MEDICAL GENETICS
LECTURE 2
CHROMOSOME ANOMALIES

Objectives

- Describe and explain the events in mitosis & meiosis.
- Define non-disjunction and describe its consequences for meiosis and mitosis.
- Classify and sub-classify chromosomal abnormalities
- Understand the common numerical autosomal disorders: trisomies 21, 13, 18.
- Understand the common numerical sex chromosome disorders: Turner`s & Klinefelter`s syndromes
- Recognize the main structural anomalies in chromosomes

Mitosis

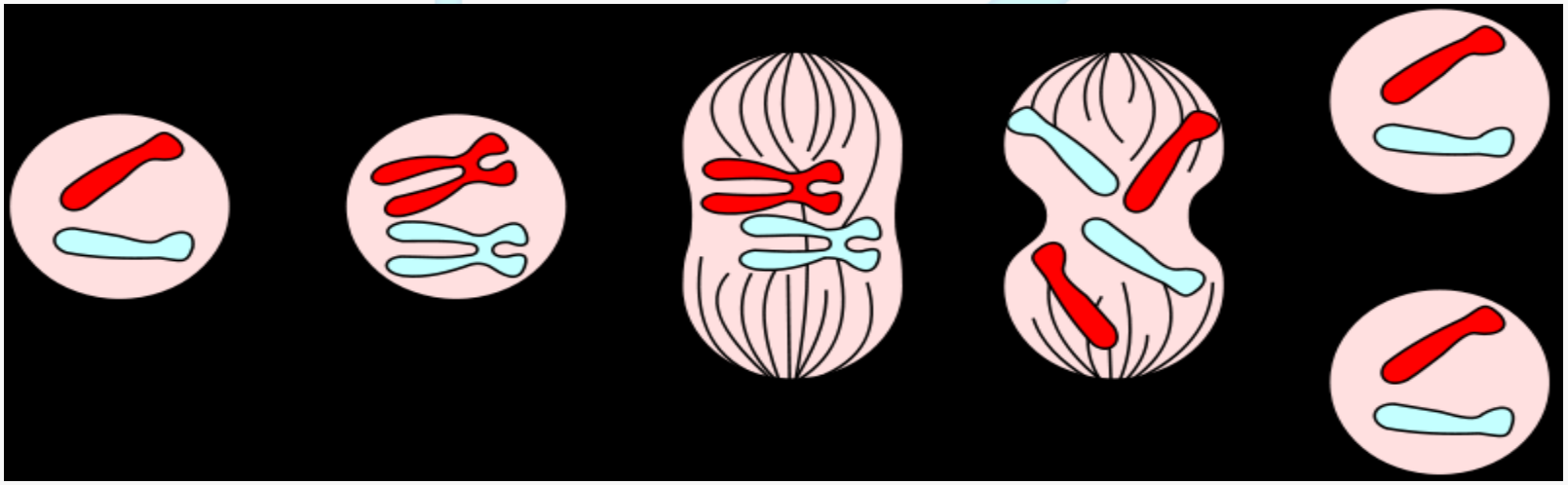
Mitosis :

- occur in somatic cells

-result: 2 daughter cells with diploid number of chromosomes

-Identical to parent cell

Followed immediately by cytokinesis which divides the nuclei, cytoplasm, organelles and cell membrane into two cells containing roughly equal shares of these cellular components.



Stages Of Mitosis

1– Interphase: *Interphase is often included in discussions of mitosis, but interphase is technically not part of mitosis.*

2- Prophase

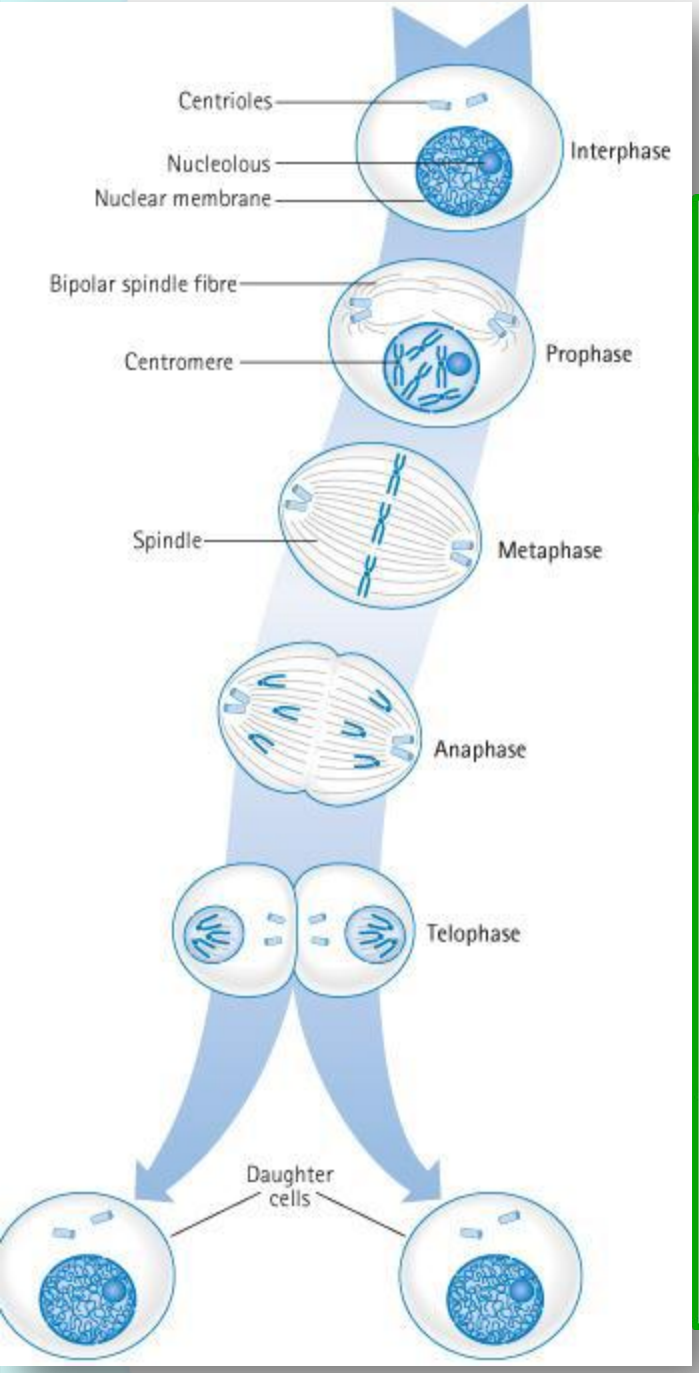
3- Metaphase

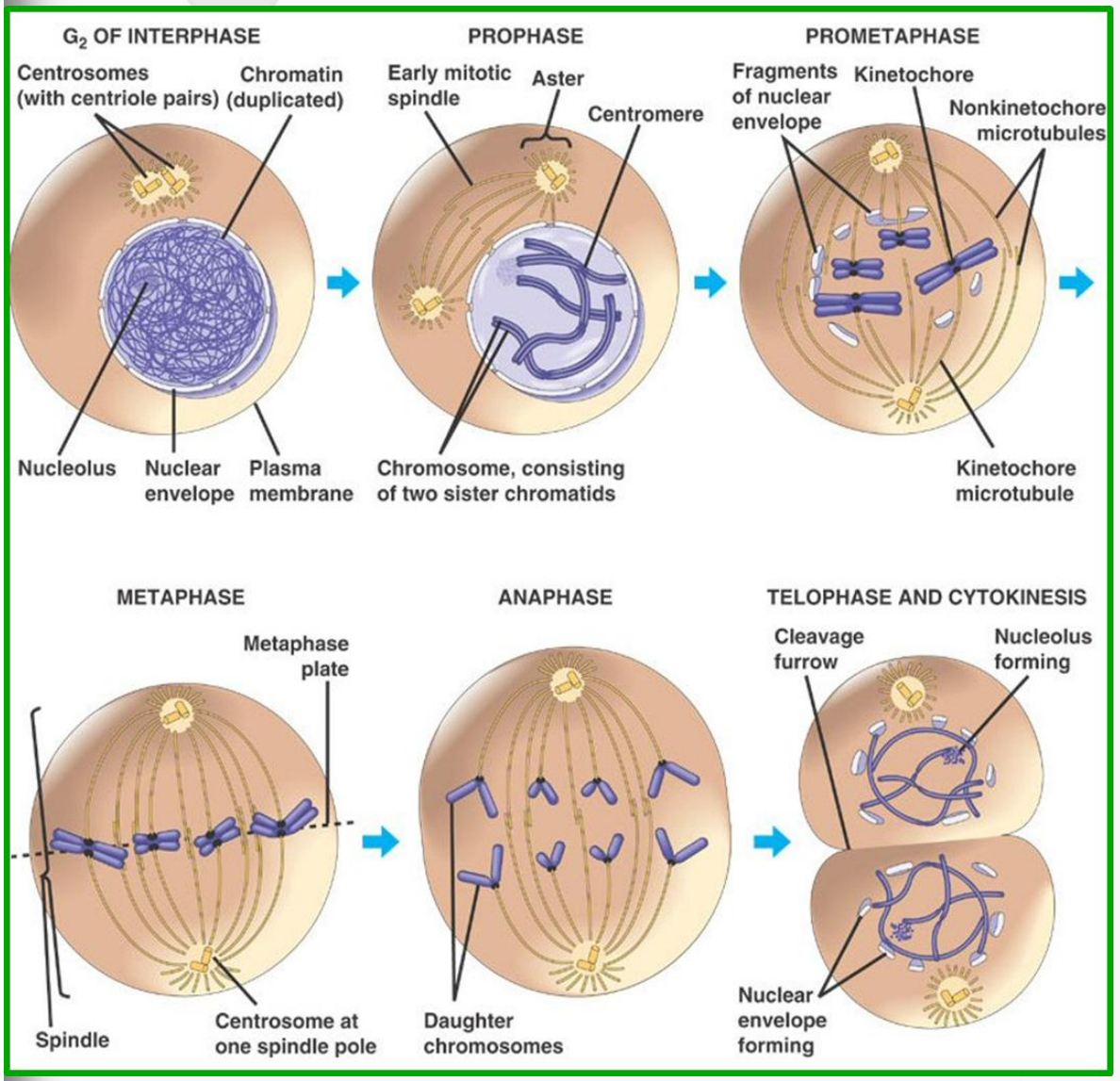
4- Anaphase

5-Telophase

6- cytokines

Mitosis

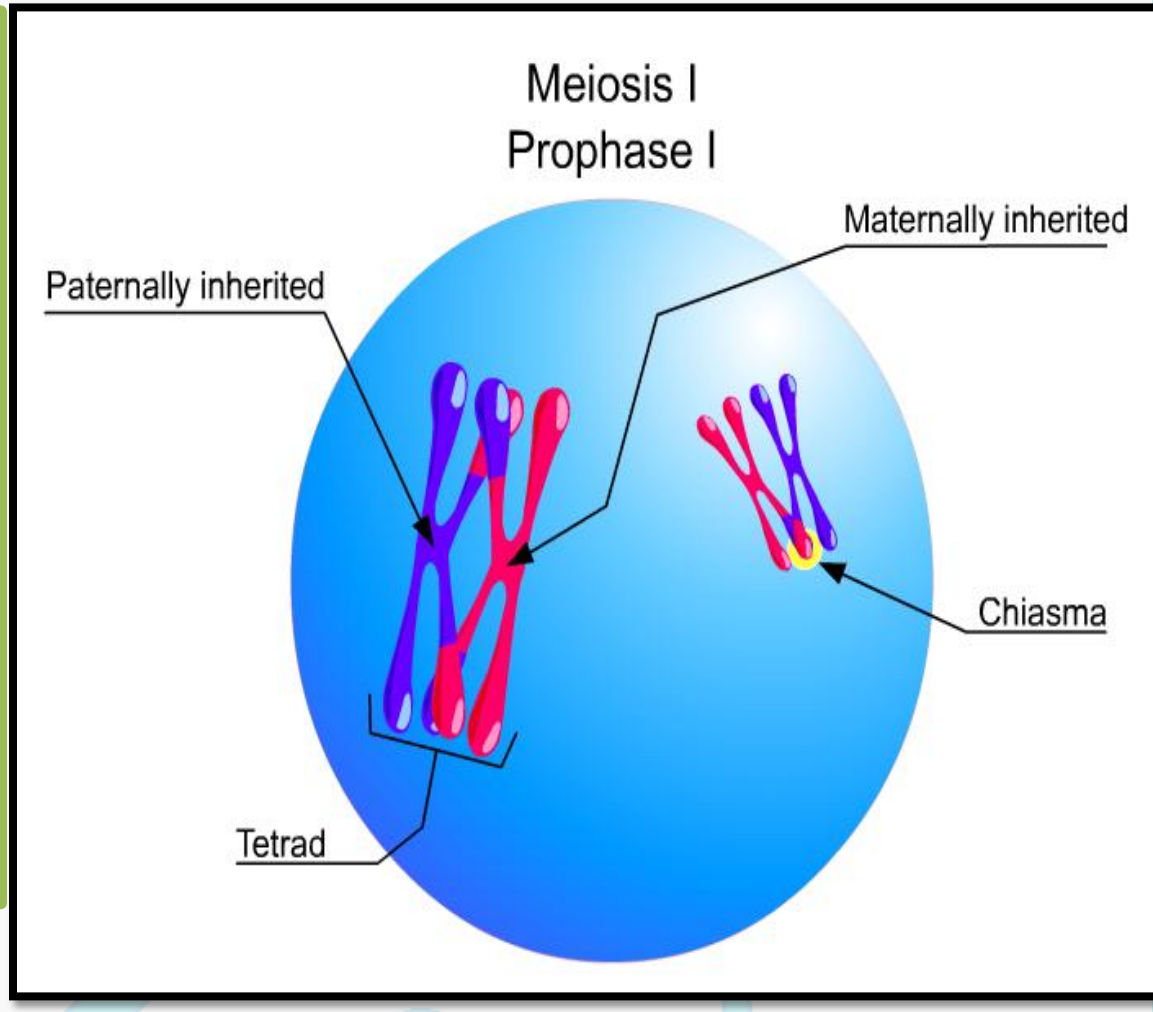

Centrioles
Nucleolous
Nuclear membrane
Interphase
Bipolar spindle fibre
Centromere
Prophase
Spindle
Metaphase
Anaphase
Telophase
Daughter cells


G2 OF INTERPHASE
Centrosomes (with centriole pairs)
Chromatin (duplicated)
Nucleolus
Nuclear envelope
Plasma membrane
PROPHASE
Early mitotic spindle
Aster
Centromere
Chromosome, consisting of two sister chromatids
PROMETAPHASE
Fragments of nuclear envelope
Kinetochore
Nonkinetochore microtubules
Kinetochore microtubule
METAPHASE
Metaphase plate
Spindle
Centrosome at one spindle pole
ANAPHASE
Daughter chromosomes
TELOPHASE AND CYTOKINESIS
Cleavage furrow
Nucleolus forming
Nuclear envelope forming

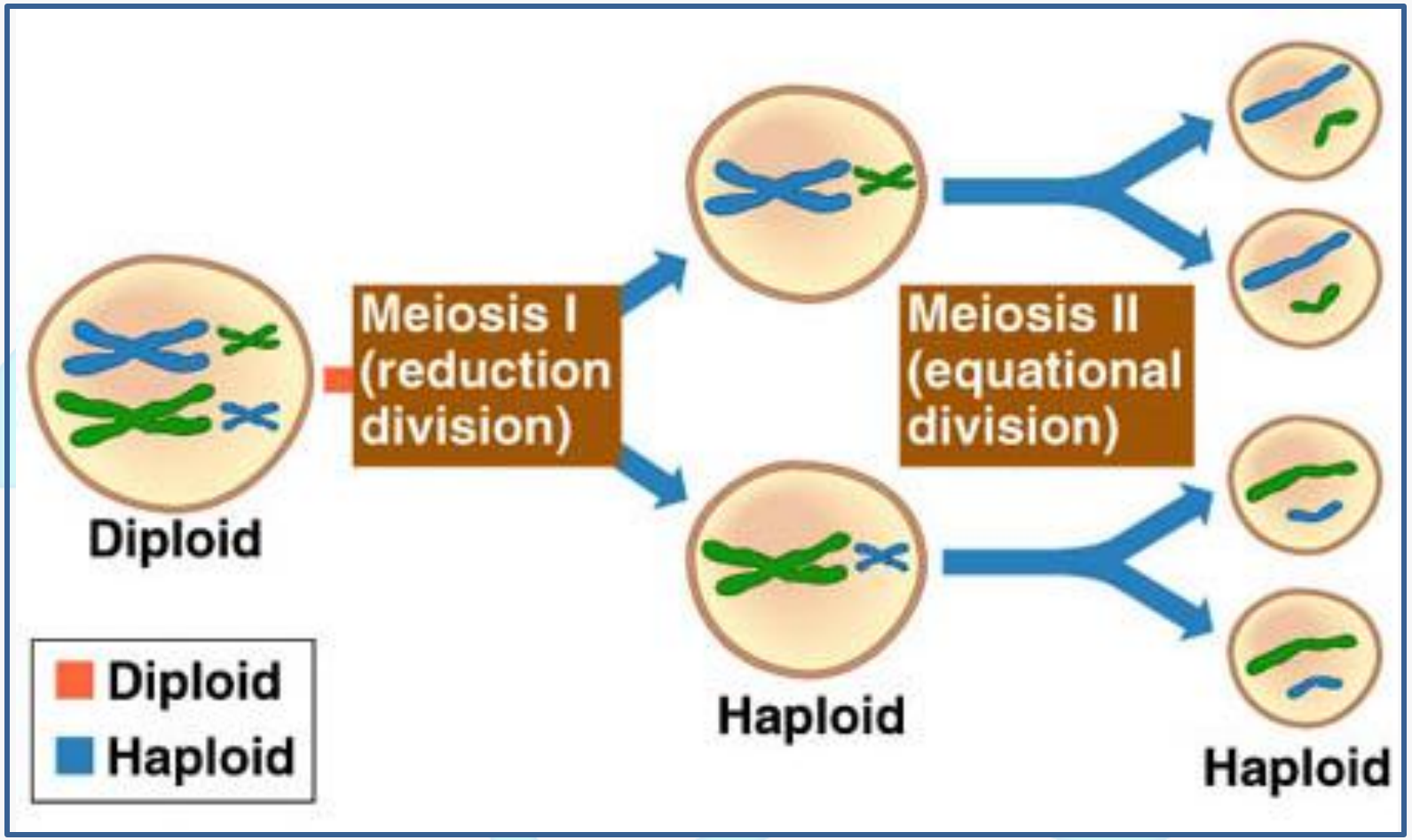
MEIOSIS

- Occur in sex cells (germ cells) producing gametes.
- Includes Crossing over , segregation
- Give 4 daughter cells with haploid number of chromosomes
- Daughter cells are genetically unique and different from parent

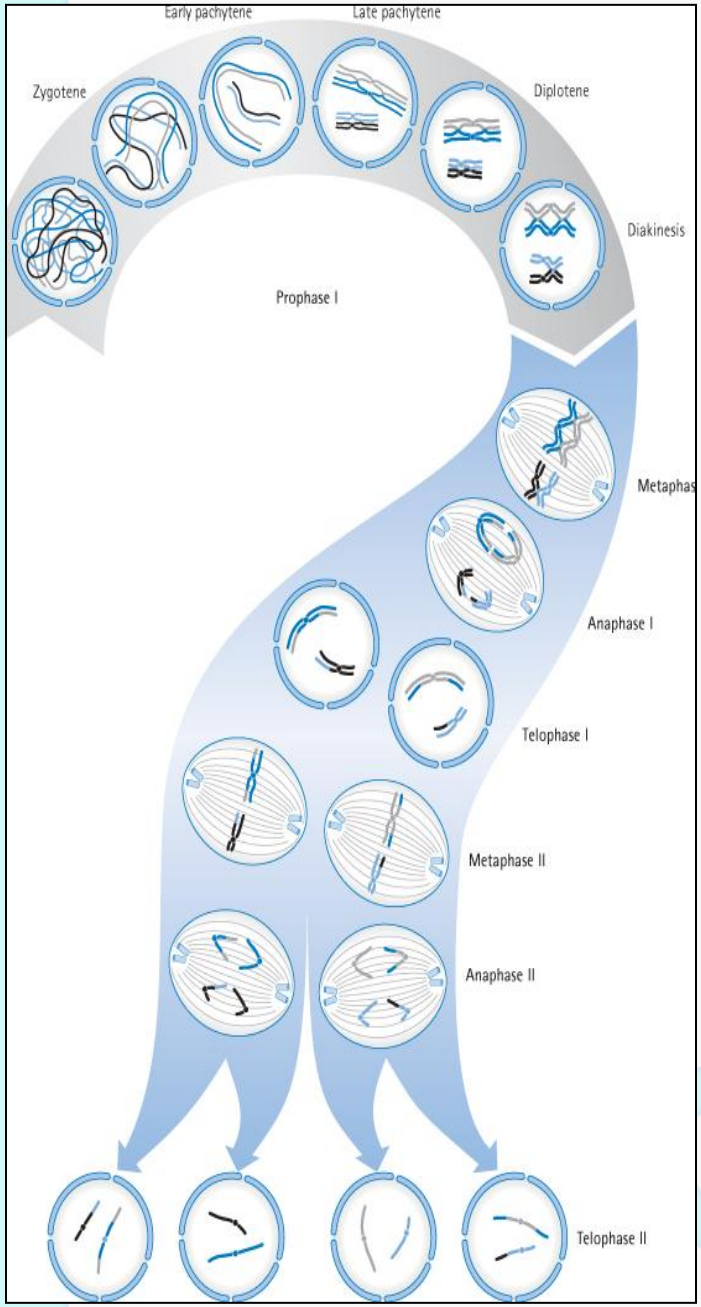
The duplicated homologous chromosomes pair, and **crossing-over** (the physical exchange of chromosome parts) occurs. Crossing-over is the process that can give rise to genetic recombination. At this point, each homologous chromosome pair is visible as a bivalent (tetrad), a tight grouping of two chromosomes, each consisting of two sister chromatids. The sites of crossing-over are seen as crisscrossed nonsister chromatids and are called chiasmata (singular: chiasma)

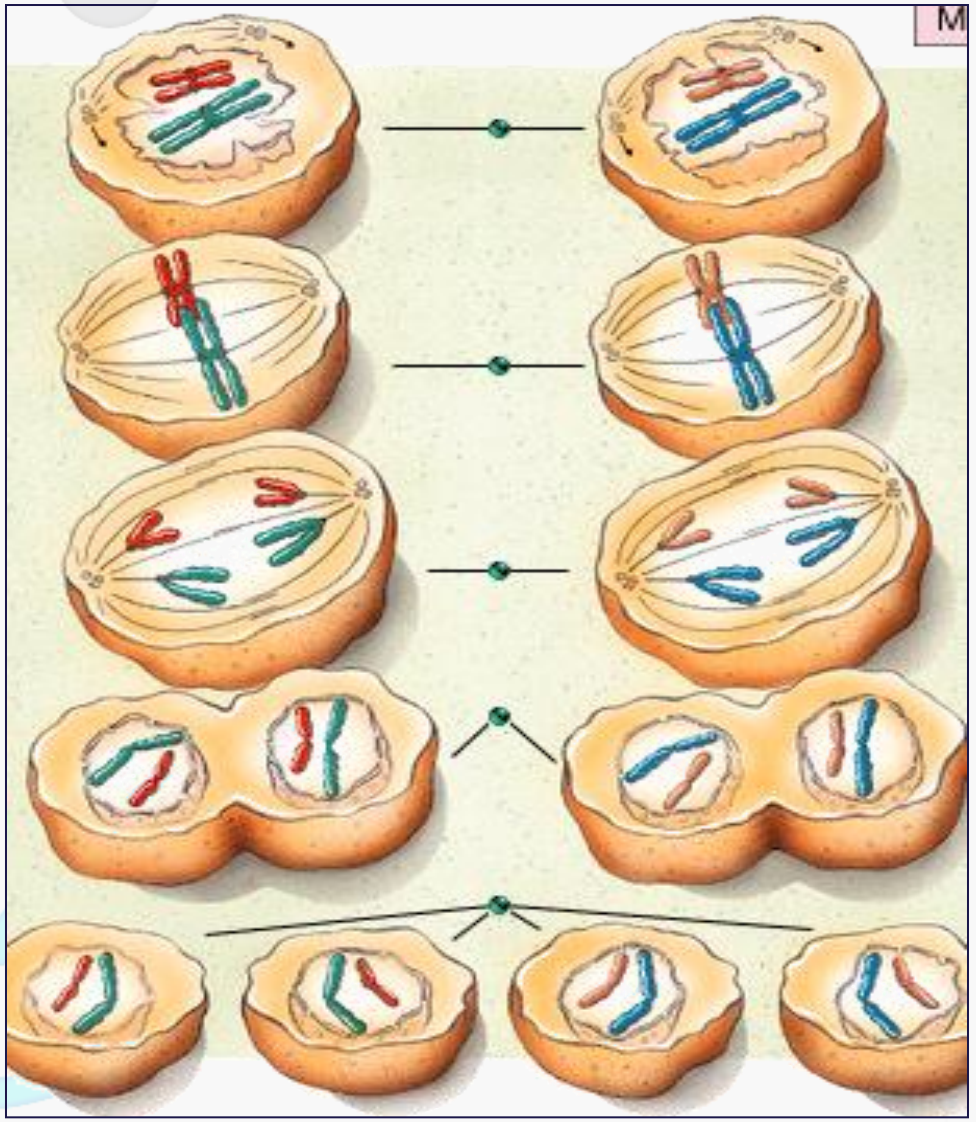


Phases of meiosis I & II



Meiosis

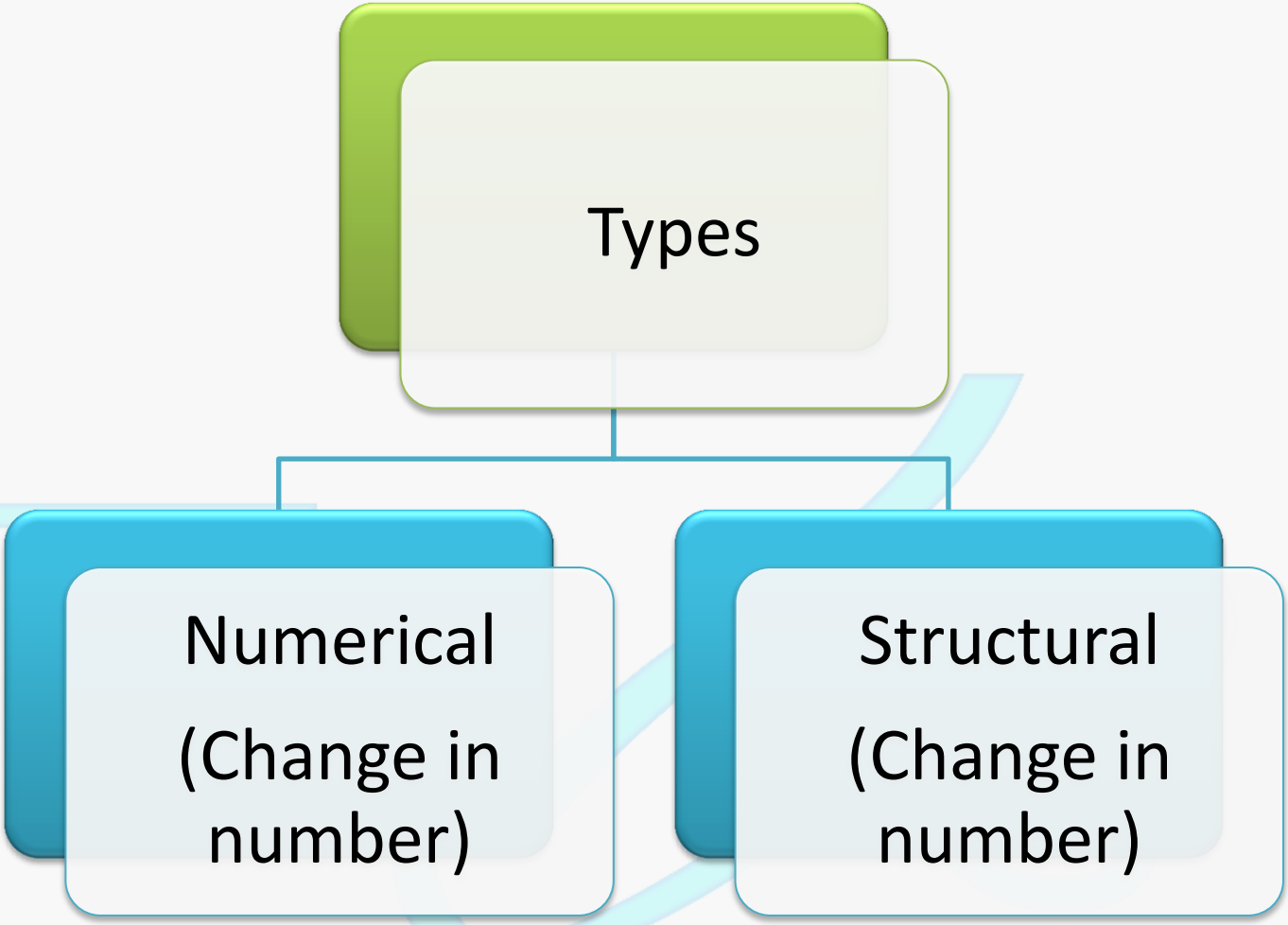

Early pachytene
Late pachytene
Zygotene
Diplotene
Diakinesis
Prophase I
Metaphas
Anaphase I
Telophase I
Metaphase II
Anaphase II
Telophase II



Comparison between Mitosis and Meiosis

Property	Mitosis	Meiosis
DNA Replication	Occurs during interphase before mitosis begins.	Occurs during interphase before meiosis begins.
Number of divisions	One	Two
Synapsis of homologous chromosomes	Does not occur.	Occurs along with crossing over between non-sister chromatids in prophase I.
Number of daughter cells and genetic composition	Two diploid (2n) daughter cells that are genetically identical to the parent cell.	4 haploid (n) daughter cells, each containing half as many chromosomes as the parent cell. Daughter cells are genetically different from the parent cell and each other.
Role in the animal body	Produces cells for growth and repair.	Produces gametes and assures genetic diversity in sexual reproduction.

CHROMOSOME ANOMALIES (شذوذ)



- **Nondisjunction** ("not coming apart") is the failure of chromosome pairs to separate properly during meiosis stage 1 or stage 2.

- As a result, one daughter cell has two chromosomes or two chromatids, and the other has none.

- **The result** of this error is a cell with an imbalance of chromosomes (Aneuploidy). Simply, an extra or missing chromosome
- Remember: It's only for one pair.

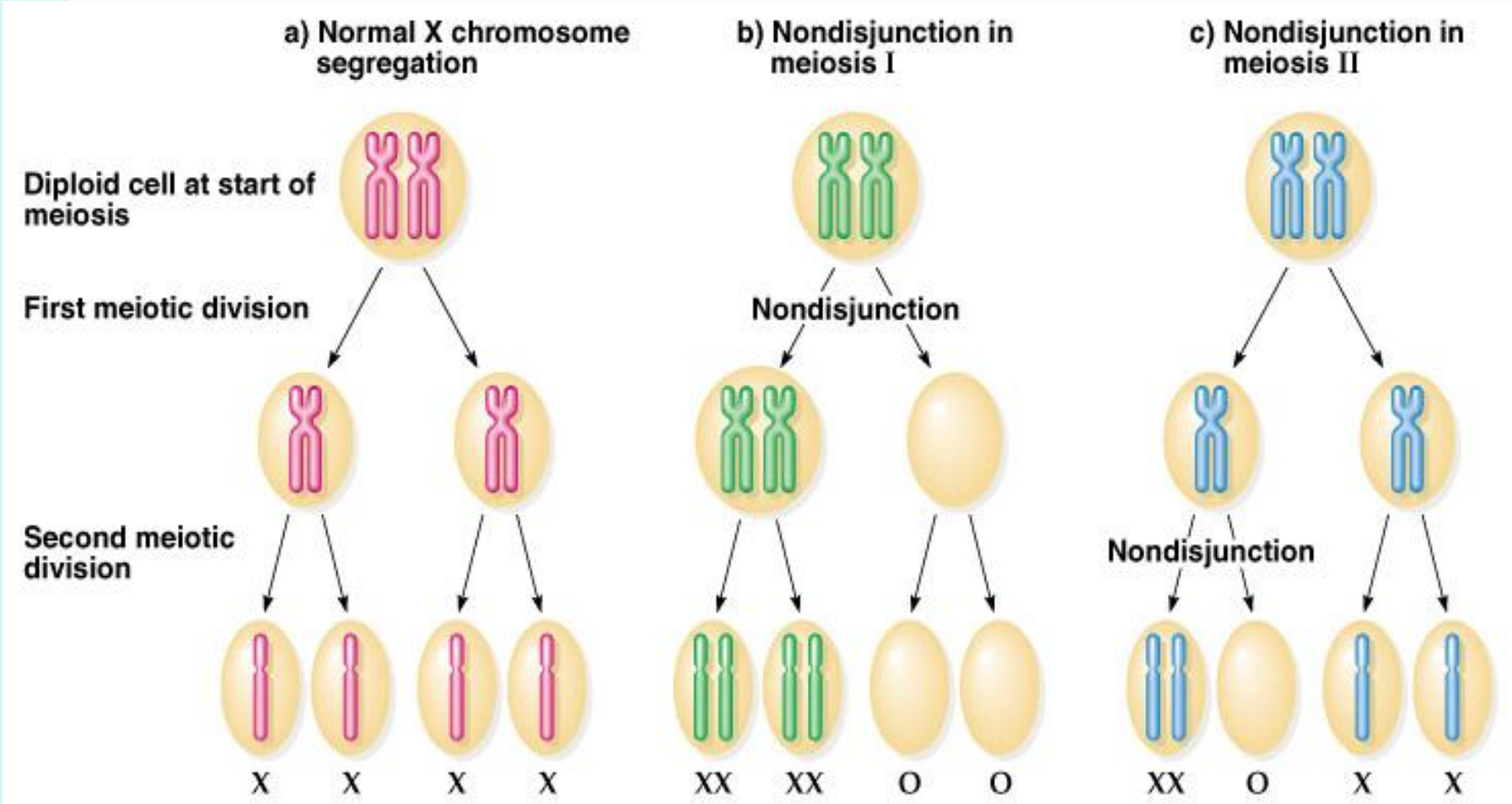
Numerical Disorders

In other words:

- Aneuploidy is: an abnormal number of chromosomes.
- The abnormality occurs when an individual is missing either a chromosome from a pair (monosomy) or has more than two chromosomes of a pair (Trisomy, Tetrasomy, etc.)

AS A RESULT OF NON-DISJUNCTION

One daughter cell has two chromosomes, or two chromatids and the other has none. In addition, some Nondisjunction occur in meiosis 1 (klinefelter), and some occur in meiosis 2 (turner). look at the figure below.



Definitions:

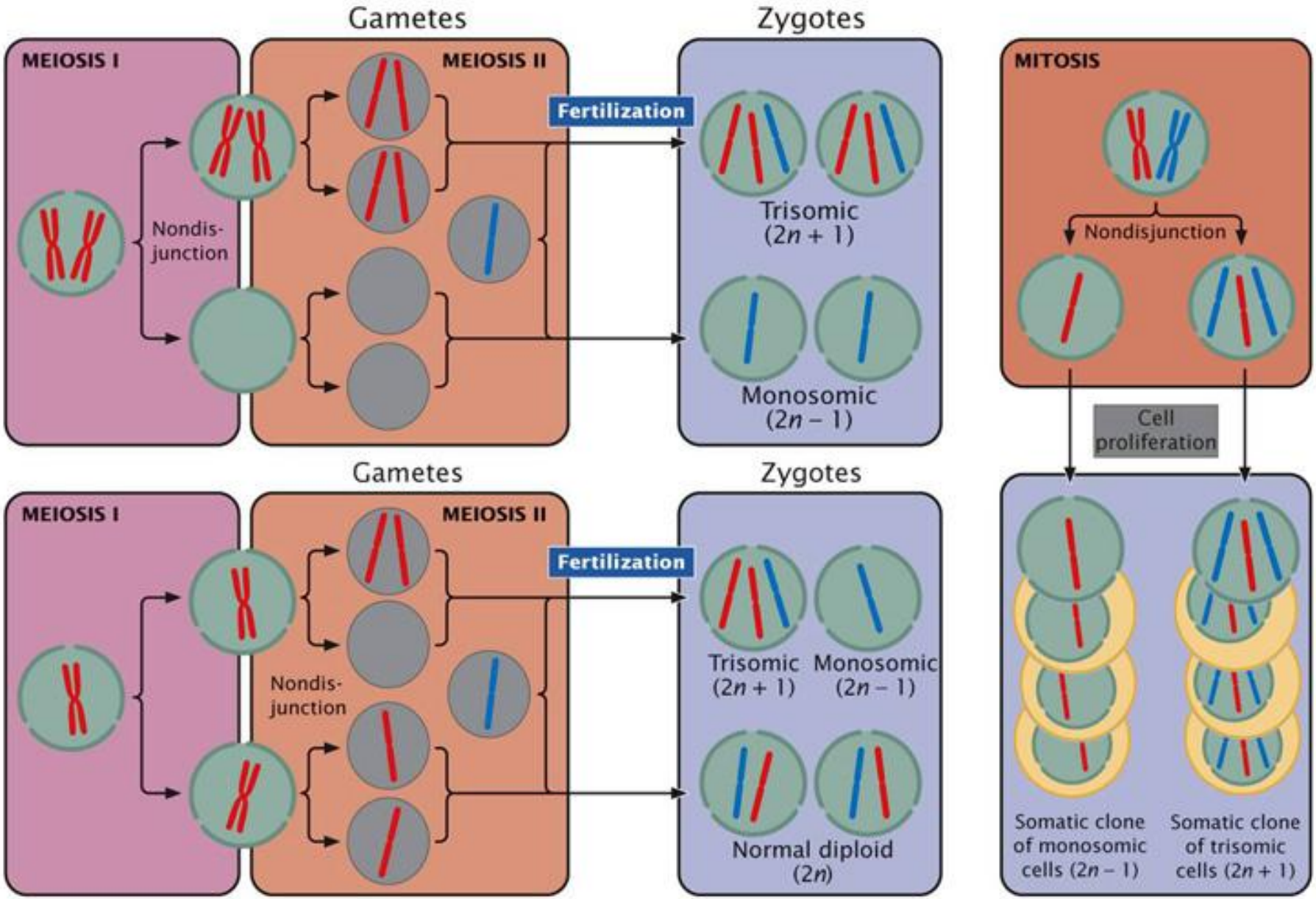
- **Monosomy**: Loss of a single chromosome (2n-1), in which the daughter cell(s) with the defect will have one chromosome missing from one of its pairs.

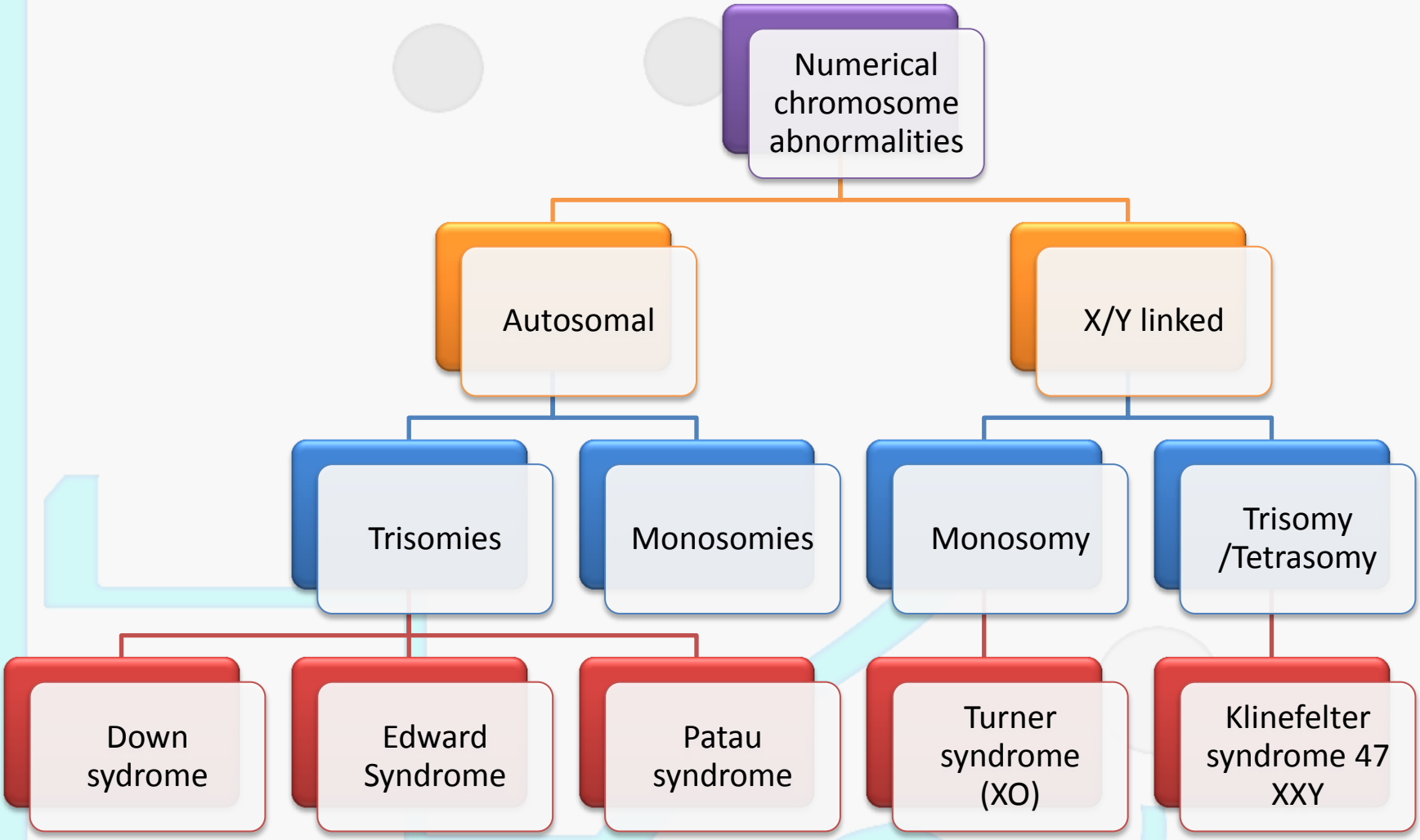
- **Trisomy**: Gaining a single chromosome, in which the daughter cell(s) with the defect will have one chromosome in addition to its pairs.

Trisomy : 3 copies instead of the normal 2.
Monosomy : The presence of one chromosome instead of the normal 2.
Tetrasomy: 4 copies instead of the normal 2.

REMEMBER!!

- If non-disjunction occurred in meiosis 1 → all gametes are abnormal (4 unbalanced gametes)
- If non disjunction occurred in meiosis 2 → half the gametes are abnormal and the other half are normal (2 normal gametes & 2 unbalanced gametes) gamete with an extra autosome + nullosomic gamete “missing one chromosome’’
- Nondisjunction on chromosome 21 (trisome)→ down syndrome (most common)


Gametes
Zygotes
MEIOSIS I
MEIOSIS II
Nondis-
junction
Fertilization
Trisomic
(2n + 1)
Monosomic
(2n – 1)
MITOSIS
Nondisjunction
Cell
proliferation
Gametes
Zygotes
MEIOSIS I
MEIOSIS II
Nondis-
junction
Fertilization
Trisomic
(2n + 1)
Monosomic
(2n – 1)
Normal diploid
(2n)
Somatic clone
of monosomic
cells (2n – 1)
Somatic clone
of trisomic
cells (2n + 1)


Numerical chromosome abnormalities
Autosomal
X/Y linked
Trisomies
Monosomies
Monosomy
Trisomy /Tetrasomy
Down sydrome
Edward Syndrome
Patau syndrome
Turner syndrome (XO)
Klinefelter syndrome 47 XXY

Autosomal Abnormalities " trisomies"

Syndrome Name	*Cause - karyotype*	*More info. about the syndrome.*	*Symptoms*
Down syndrome	Trisomy 21, which rises sharply with increasing maternal age.	Most cases develop from non-disjunction in the 1st meiotic division. The father contributing the extra chromosomes in 15% of the cases.	Include: Characteristic facial dysmorphologies. An IQ less than 50. 
Patau syndrome	Trisomy 13, most cases involve maternal non-disjunction.	50% of these babies die within the first month. Very few survive beyond the 1st year.	Multiple dysmorphic features. 
Edward's syndrome	Trisomy 18.	Most babies die in the first year and many within the first month.	

Numerical anomalies in sex chromosomes

Syndrome	Cause - Karyotype	More info.	Symptoms – characteristics
Turner's syndrome	Caused by a monosomy X (absence of entire sex chromosome, the Barr Body) 45 XO	The only viable monosomy in humans **These females live a normal , healthy and productive life**	-Webbed neck -Female individuals -They don't mature sexually -Sterile -Low hairline.. Return to the Dr's slides for more
Klinfelter syndrome	where the patient has 48, XXXY or even 49, XXXXY, or 47 XXY karyotype.	Male sex organs; unusually small testes which fail to produce normal levels of testosterone→ breast enlargement (gynaecomastia) and other feminine body characteristics. Individuals are generally severely retarded. Patients are taller and thinner than average. Return to the Dr's slides for more	

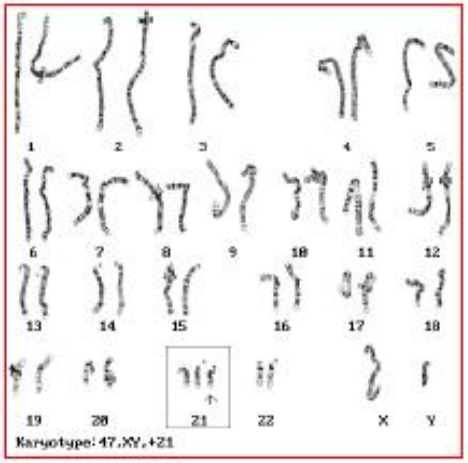
We should know that: Sex chromosome unbalance has a much less deleterious (أقل ضرر)effect on the phenotype than does autosomal aneuploidy.

– 47, XYY

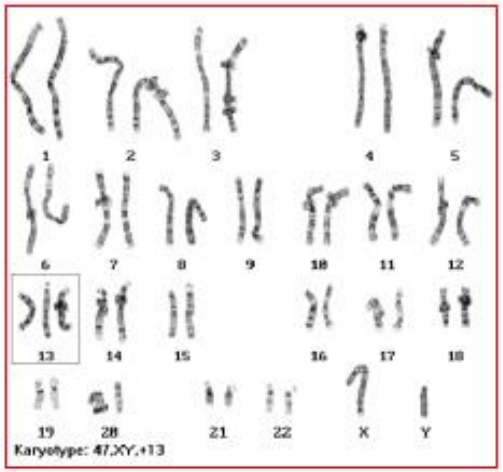
May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs.

– XXX females

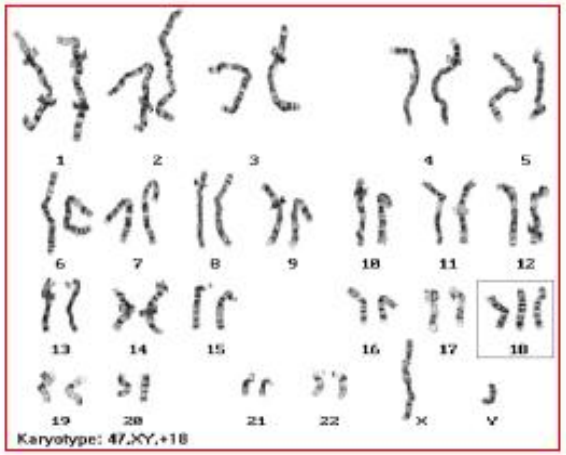
It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They do have a reduction in IQ comparable to that of Kleinfelter's males



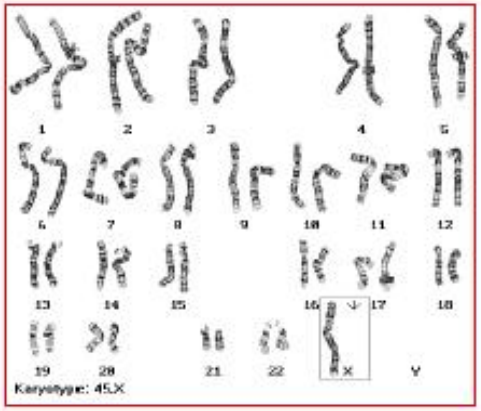
Down syndrome



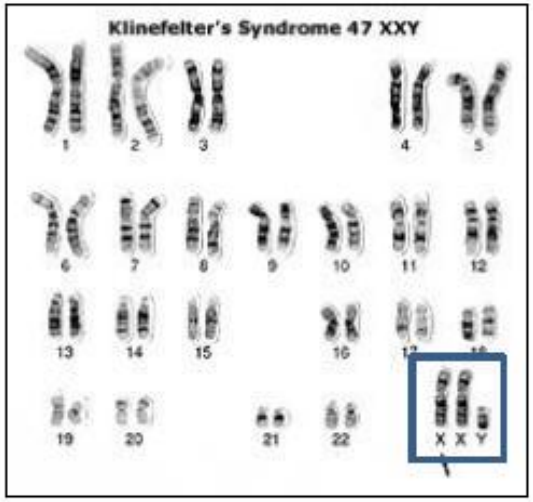
Patau Syndrome



Edward's syndrome



Turner's syndrome



Klinefelter Syndrome

Polyploidy

the condition in which a normally diploid cell or organism acquires one or more additional sets of chromosomes. It's for all pairs not only one.

Triploidies are the most frequent,

- 3N = 69 chromosomes: e.g. 69, XXX, or 69, XXY, or 69, XYY.
- Are found in 20 % of spontaneous miscarriages (الاجهاض التلقائي).

Tetraploidy

4N = 92 chromosomes.

Remember!!

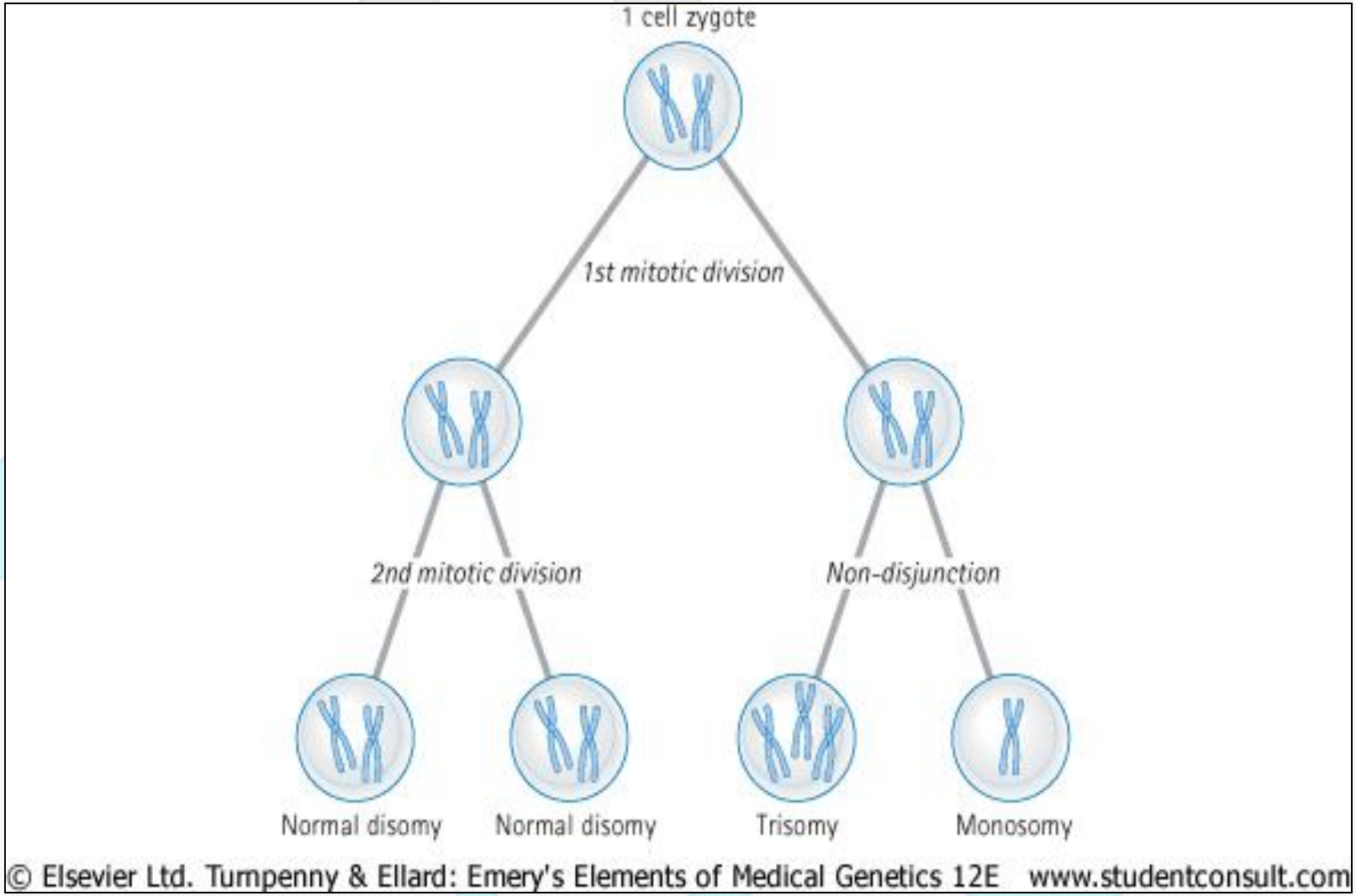
The distinction between aneuploidy and polyploidy is that aneuploidy refers to a numerical change in part of the chromosome set, whereas polyploidy refers to a numerical change in the whole set of chromosomes.

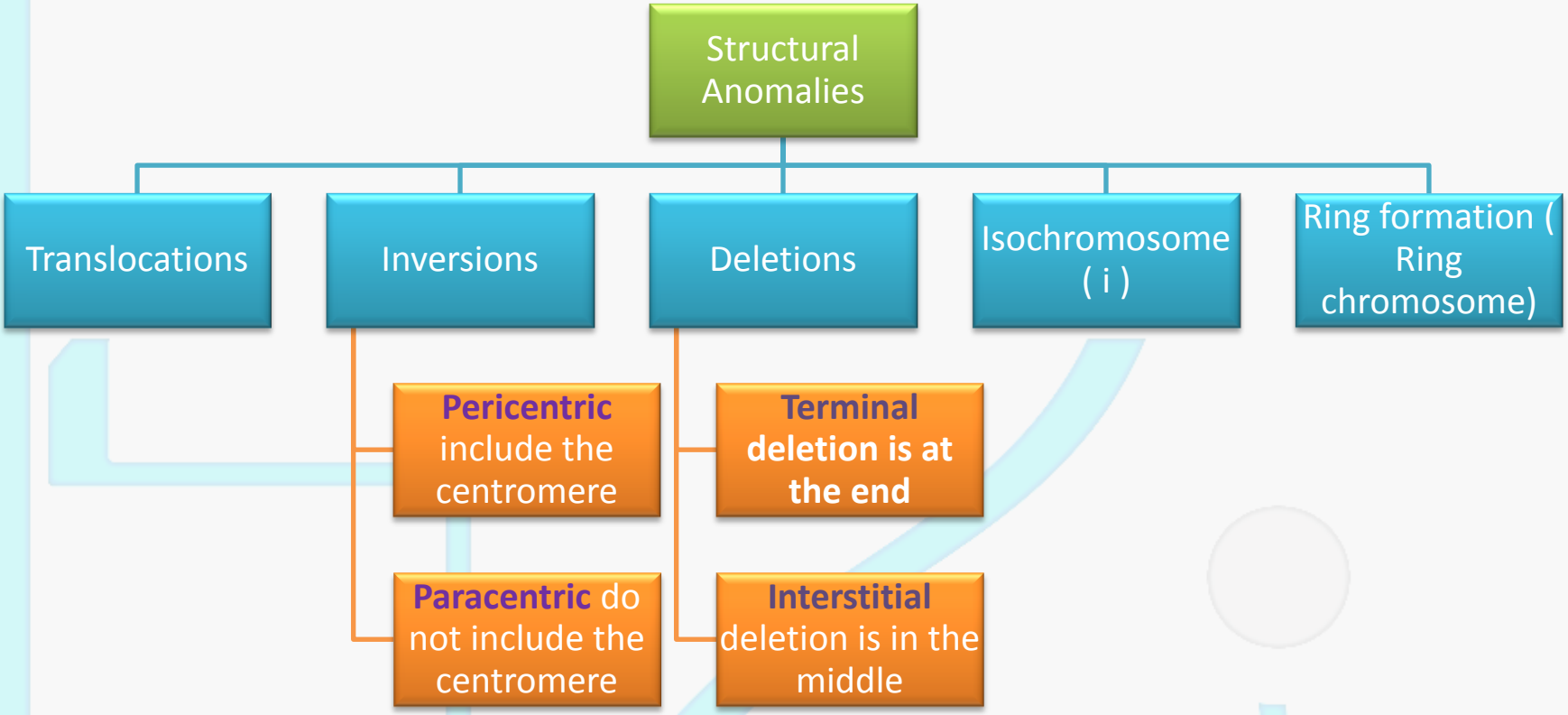
MOSAICISM

(the condition in which an organism has two or more cell populations that differ in genetic makeup)

- A mosaic individual is made of 2 (or more) cell populations, coming from only 1 zygote
- Is denoted (يرمز لها) 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

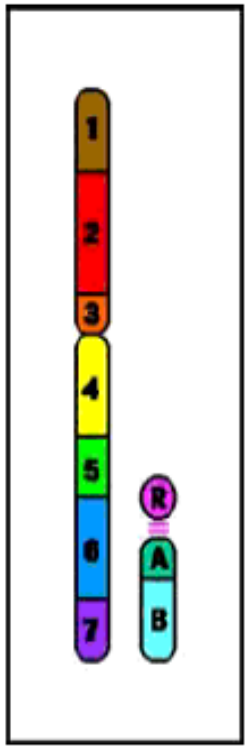
- A mosaic must not be confused with a chimeras.
- Chimerism is the presence in an individual of two or more genetically distinct cell lines derive from more than one zygote (e.g. 2 sperms fertilize 2 ova → 2 zygotes that fuse to form 1 embryo




Structural Anomalies
Translocations
Inversions
Deletions
Isochromosome (i)
Ring formation (Ring chromosome)
Pericentric include the centromere
Paracentric do not include the centromere
Terminal deletion is at the end
Interstitial deletion is in the middle

1-receprocal translocation

(تبادل)



A mutual exchange between terminal segments from the arms of 2 chromosomes.

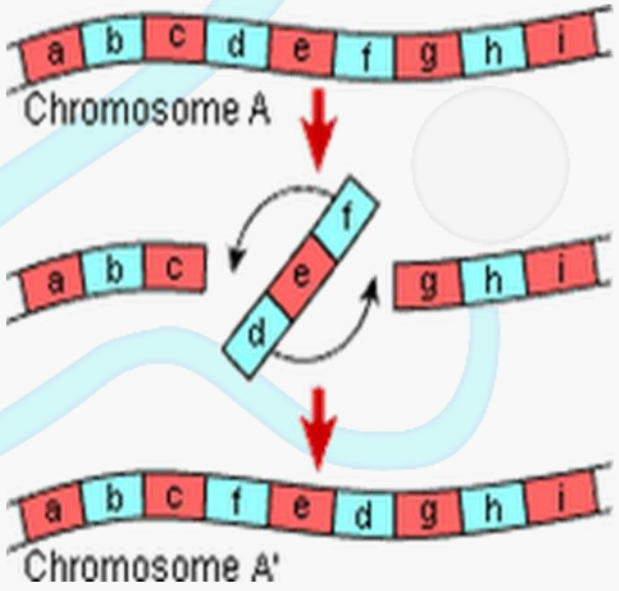
Provided that there is no loss or alteration at the points of exchange, the new rearrangement is genetically balanced, and called a Balanced rearrangement.

- Recorded as t or rcp (e.g. t(9;22)(q34;q11)).
- The carrier has a normal phenotype.

-They can occur de novo, or be transmitted through several generations.

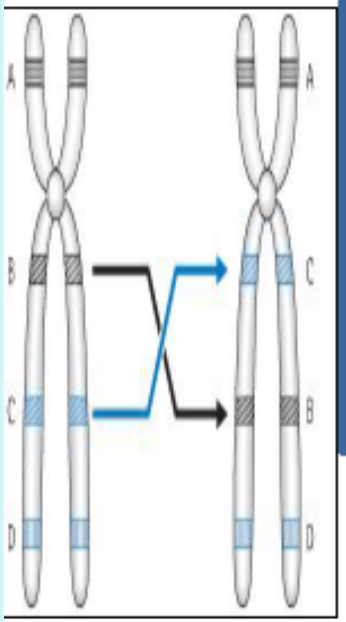
2-inversion

- Inversion occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively inverts it.
- Recorded as inv.
- Only large inversions are normally detected.
- They are balance rearrangements that rarely cause problems in carriers



Paracentric

- Are rare (or more likely rarely detected since the majority probably involve very small segments).
- when the segment involved lies wholly within one chromosome arm
- The most frequent paracentric inversions chromosomes 3, 7, and 14.



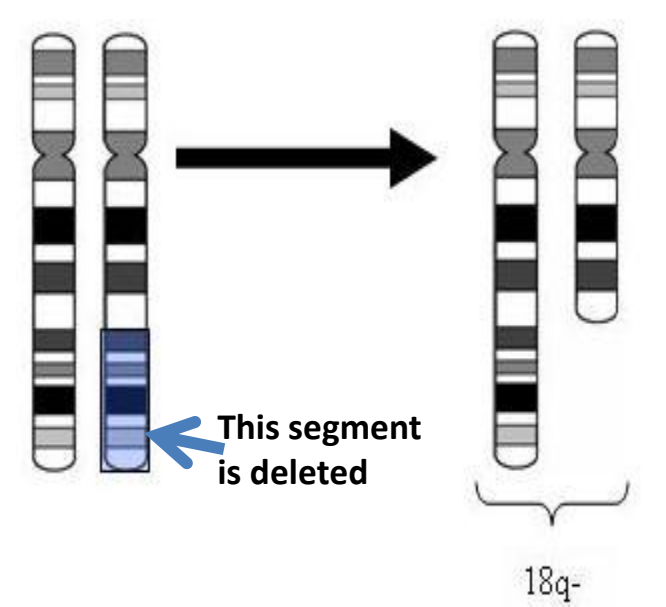
Pericentric

- when the two break-points involved are sited on opposite sides of the centromere
- A pericentric inversion can provoke miscarriages, sterility (more often in the male)

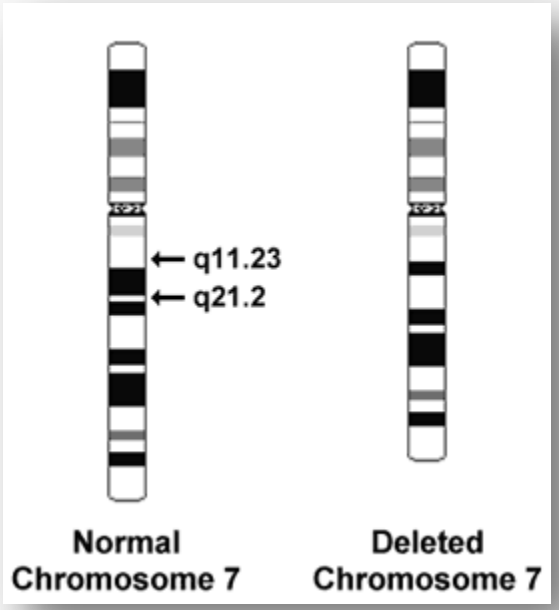
3- Deletion

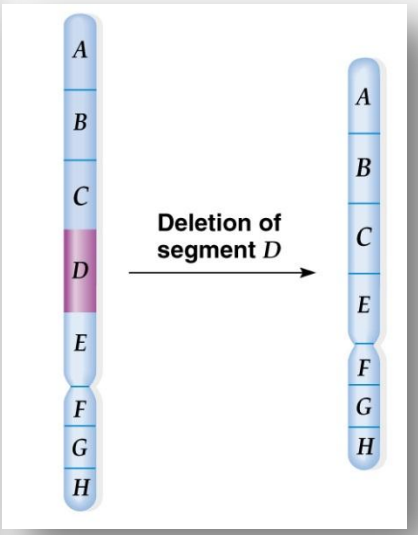
- Loss of a segment from a chromosome, either terminal or interstitial
- Invariably, but not always, results in the loss of important genetic material
- Deletion is therefore an unbalanced rearrangement.
- Recorded as del
- It has 2 points cut.

Terminal Deletion



Intersitial Deletion
(7 karyotype)





The key to the karyotype description is as follows:

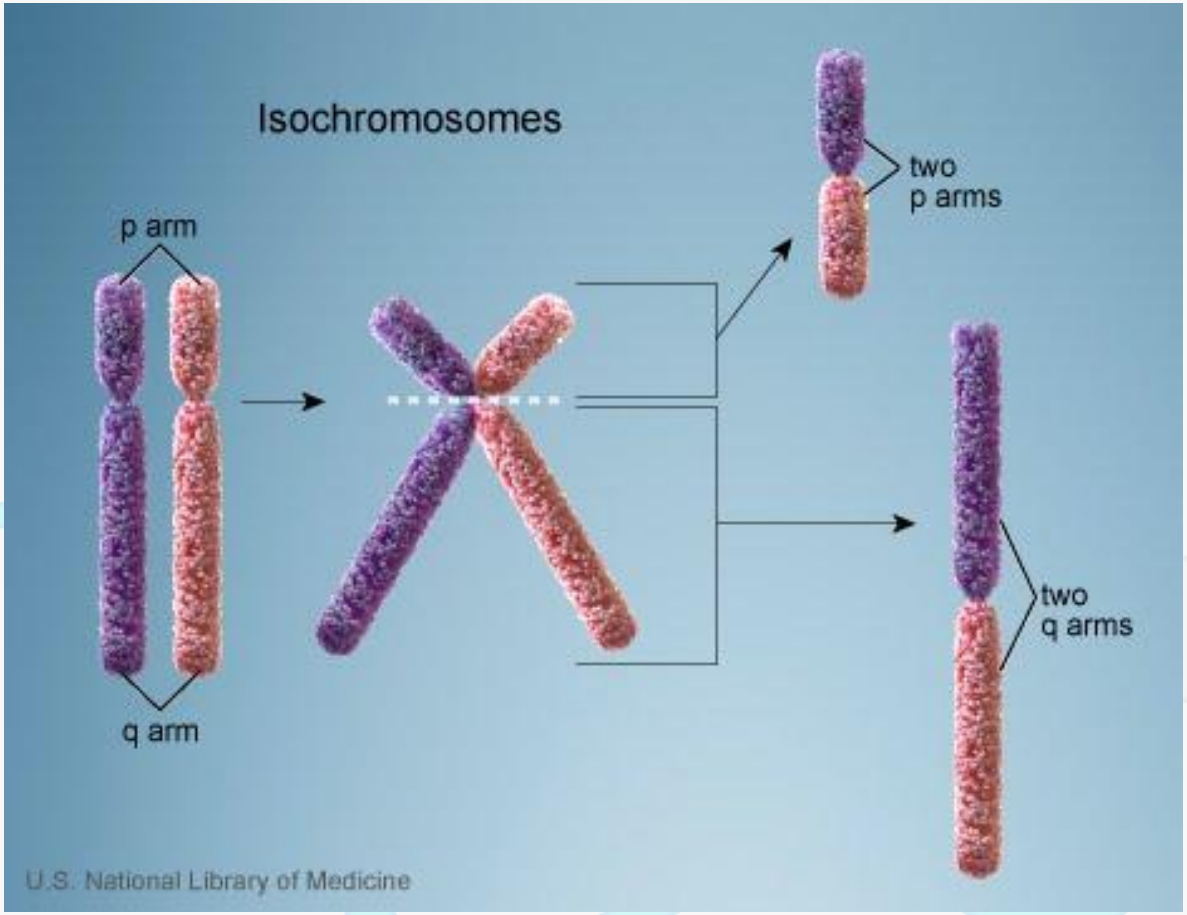
- **46: the total number of chromosomes.**
- **XY: the sex chromosomes (male).**
- **del(7): deletion in chromosome 7.**
- **(q11.23q21.2): breakpoints of the deleted segment.**

4-Isochromosome

- An isochromosome shows loss of one arm with duplication of the other
- The most commonly encountered isochromosome consists of two long arms of the X chromosome. 46,X,i(Xq)

- The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally.
- It has the same number of chromosomes (no loss).

Isochromosome

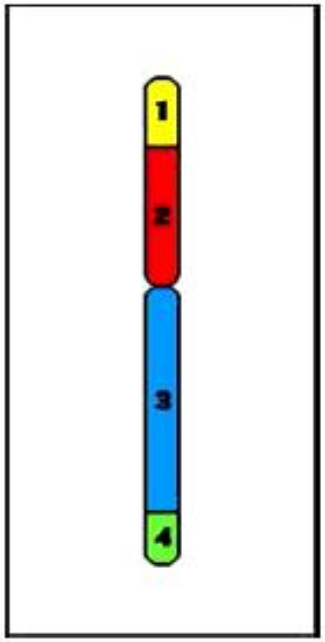


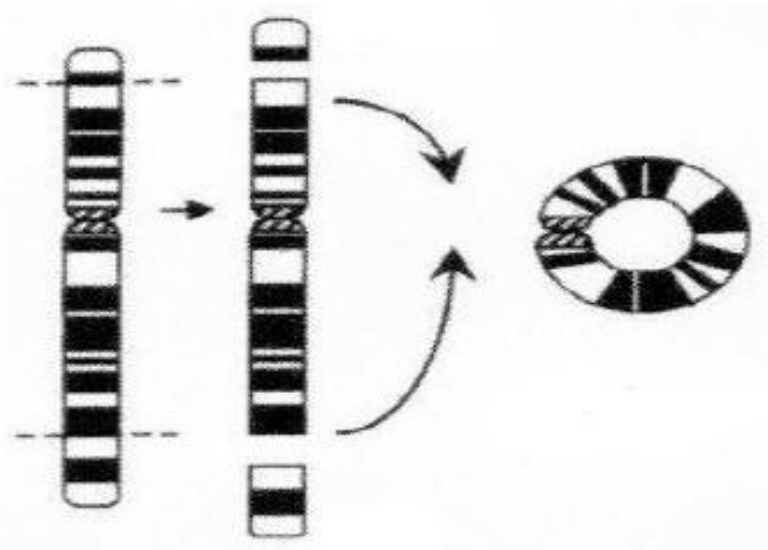
Ring formation (Ring chromosome)

A break on each arm of a chromosome → two sticky ends on the central portion → Reunion of the ends as a ring → loss of the 2 distal chromosomal fragments

Ring chromosomes are often unstable in mitosis

there is a loss of chromosomes





Take home message

- **During mitosis in somatic cell division, the two sister chromatids of each chromosome separate, with one chromatid passing to each daughter cell.**

- **During meiosis, which occurs during the final stage of gametogenesis, homologous chromosomes pair, exchange segments, and then segregate independently to the mature daughter gametes.**

  - Chromosome abnormalities can be numerical or structural.
  - Numerical abnormalities include aneuploidy and polyploidy.
  - In trisomy, a single extra chromosome is present, usually as a result of non-disjunction in the 1^{st} or 2^{nd} meiotic division.
  - In polyploidy, ≥3 complete haploid sets are present instead of the usual diploid complement.
  - Structural abnormalities include translocations (balanced or unbalanced), inversions, deletions, isochromosome & rings.