# CHROMOSOME ANOMALIES

## HUMAN GENETICS

Red: important.
Pink: F-slides
Blue: M-slides
Green: doctor's Notes
Gray: extra

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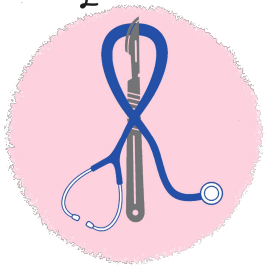


HUMAN GENETICS 441

MED441
KING SAUD UNIVERSITY

# Objectives

01 Describe and explain the events in mitosis & meiosis.

02 Define non-disjunction and describe its consequences on meiosis.

03 Classify chromosomal abnormalities: Numerical & structural.

04 Understand the common numerical autosomal disorders: trisomies 21, 13, 18.

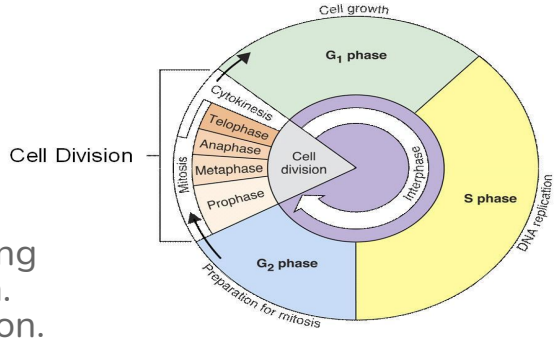
05 Understand the common numerical sex chromosome disorders: Turner`s & Klinefelter`s syndromes

06 Recognize the main structural anomalies in chromosomes.

# Cell Cycle

## 1.Interphase.

A cell cycle is a series of events that takes place in a cell as it grows and divides. A cell spends most of its time in what is called interphase, and during this time it grows, replicates its chromosomes, and prepares for cell division. The cell then leaves interphase, undergoes mitosis, and completes its division.




**G1**

One diploid

Lasts only 10-12 hours.

**S phase**

Duplications of each chromosome's DNA
Result: 2 sister chromatids
Lasts 6-8 hours

**G2**

Chromosome begins to condense and become visible.
Lasts 2-4 hours

**Ready for mitosis**

Interphase prepared 2 daughter cells=2 equal genetic information, the cell now starts dividing by mitosis.
Lasts less than 6 hours if not identical,it causes disorders.

# Cell cycle continued

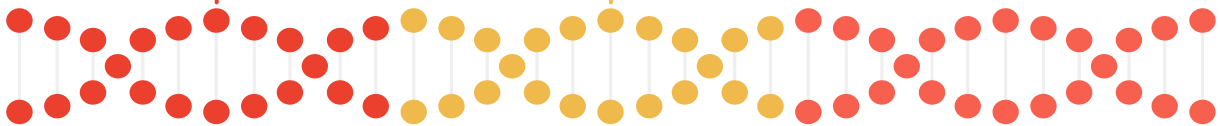
USEFUL VIDEO
HERE

## 2.Events of mitosis

**1.Prophase:**
Formation of mitotic spindles & a pair of centrosomes.

**2.Prometaphase:**
-Nuclear membrane dissolves
-Chromosomes disperse and attach to kinetochores to mitotic spindle microtubules.

**3.Metaphase:**
Chromosomes condensed and lined up at the equatorial plane.



**4.Anaphase:**
-Chromosomes separate at centromeres
-sister chromatids of each chromosome becomes an independent daughter chromosome.
Most important stage

**5.Telophase:**
Chromosomes decondense from their highly contacted state.
-Nuclear membranes reform around each of the 2 daughter nuclei.
-resume their interphase

# Meiosis

USEFUL VIDEO

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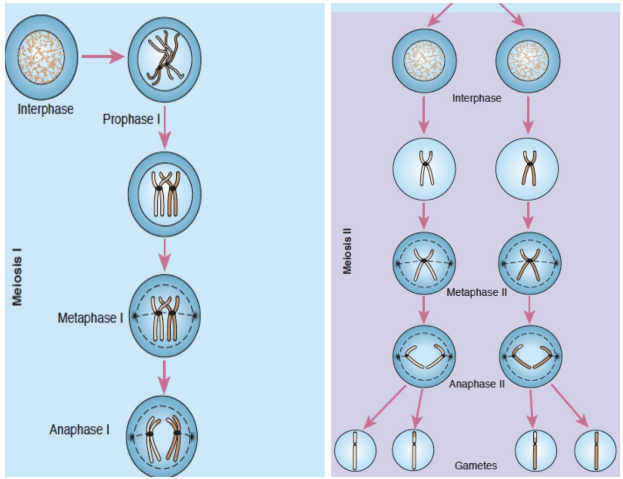
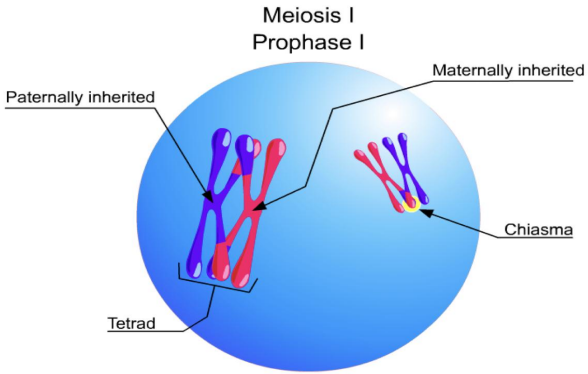
## Events of meiosis I & II



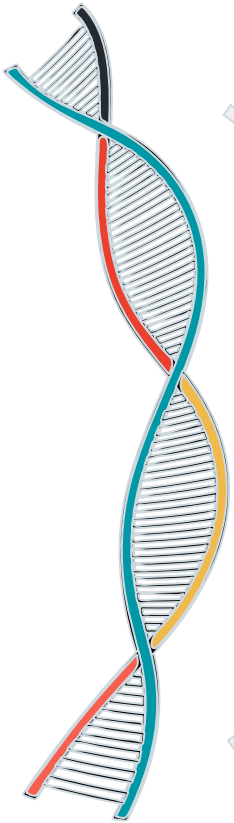




The difference between meiosis one and two is that in meiosis 2 we will have one pair of chromosomes in each cell. Normal gametes are 4 haploid Cells.
Meiosis I is a reduction division where only one member of a homologous pair enters each daughter cell which becomes haploid.
Meiosis II only splits up sister chromatids.

In meiosis and prophase 1 : the genetic material is one paternal inherited and one maternal inherited.

# Nondisjunction in meiosis

The failure of chromosomes to disjoin normally during meiosis phase 1 or phase 2. (Do not separate)



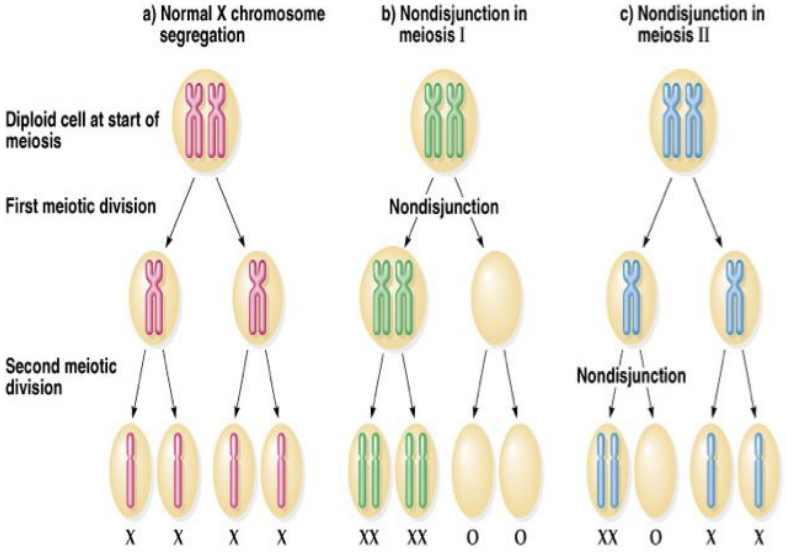
Two chromosome homologs migrate to the same daughter cell instead of disjoining normally and migrating to different daughter cells.

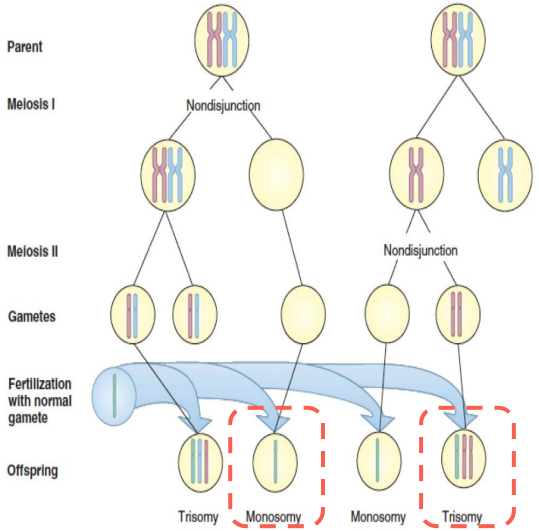
Usually happen during Anaphase 1 or Anaphase 2

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

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.(2 chromosomes)
– Nullisomic gamete (missing one chromosome)
*null means 0

When the non-disjuncted gamete is fertilized with a normal gamete, the offspring is an aneuploidy:

-monosomic(one chromosome)
-trisomic(three chromosomes)

# Types of Chromosomal Anomalies

## Numerical

Affect the number of complete haploid set (n) of chromosomes.

Most cases when fertilization happens at old maternal age

### In sex chromosomes

1.turner's syndrome (Monosomy 45,XO)
2.Klinefelter syndrome(47,XXY)

### In autosomes

1.Down syndrome (trisomy 21)
2.Edward”s syndrome (trisomy 17)
3.Patau syndrome (trisomy 13)

## Structural

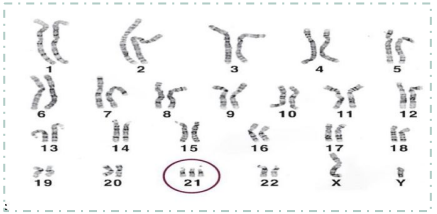
Affect the structure and organization of genomic content of the chromosome

1.Reciprocal translocation
2.Robertsonian translocation
3.Interstitial deletion
4.Inversion 5.Isochromosome
6.Ring formation

# Numerical Anomalies in Autosomes

## Down syndrome (Trisomy 21)

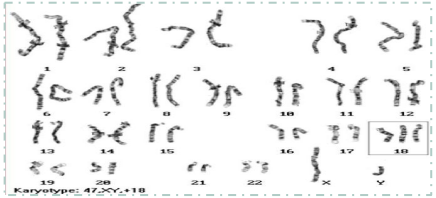
- Most cases arise from nondisjunction in the first meiotic division (of ovum cycle) - The incidence of trisomy 21 rises sharply with increasing maternal age.
- the father contributing the extra chromosome in 15% of cases - the symptoms include : characteristic facial dysmorphologies an IQ of less than 50.



Karyotype 47,XY,+21

## Edward's syndrome (Trisomy 18)

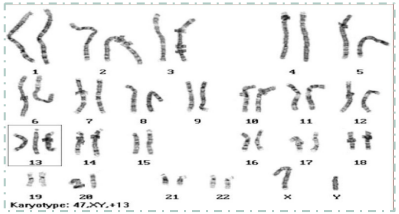
- the second most common autosomal trisomy, after Down syndrome.
- It occurs in around one in 6,000 live births.
- Most babies die in the first year and many within the first month & have a very low survival rate. (because the gene content is high)
- Common anomalies are heart abnormalities, kidney malformations, and other Internal organ disorders.



Karyotype 47,XY,+18

## Patau syndrome (Trisomy 13)

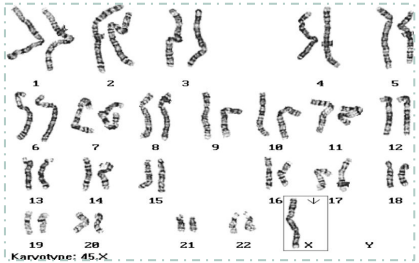
- 50 % of these babies die within the the first month and very few survive beyond the first year. - there are multiple dysmorphic features in most cases, as in Patau syndrome involve maternal non-disjunction. (Gene content is higher than Edward's)



Karyotype 47,XY, +13

# Numerical Anomalies in Sex Chromosomes

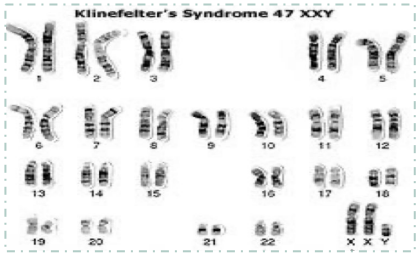
## Turner's syndrome (Females)




Karyotype 45,XO

- Occurring in 1 in 4000 phenotypic females.
- As a result of paternal meiotic non-disjunction.
- 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

- 1/600 males,due to non-disjunction of X chromosomes during meiosis I in females.
- Characteristics:

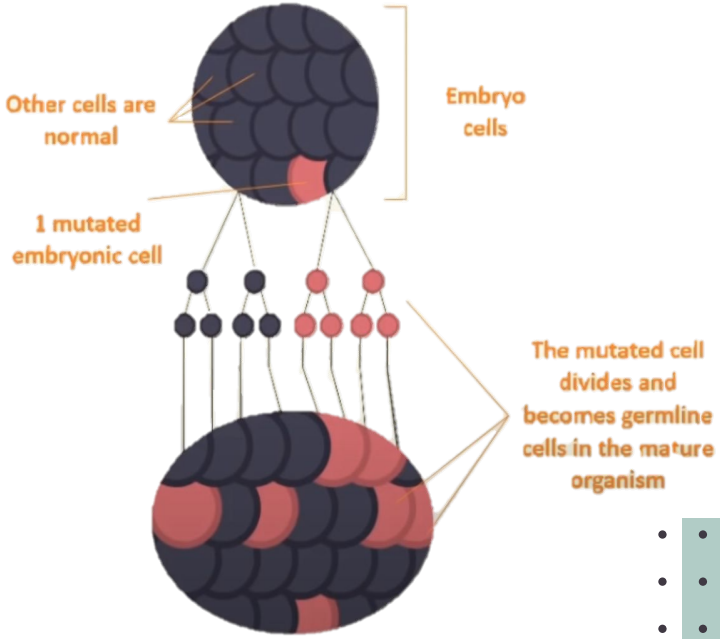
1 - Male sex organs : unusually small testes which fail to produce normal levels of testosterone -> breast enlargement (gynaecomastia) and other feminine body characteristics.

2 - 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

- It is the presence of more than one genetically distinct cell line in the body. (may be inactive)
- A mosaic individual is made of 2 (or more) cell populations, coming from only 1 zygote.
- It 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 derived from more than one zygote (e.g. 2 sperms fertilize 2 ova then the 2 zygotes fuse to form 1 embryo).




**EXTRA NOTE**

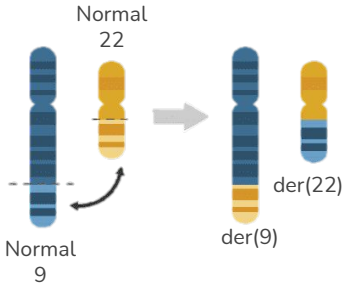
1 zygote=mosaicism
>1 zygote=chimerism

# STRUCTURAL CHROMOSOMAL ANOMALIES

## 1-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).



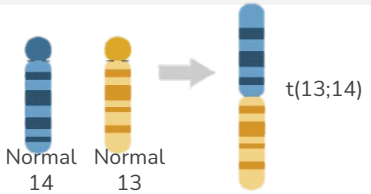

## 2-Robertsonian translocation

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 (no p arm) (13, 14, 15, 21, and 22).

Carriers have only 45 chromosomes in each cell, they are phenotypically unaffected.

the result of this translocation is not showing any phenotypic facial differences.



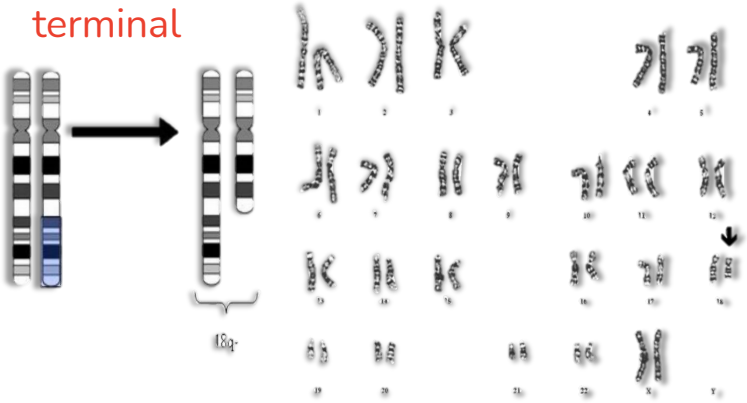
# 3-Deletion

- 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. (common in cancer)
- Indicated in nomenclature del.

**karyotype description is as follows**:

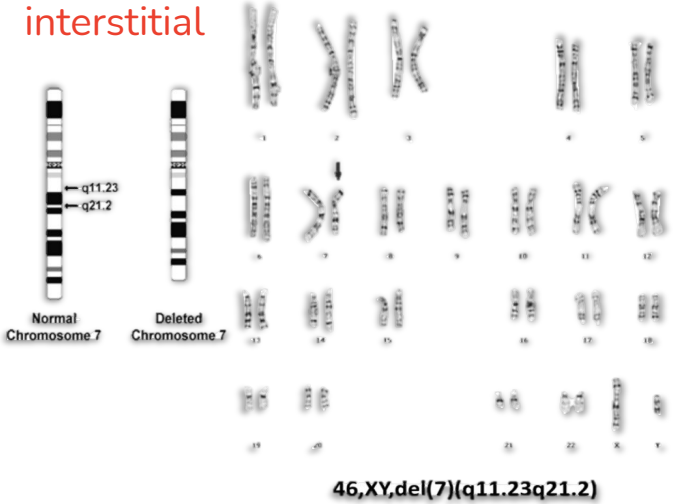
- 46: the total number of chromosomes.
- XY: the sex chromosomes (male).
- del(7): deletion in chromosome 7.
- (q11.23q21.2): breakpoints of the deleted segment.

terminal




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

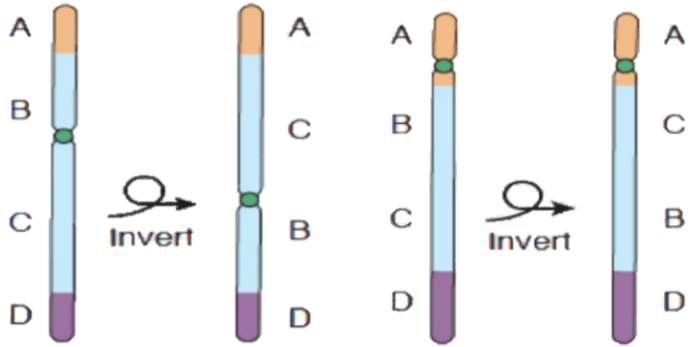
interstitial




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

# 4-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. (but it is also seen in cancer)

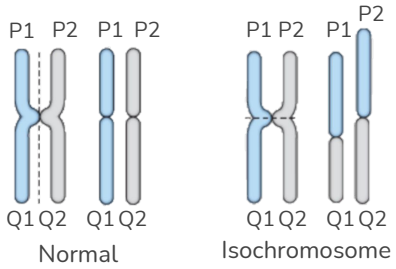



Pericentric Paracentric

Doctor's Note: the difference between peri/para is that
Peri: includes centromere in inverted part.
Para: doesn't include the centromere.

# 5-Isochromosome

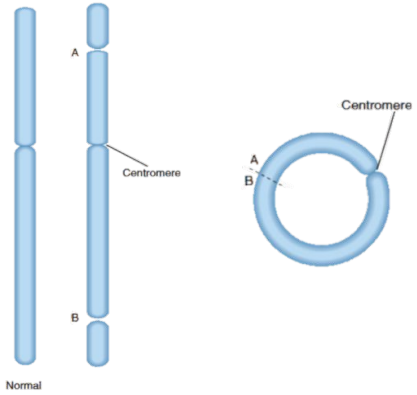
The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally.




Doctor's Note: the chromosome will have 2(P) arms and 2(Q) arms.

# 6-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 1st or 2nd 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.

# MCQs

| | | | |
|---|---|---|---|
| Q1:During mitosis, the nuclear membrane forms during : | | | |
| A. Metaphase | B. Anaphase | C.Telophase | D. Prophase |
| Q2: Nondisjunction in first meiotic division produces: | | | |
| A. 2 normal gametes | B. 4 normal gametes | C. 2 unbalanced gametes | D.4 unbalanced gametes |
| Q3:All of the following are chromosomal anomalies in autosomes EXCEPT: | | | |
| A.Down syndrome | B.Edward syndrome | C.Klinefelter's syndrome | D.Patau syndrome |
| Q4:What is the karyotype of a female with Turner's syndrome | | | |
| A.(45,XO) | B.(47,XXY) | C.(47,XY,+18) | D.(47,XY,+21) |
| Q5: When a segment of chromosome breaks, and rejoins within the chromosome effectively. | | | |
| A. Isochromosome | B. Deletion | C. Inversion | D. Translocation |

Answer Key: 1C - 2D - 3C - 4A- 5C

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Editing file

“Never stop, one day you will be Someone’s **hope**, someone’s **hero**.”