Medical Genetics

•LECTURE 2

CHROMOSOME ANOMALIES

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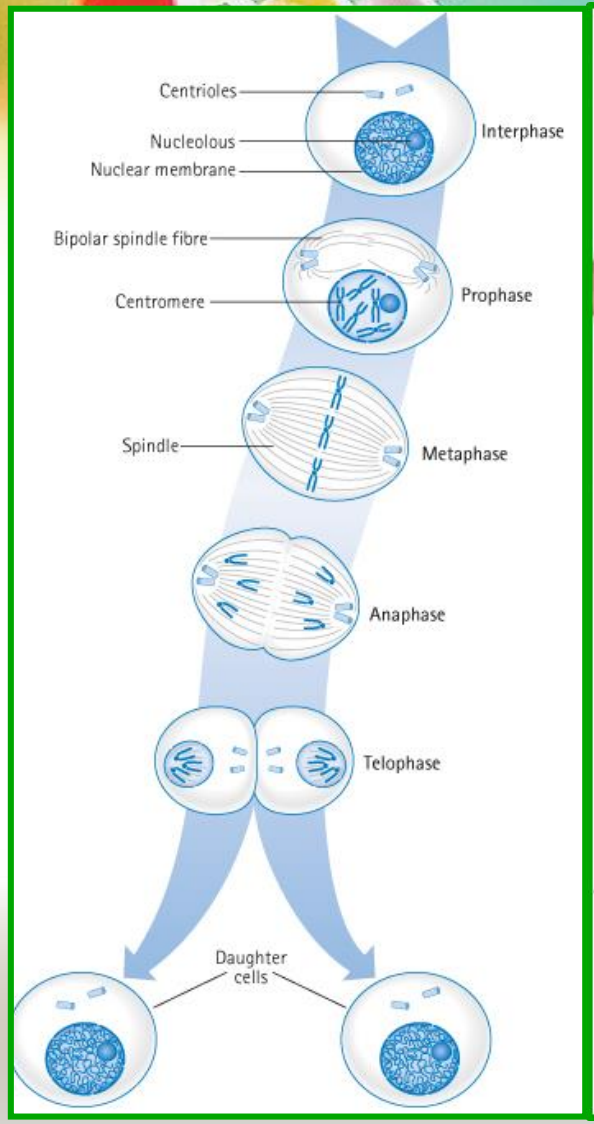
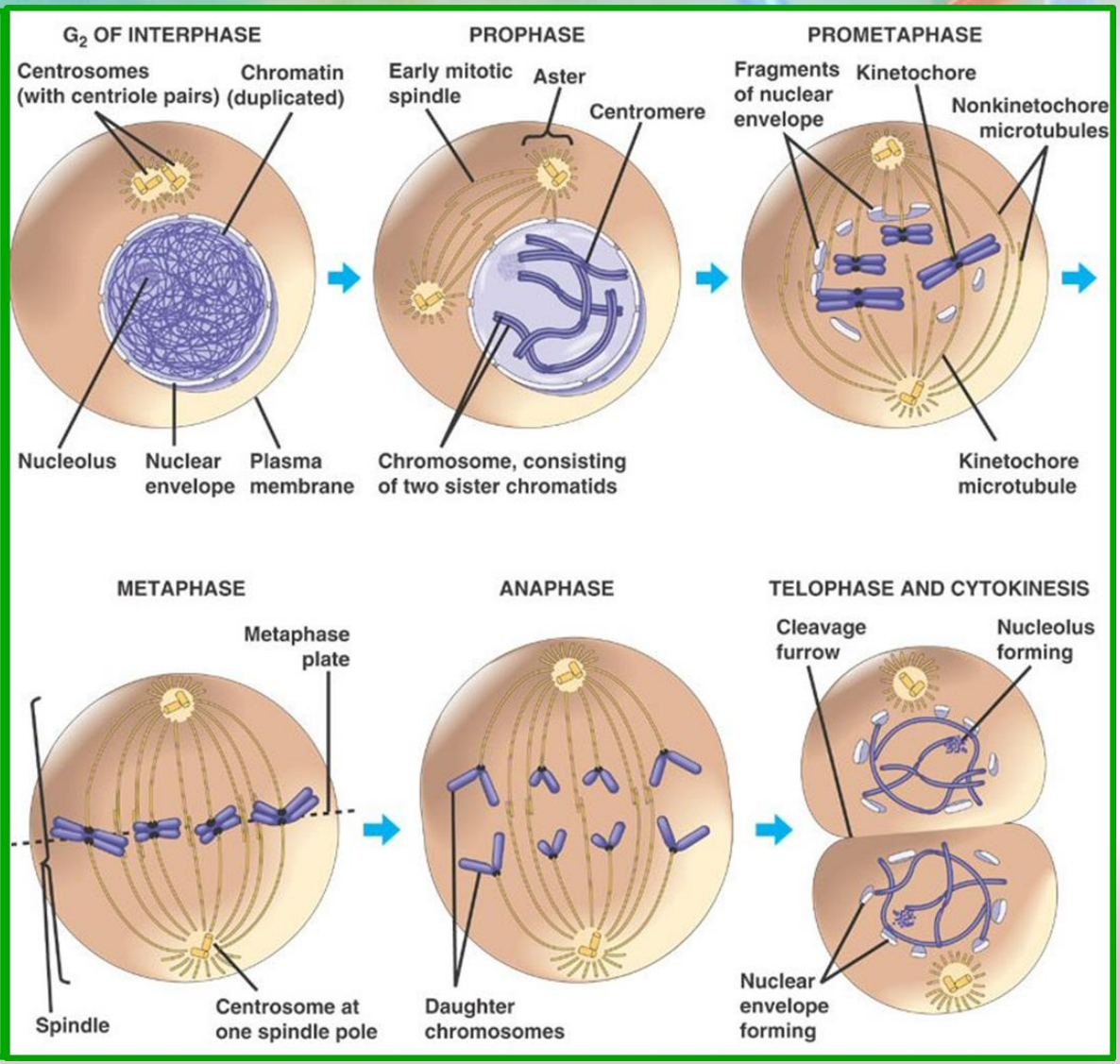
Lecture Objectives:

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

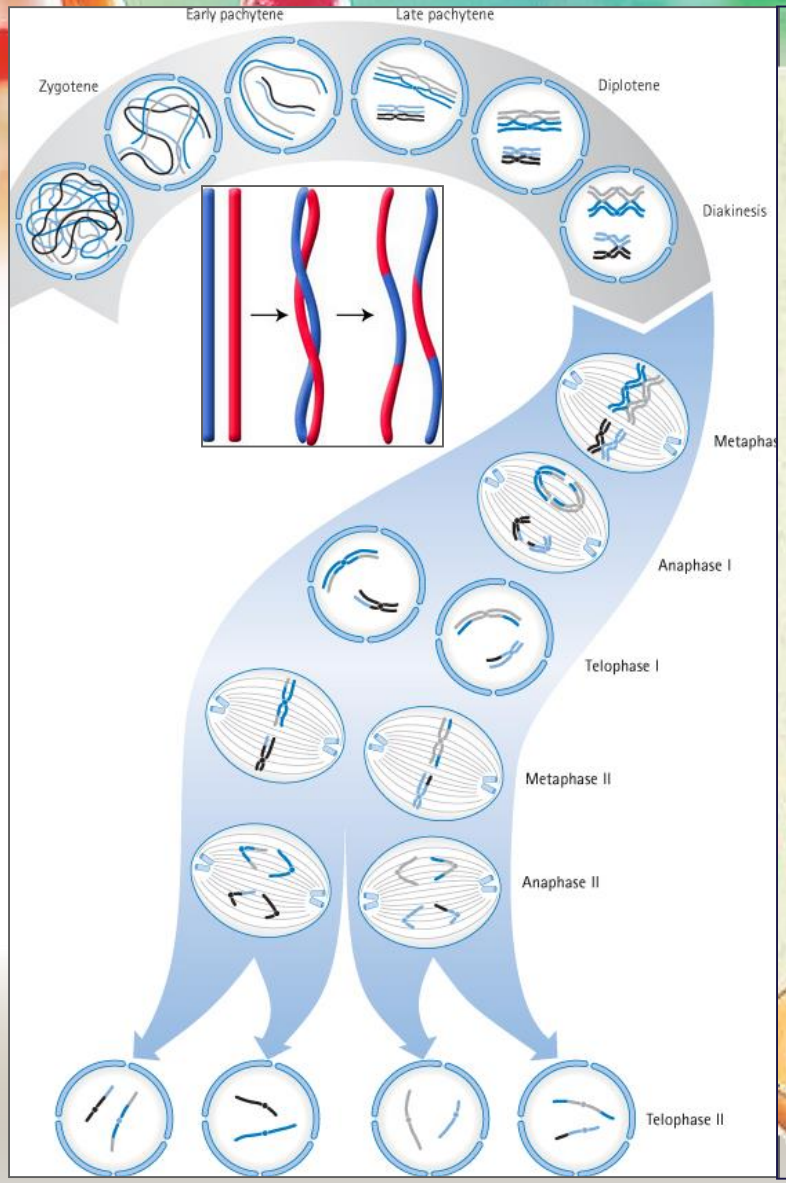
- Describe and explain the events in mitosis & meiosis.
- Define non-disjunction and describe its consequences for meiosis and mitosis.
- Classify and sub-classify chromosomal abnormalities
- Understand the common numerical autosomal disorders: trisomies 21, 13, 18.
- Understand the common numerical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

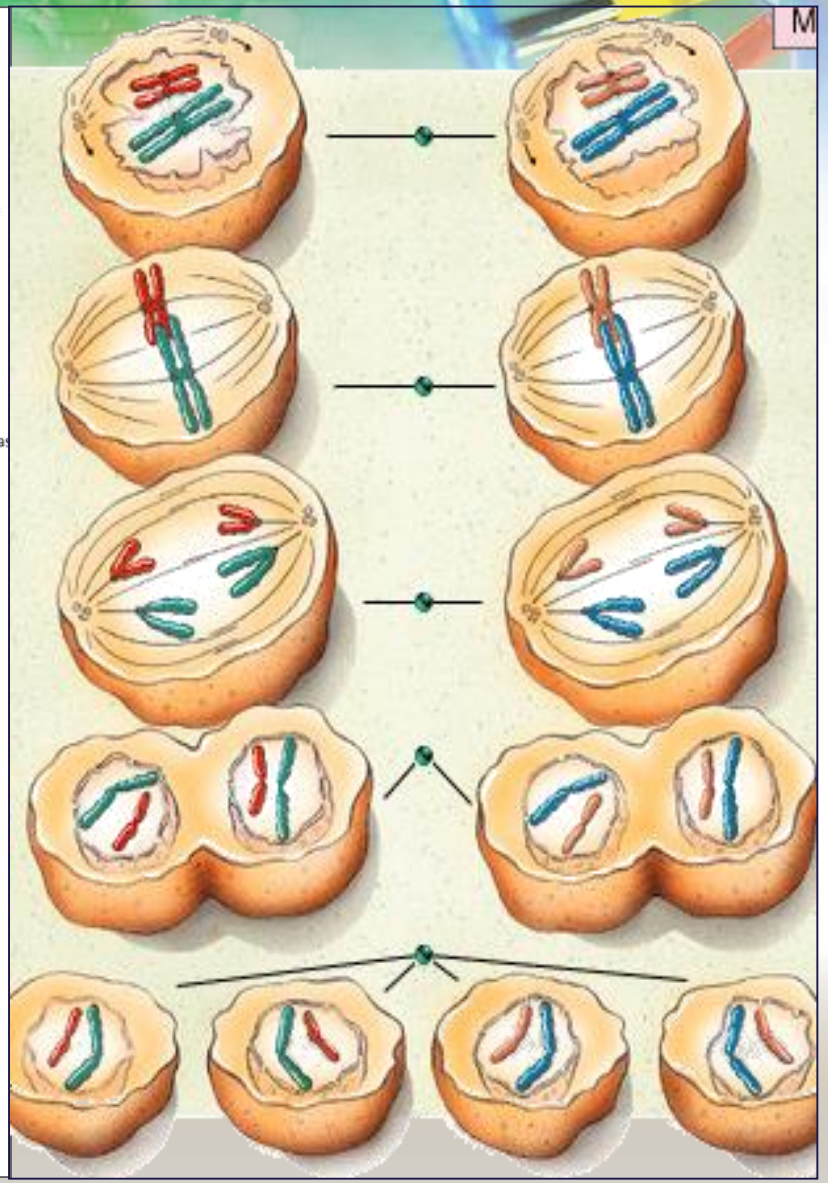
Stages of Mitosis



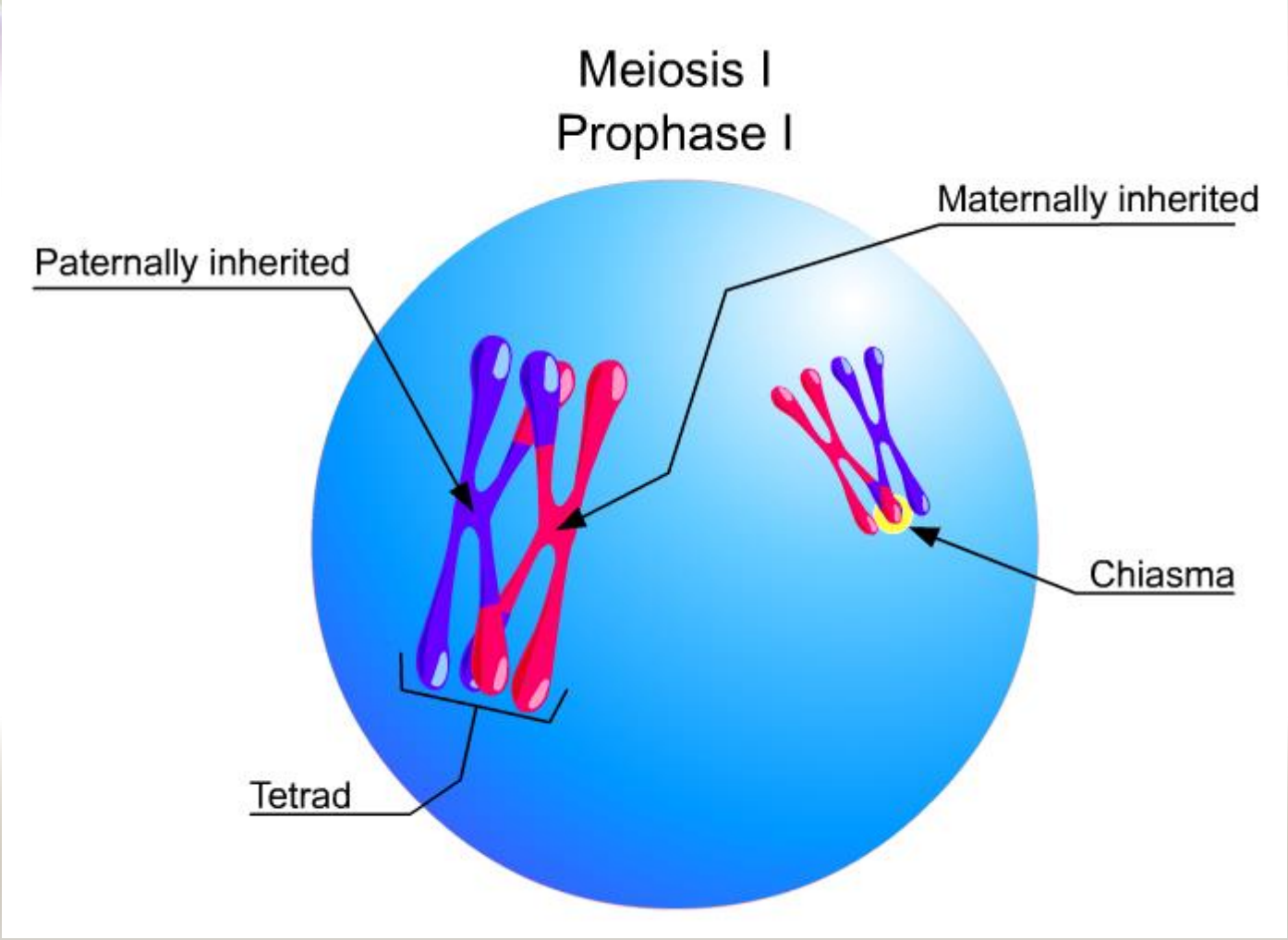


Stages of MEIOSIS

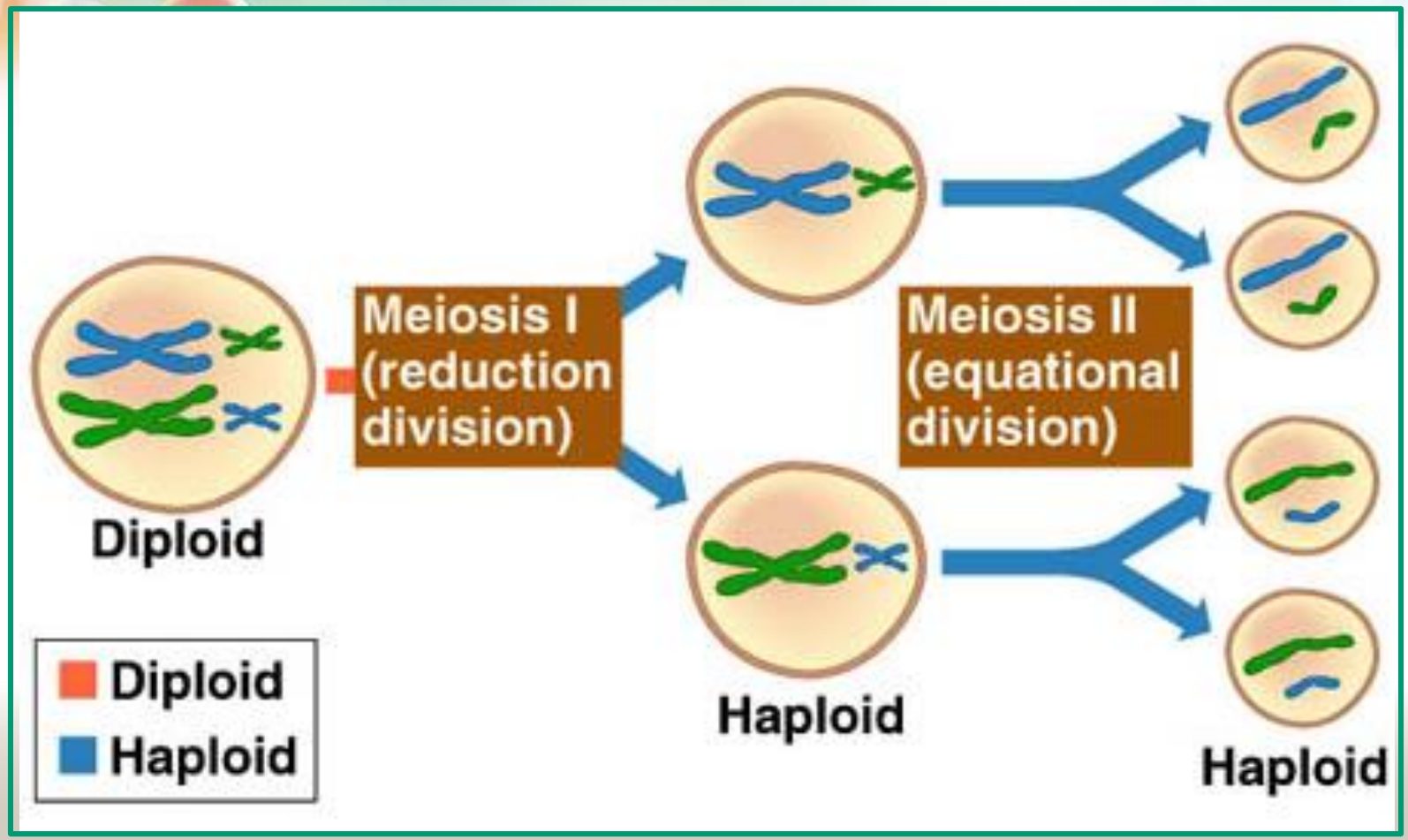




CHIASMATA


Meiosis I
Prophase I
Maternally inherited
Paternally inherited
Chiasma
Tetrad

The phases of meiosis I & II

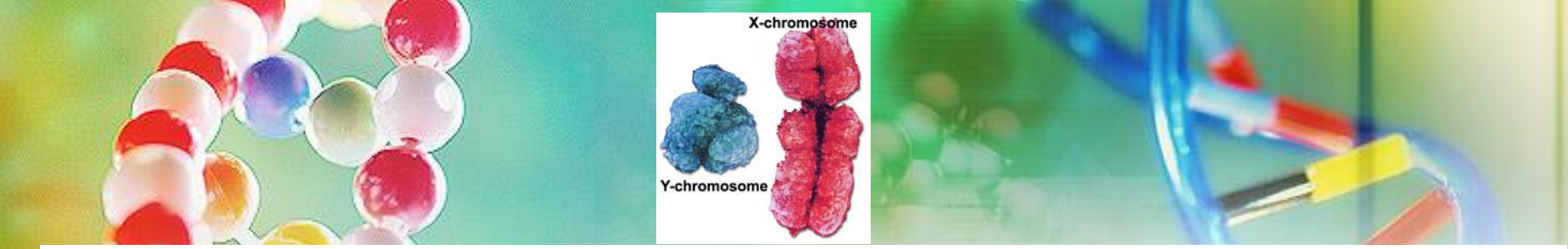


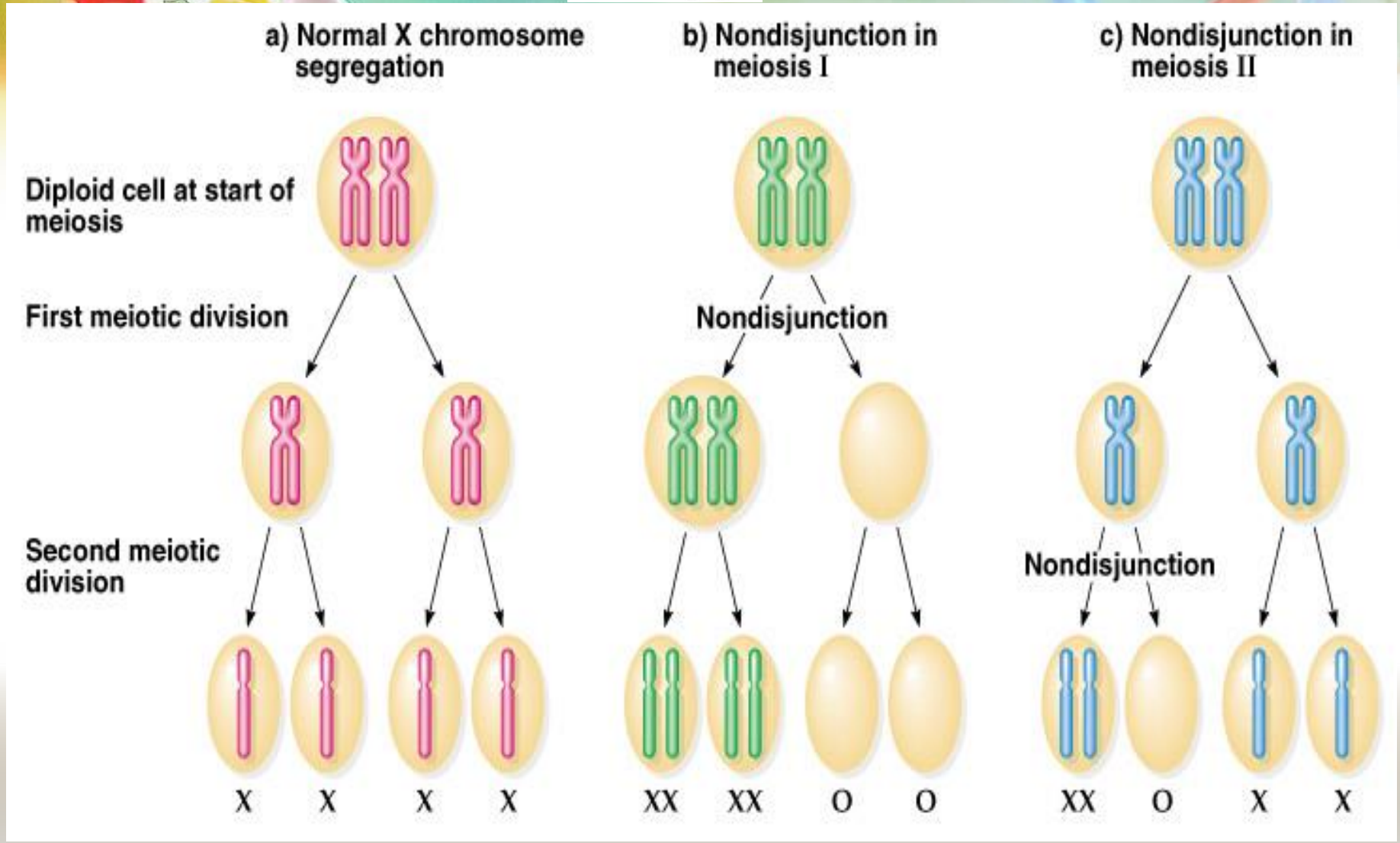
CHROMOSOME ANOMALIES

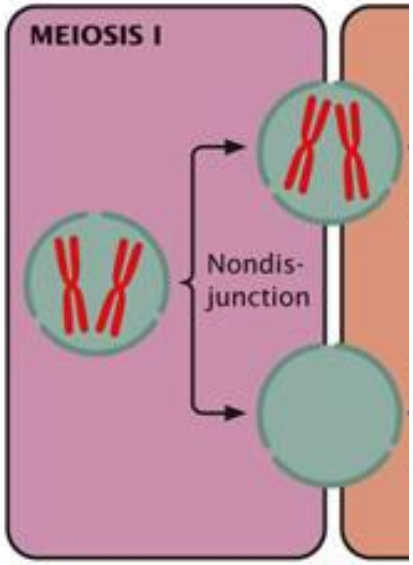
- **TYPES:**
  - **Numerical**
  - **Structural**
- **MECHANISMS**
- **NOMENCLATURE**
- **Etiology**

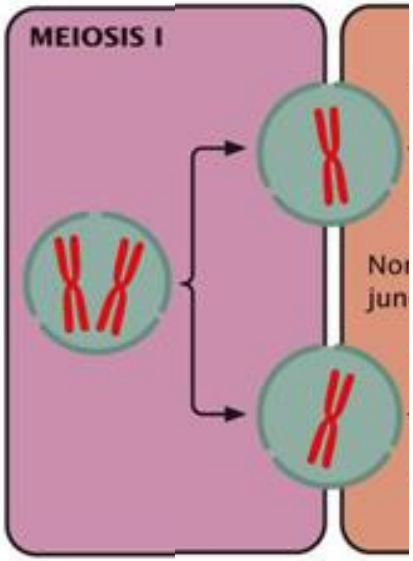
Non-disjunction in Meiosis

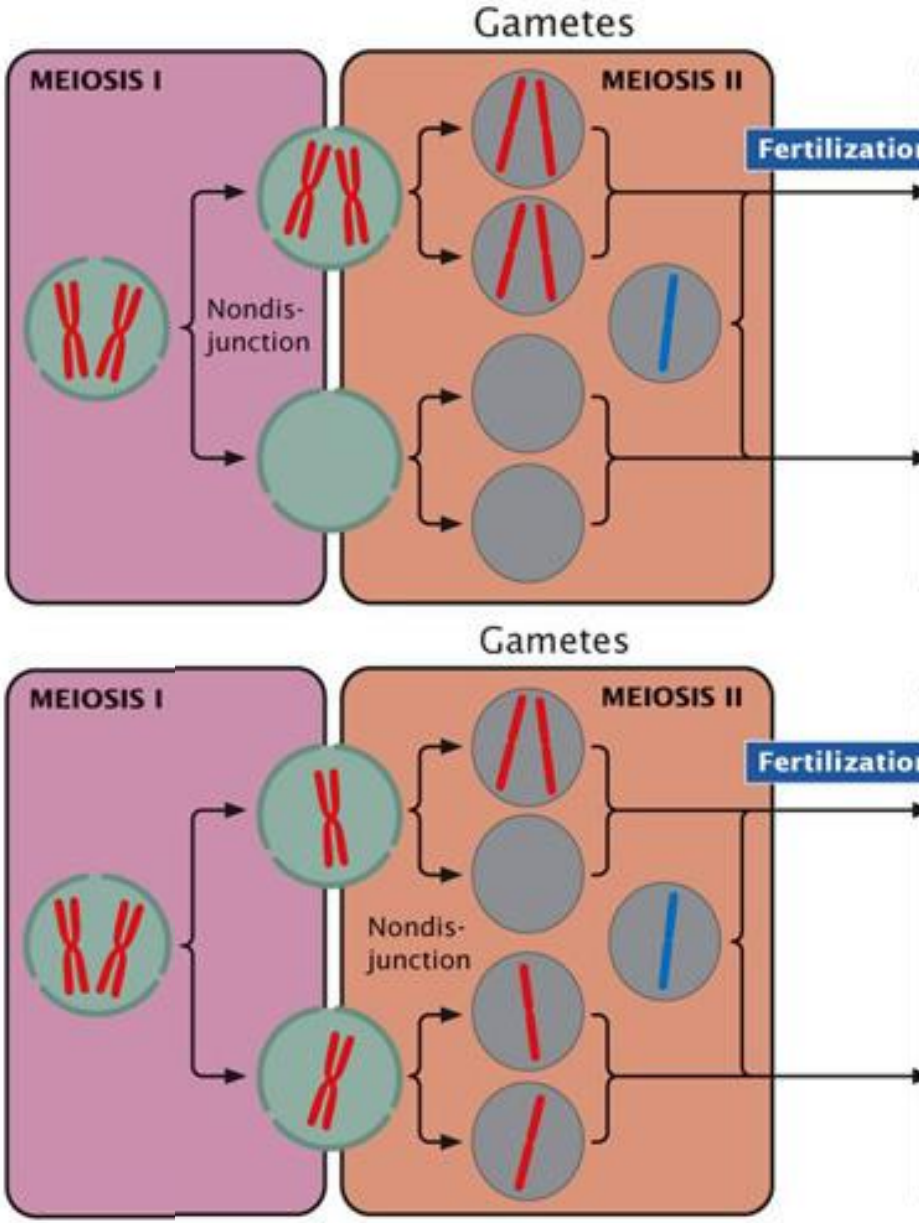
- **Nondisjunction** ("not coming apart") is the failure of chromosome pairs to separate properly during meiosis stage 1 or stage 2.
- As a result, one daughter cell has two chromosomes, and the other has none.
- The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)

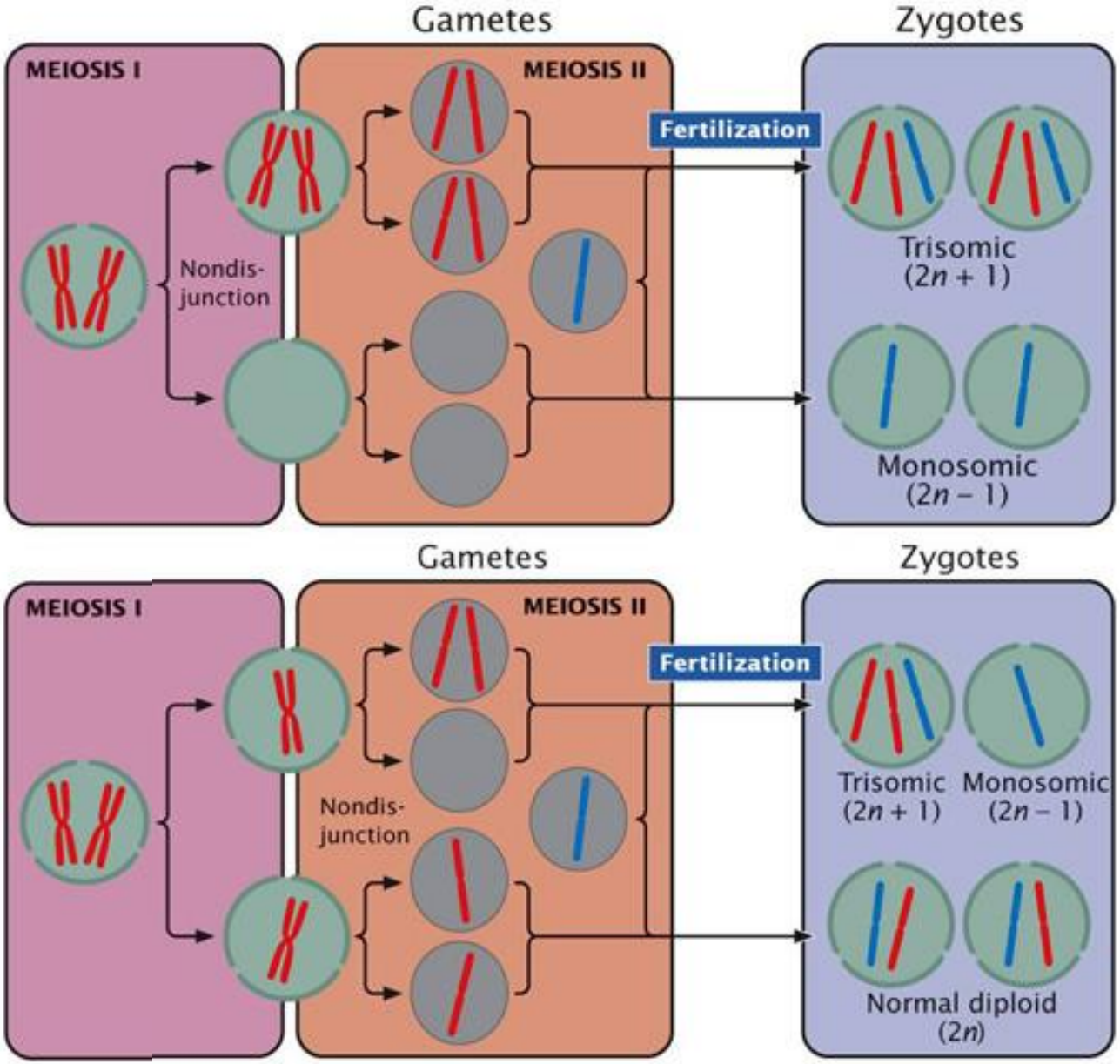

X-chromosome
Y-chromosome


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


MEIOSIS I
Nondis-
junction


MEIOSIS I


Gametes
MEIOSIS I
MEIOSIS II
Fertilizatio
Nondis-
junction
Gametes
MEIOSIS I
MEIOSIS II
Fertilizatio
Nondis-
junction


Gametes
Zygotes
MEIOSIS I
MEIOSIS II
Fertilization
Nondis-
junction
Trisomic
(2n + 1)
Monosomic
(2n – 1)
Gametes
Zygotes
MEIOSIS I
MEIOSIS II
Fertilization
Nondis-
junction
Trisomic
(2n + 1)
Monosomic
(2n – 1)
Normal diploid
(2n)

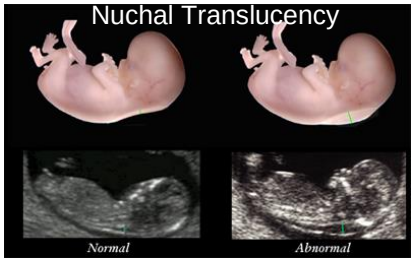
Meiotic non-disjunction

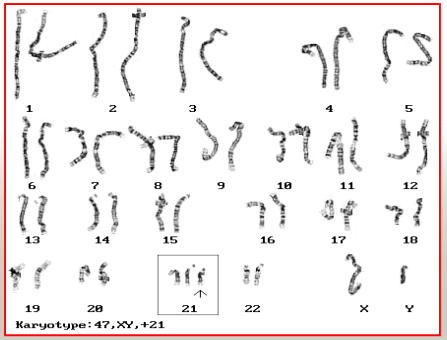
- can affect each pair of chromosomes
- is not a rare event
- non disjunction in first meiotic division produces 4 unbalanced gametes.
- non disjunction in second division produces 2 normal gametes & 2 unbalanced gametes:

Down syndrome, trisomy 21

Karyotype: 47, XY, +21

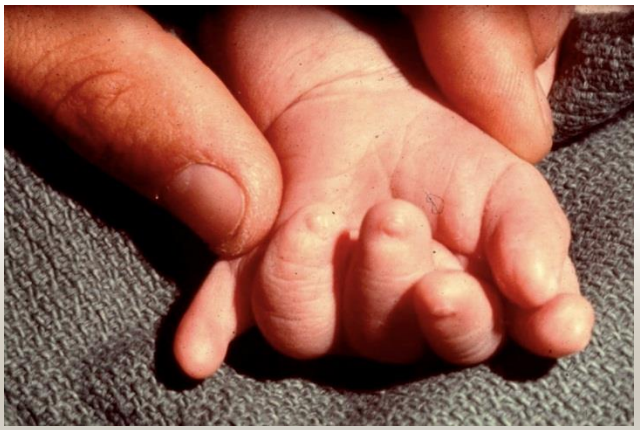
- The incidence of trisomy 21 rises sharply with increasing maternal age
- Most cases arise from non disjunction in the first meiotic division
- The father contributing the extra chromosome in 15% of cases (i.e. Down syndrome can also be the result of nondisjunction of the father's chromosome 21)
- A small proportion of cases are mosaic and these probably arise from a non disjunction event in an early zygotic division.
- The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50.





Edward's syndrome, Trisomy 18
Karyotype: 47, XY, +18

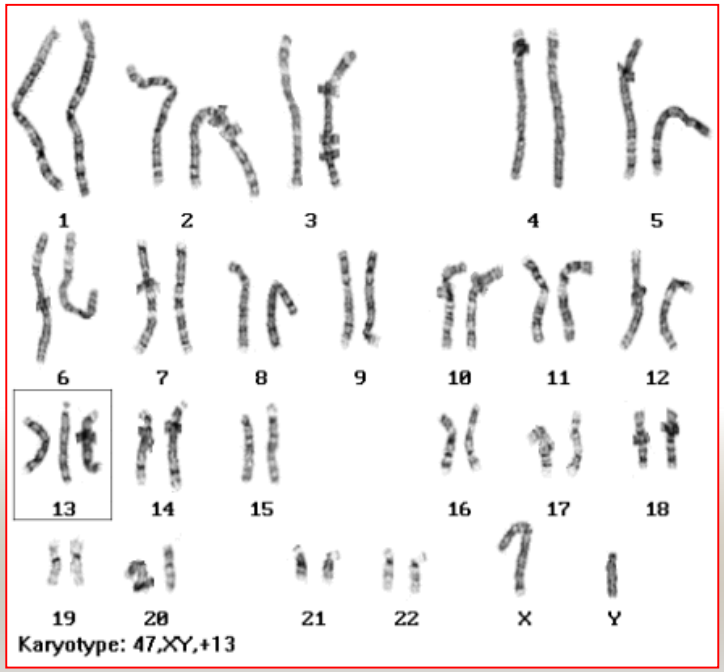
- It is the second most common autosomal trisomy, after Down syndrome, that carries to term
- It occurs in around one in 6,000 live births and around 80 percent of those affected are female
- Most babies die in the first year and many within the first month & has a very low rate of survival
- Common anomalies are heart abnormalities, kidney malformations, and other internal organ disorders



Patau Syndrome, Trisomy 13

Karyotype: 47, XY, +13

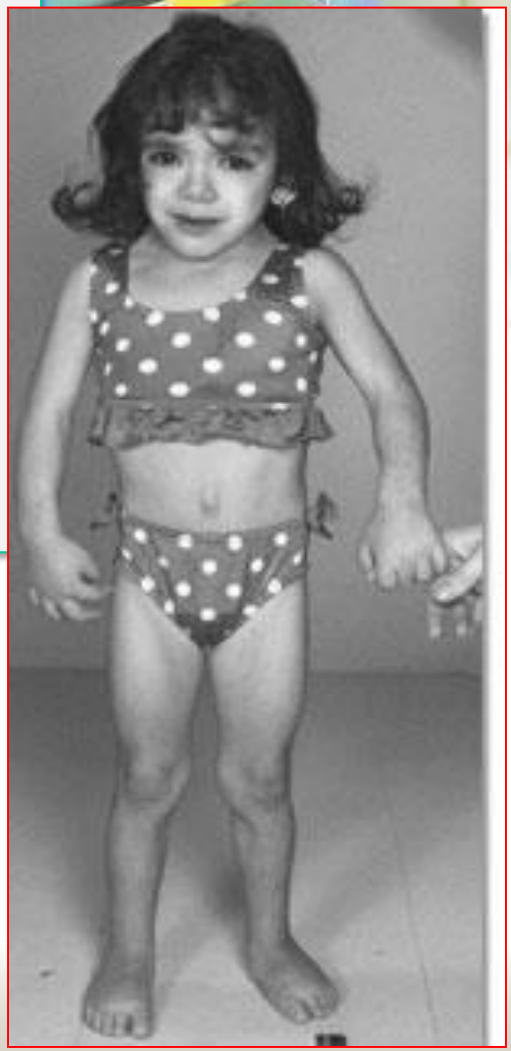
- **Fifty % of these babies die within the first month and very few survive beyond the first year.**
- **There are multiple dysmorphic features.**
- **Most cases, as in Down's syndrome, involve maternal non-disjunction.**

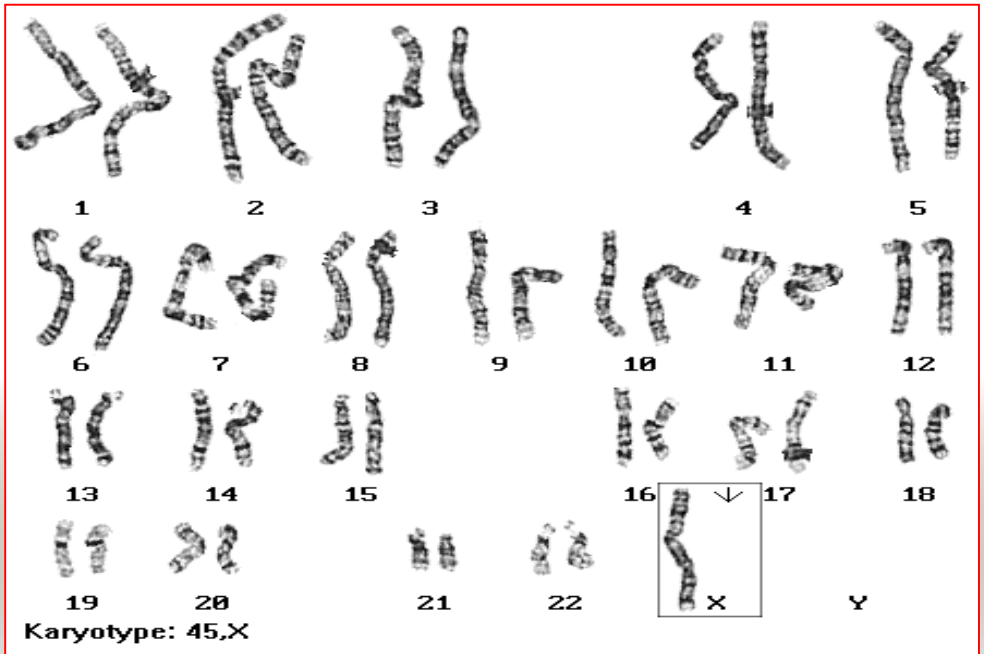


Numerical anomalies in Sex chromosomes

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

- Occurring in 1 in 5000 phenotypic females
- 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



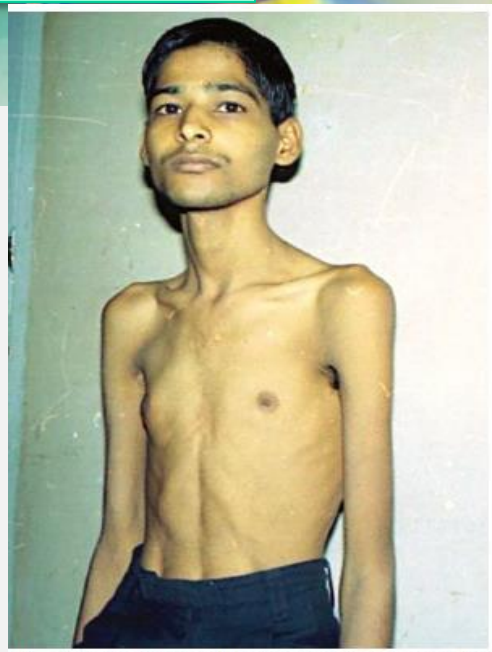


Klinefelter Syndrome: 47,XXY males

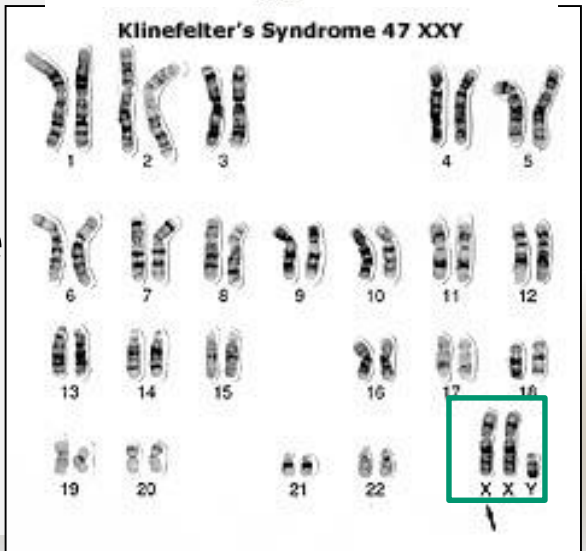
- Male sex organs; unusually small testes which fail to produce normal levels of testosterone→ breast enlargement (gynaecomastia) and other feminine body characteristic

- Patients are taller and thinner than average and may have a slight reduction in IQ but generally they have normal intelligence

- No spermatogenesis → sterile
- Very rarely more extreme forms of Klinefelte syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.



: Photograph showing development of gynecomastia in a old male after 2 months of isoniazid containing Category ATT



Sex chromosome unbalance is much less deleterious

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

Polyploidy

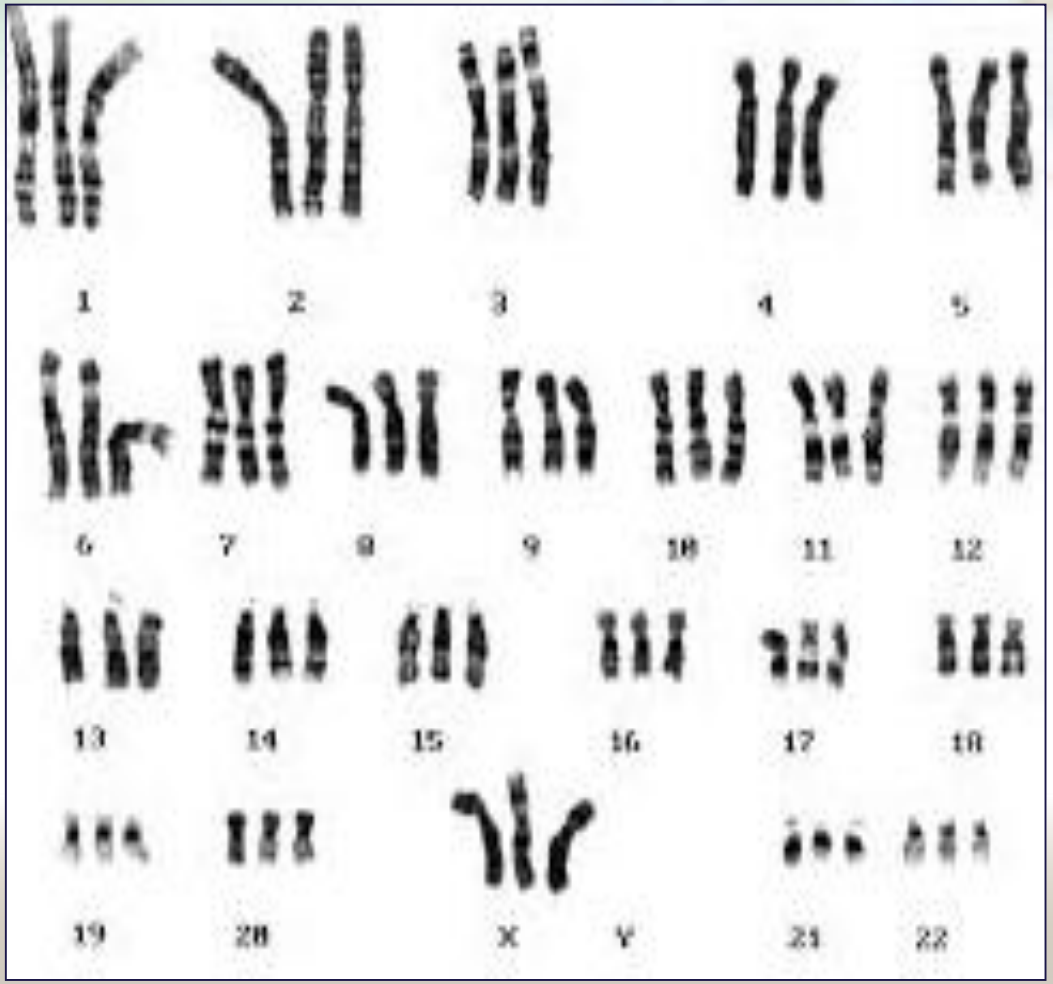
- **Triploidies are the most frequent,**

  - 3N = 69 chromosomes: e.g. 69, XXX, or 69, XXY, or 69, XYY.

  - Are found in 20 % of spontaneous miscarriages.

- **Tetraploidy,**

  4N = 92 chromosomes.

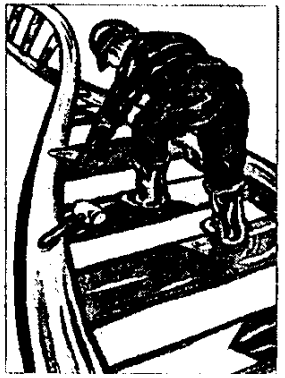


MOSAICISM

- 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
- Mosaicism is the presence of two or more populations of cells with different genotypes in one individual who has developed from a single fertilized egg.
- Mosaicism can affect any type of cell, including: Blood cells. Egg and sperm cells (gametes)

STRUCTURAL CHROMOSOMAL ANOMALIES

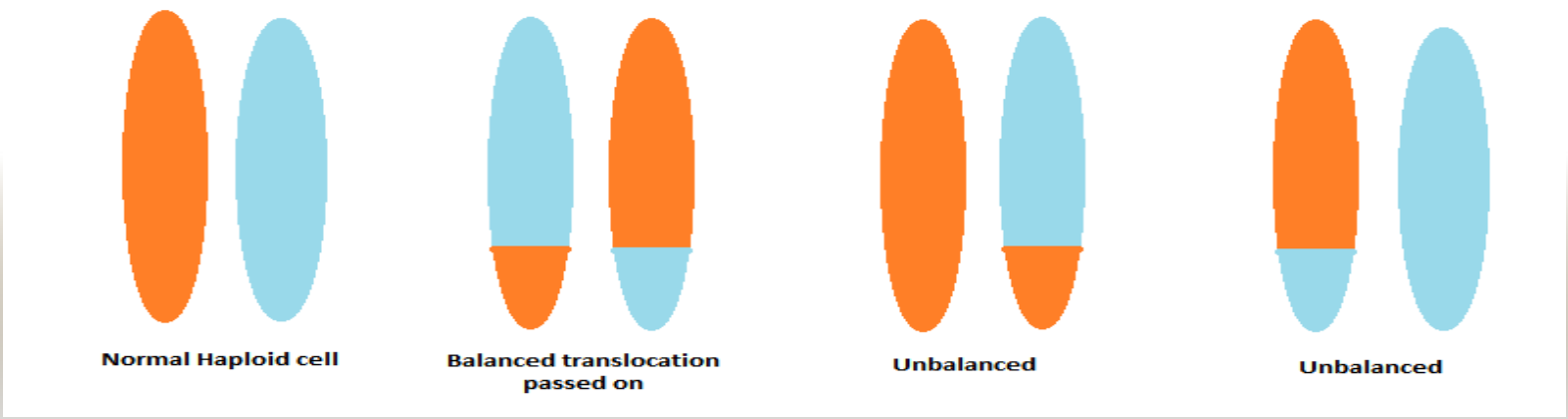
- **The most frequent Structural anomalies are:**
  - **Translocations**
  - **Inversions**
  - **Deletions**
  - **Isochromosome (i)**
  - **Ring formation (Ring chromosome)**



Reciprocal translocation:

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.

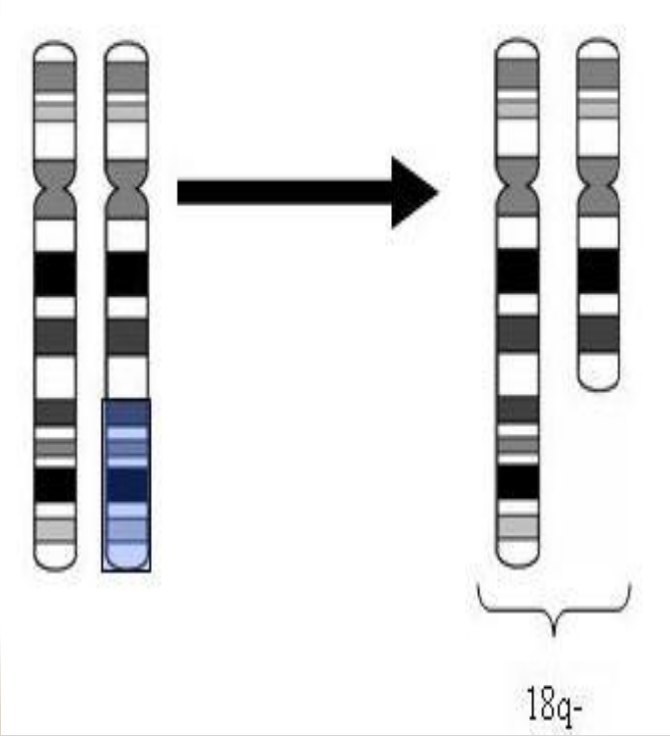


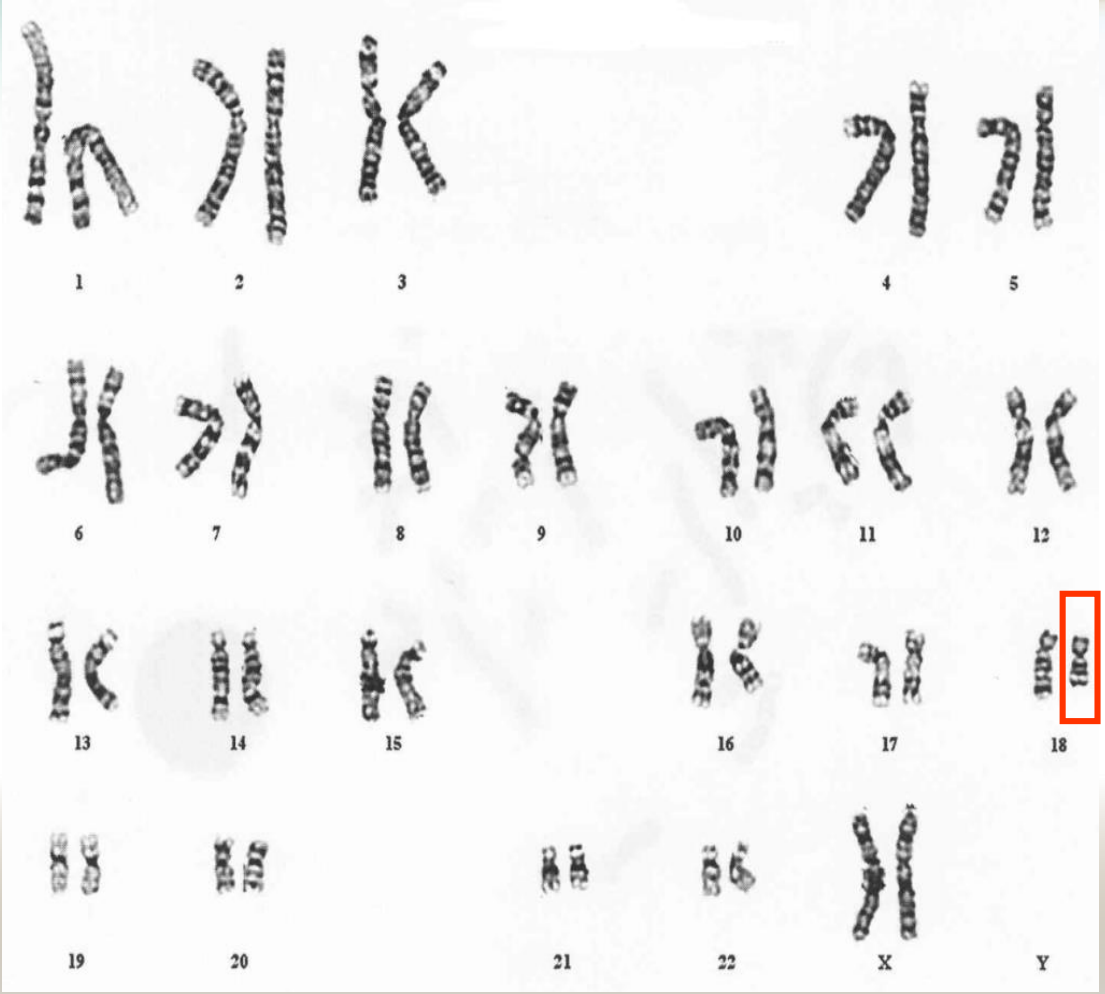
Deletion

- Loss of a segment from a chromosome, either terminal or interstitial
- Frequently results in the loss of important genetic material
- Deletion is therefore an unbalanced rearrangement.
- Recorded as del

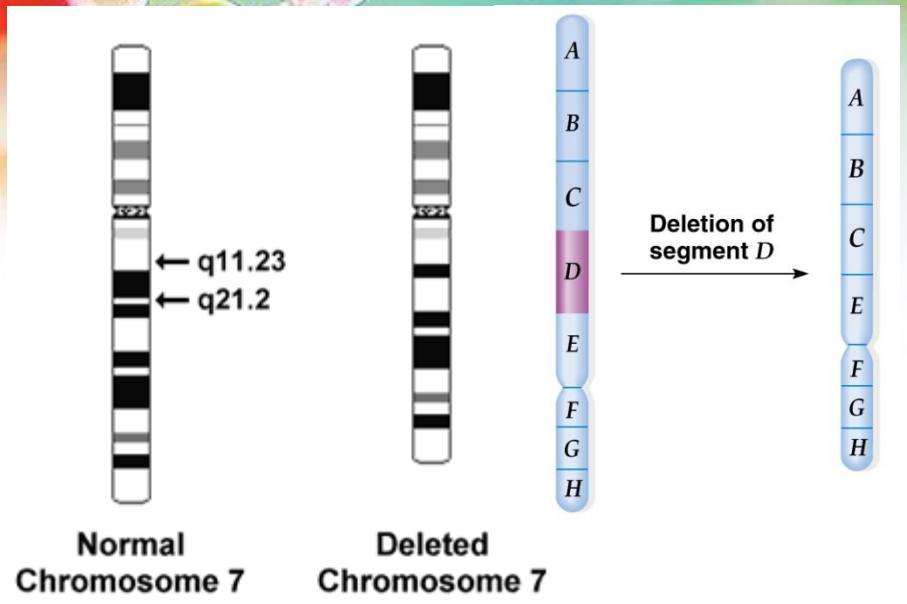
Terminal Deletion

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

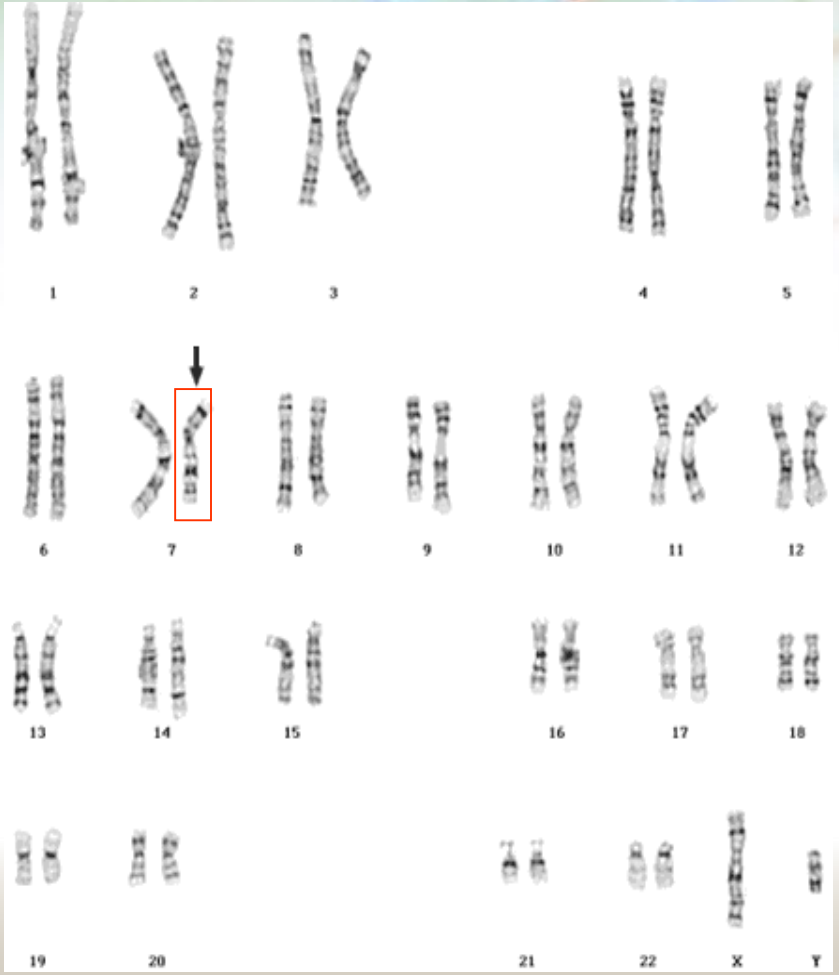




Interstitial deletion (7 Karyotype)



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

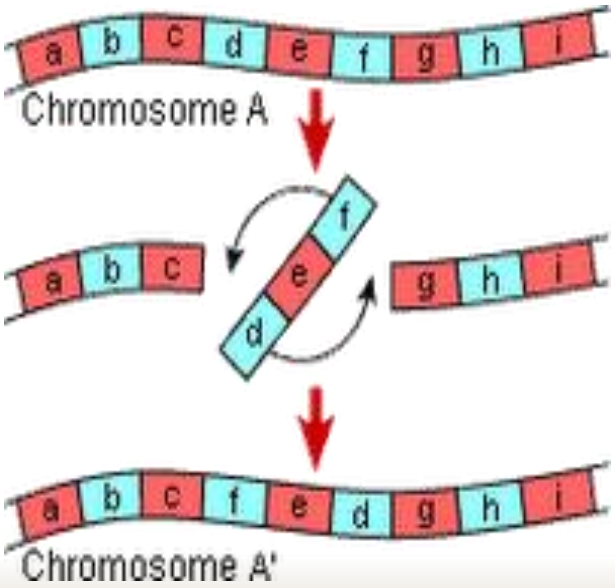


The key to the karyotype description is as follows:

- 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.

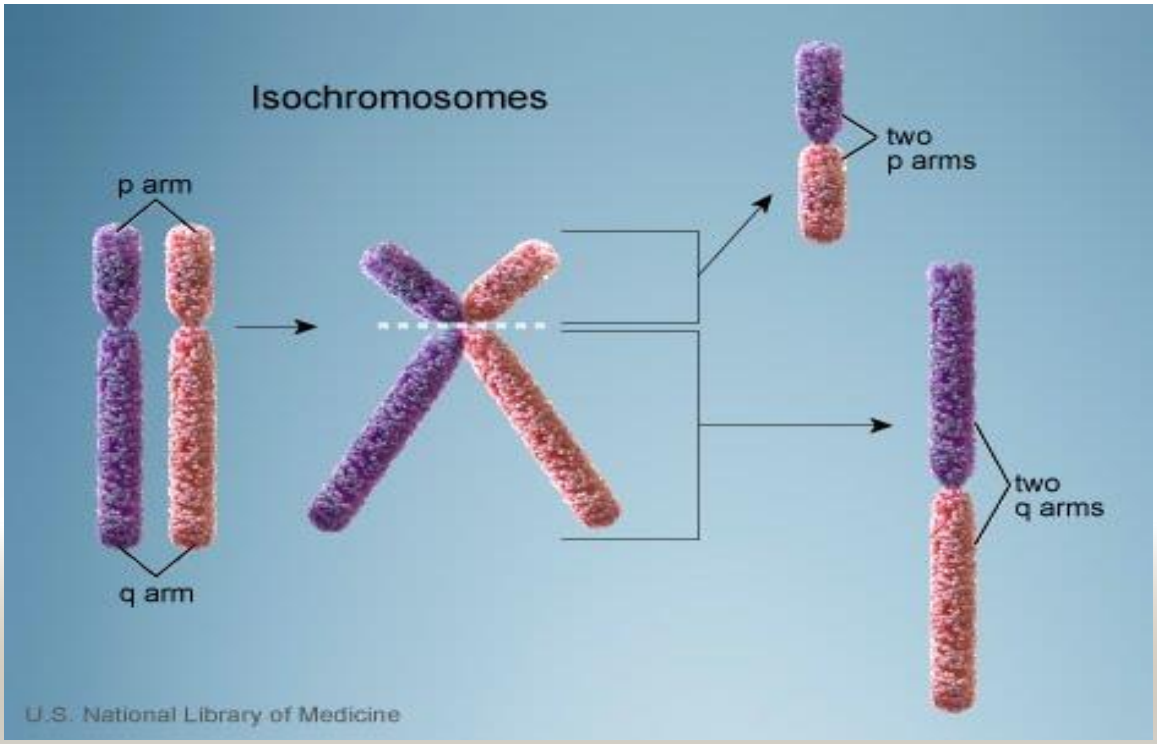
Inversion

- 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



Isochromosome

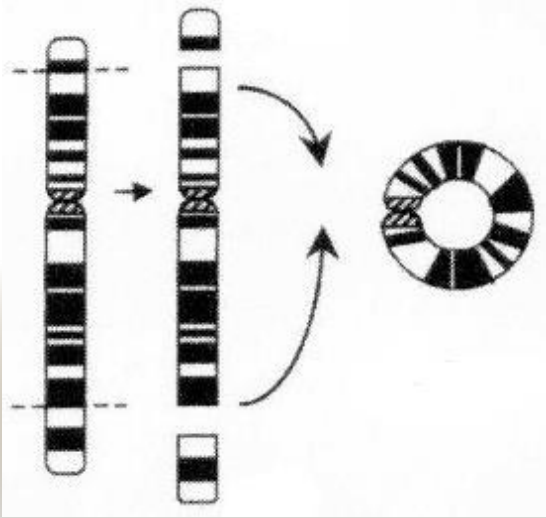
- The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally



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



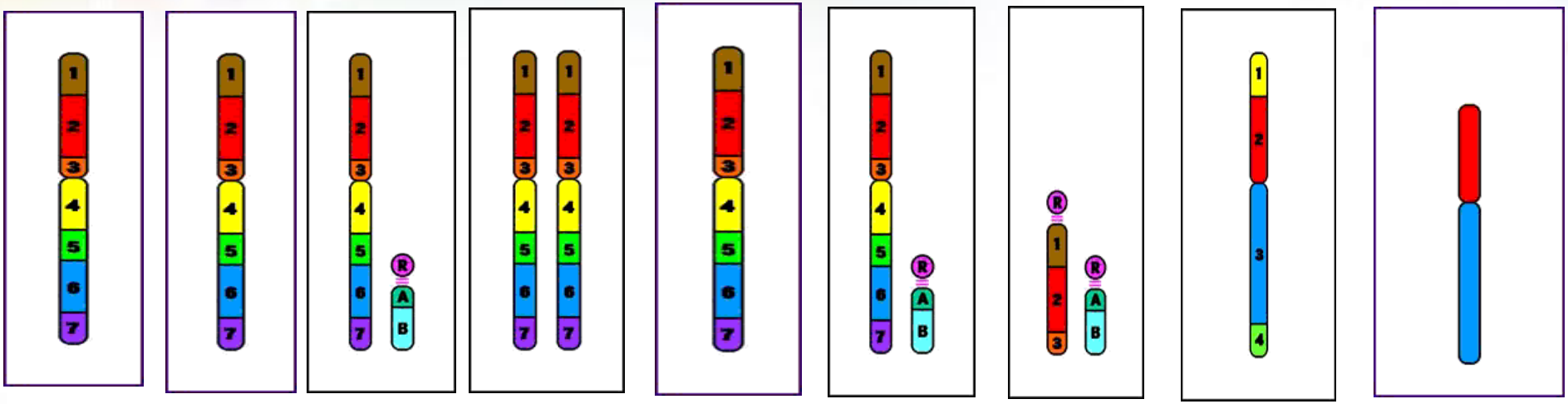
STRUCTURAL CHROMOSOMAL ANOMALIES

Deletion

Duplication

Reciprocal translocation

Ring Chromosome



Terminal Deletion

Insertion

Inversion

Robertsonian Translocation

Isochromosomes

Take home message

- 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.