

4

CHAPTER OUTLINE

- 4.1 Mechanisms of Sex Determination Among Various Species
- 4.2 Dosage Compensation and X Inactivation in Mammals
- 4.3 Properties of the X and Y Chromosome in Mammals
- 4.4 Transmission Patterns for X-linked Genes



Opposite sexes. Most species of animals, such as these male and female cardinals, are found in two sexes.

SEX DETERMINATION AND SEX CHROMOSOMES

In Chapter 2, we examined the process of sexual reproduction in which two gametes fuse with each other to begin the life of a new individual. Within a population, sexual reproduction enhances genetic diversity because the genetic material of offspring comes from two sources. For most species of animals and some species of plants, sexual reproduction is carried out by individuals of the opposite sex—females and males. The underlying mechanism by which an individual develops into a female or a male is called **sex determination**. As we will see, a variety of mechanisms promote this process.

For some species, females and males differ in their genomes. For example, you are probably already familiar with the idea that people differ with regard to X and Y chromosomes. Females are XX and males are XY, which means that females have two copies of the X chromosome, whereas males have one X and one Y chromosome. Because these chromosomes carry different genes, chromosomal differences between the sexes also result in unique phenotypes and inheritance patterns that differ from those we discussed in Chapter 3. In this chapter, we will explore

how genes located on the X chromosome exhibit a characteristic pattern of inheritance.

4.1 MECHANISMS OF SEX DETERMINATION AMONG VARIOUS SPECIES

After gametes fuse with each other during fertilization, what factor(s) determine whether the resulting zygote and embryo develop into a female or a male? Researchers have studied the process of sex determination in a wide range of species and discovered that several different mechanisms exist. In this section, we will explore some common mechanisms of sex determination in animals and plants.

Sex Differences May Depend on the Presence of Sex Chromosomes

According to the chromosome theory of inheritance, which we discussed in Chapter 3, chromosomes carry the genes that determine an organism's traits. Not surprisingly, sex determination in

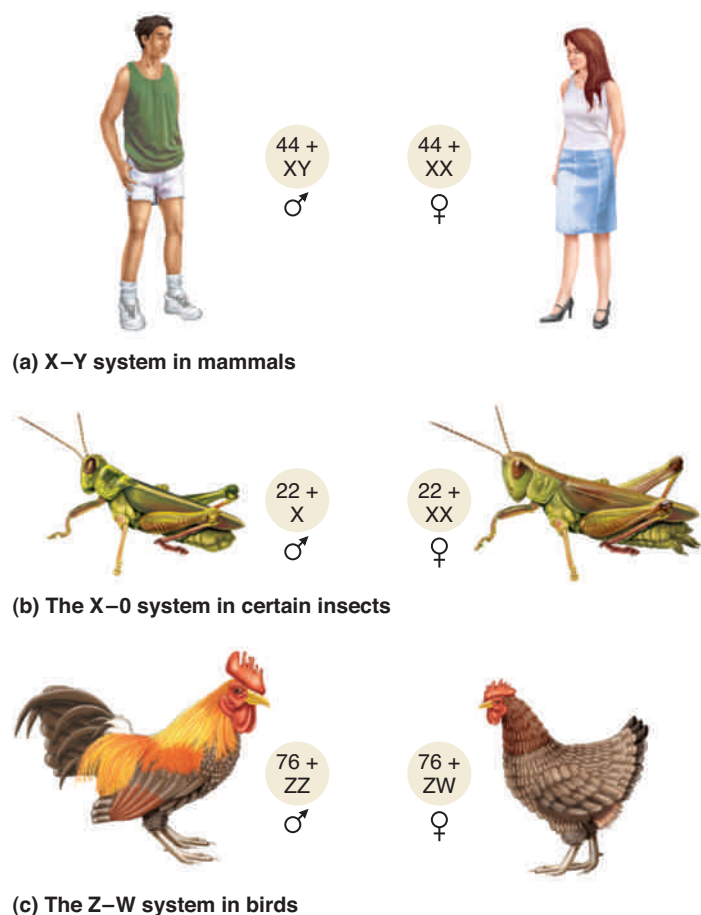


FIGURE 4.1 Sex determination via the presence of sex chromosomes. See text for a description.

Genes→Traits Certain genes that are found on the sex chromosomes play a key role in the development of sex (male vs. female). For example, in mammals, a gene on the Y chromosome initiates male development. In the X-0 system, the ratio of X chromosomes to the sets of autosomes plays a key role in governing the pathway of development toward male or female.

Concept check: What is the difference between the X-Y and X-0 systems of sex determination?

some species is due to the presence of particular chromosomes. In 1901, Clarence McClung, who studied grasshoppers, was the first to suggest that male and female sexes are due to the inheritance of particular chromosomes. Since McClung's initial observations, we now know that a pair of chromosomes, called the **sex chromosomes**, determines sex in many different species. Some examples are described in **Figure 4.1**.

In the X-Y system of sex determination, which operates in mammals, the male contains one X chromosome and one Y chromosome, whereas the female contains two X chromosomes (**Figure 4.1a**). In this case, the male is called the **heterogametic sex**. Two types of sperm are produced: one that carries only the X chromosome, and another that carries the Y. In contrast, the female is the **homogametic sex** because all eggs carry a single X chromosome. The 46 chromosomes carried by humans consist of

1 pair of sex chromosomes and 22 pairs of **autosomes**—chromosomes that are not sex chromosomes. In the human male, each of the four sperm produced during gametogenesis contains 23 chromosomes. Two sperm contain an X chromosome, and the other two have a Y chromosome. The sex of the offspring is determined by whether the sperm that fertilizes the egg carries an X or a Y chromosome.

What causes an offspring to develop into a male or female? One possibility is that two X chromosomes are required for female development. A second possibility is that the Y chromosome promotes male development. In the case of mammals, the second possibility is correct. This is known from the analysis of rare individuals who carry chromosomal abnormalities. For example, mistakes that occasionally occur during meiosis may produce an individual who carries two X chromosomes and one Y chromosome. Such an individual develops into a male. In addition, people are sometimes born with a single X chromosome and not another sex chromosome. Such individuals become females. The chromosomal basis for sex determination in mammals is rooted in the location of a particular gene on the Y chromosome. The presence of a gene on the Y chromosome called the *Sry* gene causes maleness.

Another mechanism of sex determination that involves sex chromosomes is the X-0 system that operates in many insects (**Figure 4.1b**). In some insect species, the male has only one sex chromosome (the X) and is designated X0, whereas the female has a pair (two X's). In other insect species, such as *Drosophila melanogaster*, the male is XY. For both types of insect species (i.e., X0 or XY males, and XX females), the ratio between X chromosomes and the number of autosomal sets determines sex. If a fly has one X chromosome and is diploid for the autosomes ($2n$), the ratio is $1/2$, or 0.5. This fly becomes a male even if it does not receive a Y chromosome. In contrast to mammals, the Y chromosome in the X-0 system does not determine maleness. If a fly receives two X chromosomes and is diploid, the ratio is $2/2$, or 1.0, and the fly becomes a female.

For the Z-W system, which determines sex in birds and some fish, the male is ZZ and the female is ZW (**Figure 4.1c**). The letters Z and W are used to distinguish these types of sex chromosomes from those found in the X-Y pattern of sex determination of other species. In the Z-W system, the male is the homogametic sex, and the female is heterogametic.

Sex Differences May Depend on the Number of Sets of Chromosomes

Another interesting mechanism of sex determination, known as the **haplodiploid system**, is found in bees, wasps, and ants (**Figure 4.2**). For example, in honey bees, the male, which is called a drone, is produced from unfertilized haploid eggs. Male honeybees contain a single set of 16 chromosomes. By comparison, female honeybees, both worker bees and queen bees, are produced from fertilized eggs and therefore are diploid. They contain two sets of chromosomes, for a total of 32. In this case, only females are produced by sexual reproduction.



Male honeybee (Drone)
Haploid – 16 chromosomes



Female honeybee
Diploid – 32 chromosomes

FIGURE 4.2 The haplodiploid mechanism of sex determination. In this system, males are haploid, whereas females are diploid.

Concept check: Is the male bee produced by sexual reproduction? Explain.

Sex Differences May Depend on the Environment

Although sex in many species of animals is determined by chromosomes, other mechanisms are also known. In certain reptiles and fish, sex is controlled by environmental factors such as temperature. For example, in the American alligator (*Alligator mississippiensis*), temperature controls sex development (**Figure 4.3a**). When fertilized eggs of this alligator species are incubated at 33°C, nearly 100% of them produce male individuals. In contrast, eggs incubated at a temperature a few degrees below 33°C produce nearly all females, whereas those incubated a few degrees above 33°C produce about 95% females.

Another way that sex can be environmentally determined is via behavior. Clownfish of the genus *Amphiprion* are coral reef fish that live among anemones on the ocean floor (**Figure 4.3b**). One anemone typically harbors a harem of clownfish consisting of a large female, a medium-sized reproductive male, and small nonreproductive juveniles. Clownfish are **protandrous**



(a) Sex determination via temperature.
American alligator (*A. mississippiensis*)



(b) Sex determination via behavior.
Clownfish (*Amphiprion ocellaris*)

FIGURE 4.3 Sex determination caused by environmental factors. (a) In the alligator, temperature determines whether an individual develops into a female or male. (b) In clownfish, males can change into females due to behavioral changes that occur when a dominant female dies.

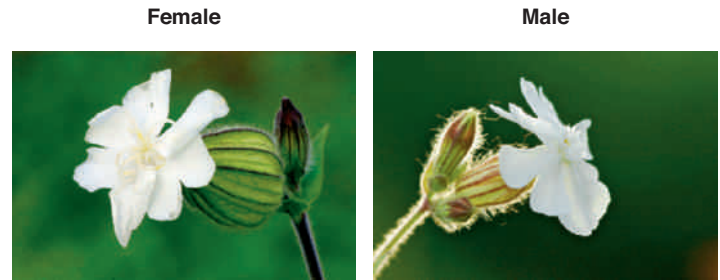
Concept check: How might global warming affect alligator populations?

hermaphrodites—they can switch from male to female! When the female of a harem dies, the reproductive male changes sex to become a female and the largest of the juveniles matures into a reproductive male. Unlike male and female humans, the opposite sexes of clownfish are not determined by chromosome differences. Male and female clownfish have the same chromosomal composition.

How can a clownfish switch from female to male? A juvenile clownfish has both male and female immature sexual organs. Hormone levels, particularly those of an androgen called



(a) American holly (*I. opaca*)



(b) Female and male flowers on separate individuals in white campion (*S. latifolia*)

FIGURE 4.4 Examples of dioecious plants in which individuals produce only male gametophytes or only female gametophytes.

(a) American holly (*Ilex opaca*). The female sporophyte, which produces red berries, is shown here. (b) White campion (*Silene latifolia*), which is often studied by researchers.

Concept check: Which are the opposite sexes in dioecious plants—the sporophytes or the gametophytes?

testosterone and an estrogen called estradiol, control the expression of particular genes. In nature, the first sexual change that usually happens is that a juvenile clownfish becomes a male. This occurs when the testosterone level becomes high, which promotes the expression of genes that encode proteins that cause the male organs to mature. Later, when the female of the harem dies, the estradiol level in the reproductive male becomes high and testosterone is decreased. This alters gene expression in a way that leads to the synthesis of some new types of proteins and prevents the synthesis of others. In other words, changes in hormones alter the composition of the proteome. When this occurs, the female organs grow and the male reproductive system degenerates. The male fish becomes female. These sex changes, which are irreversible, are due to sequential changes in the proteomes of clownfish.

What factor determines the hormone levels in clownfish? A female seems to control the other clownfish in the harem through aggressive dominance, thereby preventing the formation of other females. This aggressive behavior suppresses an area of the brain in the other clownfish that is responsible for the production of certain hormones that are needed to promote female development. If a clownfish is left by itself in an aquarium, it will automatically develop into a female because this suppression does not occur.

Dioecious Plant Species Have Opposite Sexes

In most plant species, a single diploid individual (a sporophyte) produces both female and male gametophytes, which are haploid and contain egg or sperm cells, respectively (see Chapter 2, Figure 2.15). However, some plant species are **dioecious**, which means that some individuals produce only male gametophytes, whereas others produce only female gametophytes. These include

hollies (Figure 4.4a), willows, and ginkgo trees. The genetics of sex determination in dioecious plant species is beginning to emerge. To study this process, many researchers have focused their attention on the white campion, *Silene latifolia*, which is a relatively small dioecious plant with a short generation time (Figure 4.4b). In this species, sex chromosomes, designated X and Y, are responsible for sex determination. The male plant has X and Y chromosomes, whereas the female plant is XX. Sex chromosomes are also found in other plant species such as papaya and spinach. However, in other dioecious species, cytological examination of the chromosomes does not always reveal distinct types of sex chromosomes. Even so, in these plant species, the male plants usually appear to be the heterogametic sex.

4.1 REVIEWING THE KEY CONCEPTS

- In the X-Y, X-0, and Z-W systems, sex is determined by the presence and number of particular sex chromosomes (see Figure 4.1).
- In the haplodiploid system, sex is determined by the number of sets of chromosomes (see Figure 4.2).
- In some species, such as alligators and clownfish, sex is determined by environmental factors (see Figure 4.3).
- Dioecious plants exist as individuals that produce only pollen and those that produce only eggs. Sex chromosomes sometimes determine sex in these species (see Figure 4.4).

4.1 COMPREHENSION QUESTIONS

1. Among different species, sex may be determined by
 - a. differences in sex chromosomes.
 - b. differences in the number of sets of chromosomes.
 - c. environmental factors.
 - d. all of the above.

2. In mammals, sex is determined by
 - a. the *Sry* gene on the Y chromosome.
 - b. having two copies of the X chromosome.
 - c. having one copy of the X chromosome.
 - d. both a and c.
3. An abnormal fruit fly has two sets of autosomes and is XXY. Such a fly would be
 - a. a male.
 - b. a female.
 - c. a hermaphrodite
 - d. none of the above.

4.2 DOSAGE COMPENSATION AND X INACTIVATION IN MAMMALS

Dosage compensation refers to the phenomenon in which the level of expression of many genes on the sex chromosomes (e.g., the X chromosome) is similar in both sexes, even though males and females have a different complement of sex chromosomes. This term was coined in 1932 by Hermann Muller to explain the effects of eye color mutations in *Drosophila*. Muller observed that female flies homozygous for certain alleles on the X chromosome had a similar phenotype to males, which have only one copy of the gene. He noted that an allele on the X chromosome conferring an apricot eye color produces a very similar phenotype in a female carrying two copies of the gene and in a male with just one. In contrast, a female that has one copy of the apricot allele and a deletion of the apricot allele on the other X chromosome has eyes of paler color. Therefore, one copy of the allele in the female is not equivalent to one copy of the allele in the male. Instead, two copies of the allele in the female produce a phenotype that is similar to that produced by one copy in the male. In other words, the difference in gene dosage—two copies in females versus one copy in males—is being compensated for at the level of gene expression. In this section, we will explore how this occurs in different species of animals.

Dosage Compensation Is Necessary in Some Species to Ensure Genetic Equality Between the Sexes

Dosage compensation has been studied extensively in mammals, *Drosophila*, and *Caenorhabditis elegans* (a nematode). Depending on the species, dosage compensation occurs via different mechanisms (Table 4.1). Female mammals equalize the expression of genes on the X chromosome by turning off one of their two X chromosomes. This process is known as **X inactivation**. In *Drosophila*, the male accomplishes dosage compensation by doubling the expression of most genes on the X chromosome. In *C. elegans*, the XX animal is a hermaphrodite that produces both sperm and egg cells, and an animal carrying a single X chromosome is a male that produces only sperm. The XX hermaphrodite diminishes the expression of genes on each X chromosome to approximately 50%.

In birds, the Z chromosome is a large chromosome, usually the fourth or fifth largest, and contains many genes. The W chromosome is generally a much smaller microchromosome containing a high proportion of repeat-sequence DNA that does not encode genes. Males are ZZ and females are ZW. Several years ago, researchers studied the level of expression of a Z-linked gene that encodes an enzyme called aconitase. They discovered that males express twice as much aconitase as females do. These results suggested that dosage compensation does not occur in birds. More recently, the expression of hundreds of Z-linked genes has been examined in chickens. These newer results also suggest that birds lack a general mechanism of dosage compensation that controls the expression of most Z-linked genes. Even so, the pattern of gene expression between males and females was found to vary a great deal for certain Z-linked genes. Overall, the results suggest that some Z-linked genes may be dosage-compensated, but many of them are not.

Dosage Compensation Occurs in Female Mammals by the Inactivation of One X Chromosome

In 1961, Mary Lyon proposed that dosage compensation in mammals occurs by the inactivation of a single X chromosome in

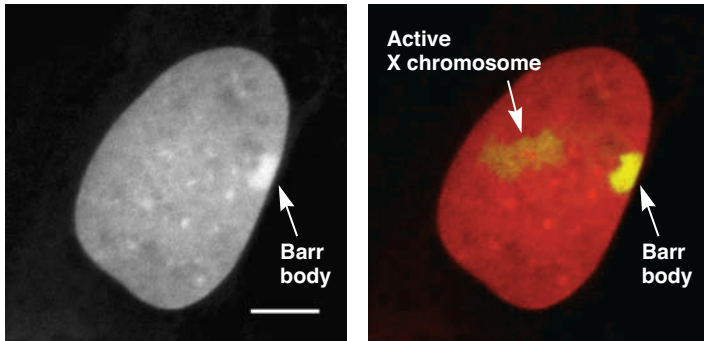
TABLE 4.1

Mechanisms of Dosage Compensation Among Different Species

Species	Sex Chromosomes in:		Mechanism of Compensation
	Females	Males	
Placental mammals	XX	XY	One of the X chromosomes in the somatic cells of females is inactivated. In certain species, the paternal X chromosome is inactivated, and in other species, such as humans, either the maternal or paternal X chromosome is randomly inactivated throughout the somatic cells of females.
Marsupial mammals	XX	XY	The paternally derived X chromosome is inactivated in the somatic cells of females.
<i>Drosophila melanogaster</i>	XX	XY	The level of expression of genes on the X chromosome in males is increased twofold.
<i>Caenorhabditis elegans</i>	XX*	XO	The XX hermaphrodite diminishes the expression of genes on each X chromosome to about 50%.

*In *C. elegans*, an XX individual is a hermaphrodite, not a female.

females. Liane Russell also proposed the same idea around the same time. This proposal brought together two lines of study. The first type of evidence came from cytological studies. In 1949, Murray Barr and Ewart Bertram identified a highly condensed structure in the interphase nuclei of somatic cells in female cats that was not found in male cats. This structure became known as the **Barr body** (Figure 4.5a). In 1960, Susumu Ohno correctly proposed that the Barr body is a highly condensed X chromosome.



(a) Nucleus with a Barr body



(b) A calico cat

FIGURE 4.5 X chromosome inactivation in female mammals.

(a) The left micrograph shows the Barr body on the periphery of a human nucleus after staining with a DNA-specific dye. Because it is compact, the Barr body is the most brightly staining. The white scale bar is 5 μm . The right micrograph shows the same nucleus using a yellow fluorescent probe that recognizes the X chromosome. The Barr body is more compact than the active X chromosome, which is to the left of the Barr body. (b) The fur pattern of a calico cat.

Genes→Traits The pattern of black and orange fur on this cat is due to random X inactivation during embryonic development. The orange patches of fur are due to the inactivation of the X chromosome that carries a black allele; the black patches are due to the inactivation of the X chromosome that carries the orange allele. In general, only heterozygous female cats can be calico. A rare exception is a male cat (XXY) that has an abnormal composition of sex chromosomes.

Concept check: Why is the Barr body more brightly staining in a cell nucleus?

In addition to this cytological evidence, Lyon was also familiar with examples in which the coat color of a mammal had a variegated pattern. Figure 4.5b is a photo of a calico cat, which is a female that is heterozygous for a gene on the X chromosome that can occur as an orange or a black allele. (The white underside is due to a dominant allele in a different gene.) The orange and black patches are randomly distributed in different female individuals. The calico pattern does not occur in male cats, but similar kinds of mosaic patterns have been identified in the female mouse. Lyon suggested that both the Barr body and the calico pattern are the result of X inactivation in the cells of female mammals.

The mechanism of X inactivation, also known as the **Lyon hypothesis**, is schematically illustrated in Figure 4.6. This

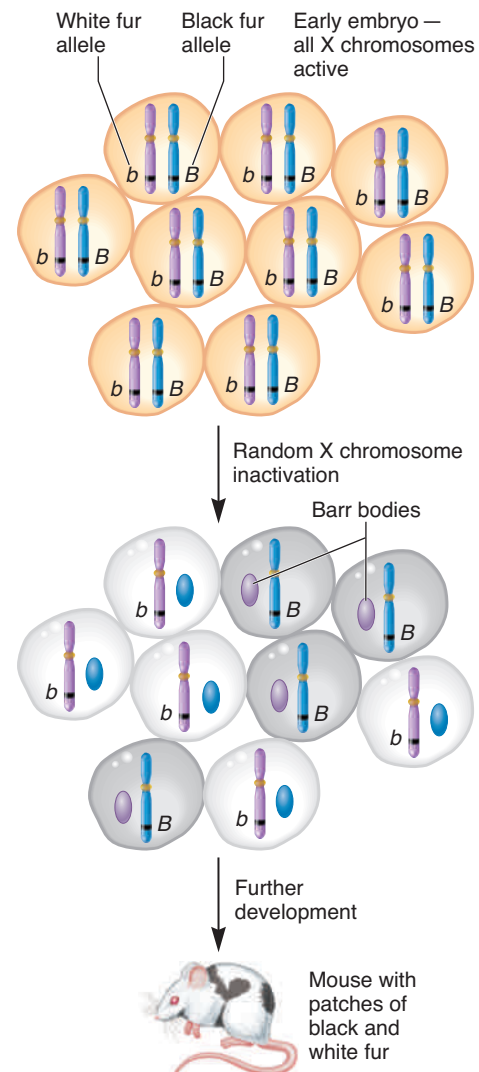


FIGURE 4.6 The mechanism of X chromosome inactivation.

Genes→Traits The top of this figure represents a mass of several cells that compose the early embryo. Initially, both X chromosomes are active. At an early stage of embryonic development, random inactivation of one X chromosome occurs in each cell. This inactivation pattern is maintained as the embryo matures into an adult.

Concept check: At which stage of development does X inactivation initially occur?

example involves a white and black variegated coat color found in certain strains of mice. As shown here, a female mouse has inherited an X chromosome from its mother that carries an allele conferring white coat color (X^b). The X chromosome from its father carries a black coat color allele (X^B). How can X inactivation explain a variegated coat pattern? Initially, both X chromosomes are active. However, at an early stage of embryonic development, one of the two X chromosomes is randomly inactivated in each somatic cell and becomes a Barr body. For example, one embryonic cell may have the X^B chromosome inactivated. As the embryo continues to grow and mature, this embryonic cell divides and may eventually give rise to billions of cells in the adult animal. The epithelial (skin) cells that are derived from this embryonic cell produce a patch of white fur because the X^B chromosome has been permanently inactivated. Alternatively, another embryonic cell may have the other X chromosome inactivated (i.e., X^b). The epithelial cells derived from this embryonic cell produce a patch of black fur. Because the primary event of X inactivation is a random process that occurs at an early stage of development, the result is an animal with some patches of white fur and other patches of black fur. This is the basis of the variegated phenotype.

During inactivation, the chromosomal DNA becomes highly compacted into a Barr body, so most of the genes on the inactivated X chromosome cannot be expressed. When cell division occurs and the inactivated X chromosome is replicated, both copies remain highly compacted and inactive. Likewise, during subsequent cell divisions, X inactivation is passed along to all future somatic cells.

Mammals Maintain One Active X Chromosome in their Somatic Cells

Since the Lyon hypothesis was confirmed, the genetic control of X inactivation has been investigated further by several laboratories. Research has shown that mammalian cells possess the ability to count their X chromosomes in their somatic cells and allow only one of them to remain active. How was this determined? A key observation came from comparisons of the chromosome composition of people who were born with normal or abnormal numbers of sex chromosomes.

Phenotype	Chromosome Composition	Number of X Chromosomes	Number of Barr Bodies
Normal female	XX	2	1
Normal male	XY	1	0
Turner syndrome (female)	X0	1	0
Triple X syndrome (female)	XXX	3	2
Klinefelter syndrome (male)	XXY	2	1

In normal females, two X chromosomes are counted and one is inactivated, whereas in males, one X chromosome is counted and none inactivated. If the number of X chromosomes exceeds two, as in triple X syndrome, additional X chromosomes are converted to Barr bodies.

X Inactivation in Mammals Depends on the X-Inactivation Center and the *Xist* Gene

Although the genetic control of inactivation is not entirely understood at the molecular level, a short region on the X chromosome called the **X-inactivation center (Xic)** is known to play a critical role. Eeva Therman and Klaus Patau identified the Xic from its key role in X inactivation. The counting of human X chromosomes is accomplished by counting the number of Xics. A Xic must be found on an X chromosome for inactivation to occur. Therman and Patau discovered that if one of the two X chromosomes in a female is missing its Xic due to a chromosome mutation, a cell counts only one Xic and X inactivation does not occur. Having two active X chromosomes is a lethal condition for a human female embryo.

Let's consider how the molecular expression of certain genes controls X inactivation. The expression of a specific gene within the Xic is required for the compaction of the X chromosome into a Barr body. This gene, discovered in 1991, is named *Xist* (for X-inactive specific transcript). The *Xist* gene on the inactivated X chromosome is active, which is unusual because most other genes on the inactivated X chromosome are silenced. The *Xist* gene product is an RNA molecule that does not encode a protein. Instead, the role of the *Xist* RNA is to coat the X chromosome and inactivate it. After coating, other proteins associate with the *Xist* RNA and promote chromosomal compaction into a Barr body.

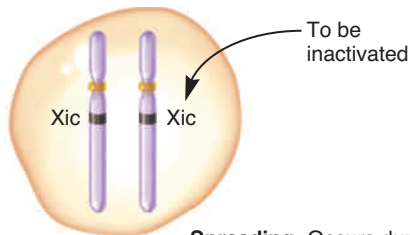
X Inactivation Occurs in Three Phases: Initiation, Spreading, and Maintenance

The process of X inactivation can be divided into three phases: initiation, spreading, and maintenance (**Figure 4.7**). During initiation, which occurs during embryonic development, one of the X chromosomes remains active, and the other is chosen to be inactivated. During the spreading phase, the chosen X chromosome is inactivated. This spreading requires the expression of the *Xist* gene. The *Xist* RNA coats the inactivated X chromosome and recruits proteins that promote compaction. The spreading phase is so named because inactivation begins near the Xic and spreads in both directions along the X chromosome.

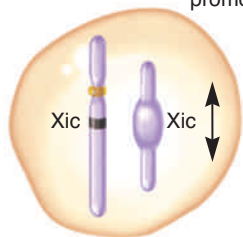
Once the initiation and spreading phases occur for a given X chromosome, the inactivated X chromosome is maintained as a Barr body during future cell divisions. When a cell divides, the Barr body is replicated, and both copies remain compacted. This maintenance phase continues from the embryonic stage through adulthood.

Some genes on the inactivated X chromosome are expressed in the somatic cells of adult female mammals. These genes are said to escape the effects of X inactivation. As mentioned, *Xist* is an example of a gene that is expressed from the highly condensed Barr body. In humans, up to a quarter of the genes on the X chromosome may escape inactivation to some degree. Many of these genes occur in clusters. Among these are the pseudoautosomal genes found on both the X and Y chromosomes in the regions of homology, which are described next. Dosage compensation is not necessary for pseudoautosomal genes because they are located on both the X and Y chromosomes.

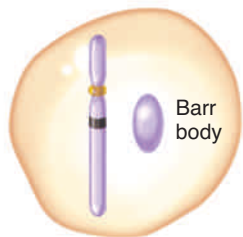
Initiation: Occurs during embryonic development. The number of X-inactivation centers (Xics) is counted and one of the X chromosomes remains active and the other is targeted for inactivation.



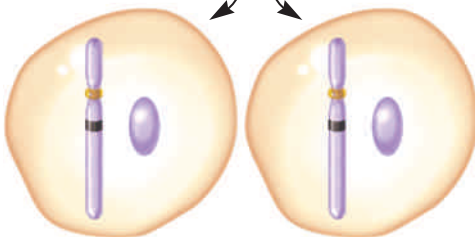
Spreading: Occurs during embryonic development. It begins at the Xic and progresses toward both ends until the entire chromosome is inactivated. The *Xist* gene encodes an RNA that coats the X chromosome and recruits proteins that promote its compaction into a Barr body.



Further spreading



Maintenance: Occurs from embryonic development through adult life. The inactivated X chromosome is maintained as such during subsequent cell divisions.



4.2 REVIEWING THE KEY CONCEPTS

- Dosage compensation often occurs in species that differ in their sex chromosomes (see Table 4.1).
- In mammals, the process of X inactivation in females compensates for the single X chromosome found in males. The inactivated X chromosome is called a Barr body. The process can lead to a variegated phenotype, such as a calico cat (see Figure 4.5).
- After it occurs during embryonic development, the pattern of X inactivation is maintained when cells divide (see Figure 4.6).
- X inactivation is controlled by the X-inactivation center (Xic) that contains the *Xist* gene. X inactivation occurs as initiation, spreading, and maintenance phases (see Figure 4.7).

4.2 COMPREHENSION QUESTIONS

1. In fruit flies, dosage compensation is achieved by
 - a. X inactivation.
 - b. turning up the expression of genes on the single X chromosome in the male twofold.
 - c. turning down the expression of genes on the two X chromosomes in the female to one half.
 - d. all of the above.
2. According to the Lyon hypothesis,
 - a. one of the X chromosomes is converted to a Barr body in somatic cells of female mammals.
 - b. one of the X chromosomes is converted to a Barr body in all cells of female mammals.
 - c. both of the X chromosomes are converted to a Barr body in somatic cells of female mammals.
 - d. both of the X chromosomes are converted to a Barr body in all cells of female mammals.
3. Which of the following is *not* a phase of X inactivation?
 - a. Initiation
 - b. Spreading
 - c. Maintenance
 - d. Erasure

4.3 PROPERTIES OF THE X AND Y CHROMOSOME IN MAMMALS

As we discussed at the beginning of this chapter, sex determination in mammals is determined by the presence of the Y chromosome, which carries the *Sry* gene. The X and Y chromosomes also differ in other ways. The X chromosome is typically much larger than the Y and carries more genes. For example, in humans, researchers estimate that the X chromosome carries about 1200 to 1500 genes, whereas the Y chromosome has 80 to 200 genes. Genes that are found on only one sex chromosome but not both are called **sex-linked genes**. Those on the X chromosome are termed **X-linked genes** and those on the Y chromosome are termed **Y-linked genes**, or **holandric genes**.

Besides sex-linked genes, the X and Y chromosomes also contain short regions of homology where the X and Y chromosomes carry the same genes, which are called **pseudoautosomal genes**. In addition to several smaller regions, the human

FIGURE 4.7 The phases of X inactivation.

Concept check: Which of these phases occurs in an adult female?

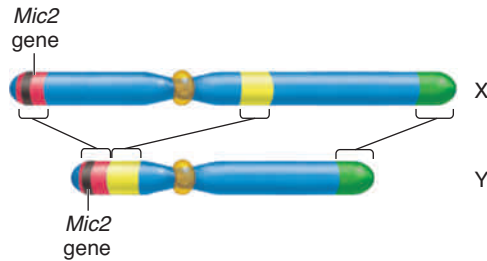


FIGURE 4.8 A comparison of the homologous and nonhomologous regions of the X and Y chromosome in humans.

The brackets show three regions of homology between the X and Y chromosome. A few pseudoautosomal genes, such as *Mic2*, are found on both the X and Y chromosomes in these small regions of homology.

Concept check: Why are the homologous regions of the X and Y chromosome important during meiosis?

sex chromosomes have three homologous regions (Figure 4.8). These regions, which are evolutionarily related, promote the necessary pairing of the X and Y chromosomes that occurs during meiosis I of spermatogenesis. Relatively few genes are located in these homologous regions. One example is a human gene called *Mic2*, which encodes a cell surface antigen. The *Mic2* gene is found on both the X and Y chromosomes. It follows a pattern of inheritance called **pseudoautosomal inheritance**. The term *pseudoautosomal* refers to the idea that the inheritance pattern of the *Mic2* gene is the same as the inheritance pattern of a gene located on an autosome even though the *Mic2* gene is actually located on the sex chromosomes. As in autosomal inheritance, males have two copies of pseudoautosomally inherited genes, and they can transmit the genes to both daughters and sons.

By comparison, genes that are found only on the X or Y chromosome exhibit transmission patterns that are quite different from genes located on an autosome. A Y-linked inheritance pattern is very distinctive—the gene is transmitted only from fathers to sons. By comparison, transmission patterns involving X-linked genes are more complex because females inherit two X chromosomes whereas males receive only one X chromosome from their mother. We will consider the complexities of X-linked inheritance patterns next.

4.3 REVIEWING THE KEY CONCEPTS

- Chromosomes that differ between males and females are termed sex chromosomes and carry sex-linked genes.
- X-linked genes are found only on the X chromosome, whereas Y-linked genes are found only on the Y chromosome. Pseudoautosomal genes are found on both the X and Y chromosomes in regions of homology (see Figure 4.8).

4.3 COMPREHENSION QUESTIONS

- 1 A Y-linked gene is passed from
 - a. father to son.
 - b. father to daughter.
 - c. father to daughter or son.
 - d. mother to son.

4.4 TRANSMISSION PATTERNS FOR X-LINKED GENES

At the beginning of this chapter, we discussed how sex determination in certain species is controlled by sex chromosomes. In fruit flies and mammals, a female is XX, whereas a male is XY. The inheritance pattern of X-linked genes, known as **X-linked inheritance**, shows certain distinctive features. For example, males transmit X-linked genes only to their daughters, and sons receive their X-linked genes from their mothers. The term **hemizygous** is used to describe the single copy of an X-linked gene in the male. A male mammal or fruit fly is said to be hemizygous for X-linked genes. Because males of certain species, such as humans, have a single copy of the X chromosome, another distinctive feature of X-linked inheritance is that males are more likely to be affected by rare, recessive X-linked disorders. We will consider the medical implications of X-linked inheritance in Chapter 23. In this section, we will examine X-linked inheritance in fruit flies and mammals.

Morgan's Experiments Showed a Connection Between a Genetic Trait and the Inheritance of a Sex Chromosome in *Drosophila*

In the early 1900s, Thomas Hunt Morgan carried out the first study that confirmed the location of a gene on a particular chromosome. In this experiment, he showed that a gene affecting eye color in fruit flies is located on the X chromosome. Morgan was trained as an embryologist, and much of his early research involved descriptive and experimental work in that field. He was particularly interested in ways that organisms change. He wrote, “The most distinctive problem of zoological work is the change in form that animals undergo, both in the course of their development from the egg (embryology) and in their development in time (evolution).” Throughout his life, he usually had dozens of different experiments going on simultaneously, many of them unrelated to each other. He jokingly said there are three kinds of experiments—those that are foolish, those that are damn foolish, and those that are worse than that!

In one of his most famous studies, Morgan engaged one of his graduate students to rear the fruit fly *Drosophila melanogaster* in the dark, hoping to produce flies whose eyes would atrophy from disuse and disappear in future generations. Even after many consecutive generations, however, the flies appeared to have no noticeable changes despite repeated attempts at inducing mutations by treatments with agents such as X-rays and radium. After 2 years, Morgan finally obtained an interesting result when a true-breeding line of *Drosophila* produced a male fruit fly with white eyes rather than the normal red eyes. Because this had been a true-breeding line of flies, this white-eyed male must have arisen from a new mutation that converted a red-eye allele (denoted w^+) into a white-eye allele (denoted w). Morgan is said to have carried this fly home with him in a jar, put it by his bedside at night while he slept, and then taken it back to the laboratory during the day.

Much like Mendel, Morgan studied the inheritance of this white-eye trait by making crosses and quantitatively analyzing their outcome. In the experiment described in **Figure 4.9**, he began with his white-eyed male and crossed it to a true-breeding red-eyed female. All of the F_1 offspring had red eyes, indicating that red is dominant to white. The F_1 offspring were then mated to each other to obtain an F_2 generation.

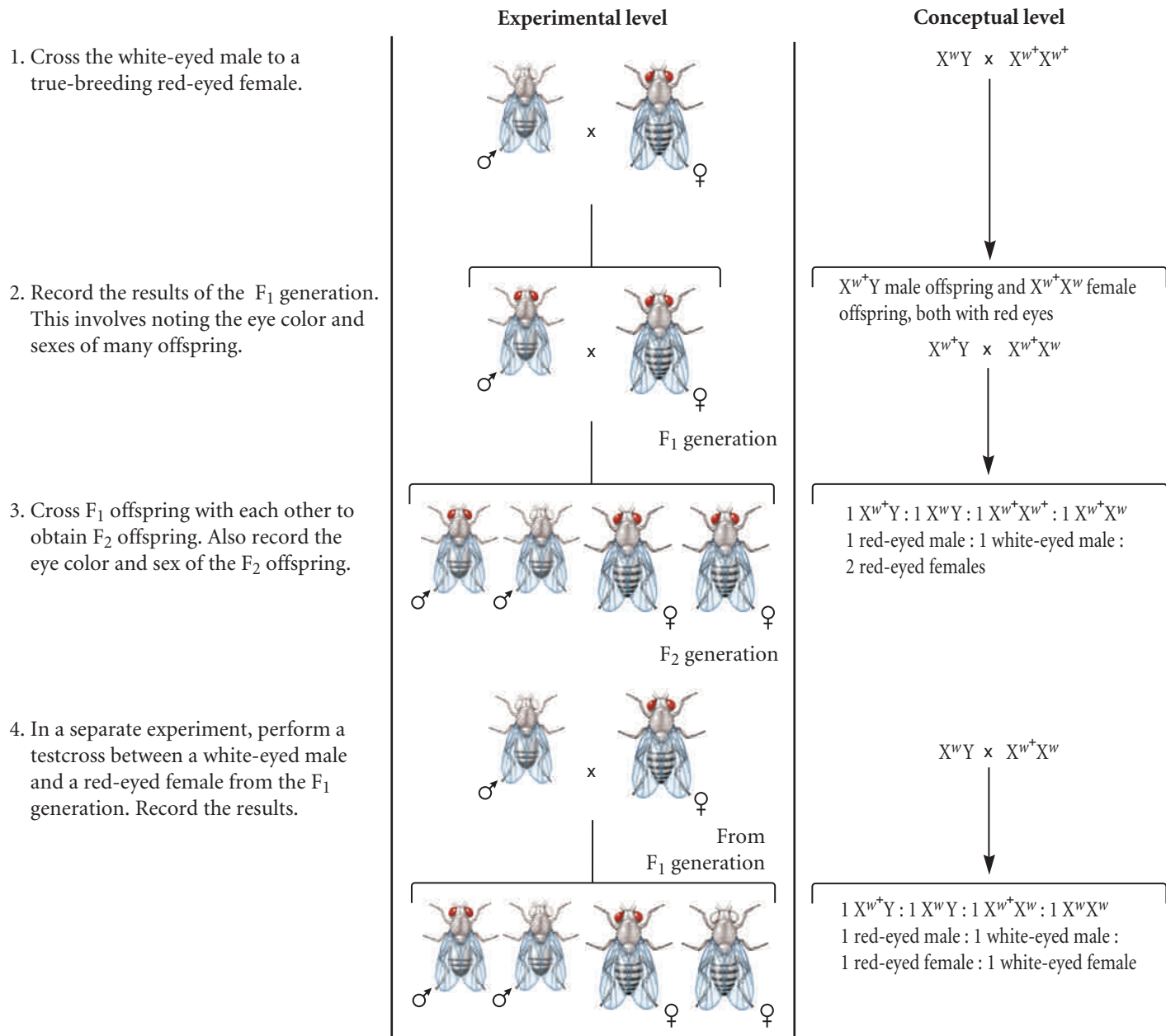
► THE GOAL

This is an example of discovery-based science rather than hypothesis testing. In this case, a quantitative analysis of genetic crosses may reveal the inheritance pattern for the white-eye allele.

► ACHIEVING THE GOAL — FIGURE 4.9 Inheritance pattern of an X-linked trait in fruit flies.

Concept check: What is the key result that suggests an X-linked inheritance pattern?

Starting material: A true-breeding line of red-eyed fruit flies plus one white-eyed male fly that was discovered in Morgan's collection of flies.



► THE DATA

Cross	Results
Original white-eyed male to red-eyed females	F ₁ generation: All red-eyed flies
F ₁ males to F ₁ females	F ₂ generation: 2459 red-eyed females 1011 red-eyed males 0 white-eyed females 782 white-eyed males
White-eyed males to F ₁ females	Testcross: 129 red-eyed females 132 red-eyed males 88 white-eyed females 86 white-eyed males

Data from T. H. Morgan (1910) Sex limited inheritance in *Drosophila*. *Science* 32, 120–122.

► INTERPRETING THE DATA

As seen in the data table, the F₂ generation consisted of 2459 red-eyed females, 1011 red-eyed males, and 782 white-eyed males. Most notably, no white-eyed female offspring were observed in the F₂ generation. These results suggested that the pattern of transmission from parent to offspring depends on the sex of the offspring and on the alleles that they carry. As shown in the Punnett square here, the data are consistent with the idea that the eye color alleles are located on the X chromosome:

F₁ male is X^{w+}Y
F₁ female is X^{w+}X^w

		Male gametes	
		♂ X ^{w+}	Y
♀	X ^{w+}	X ^{w+} X ^{w+} Red, female	X ^{w+} Y Red, male
	X ^w	X ^{w+} X ^w Red, female	X ^w Y White, male

The Punnett square predicts that the F₂ generation will not have any white-eyed females. This prediction was confirmed experimentally. These results indicated that the eye color alleles are located on the X chromosome. As mentioned earlier, genes that are physically located within the X chromosome are called **X-linked genes**, or **X-linked alleles**. However, it should also be pointed out that the experimental ratio in the F₂ generation of red eyes to white eyes is (2459 + 1011):782, which equals 4.4:1. This ratio deviates significantly from the predicted ratio of 3:1. How can this discrepancy be explained? Later work revealed that the lower-than-expected number of white-eyed flies is due to their decreased survival rate.

Morgan also conducted a **testcross** (see step 4, Figure 4.9) in which an individual with a dominant phenotype and unknown

genotype is crossed to an individual with a recessive phenotype. In this case, he mated an F₁ red-eyed female to a white-eyed male. This cross produced red-eyed males and females, and white-eyed males and females, in approximately equal numbers. The testcross data are also consistent with an X-linked pattern of inheritance. As shown in the following Punnett square, the testcross predicts a 1:1:1:1 ratio:

Testcross:
Male is X^wY
F₁ female is X^{w+}X^w

		Male gametes	
		♂ X ^w	Y
♀	X ^{w+}	X ^{w+} X ^w Red, female	X ^{w+} Y Red, male
	X ^w	X ^w X ^w White, female	X ^w Y White, male

The observed data were 129:132:88:86, which is a ratio of 1.5:1.5:1:1. Again, the lower-than-expected numbers of white-eyed males and females can be explained by a lower survival rate for white-eyed flies. In his own interpretation, Morgan concluded that red eye color and X (a sex factor that is present in two copies in the female) are combined and have never existed apart. In other words, this gene for eye color is on the X chromosome. In 1933, Morgan received the Nobel Prize in physiology or medicine.

Calvin Bridges, a graduate student in the laboratory of Morgan, also examined the transmission of X-linked traits. In his crosses, he occasionally obtained offspring that had unexpected phenotypes and abnormalities in sex chromosome composition. For example, in a cross between a white-eyed female and a red-eyed male, he occasionally observed a male offspring with red eyes. This event can be explained by nondisjunction, which is described in Chapter 8 (see Figure 8.21). In this example, the rare male offspring with red eyes was produced by a sperm carrying the X-linked red allele and by an egg that underwent nondisjunction and did not receive an X chromosome. The resulting offspring would be a male without a Y chromosome. (As shown earlier in Figure 4.1, the number of X chromosomes determines sex in fruit flies.) Together, the work of Morgan and Bridges provided an impressive body of evidence confirming the idea that traits following an X-linked pattern of inheritance are governed by genes that are physically located on the X chromosome. Bridges wrote, “There can be no doubt that the complete parallelism between the unique behavior of chromosomes and the behavior of sex-linked genes and sex in this case means that the sex-linked genes are located in and borne by the X chromosomes.” An example of Bridges’ work is described in solved problem S5 at the end of this chapter.

A self-help quiz involving this experiment can be found at www.mhhe.com/brookerconcepts.

The Inheritance Pattern of X-Linked Genes Can Be Revealed by Reciprocal Crosses

X-linked patterns are also observed in mammalian species. As an example, let's consider a human disease known as Duchenne muscular dystrophy (DMD), which was first described by the French neurologist Guillaume Duchenne in the 1860s. Affected individuals show signs of muscle weakness as early as age 3. The disease gradually weakens the skeletal muscles and eventually affects the heart and breathing muscles. Survival is rare beyond the early 30s. The gene for DMD, found on the X chromosome, encodes a protein called dystrophin that is required inside muscle cells for structural support. Dystrophin is thought to strengthen muscle cells by anchoring elements of the internal cytoskeleton to the plasma membrane. Without it, the plasma membrane becomes permeable and may rupture.

DMD is inherited in an **X-linked recessive pattern**—the allele causing the disease is recessive and located on the X chromosome. In the pedigree shown in **Figure 4.10**, several males are affected by this disorder, as indicated by filled squares. The mothers of these males are presumed heterozygotes for this X-linked recessive allele. This recessive disorder is very rare among females because daughters would have to inherit a copy of the mutant allele from their mother and a copy from an affected father.

X-linked muscular dystrophy has also been found in certain breeds of dogs such as golden retrievers (**Figure 4.11a**). Like humans, the mutation occurs in the dystrophin gene, and the symptoms include severe weakness and muscle atrophy that begin at about 6 to 8 weeks of age. Many dogs that inherit this disorder die within the first year of life, though some can live 3 to 5 years and reproduce.

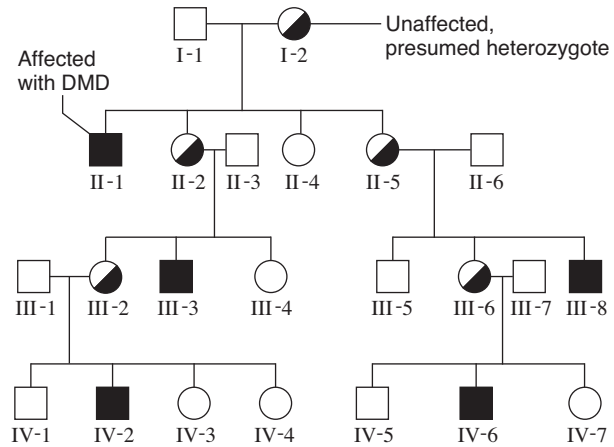


FIGURE 4.10 A human pedigree for Duchenne muscular dystrophy, an X-linked recessive trait. Affected individuals are shown with filled symbols. Females who are unaffected with the disease but have affected sons are presumed to be heterozygous carriers, as shown with half-filled symbols.

Concept check: What features of this pedigree indicate that the allele for Duchenne muscular dystrophy is X-linked?

Figure 4.11b (left side) considers a cross between an unaffected female dog with two copies of the wild-type gene and a male dog with muscular dystrophy that carries the mutant allele and has survived to reproductive age. When setting up a Punnett square involving X-linked traits, we must consider the alleles on the X chromosome as well as the observation that males may transmit a Y chromosome instead of the X chromosome. The male



(a) Male golden retriever with X-linked muscular dystrophy

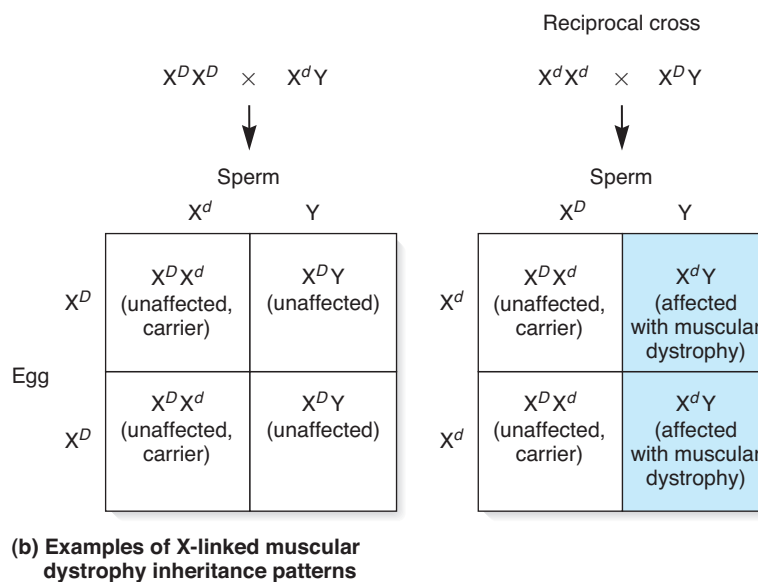


FIGURE 4.11 X-linked muscular dystrophy in dogs. (a) The male golden retriever shown here has the disease. (b) The left side shows a cross between an unaffected female and an affected male. The right shows a reciprocal cross between an affected female and an unaffected male. D represents the normal allele for the dystrophin gene, and d is the mutant allele that causes a defect in dystrophin function.

Concept check: Explain why the reciprocal cross yields a different result compared to the first cross.

makes two types of gametes: one that carries the X chromosome and one that carries the Y. The Punnett square must also include the Y chromosome even though this chromosome does not carry any X-linked genes. The X chromosomes from the female and male are designated with their corresponding alleles. When the Punnett square is filled in, it predicts the X-linked genotypes and sexes of the offspring. As seen on the left side of Figure 4.11b, none of the offspring from this cross are affected with the disorder, although all female offspring are carriers.

The right side of Figure 4.11b shows a **reciprocal cross**—a second cross in which the sexes and phenotypes are reversed. In this case, an affected female animal is crossed to an unaffected male. This cross produces female offspring that are carriers and all male offspring will be affected with muscular dystrophy.

When comparing the two Punnett squares, the outcome of the reciprocal cross yielded different results. This is expected of X-linked genes, because the male transmits the gene only to female offspring, whereas the female transmits an X chromosome to both male and female offspring. Because the male parent does not transmit the X chromosome to his sons, he does not contribute to their X-linked phenotypes. This explains why X-linked traits do not behave equally in reciprocal crosses. Experimentally, the observation that reciprocal crosses do not yield the same results is an important clue that a trait may be X-linked.

4.4 REVIEWING THE KEY CONCEPTS

- Morgan's work showed that a gene affecting eye color in fruit flies is inherited on the X chromosome (see Figure 4.9).

- X-linked inheritance is also observed in mammals. An example is Duchenne muscular dystrophy, which is an X-linked recessive disorder. For X-linked alleles, reciprocal crosses yield different results (see Figures 4.10, 4.11).

4.4 COMPREHENSION QUESTIONS

1. In Morgan's experiments, a key observation of the F_2 generation that suggested an X-linked pattern of inheritance was
 - a. a 3:1 ratio of red-eyed to white-eyed flies.
 - b. the only white-eyed flies were males.
 - c. the only white-eyed flies were females.
 - d. the only red-eyed flies were males.
2. Hemophilia is a blood clotting disorder in humans that follows an X-linked recessive pattern of inheritance. A man with hemophilia and woman without hemophilia have a daughter with hemophilia. If you let H represent the normal allele and h the hemophilia allele, what are the genotypes of the parents?
 - a. Mother is $X^H X^h$ and father is $X^h Y$.
 - b. Mother is $X^h X^h$ and father is $X^h Y$.
 - c. Mother is $X^h X^h$ and father is $X^H Y$.
 - d. Mother is $X^H X^h$ and father is $X^H Y$.
3. A cross is made between a white-eyed female fruit fly and a red-eyed male. What would be the reciprocal cross?
 - a. Female is $X^w X^w$ and male is $X^w Y$.
 - b. Female is $X^{w+} X^{w+}$ and father is $X^{w+} Y$.
 - c. Mother is $X^{w+} X^{w+}$ and father is $X^w Y$.
 - d. Mother is $X^w X^w$ and father is $X^{w+} Y$.

KEY TERMS

Page 71. sex determination

Page 72. sex chromosomes, heterogametic sex, homogametic sex, autosomes, haplodiploid system

Page 73. protandrous hermaphrodites

Page 74. dioecious

Page 75. dosage compensation, X inactivation

Page 76. Barr body, Lyon hypothesis

Page 77. X-inactivation center (X_{ic})

Page 78. sex-linked genes, X-linked genes, Y-linked genes, holandric genes, pseudoautosomal genes

Page 79. pseudoautosomal inheritance, X-linked inheritance, hemizygous

Page 81. X-linked genes, X-linked alleles, testcross

Page 82. X-linked recessive pattern

Page 83. reciprocal cross

CHAPTER SUMMARY

4.1 Mechanisms of Sex Determination Among Various Species

- In the X-Y, X-0, and Z-W systems, sex is determined by the presence and number of particular sex chromosomes (see Figure 4.1).
- In the haplodiploid system, sex is determined by the number of sets of chromosomes (see Figure 4.2).
- In some species, such as alligators and clownfish, sex is determined by environmental factors (see Figure 4.3).

- Dioecious plants exist as individuals that produce only pollen and those that produce only eggs. Sex chromosomes sometimes determine sex in these species (see Figure 4.4).

4.2 Dosage Compensation and X Inactivation in Mammals

- Dosage compensation often occurs in species that differ in their sex chromosomes (see Table 4.1).
- In mammals, the process of X inactivation in females compensates for the single X chromosome found in males. The

inactivated X chromosome is called a Barr body. The process can lead to a variegated phenotype, such as a calico cat (see Figure 4.5).

- After it occurs during embryonic development, the pattern of X inactivation is maintained when cells divide (see Figures 4.6).
- X inactivation is controlled by the X-inactivation center (Xic) that contains the *Xist* gene. X inactivation occurs as initiation, spreading, and maintenance phases (see Figure 4.7).

4.3 Properties of the X and Y Chromosome in Mammals

- Chromosomes that differ between males and females are termed sex chromosomes and carry sex-linked genes.

PROBLEM SETS & INSIGHTS

Solved Problems

- S1. A human male has an X chromosome that is missing its Xic. Is this caused by a new mutation (one that occurred during gametogenesis), or could this mutation have occurred in an earlier generation and be found in the somatic cells of one of his parents? Explain your answer. How would this mutation affect his ability to produce viable offspring?

Answer: The missing Xic must be due to a new mutation that occurred during oogenesis. A male inherits his X chromosome from his mother. If his mother had inherited an X chromosome with a missing Xic, both of her X chromosomes would remain active, and this is a lethal condition in humans. For this same reason, the male with the missing Xic could not produce living daughters, but he could produce normal sons.

- S2. In humans, why are X-linked recessive traits more likely to occur in males than females?

Answer: Because a male is hemizygous for X-linked traits, the phenotypic expression of X-linked traits depends on only a single copy of the gene. When a male inherits a recessive X-linked allele, he automatically exhibits the trait because he does not have another copy of the gene on the corresponding Y chromosome. This phenomenon is particularly relevant to the inheritance of recessive X-linked alleles that cause human disease. (Some examples will be described in Chapter 23.)

- S3. An unaffected woman (i.e., without disease symptoms) who is heterozygous for the X-linked allele causing Duchenne muscular dystrophy has children with a man with a normal allele. What are the probabilities of the following combinations of offspring?

- An unaffected son
- An unaffected son or daughter
- A family of three children, all of whom are affected

Answer: The first thing we must do is construct a Punnett square to determine the outcome of the cross. *D* represents the normal allele, and *d* is the recessive allele causing Duchenne muscular dystrophy. The mother is heterozygous, and the father has the normal allele.

- X-linked genes are found only on the X chromosome, whereas Y-linked genes are found only on the Y chromosome. Pseudoautosomal genes are found on both the X and Y chromosomes in regions of homology (see Figure 4.8).

4.4 Transmission Patterns for X-Linked Genes

- Morgan's work showed that a gene affecting eye color in fruit flies is inherited on the X chromosome (see Figure 4.9).
- X-linked inheritance is also observed in mammals. An example is Duchenne muscular dystrophy, which is an X-linked recessive disorder. For X-linked alleles, reciprocal crosses yield different results (see Figures 4.10, 4.11).

		Male gametes		
		♂ X^D	Y	
♀ Female gametes	X^D	$X^D X^D$	$X^D Y$	Phenotype ratio is 2 normal daughters : 1 normal son : 1 affected son
	X^d	$X^D X^d$	$X^d Y$	

- There are four possible children, one of whom is an unaffected son. Therefore, the probability of an unaffected son is 1/4.
 - Use the sum rule: $1/4 + 1/2 = 3/4$.
 - You could use the product rule because there would be three offspring in a row with the disorder: $(1/4)(1/4)(1/4) = 1/64 = 0.016 = 1.6\%$.
- S4. Red-green color blindness is inherited as a recessive X-linked trait. What are the following probabilities?
- A woman with phenotypically normal parents and a color-blind brother will have a color-blind son. Assume that she has no previous children.
 - The next child of a phenotypically normal woman, who has already had one color-blind son, will be a color-blind son.
 - The next child of a phenotypically normal woman, who has already had one color-blind son, and who is married to a color-blind man, will have a color-blind daughter.

Answer:

- The woman's mother must have been a heterozygote. So there is a 50% chance that the woman is a carrier. If she has children, 1/4 (i.e., 25%) will be affected sons if she is a carrier. However, there is only a 50% chance that she is a carrier. We multiply 50% times 25%, which equals $0.5 \times 0.25 = 0.125$, or a 12.5% chance.
- If she already had a color-blind son, then we know she must be a carrier, so the chance is 25%.

C. The woman is heterozygous and her husband is hemizygous for the color-blind allele. This couple will produce 1/4 offspring that are color-blind daughters. The rest are 1/4 carrier daughters, 1/4 normal sons, and 1/4 color-blind sons. Answer is 25%.

- S5. To test the chromosome theory of inheritance, which is described in Chapter 3, Calvin Bridges made crosses involving the inheritance of X-linked traits. One of his experiments concerned two different X-linked genes affecting eye color and wing size. For the eye color gene, the red-eye allele (w^+) is dominant to the white-eye allele (w). A second X-linked trait is wing size; the allele called miniature is recessive to the normal allele. In this case, m represents the miniature allele and m^+ the normal allele. A male fly carrying a miniature allele on its single X chromosome has small (miniature) wings. A female must be homozygous, mm , in order to have miniature wings.

Bridges made a cross between $X^{w,m^+} X^{w,m^+}$ female flies (white eyes and normal wings) to $X^{w^+,m} Y$ male flies (red eyes and miniature wings). He then examined the eyes, wings, and sexes of thousands of offspring. Most of the offspring were females with red eyes and normal wings, and males with white eyes and normal wings. On rare occasions (approximately 1 out of 1700 flies), however, he also obtained female offspring with white eyes or males with red eyes. He also noted the wing shape in these flies and then cytologically examined their chromosome composition using a microscope. The following results were obtained:

Offspring	Eye Color	Wing Size	Sex Chromosomes
Expected females	Red	Normal	XX
Expected males	White	Normal	XY
Unexpected females (rare)	White	Normal	XXY
Unexpected males (rare)	Red	Miniature	X0

Data from: Bridges, C. B. (1916) "Non-disjunction as proof of the chromosome theory of heredity," *Genetics* 1, 1–52, 107–163.

Explain these data.

Answer: Remember that in fruit flies, the number of X chromosomes (not the presence of the Y chromosome) determines sex. As seen in the data, the flies with unexpected phenotypes were abnormal in their sex chromosome composition. The white-eyed female flies were due to the union between an abnormal XX female gamete and a normal Y male gamete. Likewise, the unexpected male offspring contained only one X chromosome and no Y. These male offspring were due to the union between an abnormal egg without any X chromosome and a normal sperm containing one X chromosome. The wing size of the unexpected males was a particularly significant result. The red-eyed males showed a miniature wing size. As noted by Bridges, this means they inherited their X chromosome from their father rather than their mother. This observation provided compelling evidence that the inheritance of the X chromosome correlates with the inheritance of particular traits.

Conceptual Questions

- C1. In the X-Y and Z-W systems of sex determination, which sex is the heterogametic sex, the male or female?
- C2. Let's suppose that a gene affecting pigmentation is found on the X chromosome (in mammals or insects) or the Z chromosome (in birds) but not on the Y or W chromosome. It is found on an autosome in bees. This gene exists in two alleles, D (dark), which is dominant to d (light). What would be the phenotypic results of crosses between a true-breeding dark female and true-breeding light male, and the reciprocal crosses involving a true-breeding light female and true-breeding dark male, in the following species? Refer back to Figures 4.1 and 4.2 for the mechanism of sex determination in these species.
- Birds
 - Drosophila*
 - Bees
 - Humans
- C3. Assuming that such a fly would be viable, what would be the sex of a fruit fly with the following chromosomal composition?
- One X chromosome and two sets of autosomes
 - Two X chromosomes, one Y chromosome, and two sets of autosomes
 - Two X chromosomes and four sets of autosomes
 - Four X chromosomes, two Y chromosomes, and four sets of autosomes
- C4. What would be the sex of a human with the following numbers of sex chromosomes?
- XXX
 - X (also described as X0)
 - XXX
 - XXY
- C5. With regard to the numbers of sex chromosomes, explain why dosage compensation is necessary.
- C6. What is a Barr body? How is its structure different from that of other chromosomes in the cell? How does the structure of a Barr body affect the level of X-linked gene expression?
- C7. Among different species, describe three distinct strategies for accomplishing dosage compensation.
- C8. Describe when X inactivation occurs and how this leads to phenotypic results at the organism level. In your answer, you should explain why X inactivation causes results such as variegated coat patterns in mammals. Why do two different calico cats have their patches of orange and black fur in different places? Explain whether or not a variegated coat pattern due to X inactivation could occur in marsupials.
- C9. Describe the molecular process of X inactivation. This description should include the three phases of inactivation and the role of the Xic. Explain what happens to X chromosomes during embryogenesis, in adult somatic cells, and during oogenesis.
- C10. On rare occasions, an abnormal human male is born who is somewhat feminized compared with normal males. Microscopic examination of the cells of one such individual revealed that he has a single Barr body in each cell. What is the chromosomal composition of this individual?
- C11. How many Barr bodies would you expect to find in humans with the following abnormal compositions of sex chromosomes?

- A. XXY
 B. XYY
 C. XXX
 D. XO (a person with just a single X chromosome)
- C12. Certain forms of human color blindness are inherited as an X-linked recessive trait. Hemizygous males are color-blind, but heterozygous females are not. However, heterozygous females sometimes have partial color blindness.
- A. Discuss why heterozygous females may have partial color blindness.
 B. Doctors identified an unusual case in which a heterozygous female was color-blind in her right eye but had normal color vision in her left eye. Explain how this might have occurred.
- C13. A black female cat ($X^B X^b$) and an orange male cat ($X^O Y$) were mated to each other and produced a male cat that was calico. Which sex chromosomes did this male offspring inherit from its mother and father? Remember that the presence of the Y chromosome determines maleness in mammals.
- C14. What is the spreading phase of X inactivation? Why do you think it is called a spreading phase? Discuss the role of the *Xist* gene in the spreading phase of X inactivation.
- C15. A human disease known as vitamin D-resistant rickets is inherited as an X-linked dominant trait. If a male with the disease produces children with a female who does not have the disease, what is the expected ratio of affected and unaffected offspring?
- C16. Hemophilia is a X-linked recessive trait in humans. If a heterozygous woman has children with an unaffected man, what are the odds of the following combinations of children?
- A. An affected son
 B. Four unaffected offspring in a row
 C. An unaffected daughter or son
 D. Two out of five offspring that are affected
- C17. Incontinentia pigmenti is a rare, X-linked dominant disorder in humans characterized by swirls of pigment in the skin. If an affected female, who had an unaffected father, has children with an unaffected male, what would be the predicted ratios of affected and unaffected sons and daughters?

Application and Experimental Questions

- E1. Discuss the types of experimental observations that Mary Lyon brought together in proposing her hypothesis concerning X inactivation. In your own words, explain how these observations were consistent with her hypothesis.
- E2. The *Mic2* gene in humans is present on both the X and Y chromosomes. Let's suppose the *Mic2* gene exists in a dominant *Mic2* allele, which results in normal surface antigen, and a recessive *mic2* allele, which results in defective surface antigen production. Using molecular techniques, it is possible to identify homozygous and heterozygous individuals. By following the transmission of the *Mic2* and *mic2* alleles in a large human pedigree, would it be possible to distinguish between pseudoautosomal inheritance and autosomal inheritance? Explain your answer.
- E3. In Morgan's experiments, which result do you think is the most convincing piece of evidence pointing to X-linkage of the eye color gene? Explain your answer.
- E4. In his original studies of Figure 4.9, Morgan first suggested that the original white-eyed male had two copies of the white-eye allele. In this problem, let's assume that he meant the fly was $X^w Y^w$ instead of $X^w Y$. Are his data in Figure 4.9 consistent with this hypothesis? What crosses would need to be made to rule out the possibility that the Y chromosome carries a copy of the eye color gene?
- E5. How would you set up crosses to determine if a gene was Y-linked versus X-linked?
- E6. Occasionally during meiosis, a mistake can happen whereby a gamete may receive zero or two sex chromosomes rather than one. Calvin Bridges made a cross between white-eyed female flies and red-eyed male flies. As you would expect, most of the offspring were red-eyed females and white-eyed males. On rare occasions, however, he found a white-eyed female or a red-eyed male. These rare flies were not due to new gene mutations but instead were due to mistakes during meiosis in the parent flies. Consider the mechanism of sex determination in fruit flies and propose how this could happen. In your answer, describe the sex chromosome composition of these rare flies.
- E7. White-eyed flies have a lower survival rate than red-eyed flies. Based on the data in Figure 4.9, what percentage of white-eyed flies survived compared with red-eyed flies, assuming 100% survival of red-eyed flies?
- E8. A cross was made between female flies with white eyes and miniature wings (both X-linked recessive traits) to male flies with red eyes and normal wings. On rare occasions, female offspring were produced with white eyes. If we assume these females are due to errors in meiosis, what would be the most likely chromosomal composition of such flies? What would be their wing shape?
- E9. Experimentally, how do you think researchers were able to determine that the Y chromosome causes maleness in mammals, whereas the ratio of X chromosomes to the sets of autosomes causes sex determination in fruit flies?

Questions for Student Discussion/Collaboration

- Sex determination among different species seems to be caused by a wide variety of mechanisms. With regard to evolution, discuss why you think this has happened. During the evolution of life on Earth over the past 4 billion years, do you think the phenomenon of opposite sexes is a relatively recent event?
- In Figure 4.9, Morgan obtained a white-eyed male fly in a population containing many red-eyed flies that he thought were true-breeding. As mentioned in the experiment, he crossed this fly with several red-eyed sisters, and all the offspring had red eyes. But actually this is not quite true. Morgan observed 1237 red-eyed flies and 3 white-eyed males. Provide two or more explanations why he obtained 3 white-eyed males in the F_1 generation.

Answers to Comprehension Questions

4.1: d, a, b

4.2: b, a, d

4.3: a

4.4: b, a, c

Note: All answers appear at the website for this textbook; the answers to even-numbered questions are in the back of the textbook.

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Visit the website for practice tests, answer keys, and other learning aids for this chapter. Enhance your understanding of genetics with our interactive exercises, quizzes, animations, and much more.