Genetics Lecture 8

1. Patterns of Single Gene Inheritance

Single-gene disorders follow inheritance patterns depending on where the gene is located and whether the mutation is dominant or recessive.

Three very important terms:

1. **Sex-linked**
2. **Sex-influenced**
3. **Sex-limited**

2. Sex-Linked vs Sex-Influenced vs Sex-Limited

A. Sex-Linked

Gene is physically located on a sex chromosome.

-If on X chromosome → **X-linked**

-If on Y chromosome → **Y-linked**

B. Sex-Influenced

Gene is usually autosomal, but expression differs between males and females because of hormones or physiology.

Example:

Hemochromatosis
Severity often greater in males.

C. Sex-Limited

Gene may be present in both sexes, but trait expressed in only one sex.

Example:

Milk production → females only

3. X Chromosome and Gene Expression

The X chromosome contains many genes unrelated to sex determination.

Males:

-One X chromosome only

-One allele for X-linked genes

Females:

-Two X chromosomes

-Two alleles for X-linked genes

This creates a problem:

Females could theoretically produce double the amount of X-linked gene products.

This is corrected by:

Dosage Compensation

4. Dosage Compensation (VERY IMPORTANT)

Mechanism that equalizes X-linked gene expression between males and females.

Without it:

-Females = 2 X chromosomes

-Males = 1 X chromosome

Would cause imbalance of proteins and RNA.

Solution:**X-Chromosome Inactivation**

Also called:**Lyon Hypothesis**

5. Lyon Hypothesis / X-Inactivation

In female embryos (3–7 days after fertilization):

One of the two X chromosomes becomes inactive.

The inactive X condenses into:

Barr Body

This chromosome becomes transcriptionally silent.

So female cells function with one active X, like males.

6. Important Features of X-Inactivation

Random

Either maternal X or paternal X is inactivated randomly

Clonal

Once one X is inactivated in a cell, all daughter cells keep the same inactive X

Permanent

Maintained through mitosis

Mosaicism

Females become mosaics because some cells express maternal X and others paternal X

7. Genes That Escape X-Inactivation

Some genes remain active on inactive X chromosome

Especially:

-Pseudoautosomal region (PAR)

-Genes with Y chromosome counterparts

8. Barr Body (Idk but it's possible that a question will come up about it because this topic has been repeated in the past paper)

Inactive condensed X chromosome visible in nucleus during interphase.

Number of Barr Bodies Formula:

Number of X chromosomes − 1

Examples:

- XX female = 1 Barr body
- XY male = 0
- XXX female = 2
- XXY male = 1

9. Sex-Linked Inheritance

Genes on sex chromosomes follow special inheritance patterns.

Two main types:

1. X-linked recessive
2. X-linked dominant

(Y-linked is rare)

Examples to remember:

X-Linked Recessive (XLR): Hemophilia, DMD, G6PD (I mentioned in Summary of lec 5)
X-Linked Dominant (XLD): Rett Syndrome (Lethal in males) & Vitamin D-resistant rickets

10. Basic Principle

Because males have one X chromosome only:

One recessive mutation causes disease.

Male genotype:

X^aY = **Always affected (Hemizygous)**

Female needs two mutant alleles:

X^aX^a = **Affected (Rare)**

Carrier female:

X^AX^a = **Carrier (Can pass to 50% of sons)**

11. Why More Common in Males?

Males are:

Hemizygous

Only one copy of X chromosome genes

So recessive mutation is expressed immediately

Females usually need two copies

12. Features of X-Linked Recessive Inheritance (VERY IMPORTANT)

1. Much more common in males
2. No father-to-son transmission
3. Affected males linked through maternal line
4. Carrier females usually unaffected or mildly affected
5. Diagonal inheritance pattern
6. Full expression in males

13. Diagonal Inheritance

Affected grandfather → carrier daughter → affected grandson

Trait passes through females to males

14. Transmission Rules

Affected Male × Normal Female

Father = X^aY
Mother = X^AX^A

Children:

- All daughters = carriers
- All sons = normal

Carrier Female × Normal Male

Mother = X^AX^a
Father = X^AY

Children:

- 25% normal daughter
- 25% carrier daughter
- 25% normal son
- 25% affected son

16. Examples of X-Linked Recessive Diseases

- **Color Blindness**
  Usually red-green defect
  Much more common in males
- **Hemophilia**
  Clotting factor deficiency
  Bleeding tendency
- **Duchenne Muscular Dystrophy (DMD)**
  Severe muscle degeneration
  Progressive weakness
- **Becker Muscular Dystrophy**
  Milder than Duchenne

17. Mild Symptoms in Carrier Females

Because of random X-inactivation:

If many normal X chromosomes are inactivated, symptoms may appear mildly

18. Basic Principle

One mutant allele causes disease in males or females.

Male:

X^AY = affected

Female:

X^AX^a = affected

19. Features of X-Linked Dominant

1. Females affected more than males
2. No father-to-son transmission
3. Affected father passes trait to all daughters
4. Affected father passes to no sons
5. Affected heterozygous mother gives 50% risk to each child
6. Females may show milder variable disease (X-inactivation)

20. Transmission Rules

Affected Father × Normal Mother

Father = X^AY

Children:

- All daughters affected
- All sons normal

Affected Mother × Normal Father

Mother = X^AX^a

Children:

- 50% sons affected
- 50% daughters affected

21. Example of X-Linked Dominant Disease

Vitamin D Resistant Rickets
Causes soft bones due to impaired vitamin D metabolism

22. How to Distinguish AD from XLD

If affected father has:

- All daughters affected
- No sons affected

→ X-linked dominant

If sons can inherit from father:

→ Autosomal dominant

23. Y-Linked Inheritance

Rare because Y chromosome has few genes

Only males affected

Father passes trait to **all sons**

Never daughters

Usually related to:

- Male sex determination
- Spermatogenesis

24. Terms

-Hemizygous

Male has one X allele

-Obligate Carrier

Female must be carrier based on pedigree

Example: All daughters of affected X-linked recessive male

-Mosaic

Female has two populations of cells due to X-inactivation

25. High-Yield Exam Points

- Barr body = inactive X chromosome
- Lyon hypothesis = X inactivation
- Female mosaicism due to X-inactivation
- X-linked recessive more common in males
- No male-to-male transmission in any X-linked disease
- All daughters of affected XLR father are carriers
- All daughters of affected XLD father are affected
- Hemophilia = X-linked recessive
- Duchenne muscular dystrophy = X-linked recessive
- Rickets (vitamin D resistant) = X-linked dominant

26. Shortcut

- If pedigree shows:
  -Mostly males + skips females
  → X-linked recessive
  -Every generation + all daughters of affected father affected
  → X-linked dominant
  -Father to all sons only
  → Y-linked

27. Final Notes

- Females can be carriers for XLR diseases
- Males cannot be carriers (they are either affected or normal)
- X-inactivation explains variable symptoms in females
- X chromosome contains many important genes; Y has few