Sex Linkage, and Sex Determination

Sex Linkage

The phenotypic expression of an allele related to the chromosomal sex of the individual

Sex Determination

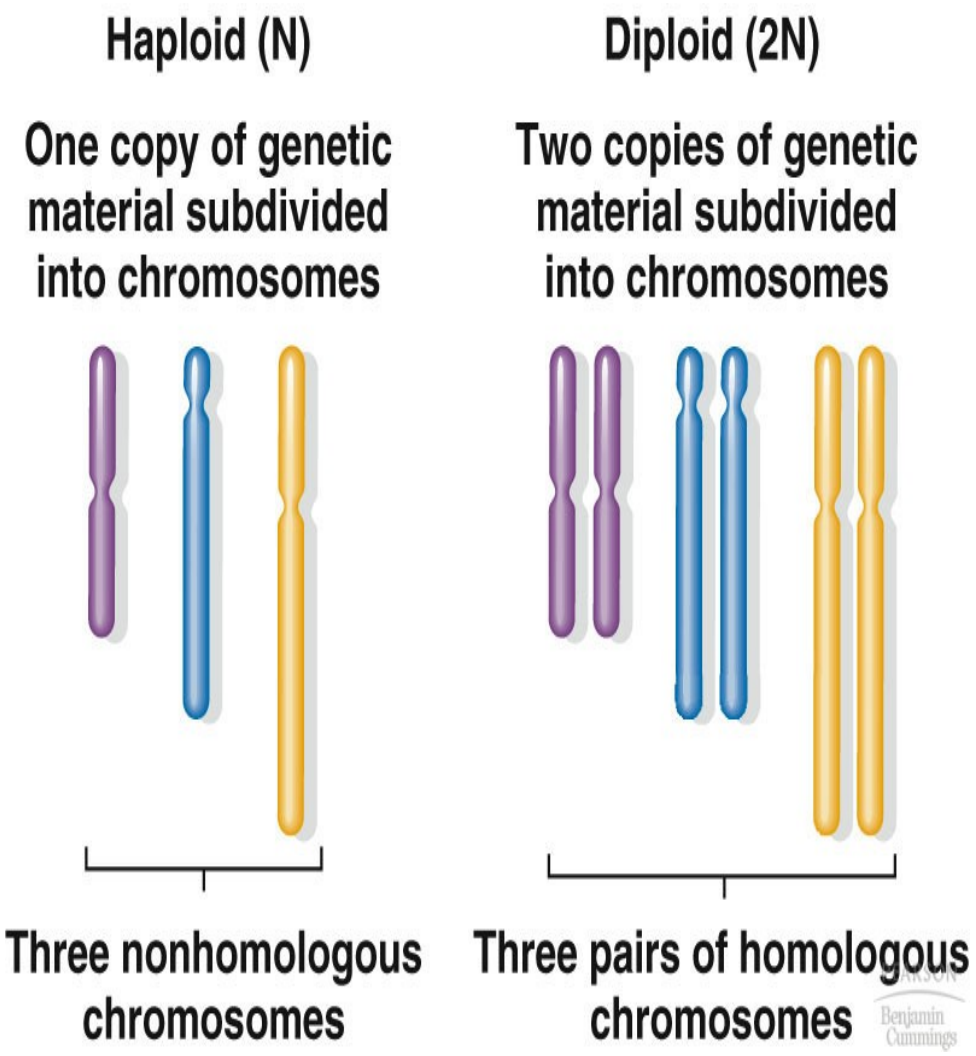
A biological system that determines the development of a sexual characteristics in an organism

Eukaryotic Chromosomes

- Eukaryotes have multiple linear chromosomes in a number characteristic of the species. Most have two versions of each chromosome, and so are diploid (2N).
  - Diploid cells are produced by haploid (N) gametes that fuse to form a zygote. The zygote then undergoes development, forming a new individual.
  - Examples of diploid organisms are humans (23 pairs) and *Drosophila melanogaster* (4 pairs).
  - The yeast *Saccharomyces cerevisiae* is haploid (16 chromosomes).

Eukaryotic Chromosomes

Chromosome pairs in diploid organisms are homologous chromosomes. One member of each pair (homolog) is inherited from each parent. Chromosomes that have different genes and do not pair are nonhomologous chromosomes



Eukaryotic Chromosomes

- ✓ Animals and some plants have male and female cells with distinct chromosome sets, due to sex chromosomes. One sex has a matched pair (e.g., human females with XX) and the other has an unmatched pair (human male with XY).
- ✓ Autosomes are chromosomes other than sex chromosomes.

Sex Chromosomes:
A chromosome that men and women have different amounts of. (X and Y in humans.)

Autosomal Chromosomes:
All the other chromosomes BESIDES the sex chromosomes.

Chromosome Theory of Inheritance

1. By the beginning of the 20th century, cytologists had observed that chromosome number is constant in all cells of a species, but varies widely between species.
2. Sutton and Boveri (1902) independently realized the parallel between Mendelian inheritance and chromosome transmission, and proposed the chromosome theory of inheritance, which states that Mendelian factors (genes) are located on chromosomes.

Sex Chromosomes

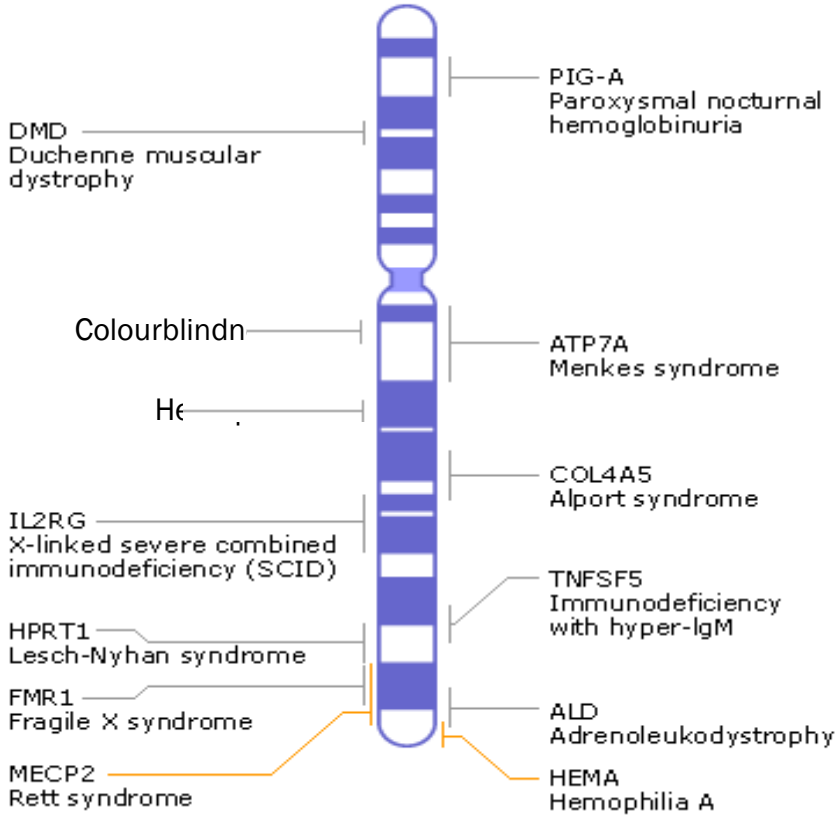
1. Behavior of sex chromosomes offers support for the chromosomal theory. In many animals sex chromosome composition relates to sex, while autosomes are constant.
2. Independent work of McClung, Stevens, and Wilson indicated that chromosomes are different in male and female insects.
   a. Stevens named the extra chromosome found in females "X."
   b. In grasshoppers, all eggs have an X, and half of the sperm produced have an X, and the other half do not. After fertilization, an unpaired X produces a male, while paired X chromosomes produce a female.
3. Other insects have a partner for the X chromosome. Stevens named it "Y." In mealworms, for example, XX individuals are female, and XY are male.

Sex Chromosomes

4. In both humans and fruit flies (*Drosophila melanogaster*) females have two X chromosomes, while males have X and Y.
   a. Males produce two kinds of gametes with respect to sex chromosomes (X or Y), and are called the heterogametic sex.
   b. Females produce gametes with only one kind of sex chromosome (X) and are called the homogametic sex.
   c. In some species the situation is reversed, with heterogametic females and homogametic males.
5. Random fusion of gametes produces an F1 that is 1/2 female (XX) and 1/2 male (XY).

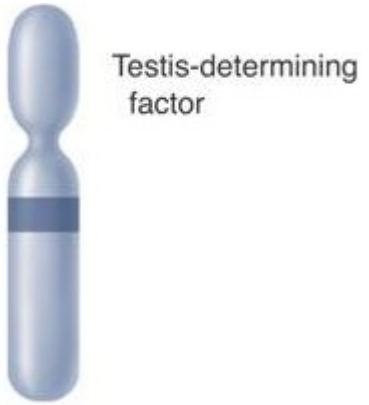
Sex Chromosomes

X chromosome



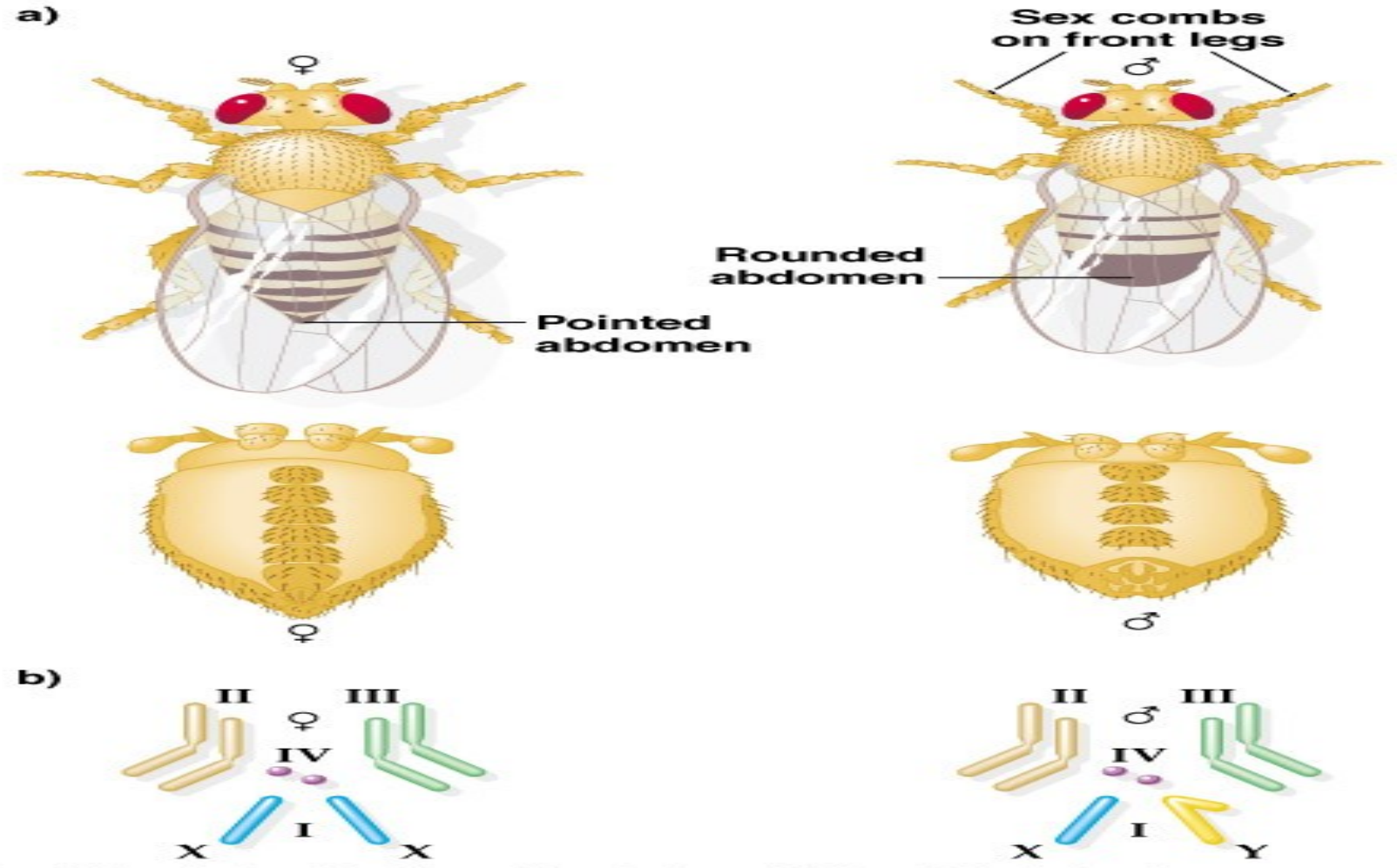
900-1600 genes

Y chromosome

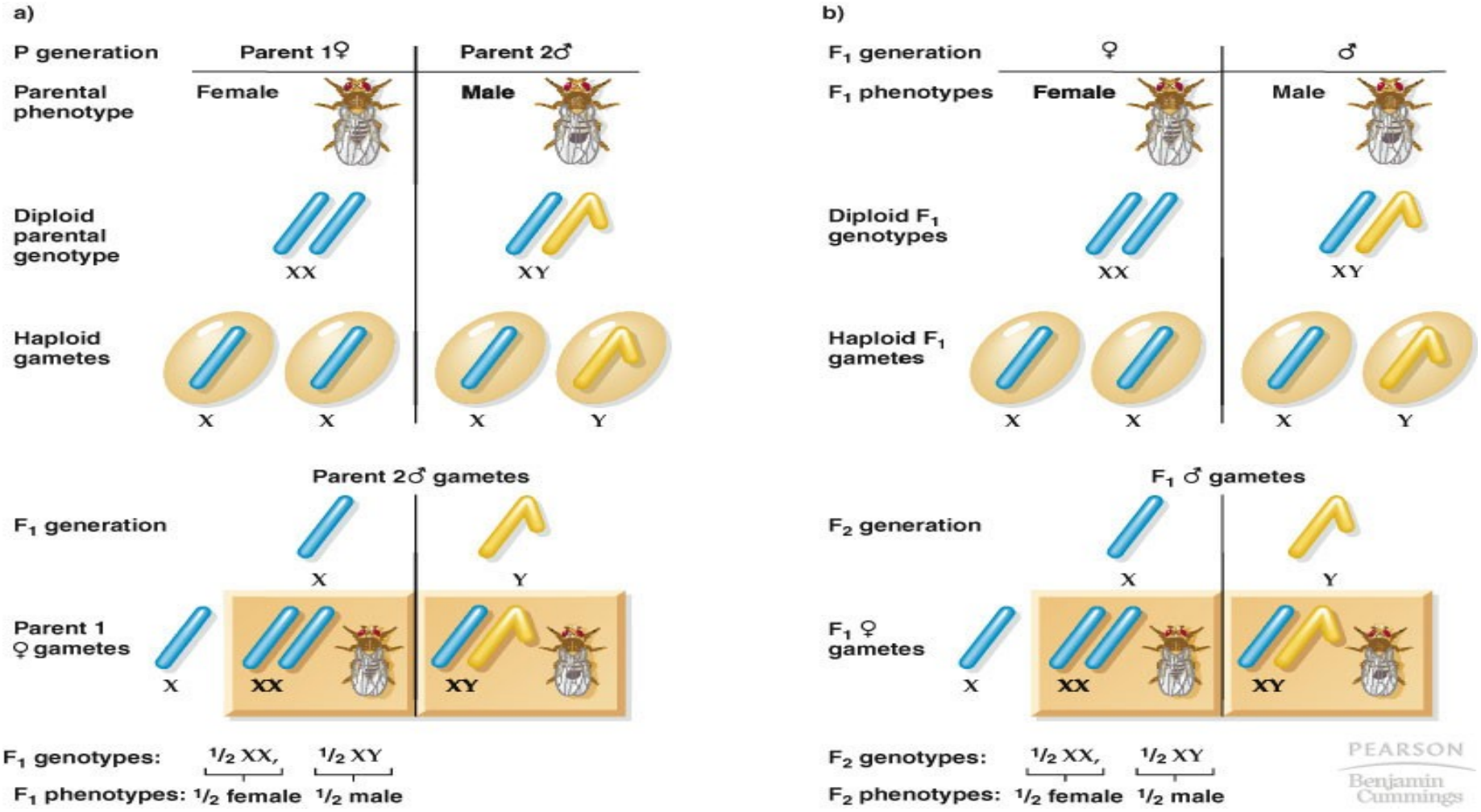


70-200 genes

Drosophila melanogaster (fruit fly), an organism used extensively in genetics experiments



Inheritance pattern of X and Y chromosomes in organisms where the female

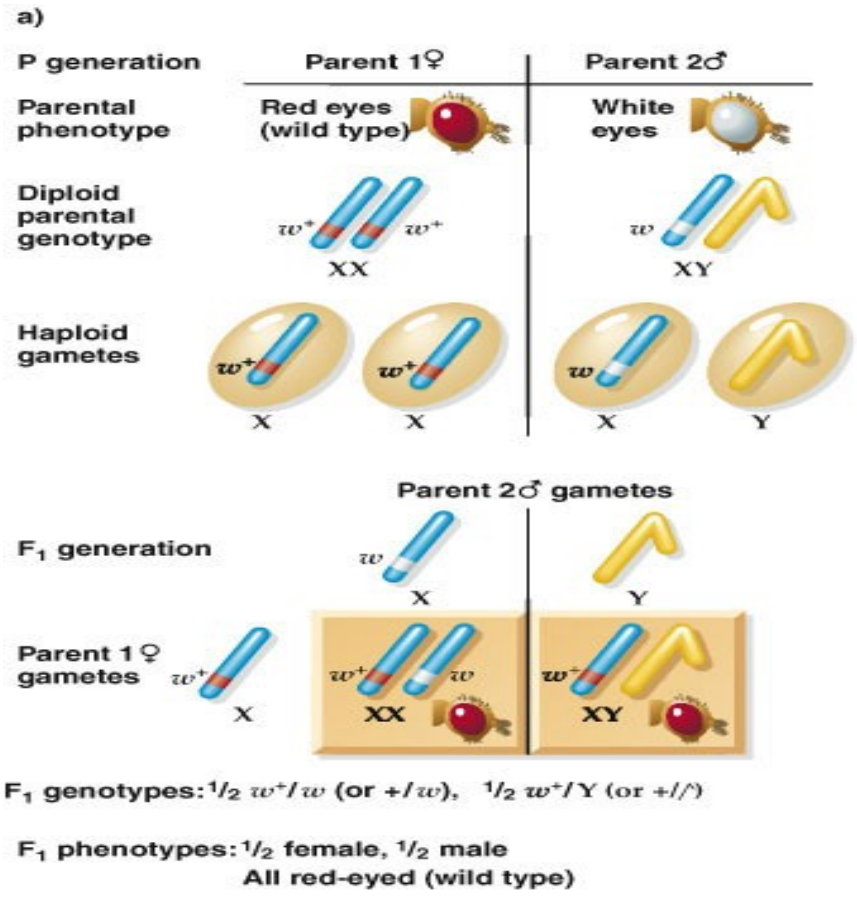


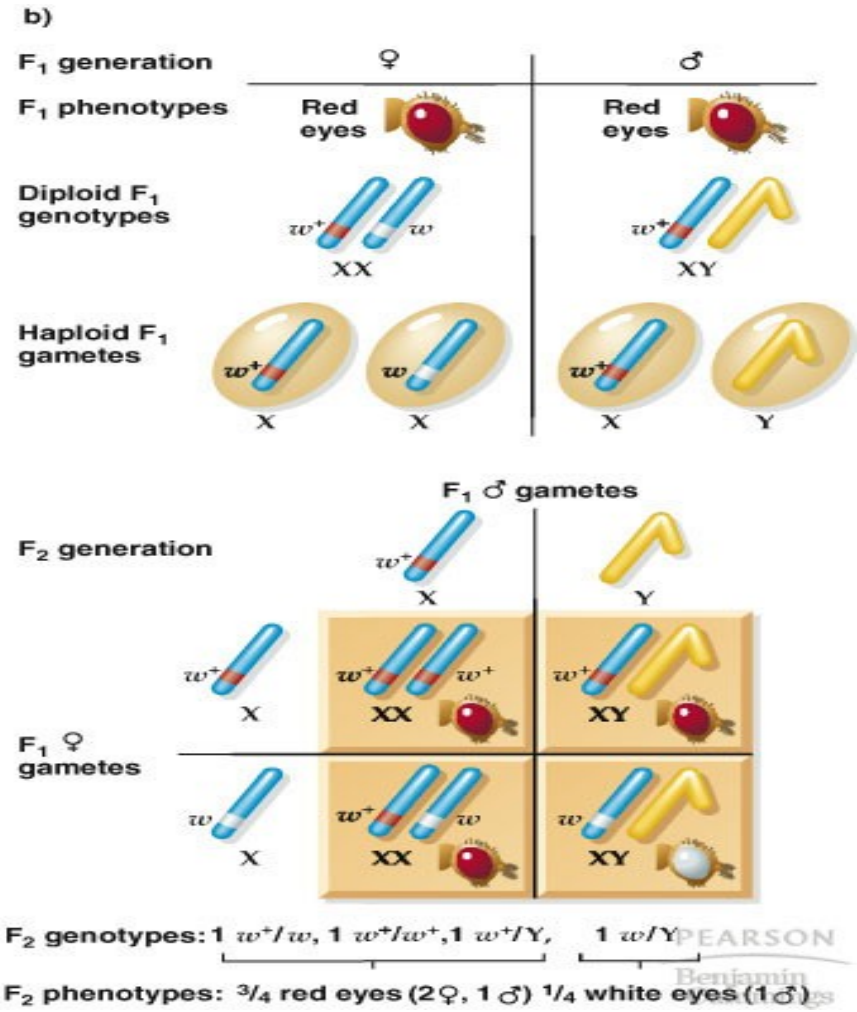
Sex Linkage

The gene for the trait is located on either the X or Y chromosome.

1. Morgan (1910) found a mutant white-eyed male fly, and used it in a series of experiments that showed a gene for eye color located on the X chromosome.
   a. First, he crossed the white-eyed male with a wild-type (red-eyed) female. All F_1 flies had red eyes. Therefore, the white-eyed trait is recessive.
   b. Next, F_1 were interbred. They produced an F_2 with:
      i. 3,470 red-eyed flies.
      ii. 782 white-eyed flies.
   c. The recessive number is too small to fit Mendelian ratios (explanation discovered later is that white-eyed flies have lower viability).
   d. All of the F_2 white-eyed flies were male.

X-linked inheritance of white eyes in *Drosophila:* Red-eyed female × white-eyed male





Sex Linkage

e. Morgan's hypothesis was that this eye color gene is located on the X chromosome. If so,

i. Males are hemizygous, because there is no homologous gene on the Y. The original mutant male's genotype was w/Y (hemizygous with the recessive allele).

ii. Females may be homozygous or heterozygous. The wild-type female in the original cross was w^+/w^+ (homozygous for red eyes).

iii. The F_1 flies were w^+/w (females) and w^+/Y (males) (females all heterozygous, males hemizygous dominant).

iv. The F_2 data complete a crisscross inheritance pattern, with transmission from the mutant fly through his daughter (who is heterozygous) to his grandson. The F_2 were:

	w^+	Y
w^+	w^+/ w^+ Red-eyed females	w^+/ Y Red-eyed males
w	w^+/ w Red-eyed females	**w/ Y** **White-eyed males**

Sex Linkage

v. Morgan's hypothesis was confirmed by an experiment reciprocal to the original cross. A white-eyed female (w/w) was crossed with a wild-type male (w^+/Y). Results of the reciprocal cross:

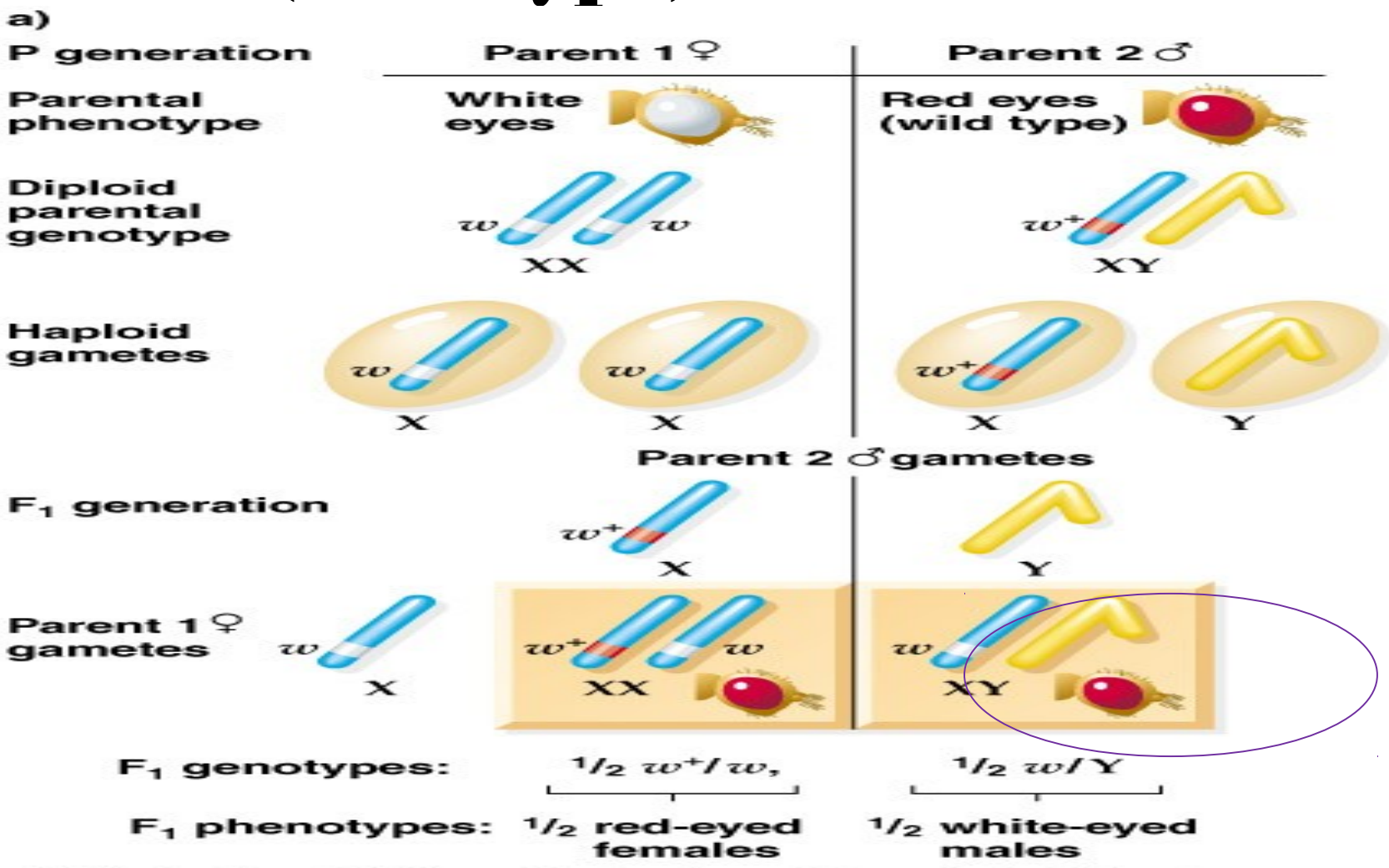
(1) All F_1 females had red eyes (w^+/w).

(2) All F_1 males had white eyes (w/Y).

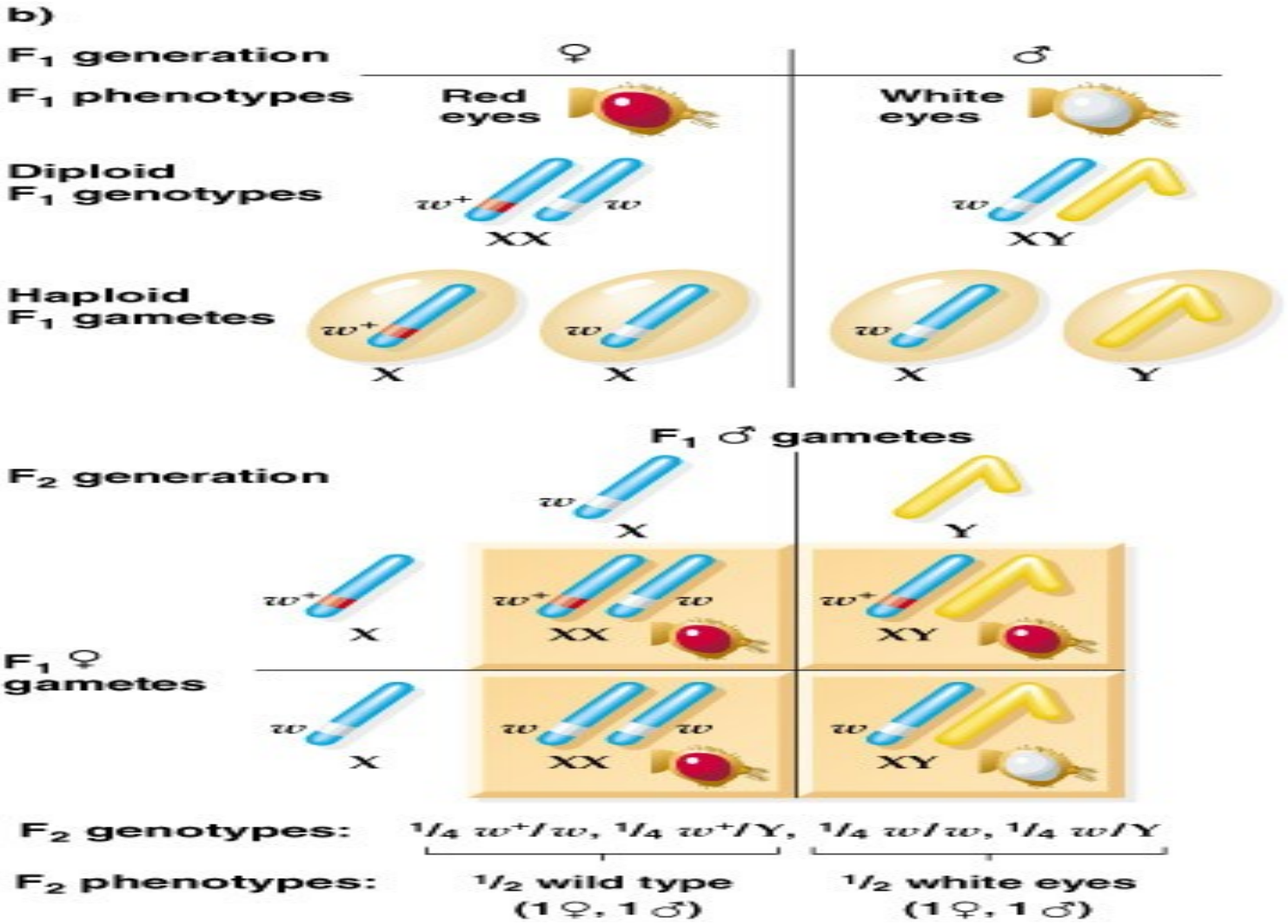
vi. These F_1 results are different from those in the original cross, where all the F_1 had red eyes. When the F_1 from the reciprocal cross interbred, the F_2 were:

	w	Y
w^+	w^+/ w Red-eyed females	w^+/ Y Red-eyed males
w	**w/ w** **White-eyed females**	**w/ Y** **White-eyed males**

Reciprocal cross : Homozygous white-eyed female × red-eyed (wild-type) male



Reciprocal cross : The F_1 flies are interbred to produce the F_2s



Sex Linkage

2. Morgan's discovery of X-linked inheritance showed that when results of reciprocal crosses are different, and ratios differ between progeny of different sexes, the gene involved is likely to be X-linked (sex-linked).
3. This was strong evidence that genes are located on chromosomes. Morgan received the 1933 Nobel Prize for Physiology or Medicine for this work.

Sex-Linked Characteristics

- X-linked characteristics
- Z-linked characteristics
- Y-linked characteristics

X-Linked White Eyes in *Drosophila*

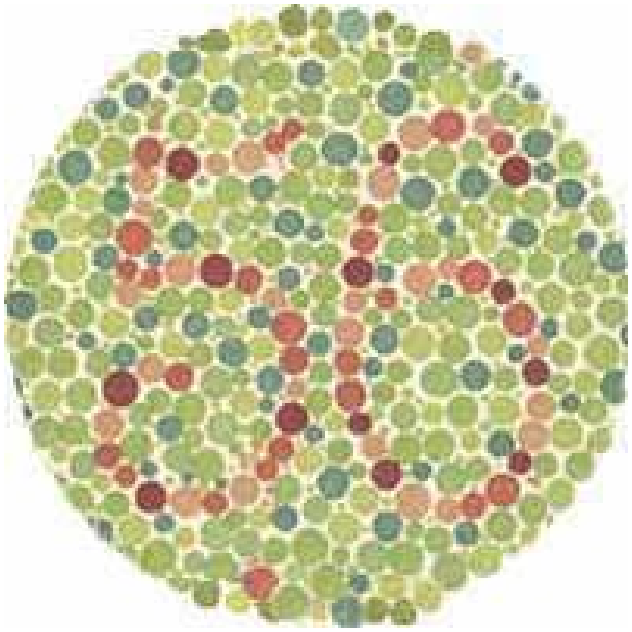
- Appearance of rare phenotypes was associated with the inheritance of particular chromosomes
- Sex-linked genes are located on the X chromosome
- The wild-type eye color of *Drosophila* is dull red, but pure lines with white eyes are available.
- Allele for white is recessive
- White-eyed females would possess two X chromosomes and one Y and that red-eyed males would possess a single X chromosome

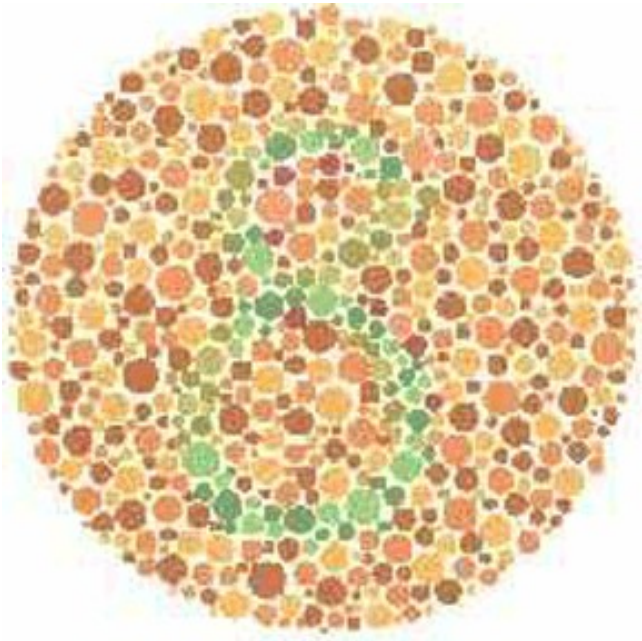
X-Linked Color Blindness in Humans

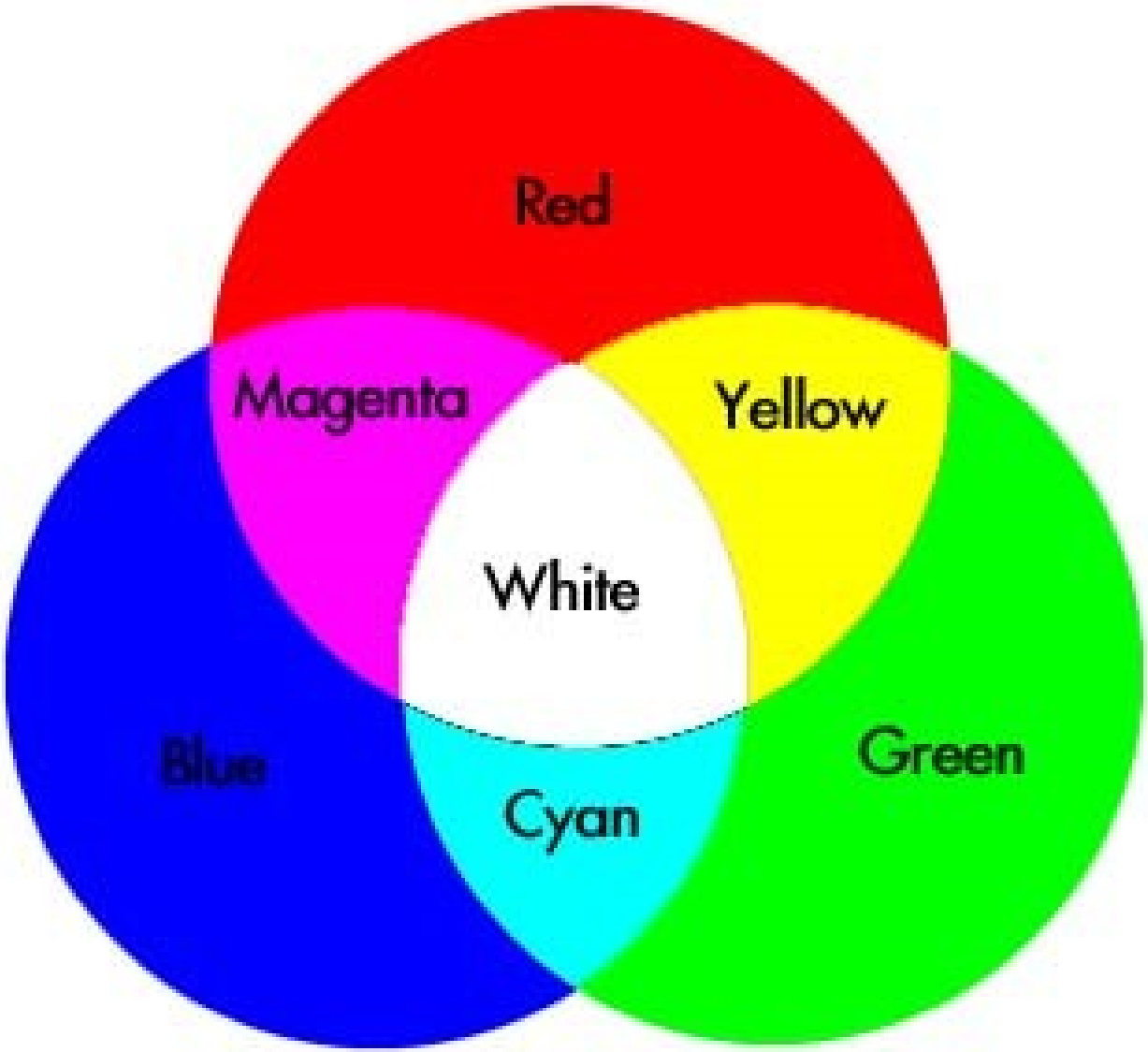
- Human eye detects only three colors—red, green and blue
- Affected woman passes the X-linked recessive trait to her sons but not to her daughters
- Affected man passes the trait to his grandsons through his daughters but never to his sons
- Pattern of inheritance exhibited by X-linked recessive characteristics is sometimes called *crisscross inheritance*

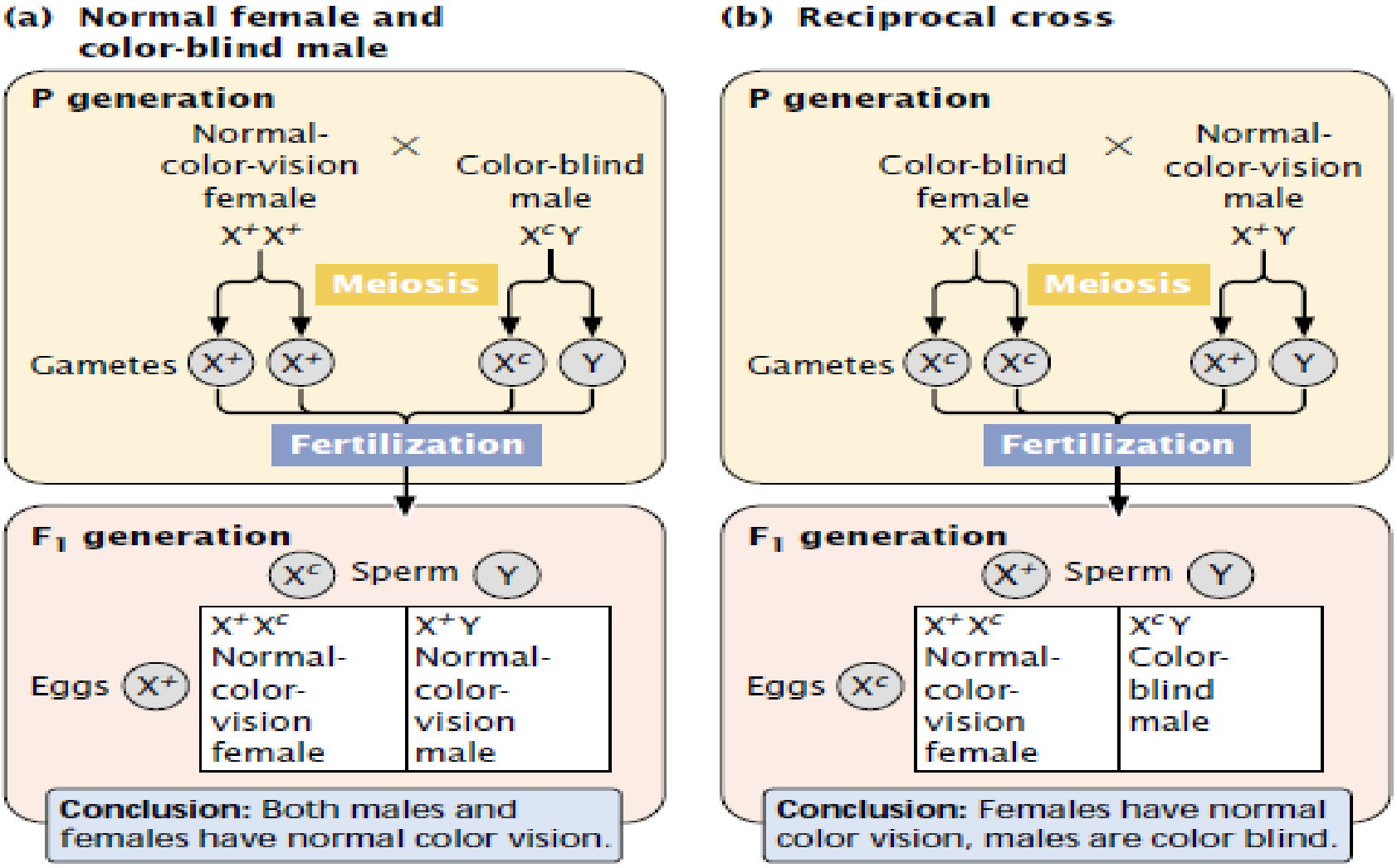
Colourblindness

Result from a defect in one of three genes found on X chromosome



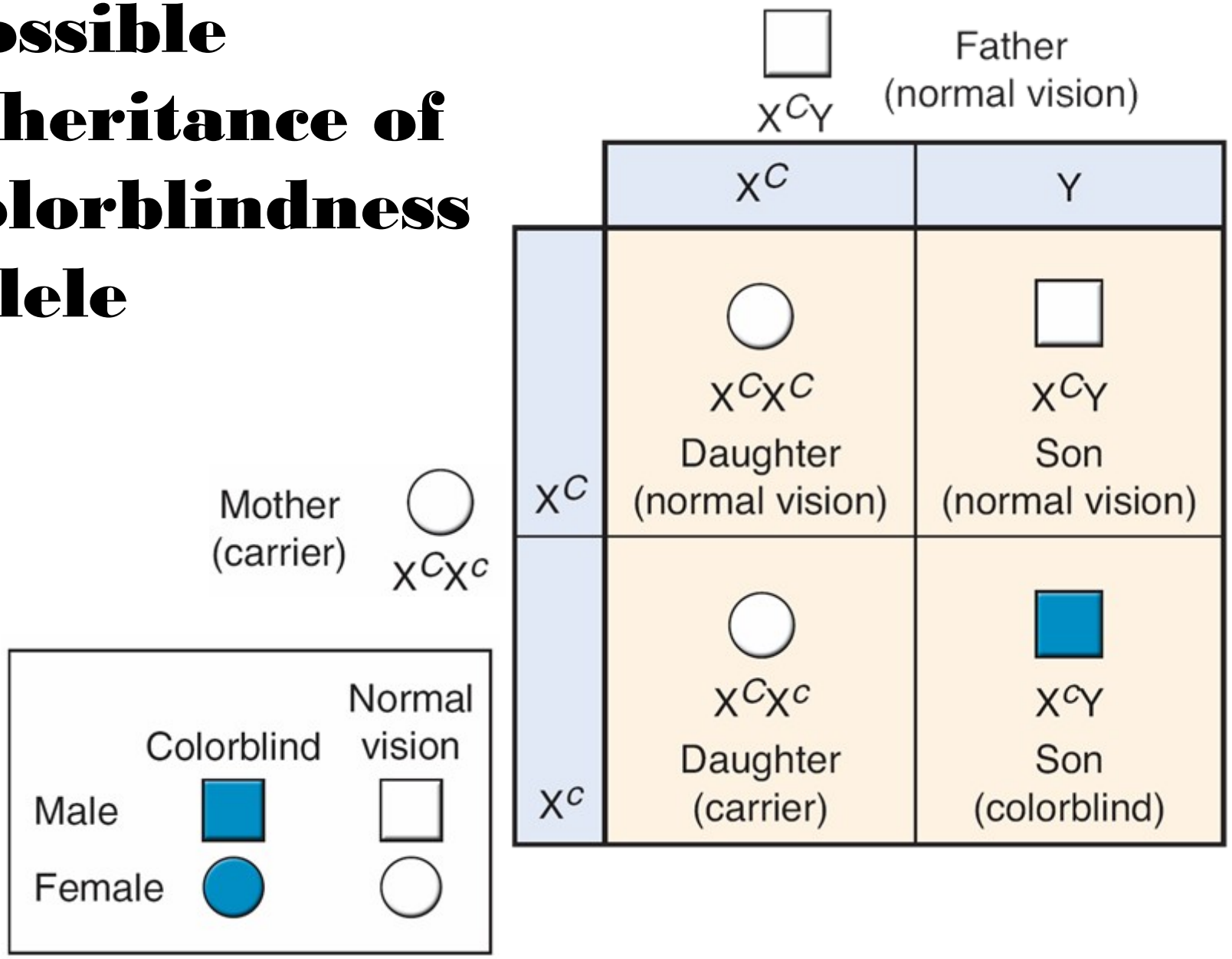



Red
Magenta
Yellow
White
Blue
Cyan
Green



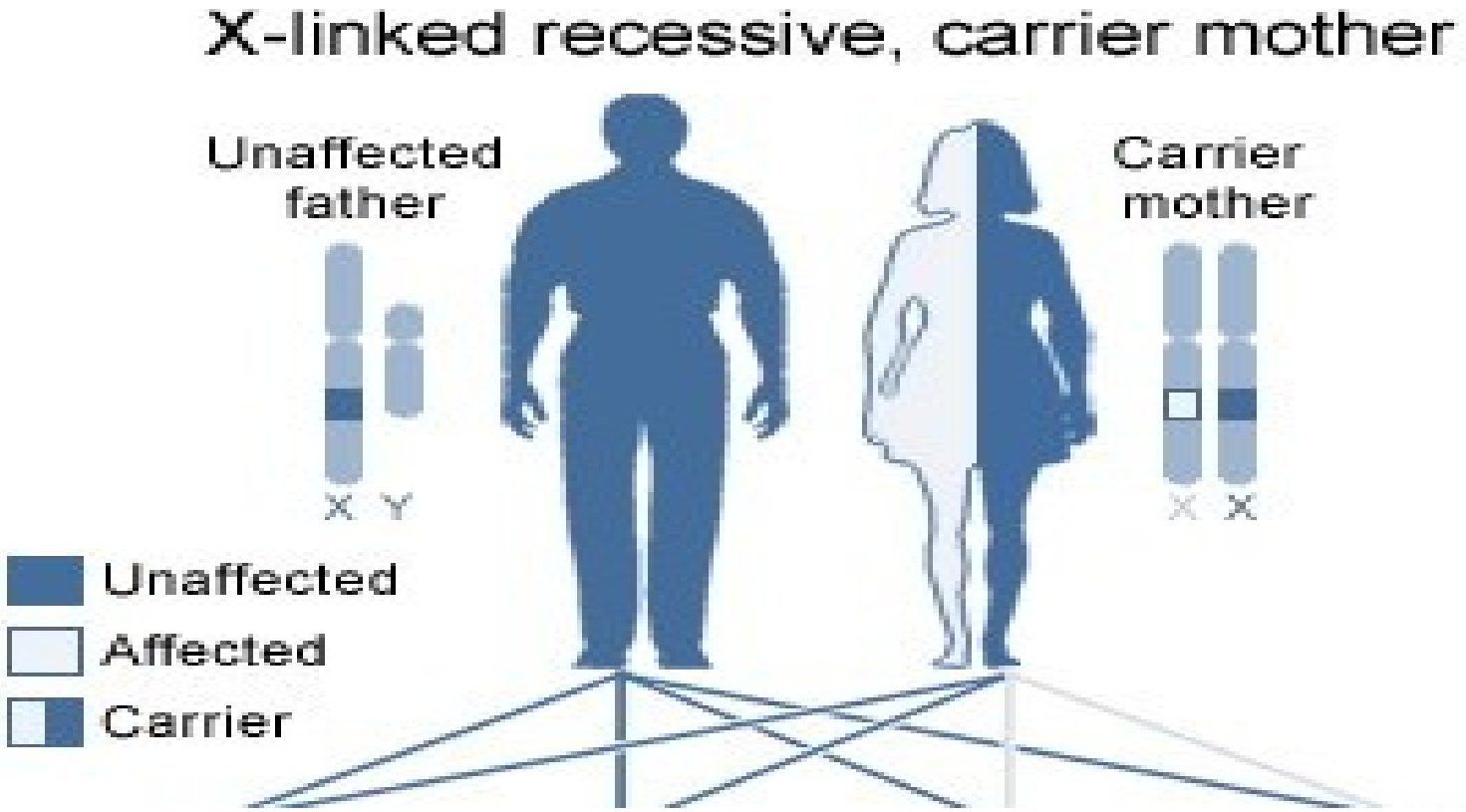
Red–green color blindness is inherited as an X-linked recessive trait in humans

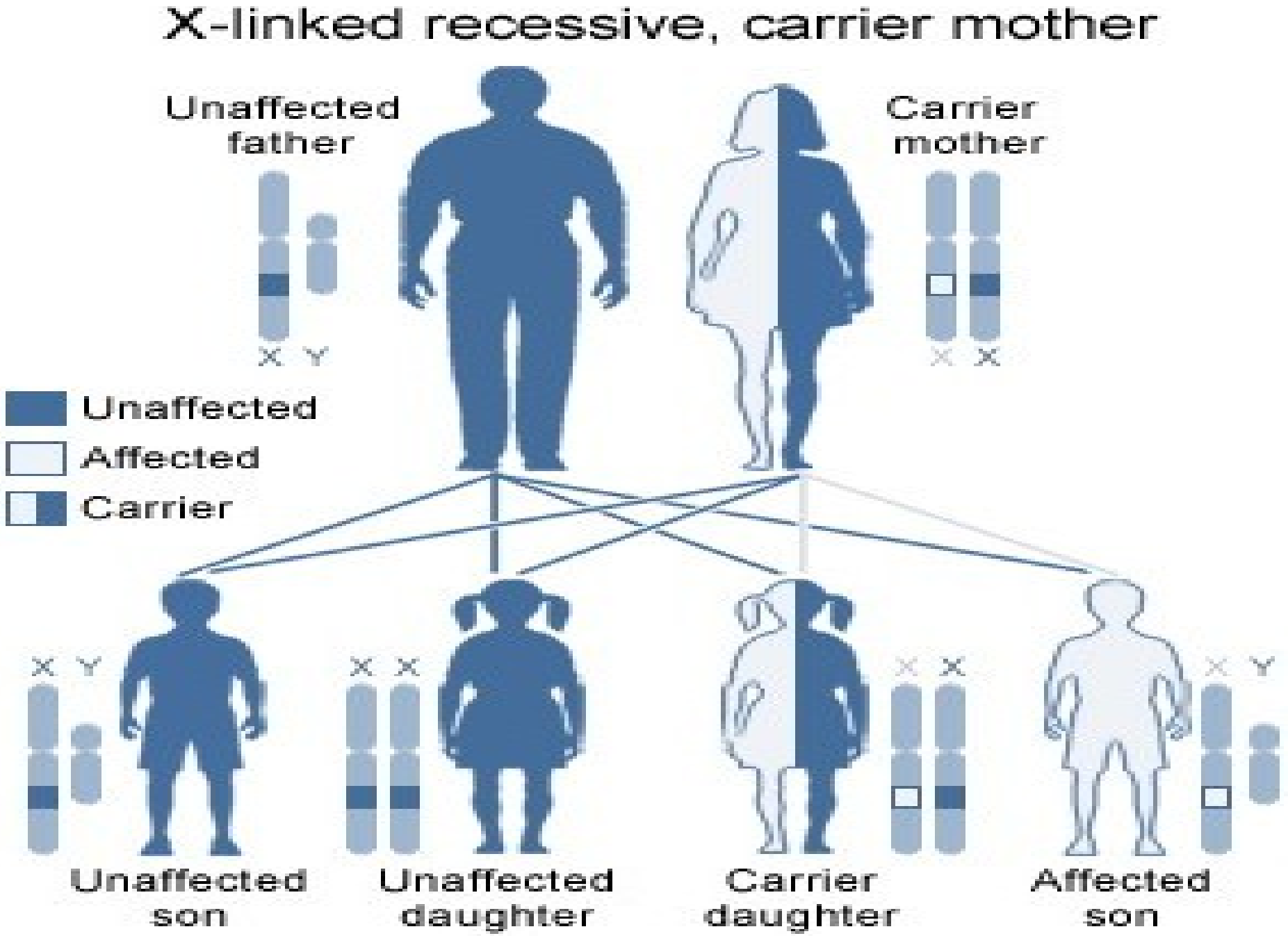
Possible Inheritance of Colorblindness Allele



Carrier

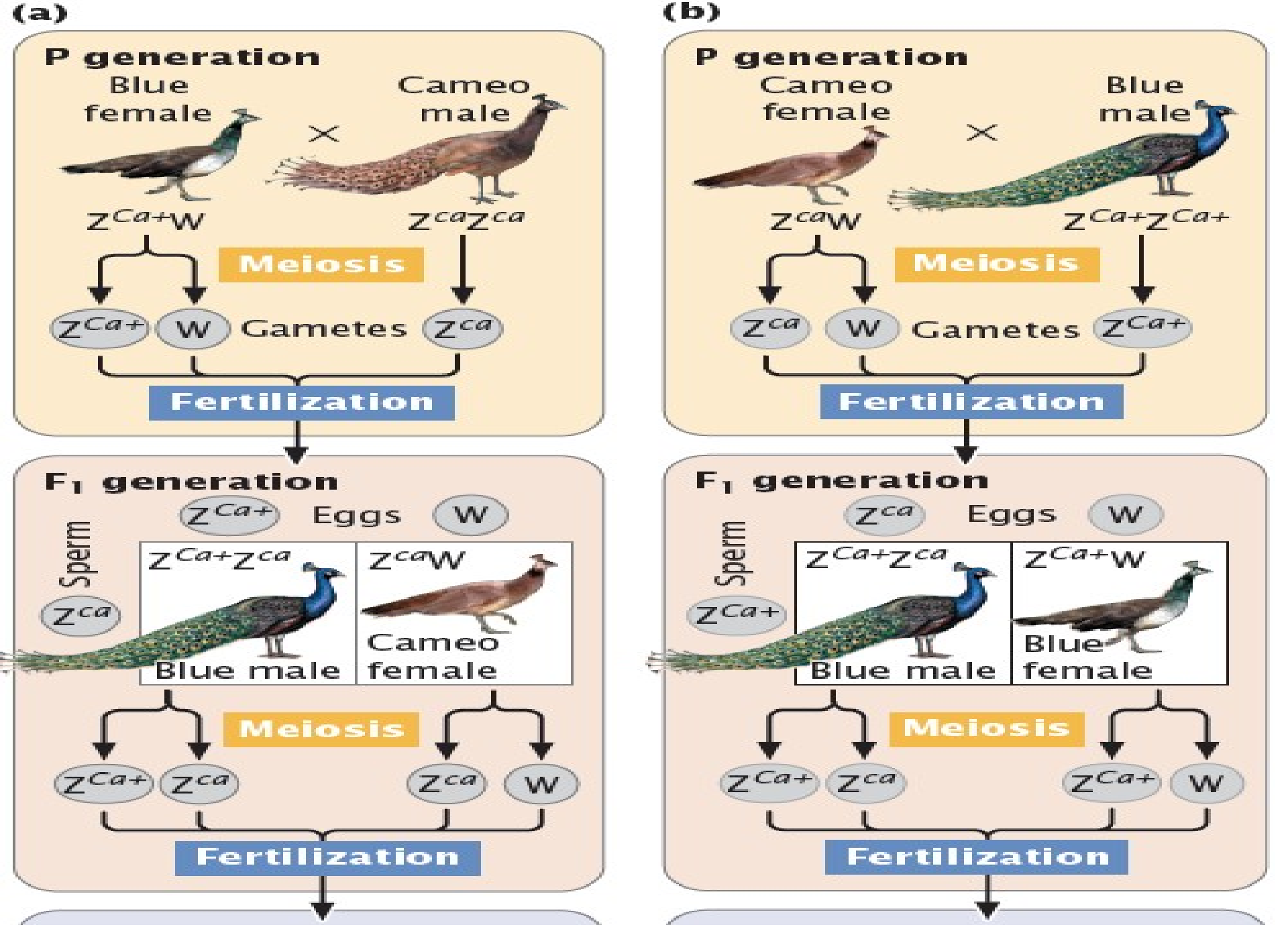
an individual that has two alleles, one damaged one and one regular

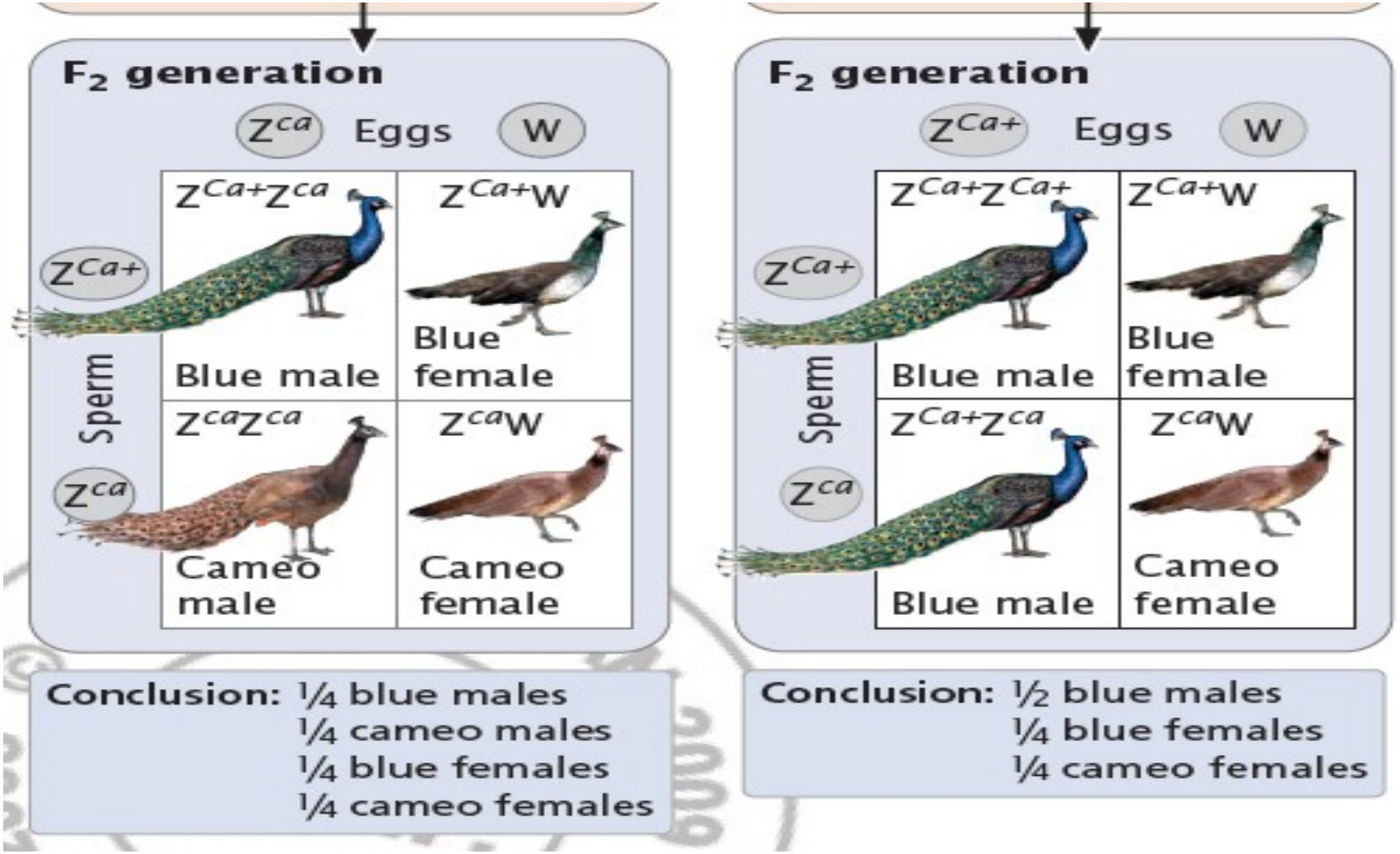



X-linked recessive, carrier mother
Unaffected father
Carrier mother
X Y
X X
Unaffected
Affected
Carrier
X Y
X X
X X
X Y
Unaffected son
Unaffected daughter
Carrier daughter
Affected son

Z-Linked Characteristics

- In organisms with ZZ-ZW sex determination
- males are the homogametic sex (ZZ)
- Females are the heterogametic sex (ZW)
- Same as that of X-linked characteristics, except that the pattern of inheritance in males and females is reversed
- Z-linked characteristic is the cameo phenotype in Indian blue peafowl


(a)
P generation
Blue female
Cameo male
$Z^{Ca+}W$
$Z^{ca}Z^{ca}$
Meiosis
Z^{Ca+}
W
Gametes
Z^{ca}
Fertilization
F_1 generation
Z^{Ca+}
Eggs
W
Sperm
Z^{ca}
$Z^{Ca+}Z^{ca}$
Blue male
$Z^{ca}W$
Cameo female
Meiosis
Z^{Ca+}
Z^{ca}
Z^{ca}
W
Fertilization
(b)
P generation
Cameo female
Blue male
$Z^{ca}W$
$Z^{Ca+}Z^{Ca+}$
Meiosis
Z^{ca}
W
Gametes
Z^{Ca+}
Fertilization
F_1 generation
Z^{ca}
Eggs
W
Sperm
Z^{Ca+}
$Z^{Ca+}Z^{ca}$
Blue male
$Z^{Ca+}W$
Blue female
Meiosis
Z^{Ca+}
Z^{ca}
Z^{Ca+}
W
Fertilization



Inheritance of the cameo phenotype in Indian blue peafowl is inherited as a Z-linked recessive trait

Y-Linked Characteristics

- Exhibit a distinct pattern of inheritance
- Present only in males
- All male offspring of a male with a Y-linked trait inherit the trait
- Relatively little genetic information on the Y chromosome

Recognizing Sex-linked Inheritance

- Alleles on sex chromosomes are inherited in predictable patterns
- Y-linked trait can be inherited only from the paternal grandfather (the father's father), never from the maternal grandfather
- X-linked characteristics also exhibit a distinctive pattern of inheritance

Sex-Linkage

When writing alleles that are sex-linked, we use a convention like that more complicated one from back at the beginning: we write the X or Y normally, and make the allele itself a superscript.

- If the A gene is on the X chromosome, then genotypes can have one of these alleles: X^A, X^a, and Y.

- If there's no allele, the Y becomes sort of like the "free square" in the middle of a bingo board. It doesn't affect the phenotype at all.

- So a man who is X^AY will have the dominant version of the trait, and a man who is X^aY will have the recessive version of the trait. He doesn't have two little-a's, true, but there's also no dominant allele to "drown out" the recessive allele.

Sex-Linkage

- if the gene is on the Y chromosome, we could have the alleles X, Y^A, or Y^a.
- if the gene is on the Y chromosome, we could have the alleles X, Y^A, or Y^a.
- *Phenotype:*
  - XX - Will not have the trait, whatever it is.
  - XY^A - Dominant phenotype
  - XY^a - Recessive phenotype

Sex-Linkage

- Phenotypes for people with a gene on the X-chromosome
  - X^BX^B- Dominant
  - X^BX^b- Dominant
  - X^bX^b - Recessive
  - X^BY - Dominant
  - X^bY - Recessive

Sex-Linkage

- Punnett Squares for sex-linked traits work like normal, except that you use the superscripts.
- A Punnett Square for a cross of X^BX^b with X^BY:

	X^B	X^b
X^B	$X^B X^B$	$X^B X^b$
Y	X^BY	X^bY

50% girl with dominant phenotype

25% boy with dominant phenotype

25% boy with recessive phenotype

Sex Determination

Some mechanisms of sex determination include:

a. Genotypic sex determination, in which sex is governed by genotype.
b. Genic sex determination, in which sex chromosomes are not involved.

Genotypic Sex Determination Systems

Genotypic sex determination may occur two different ways:

a. In the Y-chromosome mechanism of sex-determination (e.g., in mammals), the Y chromosome determines sex, conferring maleness.
b. In the X chromosome-autosome balance system (e.g., *Drosophila, Caenorhabditis elegans*) the ratio between number of X chromosomes and number of sets of autosomes determines sex. Y is required for male fertility, but does not determine sex.

Sex Determination in Mammals

1. Mammals use the Y-chromosome mechanism of sex-determination, in which the Y chromosome determines sex by conferring maleness.
2. Sex of mammals is determined by a gene on the Y chromosome, testis-determining factor. In the absence of this gene, gonads develop into ovaries.

Evidence for the Y Chromosome Mechanism of Sex Determination

1. **Understanding of the Y chromosome mechanism of sex determination came from the study of individuals with unusual chromosome complements**. In humans these aneuploidies include:
   a. **XO individuals**, who are sterile females exhibiting **Turner syndrome**. Most XO fetuses die before birth. Surviving Turner syndrome individuals become noticeable at puberty, when secondary sexual characteristics fail to develop. Other traits include:
      i. Below average height.
      ii. Weblike necks.
      iii. Poorly developed breasts.
      iv. Immature internal sexual organs.
      v. Reduced ability to interpret spatial relationships.

Evidence for the Y Chromosome Mechanism of Sex Determination

b. XXY individuals, who are male and have Klinefelter syndrome. Other traits include:

   i. Above average height.

   ii. Breast development in about 50% of XXY individuals.

   iii. Subnormal intelligence in some cases.

c. XYY individuals are male, and tend to be taller than average. Fertility is sometimes affected.

d. XXX individuals are usually normal women, although they may be slightly less fertile and a few have below average intelligence.

Evidence for the Y Chromosome Mechanism of Sex Determination

e. **Higher numbers of X and/or Y** chromosomes are sometimes found, including XXXY, XXXXY, and XXYY. The effects are similar to Klinefelter syndrome.

Table 12.2 Consequences of Various Numbers of X- and Y-Chromosome Abnormalities in Humans, Showing Role of the Y in Sex Determination

Chromosome Constitution[a]	Designation of Individual	Expected Number of Barr Bodies
46,XX	Normal ♀	1
46,XY	Normal ♂	0
45,X	Turner syndrome ♀	0
47,XXX	Triplo-X ♀	2
47,XXY	Klinefelter syndrome ♂	1
48,XXXY	Klinefelter syndrome ♂	2
48,XXYY	Klinefelter syndrome ♂	1
47,XYY	XYY syndrome ♂	0

[a] The first number indicates the total number of chromosomes in the nucleus, and the Xs and Ys indicate the sex chromosome complement.

Dosage Compensation Mechanism for X-Linked Genes in Mammals

1. Gene dosage varies between the sexes in mammals, because females have two copies of X while males have one. Early in development, gene expression from the X chromosome must be equalized to avoid death. Different dosage compensation systems have evolved in different organisms.
2. In mammals, female somatic cell nuclei contain a Barr body (highly condensed chromatin) while male nuclei not. The Lyon hypothesis explains the phenomenon:
   a. Barr body is a **condensed** and (mostly) **inactivated X chromosome**. Lyonization of one chromosome leaves one transcriptionally active X, equalizing gene dose **between the sexes**.
   b. **An X** is **randomly chosen** in each cell for inactivation early in development (in **humans**, day 16 postfertilization).

Dosage Compensation Mechanism for X-Linked Genes in Mammals

c. Descendants of that cell will have the same X inactivated, making female mammals genetic mosaics. Examples are:

    i. Calico cats, in which differing descendant cells produce patches of different color on the animal.

    ii. Women heterozygous for an X-linked allele responsible for sweat glands, who have a mosaic of normal skin and patches lacking sweat glands (anhidrotic ectodermal displasia).

d. Lyonization allows extra sex chromosomes to be tolerated well. No such mechanism exists for autosomes, and so an extra autosome is usually lethal.

e. The number of Barr bodies is the number of X chromosome minus one

Dosage Compensation Mechanism for X-Linked Genes in Mammals

h. Selection of an X for inactivation is made by the X-controlling element (*Xce*) in the *Xic* region. There are different alleles of *Xce*, and each allele has a different probability that the X chromosome carrying it will be inactivated.

i. The gene *Xist* is required for X inactivation. Uniquely, it is expressed from the inactive X.

   i. The *Xist* gene transcript is 17-kb. Although it has no ORFs, it receives splicing and a poly(A) tail.

   ii. During X inactivation, this RNA coats the chromosome to be inactivated and silences most of its genes.

   iii. Inactivation itself is not well understood, but it is known that it initiates at the *Xic* and moves in both directions, ultimately resulting in heterochrmatin.

Dosage Compensation Mechanism for X-Linked Genes in Mammals

f. X-inactivation involves three steps:

i. Chromosome counting (determining number of Xs in the cell).

ii. Selection of an X for inactivation.

iii. Inactivation itself.

g. Counting the chromosomes involves the X-inactivation center (*XIC* in humans, *Xic* in mice). Experiments in transgenic mice show that:

i. Inactivation requires the presence of at least two *Xic* sequences, one on each X chromosome.

ii. Autosomes with an *Xic* inserted are randomly inactivated, showing that *Xic* is sufficient for chromosome counting and initiation of lyonization..

Sex Determination in *Drosophila*

1. An X-chromosome-autosome balance system is used.
2. Drosophila has three pairs of autosomes, and one pair of sex chromosomes. Like humans, XX is female and XY is male. Unlike humans, Y does not determine sex.
3. An XXY fly is female, and an XO fly is male. The sex of the fly results from the ratio of the number of X chromosomes (X) to the number of sets of autosomes (A):
   a. In a normal (diploid) female Drosophila, A=2 and X=2. The X:A ratio is 1.0.
   b. In a normal (diploid) male Drosophila, A=2 and X=1. The X:A ratio is 0.5.
   c. In cases of aneuploidy (abnormal chromosome numbers):
      i. When the X:A ratio is $\geqq$1.0, the fly is female.
      ii. When the X:A ratio is$\leqq$0.5, the fly is male.
      iii. A ratio between 0.5 and 1.0 results in a sterile intersex fly with mixed male and female traits.
4. Dosage compensation in *Drosophila* results in more expression of X-linked genes in males, so the level of transcription equals that from a female's two X chromosomes.

Sex Determination in *Caenorhabditis*

1. *C. elegans*, the nematode, also uses the X-chromosome-autosome balance system to produce its two sexes, hermaphrodites and males.
   a. Self-fertilization in a hermaphrodite generally produces more hermaphrodites; only 0.2% of the offspring are male.
   b. Cross-fertilization between a hermaphrodite and a male produces approximately equal numbers of hermaphrodites and males.
2. Both hermaphrodites and males have five pairs of autosomes, so hermaphrodites (XX) have an X-chromosome-autosome ratio of 1.0, while males (XO) have a ratio of 0.5.
3. Dosage compensation limits transcription from each X chromosome of the hermaphrodite to 1⁄2 the level transcribed from the single X chromosome in the male.

Sex Chromosomes in Other Organisms

1. Sex chromosome composition in birds, butterflies, moths and some fish is opposite that of mammals, with the male the homogametic sex (ZZ) and the female heterogametic (ZW). Z-linked genes behave like X-linked genes in mammals, but the sexes are reversed.
2. . In plants, the arrangement of sex organs varies:
   a. Dioecious species (e.g., ginkgo) have plants of separate sexes, one with male parts, the other with female

   b. Monoecious species have male and female parts on the same plant.

      i. Perfect flowers (e.g., rose, buttercup) have both types of parts in the same flower..

Sex Chromosomes in Other Organisms

ii. Imperfect flowers (e.g., corn) have male and female parts in different flowers on the same plant.

3. Some dioecious plants have sex chromosomes and use an X-chromosome-autosome balance system, but many other sex determination systems also occur in dioecious plants.
4. Other eukaryotes use a genic system instead of entire sex chromosomes. A single allele determines the mating type (e.g., *MATa* and *MATα* in *Saccharomyces cerevisiae*).

Genic Sex Determination

1. Other eukaryotes use a genic system instead of entire sex chromosomes.
2. A single allele determines the mating type (e.g., *MAT*a and *MAT*a in *Saccharomyces cerevisiae*).
3. Yeast mating types have identical morphologies, but are able to fertilize gametes only from the opposite mating type.

Sex Determination Chart

Not every animal has the same sex chromosomes.

Type	Example	Male	Female	Homogametic	Heterogametic
XY	Humans & Fruit Flies	XY	XX	Female	Male
2N/ N	Bees	N	NN	Male and Female	--
XO	Grasshopper	XO	XX	Female	Male
ZW	Birds	ZZ	ZW	Male	Female
ZO	Chickens	ZZ	ZO	Male	Female

Environmental Sex Determination Systems

1. A few species use environmental sex determination systems, in which environmental factors affect the sex of progeny.
2. Some types of turtles are an example. Eggs incubated above 32° develop into females, while those below 28° become males.
3. Eggs between these temperatures produce a mix of the two sexes. Details will vary with each species using this system.
3. In this system, the environment triggers a developmental pathway which is under genetic control.

Analysis of Sex-Linked Traits in Humans

1. **X-linked traits**, like autosomal ones, can be analyzed **using pedigrees**.
2. **Human pedigree** analysis, however, is **complicated** by several factors:
   a. Data collection often relies on family recollections.
   b. If the trait is rare and the family small, there may not be enough affected individuals to establish a mechanism of inheritance.
   c. Expression of the trait may vary, resulting in affected individuals being classified as normal.
   d. More than one mutation may result in the same phenotype, and comparison of different pedigrees may show different inheritance for the "same" trait.

X-Linked Recessive Inheritance

1. Human traits involving recessive alleles on the X chromosome are X-linked recessive traits. A famous example is hemophilia A among Queen Victoria's descendants
2. **X-linked recessive** traits occur much more **frequently among males**, who are **hemizygous**. A f**emale** would express a **recessive X-linked trait** only if she were **homozygous recessive** at that locus.
3. Some characteristics of X-linked recessive inheritance:
   a. Affected **fathers transmit the recessive allele to all daughters** (who are therefore carriers), and to none of their sons.
   b. **Father-to-son transmission of X-linked alleles generally does not occur**.
   c. Many more males than females exhibit the trait.
   d. All sons of affected (homozygous recessive) mothers are expected to show the trait.
   e. With a carrier mother, about 1⁄2 of her sons will show the trait and 1⁄2 will be free of the allele.
   f. **A carrier female crossed with a normal male will have 1⁄2 carrier and 1⁄2 normal daughters**.
4. **Other X-linked recessive traits** are **Duchenne muscular dystrophy** and two forms of **color blindness**.

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Pedigree of Queen Victoria (III-2) and her descendants, showing the X-linked recessive inheritance of hemophilia

b)
Generation:

I George III Louis II Grand Duke of Hesse

II Duke of Saxe-Coburg-Gotha Edward Duke of Kent (1767–1820)

III Albert Victoria (1819–1901)

IV Victoria Empress Frederick Edward VII Alice of Hesse Helena Princess Christian Leopold Duke of Albany Beatrice

V Kaiser Wilhelm II George V Irene Princess Henry Frederick William Alix Tsarina Nikolas II 3 2 Alice of Athlone Victoria Eugenie, wife of Alfonso XIII Leopold Maurice

VI Duke of Windsor George VI Waldemar Earl Mountbatten of Burma Prince Sigismund of Prussia Henry 3 Anastasia Alexis Lady May Abel Smith ? Rupert Viscount Trematon Alfonso ? ? Gonzalo Sophie

VII Elizabeth II Prince Philip Margaret ? ? ? ? ? ? ? ? ? ? ? ? ? ? Juan Carlos

VIII Diana Charles Anne Andrew Edward ?

IX William Harry

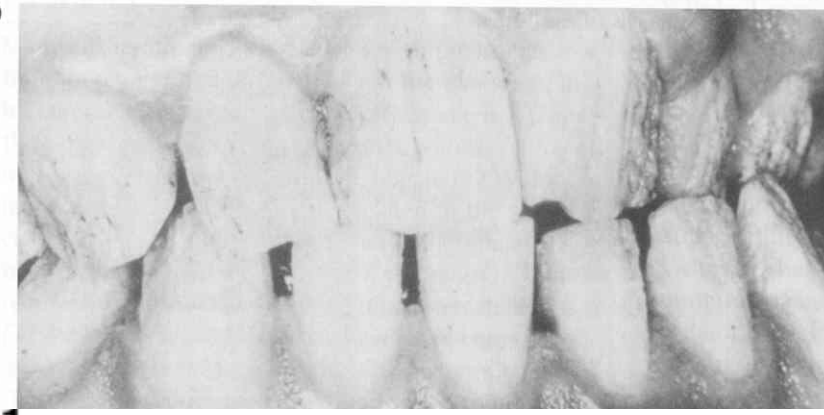
Carrier female
Hemophilic male
? Status uncertain
3 Three females, etc.

X-Linked Dominant Inheritance

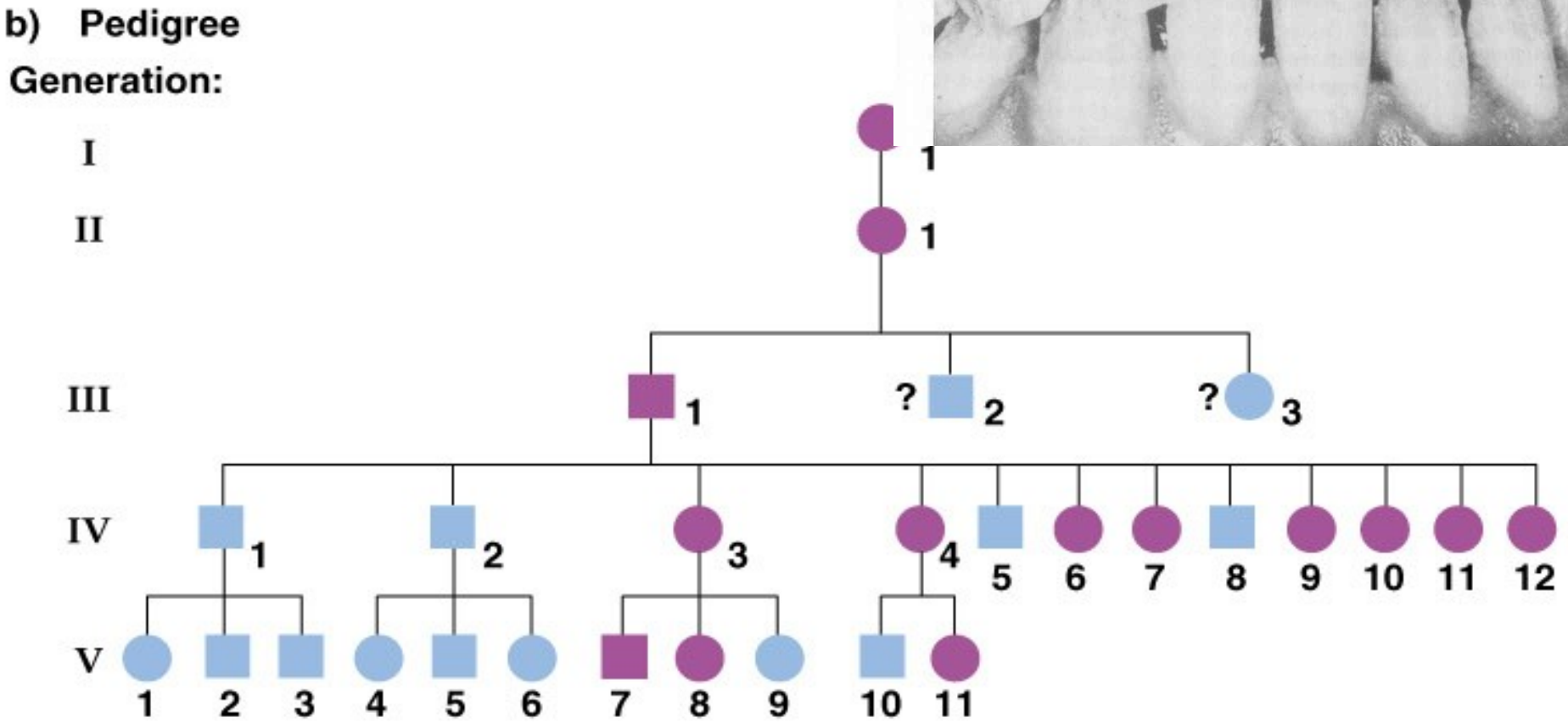
1. Only a few X-linked dominants are known.
2. Examples include:
   a. Hereditary enamel hypoplasia (faulty and discolored tooth enamel)
   b. Webbing to the tips of toes.
   c. Constitutional thrombopathy (severe bleeding due to lack of blood platelets).
3. Patterns of inheritance are the same as X-linked recessives, except that heterozygous females show the trait (although often in a milder form).

Pedigree showing the transmission of the X-linked dominant trait of faulty tooth enamel

a)

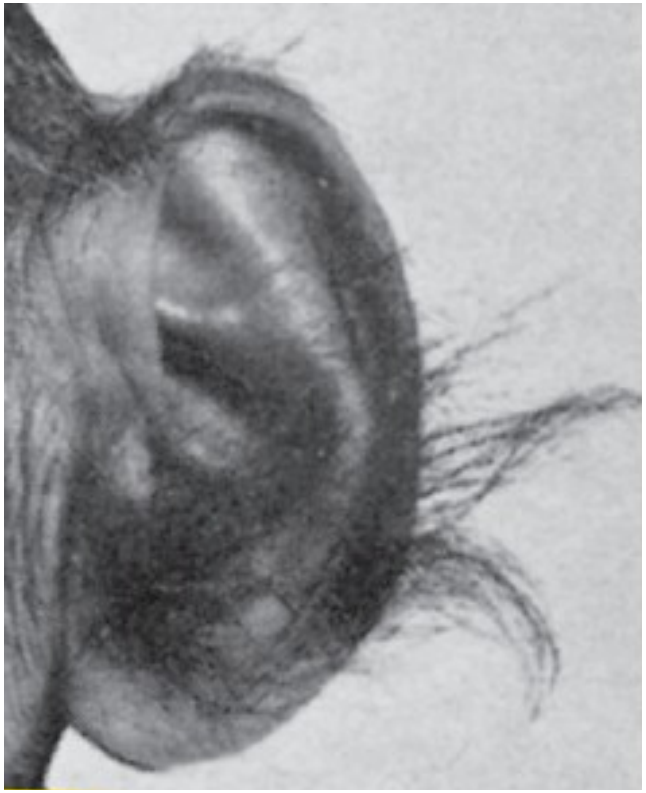


b) Pedigree



Y linked inheritance
(Holandric traits)

- There are far fewer Y-linked than X-linked genetic disorders
- This is not surprising given that the Y chromosome is smaller and has many less genes than the X chromosome.
- Y-linked inheritance shows a pattern of transmission of the mutant phenotype from father to son, and it is never observed in females.
- An example of a Y linked phenotypic trait is hairy ears.



Sex limited inheritance

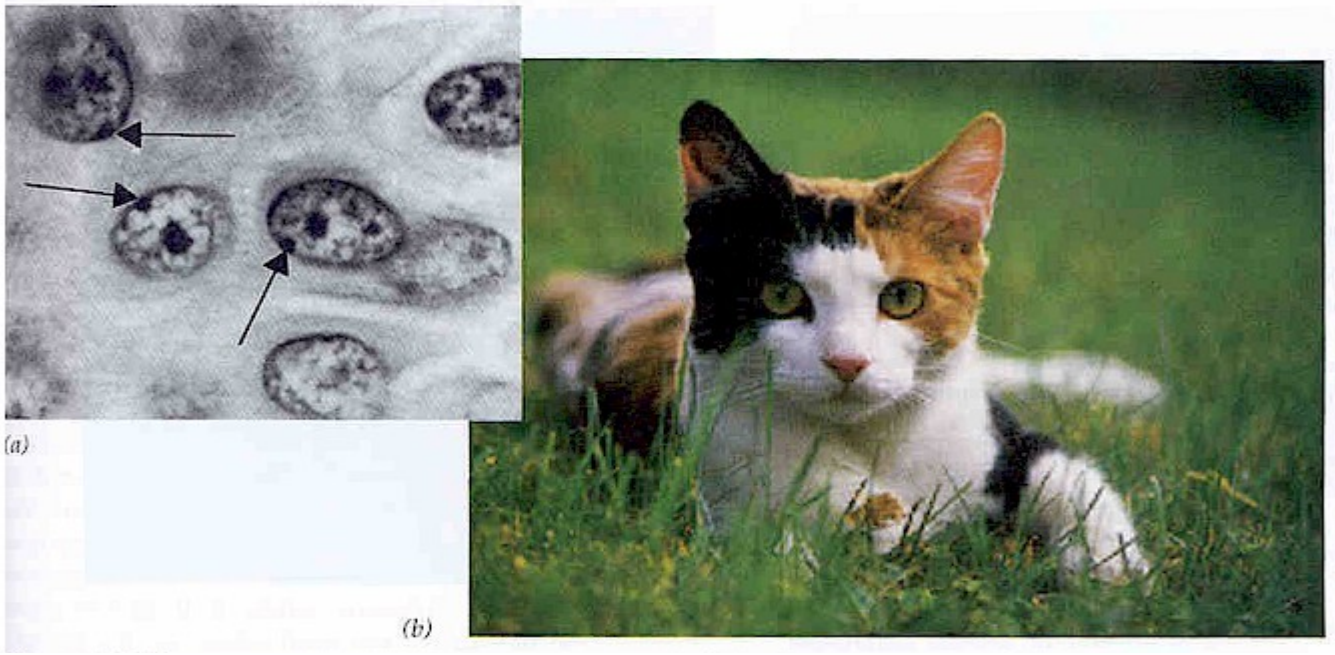
- Y-linked inheritance is often confused with **sex-limited inheritance**.
- Sex-limited traits can only occur in one sex because the feature affected is unique to that sex.
- For example, premature baldness is an autosomal dominant trait, but presumably as a result of female sex hormones, the condition is rarely expressed in the female, and then usually only after menopause.

X-inactivation

- During the growth and development of females' cells, one X chromosome is inactivated in each body cell.
- The inactivated X chromosome is visible in a female's cells as a Barr body.
- Which of the two X chromosomes becomes inactive in a cell is a matter of chance, therefore heterozygous females express different alleles in different cells.
- This is generally not noticeable in the phenotype – for example a woman heterozygous for the recessive condition haemophilia A will produce sufficient clotting factor VIII.
- Tortoise shell cats are an example where X inactivation is visible in the phenotype as one of the genes which controls coat colour is sex-linked.

X-inactivation

- One of the genes that controls coat colour in cats is sex-linked.
- It has alternative alleles X^{o} (orange) and X^{b} (black)
- If X^{o} are inactivated will produce dark fur.
- If X^{b} is inactivated will produce orange fur.

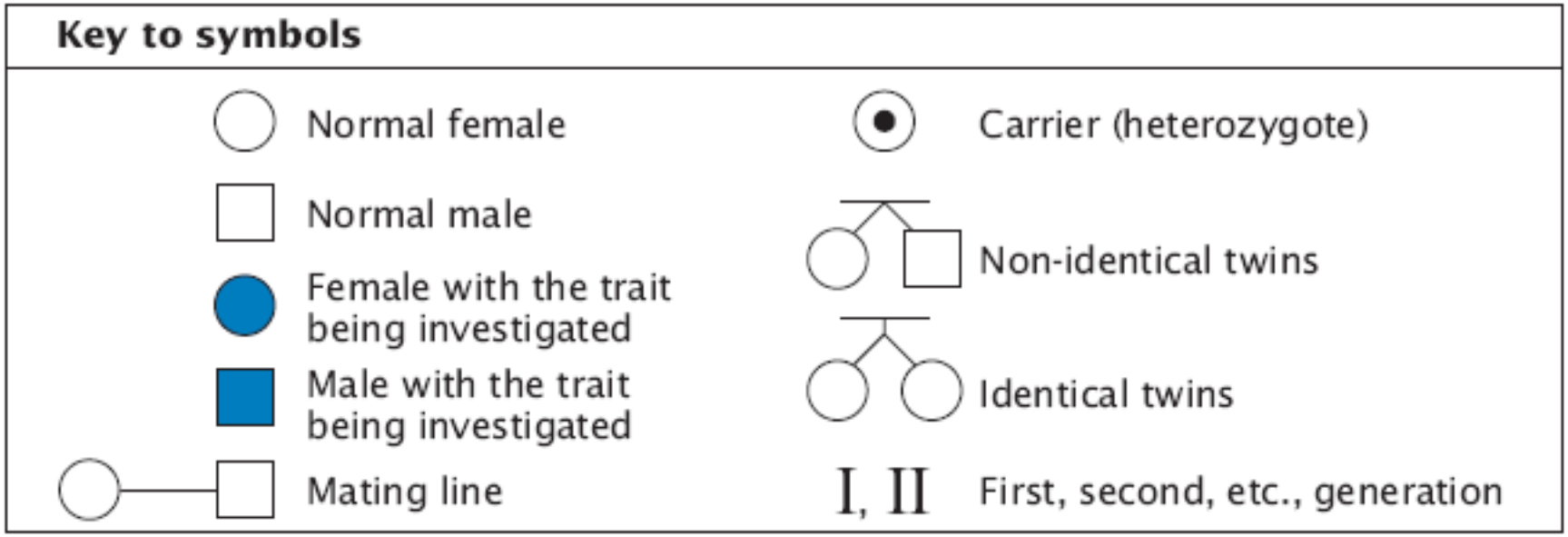


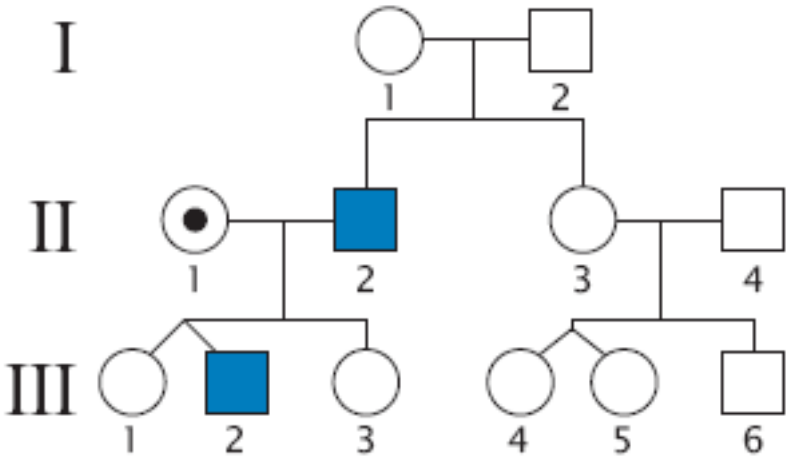
Pedigree Analysis

The technique of looking through a family tree (of humans or other organisms) for the occurrence of a particular characteristic in one family over a number of generations.

- Can be used to determine the likely mode of inheritance:
  - Autosomal dominant
  - Autosomal recessive
  - X-linked dominant
  - X-linked recessive
- When looking at pedigrees, incomplete penetrance is occasionally observed.
  - Incomplete penetrance describes the situation where a proportion of a population with a particular genotype does not show the expected phenotype.
  - Complete penetrance of a phenotype means that all individuals with a particular genotype will show the affected phenotype.

Symbols used in drawing pedigrees



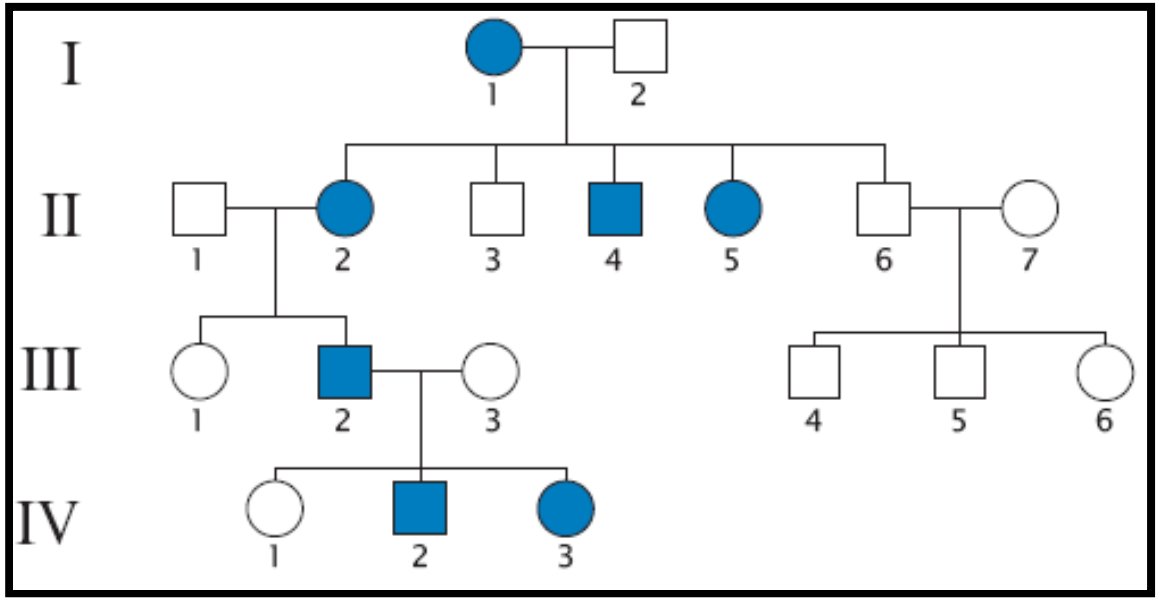


Autosomal Dominant Pattern

- An idealised pattern of inheritance of an autosomal dominant trait includes the following features:
  - both males and females can be affected
  - all affected individuals have at least one affected parent
  - transmission can be from fathers to daughters and sons, or from mothers to daughters and sons
  - once the trait disappears from a branch of the pedigree, it does not reappear
  - in a large sample, approximately equal numbers of each sex will be affected.

Examples include:

- Huntington disease
- Achondroplasia (a form of dwarfism)
- Familial form of Alzheimer disease
- Defective enamel of the teeth
- Neurofibromatosis (the 'Elephant man' disease)

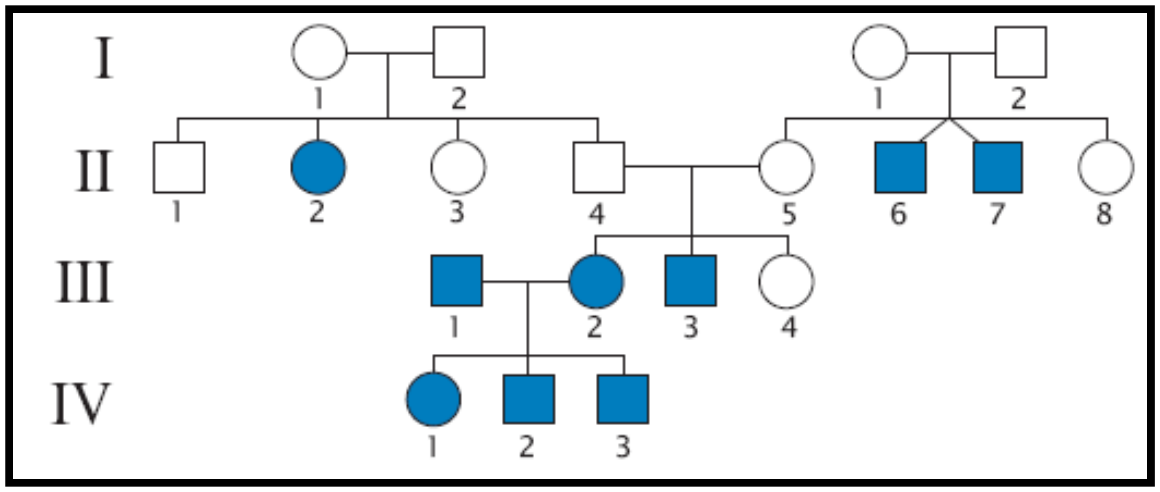


Autosomal Recessive Pattern

- An idealised pattern of inheritance of an autosomal recessive trait includes the following features:
  - both males and females can be affected
  - two unaffected parents can have an affected child
  - all the children of two persons with the condition must also show the condition
  - the trait may disappear from a branch of the pedigree, but reappear in later generations
  - over a large number of pedigrees, there are approximately equal numbers of affected females and males.

Examples include:

- Albinism
- Cystic fibrosis
- Thalassaemia
- Tay-Sachs disease
- Phenylketonuria
- Red hair colour

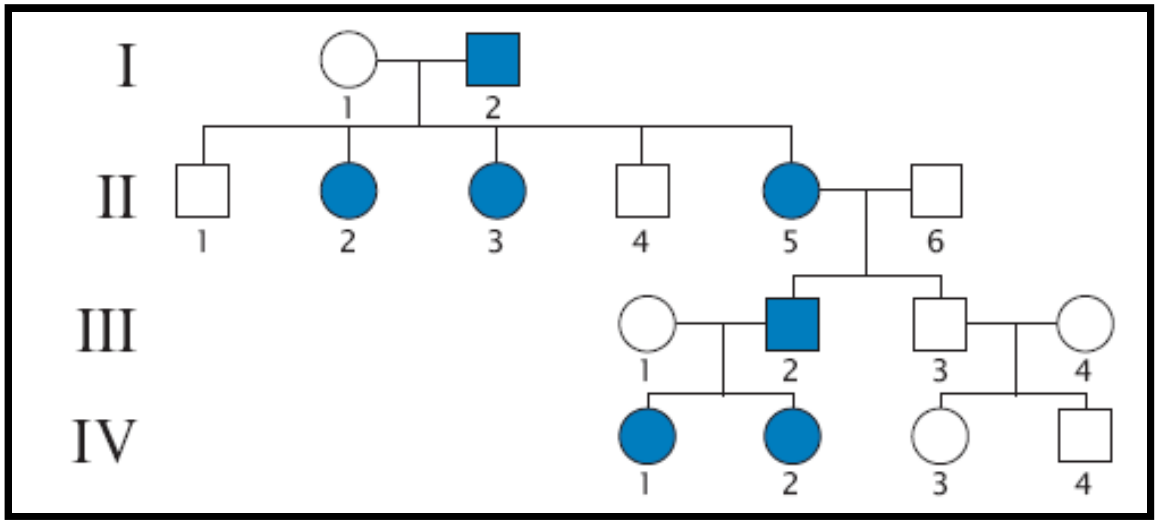


X linked Dominant Pattern

- An idealised pattern of inheritance of an X-linked dominant trait includes the following features:
  - a male with the trait passes it on to all his daughters and none of his sons
  - a female with the trait may pass it on to both her daughters and her sons
  - every affected person has at least one parent with the trait
  - if the trait disappears from a branch of the pedigree, it does not reappear
  - over a large number of pedigrees, there are more affected females than males

Examples include:

- Vitamin D resistant rickets
- Incontinentia pigmenti, a rare disorder that results in the death of affected males before birth



X linked Recessive Pattern

- An idealised pattern of inheritance of an X-linked recessive trait includes the following features:
  - all the sons of a female with the trait are affected
  - all the daughters of a male with the trait will be carriers of the trait and will not show the trait; the trait can appear in their sons
  - none of the sons of a male with the trait and an unaffected female will show the trait, unless the mother is a carrier
  - all children of two individuals with the trait will also show the trait
  - in a large sample, more males than females show the trait.

Examples include:

- Ichthyosis, an inherited skin disorder
- One form of red–green colour-blindness
- One form of severe combined immunodeficiency disease
- Haemophilia
- Fragile X syndrome
- Duchenne muscular dystrophy