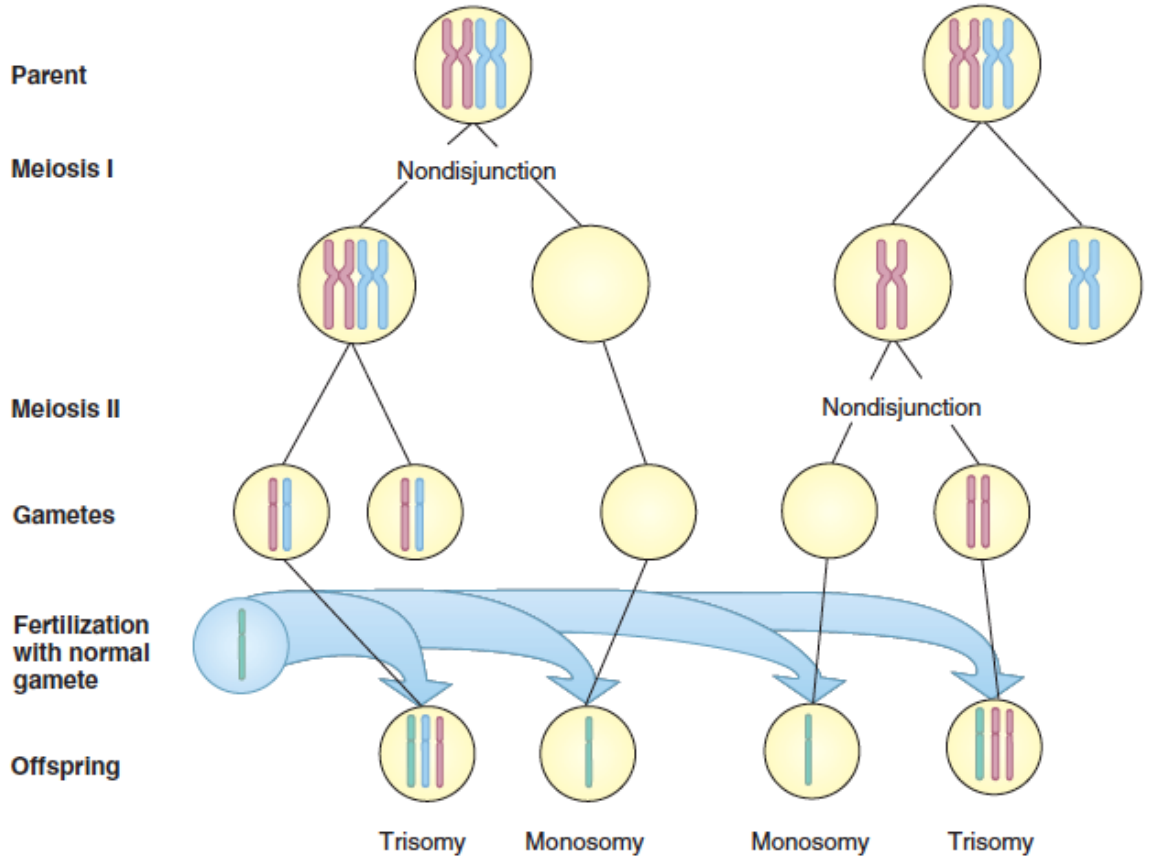
# Meiotic non-disjunction

- 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/X-linked

– Nullosomic gamete


a) Normal X chromosome segregation
b) Nondisjunction in meiosis I
c) Nondisjunction in meiosis II
Diploid cell at start of meiosis
First meiotic division
Second meiotic division
Nondisjunction
Nondisjunction
X X X X
XX XX O O
XX O X X




## 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

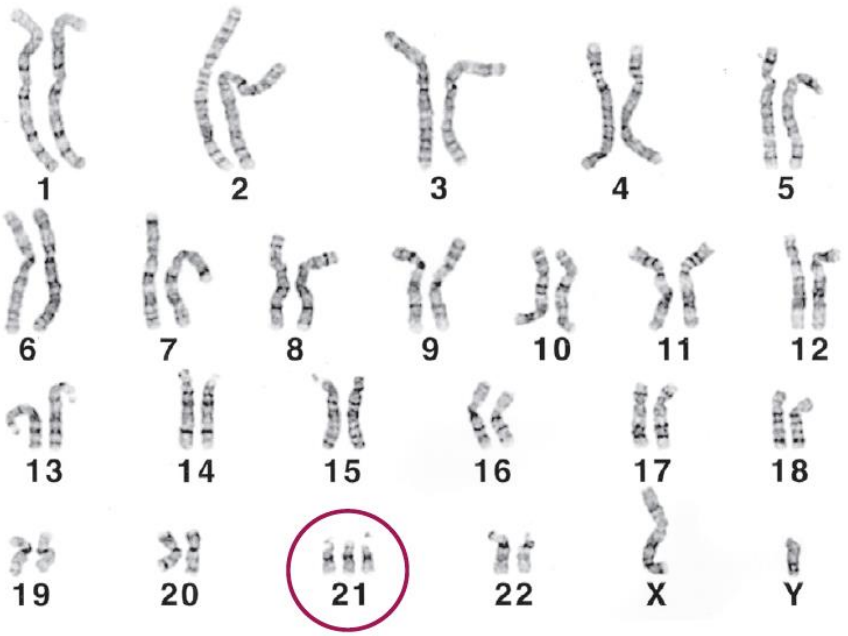
## Karyotype: 47, XY, +21

- Most cases arise from non disjunction in the first meiotic division

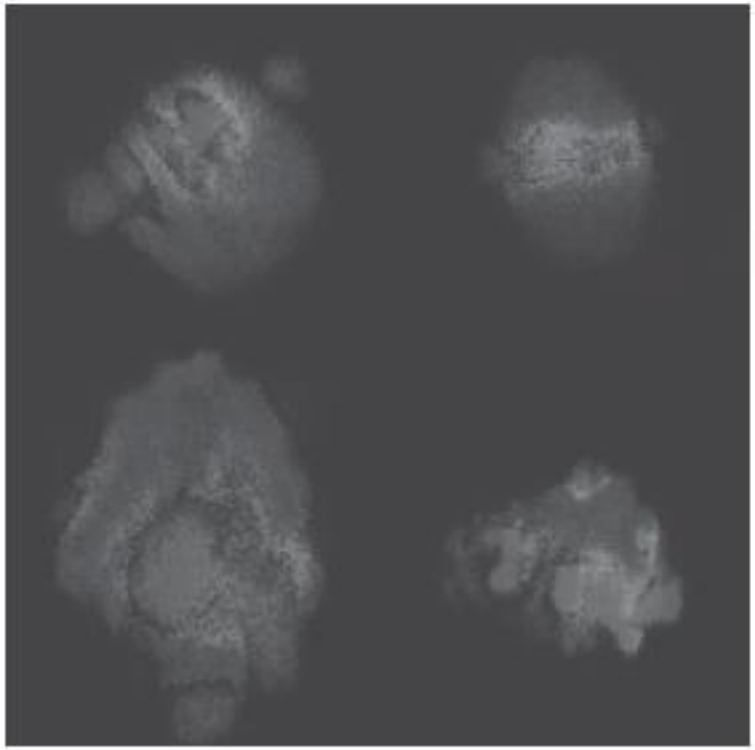
- The incidence of trisomy 21 rises sharply with increasing maternal age

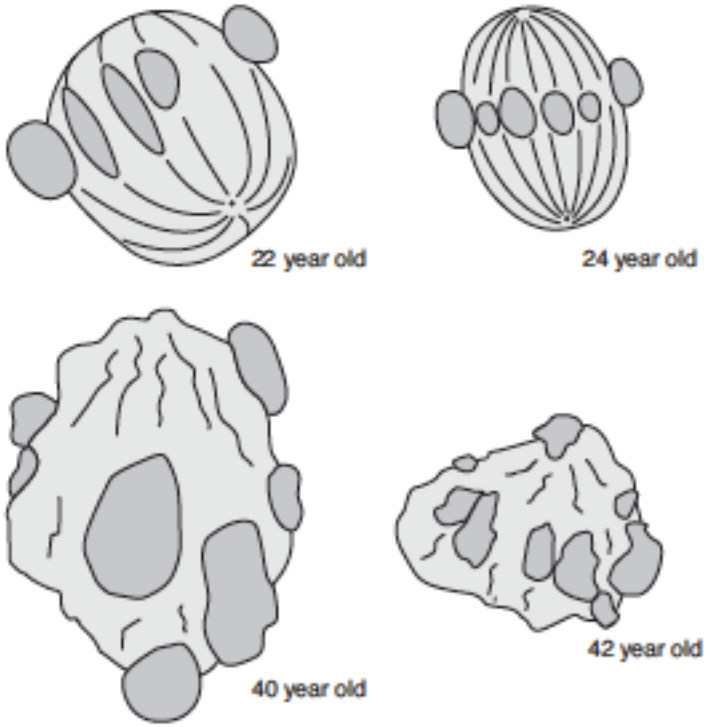
- The father contributing the extra chromosome in 15% of cases

- The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50.



# Meiosis II oöcytes from younger and older women

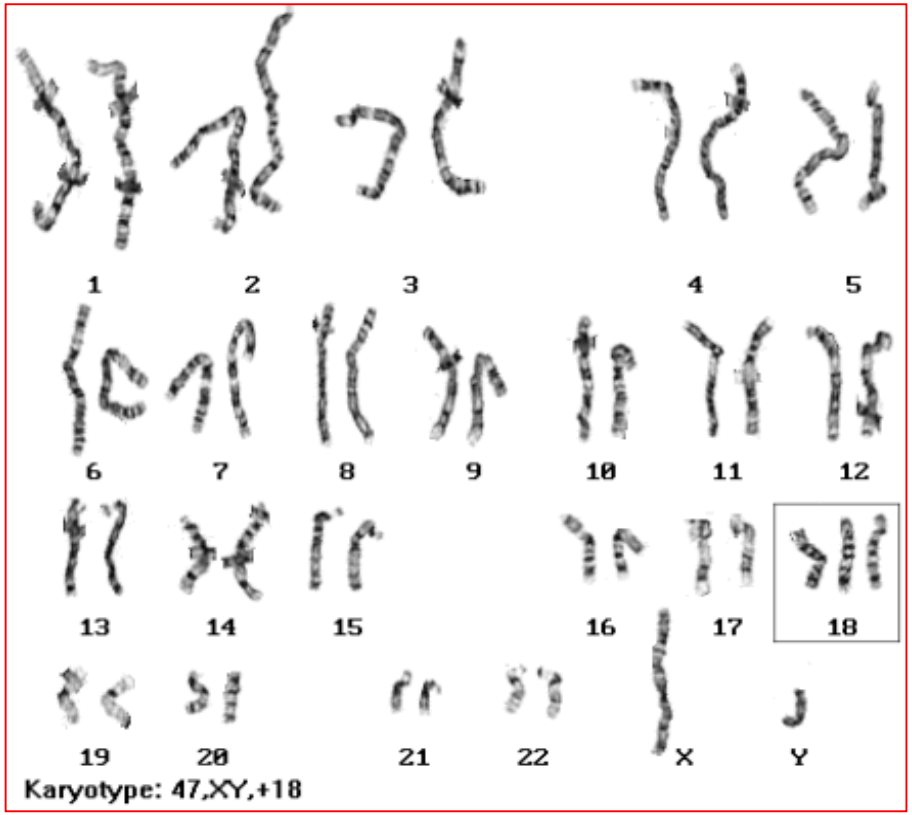




# Edward's syndrome, Trisomy 18

## 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



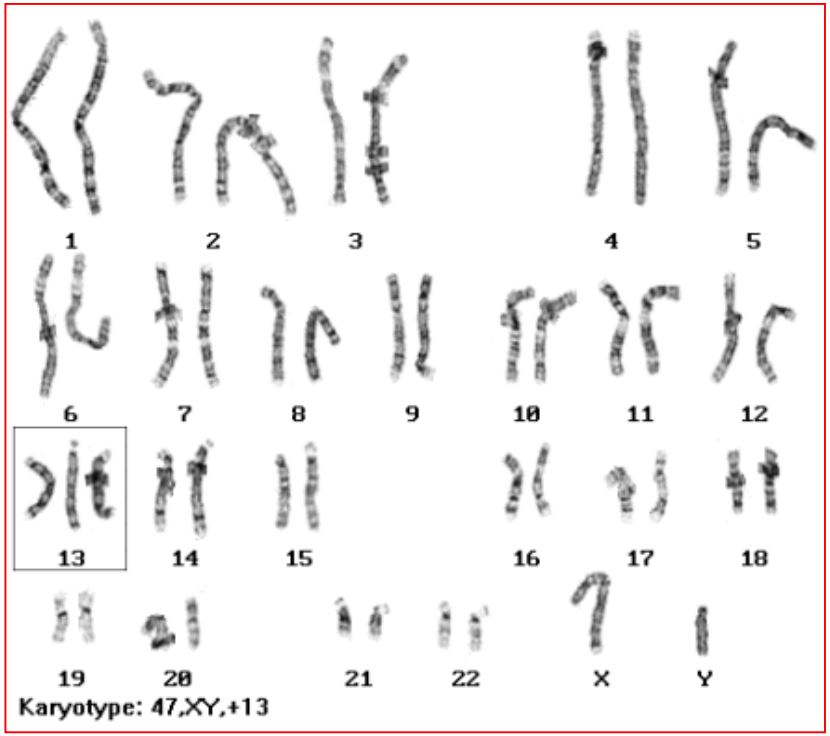
# Patau Syndrome, Trisomy 13

## 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)

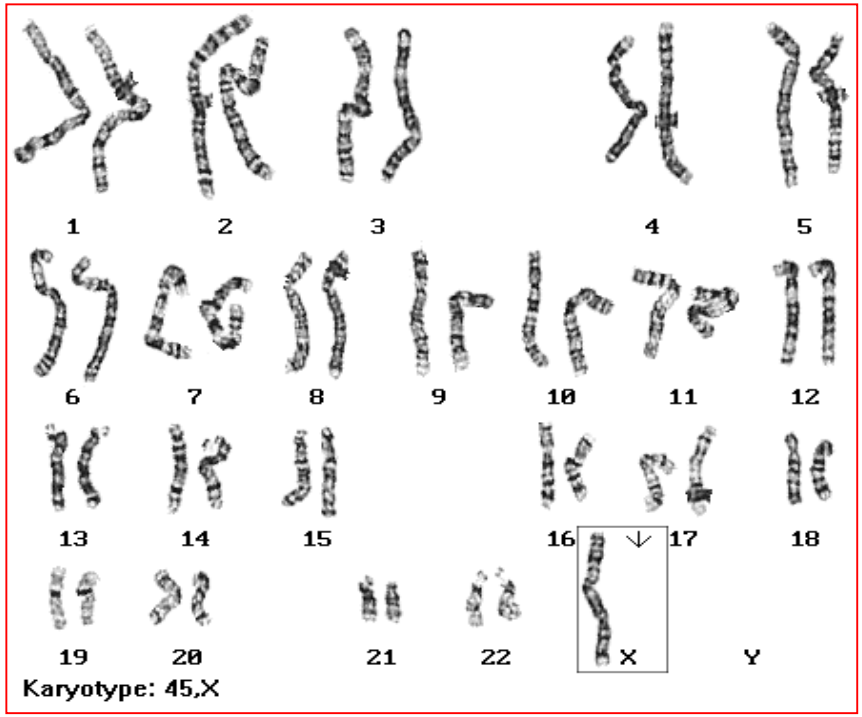
- Occurring in 1 in 4000 phenotypic females

- As a result of paternal meiotic nondisjunction

- The only viable monosomy in humans

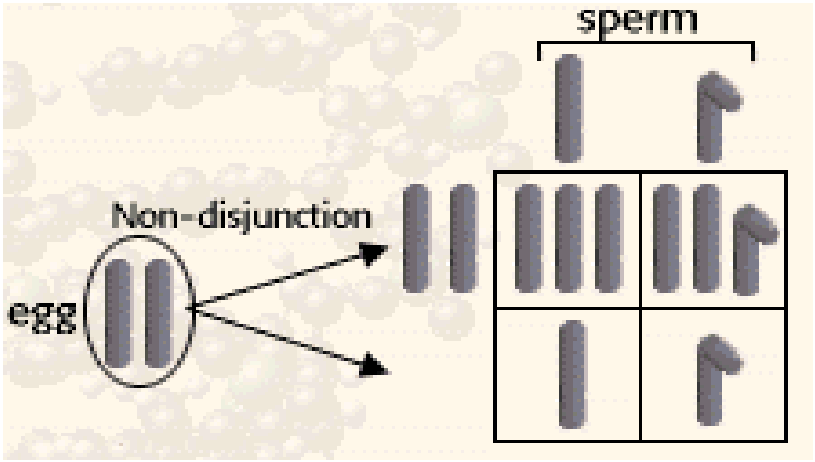
- Characteristics:

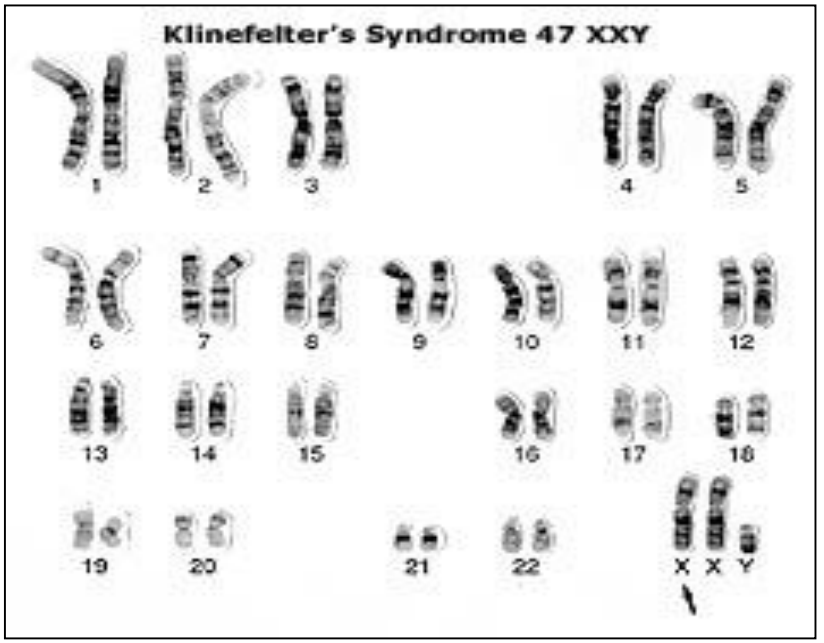
Webbed neck, Individuals are genetically female, not mature sexually, Sterile, Short stature, Broad chest, Low hairline, Streak ovaries, Normal intelligence, Normal life span



# 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

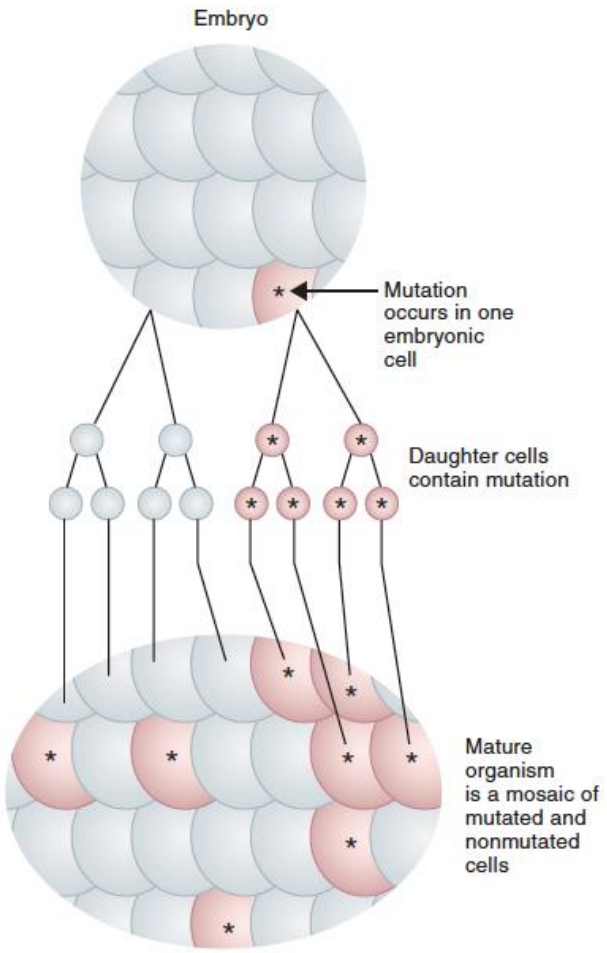


# MOSAICISM

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 <u>only 1 zygote</u>

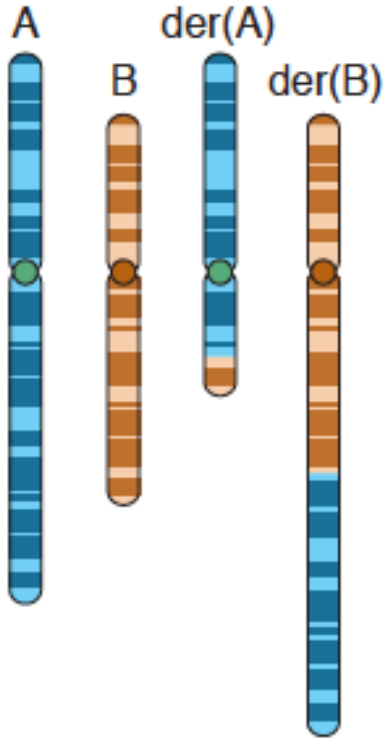


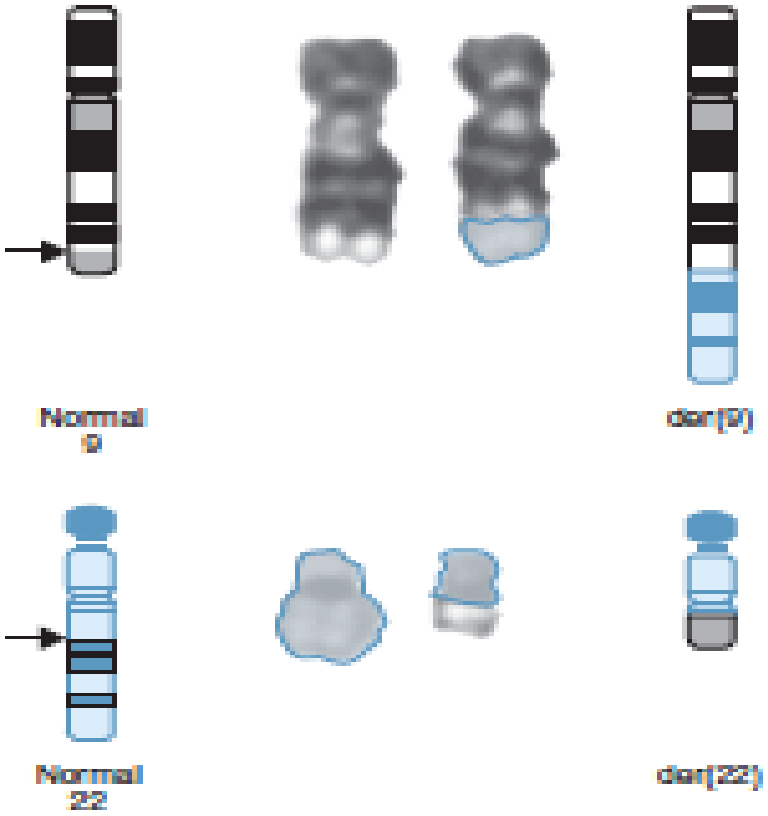
# MOSAICISM

- 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



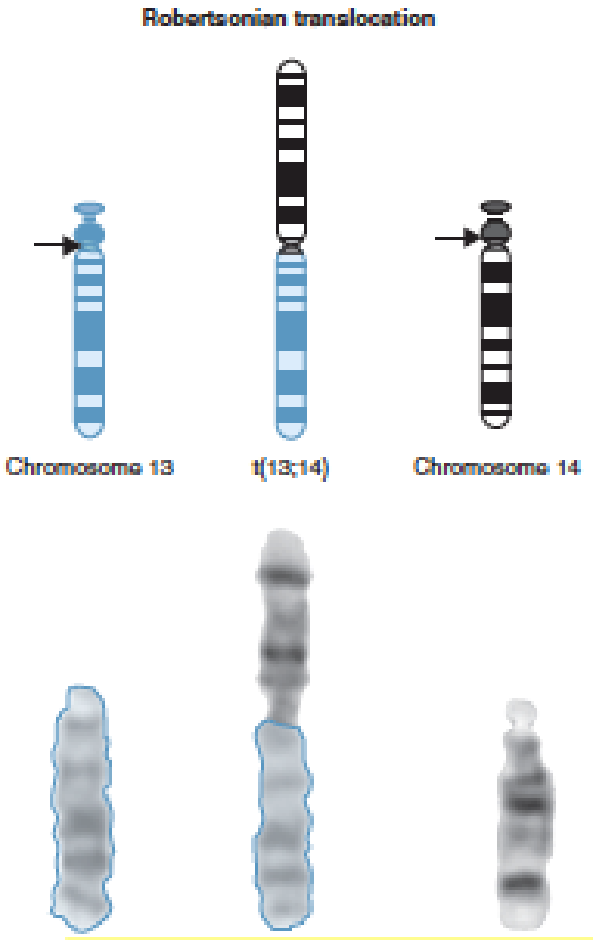

- Reciprocal translocation between chromosome 22 and the long arm of chromosome 9 (the Philadelphia chromosome).
- The occurrence of this translocation in hematopoietic cells can produce chronic myelogenous leukemia (CML)

# 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)

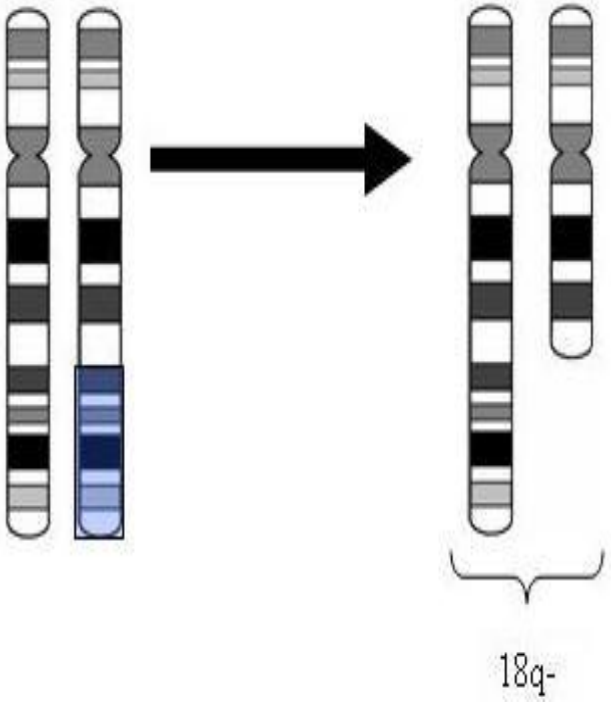
- Although carriers have only 45 chromosomes in each cell, they are phenotypically unaffected

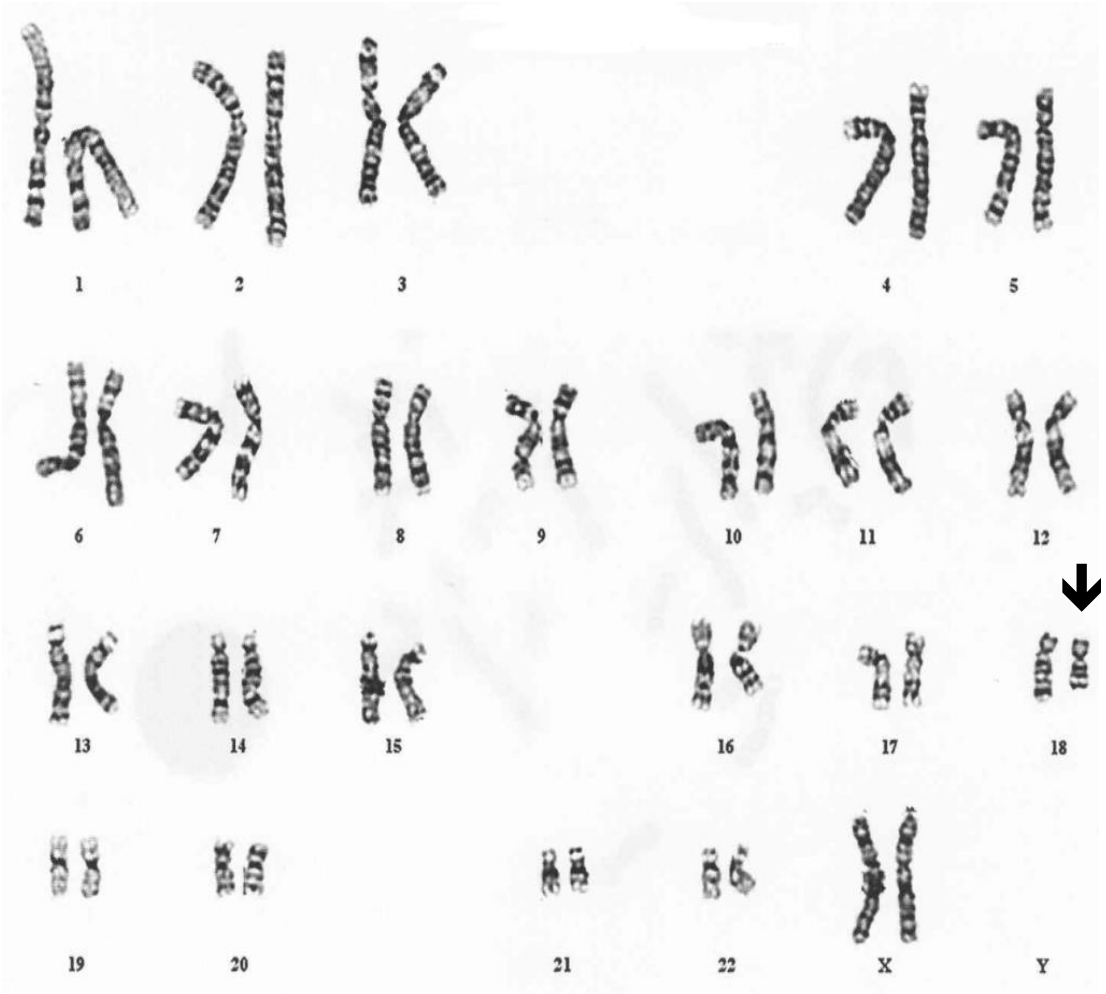


# Deletion

- **- 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**

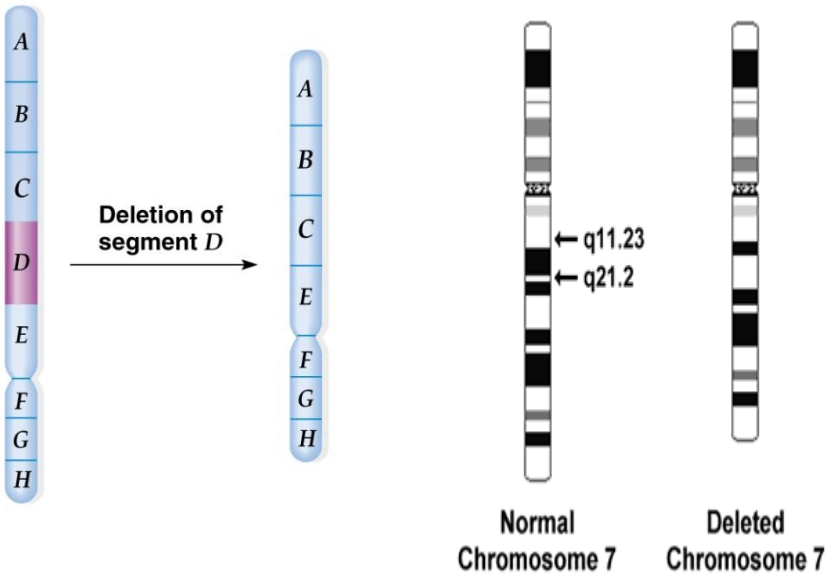
# Terminal deletion



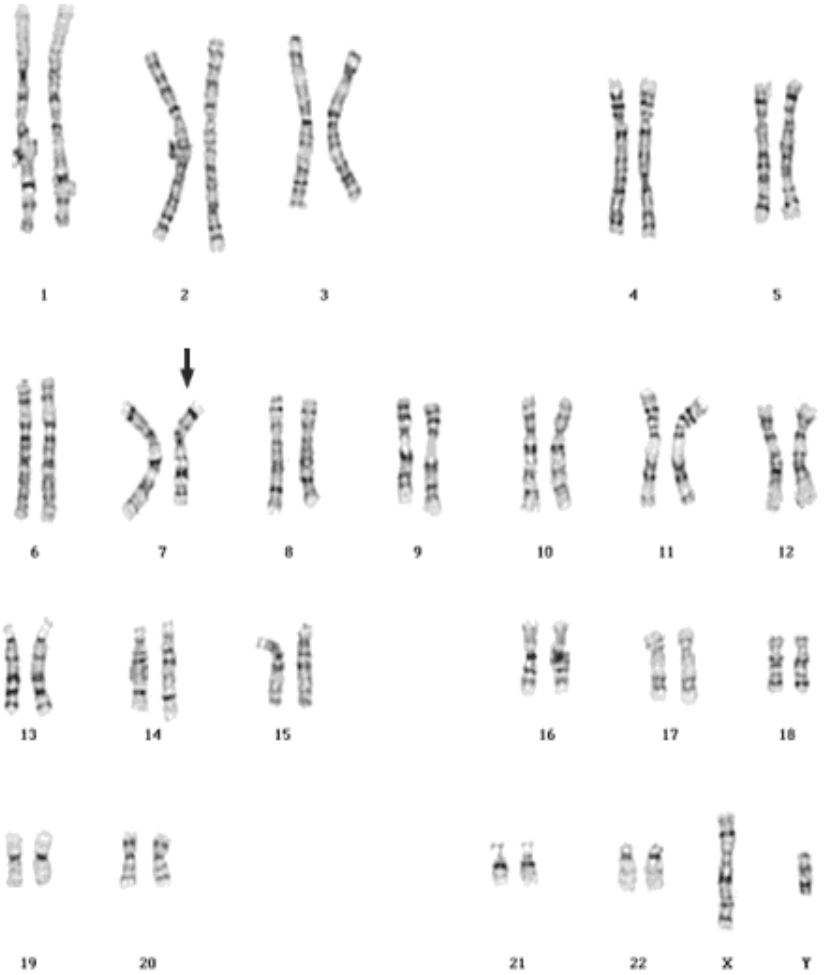




46,XX,del(18)(q21.3)

# 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.**

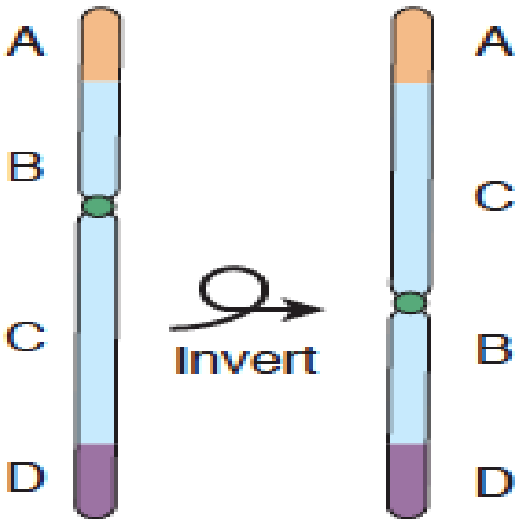
**46,XY,del(7)(q11.23q21.2)**

# Inversion

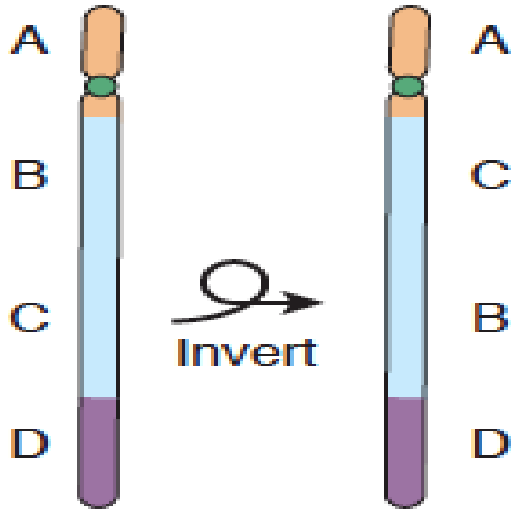
- Occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively.
- Written in nomenclature as inv.
- Only large inversions are normally detected.

They are balance rearrangements that rarely cause problems in carriers

**Pericentric**

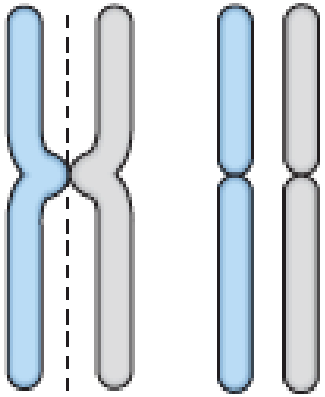



**Paracentric**

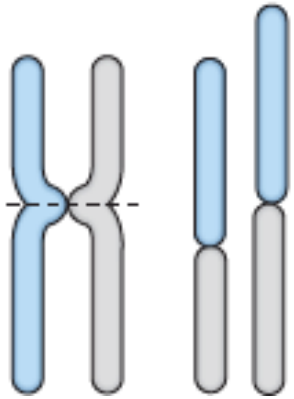


# Isochromosome

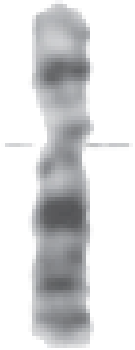
The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally



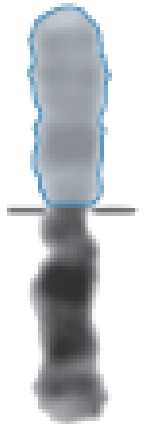
Normal



Isochromosome



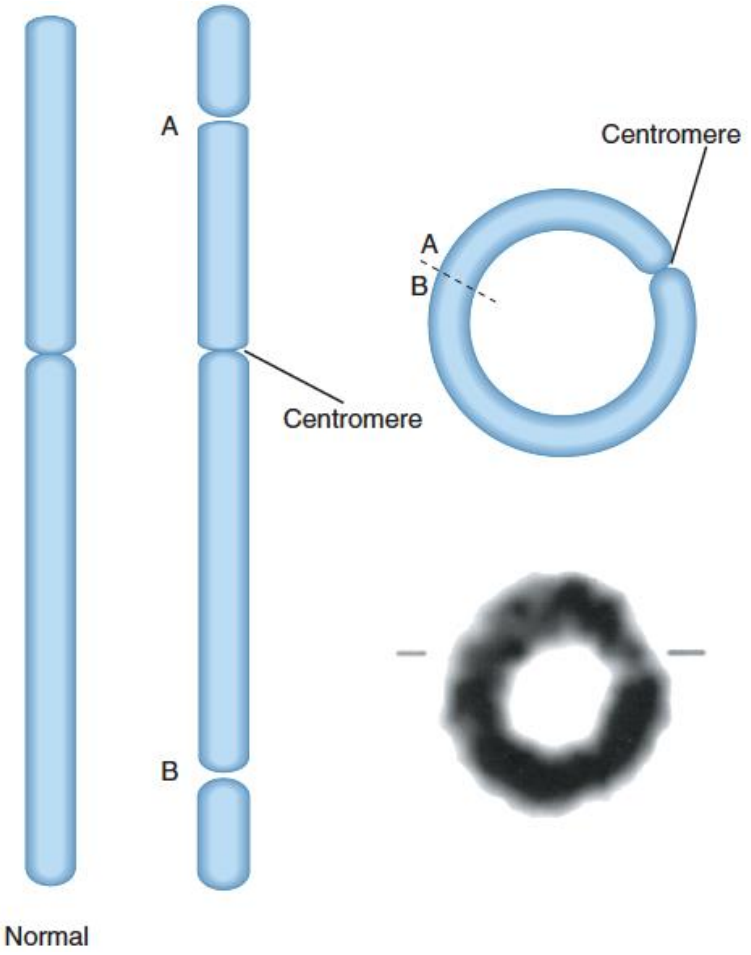
Normal



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$^{st}$ or 2$^{nd}$ meiotic division.
- Mosaicism arize from one zygote while Chimera from the fusion of two fertilized eggs
- Structural abnormalities include translocations (balanced or unbalanced), inversions, deletions, isochromosome & rings.