بسم الله الرحمن الرحيم

# X-Inactivation and Sex-Linked Pedigrees & Diseases

*Comprehensive study sheet based on the lecture slides*

**What this sheet covers**

- Dosage compensation and Lyon hypothesis
- Barr body formation, mosaicism, and escape genes
- X-linked vs Y-linked genes
- X-linked recessive inheritance, pedigree clues, and common disorders
- X-linked dominant inheritance, pedigree clues, and classic examples

اللهم ربِّ ارحمهما كما ربياني صغيرًا

## 1. Core idea: why X-inactivation exists

- Sex chromosomes do not carry equal amounts of the same genes. The X chromosome carries many genes unrelated to sex, while the Y chromosome mostly carries sex-determining genes.
- Females have two X chromosomes, but one functional X in each cell is enough for normal expression of most X-linked genes.
- X-inactivation is the built-in dosage compensation system that balances gene expression between XX females and XY males.

### Dosage compensation

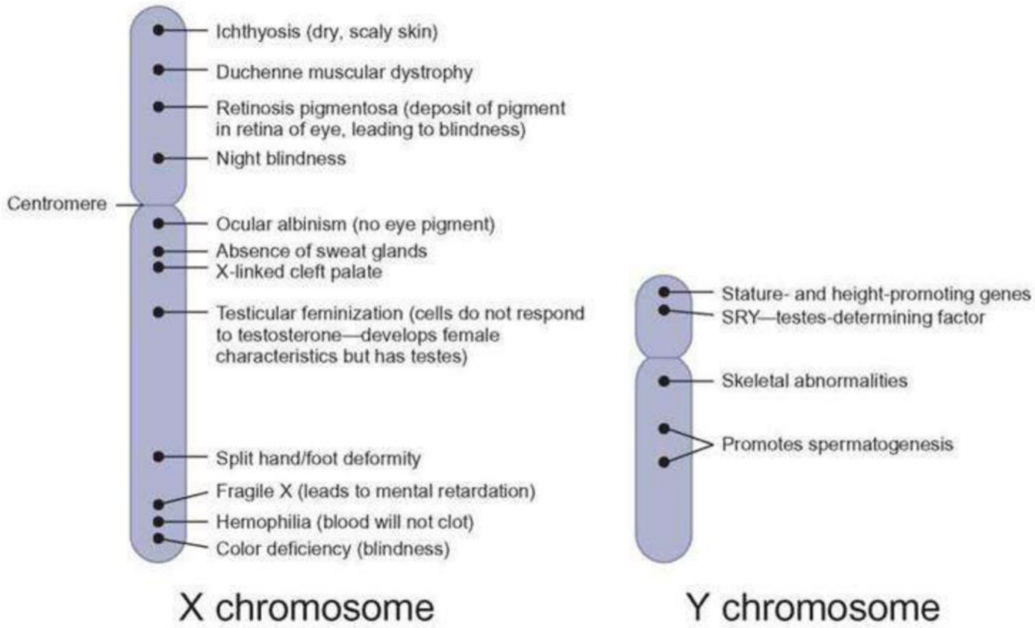
- For autosomal traits, two doses often give the normal phenotype, while one dose or more than two doses can have clinical effects.
- For X-linked traits, two doses in females and one dose in males can both produce a normal phenotype after dosage compensation.

### Lyon hypothesis and Barr body

- In early embryonic life, around 3-7 days after fertilization, one X chromosome is inactivated in each female cell.
- The inactive X condenses into a Barr body.
- Which X is inactivated is random: maternal or paternal. After that decision, all descendant cells keep the same inactive X, so the process is clonal.
- A heterozygous female for an X-linked gene becomes a mosaic because different cell clones express different X alleles.

### Genes that escape X-inactivation

- Some genes on the inactive X remain active.
- These include genes in the pseudoautosomal region, which have matching genes on the Y chromosome, plus some genes outside that region that have related Y copies and others.




*Slide figure: gene distribution on the X and Y chromosomes (page 5).*

## 2. Sex-linked genes: definitions and inheritance basics

- A gene located on either sex chromosome is called a sex-linked gene.
- Genes on the Y chromosome are Y-linked genes; there are only a few of these.
- Genes on the X chromosome are X-linked genes.

### How X-linked inheritance behaves

- X-linked genes follow special inheritance patterns because males have only one X chromosome.
- For a recessive X-linked trait to be expressed, a female needs two copies of the mutant allele, but a male needs only one because he is hemizygous.
- That is why X-linked recessive disorders are much more common in males than in females.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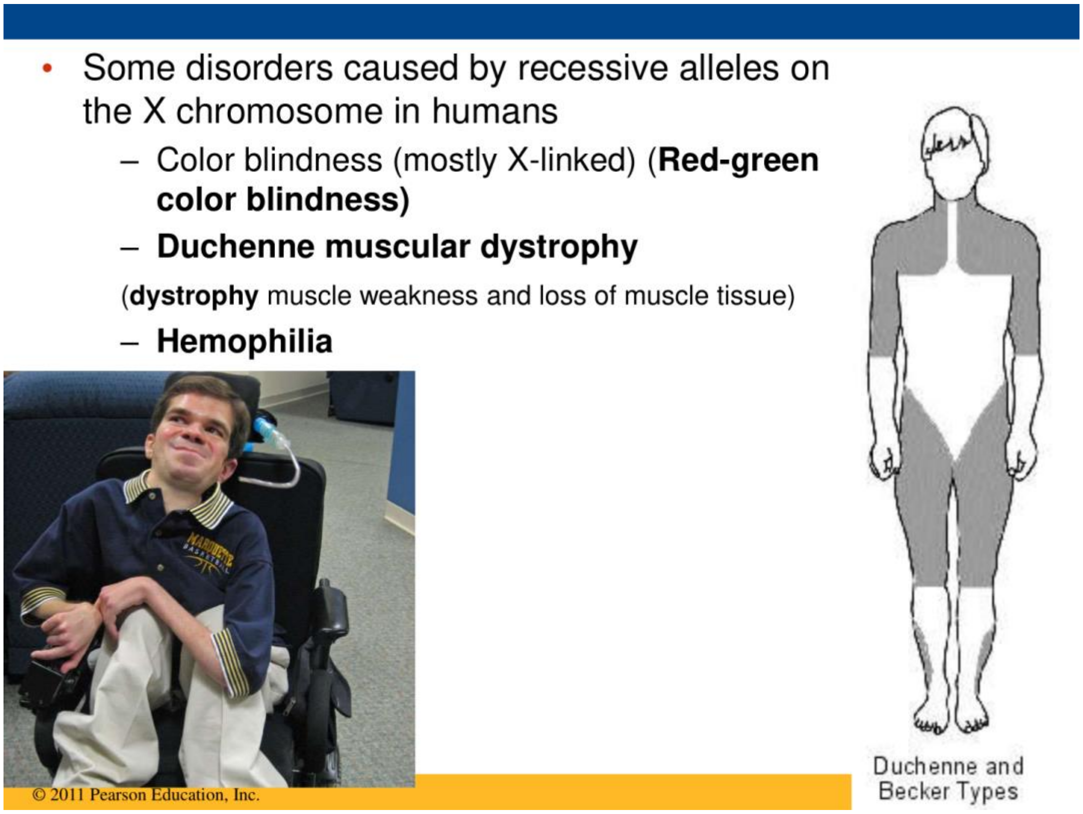



*X-linked inheritance overview from the lecture (page 10 slide image).*

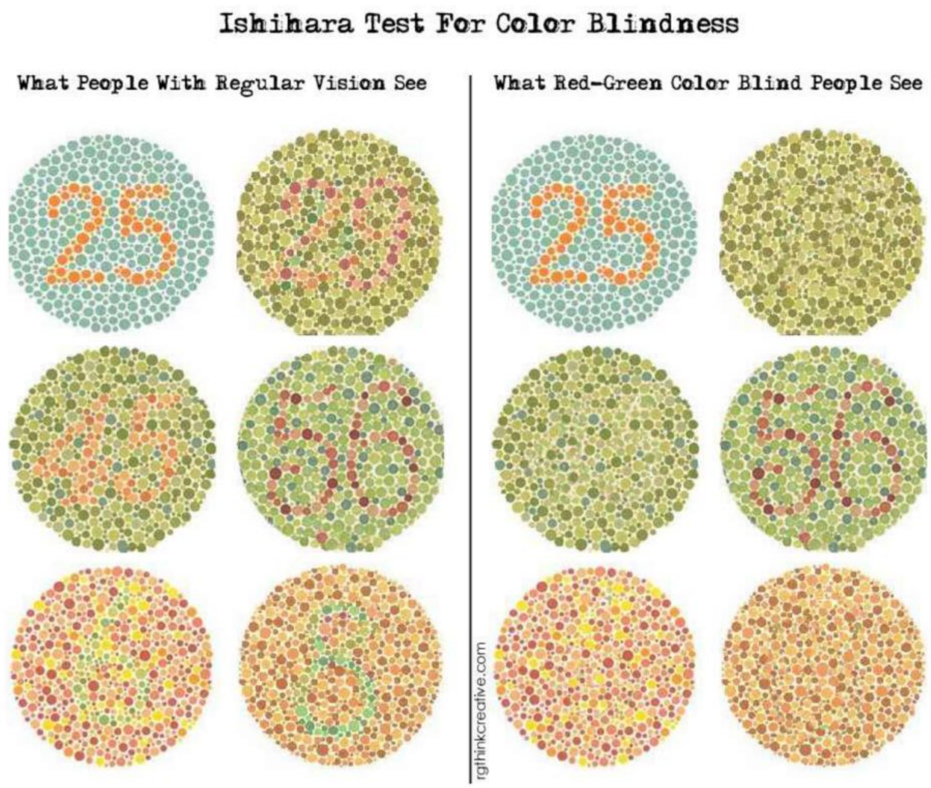
## 3. Important X-linked recessive disorders

- Color blindness, especially red-green color blindness, is usually X-linked.
- Duchenne muscular dystrophy causes progressive muscle weakness and loss of muscle tissue.
- Hemophilia is a blood-clotting disorder with prolonged bleeding and easy bruising.

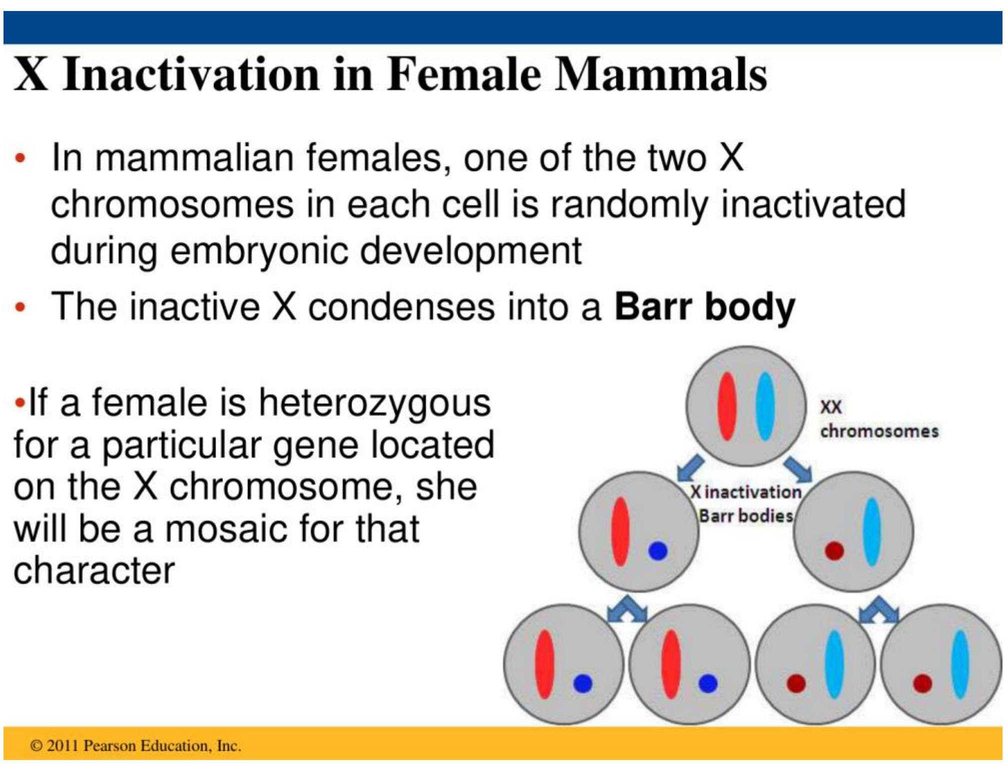
### Classic examples and features

- Hemophilia A: coagulation disorder, prolonged bleeding, easy bruising, hemorrhage, and many mutations with high heterogeneity.
- Duchenne muscular dystrophy: progressive muscle weakness, typically fatal in the 2nd or 3rd decade, with many cases due to new mutation and allelic heterogeneity; Becker muscular dystrophy is a related allelic variant.


You gotta have a heart
to endure heartbreak




*Ishihara plates illustrate red-green color blindness (page 11).*




*Random X-inactivation in female mammals creates mosaicism (page 12).*

# Examples and Features of X-Linked Recessive Inheritance

Examples:

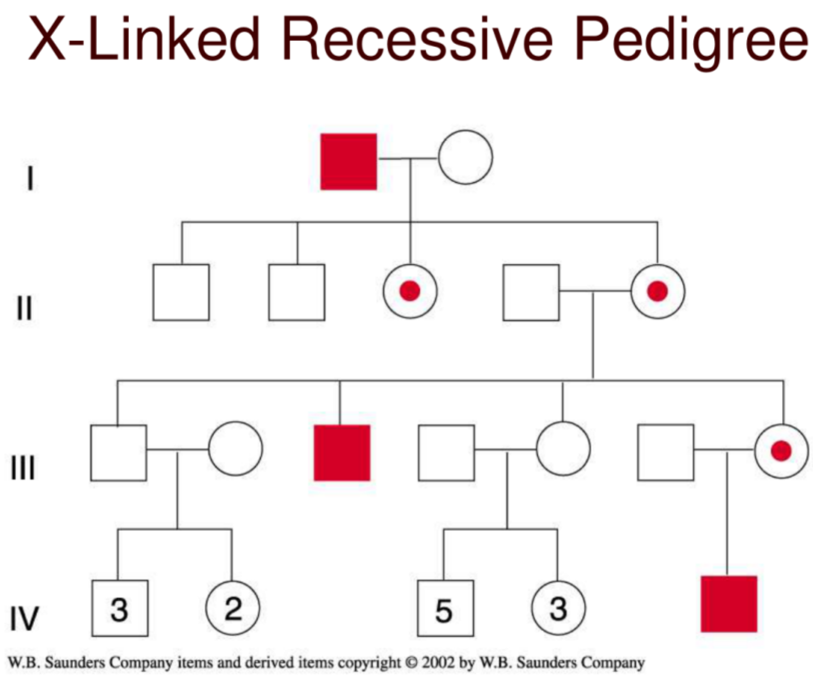
| X-Linked Recessive | |
|---|---|
| HEMOPHILIA A | Coagulation disorder<br>Prolonged bleeding<br>Easy bruising<br>Hemorrhage<br>Various mutations & very heterogeneous |
| DUCHENNE MUSCULAR DYSTROPHY | Progressive muscle weakness<br>Death typically in 2nd or 3rd decade<br>30% cases due to new mutation<br>**Allelic heterogeneity (Becker MD)** |

*Examples and features of X-linked recessive inheritance (page 13).*

Duchenne muscular dystrophy

Figure 1.4. A 15-year-old boy with Duchenne muscular dystrophy

*Clinical appearance of Duchenne muscular dystrophy (page 14).*




*Example pedigree showing X-linked recessive inheritance (page 15).*

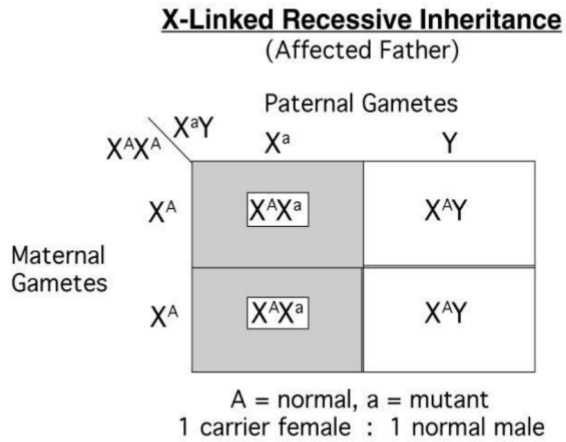
## 4. Features of X-linked recessive inheritance

**1.** Diagonal inheritance: affected males are related through females in the maternal line.
**2.** Absence of male-to-male transmission.
**3.** Trait incidence is much higher in males than females.
**4.** Full expression in hemizygous males.
**5.** No or only mild expression in carrier females because X-inactivation can dilute the effect.

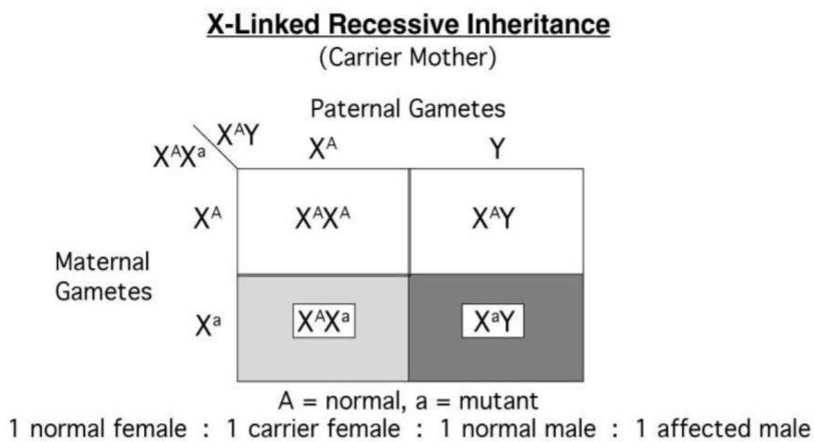
### Transmission probabilities

**1.** A son never inherits the disorder from his father.
**2.** All daughters of an affected male are obligate carriers.
**3.** Sons of carrier females have a 50% chance of inheriting the disorder.
**4.** Daughters of carrier females have a 50% chance of being carriers.


It's always the case




*Affected father: all daughters are carriers, sons are unaffected (page 18).*




*Carrier mother: 1 normal female : 1 carrier female : 1 normal male : 1 affected male (page 19).*

## 5. X-linked dominant inheritance

- X-linked dominant disorders are less common than X-linked recessive ones.
- A dominant allele on the X chromosome can cause disease in both sexes.

## Classic example

- Vitamin D resistant rickets: causes rickets, short stature, low serum phosphate, and is often less severe in heterozygous females.

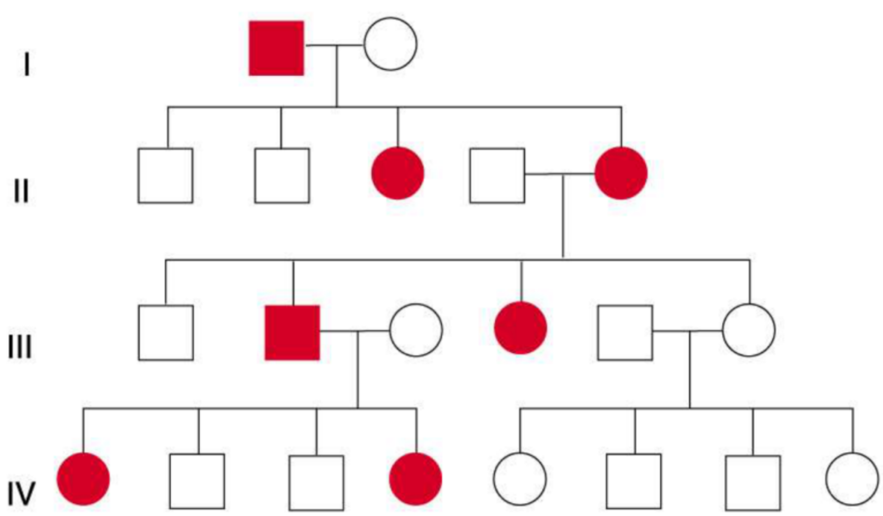
# Examples and Features of X-Linked Dominant Inheritance

X-linked Dominant

| | |
|---|---|
| VITAMIN D RESISTANT RICKETS | Rickets<br>Short stature<br>Low serum phosphate<br>**Less severe in heterozygous females** |

*Example and features of X-linked dominant inheritance (page 20).*

# X-Linked Dominant Pedigree





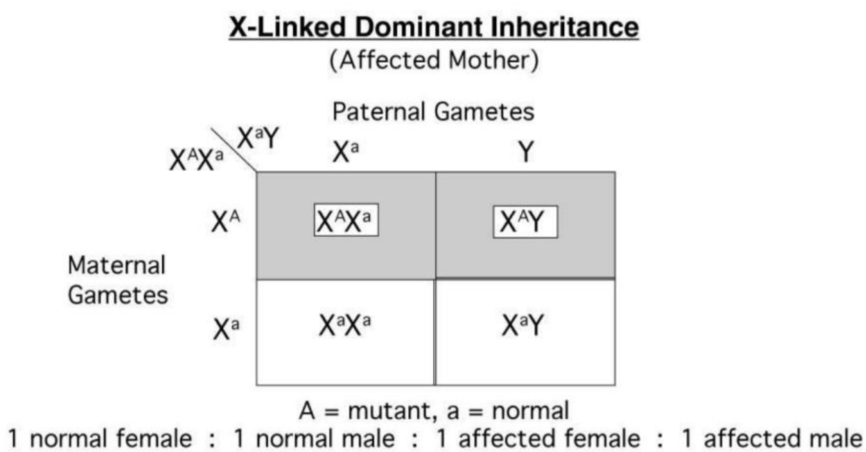

*X-linked dominant pedigree pattern (page 21).*

### Features of X-linked dominant inheritance

**1.** Twice as many females are affected as males.
**2.** There is no male-to-male transmission.
**3.** Affected males transmit the trait to all daughters and no sons.
**4.** Females usually show milder and more variable expression because of X-inactivation.
**5.** Only a few disorders are classified as X-linked dominant.

### Transmission probabilities

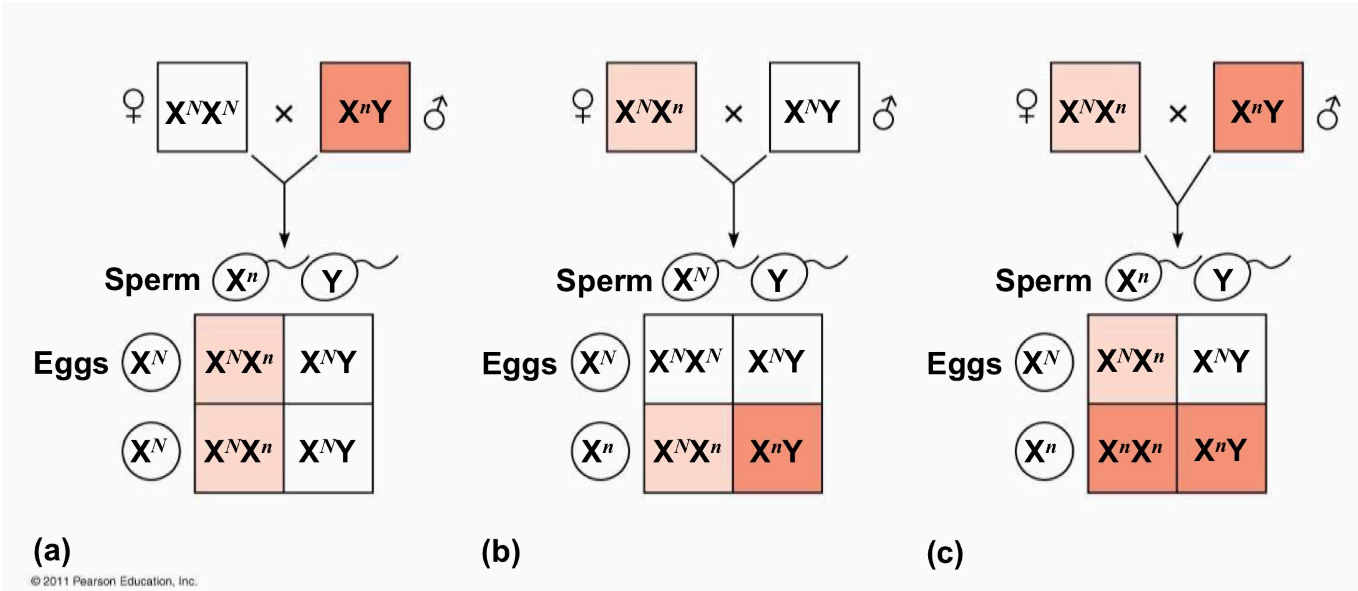
**1.** A son never inherits the disorder from his father.
**2.** All daughters of an affected male will also have the disorder.
**3.** Sons of affected females have a 50% chance of inheriting the disorder.
**4.** Daughters of affected females have a 50% chance of inheriting the disorder.
**5.** You can distinguish autosomal dominant from X-linked dominant by checking the offspring of affected males.




*Affected mother: 1 normal female : 1 normal male : 1 affected female : 1 affected male (page 24).*

## 6. High-yield comparison

| Feature | X-linked recessive | X-linked dominant |
|---|---|---|
| Who is affected more? | Males much more often | Females about twice as often as males |
| Male-to-male transmission | Absent | Absent |
| Affected father | All daughters are carriers; no sons affected | All daughters affected; no sons affected |
| Carrier/heterozygous female | Often mild or asymptomatic due to X-inactivation | Often variable, usually milder than males |




🧬 **What is a Punnett Square?**

A **Punnett square** is a simple diagram used in genetics to **predict the possible genotypes and phenotypes of offspring** from a cross between two parents.

📦 **Basic Idea**

- Each parent gives **one allele** to the offspring
- You combine them to see all possibilities

🧪 **Example (Monohybrid Cross)**

Let's say:

- **A = dominant allele**
- **a = recessive allele**
- **Cross: Aa × Aa**

🧾 **Punnett Square:**

| | A | a |
|---|---|---|
| A | AA | Aa |
| a | Aa | aa |

📊 **Results:**

- **Genotype ratio:**
  - AA → 25%
  - Aa → 50%
  - aa → 25%
- **Phenotype ratio:**
  - Dominant trait (AA + Aa) → 75%
  - Recessive trait (aa) → 25%

🎯 **Key Points (High-yield 💥)**

- Dominant allele = shows even if **one copy present**
- Recessive trait = needs **two copies (aa)**
- Punnett square helps predict **probability, not certainty**

🧠 **Quick Memory Trick**

Think of it like:

> "Each parent throws one allele into the box — mix & match"

⚡ **Types you should know:**

- **Monohybrid cross** → 1 gene (like above)
- **Dihybrid cross** → 2 genes (bigger square 4×4 😈)

## Slide coverage checklist

- Slides 1-4: sex linkage, dosage compensation, Lyon hypothesis, Barr body, escape genes
- Slides 5-9: X and Y chromosome diagram, sex-linked gene definitions, X-linked inheritance basics, recessive Punnett squares
- Slides 10-19: X-linked recessive disorders, color blindness, Duchenne muscular dystrophy, hemophilia, pedigree clues, transmission probabilities
- Slides 20-24: X-linked dominant disorders, vitamin D resistant rickets, pedigree clues, transmission probabilities

*Source: uploaded lecture PDF on X-inactivation and sex-linked pedigrees and diseases.*

وَأَن لَّيۡسَ لِلۡإِنسَٰنِ إِلَّا مَا سَعَىٰ (٣٩) وَأَنَّ سَعۡيَهُۥ سَوۡفَ يُرَىٰ (٤٠) ثُمَّ يُجۡزَىٰهُ ٱلۡجَزَآءَ ٱلۡأَوۡفَىٰ (٤١)

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