# Down's, Turner and Kleinefelter syndrome

Done by: Hadeel Al-Madany

Revised by: Aliya Al-Awaji

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

- Describe and explain the common chromosomal disorders.
- Define non-disjunction and describe its consequences for meiosis and mitosis: Down's syndrome.
- Understand the common numerical sex chromosome disorders: Turner`s & Kleinefelter`s syndromes
- Recognize the structural chromosomal anomalies

All the boxes and the last page contain extra info for you to understand

## Down's, Turner and Kleinefelter syndrome: primary care throughout the life span:

-Terms: **Aneuploidy:**

- It is an abnormal number of chromosomes, and is a type of chromosome abnormality. Or
- An abnormality involving a chromosome number that is not an exact multiple of the haploid number (one chromosome set is incomplete).

- Down syndrome, Turner syndrome, and Klinefelter syndrome constitute the most common chromosomal abnormalities encountered by primary care physicians.
- Down syndrome typically is recognized at birth, Turner syndrome usually is not recognized until adolescence, and many men with Kleinefelter syndrome are never diagnosed.
- Although each syndrome is caused by an abnormal number of chromosomes, or aneuploidy, they are distinct syndromes with learning disabilities and a predisposition toward autoimmune diseases, endocrinologic disorders, and cancers.

## When to do a chromosomal test?

- Prenatal: **maternal age >37yrs**; USS changes; Family history
- Postnatal: Learning & developmental disability; growth retardation
- Infertility: Recurrent miscarriage, primary infertility

## Human Genetic Disorders:

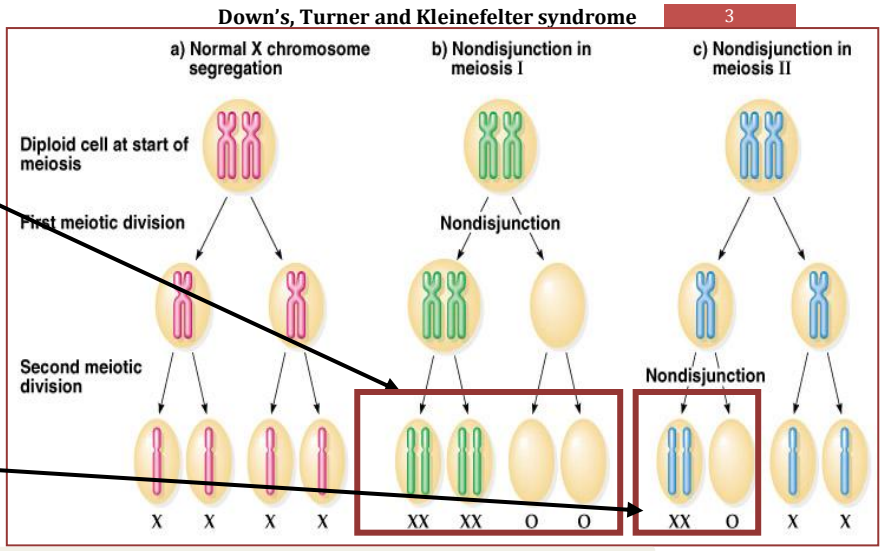
- Some genetic disorders are caused by a change in the number of chromosomes.
- nondisjunction during meiosis can create gametes having one too many or one too few chromosomes
- fertilization of these gametes creates **trisomic (e.g. Down's syndrome)** or **monosomic (e.g. Turner syndrome)** individuals
- Down syndrome is trisomy of chromosome 21

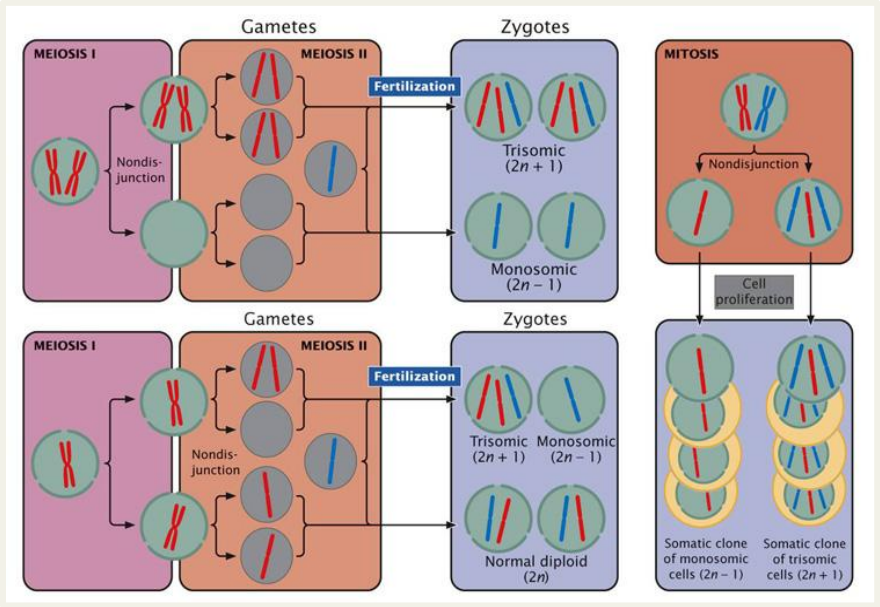
## Non-disjunction in Meiosis:

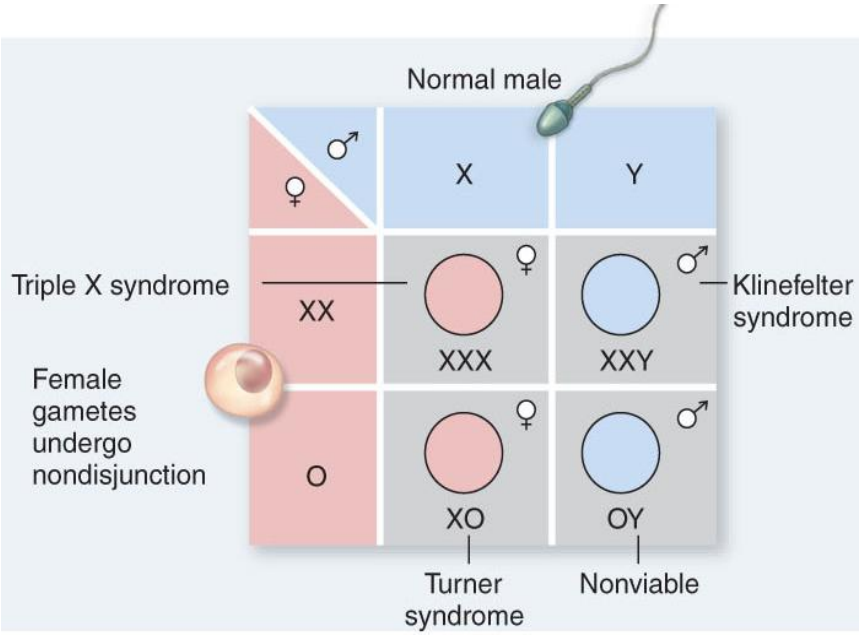
**Nondisjunction** ("not coming apart") is the failure of chromosome pairs to separate properly during **meiosis** stage 1 or stage 2. This could arise from a failure of homologous chromosomes to separate in meiosis I, or the failure of sister chromatids to separate during **meiosis II** or **mitosis**. The result of this error is a cell with an imbalance of chromosomes. Such a cell is said to be aneuploid.

- 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)

- **All gametes** are affected by nondisjunction in ***meiosis I.*** Two gametes have a single extra chromosome; two gametes are missing a single chromosome.
- **Half of the gametes** are affected by nondisjunction in ***meiosis II***. One gamete has a single extra chromosome; one gamete is missing a single chromosome.



## Common Aneuploidies:

- Most abnormalities in numbers of autosomes (anueploidies) are very serious or fatal due to gene dosage imbalances
- The fewer genes unbalanced, the less serious the condition

- **Down's syndrome**: Caused by a ***trisomy*** of chromosome number 21 (1 in 700 births)
- *mental retardation, mongoloid features, and heart defects*

- Most abnormalities of sex chromosomes **DO NOT** affect survival

- **Kleinefelter Syndrome**: Males with an ***extra X chromosome (XXY)*** (1 in 1000 male births)
- **Turner Syndrome:** Females ***missing one X chromosome (XO)*** (1 in 2500 female births)

## 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***.

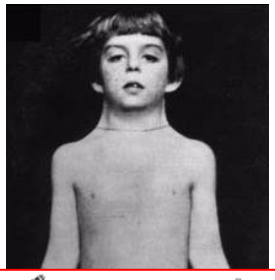
**XXX females**: It seems to do little harm, ***individuals are fertile and do not transmit the extra chromosome.***

- They do have a ***reduction in IQ comparable to that of Kleinfelter's males.***

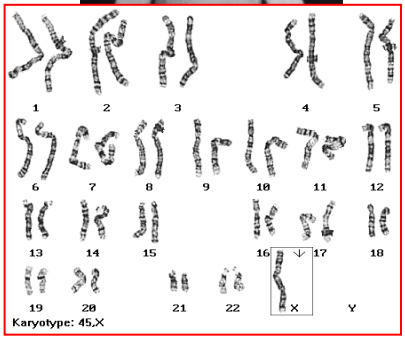
## NUMERICAL SEX CHROMOSOMAL ANOMALIES:

### What is Turner Syndrome? Monosomy X (Turner's syndrome, 45, XO)

- Relatively common disorder caused by the loss of genetic material from one of the sex chromosomes.
- Affects only females
- ***96-98% DO NOT survive to birth***
- No menstruation

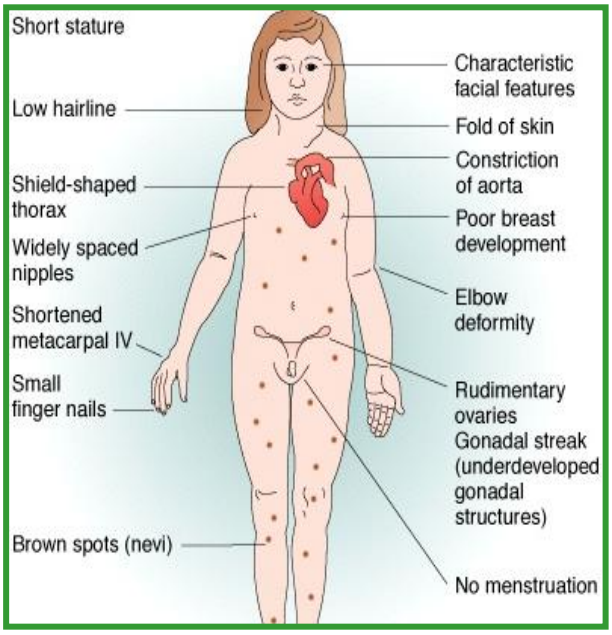


- No breast development
- No hips
- Broad shoulders and neck



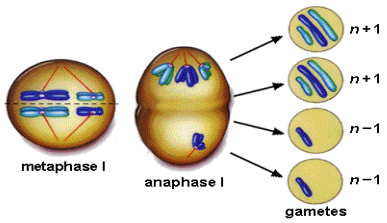
## Clinical Features:

- Short stature (143-145cm tall)
- Loss of ovarian function
- Hormone imbalances (thyroid, diabetes)
- Stress and emotional deprivation
- Diseases affecting the kidneys, heart, lungs or intestines
- Bone diseases
- Learning problems (esp. in math)




## Genetic causes:

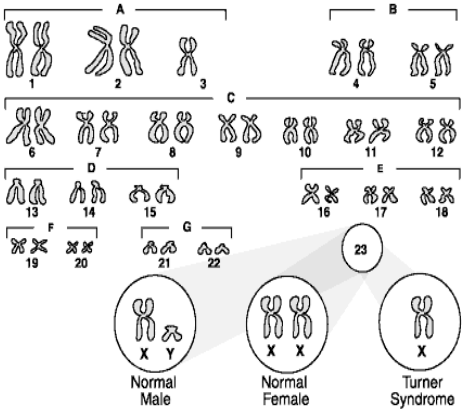
- X chromosome monosomy
- X chromosome mosaicism
- X chromosome defects




When discussing genetics, mosaicism means that the cells in a person's body do not all have the same chromosomal makeup. Some cells may be affected by a trisomy, for example, whereas other cells have a normal number of chromosomes. The degree of mosaicism can vary widely, causing minor to severe effects on a person's health.

## Diagnosis:

- Possible during infancy or early childhood
- A physical exam is the first indication
- The best test is a karyotype, (i.e. a laboratory test presenting the chromosomes).



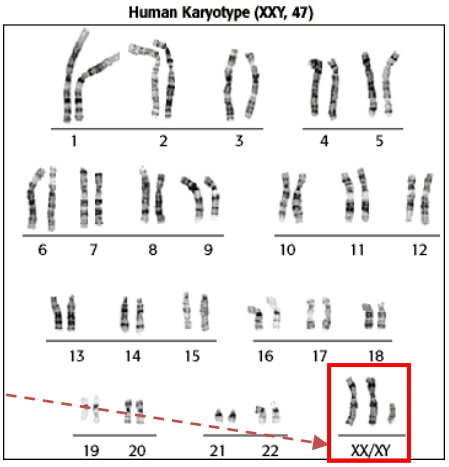

## Treatment:

- Growth hormone therapy
- Estrogen replacement therapy
- Cardiac surgery (when needed)
- In vitro fertilization (to achieve pregnancy)
- Psychological help

In vitro fertilization of an egg in a laboratory dish or test tube; *specifically*: fertilization by mixing sperm with eggs surgically removed from an ovary followed by uterine implantation of one or more of the resulting fertilized eggs.

## Is Turner Syndrome "hereditary"?

- Although it is a genetic disorder, it is **NOT** usually hereditary
- There are ***no*** known environmental causes of the syndrome
- Women with Turner Syndrome are usually **infertile**




---

## Klinefelter's Syndrome:

- 1 in 1,100 births
- 47 chromosomes XXY only 47, XXY
- #23 Trisomy
- Nondisjunction

- **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.

## Prognosis:

- People do not die from **Klinefelter syndrome**
- About 1 in every 500 to 800 males is born with this disorder. Approximately 3% of the male population have Klinefelter syndrome
- Klinefelter syndrome is not inherited but occurs during fetal development, there is no way of preventing.
- One risk factor for this condition is the mother giving birth at an older age.

## Klinefelter's Syndrome features:

- Scarce beard
- Longer fingers and arms
- Sterile
- Delicate skin
- Low mental ability
- Normal lifespan

## Symptoms of Klinefelter's syndrome:

- Smaller genitalia
- Taller than average height (longer limbs)
- Poor upper body strength (clumsy)
- Breast growth
- 20-50% have mild intention tremors

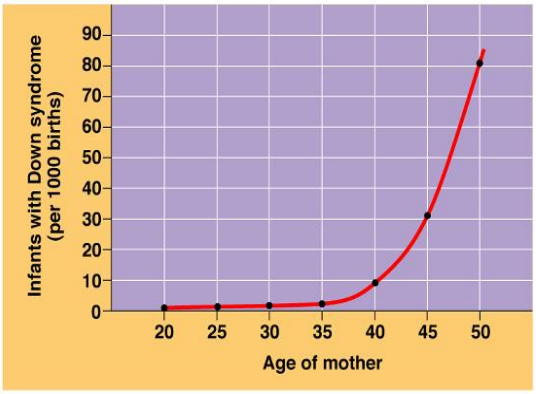
## Treatment:

- There is no cure for **Klinefelter syndrome**
- Children with Klinefelter syndrome may need special tutoring due to learning disabilities
- Surgery - for enlarged breasts
- Testosterone injections are started around the time of puberty, which may help to produce more normal development of male hormones; muscle mass, hair growth and increased sex drive
- ***Testosterone injections DO NOT increase genitalia size, but do decrease breast growth size***

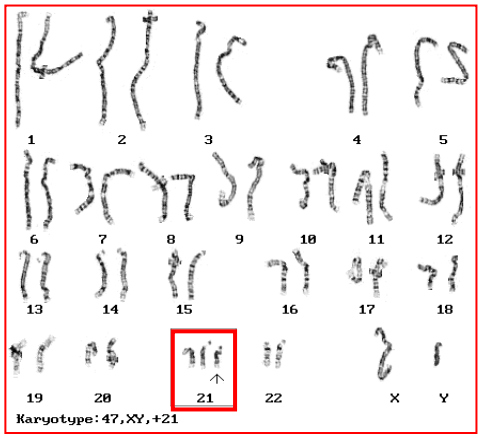
---

## STRUCTURAL ANOMALIES DOWN SYNDROME:

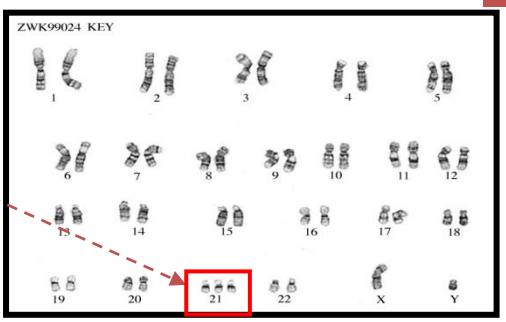
- The incidence of trisomy 21 rises sharply with ***increasing maternal age***.
- Most cases arise from non disjunction in the ***first meiotic division***.
- **The father** contributing the extra chromosome in **15% of cases** (i.e. Down syndrome can also be the result of nondisjunction of the father's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




The diagram shows the relation between increased maternal age and the incidence of trisomy 21.




Karyotype showing trisomes at the potision 21




- 47 chromosomes XY or XX
- #21 Trisomy nondisjunction

## Features:

- Short, broad hands
- Stubby fingers
- Rough skin
- Impotency in males
- Mentally retarded
- Small round face
- Protruding tongue
- Short lifespan

## Take home message

- Chromosome abnormalities can be ***numerical or structural.***
- **Numerical** abnormalities include **aneuploidy** and **polyploidy**.

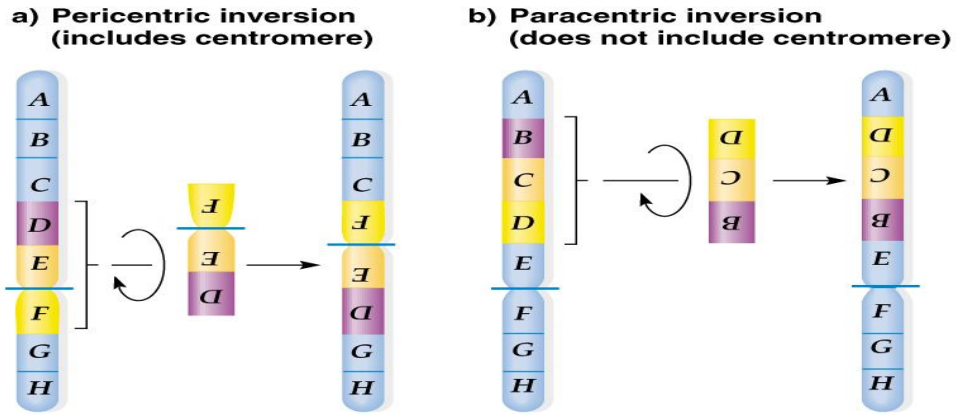
**FOR YOUR INFO: Aneuploidy** The alternation of chromosome number in a cell by adding or missing particular chromosome or chromosome set or part of a chromosome is called aneuploidy. So, chromosomal number differs from the wild type of the organism due to segregating defects. According to the difference of the number of chromosome, there are several types of aneuploidy such as monosomy (2n-1), disomy (n+1), trisomy (2n+1) and nullisomy (2n-2) where the parent phenotype is 2n. Aneuploidy occurs mainly due to the failure of segregating chromosomes properly to the opposite poles in nuclear division i.e. in mitosis or meiosis, both sister chromatids or homologous chromosomes go to one pole, or in other words, none to other.

**Polyploidy** When a cell contains more than two sets of chromosomes, polyploidy occurs. So it alters the chromosome number in a cell. Polyploidy can be seen frequently in flowering plants including important crop plants but rarely in animals, except vertebrates and invertebrates. Several types of polyploidy occur through several processes. Autopolyploidy is one type that is formed by multiplication of the genome of same species. Autopolyploidy is produced in sexual reproduction during meiosis by the non disjunction of homologous chromosomes in metaphase I or abnormal cell division in mitosis. Allopolyploidy occurs due to the combination of genomes of different species such as in hybrid species. Polyploidy also can be induced using various chemicals such as colchicine by inhibiting cell division.

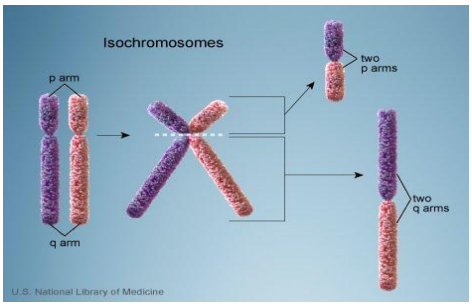
- In trisomy, a single extra chromosome is present, usually as a result of non-disjunction in the 1st or 2nd meiotic division.
- In polyploidy, ≥3 complete haploid sets are present instead of the usual diploid complement.
- Structural abnormalities include translocations (balanced or unbalanced), inversions, deletions, isochromosome & rings.

## For your info:

- **Translocation:** A mutual exchange between terminal segments from the arms of 2 chromosomes.
- **Inversion:** Chromosome segment excises and reintegrates in opposite orientation.
- Two types of inversions:
  - Pericentric = include the centromere
  - Paracentric = do not include the centromere. Generally do not result in lost DNA.




- **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.
- **An isochromosome** shows loss of one arm with duplication of the other. The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally




- **Ring:** 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