CHAPTER OUTLINE

Inheritance patterns and alleles. *In the petunia, multiple alleles can result in flowers with several different colors, such as the three shown here.*

4 EXTENSIONS OF MENDELIAN INHERITANCE

The term **Mendelian inheritance** describes inheritance patterns that obey two laws: the law of segregation and the law of independent assortment. Until now, we have mainly considered traits that are affected by a single gene that is found in two different alleles. In these cases, one allele is dominant over the other. This type of inheritance is sometimes called **simple Mendelian inheritance** because the observed ratios in the offspring readily obey Mendel's laws. For example, when two different true-breeding pea plants are crossed (e.g., tall and dwarf) and the F_1 generation is allowed to self-fertilize, the F_2 generation shows a 3:1 phenotypic ratio of tall to dwarf offspring.

In Chapter 4, we will extend our understanding of Mendelian inheritance by first examining the transmission patterns for several traits that do not display a simple dominant/recessive relationship. Geneticists have discovered an amazing diversity of mechanisms by which alleles affect the outcome of traits. Many alleles don't produce the ratios of offspring that are expected from a simple Mendelian relationship. This does not mean that Mendel was wrong. Rather, the inheritance patterns of many traits are more complex and interesting than he had realized. In this chapter, we will examine how the outcome of a trait may be influenced by a variety of factors such as the level of protein expression, the sex of the individual, the presence of multiple alleles of a given gene, and environmental effects. We will also explore how two different genes can contribute to the outcome of a single trait. Later, in Chapters 5 and 6, we will examine eukaryotic inheritance patterns that actually violate the laws of segregation or independent assortment.

4.1 INHERITANCE PATTERNS OF SINGLE GENES

We begin Chapter 4 with the further exploration of traits that are influenced by a single gene. **Table 4.1** describes the general features of several types of Mendelian inheritance patterns that have been observed by researchers. These various patterns occur because the outcome of a trait may be governed by two or more alleles in many different ways. In this section, we will examine these patterns with two goals in mind. First, we want to understand how the molecular expression of genes can account for an individual's phenotype. In other words, we will explore the underlying relationship between molecular genetics—the expression of genes to produce functional proteins—and the traits of individuals that inherit the genes. Our second goal concerns the outcome of crosses. Many of the inheritance patterns described

TABLE **4.1**

Types of Mendelian Inheritance Patterns Involving Single Genes

Type	Description
Simple Mendelian	**Inheritance:** This term is commonly applied to the inheritance of alleles that obey Mendel's laws and follow a strict dominant/recessive relationship. In Chapter 4, we will see that some genes can be found in three or more alleles, making the relationship more complex. **Molecular:** 50% of the protein, produced by a single copy of the dominant (functional) allele in the heterozygote, is sufficient to produce the dominant trait.
Incomplete dominance	**Inheritance:** This pattern occurs when the heterozygote has a phenotype that is intermediate between either corresponding homozygote. For example, a cross between homozygous red-flowered and homozygous white-flowered parents will have heterozygous offspring with pink flowers. **Molecular:** 50% of the protein, produced by a single copy of the functional allele in the heterozygote, is not sufficient to produce the same trait as the homozygote making 100%.
Incomplete penetrance	**Inheritance:** This pattern occurs when a dominant phenotype is not expressed even though an individual carries a dominant allele. An example is an individual who carries the polydactyly allele but has a normal number of fingers and toes. **Molecular:** Even though a dominant gene may be present, the protein encoded by the gene may not exert its effects. This can be due to environmental influences or due to other genes that may encode proteins that counteract the effects of the protein encoded by the dominant allele.
Overdominance	**Inheritance:** This pattern occurs when the heterozygote has a trait that is more beneficial than either homozygote. **Molecular:** Three common ways that heterozygotes gain benefits: (1) Their cells may have increased resistance to infection by microorganisms; (2) they may produce more forms of protein dimers, with enhanced function; or (3) they may produce proteins that function under a wider range of conditions.
Codominance	**Inheritance:** This pattern occurs when the heterozygote expresses both alleles simultaneously. For example, in blood typing, an individual carrying the *A* and *B* alleles will have an AB blood type. **Molecular:** The codominant alleles encode proteins that function slightly differently from each other, and the function of each protein in the heterozygote affects the phenotype uniquely.
X-linked	**Inheritance:** This pattern involves the inheritance of genes that are located on the X chromosome. In mammals and fruit flies, males are hemizygous for X-linked genes, whereas females have two copies. **Molecular:** If a pair of X-linked alleles shows a simple dominant/recessive relationship, 50% of the protein, produced by a single copy of the dominant allele in a heterozygous female, is sufficient to produce the dominant trait (in the female).
Sex-influenced inheritance	**Inheritance:** This pattern refers to the effect of sex on the phenotype of the individual. Some alleles are recessive in one sex and dominant in the opposite sex. An example is pattern baldness in humans. **Molecular:** Sex hormones may regulate the molecular expression of genes. This can influence the phenotypic effects of alleles.
Sex-limited inheritance	**Inheritance:** This refers to traits that occur in only one of the two sexes. An example is breast development in mammals. **Molecular:** Sex hormones may regulate the molecular expression of genes. This can influence the phenotypic effects of alleles. In this case, sex hormones that are primarily produced in only one sex are essential to produce a particular phenotype.
Lethal alleles	**Inheritance:** An allele that has the potential of causing the death of an organism. **Molecular:** Lethal alleles are most commonly loss-of-function alleles that encode proteins that are necessary for survival. In some cases, the allele may be due to a mutation in a nonessential gene that changes a protein to function with abnormal and detrimental consequences.

in Table 4.1 do not produce a 3:1 phenotypic ratio when two heterozygotes produce offspring. In this section, we consider how allelic interactions produce ratios that differ from a simple Mendelian pattern. However, as our starting point, we will begin by reconsidering a simple dominant/recessive relationship from a molecular perspective.

Recessive Alleles Often Cause a Reduction in the Amount or Function of the Encoded Proteins

For any given gene, geneticists refer to prevalent alleles in a natural population as **wild-type alleles.** In large populations, more than one wild-type allele may occur—a phenomenon known as **genetic polymorphism.** For example, **Figure 4.1** illustrates a striking example of polymorphism in the elderflower orchid, *Dactylorhiza sambucina*. Throughout the range of this species in Europe, both yellow- and red-flowered individuals are prevalent. Both colors are considered wild type. At the molecular level, a wild-type allele typically encodes a protein that is made in the proper amount and functions normally. As discussed in Chapter 24, wild-type alleles tend to promote the reproductive success of organisms in their native environments.

In addition, random mutations occur in populations and alter preexisting alleles. Geneticists sometimes refer to these kinds of alleles as **mutant alleles** to distinguish them from the more common wild-type alleles. Because random mutations are more likely to disrupt gene function, mutant alleles are often defective in their ability to express a functional protein. Such mutant alleles tend to be rare in natural populations. They are typically, but not always, inherited in a recessive fashion.

Among Mendel's seven traits discussed in Chapter 2, the wild-type alleles are tall plants, purple flowers, axial flowers, yellow seeds, round seeds, green pods, and smooth pods (refer back to Figure 2.4). The mutant alleles are dwarf plants, white flowers,

terminal flowers, green seeds, wrinkled seeds, yellow pods, and constricted pods. You may have already noticed that the seven wild-type alleles are dominant over the seven mutant alleles. Likewise, red eyes and normal wings are examples of wild-type alleles in *Drosophila*, and white eyes and miniature wings are recessive mutant alleles.

The idea that recessive alleles usually cause a substantial decrease in the expression of a functional protein is supported by the analysis of many human genetic diseases. Keep in mind that a genetic disease is usually caused by a mutant allele. **Table 4.2** lists several examples of human genetic diseases in which the recessive allele fails to produce a specific cellular protein in its active form. In many cases, molecular techniques have enabled researchers to clone these genes and determine the differences between the wild-type and mutant alleles. They have found that the recessive allele usually contains a mutation that causes a defect in the synthesis of a fully functional protein.

To understand why many defective mutant alleles are inherited recessively, we need to take a quantitative look at protein function. With the exception of sex-linked genes, diploid individuals have two copies of every gene. In a simple dominant/recessive relationship, the recessive allele does not affect the phenotype of the heterozygote. In other words, a single copy of the dominant allele is sufficient to mask the effects of the recessive allele. If the recessive allele cannot produce a functional protein, how do we explain the wild-type phenotype of the heterozygote? As described in **Figure 4.2**, a common explanation is that 50% of the functional protein is adequate to provide the wild-type phenotype. In this example, the *PP* homozygote and *Pp* heterozygote

FIGURE 4.1 An example of genetic polymorphism. Both yellow and red flowers are common in natural populations of the elderflower orchid, *Dactylorhiza sambucina*, and both are considered wild type.

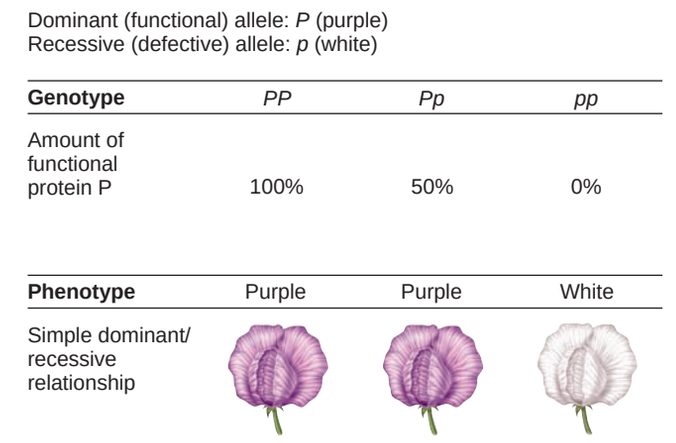


FIGURE 4.2 A comparison of protein levels among homozygous and heterozygous genotypes *PP*, *Pp*, and *pp*.
Genes →Traits In a simple dominant/recessive relationship, 50% of the protein encoded by one copy of the dominant allele in the heterozygote is sufficient to produce the wild-type phenotype, in this case, purple flowers. A complete lack of the functional protein results in white flowers.

TABLE **4.2**
Examples of Recessive Human Diseases

Disease	Protein That Is Produced by the Normal Gene*	Description
Phenylketonuria	Phenylalanine hydroxylase	Inability to metabolize phenylalanine. The disease can be prevented by following a phenylalanine-free diet. If the diet is not followed early in life, it can lead to severe mental impairment and physical degeneration.
Albinism	Tyrosinase	Lack of pigmentation in the skin, eyes, and hair.
Tay-Sachs disease	Hexosaminidase A	Defect in lipid metabolism. Leads to paralysis, blindness, and early death.
Sandhoff disease	Hexosaminidase B	Defect in lipid metabolism. Muscle weakness in infancy, early blindness, and progressive mental and motor deterioration.
Cystic fibrosis	Chloride transporter	Inability to regulate ion balance across epithelial cells. Leads to production of thick lung mucus and chronic lung infections.
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl transferase	Inability to metabolize purines, which are bases found in DNA and RNA. Leads to self-mutilation behavior, poor motor skills, and usually mental impairment and kidney failure.

*Individuals who exhibit the disease are either homozygous for a recessive allele or hemizygous (for X-linked genes in human males). The disease symptoms result from a defect in the amount or function of the normal protein.

each make sufficient functional protein to yield purple flowers. This means that the homozygous individual makes twice as much of the wild-type protein than it really needs to produce purple flowers. Therefore, if the amount is reduced to 50%, as in the heterozygote, the individual still has plenty of this protein to accomplish whatever cellular function it performs. The phenomenon that "50% of the normal protein is enough" is fairly common among many genes.

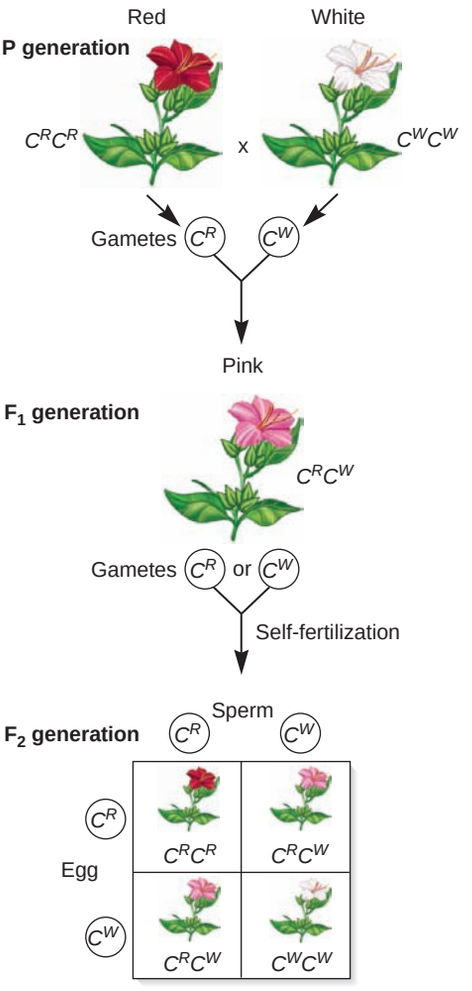
A second possible explanation for other genes is that the heterozygote actually produces more than 50% of the functional protein. Due to gene regulation, the expression of the normal gene may be increased or "up-regulated" in the heterozygote to compensate for the lack of function of the defective allele. The topic of gene regulation is discussed in Chapters 14 and 15.

Dominant Mutant Alleles Usually Exert Their Effects in One of Three Ways

Though dominant mutant alleles are much less common than recessive alleles, they do occur in natural populations. How can a mutant allele be dominant over a wild-type allele? Three explanations account for most dominant mutant alleles: a gain-of-function mutation, a dominant-negative mutation, or haploinsufficiency. Some dominant mutant alleles are due to **gain-of-function mutations.** Such mutations change the gene or the protein encoded by a gene so that it gains a new or abnormal function. For example, a mutant gene may be overexpressed and thereby produce too much of the encoded protein. A second category is **dominant-negative mutations** in which the protein encoded by the mutant gene acts antagonistically to the normal protein. In a heterozygote, the mutant protein counteracts the effects of the normal protein and thereby alters the phenotype. Finally, a third way that mutant alleles may affect phenotype is via **haploinsufficiency**. In this case, the mutant allele is a loss-of-function allele. Haploinsufficiency is used to describe patterns of inheritance in which a heterozygote (with one functional allele and one inactive allele) exhibits an abnormal or disease phenotype. An example in humans is a condition called polydactyly in which a heterozygous individual has extra fingers or toes (look ahead to Figure 4.5).

Incomplete Dominance Occurs When Two Alleles Produce an Intermediate Phenotype

Although many alleles display a simple dominant/recessive relationship, geneticists have also identified some cases in which a heterozygote exhibits **incomplete dominance**—a condition in which the phenotype is intermediate between the corresponding homozygous individuals. In 1905, the German botanist Carl Correns first observed this phenomenon in the color of the four-o'clock (*Mirabilis jalapa*). **Figure 4.3** describes Correns' experiment, in which a homozygous red-flowered four-o'clock plant was crossed to a homozygous white-flowered plant. The wild-type allele for red flower color is designated C^R and the white allele is C^W. As shown here, the offspring had pink flowers. If these F_1 offspring were allowed to self-fertilize, the F_2 generation



INTERACTIVE EXERCISE

FIGURE 4.3 Incomplete dominance in the four-o'clock plant, *Mirabilis jalapa*.

Genes →Traits When two different homozygotes (C^RC^R and C^WC^W) are crossed, the resulting heterozygote, C^RC^W, has an intermediate phenotype of pink flowers. In this case, 50% of the functional protein encoded by the C^R allele is not sufficient to produce a red phenotype.

consisted of 1/4 red-flowered plants, 1/2 pink-flowered plants, and 1/4 white-flowered plants. The pink plants in the F_2 generation were heterozygotes with an intermediate phenotype. As noted in the Punnett square in Figure 4.3, the F_2 generation displayed a 1:2:1 phenotypic ratio, which is different from the 3:1 ratio observed for simple Mendelian inheritance.

In Figure 4.3, incomplete dominance resulted in a heterozygote with an intermediate phenotype. At the molecular level, the allele that causes a white phenotype is expected to result in a lack of a functional protein required for pigmentation. Depending on the effects of gene regulation, the heterozygotes may produce only 50% of the normal protein, but this amount is not sufficient to produce the same phenotype as the C^RC^R homozygote, which may make twice as much of this protein. In this example, a reasonable explanation is that 50% of the functional protein cannot accomplish the same level of pigment synthesis that 100% of the protein can.

Dominant (functional) allele: *R* (round)
Recessive (defective) allele: *r* (wrinkled)

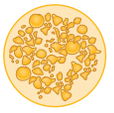
Genotype	*RR*	*Rr*	*rr*
Amount of functional (starch-producing) protein	100%	50%	0%
Phenotype	Round	Round	Wrinkled
With unaided eye (simple dominant/ recessive relationship)			
With microscope (incomplete dominance)			

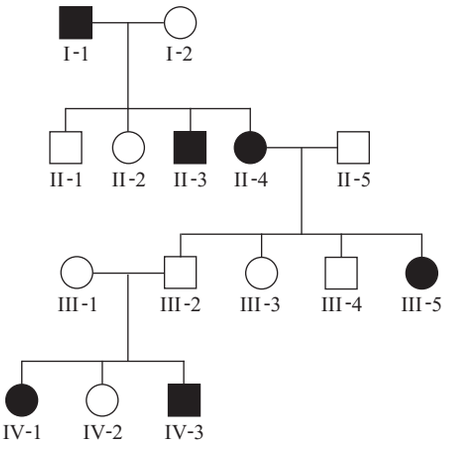
FIGURE 4.4 A comparison of phenotype at the macroscopic and microscopic levels.

Genes →Traits This illustration shows the effects of a heterozygote having only 50% of the functional protein needed for starch production. This seed appears to be as round as those of the homozygote carrying the *R* allele, but when examined microscopically, it has produced only half the amount of starch.

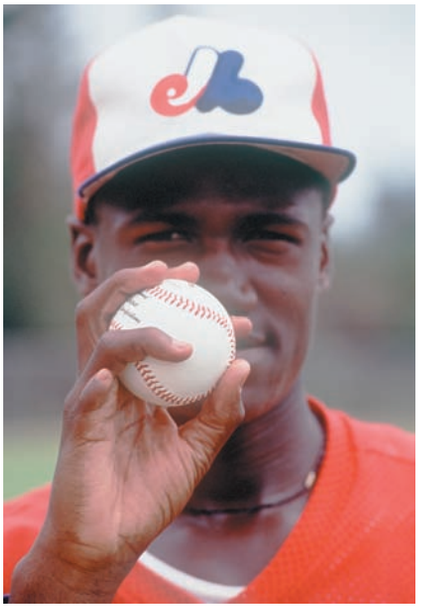
Finally, our opinion of whether a trait is dominant or incompletely dominant may depend on how closely we examine the trait in the individual. The more closely we look, the more likely we are to discover that the heterozygote is not quite the same as the wild-type homozygote. For example, Mendel studied the characteristic of pea seed shape and visually concluded that the *RR* and *Rr* genotypes produced round seeds and the *rr* genotype produced wrinkled seeds. The peculiar morphology of the wrinkled seed is caused by a large decrease in the amount of starch deposition in the seed due to a defective *r* allele. More recently, other scientists have dissected round and wrinkled seeds and examined their contents under the microscope. They have found that round seeds from heterozygotes actually contain an intermediate number of starch grains compared with seeds from the corresponding homozygotes (**Figure 4.4**). Within the seed, an intermediate amount of the functional protein is not enough to produce as many starch grains as in the homozygote carrying two copies of the *R* allele. Even so, at the level of our unaided eyes, heterozygotes produce seeds that appear to be round. With regard to phenotypes, the *R* allele is dominant to the *r* allele at the level of visual examination, but the *R* and *r* alleles show incomplete dominance at the level of starch biosynthesis.

Traits May Skip a Generation Due to Incomplete Penetrance and Vary in Their Expressivity

As we have seen, dominant alleles are expected to influence the outcome of a trait when they are present in heterozygotes. Occasionally, however, this may not occur. The phenomenon, called **incomplete penetrance,** is a situation in which an allele that is expected to cause a particular phenotype does not. **Figure 4.5a** illustrates a human pedigree for a dominant trait known as polydactyly. This trait causes the affected individual to have additional fingers or toes (or both) (**Figure 4.5b**). Polydactyly is due to an autosomal dominant allele—the allele is found in a gene located on an autosome (not a sex chromosome) and a single copy of this allele is sufficient to cause this condition. Sometimes, however, individuals carry the dominant allele but do not exhibit the trait. In Figure 4.5a, individual III-2 has inherited the polydactyly allele from his mother and passed the allele to a daughter and son. However, individual III-2 does not actually exhibit the



(a)



(b)

FIGURE 4.5 Polydactyly, a dominant trait that shows incomplete penetrance. **(a)** A family pedigree. Affected individuals are shown in black. Notice that offspring IV-1 and IV-3 have inherited the trait from a parent, III-2, who is heterozygous but does not exhibit polydactyly. **(b)** Antonio Alfonseca, a baseball player with polydactyly. His extra finger does not give him an advantage when pitching because it is small and does not touch the ball.

trait himself, even though he is a heterozygote. In our polydactyly example, the dominant allele does not always "penetrate" into the phenotype of the individual. Alternatively, for recessive traits, incomplete penetrance would occur if a homozygote carrying the recessive allele did not exhibit the recessive trait. The measure of penetrance is described at the populational level. For example, if 60% of the heterozygotes carrying a dominant allele exhibit the trait, we would say that this trait is 60% penetrant. At the individual level, the trait is either present or not.

Another term used to describe the outcome of traits is the degree to which the trait is expressed, or its **expressivity.** In the case of polydactyly, the number of extra digits can vary. For example, one individual may have an extra toe on only one foot, whereas a second individual may have extra digits on both the hands and feet. Using genetic terminology, a person with several extra digits would have high expressivity of this trait, whereas a person with a single extra digit would have low expressivity.

How do we explain incomplete penetrance and variable expressivity? Although the answer may not always be understood, the range of phenotypes is often due to environmental influences and/or due to effects of modifier genes in which one or more genes alter the phenotypic effects of another gene. We will consider the issue of the environment next. The effects of modifier genes will be discussed later in the chapter.

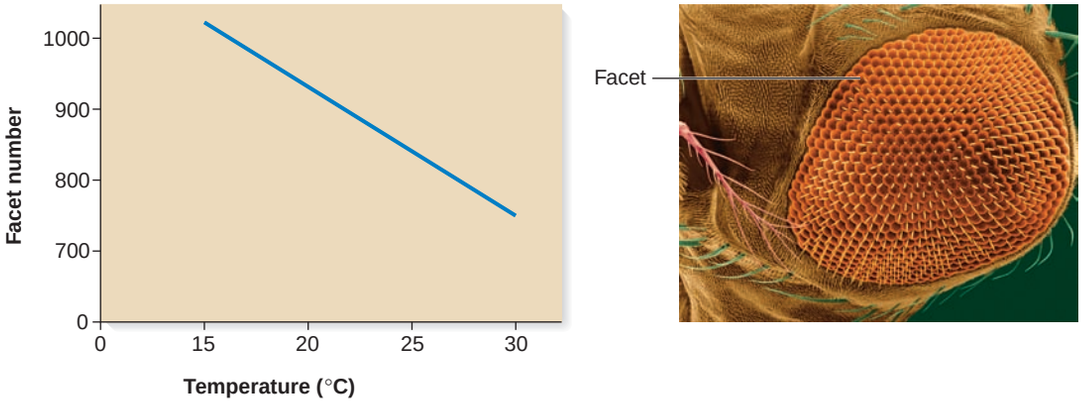
The Outcome of Traits Is Influenced by the Environment

Throughout this book, our study of genetics tends to focus on the roles of genes in the outcome of traits. In addition to genetics, environmental conditions have a great effect on the phenotype of the individual. For example, the arctic fox (*Alopex lagopus*) goes through two color phases. During the cold winter, the arctic fox is primarily white, but in the warmer summer, it is mostly brown (**Figure 4.6a**). As discussed later, such temperature-sensitive alleles affecting fur color are found among many species of mammals.

A dramatic example of the relationship between environment and phenotype can be seen in the human genetic disease known as phenylketonuria (PKU). This autosomal recessive disease is caused by a defect in a gene that encodes the enzyme phenylalanine hydroxylase. Homozygous individuals with this defective allele are unable to metabolize the amino acid phenylalanine properly. When given a standard diet containing

(a) Arctic fox in winter and summer

(b) Healthy person with PKU



(c) Norm of reaction

FIGURE 4.6 **Variation in the expression of traits due to environmental effects.** **(a)** The arctic fox in the winter and summer. **(b)** A person with PKU who has followed a restricted diet and developed normally. **(c)** Norm of reaction. In this experiment, fertilized eggs from a population of genetically identical *Drosophila melanogaster* were allowed to develop into adult flies at different environmental temperatures. This graph shows the relationship between temperature (an environmental factor) and facet number in the eyes of the resulting adult flies. The micrograph shows an eye of *D. melanogaster*.

phenylalanine, which is found in most protein-rich foods, PKU individuals manifest a variety of detrimental traits including mental impairment, underdeveloped teeth, and foul-smelling urine. In contrast, when PKU individuals are diagnosed early and follow a restricted diet free of phenylalanine, they develop normally (**Figure 4.6b**). Since the 1960s, testing methods have been developed that can determine if an individual is lacking the phenylalanine hydroxylase enzyme. These tests permit the identification of infants who have PKU. Their diets can then be modified before the harmful effects of phenylalanine ingestion have occurred. As a result of government legislation, more than 90% of infants born in the United States are now tested for PKU. This test prevents a great deal of human suffering and is also cost-effective. In the United States, the annual cost of PKU testing is estimated to be a few million dollars, whereas the cost of treating severely affected individuals with the disease would be hundreds of millions of dollars.

The examples of the arctic fox and PKU represent dramatic effects of very different environmental conditions. When considering the environment, geneticists often examine a range of conditions, rather than simply observing phenotypes under two different conditions. The term **norm of reaction** refers to the effects of environmental variation on a phenotype. Specifically, it is the phenotypic range seen in individuals with a particular genotype. To evaluate the norm of reaction, researchers begin with true-breeding strains that have the same genotypes and subject them to different environmental conditions. As an example, let's consider facet number in the eyes of fruit flies, *Drosophila melanogaster*. This species has compound eyes composed of many individual facets. **Figure 4.6c** shows the norm of reaction for facet number in genetically identical fruit flies that developed at different temperatures. As shown in the figure, the facet number varies with changes in temperature. At a higher temperature (30°C), the facet number is approximately 750, whereas at a lower temperature (15°C), it is over 1000.

Overdominance Occurs When Heterozygotes Have Superior Traits

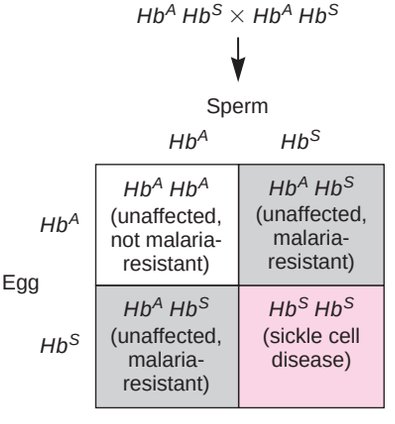
As we have just seen, the environment plays a key role in the outcome of traits. For certain genes, heterozygotes may display characteristics that are more beneficial for their survival in a particular environment. Such heterozygotes may be more likely to survive and reproduce. For example, a heterozygote may be larger, disease-resistant, or better able to withstand harsh environmental conditions. The phenomenon in which a heterozygote has greater reproductive success compared with either of the corresponding homozygotes is called **overdominance** or **heterozygote advantage.**

A well-documented example involves a human allele that causes sickle cell disease in homozygous individuals. This disease is an autosomal recessive disorder in which the affected individual produces an altered form of the protein hemoglobin, which carries oxygen within red blood cells. Most people carry the Hb^A allele and make hemoglobin A. Individuals affected with sickle cell anemia are homozygous for the Hb^S allele and produce only hemoglobin S. This causes their red blood cells to deform into a sickle shape under conditions of low oxygen concentration (**Figure 4.7a, b**). The sickling phenomenon causes the life span of these cells to be greatly shortened to only a few weeks compared with a normal span of four months, and therefore, anemia results. In addition, abnormal sickled cells can become clogged in the capillaries throughout the body, leading to localized areas of oxygen depletion. Such an event, called a crisis, causes pain and sometimes tissue and organ damage. For these reasons, the homozygous Hb^SHb^S individual usually has a shortened life span relative to an individual producing hemoglobin A.

In spite of the harmful consequences to homozygotes, the sickle cell allele has been found at a fairly high frequency among human populations that are exposed to malaria. The protozoan genus that causes malaria, *Plasmodium*, spends part of its life

(a) Normal red blood cell

(b) Sickled red blood cell



(c) Example of sickle cell inheritance pattern

INTERACTIVE EXERCISE

FIGURE 4.7 Inheritance of sickle cell disease. A comparison of **(a)** normal red blood cells and **(b)** those from a person with sickle cell disease. **(c)** The outcome of a cross between two heterozygous individuals.

cycle within the *Anopheles* mosquito and another part within the red blood cells of humans who have been bitten by an infected mosquito. However, red blood cells of heterozygotes, Hb^AHb^S, are likely to rupture when infected by this parasite, thereby preventing the parasite from propagating. People who are heterozygous have better resistance to malaria than do Hb^AHb^A homozygotes, while not incurring the ill effects of sickle cell disease. Therefore, even though the homozygous Hb^SHb^S condition is detrimental, the greater survival of the heterozygote has selected for the presence of the Hb^S allele within populations where malaria is prevalent. When viewing survival in such a region, overdominance explains the prevalence of the sickle cell allele. In Chapter 24, we will consider the role that natural selection plays in maintaining alleles that are beneficial to the heterozygote but harmful to the homozygote.

Figure 4.7c illustrates the predicted outcome when two heterozygotes have children. In this example, 1/4 of the offspring are Hb^AHb^A (unaffected, not malaria-resistant), 1/2 are Hb^AHb^S (unaffected, malaria-resistant) and 1/4 are Hb^SHb^S (sickle cell disease). This 1:2:1 ratio deviates from a simple Mendelian 3:1 phenotypic ratio.

Overdominance is usually due to two alleles that produce proteins with slightly different amino acid sequences. How can we explain the observation that two protein variants in the heterozygote produce a more favorable phenotype? There are three common explanations. In the case of sickle cell disease, the phenotype is related to the infectivity of *Plasmodium* (**Figure 4.8a**). In the heterozygote, the infectious agent is less likely to propagate within red blood cells. Interestingly, researchers have speculated that other alleles in humans may confer disease resistance in the heterozygous condition but are detrimental in the homozygous state. These include PKU, in which the heterozygous fetus may be resistant to miscarriage caused by a fungal toxin, and Tay-Sachs disease, in which the heterozygote may be resistant to tuberculosis.

A second way to explain overdominance is related to the subunit composition of proteins. In some cases, a protein functions as a complex of multiple subunits; each subunit is composed of one polypeptide. A protein composed of two subunits is called a dimer. When both subunits are encoded by the same gene, the protein is a homodimer. The prefix homo- means that the subunits come from the same type of gene although the gene may exist in different alleles. **Figure 4.8b** considers a situation in which a gene exists in two alleles that encode polypeptides designated A1 and A2. Homozygous individuals can produce only A1A1 or A2A2 homodimers, whereas a heterozygote can also produce an A1A2 homodimer. Thus, heterozygotes can produce three forms of the homodimer, homozygotes only one. For some proteins, A1A2 homodimers may have better functional activity because they are more stable or able to function under a wider range of conditions. The greater activity of the homodimer protein may be the underlying reason why a heterozygote has characteristics superior to either homozygote.

A third molecular explanation of overdominance is that the proteins encoded by each allele exhibit differences in their functional activity. For example, suppose that a gene encodes a metabolic enzyme that can be found in two forms (corresponding to the two alleles), one that functions better at a lower temperature and the other that functions optimally at a higher temperature (**Figure 4.8c**). The heterozygote, which makes a mixture of both enzymes, may be at an advantage under a wider temperature range than either of the corresponding homozygotes.

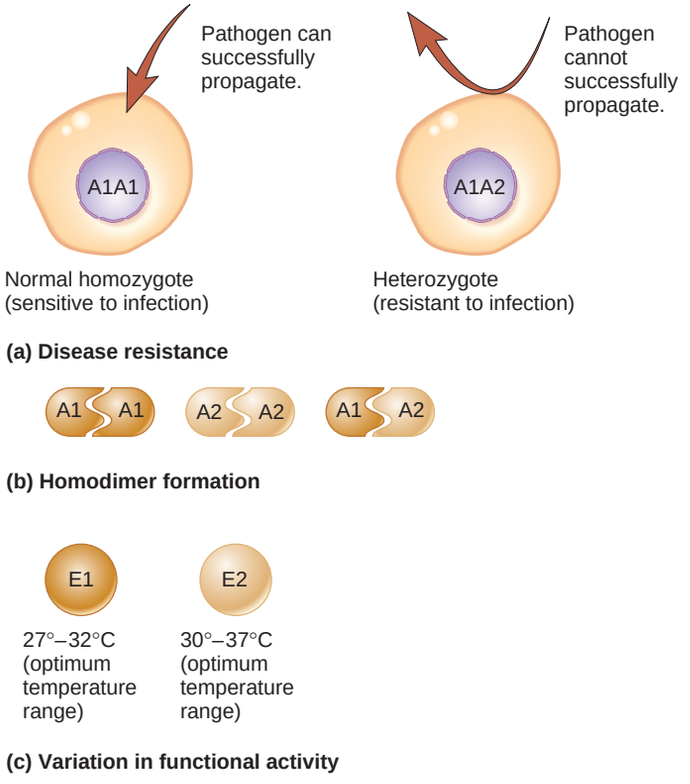


FIGURE 4.8 Three possible explanations for overdominance at the molecular level. **(a)** The successful infection of cells by certain microorganisms depends on the function of particular cellular proteins. In this example, functional differences between A1A1 and A1A2 proteins affect the ability of a pathogen to propagate in the cells. **(b)** Some proteins function as homodimers. In this example, a gene exists in two alleles designated *A1* and *A2*, which encode polypeptides also designated A1 and A2. The homozygotes that are *A1A1* or *A2A2* will make homodimers that are A1A1 and A2A2, respectively. The *A1A2* heterozygote can make A1A1 and A2A2 and can also make A1A2 homodimers, which may have better functional activity. **(c)** In this example, a gene exists in two alleles designated *E1* and *E2*. The *E1* allele encodes an enzyme that functions well in the temperature range of 27° to 32°C. *E2* encodes an enzyme that functions in the range of 30° to 37°C. A heterozygote, *E1E2*, would produce both enzymes and have a broader temperature range (i.e., 27°–37°C) in which the enzyme would function.

Many Genes Exist as Three or More Different Alleles

Thus far, we have considered examples in which a gene exists in two different alleles. As researchers have probed genes at the molecular level within natural populations of organisms, they have discovered that most genes exist in **multiple alleles.** Within a population, genes are typically found in three or more alleles.

An interesting example of multiple alleles involves coat color in rabbits. **Figure 4.9** illustrates the relationship between genotype and phenotype for a combination of four different alleles, which are designated *C* (full coat color), c^{ch} (chinchilla pattern of coat color), c^{h} (himalayan pattern of coat color), and *c* (albino). In this case, the gene encodes an enzyme called tyrosinase, which is the first enzyme in a metabolic pathway that leads to the synthesis of melanin from the amino acid tyrosine. This pathway results in the formation of two forms of melanin. Eumelanin, a black pigment, is made first, and then phaeomelanin, an orange/yellow pigment, is made from eumelanin. Alleles of other genes can also influence the relative amounts of eumelanin and phaeomelanin.

Differences in the various alleles are related to the function of tyrosinase. The *C* allele encodes a fully functional tyrosinase that allows the synthesis of both eumelanin and phaeomelanin, resulting in a full brown coat color. The *C* allele is dominant to the other three alleles. The chinchilla allele (c^{ch}) is a partial defect in tyrosinase that leads to a slight reduction in black pigment and a greatly diminished amount of orange/yellow pigment, which makes the animal look gray. The albino allele, designated *c*, is a complete loss of tyrosinase, resulting in white color. The himalayan pattern of coat color, determined by the c^{h} allele, is an example of a **temperature-sensitive allele.** The mutation in this gene has caused a change in the structure of tyrosinase, so it works enzymatically only at low temperature. Because of this property, the enzyme functions only in cooler regions of the body, primarily the tail, the paws, and the tips of the nose and ears. As shown in **Figure 4.10**, similar types of temperature-sensitive alleles have been found in other species of domestic animals, such as the Siamese cat.

Alleles of the ABO Blood Group Can Be Dominant, Recessive, or Codominant

The ABO group of antigens, which determine blood type in humans, is another example of multiple alleles and illustrates yet another allelic relationship called codominance. To understand this concept, we first need to examine the molecular characteristics of human blood types. The plasma membranes of red blood cells have groups of interconnected sugars—oligosaccharides—that act as surface antigens (**Figure 4.11a**). Antigens are molecular

(a) Full coat color *CC*, Cc^{h}, Cc^{ch}, or *Cc*.

(b) Chinchilla coat color $c^{ch}c^{ch}$, $c^{ch}c^{h}$, or $c^{ch}c$.

(c) Himalayan coat color $c^{h}c^{h}$ or $c^{h}c$.

(d) Albino coat color *cc*.

INTERACTIVE EXERCISE

FIGURE 4.9 The relationship between genotype and phenotype in rabbit coat color.

FIGURE 4.10 The expression of a temperature-sensitive conditional allele produces a Siamese pattern of coat color.

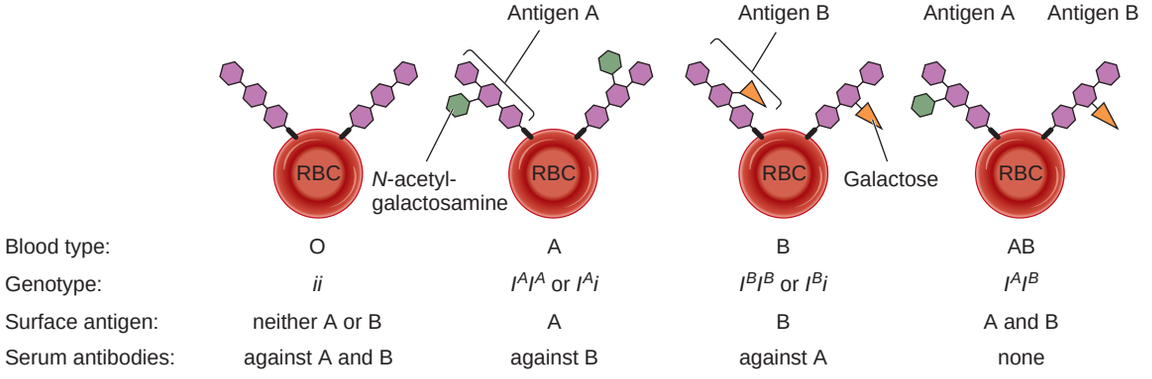
Genes →Traits The allele affecting fur pigmentation encodes a pigment-producing protein that functions only at lower temperatures. For this reason, the dark fur is produced only in the cooler parts of the animal, including the tips of the ears, nose, paws, and tail.

structures that are recognized by antibodies produced by the immune system. On red blood cells, two different types of surface antigens, known as A and B, may be found.

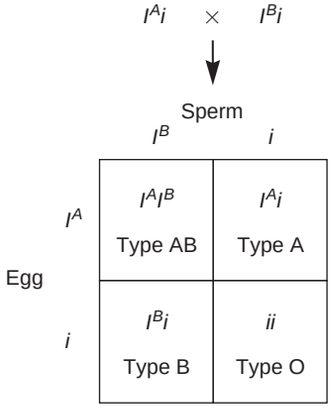
The synthesis of these surface antigens is controlled by two alleles, designated I^A and I^B, respectively. The *i* allele is recessive to both I^A and I^B. A person who is homozygous *ii* will have type O blood and does not produce either antigen. A homozygous I^AI^A or heterozygous I^Ai individual will have type A blood. The red blood cells of this individual will contain the surface antigen known as A. Similarly, a homozygous I^BI^B or heterozygous I^Bi individual will produce surface antigen B. As Figure 4.11a indicates, surface antigens A and B have significantly different molecular structures. A person who is I^AI^B will have the blood type AB and express both surface antigens A and B. The phenomenon in which two alleles are both expressed in the heterozygous individual is called **codominance.** In this case, the I^A and I^B alleles are codominant to each other.

As an example of the inheritance of blood type, let's consider the possible offspring between two parents who are I^Ai and I^Bi (**Figure 4.11b**). The I^Ai parent makes I^A and *i* gametes, and the I^Bi parent makes I^B and *i* gametes. These combine to produce I^AI^B, I^Ai, I^Bi, and *ii* offspring in a 1:1:1:1 ratio. The resulting blood types are AB, A, B, and O, respectively.

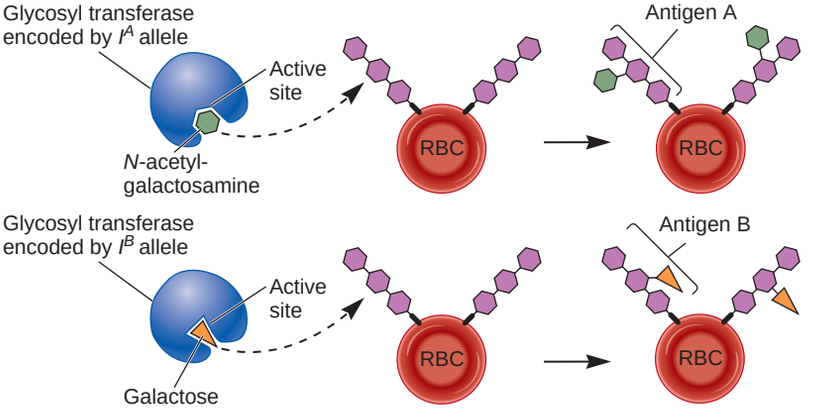
Biochemists have analyzed the oligosaccharides produced on the surfaces of cells of differing blood types. In type O, the tree is smaller than type A or type B because a sugar has not been attached to a specific site on the tree. This idea is schematically shown in Figure 4.11a. How do we explain this difference at the molecular level? The gene that determines ABO blood type encodes an enzyme called glycosyl transferase that attaches a sugar to the oligosaccharide. The *i* allele carries a mutation that renders this enzyme inactive, which prevents the attachment of an additional sugar. By comparison, the two types of glycosyl transferase encoded by the I^A and I^B alleles have different structures in their active sites. The active site is the part of the protein that recognizes the sugar molecule that will be attached to the oligosaccharide. The glycosyl transferase encoded by the I^A allele recognizes uridine diphosphate *N*-acetylgalactosamine (UDP-GalNAc) and attaches GalNAc



(a) ABO blood type



(b) Example of the ABO inheritance pattern



(c) Formation of A and B antigen by glycosyl transferase

INTERACTIVE EXERCISE

FIGURE 4.11 ABO blood type. (a) A schematic representation of blood type at the cellular level. Note: This is not drawn to scale. A red blood cell is much larger than the oligosaccharide on the surface of the cell. **(b)** The predicted offspring from parents who are I^Ai and I^Bi. **(c)** The glycosyl transferase encoded by the I^A and I^B alleles recognizes different sugars due to changes in its active site. The *i* allele results in a nonfunctional enzyme.

to the oligosaccharide (**Figure 4.11c**). GalNAc is symbolized as a green hexagon. This produces the structure of surface antigen A. In contrast, the glycosyl transferase encoded by the I^B allele recognizes UDP-galactose and attaches galactose to the oligosaccharide. Galactose is symbolized as an orange triangle. This produces the molecular structure of surface antigen B. A person with type AB blood makes both types of enzymes and thereby has a tree with both types of sugar attached.

A small difference in the structure of the oligosaccharide, namely, a GalNAc in antigen A versus galactose in antigen B, explains why the two antigens are different from each other at the molecular level. These differences enable them to be recognized by different antibodies. A person who has blood type A makes antibodies to blood type B (refer back to Figure 4.11a). The antibodies against blood type B require a galactose in the oligosaccharide for their proper recognition. Their antibodies will not recognize and destroy their own blood cells, but they will recognize and destroy the blood cells from a type B person.

With this in mind, let's consider why blood typing is essential for safe blood transfusions. The donor's blood must be an appropriate match with the recipient's blood. A person with type O blood has the potential to produce antibodies against both A and B antigens if she or he is given type A, type B, or type AB blood. After the antibodies are produced in the recipient, they will react with the donated blood cells and cause them to agglutinate (clump together). This is a life-threatening situation that causes the blood vessels to clog. Other incompatible combinations include a type A person receiving type B or type AB blood, and a type B person receiving type A or type AB blood. Because individuals with type AB blood do not produce antibodies to either A or B antigens, they can receive any type of blood and are known as universal recipients. By comparison, type O persons are universal donors because their blood can be given to type O, A, B, and AB people.

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

Let's now turn our attention to inheritance patterns of single genes in which the sexes of the parents and offspring play a critical role. As discussed in Chapter 3, many species have males and females that differ in their sex chromosome composition. In mammals, for example, females are XX and males are XY. In such species, certain traits are governed by genes that are located on a sex chromosome. For these traits, the outcome of crosses depends on the genotypes and sexes of the parents and offspring.

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

DMD is inherited in an **X-linked recessive** pattern—the allele causing the disease is recessive and located on the X chromosome. In the pedigree shown in **Figure 4.12**, several males are affected by this disorder, as indicated by filled squares. The mothers of these males are presumed heterozygotes for this X-linked recessive allele. This recessive disorder is very rare among females because daughters would have to inherit a copy of the mutant allele from their mother and a copy from an affected father.

X-linked muscular dystrophy has also been found in certain breeds of dogs such as golden retrievers (**Figure 4.13a**). Like humans, the mutation occurs in the dystrophin gene, and the symptoms include severe weakness and muscle atrophy that begin at about 6 to 8 weeks of age. Many dogs that inherit this disorder die within the first year of life, though some can live 3 to 5 years and reproduce.

Figure 4.13b (left side) considers a cross between an unaffected female dog with two copies of the wild-type gene and a male dog with muscular dystrophy that carries the mutant allele and has survived to reproductive age. When setting up a Punnett square involving X-linked traits, we must consider the alleles on the X chromosome as well as the observation that males may transmit a Y chromosome instead of the X chromosome. The male makes two types of gametes, one that carries the X chromosome and one that carries the Y. The Punnett square must also include the Y chromosome even though this chromosome does not carry any X-linked genes. The X chromosomes from the female and male are designated with their corresponding alleles. When the Punnett square is filled in, it predicts the X-linked genotypes and sexes of the offspring. As seen on the left side of Figure 4.13b, none of the offspring from this cross are affected with the disorder, although all female offspring are carriers.

The right side of Figure 4.13b shows a **reciprocal cross**—a second cross in which the sexes and phenotypes are reversed. In this case, an affected female animal is crossed to an unaffected

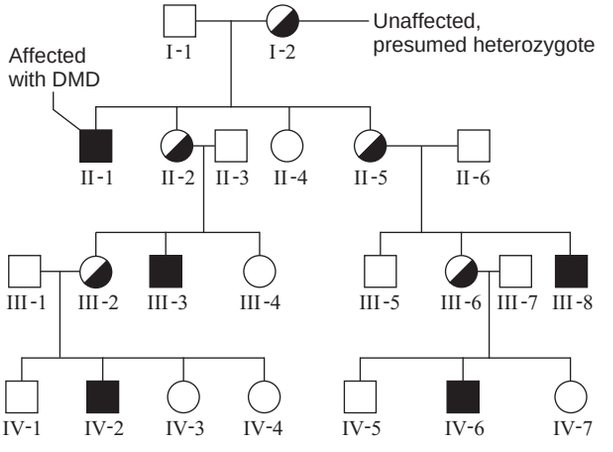
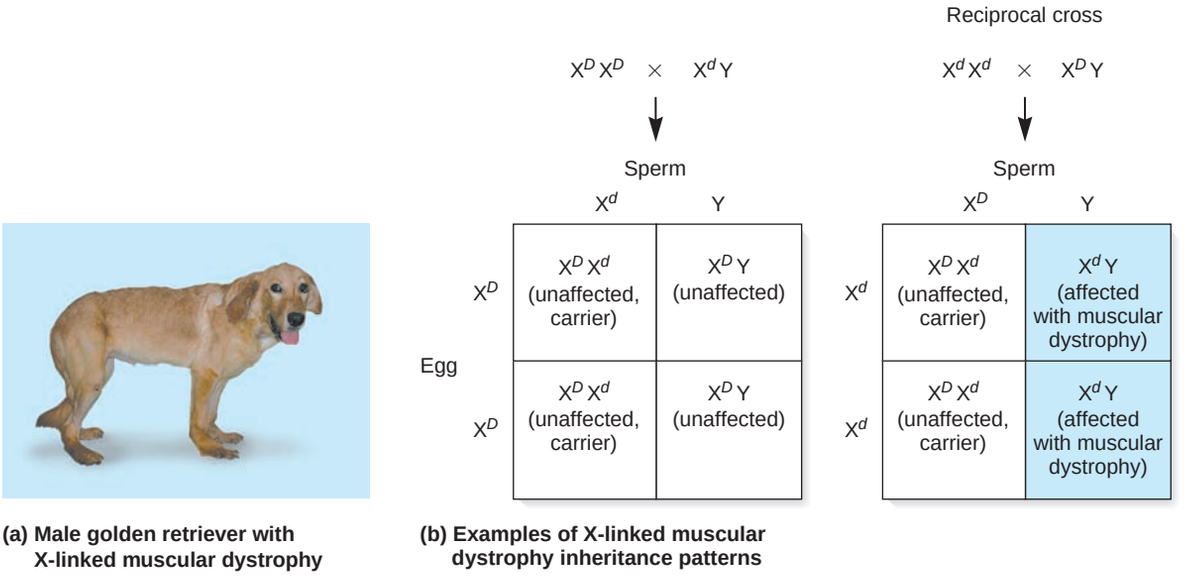


FIGURE 4.12 A human pedigree for Duchenne muscular dystrophy, an X-linked recessive trait. Affected individuals are shown with filled symbols. Females who are unaffected with the disease but have affected sons are presumed to be heterozygous carriers, as shown with half-filled symbols.



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

(b) Examples of X-linked muscular dystrophy inheritance patterns

INTERACTIVE EXERCISE

FIGURE 4.13 X-linked muscular dystrophy in dogs. (a) The male golden retriever shown here has the disease. **(b)** The left side shows a cross between an unaffected female and an affected male. The right shows a reciprocal cross between an affected female and an unaffected male. *D* represents the normal allele for the dystrophin gene, and *d* is the mutant allele that causes a defect in dystrophin function.

male. This cross produces female offspring that are carriers and all male offspring will be affected with muscular dystrophy.

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

Genes Located on Mammalian Sex Chromosomes Can Be Transmitted in an X-Linked, a Y-Linked, or a Pseudoautosomal Pattern

Our discussion of sex chromosomes has focused on genes that are located on the X chromosome but not on the Y chromosome. The term **sex-linked gene** refers to a gene that is found on one of the two types of sex chromosomes but not on both. Hundreds of X-linked genes have been identified in humans and other mammals.

The inheritance pattern of X-linked genes shows certain distinctive features. For example, males transmit X-linked genes only to their daughters, and sons receive their X-linked genes from their mothers. The term **hemizygous** is used to describe the single copy of an X-linked gene in the male. A male mammal is said to be hemizygous for X-linked genes. Because males of certain species, such as humans, have a single copy of the X chromosome, another distinctive feature of X-linked inheritance is that males are more likely to be affected by rare, recessive X-linked disorders.

By comparison, relatively few genes are located only on the Y chromosome. These few genes are called **holandric genes.** An example of a holandric gene is the *Sry* gene found in mammals. Its expression is necessary for proper male development. A Y-linked inheritance pattern is very distinctive—the gene is transmitted only from fathers to sons.

Besides sex-linked genes, the X and Y chromosomes also contain short regions of homology where the X and Y chromosomes carry the same genes. In addition to several smaller regions, the human sex chromosomes have three homologous regions (**Figure 4.14**). These regions, which are evolutionarily related, promote the necessary pairing of the X and Y chromosomes that occurs during meiosis I of spermatogenesis. Relatively

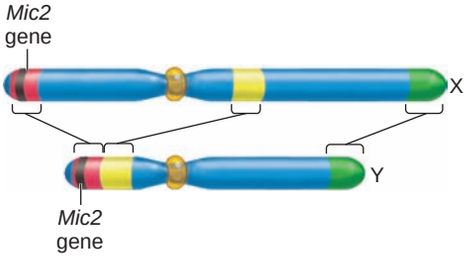


FIGURE 4.14 A comparison of the homologous and nonhomologous regions of the X and Y chromosome in humans. The brackets show three regions of homology between the X and Y chromosome. A few pseudoautosomal genes, such as *Mic2*, are found on both the X and Y chromosomes in these small regions of homology. Researchers estimate that the X chromosome contains between 900 and 1200 genes and the Y chromosome has between 70 and 300 genes.

few genes are located in these homologous regions. One example is a human gene called *Mic2*, which encodes a cell surface antigen. The *Mic2* gene is found on both the X and Y chromosomes. It follows a pattern of inheritance called **pseudoautosomal inheritance.** The term pseudoautosomal refers to the idea that the inheritance pattern of the *Mic2* gene is the same as the inheritance pattern of a gene located on an autosome even though the *Mic2* gene is actually located on the sex chromosomes. As in autosomal inheritance, males have two copies of pseudoautosomally inherited genes, and they can transmit the genes to both daughters and sons.

Some Traits Are Influenced by the Sex of the Individual

As we have just seen, the transmission pattern of sex-linked genes depends on the sex of the parents and offspring. Sex can influence traits in other ways as well. The term **sex-influenced inheritance** refers to the phenomenon in which an allele is dominant in one sex but recessive in the opposite sex. Therefore, sex influence is a phenomenon of heterozygotes. Sex-influenced inheritance should not be confused with sex-linked inheritance. The genes that govern sex-influenced traits are almost always autosomal, not on the X or Y chromosome.

In humans, the common form of pattern baldness provides an example of sex-influenced inheritance. As shown in **Figure 4.15**, the balding pattern is characterized by hair loss on the front and top of the head but not on the sides. This type of pattern baldness is inherited as an autosomal trait. (A common misconception is that this gene is X-linked.) When a male is heterozygous for the baldness allele, he will become bald.

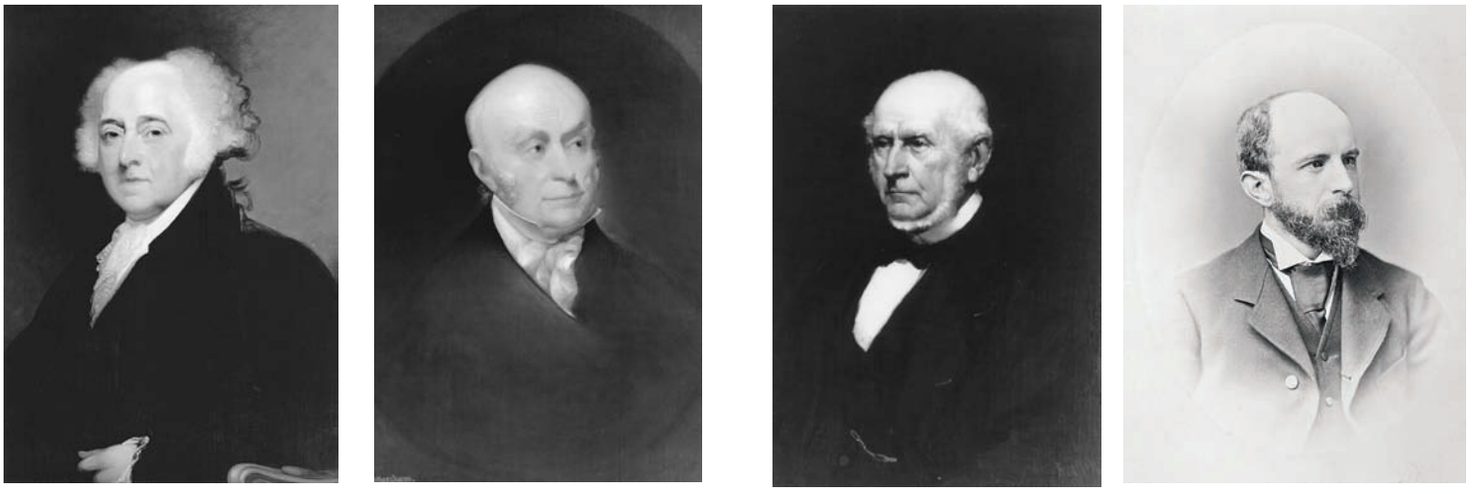
Genotype	Phenotype	
	Males	Females
BB	Bald	Bald
Bb	Bald	Nonbald
bb	Nonbald	Nonbald

In contrast, a heterozygous female will not be bald. Women who are homozygous for the baldness allele will develop the trait, but it is usually characterized by a significant thinning of the hair that occurs relatively late in life.

The sex-influenced nature of pattern baldness is related to the production of the male sex hormone testosterone. The gene that affects pattern baldness encodes an enzyme called 5-α-reductase, which converts testosterone to 5-α-dihydrotestosterone (DHT). DHT binds to cellular receptors and affects the expression of many genes, including those in the cells of the scalp. The allele that causes pattern baldness results in an overexpression of this enzyme. Because mature males normally make more testosterone than females, this allele has a greater phenotypic effect in males. However, a rare tumor of the adrenal gland can cause the secretion of abnormally large amounts of testosterone in females. If this occurs in a woman who is heterozygous *Bb*, she will become bald. If the tumor is removed surgically, her hair will return to its normal condition.

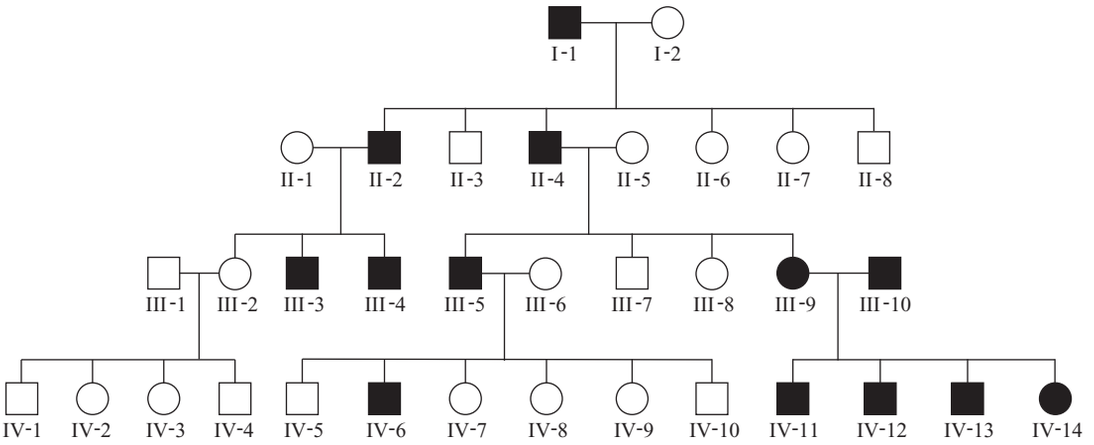
The autosomal nature of pattern baldness has been revealed by the analysis of many human pedigrees. An example is shown in **Figure 4.16a.** A bald male may inherit the bald allele from either parent, and thus a striking observation is that bald fathers can pass this trait to their sons. This could not occur if the trait was X-linked, because fathers do not transmit an X chromosome to their sons. The analyses of many human pedigrees have shown that bald fathers, on average, have at least 50% bald sons. They are expected to produce an even higher percentage of bald male offspring if they are homozygous for the bald allele or the mother also carries one or two copies of the bald allele. For example, a heterozygous bald male and heterozygous (nonbald) female will produce 75% bald sons, whereas a homozygous bald male or homozygous bald female will produce all bald sons.

Figure 4.16b shows the predicted offspring if two heterozygotes produce offspring. In this Punnett square, the phenotypes are designated for both sons and daughters. *BB* offspring are bald, and *bb* offspring are nonbald. *Bb* offspring are bald if they are sons and nonbald if they are daughters. The predicted genotypic

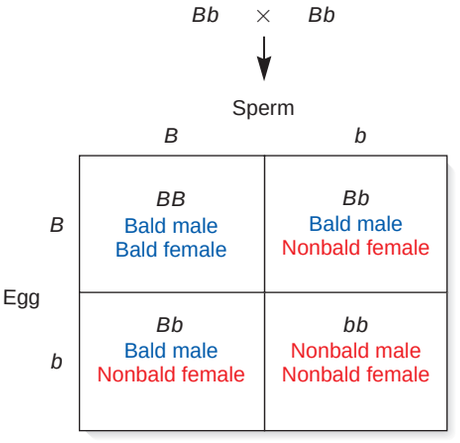


(a) John Adams (father) (b) John Quincy Adams (son) (c) Charles Francis Adams (grandson) (d) Henry Adams (great-grandson)

FIGURE 4.15 **Pattern baldness in the Adams family line.**



(a) A pedigree for human pattern baldness



(b) Example of an inheritance pattern involving baldness

FIGURE 4.16 Inheritance of pattern baldness, a sex-influenced trait involving an autosomal gene. **(a)** A family pedigree. Bald individuals are shown in black. **(b)** The predicted offspring from two heterozygous parents.

ratios from this cross would be 1 *BB* bald son to 1 *BB* bald daughter to 2 *Bb* bald sons to 2 *Bb* nonbald daughters to 1 *bb* nonbald son to 1 *bb* nonbald daughter. The predicted phenotypic ratios would be 3 bald sons to 1 bald daughter to 3 nonbald daughters to 1 nonbald son. The ratio of bald to nonbald offspring is 4:4, which is the same as 1:1.

Another example in which sex affects an organism's phenotype is provided by **sex-limited inheritance,** in which a trait occurs in only one of the two sexes. The genes that influence sex-limited traits may be autosomal or X-linked. In humans, examples of sex-limited traits are the presence of ovaries in females and the presence of testes in males. Due to these two sex-limited traits, mature females can only produce eggs, whereas mature males can only produce sperm.

Sex-limited traits are responsible for **sexual dimorphism** in which members of the opposite sex have different morphological features. This phenomenon is common among many animals species and is often striking among various species of birds in which the male has more ornate plumage than the female. As shown in **Figure 4.17**, roosters have a larger comb and wattles and longer neck and tail feathers than do hens. These sex-limited features may be found in roosters but never in normal hens.

Mutations in an Essential Gene May Result in a Lethal Phenotype

Let's now turn our attention to alleles that have the most detrimental effect on phenotype—those that result in death. An allele that has the potential to cause the death of an organism is called a **lethal allele.** These are usually inherited in a recessive manner. When the absence of a specific protein results in a lethal phenotype, the gene that encodes the protein is considered an **essential gene** for survival. Though it varies according to species, researchers estimate that approximately 1/3 of all genes are essential genes. By comparison, **nonessential genes** are not absolutely required for survival, although they are likely to be beneficial to the organism. A loss-of-function mutation in a nonessential gene will not usually cause death. On rare occasions, however, a nonessential gene may acquire a mutation that causes the gene product to be

(a) Hen (b) Rooster

FIGURE 4.17 Differences in the feathering pattern in female and male chickens, an example of sex-limited inheritance.

abnormally expressed in a way that may interfere with normal cell function and lead to a lethal phenotype. Therefore, not all lethal mutations occur in essential genes, although the great majority do.

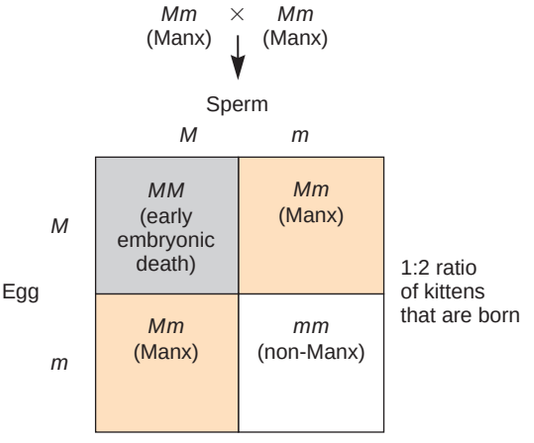
Many lethal alleles prevent cell division and thereby cause an organism to die at a very early stage. Others, however, may only exert their effects later in life, or under certain environmental conditions. For example, a human genetic disease known as Huntington disease is caused by a dominant allele. The disease is characterized by a progressive degeneration of the nervous system, dementia, and early death. The age when these symptoms appear, or the **age of onset,** is usually between 30 and 50.

Other lethal alleles may kill an organism only when certain environmental conditions prevail. Such **conditional lethal alleles** have been extensively studied in experimental organisms. For example, some conditional lethals will cause an organism to die only in a particular temperature range. These alleles, called **temperature-sensitive (ts) lethal alleles,** have been observed in many organisms, including *Drosophila*. A ts lethal allele may be fatal for a developing larva at a high temperature (30°C), but the larva will survive if grown at a lower temperature (22°C). Temperature-sensitive lethal alleles are typically caused by mutations that alter the structure of the encoded protein so it does not function correctly at the nonpermissive temperature or becomes unfolded and is rapidly degraded. Conditional lethal alleles may also be identified when an individual is exposed to a particular agent in the environment. For example, people with a defect in the gene that encodes the enzyme glucose-6-phosphate dehydrogenase (G6PD) have a negative reaction to the ingestion of fava beans. This can lead to an acute hemolytic syndrome with 10% mortality if not treated properly.

Finally, it is surprising that certain lethal alleles act only in some individuals. These are called **semilethal alleles.** Of course, any particular individual cannot be semidead. However, within a population, a semilethal allele will cause some individuals to die but not all of them. The reasons for semilethality are not always understood, but environmental conditions and the actions of other genes within the organism may help to prevent the detrimental effects of certain semilethal alleles. An example of a semilethal allele is the X-linked white-eyed allele, which is described in Chapter 3 (see Figure 3.19). Depending on the growth conditions, approximately 1/4 to 1/3 of the flies that would be expected to exhibit this white-eyed trait die prematurely.

In some cases, a lethal allele may produce ratios that seemingly deviate from Mendelian ratios. An example is an allele in a breed of cats known as Manx, which originated on the Isle of Man (**Figure 4.18a**). The Manx cat carries a dominant mutation that affects the spine. This mutation shortens the tail, resulting in a range of tail lengths from normal to tailless. When two Manx cats are crossed to each other, the ratio of offspring is 1 normal to 2 Manx. How do we explain the 1:2 ratio? The answer is that about 1/4 of the offspring die during early embryonic development (**Figure 4.18b**). In this case, the Manx phenotype is dominant, whereas the lethal phenotype occurs only in the homozygous condition.

(a) A Manx cat



(b) Example of a Manx inheritance pattern

INTERACTIVE EXERCISE

FIGURE 4.18 The Manx cat, which carries a lethal allele. **(a)** Photo of a Manx cat, which typically has a shortened tail. **(b)** Outcome of a cross between two Manx cats. Animals that are homozygous for the dominant Manx allele (*M*) die during early embryonic development.

Single Genes Have Pleiotrophic Effects

Before ending our discussion of single-gene inheritance patterns, let's take a broader look at how a single gene may affect phenotype. Although we tend to discuss genes within the context of how they influence a single trait, most genes actually have multiple effects throughout a cell or throughout a multicellular organism. The multiple effects of a single gene on the phenotype of an organism is called **pleiotrophy.** Pleiotrophy occurs for several reasons, including the following:

1. The expression of a single gene can affect cell function in more than one way. For example, a defect in a microtubule protein may affect cell division and cell movement.
2. A gene may be expressed in different cell types in a multicellular organism.
3. A gene may be expressed at different stages of development.

In all or nearly all cases, the expression of a gene is pleiotrophic with regard to the characteristics of an organism. The expression of any given gene influences the expression of many other genes in the genome, and vice versa. Pleiotrophy is revealed when researchers study the effects of gene mutations. As an example of a pleiotrophic mutation, let's consider cystic fibrosis, which is a recessive human disorder. In the late 1980s, the gene for cystic fibrosis was identified. It encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR), which regulates ionic balance by allowing the transport of chloride ions (Cl^-) across epithelial cell membranes.

The mutation that causes cystic fibrosis diminishes the function of this Cl^- transporter, affecting several parts of the body in different ways. Because the movement of Cl^- affects water transport across membranes, the most severe symptom of cystic fibrosis is thick mucus in the lungs that occurs because of a water imbalance. In sweat glands, the normal Cl^- transporter has the function of recycling salt out of the glands and back into the skin before it can be lost to the outside world. Persons with cystic fibrosis have excessively salty sweat due to their inability to recycle salt back into their skin cells—a common test for cystic fibrosis is measurement of salt on the skin. Another effect is seen in the reproductive system of males who are homozygous for the cystic fibrosis allele. Males with cystic fibrosis may be infertile because the vas deferens, the tubules that transport sperm from the testes, may be absent or undeveloped. Presumably, a normally functioning Cl^- transporter is needed for the proper development of the vas deferens in the embryo. Taken together, we can see that a defect in CFTR has multiple effects throughout the body.

4.2 GENE INTERACTIONS

In Section 4.1, we considered the effects of a single gene on the outcome of a trait. This approach helps us to understand the various ways that alleles can influence traits. Researchers often examine the effects of a single gene on the outcome of a single trait as a way to simplify the genetic analysis. For example, Mendel studied one gene that affected the height of pea plants—tall versus dwarf alleles. Actually, many other genes in pea plants also affect height, but Mendel did not happen to study variants in those other height genes. How then did Mendel study the effects of a single gene? The answer lies in the genotypes of his strains. Although many genes affect the height of pea plants, Mendel chose true-breeding strains that differed with regard to only one of those genes. As a hypothetical example, let's suppose that pea plants have 10 genes affecting height, which we will call *K*, *L*, *M*, *N*, *O*, *P*, *Q*, *R*, *S*, and *T*. The genotypes of two hypothetical strains of pea plants may be

Tall strain: *KK LL MM NN OO PP QQ RR SS* ***TT***
Dwarf strain: *KK LL MM NN OO PP QQ RR SS* ***tt***

In this example, the alleles affecting height may differ at only a single gene. One strain is *TT* and the other is *tt*, and this accounts for the difference in their height. If we make crosses between these tall and dwarf strains, the genotypes of the F_2 offspring will differ with regard to only one gene; the other nine genes will be identical in all of them. This approach allows a researcher to study the effects of a single gene even though many genes may affect a single trait.

Researchers now appreciate that essentially all traits are affected by the contributions of many genes. Morphological features such as height, weight, growth rate, and pigmentation are all affected by the expression of many different genes in combination with environmental factors. In this section, we will further our understanding of genetics by considering how the allelic variants of two different genes affect a single trait. This phenomenon is known as **gene interaction.** Table 4.3 considers several examples in which two different genes interact to influence the outcome of particular traits. In this section, we will examine these examples in greater detail.

TABLE **4.3**
Types of Mendelian Inheritance Patterns Involving Two Genes

Type	Description
Epistasis	An inheritance pattern in which the alleles of one gene mask the phenotypic effects of the alleles of a different gene.
Complementation	A phenomenon in which two different parents that express the same or similar recessive phenotypes produce offspring with a wild-type phenotype.
Modifying genes	A phenomenon in which an allele of one gene modifies the phenotypic outcome of the alleles of a different gene.
Gene redundancy	A pattern in which the loss of function in a single gene has no phenotypic effect, but the loss of function of two genes has an effect. Functionality of only one of the two genes is necessary for a normal phenotype; the genes are functionally redundant.
Intergenic suppressors	An inheritance pattern in which the phenotypic effects of one mutation are reversed by a suppressor mutation in another gene.

A Cross Involving a Two-Gene Interaction Can Produce Four Distinct Phenotypes

The first case of two different genes interacting to affect a single trait was discovered by William Bateson and Reginald Punnett in 1906 while they were investigating the inheritance of comb morphology in chickens. Several common varieties of chicken possess combs with different morphologies, as illustrated in **Figure 4.19a**. In their studies, Bateson and Punnett crossed a Wyandotte breed having a rose comb to a Brahma having a pea comb. All F_1 offspring had a walnut comb.

When these F_1 offspring were mated to each other, the F_2 generation consisted of chickens with four types of combs in the following phenotypic ratio: 9 walnut : 3 rose : 3 pea : 1 single comb. As we have seen in Chapter 2, a 9:3:3:1 ratio is obtained in the F_2 generation when the F_1 generation is heterozygous for two different genes and these genes assort independently. However, an important difference here is that we have four distinct categories of a single trait. Based on the 9:3:3:1 ratio, Bateson and Punnett reasoned that a single trait (comb morphology) was determined by two different genes.

R (rose comb) is dominant to *r*.
P (pea comb) is dominant to *p*.
R and *P* (walnut comb) are codominant.
rrpp produces a single comb.

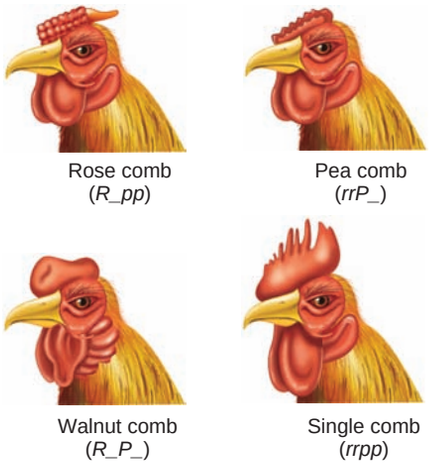
As shown in the Punnett square of **Figure 4.19b**, each of the genes can exist in two alleles, and the two genes show independent assortment.

A Cross Involving a Two-Gene Interaction Can Produce Two Distinct Phenotypes Due to Epistasis

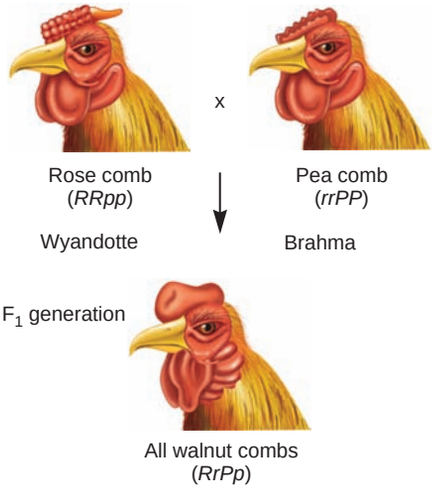
Bateson and Punnett also discovered an unexpected gene interaction when studying crosses involving the sweet pea, *Lathyrus odoratus*. The wild sweet pea has purple flowers. However, they obtained several true-breeding mutant varieties with white flowers. Not surprisingly, when they crossed a true-breeding purple-flowered plant to a true-breeding white-flowered plant, the F_1 generation contained all purple-flowered plants and the F_2 generation (produced by self-fertilization of the F_1 generation) consisted of purple- and white-flowered plants in a 3:1 ratio.

A surprising result came in an experiment where they crossed two different varieties of white-flowered plants (**Figure 4.20**). All of the F_1 generation plants had purple flowers! Bateson and Punnett then allowed the F_1 offspring to self-fertilize. The F_2 generation resulted in purple and white flowers in a ratio of 9 purple to 7 white. From this result, Bateson and Punnett deduced that two different genes were involved, with the following relationship:

C (one purple-color-producing) allele is dominant to *c* (white).
P (another purple-color-producing) allele is dominant to *p* (white).
cc or *pp* masks the *P* or *C* alleles, producing white color.



(a) Comb types



F_1 (*RrPp*) x F_1 (*RrPp*)

F_2 generation

	RP	*Rp*	*rP*	*rp*
RP	*RRPP* Walnut	*RRPp* Walnut	*RrPP* Walnut	*RrPp* Walnut
Rp	*RRPp* Walnut	*RRpp* Rose	*RrPp* Walnut	*Rrpp* Rose
rP	*RrPP* Walnut	*RrPp* Walnut	*rrPP* Pea	*rrPp* Pea
rp	*RrPp* Walnut	*Rrpp* Rose	*rrPp* Pea	*rrpp* Single

(b) The crosses of Bateson and Punnett

INTERACTIVE EXERCISE

FIGURE 4.19 Inheritance of comb morphology in chickens. This trait is influenced by two different genes, which can each exist in two alleles. **(a)** Four phenotypic outcomes are possible. The underline symbol indicates the allele could be either dominant or recessive. **(b)** The crosses of Bateson and Punnett examined the interaction of the two genes.

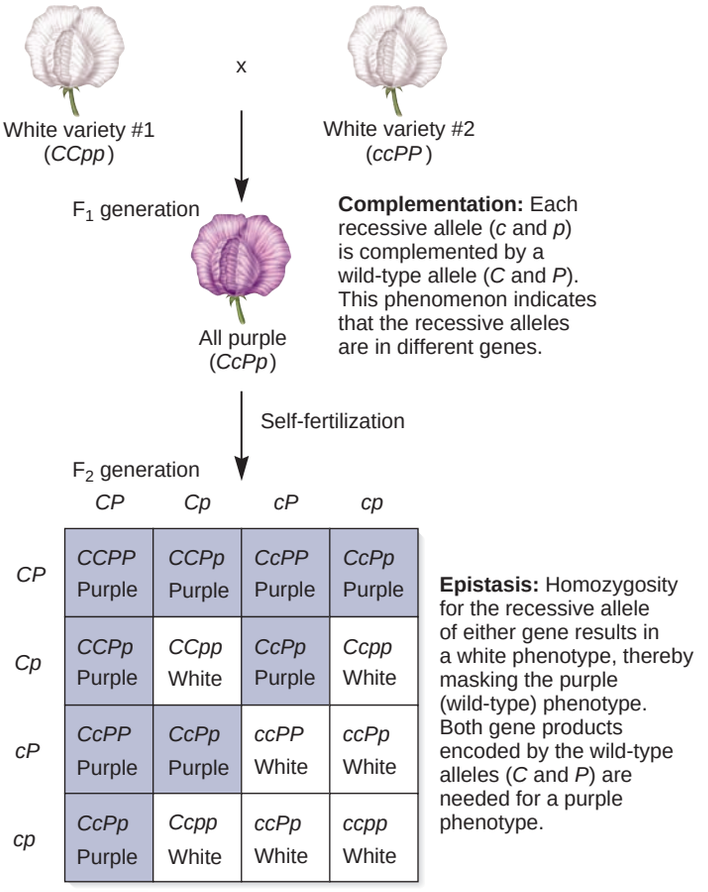
When the alleles of one gene mask the phenotypic effects of the alleles of another gene, the phenomenon is called **epistasis.** Geneticists consider epistasis relative to a particular phenotype. If possible, geneticists use the wild-type phenotype as their reference phenotype when describing an epistatic interaction. In this case, purple flowers are wild type. Homozygosity for the white allele of one gene masks the expression of the purple-producing allele of another gene. In other words, the *cc* genotype is epistatic to a purple phenotype, and the *pp* genotype is also epistatic to a purple phenotype. At the level of genotypes, *cc* is epistatic to *PP* or *Pp*, and *pp* is epistatic to *CC* or *Cc*. This is an example of **recessive epistasis**. As seen in Figure 4.20, this epistatic interaction produces only two phenotypes—purple or white flowers—in a 9:7 ratio.

Epistatis often occurs because two (or more) different proteins participate in a common function. For example, two or more proteins may be part of an enzymatic pathway leading to the formation of a single product. To illustrate this idea, let's consider the formation of a purple pigment in the sweet pea.

Colorless precursor $\xrightarrow{\text{Enzyme C}}$ Colorless intermediate $\xrightarrow{\text{Enzyme P}}$ **Purple pigment**

In this example, a colorless precursor molecule must be acted on by two different enzymes to produce the purple pigment. Gene *C* encodes a functional protein called enzyme C, which converts the colorless precursor into a colorless intermediate. Two copies of the recessive allele (*cc*) result in a lack of production of this enzyme in the homozygote. Gene *P* encodes a functional enzyme P, which converts the colorless intermediate into the purple pigment. Like the *c* allele, the recessive *p* allele encodes a defective enzyme P. If an individual is homozygous for either recessive allele (*cc* or *pp*), it will not make any functional enzyme C or enzyme P, respectively. When one of these enzymes is missing, purple pigment cannot be made, and the flowers remain white.

The parental cross shown in Figure 4.20 illustrates another genetic phenomenon called **complementation.** This term refers to the production of offspring with a wild-type phenotype from parents that both display the same or similar recessive phenotype. In this case, purple-flowered F_1 offspring were obtained from two white-flowered parents. Complementation typically occurs because the recessive phenotype in the parents is due to homozgyosity at two different genes. In our sweet pea example, one parent is *CCpp* and the other is *ccPP*. In the F_1 offspring, the *C* and *P* alleles, which are wild-type and dominant, complement the *c* and *p* alleles, which are recessive. The offspring must have one wild-type allele of both genes to display the wild-type phenotype. Why is complementation an important experimental observation? When geneticists observe complementation in a genetic cross, the results suggest that the recessive phenotype in the two parent strains is caused by mutant alleles in two different genes.



INTERACTIVE EXERCISE

FIGURE 4.20 A cross between two different white varieties of the sweet pea.

Genes →Traits The color of the sweet pea flower is controlled by two genes, which are epistatic to each other and show complementation. Each gene is necessary for the production of an enzyme required for pigment synthesis. The recessive allele of either gene encodes a defective enzyme. If an individual is homozygous recessive for either of the two genes, the purple pigment cannot be synthesized. This results in a white phenotype.

A Cross Involving a Two-Gene Interaction Can Produce Three Distinct Phenotypes Due to Epistasis

Thus far, we have observed two different gene interactions: one producing four phenotypes and the other producing only two. Coat color in rodents provides an example that produces three phenotypes. If a true-breeding black rat is crossed to a true-breeding albino rat, the result is a rat with agouti coat color. Animals with agouti coat color have black pigmentation at the tips of each hair that changes to orange pigmentation near the root. If two agouti animals of the F_1 generation are crossed to each other, they produce agouti, black, and albino offspring in a 9:3:4 ratio (**Figure 4.21**).

How do we explain this ratio? This cross involves two genes that are called *A* (for agouti) and *C* (for colored). The dominant *A* allele of the agouti gene encodes a protein that regulates hair color such that the pigmentation shifts from black (eumelanin) at the tips to orange (phaeomelanin) near the roots. The recessive

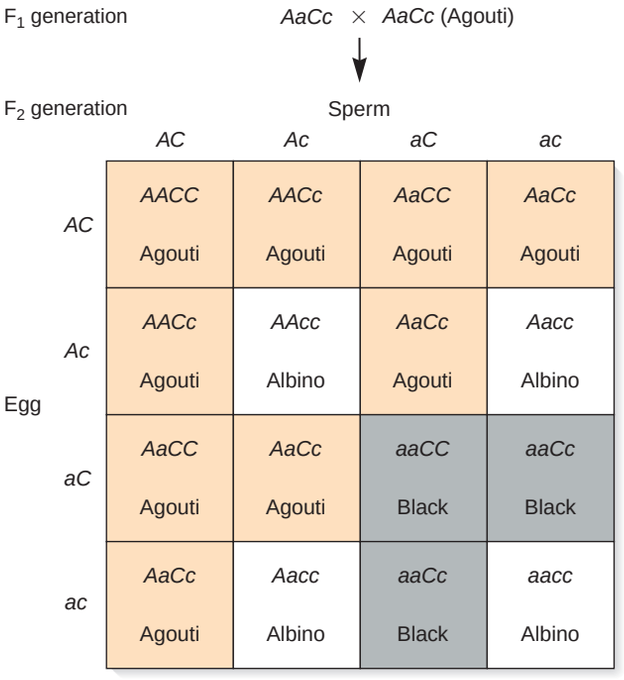


FIGURE 4.21 **Inheritance pattern of coat color in rats involving a gene interaction between the agouti gene (*A* or *a*) and the colored gene (*C* or *c*).**

allele, *a*, inhibits the shift to orange pigmentation and thereby results in black pigment production throughout the entire hair, when an animal is *aa*. As with rabbits, the colored gene encodes tyrosinase, which is needed for the first step in melanin synthesis. The *C* allele allows pigmentation to occur, whereas the *c* allele causes the loss of tyrosinase function. The *C* allele is dominant to the *c* allele; *cc* homozygotes are albino and have white coat color.

As shown at the top of Figure 4.21, the F_1 rats are heterozygous for the two genes. In this case, *C* is dominant to *c*, and *A* is dominant to *a*. If a rat has at least one copy of both dominant alleles, the result is agouti coat color. Let's consider agouti as our reference phenotype. In the F_2 generation, if a rat has a dominant *A* allele but is *cc* homozygous, it will be albino and develop a white coat. The *c* allele is epistatic to *A* and masks pigment production.

By comparison, if an individual has a dominant *C* allele and is homozygous *aa*, the coat color is black. How can we view the effects of the *aa* genotype when an individual carries a *C* allele? Because the *aa* genotype actually masks orange pigmentation, the black phenotype could be viewed as epistasis. However, many geneticists would not view this effect as epistasis but instead would call it a **gene modifier effect**—the alleles of one gene modify the phenotypic effect of the alleles of a different gene. From this alternative viewpoint, the pigmentation is not totally masked, but instead the agouti color is modified to black. Another example of a gene modifer effect is described next.

EXPERIMENT 4A

Bridges Observed an 8:4:3:1 Ratio Because the Cream-Eye Gene Can Modify the X-Linked Eosin Allele But Not the Red or White Alleles

As we have seen, geneticists view epistasis as a situation in which the alleles of a given gene mask the phenotypic effects of the alleles of another gene. In some cases, however, two genes may interact to influence a particular phenotype, but the interaction of particular alleles seems to modify the phenotype, not mask it.

Calvin Bridges discovered an early example in which one gene modifies the phenotypic effects of an X-linked eye color gene in *Drosophila*. As discussed in Chapter 3, the X-linked red allele (w^+) is dominant to the white allele (w). Besides these two alleles, Thomas Hunt Morgan and Calvin Bridges found another allele of this gene that they called eosin (w-e), which results in eyes that are a pale orange color. The red allele is dominant to the eosin allele. In addition, the expression of the eosin allele depends on the number of copies of the allele. When females have two copies of this allele, they have eosin eyes. When females are heterozygous for the eosin allele and white allele, they have light-eosin eyes. Within true-breeding cultures of flies with eosin eyes, he occasionally found a fly that had a noticeably different eye color. In particular, he identified a rare fly with cream-colored eyes. Bridges reasoned that this new eye color could be explained in two different ways. One possibility is that the cream-colored phenotype could be the result of a new mutation that changed the eosin allele into a cream allele. A second possibility is that a different gene may have incurred a mutation that modified the phenotypic expression of the eosin allele. This second possibility is an example of a gene interaction. To distinguish between these two possibilities, he carried out the crosses described in **Figure 4.22**. He crossed males with cream-colored eyes to wild-type females and then allowed the F_1 generation flies, which all had red eyes, to mate with each other. As shown in the data, all F_2 females had red eyes, but males had red eyes, eosin eyes, or cream eyes.

THE HYPOTHESES

Cream-colored eyes in fruit flies are due to the effect of an allele that is in the same gene as the eosin allele or in a second gene that modifies the expression of the eosin allele.

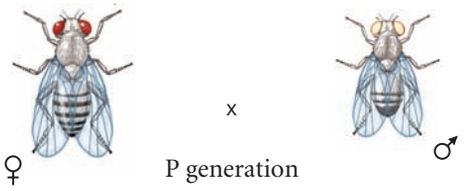
TESTING THE HYPOTHESES — FIGURE 4.22 A gene interaction between the cream allele and eosin allele.

INTERACTIVE EXERCISE

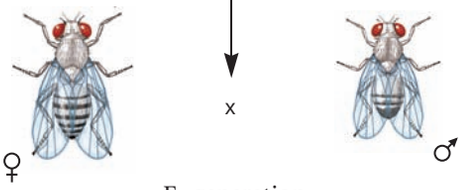
Starting material: From a culture of flies with eosin eyes, Bridges obtained a fly with cream-colored eyes and used it to produce a true-breeding culture of flies with cream-colored eyes. The allele was called *cream a* (c^a).

1. Cross males with cream-colored eyes to wild-type females.
2. Observe the F_1 offspring and then allow the offspring to mate with each other.
3. Observe and record the eye color and sex of the F_2 generation.

Experimental level



P generation



F_1 generation

F_2 generation (see The Data)

Conceptual level

$CCX^{w^+}X^{w^+}$ x $c^ac^aX^{w-e}Y$

Predicted outcome: $Cc^aX^{w^+}X^{w-e}$ and $Cc^aX^{w^+}Y$

Red-eyed females and males

Allow F_1 offspring to mate.

Predicted outcome: See Punnett square and The Data.

THE DATA

Cross	*Outcome*
P cross:	
Cream-eyed male × wild-type female	F_1: All red eyes
F_1 cross:	
F_1 brother × F_1 sister	F_2: 104 females with red eyes 47 males with red eyes 44 males with eosin eyes 14 males with cream eyes

Data from Calvin Bridges (1919) Specific modifiers of eosin eye color in *Drosophila melanogaster. J. Experimental Zoology 28*, 337–384.

INTERPRETING THE DATA

To interpret these data, keep in mind that Bridges already knew that the eosin allele is X-linked. However, he did not know whether the cream allele was in the same gene as the eosin allele, in a different gene on the X chromosome, or on an autosome. The F_2 generation indicates that the cream allele is not in the same gene as the eosin allele. If the cream allele was in the same gene as the eosin allele, none of the F_2 males would have had eosin eyes; there would have been a 1:1 ratio of red-eyed males and cream-eyed males in the F_2 generation. This result was not obtained. Instead, the actual results are consistent with the idea that the male flies of the parental generation possessed both the eosin and cream alleles. Therefore, Bridges concluded that the cream allele was an allele of a different gene.

One possibility is that the cream allele is an autosomal recessive allele. If so, we can let *C* represent the dominant allele (which does not modify the eosin phenotype) and c^a represent the cream allele that modifies the eosin color to cream. We already know that the eosin allele is X-linked and recessive to the red allele. The parental cross is expected to produce all red-eyed F_1 flies in which the males are $Cc^aX^{w+}Y$ and the females are $Cc^aX^{w+}X^{w-e}$. When these F_1 offspring are allowed to mate with each other, the Punnett square shown here would predict the following outcome:

$Cc^aX^{w^+}X^{w-e}$ × $Cc^aX^{w^+}Y$

Sperm

Egg \ ♂ Sperm	CX^{w^+}	CY	$c^aX^{w^+}$	c^aY
CX^{w^+}	$CCX^{w^+}X^{w^+}$	$CCX^{w^+}Y$	$Cc^aX^{w^+}X^{w^+}$	$Cc^aX^{w^+}Y$
CX^{w-e}	$CCX^{w^+}X^{w-e}$	$CCX^{w-e}Y$	$Cc^aX^{w^+}X^{w-e}$	$Cc^aX^{w-e}Y$
$c^aX^{w^+}$	$Cc^aX^{w^+}X^{w^+}$	$Cc^aX^{w^+}Y$	$c^ac^aX^{w^+}X^{w^+}$	$c^ac^aX^{w^+}Y$
c^aX^{w-e}	$Cc^aX^{w^+}X^{w-e}$	$Cc^aX^{w-e}Y$	$c^ac^aX^{w^+}X^{w-e}$	$c^ac^aX^{w-e}Y$

Outcome:

1 $CCX^{w^+}X^{w^+}$: 1 $CCX^{w^+}X^{w-e}$: 2 $Cc^aX^{w^+}X^{w^+}$: 2 $Cc^aX^{w^+}X^{w-e}$: 1 $c^ac^aX^{w^+}X^{w^+}$: 1 $c^ac^aX^{w^+}X^{w-e}$ = **8 red-eyed females**

1 $CCX^{w^+}Y$: 2 $Cc^aX^{w^+}Y$: 1 $c^ac^aX^{w^+}Y$ = **4 red-eyed males**

1 $CCX^{w-e}Y$: 2 $Cc^aX^{w-e}Y$ = **3 light eosin-eyed males**

1 $c^ac^aX^{w-e}Y$ = **1 cream-eyed male**

This phenotypic outcome proposes that the specific modifier allele, c^a, can modify the phenotype of the eosin allele but not the red-eye allele. The eosin allele can be modified only when the c^a allele is homozygous. The predicted 8:4:3:1 ratio agrees reasonably well with Bridges's data.

A self-help quiz involving this experiment can be found at www.mhhe.com/brookergenetics4e.

Due to Gene Redundancy, Loss-of-Function Alleles May Have No Effect on Phenotype

During the past several decades, researchers have discovered new kinds of gene interactions by studying model organisms such as *Escherichia coli* (a bacterium), *Saccharomyces cerevisiae* (baker's yeast), *Arabidopsis thaliana* (a model plant), *Drosophila melanogaster* (fruit fly), *Caenorhabditis elegans* (a nematode worm), and *Mus musculus* (the laboratory mouse). The isolation of mutants that alter the phenotypes of these organisms has become a powerful tool for investigating gene function and has provided ways for researchers to identify new kinds of gene interactions. With the advent of modern molecular techniques (described in Chapters 16, 18, and 19), a common approach for investigating gene function is to intentionally produce loss-of-function alleles in a gene of interest. When a geneticist abolishes gene function by creating an organism that is homozygous for a loss-of-function allele, the resulting organism is said to have undergone a **gene knockout.**

Why are gene knockouts useful? The primary reason for making a gene knockout is to understand how a gene affects the structure and function of cells or the phenotypes of organisms. For example, if a researcher knocked out a particular gene in a mouse and the resulting animal was unable to hear, the researcher would suspect that the role of the functional gene is to promote the formation of ear structures that are vital for hearing.

Interestingly, by studying many gene knockouts in a variety of experimental organisms, geneticists have discovered that many knockouts have no obvious effect on phenotype at the cellular level or the level of discernible traits. To explore gene function further, researchers may make two or more gene knockouts in the same organism. In some cases, gene knockouts in two different genes produce a phenotypic change even though the single knockouts have no effect (**Figure 4.23**). Geneticists may attribute this change to **gene redundancy**—the phenomenon that one gene can compensate for the loss of function of another gene.

Gene redundancy may be due to different underlying causes. One common reason is gene duplication. Certain genes have been duplicated during evolution, so a species may contain two or more copies of similar genes. These copies, which are not identical due to the accumulation of random changes during evolution, are called **paralogs.** When one gene is missing, a paralog may be able to carry out the missing function. For example, genes *A* and *B* in Figure 4.23 could be paralogs of each other. Alternatively, gene redundancy may involve proteins that are involved in a common cellular function. When one of the proteins is missing due to a gene knockout, the function of another protein may be increased to compensate for the missing protein and thereby overcome the defect.

Let's explore the consequences of gene redundancy in a genetic cross. George Shull conducted one of the first studies

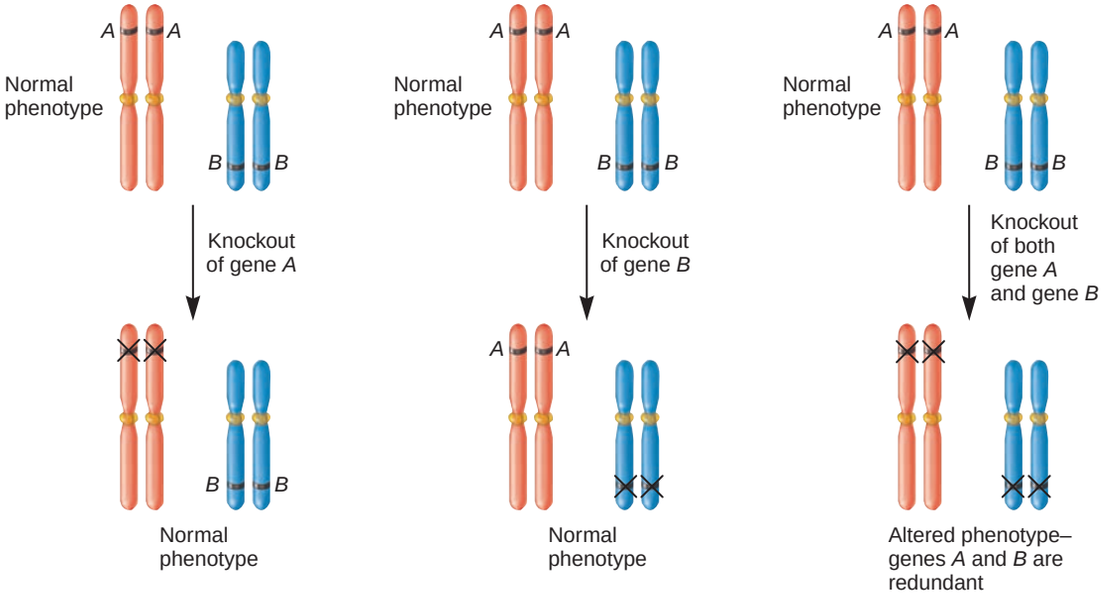


FIGURE 4.23 **A molecular explanation for gene redundancy.** To have a normal phenotype, an organism must have a functional copy of gene *A* or gene *B*, but not both. If both gene *A* and gene *B* are knocked out, an altered phenotype occurs.

that illustrated the phenomenon of gene redundancy. His work involved a weed known as shepherd's purse, a member of the mustard family. The trait he followed was the shape of the seed capsule, which is commonly triangular (**Figure 4.24**). Strains producing smaller ovate capsules are due to loss-of-function alleles in two different genes (*ttvv*). The ovate strain is an example of a double gene knockout. When Shull crossed a true-breeding plant with triangular capsules to a plant having ovate capsules, the F_1 generation all had triangular capsules. When the F_1 plants were self-fertilized, a surprising result came in the F_2 generation. Shull observed a 15:1 ratio of plants having triangular capsules to ovate capsules. The result can be explained by gene redundancy. Having one functional copy of either gene (*T* or *V*) is sufficient to produce the triangular phenotype. *T* and *V* are functional alleles of redundant genes. Only one of them is necessary for a triangular shape. When the functions of both genes are knocked out, as in the *ttvv* homozygote, the capsule becomes smaller and ovate.

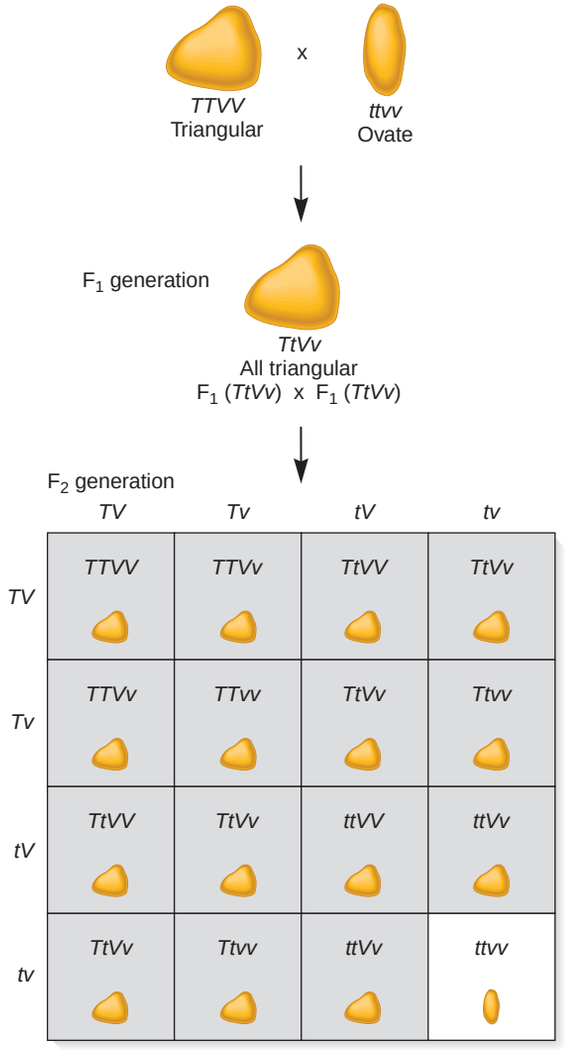


FIGURE 4.24 Inheritance of capsule shape in shepherd's purse, an example of gene redundancy. In this case, triangular shape requires a dominant allele in one of two genes, but not both. The *T* and *V* alleles are redundant.

The Phenotypic Effects of a Mutation Can Be Reversed by a Suppressor Mutation

When studying an experimental organism, a common approach to gain a deeper understanding of gene interaction is the isolation of a **suppressor mutation**—a second mutation that reverses the phenotypic effects of a first mutation. When a suppressor mutation is in a different gene than the first mutation, it is called an **intergenic** (or **extragenic**) **suppressor.**

What type of information might a researcher gain from the analysis of intergenic suppressor mutants? Usually, the primary goal is to identify proteins that participate in a common cellular process that ultimately affects the traits of an organism. In *Drosophila*, several different proteins work together in a signaling pathway that determines whether certain parts of the body contain sensory cells, such as those that make up mechanosensory bristles. Researchers have isolated dominant mutants that result in flies with fewer bristles. The mutated gene was named *Hairless* to reflect this phenotype. In this case, the wild-type allele is designated *h*, and the dominant mutant is *H*. After the *Hairless* mutant was obtained, researchers then isolated mutants that suppressed the hairless phenotype. Such suppressor mutants, which are in a different gene, produced flies that have a wild-type number of bristles. These mutants, which are also dominant, are in a gene that was named *Suppressor of Hairless*. The wild-type allele is designated *soh*, and the dominant mutant allele is *SoH*.

How do we explain the effects of these mutations at the molecular level? Let's first consider the functions of the proteins encoded by the normal (wild-type) genes (**Figure 4.25**). The role of the SoH protein, encoded by the *soh* allele of the *Suppressor of Hairless* gene, is to prevent the formation of sensory structures such as bristles in regions of the body where they should not be made. The Hairless protein is made in regions of the body where bristles should form, and binds to the SoH protein and inhibits its function. When the Hairless protein is properly expressed on the surface of the fly, as in an *hh* homozygote, bristles will form there.

Now let's consider the effects of a single mutation in the *Hairless* gene. In a heterozygote carrying the dominant allele (*H*), only half the amount of functional Hairless protein is made. This is not enough to inhibit all of the SoH proteins that are made. Therefore, the uninhibited SoH proteins prevent bristle formation and result in a hairless (bristleless) phenotype.

What happens in the double mutant? The suppressor mutation eliminates one of the two functional *soh* alleles. The double mutant expresses only one functional *h* allele and one functional *soh* allele. In the double mutant, the reduced amount of Hairless protein is able to inhibit the reduced amount of the SoH protein. Therefore, the ability of the SoH proteins to prevent bristle formation is stopped. Bristles form in the double heterozygote.

The analysis of a mutant and its suppressor often provides key information that two proteins participate in a common function. In some cases, the analysis reveals that two proteins physically interact with each other. As we have just seen, this type of interaction occurs between the Hairless and SoH proteins. Alternatively, two distinct proteins encoded by different genes may

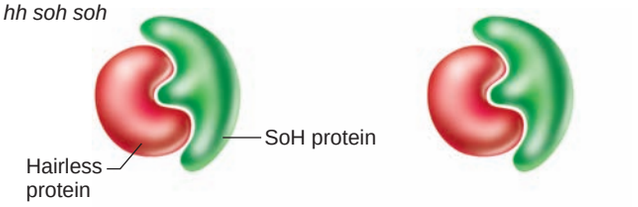
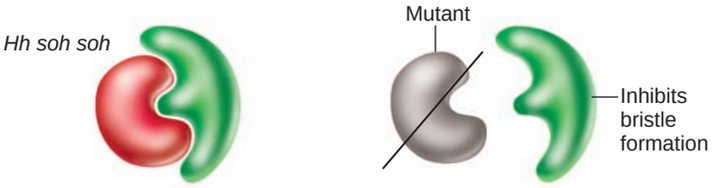
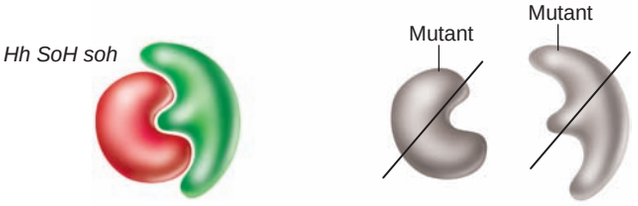
Genotype	Amount of functional Hairless protein	Amount of functional SoH protein	SoH proteins completely inhibited by Hairless proteins?	Normal bristle formation?
hh soh soh 	100%	100%	Yes	Yes
Hh soh soh 	~50%	100%	No	No
Hh SoH soh 	~50%	~50%	Yes	Yes

FIGURE 4.25 **An example of a gene interaction involving an intergenic suppressor.** The *Hairless* mutation, which produces the dominant *H* allele, results in flies with fewer bristles. A dominant suppressor mutation in a second gene restores bristle formation. This dominant allele is designated *SoH*. Examination of the interactions between the mutant and its suppressor reveals that the Hairless and SoH proteins physically interact with each other to determine whether bristles are formed.

participate in a common function, but do not directly interact with each other. For example, two enzymes may be involved in a biochemical pathway that leads to the synthesis of an amino acid. A mutation that greatly decreases the amount of one enzyme may limit the ability of an organism to make the amino acid. If this occurs, the amino acid would have to be supplied to the organism for it to survive. A suppressor mutation could increase the function of another enzyme in the pathway and thereby restore the ability of the organism to make an adequate amount of the amino acid. Such a suppressor would alleviate the need for the organism to have the amino acid supplemented in its diet.

Other suppressors exert their effects by altering the amount of protein encoded by a mutant gene. For example, a mutation may decrease the functional activity of a protein that is needed for sugar metabolism. An organism harboring such a mutation may not be able to metabolize the sugar at a sufficient rate for growth or survival. A suppressor mutation in a different gene could alter genetic regulatory proteins and thereby increase the amount of the protein encoded by the mutant gene. (The proteins involved in gene regulation are described in Chapters 14 and 15.) This suppressor mutation would increase the amount of the defective protein and thereby result in a faster rate of sugar metabolism.

KEY TERMS

Page 71. Mendelian inheritance, simple Mendelian inheritance
Page 72. wild-type alleles, genetic polymorphism, mutant alleles
Page 74. gain-of-function mutations, dominant-negative mutations, haploinsufficiency, incomplete dominance
Page 75. incomplete penetrance
Page 76. expressivity
Page 77. norm of reaction, overdominance, heterozygote advantage
Page 79. multiple alleles, temperature-sensitive allele
Page 80. codominance
Page 81. X-linked recessive, reciprocal cross
Page 82. sex-linked gene, hemizygous, holandric genes
Page 83. pseudoautosomal inheritance, sex-influenced inheritance
Page 84. sex-limited inheritance, sexual dimorphism, lethal allele, essential gene, nonessential genes
Page 85. age of onset, conditional lethal alleles, temperature-sensitive lethal alleles, semilethal alleles
Page 86. pleiotrophy, gene interaction
Page 88. epistasis, recessive epistasis, complementation
Page 89. gene modifier effect
Page 91. gene knockout, gene redundancy, paralogs
Page 92. suppressor mutation, intergenic (extragenic) suppressor

CHAPTER SUMMARY

- Mendelian inheritance patterns obey Mendel's laws.

4.1 Inheritance Patterns of Single Genes

- Several inheritance patterns involving single genes differ from those observed by Mendel (see Table 4.1).
- Wild-type alleles are prevalent in a population. When a gene exists in two or more wild-type alleles, this is a genetic polymorphism (see Figure 4.1).
- Recessive alleles are often due to mutations that result in a reduction or loss of function of the encoded protein (see Figure 4.2 and Table 4.2).
- Dominant alleles are most commonly caused by gain-of-function mutations, dominant negative mutations, or haploinsufficiency.
- Incomplete dominance is an inheritance pattern in which the heterozygote has an intermediate phenotype (see Figure 4.3).
- Whether we judge an allele to be dominant or incompletely dominant may depend on how closely we examine the phenotype (see Figure 4.4).
- Incomplete penetrance is a situation in which an allele that is expected to be expressed is not expressed (see Figure 4.5).
- Traits may vary in their expressivity.
- The outcome of traits is influenced by the environment (see Figure 4.6).
- Overdominance is an inheritance pattern in which the heterozygote has greater reproductive success (see Figures 4.7, 4.8).
- Most genes exist in multiple alleles in a population. Some alleles are temperature-sensitive (see Figures 4.9, 4.10).
- Some alleles, such as those that produce A and B blood antigens, are codominant (see Figure 4.11).
- X-linked inheritance patterns show differences between males and females, and are revealed in reciprocal crosses (see Figures 4.12, 4.13).
- The X and Y chromosomes carry different sets of genes, but they do have regions of short homology that can lead to pseudoautosomal inheritance (see Figure 4.14).
- For sex-influenced traits such as pattern baldness in humans, heterozygous males and females have different phenotypes (see Figures 4.15, 4.16).
- Sex-limited traits are expressed in only one sex, thereby resulting in sexual dimorphism (see Figure 4.17).
- Lethal alleles most commonly occur in essential genes. Lethal alleles may result in inheritance patterns that yield unexpected ratios (see Figure 4.18).
- Single genes have pleiotrophic effects.

4.2 Gene Interactions

- A gene interaction is a situation in which two or more genes affect a single phenotype (see Table 4.3).
- Bateson and Punnett discovered the first case of a gene interaction affecting comb morphology in chickens (see Figure 4.19).
- Epistasis is a situation in which the allele of one gene masks the phenotypic expression of the alleles of a different gene (see Figures 4.20, 4.21).
- A gene modifier effect is a situation in which an allele of one gene modifies (but does not completely mask) the phenotypic effects of the alleles of a different gene. An example is the cream eye color observed by Bridges (see Figure 4.22).
- Two different genes may have redundant functions, which is revealed in a double gene knockout (see Figures 4.23, 4.24).
- An intergenic suppressor mutation reverses the effects of a mutation in a different gene (see Figure 4.25).

PROBLEM SETS & INSIGHTS

Solved Problems

S1. In humans, why are X-linked recessive traits more likely to occur in males than females?

Answer: Because a male is hemizygous for X-linked traits, the phenotypic expression of X-linked traits depends on only a single copy of the gene. When a male inherits a recessive X-linked allele, he will automatically exhibit the trait because he does not have another copy of the gene on the corresponding Y chromosome. This phenomenon is particularly relevant to the inheritance of recessive X-linked alleles that cause human disease. (Some examples will be described in Chapter 22.)

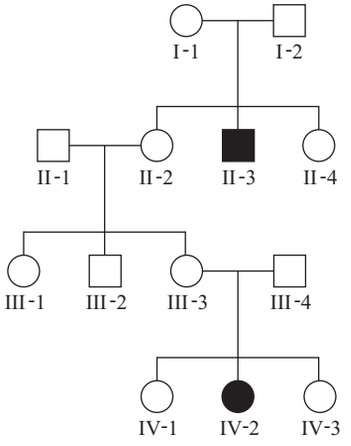
S2. In Ayrshire cattle, the spotting pattern of the animals can be either red and white or mahogany and white. The mahogany and white pattern is caused by the allele *M*. The red and white phenotype is controlled by the allele *m*. When mahogany and white animals are mated to red and white animals, the following results are obtained:

Genotype	Phenotype	
	Females	**Males**
MM	Mahogany and white	Mahogany and white
Mm	Red and white	Mahogany and white
mm	Red and white	Red and white

Explain the pattern of inheritance.

Answer: The inheritance pattern for this trait is sex-influenced inheritance. The *M* allele is dominant in males but recessive in females, whereas the *m* allele is dominant in females but recessive in males.

S3. The following pedigree involves a single gene causing an inherited disease. If you assume that incomplete penetrance is *not* occurring, indicate which modes of inheritance are *not* possible. (Affected individuals are shown as filled symbols.)



A. Recessive

B. Dominant

C. X-linked, recessive

D. Sex-influenced, dominant in females

E. Sex-limited, recessive in females

Answer:

A. It could be recessive.

B. It is probably not dominant unless it is incompletely penetrant.

C. It could not be X-linked recessive because individual IV-2 does not have an affected father.

D. It could not be sex-influenced, dominant in females because individual II-3 (who would have to be homozygous) has an unaffected mother (who would have to be heterozygous and affected).

E. It is not sex-limited because individual II-3 is an affected male and IV-2 is an affected female.

S4. Red-green color blindness is inherited as a recessive X-linked trait. What are the following probabilities?

A. A woman with phenotypically normal parents and a color-blind brother will have a color-blind son. Assume that she has no previous children.

B. The next child of a phenotypically normal woman, who has already had one color-blind son, will be a color-blind son.

C. The next child of a phenotypically normal woman, who has already had one color-blind son, and who is married to a color-blind man, will have a color-blind daughter.

Answer:

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

B. If she already had a color-blind son, then we know she must be a carrier, so the chance is 25%.

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

S5. Pattern baldness is an example of a sex-influenced trait that is dominant in males and recessive in females. A couple, neither of whom is bald, produced a bald son. What are the genotypes of the parents?

Answer: Because the father is not bald, we know he must be homozygous, *bb*. Otherwise, he would be bald. A female who is not bald can be either *Bb* or *bb*. Because she has produced a bald son, we know that she must be *Bb* in order to pass the *B* allele to her son.

S6. Two pink-flowered four-o'clocks were crossed to each other. What are the following probabilities for the offspring?

A. A plant will be red-flowered.

B. The first three plants examined will be white.

C. A plant will be either white or pink.

D. A group of six plants contain one pink, two whites, and three reds.

Answer: The first thing we need to do is construct a Punnett square to determine the individual probabilities for each type of offspring.

Because flower color is incompletely dominant, the cross is *Rr* × *Rr*.

♀ \ ♂	*R*	*r*
R	*RR* Red	*Rr* Pink
r	*Rr* Pink	*rr* White

The phenotypic ratio is 1 red to 2 pink to 1 white. In other words, 1/4 are expected to be red, 1/2 pink, and 1/4 white.

A. The probability of a red-flowered plant is 1/4, which equals 25%.

B. Use the product rule.

$1/4 \times 1/4 \times 1/4 = 1/64 = 1.6\%$

C. Use the sum rule because these are mutually exclusive events. A given plant cannot be both white and pink.

$1/4 + 1/2 = 3/4 = 75\%$

D. Use the multinomial expansion equation. See solved problem S7 in Chapter 2 for an explanation of the multinomial expansion equation. In this case, three phenotypes are possible.

$$P = \frac{n!}{a!b!c!} p^a q^b r^c$$

where

n = total number of offspring = 6
a = number of reds = 3
p = probability of reds = (1/4)
b = number of pinks = 1
q = probability of pink = (1/2)
c = number of whites = 2
r = probability of whites = (1/4)

If we substitute these values into the equation,

$$P = \frac{6!}{3!1!2!} (1/4)^3(1/2)^1(1/4)^2$$

$$P = 0.029 = 2.9\%$$

This means that 2.9% of the time we would expect to obtain six plants, three with red flowers, one with pink flowers, and two with white flowers.

Conceptual Questions

C1. Describe the differences among dominance, incomplete dominance, codominance, and overdominance.

C2. Discuss the differences among sex-influenced, sex-limited, and sex-linked inheritance. Describe examples.

C3. What is meant by a gene interaction? How can a gene interaction be explained at the molecular level?

C4. Let's suppose a recessive allele encodes a completely defective protein. If the functional allele is dominant, what does that tell you about the amount of the functional protein that is sufficient to cause the phenotype? What if the allele shows incomplete dominance?

C5. A nectarine is a peach without the fuzz. The difference is controlled by a single gene that is found in two alleles, *D* and *d*. At the molecular level, would it make more sense to you that the nectarine is homozygous for a recessive allele or that the peach is homozygous for the recessive allele? Explain your reasoning.

C6. An allele in *Drosophila* produces a "star-eye" trait in the heterozygous individual. However, the star-eye allele is lethal in homozygotes. What would be the ratio and phenotypes of surviving flies if star-eyed flies were crossed to each other?

C7. A seed dealer wants to sell four-o'clock seeds that will produce only red, white, or pink flowers. Explain how this should be done.

C8. The serum from one individual (let's call this person individual 1) is known to agglutinate the red blood cells from a second individual (individual 2). List the pairwise combinations of possible genotypes that individuals 1 and 2 could be. If individual 1 is the parent of individual 2, what are his or her possible genotypes?

C9. Which blood phenotypes (A, B, AB, and/or O) provide an unambiguous genotype? Is it possible for a couple to produce a family of children with all four blood types? If so, what would the genotypes of the parents have to be?

C10. A woman with type B blood has a child with type O blood. What are the possible genotypes and blood types of the father?

C11. A type A woman is the daughter of a type O father and type A mother. If she has children with a type AB man, what are the following probabilities?

A. A type AB child

B. A type O child

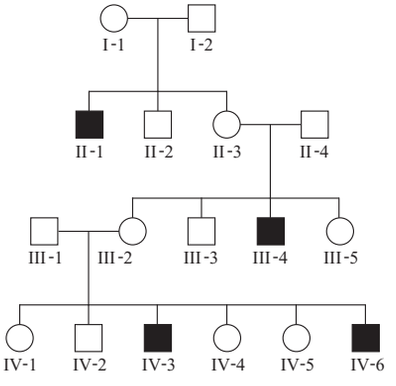
C. The first three children with type AB blood

D. A family containing two children with type B blood and one child with type AB

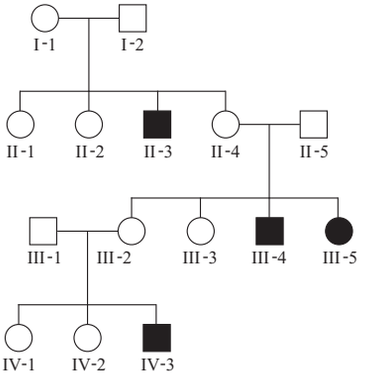
C12. In Shorthorn cattle, coat color is controlled by a single gene that can exist as a red allele (*R*) or white allele (*r*). The heterozygotes (*Rr*) have a color called roan that looks less red than the *RR* homozygotes. However, when examined carefully, the roan phenotype in cattle is actually due to a mixture of completely red hairs and completely white hairs. Should this be called incomplete dominance, codominance, or something else? Explain your reasoning.

C13. In chickens, the Leghorn variety has white feathers due to an autosomal dominant allele. Silkies have white feathers due to a recessive allele in a second (different) gene. If a true-breeding white Leghorn is crossed to a true-breeding white Silkie, what is the expected phenotype of the F_1 generation? If members of the F_1 generation are mated to each other, what is the expected phenotypic outcome of the F_2 generation? Assume the chickens in the parental generation are homozygous for the white allele at one gene and homozygous for the brown allele at the other gene. In subsequent generations, nonwhite birds will be brown.

C14. Propose the most likely mode of inheritance (autosomal dominant, autosomal recessive, or X-linked recessive) for the following pedigrees. Affected individuals are shown with filled (black) symbols.



(a)



(b)

C15. A human disease known as vitamin D-resistant rickets is inherited as an X-linked dominant trait. If a male with the disease produces children with a female who does not have the disease, what is the expected ratio of affected and unaffected offspring?

C16. Hemophilia is an X-linked recessive trait in humans. If a heterozygous woman has children with an unaffected man, what is the probability of the following combinations of children?

A. An affected son

B. Four unaffected offspring in a row

C. An unaffected daughter or son

D. Two out of five offspring that are affected

C17. Incontinentia pigmenti is a rare, X-linked dominant disorder in humans characterized by swirls of pigment in the skin. If an affected female, who had an unaffected father, has children with an unaffected male, what would be the predicted ratios of affected and unaffected sons and daughters?

C18. With regard to pattern baldness in humans (a sex-influenced trait), a woman who is not bald and whose mother is bald has children with a bald man whose father is not bald. What are their probabilities of having the following types of families?

A. Their first child will not become bald.

B. Their first child will be a male who will not become bald.

C. Their first three children will be females who are not bald.

C19. In rabbits, the color of body fat is controlled by a single gene with two alleles, designated *Y* and *y*. The outcome of this trait is affected by the diet of the rabbit. When raised on a standard vegetarian diet, the dominant *Y* allele confers white body fat, and the *y* allele confers yellow body fat. However, when raised on a xanthophyll-free diet, the homozygote *yy* animal has white body fat. If a heterozygous animal is crossed to a rabbit with yellow body fat, what are the proportions of offspring with white and yellow body fat when raised on a standard vegetarian diet? How do the proportions change if the offspring are raised on a xanthophyll-free diet?

C20. A Siamese cat that spends most of its time outside was accidentally injured in a trap and required several stitches in its right front paw. The veterinarian had to shave the fur from the paw and leg, which originally had rather dark fur. Later, when the fur grew back, it was much lighter than the fur on the other three legs. Do you think this injury occurred in the hot summer or cold winter? Explain your answer.

C21. A true-breeding male fly with eosin eyes is crossed to a white-eyed female that is heterozygous for the wild-type (*C*) and cream alleles (c^a). What are the expected proportions of their offspring?

C22. The trait of hen- versus cock-feathering is a sex-limited trait controlled by a single gene. Females always exhibit hen-featuring as do *HH* and *Hh* males. Only *hh* males show cock-featuring. Starting with two heterozygous fowl that are hen-feathered, explain how you would obtain a true-breeding line that always produced cock-feathered males.

C23. In the pedigree shown here for a trait determined by a single gene (affected individuals are shown in black), state whether it would be possible for the trait to be inherited in each of the following ways:

A. Recessive

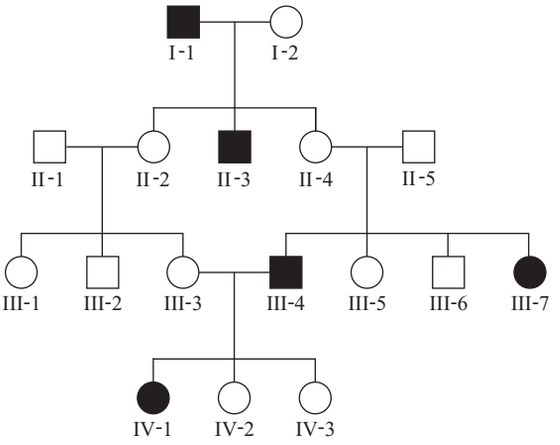
B. X-linked recessive

C. Dominant, complete penetrance

D. Sex-influenced, dominant in males

E. Sex-limited

F. Dominant, incomplete penetrance



C24. The pedigree shown here also concerns a trait determined by a single gene (affected individuals are shown in black). Which of the following patterns of inheritance are possible?

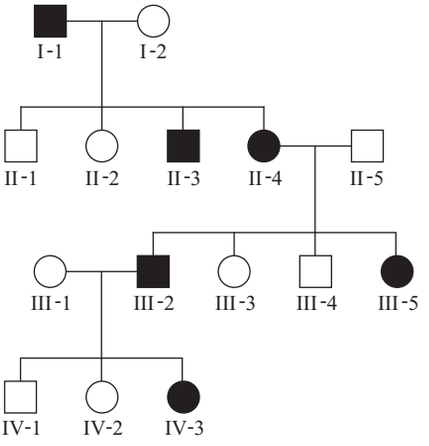
A. Recessive

B. X-linked recessive

C. Dominant

D. Sex-influenced, recessive in males

E. Sex-limited



C25. Let's suppose you have pedigree data from thousands of different families involving a particular genetic disease. How would you decide whether the disease is inherited as a recessive trait as opposed to one that is dominant with incomplete penetrance?

C26. Compare phenotypes at the molecular, cellular, and organism levels for individuals who are homozygous for the hemoglobin allele, Hb^AHb^A, and the sickle cell allele, Hb^SHb^S.

C27. A very rare dominant allele that causes the little finger to be crooked has a penetrance value of 80%. In other words, 80% of heterozygotes carrying the allele will have a crooked little finger. If a homozygous unaffected person has children with a heterozygote carrying this mutant allele, what is the probability that an offspring will have little fingers that are crooked?

C28. A sex-influenced trait in humans is one that affects the length of the index finger. A "short" allele is dominant in males and

recessive in females. Heterozygous males have an index finger that is significantly shorter than the ring finger. The gene affecting index finger length is located on an autosome. A woman with short index fingers has children with a man who has normal index fingers. They produce five children in the following order: female, male, male, female, male. The oldest female offspring marries a man with normal fingers and then has one daughter. The youngest male among the five children marries a woman with short index fingers, and then they have two sons. Draw the pedigree for this family. Indicate the phenotypes of every individual (filled symbols for individuals with short index fingers and open symbols for individuals with normal index fingers).

C29. In horses, there are three coat-color patterns termed cremello (beige), chestnut (brown), and palomino (golden with light mane and tail). If two palomino horses are mated, they produce about 1/4 cremello, 1/4 chestnut, and 1/2 palomino offspring. In contrast, cremello horses and chestnut horses breed true. (In other words, two cremello horses will produce only cremello offspring and two chestnut horses will produce only chestnut offspring.) Explain this pattern of inheritance.

C30. Briefly describe three explanations for how a suppressor mutation exerts its effects at the molecular level.

Experimental Questions

E1. Mexican hairless dogs have little hair and few teeth. When a Mexican hairless is mated to another breed of dog, about half of the puppies are hairless. When two Mexican hairless dogs are mated to each other, about 1/3 of the surviving puppies have hair, and about 2/3 of the surviving puppies are hairless. However, about two out of eight puppies from this type of cross are born grossly deformed and do not survive. Explain this pattern of inheritance.

E2. In chickens, some varieties have feathered shanks (legs), but others do not. In a cross between a Black Langhans (feathered shanks) and Buff Rocks (unfeathered shanks), the shanks of the F_1 generation are all feathered. When the F_1 generation is crossed, the F_2 generation contains chickens with feathered shanks to unfeathered shanks in a ratio of 15:1. Suggest an explanation for this result.

E3. In sheep, the formation of horns is a sex-influenced trait; the allele that results in horns is dominant in males and recessive in females. Females must be homozygous for the horned allele to have horns. A horned ram was crossed to a polled (unhorned) ewe, and the first offspring they produced was a horned ewe. What are the genotypes of the parents?

E4. A particular breed of dog can have long hair or short hair. When true-breeding long-haired animals were crossed to true-breeding short-haired animals, the offspring all had long hair. The F_2 generation produced a 3:1 ratio of long- to short-haired offspring. A second trait involves the texture of the hair. The two variants are wiry hair and straight hair. F_1 offspring from a cross of these two varieties all had wiry hair, and F_2 offspring showed a 3:1 ratio of wiry-haired to straight-haired puppies. Recently, a breeder of the short-, wiry-haired dogs found a female puppy that was albino. Similarly, another breeder of the long-, straight-haired dogs found a male puppy that was albino. Because the albino trait is always due to a recessive allele, the two breeders got together and mated the two dogs. Surprisingly, all of the puppies in the litter had black hair. How would you explain this result?

E5. In the clover butterfly, males are always yellow, but females can be yellow or white. In females, white is a dominant allele. Two yellow butterflies were crossed to yield an F_1 generation consisting of 50% yellow males, 25% yellow females, and 25% white females. Describe how this trait is inherited and the genotypes of the parents.

E6. The *Mic2* gene in humans is present on both the X and Y chromosome. Let's suppose the *Mic2* gene exists in a dominant *Mic2* allele, which results in normal surface antigen, and a recessive *mic2* allele, which results in defective surface antigen production. Using molecular techniques, it is possible to identify homozygous and heterozygous individuals. By following the transmission of the *Mic2* and *mic2* alleles in a large human pedigree, would it be possible to distinguish between pseudoautosomal inheritance and autosomal inheritance? Explain your answer.

E7. Duroc Jersey pigs are typically red, but a sandy variation is also seen. When two different varieties of true-breeding sandy pigs were crossed to each other, they produced F_1 offspring that were red. When these F_1 offspring were crossed to each other, they produced red, sandy, and white pigs in a 9:6:1 ratio. Explain this pattern of inheritance.

E8. As discussed in this chapter, comb morphology in chickens is governed by a gene interaction. Two walnut comb chickens were crossed to each other. They produced only walnut comb and rose comb offspring, in a ratio of 3:1. What are the genotypes of the parents?

E9. In certain species of summer squash, fruit color is determined by two interacting genes. A dominant allele, *W*, determines white color, and a recessive allele (*w*) allows the fruit to be colored. In a homozygous *ww* individual, a second gene determines fruit color: *G* (green) is dominant to *g* (yellow). A white squash and a yellow squash were crossed, and the F_1 generation yielded approximately 50% white fruit and 50% green fruit. What are the genotypes of the parents?

E10. Certain species of summer squash exist in long, spherical, or disk shapes. When a true-breeding long-shaped strain was crossed to a true-breeding disk-shaped strain, all of the F_1 offspring were disk-shaped. When the F_1 offspring were allowed to self-fertilize, the F_2 generation consisted of a ratio of 9 disk-shaped to 6 round-shaped to 1 long-shaped. Assuming the shape of summer squash is governed by two different genes, with each gene existing in two alleles, propose a mechanism to account for this 9:6:1 ratio.

E11. In a species of plant, two genes control flower color. The red allele (*R*) is dominant to the white allele (*r*); the color-producing allele (*C*) is dominant to the non-color-producing allele (*c*). You suspect that either an *rr* homozygote or a *cc* homozygote will produce white flowers. In other words, *rr* is epistatic to *C*, and *cc* is epistatic to *R*. To test your hypothesis, you allowed heterozygous plants (*RrCc*) to self-fertilize and counted the offspring. You obtained the following data: 201 plants with red flowers and 144 with white flowers. Conduct a chi-square analysis to see if your observed data are consistent with your hypothesis.

E12. In *Drosophila*, red eyes is the wild-type phenotype. Several different genes (with each gene existing in two or more alleles) are known to affect eye color. One allele causes purple eyes, and a different allele causes sepia eyes. Both of these alleles are recessive compared with red eye color. When flies with purple eyes were crossed to flies with sepia eyes, all of the F_1 offspring had red eyes. When the F_1 offspring were allowed to mate with each other, the following data were obtained:

146 purple eyes

151 sepia eyes

50 purplish sepia eyes

444 red eyes

Explain this pattern of inheritance. Conduct a chi-square analysis to see if the experimental data fit your hypothesis.

E13. As mentioned in Experimental Question E12, red eyes is the wild-type phenotype in *Drosophila*, and several different genes (with each gene existing in two or more alleles) affect eye color. One allele causes purple eyes, and a different allele causes vermilion eyes. The purple and vermilion alleles are recessive compared with red eye color. The following crosses were made, and the following data were obtained:

Cross 1: Males with vermilion eyes × females with purple eyes

354 offspring, all with red eyes

Cross 2: Males with purple eyes × females with vermilion eyes

212 male offspring with vermilion eyes

221 female offspring with red eyes

Explain the pattern of inheritance based on these results. What additional crosses might you make to confirm your hypothesis?

E14. Let's suppose you were looking through a vial of fruit flies in your laboratory and noticed a male fly that has pink eyes. What crosses would you make to determine if the pink allele is an X-linked gene? What crosses would you make to determine if the pink allele is an allele of the same X-linked gene that has white and eosin alleles? Note: The white and eosin alleles are discussed in Figure 4.22.

E15. When examining a human pedigree, what features do you look for to distinguish between X-linked recessive inheritance versus autosomal recessive inheritance? How would you distinguish X-linked dominant inheritance from autosomal dominant inheritance in a human pedigree?

E16. The cream allele is a modifier of eosin and the cream allele is autosomal. By comparison, the red and eosin alleles are X-linked. Based on these ideas, conduct a chi-square analysis to determine if Bridges' data of Figure 4.22 agree with the predicted ratio of 8 red-eyed females, 4 red-eyed males, 3 light eosin-eyed males, and 1 cream-eyed male.

Questions for Student Discussion/Collaboration

1. Let's suppose a gene exists as a functional wild-type allele and a nonfunctional mutant allele. At the organism level, the wild-type allele is dominant. In a heterozygote, discuss whether dominance occurs at the cellular or molecular level. Discuss examples in which the issue of dominance depends on the level of examination.
2. A true-breeding rooster with a rose comb, feathered shanks, and cock-feathering was crossed to a hen that is true-breeding for pea comb and unfeathered shanks but is heterozygous for hen-feathering. If you assume these genes can assort independently, what is the expected outcome of the F_1 generation?
3. In oats, the color of the chaff is determined by a two-gene interaction. When a true-breeding black plant was crossed to a true-breeding white plant, the F_1 generation was composed of all black plants. When the F_1 offspring were crossed to each other, the ratio produced was 12 black to 3 gray to 1 white. First, construct a Punnett square that accounts for this pattern of inheritance. Which genotypes produce the gray phenotype? Second, at the level of protein function, how would you explain this type of inheritance?

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

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