4 Sex Determination and Sex-Linked Characteristics

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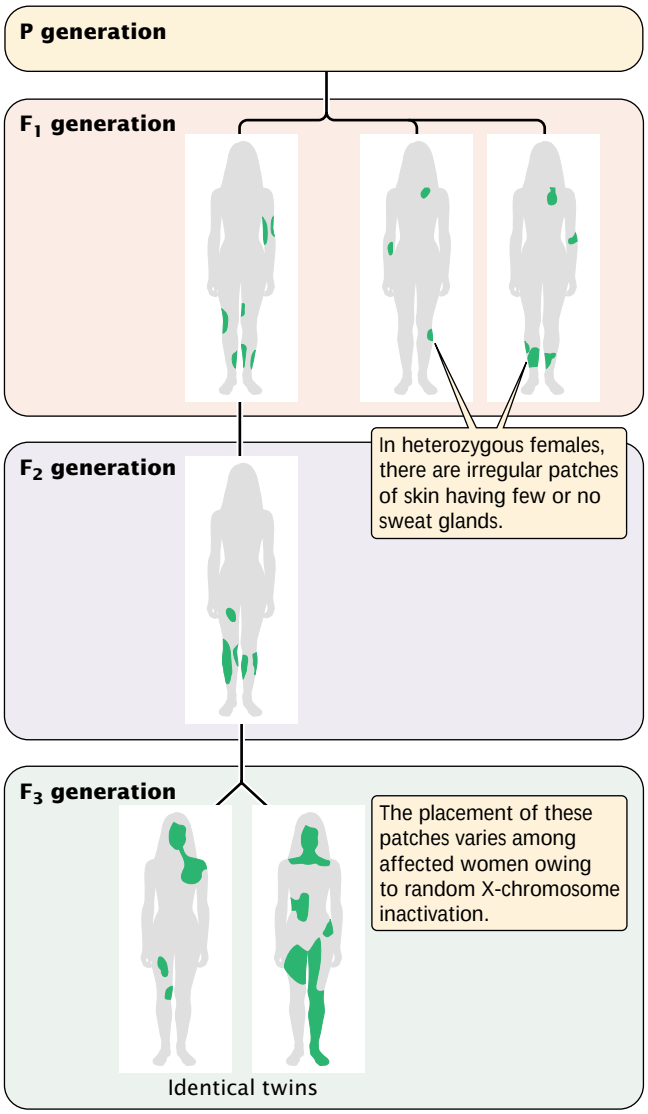
The Toothless, Hairless Men of Sind

In 1875, Charles Darwin, author of *On the Origin of Species*, wrote of a peculiar family of Sind, a province in northwest India,

> in which ten men, in the course of four generations, were furnished in both jaws taken together, with only four small and weak incisor teeth and with eight posterior molars. The men thus affected have little hair on the body, and become bald early in life. They also suffer much during hot weather from excessive dryness of the skin. It is remarkable that no instance has occurred of a daughter being thus affected. . . . Though daughters in the above family are never affected, they transmit the tendency to their sons; and no case has occurred of a son transmitting it to his sons.

These men possessed a genetic condition now known as anhidrotic ectodermal dysplasia, which (as noted by Darwin) is characterized by small teeth, no sweat glands, and sparse body hair. Darwin also noted several key features of the inheritance of this disorder: although it occurs primarily in men, fathers never transmit the trait to their sons; unaffected daughters, however, may pass the trait to their sons (the grandsons of affected men). These features of inheritance are the hallmarks of a sex-linked trait, a major focus of this chapter. Although Darwin didn't understand the mechanism of heredity, his attention to detail and remarkable ability to focus on crucial observations allowed him to identify the essential features of this genetic disease 25 years before Mendel's principles of heredity became widely known.

Darwin claimed that the daughters of this Hindu family were never affected, but it's now known that some women do have mild cases of anhidrotic ectodermal dysplasia. In these women, the symptoms of the disorder appear on only some parts of the body. For example, some regions of the jaw are missing teeth, whereas other regions have normal teeth. There are irregular patches of skin having few or no sweat



4.1 Three generations of women heterozygous for the X-linked recessive disorder anhidrotic ectodermal dysplasia, which is inherited as an X-linked recessive trait. (After A. P. Mance and J. Mance, *Genetics: Human Aspects,* Sinauer, 1990, p. 133.)

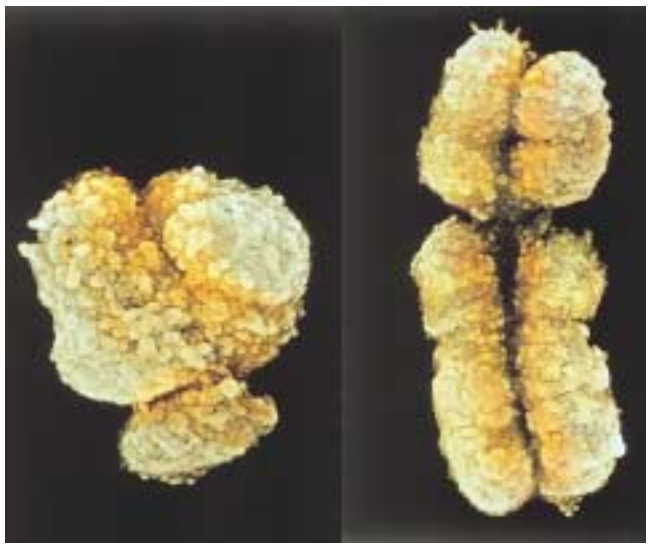
glands; the placement of these patches varies among affected women (FIGURE 4.1). The patchy occurrence of these features is explained by the fact that the gene for anhidrotic ectodermal dysplasia is located on a sex chromosome.

www.whfreeman.com/pierce Additional information about anhidrotic ectodermal dysplasia, including symptoms, history, and genetics

In Chapter 3, we studied Mendel's principles of segregation and independent assortment and saw how these principles explain much about the nature of inheritance. After Mendel's principles were rediscovered in 1900, biologists began to conduct genetic studies on a wide array of different organisms. As they applied Mendel's principles more widely, exceptions were observed, and it became necessary to devise extensions to his basic principles of heredity.

In this chapter, we explore one of the major extensions to Mendel's principles: the inheritance of characteristics encoded by genes located on the sex chromosomes, which differ in males and females (FIGURE 4.2). These characteristics and the genes that produce them are referred to as sex linked. To understand the inheritance of sex-linked characteristics, we must first know how sex is determined—why some members of a species are male and others are female. Sex determination is the focus of the first part of the chapter. The second part examines how characteristics encoded by genes on the sex chromosomes are inherited. In Chapter 5, we will explore some additional ways in which sex and inheritance interact.

As we consider sex determination and sex-linked characteristics, it will be helpful to think about two important principles. First, there are several different mechanisms of sex determination and, ultimately, the mechanism of sex determination controls the inheritance of sex-linked characteristics. Second, like other pairs of chromosomes, the X and Y sex chromosomes may pair in the course of meiosis and segregate, but throughout most of their length they are not homologous (their gene sequences don't code for the same characteristics): most genes on the X chromosome are different from genes on the Y chromosome. Consequently, males and females do not possess the same number of alleles at sex-linked loci. This difference in the number of sex-linked alleles produces the distinct patterns of inheritance in males and females.



4.2 The sex chromosomes of males (Y) and females (X) are different. (Biophoto Associates/Photo Researchers.)

Sex Determination

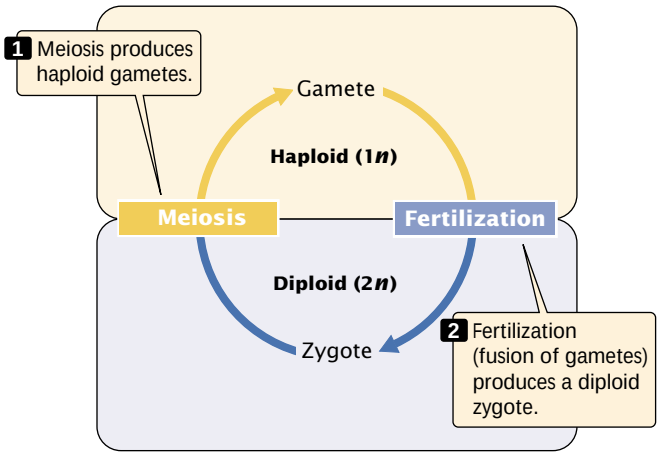
Sexual reproduction is the formation of offspring that are genetically distinct from their parents; most often, two parents contribute genes to their offspring. Among most eukaryotes, sexual reproduction consists of two processes that lead to an alternation of haploid and diploid cells: meiosis produces haploid gametes, and fertilization produces diploid zygotes (◖ FIGURE 4.3).

The term **sex** refers to sexual phenotype. Most organisms have only two sexual phenotypes: male and female. The fundamental difference between males and females is gamete size: males produce small gametes; females produce relatively large gametes (◖ FIGURE 4.4).

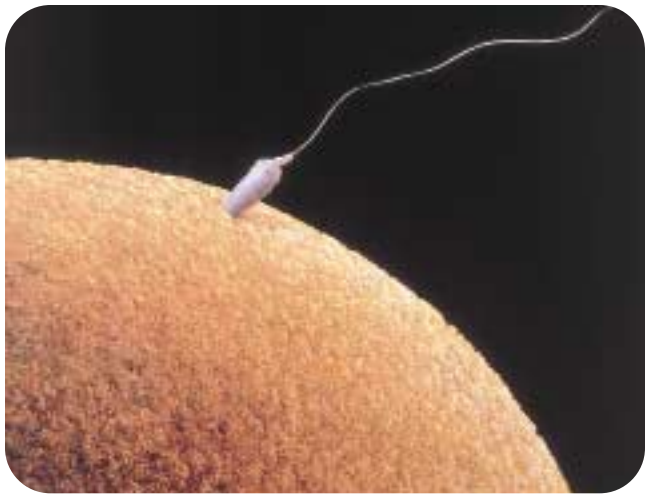
The mechanism by which sex is established is termed **sex determination.** We define the sex of an individual in terms of the individual's phenotype—ultimately, the type of gametes that it produces. Sometimes an individual has chromosomes or genes that are normally associated with one sex but a morphology corresponding to the opposite sex. For instance, the cells of female humans normally have two X chromosomes, and the cells of males have one X chromosome and one Y chromosome. A few rare persons have male anatomy, although their cells each contain two X chromosomes. Even though these people are genetically female, we refer to them as male because their sexual phenotype is male.

Concepts

In sexual reproduction, parents contribute genes to produce an offspring that is genetically distinct from both parents. In eukaryotes, sexual reproduction consists of meiosis, which produces haploid gametes, and fertilization, which produces a diploid zygote.



◖ 4.3 **In most eukaryotic organisms, sexual reproduction consists of an alternation of haploid (1*n*) and diploid (2*n*) cells.**



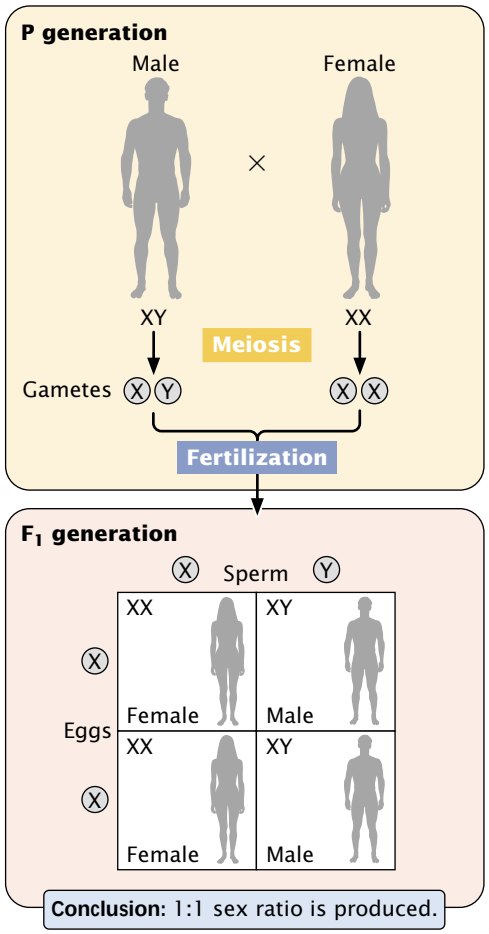
◖ 4.4 **Male and female gametes (sperm and egg, respectively) differ in size. In this photograph, a human sperm (with flagellum) penetrates a human egg cell.** (Francis Leroy, Biocosmos/Science Photo Library/Photo Researchers.)

There are many ways in which sex differences arise. In some species, both sexes are present in the same individual, a condition termed **hermaphroditism**; organisms that bear both male and female reproductive structures are said to be **monoecious** (meaning "one house"). Species in which an individual has either male or female reproductive structures are said to be **dioecious** (meaning "two houses"). Humans are dioecious. Among dioecious species, the sex of an individual may be determined chromosomally, genetically, or environmentally.

Chromosomal Sex-Determining Systems

The chromosome theory of inheritance (discussed in Chapter 3) states that genes are located on chromosomes, which serve as the vehicles for gene segregation in meiosis. Definitive proof of this theory was provided by the discovery that the sex of certain insects is determined by the presence or absence of particular chromosomes.

In 1891, Hermann Henking noticed a peculiar structure in the nuclei of cells from male insects. Understanding neither its function nor its relation to sex, he called this structure the X body. Later, Clarence E. McClung studied Henking's X body in grasshoppers and recognized that it was a chromosome. McClung called it the accessory chromosome, but eventually it became known as the X chromosome, from Henking's original designation. McClung observed that the cells of female grasshoppers had one more chromosome than the cells of male grasshoppers, and he concluded that accessory chromosomes played a role in sex determination. In 1905, Nettie Stevens and Edmund Wilson demonstrated that, in grasshoppers and other insects, the cells of females have two X chromosomes, whereas the cells of males have a single X. In some insects, they counted the same number of chromosomes in



4.5 Inheritance of sex in organisms with X and Y chromosomes results in equal numbers of male and female offspring.

cells of males and females but saw that one chromosome pair was different: two X chromosomes were found in female cells, whereas a single X chromosome plus a smaller chromosome, which they called Y, was found in male cells.

Stevens and Wilson also showed that the X and Y chromosomes separate into different cells in sperm formation; half of the sperm receive an X chromosome and half receive a Y. All egg cells produced by the female in meiosis receive one X chromosome. A sperm containing a Y chromosome unites with an X-bearing egg to produce an XY male, whereas a sperm containing an X chromosome unites with an X-bearing egg to produce an XX female (FIGURE 4.5). This accounts for the 50:50 sex ratio observed in most dioecious organisms. Because sex is inherited like other genetically determined characteristics, Stevens and Wilson's discovery that sex was associated with the inheritance of a particular chromosome also demonstrated that genes are on chromosomes.

As Stevens and Wilson found for insects, sex is frequently determined by a pair of chromosomes, the **sex chromosomes,** which differ between males and females. The nonsex chromosomes, which are the same for males and females, are called **autosomes.** We think of sex in these organisms as being determined by the presence of the sex chromosomes, but in fact the individual genes located on the sex chromosomes are usually responsible for the sexual phenotypes.

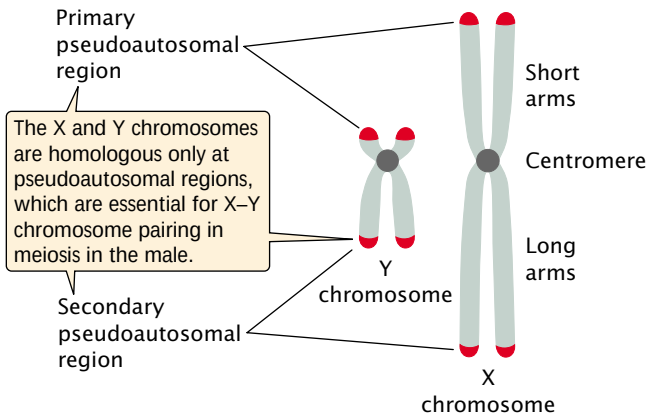
XX-XO sex determination

The mechanism of sex determination in the grasshoppers studied by McClung is one of the simplest mechanisms of chromosomal sex determination and is called the XX-XO system. In this system, females have two X chromosomes (XX), and males possess a single X chromosome (XO). There is no O chromosome; the letter O signifies the absence of a sex chromosome.

In meiosis in females, the two X chromosomes pair and then separate, with one X chromosome entering each haploid egg. In males, the single X chromosome segregates in meiosis to half the sperm cells—the other half receive no sex chromosome. Because males produce two different types of gametes with respect to the sex chromosomes, they are said to be the **heterogametic sex.** Females, which produce gametes that are all the same with respect to the sex chromosomes, are the **homogametic sex.** In the XX-XO system, the sex of an individual is therefore determined by which type of male gamete fertilizes the egg. X-bearing sperm unite with X-bearing eggs to produce XX zygotes, which eventually develop as females. Sperm lacking an X chromosome unite with X-bearing eggs to produce XO zygotes, which develop into males.

XX-XY sex determination

In many species, the cells of males and females have the same number of chromosomes, but the cells of females have two X chromosomes (XX) and the cells of males have a single X chromosome and a smaller sex chromosome called the Y chromosome (XY). In humans and many other organisms, the Y chromosome is acrocentric (FIGURE 4.6), not Y shaped as is commonly assumed. In this type of sex-determining system, the male is the heterogametic sex—half of his gametes have an X chromosome and half have a Y chromosome. The female is the



4.6 The X and Y chromosomes in humans differ in size and genetic content. They are homologous only at the pseudoautosomal regions

homogametic sex—all her egg cells contain a single X chromosome. Many organisms, including some plants, insects, and reptiles, and all mammals (including humans), have the XX-XY sex-determining system.

Although the X and Y chromosomes are not generally homologous, they do pair and segregate into different cells in meiosis. They can pair because these chromosomes are homologous at small regions called the **pseudoautosomal regions** (see Figure 4.6), in which they carry the same genes. Genes found in these regions will display the same pattern of inheritance as that of genes located on autosomal chromosomes. In humans, there are pseudoautosomal regions at both tips of the X and Y chromosomes.

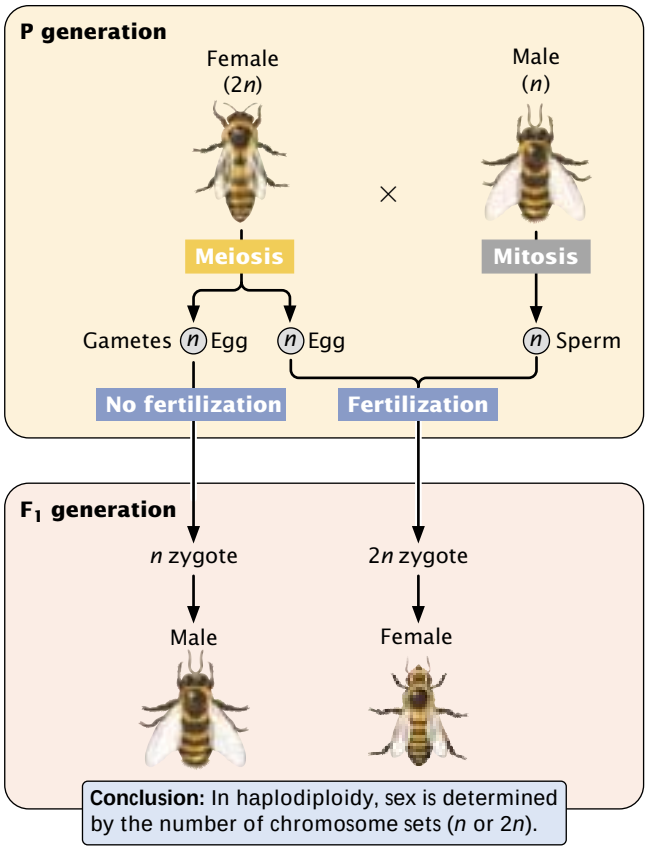
ZZ-ZW sex determination In this system, the female is heterogametic and the male is homogametic. To prevent confusion with the XX-XY system, the sex chromosomes in this system are labeled Z and W, but the chromosomes do not resemble Zs and Ws. Females in this system are ZW; after meiosis, half of the eggs have a Z chromosome and the other half have a W. Males are ZZ; all sperm contain a single Z chromosome. The ZZ-ZW system is found in birds, moths, some amphibians, and some fishes.

Concepts

In XX-XO sex determination, the male is XO and heterogametic, and the female is XX and homogametic. In XX-XY sex determination, the male is XY and the female is XX; in this system the male is heterogametic. In ZZ-ZW sex determination, the female is ZW and the male is ZZ; in this system the female is the heterogametic sex.

Haplodiploidy Some insects in the order Hymenoptera (bees, wasps, and ants) have no sex chromosomes; instead, sex is based on the number of chromosome sets found in the nucleus of each cell. Males develop from unfertilized eggs, and females develop from fertilized eggs. The cells of male hymenopterans possess only a single set of chromosomes (they are haploid) inherited from the mother. In contrast, the cells of females possess two sets of chromosomes (they are diploid), one set inherited from the mother and the other set from the father (Figure 4.7).

The haplodiploid method of sex determination produces some odd genetic relationships. When both parents are diploid, siblings on average have half their genes in common because they have a 50% chance of receiving the same allele from each parent. In these insects, males produce sperm by mitosis (they are already haploid); so all offspring receive the same set of paternal genes. The diploid females produce eggs by normal meiosis. Therefore, sisters have a 50% chance of receiving the same allele from their mother and a 100% chance of receiving the same allele from their father; the average relatedness between sisters is therefore 75%. Brothers have a 50% chance of receiving the same copy of each of their mother's two alleles at any particular locus; so their average relatedness is only 50%. The greater genetic relatedness among female siblings in insects with haplodiploid sex determination may contribute to the high degree of social cooperation that exists among females (the workers) of these insects.



4.7 In insects with haplodiploidy, males develop from unfertilized eggs and are haploid; females develop from fertilized eggs and are diploid.

Concepts

Some insects possess haplodiploid sex determination, in which males develop from unfertilized eggs and are haploid; females develop from fertilized eggs and are diploid.

Genic Sex-Determining Systems

In some plants and protozoans, sex is genetically determined, but there are no obvious differences in the chromosomes of males and females—there are no sex chromosomes. These

organisms have **genic sex determination;** genotypes at one or more loci determine the sex of an individual.

It is important to understand that, even in chromosomal sex-determining systems, sex is actually determined by individual genes. For example, in mammals, a gene (*SRY,* discussed later in this chapter) located on the Y chromosome determines the male phenotype. In both genic sex determination and chromosomal sex determination, sex is controlled by individual genes; the difference is that, with chromosomal sex determination, the chromosomes that carry those genes *appear* different in males and females.

Environmental Sex Determination

Genes have had a role in all of the examples of sex determination discussed thus far, but sex is determined fully or in part by environmental factors in a number of organisms.

One fascinating example of environmental sex determination is seen in the marine mollusk *Crepidula fornicata*, also known as the common slipper limpet (FIGURE 4.8). Slipper limpets live in stacks, one on top of another. Each limpet begins life as a swimming larva. The first larva to settle on a solid, unoccupied substrate develops into a female limpet. It then produces chemicals that attract other larvae, which settle on top of it. These larvae develop into males, which then serve as mates for the limpet below. After a period of time, the males on top develop into females and, in turn, attract additional larvae that settle on top of the stack, develop into males, and serve as mates for the limpets under them. Limpets can form stacks of a dozen or more animals; the uppermost animals are always male. This type of sexual development is called **sequential hermaphroditism;** each individual animal can be both male and female, although not at the same time. In *Crepidula fornicata*, sex is determined environmentally by the limpet's position in the stack.

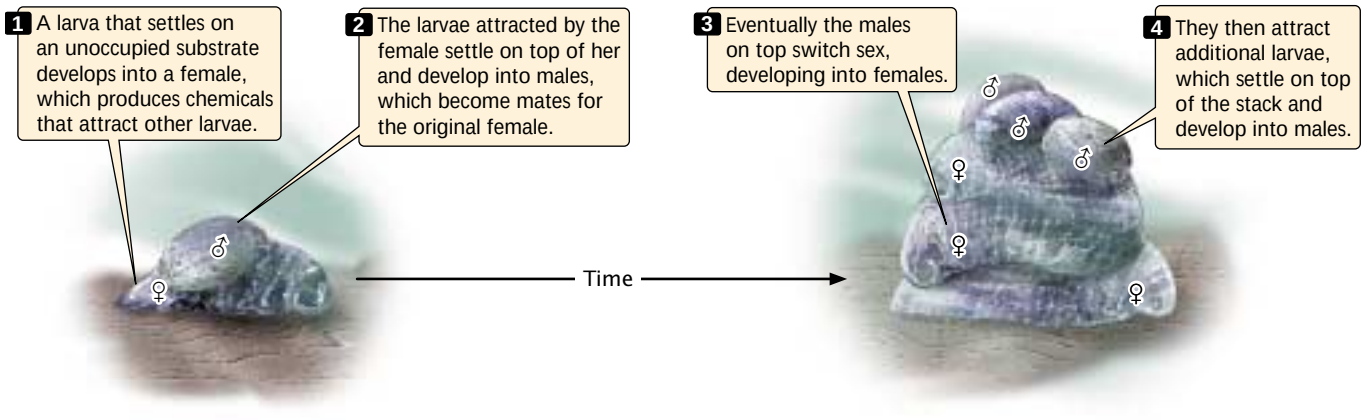
Environmental factors are also important in determining sex in many reptiles. Although most snakes and lizards have sex chromosomes, in many turtles, crocodiles, and alligators, temperature during embryonic development determines sexual phenotype. In turtles, for example, warm temperatures produce females during certain times of the year, whereas cool temperatures produce males. In alligators, the reverse is true.

Concepts

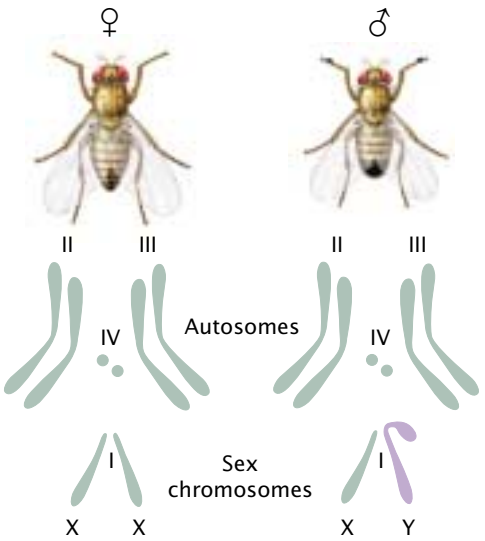
In genic sex determination, sex is determined by genes at one or more loci, but there are no obvious differences in the chromosomes of males and females. In environmental sex determination, sex is determined fully or in part by environmental factors.

Sex Determination in *Drosophila*

The fruit fly *Drosophila melanogaster,* has eight chromosomes: three pairs of autosomes and one pair of sex chromosomes (FIGURE 4.9). Normally, females have two X chromosomes and males have an X chromosome and a Y chromosome. However, the presence of the Y chromosome does not determine maleness in *Drosophila;* instead, each fly's sex is determined by a balance between genes on the autosomes and genes on the X chromosome. This type of sex determination is called the **genic balance system.** In this system, a number of genes seem to influence sexual development. The X chromosome contains genes with female-producing effects, whereas the autosomes contain genes with male-producing effects. Consequently, a fly's sex is determined by the **X:A ratio,** the number of X chromosomes divided by the number of haploid sets of autosomal chromosomes.



4.8 In *Crepidula fornicata,* the common slipper limpet, sex is determined by an environmental factor, the limpet's position in a stack of limpets.



4.9 The chromosomes of *Drosophila melanogaster* ($2n = 8$) consist of three pairs of autosomes (labelled I, II, and III) and one pair of sex chromosomes (labelled X and Y).

An X:A ratio of 1.0 produces a female fly; an X:A ratio of 0.5 produces a male. If the X:A ratio is less than 0.5, a male phenotype is produced, but the fly is weak and sterile—such flies are sometimes called metamales. An X:A ratio between 1.0 and 0.50 produces an intersex fly, with a mixture of male and female characteristics. If the X:A ratio is greater than 1.0, a female phenotype is produced, but these flies (called metafemales) have serious developmental problems and many never emerge from the pupal case. Table 4.1 presents some different chromosome complements in *Drosophila* and their associated sexual phenotypes. Flies with two sets of autosomes and XXY sex chromosomes (an X:A ratio of 1.0) develop as fully fertile females, in spite of the presence of a Y chromosome. Flies with only a single X (an X:A ratio of 0.5), develop as males, although they are sterile. These observations confirm that the Y chromosome does not determine sex in *Drosophila*.

Mutations in genes that affect sexual phenotype in *Drosophila* have been isolated. For example, the *transformer* mutation converts a female with an X:A ratio of 1.0 into a phenotypic male, whereas the *doublesex* mutation transforms normal males and females into flies with intersex phenotypes. Environmental factors, such as the temperature of the rearing conditions, also can affect the development of sexual characteristics.

Concepts

The sexual phenotype of a fruit fly is determined by the ratio of the number of X chromosomes to the number of haploid sets of autosomal chromosomes (the X:A ratio).

www.whfreeman.com/pierce Links to many Internet resources on the genetics of *Drosophila melanogaster*

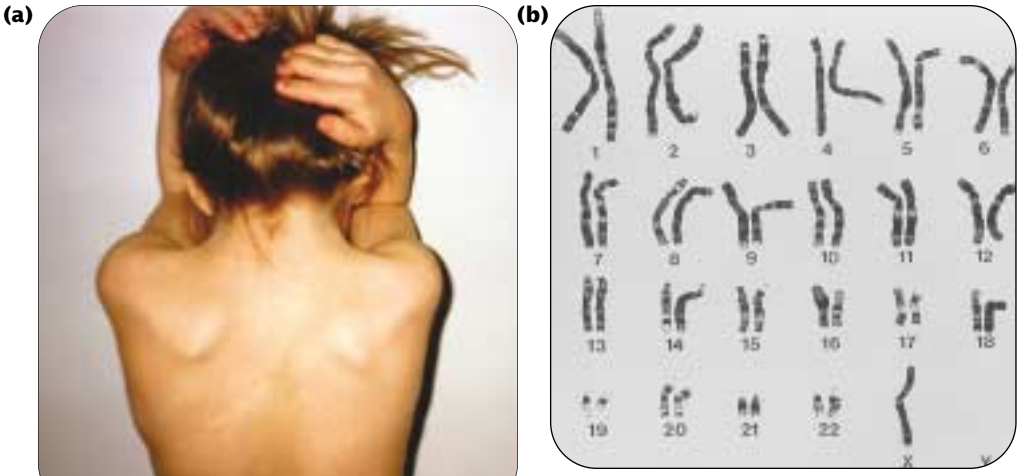
Sex Determination in Humans

Humans, like *Drosophila*, have XX-XY sex determination, but in humans the presence of a gene on the Y chromosome determines maleness. The phenotypes that result from abnormal numbers of sex chromosomes, which arise when the sex chromosomes do not segregate properly in meiosis or mitosis, illustrate the importance of the Y chromosome in human sex determination.

Turner syndrome Persons who have **Turner syndrome** are female; they do not undergo puberty and their female

Table 4.1 Chromosome complements and sexual phenotypes in *Drosophila*

Sex-Chromosome Complement	Haploid Sets of Autosomes	X:A Ratio	Sexual Phenotype
XX	AA	1.0	Female
XY	AA	0.5	Male
XO	AA	0.5	Male
XXY	AA	1.0	Female
XXX	AA	1.5	Metafemale
XXXY	AA	1.5	Metafemale
XX	AAA	0.67	Intersex
XO	AAA	0.33	Metamale
XXXX	AAA	1.3	Metafemale



4.10 Persons with Turner syndrome have a single X chromosome in their cells. (a) Characteristic physical features. (b) Chromosomes from a person with Turner syndrome. (Part a, courtesy of Dr. Daniel C. Postellon, Devos Children's Hospital; Part b, Dept. of Clinical Cytogenics, Addenbrookes Hospital/Science Photo Library/Photo Reseachers.)

secondary sex characteristics remain immature: menstruation is usually absent, breast development is slight, and pubic hair is sparse. This syndrome is seen in 1 of 3000 female births. Affected women are frequently short and have a low hairline, a relatively broad chest, and folds of skin on the neck (FIGURE 4.10). Their intelligence is usually normal. Most women who have Turner syndrome are sterile. In 1959, C. E. Ford used new techniques to study human chromosomes and discovered that cells from a 14-year-old girl with Turner syndrome had only a single X chromosome; this chromosome complement is usually referred to as XO.

There are no known cases in which a person is missing both X chromosomes, an indication that at least one X chromosome is necessary for human development. Presumably, embryos missing both Xs are spontaneously aborted in the early stages of development.

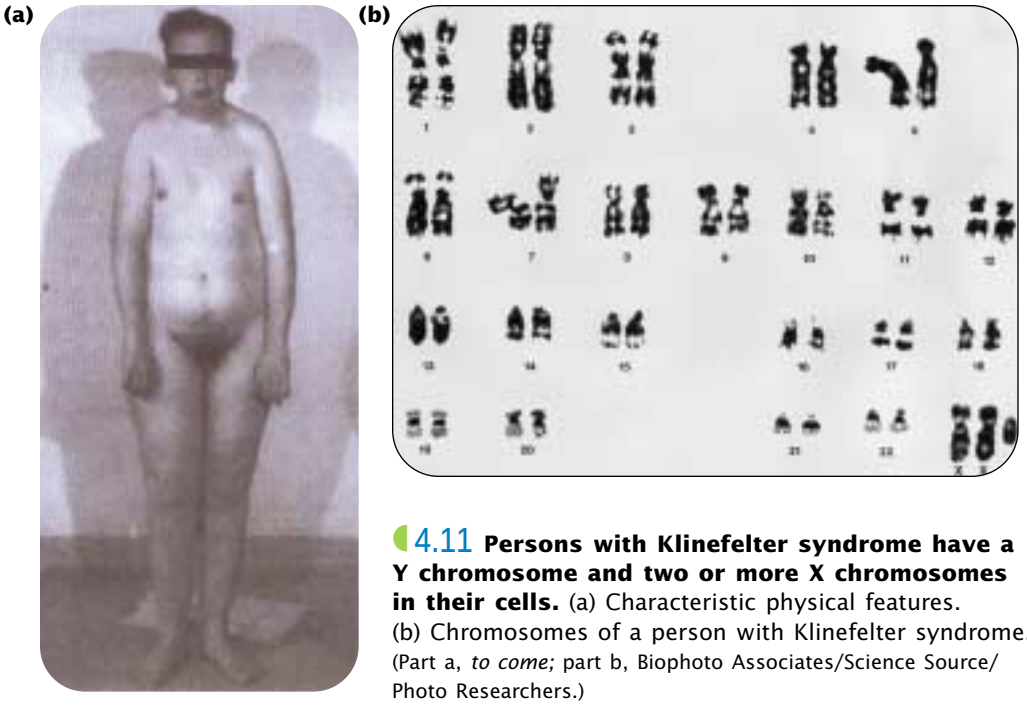
Klinefelter syndrome Persons who have **Klinefelter syndrome,** which occurs with a frequency of about 1 in 1000 male births, have cells with one or more Y chromosomes and multiple X chromosomes. The cells of most males having this condition are XXY, but cells of a few Klinefelter males are XXXY, XXXXY, or XXYY. Persons with this condition, though male, frequently have small testes, some breast enlargement, and reduced facial and pubic hair (FIGURE 4.11). They are often taller than normal and sterile; most have normal intelligence.

Poly-X females In about 1 in 1000 female births, the child's cells possess three X chromosomes, a condition often referred to as **triplo-X syndrome.** These persons have no distinctive features other than a tendency to be tall and thin. Although a few are sterile, many menstruate regularly and are fertile. The incidence of mental retardation among triple-X females is slightly greater than in the general population, but most XXX females have normal intelligence. Much rarer are women whose cells contain four or five X chromosomes. These women usually have normal female anatomy but are mentally retarded and have a number of physical problems. The severity of mental retardation increases as the number of X chromosomes increases beyond three.

www.whfreeman.com/pierce Further information about sex-chromosomal abnormalities in humans

The role of sex chromosomes The phenotypes associated with sex-chromosome anomalies allow us to make several inferences about the role of sex chromosomes in human sex determination.

1. The X chromosome contains genetic information essential for both sexes; at least one copy of an X chromosome is required for human development.
2. The male-determining gene is located on the Y chromosome. A single copy of this chromosome, even in the presence of several X chromosomes, produces a male phenotype.
3. The absence of the Y chromosome results in a female phenotype.
4. Genes affecting fertility are located on the X and Y chromosomes. A female usually needs at least two copies of the X chromosome to be fertile.
5. Additional copies of the X chromosome may upset normal development in both males and females, producing physical and mental problems that increase as the number of extra X chromosomes increases.



4.11 Persons with Klinefelter syndrome have a Y chromosome and two or more X chromosomes in their cells. (a) Characteristic physical features. (b) Chromosomes of a person with Klinefelter syndrome. (Part a, *to come;* part b, Biophoto Associates/Science Source/ Photo Researchers.)

The male-determining gene in humans The Y chromosome in humans and all other mammals is of paramount importance in producing a male phenotype. However, scientists discovered a few rare XX males whose cells apparently lack a Y chromosome. For many years, these males presented a real enigma: How could a male phenotype exist without a Y chromosome? Close examination eventually revealed a small part of the Y chromosome attached to another chromosome. This finding indicates that it is not the entire Y chromosome that determines maleness in humans; rather, it is a gene on the Y chromosome.

Early in development, all humans possess undifferentiated gonads and both male and female reproductive ducts. Then, about 6 weeks after fertilization, a gene on the Y chromosome becomes active. By an unknown mechanism, this gene causes the neutral gonads to develop into testes, which begin to secrete two hormones: testosterone and Mullerian-inhibiting substance. Testosterone induces the development of male characteristics, and Mullerian-inhibiting substance causes the degeneration of the female reproductive ducts. In the absence of this male-determining gene, the neutral gonads become ovaries, and female features develop.

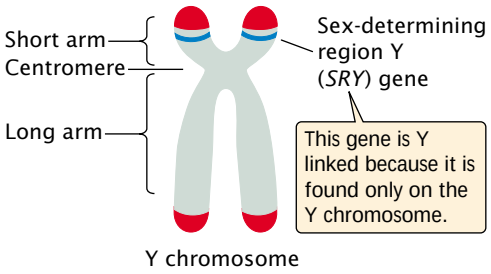
In 1987, David Page and his colleagues at the Massachusetts Institute of Technology located what appeared to be the male-determining gene near the tip of the short arm of the Y chromosome. They had examined the DNA of several XX males and XY females. The cells of one XX male that they studied possessed a very small piece of a Y chromosome attached to one of the Xs. This piece came from a section, called 1A, of the Y chromosome. Because this person had a male phenotype, they reasoned that the male-determining gene must reside within the 1A section of the Y chromosome.

Examination of the Y chromosome of a 12 year-old XY girl seemed to verify this conclusion. In spite of the fact that she possessed more than 99.8% of a Y chromosome, this XY person had a female phenotype. Page and his colleagues assumed that the male-determining gene must reside within the 0.2% of the Y chromosome that she was missing. Further examination showed that this Y chromosome was indeed missing part of section 1A. They then sequenced the DNA within section 1A of normal males and found a gene called *ZFY,* which appeared to be the testis-determining factor.

Within a few months, however, results from other laboratories suggested that *ZFY* might not in fact be the male-determining gene. Marsupials (pouched mammals), which also have XX-XY sex determination, were found to possess a *ZFY* gene on an autosomal chromosome, not on the Y chromosome. Furthermore, several human XX males were found who did not possess a copy of the *ZFY* gene.

A new candidate for the male-determining gene, called the **sex-determining region Y** (*SRY*) **gene,** was discovered in 1990 (◖ FIGURE 4.12). This gene is found in XX males and is missing from all XY females; it is also found on the Y chromosome of all mammals examined to date. Definitive proof that *SRY* is the male-determining gene came when scientists placed a copy of this gene into XX mice by means of genetic engineering. The XX mice that received this gene, although sterile, developed into anatomical males.

The *SRY* gene encodes a protein that binds to DNA and causes a sharp bend in the molecule. This alteration of DNA structure may affect the expression of other genes that



4.12 The *SRY* gene is on the Y chromosome and causes the development of male characteristics.

encode testis formation. Although *SRY* is the primary determinant of maleness in humans, other genes (some X linked, others Y linked, and still others autosomal) also play a role in fertility and the development of sex differences.

Concepts

The presence of the *SRY* gene on the Y chromosome causes a human embryo to develop as a male. In the absence of this gene, a human embryo develops as a female.

www.whfreeman.com/pierce Additional information on the *SRY* gene

Androgen-insensitivity syndrome Several genes besides *SRY* influence sexual development in humans, as illustrated by women with androgen-insensitivity syndrome. These persons have female external sexual characteristics and psychological orientation. Indeed, most are unaware of their condition until they reach puberty and fail to menstruate. Examination by a gynecologist reveals that the vagina ends blindly and that the uterus, oviducts, and ovaries are absent. Inside the abdominal cavity lies a pair of testes, which produce levels of testosterone normally seen in males. The cells of a woman with androgen-insensitivity syndrome contain an X and a Y chromosome.

How can a person be female in appearance when her cells contain a Y chromosome and she has testes that produce testosterone? The answer lies in the complex relation between genes and sex in humans. In a human embryo with a Y chromosome, the *SRY* gene causes the gonads to develop into testes, which produce testosterone. Testosterone stimulates embryonic tissues to develop male characteristics. But, for testosterone to have its effects, it must bind to an androgen receptor. This receptor is defective in females with androgen-insensitivity syndrome; consequently, their cells are insensitive to testosterone, and female characteristics develop. The gene for the androgen receptor is located on the X chromosome; so persons with this condition always inherit it from their mothers. (All XY persons inherit the X chromosome from their mothers.)

Androgen-insensitivity syndrome illustrates several important points about the influence of genes on a person's sex. First, this condition demonstrates that human sexual development is a complex process, influenced not only by the *SRY* gene on the Y chromosome, but also by other genes found elsewhere. Second, it shows that most people carry genes for both male and female characteristics, as illustrated by the fact that those with androgen-insensitivity syndrome have the capacity to produce female characteristics, even though they have male chromosomes. Indeed, the genes for most male and female secondary sex characteristics are present not on the sex chromosomes but on autosomes. The key to maleness and femaleness lies not in the genes but in the control of their expression.

www.whfreeman.com/pierce Additional information on androgen-insensitivity syndrome

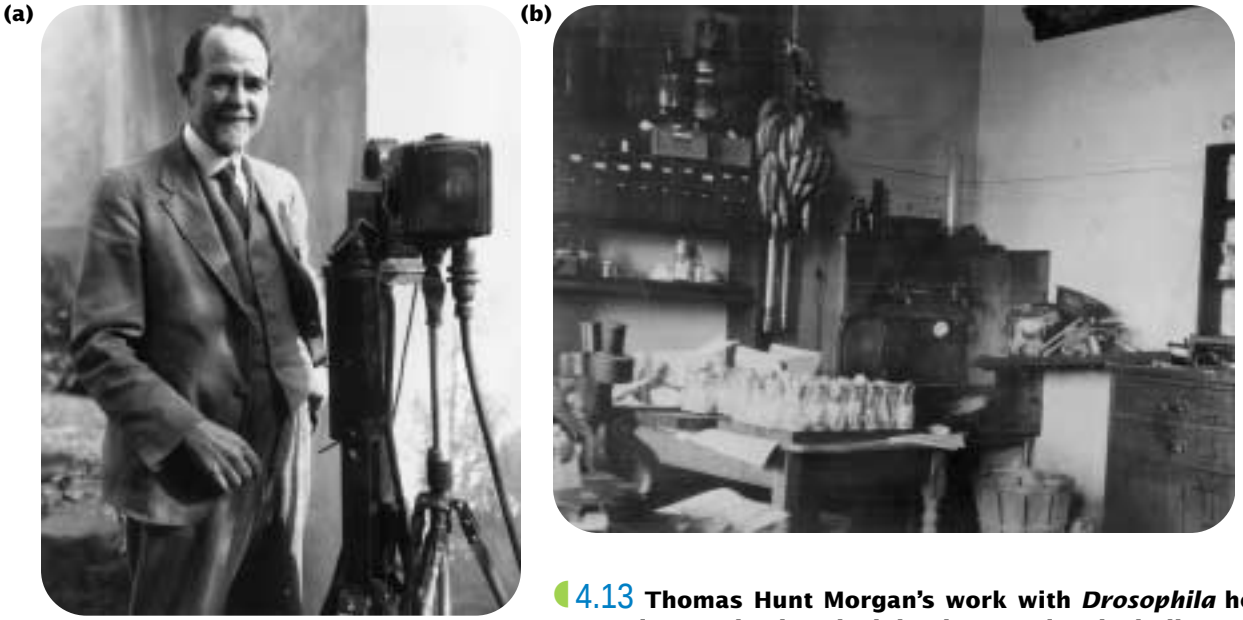
Sex-Linked Characteristics

Sex-linked characteristics are determined by genes located on the sex chromosomes. Genes on the X chromosome determine **X-linked characteristics;** those on the Y chromosome determine **Y-linked characteristics.** Because little genetic information exists on the Y chromosome in many organisms, most sex-linked characteristics are X linked. Males and females differ in their sex chromosomes; so the pattern of inheritance for sex-linked characteristics differs from that exhibited by genes located on autosomal chromosomes.

X-Linked White Eyes in *Drosophila*

The first person to explain sex-linked inheritance was the American biologist Thomas Hunt Morgan (**Figure 4.13a**). Morgan began his career as an embryologist, but the discovery of Mendel's principles inspired him to begin conducting genetic experiments, initially on mice and rats. In 1909, Morgan switched to *Drosophila melanogaster;* a year later, he discovered among the flies of his laboratory colony a single male that possessed white eyes, in stark contrast with the red eyes of normal fruit flies. This fly had a tremendous effect on the future of genetics and on Morgan's career as a biologist. With his white-eyed male, Morgan unraveled the mechanism of X-linked inheritance, ushering in the "golden age" of *Drosophila* genetics that lasted from 1910 until 1930.

Morgan's laboratory, located on the top floor of Schermerhorn Hall at Columbia University, became known as the Fly Room (**Figure 4.13b**). To say that the Fly Room was unimpressive is an understatement. The cramped room, only about 16 × 23 feet, was filled with eight desks, each occupied by a student and his experiments. The primitive laboratory equipment consisted of little more than milk bottles for rearing the flies and hand-held lenses for observing their traits. Later, microscopes replaced the hand-held lenses, and crude incubators were added to maintain the fly



4.13 Thomas Hunt Morgan's work with *Drosophila* helped unravel many basic principles in genetics, including X-linked inheritance. (a) Morgan. (b) The Fly Room, where Morgan and his students conducted genetic research. (Part a, World Wide Photos; Part b, American Philisophical Society.)

cultures, but even these additions did little to increase the physical sophistication of the laboratory. Morgan and his students were not tidy: cockroaches were abundant (living off spilled *Drosophila* food), dirty milk bottles filled the sink, ripe bananas—food for the flies—hung from the ceiling, and escaped fruit flies hovered everywhere.

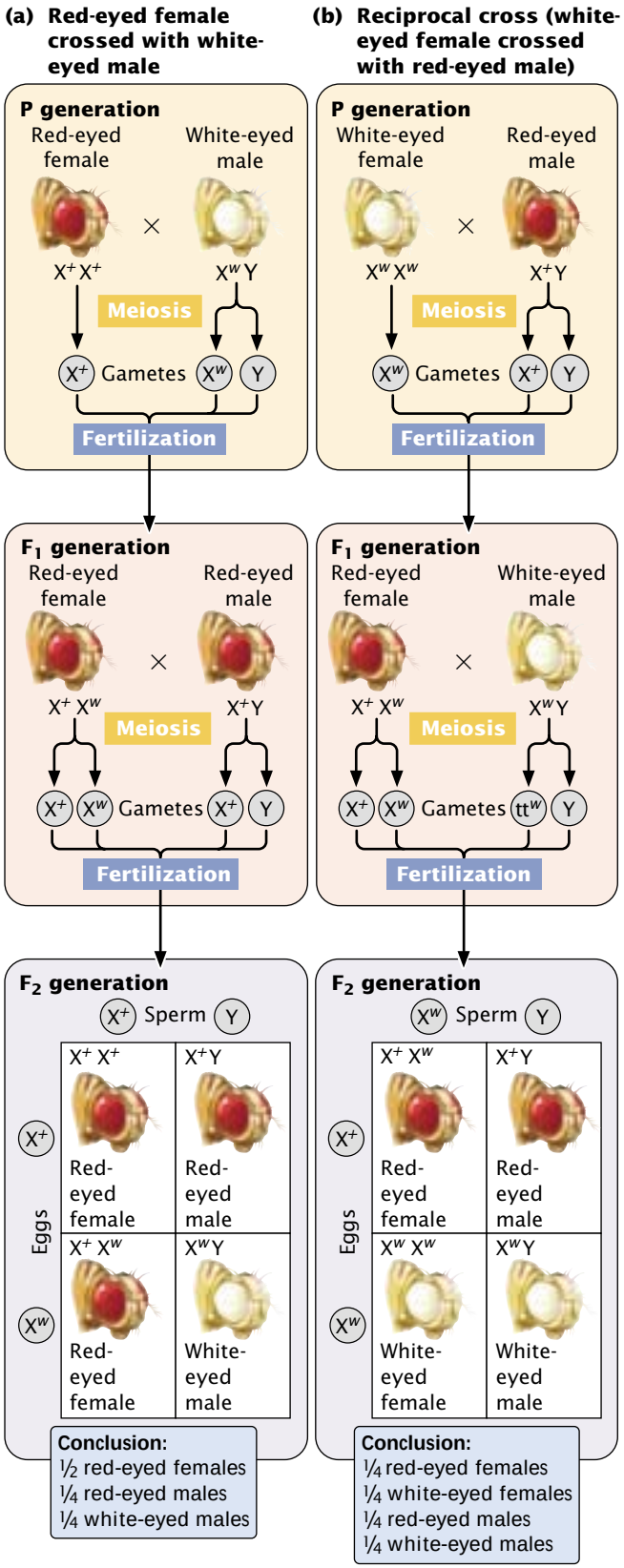
In spite of its physical limitations, the Fly Room was the source of some of the most important research in the history of biology. There was daily excitement among the students, some of whom initially came to the laboratory as undergraduates. The close quarters facilitated informality and the free flow of ideas. Morgan and the Fly Room illustrate the tremendous importance of "atmosphere" in producing good science.

To explain the inheritance of the white-eyed characteristic in fruit flies, Morgan systematically carried out a series of genetic crosses (FIGURE 4.14a). First, he crossed pure-breeding, red-eyed females with his white-eyed male, producing F_1 progeny that all had red eyes. (In fact, Morgan found three white-eyed males among the 1237 progeny, but he assumed that the white eyes were due to new mutations.) Morgan's results from this initial cross were consistent with Mendel's principles: a cross between a homozygous dominant individual and a homozygous recessive individual produces heterozygous offspring exhibiting the dominant trait. His results suggested that white eyes were a simple recessive trait. However, when Morgan crossed the F_1 flies with one another, he found that all the female F_2 flies possessed red eyes but that half the male F_2 flies had red eyes and the other half had white eyes. This finding was clearly not the expected result for a simple recessive trait, which should appear in $\frac{1}{4}$ of both male and female F_2 offspring.

To explain this unexpected result, Morgan proposed that the locus affecting eye color was on the X chromosome (that eye color was X linked). He recognized that the eye-color alleles were present only on the X chromosome—no homologous allele was present on the Y chromosome. Because the cells of females possess two X chromosomes, females could be homozygous or heterozygous for the eye-color alleles. The cells of males, on the other hand, possess only a single X chromosome and can carry only a single eye-color allele. Males therefore cannot be either homozygous or heterozygous but are said to be **hemizygous** for X-linked loci.

To verify his hypothesis that the white-eye trait is X linked, Morgan conducted additional crosses. He predicted that a cross between a white-eyed female and a red-eyed male would produce all red-eyed females and all white-eyed males (FIGURE 4.14b). When Morgan performed this cross, the results were exactly as predicted. Note that this cross is the reciprocal of the original cross and that the two reciprocal crosses produced different results in the F_1 and F_2 generations. Morgan also crossed the F_1 heterozygous females with their white-eyed father, the red-eyed F_2 females with white-eyed males, and white-eyed females with white-eyed males. In all of these crosses, the results were consistent with Morgan's conclusion that white eyes is an X-linked characteristic.

www.whfreeman.com/pierce More information on the life of Thomas Hunt Morgan



4.14 Morgan's X-linked crosses for white eyes in fruit flies. (a) Original and F_1 crosses. (b) Reciprocal crosses.

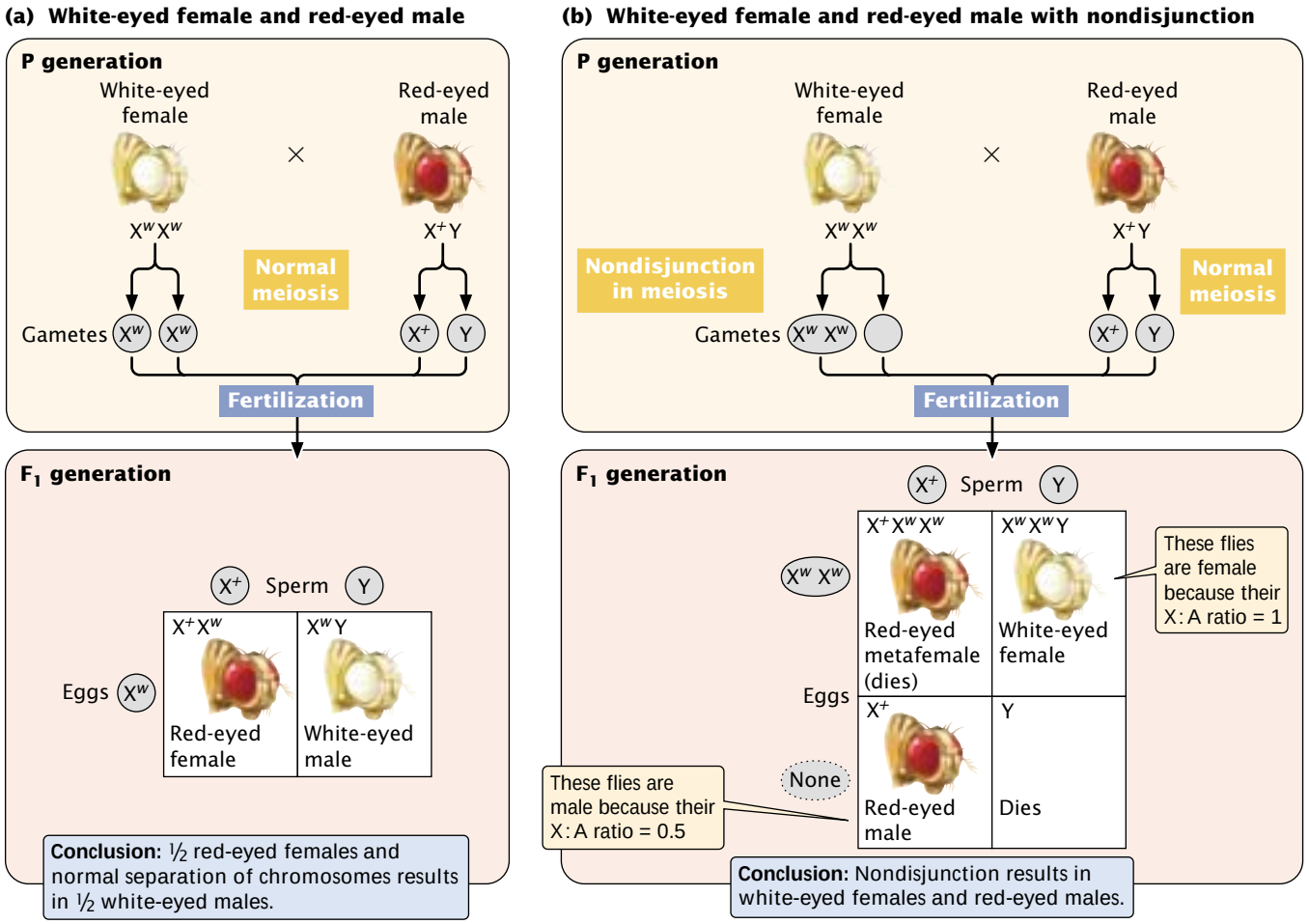
Nondisjunction and the Chromosome Theory of Inheritance

When Morgan crossed his original white-eyed male with homozygous red-eyed females, all 1237 of the progeny had red eyes, except for three white-eyed males. As already mentioned, Morgan attributed these white-eyed F_1 males to the occurrence of further mutations. However, flies with these unexpected phenotypes continued to appear in his crosses. Although uncommon, they appeared far too often to be due to mutation. Calvin Bridges, one of Morgan's students, set out to investigate the genetic basis of these exceptions.

Bridges found that, when he crossed a white-eyed female (X^wX^w) with a red-eyed male (X^+Y), about 2.5% of the male offspring had red eyes and about 2.5% of the female offspring had white eyes (Figure 4.15a). In this cross, every male fly should inherit its mother's X chromosome and should be X^wY with white eyes. Every female fly should inherit a dominant red-eye allele on its father's X chromosome, along with a white-eyed allele on its mother's X chromosome; thus, all the female progeny should be X^+X^w and have red eyes. The appearance of red-eyed males and white-eyed females in this cross was therefore unexpected.

To explain this result, Bridges hypothesized that, occasionally, the two X chromosomes in females fail to separate during anaphase I of meiosis. Bridges termed this failure of chromosomes to separate **nondisjunction.** When nondisjunction occurs, some of the eggs receive two copies of the X chromosome and others do not receive an X chromosome (Figure 4.15b). If these eggs are fertilized by sperm from a red-eyed male, four combinations of sex chromosomes are produced. When an egg carrying two X chromosomes is fertilized by a Y-bearing sperm, the resulting zygote is X^wX^wY. Sex in *Drosophila* is determined by the X:A ratio (see Table 4.1); in this case the X:A ratio is 1.0, so the X^wX^wY zygote develops into a white-eyed female. An egg with two X chromosomes that is fertilized by an X-bearing sperm produces $X^wX^wX^+$, which usually dies. An egg with no X chromosome that is fertilized by an X-bearing sperm produces X^+O, which develops into a red-eyed male. If the egg with no X chromosome is fertilized by a Y-bearing sperm, the resulting zygote with only a Y chromosome and no X chromosome dies. Rare nondisjunction of the X chromosomes among white-eyed females therefore produces a few red-eyed males and white-eyed females, which is exactly what Bridges found in his crosses.

Bridges's hypothesis predicted that the white-eyed females would possess two X chromosomes and one Y and that red-eyed males would possess a single X chromosome. To verify his hypothesis, Bridges examined the chromosomes of his flies and found precisely what he predicted. The significance of Bridges's study was not that it explained



4.15 Bridges conducted experiments that proved that the gene for white eyes is located on the X chromosome. (a) A white-eyed female was crossed with a red-eyed male. (b) Rare nondisjunction produced a few eggs with two copies of the X^w chromosome and other eggs with no X chromosome.

the appearance of an occasional odd fly in his culture but that he was able to predict a fly's chromosomal makeup on the basis of its eye-color genotype. This association between genotype and chromosomes gave unequivocal evidence that sex-linked genes were located on the X chromosome and confirmed the chromosome theory of inheritance.

Concepts

By showing that the appearance of rare phenotypes was associated with the inheritance of particular chromosomes, Bridges proved that sex-linked genes are located on the X chromosome and that the chromosome theory of inheritance is correct.

X-Linked Color Blindness in Humans

To further examine X-linked inheritance, let's consider another X-linked characteristic: red–green color blindness in humans. Within the human eye, color is perceived in light-sensing cone cells that line the retina. Each cone cell contains one of three pigments capable of absorbing light of a particular wavelength; one absorbs blue light, a second absorbs red light, and a third absorbs green light. The human eye actually detects only three colors—red, green, and blue—but the brain mixes the signals from different cone cells to create the wide spectrum of colors that we perceive. Each of the three pigments is encoded by a separate locus; the locus for the blue pigment is found on chromosome 7, and those for green and red pigments lie close together on the X chromosome.

The most common types of human color blindness are caused by defects of the red and green pigments; we will refer

to these conditions as red–green color blindness. Mutations that produce defective color vision are generally recessive and, because the genes coding for the red and green pigments are located on the X chromosome, red–green color blindness is inherited as an X-linked recessive characteristic.

We will use the symbol X^c to represent an allele for red–green color blindness and the symbol X^+ to represent an allele for normal color vision. Females possess two X chromosomes; so there are three possible genotypes among females: X^+X^+ and X^+X^c, which produce normal vision, and X^cX^c, which produces color blindness. Males have only a single X chromosome and two possible genotypes: X^+Y, which produces normal vision, and X^cY which produces color blindness.

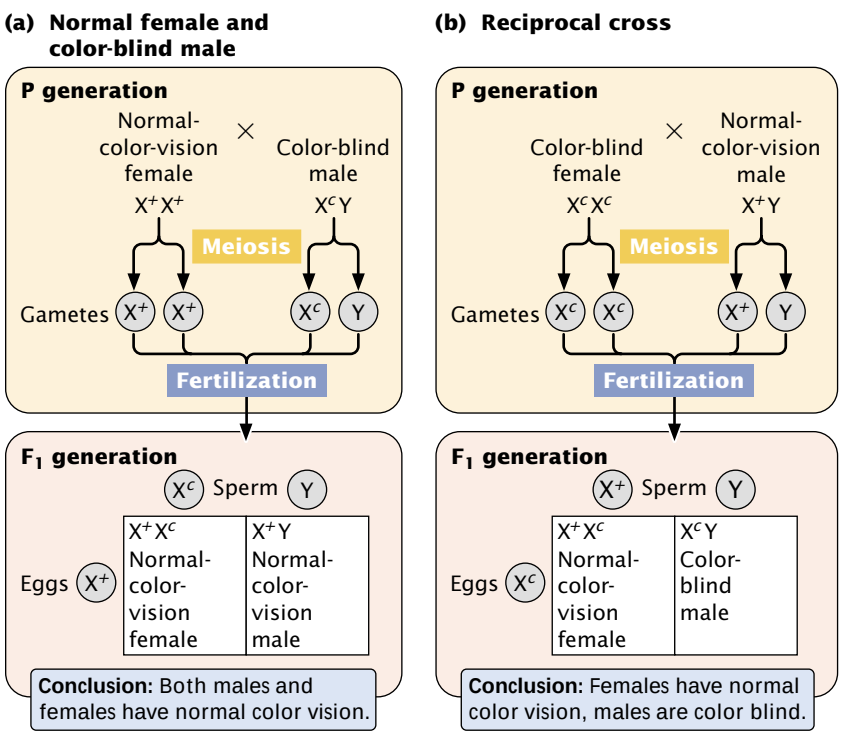
If a color-blind man mates with a woman homozygous for normal color vision (**Figure 4.16a**), all of the gametes produced by the woman will contain an allele for normal color vision. Half of the man's gametes will receive the X chromosome with the color-blind allele, and the other half will receive the Y chromosome, which carries no alleles affecting color vision. When an X^c-bearing sperm unites with the X^+-bearing egg, a heterozygous female with normal vision (X^+X^c) is produced. When a Y-bearing sperm unites with the X^+-bearing egg, a hemizygous male with normal vision (X^+Y) is produced (see Figure 4.16a).

In the reciprocal cross between a color-blind woman and a man with normal color vision (**Figure 4.16b**), the woman produces only X^c-bearing gametes. The man produces some gametes that contain the X^+ chromosome and others that contain the Y chromosome. Males inherit the X chromosome from their mothers; because both of the mother's X chromosomes bear the X^c allele in this case, all the male offspring will be color blind. In contrast, females inherit an X chromosome from both parents; thus the female offspring of this reciprocal cross will all be heterozygous with normal vision. Females are color blind only when color-blind alleles have been inherited from both parents, whereas a color-blind male need inherit a color-blind allele from his mother only; for this reason, color blindness and most other rare X-linked recessive characteristics are more common in males.

In these crosses for color blindness, notice that an affected woman passes the X-linked recessive trait to her sons but not to her daughters, whereas an affected man passes the trait to his grandsons through his daughters but never to his sons. X-linked recessive characteristics seem to alternate between the sexes, appearing in females one generation and in males the next generation; thus, this pattern of inheritance exhibited by X-linked recessive characteristics is sometimes called *crisscross inheritance*.

Concepts

Characteristics determined by genes on the sex chromosomes are called sex-linked characteristics. Diploid females have two alleles at each X-linked locus, whereas diploid males possess a single allele at each X-linked locus. Females inherit X-linked alleles from both parents, but males inherit a single X-linked allele from their mothers.



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

Symbols for X-Linked Genes

There are several different ways to record genotypes for X-linked traits. Sometimes the genotypes are recorded in the same fashion as for autosomal characteristics—the hemizygous males are simply given a single allele: the genotype of a female *Drosophila* with white eyes would be *ww*, and the genotype of a white-eyed hemizygous male would be *w*. Another method is to include the Y chromosome, designating it with a diagonal slash (/). With this method, the white-eyed female's genotype would still be *ww* and the white-eyed male's genotype would be *w*/. Perhaps the most useful method is to write the X and Y chromosomes in the genotype, designating the X-linked alleles with superscripts, as we have done in this chapter. With this method, a white-eyed female would be X^wX^w and a white-eyed male X^wY. Using Xs and Ys in the genotype has the advantage of reminding us that the genes are X linked and that the male must always have a single allele, inherited from the mother.

Dosage Compensation

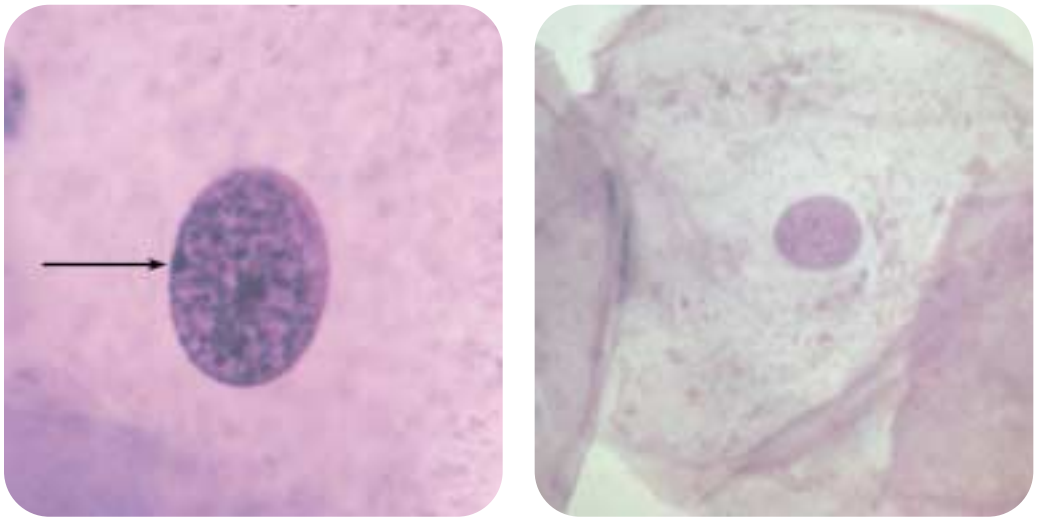
The presence of different numbers of X chromosomes in males and females presents a special problem in development. Because females have two copies of every X-linked gene and males possess one copy, the amount of gene product (protein) from X-linked genes would normally differ in the two sexes—females would produce twice as much gene product as males. This difference could be highly detrimental because protein concentration plays a critical role in development. Animals overcome this potential problem through **dosage compensation,** which equalizes the amount of protein produced by X-linked genes in the two sexes. In fruit flies, dosage compensation is achieved by a doubling of the activity of the genes on the X chromosome of the male. In the worm *Caenorhabditis elegans*, it is achieved by a halving of the activity of genes on both of the X chromosomes in the female. Placental mammals use yet another mechanism of dosage compensation; genes on one of the X chromosomes in the female are completely inactivated.

In 1949, Murray Barr observed condensed, darkly staining bodies in the nuclei of cells from female cats (FIGURE 4.17); this darkly staining structure became known as a **Barr body.** Mary Lyon proposed in 1961 that the Barr body was an inactive X chromosome; her hypothesis (now proved) has become known as the **Lyon hypothesis.** She suggested that, within each female cell, one of the two X chromosomes becomes inactive; which X chromosome is inactivated is random. If a cell contains more than two X chromosomes, all but one of them is inactivated. The number of Barr bodies present in human cells with different complements of sex chromosomes is shown in Table 4.2.

As a result of X inactivation, females are functionally hemizygous at the cellular level for X-linked genes. In females that are heterozygous at an X-linked locus, approximately 50% of the cells will express one allele and 50% will express the other allele; thus, in heterozygous females, proteins encoded by both alleles are produced, although not within the same cell. This functional hemizygosity means that cells in females are not identical with respect to the expression of the genes on the X chromosome; females are mosaics for the expression of X-linked genes.

X inactivation takes place relatively early in development—in humans, within the first few weeks of development. Once an X chromosome becomes inactive in a cell, it remains inactivated and is inactive in all somatic cells that descend from the cell. Thus, neighboring cells tend to have the same X chromosome inactivated, producing a patchy pattern (mosaic) for the expression of an X-linked characteristic in heterozygous females.

This patchy distribution can be seen in tortoiseshell cats (FIGURE 4.18). Although many genes contribute to coat color and pattern in domestic cats, a single X-linked locus determines the presence of orange color. There are possible



4.17 A Barr body is an inactivated X chromosome. (a) Female cell with a Barr body (indicated by arrow). (b) Male cell without a Barr body. (Part a, George Wilder/Visuals Unlimited; part b, M. Abbey/Photo Researchers.)

Table 4.2 Number of Barr bodies in human cells with different complements of sex chromosomes

Sex Chromosomes	Syndrome	Number of Barr Bodies
XX	None	1
XY	None	0
XO	Turner	0
XXY	Klinefelter	1
XXYY	Klinefelter	1
XXXY	Klinefelter	2
XXXXY	Klinefelter	3
XXX	Triplo-X	2
XXXX	Poly-X female	3
XXXXX	Poly-X female	4

4.18 The patchy distribution of color on tortoiseshell cats results from the random inactivation of one X chromosome in females. (David Falconer/Words & Pictures/Picture Quest.)

two alleles at this locus: X^+, which produces nonorange (usually black) fur, and X^o, which produces orange fur. Males are hemizygous and thus may be black (X^+Y) or orange (X^oY) but not black *and* orange. (Rare tortoiseshell males can arise from the presence of two X chromosomes, X^+X^oY.) Females may be black (X^+X^+), orange (X^oX^o), or tortoiseshell (X^+X^o), the tortoiseshell pattern arising from a patchy mixture of black and orange fur. Each orange patch is a clone of cells derived from an original cell with the black allele inactivated, and each black patch is a clone of cells derived from an original cell with the orange allele inactivated. The mosaic pattern of gene expression associated with dosage compensation also produces the patchy distribution of sweat glands in women heterozygous for anhidrotic ectodermal dysplasia (see introduction to this chapter).

Lyon's hypothesis suggests that the presence of variable numbers of X chromosomes should not be detrimental in mammals, because any X chromosomes beyond one should be inactivated. However, persons with Turner syndrome (XO) differ from normal females, and those with Klinefelter syndrome (XXY) differ from normal males. How do these conditions arise in the face of dosage compensation? The reason may lie partly in the fact that there is a short period of time, very early in development, when all X chromosomes are active. If the number of X chromosomes is abnormal, any X-linked genes expressed during this early period will produce abnormal levels of gene product. Furthermore, the phenotypic abnormalities may arise because some X-linked genes escape inactivation, although how they do so isn't known.

Exactly how an X chromosome becomes inactivated is not completely understood either, but it appears to entail the addition of methyl groups ($-CH_3$) to the DNA. The *XIST* (for X inactive-specific transcript) gene, located on the X chromosome, is required for inactivation. Only the copy of *XIST* on the inactivated X chromosome is expressed, and it continues to be expressed during inactivation (unlike most other genes on the inactivated X chromosome). Interestingly, *XIST* does not encode a protein; it produces an RNA molecule that binds to the inactivated X chromosome. This binding is thought to prevent the attachment of other proteins that participate in transcription and, in this way, it brings about X inactivation.

Concepts

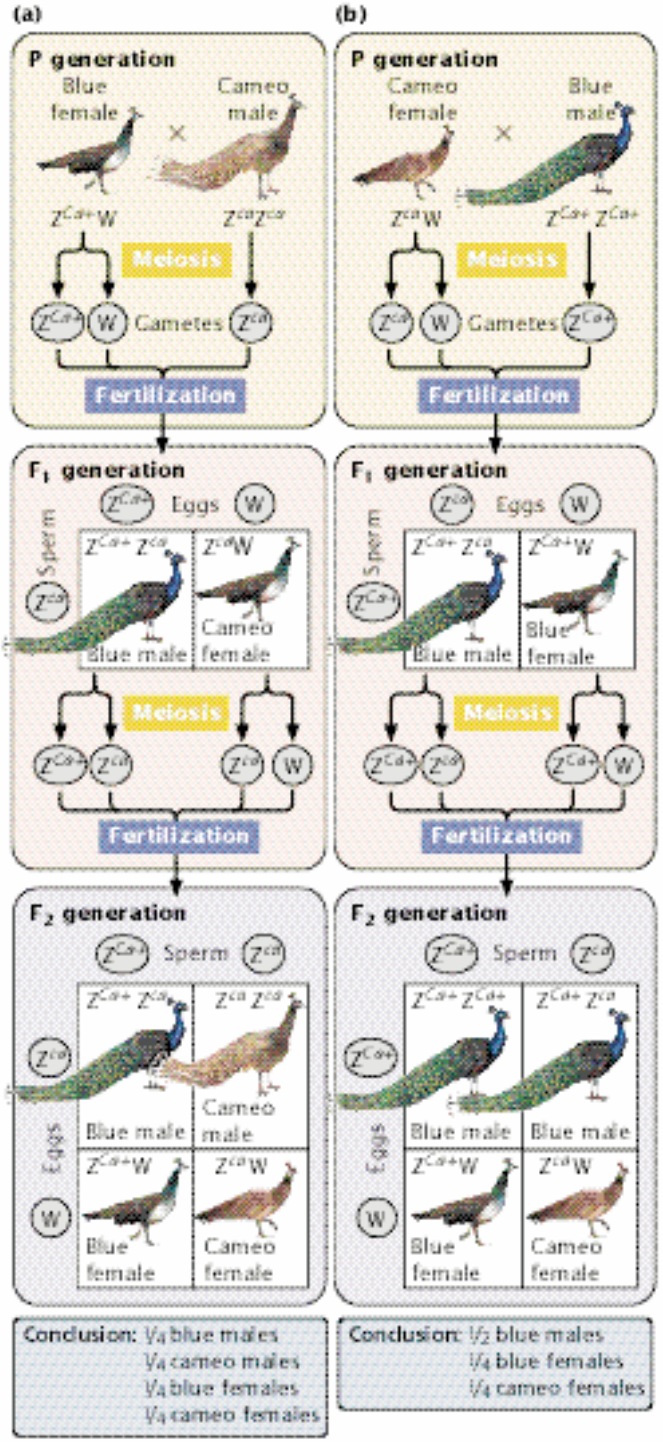
In mammals, dosage compensation ensures that the same amount of X-linked gene product will be produced in the cells of both males and females. All but one X chromosome is randomly inactivated in each cell; which X chromosome is inactivated is random and varies from cell to cell.

www.whfreeman.com/pierce Current information on *XIST* and X-chromosome inactivation in humans

Z-Linked Characteristics

In organisms with ZZ-ZW sex determination, the males are the homogametic sex (ZZ) and carry two sex-linked (usually referred to as Z-linked) alleles; thus males may be homozygous or heterozygous. Females are the heterogametic sex (ZW) and possess only a single Z-linked allele. Inheritance of Z-linked characteristics is the same as that of X-linked characteristics, except that the pattern of inheritance in males and females is reversed.

An example of a Z-linked characteristic is the cameo phenotype in Indian blue peafowl (*Pavo cristatus*). In these birds, the wild-type plumage is a glossy, metallic blue. The female peafowl is ZW and the male is ZZ. Cameo plumage, which produces brown feathers, results from a Z-linked allele (Z^{ca}) that is recessive to the wild-type blue allele (Z^{Ca+}). If a blue-colored female ($Z^{Ca+}W$) is crossed with a cameo male ($Z^{ca}Z^{ca}$), all the F_1 females are cameo ($Z^{ca}W$) and all the F_1 males are blue ($Z^{Ca+}Z^{ca}$) (FIGURE 4.19). When the F_1 are interbred, 1/4 of the F_2 are blue males ($Z^{Ca+}Z^{ca}$), 1/4 are blue females ($Z^{Ca+}W$), 1/4 are cameo males ($Z^{ca}Z^{ca}$), and 1/4 are cameo females ($Z^{ca}W$). The reciprocal cross of a cameo female with a homozygous blue male produces an F_1 generation in which all offspring are blue and an F_1 consisting of 1/2 blue males ($Z^{Ca+}Z^{ca}$ and $Z^{Ca+}Z^{Ca+}$), 1/4 blue females (Z^{Ca+} W), and 1/4 cameo females (Z^{ca} W).



4.19 Inheritance of the cameo phenotype in Indian blue peafowl is inherited as a Z-linked recessive trait. (a) Blue female crossed with cameo male. (b) Reciprocal cross of cameo female crossed with homozygous blue male.

In organisms with ZZ-ZW sex determination, the female always inherits her W chromosome from her mother, and she inherits her Z chromosome, along with any Z-linked alleles, from her father. In this system, the male inherits Z chromosomes, along with any Z-linked alleles, from both the mother and the father. This pattern of inheritance is the reverse of X-linked alleles in organisms with XX-XY sex determination.

Y-Linked Characteristics

Y-linked traits exhibit a distinct pattern of inheritance and are present only in males, because only males possess a Y chromosome. All male offspring of a male with a Y-linked trait will display the trait (provided that the penetrance—see Chapter 3—is 100%), because every male inherits the Y chromosome from his father.

In humans and many other organisms, there is relatively little genetic information on the Y chromosome, and few characteristics exhibit Y-linked inheritance. More than 20 genes have been identified outside the pseudoautosomal region on the human Y chromosome, including the *SRY* gene and the *ZFY* gene. A possible Y-linked human trait is hairy ears, a trait that is common among men in some parts of the Middle East and India, affecting as many as 70% of adult men in some regions. This trait displays variable expressivity—some men have only a few hairs on the outer ear, whereas others have ears that are covered with hair. The age at which this trait appears also is quite variable.

Only men have hairy ears and, in many families, the occurrence of the trait is entirely consistent with Y-linked inheritance. In a few families, however, not all sons of an affected man display the trait, which implies that the trait has incomplete penetrance. Some investigators have concluded that the hairy-ears trait is not Y-linked, but instead is an autosomal dominant trait expressed only in men (sex-limited expression, discussed more fully in Chapter 5). Distinguishing between a Y-linked characteristic with incomplete penetrance and an autosomal dominant characteristic expressed only in males is difficult, and the pattern of inheritance of hairy ears is consistent with both modes of inheritance.

The function of most Y-linked genes is poorly understood, but some appear to influence male sexual development

and fertility. Some Y-linked genes have counterparts on the X chromosome that encode similar proteins in females.

DNA sequences in the Y chromosome undergo mutation over time and vary among individuals. Like Y-linked traits, these variants—called genetic markers—are passed from father to son and can be used to study male ancestry. Although the markers themselves do not code for any physical traits, they can be detected with molecular methods. Much of the Y chromosome is nonfunctional; so mutations readily accumulate. Many of these mutations are unique; they arise only once and are passed down through the generations without recombination. Individuals possessing the same set of mutations are therefore related, and the distribution of these genetic markers on Y chromosomes provides clues about genetic relationships of present-day people.

Y-linked markers have been used to study the offspring of Thomas Jefferson, principal author of the Declaration of Independence and third president of the United States. In 1802, Jefferson was accused by a political enemy of fathering a child by his slave Sally Hemings, but the evidence was circumstantial. Hemings, who worked in the Jefferson household and accompanied Jefferson on a trip to Paris, had five children. Jefferson was accused of fathering the first child, Tom, but rumors about the paternity of the other children circulated as well. Hemings's last child, Eston, bore a striking resemblance to Jefferson, and her fourth child, Madison, testified late in life that Jefferson was the father of all Hemings's children. Ancestors of Hemings's children maintained that they were descendants of the Jefferson line, but some Jefferson descendants refused to recognize their claim.

To resolve this long-standing controversy, geneticists examined markers from the Y chromosomes of male-line descendants of Hemings's first son (Thomas Woodson), her last son (Eston Hemings), and a paternal uncle of Thomas Jefferson with whom Jefferson had Y chromosomes in common. (Descendants of Jefferson's uncle were used because Jefferson himself had no verified male descendants.) Geneticists determined that Jefferson possessed a rare and distinctive set of genetic markers on his Y chromosome. The same markers were also found on the Y chromosomes of the male-line descendants of Eston Hemings. The probability of such a match arising by chance is less than 1%. (The markers were not found on the Y chromosomes of the descendants of Thomas Woodson.) Together with the circumstantial historical evidence, these matching markers strongly suggest that Jefferson fathered Eston Hemings but not Thomas Woodson.

Another study utilizing Y-linked genetic markers focused on the origins of the Lemba, an African tribe comprising 50,000 people who reside in South Africa and parts of Zimbabwe. Members of the Lemba tribe are commonly referred to as the black Jews of South Africa. This name derives from cultural practices of the tribe, including circumcision and food taboos, which superficially resemble those of Jewish people. Lemba oral tradition suggests that the tribe came from "Sena in the north by boat," Sena being variously identified as Sanaa in Yemen, Judea, Egypt, or Ethiopia. Legend says that the original group was entirely male, that half of their number was lost at sea, and that the survivors made their way to the coast of Africa, where they settled.

Today, most Lemba belong to Christian churches, are Muslims, or claim to be Lemba in religion. Their religious practices have little in common with Judaism and, with the exception of their oral tradition and a few cultural practices, there is little to suggest a Jewish origin.

To reveal the genetic origin of the Lemba, scientists examined genetic markers on their Y chromosomes. Swabs of cheek cells were collected from 399 males in several populations: the Lemba in Africa, Bantu (another South African tribe), two groups from Yemen, and several groups of Jews. DNA was extracted and analyzed for alleles at 12 loci. This analysis of genetic markers revealed that Y chromosomes in the Lemba were of two types: those of Bantu origin and those similar to chromosomes found in Jewish and Yemen populations. Most importantly, members of one Lemba clan carried a large number of Y chromosomes that had a rare combination of alleles also found on the Y chromosomes of members of the Jewish priesthood. This set of alleles is thought to be an important indicator of Judaic origin. These findings are consistent with the Lemba oral tradition and strongly suggest a genetic contribution from Jewish populations.

Concepts

Y-linked characteristics exhibit a distinct pattern of inheritance: they are present only in males, and all male offspring of a male with a Y-linked trait inherit the trait.

www.whfreeman.com/pierce An over overview of the use of Y-linked markers in studies of ancestry

Connecting Concepts

Recognizing Sex-linked Inheritance

What features should we look for to identify a trait as sex linked? A common misconception is that any genetic characteristic in which the phenotypes of males and females differ must be sex linked. In fact, the expression of many *autosomal* characteristics differs between males and females. The genes that code for these characteristics are the same in both sexes, but their expression is influenced by sex hormones. The different sex hormones of males and females cause the same genes to generate different phenotypes in males and females.

Another misconception is that any characteristic that is found more frequently in one sex is sex linked. A number of

autosomal traits are expressed more commonly in one sex than in the other, because the penetrance of the trait differs in the two sexes; these traits are said to be sex influenced. For some autosomal traits, the penetrance in one sex is so low that the trait is expressed in only one sex; these traits are said to be sex limited. Both sex-influenced and sex-limited characteristics will be discussed in more detail in Chapter 5.

Several features of sex-linked characteristics make them easy to recognize. Y-linked traits are found only in males, but this fact does not guarantee that a trait is Y linked, because some autosomal characteristics are expressed only in males. A Y-linked trait is unique, however, in that all the male offspring of an affected male will express the father's phenotype, provided the penetrance of the trait is 100%. This need not be the case for autosomal traits that are sex-limited to males. Even when the penetrance is less than 100%, a Y-linked trait can be inherited only from the father's side of the family. Thus, a Y-linked trait can be inherited only from the paternal grandfather (the father's father), never from the maternal grandfather (the mother's father).

X-linked characteristics also exhibit a distinctive pattern of inheritance. X linkage is a possible explanation when the results of reciprocal crosses differ. If a characteristic is X linked, a cross between an affected male and an unaffected female will not give the same results as a cross between an affected female and an unaffected male. For almost all autosomal characteristics, the results of reciprocal crosses are the same. We should not conclude, however, that, when the reciprocal crosses give different results, the characteristic is X linked. Other sex-associated forms of inheritance, discussed in Chapter 5, also produce different results in reciprocal crosses. The key to recognizing X-linked inheritance is to remember that a male always inherits his X chromosome from his mother, not from his father. Thus, an X-linked characteristic is not passed directly from father to son; if a male clearly inherits a characteristic from his father—and the mother is not heterozygous—it cannot be X linked.

Connecting Concepts Across Chapters

In this chapter, we have examined sex determination and the inheritance of traits encoded by genes located on the sex chromosomes. An important theme has been that sex is determined in a variety of different ways—not all organisms have the familiar XX-XY system seen in humans. Even among organisms with XX-XY sex determination, the sexual phenotype of an individual can be shaped by very different mechanisms.

The discussion of sex determination lays the foundation for an understanding of sex-linked inheritance, covered in the last part of the chapter. Because males and females differ in sex chromosomes, which are not homologous, they do not possess the same number of alleles at sex-linked loci, and the patterns of inheritance for sex-linked characteristics are different from those for autosomal characteristics. This material augments the principles of inheritance presented in Chapter 3. The chromosome theory of inheritance, which states that genes are located on chromosomes, was first elucidated through the study of sex-linked traits. This theory provided the first clues about the physical basis of heredity, which we will explore in more detail in Chapters 10 and 11.

The ways in which sex and heredity interact are explored further in Chapter 5, where we consider additional exceptions to Mendel's principles, including sex-limited and sex-influenced traits, cytoplasmic inheritance, genetic maternal effect, and genomic imprinting. The inheritance of human sex-linked characteristics will be discussed in Chapter 6, and we will take a more detailed look at chromosome abnormalities, including abnormal sex chromosomes, in Chapter 9.

CONCEPTS SUMMARY

- Sexual reproduction is the production of offspring that are genetically distinct from the parents. Among diploid eukaryotes, sexual reproduction consists of two processes: meiosis, which produces haploid gametes, and fertilization, in which gametes unite to produce diploid zygotes.
- Most organisms have two sexual phenotypes—males and females. Males produce small gametes; females produce large gametes. The sex of an individual normally refers to the individual's sexual phenotype, not its genetic makeup.
- The mechanism by which sex is specified is termed sex determination. Sex may be determined by differences in specific chromosomes, ploidy level, genotypes, or environment.
- Sex chromosomes differ in number and appearance between males and females; other, nonsex chromosomes are termed autosomes. In organisms with chromosomal sex-determining systems, the homogametic sex produces gametes that are all identical with regard to sex chromosomes; the heterogametic sex produces two types of gametes, which differ in their sex-chromosome composition.
- In the XX-XO system, females possess two X chromosomes, and males possess a single X chromosome.
- In the XX-XY system, females possess two X chromosomes, and males possess a single X and a single Y chromosome. The X and Y chromosomes are not homologous, except at

the pseudoautosomal region, which is essential to pairing in meiosis in males.

- In the ZZ-ZW system of sex determination, males possess two Z chromosomes and females possess an L_Z and a L_W chromosome.
- In some organisms, ploidy level determines sex; males develop from unfertilized eggs (and are haploid) and females develop from fertilized eggs (and are diploid). Other organisms have genic sex determination, in which genotypes at one or more loci determine the sex of an individual. Still others have environmental sex determination.
- In *Drosophila melanogaster*, sex is determined by a balance between genes on the X chromosomes and genes on the autosomes, the X:A ratio. An X:A ratio of 1.0 produces a female; an X:A ratio of 0.5 produces a male; and an X:A ratio between 1.0 and 0.5 produces an intersex.
- In humans, sex is ultimately determined by the presence or absence of the *SRY* gene located on the Y chromosome.
- Sex-linked characteristics are determined by genes on the sex chromosomes; X-linked characteristics are encoded by genes on the X chromosome, and Y-linked characteristics are encoded by genes on the Y chromosome.
- A female inherits X-linked alleles from both parents; a male inherits X-linked alleles from his female parent only.

IMPORTANT TERMS

sex (p. 78)
sex determination (p. 78)
hermaphroditism (p. 78)
monoecious (p. 78)
dioecious (p. 78)
sex chromosomes (p. 79)
autosomes (p. 79)
heterogametic sex (p. 79)
homogametic sex (p. 79)
pseudoautosomal region (p. 80)
genic sex determination (p. 81)
sequential hermaphroditism (p. 81)
genic balance system (p. 81)
X:A ratio (p. 81)
Turner syndrome (p. 82)
Klinefelter syndrome (p. 83)
triplo-X syndrome (p. 83)
sex-determining region Y (*SRY*) gene (p. 84)
sex-linked characteristic (p. 85)
X-linked characteristic (p. 85)
Y-linked characteristic (p. 85)
hemizygous (p. 86)
nondisjunction (p. 86)
dosage compensation (p. 90)
Barr body (p. 90)
Lyon hypothesis (p. 90)

Worked Problems

1. A fruit fly has XXXYY sex chromosomes; all the autosomal chromosomes are normal. What sexual phenotype will this fly have?

• Solution

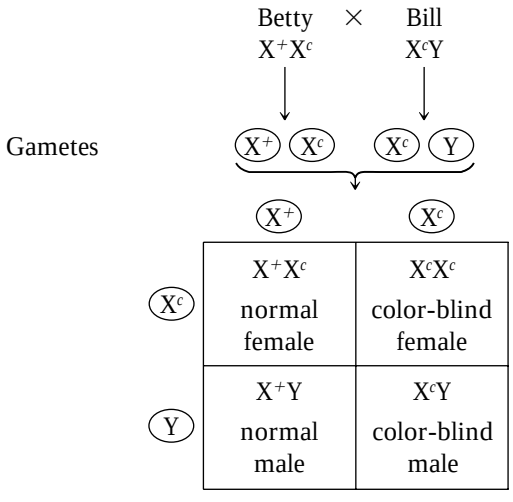
Sex in fruit flies is determined by the X:A ratio—the ratio of the number of X chromosomes to the number of haploid autosomal sets. An X:A ratio of 1.0 produces a female fly; an X:A ratio of 0.5 produces a male. If the X:A ratio is greater than 1.0, the fly is a metafemale; if it is less than 0.5, the fly is a metamale; if the X:A ratio is between 1.0 and 0.5, the fly is an intersex.

This fly has three X chromosomes and normal autosomes. Normal diploid flies have two autosomal sets of chromosomes; so the X:A ratio in this case is $\frac{3}{2}$ or 1.5. Thus, this fly is a metafemale.

2. Color blindness in humans is most commonly due to an X-linked recessive allele. Betty has normal vision, but her mother is color blind. Bill is color blind. If Bill and Betty marry and have a child together, what is the probability that the child will be color blind?

• Solution

Because color blindness is an X-linked recessive characteristic, Betty's color-blind mother must be homozygous for the color-blind allele (X^cX^c). Females inherit one X chromosome from each of their parents; so Betty must have inherited a color-blind allele from her mother. Because Betty has normal color vision, she must have inherited an allele for normal vision (X^+) from her father; thus Betty is heterozygous (X^+X^c). Bill is color blind. Because males are hemizygous for X-linked alleles, he must be (X^cY). A mating between Betty and Bill is represented as:

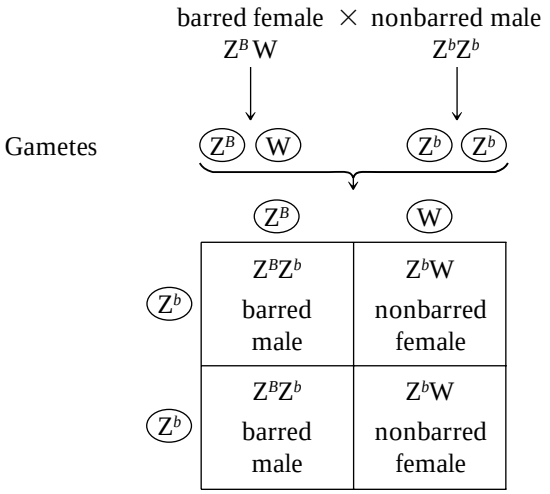


Thus, $\frac{1}{4}$ of the children are expected to be female with normal color vision, $\frac{1}{4}$ female with color blindness, $\frac{1}{4}$ male with normal color vision, and $\frac{1}{4}$ male with color blindness.

3. Chickens, like all birds, have ZZ-ZW sex determination. The bar-feathered phenotype in chickens results from a Z-linked allele that is dominant over the allele for nonbar feathers. A barred female is crossed with a nonbarred male. The F_1 from this cross are intercrossed to produce the F_2. What will the phenotypes and their proportions be in the F_1 and F_2 progeny?

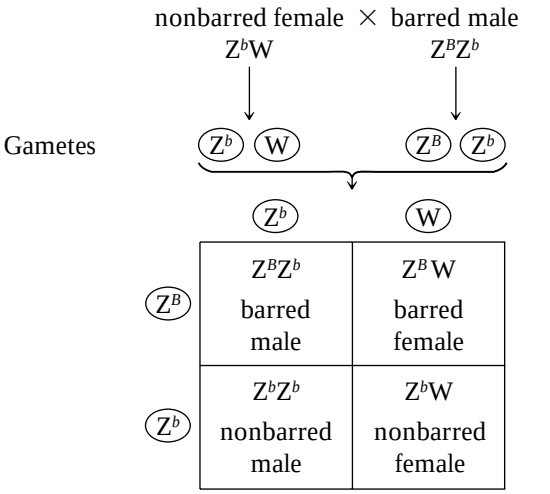
• Solution

With the ZZ-ZW system of sex determination, females are the heterogametic sex, possessing a Z chromosome and a W chromosome; males are the homogametic sex, with two Z chromosomes. In this problem, the barred female is hemizygous for the bar phenotype (Z^BW). Because bar is dominant over nonbar, the nonbarred male must be homozygous for nonbar (Z^bZ^b). Crossing these two chickens, we obtain:



Thus, all the males in the F_1 will be barred (Z^BZ^b), and all the females will be nonbarred (Z^bW).

The F_1 are now crossed to produce the F_2:



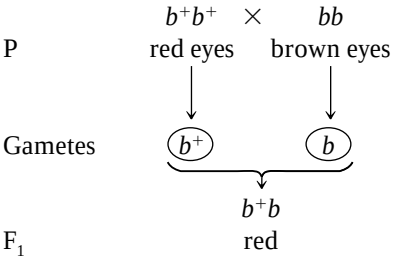
So, ¼ of the F_2 are barred males, ¼ are nonbarred males, ¼ are barred females, and ¼ are nonbarred females.

4. In *Drosophila melanogaster*, forked bristles are caused by an allele (X^f) that is X linked and recessive to an allele for normal bristles (X^+). Brown eyes are caused by an allele (*b*) that is autosomal and recessive to an allele for red eyes (b^+). A female fly that is homozygous for normal bristles and red eyes mates with a male fly that has forked bristles and brown eyes. The F_1 are intercrossed to produce the F_2. What will the phenotypes and proportions of the F_2 flies be from this cross?

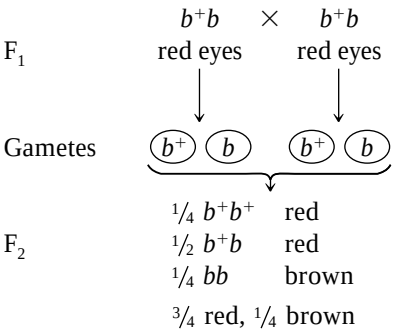
• Solution

This problem is best worked by breaking the cross down into two separate crosses, one for the X-linked genes that determine the type of bristles and one for the autosomal genes that determine eye color.

Let's begin with the autosomal characteristics. A female fly that is homozygous for red eyes (b^+b^+) is crossed with a male with brown eyes. Because brown eyes are recessive, the male fly must be homozygous for the brown-eyed allele (*bb*). All of the offspring of this cross will be heterozygous (b^+b) and will have brown eyes:

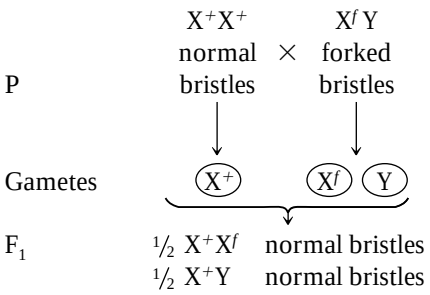


The F_1 are then intercrossed to produce the F_2. Whenever two individuals heterozygous for an autosomal recessive characteristic are crossed, ¾ of the offspring will have the dominant trait and ¼ will have the recessive trait; thus, ¾ of the F_2 flies will have red eyes and ¼ will have brown eyes:

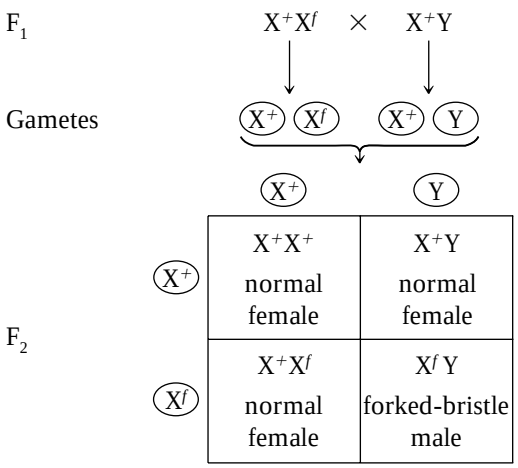


Next, we work out the results for the X-linked characteristic. A female that is homozygous for normal bristles (X^+X^+) is crossed with a male that has forked bristles (X^fY). The female F_1 from this cross are heterozygous (X^+X^f), receiving an X chromosome with a normal-bristle allele from their mother (X^+) and an X chromosome with a forked-bristle allele (X^f) from their father. The male F_1 are hemizygous (X^+Y), receiving an X

chromosome with a normal-bristle allele from their mother (X^+) and a Y chromosome from their father:

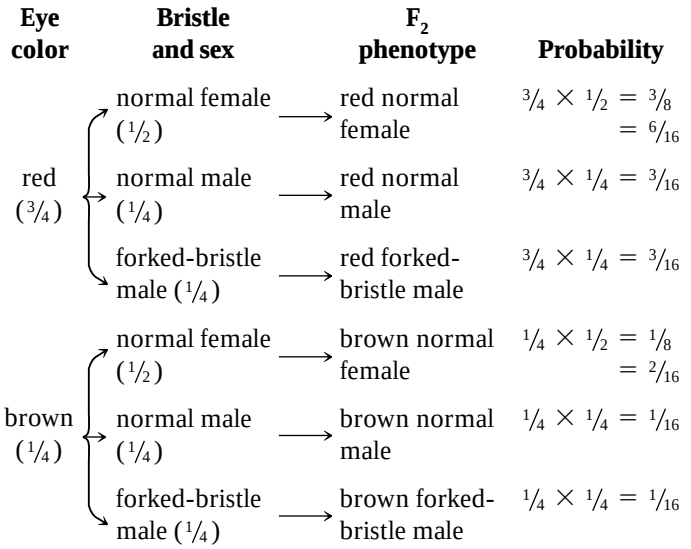


When these F_1 are intercrossed, ½ of the F_2 will be normal-bristle females, ¼ will be normal-bristle males, and ¼ will be forked-bristle males:



½ normal female, ¼ normal male, ¼ forked bristle male

To obtain the phenotypic ratio in the F_2, we now combine these two crosses by using the multiplicative rule of probability and the branch diagram:



COMPREHENSION QUESTIONS

* 1. What is the most defining difference between males and females?

2. How do monoecious organisms differ from dioecious organisms?

3. Describe the XX-XO system of sex determination. In this system, which is the heterogametic sex and which is the homogametic sex?

4. How does sex determination in the XX-XY system differ from sex determination in the ZZ-ZW system?

* 5. What is the pseudoautosomal region? How does the inheritance of genes in this region differ from the inheritance of other Y-linked characteristics?

* 6. How is sex determined in insects with haplodiploid sex determination?

7. What is meant by genic sex determination?

8. How does sex determination in *Drosophila* differ from sex determination in humans?

9. Give the typical sex chromosomes found in the cells of people with Turner syndrome, Klinefelter syndrome, and androgen insensitivity syndrome, as well as in poly-X females.

* 10. What characteristics are exhibited by an X-linked trait?

11. Explain how Bridges's study of nondisjunction in *Drosophila* helped prove the chromosome theory of inheritance.

12. Explain why tortoiseshell cats are almost always female and why they have a patchy distribution of orange and black fur.

13. What is a Barr body? How is it related to the Lyon hypothesis?

* 14. What characteristics are exhibited by a Y-linked trait?

APPLICATION QUESTIONS AND PROBLEMS

*15. What is the sexual phenotype of fruit flies having the following chromosomes?

	Sex chromosomes	Autosomal chromosomes
(a)	XX	all normal
(b)	XY	all normal
(c)	XO	all normal
(d)	XXY	all normal
(e)	XYY	all normal
(f)	XXYY	all normal
(g)	XXX	all normal
(h)	XX	four haploid sets
(i)	XXX	four haploid sets
(j)	XXX	three haploid sets
(k)	X	three haploid sets
(l)	XY	three haploid sets
(m)	XX	three haploid sets

16. For parts *a* through *g* in problem 15 what would the human sexual phenotype (male or female) be?

*17. Joe has classic hemophilia, which is an X-linked recessive disease. Could Joe have inherited the gene for this disease from the following persons?

	Yes	No
(a) His mother's mother	____	____
(b) His mother's father	____	____
(c) His father's mother	____	____
(d) His father's father	____	____

*18. In *Drosophila*, yellow body is due to an X-linked gene that is recessive to the gene for gray body.

(a) A homozygous gray female is crossed with a yellow male. The F_1 are intercrossed to produce F_2. Give the genotypes and phenotypes, along with the expected proportions, of the F_1 and F_2 progeny.

(b) A yellow female is crossed with a gray male. The F_1 are intercrossed to produce the F_2. Give the genotypes and phenotypes, along with the expected proportions, of the F_1 and F_2 progeny.

(c) A yellow female is crossed with a gray male. The F_1 females are backcrossed with gray males. Give the genotypes and phenotypes, along with the expected proportions, of the F_2 progeny.

(d) If the F_2 flies in part b mate randomly, what are the expected phenotypic proportions of flies in the F_3?

*19. Both John and Cathy have normal color vision. After 10 years of marriage to John, Cathy gave birth to a color-blind daughter. John filed for divorce, claiming he is not the father of the child. Is John justified in his claim of nonpaternity? Explain why. If Cathy had given birth to a color-blind son, would John be justified in claiming nonpaternity?

20. Red–green color blindness in humans is due to an X-linked recessive gene. A woman whose father is color blind possesses one eye with normal color vision and one eye with color blindness.

(a) Propose an explanation for this woman's vision pattern.

(b) Would it be possible for a man to have one eye with normal color vision and one eye with color blindness?

*21. Bob has XXY chromosomes (Klinefelter syndrome) and is color blind. His mother and father have normal color vision, but his maternal grandfather is color blind. Assume that Bob's chromosome abnormality arose from nondisjunction in meiosis. In which parent and in which meiotic division did nondisjunction occur? Explain your answer.

22. In certain salamanders, it is possible to alter the sex of a genetic female, making her into a functional male; these salamanders are called sex-reversed males. When a sex-reversed male is mated with a normal female, approximately $^2/_3$ of the offspring are female and $^1/_3$ are male. How is sex determined in these salamanders? Explain the results of this cross.

23. In some mites, males pass genes to their grandsons, but they never pass genes to male offspring. Explain.

24. The Talmud, an ancient book of Jewish civil and religious laws, states that if a woman bears two sons who die of bleeding after circumcision (removal of the foreskin from the penis), any additional sons that she has should not be circumcised. (The bleeding is most likely due to the X-linked disorder hemophilia.) Furthermore, the Talmud states that the sons of her sisters must not be circumcised, whereas the sons of her brothers should. Is this religious law consistent with sound genetic principles? Explain your answer.

*25. Miniature wings (X^m) in *Drosophila* result from an X-linked allele that is recessive to the allele for long wings (X^+). Give the genotypes of the parents in the following crosses.

	Male parent	Female parent	Male offspring	Female offspring
(a)	long	long	231 long, 250 miniature	560 long
(b)	miniature	long	610 long	632 long
(c)	miniature	long	410 long, 417 miniature	412 long, 415 miniature
(d)	long	miniature	753 miniature	761 long
(e)	long	long	625 long	630 long

*26. In chickens, congenital baldness results from a Z-linked recessive gene. A bald rooster is mated with a normal hen.

The F_1 from this cross are interbred to produce the F_2. Give the genotypes and phenotypes, along with their expected proportions, among the F_1 and F_2 progeny.

27. In the eastern mosquito fish *(Gambusia affinis holbrooki)*, which has XX-XY sex determination, spotting is inherited as a Y-linked trait. The trait exhibits 100% penetrance when the fish are raised at 22°C, but the penetrance drops to 42% when the fish are raised at 26°C. A male with spots is crossed with a female without spots, and the F_1 are intercrossed to produce the F_2. If all the offspring are raised at 22°C, what proportion of the F_1 and F_2 will have spots? If all the offspring are raised at 26°C, what proportion of the F_1 and F_2 will have spots?

*28. How many Barr bodies would you expect to see in human cells containing the following chromosomes?

(a) XX **(d)** XXY **(g)** XYY
(b) XY **(e)** XXYY **(h)** XXX
(c) XO **(f)** XXXY **(i)** XXXX

29. Red–green color blindness is an X-linked recessive trait in humans. Polydactyly (extra fingers and toes) is an autosomal dominant trait. Martha has normal fingers and toes and normal color vision. Her mother is normal in all respects, but her father is color blind and polydactylous. Bill is color blind and polydactylous. His mother has normal color vision and normal fingers and toes. If Bill and Martha marry, what types and proportions of children can they produce?

*30. Miniature wings in *Drosophila melanogaster* result from an X-linked gene (X^m) that is recessive to an allele for long wings (X^+). Sepia eyes are produced by an autosomal gene (s) that is recessive to an allele for red eyes (s^+).

(a) A female fly that has miniature wings and sepia eyes is crossed with a male that has normal wings and is homozygous for red eyes. The F_1 are intercrossed to produce the F_2. Give the phenotypes and their proportions expected in the F_1 and F_2 flies from this cross.

(b) A female fly that is homozygous for normal wings and has sepia eyes is crossed with a male that has miniature wings and is homozygous for red eyes. The F_1 are intercrossed to produce the F_2. Give the phenotypes and proportions expected in the F_1 and F_2 flies from this cross.

31. Suppose that a recessive gene that produces a short tail in mice is located in the pseudoautosomal region. A short-tailed male is mated with a female mouse that is homozygous for a normal tail. The F_1 from this cross are intercrossed to produce the F_2. What will the phenotypes and proportions of the F_1 and F_2 mice be from this cross?

*32. A color-blind female and a male with normal vision have three sons and six daughters. All the sons are color blind. Five of the daughters have normal vision, but one of them is color blind. The color-blind daughter is 16 years old, is short for her age, and has never undergone puberty. Propose an explanation for how this girl inherited her color blindness.

CHALLENGE QUESTIONS

33. On average, what proportion of the X-linked genes in the first individual is the same as that in the second individual?

(a) A male and his mother
(b) A female and her mother
(c) A male and his father
(d) A female and her father
(e) A male and his brother
(f) A female and her sister
(g) A male and his sister
(h) A female and her brother

34. A geneticist discovers a male mouse in his laboratory colony with greatly enlarged testes. He suspects that this trait results from a new mutation that is either Y linked or autosomal dominant. How could he determine whether the trait is autosomal dominant or Y linked?

35. Amanda is a genetics student at a small college in Connecticut. While counting her fruit flies in the laboratory one afternoon, she observed a strange species of fly in the room. Amanda captured several of the flies and began to raise them. After having raised the flies for several generations, she discovered a mutation in her colony that produces yellow eyes, in contrast with normal red eyes, and Amanda determined that this trait is definitely X-linked recessive. Because yellow eyes are X linked, she assumed that either this species has the XX-XY system of sex determination with genic balance similar to *Drosophila* or it has the XX-XO system of sex determination.

How can Amanda determine whether sex determination in this species is XX-XY or XX-XO? The chromosomes of this species are very small and hard for Amanda to see with her student microscope, so she can only conduct crosses with flies having the yellow-eye mutation. Outline the crosses that Amanda should conduct and explain how they will prove XX-XY or XX-XO sex determination in this species.

36. Occasionally, a mouse X chromosome is broken into two pieces and each piece becomes attached to a different autosomal chromosome. In this event, only the genes on one of the two pieces undergo X inactivation. What does this observation indicate about the mechanism of X-chromosome inactivation?

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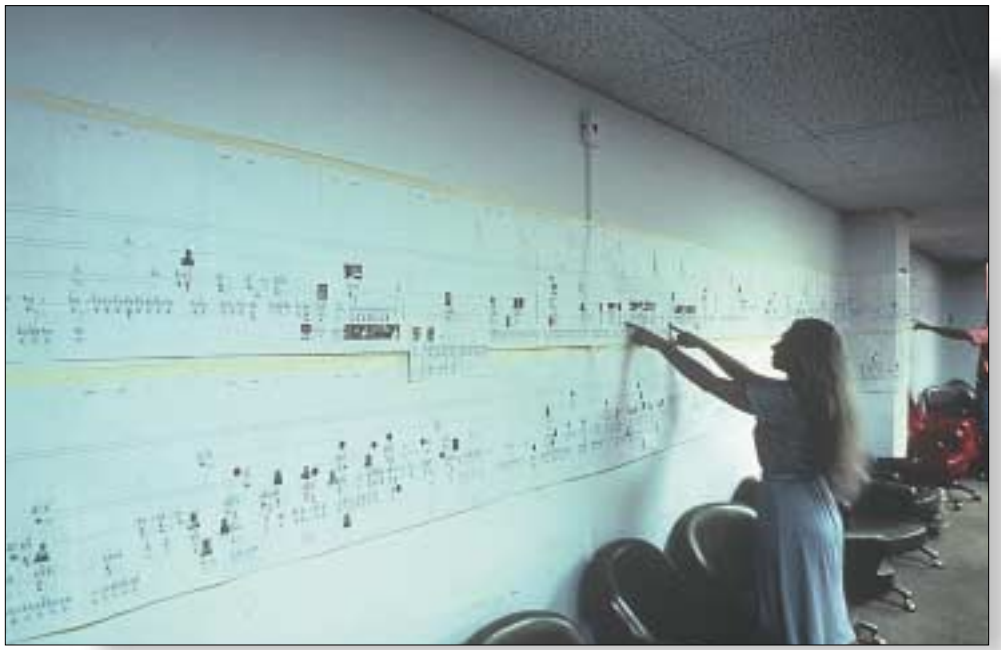
5 Extensions and Modifications of Basic Principles

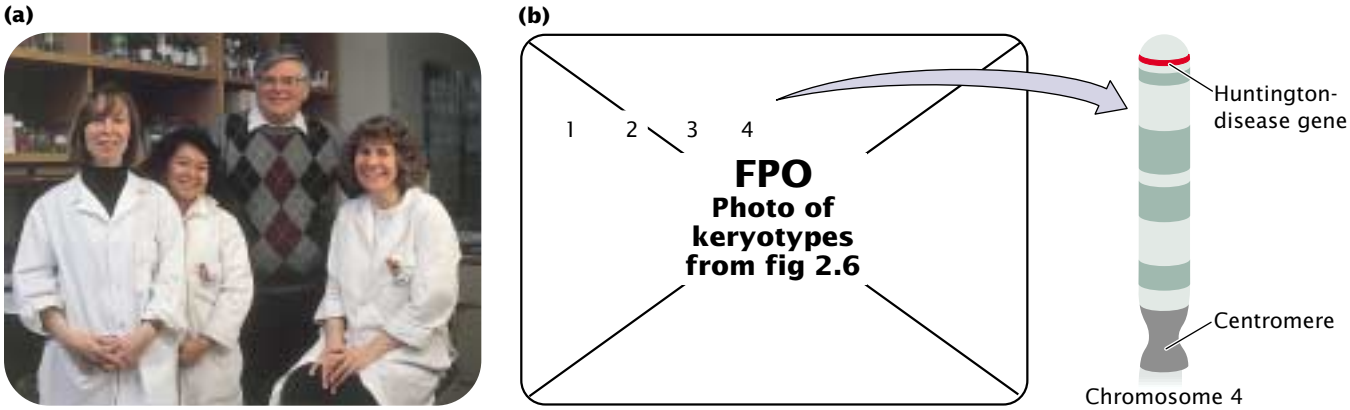


This is Chapter 5 Opener photo legend to position here. (Nancy Wexler, HDF/Neurology, Columbia University.)

Was Mendel Wrong?

In 1872, a physician from Long Island, New York named George Huntington described a medical condition characterized by jerky, involuntary movements. Now known as Huntington disease, the condition typically appears in middle age. The initial symptoms are subtle, consisting of mild behavioral and neurological changes; but, as the disease progresses, speech is impaired, walking becomes difficult, and psychiatric problems develop that frequently lead to insanity. Most people who have Huntington disease live for 10 to 30 years after the disease begins; there is currently no cure or effective treatment.

Huntington disease appears with equal frequency in males and females, rarely skips generations and, when one parent has the disorder, approximately half of the children will be similarly affected. These are the hallmarks of an autosomal dominant trait—with one exception. The disorder occasionally arises before the age of 15 and, in these cases, progresses much more rapidly than it does when it arises in middle age. Among younger patients, the trait is almost always inherited from the father. According to Mendel's principles of heredity (Chapter 3), males and females transmit autosomal traits with equal frequency, and reciprocal crosses should yield identical results; yet, for juvenile cases of Huntington



5.1 The gene for Huntington disease. (a) James Gusella and colleagues, whose research located the Huntington gene. (b) The gene has been mapped to the tip of chromosome 4. (Part a, Sam Ogden; part b, left courtesy of Dr. Thomas Ried and Dr. Evelin Schrock.)

disease, Mendel's principles do not apply. Was Mendel wrong?

In 1983, a molecular geneticist at Massachusetts General Hospital named James Gusella determined that the gene causing Huntington disease is located near the tip of the short arm of chromosome 4. Gusella determined its location by analyzing DNA from members of the largest known family with Huntington disease, about 7000 people who live near Lake Maracaibo in Venezuela, more than 100 of whom have Huntington disease. Many experts predicted that, with the general location of the Huntington gene pinned down, the actual DNA sequence would be isolated within a few years. Despite intensive efforts, finding the gene took 10 years. When it was finally isolated in the spring of 1993 (**Figure 5.1**), the gene turned out to be quite different from any of those that code for the traits studied by Mendel.

The mutation that causes Huntington disease consists of an unstable region of DNA capable of expanding and contracting as it is passed from generation to generation. When the region expands, Huntington disease results. The degree of expansion affects the severity and age of onset of symptoms; the juvenile form of Huntington disease results from rapid expansion of the region, which occurs primarily when the gene is transmitted from father to offspring.

This genetic phenomenon—the earlier appearance of a trait as it is passed from generation to generation—is called anticipation. Like a number of other genetic phenomena, anticipation does not adhere to Mendel's principles of heredity. This lack of adherence doesn't mean that Mendel was wrong; rather, it means that Mendel's principles are not, by themselves, sufficient to explain the inheritance of all genetic characteristics. Our modern understanding of genetics has been greatly enriched by the discovery of a number of modifications and extensions of Mendel's basic principles, which are the focus of this chapter.

An important extension of Mendel's principles of heredity—the inheritance of sex-linked characteristics—was introduced in Chapter 4. In this chapter, we will examine a number of additional refinements of Mendel's basic tenets. We begin by reviewing the concept of dominance, emphasizing that dominance entails interactions between genes at one locus (allelic genes) and affects the way in which genes are expressed in the phenotype. Next, we consider lethal alleles and their effect on phenotypic ratios, followed by a discussion of multiple alleles. We then turn to interaction among genes at different loci (nonallelic genes). The phenotypic ratios produced by gene interaction are related to the ratios encountered in Chapter 3. In the latter part of the chapter, we will consider ways in which sex interacts with heredity. Our last stop will be a discussion of environmental influences on gene expression.

The modifications and extensions of hereditary principles discussed in this chapter do not invalidate Mendel's important contributions; rather, they enlarge our understanding of heredity by building on the framework provided by his principles of segregation and independent assortment. These modifications rarely alter the way in which the genes are inherited; rather, they affect the ways in which the genes determine the phenotype.

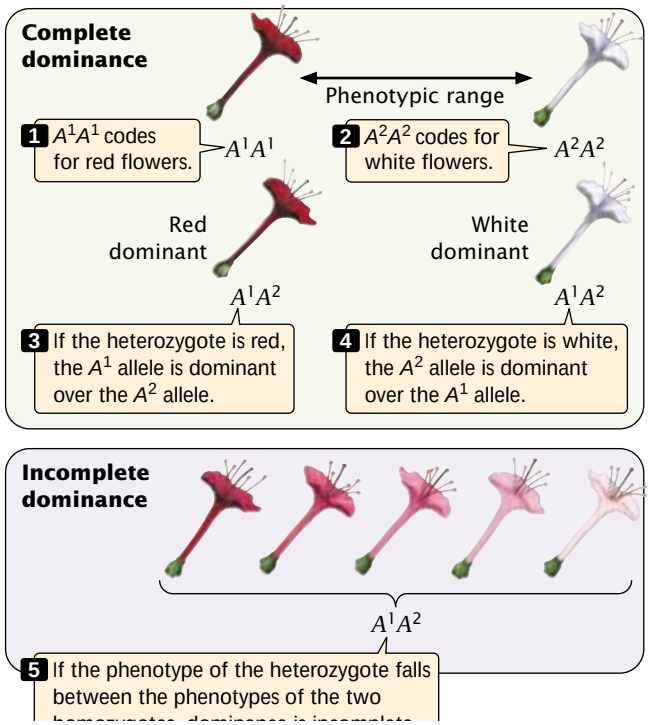
www.whfreeman.com/pierce Additional information about Huntington disease

Dominance Revisited

One of Mendel's important contributions to the study of heredity is the concept of *dominance*—the idea that an individual possesses two different alleles for a characteristic, but the trait enclosed by only one of the alleles is observed in the phenotype. With dominance, the heterozygote possesses the same phenotype as one of the homozygotes. When biologists began to apply Mendel's principles to organisms other then peas, it quickly became apparent that many characteristics do not exhibit this type of dominance. Indeed, Mendel

himself was aware that dominance is not universal, because he observed that a pea plant heterozygous for long and short flowering times had a flowering time that was intermediate between those of its homozygous parents. This situation, in which the heterozygote is intermediate in phenotype between the two homozygotes, is termed *incomplete dominance.*

Dominance can be understood in regard to how the phenotype of the heterozygote relates to the phenotypes of the homozygotes. In the example presented in FIGURE 5.2, flower color potentially ranges from red to white. One homozygous genotype, A^1A^1, codes for red flowers, and another, A^2A^2, codes for white flowers. Where the heterozygote falls on the range of phenotypes determines the type of dominance. If the heterozygote (A^1A^2) has flowers that are the same color as those of the A^1A^1 homozygote (red), then the A^1 allele is *completely dominant* over the A^2 allele; that is, red is dominant over white. If, on the other hand, the heterozygote has flowers that are the same color as the A^2A^2 homozygote (white), then the A^2 allele is completely dominant, and white is dominant over red. When the heterozygote falls in between the phenotypes of the two homozygotes, dominance is incomplete. With incomplete dominance, the heterozygote need not be exactly intermediate (pink in our example) between the two homozygotes; it might be a slightly lighter shade of red or a slightly pink shade of white. As long as the heterozygote's phenotype can be differentiated and falls within the range of the two homozygotes, dominance is incomplete. The important thing to remember about dominance is that it affects the phenotype that genes produce, but not the way in which genes are *inherited.*



5.2 The type of dominance exhibited by a trait depends on how the phenotype of the heterozygote relates to the phenotypes of the homozygotes.

Table 5.1 Differences between dominance, incomplete dominance, and codominance

Type of Dominance	Definition
Dominance	Phenotype of the heterozygote is the same as the phenotype of one of the homozygotes
Incomplete dominance	Phenotype of the heterozygote is intermediate (falls within the range) between the phenotypes of the two homozygotes
Codominance	Phenotype of the heterozygote includes the phenotypes of both homozygotes

Another type of interaction between alleles is **codominance,** in which the phenotype of the heterozygote is not intermediate between the phenotypes of the homozygotes; rather, the heterozygote simultaneously expresses the phenotypes of both homozygotes. An example of codominance is seen in the MN blood types.

The MN locus codes for one of the types of antigens on red blood cells. Unlike antigens foreign to the ABO and Rh blood groups (which also code for red-blood-cell antigens), foreign MN antigens do not elicit a strong immunological reaction, and therefore the MN blood types are not routinely considered in blood transfusions. At the MN locus, there are two alleles: the L^M allele, which codes for the M antigen; and the L^N allele, which codes for the N antigen. Homozygotes with genotype L^ML^M express the M antigen on their red blood cells and have the M blood type. Homozygotes with genotype L^NL^N express the N antigen and have the N blood type. Heterozygotes with genotype L^ML^N exhibit codominance and express both the M and the N antigens; they have blood type MN. The differences between dominance, incomplete dominance, and codominance are summarized in Table 5.1.

The type of dominance that a character exhibits frequently depends on the level of the phenotype examined. An example is cystic fibrosis, one of the more common genetic disorders found in Caucasians and usually considered to be a recessive disease. People who have cystic fibrosis produce large quantities of thick, sticky mucus, which plugs up the airways of the lungs and clogs the ducts leading from the pancreas to the intestine, causing frequent respiratory infections and digestive problems. Even with medical treatment, patients with cystic fibrosis suffer chronic, life-threatening medical problems.

The gene responsible for cystic fibrosis resides on the long arm of chromosome 7. It encodes a protein termed *cystic fibrosis transmembrane conductance regulator*, mercifully abbreviated CFTR, which acts as a gate in the cell membrane and regulates the movement of chloride ions into and out of the cell. Patients with cystic fibrosis have a mutated, dysfunctional form of CFTR that causes the channel to stay closed, and so chloride ions build up in the cell. This buildup causes the formation of thick mucus and produces the symptoms of the disease.

Most people have two copies of the normal allele for CFTR, and produce only functional CFTR protein. Those with cystic fibrosis possess two copies of the mutated CFTR allele, and produce only the defective CFTR protein. Heterozygotes, with one normal and one defective CFTR allele, produce both functional and defective CFTR protein. Thus, at the molecular level, the alleles for normal and defective CFTR are codominant, because both alleles are expressed in the heterozygote. However, because one normal allele produces enough functional CFTR protein to allow normal chloride transport, the heterozygote exhibits no adverse effects, and the mutated CFTR allele appears to be recessive at the physiological level.

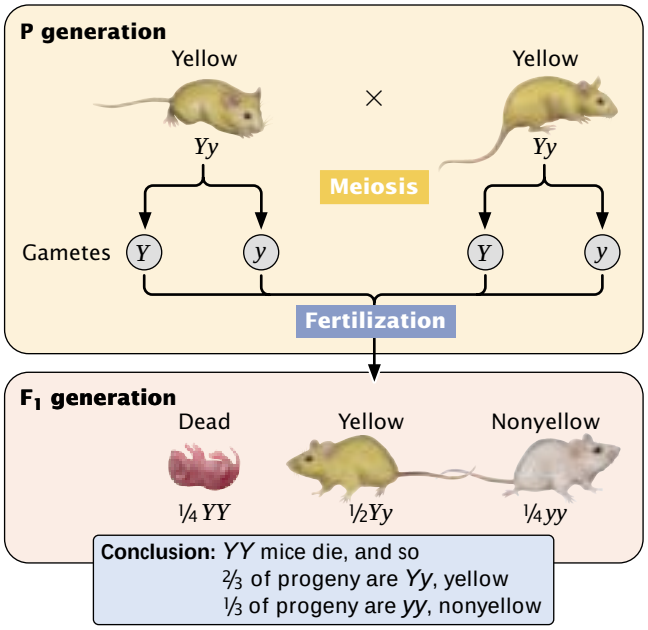
In summary, several important characteristics of dominance should be emphasized. First, dominance is a result of interactions between genes at the same locus; in other words, dominance is *allelic* interaction. Second, dominance does not alter the way in which the genes are inherited; it only influences the way in which they are expressed as a phenotype. The allelic interaction that characterizes dominance is therefore interaction between the *products* of the genes. Finally, dominance is frequently "in the eye of the beholder," meaning that the classification of dominance depends on the level at which the phenotype is examined. As we saw with cystic fibrosis, an allele may exhibit codominance at one level and be recessive at another level.

Concepts

Dominance entails interactions between genes at the same locus (allelic genes) and is an aspect of the phenotype; dominance does not affect the way in which genes are inherited. The type of dominance exhibited by a characteristic frequently depends on the level of the phenotype examined.

Lethal Alleles

In 1905, Lucien Cuenot reported a peculiar pattern of inheritance in mice. When he mated two yellow mice, approximately $^2/_3$ of their offspring were yellow and $^1/_3$ were nonyellow. When he test-crossed the yellow mice, he found that all were heterozygous; he was never able to obtain a yellow mouse that bred true. There was a great deal of discussion about Cuenot's results among his colleagues, but it was eventually realized that the yellow allele must be lethal when homozygous (Figure 5.3). A **lethal allele** is one that causes death at an early stage of development—often before birth—and so a some genetypes may not appear among the progeny.



5.3 A 2 : 1 ratio among the progeny of a cross results from the segregation of a lethal allele.

Cuenot originally crossed two mice heterozygous for yellow: *Yy* × *Yy*. Normally, this cross would be expected to produce $^1/_4$ *YY*, $^1/_2$ *Yy*, and $^1/_4$ *yy* (see Figure 5.3). The homozygous *YY* mice are conceived but never complete development, which leaves a 2:1 ratio of *Yy* (yellow) to *yy* (nonyellow) in the observed offspring; all yellow mice are heterozygous *(Yy)*.

Another example of a lethal allele, originally described by Erwin Baur in 1907, is found in snapdragons. The *aurea* strain in these plants has yellow leaves. When two plants with yellow leaves are crossed, $^2/_3$ of the progeny have yellow leaves and $^1/_3$ have green leaves. When green is crossed with green, all the progeny have green leaves; however, when yellow is crossed with green, $^1/_2$ of the progeny are green and $^1/_2$ are yellow, confirming that all yellow-leaved snapdragons are heterozygous. A 2:1 ratio is almost always produced by a recessive lethal allele; so observing this ratio among the progeny of a cross between individuals with the same phenotype is a strong clue that one of the alleles is lethal.

In both of these examples, the lethal alleles are recessive because they cause death only in homozygotes. Unlike its effect on *survival*, the effect of the allele on *color* is dominant; in both mice and snapdragons, a single copy of the allele in the heterozygote produces a yellow color. Lethal alleles also can be dominant; in this case, homozygotes and

heterozygotes for the allele die. Truly dominant lethal alleles cannot be transmitted unless they are expressed after the onset of reproduction, as in Huntington disease.

Concepts

A lethal allele causes death, frequently at an early developmental stage, and so one or more genotypes are missing from the progeny of a cross. Lethal alleles may modify the ratio of progeny resulting from a cross.

Multiple Alleles

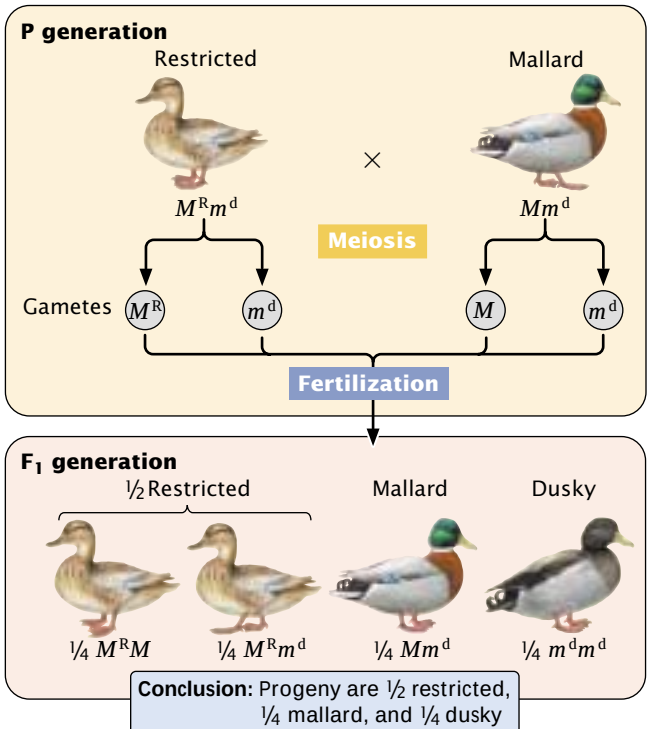
Most of the genetic systems that we have examined so far consist of two alleles. In Mendel's peas, for instance, one allele coded for round seeds and another for wrinkled seeds; in cats, one allele produced a black coat and another produced a gray coat. For some loci, more than two alleles are present within a group of individuals—the locus has **multiple alleles.** (Multiple alleles may also be referred to as an *allelic series.*) Although there may be more than two alleles present within a *group,* the genotype of each diploid *individual* still consists of only two alleles. The inheritance of characteristics encoded by multiple alleles is no different from the inheritance of characteristics encoded by two alleles, except that a greater variety of genotypes and phenotypes are possible.

Duck-Feather Patterns

An example of multiple alleles is seen at a locus that determines the feather pattern of mallard ducks. One allele, M, produces the wild-type *mallard* pattern. A second allele, M^R, produces a different pattern called *restricted,* and a third allele, m^d, produces a pattern termed *dusky.* In this allelic series, restricted is dominant over mallard and dusky, and mallard is dominant over dusky: $M^R > M > m^d$. The six genotypes possible with these three alleles and their resulting phenotypes are:

Genotype	Phenotype
M^RM^R	restricted
M^RM	restricted
M^Rm^d	restricted
MM	mallard
Mm^d	mallard
m^dm^d	dusky

In general, the number of genotypes possible will be $[n(n+1)]/2$, where n equals the number of different alleles at a locus. Working crosses with multiple alleles is no different from working crosses with two alleles; Mendel's principle of segregation still holds, as shown in the cross between a restricted duck and a mallard duck (FIGURE 5.4).



5.4 Mendel's principle of segregation applies to crosses with multiple alleles. In this example, three alleles determine the type of plumage in mallard ducks: M^R (Restricted) > M (Mallard) > m^d (Dusky).

The ABO Blood Group

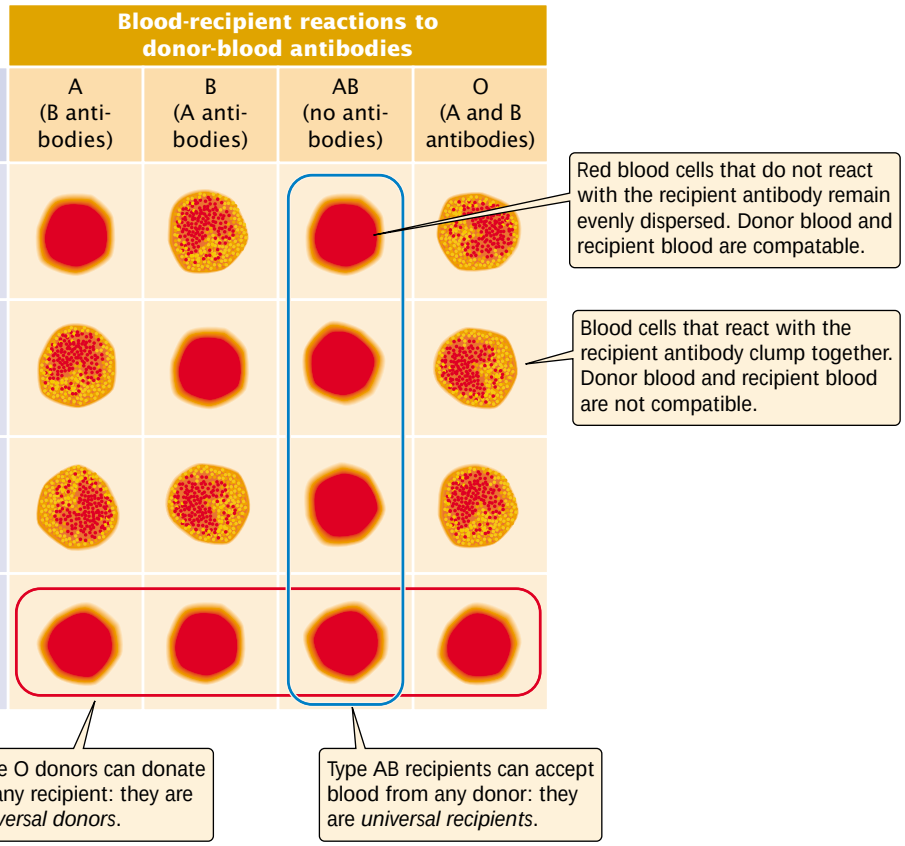
Another multiple-allele system is at the locus for the ABO blood group. This locus determines your ABO blood type and, like the MN locus, codes for antigens on red blood cells. The three common alleles for the ABO blood group locus are: I^A, which codes for the A antigen; I^B, which codes for the B antigen; and i, which codes for no antigen (O). We can represent the dominance relations among the ABO alleles as follows: $I^A > i$, $I^B > i$, $I^A = I^B$. The I^A and I^B alleles are both dominant over i and are codominant with each other; the AB phenotype is due to the presence of an I^A allele and an I^B allele, which results in the production of A and B antigens on red blood cells. An individual with genotype ii produces neither antigen and has blood type O. The six common genotypes at this locus and their phenotypes are shown in FIGURE 5.5a.

Antibodies are produced against any foreign antigens (see Figure 5.5a). For instance, a person having blood type A produces B antibodies, because the B antigen is foreign. A person having blood type B produces A antibodies, and someone having blood type AB produces neither A nor B antibodies, because neither A nor B antigen is foreign. A person having blood type O possesses no A or B antigens; consequently that person produces both A antibodies and B antibodies. The presence of antibodies against foreign ABO antigens means

(a)

Phenotype (blood type)	Genotype	Antigen type	Antibodies made by body
A	I^AI^A or I^Ai	A	B
B	I^BI^B or I^Bi	B	A
AB	I^AI^B	A and B	None
O	ii	None	A and B

(b)



5.5 ABO blood types and possible blood transfusions.

that successful blood transfusions are possible only between persons with certain compatible blood types (FIGURE 5.5b).

The inheritance of alleles at the ABO locus can be illustrated by a paternity suit involving the famous movie actor Charlie Chaplin. In 1941, Chaplin met a young actress named Joan Barry, with whom he had an affair. The affair ended in February 1942 but, 20 months later, Barry gave birth to a baby girl and claimed that Chaplin was the father. Barry then sued for child support. At this time, blood typing had just come into widespread use, and Chaplin's attorneys had Chaplin, Barry, and the child blood typed. Barry had blood type A, her child had blood type B, and Chaplin had blood type O. Could Chaplin have been the father of Barry's child?

Your answer should be no. Joan Barry had blood type A, which can be produced by either genotype I^AI^A or I^Ai. Her baby possessed blood type B, which can be produced by either genotype I^BI^B or I^Bi. The baby could not have inherited the I^B allele from Barry (Barry could not carry an I^B allele if she were blood type A); therefore the baby must have inherited the i allele from her. Barry must have had genotype I^Ai, and the baby must have had genotype I^Bi. Because the baby girl inherited her i allele from Barry, she must have inherited the I^B allele from her father. With blood type O, produced only by genotype ii, Chaplin could not have been the father of Barry's child. In the course of the trial to settle the paternity suit, three pathologists came to the witness stand and declared that it was genetically impossible for Chaplin to have fathered the child. Nevertheless, the jury ruled that Chaplin was the father and ordered him to pay child support and Barry's legal expenses.

Concepts

More than two alleles (multiple alleles) may be present within a group of individuals, although each diploid individual still has only two alleles at that locus.

Gene Interaction

In the dihybrid crosses that we examined in Chapter 3, each locus had an independent effect on the phenotype. When Mendel crossed a homozygous round and yellow plant *(RRYY)* with a homozygous wrinkled and green plant *(rryy)* and then self-fertilized the F_1, he obtained F_2 progeny in the following proportions:

$^9/_{16}$	*R_Y_*	round, yellow
$^3/_{16}$	*R_yy*	round, green
$^3/_{16}$	*rrY_*	wrinkled, yellow
$^1/_{16}$	*rryy*	wrinkled, green

In this example, the genes showed two kinds of independence. First, the genes at each locus are independent in their *assortment* in meiosis, which is what produces the 9:3:3:1 ratio of phenotypes in the progeny, in accord with Mendel's principle of independent assortment. Second, the genes are independent in their *phenotypic expression;* the *R* and *r* alleles affect only the shape of the seed and have no influence on the color of the endosperm; the *Y* and *y* alleles affect only color and have no influence on the shape of the seed.

Frequently, genes exhibit independent assortment but do not act independently in their phenotypic expression; instead, the effects of genes at one locus depend on the presence of genes at other loci. This type of interaction between the effects of genes at different loci (genes that are not allelic) is termed **gene interaction.** With gene interaction, the products of genes at different loci combine to produce new phenotypes that are not predictable from the single-locus effects alone. In our consideration of gene interaction, we'll focus primarily on interaction between the effects of genes at two loci, although interactions among genes at three, four, or more loci are common.

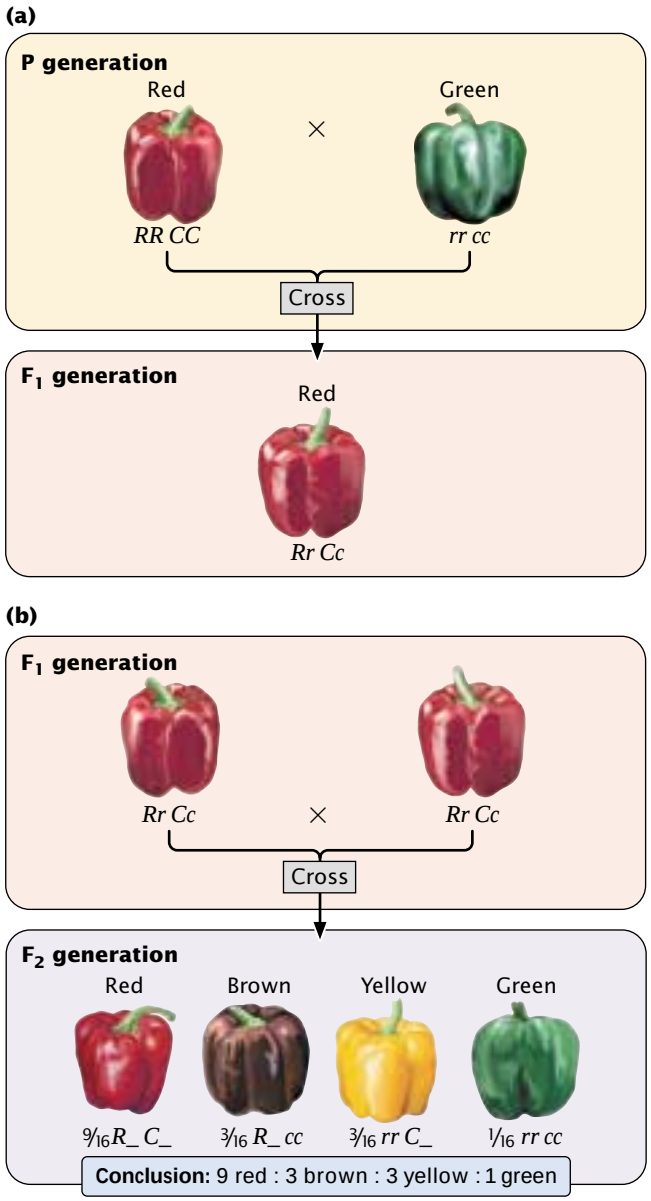
Concepts

In gene interaction, genes at different loci contribute to the determination of a single phenotypic characteristic.

Gene Interaction That Produces Novel Phenotypes

Let's first examine gene interaction in which genes at two loci interact to produce a single characteristic. Fruit color in the pepper *Capsicum annuum* is determined in this way. This plant produces peppers in one of four colors: red, brown, yellow, or green. If a homozygous plant with red peppers is crossed with a homozygous plant with green peppers, all the F_1 plants have red peppers (Figure 5.6a). When the F_1 are crossed with one another, the F_2 are in a ratio of 9 red : 3 brown : 3 yellow : 1 green (Figure 5.6b). This dihybrid ratio (Chapter 3) is produced by a cross between two plants that are both heterozygous for two loci (*RrCc* × *RrCc*). In peppers, a dominant allele *R* at the first locus produces a red pigment; the recessive allele *r* at this locus produces no red pigment. A dominant allele *C* at the second locus causes decomposition of the green pigment chlorophyll; the recessive allele *c* allows chlorophyll to persist. The genes at the two loci then interact to produce the colors seen in F_2 peppers:

Genotype	Phenotype
*R_C_*	red
R_cc	brown
*rrC_*	yellow
rrcc	green



5.6 Gene interaction in which two loci determine a single characteristic, fruit color, in the pepper *Capsicum annuum*.

To illustrate how Mendel's rules of heredity can be used to understand the inheritance of characteristics determined by gene interaction, let's consider a testcross between an F_1 plant from the cross in Figure 5.6 (*RrCc*) and a plant with green peppers (*rrcc*). As outlined in Chapter 3 (p. 000) for independent loci, we can work this cross by breaking it down into two simple crosses. At the first locus, the heterozygote *Rr* is crossed with the homozygote *rr;* this cross produces ½ *Rr* and ½ *rr* progeny. Similarly, at the second locus, the heterozygous genotype *Cc* is crossed with the homozygous genotype *cc*, producing ½ *Cc* and ½ *cc* progeny. In accord with Mendel's principle of

5.7 A chicken's comb is determined by gene interaction between two loci. (a) A walnut comb is produced when there is a dominant allele at each of two loci (*R_P_*). (b) A rose comb occurs when there is a dominant allele only at the first locus (*R_pp*). (c) A pea comb occurs when there is a dominant allele only at the second locus (*ppR_*). (d) A single comb is produced by the presence of only recessive alleles at both loci (*rrpp*). (Parts a and d, R. OSF Dowling/Animals Animals; part b, Robert Maier/Animals Animals; part c, George Godfrey/Animals Animals.)

independent assortment, these single-locus ratios can be combined by using the multiplication rule: the probability of obtaining the genotype *RrCc* is the probability of *Rr* ($\frac{1}{2}$) multiplied by the probability of *Cc* ($\frac{1}{2}$), or $\frac{1}{4}$. The probability of each progeny genotype resulting from the testcross is:

Progeny genotype	Probability at each locus	Overall probability	Phenotype
RrCc	$\frac{1}{2} \times \frac{1}{2} =$	$\frac{1}{4}$	red peppers
Rrcc	$\frac{1}{2} \times \frac{1}{2} =$	$\frac{1}{4}$	brown peppers
rrCc	$\frac{1}{2} \times \frac{1}{2} =$	$\frac{1}{4}$	yellow peppers
rrcc	$\frac{1}{2} \times \frac{1}{2} =$	$\frac{1}{4}$	green peppers

When you work problems with gene interaction, it is especially important to determine the probabilities of single-locus genotypes and to multiply the probabilities of *genotypes*, not phenotypes, because the phenotypes cannot be determined without considering the effects of the genotypes at all the contributing loci.

Another example of gene interaction that produces novel phenotypes is seen in the genes that determine comb shape in chickens. The comb is the fleshy structure found on the head of a chicken. Genes at two loci (*R*, *r* and *P*, *p*) interact to determine the four types of combs shown in FIGURE 5.7. A walnut comb is produced when at least one dominant allele *R* is present at the first locus and at least one dominant allele *P* is present at the second locus (genotype *R_P_*). A chicken with at least one dominant allele at the first locus and two recessive alleles at the second locus (genotype *R_pp*) possesses a rose comb. If two recessive alleles are present at the first locus and at least one dominant allele is present at the second (genotype *rrP_*), the chicken has a pea comb. Finally, if two recessive alleles are present at both loci (*rrpp*), the bird has a single comb.

Gene Interaction with Epistasis

Sometimes the effect of gene interaction is that one gene masks (hides) the effect of another gene at a different locus, a phenomenon known as **epistasis.** This phenomenon is similar to dominance, except that dominance entails the masking of genes at the *same* locus (allelic genes). In epistasis, the gene that does the masking is called the **epistatic gene;** the gene whose effect is masked is a **hypostatic gene.** Epistatic genes may be recessive or dominant in their effects.

Recessive epistasis Recessive epistasis is seen in the genes that determine coat color in Labrador retrievers. These dogs may be black, brown, or yellow; their different coat colors are determined by interactions between genes at two loci (although a number of other loci also help to determine coat color; see p. 000). One locus determines the type of pigment produced by the skin cells: a dominant allele *B* codes for black pigment, whereas a recessive allele *b* codes for brown pigment. Alleles at a second locus affect the *deposition* of the pigment in the shaft of the hair; allele *E* allows dark pigment (black or brown) to be deposited, whereas a recessive allele *e* prevents the deposition of dark pigment, causing the hair to be yellow. The presence of genotype *ee* at the second locus therefore masks the expression of the black and brown alleles at the first locus. The

genotypes that determine coat color and their phenotypes are:

Genotype	Phenotype
*B_ E_*	black
*bbE_*	brown (frequently called chocolate)
B_ee	yellow
bbee	yellow

If we cross a black Labrador homozygous for the dominant alleles with a yellow Labrador homozygous for the recessive alleles and then intercross the F_1, we obtain progeny in the F_2 in a 9:3:4 ratio:

P *BBEE* × *bbee*
black yellow
↓
F_1 *BbEe*
black
↓ Intercross
F_2 $^9/_{16}$ *B_E_* black
$^3/_{16}$ *bbE_* brown
$^3/_{16}$ *B_ee* yellow } $^4/_{16}$ yellow
$^1/_{16}$ *bbee* yellow }

Notice that yellow dogs can carry alleles for either black or brown pigment, but these alleles are not expressed in their coat color.

In this example of gene interaction, allele *e* is epistatic to *B* and *b*, because *e* masks the expression of the alleles for black and brown pigments, and alleles *B* and *b* are hypostatic to *e*. In this case, *e* is a recessive epistatic allele, because two copies of *e* must be present to mask of the black and brown pigments.

Dominant epistasis Dominant epistasis is seen in the interaction of two loci that determine fruit color in summer squash, which is commonly found in one of three colors: yellow, white, or green. When a homozygous plant that produces white squash is crossed with a homozygous plant that produces green squash and the F_1 plants are crossed with each other, the following results are obtained:

P plants with white squash × plants with green squash
↓
F_1 plants with white squash
↓ Intercross
F_2 $^{12}/_{16}$ plants with white squash
$^3/_{16}$ plants with yellow squash
$^1/_{16}$ plants with green squash

How can gene interaction explain these results?

In the F_2, $^{12}/_{16}$ or $^3/_4$ of the plants produce white squash and $^3/_{16} + {}^1/_{16} = {}^4/_{16} = {}^1/_4$ of the plants produce squash having color. This outcome is the familiar 3:1 ratio produced by a cross between two heterozygous individuals, which suggests that a dominant allele at one locus inhibits the production of pigment, resulting in white progeny. If we use the symbol *W* to represent the dominant allele that inhibits pigment production, then genotype *W_* inhibits pigment production and produces white squash, whereas *ww* allows pigment and results in colored squash.

Among those *ww* F_2 plants with pigmented fruit, we observe $^3/_{16}$ yellow and $^1/_{16}$ green (a 3:1 ratio). This outcome is because a second locus determines the type of pigment produced in the squash, with yellow (*Y_*) dominant over green *(yy)*. This locus is expressed only in *ww* plants, which lack the dominant inhibitory allele *W*. We can assign the genotype *wwY_* to plants that produce yellow squash and the genotype *wwyy* to plants that produce green squash. The genotypes and their associated phenotypes are:

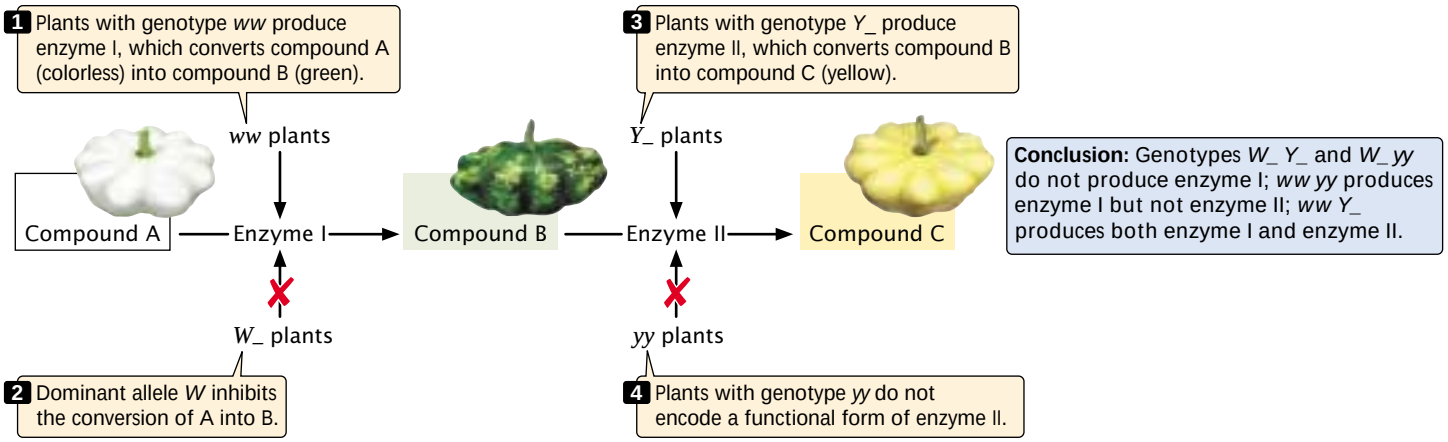
*W_Y_*	white squash
W_yy	white squash
*wwY_*	yellow squash
wwyy	green squash

Allele *W* is epistatic to *Y* and *y*—it suppresses the expression of these pigment-producing genes. *W* is a dominant epistatic allele because, in contrast with *e* in Labrador retriever coat color, a single copy of the allele is sufficient to inhibit pigment production.

Summer squash provides us with a good opportunity for considering how epistasis often arises when genes affect a series of steps in a biochemical pathway. Yellow pigment in the squash is most likely produced in a two-step biochemical pathway (**Figure 5.8**). A colorless (white) compound (designated A in Figure 5.8) is converted by enzyme I into green compound B, which is then converted into compound C by enzyme II. Compound C is the yellow pigment in the fruit.

Plants with the genotype *ww* produce enzyme I and may be green or yellow, depending on whether enzyme II is present. When allele *Y* is present at a second locus, enzyme II is produced and compound B is converted into compound C, producing a yellow fruit. When two copies of *y*, which does not encode a functional form of enzyme II, are present, squash remain green. The presence of *W* at the first locus inhibits the conversion of compound A into compound B; plants with genotype *W_* do not make compound B and their fruit remains white, regardless of which alleles are present at the second locus.

Many cases of epistasis arise in this way. A gene (such as *W*) that has an effect on an early step in a biochemical pathway will be epistatic to genes (such as *Y* and *y*) that affect subsequent steps, because the effect of the enzyme in the later step depends on the product of the earlier reaction.



5.8 Yellow pigment in summer squash is produced in a two-step pathway.

Duplicate recessive epistasis Let's consider one more detailed example of epistasis. Albinism is the absence of pigment and is a common genetic trait in many plants and animals. Pigment is almost always produced through a multistep biochemical pathway; thus, albinism may entail gene interaction. Robert T. Dillon and Amy R. Wethington found that albinism in the common freshwater snail *Physa heterostroha* can result from the presence of either of two recessive alleles at two different loci. Inseminated snails were collected from a natural population and placed in cups of water, where they laid eggs. Some of the eggs hatched into albino snails. When two albino snails were crossed, all of the F_1 were pigmented. On intercrossing the F_1, the F_2 consisted of $^9/_{16}$ pigmented snails and $^7/_{16}$ albino snails. How did this 9:7 ratio arise?

The 9:7 ratio seen in the F_2 snails can be understood as a modification of the 9:3:3:1 ratio obtained when two individuals heterozygous for two loci are crossed. The 9:7 ratio arises when dominant alleles at both loci (*A_B_*) produce pigmented snails; any other genotype produces albino snails:

P *aaBB* albino × *AAbb* albino

↓

F_1 *AaBb* pigmented

↓ Intercross

F_2 $^9/_{16}$ *A_B_* pigmented
$^3/_{16}$ *aaB_* albino
$^3/_{16}$ *A_bb* albino
$^1/_{16}$ *aabb* albino
} $^7/_{16}$ albino

The 9:7 ratio in these snails is probably produced by a two-step pathway of pigment production (Figure 5.9). Pigment (compound C) is produced only after compound A has been converted into compound B by enzyme I and after compound B has been converted into compound C by enzyme II. At least one dominant allele *A* at the first locus is required to produce enzyme I; similarly, at least one dominant allele *B* at the second locus is required to produce enzyme II. Albinism arises from the absence of compound C, which may happen in three ways. First, two recessive alleles at the first locus (genotype *aaB_*) may prevent the production of enzyme I, and so compound B is never produced. Second, two recessive alleles at the second locus (genotype *A_bb*) may prevent the production of enzyme II. In this case, compound B is never converted into compound C. Third, two recessive alleles may be present at both loci (*aabb*), causing the absence of both enzyme I and enzyme II. In this example of gene interaction, *a* is epistatic to *B*, and *b* is epistatic to *A; both* are recessive epistatic alleles because the presence of two copies of either allele *a* or *b* is necessary to suppress pigment production. This example differs from the suppression of coat color in Labrador retrievers in that recessive alleles at either of two loci are capable of suppressing pigment production in the snails, whereas recessive alleles at a single locus suppress pigment expression in Labs.

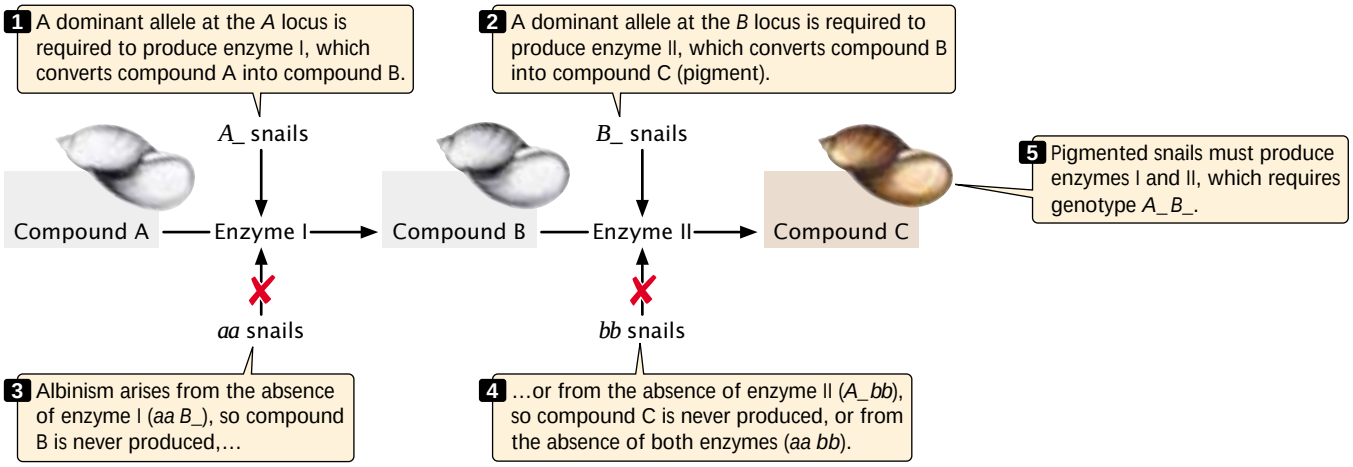
Concepts

Epistasis is the masking of the expression of one gene by another gene at a different locus. The epistatic gene does the masking; the hypostatic gene is masked. Epistatic genes can be dominant or recessive.

Connecting Concepts

Interpreting Ratios Produced by Gene Interaction

A number of modified ratios that result from gene interaction are shown in Table 5.2. Each of these examples represents a modification of the basic 9:3:3:1 dihybrid ratio.



5.9 Pigment is produced in a two-step pathway in snails.

In interpreting the genetic basis of modified ratios, we should keep several points in mind. First, the inheritance of the genes producing these characteristics is no different from the inheritance of genes coding for simple genetic characters. Mendel's principles of segregation and independent assortment still apply; each individual possesses two alleles at each locus, which separate in meiosis, and genes at the different loci assort independently. The only difference is in how the *products* of the genotypes interact to produce the phenotype. Thus, we cannot consider the expression of genes at each locus separately, but must take into consideration how the genes at different loci interact.

A second point is that in the examples that we have considered, the phenotypic proportions were always in sixteenths because, in all the crosses, pairs of alleles segregated at two independently assorting loci. The probability of inheriting one of the two alleles at a locus is $\frac{1}{2}$. Because there are two loci, each with two alleles, the probability of inheriting any particular combination of genes is $(\frac{1}{2})^4 = \frac{1}{16}$. For a trihybrid cross, the progeny proportions should be in sixty-fourths, because $(\frac{1}{2})^6 = \frac{1}{64}$. In general, the progeny proportions should be in fractions of $(\frac{1}{2})^{2n}$, where n equals the number of loci with two alleles segregating in the cross.

Table 5.2 Modified dihybrid—phenotypic ratios due to gene interaction

Ratio	Genotype				Type of Interaction	Example
	*A_B_*	*A_bb*	*aaB_*	*aabb*		
9:3:3:1	9	3	3	1	None	Seed shape and endosperm color in peas
9:3:4	9	3	4		Recessive epistasis	Coat color in Labrador retrievers
12:3:1	12		3	1	Dominant epistasis	Color in squash
9:7	9	7			Duplicate recessive epistasis	Albinism in snails
9:6:1	9	6		1	Duplicate interaction	—
15:1	15			1	Duplicate dominant epistasis	—
13:3	13		3		Dominant and recessive epistasis	—

*Reading across, each row gives the phenotypic ratios of progeny from a dihybrid cross (*AaBb* × *AaBb*).

Crosses rarely produce exactly 16 progeny; therefore, modifications of a dihybrid ratio are not always obvious. Modified dihybrid ratios are more easily seen if the number of individuals of each phenotype is expressed in sixteenths:

$$\frac{x}{16} = \frac{\text{number of progeny with a phenotype}}{\text{total number of progeny}}$$

where $x/16$ equals the proportion of progeny with a particular phenotype. If we solve for x (the proportion of the particular phenotype in sixteenths), we have:

$$x = \frac{\text{number of progeny with a phenotype} \times 16}{\text{total number of progeny}}$$

For example, suppose we cross two homozygous individuals, interbreed the F_1 and obtain 63 red, 21 brown, and 28 white F_2 individuals. Using the preceding formula, the phenotypic ratio in the F_2 is: red $= (63 \times 16)/112 = 9$; brown $= (21 \times 16)/112 = 3$; and white $= (28 \times 16)/112 = 4$. The phenotypic ratio is 9:3:4

A final point to consider is how to assign genotypes to the phenotypes in modified ratios owing to gene interaction. Don't try to *memorize* the genotypes associated with all the modified ratios in Table 5.2. Instead, practice relating modified ratios to known ratios, such as the 9:3:3:1 dihybrid ratio. Suppose we obtain $^{15}/_{16}$ green progeny and $^{1}/_{16}$ white progeny in a cross between two plants. If we compare this 15:1 ratio with the standard 9:3:3:1 dihybrid ratio, we see that $^{9}/_{16} + {}^{3}/_{16} + {}^{3}/_{16}$ equals $^{15}/_{16}$. All the genotypes associated with these proportions in the dihybrid cross (*A_B_*, *A_bb*, and *aaB_*) must give the same phenotype, the green progeny. Genotype *aabb* makes up $^{1}/_{16}$ of the progeny in a dihybrid cross, the white progeny in this cross.

In assigning genotypes to phenotypes in modified ratios, students sometimes become confused about which letters to assign to which phenotype. Suppose we obtain the following phenotypic ratio: $^{9}/_{16}$ black : $^{3}/_{16}$ brown : $^{4}/_{16}$ white. Which genotype do we assign to the brown progeny, *A_bb* or *aaB_*? Either answer is correct, because the letters are just arbitrary symbols for the genetic information. The important thing to realize about this ratio is that the brown phenotype arises when two recessive alleles are present at one locus.

Concepts

Gene interaction frequently produces modified phenotypic ratios. These modified ratios can be understood by relating them to other known ratios.

The Complex Genetics of Coat Color in Dogs

Coat color in dogs is an excellent example of how complex interactions between genes may take part in the determination of a phenotype. Domestic dogs come in an amazing variety of shapes, sizes, and colors. For thousands of years, humans have been breeding dogs for particular traits, producing the large number of types that we see today. Each breed of dog carries a selection of genes from the ancestral dog gene pool; these genes define the features of a particular breed.

One of the most obvious differences between dogs is coat color. The genetics of coat color in dogs is quite complex; many genes participate, and there are numerous interactions between genes at different loci. We will consider seven loci (in the list that follows) that are important in producing many of the noticeable differences in color and pattern among breeds of dogs. In interpreting the genetic basis of differences in coat color of dogs, consider how the expression of a particular gene is modified by the effects of other genes. Keep in mind that additional loci not listed here can modify the colors produced by these seven loci and that not all geneticists agree on the genetics of color variation in some breeds.

1. Agouti (A) locus—This locus has five common alleles that determine the depth and distribution of color in a dog's coat:

A^s	Solid black pigment.
a^w	Agouti, or wolflike gray. Hairs encoded by this allele have a "salt and pepper" appearance, produced by a band of yellow pigment on a black hair.
a^y	Yellow. The black pigment is markedly reduced; so the entire hair is yellow.
a^s	Saddle markings (dark color on the back, with extensive tan markings on the head and legs).
a^t	Bicolor (dark color over most of the body, with tan markings on the feet and eyebrows).

   A^s and a^y are generally dominant over the other alleles, but the dominance relations are complex and not yet completely understood.

2. Black (B) locus—This locus determines whether black pigment can be formed. The actual color of a dog's fur depends on the effects of genes at other loci (such as the A, C, D, and E loci). Two alleles are common:

B	Allows black pigment to be produced; the dog will be black if it also possesses certain alleles at the A, C, D, and E loci.
b	Black pigment cannot be produced; pigmented dogs can be chocolate, liver, tan, or red.

   B is dominant over *b*.

3. Albino (C) locus—This locus determines whether full color will be expressed. There are five alleles at this locus:

C	Color fully expressed.
c^{ch}	Chinchilla. Less color is expressed, and pigment is completely absent from the base of the long hairs, producing a pale coat.
c^d	All white coat with dark nose and dark eyes.
c^b	All white coat with blue eyes.
c	Fully albino. The dogs have an all-white coat with pink eyes and nose.

5.10 Coat color in dogs is determined by interactions between genes at a number of loci. (a) Most Labrador retrievers are genotype $A^sA^sCCDDSStt$, varing only at the *B* and *E* loci. (b) Most beares are genotype $a^sa^sBBCCDDs^ps^ptt$. (c) Dalmations are genotype $A^sA^sCCDDEEs^ws^wTT$, varing at the *B* locus so that the dogs are black (*B_*) or brown (*bb*). (Part a, Robert Maier/Animals Animals; part b, Ralph Reinhold/Animals Animals; part c, Robert Percy/ Animals Animals.)

The dominance relations among these alleles is presumed to be $C > c^{ch} > c^d > c^b > c$, but the c^{ch} and *c* alleles are rare, and crosses including all possible genotypes have not been completed.

4. Dilution (D) locus—This locus, with two alleles, determines whether the color will be diluted. For example, diluted black pigment appears bluish, and diluted yellow appears cream. The diluted effect is produced by an uneven distribution of pigment in the hair shaft:

   D Intense pigmentation.
   d Dilution of pigment.

   D is dominant over *d*.

5. Extension (E) locus—Four alleles at this locus determine where the genotype at the A locus is expressed. For example, if a dog has the A^s allele (solid black) at the A locus, then black pigment will either be extended throughout the coat or be restricted to some areas, depending on the alleles present at the E locus. Areas where the A locus is not expressed may appear as yellow, red, or tan, depending on the presence of particular genes at other loci. When A^s is present at the A locus, the four alleles at the E locus have the following effects:

   E^m Black mask with a tan coat.
   E The A locus expressed throughout (solid black).
   e^{br} Brindle, in which black and yellow are in layers to give a tiger-striped appearance.
   e No black in the coat, but the nose and eyes may be black.

   The dominance relations among these alleles are poorly known.

6. Spotting (S) locus—Alleles at this locus determine whether white spots will be present. There are four common alleles:

   S No spots.
   s^i Irish spotting; numerous white spots.
   s^p Piebald spotting; various amounts of white.
   s^w Extreme white piebald; almost all white.

   S is completely dominant over s^i, s^p, and s^w; s^i and s^p are dominant over s^w ($S > s^i, s^p > s^w$). The relation between of s^i and s^p is poorly defined; indeed, they may not be separate alleles. Genes at other poorly known loci also modify spotting patterns.

7. Ticking (T) locus—This locus determines the presence of small colored spots on the white areas, which is called ticking:

   T Ticking; small colored spots on the areas of white.
   t No ticking.

   T is dominant over *t*. Ticking cannot be expressed if a dog has a solid coat (*S_*).

To illustrate how genes at these loci interact in determining a dog's coat color, let's consider a few examples:

Labrador retriever- Labrador retrievers (**Figure 5.10a**) may be black, brown, or yellow. Most are homozygous $A^sA^sCCDDSStt$; thus, they vary only at the B and E loci. The A^s, *C*, and *D* alleles allow dark pigment to be expressed; whether a dog is black depends on which genes are present at the B and E loci. As discussed earlier in the chapter, all black Labradors must carry at least one *B* allele and one *E* allele (*B_E_*). Brown dogs are homozygous *bb* and have at least one *E* allele (*bbE_*). Yellow dogs are a result of the presence of *ee* (*B_ee* or *bbee*). Labrador retrievers are homozygous for the *S* allele, which produces a solid color; the few white spots that appear in some dogs of this breed are due to other modifying genes. The allele for ticking, *T*, is presumed not to exist in Labradors; however, Labrador retrievers have solid coats and ticking is expressed only in spotted dogs; so its absence is uncertain.

Beagle- Most beagles are homozygous a^sa^s $BBCCDDs^ps^ptt$, although other alleles at these loci are occasionally present. The a^s allele produces the saddle markings—dark back and sides, with tan head

and legs—that are characteristic of the breed (FIGURE 5.10b). Alleles *B, C,* and *D* allow black to be produced, but its distribution is limited by the a^s allele. Genotype *ee* does occasionally arise, leading to a few all-tan beagles. White spotting in beagles is due to the s^p allele. Ticking can appear, but most beagles are *tt*.

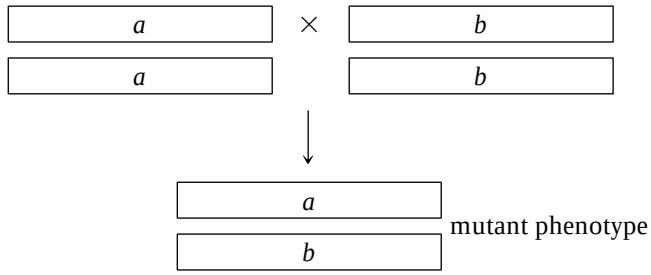
Dalmatian- Dalmatians (FIGURE 5.10c) have an interesting genetic makeup. Most are homozygous A^sA^s *CCDDEE*s^ws^w*TT*; so they vary only at the B locus. Notice that these dogs possess genotype A^sA^s*CCDDEE*, which allows for a solid coat that would be black, if genotype *B_* is present, or brown (called liver), if genotype *bb* is present. However, the presence of the s^w allele produces a white coat, masking the expression of the solid color. The dog's color appears only in the pigmented spots, which are due to the presence of the ticking allele *T*. Table 5.3 gives the common genotypes of other breeds of dogs.

www.whfreeman.com/pierce Information on dog genetics, including the Dog Genome Project

Complementation: Determining Whether Mutations Are at the Same or Different Loci

How do we know whether different mutations that affect a characteristic occur at the same locus (are allelic) or at different loci? In fruit flies, for example, *white* is an X-linked mutation that produces white eyes instead of the red eyes found in wild-type flies. *Apricot* is an X-linked recessive mutation that produces light orange-colored eyes. Do the white and apricot mutations occur at the same locus or at different loci? We can use the complementation test to answer this question.

To carry out a **complementation test,** parents that are homozygous for different mutations are crossed, producing offspring that are heterozygous. If the mutations are allelic (occur at the same locus), then the heterozygous offspring have only mutant alleles (*ab*) and exhibit a mutant phenotype:

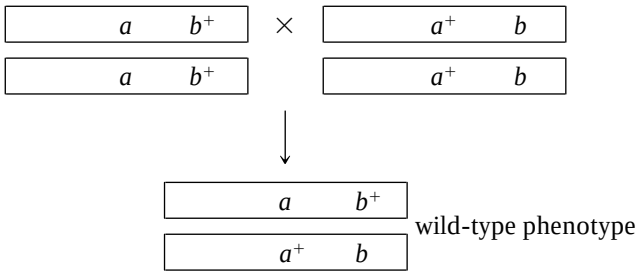


If, on the other hand, the mutations occur at different loci, each of the homozygous parents possesses wild-type genes at the other locus (*aa* b^+b^+ and a^+a^+ *bb*); so the heterozygous offspring inherit a mutant and a wild-type allele at each locus. In this case, the mutations complement each other and the heterozygous offspring have the wild-type phenotype:

Table 5.3 Common genotypes in different breeds of dogs

Breed	Usual Homozygous Genes*	Other Genes Present Within the Breed
Basset hound	*BBCCDDEEtt*	a^y, a^t *S*, s^p, s^i
Beagle	a^sa^s*BBCCDDs*^{p}s^p*tt*	*E, e*
English bulldog	*BBCCDDtt*	A^s, a^y, a^t E^m, *E*, e^{br} *S*, s^i, s^p, s^w
Chihuahua	*tt*	A^s, a^y, a^s, a^t *B, b* *C*, c^{ch} *D, d* E^m, *E*, e^{br}, *e* *S*, s^i s^p, s^w
Collie	*BBCCEEtt*	a^y, a^t *D, d* s^i, s^w
Dalmatian	A^sA^s*CCDDEEs*^{w}s^w*TT*	*B, b*
Doberman	a^ta^t*CCEESStt*	*B, b* *D, d*
German shepherd	*BBDDSStt*	a^y, a^g, a^s, a^t *C*, c^{ch} E^m, *E, e*
Golden retriever	A^sA^s*BBDDSStt*	*C*, c^{ch} *E, e*
Greyhound	*BBtt*	A^s, a^y *C*, c^{ch} *D, d* *E*, e^{br}, *e* *S*, s^p, s^w, s^i
Irish setter	*BBCCDDeeSStt*	*A*, a^t
Labrador retriever	A^sA^s*CCDDSStt*	*B, b* *E, e*
Poodle	*SStt*	A^s, a^t *B, b* *C*, c^{ch} *D, d* *E, e*
Rottweiler	a^ta^t*BBCCDDEESStt*	
St. Bernard	a^ya^y*BBCCDDtt*	E^m, *E* s^i, s^p, s^w

*Most dogs in the breed are homozygous for these genes; a few individual dogs may possess other alleles at these loci.
Source: Data from M. B. Willis, *Genetics of the Dog* (London: Witherby, 1989).



Complementation occurs when an individual possessing two mutant genes has a wild-type phenotype and is an indicator that the mutations are nonallelic genes.

When the complementation test is applied to white and apricot mutations, all of the heterozygous offspring have light-colored eyes, demonstrating that white and apricot are produced by mutations that occur at the same locus and are allelic.

Interaction Between Sex and Heredity

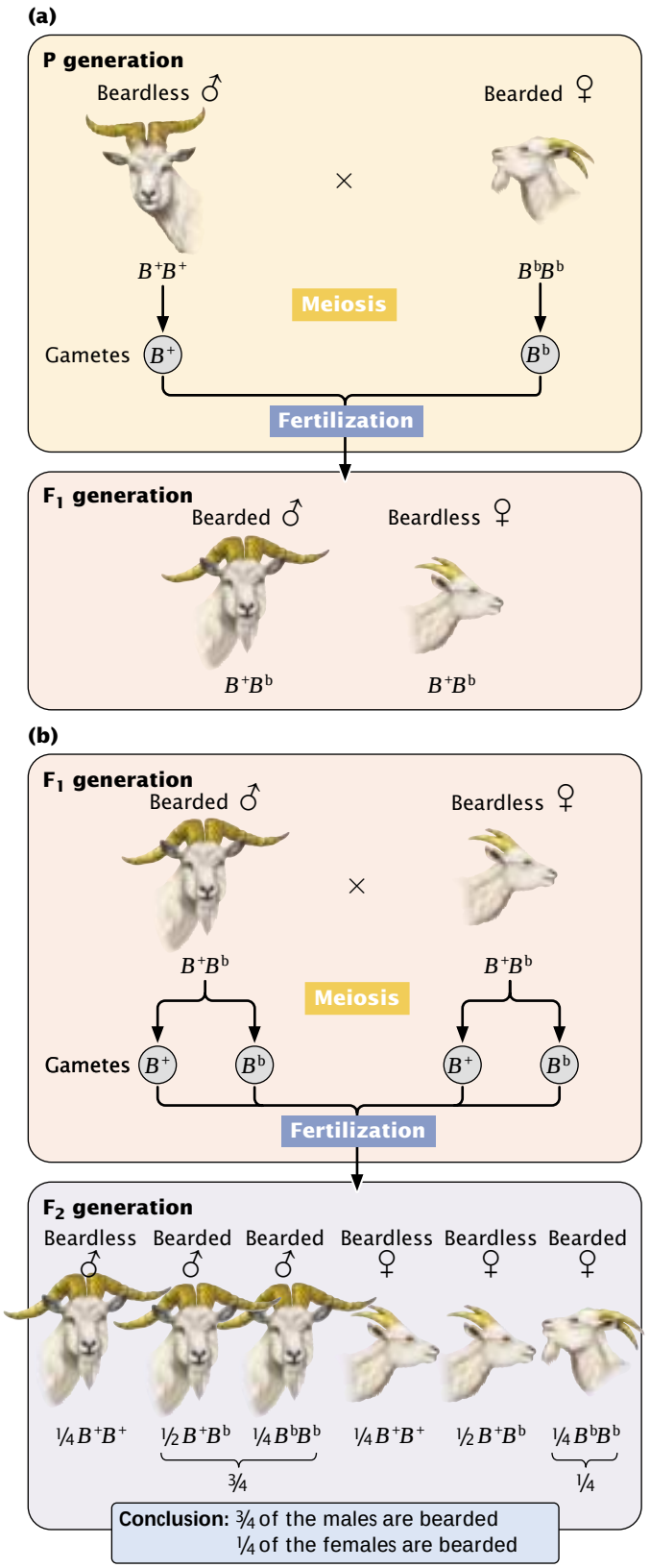
In Chapter 4, we considered characteristics encoded by genes located on the sex chromosomes and how their inheritance differs from the inheritance of traits encoded by autosomal genes. Now we will examine additional influences of sex, including the effect of the sex of an individual on the expression of genes on autosomal chromosomes, characteristics determined by genes located in the cytoplasm, and characteristics for which the genotype of only the maternal parent determines the phenotype of the offspring. Finally, we'll look at situations in which the expression of genes on autosomal chromosomes is affected by the sex of the parent from whom they are inherited.

Sex-Influenced and Sex-Limited Characteristics

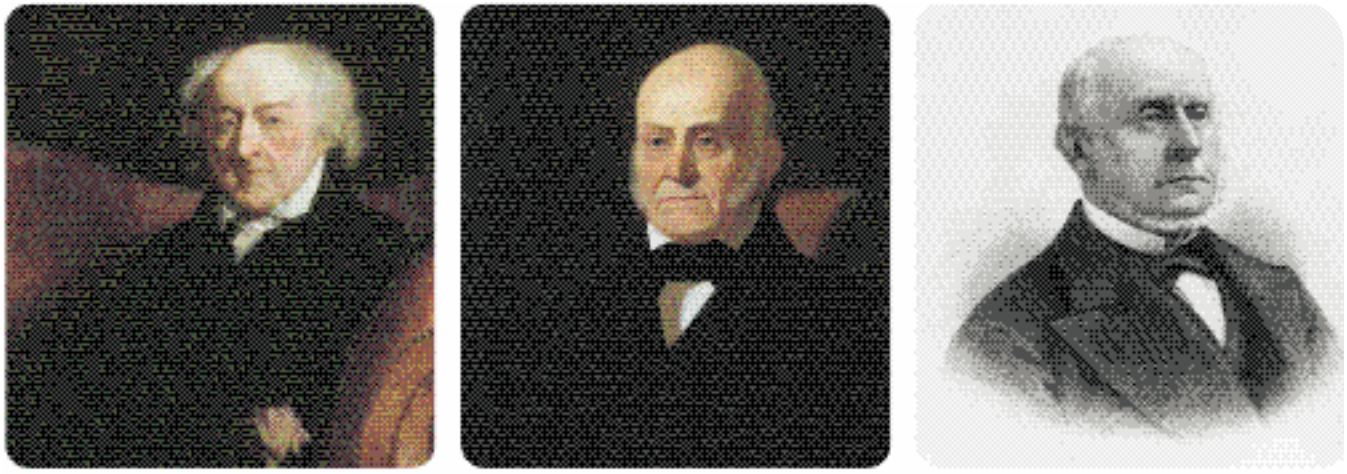
Sex influenced characteristics are determined by autosomal genes and are inherited according to Mendel's principles, but they are expressed differently in males and females. In this case, a particular trait is more readily expressed in one sex; in other words, the trait has higher penetrance (see p. 000 in Chapter 3) in one of the sexes.

For example, the presence of a beard on some goats is determined by an autosomal gene (B^b) that is dominant in males and recessive in females. In males, a single allele is required for the expression of this trait: both the homozygote (B^bB^b) and the heterozygote (B^bB^+) have beards, whereas the B^+B^+ male is beardless. In contrast, females require two alleles in order for this trait to be expressed: the homozygote B^bB^b has a beard, whereas the heterozygote (B^bB^+) and the other homozygote (B^+B^+) are beardless. The key to understanding the expression of the bearded gene is to look at the heterozygote. In males (for which the presence of a beard is dominant), the heterozygous genotype produces a beard but, in females (for which the presence of a beard is recessive and its absence is dominant), the heterozygous genotype produces a goat without a beard.

FIGURE 5.11a illustrates a cross between a beardless male (B^+B^+) and a bearded female (B^bB^b). The alleles



5.11 Genes that encode sex-influenced traits are inherited according to Mendel's principles but are expressed differently in males and females.



(a) (b) (c)

5.12 Pattern baldness is a sex-influenced trait. This trait is seen in three generations of the Adams family: (a) John Adams (1735–1826), the second president of the United States, was father to (b) John Quincy Adams (1767–1848), who was father to (c) Charles Francis Adams (1807–1886). Pattern baldness results from an autosomal gene that is thought to be dominant in males and recessive in females. (Part (a) National Museum of American Art, Washington, D.C./Art Resource, NY; (b) National Portrait Gallery, Washington, D.C./Art Resource, N.Y.; (c) Bettmann/Corbis.)

separate into gametes according to Mendel's principle of segregation, and all the F_1 are heterozygous (B^+B^b). Because the trait is dominant in males and recessive in females, all the F_1 males will be bearded, and all the F_1 females will be beardless. When the F_1 are crossed with one another, $\frac{1}{4}$ of the F_2 progeny are B^bB^b, $\frac{1}{2}$ are B^bB^+, and $\frac{1}{4}$ are B^+B^+ (Figure 5.11b). Because male heterozygotes are bearded, $\frac{3}{4}$ of the males in the F_2 possess beards; because female heterozygotes are beardless, only $\frac{1}{4}$ of the females in F_2 are bearded.

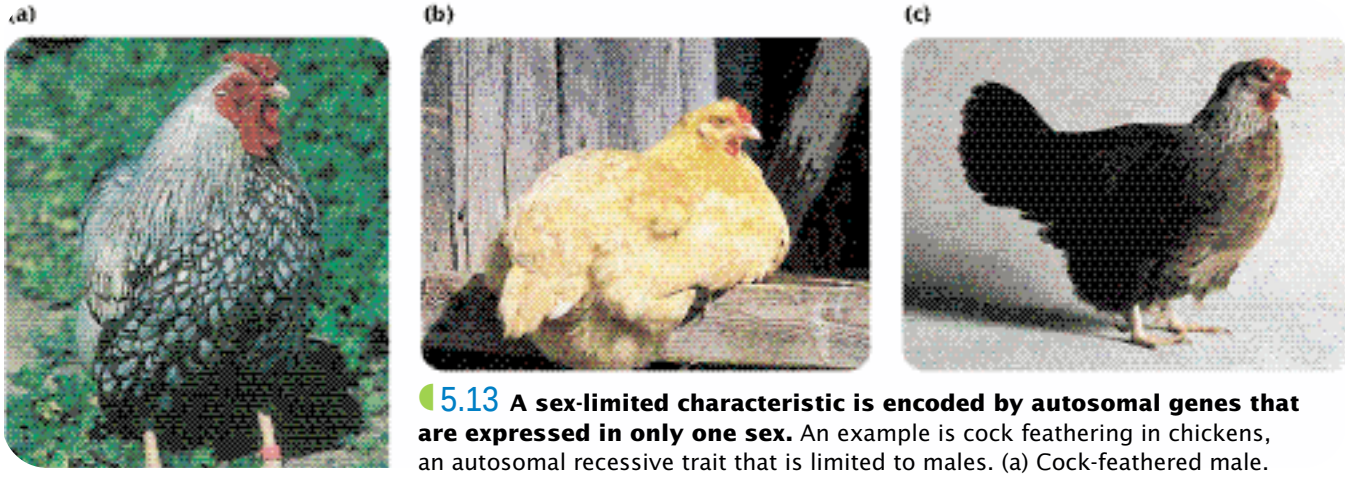
An example of a sex-influenced characteristic in humans is pattern baldness, in which hair is lost prematurely from the front and the top of the head (Figure 5.12). Pattern baldness is an autosomal character believed to be dominant in males and recessive in females, just like beards in goats. Contrary to a popular misconception, a man does not inherit pattern baldness from his mother's side of the family (which would be the case if the character were X linked, but it isn't). Pattern baldness is autosomal; men and women can inherit baldness from either their mothers or their fathers. Men require only a single allele for baldness to become bald, whereas women require two alleles for baldness, and so pattern baldness is much more common among men. Furthermore, pattern baldness is expressed weakly in women; those with the trait usually have only a mild thinning of the hair, whereas men frequently lose all the hair on the top of the head. The expression of the allele for pattern baldness is clearly enhanced by the presence of male sex hormones; males who are castrated at an early age rarely become bald (but castration is not a recommended method for preventing baldness).

An extreme form of sex-influenced inheritance, a **sex-limited characteristic** is encoded by autosomal genes that are expressed in only one sex—the trait has zero penetrance in the other sex. In domestic chickens, some males display a plumage pattern called cock feathering (Figure 5.13a). Other males and all females display a pattern called hen feathering (Figure 5.13b and c). Cock feathering is an autosomal recessive trait that is sex limited to males. Because the trait is autosomal, the genotypes of males and females are the same, but the phenotypes produced by these genotypes differ in males and females:

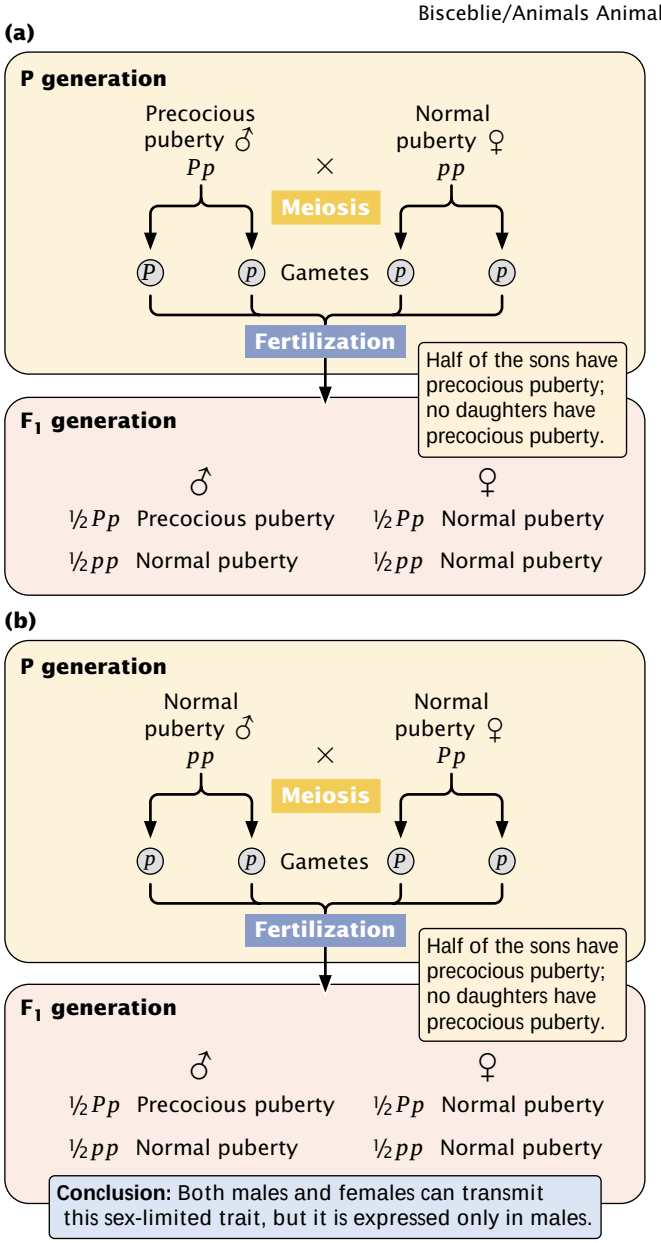
Genotype	Male phenotype	Female phenotype
HH	hen feathering	hen feathering
Hh	hen feathering	hen feathering
hh	cock feathering	hen feathering

An example of a sex-limited characteristic in humans is male-limited precocious puberty. There are several types of precocious puberty in humans, most of which are not genetic. Male-limited precocious puberty, however, results from an autosomal dominant allele (*P*) that is expressed only in males; females with the gene are normal in phenotype. Males with precocious puberty undergo puberty at an early age, usually before the age of 4. At this time, the penis enlarges, the voice deepens, and pubic hair develops. There is no impairment of sexual function; affected males are fully fertile. Most are short as adults, because the long bones stop growing after puberty.

Because the trait is rare, affected males are usually heterozygous (*Pp*). A male with precocious puberty who mates



5.13 A sex-limited characteristic is encoded by autosomal genes that are expressed in only one sex. An example is cock feathering in chickens, an autosomal recessive trait that is limited to males. (a) Cock-feathered male. (b) and (c) Hen-feathered females. (Part a, Richard Kolar/Animals Animals; part b, Michael Bisceblie/Animals Animals; part c, R. OSF Dowling/Animals Animals.)



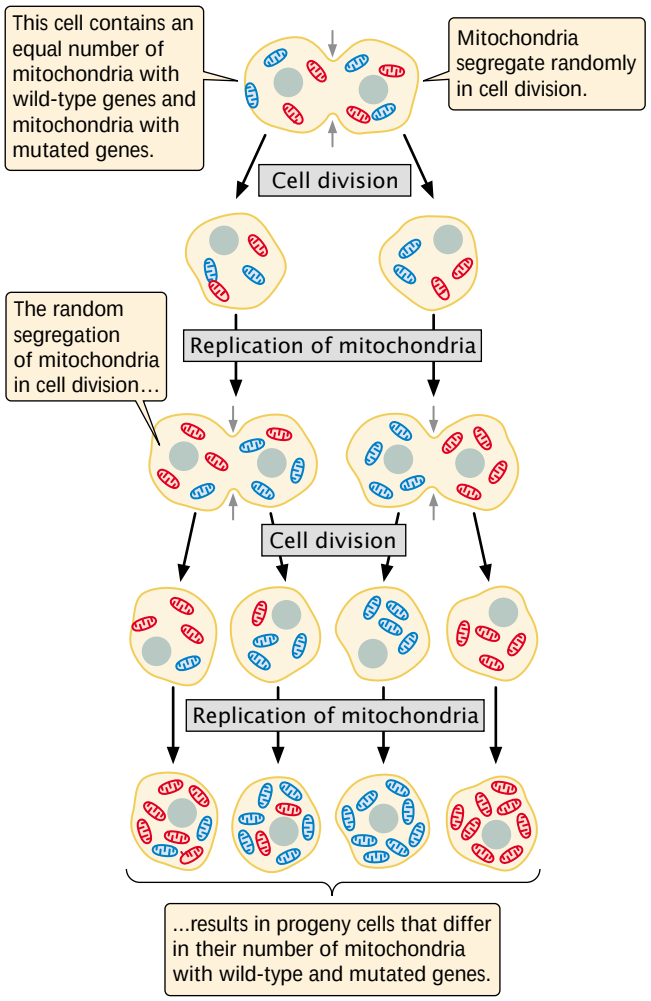
with a woman who has no family history of this condition will transmit the allele for precocious puberty to ½ of the children (Figure 5.14a), but it will be expressed only in the sons. If one of the heterozygous daughters (*Pp*) mates with a male who has normal puberty (*pp*), ½ of the sons will exhibit precocious puberty (Figure 5.14b). Thus a sex-limited characteristic can be inherited from either parent, although the trait appears in only one sex.

The results of molecular studies reveal that the underlying genetic defect in male-limited precocious puberty affects the receptor for luteinizing hormone (LH). This hormone normally attaches to receptors found on certain cells of the testes and stimulates these cells to produce testosterone. During normal puberty in males, high levels of LH stimulate the increased production of testosterone, which, in turn, stimulates the anatomical and physiological changes associated with puberty. The *P* allele for precocious puberty codes for a defective LH receptor, which stimulates testosterone production even in the absence of LH. Boys with this allele produce high levels of testosterone at an early age, when levels of LH are low. Defective LH receptors are also found in females who carry the precocious-puberty gene, but their presence does not result in precocious puberty, because additional hormones are required along with LH to induce puberty in girls.

Concepts

Sex-influenced characteristics are traits encoded by autosomal genes that are more readily expressed in one sex. Sex-limited characteristics are encoded by autosomal genes whose expression is limited to one sex.

5.14 Sex-limited characteristics are inherited according to Mendel's principles. Precocious puberty is an autosomal dominant trait that is limited to males.



5.15 Cytoplasmically inherited characteristics frequently exhibit extensive phenotypic variation because cells and individual offspring contain various proportions of cytoplasmic genes. Mitochondria that have wild-type mtDNA are shown in red; those having mutant mtDNA are shown in blue.

Cytoplasmic Inheritance

Mendel's principles of segregation and independent assortment are based on the assumption that genes are located on chromosomes in the nucleus of the cell. For the majority of genetic characteristics, this assumption is valid, and Mendel's principles allow us to predict the types of offspring that will be produced in a genetic cross. However, not all the genetic material of a cell is found in the nucleus; some characteristics are encoded by genes located in the cytoplasm. These characteristics exhibit **cytoplasmic inheritance**.

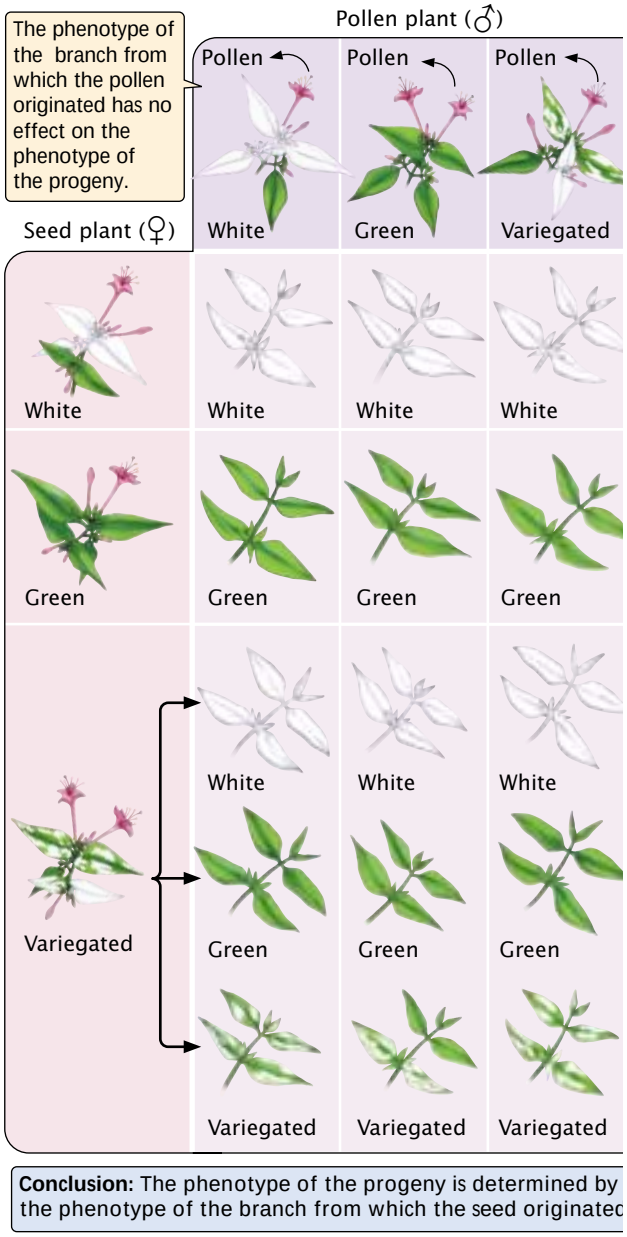
A few organelles, notably chloroplasts and mitochondria, contain DNA. Each human mitochondrion contains about 15,000 nucleotides of DNA, encoding 37 genes. Compared with that of nuclear DNA, which contains some 3 billion nucleotides encoding perhaps 35,000 genes, the amount of mitochondrial DNA (mtDNA) is very small; nevertheless, mitochondrial and chloroplast genes encode some important characteristics. The molecular details of this extranuclear DNA are discussed in Chapter 20; here, we will focus on *patterns* of cytoplasmic inheritance.

Cytoplasmic inheritance differs from the inheritance of characteristics encoded by nuclear genes in several important respects. A zygote inherits nuclear genes from both parents, but typically all of its cytoplasmic organelles, and thus all its cytoplasmic genes, come from only one of the gametes, usually the egg. Sperm generally contributes only a set of nuclear genes from the male parent. In a few organisms, cytoplasmic genes are inherited from the male parent, or from both parents; however, for most organisms, all the cytoplasm is inherited from the egg. In this case, cytoplasmically inherited maits are present in both males and females and are passed from mother to offspring, never from father to offspring. Reciprocal crosses, therefore, give different results when cytoplasmic genes encode a trait.

Cytoplasmically inherited characteristics frequently exhibit extensive phenotypic variation, because there is no mechanism analogous to mitosis or meiosis to ensure that cytoplasmic genes are evenly distributed in cell division. Thus, different cells and individuals will contain various proportions of cytoplasmic genes.

Consider mitochondrial genes. There are thousands of mitochondria in each cell, and each mitochondrion contains from 2 to 10 copies of mtDNA. Suppose that half of the mitochondria in a cell contain a normal wild-type copy of mtDNA and the other half contain a mutated copy (FIGURE 5.15). In cell division, the mitochondria segregate into progeny cells at random. Just by chance, one cell may receive mostly mutated mtDNA and another cell may receive mostly wild-type mtDNA (see Figure 5.15). In this way, different progeny from the same mother and even cells within an individual offspring may vary in their phenotype. Traits encoded by chloroplast DNA (cpDNA) are similarly variable.

In 1909, cytoplasmic inheritance was recognized by Carl Correns as one of the first exceptions to Mendel's principles. Correns, one of the biologists who rediscovered Mendel's work, studied the inheritance of leaf variegation in the four-o'clock plant, *Mirabilis jalapa*. Correns found that the leaves and shoots of one variety of four-o'clock were variegated, displaying a mixture of green and white splotches. He also noted that some branches of the variegated strain had all-green leaves; other branches had all-white leaves. Each branch produced flowers; so Correns was able to cross flowers from variegated, green, and white branches in all combinations (FIGURE 5.16). The seeds from green branches always gave rise to green progeny, no matter whether the pollen was from a green, white, or variegated branch. Similarly, flowers on white branches always produced white progeny. Flowers on the variegated branches gave rise to green, white, and variegated progeny, in no particular ratio.



5.16 Crosses for leaf type in four o'clocks illustrate cytoplasmic inheritance.

Corren's crosses demonstrated cytoplasmic inheritance of variegation in the four-o'clocks. The phenotypes of the offspring were determined entirely by the maternal parent, never by the paternal parent (the source of the pollen). Furthermore, the production of all three phenotypes by flowers on variegated branches is consistent with the occurrence of cytoplasmic inheritance. Variegation in these plants is caused by a defective gene in the cpDNA, which results in a failure to produce the green pigment chlorophyll. Cells from green branches contain normal chloroplasts only, cells from white branches contain abnormal chloroplasts only, and cells from variegated branches contain a mixture of normal and abnormal chloroplasts. In the flowers from variegated branches, the random segregation of chloroplasts in the course of oogenesis produces some egg cells with normal cpDNA, which develop into green progeny; other egg cells with only abnormal cpDNA develop into white progeny; and, finally, still other egg cells with a mixture of normal and abnormal cpDNA develop into variegated progeny.

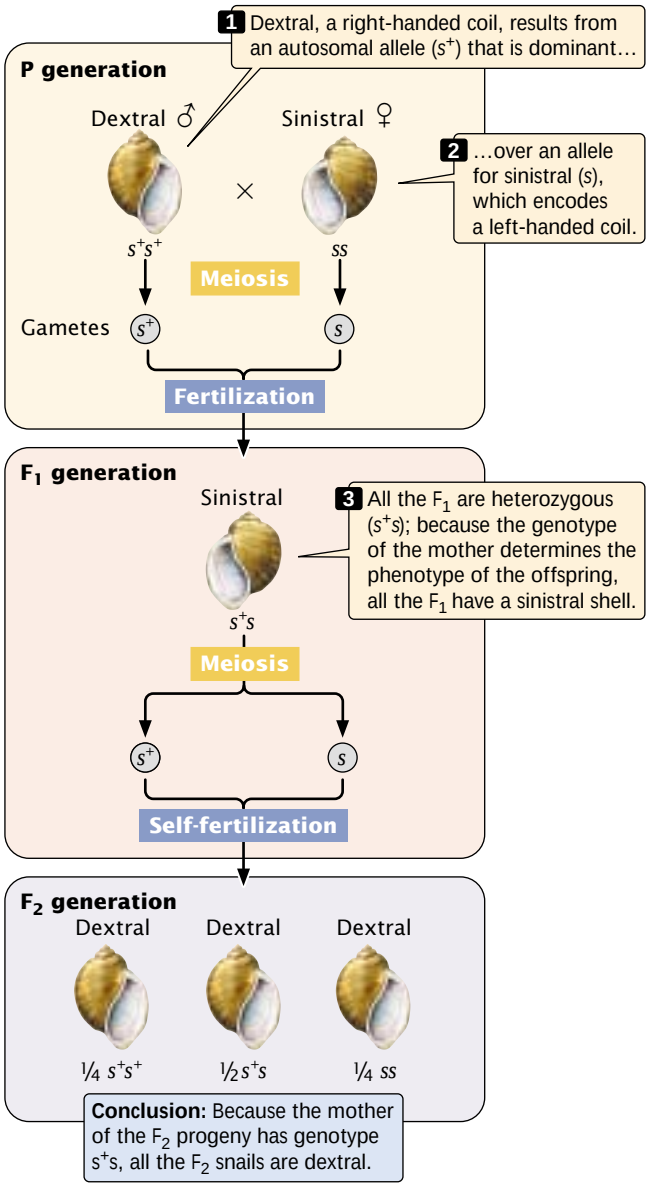
In recent years, a number of human diseases (mostly rare) that exhibit cytoplasmic inheritance have been identified. These disorders arise from mutations in mtDNA, most of which occur in genes coding for components of the electron-transport chain, which generates most of the ATP (adenosine triphosphate) in aerobic cellular respiration. One such disease is Leber hereditary optic neuropathy. Patients who have this disorder experience rapid loss of vision in both eyes, resulting from the death of cells in the optic nerve. Loss of vision typically occurs in early adulthood (usually between the ages of 20 and 24), but it can occur any time after adolescence. There is much clinical variability in the severity of the disease, even within the same family. Leber hereditary optic neuropathy exhibits maternal inheritance: the trait is always passed from mother to child.

Genetic Maternal Effect

A genetic phenomenon that is sometimes confused with cytoplasmic inheritance is **genetic maternal effect,** in which the phenotype of the offspring is determined by the genotype of the mother. In cytoplasmic inheritance, the genes for a characteristic are inherited from only one parent, usually the mother. In genetic maternal effect, the genes are inherited from both parents, but the offspring's phenotype is determined not by its own genotype but by the genotype of its mother.

Genetic maternal effect frequently arises when substances present in the cytoplasm of an egg (encoded by the mother's genes) are pivotal in early development. An excellent example is shell coiling of the snail *Limnaea peregra.* In most snails of this species, the shell coils to the right, which is termed dextral coiling. However, some snails possess a left-coiling shell, exhibiting sinistral coiling. The direction of coiling is determined by a pair of alleles; the allele for dextral (s^+) is dominant over the allele for sinistral *(s)*. However, the direction of coiling is determined not by that snail's own genotype, but by the genotype of its *mother.* The direction of coiling is affected by the way in which the cytoplasm divides soon after fertilization, which in turn is determined by a substance produced by the mother and passed to the offspring in the cytoplasm of the egg.

If a male homozygous for dextral alleles (s^+s^+) is crossed with a female homozygous for sinistral alleles (*ss*), all of the F_1 are heterozygous (s^+s) and have a sinistral shell, because the genotype of the mother (*ss*) codes for sinistral (Figure 5.17). If these F_1 snails are self-fertilized, the genotypic ratio of the F_2 is 1 s^+s^+ : 2 s^+s : 1 *ss*. The phenotype of all F_2 snails will be dextral regardless of their genotypes, because the genotype of their mother (s^+s) encodes a right-coiling shell and determines their phenotype.



5.17 In genetic maternal effect, the genotype of the maternal parent determines the phenotype of the offspring. Shell coiling in snails is a trait that exhibits genetic maternal effect.

Notice that the phenotype of the progeny is not necessarily the same as the phenotype of the mother, because the progeny's phenotype is determined by the mother's *genotype*, not her phenotype. Neither the male parent's nor the offspring's own genotype has any role in the offspring's phenotype. A male does influence the phenotype of the F_2 generation; by contributing to the genotypes of his daughters, he affects the phenotypes of their offspring. Genes that exhibit genetic maternal effect are therefore transmitted through males to future generations. In contrast, the genes that exhibit cytoplasmic inheritance are always transmitted through only one of the sexes (usually the female).

Concepts

Characteristics exhibiting cytoplasmic inheritance are encoded by genes in the cytoplasm and are usually inherited from one parent, most commonly the mother. In genetic maternal effect, the genotype of the mother determines the phenotype of the offspring.

Genomic Imprinting

One of the basic tenets of Mendelian genetics is that the parental origin of a gene does not affect its expression—reciprocal crosses give identical results. We have seen that there are some genetic characteristics—those encoded by X-linked genes and cytoplasmic genes—for which reciprocal crosses do not give the same results. In these cases, males and females do not contribute the same genetic material to the offspring. With regard to autosomal genes, males and females contribute the same number of genes, and paternal and maternal genes have long been assumed to have equal effects. The results of recent studies, however, have identified several mammalian genes whose expression is significantly affected by their parental origin. This phenomenon, the differential expression of genetic material depending on whether it is inherited from the male or female parent, is called **genomic imprinting.**

Genomic imprinting has been observed in mice in which a particular gene has been artificially inserted into a mouse's DNA (to create a transgenic mouse). In these mice, the inserted gene is faithfully passed from generation to generation, but its expression may depend on which parent transmitted the gene. For example, when a transgenic male passes an imprinted gene to his offspring, they express the gene; but, when his daughter transmits the same gene to her offspring, they don't express it. In turn, her son's offspring express it, but her daughter's offspring don't. Both male and female offspring possess the gene for the trait; the key to whether the gene is expressed is the sex of the parent transmitting the gene. In the present example, the gene is expressed only when it is transmitted by a male parent. The reverse situation, expression of a trait when the gene is transmitted by the female parent, also occurs.

Genomic imprinting has been implicated in several human disorders, including Prader-Willi and Angelman syndromes. Children with Prader-Willi syndrome have small hands and feet, short stature, poor sexual development, and mental retardation; they develop voracious appetites and frequently become obese. Many persons with Prader-Willi syndrome are missing a small region of chromosome 15 called q11–13. The deletion of this region is always inherited from the father in persons with Prader-Willi syndrome.

The deletions of q11–13 on chromosome 15 can also be inherited from the *mother*, but this inheritance results in a completely different set of symptoms, producing Angelman

Table 5.4 Sex influences on heredity

Genetic Phenomenon	Phenotype Determined by
Sex-linked characteristic	genes located on the sex chromosome
Sex-influenced characteristic	genes on autosomal chromosomes that are more readily expressed in one sex
Sex-limited characteristic	autosomal genes whose expression is limited to one sex
Genetic maternal effect	nuclear genotype of the maternal parent
Cytoplasmic inheritance	cytoplasmic genes, which are usually inherited entirely from only one parent
Genomic imprinting	genes whose expression is affected by the sex of the transmitting parent

syndrome. Children with Angelman syndrome exhibit frequent laughter, uncontrolled muscle movement, a large mouth, and unusual seizures. The deletion of segment q11–13 from chromosome 15 has severe effects on the human phenotype, but the specific effects depend on which parent contributes the deletion. For normal development to take place, copies of segment q11–13 of chromosome 15 from both male and female parents are apparently required.

Several other human diseases also appear to exhibit genomic imprinting. Although the precise mechanism of this phenomenon is unknown, methylation of DNA—the addition of methyl (CH_3) groups to DNA nucleotides (see Chapters 10 and 16)—is essential to the process of genomic imprinting, as demonstrated by the observation that mice deficient in DNA methylation do not exhibit imprinting. Some of the ways in which sex interacts with heredity are summarized in Table 5.4.

Concepts

In genomic imprinting, the expression of a gene is influenced by the sex of the parent who transmits the gene to the offspring.

www.whfreeman.com/pierce Additional information about genomic imprinting, Prader-Willi syndrome, and Angelman syndrome

Anticipation

Another genetic phenomenon that is not explained by Mendel's principles is **anticipation,** in which a genetic trait becomes more strongly expressed or is expressed at an earlier age as it is passed from generation to generation. In the early 1900s, several physicians observed that patients with moderate to severe myotonic dystrophy—an autosomal dominant muscle disorder—frequently had ancestors who were only mildly affected by the disease. These observations led to the concept of anticipation. However, the concept quickly fell out of favor with geneticists because there was no obvious mechanism to explain it; traditional genetics held that genes are passed unaltered from parents to offspring. Geneticists tended to attribute anticipation to observational bias.

The results of recent research have reestablished anticipation as a legitimate genetic phenomenon. The mutation causing myotonic dystrophy consists of an unstable region of DNA that can increase or decrease in size as the gene is passed from generation to generation, much like the gene that causes Huntington disease. The age of onset and the severity of the disease are correlated with the size of the unstable region; an increase in the size of the region through generations produces anticipation. The phenomenon has now been implicated in several genetic diseases. We will examine these interesting types of mutations in more detail in Chapter 17.

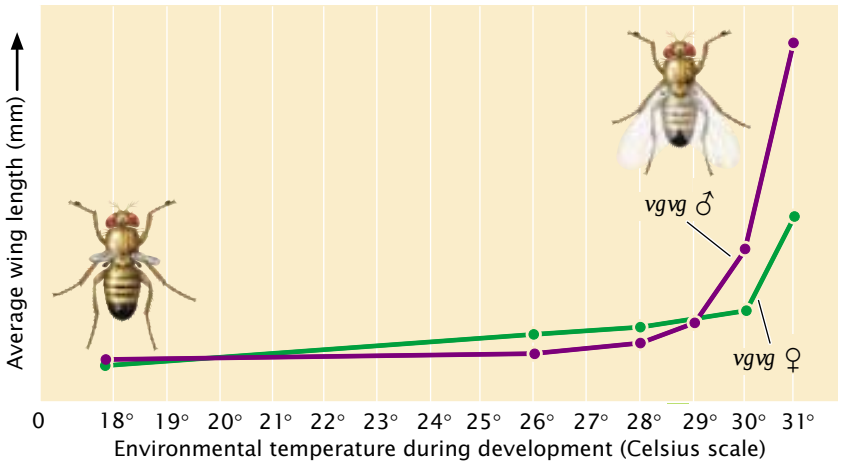
Concepts

Anticipation is the stronger or earlier expression of a genetic trait through succeeding generations. It is caused by an unstable region of DNA that increases or decreases in size.

Interaction Between Genes and Environment

In Chapter 3, we learned that each phenotype is the result of a genotype developing within a specific environment; the genotype sets the potential for development, but how the phenotype actually develops within the limits imposed by the genotype depends on environmental effects. Stated another way, each genotype may produce several different phenotypes, depending on the environmental conditions in which development occurs. For example, genotype *GG* may produce a plant that is 10 cm high when raised at 20°C, but the same genotype may produce a plant that is 18 cm high when raised at 25°C. The range of phenotypes produced by a genotype in different environments (in this case, plant height) is called the **norm of reaction** (◖ FIGURE 5.18).

For most of the characteristics discussed so far, the effect of the environment on the phenotype has been slight.



5.18 Norm of reaction is the range of phenotypes produced by a genotype in different environments. This norm of reaction is for vestigial wings in *Drosophila melanogaster.* (Data from M. H. Harnly, *Journal of Experimental Zoology* 56:363–379, 1936.)

Mendel's peas with genotype *yy*, for example, developed yellow endosperm regardless of the environment in which they were raised. Similarly, persons with genotype I^AI^A have the A antigen on their red blood cells regardless of their diet, socioeconomic status, or family environment. For other phenotypes, however, environmental effects play a more important role.

Environmental Effects on Gene Expression

The expression of some genotypes is critically dependent on the presence of a specific environment. For example, the *himalayan* allele in rabbits produces dark fur at the extremities of the body—on the nose, ears, and feet (FIGURE 5.19). The dark pigment develops, however, only when the rabbit is reared at 25°C or less; if a Himalayan rabbit is reared at 30°C, no dark patches develop. The expression of the *himalayan* allele is thus temperature dependent—an enzyme necessary for the production of dark pigment is inactivated at higher temperatures. The pigment is normally restricted to the nose, feet, and ears of Himalayan rabbits because the animal's core body temperature is normally above 25°C and the enzyme is functional only in the cells of the relatively cool extremities. The *himalayan* allele is an example of a **temperature-sensitive allele,** an allele whose product is functional only at certain temperatures.

Some types of albinism in plants are temperature dependent. In barley, an autosomal recessive allele inhibits chlorophyll production, producing albinism when the plant is grown below 7°C. At temperatures above 18°C, a plant homozygous for the albino allele develops normal chlorophyll and is green. Similarly, among *Drosophila melanogaster* homozygous for the autosomal mutation *vestigial*, greatly reduced wings develop at 25°C, but wings near normal size develop at higher temperatures (see Figure 5.18).

Environmental factors also play an important role in the expression of a number of human genetic diseases. Glucose-6-phosphate dehydrogenase is an enzyme taking part in supplying energy to the cell. In humans, there are a number of genetic variants of glucose-6-phosphate dehydrogenase, some of which destroy red blood cells when the body is stressed by infection or by the ingestion of certain drugs or foods. The symptoms of the genetic disease appear only in the presence of these specific environmental factors.

Another genetic disease, phenylketonuria (PKU), is due to an autosomal recessive allele that causes mental retardation. The disorder arises from a defect in an enzyme that normally metabolizes the amino acid phenylalanine. When this enzyme is defective, phenylalanine is not metabolized, and its buildup causes brain damage in children. A simple

5.19 The expression of some genotypes depends on specific environments. The expression of a temperature-sensitive allele, *himalayan,* is shown in rabbits reared at different temperatures.

Reared at 20°C or less

Reared at temperatures above 30°C

environmental change, putting an affected child on a low-phenylalanine diet, prevents retardation.

These examples illustrate the point that genes and their products do not act in isolation; rather, they frequently interact with environmental factors. Occasionally, environmental factors alone can produce a phenotype that is the same as the phenotype produced by a genotype; this phenotype is called a **phenocopy.** In fruit flies, for example, the autosomal recessive mutation *eyeless* produces greatly reduced eyes. The eyeless phenotype can also be produced by exposing the larvae of normal flies to sodium metaborate.

Concepts

The expression of many genes is modified by the environment. The range of phenotypes produced by a genotype in different environments is called the norm of reaction. A phenocopy is a trait produced by environmental effects that mimics the phenotype produced by a genotype.

The Inheritance of Continuous Characteristics

So far, we've dealt primarily with characteristics that have only a few distinct phenotypes. In Mendel's peas, for example, the seeds were either smooth or wrinkled, yellow or green; the coats of dogs were black, brown, or yellow; blood types were of four distinct types, A, B, AB, or O. Characteristics such as these, which have a few easily distinguished phenotypes, are called **discontinuous characteristics.**

Not all characteristics exhibit discontinuous phenotypes. Human height is an example of such a character; people do not come in just a few distinct heights but, rather, display a continuum of heights. Indeed, there are so many possible phenotypes of human height that we must use a measurement to describe a person's height. Characteristics that exhibit a continuous distribution of phenotypes are termed **continuous characteristics.** Because such characteristics have many possible phenotypes and must be described in quantitative terms, continuous characteristics are also called **quantitative characteristics.**

Continuous characteristics frequently arise because genes at many loci interact to produce the phenotypes. When a single locus with two alleles codes for a characteristic, there are three genotypes possible: *AA*, *Aa*, and *aa*. With two loci, each with two alleles, there are $3^2 = 9$ genotypes possible. The number of genotypes coding for characteristic is 3^n, where n equals the number of loci with two alleles that influence the characteristic. For example, when a characteristic is determined by eight loci, each with two alleles, there are $3^8 = 6561$ different genotypes possible for this character. If each genotype produces a different phenotype, many phenotypes will be possible. The slight differences between the phenotypes will be indistinguishable, and the characteristic will appear continuous. Characteristics encoded by genes at many loci are called **polygenic characteristics.**

The converse of polygeny is **pleiotropy,** in which one gene affects multiple characteristics. Many genes exhibit pleiotropy. PKU, mentioned earlier, results from a recessive allele; persons homozygous for this allele, if untreated, exhibit mental retardation, blue eyes, and light skin color.

Frequently the phenotypes of continuous characteristics are also influenced by environmental factors. Each genotype is capable of producing a range of phenotypes—it has a relatively broad norm of reaction. In this situation, the particular phenotype that results depends on both the genotype and the environmental conditions in which the genotype develops. For example, there may be only three genotypes coding for a characteristic, but, because each genotype has a broad norm of reaction, the phenotype of the character exhibits a continuous distribution. Many continuous characteristics are both polygenic and influenced by environmental factors; such characteristics are called **multifactorial** because many factors help determine the phenotype.

The inheritance of continuous characteristics may appear to be complex, but the alleles at each locus follow Mendel's principles and are inherited in the same way as alleles coding for simple, discontinuous characteristics. However, because many genes participate, environmental factors influence the phenotype, and the phenotypes do not sort out into a few distinct types, we cannot observe the distinct ratios that have allowed us to interpret the genetic basis of discontinuous characteristics. To analyze continuous characteristics, we must employ special statistical tools, as will be discussed in Chapter 22.

Concepts

Discontinuous characteristics exhibit a few distinct phenotypes; continuous characteristics exhibit a range of phenotypes. A continuous characteristic is frequently produced when genes at many loci and environmental factors combine to determine a phenotype.

Connecting Concepts Across Chapters

This chapter introduced a number of modifications and extensions of the basic concepts of heredity that we learned in Chapter 3. A major theme has been gene expression: how interactions between genes, interactions between genes and sex, and interactions between genes and the environment affect the phenotypic expression of genes. The modifications and extensions discussed in this chapter do not alter the way that genes are inherited, but they do modify the way in which the genes determine the phenotype.

A number of topics introduced in this chapter will be explored further in other chapters of the book. Here we have purposefully ignored many aspects of the nature of gene expression because our focus has been on the "big picture" of how these interactions affect phenotypic ratios in genetic crosses. In subsequent chapters, we will explore the molecular details of gene expression, including transcription (Chapter 13), translation (Chapter 15), and the control of gene expression (Chapter 16). The molecular nature of anticipation will be examined in more detail in Chapter 17, and DNA methylation, the basis of genomic imprinting, will be discussed in Chapter 10. Complementation testing will be revisited in Chapter 8, and the role of multiple genes and environmental factors in the inheritance of continuous characteristics will be studied more thoroughly in Chapter 22.

CONCEPTS SUMMARY

- Dominance always refers to genes at the same locus (allelic genes) and can be understood in regard to how the phenotype of the heterozygote relates to the phenotypes of the homozygotes.
- Dominance is complete when a heterozygote has the same phenotype as a homozygote. Dominance is incomplete when the heterozygote has a phenotype intermediate between those of two parental homozygotes. Codominance is the result when the heterozygote exhibits traits of both parental homozygotes.
- The type of dominance does not affect the inheritance of an allele; it does affect the phenotypic expression of the allele. The classification of dominance may depend on the level of the phenotype examined.
- Lethal alleles cause the death of an individual possessing them, usually at an early stage of development, and may alter phenotypic ratios.
- Multiple alleles refers to the presence of more than two alleles at a locus within a group. Their presence increases the number of genotypes and phenotypes possible.
- Gene interaction refers to interaction between genes at different loci to produce a single phenotype. An epistatic gene at one locus suppresses or masks the expression of hypostatic genes at different loci. Gene interaction frequently produces phenotypic ratios that are modifications of dihybrid ratios.
- A complementation test, in which individuals homozygous for different mutations are crossed, can be used to determine if the mutations occur at the same locus or at different loci.
- Sex-influenced characteristics are encoded by autosomal genes that are expressed more readily in one sex.
- Sex-limited characteristics are encoded by autosomal genes expressed in only one sex. Both males and females possess sex-limited genes and transmit them to their offspring.
- In cytoplasmic inheritance, the genes for the characteristic are found in the cytoplasm and are usually inherited from a single (usually maternal parent).
- Genetic maternal effect is present when an offspring inherits genes from both parents, but the nuclear genes of the mother determine the offspring's phenotype.
- Genomic imprinting refers to characteristics encoded by autosomal genes whose expression is affected by the sex of the parent transmitting the genes.
- Anticipation refers to a genetic trait that is more strongly expressed or is expressed at an earlier age in succeeding generations.
- Phenotypes are often modified by environmental effects. The range of phenotypes that a genotype is capable of producing in different environments is the norm of reaction. A phenocopy is a phenotype produced by an environmental effect that mimics a phenotype produced by a genotype.
- Discontinuous characteristics are characteristics with a few distinct phenotypes; continuous characteristics are those that exhibit a wide range of phenotypes. Continuous characteristics are frequently produced by the combined effects of many genes and environmental effects.

IMPORTANT TERMS

codominance (p. 103)
lethal allele (p. 104)
multiple alleles (p. 105)
gene interaction (p. 107)
epistasis (p. 108)
epistatic gene (p. 108)
hypostatic gene (p. 108)
complementation test (p. 114)
complementation (p. 115)
sex-influenced characteristic (p. 115)
sex-limited characteristic (p. 116)
cytoplasmic inheritance (p. 118)
genetic maternal effect (p. 119)
genomic imprinting (p. 120)
anticipation (p. 121)
norm of reaction (p. 121)
temperature-sensitive allele (p. 122)
phenocopy (p. 123)
discontinuous characteristic (p. 123)
continuous characteristic (p. 123)
quantitative characteristic (p. 123)
polygenic characteristic (p. 123)
pleiotropy (p. 123)
multifactorial characteristic (p. 123)