



Kleinfelter, Turner & Down Syndrome

Editing file



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-  **Important**
-  **Original content**
-  **Only in girls slides**
-  **Only in boys slides**
-  **Doctor's notes**



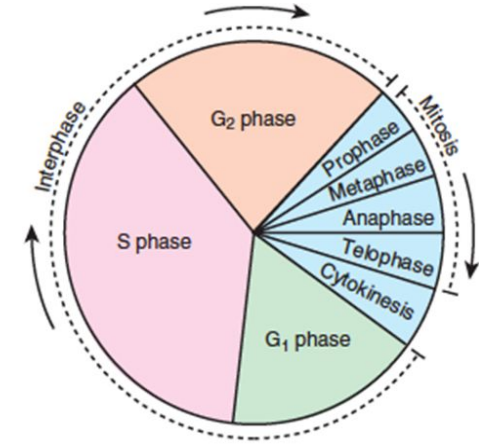
Objectives:

- ◀ 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 syndromes.

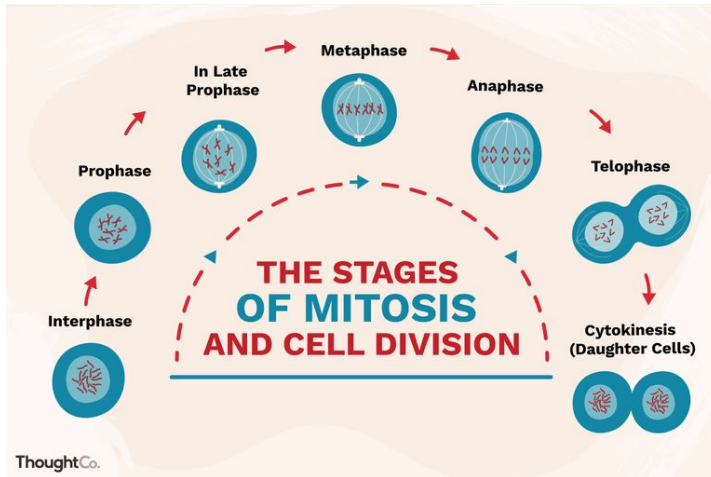
According to female's doc (nomenclature of syndromes is super imp)

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



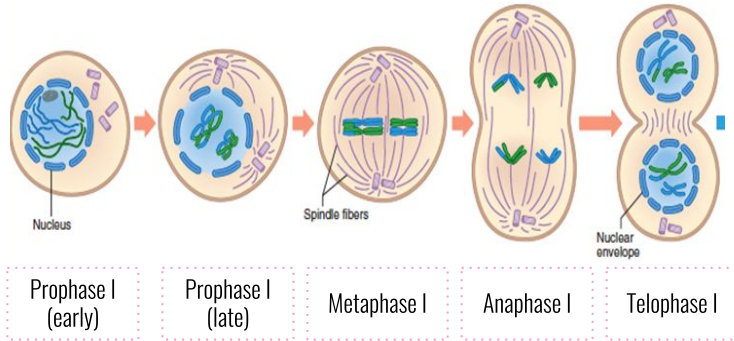
1. **Interphase:** Chromosomes are uncondensed.
2. **Prophase:** Condensed chromosomes take up stain, the spindle assembles, centrioles appears and the nuclear envelope breaks down.
3. **Metaphase:** Chromosomes align.
4. **Anaphase:** Centromeres part and chromatids.
5. **Telophase:** The spindle disassembles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



Stages of Meiosis I & II

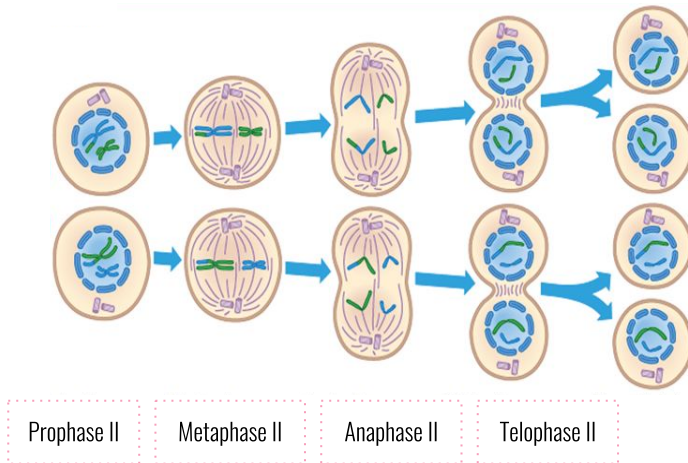


Meiosis I



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 chromosome.
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.

Meiosis II



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

Mitosis <i>Any division post-zygotic (After fertilization)</i>	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

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).

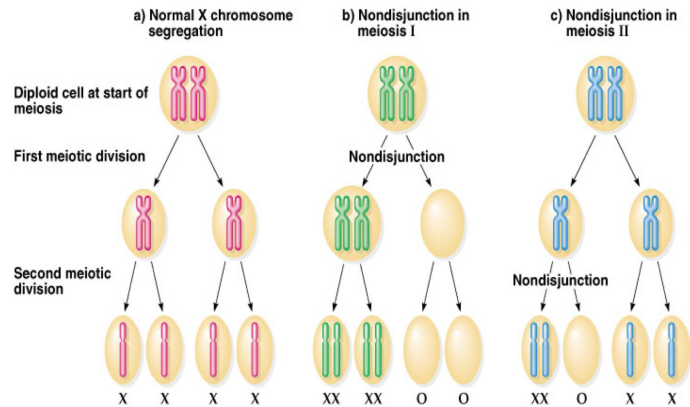
- Is not a rare event.
- Can affect each pair of chromosomes.
 - ◆ As a result, one daughter cell has two chromosomes or two chromatids and the other has none.
- Chromosomal abnormality:
 - ◆ Numerical
 - ◆ structural

In this case it's numerical abnormality.

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

Autosomal
Trisomy 21 (Down syndrome)

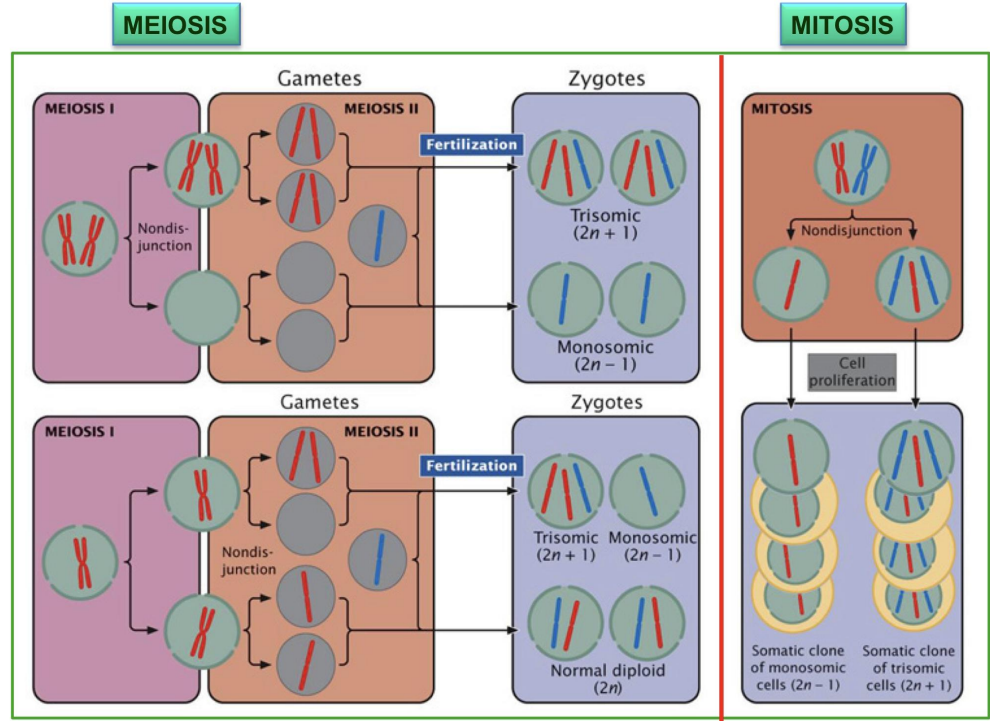
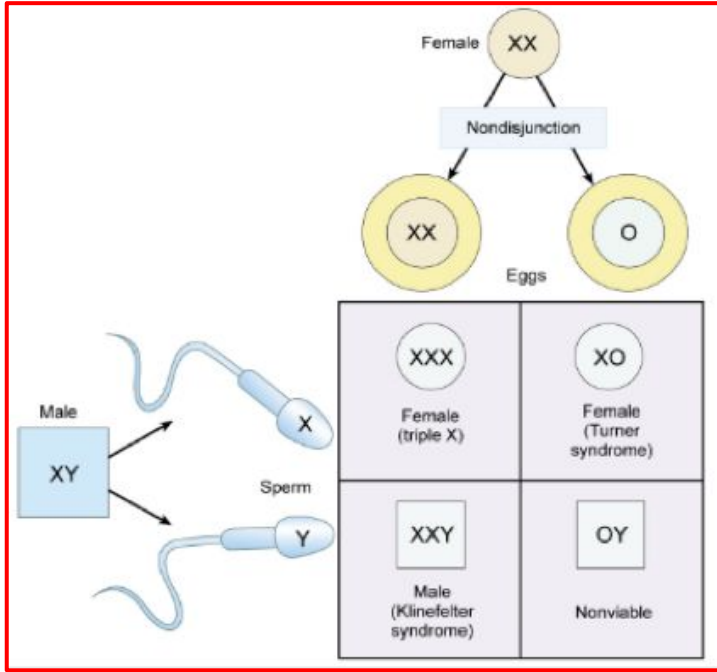
Sex Chromosomes
47XXY (Klinefelter syndrome)
45X (Turner syndrome).



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

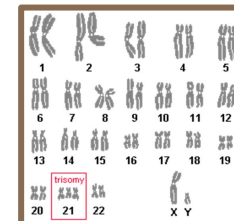
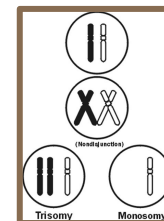
B: Result of Nondisjunction in Meiosis I:
2 gametes with diploid number of X chromosome, and 2 gametes lacking X chromosomes.

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.



If the nondisjunction occurred in meiosis I the result is 100% abnormal cells.
 If the nondisjunction occurred in meiosis II the result is 50% abnormal cells.

Down Syndrome (47, XY, +21)



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

Source of extra chromosome: Mothers & ↑ with age.

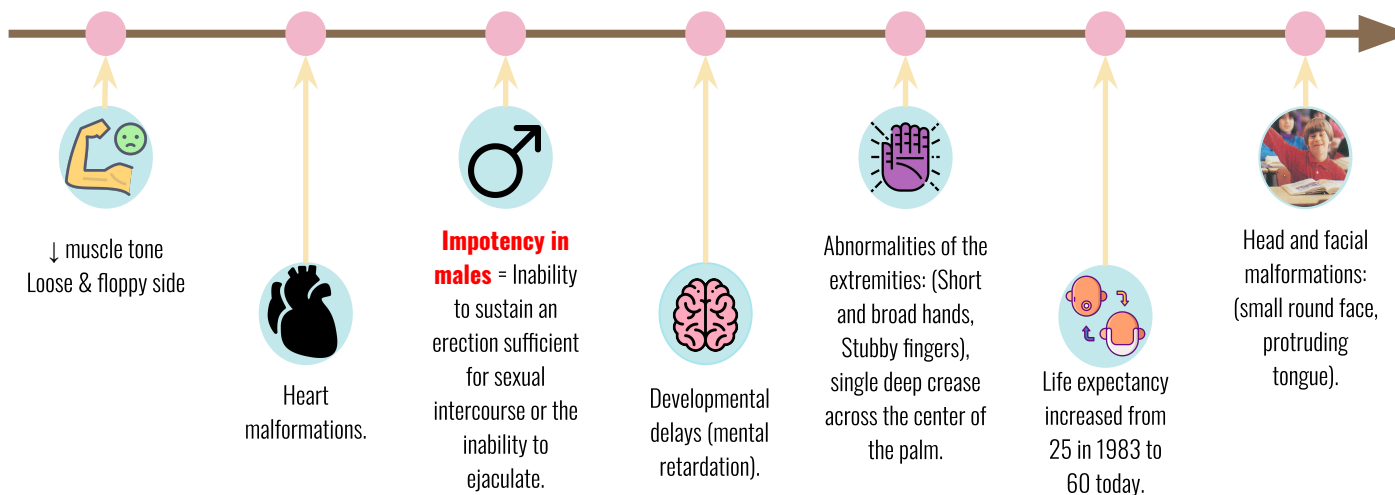
Advanced maternal age was significantly associated with both **meiosis I (MI)** and **meiosis II (MII)**.

Epidemiology:

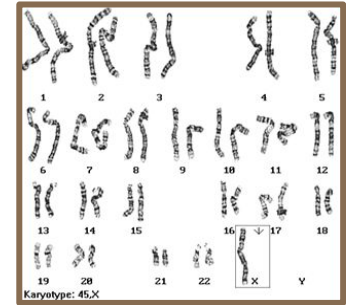
Nondisjunction occurred in MII, mothers were 15.1 times more likely to be ≥40 years compared to 8.5 times of nondisjunction in MI.

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

Features of Down Syndrome

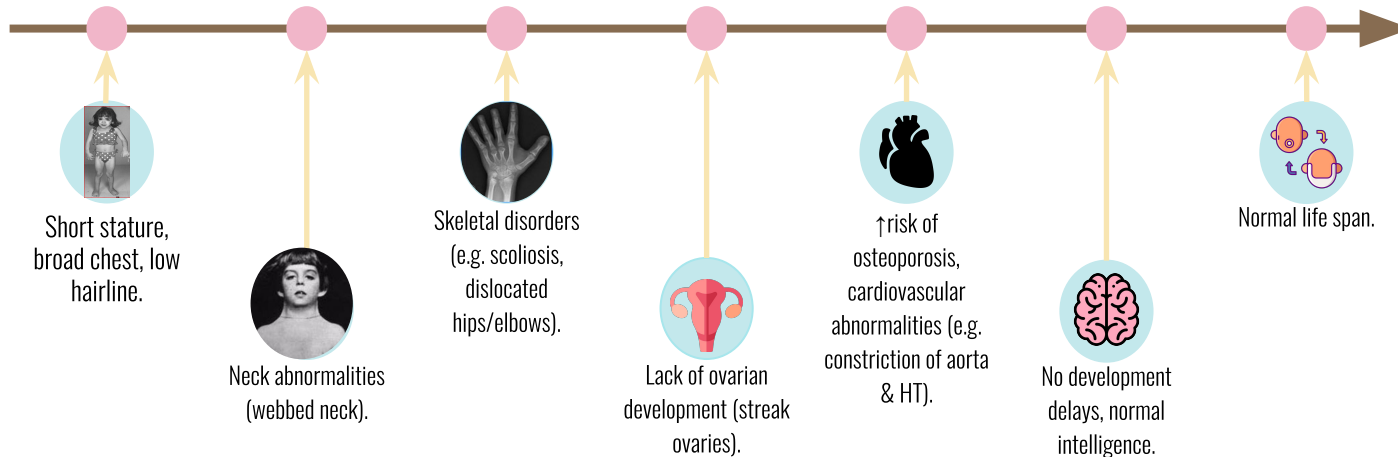


Turner Syndrome (45, XO)



- **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.

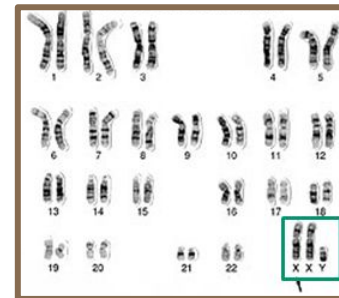
Features of Turner Syndrome



- **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).

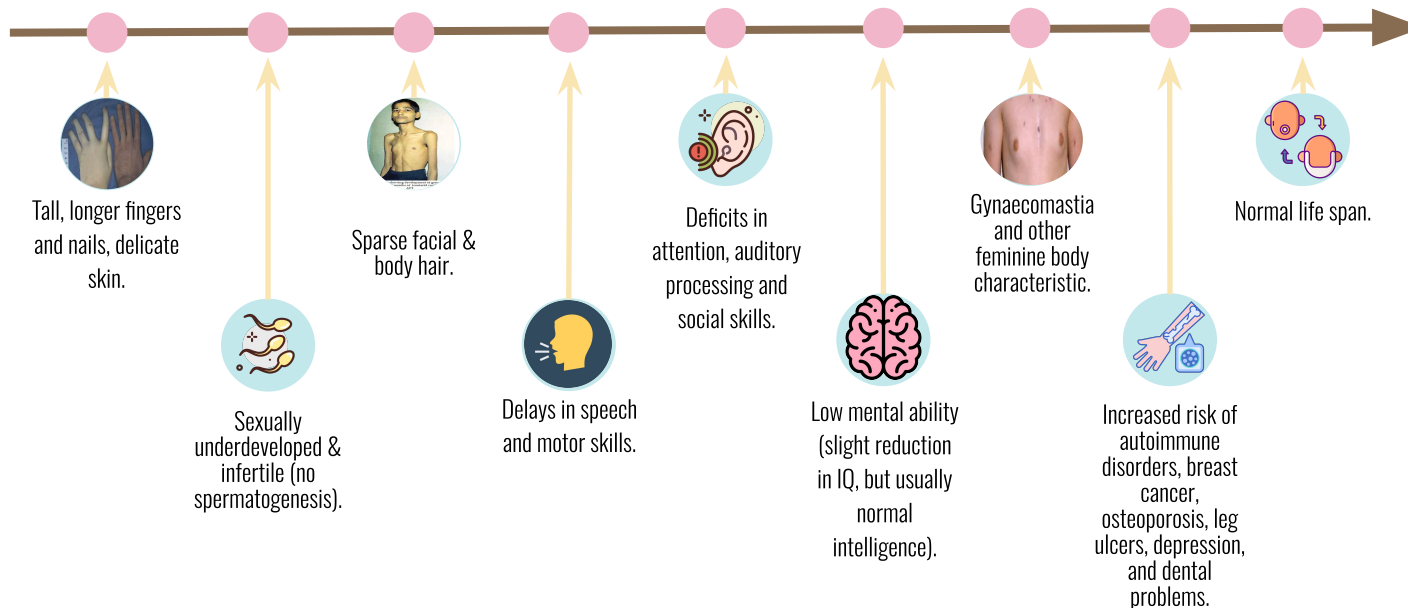


Klinefelter Syndrome (47, XXY)



- **Occurrence:** 1 in 2500 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.

Features of Klinefelter Syndrome



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.

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 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.

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).

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

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

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.