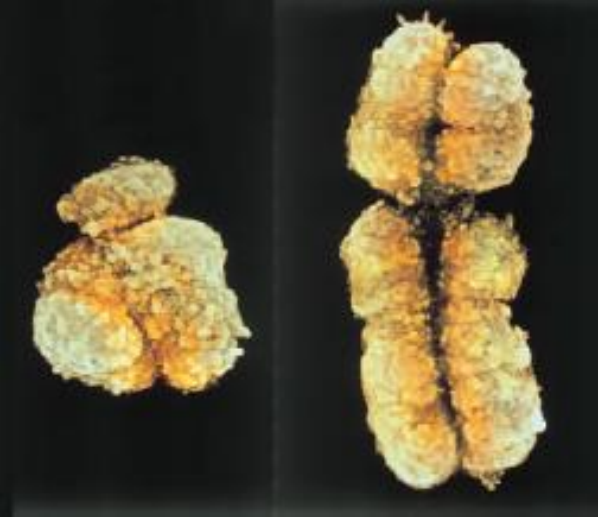
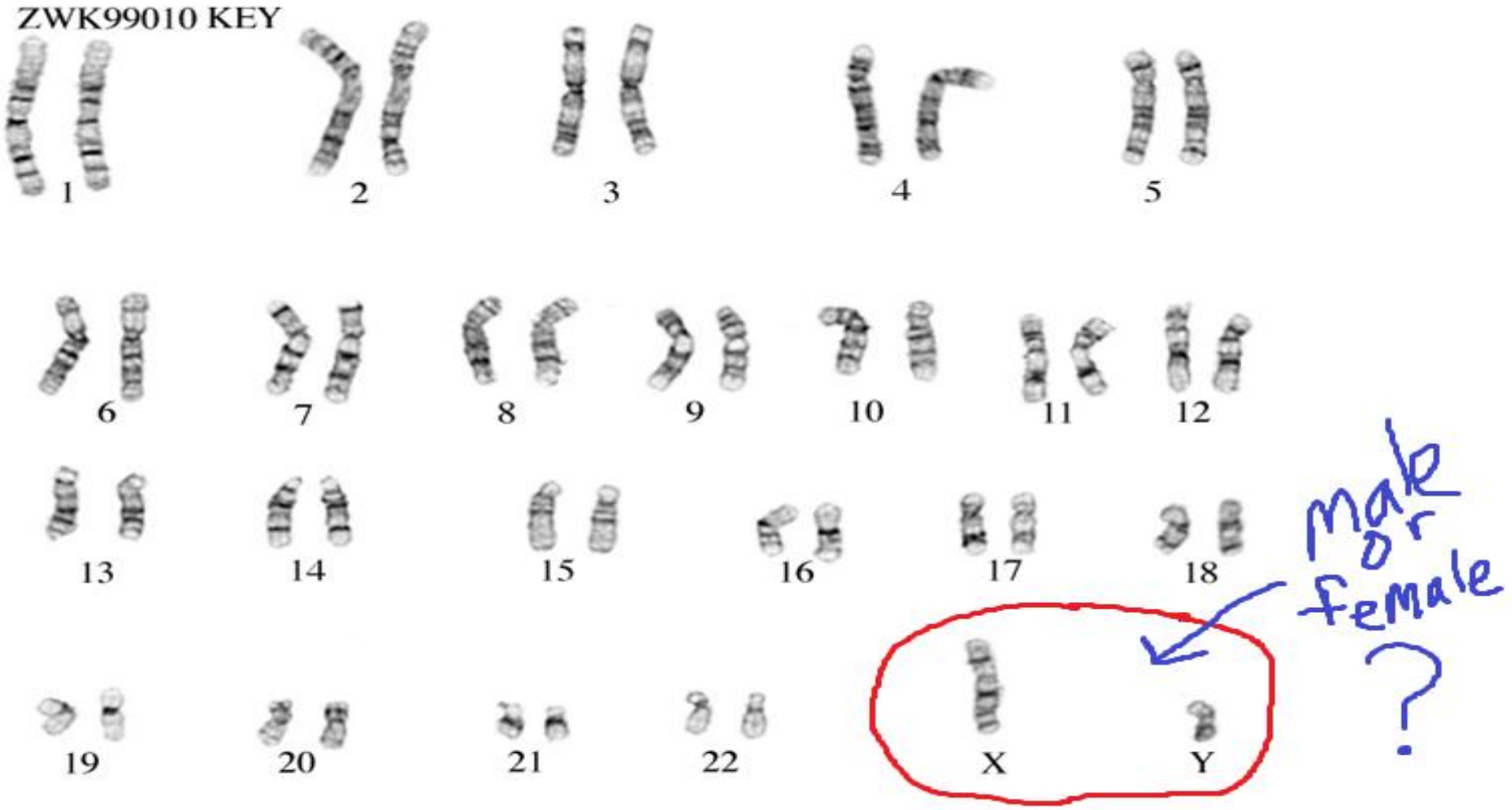


SEX-LINKED INHERITANCE

Dr Rasime Kalkan

Human Karyotype

Picture of Human Chromosomes
22 Autosomes and 2 Sex Chromosomes



Autosomal vs. Sex-Linked

Traits can be either:

- Autosomal: traits (genes) are located on the non-sex chromosomes
- Sex-Linked: traits (genes) are located on the sex chromosomes
- Sex chromosomes determine gender (X & Y)
- XX genotype for females
- XY genotype for males

Human Sex Chromosomes

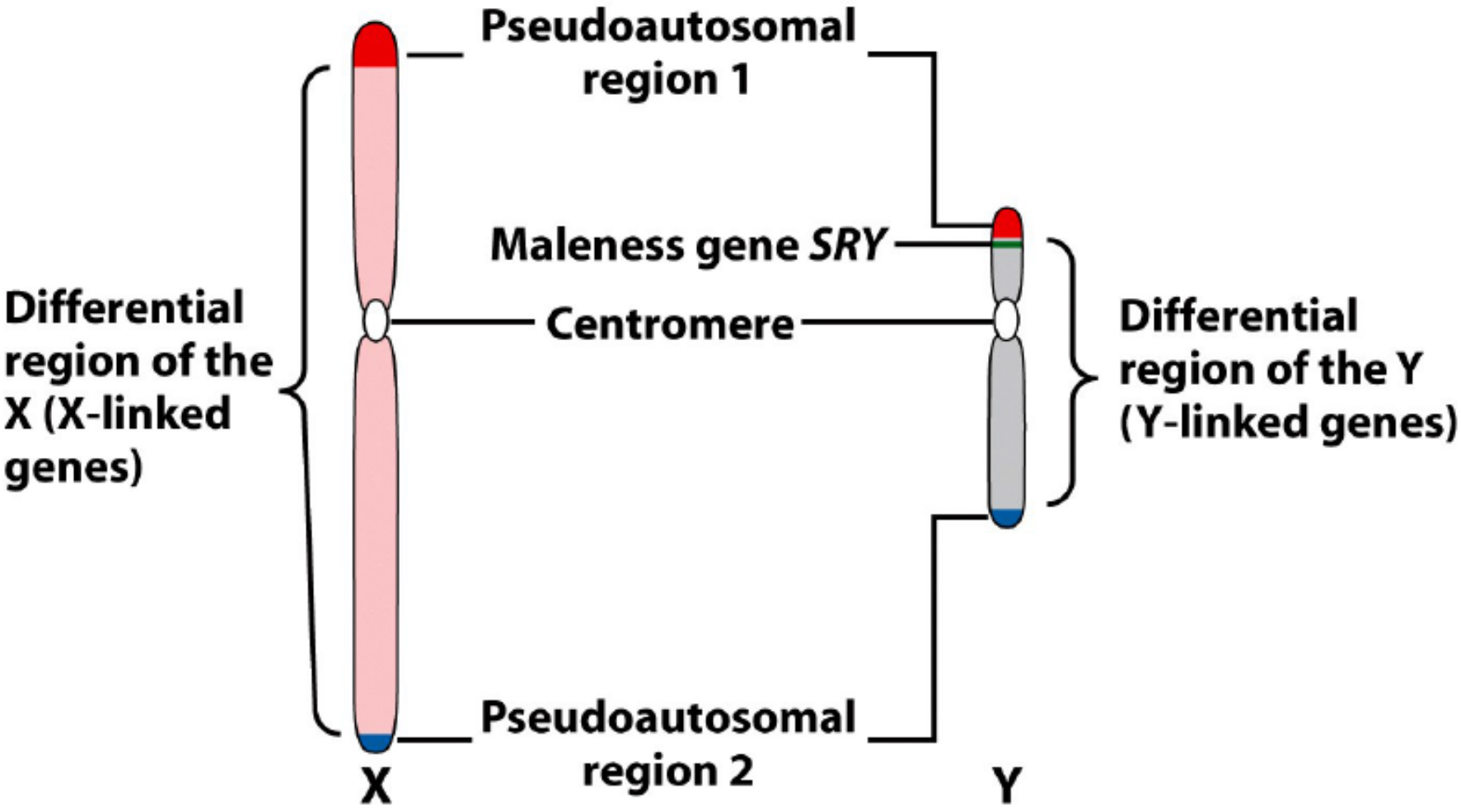
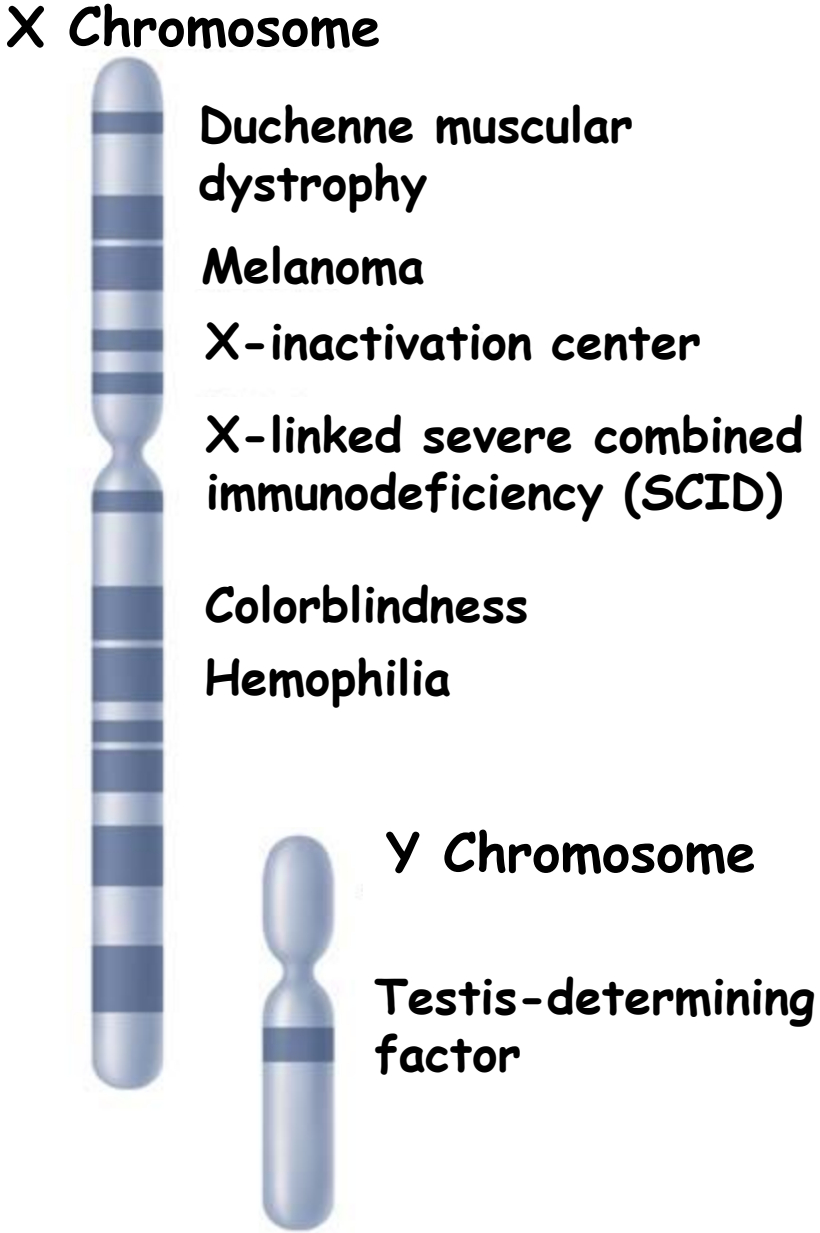
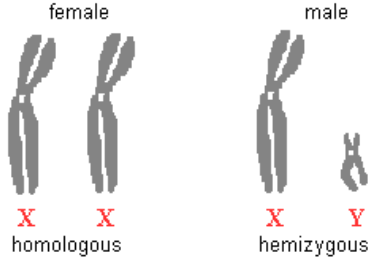


Figure 2-25
Introduction to Genetic Analysis, Ninth Edition

Sex-Linked Genes

The Y chromosome is much smaller than the X chromosome and appears to contain fewer genes.



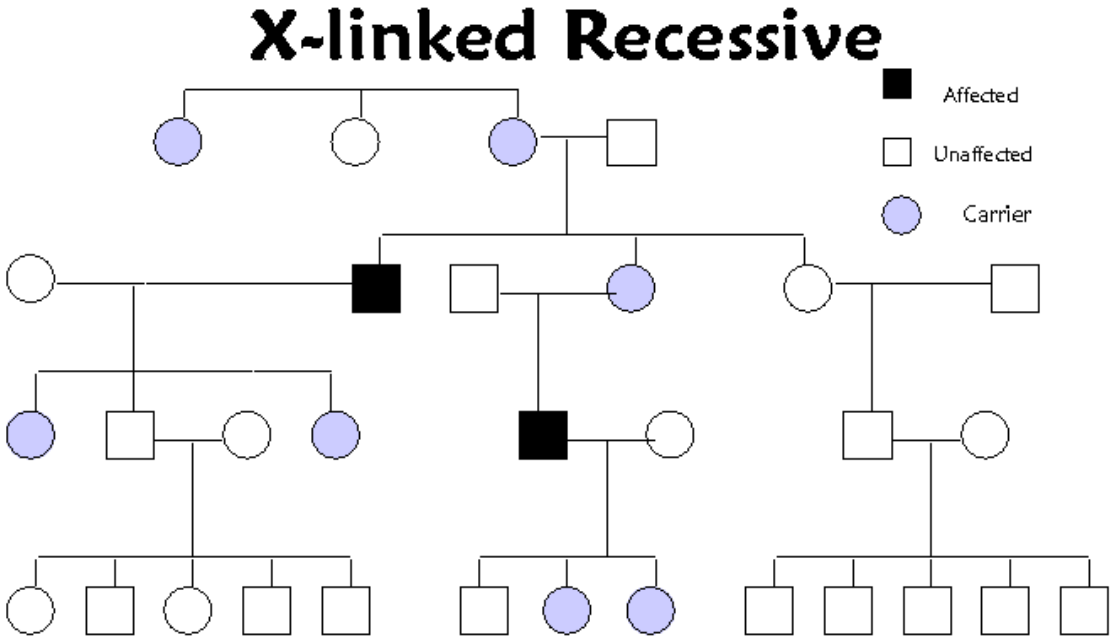


Sex-Linked Genes

- Genes unrelated to gender on the X chromosome.
- Females have **two** X chromosomes (so they can be heterozygous or homozygous for each of these genes)
- Males have **one copy** of the sex-linked genes.
- Thus, the male is referred to as **hemizygous**.

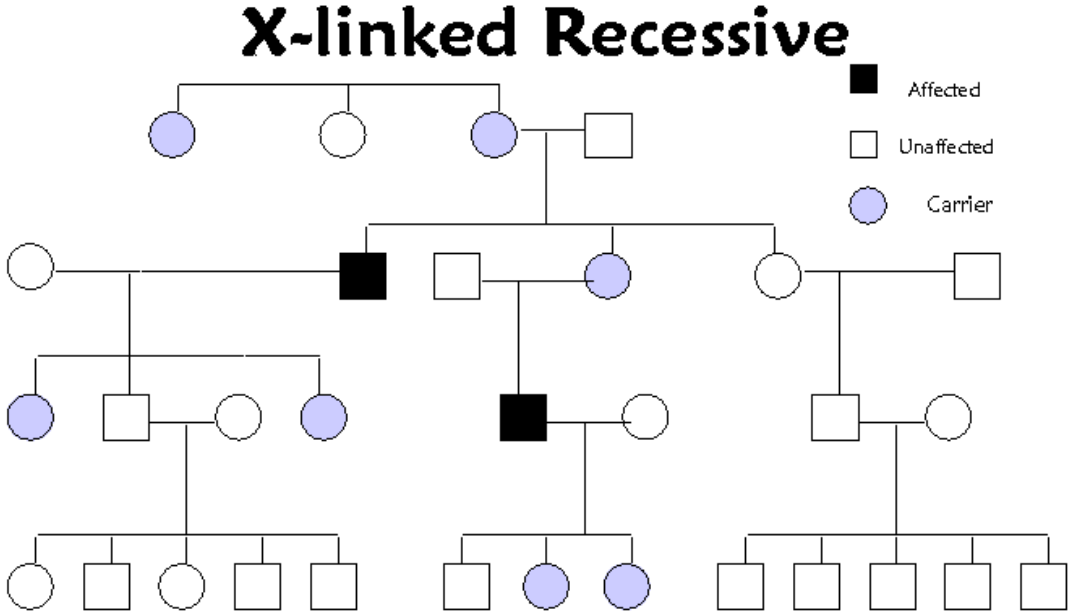
X – linked Recessive Inheritance

- Refers to those situations where a recessive allele on the X chromosome can lead to a trait/condition or disorder.



X – linked Recessive Inheritance

- Males are affected more often than females.
- Affected males will transmit the allele to all daughters, but not to sons.
- Homozygous recessive females can arise only from matings in which the father is affected and the mother is affected or a carrier.



Typical features of X-linked recessive inheritance

- Never passed from father to son.
- Males are much more likely to be affected because they only need one copy of the mutant allele to express the phenotype.
- Affected males get the disease from their mothers and all of their daughters are obligate carriers.
- Sons of heterozygous females have a 50% chance of receiving the mutant allele.
- These disorders are typically passed from an affected grandfather to 50% of his grandsons.

X-linked recessive

- Heterozygous females are usually unaffected, but some may express the condition with variable severity as determined by the pattern of X inactivaiton.

- The mutant allele may be transmitted through a series of carrier females; if so, the effected males in a kindred are related through females.

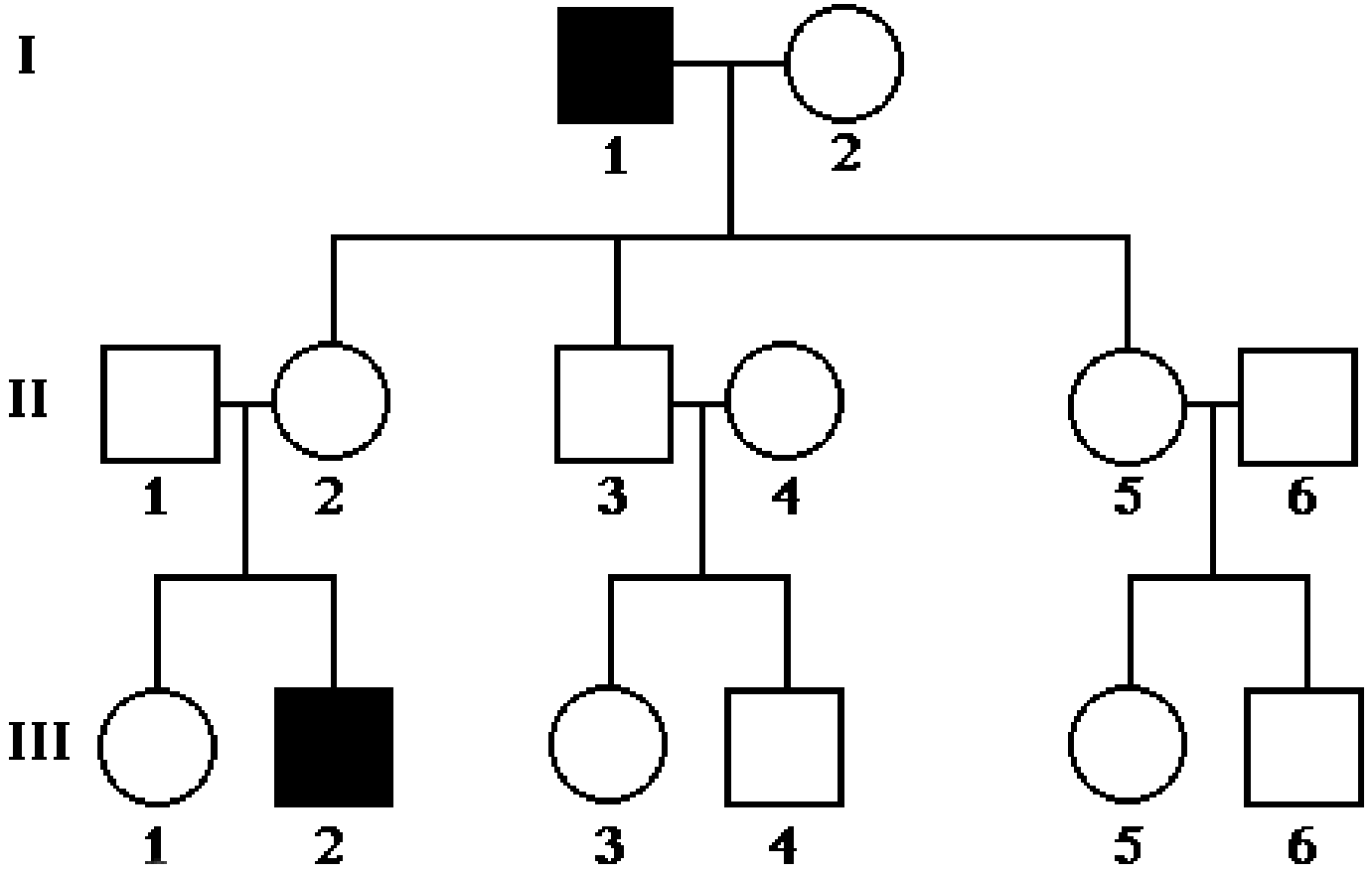
- A significant proportion of isolated cases are due to new mutation.

- Many X-linked recessive disorders are well-known, including color blindness, hemophilia, and Duchenne muscular dystrophy.

Manifesting Heterozygous or unbalanced (skewed) inactivation for X linked disease

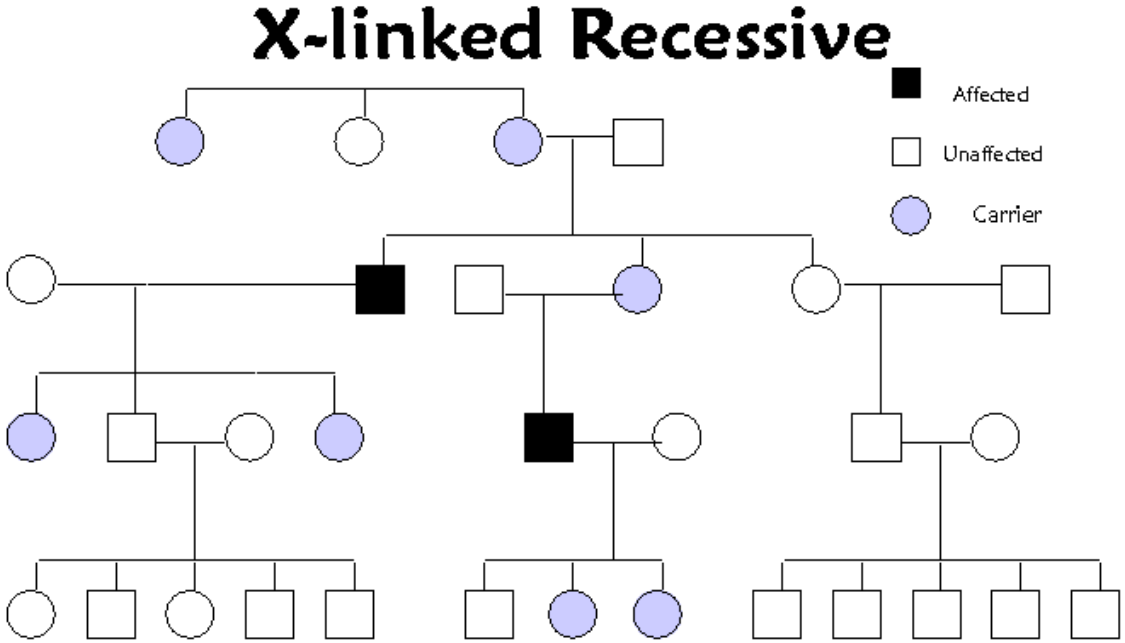
- In those rare instances in which a female carrier of a recessive X linked allele has phenotypic expression of the disease, she is referred to as a Manifesting Heterozygous.

The pattern for the pedigree of X-linked recessive inheritance



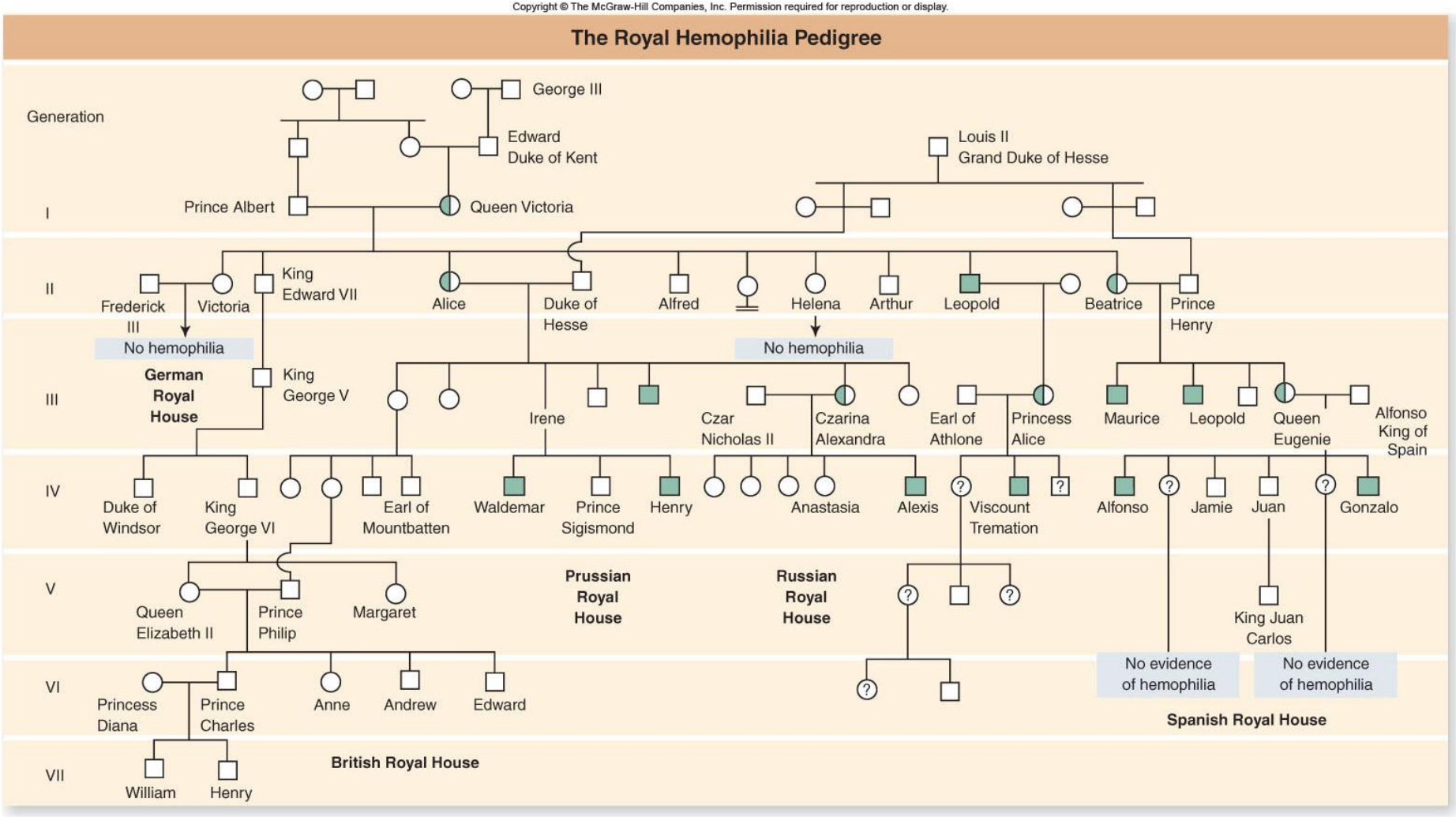
X – linked Recessive Disorders

- Hemophilia which is the inability of the blood to clot properly.
- Duchenne Muscular Dystrophy which causes progressive and degenerative muscle weakness.

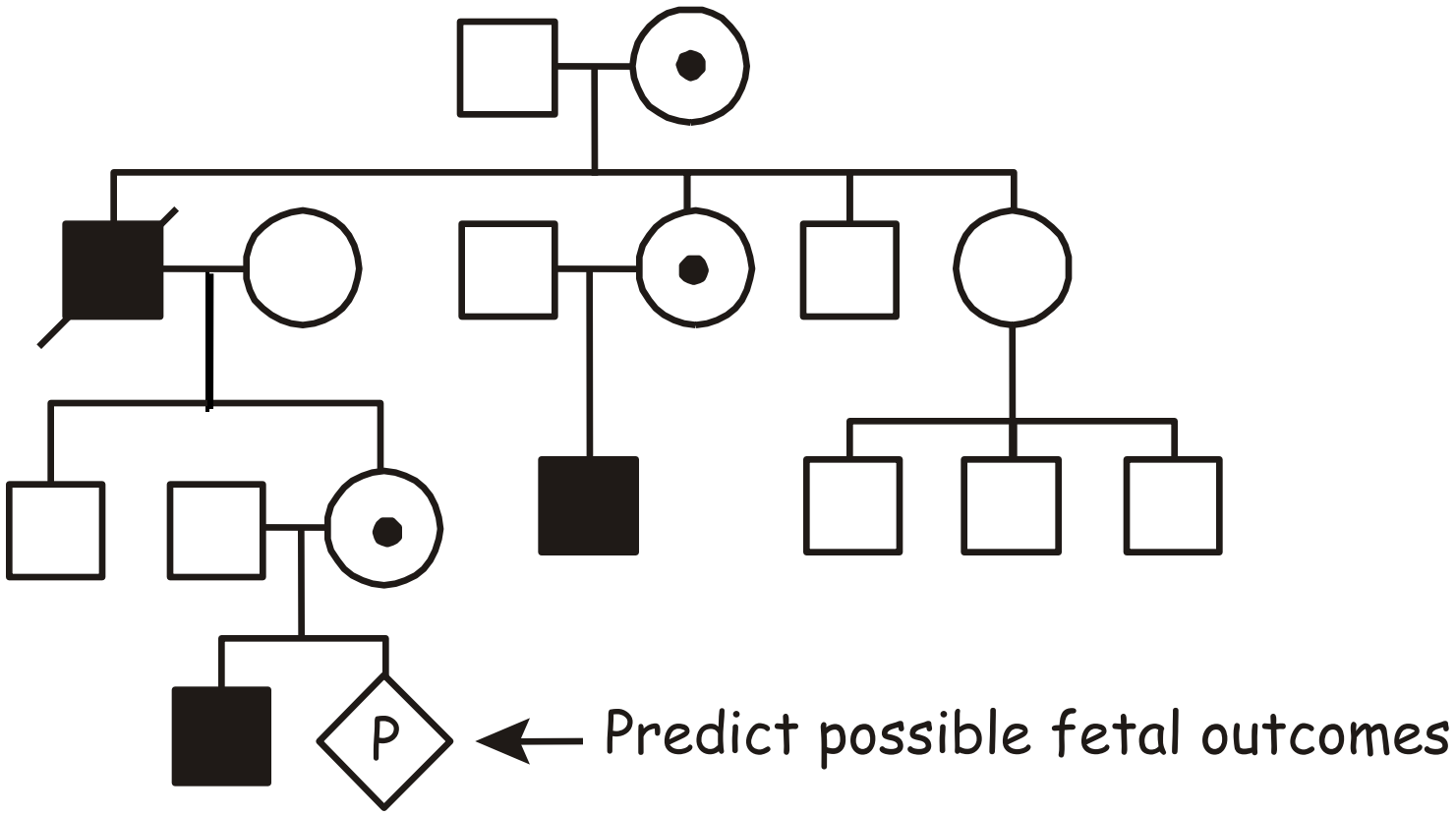


Hemophilia

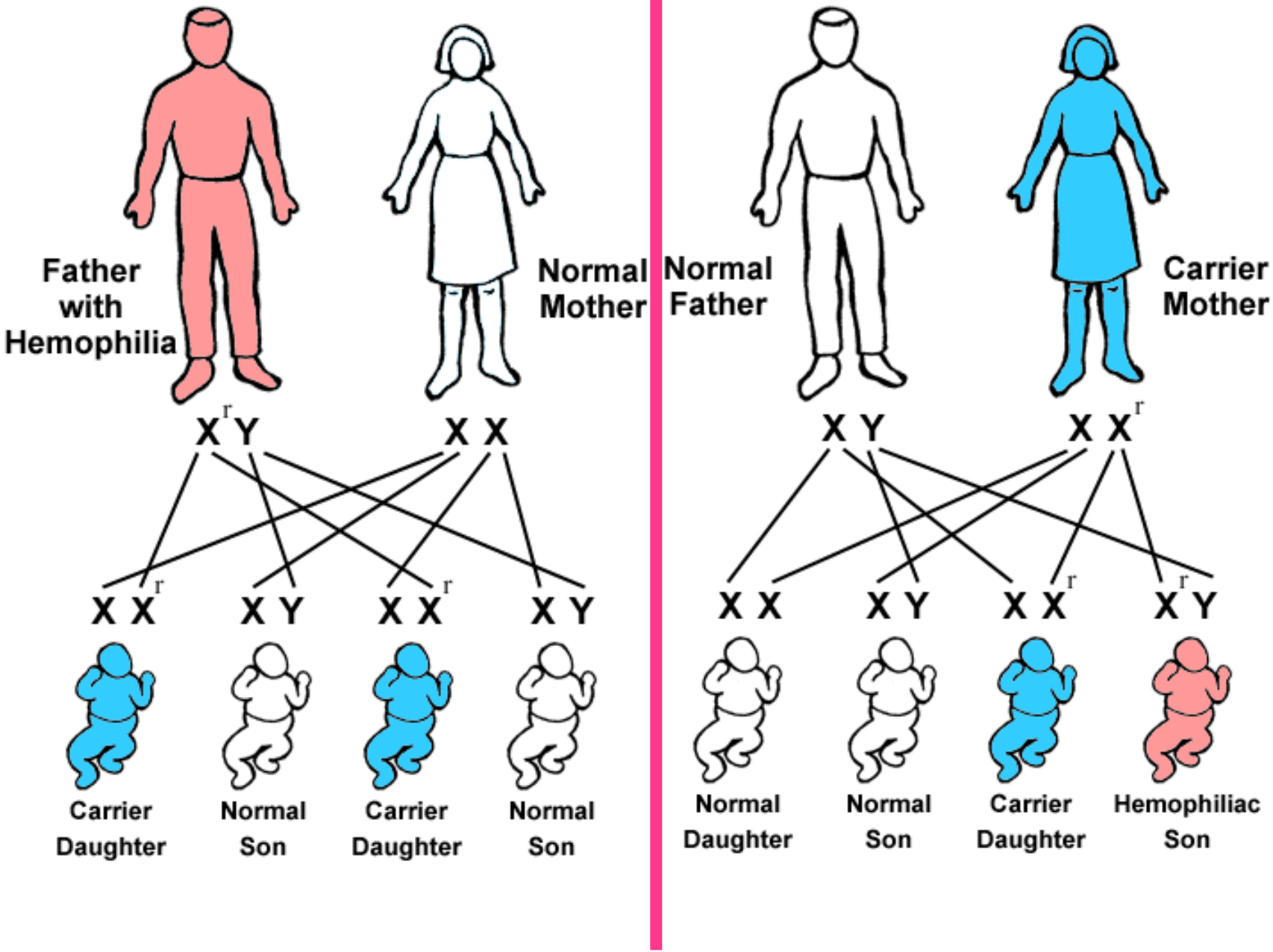
- Disease that affects a single protein in a cascade of proteins involved in the formation of blood clots
- Form of hemophilia is caused by an X-linked recessive allele
  - Heterozygous females are asymptomatic carriers
- Allele for hemophilia was introduced into a number of different European royal families by Queen Victoria of England



Example: hemophilia A



Example: hemophilia A



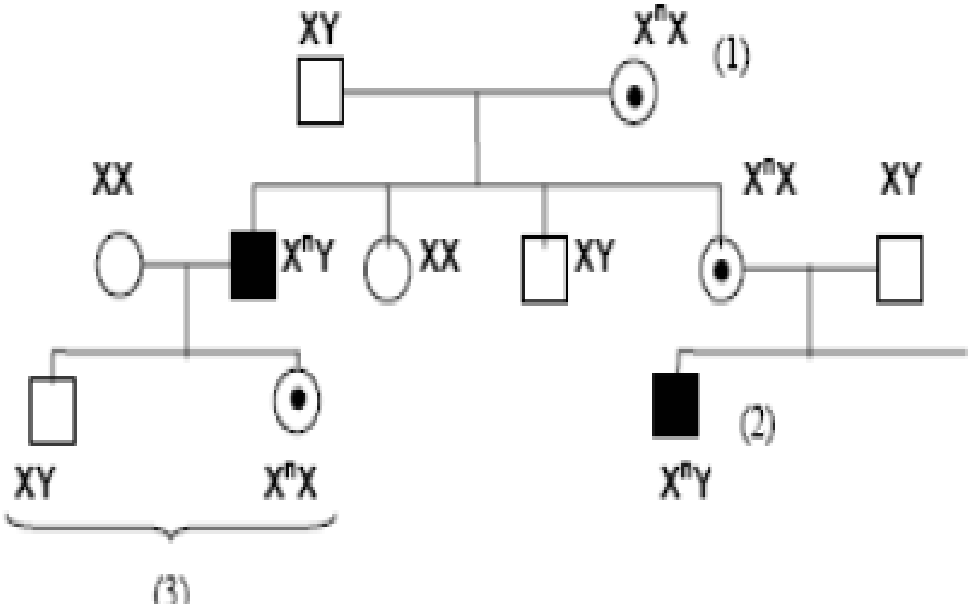
Overview of XR trait

- A number of recessive mutations are X linked.
- Their transmission is described by the followins rules:

❑ Females can be carriers of recessive disorders

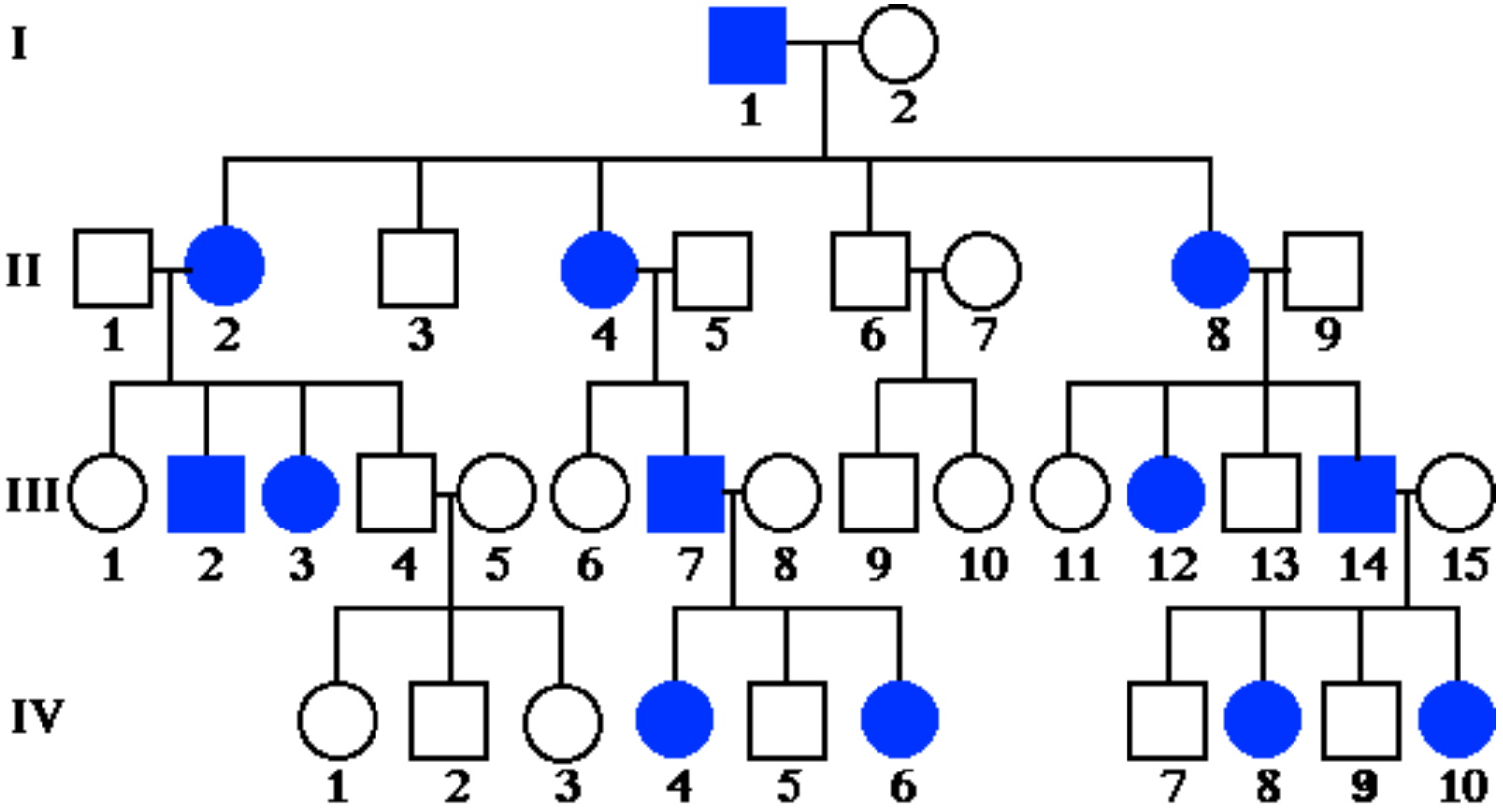
❑ Males expresses the respective phenothype because they are HEMIZYGOUS for X chromosome. They receive their X from the mother.

❑ Sons of affected males are healty but daughters become carriers.



X – Linked Dominant Inheritance

- Refers to situations where a single dominant allele on the X chromosome can lead to a trait/condition.
- XD can distinguished from autosomal dominant inheritance by the lack of male to male transmission.



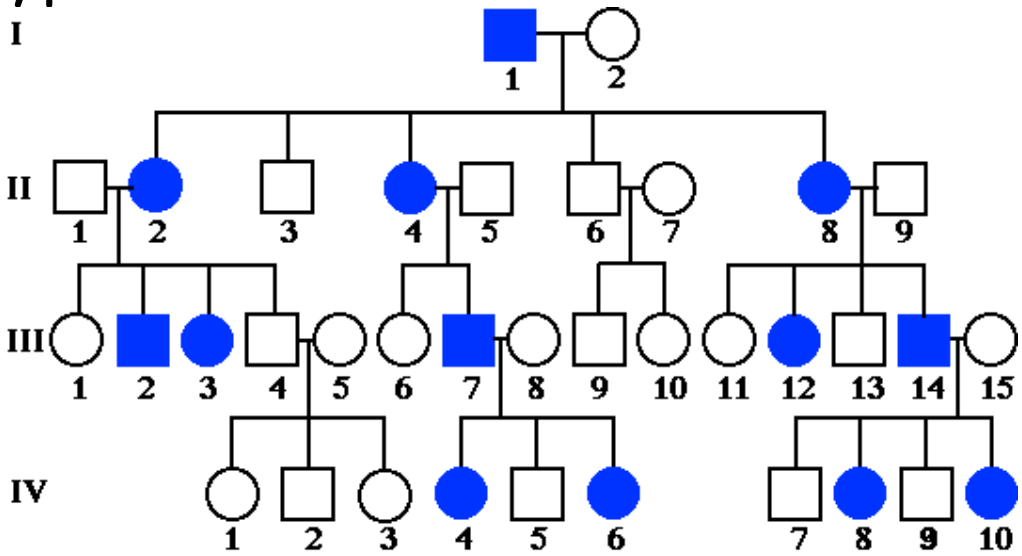
Pedigree 5. X-linked dominant inheritance.

X-Linked Dominant Inheritance

- Affected fathers transmit the disorder to ALL of their daughters none of their sons
- The pattern of inheritance through females is no different from AD pattern
- Each child of an affected female has a 50% chance of inheriting the trait, regardless of sex
- Rare X-linked dominant phenotypes are about twice as common in females, though the expression is much milder in females who are almost always heterozygous

X – Linked Dominant Inheritance

- 1. Usually half the children of an affected female will be affected, regardless of sex.
- 2. All the daughters of an affected male will be affected but none of the sons.
- 3. Affected females typically have milder expression of the phenotype.



Pedigree 5. X-linked dominant inheritance.

X-linked dominant

- Hereditary pattern in which a dominant gene on the X chromosome causes a characteristic to be manifested in the offspring.

- X-linked dominant diseases are those that are expressed in females when only a single copy of the mutated gene is present.

- Very few X-linked dominant diseases have been identified (e.g. hypophosphatemic rickets, Alport syndrome, diabetes insipidus)
  - hypophosphatemic rickets or vitamin D resistant rickets >>>low serum phosphorus, skeletal abnormalities
  - Alport syndrome, which involves progressive hearing loss and progressive kidney problems.

Characteristics of X-linked dominant diseases include:

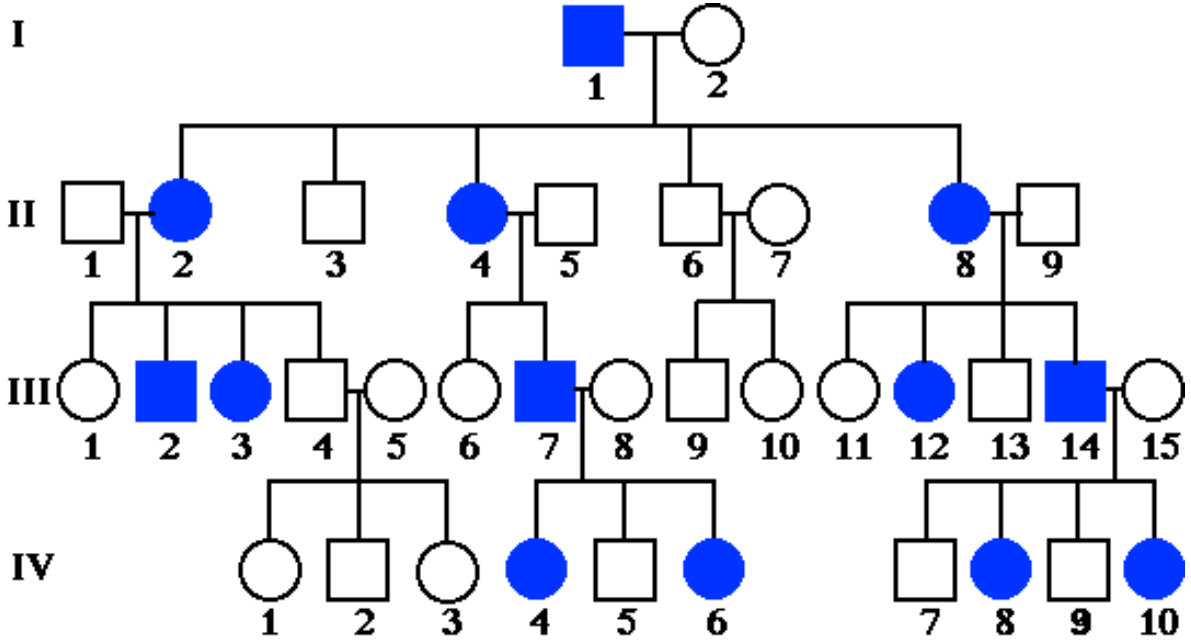
- Never passed from father to son.
- Affected males produce only affected females. An affected male only has one X chromosome to pass on to his daughters
- Affected females produce 50% normal and 50% affected offspring.. >>>> heterozygous
- Males are usually more severely affected than females. Some X-linked dominant traits may even be lethal to males.
- Females are more likely to be affected. Since females have 2 X chromosomes, they have 2 "chances" to inherit the mutated allele.

Characteristics of X-Linked Dominant Inheritance

- Affected fathers with normal mates have no affected sons and no normal daughters
- For rare pehnotypes, affected females are about twice as common as affected males (unless disease is lethal in males), but affected females typically have milder (though variable) expression
- Both male and female offspring of a heterozygous female have a 50% risk of inheriting the phenotype. The pedigree pattern is similar to AD inheritance

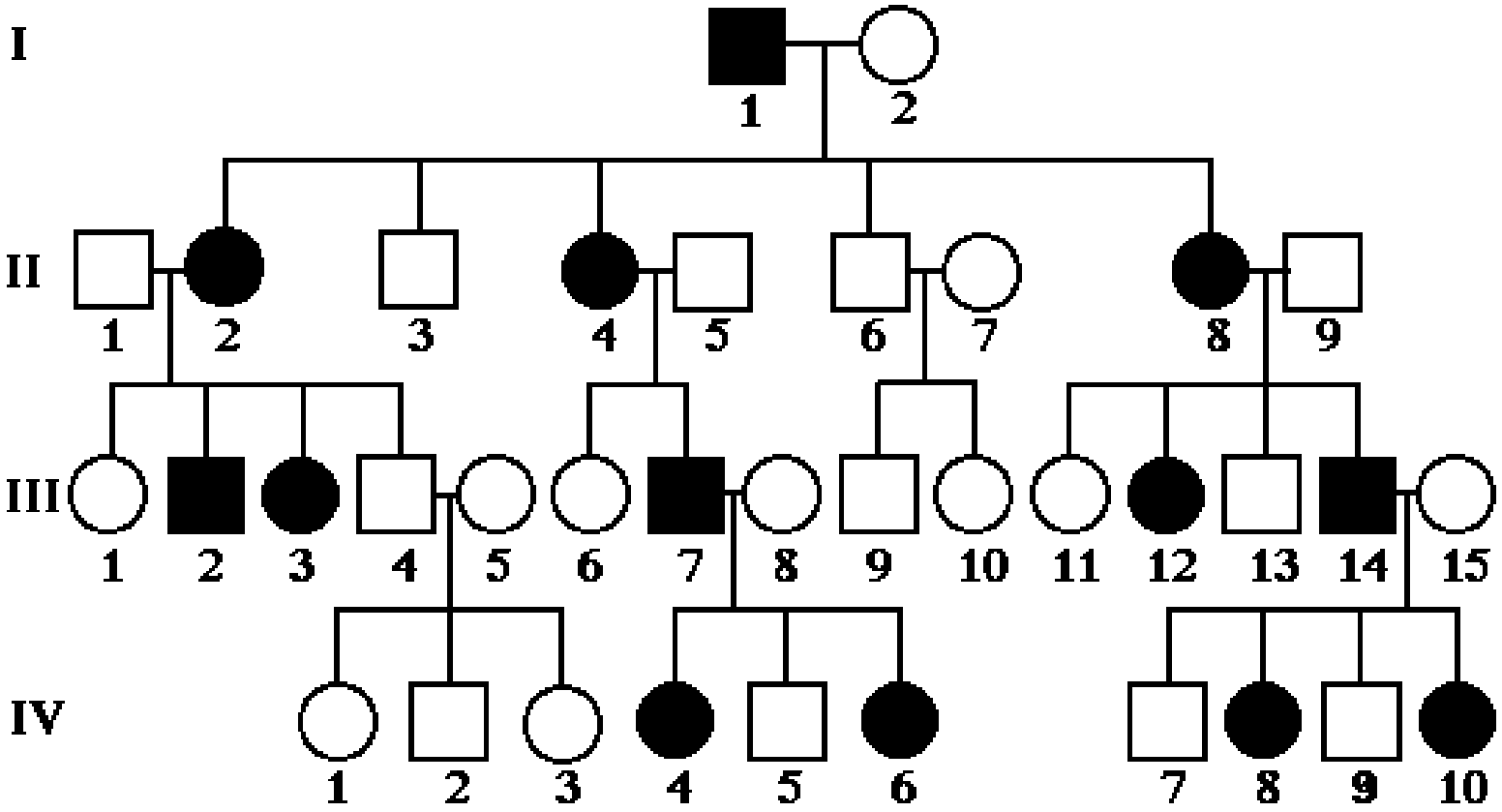
X – Linked Dominant Example

- Vitamin D resistant rickets which can lead to bone deformities, particularly in the lower limbs (bowed legs).



Pedigree 5. X-linked dominant inheritance.

The pattern for the pedigree of X-linked dominant inheritance



X-linked Dominant Disorders with Male Lethality

- Some rare genetic defects expressed exclusively or almost exclusively in females appear to be XD lethal in males before birth or early infancy
- Typical pedigrees: transmission by affected female → affected daughters, normal daughters, normal sons in equal proportions.
- Rett syndrome meets criteria for an XD that is usually lethal in hemizygous males.
- The syndrome is characterized by normal prenatal and neonatal growth and development, followed by rapid onset of neurological symptoms and loss of milestones between 6 and 18 months of age.

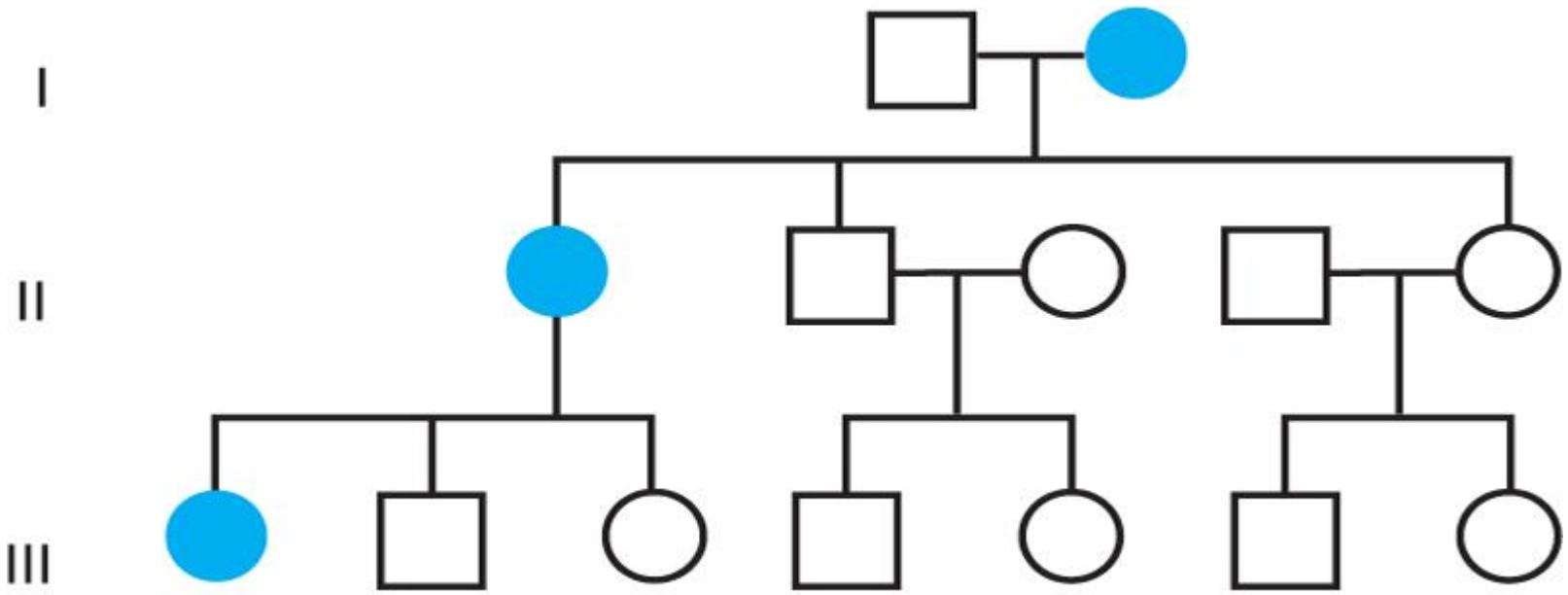
Rett syndrome cont.

- Children become spastic and ataxic, develop autistic features and irritable behavior with outbursts of crying, and demonstrate characteristic purposeless wringing or flapping movements of hands and arms.
- Head growth slows and microcephaly develops. Seizures are common (~50%)
- Mental deterioration stops after a few years and the patients can then survive for many decades with a stable but severe neurological disability.

Typical appearance and hand posture of girls with Rett syndrome

Rett syndrome cont.

- Males who survive with the syndrome usually have two X chromosomes (as in 47,XXY or in a 46,X,der(X) male with the male determining SRY gene translocated to an X) or are mosaic for a mutation that is absent in most of their cells
- There are a few apparently unaffected women who have given birth to more than one child with Rett syndrome. ? X-inactivation pattern in a heterozygous female. ? Germline mosaic



Pedigree pattern demonstrating an X-linked dominant disorder, lethal in males during the prenatal period.

New Mutation in X-linked Disorders

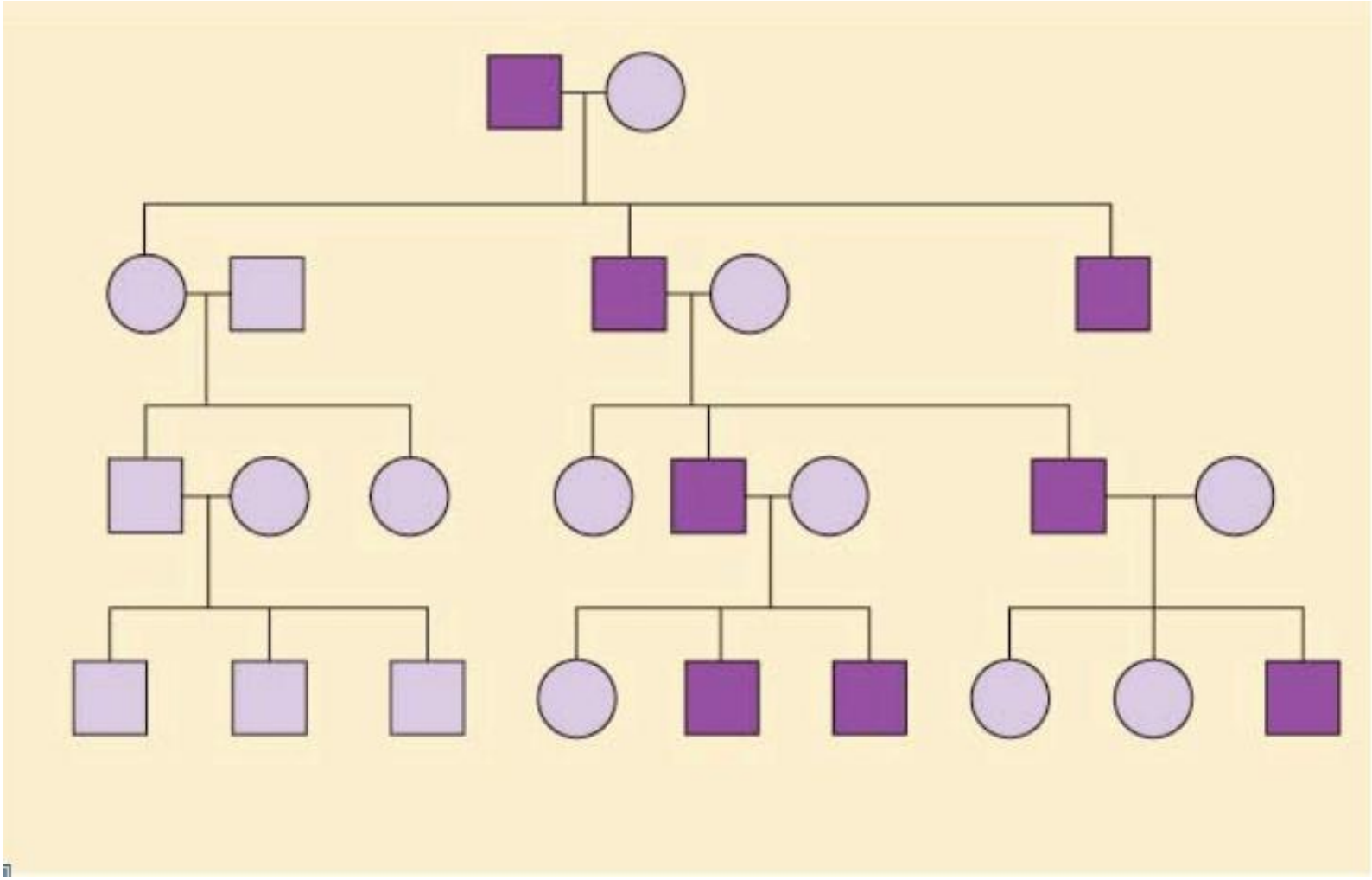
- For a sex-linked recessive disorder with zero fitness, such as Duchenne muscular dystrophy, 1/3 of disease alleles are in males and are lost with each generation. Thus, 1/3 of disease alleles must be replaced with a new mutation in each generation
- DMD is said to be genetic lethal because affected males usually fail to reproduce
- For hemophilia, in which reproduction is reduced but not eliminated, a proportionately smaller fraction of cases will be due to new mutation

•New mutation constitute a significant franction of isolated cases of many X linked diseases

Y-Linked Traits

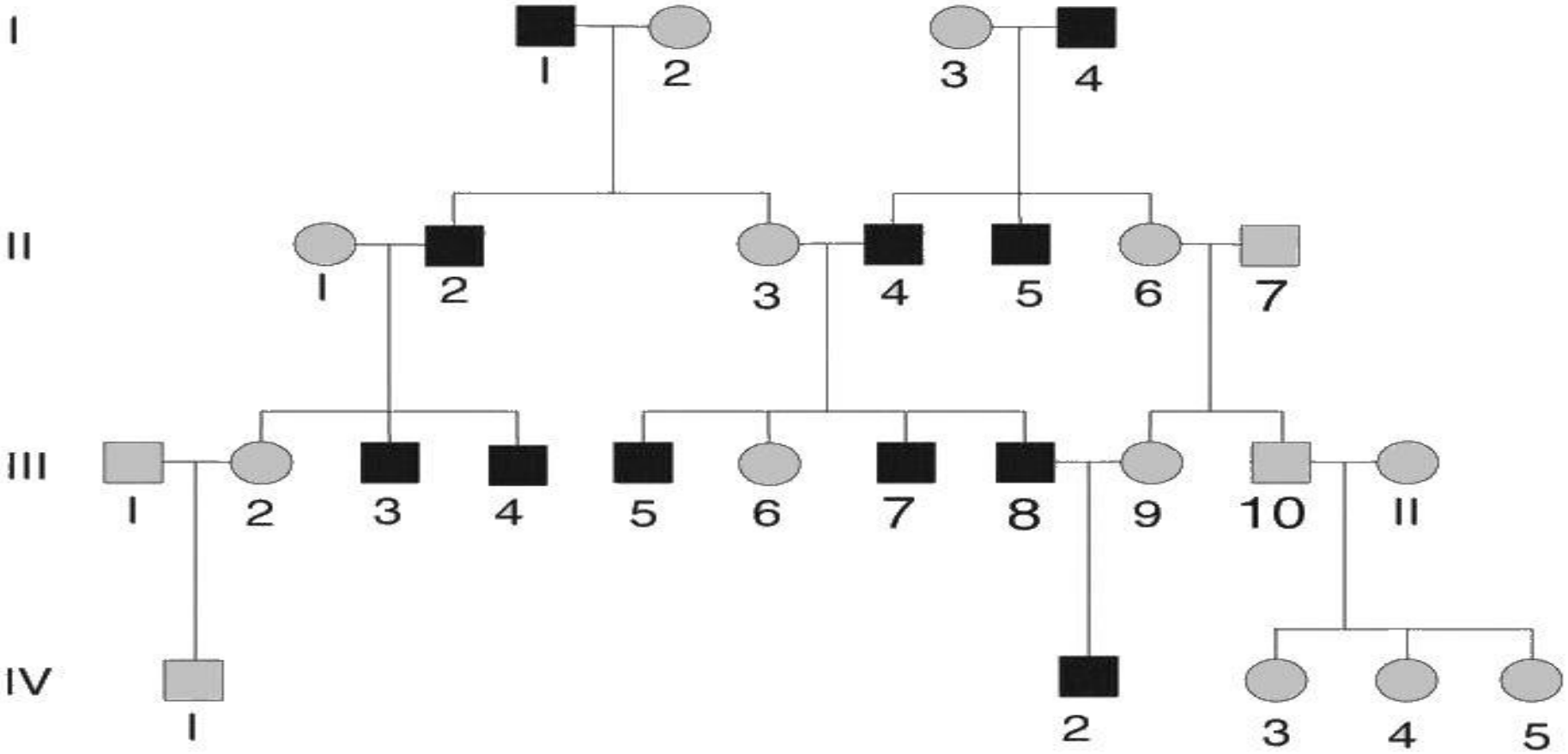
- Only males have Y chromosomes
- Passed from father to sons
- All Y-linked traits are expressed
- Approximately three dozen Y-linked traits have been discovered

Pedigree for Y-Linked Trait



Y-Linked Traits

- **No** affected **females**
- **ALL sons** of affected males are also **affected**



Y-linked Inheritance

- **Y-linked (holandric) genes: < than 50 and NOT** essential. They are transmitted from father to son and appear only in males
- **ZFY: The terminal portion of the short arm of the human Y (Yp)** chromosome encodes a zinc-finger DNA binding protein (*ZFY) with the* potential for regulating the expression of other genes. A highly homologous gene, *ZFX, is encoded on Xp.*
- **H-YA: Male specific Histocompatibility Antigen**
- **AZF2: Azoospermia factor**
- **TSPY: Testis-specific protein**
- **SRY: Sex-determining Region Y gene. Testis determining factor**
- **X- linked several genes: many, not involved in** sex determination