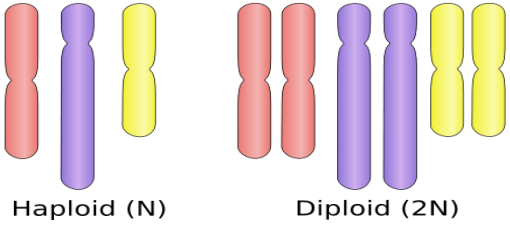
# Human Genetics

CHROMOSOME ANOMALIES

# Lecture Objectives :

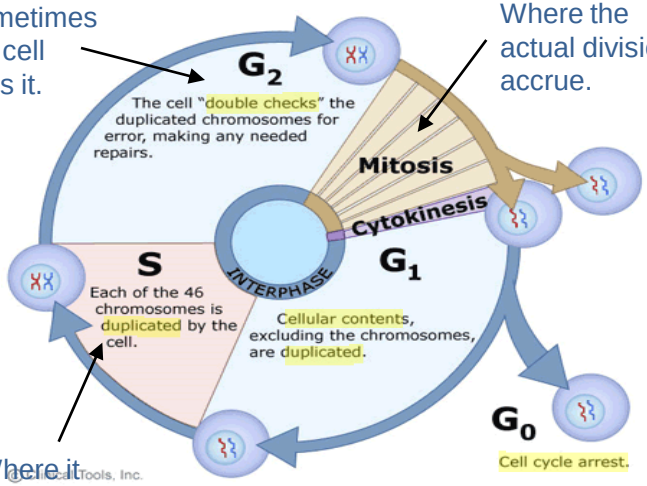
**By the end of this lecture, the students should be able to:**

- 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



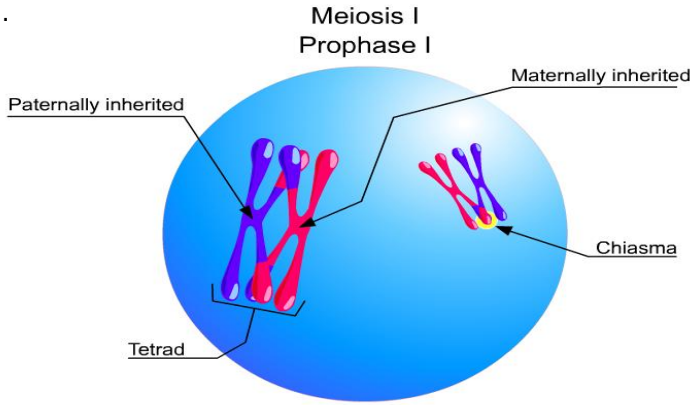

Sometimes the cell miss it.

Where the actual division accrue.

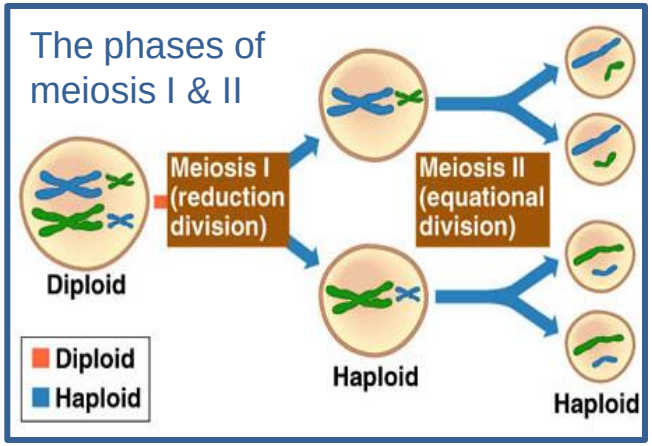


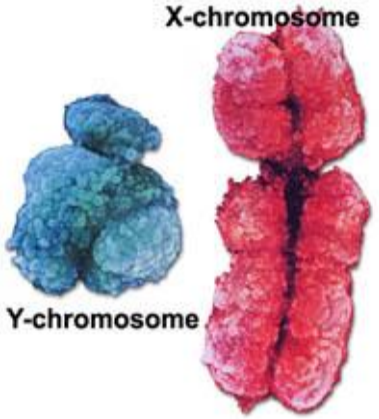

Where it duplicate the chromosome

.




A CHIASMATA is a point where two homologous non-sister chromaids exchange genetic material during chromosomal crossover during meiosis

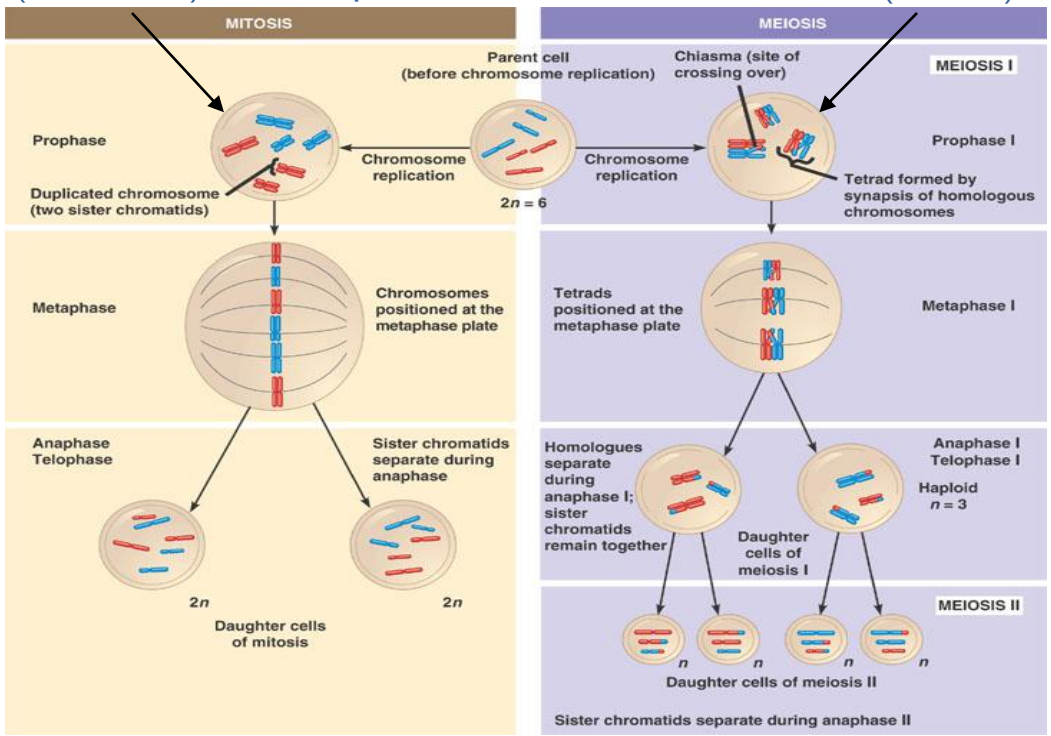



(Somatic cells).

The phases of meiosis & mitosis

(Sex cells).




(Thetse pictures are for your general understanding)

# CHROMOSOME ANOMALIES

## Structural

- Translocations
- Inversions
- Deletions
  (terminal or interstitial)
- Isochromosome ( i )
- Ring formation
  (Ring chromosome)

## Numerical

### Mosaicism & Chimerism

### Sex chromosome

#### Monosomy

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

#### Trisomy

- Klinefelter Syndrome: 47,XXY males
- 47, XYY
- XXX females

### Polyploidy

- Triploidies are the most frequent
  3N = 69
- Tetraploidy
  4N = 92

### autosomes

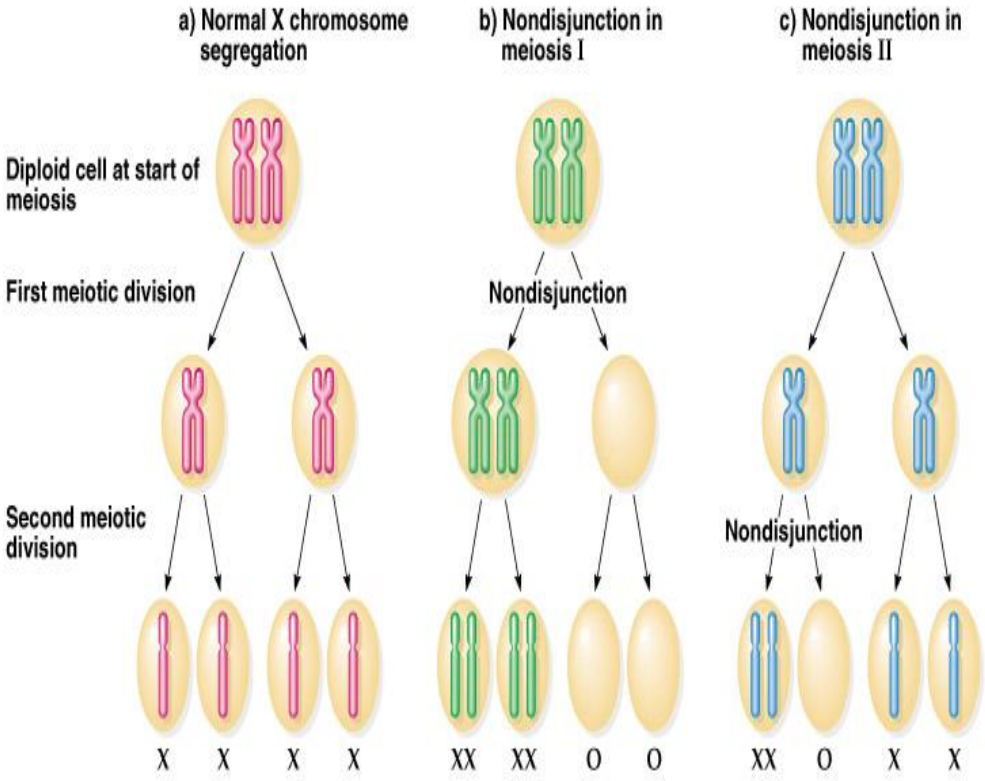
#### Trisomy

- Patau Syndrome
  47, XY, +13
- Edward's syndrome
  47, XY, +18
- Down syndrome
  47, XY, +21
  - non disjunction in the 1st meiotic division
  - nondisjunction of the father's chromosome 21.
  - non disjunction event in an early zygotic division.

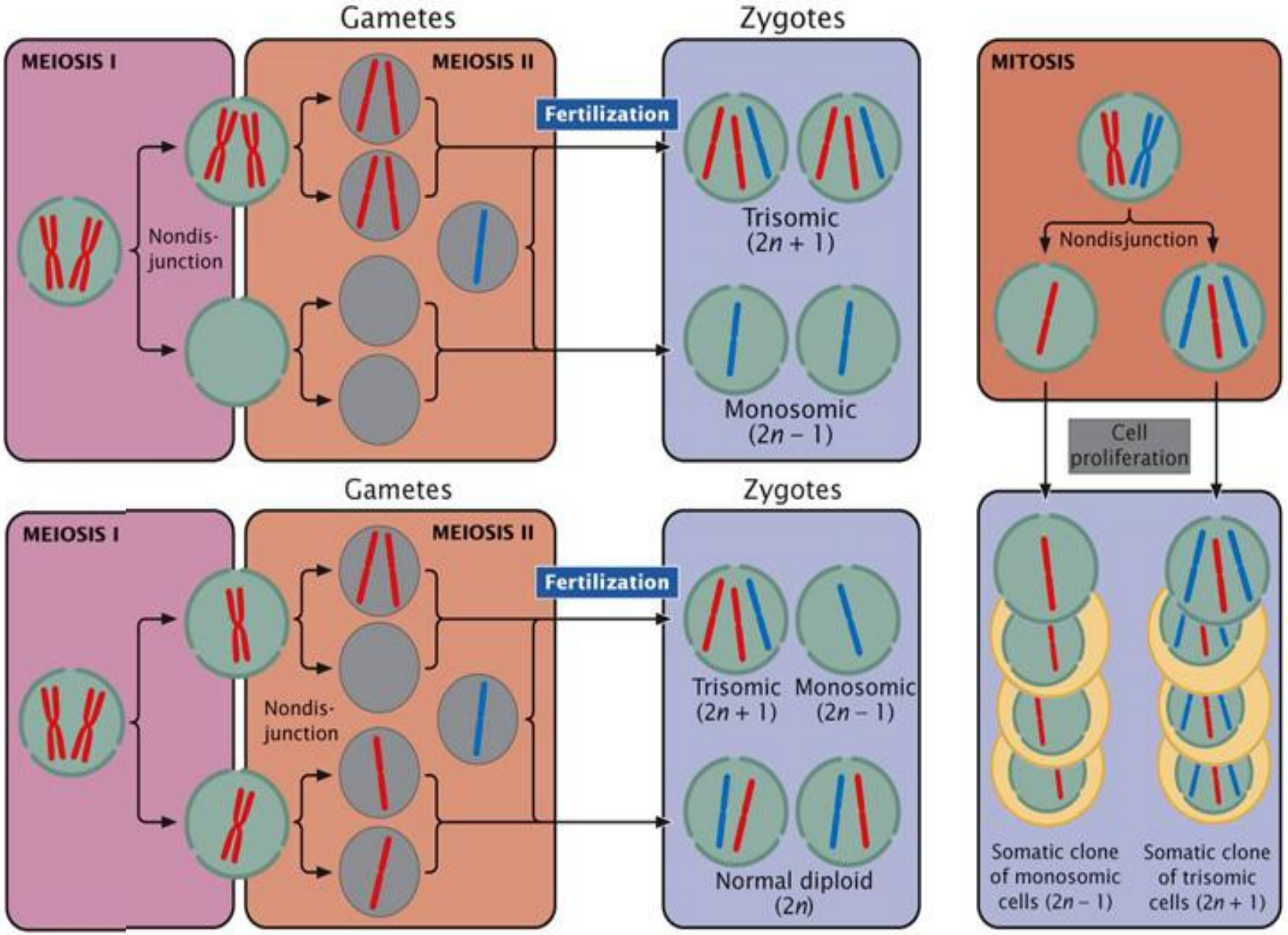
# Non-disjunction

## In meiotic/meiosis:

- **Nondisjunction** ("not coming apart") **:** the failure of chromosome pairs to separate properly during meiosis 1 or 2.
- As a result, one daughter cell has two chromosomes or two chromatids, and the other has none.
- The result **:** cell with imbalance chromosomes (Aneuploidy)
- can affect each pair of chromosomes
- not a rare event
- in first division → produces 4 unbalanced gametes.
- in second division → produces 2 normal gametes & 2 unbalanced gametes:
- Gamete with an extra autosome
- Nullosomic gamete (missing one chromosome)




**Gamete:** a mature haploid male/female germ cell which is able to form a zygote.
**Autosome:** a chromosome that is not an allosome (i.e., not a sex chromosome).


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 Anomalies in autosomes

## Edward's Syndrome

Karyotype: 47, XY, +18

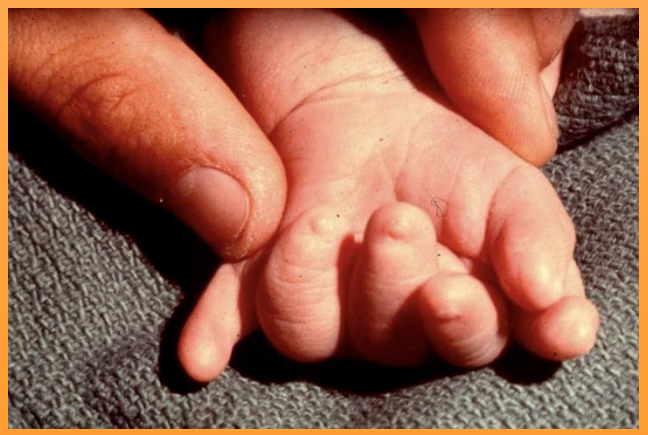
(Trisomy)

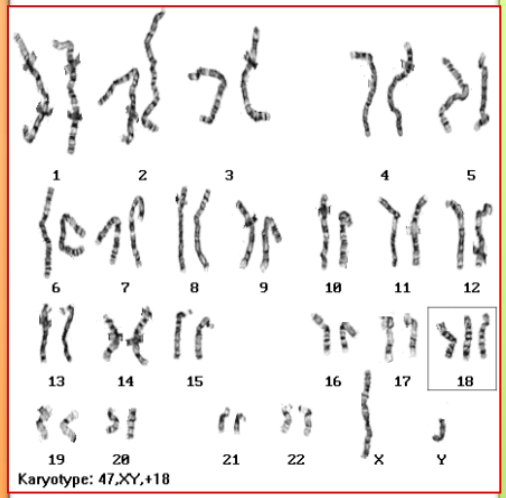
-It is the second most common autosomal trisomy, after Down syndrome, that carries to term.

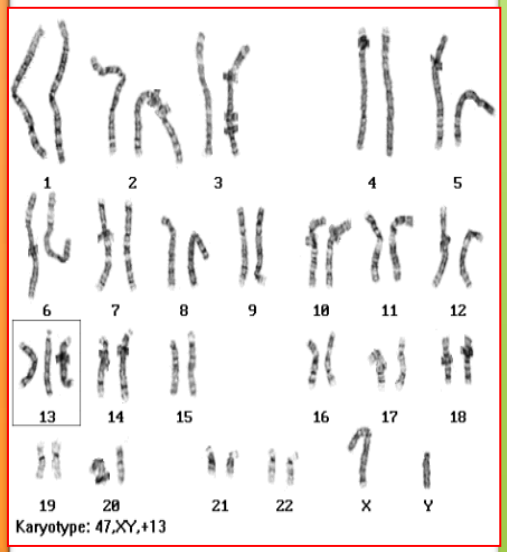
-It occurs in around one in 6,000 live births and around 80% of those affected are females

-Most babies die in the first year and many within the first month and has a very low rate of survival.

-Common anamolies are heart abnormalities, kidney malformations and other internal organ disorders.






## Patau Syndrome

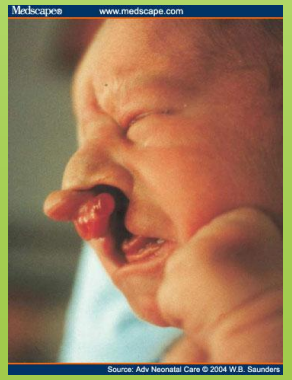
Karyotype: 47, XY, +13

(Trisomy)

-50% of these babies die within the first month and very few survive beyond the first year

-There are multiple dysmorphic features.

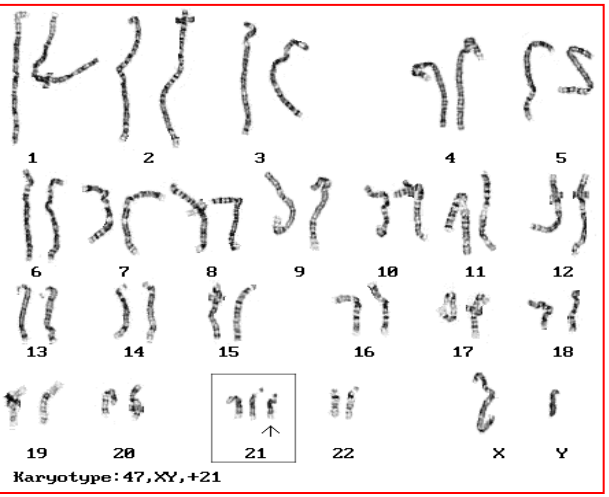
-Most cases, as in Down's syndrome, involve maternal nondisjunction.



# Down syndrome

## Karyotype: 47, XY, +21 (Trisomy)

The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50.




**Causes of Down syndrome (trisomy 21 )**

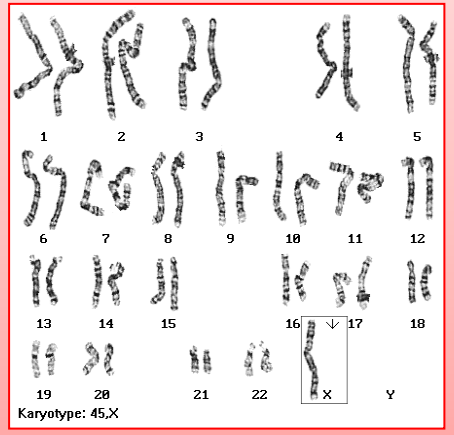
- The incidence rises sharply with increasing maternal age
- Most cases arise from non disjunction in the first meiotic division
- The father contributing the extra chromosome in 15% of cases (i.e. Down syndrome can also be the result of nondisjunction of the father's chromosome 21)
- A small proportion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

# Numerical Anomalies in Sex chromosomes

## Turner's syndrome

**Karyotype: 45, XO (Monosomy)**

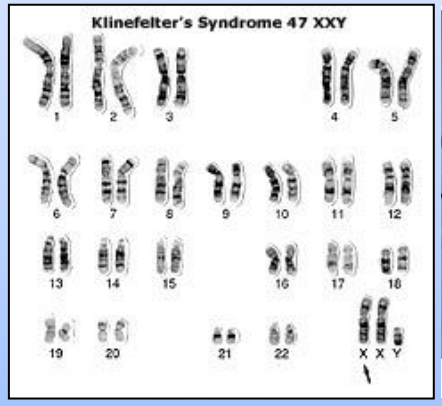
-Occurring in 1 in 5,000 phenotypic females
  -The only viable monosomy in humans
-Characteristics:
1-Webbed neck
2-Individuals are genetically female
3-Not mature sexually
4-Sterile
5-Short stature
6-Broad chest
7-Low hairline
8-Streak ovaries
9-Normal intelligence
10-Normal life span




## Klinefelter Syndrome

**Karyotype: 47,XXY (Trisomy)**

-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.





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

**Sex chromosome unbalance of much less deleterious effects:**

**47, XYY males**

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

**47 ,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.
-Found in 20% of spontaneous miscarriages.
-Tetraploidy
4N=92 chromosomes

NOTE:
Polyploidy (3N,4N) usually don't survive & miscarriage happens.

**Can an individual have a combination of cells:**

-Some cells with normal chromosomal number.
-Some cells with numerical chromosomal anomalies.

# Mosaicism VS Chimerism

## Mosaicism

- Mosaic Chromosome Syndrome is caused by the presence of an extra chromosome in **some** of the body's cells coming from **one zygote**.
- Numerical mosaic anomaly is usually due to a mitotic non-disjunction
- Is denoted by a slash between the various clones observed e.g. (46, XY / 47, XY, +21).

- Fun Fact: children born with **mosaic Down syndrome** have a higher IQ than children born with "complete" Down syndrome.

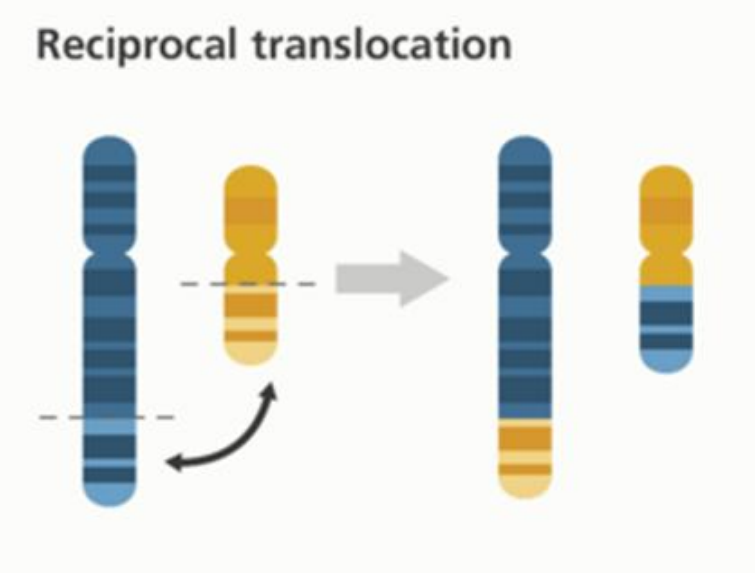
## Chimerism

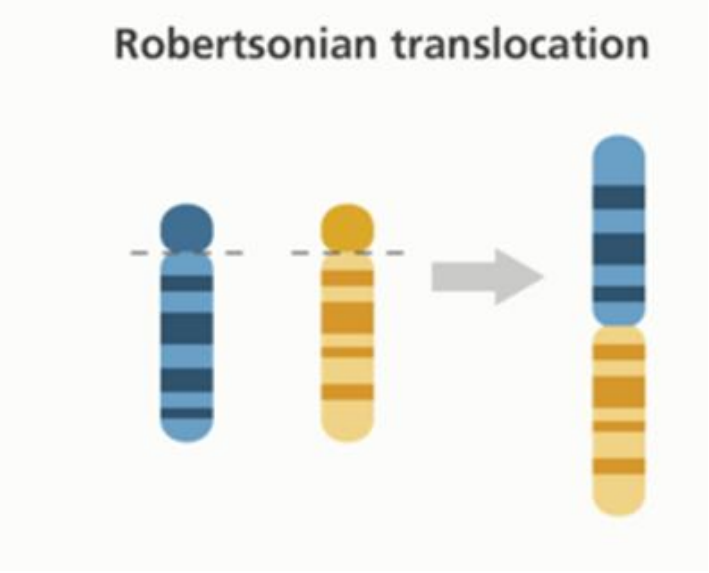
- The presence of two or more genetically distinct cell lines derived from **different zygotes (**2 zygotes that fuse to form 1 embryo).
- A person could be a chimera without ever knowing. He or she will have two distinct sets of DNA.
- Fun Fact: A chimera could have one organ with different DNA to that in the rest of their body. In some cases, they may have visible signs such as differently-colored eyes.

# Structural Chromosomal Anomalies

- Translocations
- Deletions
- Inversions
- Isochromosomes
- Ring Formation (Ring Chromosome)
- Duplications

# Translocation has two main types:



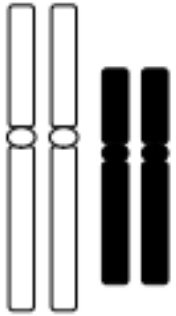




**Reciprocal:** segments from **two different chromosomes** are exchanged.

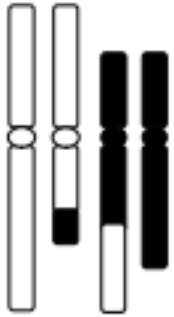
**Robertsonian:** an **entire chromosome** attaches to another.

# Reciprocal Translocations

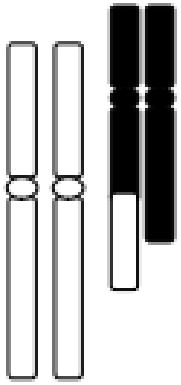
- There are two main types <u>under reciprocal translocations:</u>
  - Balanced
  - Unbalanced
- **A balanced reciprocal translocation** occurs when the chromosomes have been rearranged so that **no chromosome material has been lost or gained**.
- An **unbalanced reciprocal translocation** in which there is an extra piece of one chromosome and/or a missing piece of another chromosome.



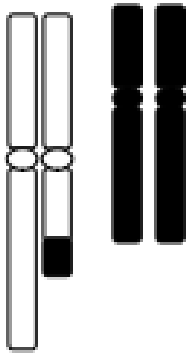
1. Normal chromosome arrangement in a child



2. Balanced translocation in a child



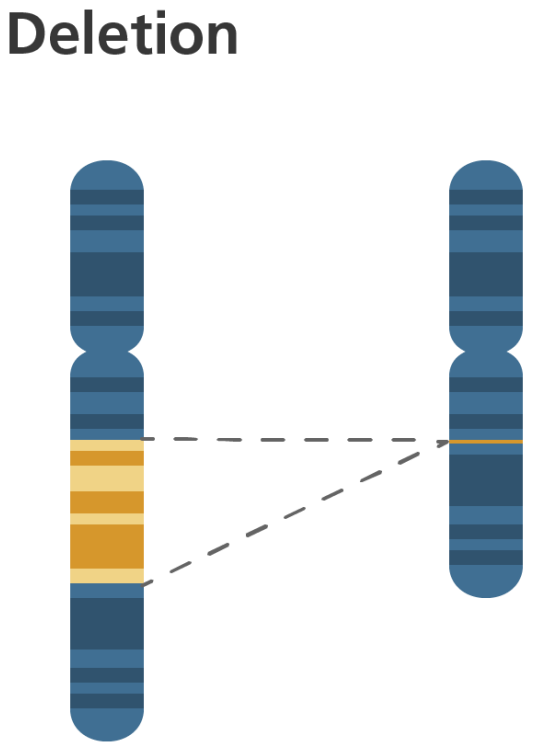
3. Unbalanced translocation in a child



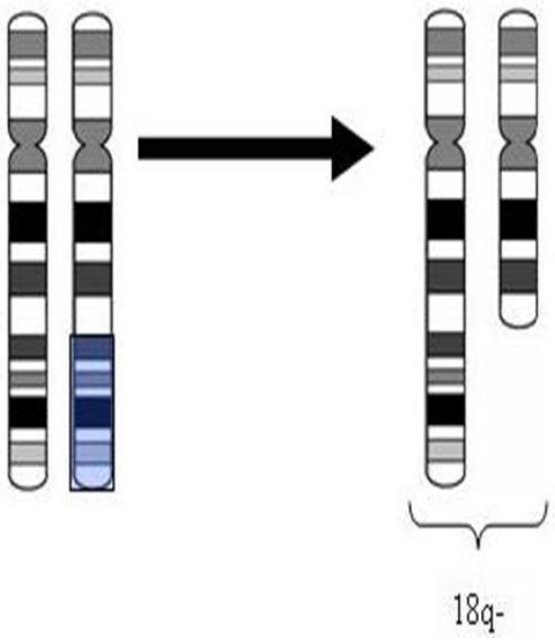
4. Unbalanced translocation in a child

# Deletion (Unbalanced Rearrangement)

- The term **chromosome deletion** means that part of a chromosome has been lost or deleted.
- A deletion can happen on any chromosome, and along any part of the chromosome.
- The deletion can be any size.
- If the material (genes) that has been deleted contains important instructions for the body, that person may have learning disability, developmental delay and health problems.
- The seriousness of these depends on how much of the chromosome has been deleted, and where the deletion is.
- It is recorded as "del".

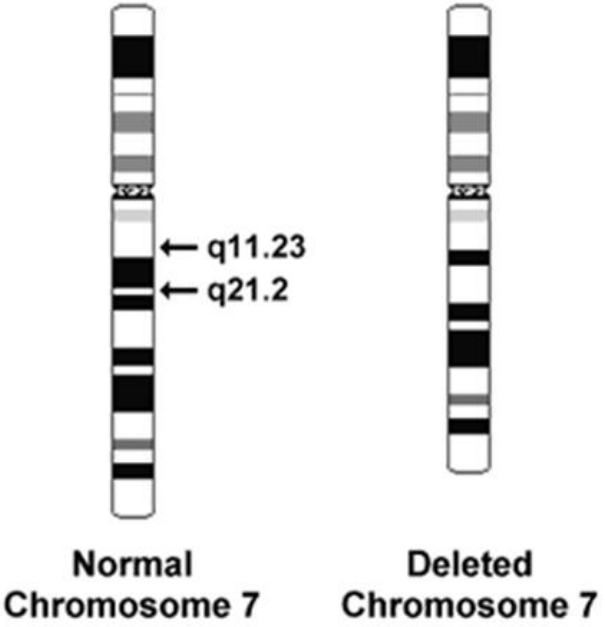


## Terminal Deletion




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

## Interstitial Deletion



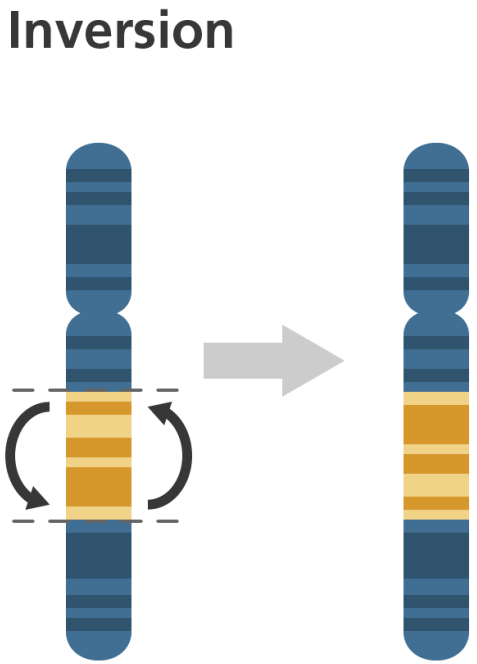

46,XY,del(7)(q11.23q21.2)

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.

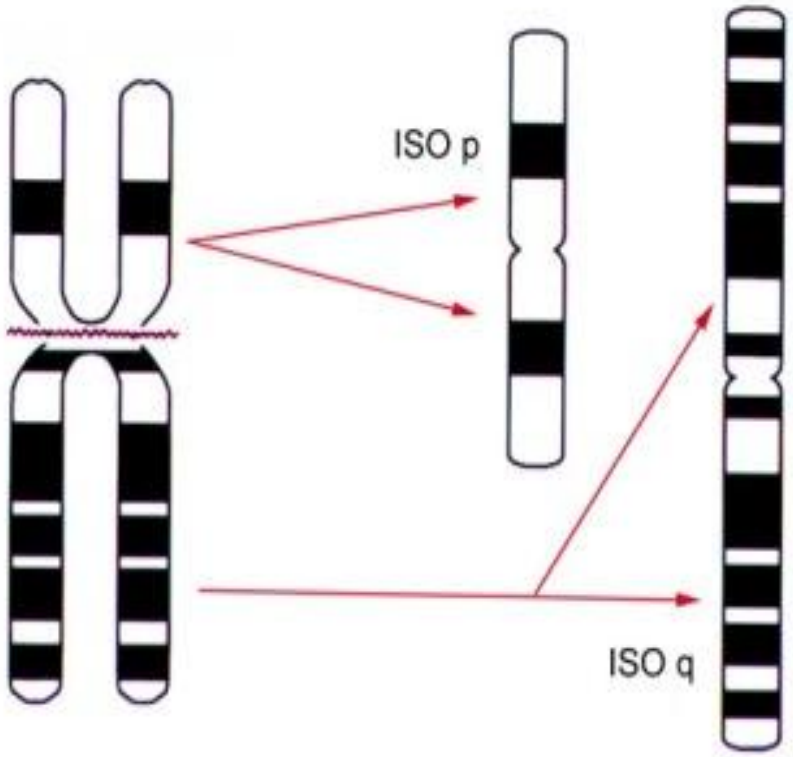
# Inversion

- Chromosome inversion means that part of a chromosome has turned so that the sequence of genes in the chromosome is partly reversed.
- In the **majority of cases this does not cause any health problems** to the person carrying the inversion.
- Only large inversions are normally detected.
- It is recorded as “inv”.



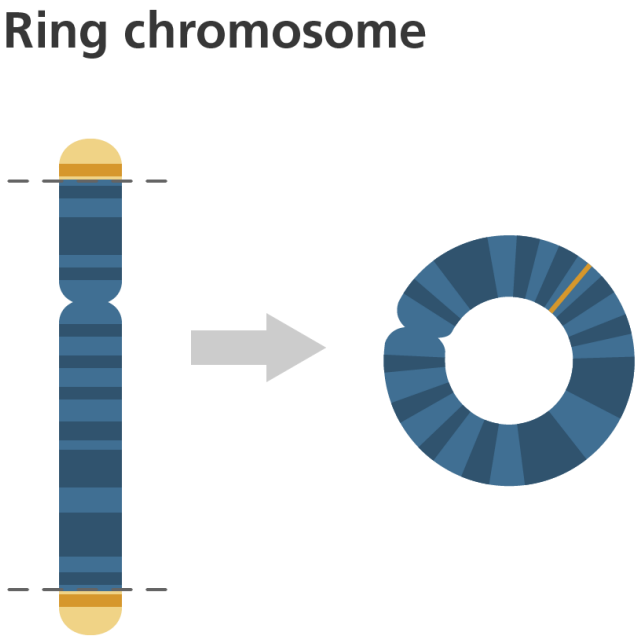
# Isochromosomes

- An isochromosome is a chromosome with **two identical arms.**
- Instead of one long (q) arm and one short (p) arm, an isochromosome has two long arms or two short arms.
- As a result, these abnormal chromosomes have an extra copy of some genes and are missing copies of other genes.
- The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally.



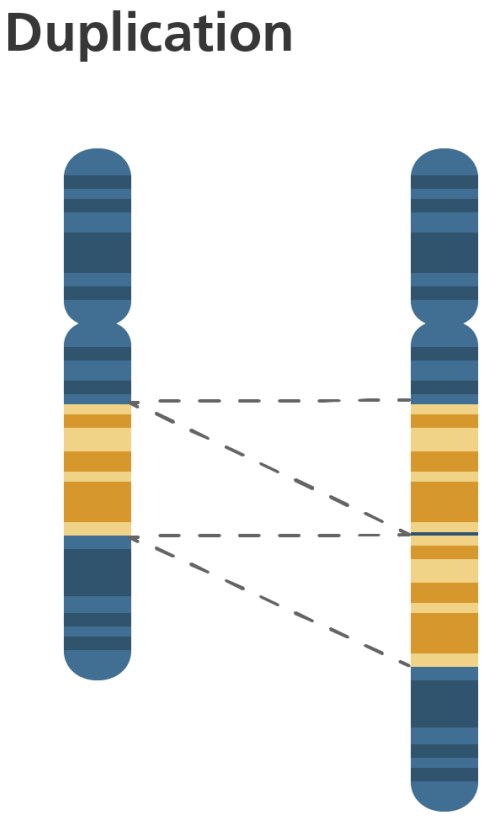
# Ring Formation

- This usually happens when the two ends of the same chromosome are deleted.
- The remaining ends of the chromosome are 'sticky' and join together to make a **ring** shape.
- The effect this has on the person usually depends on how much chromosome material, and therefore 'information' , was deleted before the chromosome formed a 'ring'.
- Ring chromosomes are often unstable in mitosis



# Duplication

- A mutation causing part of the chromosome to be repeated, resulting in extra genetic material.




# Quiz Yourself:

https://www.onlineexambuilder.com/human-genetics-lecture-2/exam-41306

# 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.



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