Genetics Lecture 5

1. Chromosomal Basis of Sex
In humans, sex determination depends on sex chromosomes. Females are 46,XX and males are 46,XY. The presence of the Y chromosome determines male development due to the SRY gene. In the absence of the Y chromosome (or SRY), development follows the default female pathway.

2. SRY Gene (VERY IMPORTANT)
The SRY gene (Sex-Determining Region Y) is located on the short arm (p arm) of the Y chromosome. It encodes a transcription factor that initiates male differentiation by activating genes responsible for testis development. If SRY is absent or mutated, an XY individual develops as a phenotypic female.

3. Pseudoautosomal Regions (PAR)
PAR regions are homologous segments located at the ends of X and Y chromosomes (both p and q arms). These regions allow pairing and recombination during meiosis. Outside these regions, X and Y chromosomes are genetically different.

4. Y Chromosome Structure
The Y chromosome contains unique sequences not found on the X chromosome. Important regions include:
- SRY → male determination
- AZF (Azoospermia Factor) → sperm production
Deletion of AZF leads to male infertility (azoospermia). The distal q arm contains heterochromatin and has no major clinical significance.

5. X Chromosome Clinical Importance
The X chromosome contains many important genes, including:
- DMD gene → Duchenne muscular dystrophy
- F8 gene → Hemophilia A
- FMR1 gene → Fragile X syndrome
- HGPRT gene → Lesch-Nyhan syndrome
Mutations in these genes lead to X-linked disorders.

6. Structural Chromosomal Abnormalities
Structural abnormalities result from chromosome breakage and incorrect repair. They include deletion, duplication, inversion, and translocation. These can disrupt gene function and lead to disease.

7. Cri-du-chat Syndrome
This syndrome results from deletion of the short arm of chromosome 5. It is characterized by intellectual disability and a characteristic cat-like cry. Most affected individuals die in early childhood.

8. Translocations and Cancer
Certain cancers are caused by chromosomal translocations. A classic example is t(9;22), which produces the Philadelphia chromosome and leads to chronic myelogenous leukemia (CML).

9. BCR-ABL Fusion Gene
The translocation moves the ABL gene (chromosome 9) to chromosome 22, where it fuses with the BCR gene. This creates the BCR-ABL fusion gene, which encodes a constitutively active tyrosine

kinase. This results in uncontrolled cell proliferation (cancer).

10. Robertsonian Translocation
A specialized translocation occurring between acrocentric chromosomes (13,14,15,21,22). The short arms are lost, and the long arms fuse. Carriers have 45 chromosomes but are usually phenotypically normal.

11. Gamete Formation in Translocation Carriers
Balanced carriers can produce multiple types of gametes. After fertilization, outcomes may include normal offspring, balanced carriers, or individuals with trisomy/monosomy. There is a significant risk of abnormal offspring.

12. Triploidy
Triploidy is the presence of three sets of chromosomes (3n = 69). It is commonly caused by dispermy (two sperm fertilizing one egg). Other causes include diploid gametes. It leads to severe abnormalities and is usually fatal.

13. Tetraploidy
Tetraploidy (4n = 92) results from failure of mitotic division (endomitosis). It is incompatible with life.

14. Molar Pregnancy
Complete mole: only paternal chromosomes (no fetus). Partial mole: triploidy with abnormal fetal development. Associated with abnormal trophoblastic proliferation.

15. Mosaicism
Mosaicism results from post-zygotic mutations during mitosis. The individual has two or more genetically different cell lines. Severity depends on timing of the mutation (earlier = more severe).

16. Chimera
A chimera results from fusion of two different zygotes. The individual contains genetically distinct cell populations from different origins.

17. High-Yield
- SRY gene determines male development
- AZF deletion → infertility
- t(9;22) → CML (Philadelphia chromosome)
- Triploidy = 69 chromosomes
- Mosaicism = post-zygotic
- Chimera = fusion of two zygotes
- Robertsonian translocation → 45 chromosomes but normal phenotype