Genetics Lecture

1. Normal Chromosome Segregation

During meiosis I, homologous chromosomes separate, while during meiosis II and mitosis, sister chromatids separate. This ensures equal distribution of genetic material into daughter cells.

Accurate segregation is critical for maintaining the normal chromosome number (46 in humans). Any disruption leads to chromosomal abnormalities.

2. Nondisjunction

Nondisjunction is the failure of chromosomes to separate properly during cell division.

- In meiosis I: homologous chromosomes fail to separate → all gametes abnormal (50% n+1, 50% n−1).

- In meiosis II: sister chromatids fail → 50% normal, 25% n+1, 25% n−1.

This leads to abnormal gametes, which upon fertilization produce abnormal zygotes.

3. Aneuploidy

Aneuploidy refers to an abnormal number of chromosomes that is not a multiple of the haploid number.

- Monosomy (2n−1): missing one chromosome (usually lethal).

- Trisomy (2n+1): extra chromosome (may survive depending on chromosome).

Aneuploidy can affect autosomes or sex chromosomes.

4. Polyploidy & Euploidy

Euploidy: exact multiples of haploid number (n, 2n, 3n, etc.).

Polyploidy: more than two sets of chromosomes (triploidy 3n, tetraploidy 4n).

Polyploidy is common in plants but rare and usually lethal in humans.

5. Chromosomal Structural Abnormalities

- Deletion: loss of a segment → loss of genes.

- Duplication: repeated segment → gene dosage effect.

- Inversion: segment reversed within chromosome.

- Translocation: exchange between non-homologous chromosomes.

Balanced rearrangements: no genetic material lost (often asymptomatic).

Unbalanced rearrangements: gain/loss of DNA → disease.

6. Recombination vs Translocation

Recombination: normal process during prophase I involving homologous chromosomes.

Translocation: abnormal exchange between non-homologous chromosomes, may cause disease (e.g., leukemia).

7. Chromosomal Disorders

Chromosomal abnormalities lead to syndromes with characteristic clinical features.

Down Syndrome (Trisomy 21)

Most common viable autosomal trisomy.

Cause: nondisjunction (mainly maternal origin, especially meiosis I).

Risk increases with advanced maternal age (>35 years).

Clinical features:

- Intellectual disability (IQ 25–50)

- Flat facial profile, epicanthic folds

- Low nasal bridge, protruding tongue

- Hypotonia

- Congenital heart defects (VSD, AV canal)

- Simian crease, gap between toes

- Increased leukemia risk

8. Origin of Extra Chromosome

Short tandem repeats (STRs) are used to trace parental origin.

PCR + gel electrophoresis allows identification of chromosome origin.

Most trisomy 21 cases are maternal (~94%).

9. Partial Trisomy 21

Occurs when extra chromosome 21 material is attached to another chromosome.

Even with 46 chromosomes, the genetic effect is equivalent to trisomy.

Often due to balanced translocation in a parent.

10. Other Viable Trisomies

Trisomy 18 (Edwards syndrome):

- Severe developmental delay
- Congenital heart disease (95%)
- Clenched fists, rocker-bottom feet
- Prominent occiput, low-set ears

Trisomy 13 (Patau syndrome):

- Severe intellectual disability
- Cleft lip/palate
- Polydactyly
- Microcephaly, eye defects
- Polycystic kidneys

11. Key Principles

- Only trisomy 13, 18, and 21 are compatible with life.

- Most other trisomies and all autosomal monosomies are lethal.

- Monosomy is more severe than trisomy because of loss of genetic material.

- Sex chromosome aneuploidies are generally less severe.

12. Important Clinical Insights

- Maternal age is a major risk factor for nondisjunction.

- Genetic testing (karyotyping, STR analysis) is essential for diagnosis.

- Balanced carriers may be asymptomatic but can produce affected offspring.

Conclusion

Chromosomal abnormalities arise due to errors in segregation or structural rearrangements. Understanding these mechanisms is essential for clinical diagnosis, genetic counseling, and predicting disease risk.