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

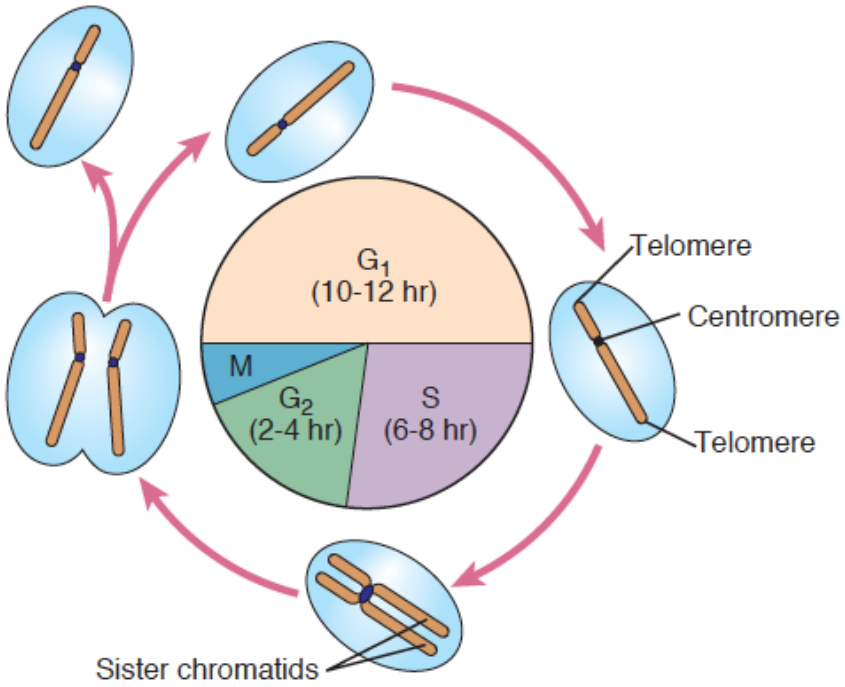
Typical mitotic cell cycle

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.

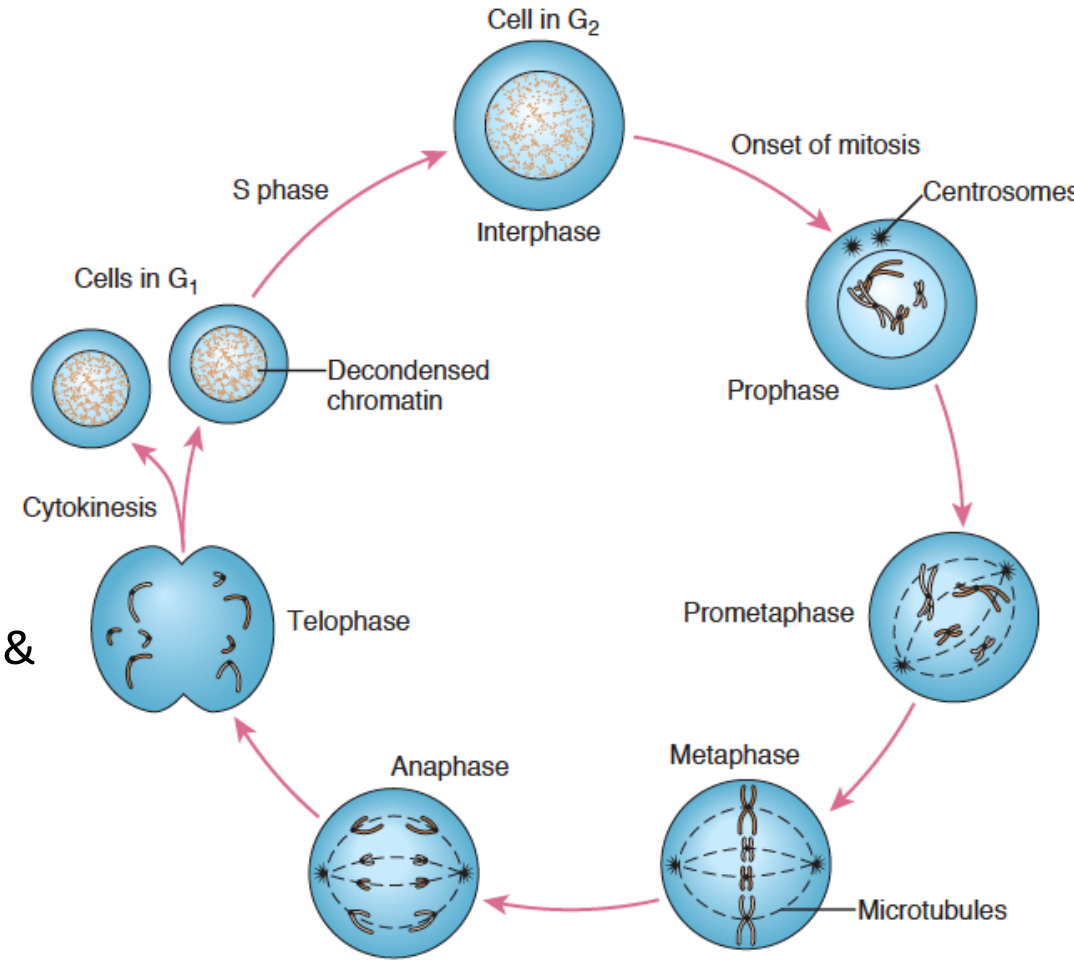
Chromosomes condensed & line up at the equatorial plane

Anaphase.

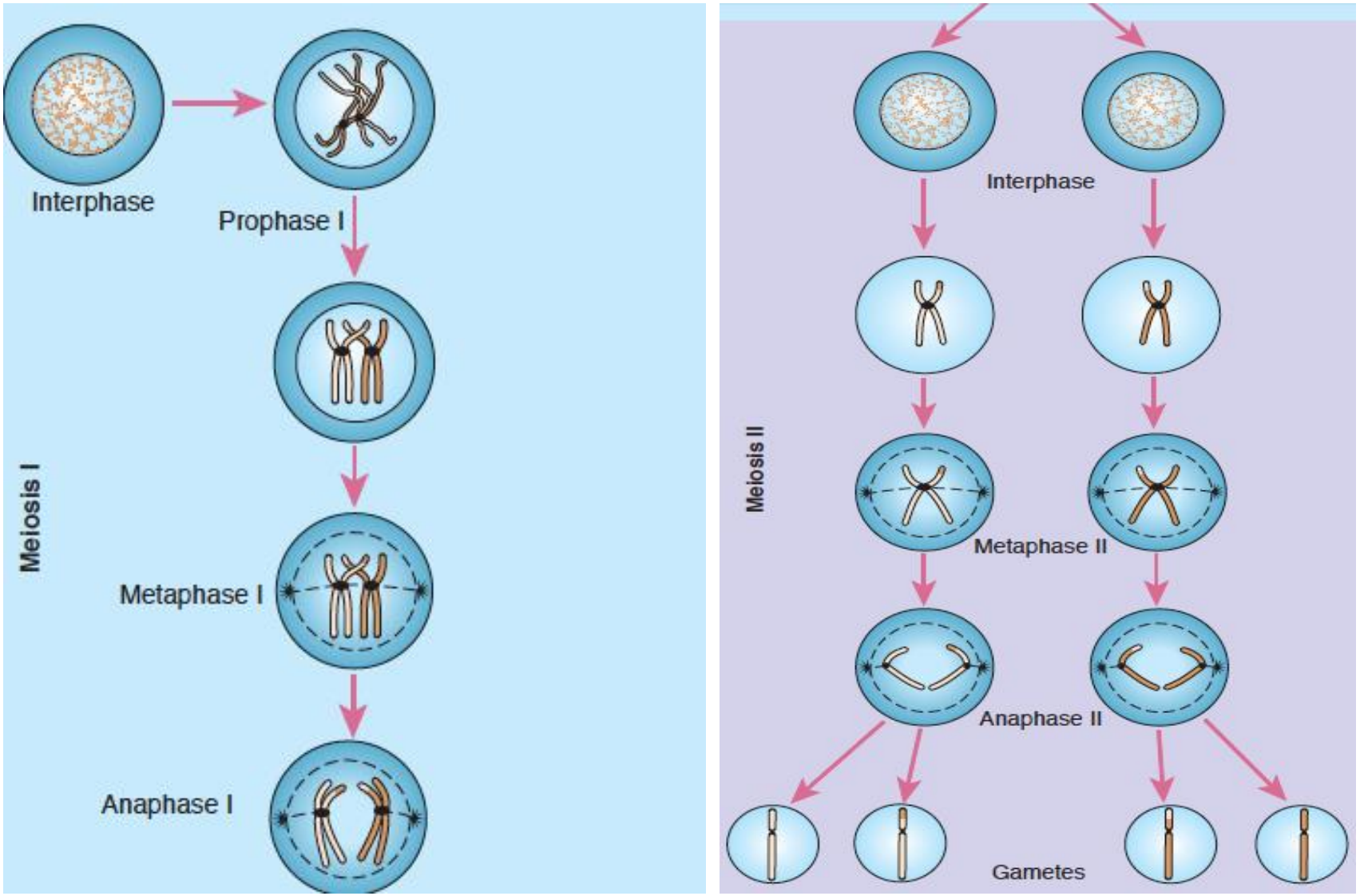
- Chromosomes separate at centromere &
- Sister chromatids of each chromosome become independent daughter chromosomes

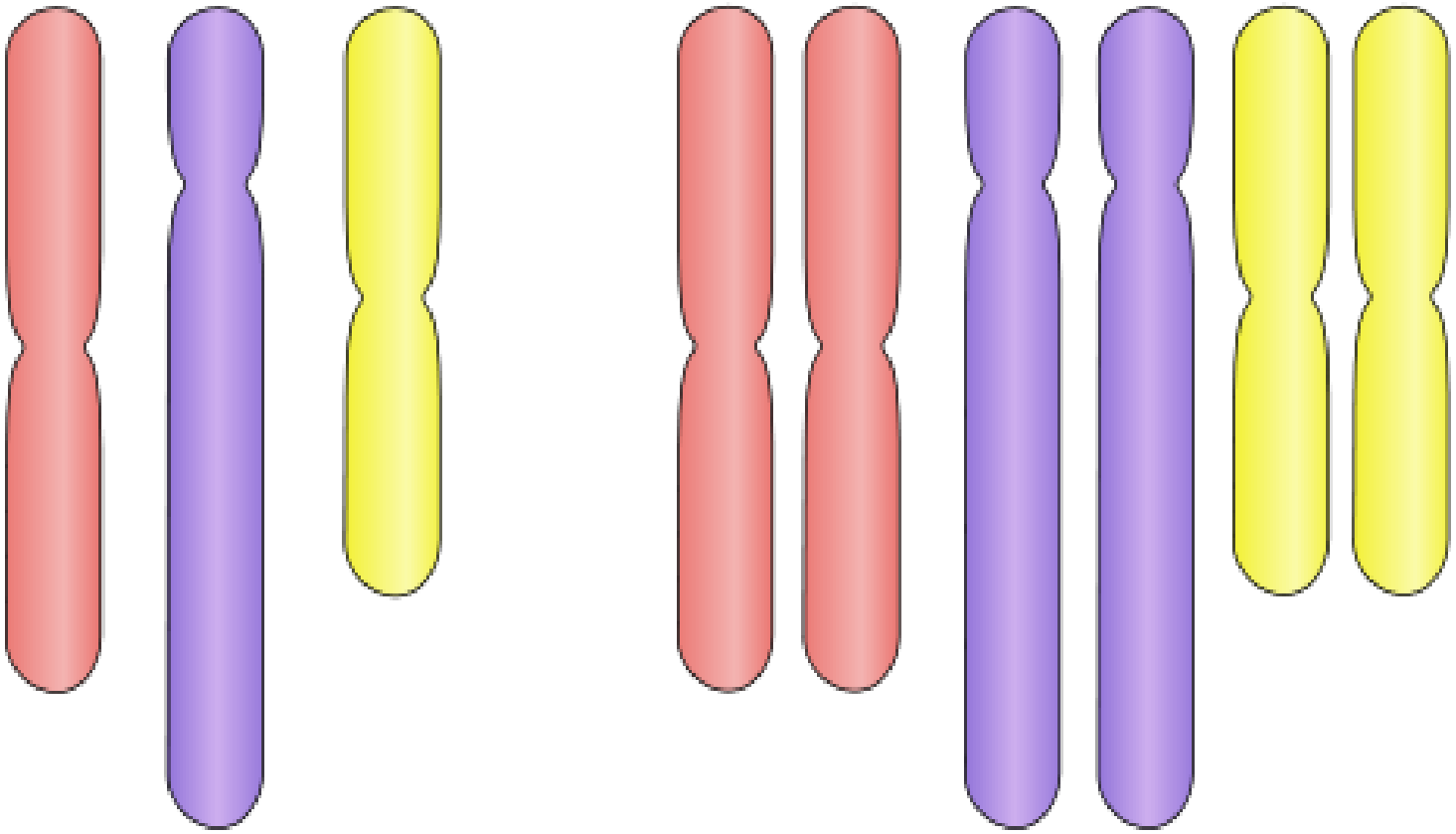
Telophase.

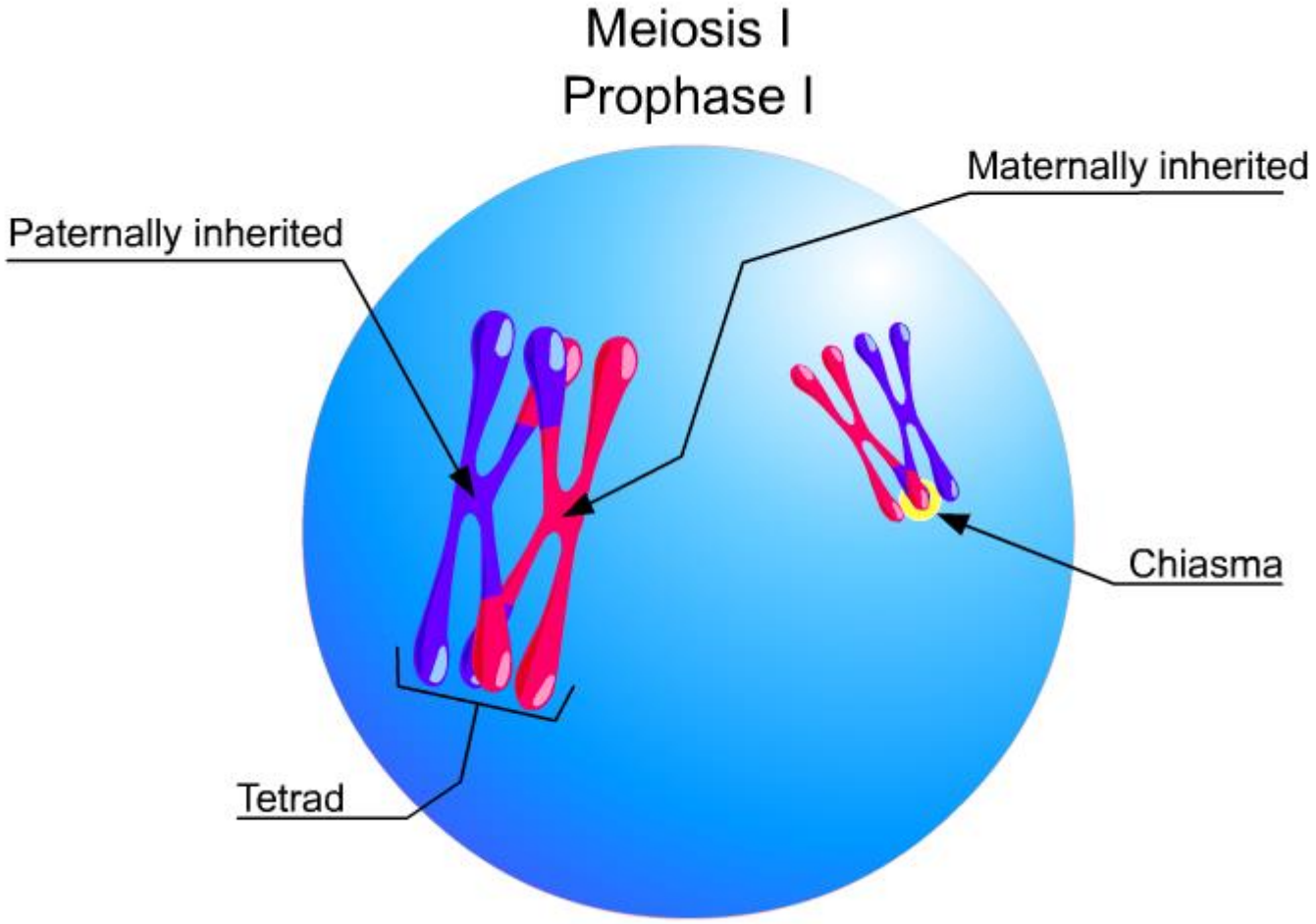
- Chromosomes de-condense from their highly contracted state,
- Nuclear membrane re-form around each of the two daughter nuclei,
- resume their interphase



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.

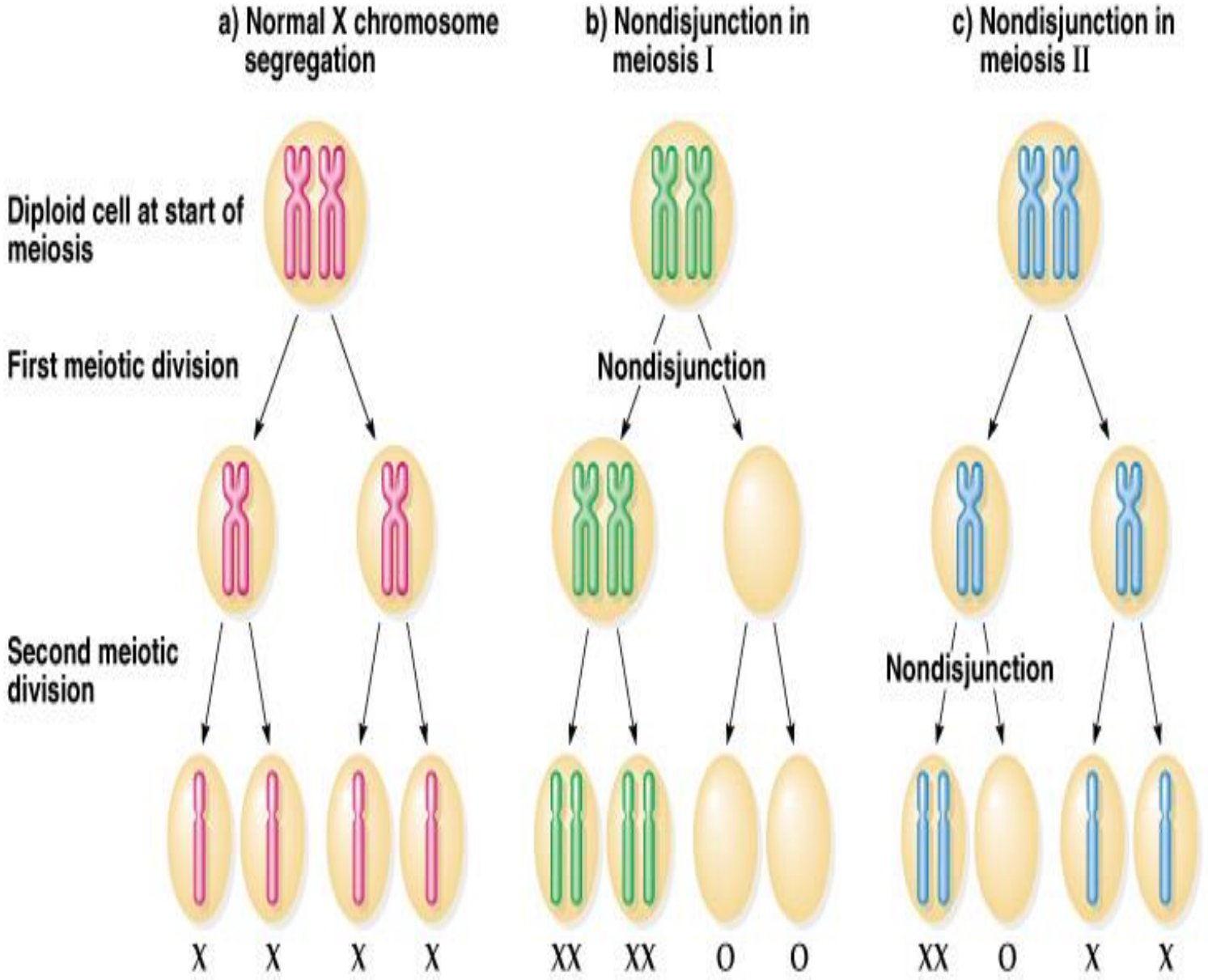
- The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)

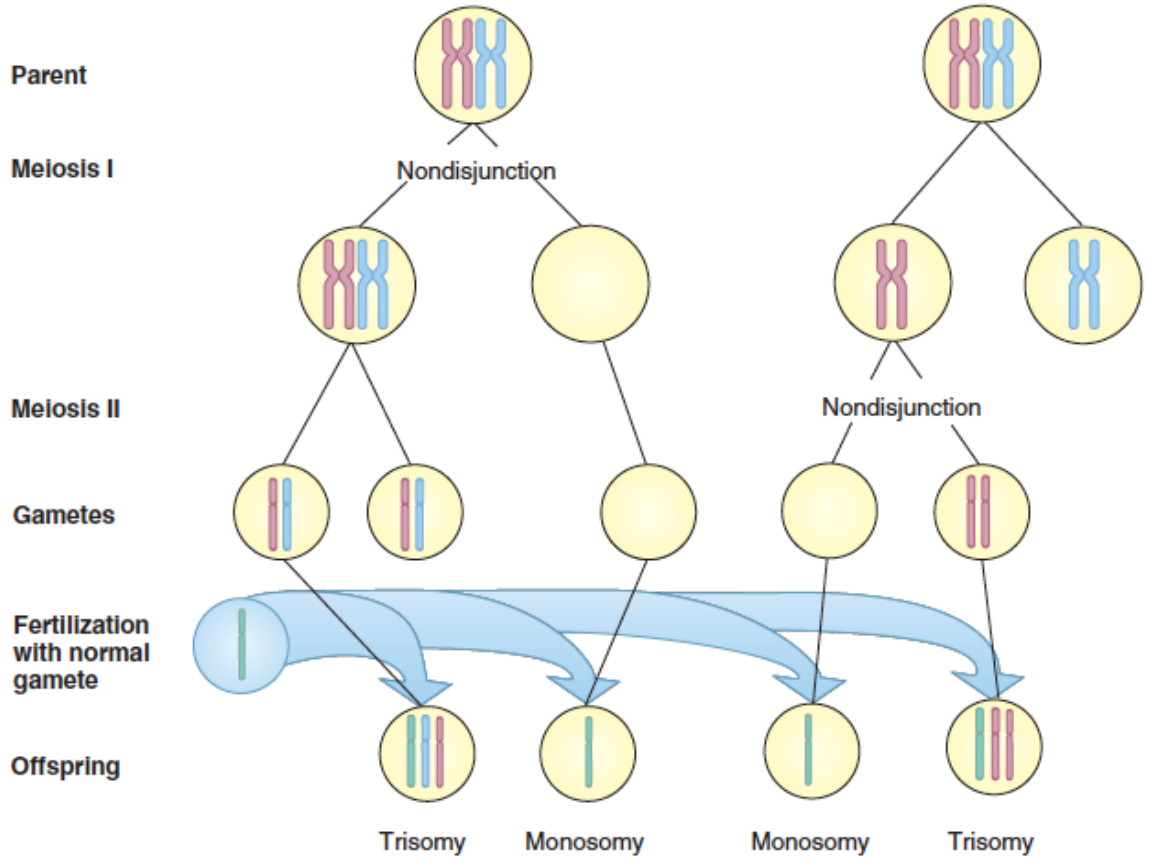
Meiotic non-disjunction

- 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

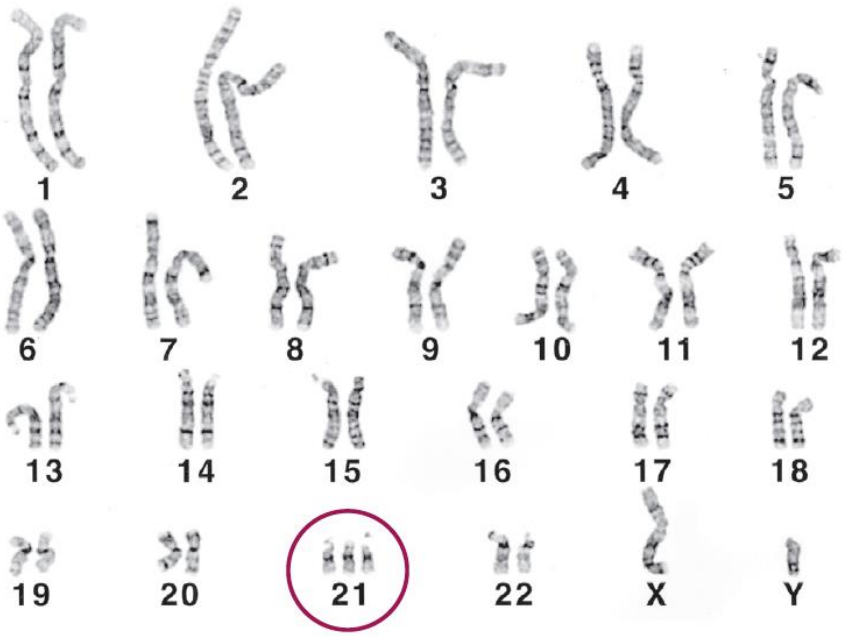
Karyotype: 47, XY, +21

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

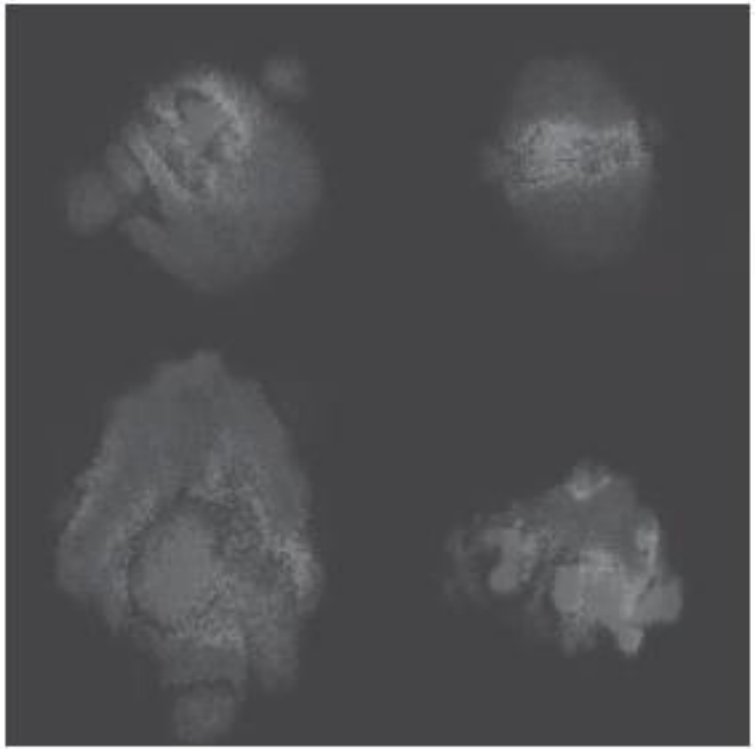
- The incidence of trisomy 21 rises sharply with increasing maternal age

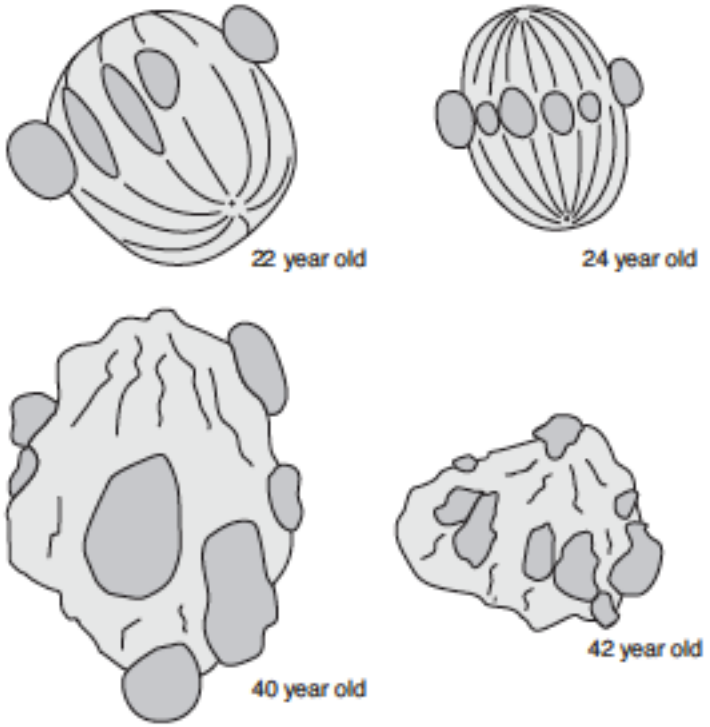
- The father contributing the extra chromosome in 15% of cases

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



Meiosis II oöcytes from younger and older women

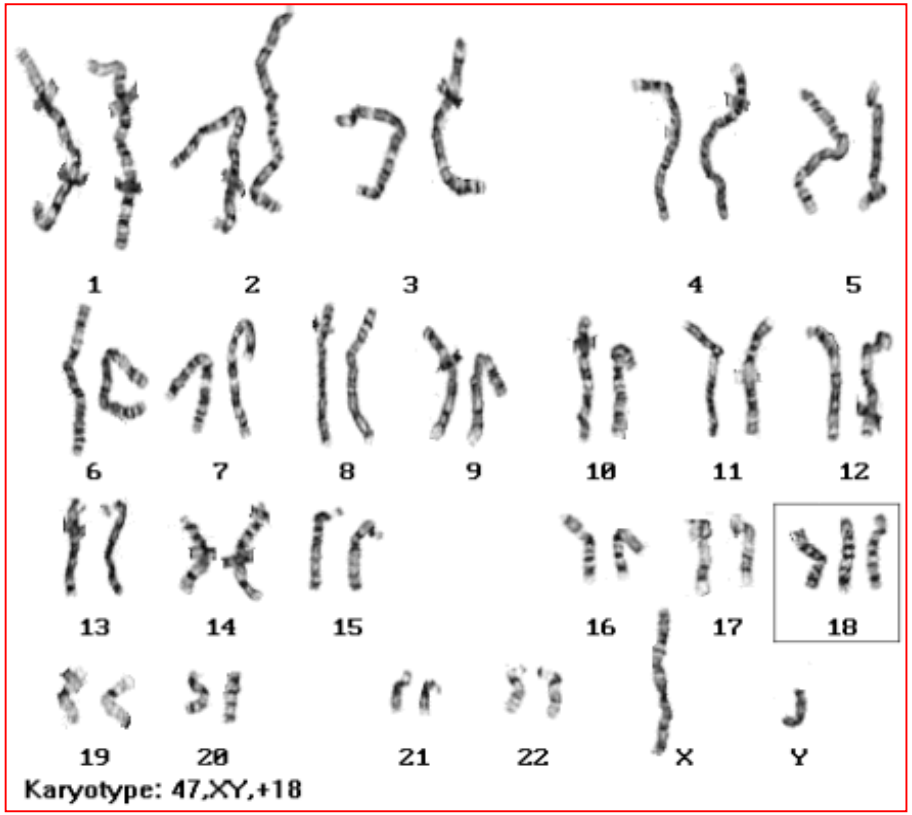




Edward's syndrome, Trisomy 18

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



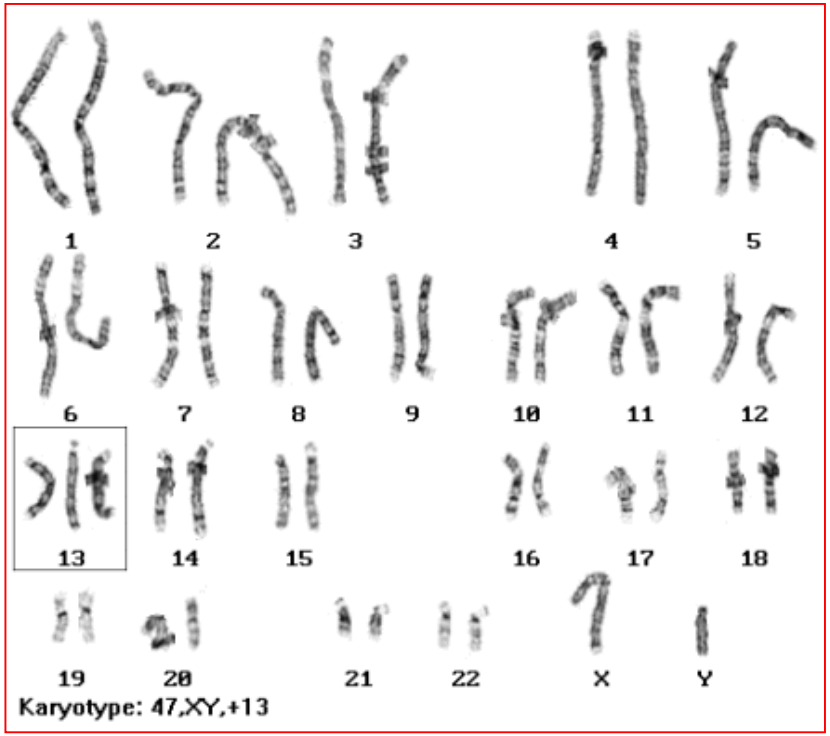
Patau Syndrome, Trisomy 13

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)

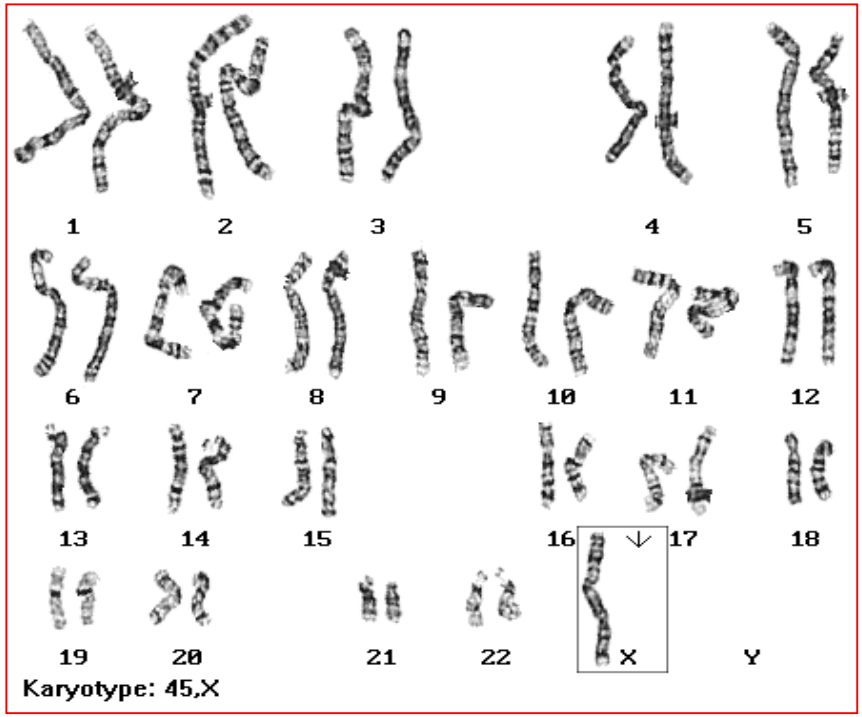
- Occurring in 1 in 4000 phenotypic females

- As a result of paternal meiotic nondisjunction

- The only viable monosomy in humans

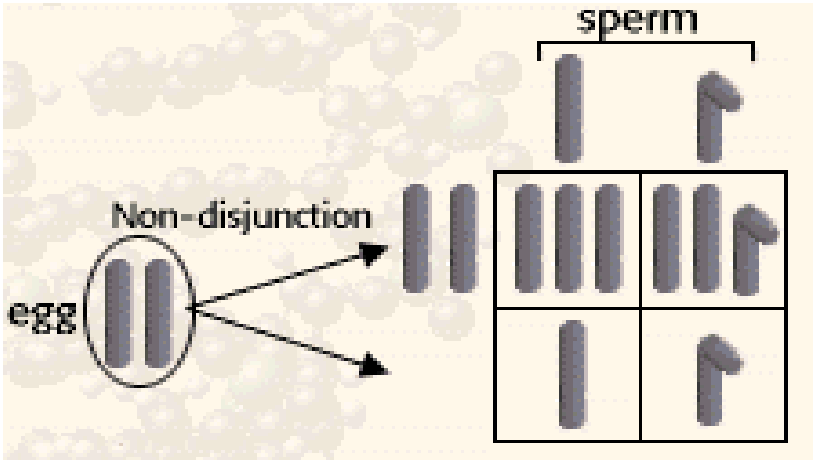
- Characteristics:

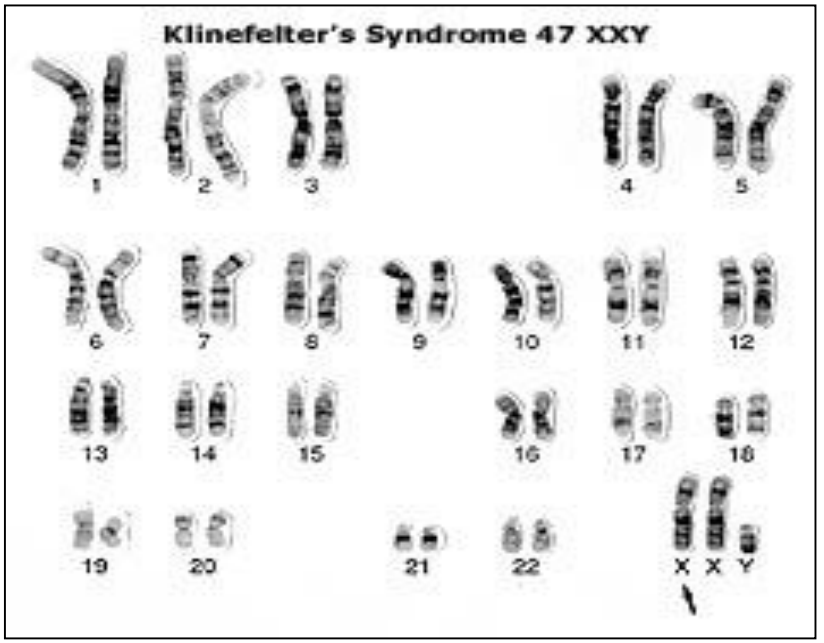
Webbed neck, Individuals are genetically female, not mature sexually, Sterile, Short stature, Broad chest, Low hairline, Streak ovaries, Normal intelligence, Normal life span



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

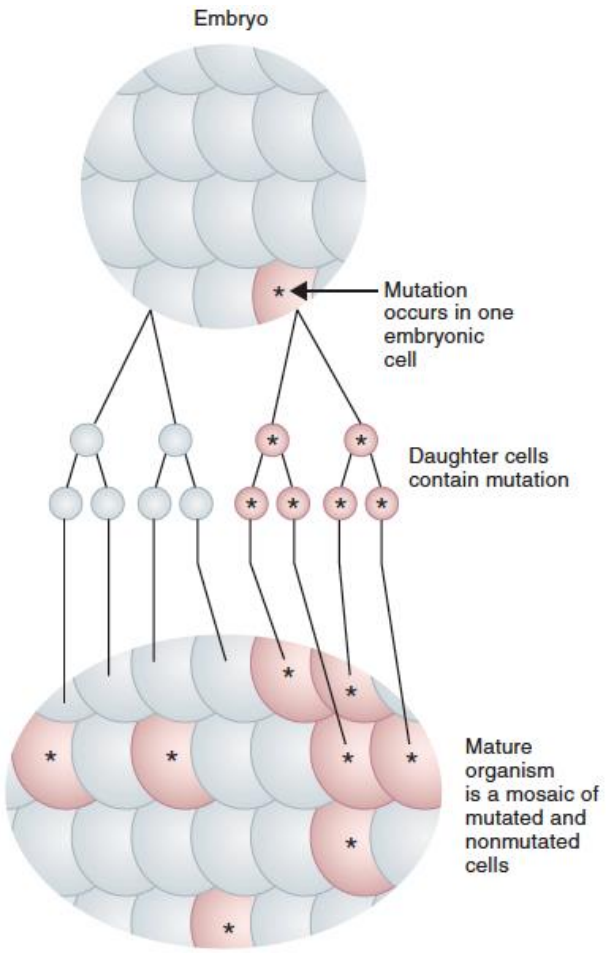




MOSAICISM

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>

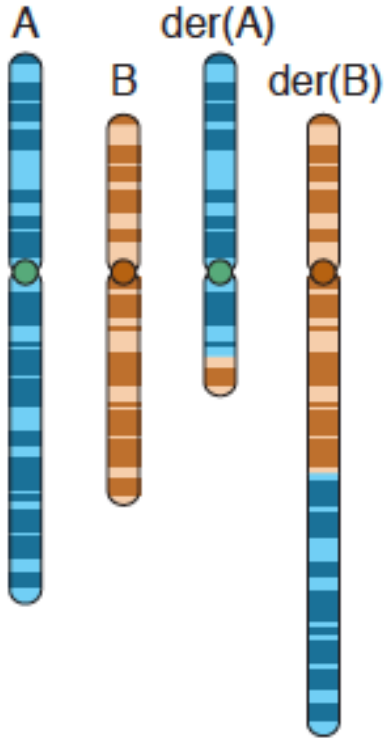


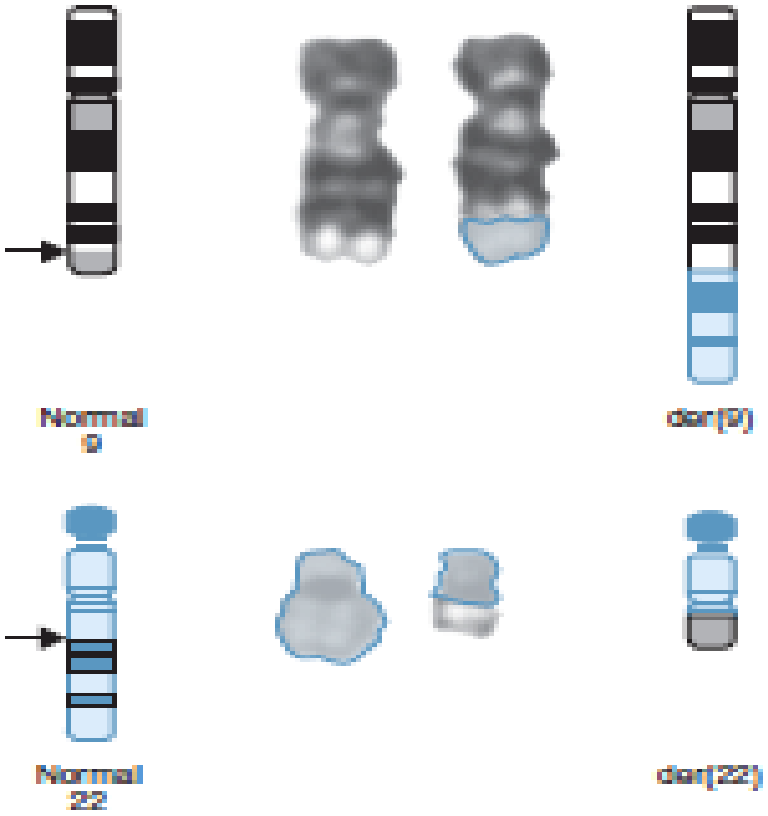
MOSAICISM

- 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





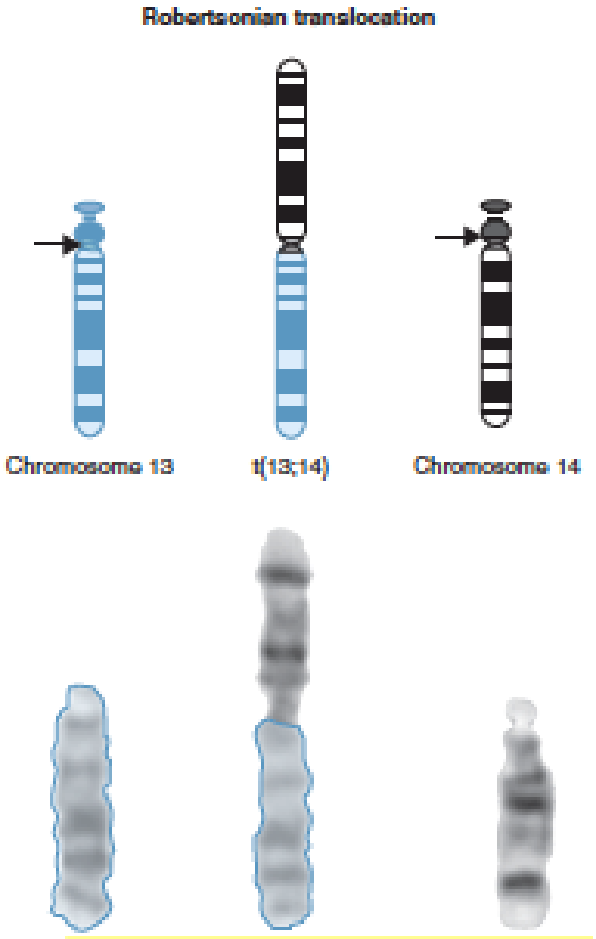
- Reciprocal translocation between chromosome 22 and the long arm of chromosome 9 (the Philadelphia chromosome).
- The occurrence of this translocation in hematopoietic cells can produce chronic myelogenous leukemia (CML)

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)

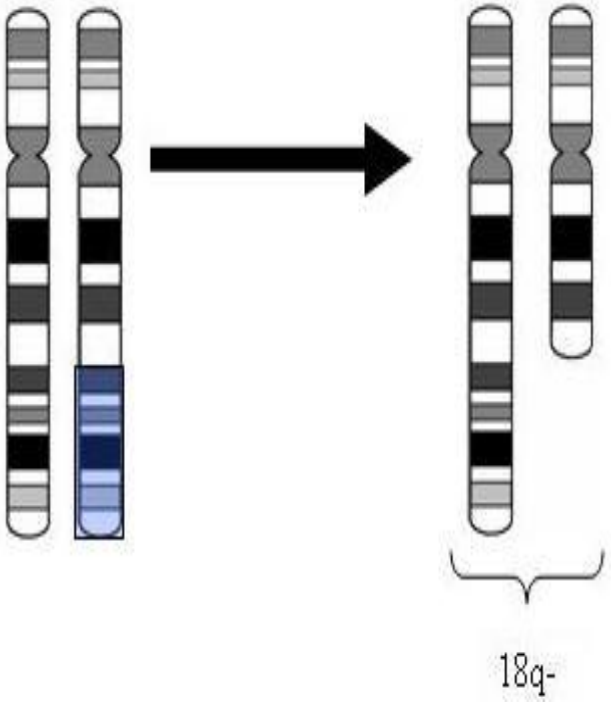
- Although carriers have only 45 chromosomes in each cell, they are phenotypically unaffected

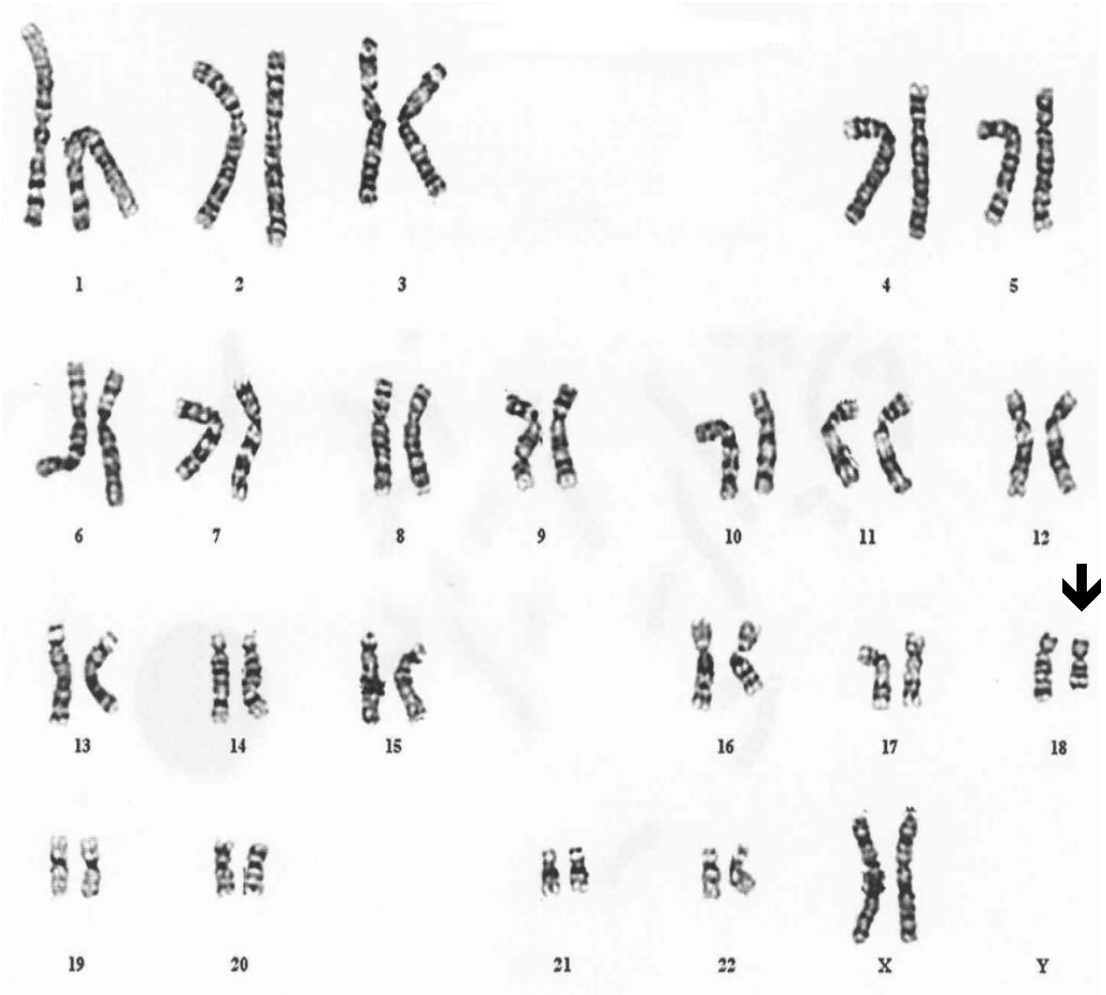


Deletion

- **- 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**

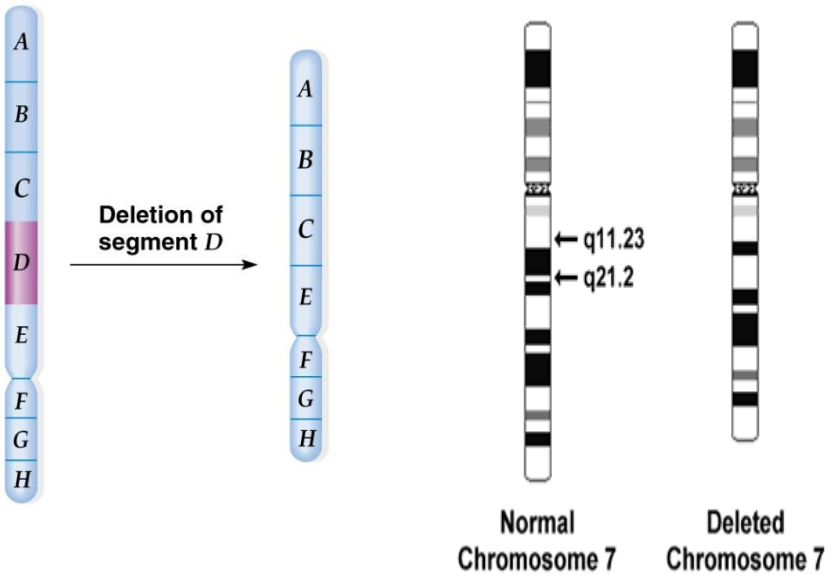
Terminal deletion



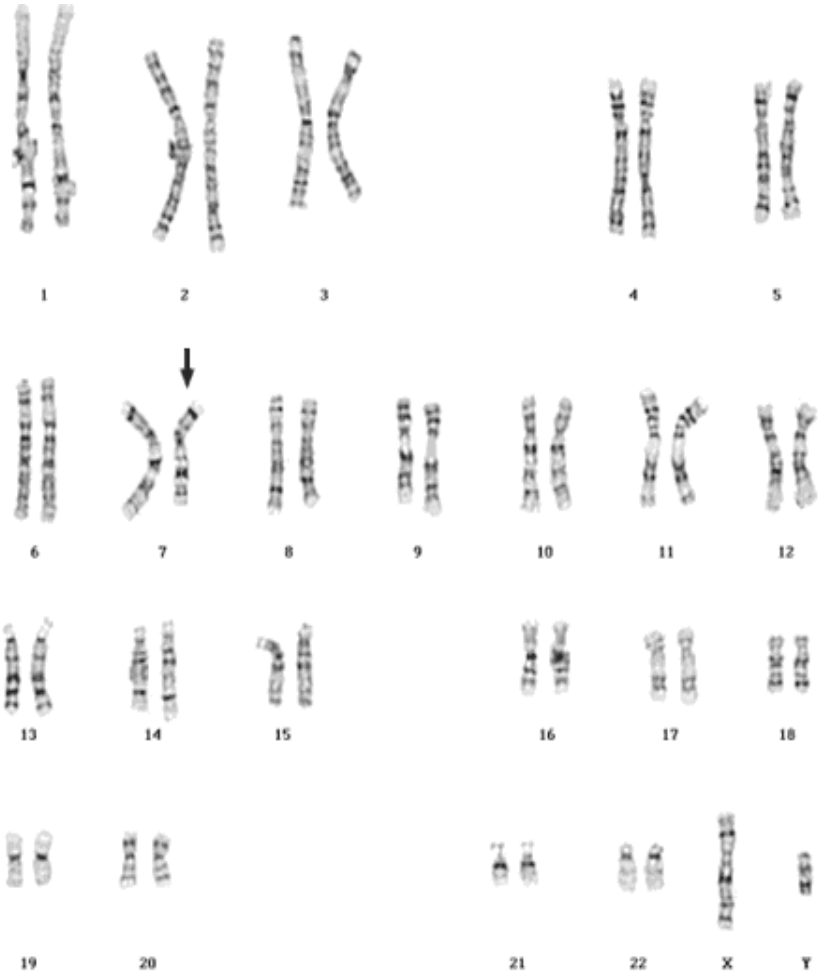


46,XX,del(18)(q21.3)

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.**

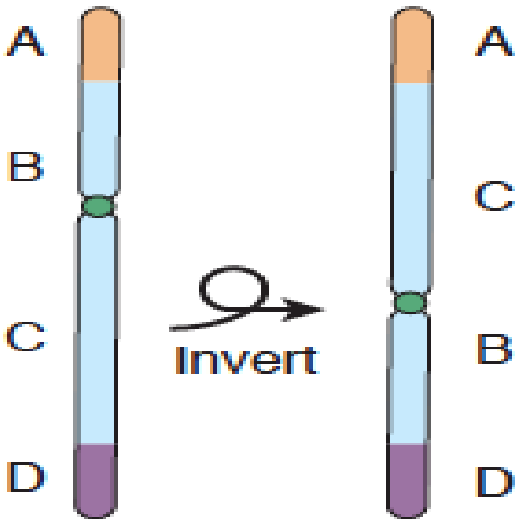
46,XY,del(7)(q11.23q21.2)

Inversion

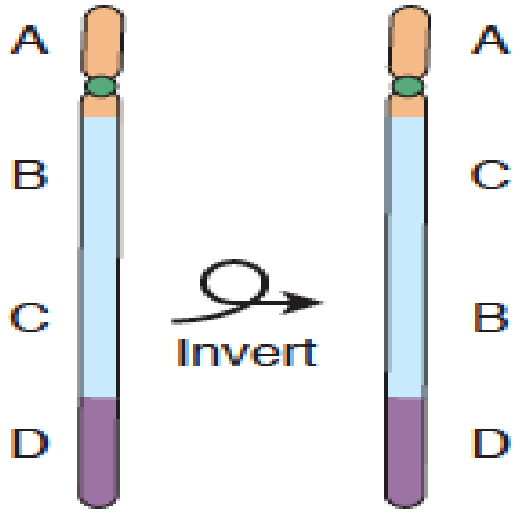
- Occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively.
- Written in nomenclature as inv.
- Only large inversions are normally detected.

They are balance rearrangements that rarely cause problems in carriers

Pericentric

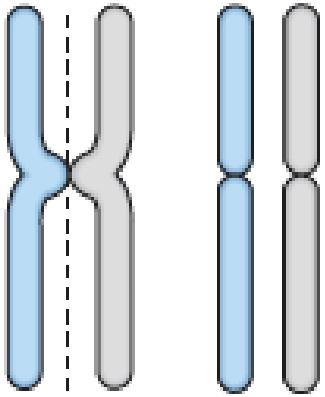


Paracentric

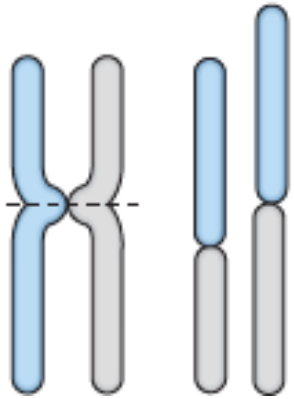


Isochromosome

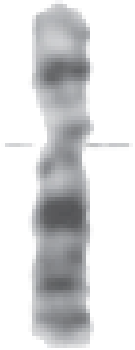
The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally



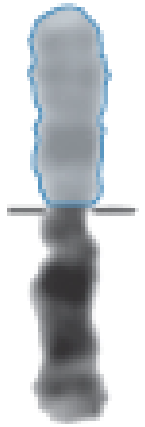
Normal



Isochromosome



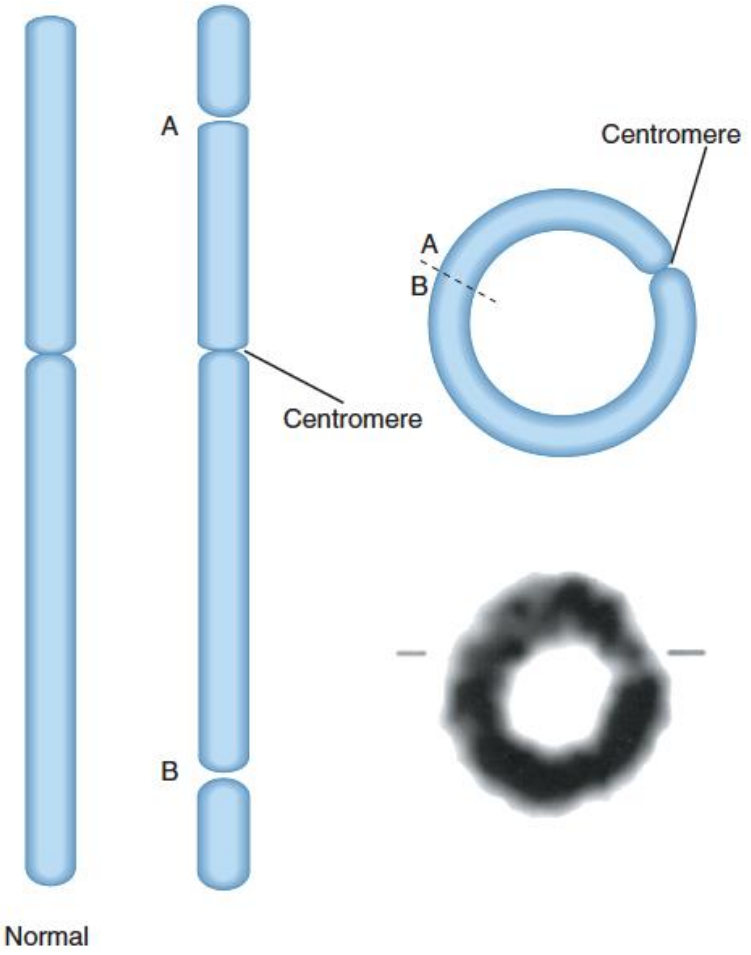
Normal



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.