Klinefelter, Turner & Down Syndrome

RED: Important
GREEN: Doctors notes
Gray: Just go through it

OBJECTIVES

Define nondisjunction and describe its consequences for meiosis and mitosis.

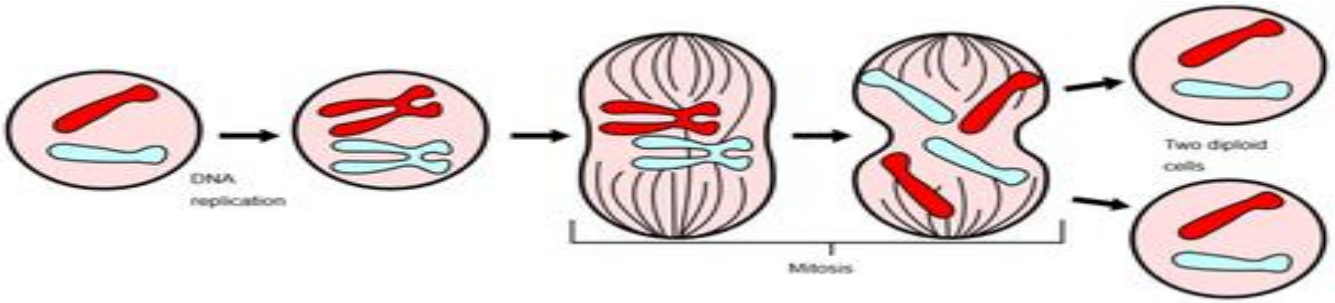
Classify chromosomal abnormalities.

Understand the common numerical chromosomal disorders: monosomy and trisomy.

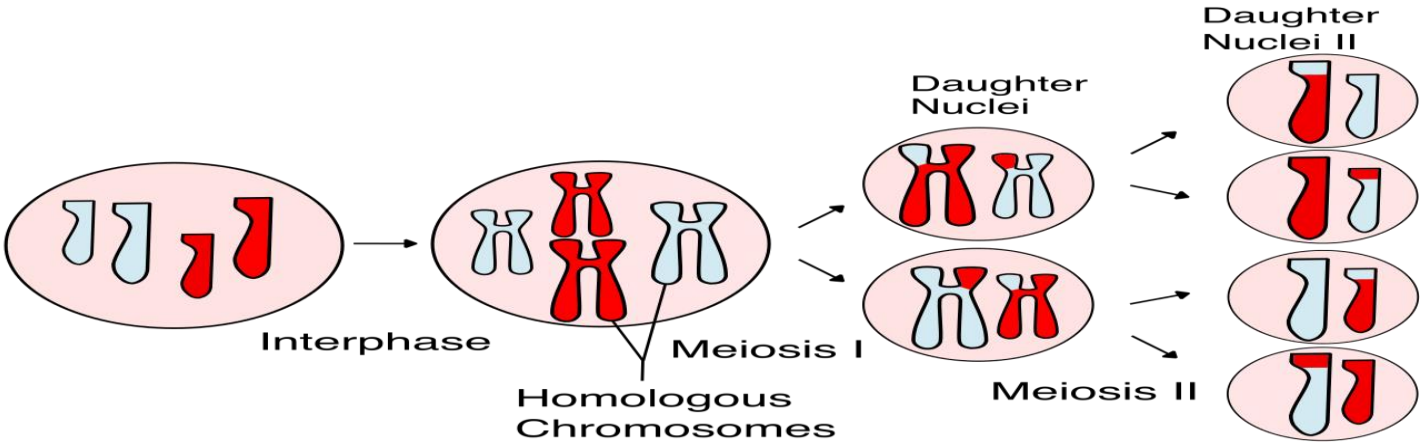
Understand the common numerical sex chromosome disorders: Down, Turner & Klinefelter syndromes.

The main focus of this lecture is to know the total number of chromosomes, the gender, when does this syndrome happen, the name of the syndrome, and how to test.

MITOSIS



MEIOSIS



Nondisjunction (happens rarely)

Not coming apart

In case of Meiosis I , it is the failure of a chromosome pair to separate properly, as a result, one daughter cell has two chromosomes and the other has none.

In case of Mitosis or Meiosis II , it is the failure of two chromatids of a chromosome to separate properly, as a result, one daughter cell has two chromatids and the other has none.

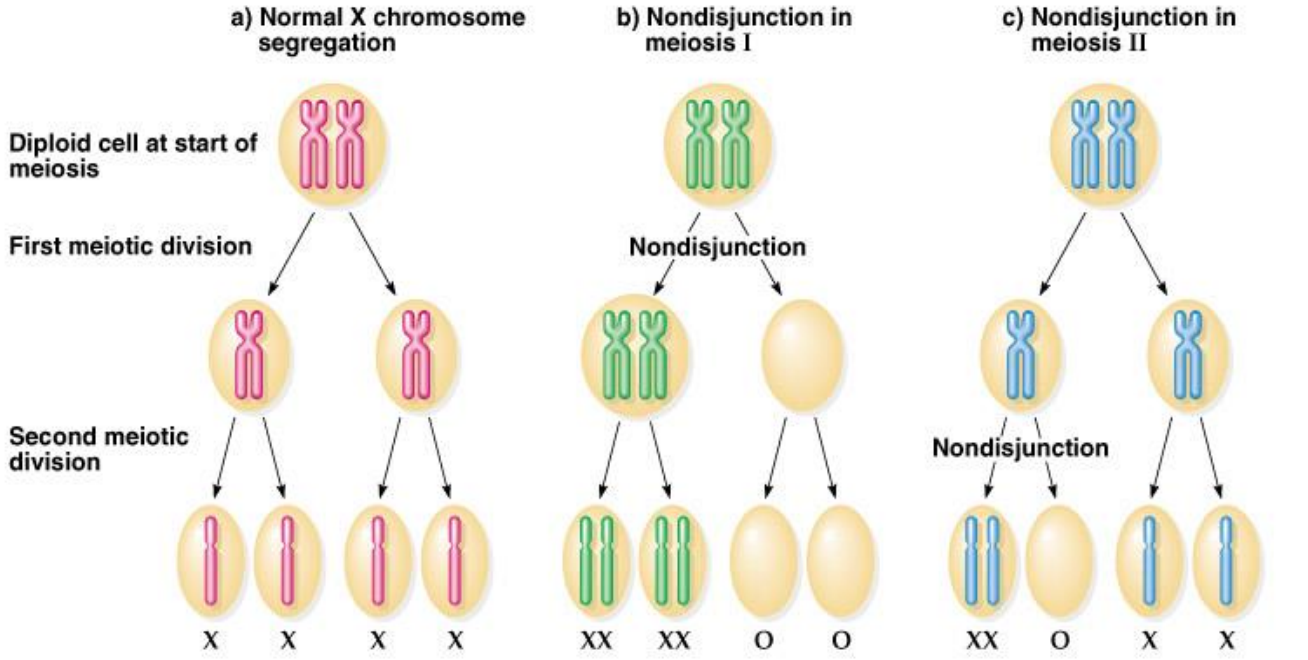
The difference between a Chromosome and a Chromatid:
Chromatid is one out of the two similar copies of DNA that makes up a single chromosome.

Nondisjunction can affect each pair of chromosomes.

The result is an imbalance of chromosomes termed **ANEUPLOIDY.**

There is no treatment for the abnormalities (yet) only management of symptoms.

NONDISJUNCTION illustration



The resulting gametes

4 haploid gametes

2 gametes with diploid number of X chromosome, and 2 gametes lacking X chromosome

2 gametes with haploid number of X chromosome, 1 gamete with diploid number of X chromosome, and 1 gamete lacking X chromosome

. Nullsomy : a term used when the cell has no chromosomes.

. In general the X chromosome has more genetic importance than Y chromosome

Aneuploidy

Aneuploidy is the presence of an abnormal number of chromosomes in a cell (whether it's an increase or a decrease).

Aneuploidy can occur in autosomal chromosomes as in **(Down syndrome)** which is Trisomy 21.

Or it can occur in sex chromosomes as in **(Klinefelter Syndrome)** in which a male has 2 or more X chromosomes. Or as in **(Turner Syndrome)** in which a female has only one X chromosome.

Down Syndrome (Karyotype: 47, XY or XX, +21)

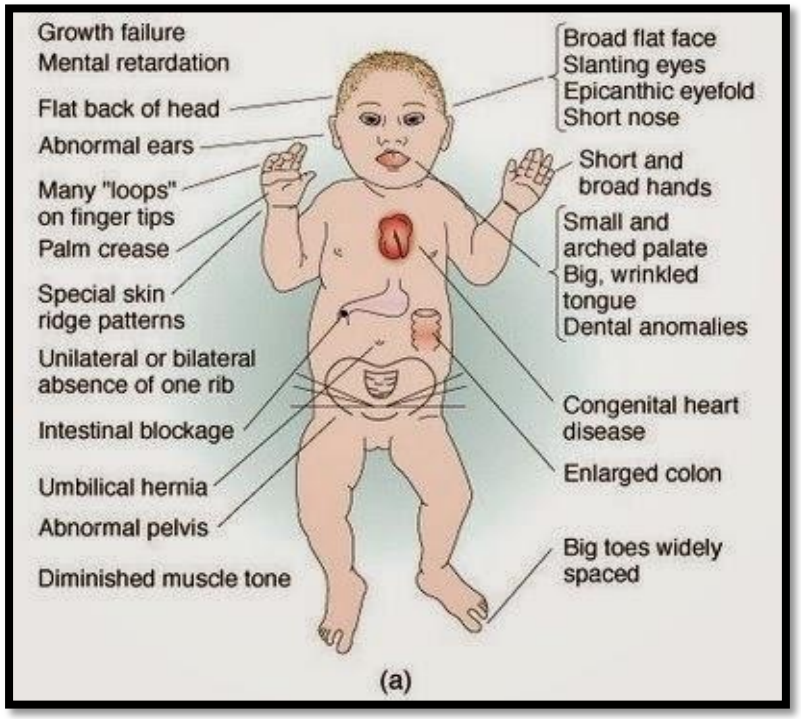
Patients with down syndrome have 3 copies of chromosome number 21.
Most cases arise from nondisjunction in the first meiotic division.
The incidence increases with increased maternal age.
Also if the mother is pregnant at very young age (11 or 12) this is also a risk factor for giving birth to a down syndrome baby.
Mothers are the source of the extra chromosome in the majority of cases, however in 15% of the cases the father contributes the extra 21 chromosome.

A small proportion of cases are mosaic and these probably arise from a nondisjunction event in an early zygotic division.

Mosaicism In Down syndrome means that some cells of the body have trisomy 21, and some have the typical number of chromosomes.

FEATURES OF DOWN SYNDROME

- Low muscle tone.
- Head and facial malformations: (Small round face, protruding tongue).
- Abnormalities of the extremities: (Short and broad hands, Stubby fingers).
- Developmental delays (mental retardation).
- Heart malformations.
- Increased risk of infectious disease.
- Rough skin.
- Impotency in males.
- Early death (Short lifespan).



The features are important to know.

They used to live until the age of 30 but now their life span increased so they could live up to the age of 60.

Turner syndrome (45, XO)

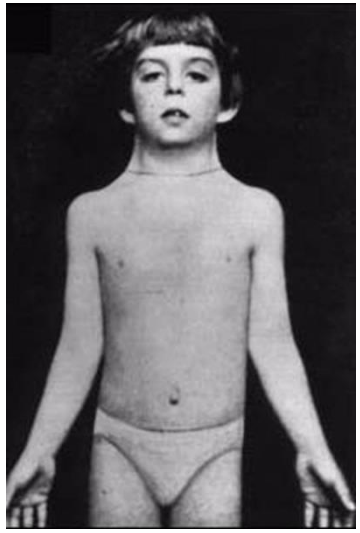
Monosomy of sex chromosome i.e. only one X chromosome is present.

Occurrence – 1 in 2500 live female births.

96-98% do not survive to birth.

The only viable monosomy in humans.

Individuals are genetically female, not mature sexually and sterile.



There is no association between developmental delays and any sex chromosomal abnormality. This indicates that genes affecting mental development and ability lie only on autosomal chromosomes. Early death is also not associated with any of the sex linked chromosomal abnormalities.

For your information:
Synthetic Human Growth Hormone is prescribed for females affected with Turner's.

FEATURES OF TURNER SYNDROME

Short stature, Broad chest, Low hairline.

Neck abnormalities (webbed neck).

Skeletal disorders (e.g. scoliosis, dislocated hips/elbows).

Lack of ovarian development (Streak ovaries).

Increased risk of cardiovascular anomalies e.g. constriction of aorta and hypertension.

Bicuspid aortic valve.

Coarctation of aorta.

Thoracic aortic aneurysm (aortic root dilatation).

No developmental delays, Normal intelligence.

Normal life span.

Short 4th metacarpal/metatarsal bone (± short 3rd and 5th).

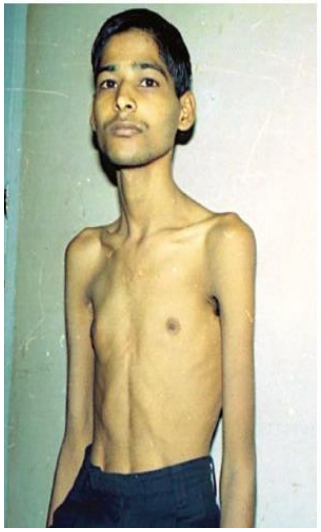
Osteoporosis (due to lack of estrogen).

Scoliosis.

Women with Turner syndrome are almost universally infertile.

Klinefelter Syndrome (47,XXY)

It's the set of symptoms that results from two or more X chromosomes in males.
1 case in 1,100 births.



Features of Klinefelter Syndrome

Tall

Sexually underdeveloped & infertile (no spermatogenesis).

In some cases testicular function is preserved.

Sparse facial and body hair (very small amount).

Delays in speech and motor skills.

Deficits in attention, auditory processing and social skills.

Low mental ability (slight reduction in IQ, but usually normal intelligence).

Longer fingers and arms.

Delicate skin.

Gynaecomastia and other feminine body characteristic.

Increased risk of autoimmune disorders, breast cancer, osteoporosis, leg ulcers, depression, and dental problems.

Normal life span.

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.

Treatment includes testosterone therapy and assisted learning.

Pre-natal

When to perform?

If maternal age is above 37 Years old, If the physician notices changes during Ultrasound or if there is a family history of abnormalities.

Triple test:

A test done during pregnancy which includes three tests:

Alpha fetoprotein (AFP), Human chorionic gonadotropin (hCG), and Estriol.

If +ve it indicates the fetus is at a risk of having diseases due to chromosomal abnormalities .

Chromosomal testing

the incidence is increasing due 2 factors
1/relative marriage
2/ people keep ignore doing test to prevent these abnormalities from happening

Infertility

When to perform ?

In case of recurrent miscarriage or primary infertility.

Post-natal

When to perform ?

If the baby has learning & developmental disability or growth retardation.

OTHER TESTS

The doctor didn't focus much on this slide and said just read it!

Rapid Aneuploidy Screening by Fluorescence in situ hybridization (FISH):

Available on amniocentesis sample

Uncultured amniocytes

FISH probes for X,Y, 21

Result in 24-48 hours

Proceed onto full karyotype (11-14 days)

Quantitative Fluorescence PCR (qf PCR): Used for trisomy screening.

This test is able to measure the number of copies of a chromosome.

Cell-free fetal DNA (from maternal plasma)

It is a non-invasive prenatal diagnostic tool done at 6-8 weeks of gestation to check for chromosomal aneuploidy.

It can also be used to determine the fetus sex.
How ? By looking for presence of Y chromosome material.

Check your understanding

1.Which of the following is the karyotype of Turner's syndrome?

A. 47, XYY
B. 45, XO
C. 47, XXX
D. 47, XXY

2.Which of the following syndromes is not related to sex chromosomes imbalance?

A. jakob syndrome
B. triple x syndrome
C. down syndrome
D. klienfelter syndrome

3. A patient came to the clinic having the following features: small round face, protruding tongue, mental retardation and a rough skin. which of the following describes the patient best?

A. His Karyotype is 47, XY +21
B. The patient will have less life span than normal
C. Increased mother age is the cause in most cases.
D. All of the above is true

4. Which of the following is true regarding Klinefelter syndrome?

A. 47, XXY
B. 47, XYY
C. 45, XO
D. 47, XXX

Answers: 1. B 2. C 3. D 4.A

Take home message

Normal human karyotype is 46, XY or 46, XX

Chromosome abnormalities can be numerical or structural.

Numerical abnormalities include aneuploidy and polyploidy.

In monosomy or trisomy, a single extra chromosome is absent or present, usually as a result of nondisjunction in the 1st or 2nd meiotic division.

Structural abnormalities include translocations, inversions, deletions, isochromosome & rings.

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