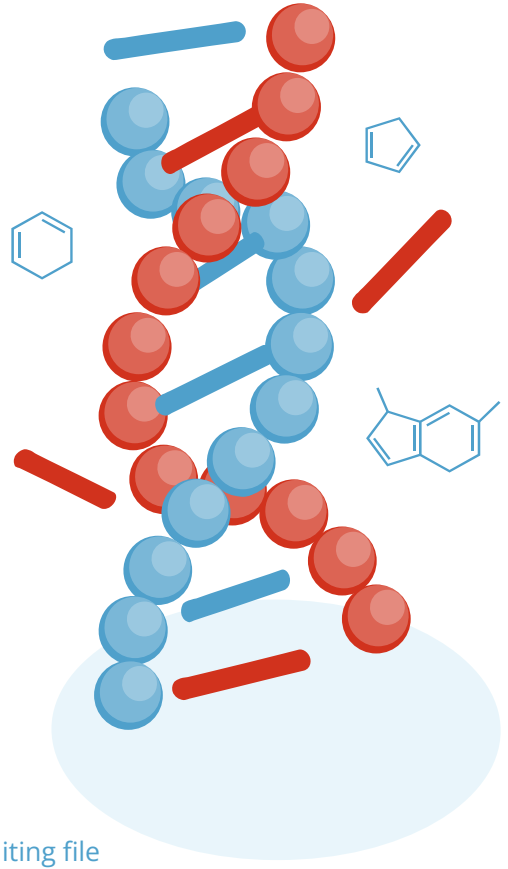
Klinefelter, Turner & Down Syndrome

Reproductive Block



Editing file

Color index:

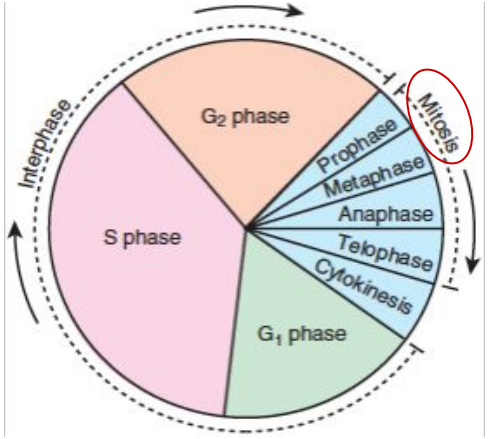
- Main Text
- Important
- Female's Slides
- Male's Slides
- Drs' notes
- Extra Info

Objectives

- Describe cell cycle and stages of mitosis and meiosis
- Define non-disjunction and describe its consequences for mitosis and meiosis.
- Classify chromosomal abnormalities.
- Understand the common numerical chromosomal disorders monosomy and trisomy.
- Understand the common numerical autosomal & sex chromosome disorders; Down, Turner, & klinefelter syndromes.

The Cell Cycle

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



Team 442:

1. Cell cycle is the name we give the process through which cells replicate and make two new cells.
2. Cell cycle has different stages called G1, S, G2, and M. G1 is the stage where the cell is preparing to divide. To do this, it then moves into the S phase where the cell copies all the DNA. So, S stands for DNA synthesis.
3. After the DNA is copied and there's a complete extra set of all the genetic material, the cell moves into the G2 stage, where it organizes and condenses the genetic material, or starts to condense the genetic material, and prepares to divide.
4. The next stage is M. M stands for mitosis. This is where the cell actually partitions the two copies of the genetic material into the two daughter cells.
5. After M phase completes, cell division occurs and two cells are left, and the cell cycle can begin again.

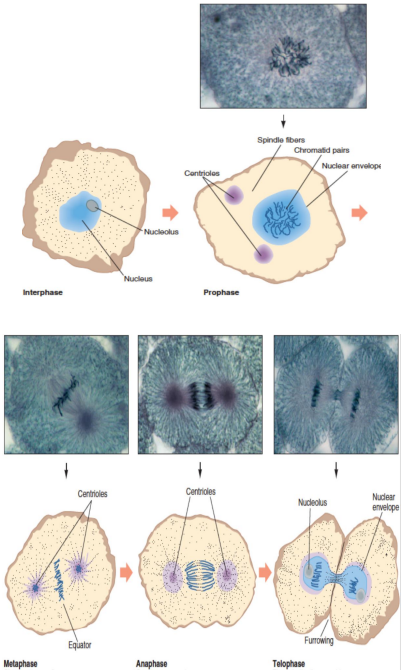
Source:https://www.genome.gov/genetics-glossary/Cell-Cycle#:~:text=A%20cell%20cycle%20is%20a,mitosis%2C%20and%20completes%20its%20division.

Mitosis in a human cell

Stages

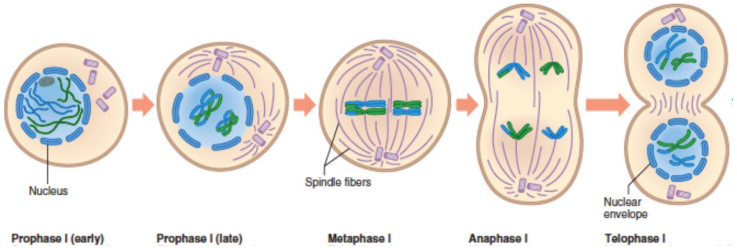
Interphase	Chromosomes are uncondensed
Prophase	Condensed chromosomes take up stain, the spindle assembles, centrioles appears and the nuclear envelope breaks down.
Metaphase	Chromosomes align.
Anaphase	Centromeres part and chromatids separate.
Telophase	The spindle disassembles and the nuclear envelope re-forms

Two identical diploid daughter cells (2n).



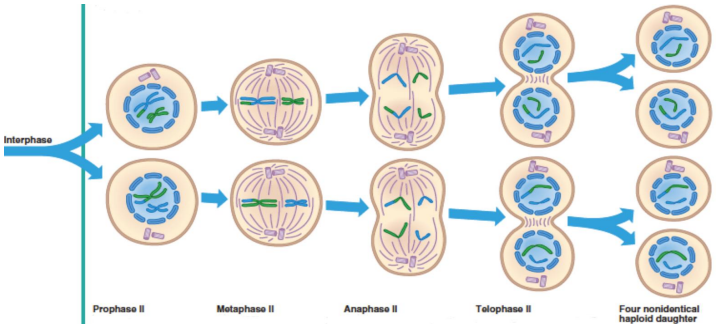
Stages of Meiosis: Meiosis I

Stages	**Prophase (early)**	Synapsis and crossing over occurs
	Prophase (late)	Chromosomes condense, become visible. Spindle forms. Nuclear envelope fragments. Spindle fibers attach to each chromosomes..
	Metaphase I	Paired homologous chromosomes align along equator of cell.
	Anaphase I	Homologous chromosomes separate to opposite poles of the cell.
	Telophase I	Nuclear envelope partially assemble around chromosomes. Spindle disappears. Cytokinesis divides cell into two.



Stages of Meiosis: Meiosis II

Stages		
	Prophase II	Nuclear envelope fragments. Spindle forms and fibers attach to both chromosomes.
	Metaphase II	Chromosomes align along equator of cell.
	Anaphase II	Sister chromatids separate to opposite poles of cell
	Telophase II	Nuclear envelopes assemble around two daughter nuclei. Chromosomes decondensed. Spindle disappears. Cytokinesis divides cells cytokinesis divides cells.
	Four non-identical haploid daughter cells (1n).	



Comparison between Mitosis & Meiosis

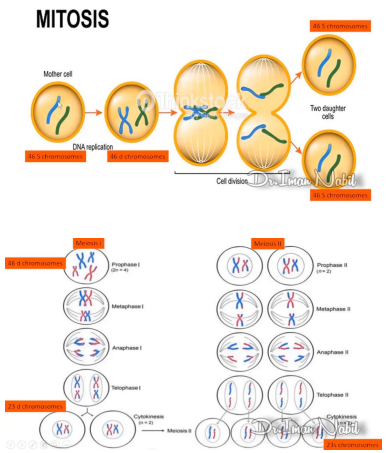
Cell Division	Mitosis	Meiosis
Number of Division	One division.	Two divisions.
Number of Daughter cells (DCs) per cycle	**Two** daughter cells per cycle.	**Four** daughter cells per cycle.
Similarities (identical) of DCs to the Parent Cell	Genetically identical to the parent cells.	Genetically different to the parent cells.
Chromosomal number of DCs to the Parent Cell	Chromosome number of the daughter cells same as parent cells (2n).	Chromosome number of the daughter cells half that of parent cells (1n).
Type of Cell	Occurs in **somatic cells.**	Occurs in **germline cells.**
Occurance	Occurs throughout **life cycle.**	In humans, complete after **sexual maturity.**
Uses	Used for growth, repair, and asexual reproduction.	Used for sexual reproduction, producing new gene combinations.

Summary of Chromosome & Chromatid Num
During Mitosis, Meiosis I & II in Humans

Dr: you have to understand the numbers

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

Extra for understanding:

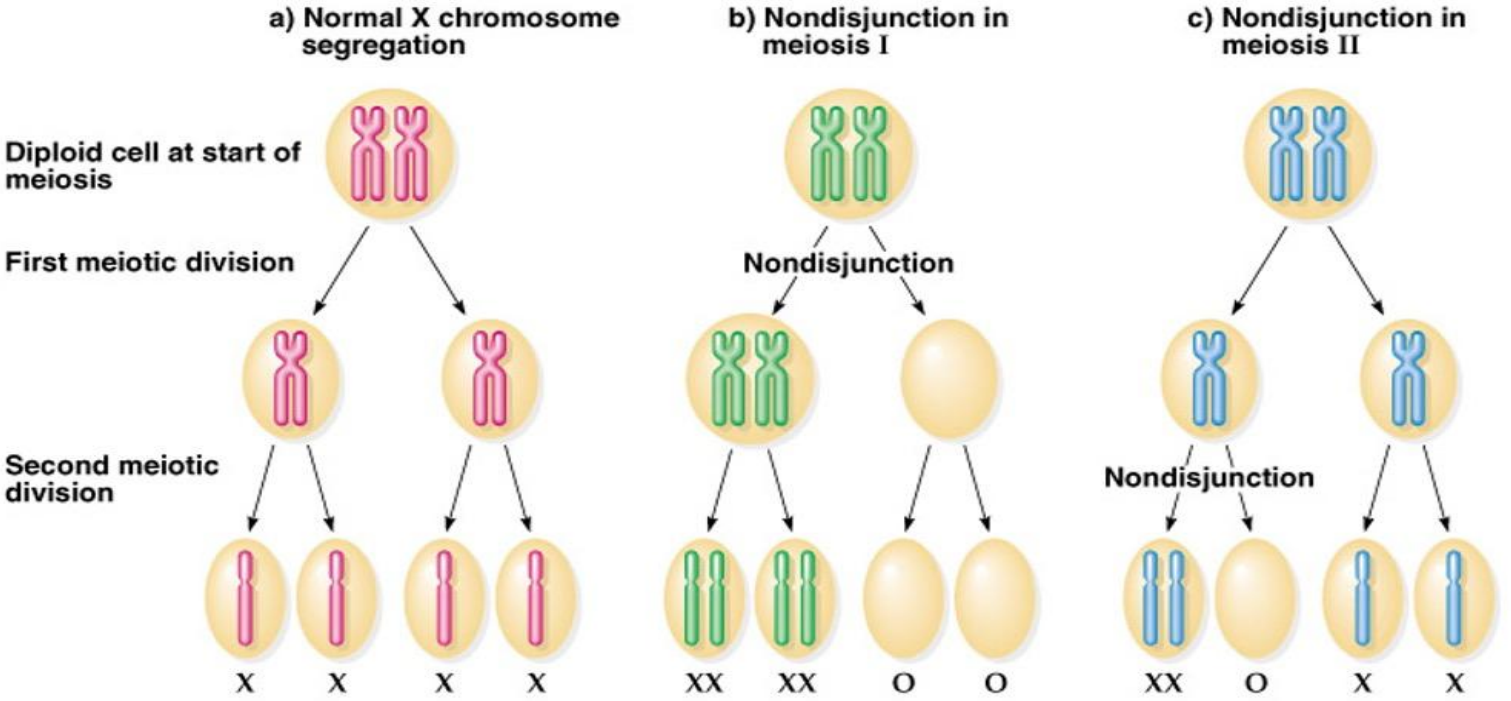


- During the stages of meiosis and mitosis, the chromatid count never changes. Only the number of chromosomes changes (by doubling) during anaphase when sister chromatids are separated. During meiosis I, neither the chromosome number nor the chromatid number change until after telophase I is complete.

Nondisjunction in Meiosis

Nondisjunction "not coming apart" : is the failure of a chromosome pair to separate properly during meiosis I, or of two chromatids of chromosome to separate properly during meiosis II or mitosis.

- Can affect each pair of a chromosome.
- Is **not a rare** event.
- As a result, one daughter cell has two chromosome, and the other has none.
- The result of this error is cell with an imbalance of chromosomes (**Aneuploidy**).

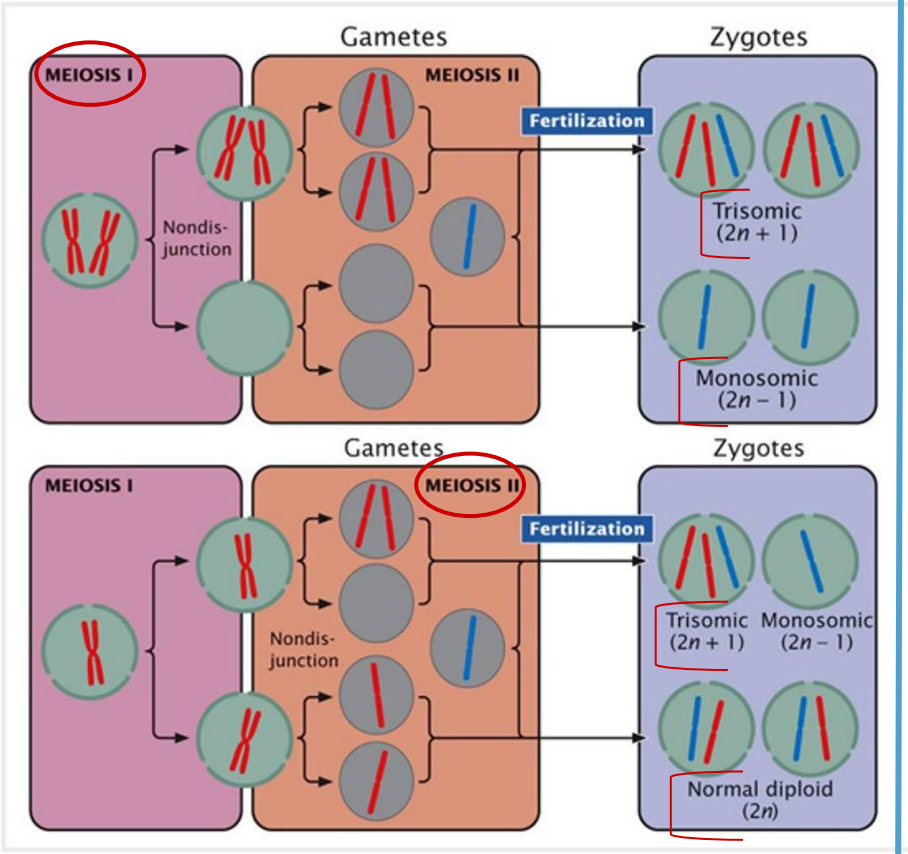


4 haploid gametes.

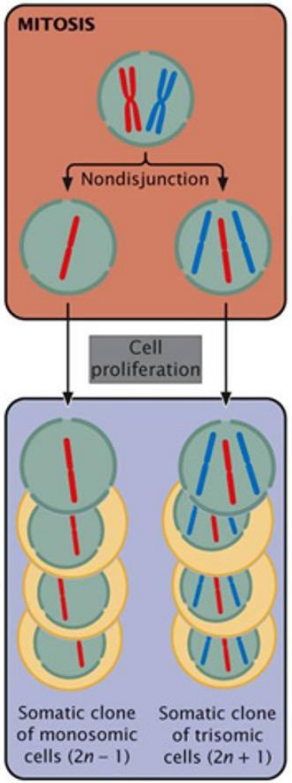
2 gametes with diploid number of X chromosome, and 2 gametes lacking X chromosome.

2 gametes with haploid number of X chromosome (on the right), 1 gamete with diploid number of X chromosome (left), 1 gametes lacking X chromosome

Meiosis



Mitosis



- Nondisjunction occurs in **Meiosis** more commonly than **Mitosis**

Aneuploidy

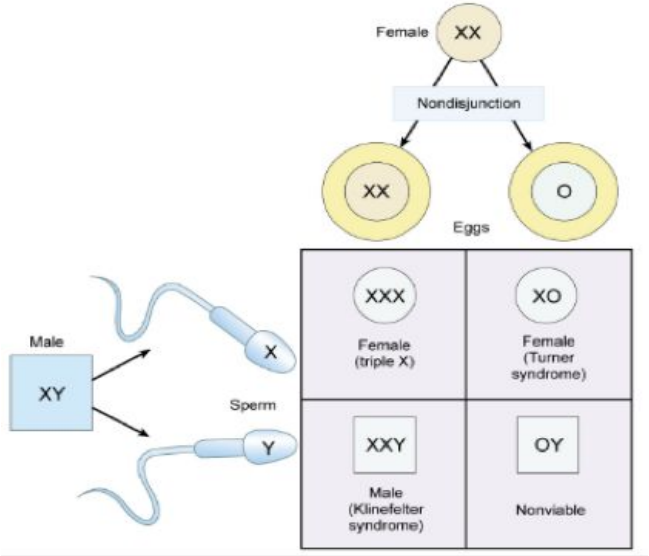
- **Aneuploidy**: The result of this error is cell with an imbalance of chromosomes.

Autosomal

- Trisomy 21 (Down syndrome)

Sex chromosome

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



DOWN SYNDROME (47,XY,+21)

KARYOTYPE:47,XY,+21

- Mostly caused by: Nondisjunction restricted to **Meiotic** errors in the egg.
- Source of extra chromosome: Mothers in the majority of cases
- Advanced maternal age was significantly associated with both meiosis I (MI) and meiosis II (MII).

Epidemiology:

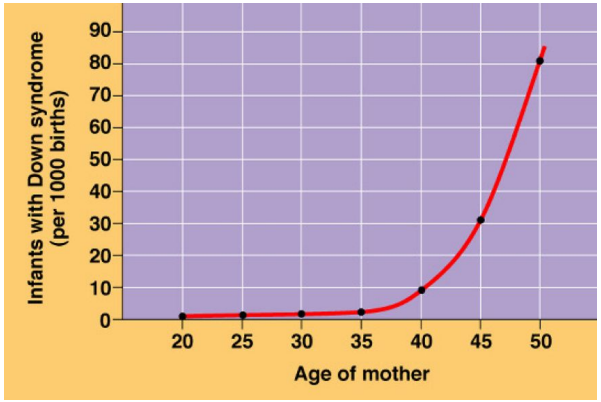
Nondisjunction occurred in **MII**, mothers were 15.1 times more likely to be **≥40 years** compared to 8.5 times of nondisjunction in **MI**.

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

Mosaic: Post-fertilization (or postzygotic) Mitotic error.

يعني الـ germline cell مرت طبيعي بالـ meiosis وصار لها fertilization ، بعدها بتدخل بمرحلة الـ mitosis وهنا يصير لها الـ error وتصير تنسخ نفسها غلط)

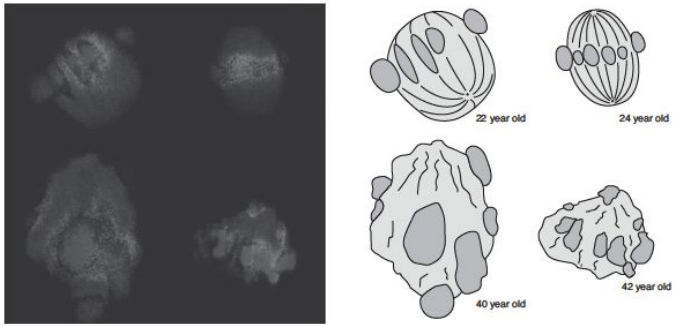
- The incidence of trisomy 21 rises sharply with **increasing maternal age**



Team 439:

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

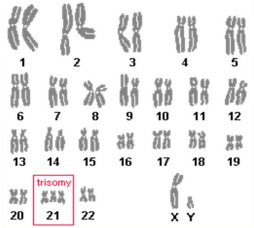
- Meiosis II oöcytes from younger and older women

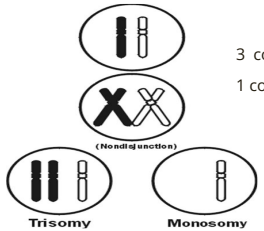


Team 439:

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

Features of Down Syndrome





3 copies = trisomy

1 copy = monosomy

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

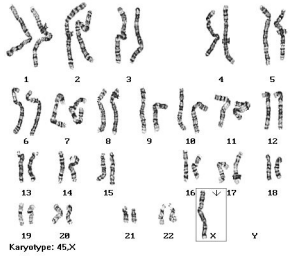
Sex Chromosome Imbalance is Much Less Deleterious

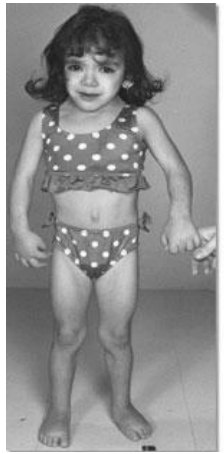
1. **Klinefelter Syndrome (47,XXY).**
2. **47,XYY Syndrome:** (May be *without any symptoms*. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs).
3. **Trisomy X (47,XXX) females:** (It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They do have a **reduction in IQ** comparable to that of Klinefelter males).
4. **Turner Syndrome (45,X and variants).**

Turner Syndrome (45, XO)

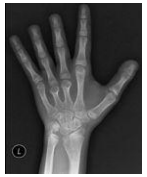
What is turner syndrome ?

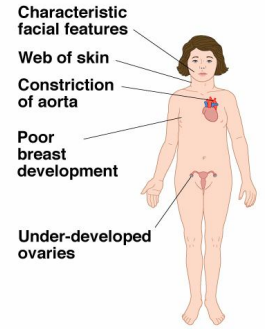
- Monosomy of sex chromosome: (Monosomy X: 45, XO) i.e. only one X chromosome is present.
- The only viable monosomy in humans.
- Individuals are genetically **female**, not mature sexually and sterile.
- Occurrence: 1 in 2500 live female births.
- 96-98% do not survive to birth
- Signs do not become evident until **puberty**





Features



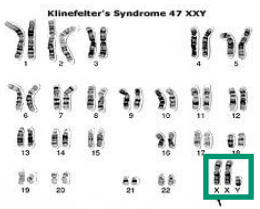


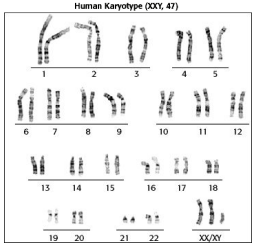
1. **Short stature**, broad chest, low hairline.
2. Neck abnormalities (webbed neck).
3. Skeletal disorders (e.g. scoliosis, dislocated hips/elbows).
4. **Lack of ovarian development (streak ovaries).**
5. Increased risk of osteoporosis, cardiovascular abnormalities (e.g. constriction of aorta & HT).
6. Normal life span.
7. No development delays, **normal intelligence.**
8. Cardiovascular: (Bicuspid aortic valve, Coarctation of aorta, Thoracic aortic aneurysm (aortic root dilatation)
9. Skeletal: (Short stature, Short 4th metacarpal/metatarsal bone (± short 3rd and 5th), Osteoporosis (due to lack of estrogen), Scoliosis).
10. Reproductive: (Women with Turner syndrome are almost universally infertile).

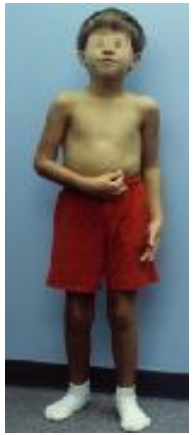
Klinefelter Syndrome (47, XXY)

What is Klinefelter syndrome ?

- Occurrence: 1 in 1100 births (liveborn **males**)
- 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.

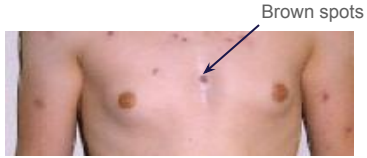


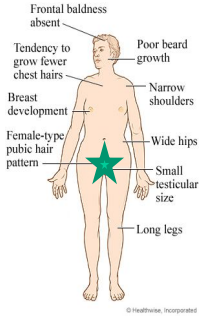




Features

1. **Tall,** longer fingers and arms, delicate skin.
2. **Sexually underdeveloped & infertile (no spermatogenesis).**
3. Sparse facial & body hair.
4. Delays in speech and motor skills.
5. Deficits in attention, auditory processing and social skills.
6. **Low mental ability** (slight reduction in IQ, but usually Normal intelligence).
7. **Gynaecomastia** and other feminine body characteristic.
8. Increased risk of autoimmune disorders, breastCancer, osteoporosis, leg ulcers, depression,and dental problems.
9. Normal life span.





Chromosomal Tests

When to do a chromosomal test

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**)

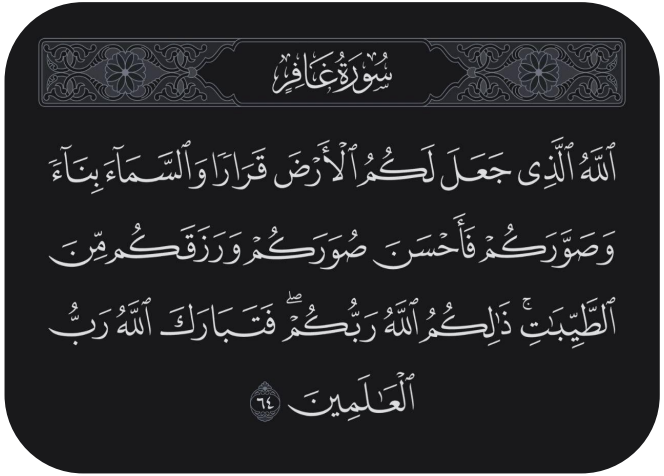
- Available on amniocentesis sample.
- Uncultured amniocytes.
- FISH probes for **X,Y, 21**.
- Result in 24-48 hours.
- Proceed onto full karyotype (11-14 days).

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 massage

- 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.



Test Yourself! MCQs

Answers: D, C, C, A, A, C

Q1: Nondisjunction refers to the failure of chromosomes to separate properly during:
A. DNA replication
B. Transcription
C. Translation
D. Cell division

Q2: Nondisjunction during meiosis I can result in which of the following conditions?
A. Trisomy
B. Monosomy
C. Both trisomy and monosomy
D. Neither trisomy nor monosomy

Q3: An increased risk of nondisjunction is associated with which factor?
A. Genetic factors only in the mother
B. Optimal nutrient intake during pregnancy
C. Advanced maternal age
D. Living at high altitudes

Q4: What is the chromosomal anomaly in Turner syndrome?
A. 45 XO
B. 46XX
C. 46XY
D. 47XXY

Q5: 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.

Q6: Which of the following is caused by autosomal chromosomal aneuploidy?
A. Klinefelter
B. Turner
C. Down syndrome
D. Trisomy X

Textbook Questions !

Answers: A, C, B. Explanations

Q1: A 25-year-old woman with amenorrhea has never had menarche. On physical examination, she is 145 cm (4 ft 9 in) tall. She has a webbed neck, a broad chest, and widely spaced nipples. Strong pulses are palpable in the upper extremities, but there are only weak pulses in the lower extremities. On abdominal MR imaging, the ovaries are small, elongated, and tubular. Which of the following karyotypes is most likely to be present in this patient?

A. 45,X/46,XX **B.** 47,XXY **C.** 47,XX,+16 **D.** 47,XXX

Q2: A 22-year-old primigravida notes absent fetal movement for 2 days. The fetus is delivered stillborn at 19 weeks' gesta-tion. The macerated fetus shows marked hydrops fetalis and a large posterior cystic hygroma of the neck. At autopsy, internal anomalies are seen, including aortic coarctation and a horseshoe kidney. Which of the following karyotypes is most likely to be present in cells obtained from the fetus?

A. 47,XX,+18 **B.** 47,XX,+21 **C.** 45,X **D.** 48,XXXY

Q3: A 27-year-old man comes to the physician for an infer-tility workup. He and his wife have been trying to conceive a child for 6 years. Physical examination shows bilateral gyneco-mastia, reduced testicular size, reduced body hair, and increased length between the soles of his feet and the pubic bone. A semen analysis indicates oligospermia. Laboratory studies show increased follicle-stimulating hormone level and slightly decreased testosterone level. Which of the following karyotypes is most likely to be present in this man?

A. 46XX/47XX,+21 **B.** 47,XXY **C.** 47,XYY **D.** 47,XXX

Team Leaders

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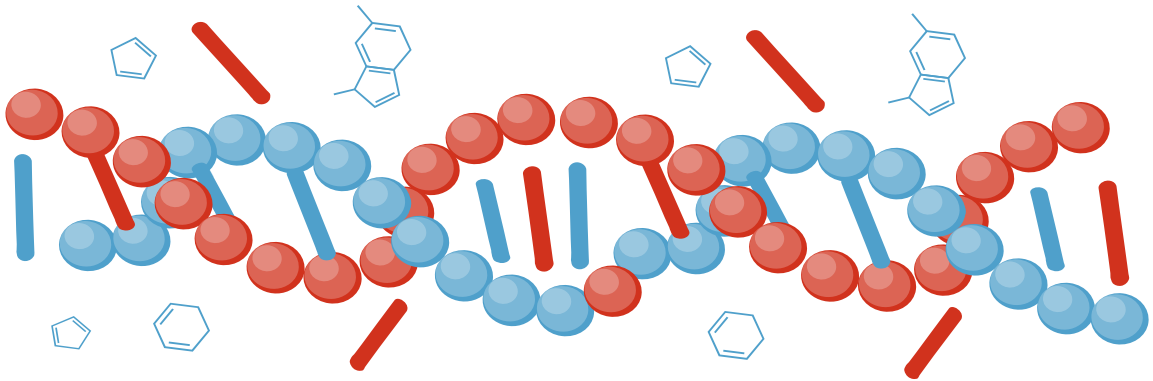

Wish You All the Best !!