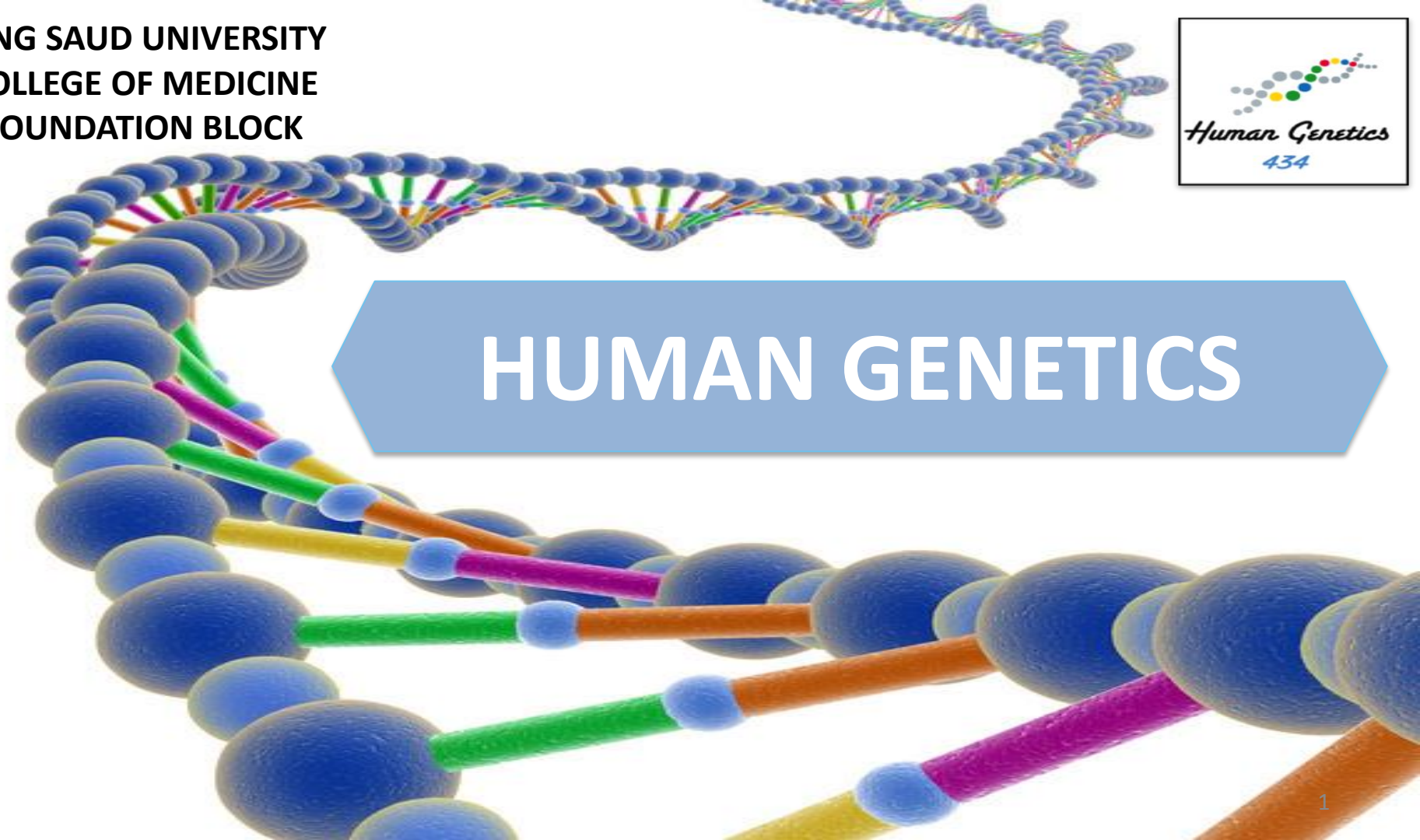
KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
FOUNDATION BLOCK

Human Genetics
434



# HUMAN GENETICS

# OBJECTIVES :

- 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

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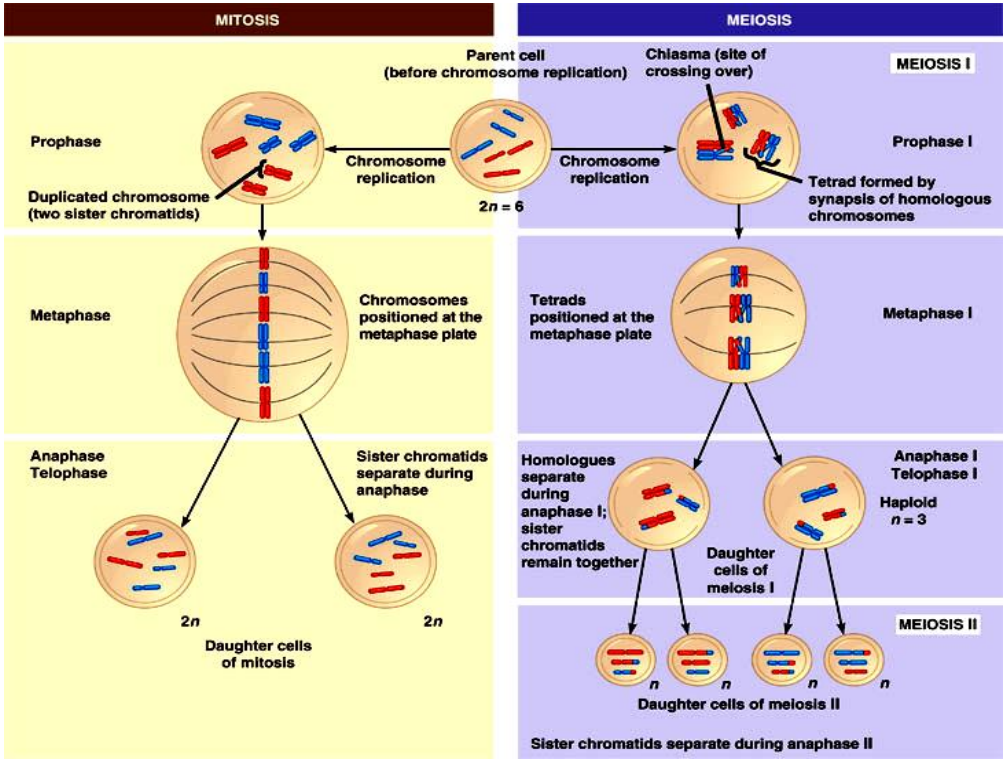
# CHROMOSOME ANOMALIES




**The phases of meiosis and mitosis**

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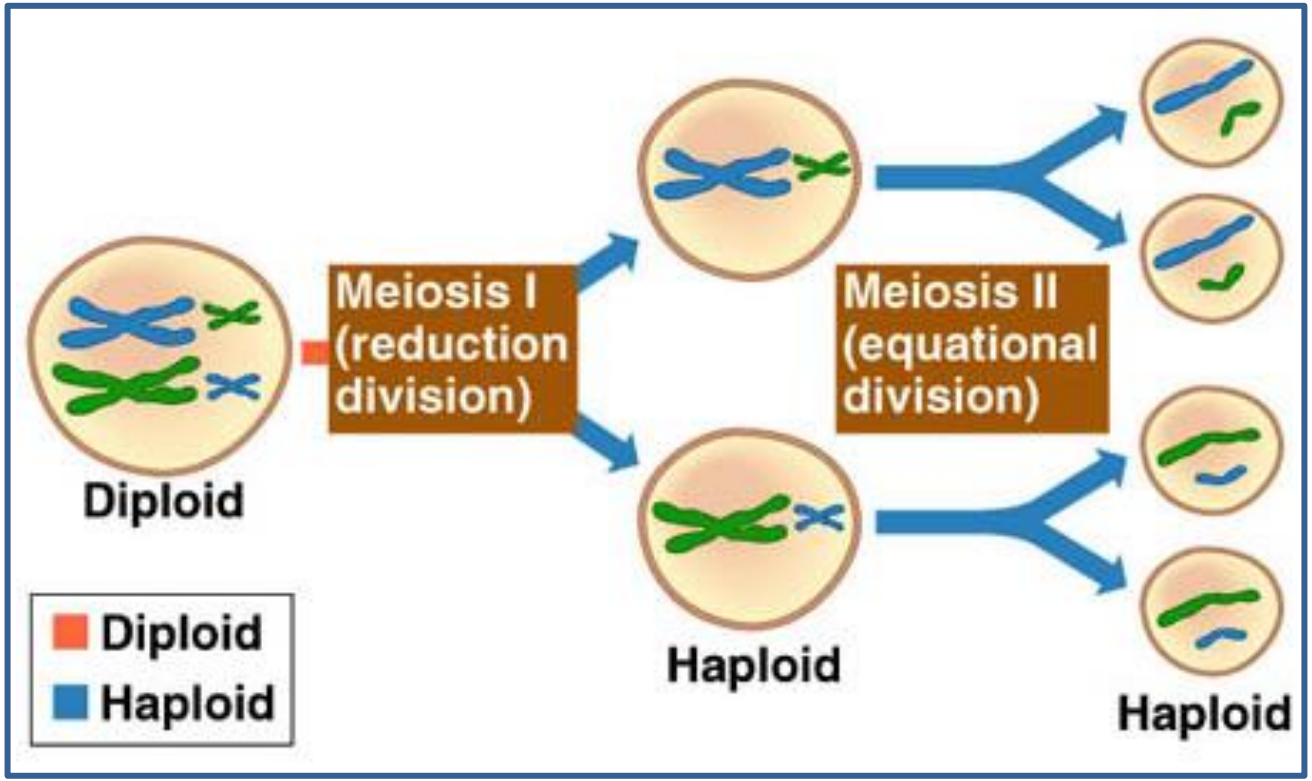


**The phases of meiosis I& II**

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# 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)

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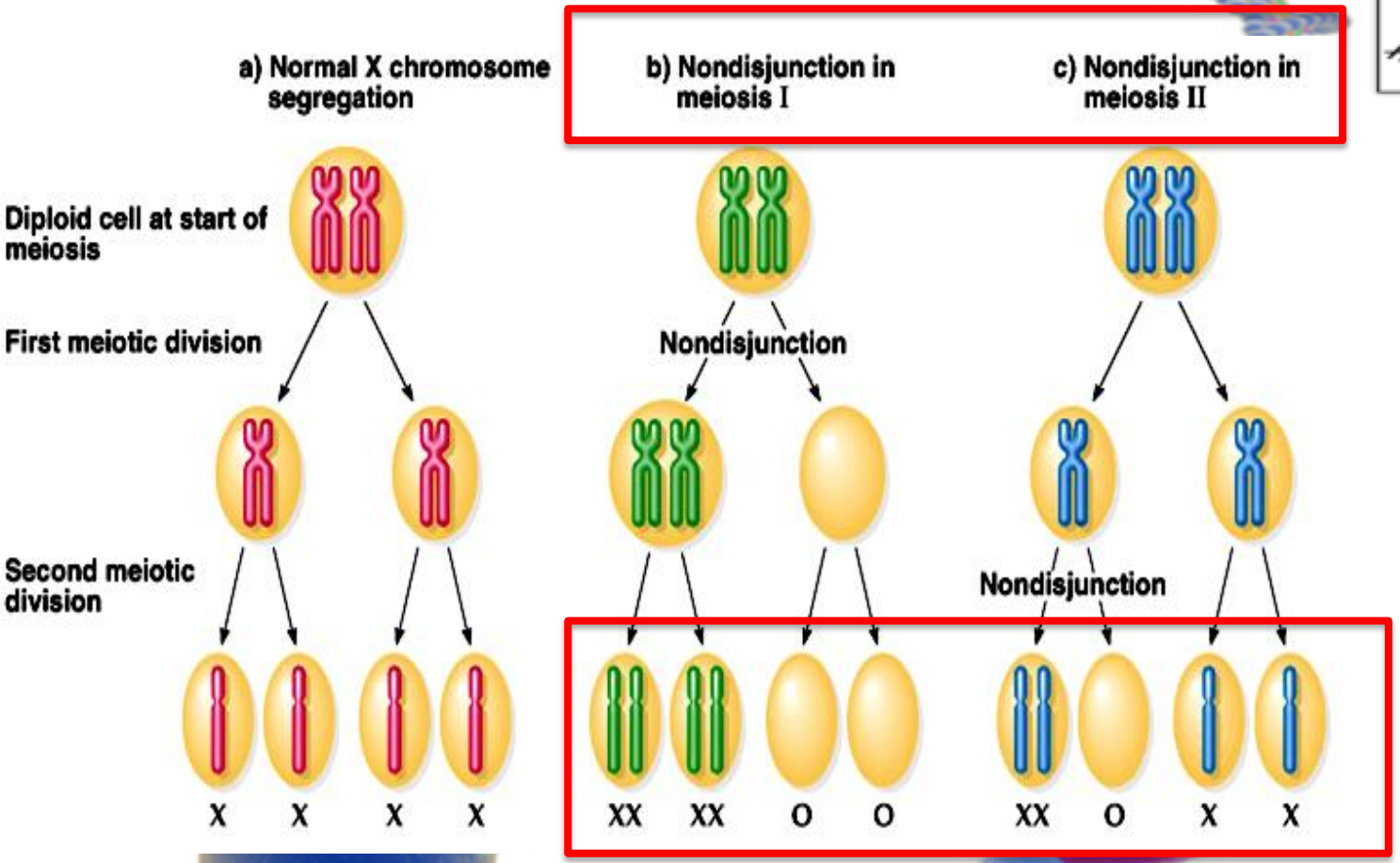
a) Normal X chromosome segregation
b) Nondisjunction in meiosis I
c) Nondisjunction in meiosis II
Diploid cell at start of meiosis
First meiotic division
Second meiotic division
Nondisjunction
Nondisjunction
X X X X
XX XX O O
XX O X X

# 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(1)

(1)
1)Gamete with an extra autosome

2)**Nullosomic** gamete (missing one chr.)

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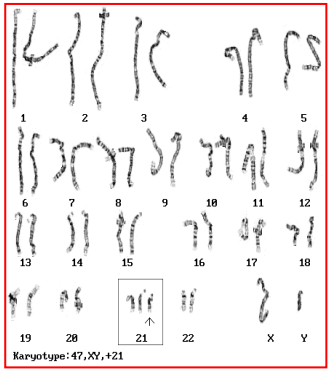
# NUMERICAL CHROMOSOME ANOMALIES IN AUTOSOME :

## 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.
- 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.**

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# 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**

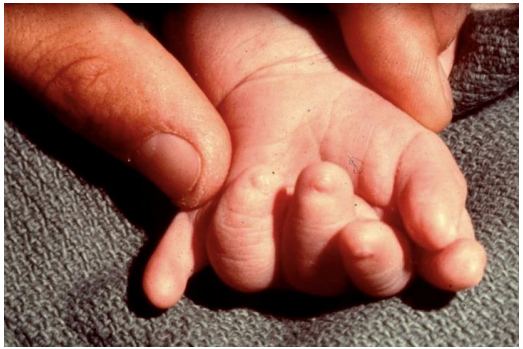
❖A mosaic must not be confused with a chimeras.

❖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

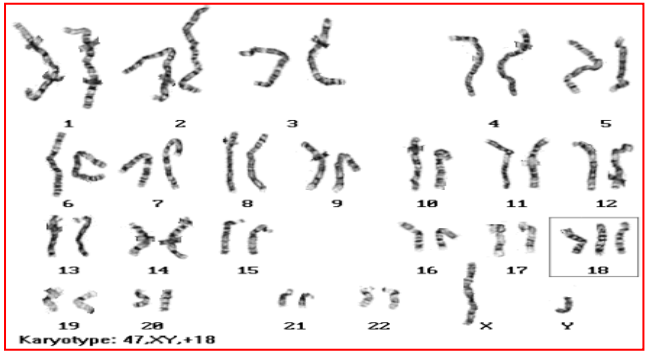
Can an individual have A combination of cells?
some cells with normal chromosomal numbers, & -some cells with numerical chromosomal anomalies? YES

# Edward's syndrome, TRISOMY 18

## Karyotype: 47, XY, +18



- It is the **second** most common autosomal trisomy, after Down syndrome.
- 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.

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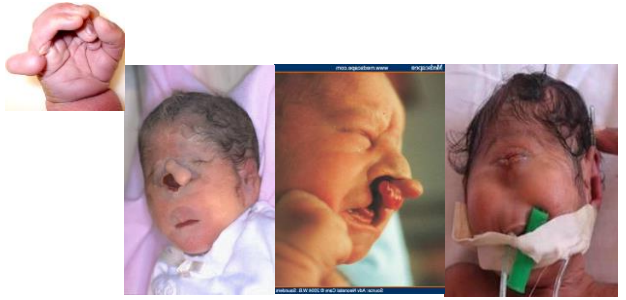
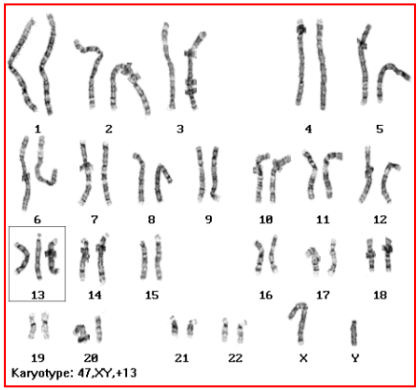
# Patau Syndrome, TRISOMY 13

## Karyotype: 47, XY, +13






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

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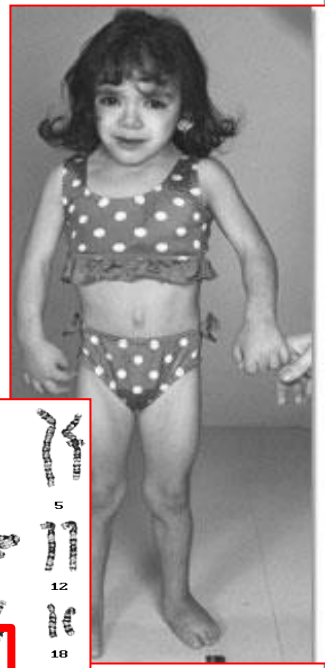
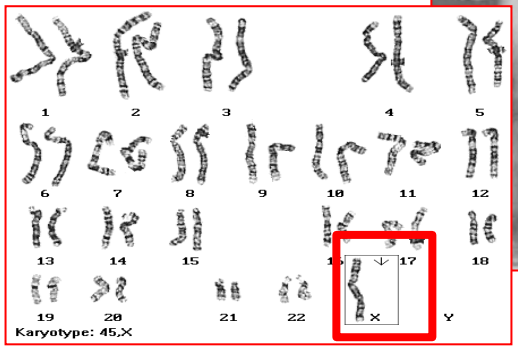
# NUMERICAL CHROMOSOME ANOMALIES IN SEX CHROMOSOMES :

## Turner's syndrome(Monosomy X)

**Karyotype: 45, X0**

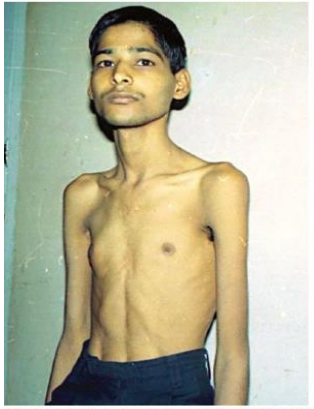


- Occurring in 1 in 5000 phenotypic females.
- The **only** viable **monosomy** in humans.
- Characteristics: Webbed neck**, Individuals are genetically female**, not mature sexually, **Sterile**, Short stature, Broad chest, Low hairline, Streak ovaries, **Normal intelligence**, **Normal life span.**



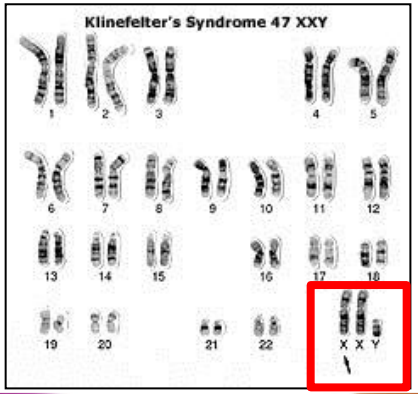
# Klinefelter Syndrome: MALES

## Karyotype: 47, XXY



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

- **Male sex organs**; unusually small testes which fail to produce normal levels of testosterone, breast enlargement.
- No spermatogenesis → **sterile**
- Patients are taller and thinner than average and may have a slight reduction in IQ but generally they have **normal intelligence**
- 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.

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# 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

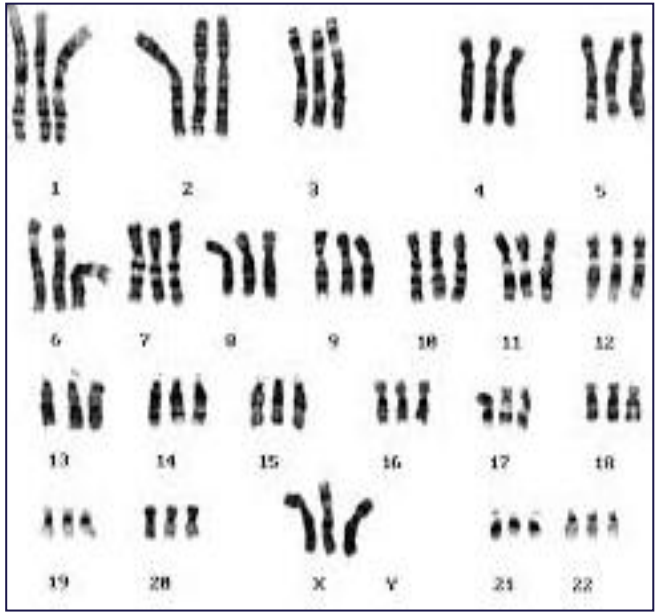
- It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They do have a reduction in IQ comparable to that of Kleinfelter's males

# 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.**



# STRUCTURAL CHROMOSOMAL ANOMALIES

✧**The most frequent Structural anomalies are:**

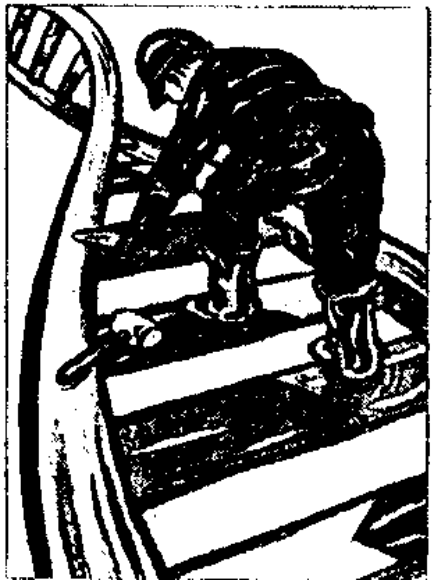
Translocations

Inversions

Deletions

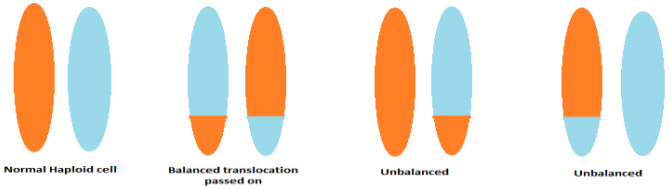
Isochromosome ( i )

Ring formation ( Ring chromosome)



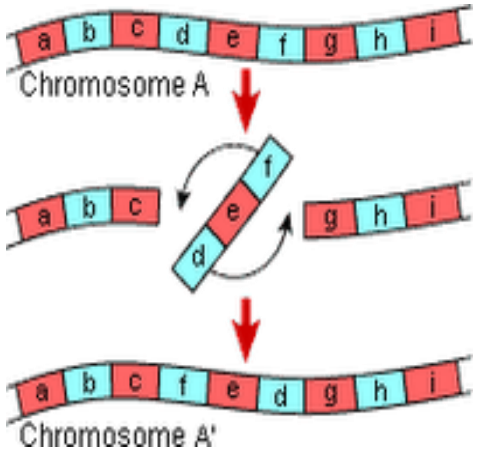
# Reciprocal translocation:

- 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, called a **Balanced rearrangement.**




# Inversion

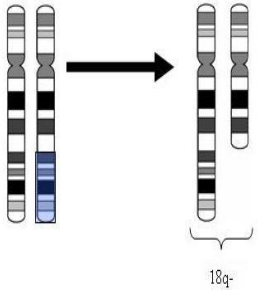
- Inversion occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively inverts it.

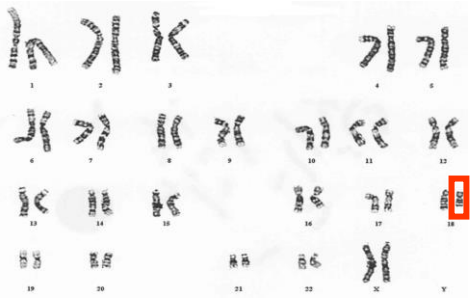


# Deletion

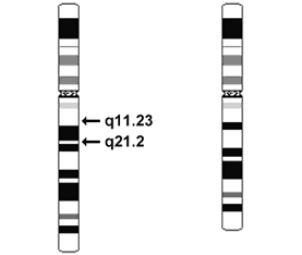
- Loss of a segment from a chromosome, either **terminal or interstitial.**
- Invariably, but not always, results in the loss of important genetic material
- Deletion is therefore **an unbalanced rearrangement.**

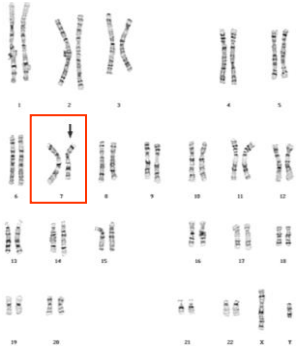
## Terminal Deletion



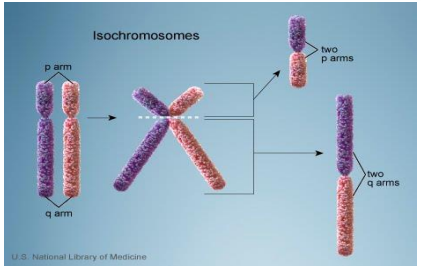
## Interstitial deletion



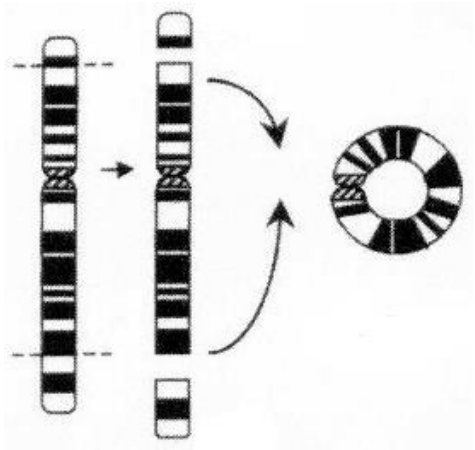
# Isochromosome

- 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 fragment.**



# 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.

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Done by :

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