Revised & Approved
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HUMAN GENETICS

Objectives :

- Describe cell cycle and stages of mitosis and meiosis.
- 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 autosomal & sex chromosome disorders:(Down,Turner & Klinefelter)

Special thanks to
Human genetics Team #438

Team leaders:
Sarah alqahtani
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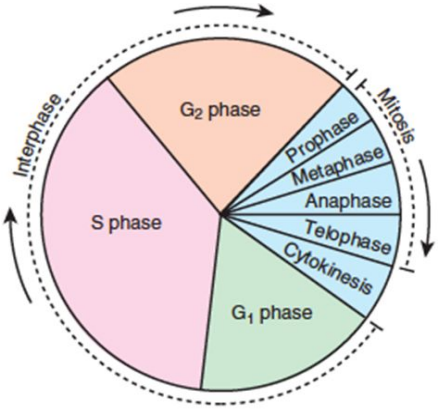
Dr's notes
Important
Extra notes
** Only in girls slides
** Only in boys slides

According to female's doc (karyotypes is super imp) | + everything RED is IMP

IMP Read according to the females doctor but you should know the end results of cell cycle mitosis or meiosis I & II (haploid/diploid + # of cells)

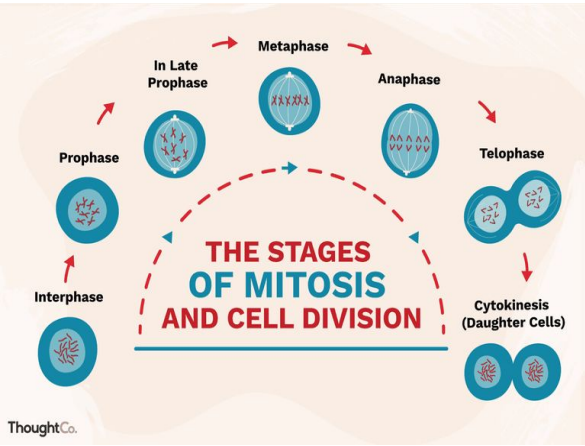
The Cell Cycle

- **Interphase** = Cellular components are replicated.
  - **G1 and G2** = Cell duplicates specific molecules and structures.
  - **S phase** = Cell replicates DNA.
- **Mitosis** = Cell distributes its contents into two daughter cells.



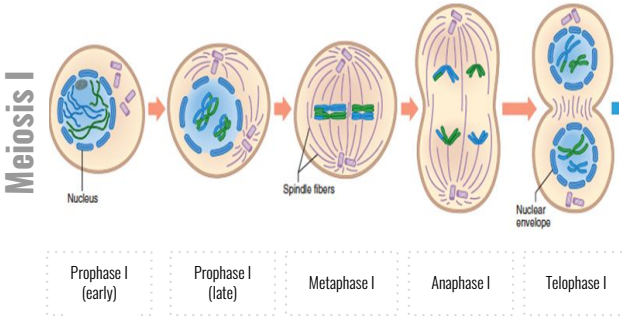
Stages of Mitosis

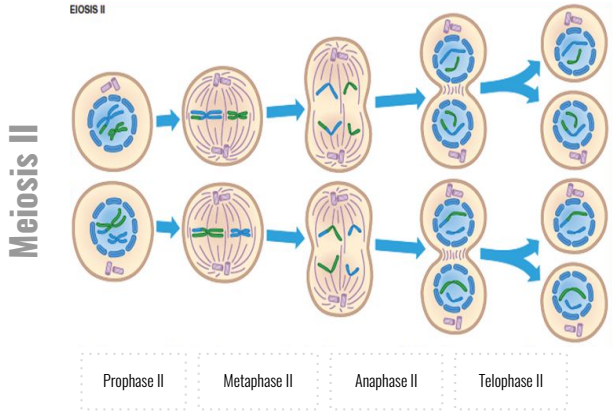
Main Point here is we have 2 main phases, the interphase and the metaphase and the one contributing more to nondisjunction is metaphase.



1. **Interphase:** Chromosomes are uncondensed.
2. **Prophase:** Condensed chromosomes take up stain, the spindle assembles, centrioles appears and the nuclear envelope breaks down.
3. **Metaphase:** Chromosomes align.
4. **Anaphase:** Centromeres part and chromatids.
5. **Telophase:** The spindle disassembles and the nuclear envelope re-forms.
6. **Two identical diploid daughter cells (2n).**

Stages of Meiosis I & II





1. **Prophase I (early):** Synapsis and crossing over occurs.
2. **Prophase I (late):** Chromosomes condense, become visible. Spindle forms. Nuclear envelope fragments. Spindle fibers attach to each chromosomes.
3. **Metaphase I:** Paired homologous chromosomes align along equator of cell.
4. **Anaphase I:** Homologous chromosomes separate to opposite poles of the cell.
5. **Telophase I:** Nuclear envelope partially assemble around chromosomes. Spindle disappears. Cytokinesis divides cell into two.
6. **Prophase II:** Nuclear envelope fragments. Spindle forms and fibers attach to both chromosomes.
7. **Metaphase II:** Chromosomes align along equator of cell.
8. **Anaphase II:** Sister chromatids separate to opposite poles of cell.
9. **Telophase II:** Nuclear envelopes assemble around two daughter nuclei. Chromosomes decondense. Spindle disappears.
10. **Four non-identical haploid daughter cells (1n).**

Comparison Between Mitosis & Meiosis [IMP]

Mitosis happens as 1 stage, after fertilization in adult cells.

Meiosis happens as 2 Stages, In gametes (germ cells: sperm or ova).

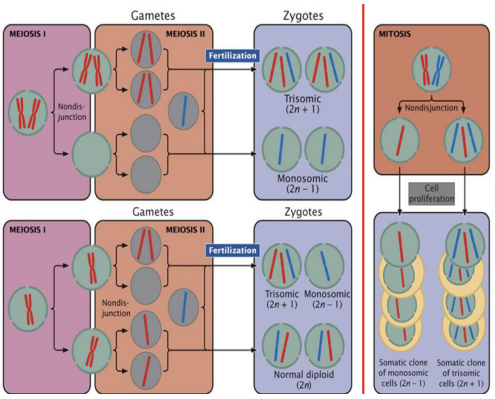
Mitosis	Meiosis
One division	Two divisions
Two daughter cells per cycle	Four daughter cells per cycle
Daughter cells genetically identical	Daughter cells genetically different
Chromosome number of daughter cells same as that of parent cell (2n) (Diploid)	Chromosome number of daughter cells half that of parent cell (1n) (haploid)
Occurs in somatic cells	Occurs in germline cells
Occurs throughout life cycle	In humans, completes after sexual maturity
Used for growth, repair & asexual reproduction	Used for sexual reproduction & producing new gene combinations

Summary of The Chromosome and Chromatid Number During Mitosis, Meiosis I & II in Humans

Phase (Mitosis)	# Chromosomes	# Chromatids
Prophase	46	92
Metaphase	46	92
Anaphase	92	92
Telophase	92	92
End of Mitosis (separated cells)	46	46
Phase (Meiosis I)	# Chromosomes	# Chromatids
Prophase I	46	92
Metaphase I	46	92
Anaphase I	46	92
Telophase I	46	92
End of Meiosis I (separated cells)	23	46
Phase (Meiosis II)	# Chromosomes	# Chromatids
Prophase II	23	46
Metaphase II	23	46
Anaphase II	46	46
Telophase II	46	46
End of Meiosis II (separated cells)	23	23

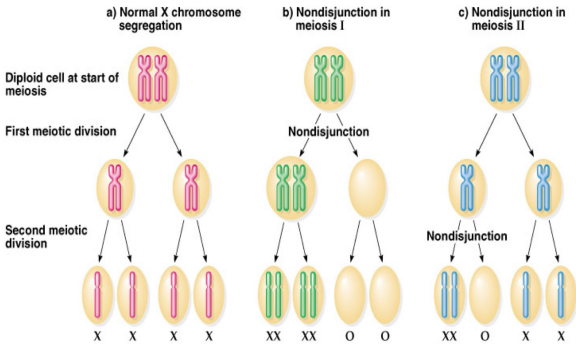
Nondisjunction "not coming apart" in Meiosis [IMP]

It is the failure of a chromosome pair to separate properly during meiosis I, or of two chromatids of a chromosome to separate properly during meiosis II or mitosis (not coming apart).



Stage where chromosomes are already mature but fail to disconnect from each other and this results in certain chromosomes going to a particular nucleus and this results in us having an extra chromosome in one cell and monosomy in another cell.

- Is not a rare event.
- Can affect each pair of chromosomes.
  - As a result, one daughter cell has two chromosomes or two chromatids and the other has none.
- Chromosomal abnormality: Numerical structural , In this case it's numerical abnormality.



Comparison between normal case with aneuploidy

A: **Result of normal chromosome segregation:**
4 haploid gametes.

B: **Result of Nondisjunction in Meiosis I:**
2 gametes with diploid number of X chromosome, and 2 gametes lacking X chromosomes.
All the gametes by this disjunction are up abnormal

C: **Result of nondisjunction in Meiosis II:**
2 gametes with haploid number of X chromosome, 1 gamete with diploid chromosome, and 1 gamete lacking X chromosome
Here 50% end up having normal gametes and 50 % abnormal .

Disomic gametes = 1 gamete with diploid number of X chromosome.
Nullisomic gametes = 1 gamete lacking X chromosome.

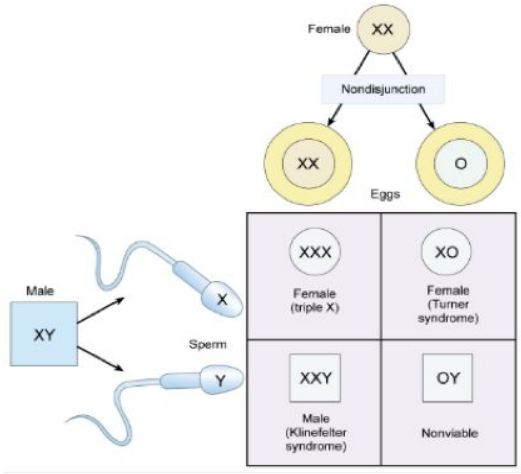
The result of this error is a cell with an imbalance of chromosomes (**Aneuploidy**). [IMP]

Autosomal

Trisomy 21
(Down syndrome)

Sex Chromosomes

47XXY (Klinefelter syndrome)
45X (Turner syndrome).



Know what each of these 4 events are called

IMP

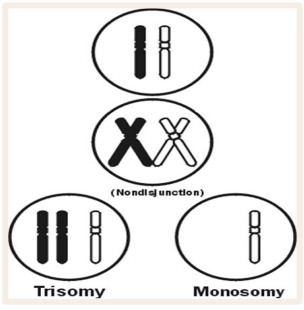
According to female's doc: nomenclature is important, understand the features and link them to the syndrome, read the rest with cup of coffee :)

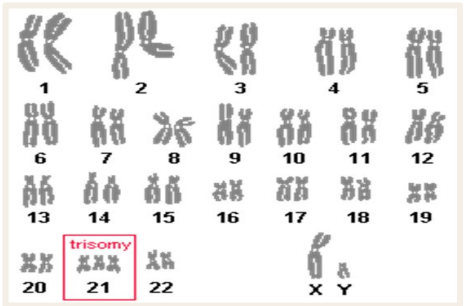
Down Syndrome (47, XY, +21)

Mostly caused by: Nondisjunction restricted to meiotic errors in the egg.

Source of extra chromosome: Mothers & ↑ with age.

Advanced maternal age was significantly associated with both **meiosis I (MI)** and **meiosis II (MII)**.





Epidemiology:

Nondisjunction occurred in MII, mothers were 15.1 times more likely (with about 50% of embryos harboring this abnormality) to be ≥40 years compared to 8.5 times of nondisjunction in MI.

A small proportion of cases are mosaic and these probably arise from a nondisjunction event in an early zygotic division = mitotic.
Affecting the genotype and therefore phenotype as per dosage.

Male Dr:
What is the difference between autosomes and X-linked?
ANS-> Autosomes are any chromosomes other than the X and Y.

Down syndrome is an autosomal abnormality and we use the ICN system (international system used by clinicians) to report it as 47,XY,+21.
This system depends on 3 variable which are the chromosome number, the abnormality, and whether its male or female.

Reason for the association of down syndrome with advanced maternal age is due the harboring abnormalities especially with nondisjunction at meiosis 2 (anaphase), this will cause a defect in the ovum development including smaller chromosome size and more difficulty to disjunct (separate) chromosomes during anaphase.

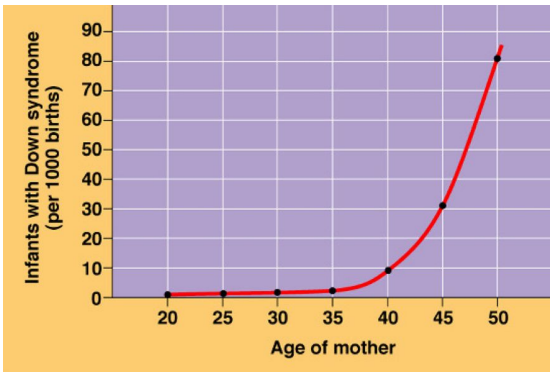
What is the mosaic abnormality?
ANS-> Harboring 2 genotypes (the normal and abnormal genotypes) at the same time.

Features of Down Syndrome male Dr: we will only focus on reproductive features ;)

- ↓ muscle tone
  Loose & floppy side
- Heart malformations.
- **Impotency in males** = Inability to sustain an erection sufficient for sexual intercourse or the inability to ejaculate.
- Developmental delays (mental retardation).
- Abnormalities of the extremities: (Short and broad hands, Stubby fingers), single deep crease across the center of the palm.
- Life expectancy increased from 25 in 1983 to 60 today.
- Head and facial malformations: (small round face, protruding tongue).

Down Syndrome (47, XY, +21) cont...

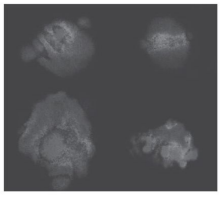
Genetic counseling is required from the age of 35 onwards . Mosaic Down syndrome, or mosaicism, is a rare form of Down syndrome. Down syndrome is a genetic disorder that results in an extra copy of chromosome 21. People with mosaic Down syndrome have a mixture of cells. Some have two copies of chromosome 21, and some have three. And so the greater the number number of cells with the copies the greater the abnormalities shown in the phenotype and the worse the condition

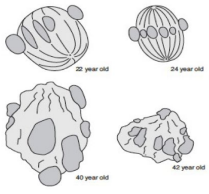


The incidence of trisomy 21 rises sharply with increasing maternal age

photomicrographs here show a disruption in the ova in old aged compared to young aged women.

Meiosis II oöcytes from younger and older women





- Impotency in males with Down syndrome result due a problems with the muscles themselves.

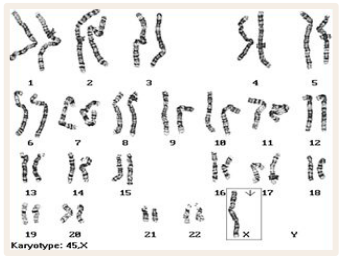
Sex Chromosome Imbalance is Much Less Deleterious

1. **Klinefelter Syndrome** (47,XXY).
2. **47,XYY Syndrome** (May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs).
3. **Trisomy X** (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 males).
4. **Turner Syndrome** (45,X and variants).

Mele Dr: these are the most frequent abnormalities are at the level of the X and Y sex chromosomes, while other abnormalities called double hits involve both anueploidy (numerical abnormality) and a structural abnormality at the sane time

IMP According to female's doc: nomenclature is important, understand the features and link them to the syndrome, read the rest.

Turner Syndrome (45, XO)

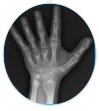


- **Monosomy of sex chromosome:** (Monosomy X: 45, XO) i.e. only one X chromosome is present.
- The only viable monosomy in humans.
- Individuals are genetically female, not mature sexually and sterile.
- **Occurrence:** 1 in 2500 live female births.
- They hardly survive.

Features of Turner Syndrome


Short stature, broad chest, low hairline.


Neck abnormalities (webbed neck).


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

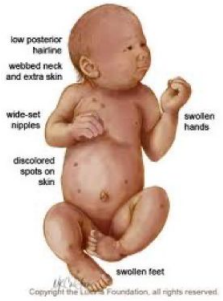

Lack of ovarian development (streak ovaries).


↑risk of osteoporosis, cardiovascular abnormalities (e.g. constriction of aorta & HT).


No development delays, normal intelligence.


Normal life span.

- **Cardiovascular:** (Bicuspid aortic valve, Coarctation of aorta, Thoracic aortic aneurysm (aortic root dilatation)).
- **Skeletal:** (Short stature, Short 4th metacarpal/metatarsal bone (± short 3rd and 5th), Osteoporosis (due to lack of estrogen), Scoliosis).
- **Reproductive:** (Women with Turner syndrome are almost universally infertile).

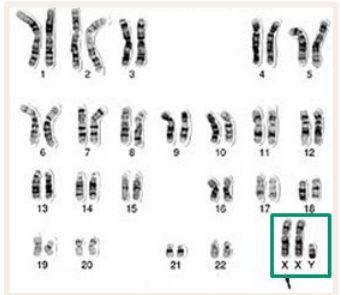


Male Dr: general phenotype mainly includes short stature.
Here we will only focus on the reproductive features as well ;)
What do we call the ovaries in turner syndrome female patients that lack ovarian development?
ANS-> Streak ovaries, and since its due to a loss of an X chromosome it can't be treated.

IMP According to female's doc: nomenclature is important, understand the features and link them to the syndrome, read the rest.

Klinefelter Syndrome (47, XXY)

- **Occurrence:** 1 in 1100 live female births
- **Treatment**: Testosterone therapy and assisted learning, In some cases testicular function is preserved.
- Aggressive outcome but survival rate is higher than Turner's.



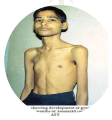
Very rarely more extreme forms of Klinefelter syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.

Mele Dr: Features I'm concerned with are underdeveloped male organs, azoospermia, and the male becomes sterile.
MALE DR: WHAT I HAVE MENTIONED TO YOU IS WHAT IS IMPORTANT IN THE EXAM ;)

Features of Klinefelter Syndrome

Tall, longer fingers and nails, delicate skin.

Sexually underdeveloped & infertile (no spermatogenesis).

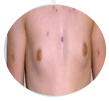


Sparse facial & body hair.

Delays in speech and motor skills.

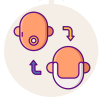
Deficits in attention, auditory processing and social skills.

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



Gynaecomastia and other feminine body characteristic.

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



Normal life span.

IMP

According to female's doc: read it while drinking coffee

Chromosomal Tests

- **Prenatal:** Maternal age > 37 yrs; Ultrasound scan (USS) changes; Family history.
- **Triple test:**
  - Measuring the alpha fetoprotein (AFP) = detect the vast majority of neural tube defects and and a small portion of trisomy 21–affected pregnancies.
  - Human chorionic gonadotropin (hCG), and estriol): if positive it indicates an increased risk of trisomy 21 and 18.
- **Postnatal:** Learning & developmental disability; growth retardation.
- **Infertility:** Recurrent miscarriage, primary infertility.

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).

New Techniques

- Quantitative Fluorescence PCR (qf PCR): is able to measure number of copies of a chromosome – used for trisomy screening.
- Cell-free fetal DNA from maternal plasma at 6-8 weeks of gestation. It is a non-invasive prenatal diagnostic tool for chromosomal aneuploidy. It can be used to determine the fetus sex: look for presence of Y chromosome material.

TAKE HOME MESSAGES

- 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.

QUIZ

Q1. Nondisjunction defect in the meiotic cell division happens at which phase?

A. Prophase.
B. Metaphase.
C. Anaphase.
D. Telophase.

Q2. Meiosis occurs in which one of the following cells?

A. Somatic cells.
B. Germline cells.
C. Ovum and sperm.
D. B & C.

Q3. A 16 years old girl presented to the hospital complaining of delayed puberty, on examination the doctor noticed the that patient is short with a webbed neck, chromosomal karyotyping showed 45,X . What is the diagnosis?

A. Klinefelter syndrome.
B. Down Syndrome.
C. Turner Syndrome.
D. Constitutional delayed puberty.

Q4. Which of the following chromosome complements will not be viable?

A. XXX.
B. XO or X.
C. XXY.
D. OY or Y.

Q5. Which one of the following tests is the best for detecting a chromosomal abnormality?

A. FISH.
B. Karyotyping.
C. PCR.
D. A & B.

Q6. Which one of the following chromosomal disorders correlates with the karyotype 47,XXY?

A. Klinefelter Syndrome.
B. Down Syndrome.
C. Turner Syndrome.
D. Trisomy X.

Q7. Which one of the following is the result of nondisjunction in meiosis I?

A. 2 haploid , 1 nullisomy , 1 Diosomy.
B. 2 Diosomy , 2 nullisomy.
C. 4 Haploid.
D. 3 Haploid , 1 nullisomy.

Q8. Which of the following chromosome complements will be least phenotypically affected?

A. XXX.
B. XO or X.
C. XXY.
D. OY or Y.

Answers: 1) C, 2) D, 3) C, 4) D, 5) D, 6) A, 7) B, 8) A