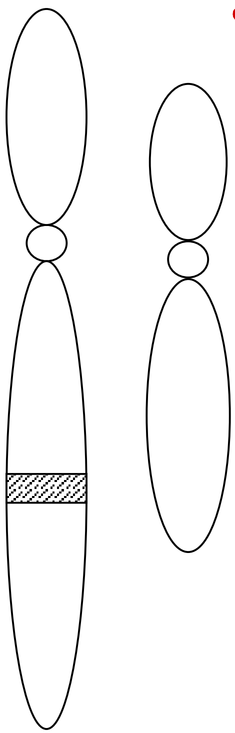
Sex Linkage and X-Inactivation

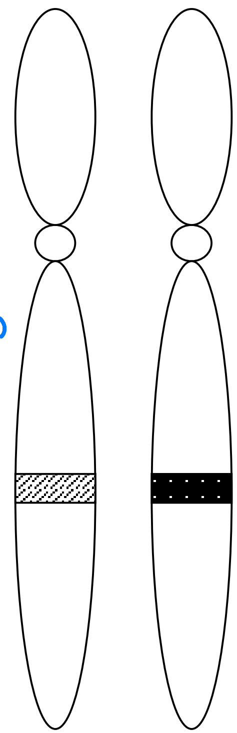
*3 important terms:

1. sex-linked : a "sex-linked" gene is a gene that is physically located on the sex chromosome → x-linked → females : homozygous OR heterozygous. / males : have only 1 ch. X (most of the genes on ch. X do NOT have an allele on ch. Y) } i.e.: * Fragile X (FMR) is a disease caused by a gene mutation on ch.X which doesn't have an allele on ch.Y
   * Duchenne Muscular Dystrophy is also caused by a genetic mutation on ch.X (not found on ch.Y)
   → y-linked
2. sex-influenced
3. sex-limited

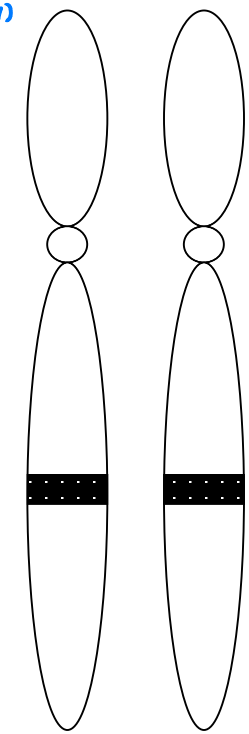
} does NOT necessarily mean the gene itself is on the sex chromosome BUT the clinical features are limited to 1 sex OR influenced by sex. i.e.: Hemochromatosis (iron overload in the blood) is a sex-influenced disease bcz the gene itself is located on an autosomal chromosome but the severity of the disease is impacted by the biological sex of the individual (females are more impacted)



X^A Y



X^A X^a



X^a X^a

Dosage compensation

1. For autosomal traits, two doses lead to a normal phenotype, while one dose or more than two doses often have clinical significance

2. For X-linked traits two doses in females and one dose in males both lead to a normal phenotype

X-inactivation in females allows compensation for this difference in dosage for X-linked traits

- Lyon hypothesis

- In early embryonic life (3-7 days after fertilization) one X chromosome is inactivated. The inactive X chromosome is condensed in a Barr body.

- Inactivation of the maternal or paternal X chromosome is random, but once it occurs, the same X will be inactive in all descendants of a particular cell.

* most of the genes on the condensed ch. X are inactive BUT

- Some genes on the inactive X chromosome remain active, i.e., escape inactivation. These include the genes in the pseudoautosomal region that have matching genes on the Y chromosome, genes outside the pseudoautosomal region that have related copies on the Y chromosomes, and others.

↳ especially some genes that are located on the surface of the chromosome

→ these genes have 2 copies/alleles.

X-Inactivation

- Allows dosage compensation between males and females for genes on the X chromosome
- In females, early in embryonic life, one of the X chromosomes is inactivated
- The process is random and clonal
- Some genes escape X-inactivation

* Normally a gene on ch.X physically has 1 allele in males & 2 alleles in females.

↓

Transcription factors & RNA polymerase will bind to these locations on ch.X where gene expression takes place.

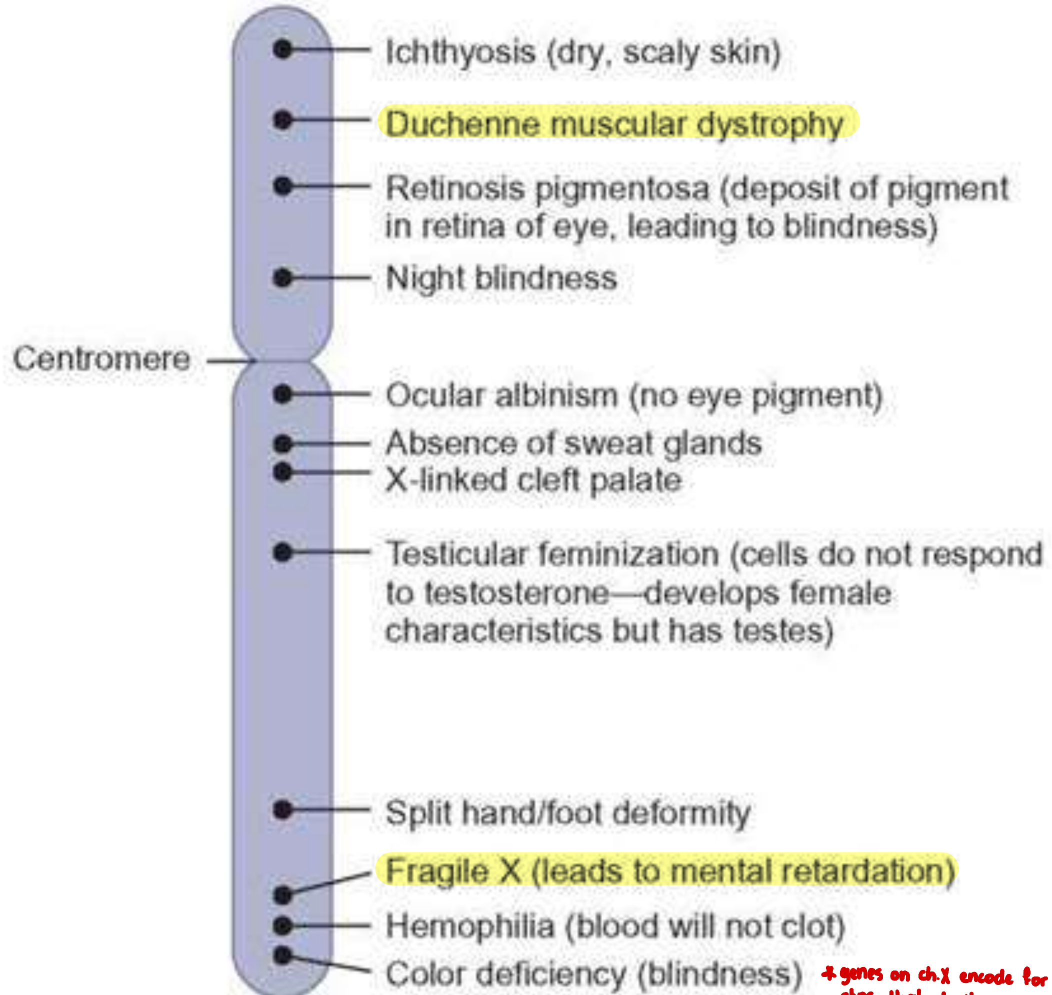
- 1 allele (male) ↓ RNA polymerase & TFs will bind to only 1 allele.
- 2 alleles (female) ↓ RNA polymerase & TFs will bind to both maternal & paternal alleles

* females will have 1 extra physical copy of the gene therefore higher expression level than males for the same gene.

* this creates a difference in expression levels between males & females (differential expression) → abnormal; meanwhile autosomal genes are expressed in comparable amounts between both sexes.

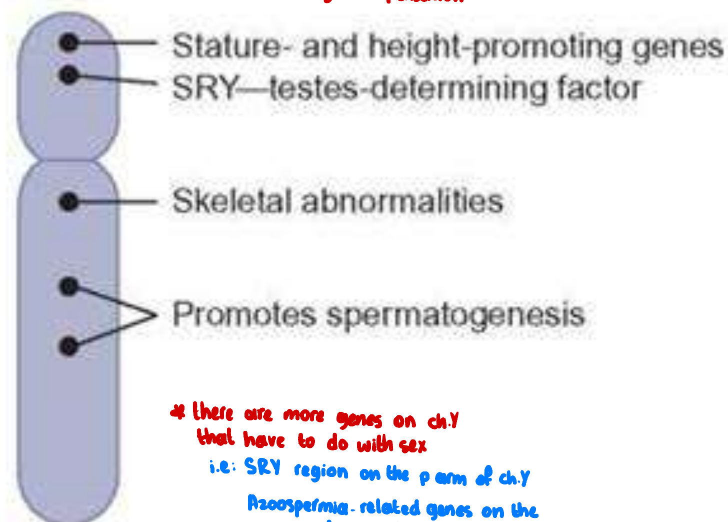
⇓

this problem is solved by "Dosage Compensation"



X chromosome

* genes on ch.X encode for ptns that don't necessarily have to do with sex.
i.e: Duchenne Muscular Dystrophy
Hemophilia
Color blindness
⋮



Y chromosome

* there are more genes on ch.Y that have to do with sex
i.e: SRY region on the p arm of ch.Y
Azoospermia-related genes on the q arm of ch.Y (AZF)

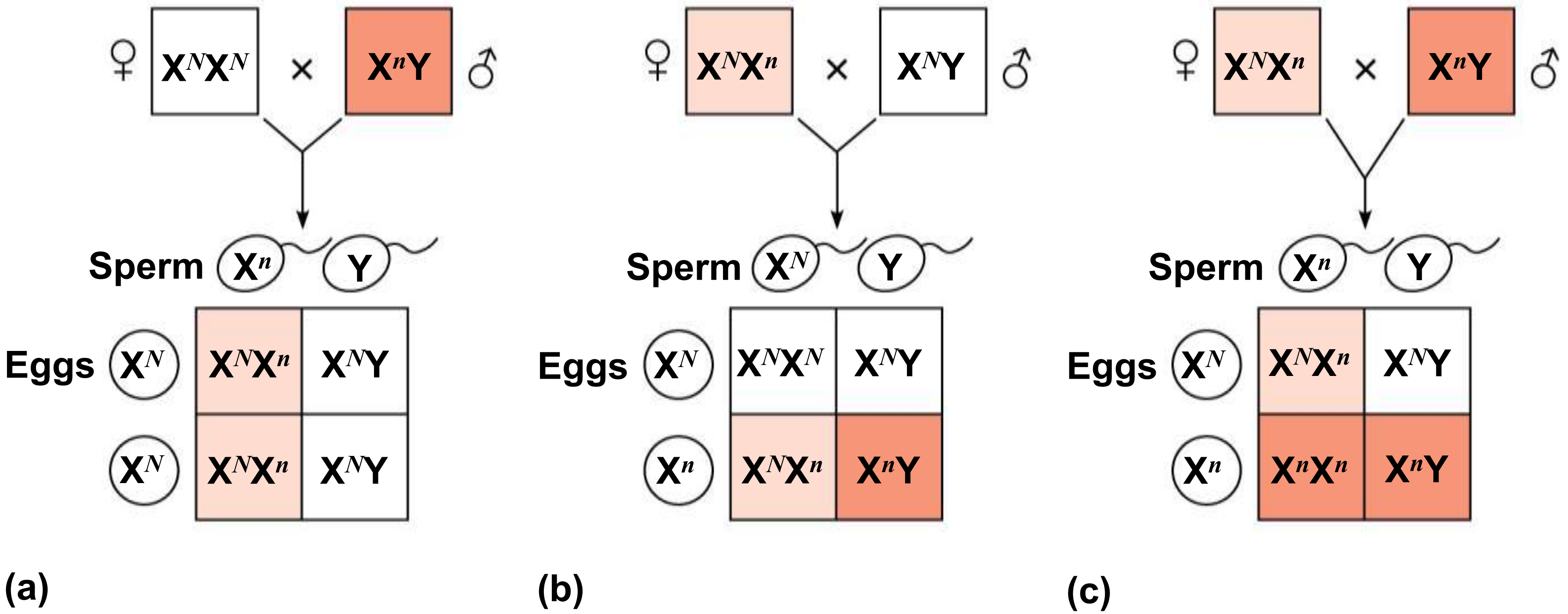
- A gene that is located on either sex chromosome is called a **sex-linked gene**
- Genes on the Y chromosome are called Y-linked genes; there are **few** of these
- Genes on the X chromosome are called **X-linked genes**

Inheritance of X-Linked Genes

- X chromosome have genes for many characters **unrelated** to sex, whereas the Y chromosome mainly encodes genes **related** to sex determination

- X-linked genes follow specific patterns of inheritance
- For a recessive X-linked trait to be expressed
  - A female needs two copies of the allele (**homozygous**)
  - A male needs only one copy of the allele (**hemizygous**)
- X-linked recessive disorders are much **more** common in males than in females

Figure 15.7


♀ X^N X^N × X^n Y ♂
Sperm X^n Y
Eggs X^N X^N
X^N X^n X^N Y
X^N X^n X^N Y
(a)
♀ X^N X^n × X^N Y ♂
Sperm X^N Y
Eggs X^N X^n
X^N X^N X^N Y
X^N X^n X^n Y
(b)
♀ X^N X^n × X^n Y ♂
Sperm X^n Y
Eggs X^N X^n
X^N X^n X^N Y
X^n X^n X^n Y
(c)

- Some disorders caused by recessive alleles on the X chromosome in humans
  - Color blindness (mostly X-linked) (**Red-green color blindness**)
  - **Duchenne muscular dystrophy**

  (**dystrophy** muscle weakness and loss of muscle tissue)
  - **Hemophilia**

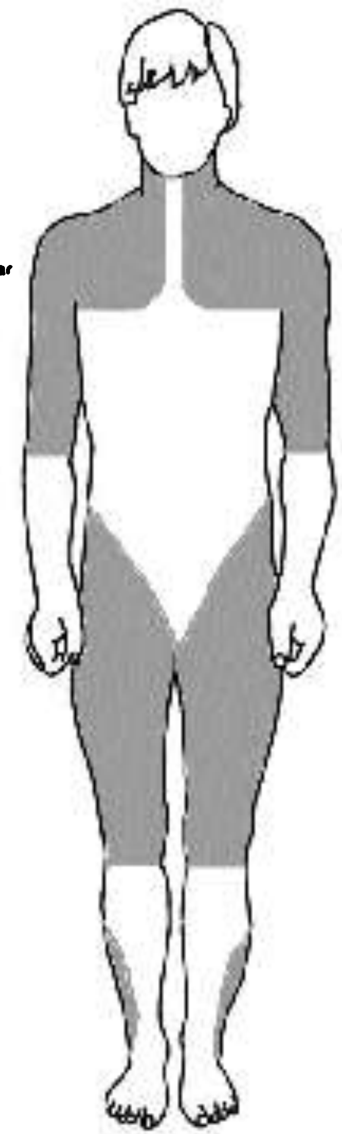
* there are different types of color blindness, one of them is Red-green color blindness which is a X-linked recessive disease.

* DMD gene (Duchenne Muscular Dystrophy gene) is located on the p arm of ch. X

* the type of mutation & therefore disease severity are variable to a point where clinically they can cause 2 diseases clinically (depending on disease severity)
  → Duchenne Muscular Dystrophy
  → Becker Muscular Dystrophy.

Q: Which sex is expected to have more individuals with color blindness?

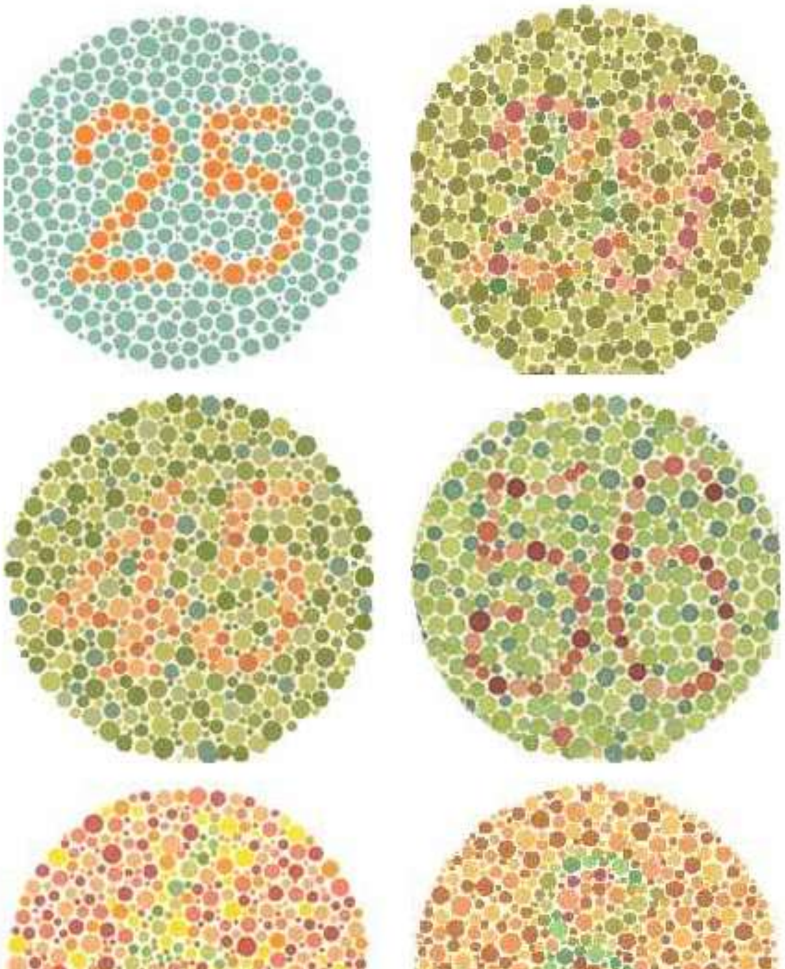
A: Males, bcz they have only 1 ch.X so if it's mutated there is no compensation for the mutated allele.
In contrast to females, if 1 allele is mutated the other allele is compensating.
(same with other X-linked recessive diseases)



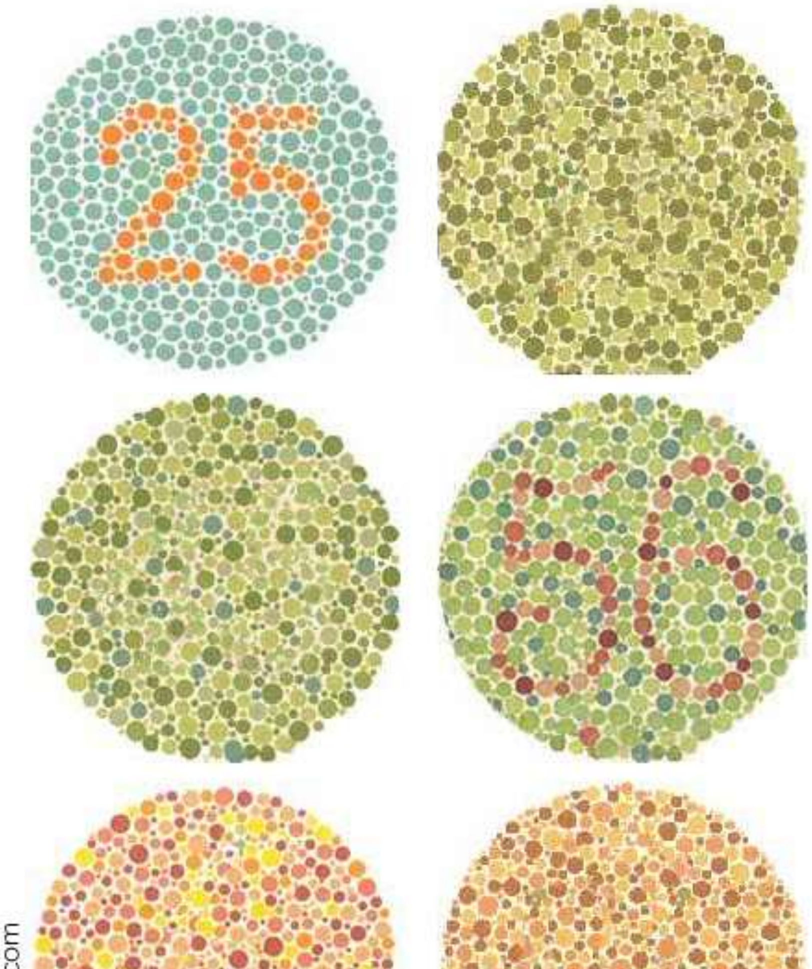
Duchenne and Becker Types

Ishihara Test For Color Blindness

What People With Regular Vision See

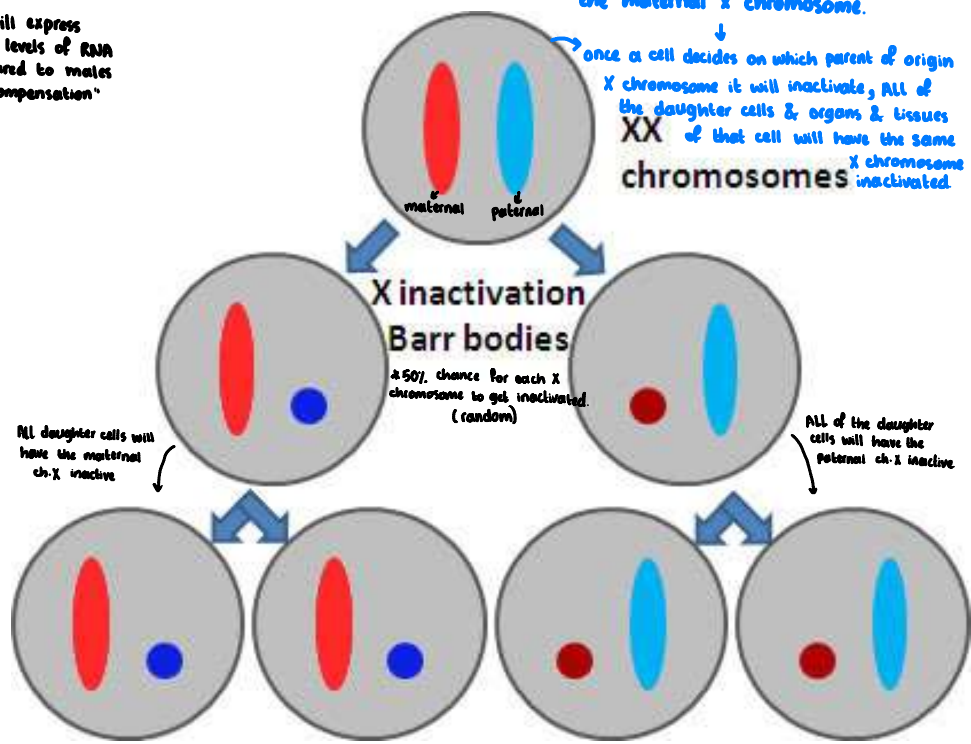


What Red-Green Color Blind People See



X Inactivation in Female Mammals

- In mammalian females, one of the two X chromosomes in each cell is randomly inactivated during embryonic development
  - ↳ regardless of the parent of origin
  - ↳ this process takes place a few days after fertilization, each cell will individually decide on condensing & therefore inactivating 1 of the 2 X chromosomes
  - one cell could decide on inactivating the paternal X chromosome while another cell decides on inactivating the maternal X chromosome.
  - ↓ once a cell decides on which parent of origin X chromosome it will inactivate, ALL of the daughter cells & organs & tissues of that cell will have the same X chromosome inactivated.
- The inactive X condenses into a **Barr body**
  - ↳ this condensed/inactive ch. X will NOT be accessible to RNA polymerase & TFs
  - during the interphase in females we will notice that 1 of the 2 X chromosomes is NOT decondensed therefore its genes are NOT expressed. ⇒ in reality, females will express comparable & similar levels of RNA from their ch. X compared to males bcz of "dosage compensation"
- If a female is heterozygous for a particular gene located on the X chromosome, she will be a mosaic for that character



Examples and Features of X-Linked Recessive Inheritance

Examples:

X-Linked Recessive	
HEMOPHILIA A (there are different types of Hemophilia)	Coagulation disorder Prolonged bleeding Easy bruising Hemorrhage (+ internal hemorrhage) Various mutations & very heterogeneous → disease heterogeneity depending on the variant. (disease severity is variable based on the mutation)
DUCHENNE MUSCULAR DYSTROPHY	Progressive muscle weakness → deteriorates with time. Death typically in 2nd or 3rd decade 30% cases due to new mutation (Spontaneous / de novo mutation.) → it means that this mutation that the patient has is NOT seen in the parents. (it occured during oogenesis / spermatogenesis) Allelic heterogeneity (Becker MD)

↳ a DMD is a big gene in terms of size
a depending on how dysfunctional a mutation is (completely inactive ptn, residual activity...)

- → Severe damage : Duchenne MD
- → Milder damage: Becker MD

} even though the mutated gene is the same, the severity is different to a point that they are clinically considered as 2 different diseases.

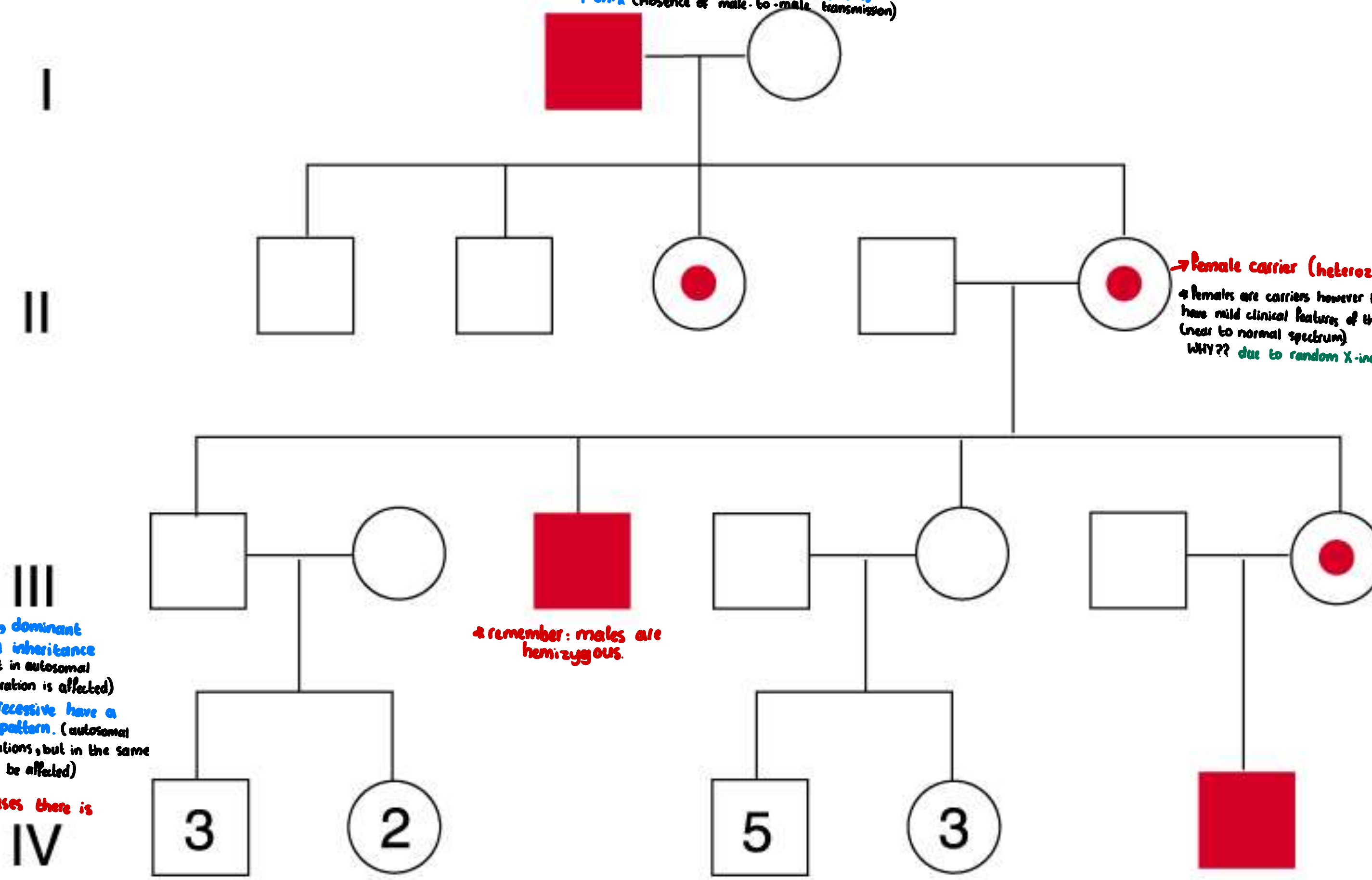
Duchenne muscular dystrophy

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

X-Linked Recessive Pedigree

* we expect to have more males affected than females in a x-linked recessive pedigree

→ this X chromosome that the affected father has will be passed on to ALL his daughters.
→ NONE of the sons will inherit this ch.X (Absence of male-to-male transmission)



→ female carrier (heterozygous)
* females are carriers however they could have mild clinical features of the disease (near to normal spectrum).
WHY?? due to random X-inactivation

* remember: males are hemizygous.

* note:
1. as mentioned previously, dominant disorders have a vertical inheritance pattern. (which means that in autosomal dominant diseases every generation is affected) meanwhile, autosomal recessive have a horizontal inheritance pattern. (autosomal recessive diseases skip generations, but in the same generation >1 individual can be affected)
2. in x-linked recessive diseases there is a "Diagonal pattern". ← mode of inheritance
3. in the exam, there will NOT be a highlight on which females are carriers & which aren't bcz usually we don't know that yet when we are building the pedigree unless genetic testing is performed before the pedigree. (typically a pedigree is built before genetic testing)

Features of X-Linked Recessive Inheritance

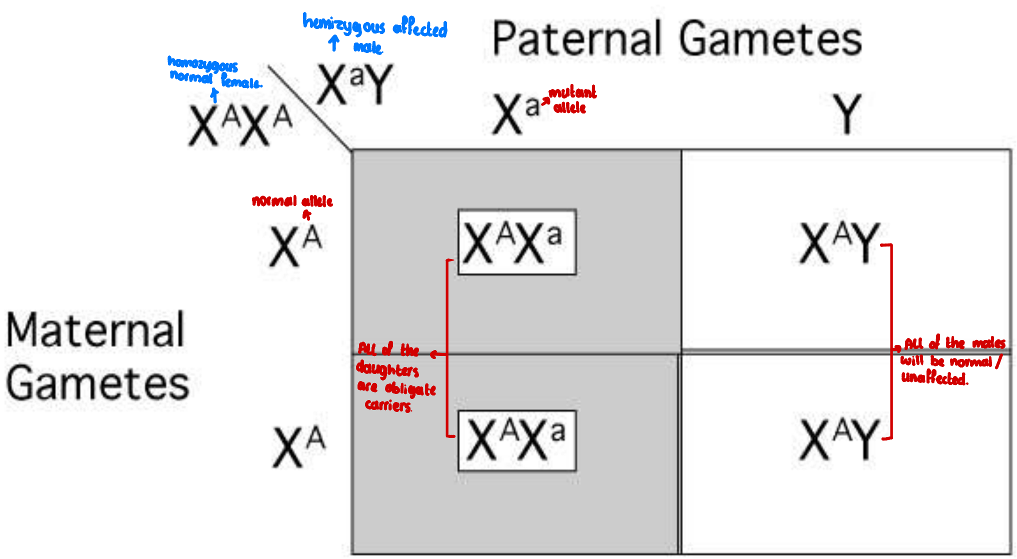
1. Diagonal inheritance – affected males related through females of the maternal line
   * bcz males ONLY inherit ch. X from their mothers
   * when the mother is heterozygous there's a 50% chance that her son will be hemizygous for that mutation
2. Absence of male-to-male transmission
3. Incidence of trait much higher in males than females
4. Full expression in hemizygous males
5. No or mild expression in carrier females due to X-inactivation

Transmission probabilities and use of the Punnett square

1. A son never inherits the disorder from his father.
2. All daughters of a male with the disorder 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 too.

X-Linked Recessive Inheritance

(Affected Father)



A = normal, a = mutant

1 carrier female : 1 normal male

X-Linked Recessive Inheritance

(Carrier Mother)
- daughters
  - 50% : carriers
  - 50% : homozygous wild-type.
- sons
  - 50% : affected.
  - 50% : unaffected.

Paternal Gametes * OR regardless of gender
- 25% : homozygous wild-type.
- 25% : hemizygous wild-type.
- 25% : heterozygous unaffected.
- 25% : hemizygous affected.

unaffected father: X^AY

heterozygous /carrier mother: X^AX^a

Maternal Gametes \ Paternal Gametes	X^A	Y
X^A	X^AX^A	X^AY
X^a	X^AX^a	X^aY

A = normal, a = mutant

1 normal female : 1 carrier female : 1 normal male : 1 affected male

Examples and Features of X-Linked Dominant Inheritance

* 1 mutant allele is enough to cause the disease whether it's X-linked or autosomal.

X-linked Dominant

VITAMIN D RESISTANT RICKETS	Rickets Short stature Low serum phosphate Less severe in heterozygous females

→ heterozygous females are affected BUT the disease severity is less than in hemizygous males due to X-inactivation.

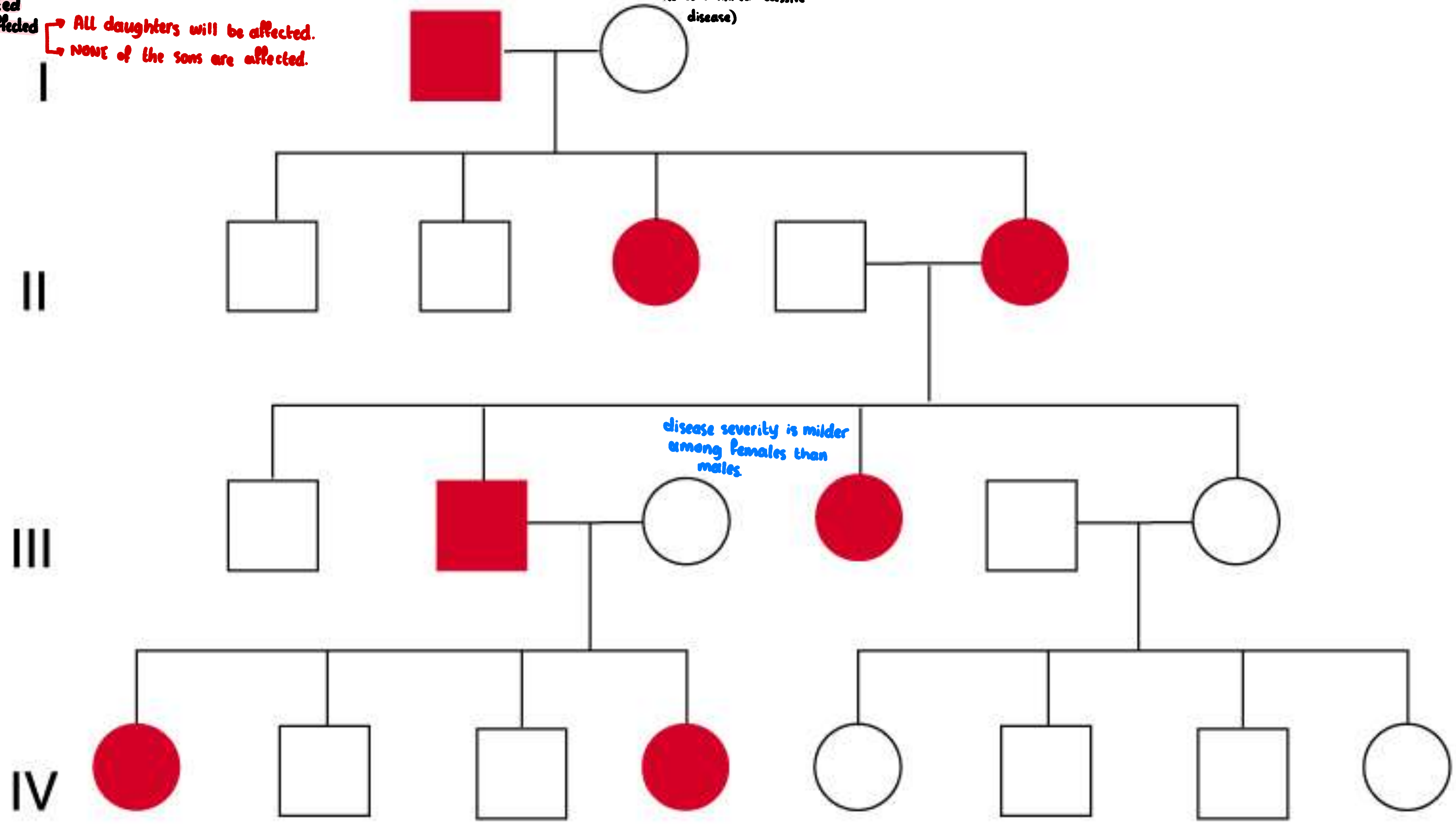
X-Linked Dominant Pedigree

* there's NO male-to-male transmission bcz it's X-linked.

* since it's dominant, every generation is affected with the disease.

* there are more females affected than males (opposite to X-linked recessive disease)

* in this pedigree, the male is hemizygous affected & the mother is unaffected
→ All daughters will be affected.
→ NONE of the sons are affected.



Features of X-Linked Dominant Inheritance

1. Twice as many females with the disorder as males
2. Absence of male-to-male transmission
3. Males with the disorder transmit it to all daughters and no sons
4. Females usually have more mild and variable expression due to X-inactivation
5. Few disorders classified as X-linked dominant

Transmission probabilities and use of the Punnett square

*v.imp. note:
in dominant diseases (whether X-linked or autosomal) we assume that the affected individual is heterozygous unless indicated otherwise.

*IMPORTANT:

1. A son never inherits the disorder from his father
2. All daughters of male with the disorder will also have the disorder
3. Sons of affected females have a 50% chance of inheriting the disorder
4. Daughters of affected females also have a 50% chance of inheriting the disorder
5. Can distinguish between autosomal and X-linked dominant by looking at offspring of affected males

X-Linked Dominant Inheritance

(Affected Mother)

regardless of gender → 50%: affected.
→ 50%: unaffected.

Paternal Gametes

affected mother ↑ X^AX^a ; normal father ↑ X^aY

Maternal Gametes	X^a	Y
X^A	X^AX^a	X^AY
X^a	X^aX^a	X^aY

A = mutant, a = normal

1 normal female : 1 normal male : 1 affected female : 1 affected male