



### Numerical chromosome aberrations

Are defined as a gain or loss of one or more whole chromosome(s) (whether an autosome or a sex chromosome) or a whole set of chromosomes. The normal chromosome count is 46 (i.e.  $2n = 46$ ) as it is arranged in two sets of chromosomes. The numerical anomalies, when one or more chromosomes are in excess or missing, ultimately modify the entire genome size, so they can be considered genome mutations as well.

are those that cause a change (addition or deletion) in the number of chromosomes. They are further classified as **euploidy changes or aneuploidy changes**.

- **Euploidy** is the condition when an organism gains or losses one or more complete set of chromosomes, thus causing change in the ploidy number. For example, triploid ( $3n$ ), tetraploid ( $4n$ ) etc.
- **Aneuploidy** is the condition when an organism gains or losses one or more chromosomes and not the entire set. For example, trisomy ( $2n + 1$ ), monosomy ( $2n - 1$ ) In humans, euploidy conditions do not exist because the extent of abnormality is too large to sustain life. Aneuploidy conditions, however, are more common and are manifested in disorders such as Down syndrome, Klinefelter syndrome and Turner syndrome. We shall discuss these changes in detail later in the unit

- **Euploidy classify three type:**

1-Monoploidy( $x$ )

2-Diploidy ( $2x$ )

3-Polyploidy ( $3x, 4x, 5x$  etc)

- **Aneuploidy 2type:**

1-Hypoloidy :

**Monosomy( $2n-1$ )and Nullisomy ( $2n-2$ )**

2-Hyperploidy:

**Trisomy( $2n+1$ )and Tetrasomy( $2n+2$ )**

**Nondisjunction** - Mistake in cell division where chromosomes do not separate properly in anaphase. Usually in meiosis, although in mitosis occasionally. In meiosis, can occur in anaphase I or II. **Polyploidy** – complete extra sets ( $3n$ , etc.) – fatal in



humans, most animals.

**Aneuploidy** – missing one copy or have an extra copy of a single chromosome. Three copies of a chromosome in your somatic cells: TRISOMY. One copy of a chromosome in your somatic cells: Monosomy. Most trisomies and monosomies are lethal well before birth in humans.

Generally, **autosomal aneuploids** tend to be spontaneously aborted. Over 1/5 of human pregnancies are lost spontaneously after implantation. Chromosomal abnormalities are the leading known cause of pregnancy loss. Data indicate that minimum 10-15% of conceptions have a chromosomal abnormality. At least 95% of these conceptions spontaneously abort (often without being noticed).

### *The most common numerical chromosomal abnormalities*

**chromosome disorder autosomes** :- the majority of human chromosomal abnormalities occur in autosomes. There are three trisomies that results in baby which can survive for time after birth ; the other are too devastating and baby usually dies in utero.

#### **A-Down syndrome (Trisomy 21)**

Trisomy 21 is the cause of **Down syndrome**. Although the non-disjunction of chromosome 21 is not the only cause of Down syndrome -a smaller proportion of the cases is due to either centric fusion or translocation - it is the most common type. Despite the fact that trisomy 21 fetuses die in utero the average population frequency of Down syndrome is 1:650, but this value increases dramatically with maternal age, at 45 years of age it is more than 1:100 (figure 4.1).

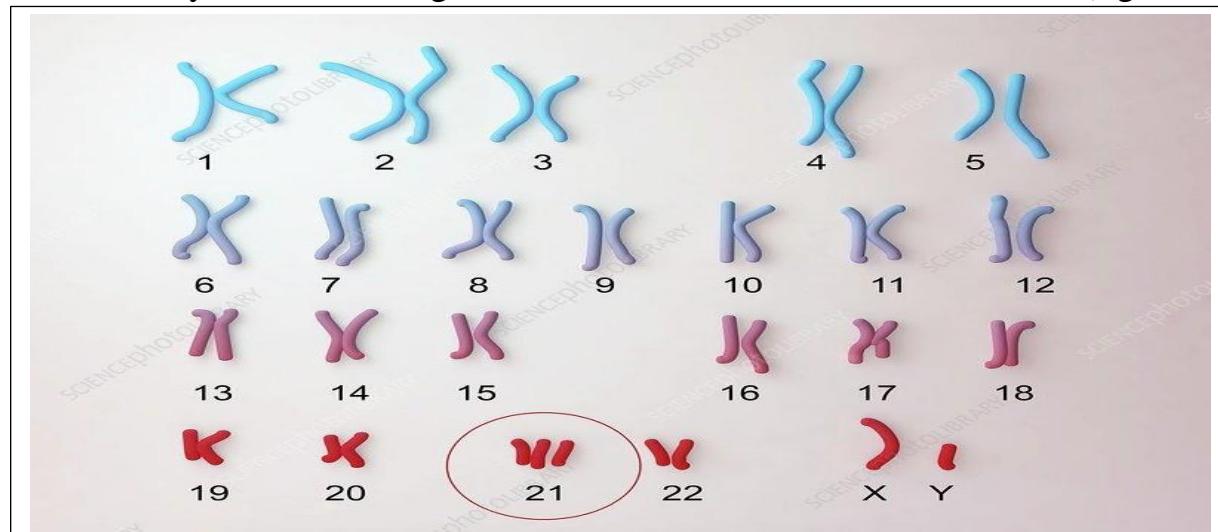


Figure 4.1 Down's syndrome karyotype



### B-Patau syndrome (Trisomy 13)

Trisomy 13 is the **Patau syndrome**. Similar to Down syndrome it is most commonly derived from maternal non-disjunction. 65% of such non-disjunctions derived from the first meiotic division. Frequency of birth is 1:12 500 - 1:21 700. Only <5% of these infants survive the first year of life (figure 4.2).

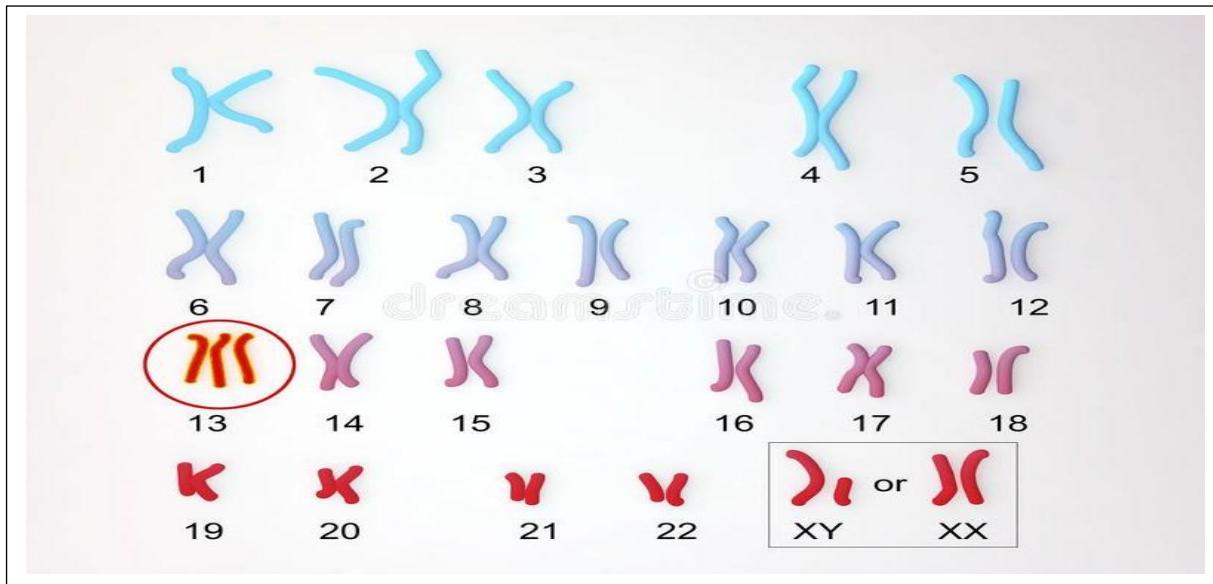


Figure 4.2 Patau's syndrome karyotype

### C-Edwards syndrome.( Trisomy 18)

Trisomy 18 is the **Edwards syndrome**. It is primarily due to maternal non-disjunction. 95% of the cases are due to non-disjunction in the first meiotic division. The frequency is 1:6000 -1:10000 live-born but the frequency at the time of conception can be much higher, since approx. 95% of the fetuses die within the womb. 30% of the Edwards syndromic abnormal newborns die within one month, > 95% of them die within a year (figure 4.3).

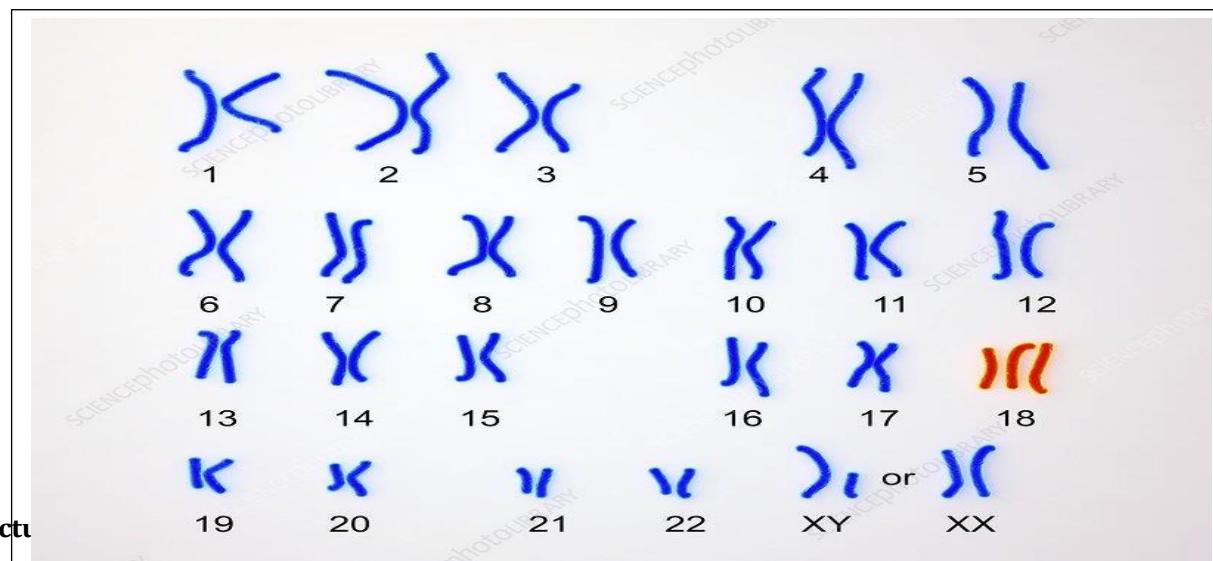
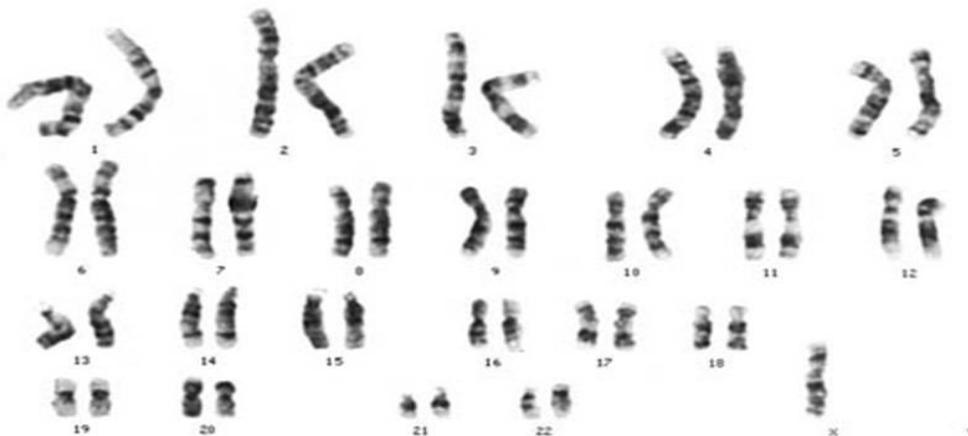




Figure 4.3 Edwards syndrome karyotype

### 2-1 chromosome disorder of sex chromosome :-

#### A-Turnersyndrome



Turner syndrome is related to the X chromosome, which is one of the two sex chromosomes. People typically have two sex chromosomes in each cell: females have two X chromosomes, while males have one X chromosome and one Y chromosome.

Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. The missing genetic material affects development before and after birth (figure 4.4).

About half of individuals with Turner syndrome have monosomy X, which means each cell in the individual's body has only one copy of the X chromosome instead of the usual two sex chromosomes. Turner syndrome can also occur if one of the sex chromosomes is partially missing or rearranged rather than completely absent. Some women with Turner syndrome have a chromosomal change in only some of their cells, which is known as mosaicism. Women with Turner syndrome caused by X chromosome mosaicism are said to have mosaic Turner syndrome.

The main symptom of Turner syndrome is short stature, grow more slowly than their peers during childhood and adolescence, have small ovaries, don't make enough sex hormones and low hairline at the back of the neck.

#### B-XXY male (Klinefelter syndrome)

Klinefelter syndrome (KS) is a genetic condition where there's an extra X chromosome present in a male's genetic code. Instead of having a total of 46 chromosomes, they have 47 — with two copies of the X chromosome and one copy of the Y chromosome (47,XXY).



Klinefelter syndrome can be caused by:

- One extra copy of the X chromosome in each cell (XXY), the most common cause
- An extra X chromosome in some of the cells (mosaic Klinefelter syndrome), with fewer symptoms
- More than one extra copy of the X chromosome, which is rare and results in a severe form

Signs and symptoms may include:

Taller than average stature, Longer legs, shorter torso and broader hips compared with other boys, After puberty, less muscle and less facial and body hair compared with other teens and Small, firm testicles.

### ***C-XYY male (XYY syndrome) "superman" or Jacobs syndrome***

In this case ***normal, slightly taller than the average males have 47,XYY karyotype.*** The birth rate is 1:1000. They derived only from paternal second meiotic non-disjunction. In contrast to all meiotic non-disjunctions, ***the formation is not affected by age.***

Usually tall, with heavy acne; some correlation with mild mental retardation and with aggressiveness; usually still fertile.

### ***D- XXX female (triple X syndrome)***

Triple X syndrome can also be referred to as trisomy X syndrome or 47,XXX. Triple X syndrome happens when a female is born with an extra X chromosome, and therefore has a total of 47 chromosomes.

For some girls and women with triple X syndrome, all of their cells contain three X chromosomes. In other females with triple X syndrome, some cells have three X chromosomes while other have the usual two X chromosomes — this is referred to as mosaicism. The degree of mosaicism (the number of cells with three X chromosomes) may vary from a small percentage to close to 100%.

The condition occurs in about one out of every 1,000 female births. There is a great degree of variation among girls and women with triple X syndrome. Some individuals do not experience any symptoms or their symptoms are so mild that they go unnoticed. Other girls and women may have certain characteristics — as well as psychological or medical problems — associated with triple X syndrome. Symptoms may be more pronounced in females with a higher percentage of cells with three X chromosomes.



One consistent physical characteristic is that females with triple X are taller than girls of the same age, wide-spaced eyes (known as hypertelorism), poor muscle tone (known as hypotonia) and dysfunction and/or failure of the ovaries, which can be associated with fertility problems.

### 2-2 Mixoploid mutations

In mixoploidy or in mutations associated with mixed ploidy usually two (sometimes more) cell lines with different chromosome numbers are found within an organism.

There are two forms: **mosaicism and chimerism**

In genetics a mosaic is a living creature, where two cell lines of different chromosome numbers, but of the same origin are present in the body. They are either **aneuploid or polyploid mosaics**.

In the case of **gonadal mosaicism** only the cells in the germ line have abnormal chromosome number, thus the risk of numerical aberrations in the offspring is high. Unfortunately, the detection of such defects is still not possible routinely, but the birth of an abnormal offspring of the patient can indicate this. Mosaicism in a broader sense is a somatic mutation, when different mutants (alleles) of a given gene are located in different organs or in different cells of the same organ (for example eyes with different colors: one is blue and the other is brown or a blue eye with brown spots).

After the lion-headed, bird-legged, snake-tailed monster of Greek mythology the creature that has two cell lines of different origin - derived from different zygotes - is called **chimera**. A chimera is derived either from fusion of fraternal twins, or from double fertilization of an egg and a polar body (polocyte), or from transplacental haematopoietic stem cells exchange between fraternal twins (blood group chimerism). Recently, the chimera referred to as transgenic animals / plants, which contain cells of different origin, derived from either the fusion of few-cell-embryos, or via the microinjection of foreign genes into fertilized oocytes.

### 2-4. Uniparental disomy (UPD)

**Uniparental disomy (UPD)** is a genetic abnormality that cannot be easily detected by traditional cytogenetic methods; instead, it is identified using modern molecular techniques.

#### What is UPD?

UPD occurs when a person has a **normal chromosome number (46)**, but **both copies of a particular chromosome come from the same parent**—either the mother or the father—instead of one from each parent.

#### How does UPD form?



UPD typically results from **two sequential chromosomal abnormalities**:

#### 1. **Meiotic nondisjunction**

- This leads to the formation of a **trisomic zygote** (having three copies of a chromosome).

#### 2. **Anaphase lag during early embryonic divisions**

- One of the three chromosomes is lost, restoring the normal chromosome number but leaving the two remaining copies from the same parent.

### Types of UPD

The type depends on whether nondisjunction occurred in the first or second meiotic division:

#### 1. **Uniparental Heterodisomy**

Arises from **nondisjunction in Meiosis I**.

The child inherits **two different homologous chromosomes** from the same parent (one from each grandparent).

#### 2. **Uniparental Isodisomy**

- Arises from **nondisjunction in Meiosis II**.

The child inherits **two identical copies** of the chromosome (both from the same grandparent).

### Clinical significance

UPD can cause clinical symptoms due to **genomic imprinting**, where gene expression depends on whether the gene is inherited from the mother or the father.

### Important example:

Some cases of:

- **Prader–Willi syndrome**
- **Angelman syndrome**