



Medical Genetics

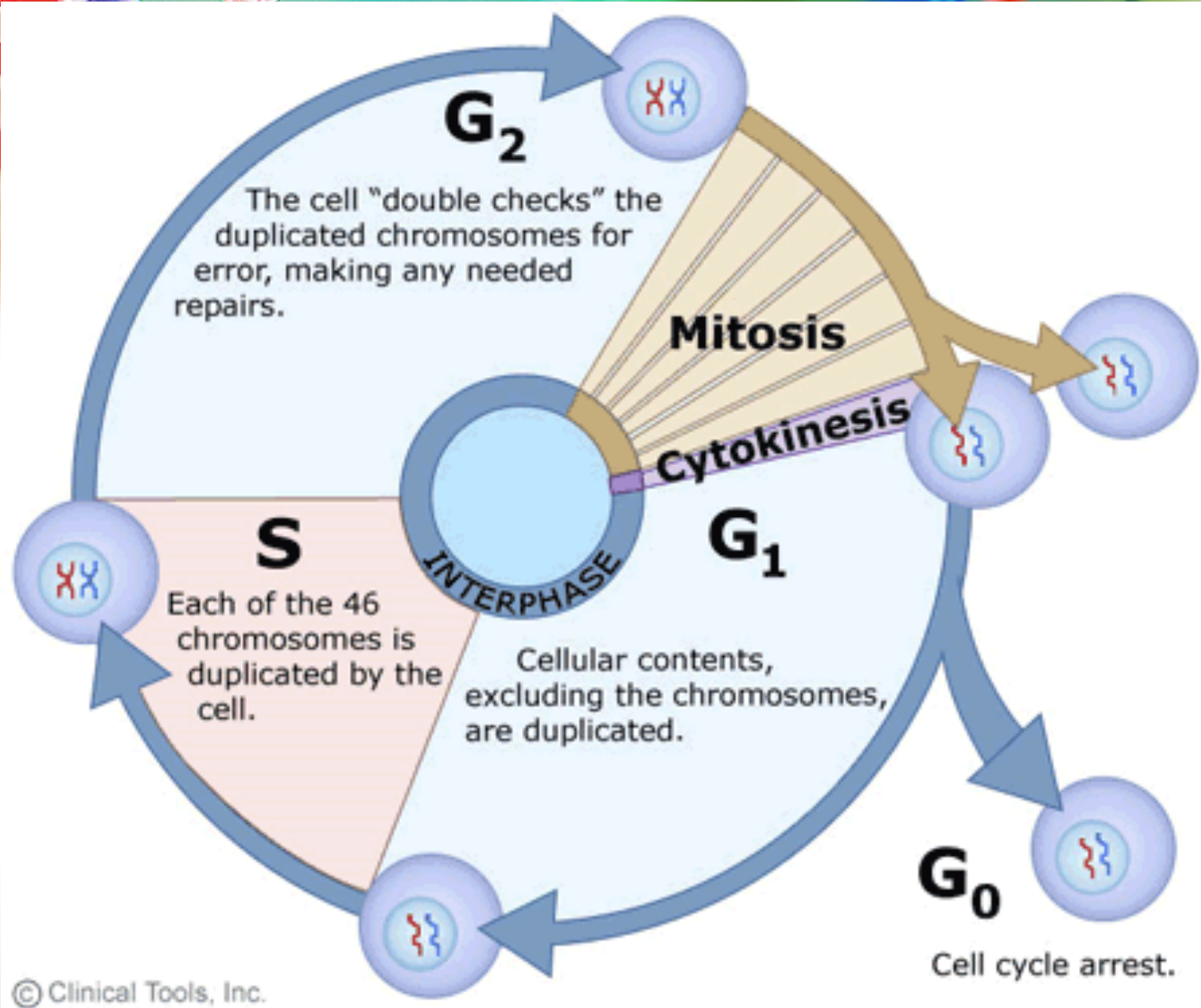
LECTURE 2 CHROMOSOME ANOMALIES



Lecture Objectives:

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

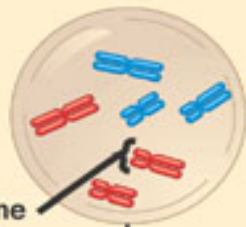
- Describe and explain the events in mitosis & meiosis.
- Define non-disjunction and describe its consequences for meiosis and mitosis.
- Classify chromosomal abnormalities
- Understand the common numerical autosomal disorders: trisomies 21, 13, 18.
- Understand the common numerical sex chromosome disorders: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



MITOSIS

Prophase

Duplicated chromosome (two sister chromatids)



Chromosome replication

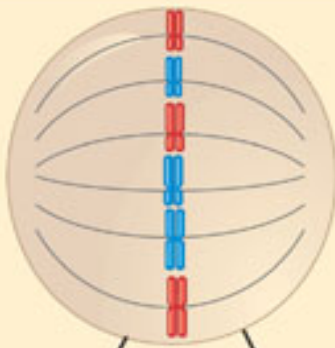


$2n = 6$

Chromosome replication

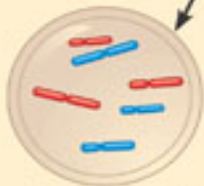
Metaphase

Chromosomes positioned at the metaphase plate



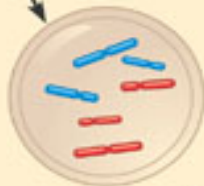
Anaphase
Telophase

Sister chromatids separate during anaphase



$2n$

Daughter cells of mitosis



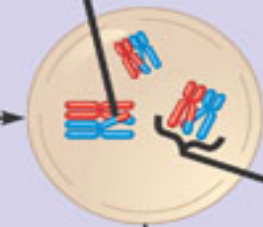
$2n$

MEIOSIS

MEIOSIS I

Prophase I

Chiasma (site of crossing over)



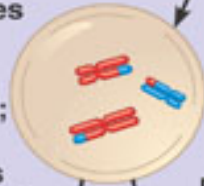
Tetrad formed by synapsis of homologous chromosomes

Tetrads positioned at the metaphase plate

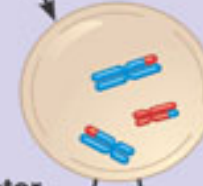


Metaphase I

Homologues separate during anaphase I; sister chromatids remain together



Daughter cells of meiosis I



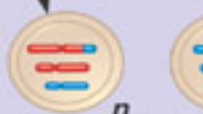
Anaphase I
Telophase I

Haploid
 $n = 3$

MEIOSIS II



n



n



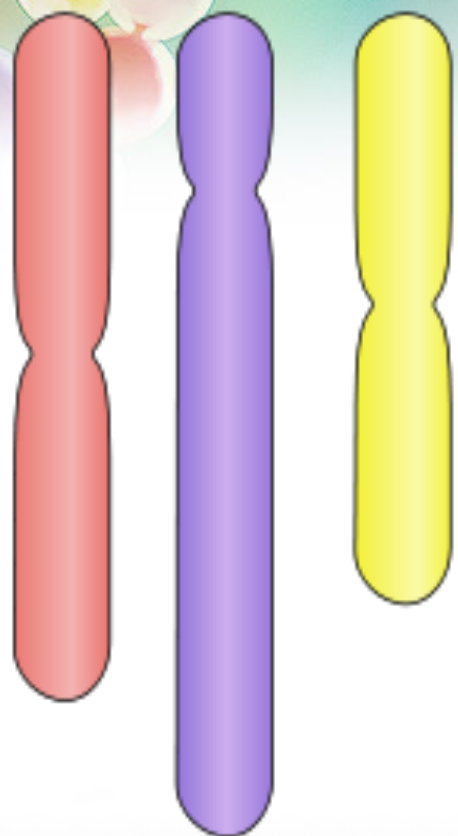
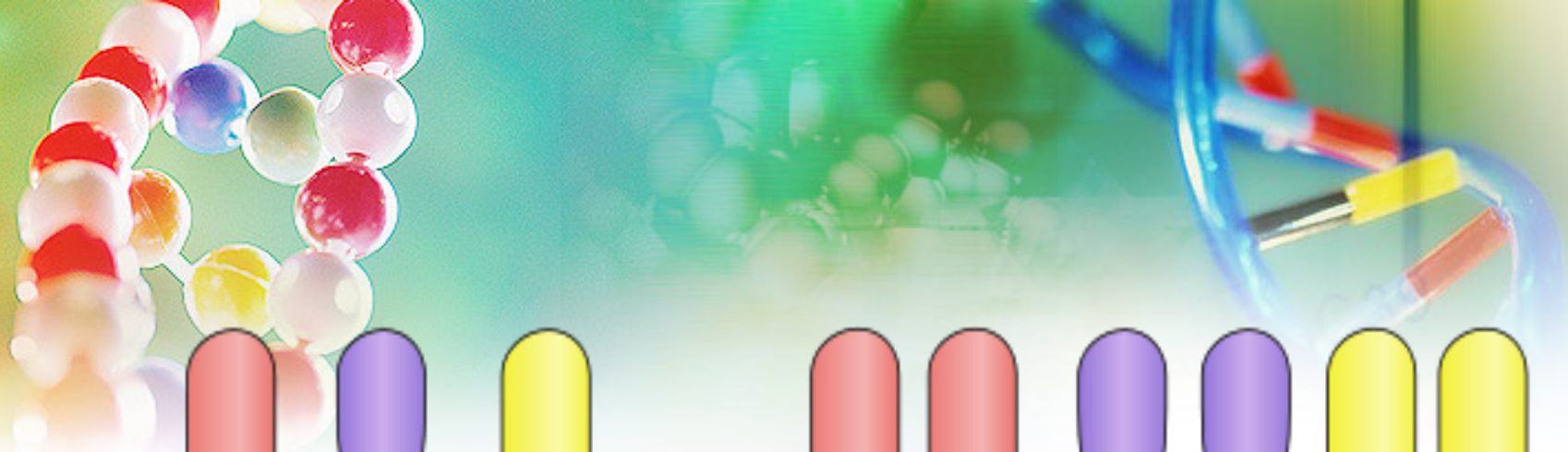
n



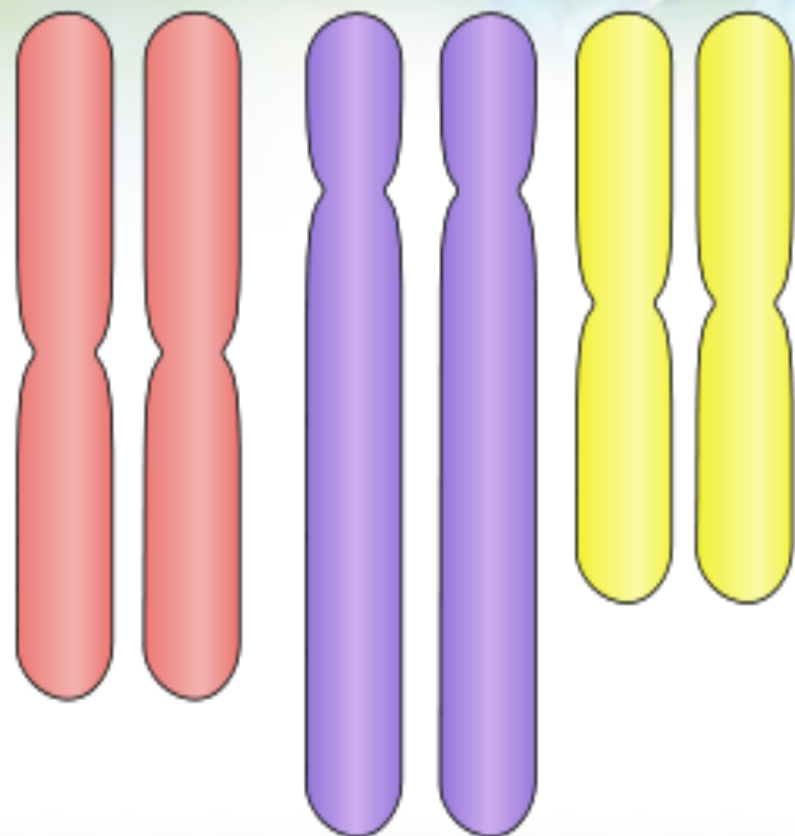
n

Daughter cells of meiosis II

Sister chromatids separate during anaphase II



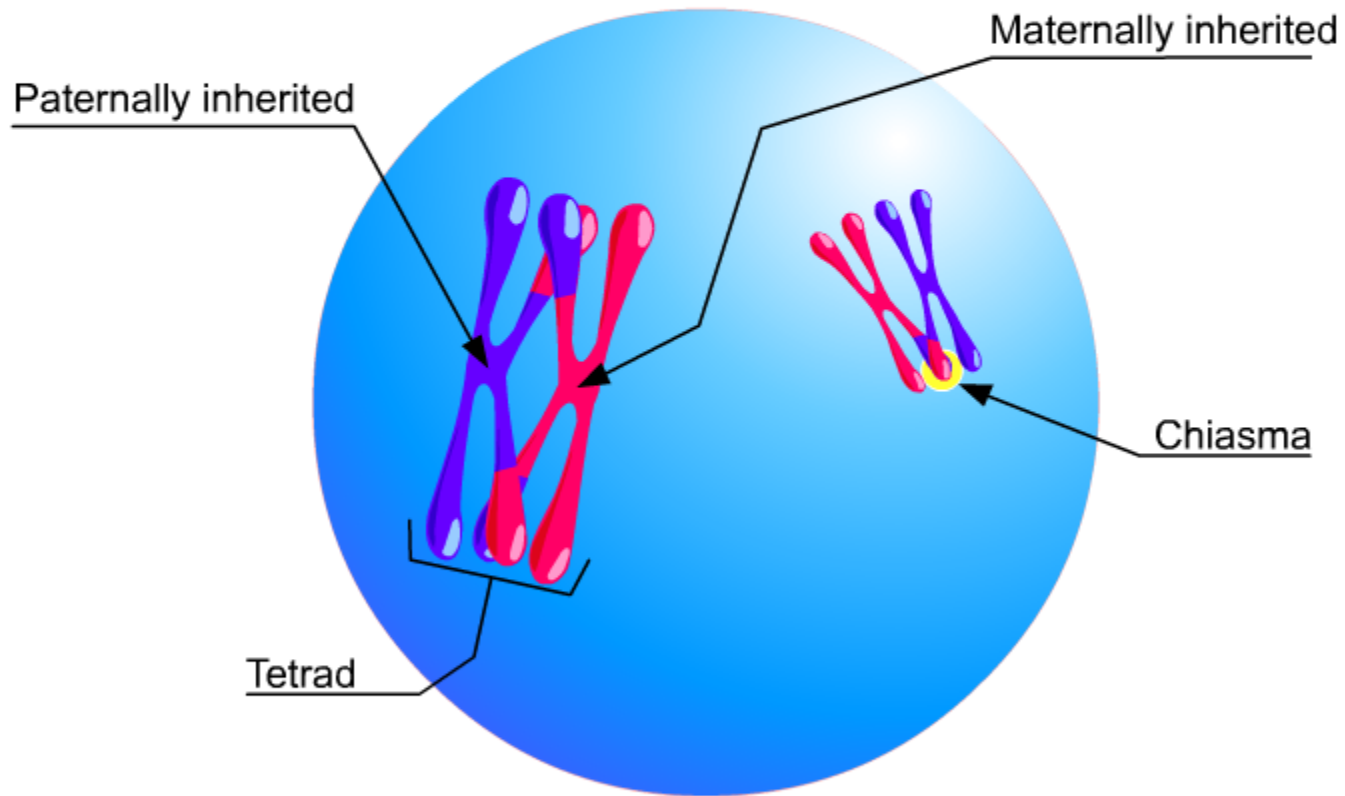
Haploid (N)



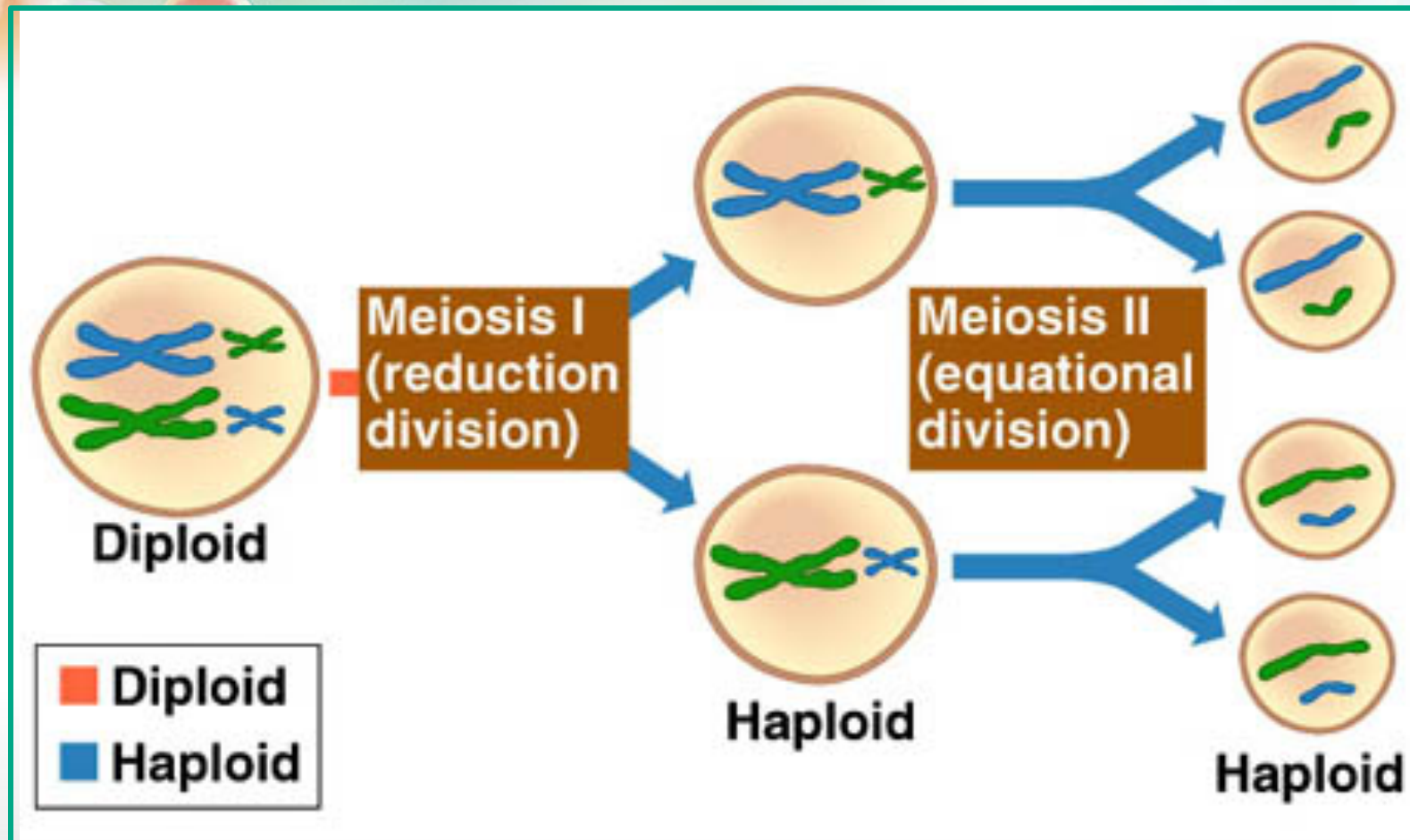
Diploid (2N)



Meiosis I Prophase I



The phases of meiosis I & II



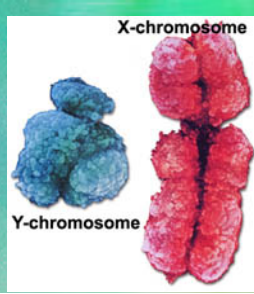


CHROMOSOME ANOMALIES

- **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 or two chromatids, and the other has none.
- ❖ The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)

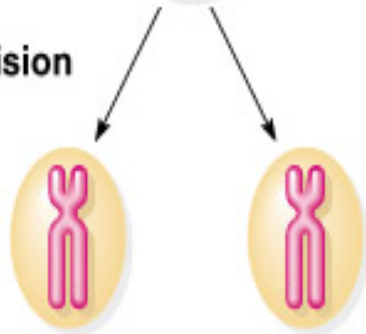


a) Normal X chromosome segregation

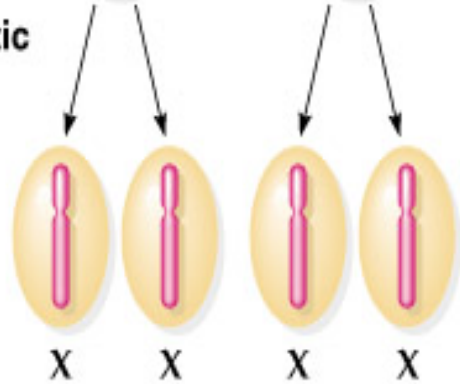
Diploid cell at start of meiosis

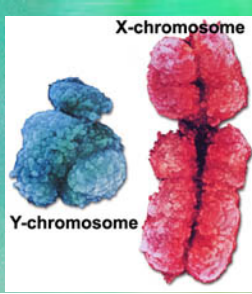


First meiotic division



Second meiotic division





a) Normal X chromosome segregation

b) Nondisjunction in meiosis I

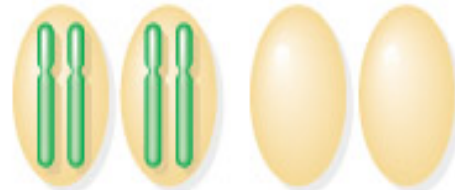
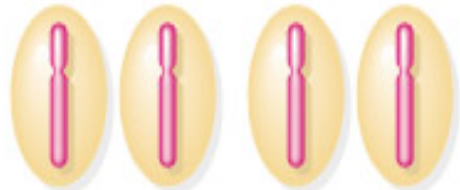
Diploid cell at start of meiosis



First meiotic division

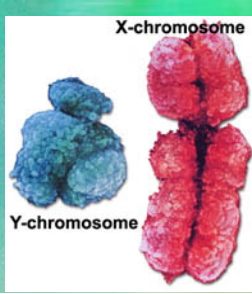


Second meiotic division



X X X X

XX XX O O



a) Normal X chromosome segregation

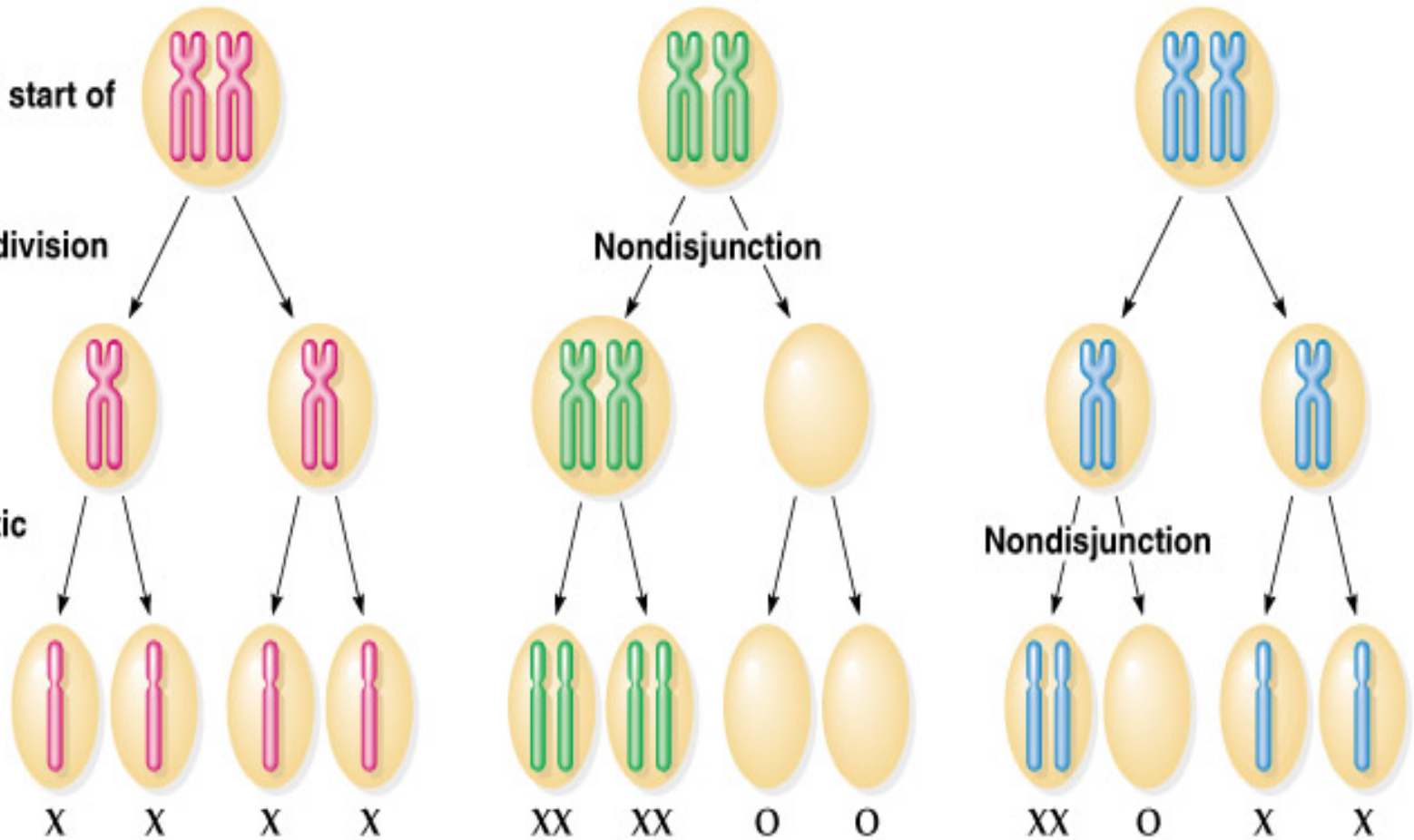
b) Nondisjunction in meiosis I


c) Nondisjunction in meiosis II

Diploid cell at start of meiosis

First meiotic division

Second meiotic division





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

Nullosoomic gamete (missing one chromosome)



NUMERICAL CHROMOSOMAL ANOMALIES

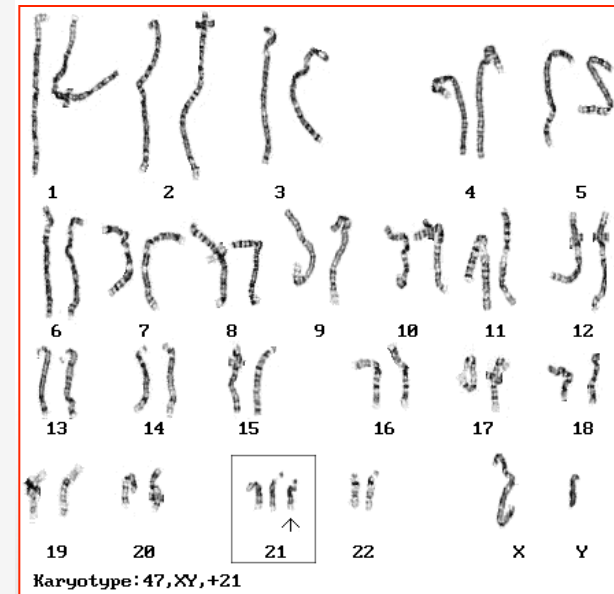


Numerical anomalies in autosomes

Down syndrome, trisomy 21

Karyotype: 47, XY, +21

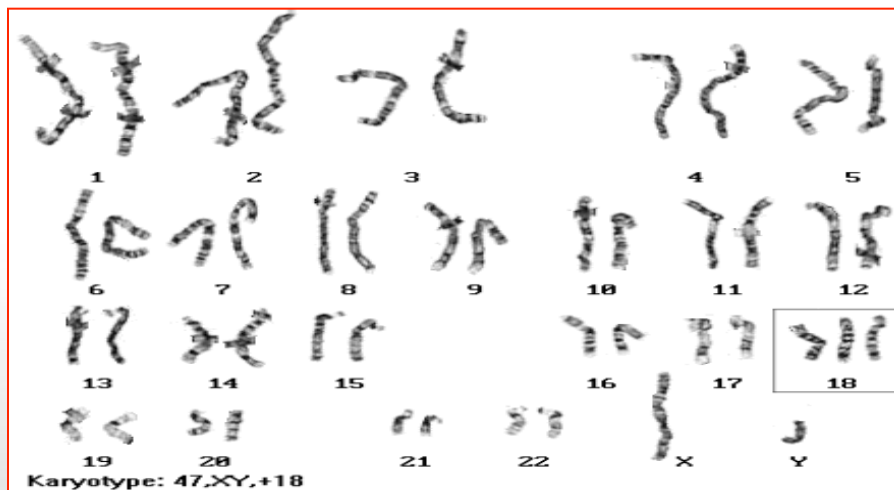
- The incidence of trisomy 21 rises sharply with increasing maternal age
- Most cases arise from non disjunction in the first meiotic division
- The father contributing the extra chromosome in 15% of cases (i.e. Down syndrome can also be the result of nondisjunction of the father's chromosome 21)
- A 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

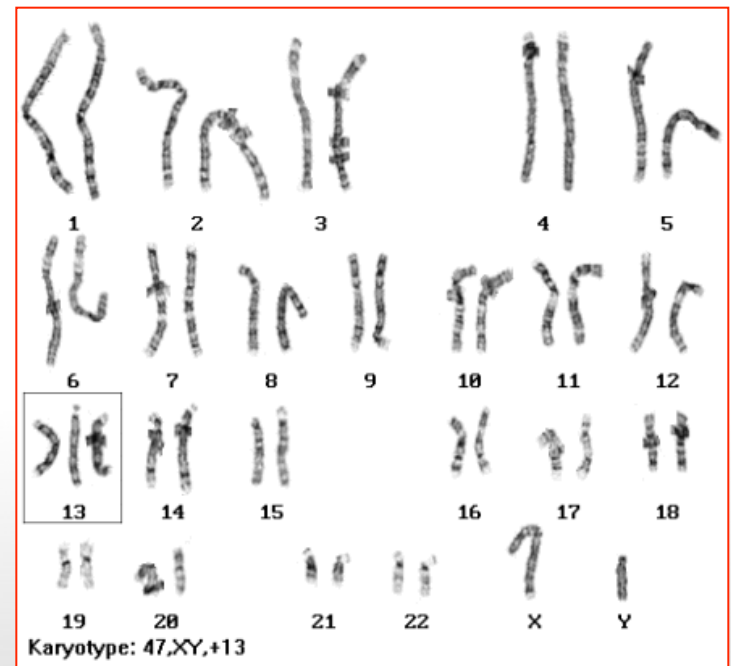
- It is the second most common autosomal trisomy, after Down syndrome, that carries to term
- It occurs in around one in 6,000 live births and around 80 percent of those affected are female
- Most babies die in the first year and many within the first month & has a very low rate of survival
- Common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

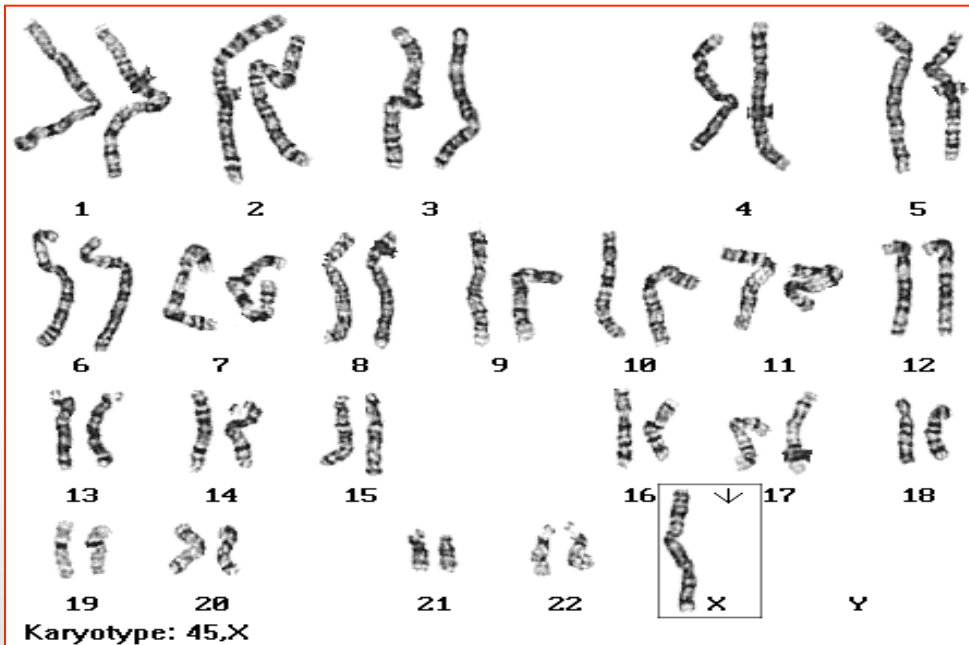




Numerical anomalies in Sex chromosomes

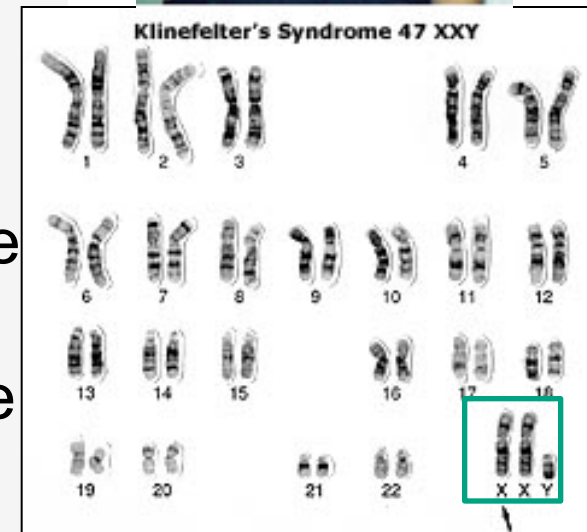
Monosomy X (Turner's syndrome, 45, XO)

- ❖ 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 Klinefelter syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.





Sex chromosome unbalance Of much less deleterious effect

47, XYY

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

XXX females

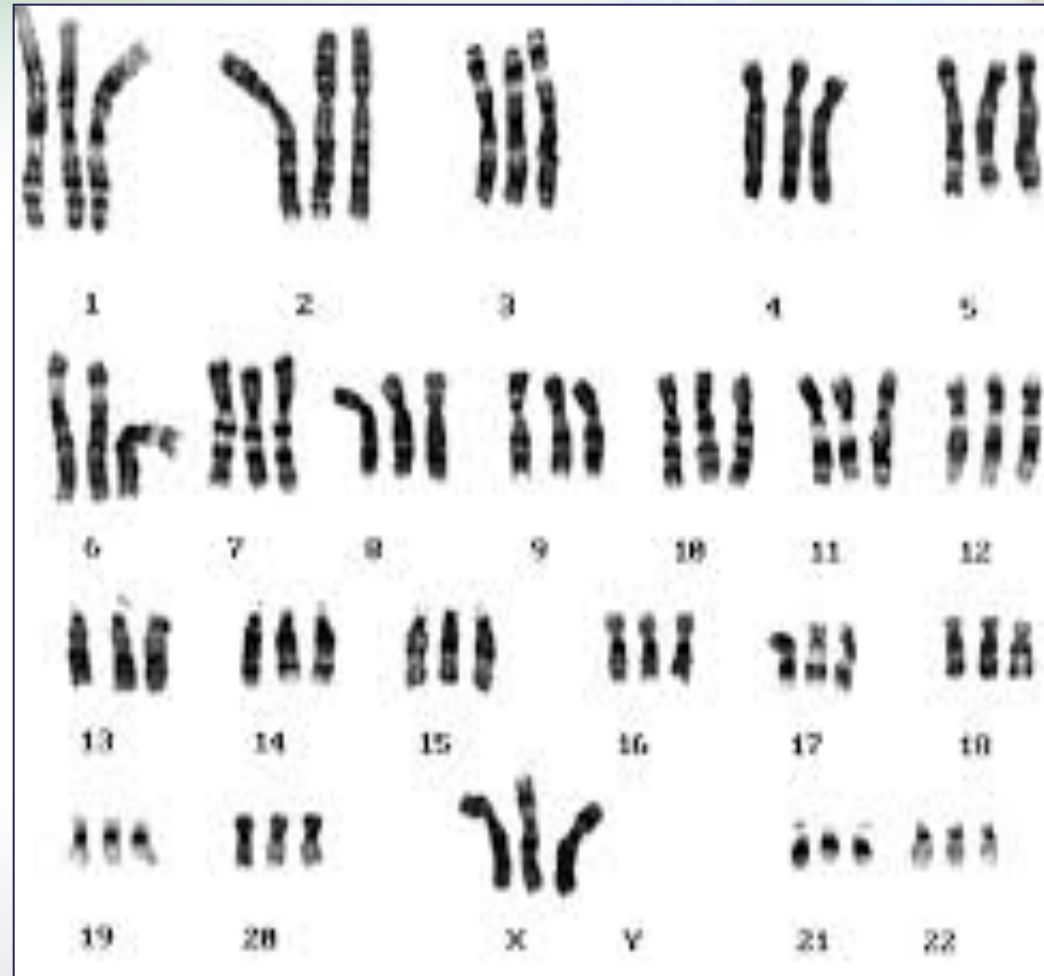
It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They do have a reduction in IQ comparable to that of Klinefelter's males



Numerical anomalies affecting the number of complete haploid set (n) of chromosomes

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.





Can an individual have A combination of cells:

- some cells with normal chromosomal numbers, &
- some cells with numerical chromosomal anomalies?



MOSAICISM

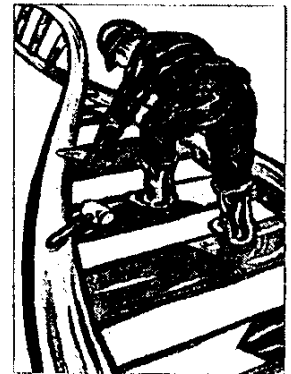
- ❖ A mosaic individual is made of 2 (or more) cell populations, coming from only 1 zygote
- ❖ Is denoted by a slash between the various clones observed (e.g. 46, XY / 47, XY, +21).
- ❖ Numerical mosaic anomaly is usually due to a mitotic non-disjunction
- ❖ A mosaic must not be confused with a chimeras.
- ❖ 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)



STRUCTURAL CHROMOSOMAL ANOMALIES

STRUCTURAL CHROMOSOMAL ANOMALIES

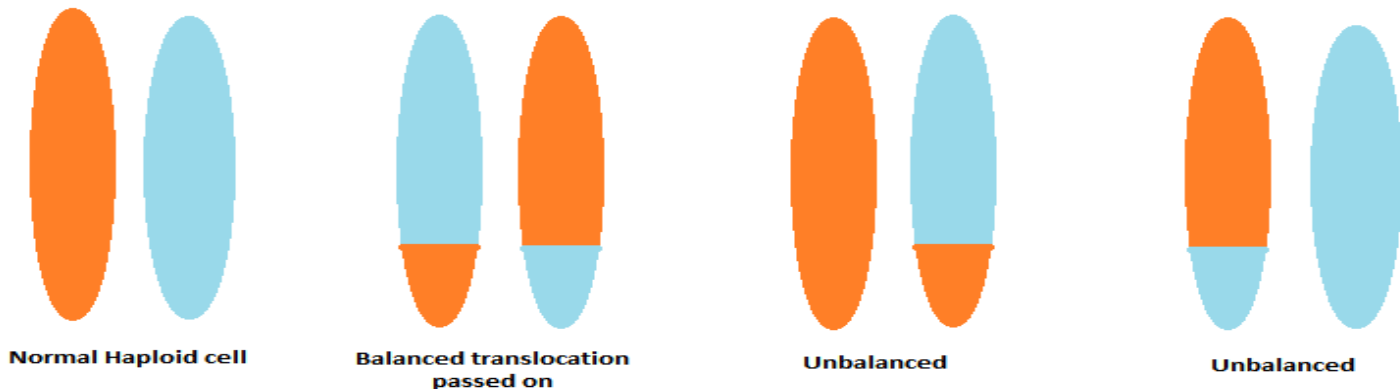
- **The most frequent Structural anomalies are:**
 - Translocations
 - Inversions
 - Deletions (terminal or interstitial)
 - Isochromosome (i)
 - Ring formation (Ring chromosome)



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.



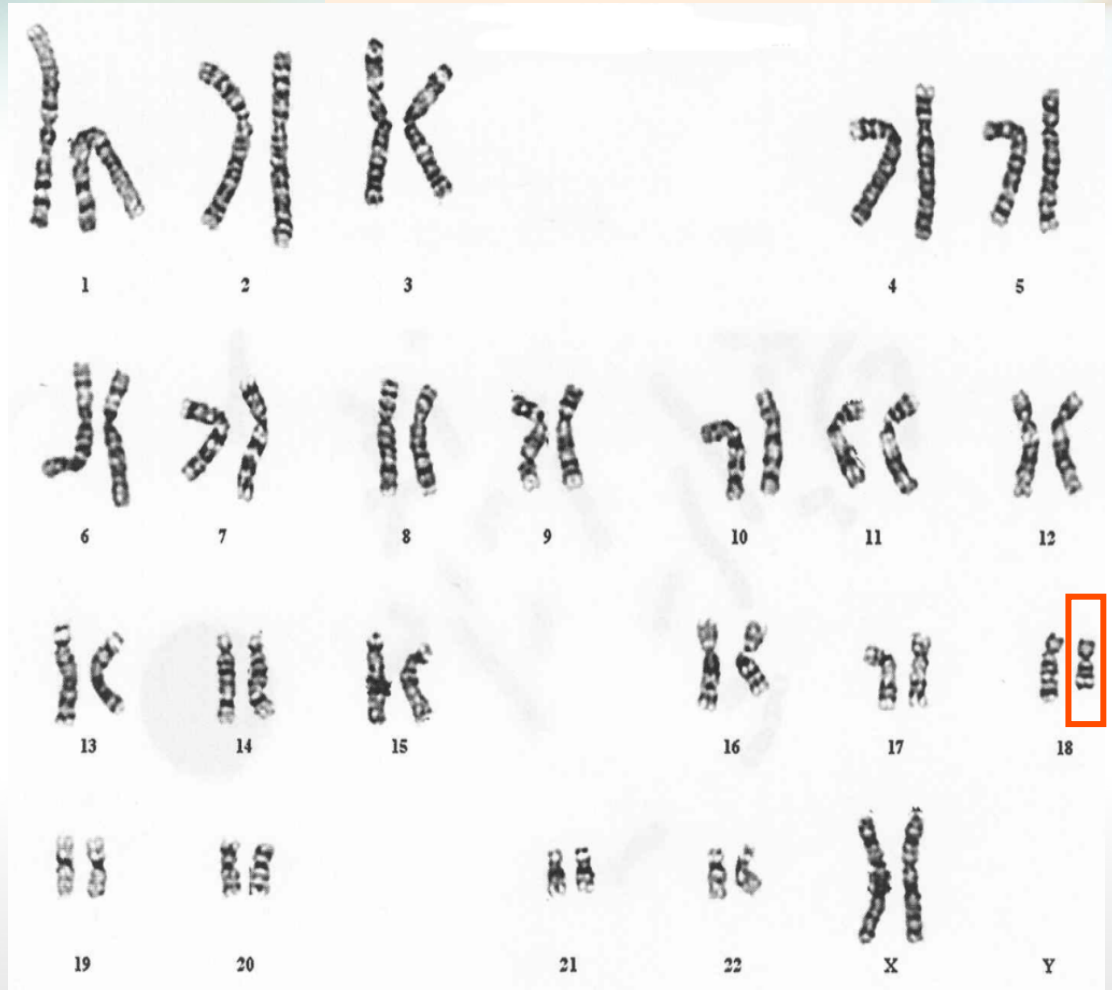
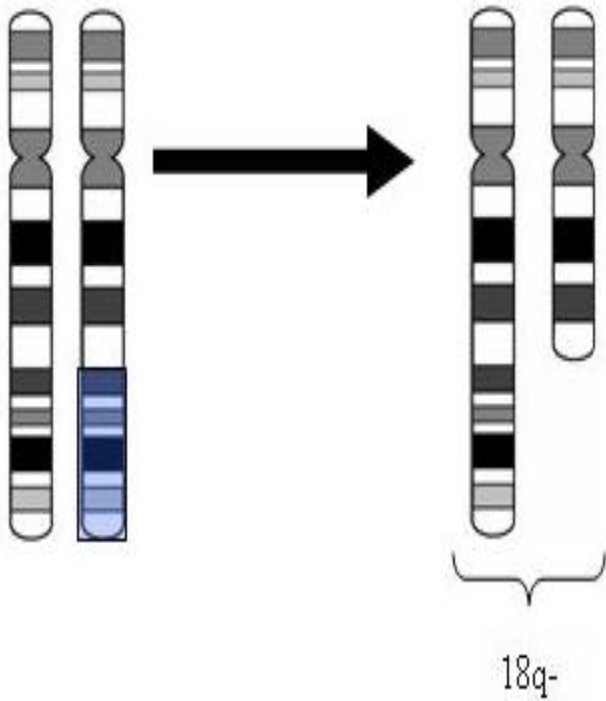


Deletion

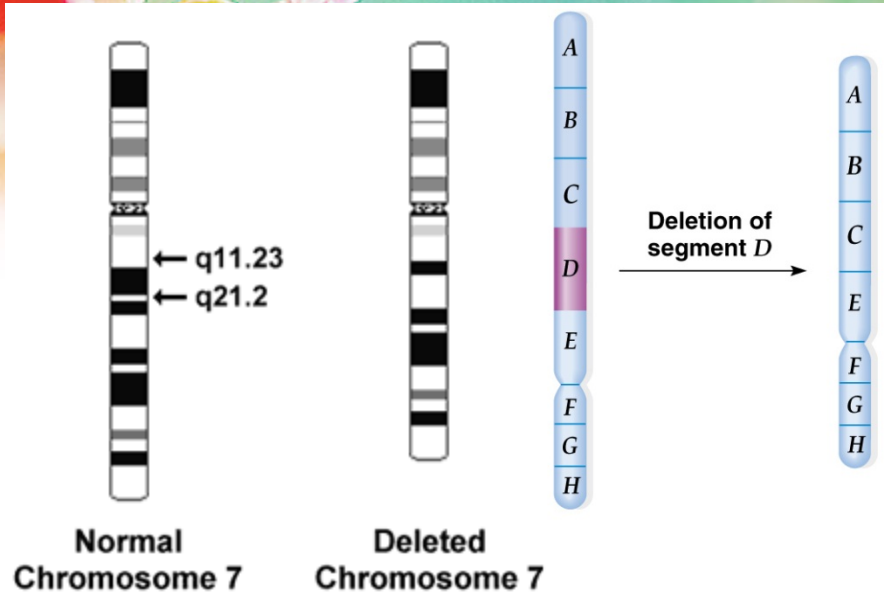
- ❖ Loss of a segment from a chromosome, either terminal or interstitial
- ❖ Invariably, but not always, results in the loss of important genetic material
- ❖ Deletion is therefore an unbalanced rearrangement.
- ❖ Recorded as **del**

Terminal Deletion

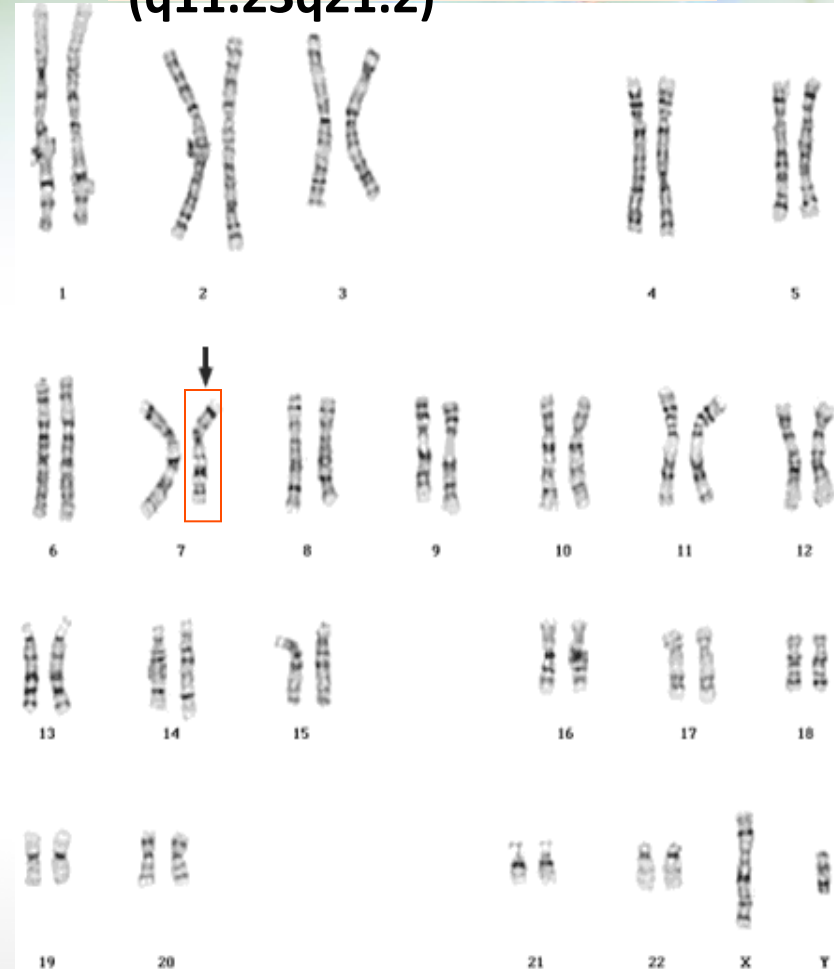
46,XX,del(18)(q21.3).



Interstitial deletion (7 Karyotype)



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

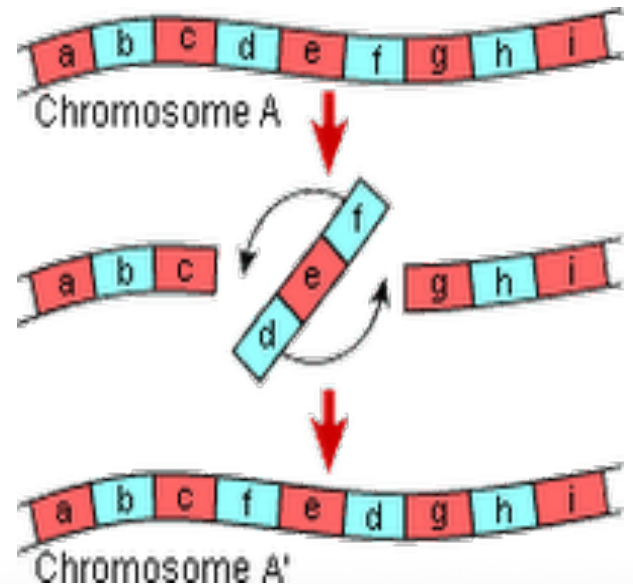


The key to the karyotype description is as follows:

- 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.

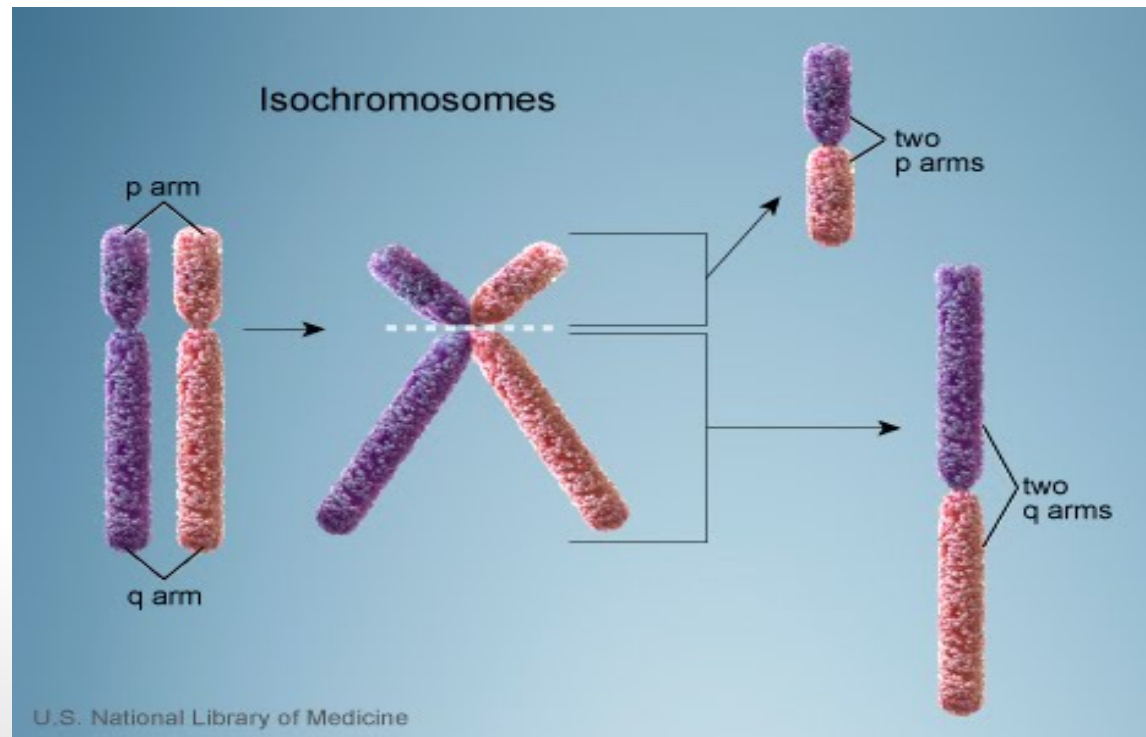
Inversion

- 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

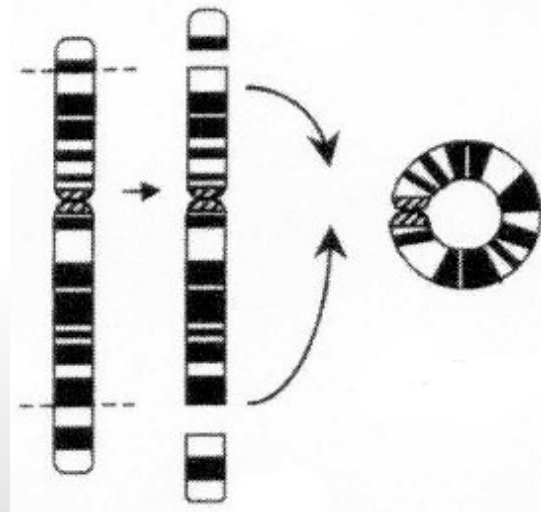
- The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally



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



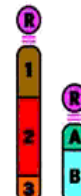
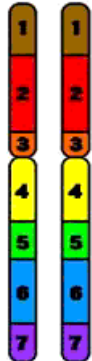
STRUCTURAL CHROMOSOMAL ANOMALIES

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 1st or 2nd 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.**



THANK YOU 😊