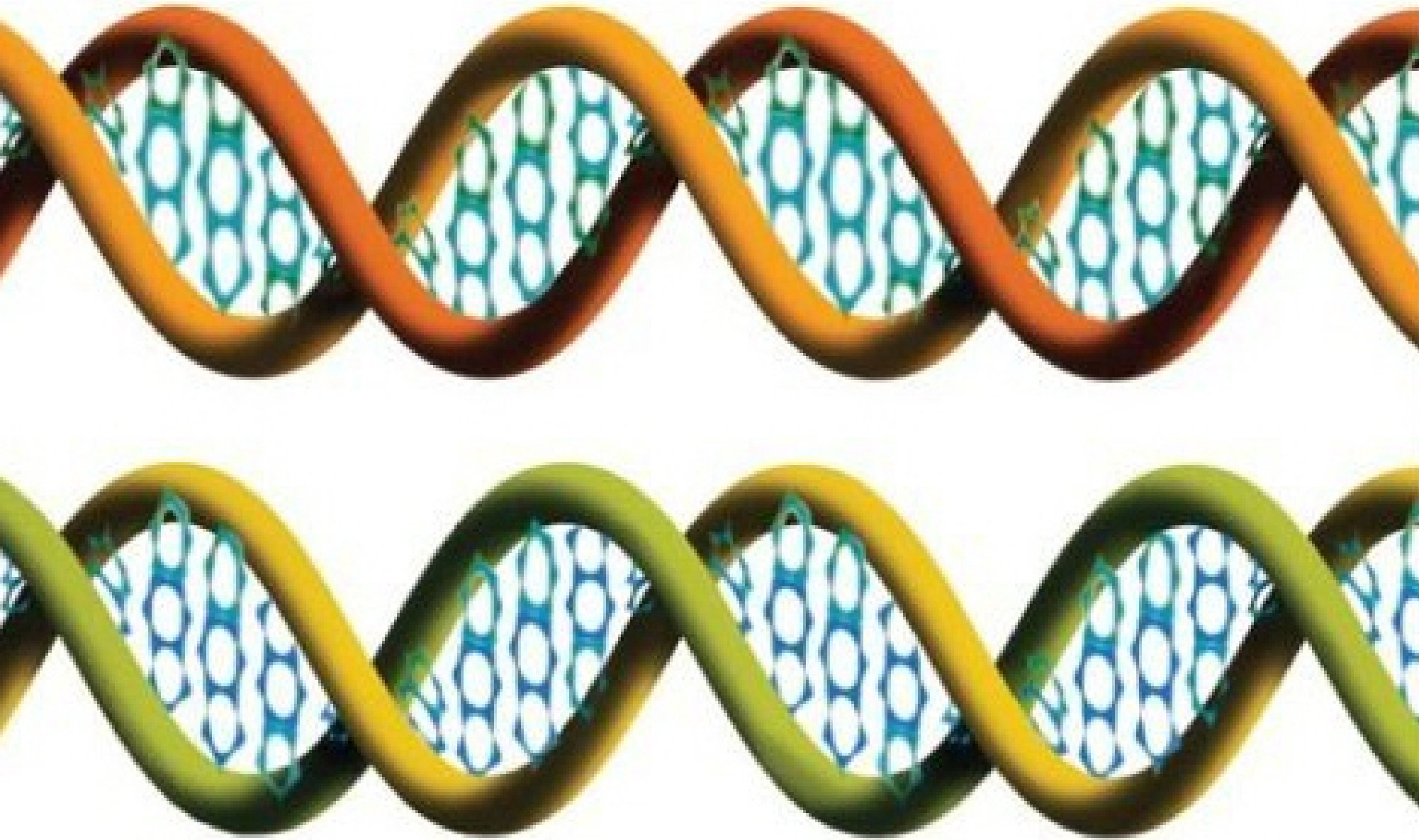
BENJAMIN A. PIERCE

GENETICS

A Conceptual Approach



The New Genetics
ETHICS • SCIENCE • TECHNOLOGY

Mapping the Human Genome—Where does it lead, and what does it mean?

by Arthur L. Caplan and Kelly A. Carroll

In June 2000, scientists from the Human Genome Project and Celera Genomics stood at a podium with former President Bill Clinton to announce a stunning achievement—they had successfully constructed a sequence of the entire huan genome. Soon this process of identifying and sequencing each and every human gene became characterized as "mapping the human genome". As with maps of the physical world, the map of the human genome provides a picture of locations, terrains, and structures. But, like explorers, scientists must continue to decipher what each location on the map can tell us about diseases, human health, and biology. The map accelerates this process, as it allows researchers to identify key structural dimensions of the gene they are exploring, and reminds them where they have been and where they have yet to explore.

What does the map of the human genome depict? when researchers discuss the sequencing of the genome, they are describing the identification of the patterns and order of the 3 billion human DNA base pairs. While this provides valuable information about overall structure and the evolution of humans in relation to other organisms, researchers really wanted the key information encoded in just 2% of this enormous map—the information that makes most of the proteins that compose you and me. Comprised of DNA, genes are the basic units of heredity; they hold all of the information required to make the proteins that regulate most life functions, from digesting food to battling diseases. Proteins stand as the link between genes and pharmaceutical drug development, they show which genes are being expressed at any given moment, and provide information about gene function.

Knowing our genes will lead to greater understanding and radically improved treatment of many diseases. However, sequencing the entire human genome, in conjunction with sequencing of various nonhuman genomes under the same project, has raised fundamental questions about what it means to be human. After all, fruit flies possess about one-third the number of genes as humans, and an ear of corn has approximately the same number of genes as a human! In addition, the overall DNA sequence of a chimpanzee is about 99% the same as the human genome sequence. As the genomes of other species become available, the similarities to the human genome in both structure and sequence pattern will continue to be identified. At a basic level, the discovery of so many commonalities and links and ancestral trees with other species adds credence to principles of evolution and Darwinism.

Some of the most anticipated developments and potential benefits of the Human Genome Project directly affect human health; researchers, practicing physicians, and the general public eagerly await the development of targeted pharmaceutical agents and more specific diagnostic tests. Pharmacogenomics is at the intersection of genetics and pharmacology; it is the study of how one's genetic makeup will affect his or her response to various drugs. In the future, medicine will potentially be safer, cheaper, and more disease specific, all while causing fewer side effects and acting more effectively, the first time around.

There are however some hard ethical questions that follow in the wake of new genetic knowledge. Patients will have to undergo genetic testing in order to match drugs to their genetic makeup. Who will have access to these result—just the health care practitioner, or the patient's insurance company, employer/school, and/or family members? While the tests were administered for one case, will the information derived from them be used for other purposes, such as for identification of other conditions/future diseases, or even in research studies?

How should researchers conduct studies in pharmacogenomics? Often they need to group study subjects by some kind of identifiabe traits that they believe will assist in separating groups of drugs, and in turn they separate people into populations. The order of almost all of the DNA base pairs (99.9%) is exactly the same in all humans. So, this leaves a small window of difference. There is potential for stigmatization of individuals and groups, of people based on race and ethnicity inherent in genomic research and analysis. As scientists continue drug development, they must be careful to not further such ideas, especially as studies of nuclear DNA indicate that there is often more genetic variation within "races" or cultures, than between "races" or cultures. Stigmatization or discrimination can occur through genetic testing and human subjects research on populations.

These are just a few of the ethical issues arising out of one development of the Human Genome Project. The potential applications of genome research are staggering, and the mapping is just the beginning. Realizing this was simply a starting point, the draft sequences of the human genome released in February 2001 by the publicly funded Human Genome Project and the private company, Celera Genomics, are freely available on the Internet. A long road lies ahead, where scientists will be charged with exploring and understanding the functions of and relationships between genes and proteins. With such exploration comes a responsibility to acknowledge and address the ethical, legal, and social implications of this exciting research.

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

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

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

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

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

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

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

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

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

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

CHALLENGE QUESTIONS

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

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

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

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

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

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

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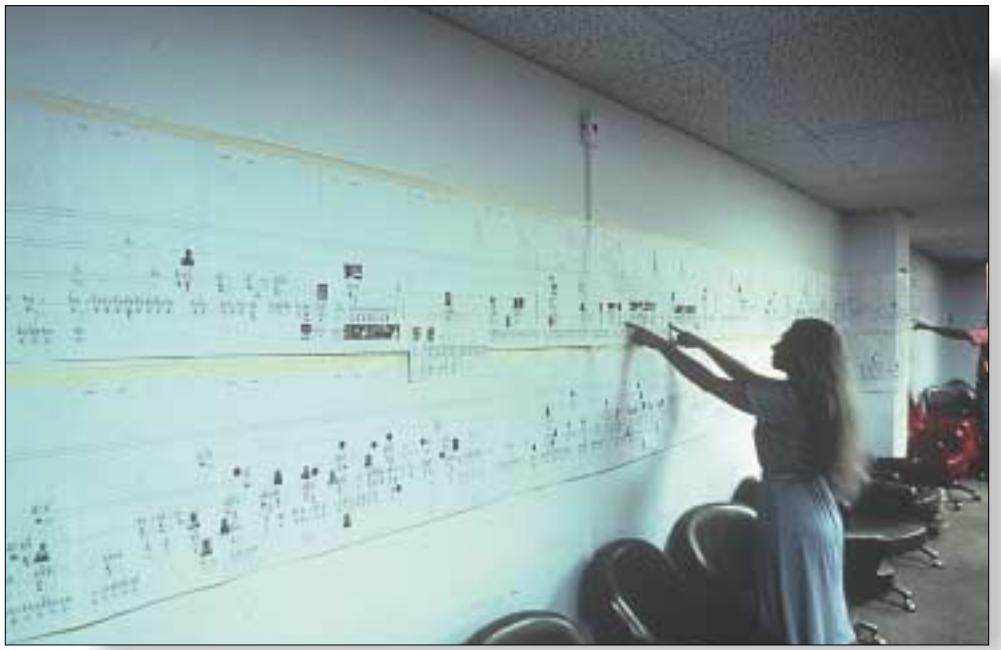
5 Extensions and Modifications of Basic Principles



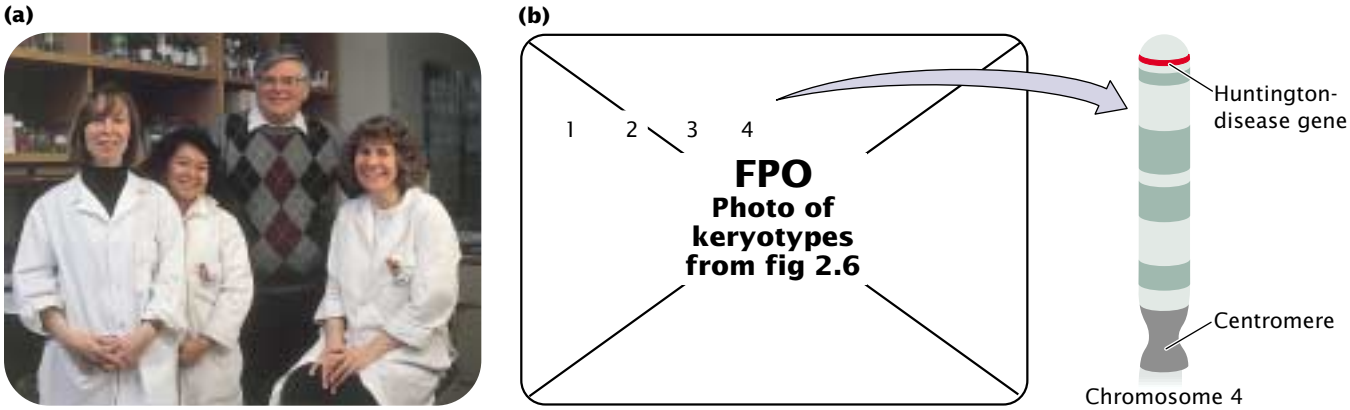
This is Chapter 5 Opener photo legend to position here. (Nancy Wexler, HDF/Neurology, Columbia University.)

- Was Mendel Wrong?
- Dominance Revisited
- Lethal Alleles
- Multiple Alleles
  - Duck-Feather Patterns
  - The ABO Blood Group
- Gene Interaction
  - Gene Interaction That Produces Novel Phenotypes
  - Gene Interaction with Epistasis
  - The Complex Genetics of Coat Color in Dogs
- The Interaction Between Sex and Heredity
  - Sex-Influenced and Sex-Limited Characteristics
  - Cytoplasmic Inheritance
  - Genetic Maternal Effects
  - Genomic Imprinting
- Anticipation
- Interaction Between Genes and Environment
  - Environmental Effects on Gene Expression
  - The Inheritance of Continuous Characteristics

Was Mendel Wrong?

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

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



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

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

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

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

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

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

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

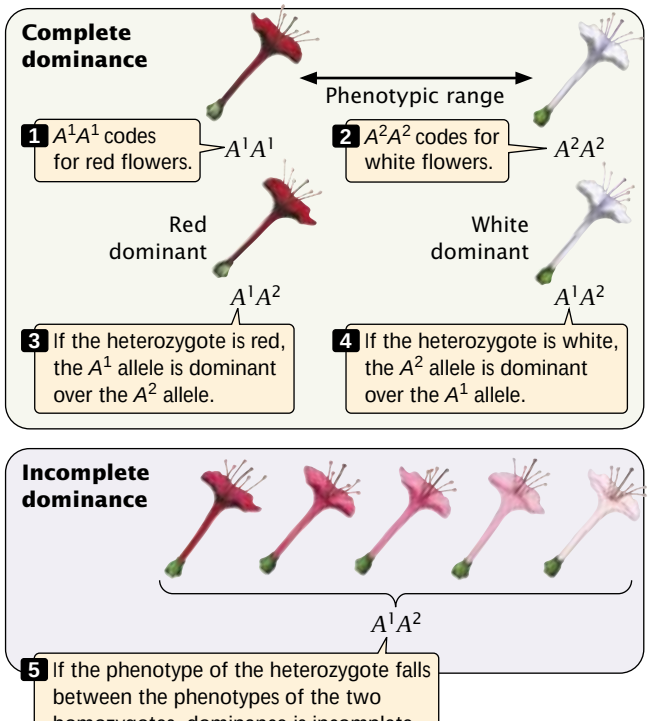
www.whfreeman.com/pierce Additional information about Huntington disease

Dominance Revisited

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

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

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



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

Table 5.1 Differences between dominance, incomplete dominance, and codominance

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

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

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

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

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

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

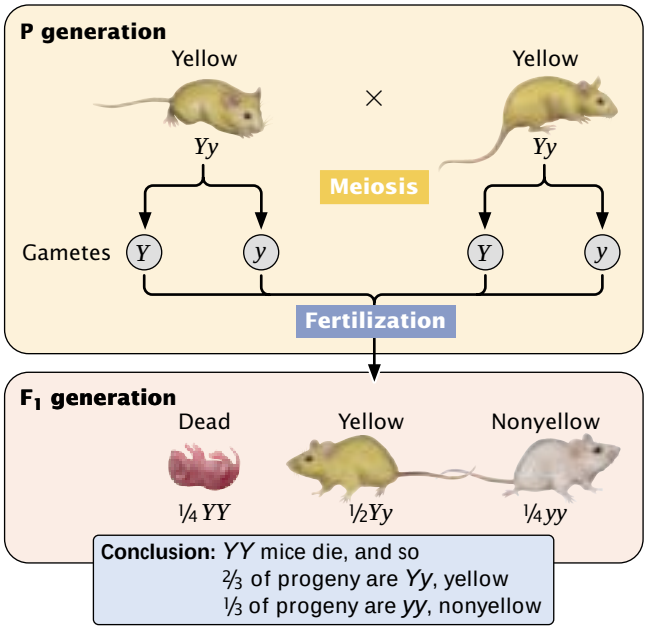
In summary, several important characteristics of dominance should be emphasized. First, dominance is a result of interactions between genes at the same locus; in other words, dominance is *allelic* interaction. Second, dominance does not alter the way in which the genes are inherited; it only influences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

Concepts

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

Lethal Alleles

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



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

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

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

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

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

Concepts

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

Multiple Alleles

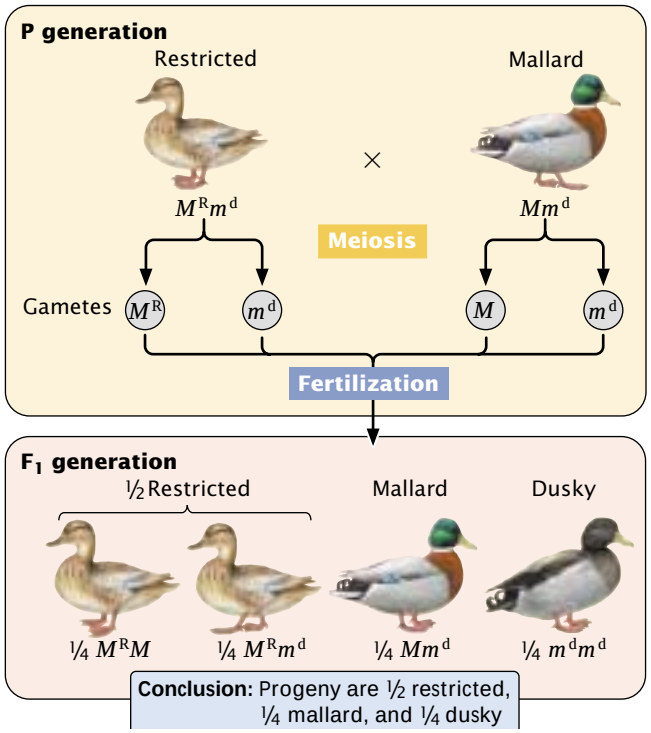
Most of the genetic systems that we have examined so far consist of two alleles. In Mendel's peas, for instance, one allele coded for round seeds and another for wrinkled seeds; in cats, one allele produced a black coat and another produced a gray coat. For some loci, more than two alleles are present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

Duck-Feather Patterns

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

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

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



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

The ABO Blood Group

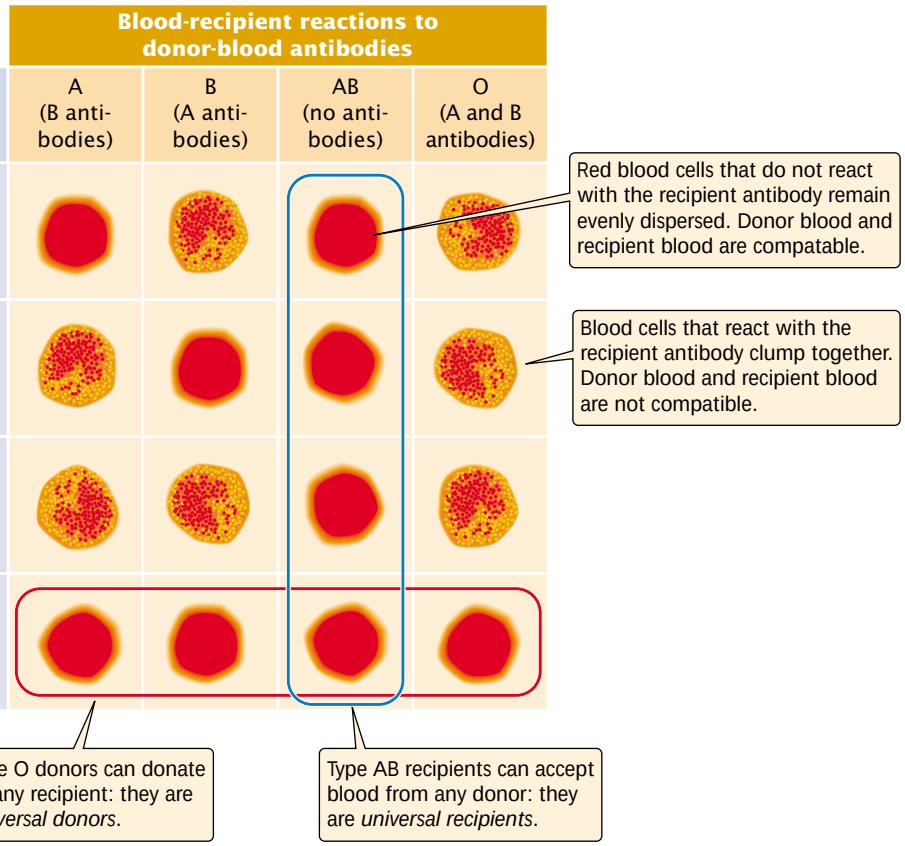
Another multiple-allele system is at the locus for the ABO blood group. This locus determines your ABO blood type and, like the MN locus, codes for antigens on red blood cells. The three common alleles for the ABO blood group locus are: I^A, which codes for the A antigen; I^B, which codes for the B antigen;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

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

(a)

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

(b)



5.5 ABO blood types and possible blood transfusions.

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

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

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

Concepts

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

Gene Interaction

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

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

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

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

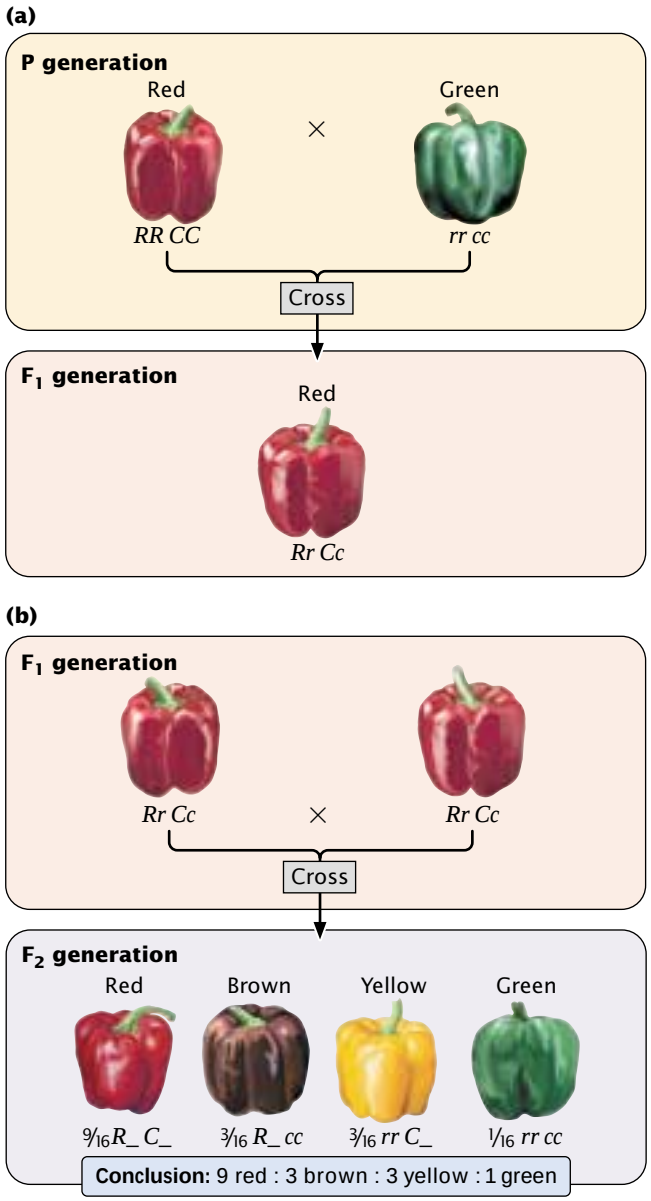
Concepts

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

Gene Interaction That Produces Novel Phenotypes

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

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



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

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

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

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

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

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

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

Gene Interaction with Epistasis

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

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

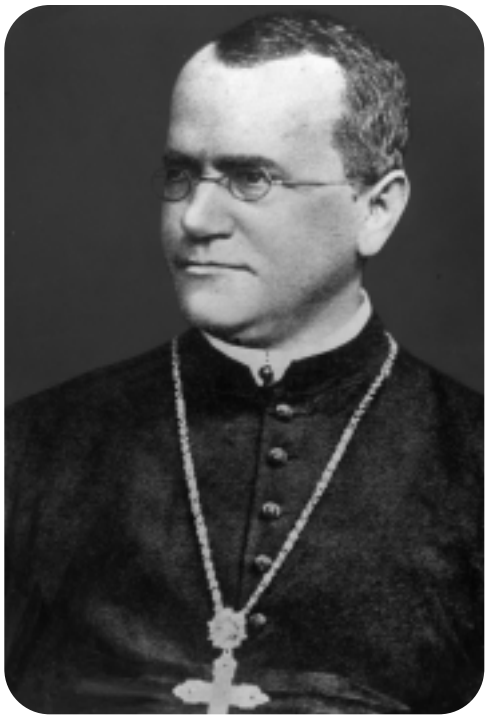
1.9 **Preformationism was a popular idea of inheritance in the seventeenth and eighteenth centuries.** Shown here is a drawing of a homunculus inside a sperm. (Science VU/Visuals Unlimited.)

of parental traits. This idea suggested that the genetic material itself blends, much as blue and yellow pigments blend to make green paint. Once blended, genetic differences could not be separated out in future generations, just as green paint cannot be separated out into blue and yellow pigments. Some traits do *appear* to exhibit blending inheritance; however, we realize today that individual genes do not blend.

Nehemiah Grew (1641–1712) reported that plants reproduce sexually by using pollen from the male sex cells. With this information, a number of botanists began to experiment with crossing plants and creating hybrids. Foremost among these early plant breeders was Joseph Gottleib Kölreuter (1733–1806), who carried out numerous crosses and studied pollen under the microscope. He observed that many hybrids were intermediate between the parental varieties. Because he crossed plants that differed in many traits, Kölreuter was unable to discern any general pattern of inheritance. In spite of this limitation, Kölreuter's work set the foundation for the modern study of genetics. Subsequent to his work, a number of other botanists began to experiment with hybridization, including Gregor Mendel (1822–1884) (FIGURE 1.10), who went on to discover the basic principles of heredity. Mendel's conclusions, which were unappreciated for 45 years, laid the foundation for our modern understanding of heredity, and he is generally recognized today as the father of genetics.

Developments in cytology (the study of cells) in the 1800s had a strong influence on genetics. Robert Brown (1773–1858) described the cell nucleus in 1833. Building on the work of others, Matthis Jacob Schleiden (1804–1881) and Theodor Schwann (1810–1882) proposed the concept of the **cell theory** in 1839. According to this theory, all life is composed of cells, cells arise only from preexisting cells, and the cell is the fundamental unit of structure and function in living organisms. Biologists began to examine cells to see how traits were transmitted in the course of cell division.

Charles Darwin (1809–1882), one of the most influential biologists of the nineteenth century, put forth the theory of evolution through natural selection and published his ideas in *On the Origin of Species* in 1856. Darwin recognized that heredity was fundamental to evolution, and he



1.10 **Gregor Mendel was the founder of modern genetics.** Mendel first discovered the principles of heredity by crossing different varieties of pea plants and analyzing the pattern of transmission of traits in subsequent generations. (Hulton/Archive by Getty Images.)

genotypes that determine coat color and their phenotypes are:

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

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

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

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

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

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

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

How can gene interaction explain these results?

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

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

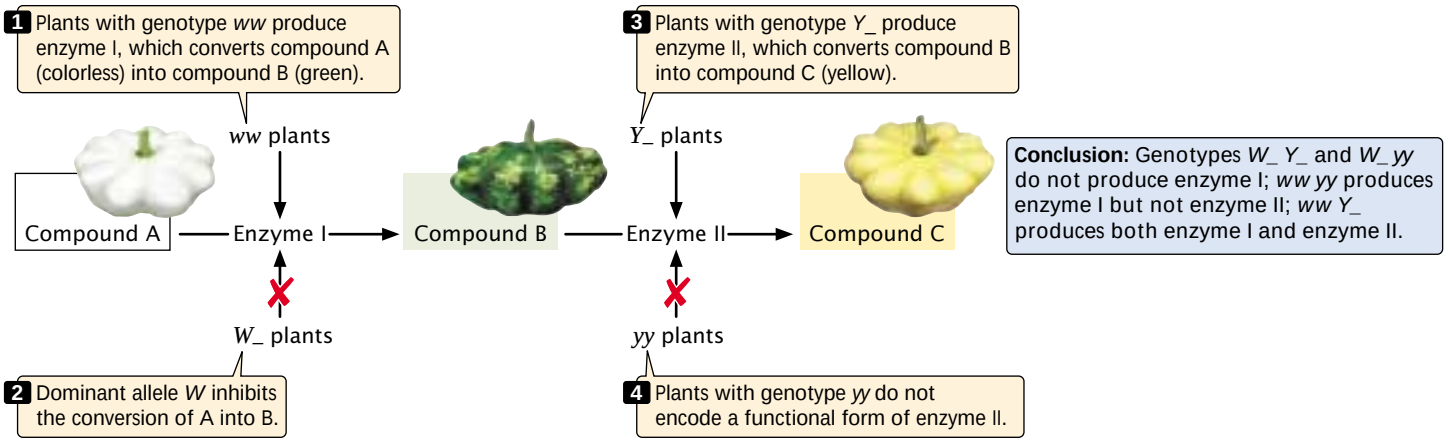
*W_Y_*	white squash
W_yy	white squash
*wwY_*	yellow squash
wwyy	green squash

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

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

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

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



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

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

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

P *aaBB* albino × *AAbb* albino

↓

F_1 *AaBb* pigmented

↓ Intercross

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

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

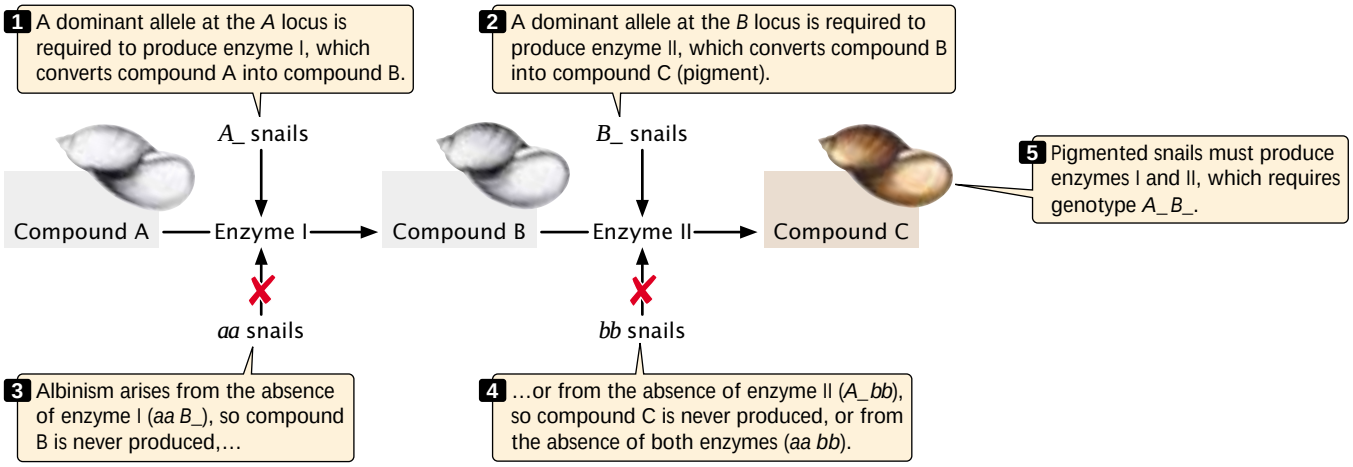
Concepts

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

Connecting Concepts

Interpreting Ratios Produced by Gene Interaction

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



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

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

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

Table 5.2 Modified dihybrid—phenotypic ratios due to gene interaction

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

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

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

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

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

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

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

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

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

Concepts

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

The Complex Genetics of Coat Color in Dogs

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

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

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

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

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

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

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

   B is dominant over *b*.

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

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

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

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

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

   D Intense pigmentation.
   d Dilution of pigment.

   D is dominant over *d*.

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

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

   The dominance relations among these alleles are poorly known.

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

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

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

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

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

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

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

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

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

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

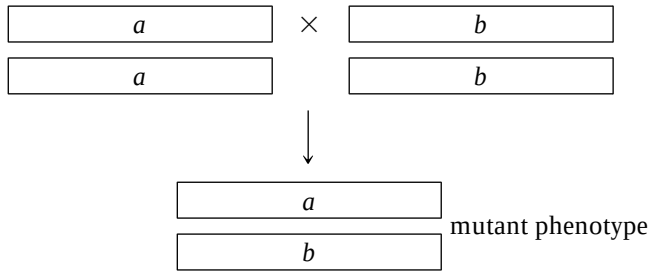
Dalmatian- Dalmatians (FIGURE 5.10c) have an interesting genetic makeup. Most are homozygous A^sA^s *CCDDEE*s^ws^w*TT*; so they vary only at the B locus. Notice that these dogs possess genotype A^sA^s*CCDDEE*, which allows for a solid coat that would be black, if genotype *B_* is present, or brown (called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

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

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

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

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

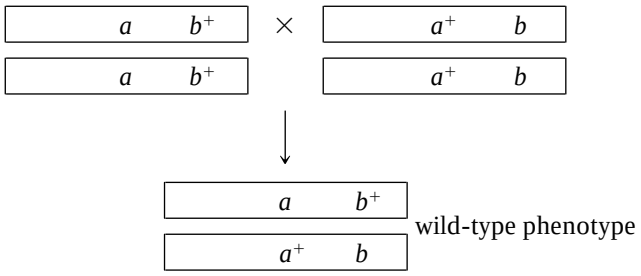


If, on the other hand, the mutations occur at different loci, each of the homozygous parents possesses wild-type genes at the other locus (*aa* b^+b^+ and a^+a^+ *bb*); so the heterozygous offspring inherit a mutant and a wild-type allele at each locus. In this case, the mutations complement each other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

Table 5.3 Common genotypes in different breeds of dogs

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

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



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

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

Interaction Between Sex and Heredity

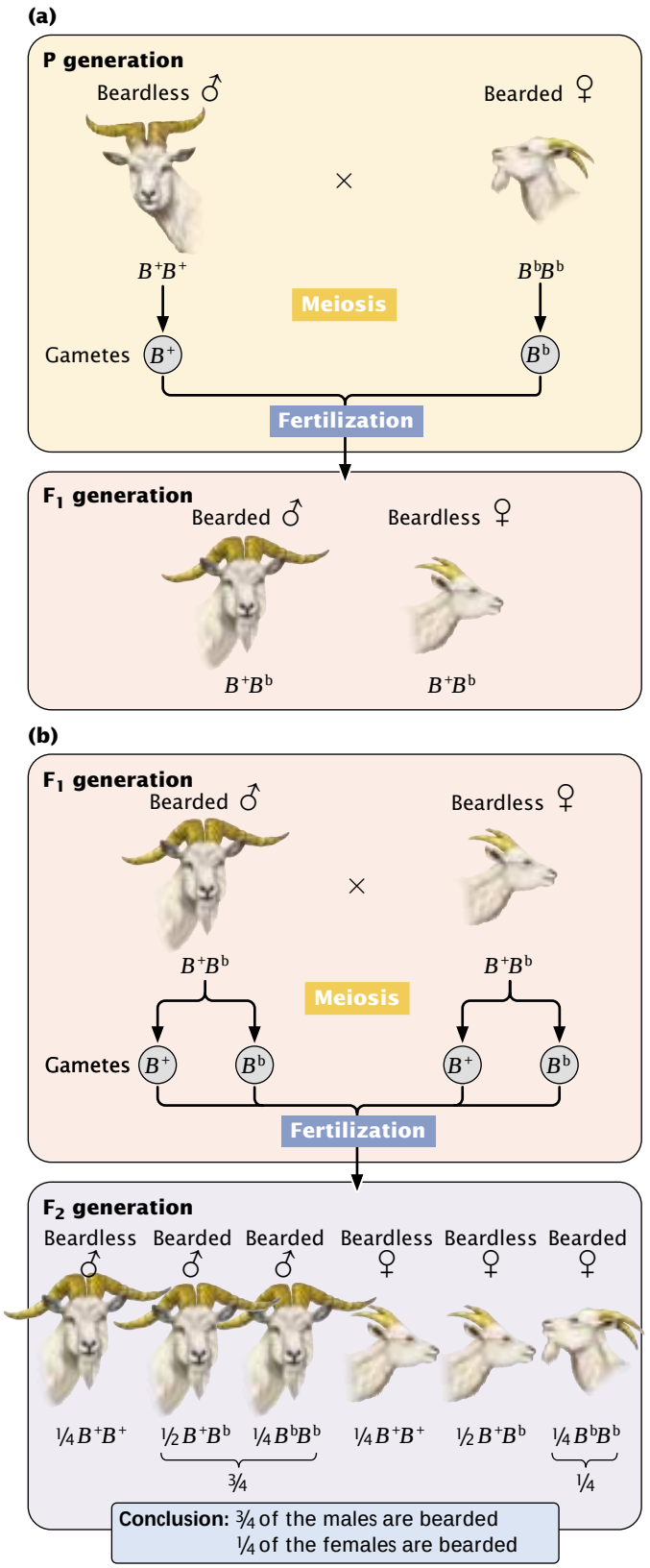
In Chapter 4, we considered characteristics encoded by genes located on the sex chromosomes and how their inheritance differs from the inheritance of traits encoded by autosomal genes. Now we will examine additional influences of sex, including the effect of the sex of an individual on the expression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

Sex-Influenced and Sex-Limited Characteristics

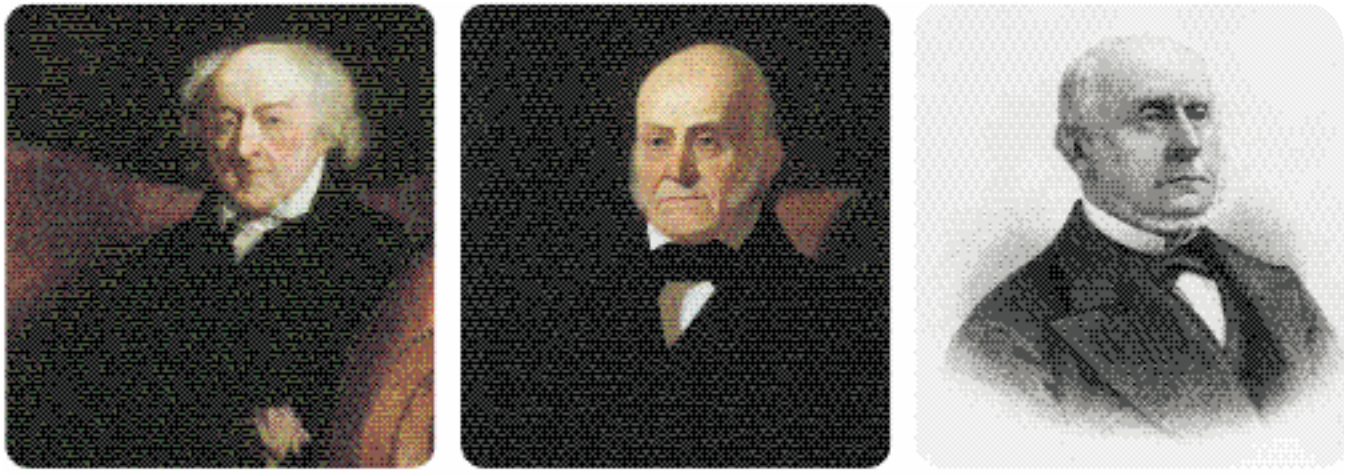
Sex influenced characteristics are determined by autosomal genes and are inherited according to Mendel's principles, but they are expressed differently in males and females. In this case, a particular trait is more readily expressed in one sex; in other words, the trait has higher penetrance (see p.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

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

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



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



(a) (b) (c)

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

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

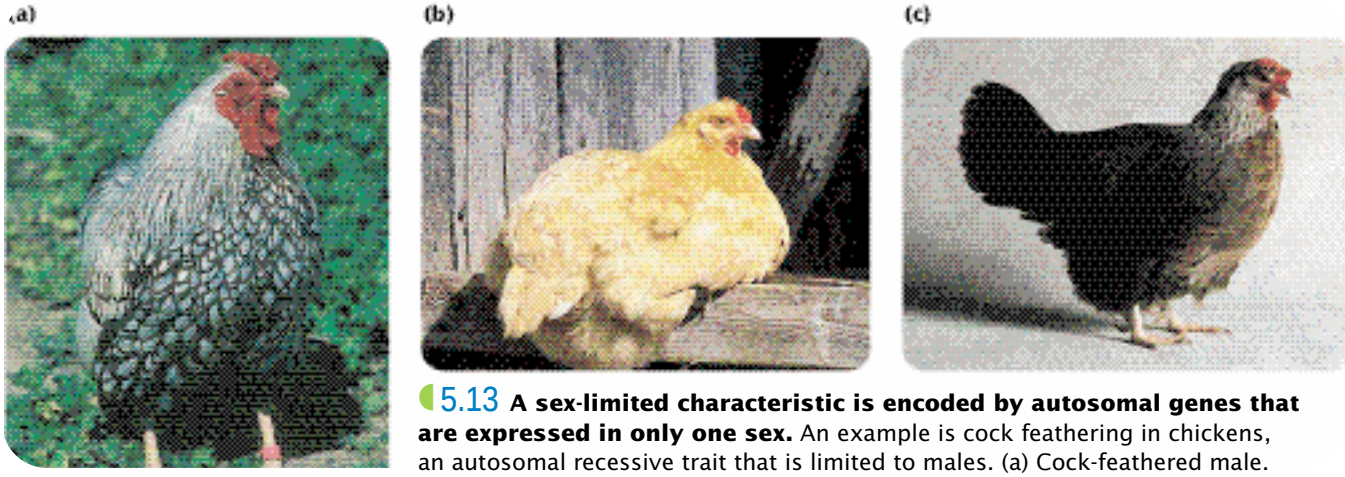
An example of a sex-influenced characteristic in humans is pattern baldness, in which hair is lost prematurely from the front and the top of the head (Figure 5.12). Pattern baldness is an autosomal character believed to be dominant in males and recessive in females, just like beards in goats. Contrary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

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

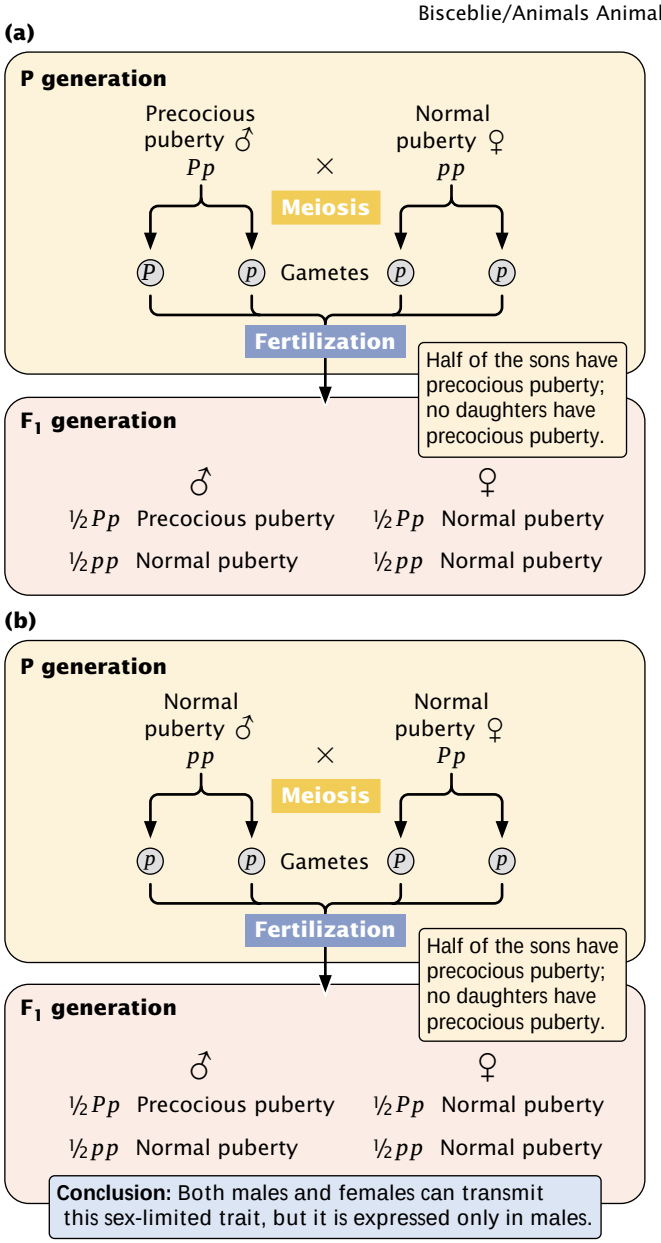
Genotype	Male phenotype	Female phenotype
HH	hen feathering	hen feathering
Hh	hen feathering	hen feathering
hh	cock feathering	hen feathering

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

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



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



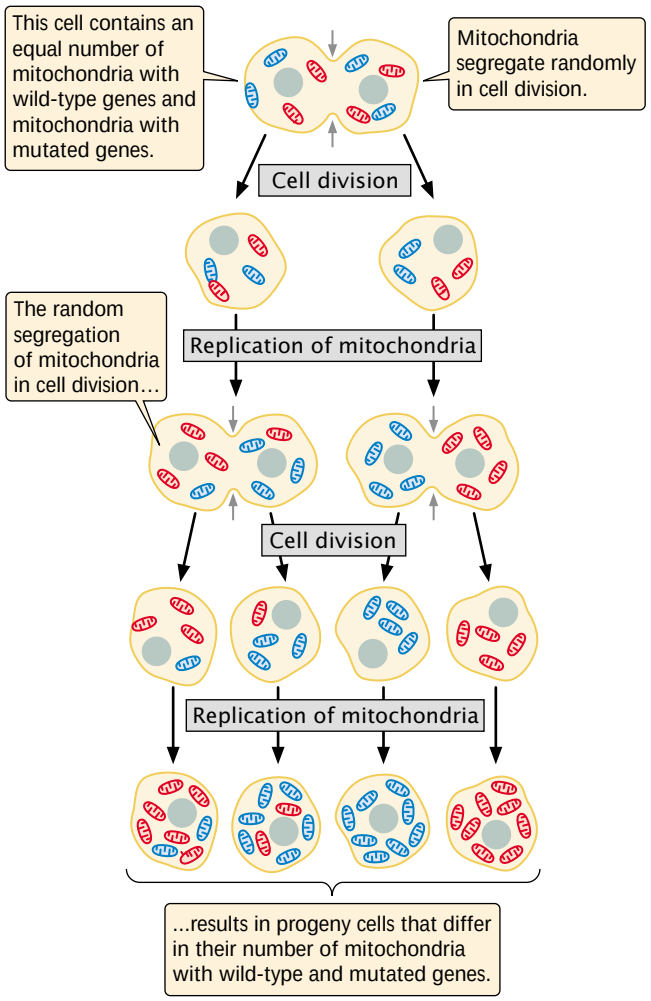
with a woman who has no family history of this condition will transmit the allele for precocious puberty to ½ of the children (Figure 5.14a), but it will be expressed only in the sons. If one of the heterozygous daughters (*Pp*) mates with a male who has normal puberty (*pp*), ½ of the sons will exhibit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

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

Concepts

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

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



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

Cytoplasmic Inheritance

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

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

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

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

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

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

conducted extensive genetic crosses with pigeons and other organisms. However, he never understood the nature of inheritance, and this lack of understanding was a major omission in his theory of evolution.

In the last half of the nineteenth century, the invention of the microtome (for cutting thin sections of tissue for microscopic examination) and the development of improved histological stains stimulated a flurry of cytological research. Several cytologists demonstrated that the nucleus had a role in fertilization. Walter Flemming (1843–1905) observed the division of chromosomes in 1879 and published a superb description of mitosis. By 1885, it was generally recognized that the nucleus contained the hereditary information.

Near the close of the nineteenth century, August Weismann (1834–1914) finally laid to rest the notion of the inheritance of acquired characteristics. He cut off the tails of mice for 22 consecutive generations and showed that the tail length in descendants remained stubbornly long. Weismann proposed the **germ-plasm theory,** which holds that the cells in the reproductive organs carry a complete set of genetic information that is passed to the gametes (see Figure 1.8b).

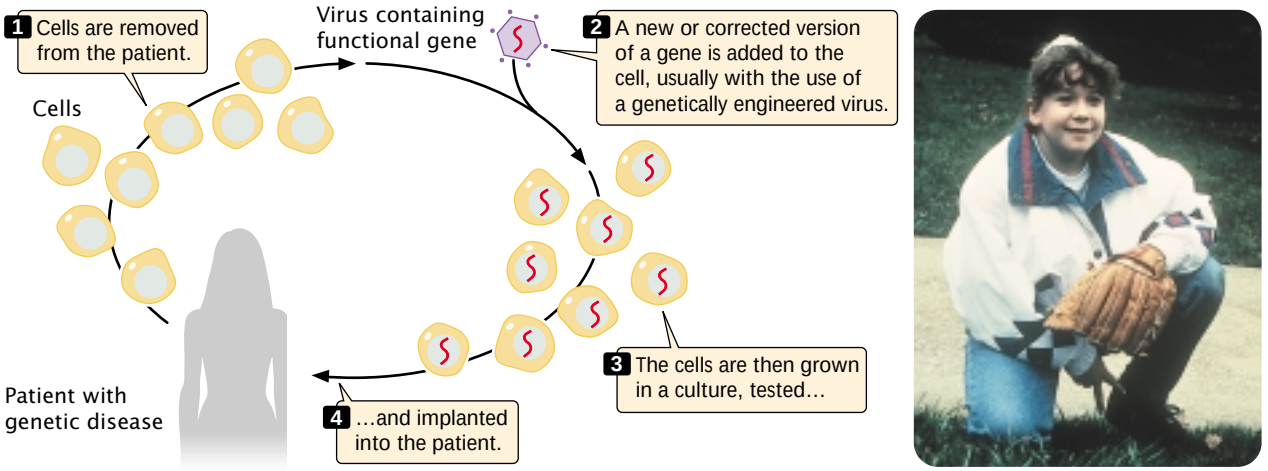
Twentieth-Century Genetics

The year 1900 was a watershed in the history of genetics. Gregor Mendel's pivotal 1866 publication on experiments with pea plants, which revealed the principles of heredity, was "rediscovered," as discussed in more detail in Chapter 3. The significance of his conclusions was recognized, and other biologists immediately began to conduct similar genetic studies on mice, chickens, and other organisms. The results of these investigations showed that many traits indeed follow Mendel's rules.

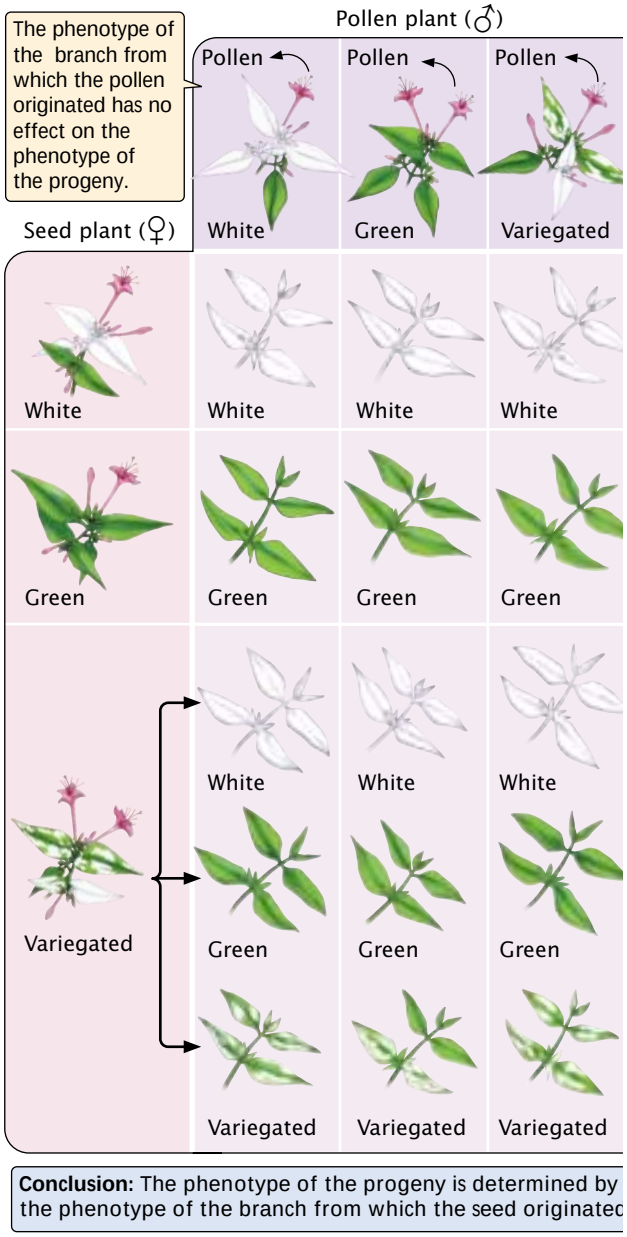
Walter Sutton (1877–1916) proposed in 1902 that genes are located on chromosomes. Thomas Hunt Morgan (1866–1945) discovered the first genetic mutant of fruit flies in 1910 and used fruit flies to unravel many details of transmission genetics. Ronald A. Fisher (1890–1962), John B. S. Haldane (1892–1964), and Sewall Wright (1889–1988) laid the foundation for population genetics in the 1930s.

Geneticists began to use bacteria and viruses in the 1940s; the rapid reproduction and simple genetic systems of these organisms allowed detailed study of the organization and structure of genes. At about this same time, evidence accumulated that DNA was the repository of genetic information. James Watson (b. 1928) and Francis Crick (b. 1916) described the three-dimensional structure of DNA in 1953, ushering in the era of molecular genetics.

By 1966, the chemical structure of DNA and the system by which it determines the amino acid sequence of proteins had been worked out. Advances in molecular genetics led to the first recombinant DNA experiments in 1973, which touched off another revolution in genetic research. Walter Gilbert (b. 1932) and Frederick Sanger (b. 1918) developed methods for sequencing DNA in 1977. The polymerase chain reaction, a technique for quickly amplifying tiny amounts of DNA, was developed by Kary Mullis (b. 1944) and others in 1986. In 1990, gene therapy was used for the first time to treat human genetic disease in the United States (FIGURE 1.11), and the Human Genome Project was launched. By 1995, the first complete DNA sequence of a free-living organism—the bacterium *Haemophilus influenzae*—was determined, and the first complete sequence of a eukaryotic organism (yeast) was reported a year later. At the beginning of the twenty-first century, the human genome sequence was determined, ushering in a new era in genetics.



1.11 Gene therapy applies genetic engineering to the treatment of human diseases. (J. Coate, MDBD/Science VU/Visuals Unlimited.)



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

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

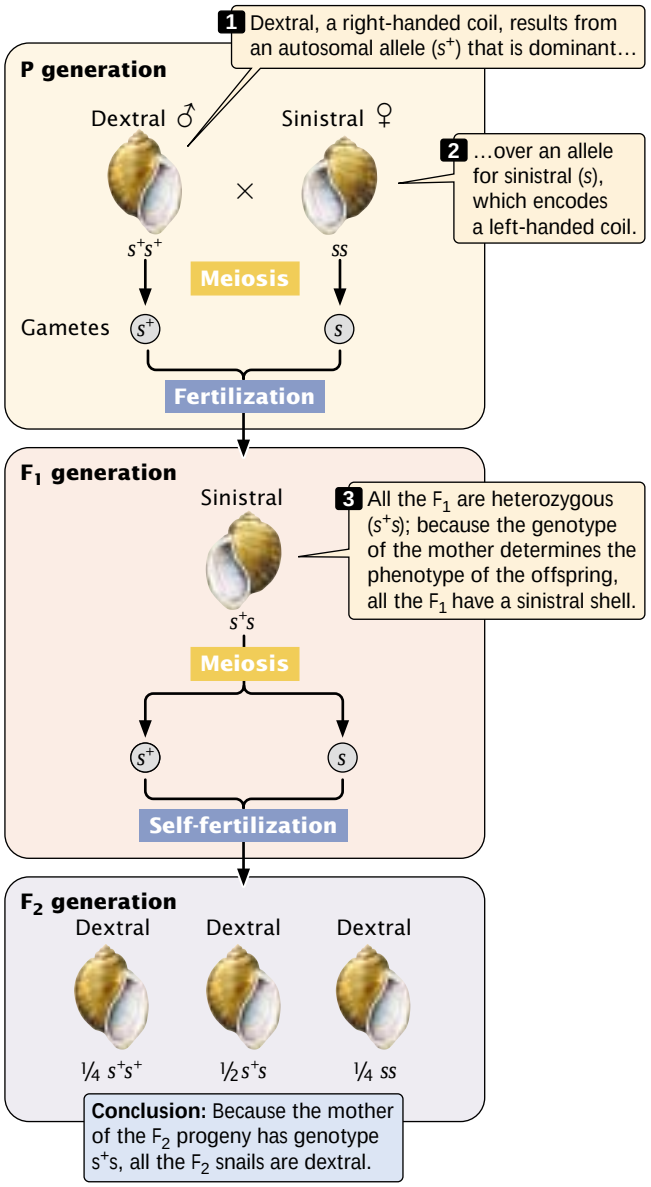
In recent years, a number of human diseases (mostly rare) that exhibit cytoplasmic inheritance have been identified. These disorders arise from mutations in mtDNA, most of which occur in genes coding for components of the electron-transport chain, which generates most of the ATP (adenosine triphosphate)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

Genetic Maternal Effect

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

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

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



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

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

Concepts

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

Genomic Imprinting

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

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

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

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

Table 5.4 Sex influences on heredity

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

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

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

Concepts

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

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

Anticipation

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

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

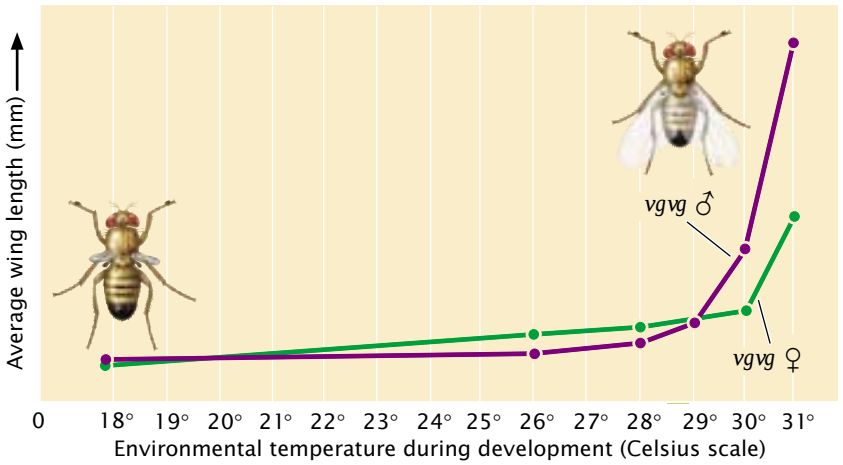
Concepts

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

Interaction Between Genes and Environment

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

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



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

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

Environmental Effects on Gene Expression

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

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

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

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

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

Reared at 20°C or less

Reared at temperatures above 30°C

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

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

Concepts

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

The Inheritance of Continuous Characteristics

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

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

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

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

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

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

Concepts

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

Connecting Concepts Across Chapters

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

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

CONCEPTS SUMMARY

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

IMPORTANT TERMS

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

Worked Problems

1. The type of plumage found in mallard ducks is determined by three alleles at a single locus: M^R, which codes for restricted plumage; M, which codes for mallard plumage; and m^d, which codes for dusky plumage. The restricted phenotype is dominant over mallard and dusky; mallard is dominant over dusky ($M^R > M > m^d$). Give the expected phenotypes and proportions of offspring produced by the following crosses.

(a) $M^R M \times m^d m^d$
(b) $M^R m^d \times M m^d$
(c) $M^R m^d \times M^R M$
(d) $M^R M \times M m^d$

• Solution

We can determine the phenotypes and proportions of offspring by (1) determining the types of gametes produced by each parent and (2) combining the gametes of the two parents with the use of a Punnett square

(a) Parents $M^R M \times m^d m^d$

Gametes M^R, M and m^d

	M^R	M
m^d	$M^R m^d$ restricted	$M m^d$ mallard

½ restricted, ½ mallard

(b) Parents $M^R m^d \times M m^d$

Gametes M^R, m^d and M, m^d

	M	m^d
M^R	$M^R M$ restricted	$M^R m^d$ restricted
m^d	$M m^d$ mallard	$m^d m^d$ dusky

½ restricted, ¼ mallard, ¼ dusky

(c) Parents $M^R m^d \times M^R M$

Gametes M^R, m^d and M^R, M

	M^R	M
M^R	$M^R M^R$ restricted	$M^R M$ restricted
m^d	$M^R m^d$ restricted	$M m^d$ mallard

¾ restricted, ¼ mallard

(d) Parents $M^R M \times M m^d$

Gametes M^R, M and M, m^d

	M	m^d
M^R	$M^R M$ restricted	$M^R m^d$ restricted
M	MM mallard	$M m^d$ mallard

½ restricted, ½ mallard

2. A homozygous strain of yellow corn is crossed with a homozygous strain of purple corn. The F_1 are intercrossed, producing an ear of corn with 119 purple kernels and 89 yellow kernels (the progeny).

(a) What is the genotype of the yellow kernels?

(b) Give a genetic explanation for the differences in kernel color in this cross.

• Solution

(a) We should first consider whether the cross between yellow and purple strains might be a monohybrid cross for a simple dominant trait, which would produce a 3:1 ratio in the F_2 ($Aa \times Aa \rightarrow ¾\ A\_$ and $¼\ aa$). Under this hypothesis, we would expect 156 purple progeny and 52 yellow progeny:

Phenotype	Genotype	Observed number	Expected number
purple	$A\_$	119	$¾ \times 208 = 156$
yellow	aa	89	$¼ \times 208 = 52$
total		208	

We see that the expected numbers do not closely fit the observed numbers. If we performed a chi-square test (see Chapter 3), we would obtain a calculated chi-square value of 35.08, which has a probability much less than 0.05, indicating that it is extremely unlikely that, when we expect a 3:1 ratio, we would obtain 119 purple progeny and 89 yellow progeny. Therefore we can reject the hypothesis that these results were produced by a monohybrid cross.

Another possible hypothesis is that the observed F_2 progeny are in a 1:1 ratio. However, we learned in Chapter 3 that a 1:1 ratio is produced by a cross between a heterozygote and a homozygote (*Aa* × *aa*) and, from the information given, the cross was not between a heterozygote and a homozygote, because the original parental strains were both homozygous. Furthermore, a chi-square test comparing the observed numbers with an expected 1:1 ratio yields a calculated chi-square value of 4.32, which has a probability of less than .05.

Next, we should look to see if the results can be explained by a dihybrid cross (*AaBb* × *AaBb*). A dihybrid cross results in phenotypic proportions that are in sixteenths. We can apply the formula given earlier in the chapter to determine the number of sixteenths for each phenotype:

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

$$x_{(\text{purple})} = \frac{119 \times 16}{208} = 9.15$$

$$x_{(\text{yellow})} = \frac{89 \times 16}{208} = 6.85$$

Thus, purple and yellow appear approximately a 9:7 ratio. We can test this hypothesis with a chi-square test:

Phenotype	Genotype	Observed number	Expected number
purple	?	119	$^9/_{16} \times 208 = 117$
yellow	?	89	$^7/_{16} \times 208 = 91$
total		208	

$$\chi^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}} = \frac{(119 - 117)^2}{117} + \frac{(89 - 91)^2}{91}$$

$$= 0.034 + 0.44 = 0.078$$

Degree of freedom $= n - 1 = 2 - 1 = 1$

$P > .05$

The probability associated with the chi-square value is greater than .05, indicating that there is a relatively good fit between the observed results and a 9:7 ratio.

We now need to determine how a dihybrid cross can produce a 9:7 ratio and what genotypes correspond to the two phenotypes. A dihybrid cross without epistasis produces a 9:3:3:1 ratio:

AaBb × *AaBb*

↓

*A_B_*	$^9/_{16}$
A_bb	$^3/_{16}$
*aaB_*	$^3/_{16}$
aabb	$^1/_{16}$

Because $^9/_{16}$ of the progeny from the corn cross are purple, purple must be produced by genotypes *A_B_*; in other words, individual kernels that have at least one dominant allele at the first locus and at least one dominant allele at the second locus are purple. The proportions of all the other genotypes (*A_bb*, *aaB_*, and *aabb*) sum to $^7/_{16}$, which is the proportion of the progeny in the corn cross that are yellow, so any individual kernel that does not have a dominant allele at both the first and the second locus is yellow.

(b) Kernel color is an example of duplicate recessive epistasis, where the presence of two recessive alleles at either the first locus or the second locus or both suppresses the production of purple pigment.

3. A geneticist crosses two yellow mice with straight hair and obtains the following progeny:

$^1/_2$ yellow, straight
$^1/_6$ yellow, fuzzy
$^1/_4$ gray, straight
$^1/_{12}$ gray, fuzzy

(a) Provide a genetic explanation for the results and assign genotypes to the parents and progeny of this cross.

(b) What additional crosses might be carried out to determine if your explanation is correct?

• Solution

(a) This cross concerns two separate characteristics—color and type of hair; so we should begin by examining the results for each characteristic separately. First, let's look at the inheritance of color. Two yellow mice are crossed producing $^1/_2 + ^1/_6 = ^3/_6 + ^1/_6 = ^4/_6 = ^2/_3$ yellow mice and $^1/_4 + ^1/_{12} = ^3/_{12} + ^1/_{12} = ^4/_{12} = ^1/_3$ gray mice. We learned in this chapter that a 2:1 ratio is often produced when a recessive lethal gene is present:

Yy × *Yy*

↓

YY	$^1/_4$ die
Yy	$^1/_2$ yellow, becomes $^2/_3$
yy	$^1/_4$ gray, becomes $^1/_3$

Now, let's examine the inheritance of the hair type. Two mice with straight hair are crossed, producing $^1/_2 + ^1/_4 = ^2/_4 + ^1/_4 = ^3/_4$ mice with straight hair and $^1/_6 + ^1/_{12} = ^2/_{12} + ^1/_{12} = ^3/_{12} = ^1/_4$ mice with fuzzy hair. We learned in Chapter 3 that a

3:1 ratio is usually produced by a cross between two individuals heterozygous for a simple dominant allele:

$$Ss \times Ss$$

$$\downarrow$$

SS	$\frac{1}{4}$ straight	$\frac{3}{4}$ straight
Ss	$\frac{1}{2}$ straight	
ss	$\frac{1}{4}$ fuzzy	

We can now combine both loci and assign genotypes to all the individuals in the cross:

P yellow, straight *YySs* × yellow, straight *YySs*

$$\downarrow$$

Phenotype	Genotype	Probability at each locus	Combined probability
yellow, straight	*YyS_*	$\frac{2}{3} \times \frac{3}{4}$	$= \frac{6}{12} = \frac{1}{2}$
yellow, fuzzy	*Yyss*	$\frac{2}{3} \times \frac{1}{4}$	$= \frac{2}{12} = \frac{1}{6}$
gray, straight	*yyS_*	$\frac{1}{3} \times \frac{3}{4}$	$= \frac{3}{12} = \frac{1}{4}$
gray, fuzzy	*yyss*	$\frac{1}{3} \times \frac{1}{4}$	$= \frac{1}{12}$

(b) We could carry out a number of different crosses to test our hypothesis that yellow is a recessive lethal and straight is dominant over fuzzy. For example, a cross between any two yellow individuals should always produce $\frac{2}{3}$ yellow and $\frac{1}{3}$ gray, and a cross between two gray individuals should produce all gray offspring. A cross between two fuzzy individuals should always produce all fuzzy offspring.

4. In some sheep, the presence of horns is produced by an autosomal allele that is dominant in males and recessive in females. A horned female is crossed with a hornless male. One of the resulting F_1 females is crossed with a hornless male. What proportion of the male and female progeny from this cross will have horns?

• Solution

The presence of horns in these sheep is an example of a sex-influenced characteristic. Because the phenotypes associated with the genotypes differ for the two sexes, let's begin this problem by writing out the genotypes and phenotypes for each sex. We will let *H* represent the allele that codes for horns and H^+ represent the allele for hornless. In males, the allele for horns is dominant over the allele for hornless, which means that males homozygous (*HH*) and heterozygous (H^+H) for this gene are horned. Only males homozygous for the recessive hornless allele (H^+H^+) will be hornless. In females, the allele for horns is recessive, which means that only females homozygous for this allele (*HH*) will be horned; females heterozygous (H^+H) and homozygous (H^+H^+) for the hornless allele will be hornless. The following table summarizes genotypes and associated phenotypes:

Genotype	Male phenotype	Female phenotype
HH	horned	horned
HH^+	horned	hornless
H^+H^+	hornless	hornless

In the problem, a horned female is crossed with a hornless male. From the preceding table, we see that a horned female must be homozygous for the allele for horns (*HH*) and a hornless male must be homozygous for the allele for hornless (H^+H^+); so all the F_1 will be heterozygous; the F_1 males will be horned and the F_1 females will be hornless, as shown below:

P $H^+H^+ \times HH$

$$\downarrow$$

F_1 H^+H H^+H

horned males and hornless females

A heterozygous hornless F_1 female (H^+H) is then crossed with a hornless male (H^+H^+):

$H^+H \times H^+H^+$

horned female hornless male

$$\downarrow$$

		Males	Females
$\frac{1}{2}$	H^+H^+	hornless	hornless
$\frac{1}{2}$	H^+H	horned	hornless

Therefore, $\frac{1}{2}$ of the male progeny will be horned but none of the female progeny will be horned.

COMPREHENSION QUESTIONS

* 1. How do incomplete dominance and codominance differ?
* 2. Explain how dominance and epistasis differ.
3. What is a recessive epistatic gene?
4. What is a complementation test and what is it used for?
* 5. What is genomic imprinting?
6. What characteristics do you expect to see in a trait that exhibits anticipation?
* 7. What characteristics are exhibited by a cytoplasmically inherited trait?
8. What is the difference between genetic maternal effect and genomic imprinting?
9. What is the difference between a sex-influenced gene and a gene that exhibits genomic imprinting?
* 10. What are continuous characteristics and how do they arise?

APPLICATION QUESTIONS AND PROBLEMS

* 11. Palomino horses have a golden yellow coat, chestnut horses have a brown coat, and cremello horses have a coat that is almost white. A series of crosses between the three different types of horses produced the following offspring:

Cross	Offspring
palomino × palomino	13 palomino, 6 chestnut, 5 cremello
chestnut × chestnut	16 chestnut
cremello × cremello	13 cremello
palomino × chestnut	8 palomino, 9 chestnut
palomino × cremello	11 palomino, 11 cremello
chestnut × cremello	23 palomino

(a) Explain the inheritance of the palomino, chestnut, and cremello phenotypes in horses.

(b) Assign symbols for the alleles that determine these phenotypes, and list the genotypes of all parents and offspring given in the preceding table.

* 12. The L^M and L^N alleles at the MN blood group locus exhibit codominance. Give the expected genotypes and phenotypes and their ratios in progeny resulting from the following crosses.

(a) $L^ML^M \times L^ML^N$

(b) $L^NL^N \times L^NL^N$

(c) $L^ML^N \times L^ML^N$

(d) $L^ML^N \times L^NL^N$

(e) $L^ML^M \times L^NL^N$

13. In the pearl millet plant, color is determined by three alleles at a single locus: Rp^1 (red), Rp^2 (purple), and rp (green). Red is dominant over purple and green, and purple is dominant over green ($Rp^1 > Rp^2 > rp$). Give the expected phenotypes and ratios of offspring produced by the following crosses.

(a) $Rp^1/Rp^2 \times Rp^1/rp$

(b) $Rp^1/rp \times Rp^2/rp$

(c) $Rp^1/Rp^2 \times Rp^1/Rp^2$

(d) $Rp^2/rp \times rp/rp$

(e) $rp/rp \times Rp^1/Rp^2$

* 14. Give the expected genotypic and phenotypic ratios for the following crosses for ABO blood types.

(a) $I^Ai \times I^Bi$

(b) $I^AI^B \times I^Ai$

(c) $I^AI^B \times I^AI^B$

(d) $ii \times I^Ai$

(e) $I^AI^B \times ii$

15. If there are five alleles at a locus, how many genotypes may there be at this locus? How many different kinds of homozygotes will there be? How many genotypes and homozygotes would there be with eight alleles?

16. Turkeys have black, bronze, or black-bronze plumage. Examine the results of the following crosses:

Parents	Offspring
Cross 1: black and bronze	all black
Cross 2: black and black	¾ black, ¼ bronze
Cross 3: black-bronze and black-bronze	all black-bronze
Cross 4: black and bronze	½ black, ¼ bronze, ¼ black-bronze
Cross 5: bronze and black-bronze	½ bronze, ½ black-bronze
Cross 6: bronze and bronze	¾ bronze, ¼ black-bronze

Do you think these differences in plumage arise from incomplete dominance between two alleles at a single locus? If yes, support your conclusion by assigning symbols to each allele and providing genotypes for all turkeys in the crosses. If your answer is no, provide an alternative explanation and assign genotypes to all turkeys in the crosses.

17. In rabbits, an allelic series helps to determine coat color: C (full color), c^{ch} (chinchilla, gray color), c^h (himalayan, white with black extremities), and c (albino, all white). The C allele is dominant over all others, c^{ch} is dominant over c^h and c, c^h is dominant over c, and c is recessive to all the other alleles. This dominance hierarchy can be summarized as $C > c^{ch} > c^h > c$. The rabbits in the following list are crossed and produce the progeny shown. Give the genotypes of the parents for each cross:

Phenotypes of parents	Phenotypes of offspring
(a) full color × albino	½ full color, ½ albino
(b) himalayan × albino	½ himalayan, ½ albino
(c) full color × albino	½ full color, ½ chinchilla
(d) full color × himalayan	½ full color, ¼ himalayan, ¼ albino
(e) full color × full color	¾ full color, ¼ albino

18. In this chapter we considered Joan Barry's paternity suit against Charlie Chaplin and how, on the basis of blood types, Chaplin could not have been the father of her child.

(a) What blood types are possible for the father of Barry's child?

(b) If Chaplin had possessed one of these blood types, would that prove that he fathered Barry's child?

The Future of Genetics

The information content of genetics now doubles every few years. The genome sequences of many organisms are added to DNA databases every year, and new details about gene structure and function are continually expanding our knowledge of heredity. All of this information provides us with a better understanding of numerous biological processes and evolutionary relationships. The flood of new genetic information requires the continuous development of sophisticated computer programs to store, retrieve, compare, and analyze genetic data and has given rise to the field of bioinformatics, a merging of molecular biology and computer science.

In the future, the focus of DNA-sequencing efforts will shift from the genomes of different species to individual differences within species. It is reasonable to assume that each person may some day possess a copy of his or her entire genome sequence. New genetic microchips that simultaneously analyze thousands of RNA molecules will provide information about the activity of thousands of genes in a given cell, allowing a detailed picture of how cells respond to external signals, environmental stresses, and disease states. The use of genetics in the agricultural, chemical, and health-care fields will continue to expand; some predict that biotechnology will be to the twenty-first century what the electronics industry was to the twentieth century. This ever-widening scope of genetics will raise significant ethical, social, and economic issues.

This brief overview of the history of genetics is not intended to be comprehensive; rather it is designed to provide a sense of the accelerating pace of advances in genetics. In the chapters to come, we will learn more about the experiments and the scientists who helped shape the discipline of genetics.

www.whfreeman.com/pierce More information about the history of genetics

Concepts

Developments in plant hybridization and cytology in the eighteenth and nineteenth centuries laid the foundation for the field of genetics today. After Mendel's work was rediscovered in 1900, the science of genetics developed rapidly and today is one of the most active areas of science.

Basic Concepts in Genetics

Undoubtedly, you learned some genetic principles in other biology classes. Let's take a few moments to review some of these fundamental genetic concepts.

Cells are of two basic types: eukaryotic and prokaryotic- Structurally, cells consist of two basic types, although, evolutionarily, the story is more complex (see Chapter 2). Prokaryotic cells lack a nuclear membrane and possess no membrane-bounded cell organelles, whereas eukaryotic cells are more complex, possessing a nucleus and membrane-bounded organelles such as chloroplasts and mitochondria.

A gene is the fundamental unit of heredity- The precise way in which a gene is defined often varies. At the simplest level, we can think of a gene as a unit of information that encodes a genetic characteristic. We will enlarge this definition as we learn more about what genes are and how they function.

Genes come in multiple forms called alleles- A gene that specifies a characteristic may exist in several forms, called alleles. For example, a gene for coat color in cats may exist in alleles that encode either black or orange fur.

Genes encode phenotypes- One of the most important concepts in genetics is the distinction between traits and genes. Traits are not inherited directly. Rather, genes are inherited and, along with environmental factors, determine the expression of traits. The genetic information that an individual organism possesses is its genotype; the trait is its phenotype. For example, the A blood type is a phenotype; the genetic information that encodes the blood type A antigen is the genotype.

Genetic information is carried in DNA and RNA- Genetic information is encoded in the molecular structure of nucleic acids, which come in two types: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids are polymers consisting of repeating units called nucleotides; each nucleotide consists of a sugar, a phosphate, and a nitrogenous base. The nitrogenous bases in DNA are of four types (abbreviated A, C, G, and T), and the sequence of these bases encodes genetic information. Most organisms carry their genetic information in DNA, but a few viruses carry it in RNA. The four nitrogenous bases of RNA are abbreviated A, C, G, and U.

Genes are located on chromosomes- The vehicles of genetic information within the cell are chromosomes **(FIGURE 1.12)**, which consist of DNA and associated proteins. The cells of each species have a characteristic number of chromosomes; for example, bacterial cells normally possess a single chromosome; human cells possess 46; pigeon cells possess 80. Each chromosome carries a large number of genes.

* 19. A woman has blood type A MM. She has a child with blood type AB MN. Which of the following blood types could *not* be that of the child's father? Explain your reasoning.

George	O	NN
Tom	AB	MN
Bill	B	MN
Claude	A	NN
Henry	AB	MM

20. Allele *A* is epistatic to allele *B*. Indicate whether each of the following statements is true or false. Explain why.

(a) Alleles *A* and *B* are at the same locus.

(b) Alleles *A* and *B* are at different loci.

(c) Alleles *A* and *B* are always located on the same chromosome.

(d) Alleles *A* and *B* may be located on different, homologous chromosomes.

(e) Alleles *A* and *B* may be located on different, nonhomologous chromosomes.

* 21. In chickens, comb shape is determined by alleles at two loci (*R*, *r* and *P*, *p*). A walnut comb is produced when at least one dominant allele *R* is present at one locus and at least one dominant allele *P* is present at a second locus (genotype *R_P_*). A rose comb is produced when at least one dominant allele is present at the first locus and two recessive alleles are present at the second locus (genotype *R_pp*). A pea comb is produced when two recessive alleles are present at the first locus and at least one dominant allele is present at the second (genotype *rrP_*). If two recessive alleles are present at the first and at the second locus (*rrpp*), a single comb is produced. Progeny with what types of combs and in what proportions will result from the following crosses?

(a) *RRPP* × *rrpp*

(b) *RrPp* × *rrpp*

(c) *RrPp* × *RrPp*

(d) *Rrpp* × *Rrpp*

(e) *Rrpp* × *rrPp*

(f) *Rrpp* × *rrpp*

* 22. Eye color of the Oriental fruit fly (*Bactrocera dorsalis*) is determined by a number of genes. A fly having wild-type eyes is crossed with a fly having yellow eyes. All the F_1 flies from this cross have wild-type eyes. When the F_1 are interbred, $^9/_{16}$ of the F_2 progeny have wild-type eyes, $^3/_{16}$ have amethyst eyes (a bright, sparkling blue color), and $^4/_{16}$ have yellow eyes.

(a) Give genotypes for all the flies in the P, F_1, and F_2 generations.

(b) Does epistasis account for eye color in Oriental fruit flies? If so, which gene is epistatic and which gene is hypostatic?

23. A variety of opium poppy (*Papaver somniferum* L.) having lacerate leaves was crossed with a variety that has normal leaves. All the F_1 had lacerate leaves. Two F_1 plants were interbred to produce the F_2. Of the F_2, 249 had lacerate leaves and 16 had normal leaves. Give genotypes for all the plants in the P, F_1, and F_2 generations. Explain how lacerate leaves are determined in the opium poppy.

* 24. A dog breeder liked yellow and brown Labrador retrievers. In an attempt to produce yellow and brown puppies, he bought a yellow Labrador male and a brown Labrador female and mated them. Unfortunately, all the puppies produced in this cross were black. (See p. 000 for a discussion of the genetic basis of coat color in Labrador retrievers.)

(a) Explain this result.

(b) How might the breeder go about producing yellow and brown Labradors?

25. When a yellow female Labrador retriever was mated with a brown male, half of the puppies were brown and half were yellow. The same female, when mated with a different brown male, produced all brown males. Explain these results.

* 26. In summer squash, a plant that produces disc-shaped fruit is crossed with a plant that produces long fruit. All the F_1 have disc-shaped fruit. When the F_1 are intercrossed, F_2 progeny are produced in the following ratio: $^9/_{16}$ disc-shaped fruit: $^6/_{16}$ spherical fruit: $^1/_{16}$ long fruit. Give the genotypes of the F_2 progeny.

27. In sweet peas, some plants have purple flowers and other plants have white flowers. A homozygous variety of pea that has purple flowers is crossed with a homozygous variety that has white flowers. All the F_1 have purple flowers. When these F_1 are self-fertilized, the F_2 appear in a ratio of $^9/_{16}$ purple to $^7/_{16}$ white.

(a) Give genotypes for the purple and white flowers in these crosses.

(b) Draw a hypothetical biochemical pathway to explain the production of purple and white flowers in sweet peas.

28. For the following questions, refer to p. 000 for a discussion of how coat color and pattern are determined in dogs.

(a) Explain why Irish setters are reddish in color.

(b) Will a cross between a beagle and a Dalmatian produce puppies with ticking? Why or why not?

(c) Can a poodle crossed with any other breed produce spotted puppies? Why or why not?

(d) If a St. Bernard is crossed with a Doberman, will the offspring have solid, yellow, saddle, or bicolor coats?

(e) If a Rottweiler is crossed with a Labrador retriever, will the offspring have solid, yellow, saddle, or bicolor coats?

*29. When a Chinese hamster with white spots is crossed with another hamster that has no spots, approximately ½ of the offspring have white spots and ½ have no spots. When two hamsters with white spots are crossed, ⅔ of the offspring possess white spots and ⅓ have no spots.

(a) What is the genetic basis of white spotting in Chinese hamsters?

(b) How might you go about producing Chinese hamsters that breed true for white spotting?

30. Male-limited precocious puberty results from a rare, sex-limited autosomal allele (*P*) that is dominant over the allele for normal puberty (*p*) and is expressed only in males. Bill undergoes precocious puberty, but his brother Jack and his sister Beth underwent puberty at the usual time, between the ages of 10 and 14. Although Bill's mother and father underwent normal puberty, two of his maternal uncles (his mother's brothers) underwent precocious puberty. All of Bill's grandparents underwent normal puberty. Give the most likely genotypes for all the relatives mentioned in this family.

*31. Pattern baldness in humans is a sex-influenced trait that is autosomal dominant in males and recessive in females. Jack has a full head of hair. JoAnn also has a full head of hair, but her mother is bald. (In women, pattern baldness is usually expressed as a thinning of the hair.) If Jack and JoAnn marry, what proportion of their children are expected to be bald?

32. In goats, a beard is produced by an autosomal allele that is dominant in males and recessive in females. We'll use the symbol B^b for the beard allele and B^+ for the beardless allele. Another independently assorting autosomal allele that produces a black coat (*W*) is dominant over the allele for white coat (*w*). Give the phenotypes and their expected proportions for the following crosses.

(a) B^+B^b *Ww* male × B^+B^b *Ww* female

(b) B^+B^b *Ww* male × B^+B^b *ww* female

(c) B^+B^+ *Ww* male × B^bB^b *Ww* female

(d) B^+B^b *Ww* male × B^bB^b *ww* female

33. In the snail *Limnaea peregra*, shell coiling results from a genetic maternal effect. An autosomal allele for a right-handed shell (s^+), called dextral, is dominant over the allele for a left-handed shell *(s)*, called sinistral. A pet snail called Martha is sinistral and reproduces only as a female (the snails are hermaphroditic). Indicate which of the following statements are true and which are false. Explain your reasoning in each case.

(a) Martha's genotype *must* be *ss*.

(b) Martha's genotype *cannot* be s^+s^+.

(c) All the offspring produced by Martha *must* be sinistral.

(d) At least some of the offspring produced by Martha *must* be sinistral.

(e) Martha's mother *must* have been sinistral.

(f) All Martha's brothers *must* be sinistral.

34. In unicorns, two autosomal loci interact to determine the type of tail. One locus controls whether a tail is present at all; the allele for a tail (*T*) is dominant over the allele for tailless (*t*). If a unicorn has a tail, then alleles at a second locus determine whether the tail is curly or straight. Farmer Baldridge has two unicorns with curly tails. When he crosses these two unicorns, ½ of the progeny have curly tails, ¼ have straight tails, and ¼ do not have a tail. Give the genotypes of the parents and progeny in Farmer Baldridge's cross. Explain how he obtained the 2:1:1 phenotypic ratio in his cross.

* 35. Phenylketonuria (PKU) is an autosomal recessive disease that results from a defect in an enzyme that normally metabolizes the amino acid phenylalanine. When this enzyme is defective, high levels of phenylalanine cause brain damage. In the past, most children with PKU became mentally retarded. Fortunately, mental retardation can be prevented in these children today by carefully controlling the amount of phenylalanine in the diet. As a result of this treatment, many people with PKU are now reaching reproductive age with no mental retardation. By the end of the teen years, when brain development is complete, many people with PKU go off the restrictive diet. Children born to women with PKU (who are no longer on a phenylalanine-restricted diet) frequently have low birth weight, developmental abnormalities, and mental retardation, even though they are heterozygous for the recessive PKU allele. However, children of men with PKU do not have these problems. Provide an explanation for these observations.

36. In 1983, a sheep farmer in Oklahoma noticed a ram in his flock that possessed increased muscle mass in his hindquarters. Many of the offspring of this ram possessed the same trait, which became known as the callipyge mutant (*callipyge* is Greek for "beautiful buttocks"). The mutation that caused the callipyge phenotype was eventually mapped to a position on the sheep chromosome 18.

When the male callipyge offspring of the original mutant ram were crossed with normal females, they produced the following progeny: ¼ male callipyge, ¼ female callipyge, ¼ male normal, and ¼ female normal. When female callipyge offspring of the original mutant ram were crossed with normal males, all of the offspring were normal. Analysis of the chromosomes of these offspring of callipyge females showed that half of them received a chromosome 18 with the callipyge gene from their mother. Propose an explanation for the inheritance of the callipyge gene. How might you test your explanation?

CHALLENGE QUESTION

37. Suppose that you are tending a mouse colony at a genetics research institute and one day you discover a mouse with twisted ears. You breed this mouse with twisted ears and find that the trait is inherited. Both male and female mice have twisted ears, but when you cross a twisted-eared male with a normal-eared female, you obtain different results from those obtained when you cross a twisted-eared female with normal-eared male—the reciprocal crosses give different results. Describe how you would go about determining whether this trait results from a sex-linked gene, a sex-influenced gene, a genetic maternal effect, a cytoplasmically inherited gene, or genomic imprinting. What crosses would you conduct and what results would be expected with these different types of inheritance?

SUGGESTED READINGS

Barlow, D. P. 1995. Gametic imprinting in mammals. *Science* 270:1610–1613.
Discusses the phenomenon of genomic imprinting.

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A nice review of the history of anticipation.

Li, E., C. Beard, and R. Jaenisch. 1993. Role for DNA methylation in genomic imprinting. *Nature* 366:362–365.
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Morell, V. 1993. Huntington's gene finally found. *Science* 260:28–30.
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Ostrander, E. A., F. Galibert, and D. F. Patterson. 2000. Canine genetics comes of age. *Trends in Genetics* 16:117–123.
Review of the use of dog genetics for understanding human genetic diseases.

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Discusses some of the possible evolutionary reasons for genomic imprinting.

Sapienza, C. 1990. Parental imprinting of genes. *Scientific American* 263 (October):52–60.
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Skuse, D. H., R. S. James, D. V. M. Bishop, B. Coppin, P. Dalton, G. Aamodt-Leeper, M. Bacarese-Hamilton, C. Creswell, R. McGurk, and P. A. Jacobs. 1997. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* 387:705–708.
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Thomson, G., and M. S. Esposito. 1999. The genetics of complex diseases. *Trends in Genetics* 15:M17–M20.
Discussion of human multifactorial diseases and the effect of the Human Genome Project on the identification of genes influencing these diseases.

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More discussion of cytoplasmically inherited mitochondrial mutations.

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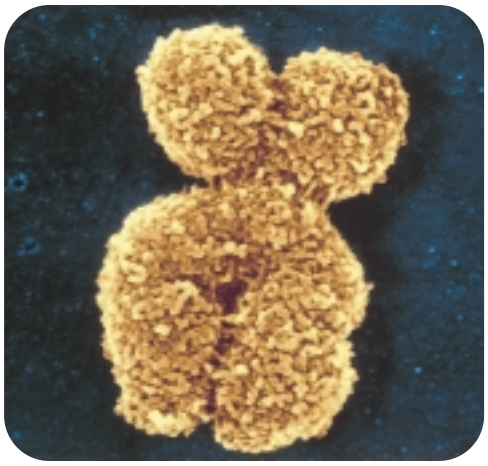

1.12 Genes are carried on chromosomes.
(Biophoto Associates/Science Source/Photo Researchers.)

Chromosomes separate through the processes of mitosis and meiosis- The processes of mitosis and meiosis ensure that each daughter cell receives a complete set of an organism's chromosomes. Mitosis is the separation of replicated chromosomes during the division of somatic (nonsex) cells. Meiosis is the pairing and separation of replicated chromosomes during the division of sex cells to produce gametes (reproductive cells).

Genetic information is transferred from DNA to RNA to protein- Many genes encode traits by specifying the structure of proteins. Genetic information is first transcribed from DNA into RNA, and then RNA is translated into the amino acid sequence of a protein.

Mutations are permanent, heritable changes in genetic information- Gene mutations affect only the genetic information of a single gene; chromosome mutations alter the number or the structure of chromosomes and therefore usually affect many genes.

Some traits are affected by multiple factors- Some traits are influenced by multiple genes that interact in complex ways with environmental factors. Human height, for example, is affected by hundreds of genes as well as environmental factors such as nutrition.

Evolution is genetic change- Evolution can be viewed as a two-step process: first, genetic variation arises and, second, some genetic variants increase in frequency, whereas other variants decrease in frequency.

www.whfreeman.com/pierce A glossary of genetics terms

Connecting Concepts Across Chapters

This chapter introduces the study of genetics, outlining its history, relevance, and some fundamental concepts. One of the themes that emerges from our review of the history of genetics is that humans have been interested in, and using, genetics for thousands of years, yet our understanding of the mechanisms of inheritance are relatively new. A number of ideas about how inheritance works have been proposed throughout history, but many of them have turned out to be incorrect. This is to be expected, because science progresses by constantly evaluating and challenging explanations. Genetics, like all science, is a self-correcting process, and thus many ideas that are proposed will be discarded or modified through time.

CONCEPTS SUMMARY

- Genetics is central to the life of every individual: it influences our physical features, susceptibility to numerous diseases, personality, and intelligence.
- Genetics plays important roles in agriculture, the pharmaceutical industry, and medicine. It is central to the study of biology.
- Genetic variation is the foundation of evolution and is critical to understanding all life.
- The study of genetics can be divided into transmission genetics, molecular genetics, and population genetics.
- The use of genetics by humans began with the domestication of plants and animals.
- The ancient Greeks developed the concept of pangenesis and the concept of the inheritance of acquired characteristics. Ancient Romans developed practical measures for the breeding of plants and animals.
- In the seventeenth century, biologists proposed the idea of preformationism, which suggested that a miniature adult is present inside the egg or the sperm and that a person inherits all of his or her traits from one parent.
- Another early idea, blending inheritance, proposed that genetic information blends during reproduction and offspring are a mixture of the parental traits.
- By studying the offspring of crosses between varieties of peas, Gregor Mendel discovered the principles of heredity.
- Darwin developed the concept of evolution by natural selection in the 1800s, but he was unaware of Mendel's work and was not able to incorporate genetics into his theory.

- Developments in cytology in the nineteenth century led to the understanding that the cell nucleus is the site of heredity.
- In 1900, Mendel's principles of heredity were rediscovered. Population genetics was established in the early 1930s, followed closely by biochemical genetics and bacterial and viral genetics. Watson and Crick discovered the structure of DNA in 1953, which stimulated the rise of molecular genetics.
- Advances in molecular genetics have led to gene therapy and the Human Genome Project.
- Cells come in two basic types: prokaryotic and eukaryotic.
- Genetics is the study of genes, which are the fundamental units of heredity.
- The genes that determine a trait are termed the genotype; the trait that they produce is the phenotype.
- Genes are located on chromosomes, which are made up of nucleic acids and proteins and are partitioned into daughter cells through the process of mitosis or meiosis.
- Genetic information is expressed through the transfer of information from DNA to RNA to proteins.
- Evolution requires genetic change in populations.

IMPORTANT TERMS

transmission genetics (p. 5)
molecular genetics (p. 5)
population genetics (p. 6)
pangenesis (p. 7)
inheritance of acquired characteristics (p. 7)
preformationism (p. 8)
blending inheritance (p. 8)
cell theory (p. 10)
germ-plasm theory (p. 11)

COMPREHENSION QUESTIONS

Answers to questions and problems preceded by an asterisk will be found at the end of the book.

1. Outline some of the ways in which genetics is important to each of us.
* 2. Give at least three examples of the role of genetics in society today.
3. Briefly explain why genetics is crucial to modern biology.
* 4. List the three traditional subdisciplines of genetics and summarize what each covers.
5. When and where did agriculture first arise? What role did genetics play in the development of the first domesticated plants and animals?
* 6. Outline the notion of pangenesis and explain how it differs from the germ-plasm theory.
* 7. What does the concept of the inheritance of acquired characteristics propose and how is it related to the notion of pangenesis?
* 8. What is preformationism? What did it have to say about how traits are inherited?
9. Define blending inheritance and contrast it with preformationism.
10. How did developments in botany in the seventeenth and eighteenth centuries contribute to the rise of modern genetics?
11. How did developments in cytology in the nineteenth century contribute to the rise of modern genetics?
*12. Who first discovered the basic principles that laid the foundation for our modern understanding of heredity?
13. List some advances in genetics that have occurred in the twentieth century.
*14. Briefly define the following terms: **(a)** gene; **(b)** allele; **(c)** chromosome; **(d)** DNA; **(e)** RNA; **(f)** genetics; **(g)** genotype; **(h)** phenotype; **(i)** mutation; **(j)** evolution.
15. What are the two basic cell types (from a structural perspective) and how do they differ?
16. Outline the relations between genes, DNA, and chromosomes.

APPLICATION QUESTIONS AND PROBLEMS

*17. Genetics is said to be both a very old science and a very young science. Explain what is meant by this statement.
18. Find at least one newspaper article that covers some aspect of genetics. Briefly summarize the article. Does this article focus on transmission, molecular, or population genetics?
19. The following concepts were widely believed at one time but are no longer accepted as valid genetic theories. What experimental evidence suggests that these concepts are incorrect and what theories have taken their place?
(a) pangenesis; **(b)** the inheritance of acquired characteristics; **(c)** preformationism; **(d)** blending inheritance.

CHALLENGE QUESTIONS

20. Describe some of the ways in which your own genetic makeup affects you as a person. Be as specific as you can.
21. Pick one of the following ethical or social issues and give your opinion on this issue. For background information, you might read one of the articles on ethics listed and marked with an asterisk in Suggested Readings at the end of this chapter.

    (a) Should a person's genetic makeup be used in determining his or her eligibility for life insurance?

    (b) Should biotechnology companies be able to patent newly sequenced genes?

    (c) Should gene therapy be used on people?

    (d) Should genetic testing be made available for inherited conditions for which there is no treatment or cure?

    (e) Should governments outlaw the cloning of people?

SUGGESTED READINGS

Articles on ethical issues in genetics are preceded by an asterisk.

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*Friedmann, T. 2000. Principles for human gene therapy studies. *Science* 287:2163–2165.

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An update on the status of gene therapy.

1 Introduction to Genetics

Alexis, heir to the Russian throne, and his father Tsar Nicholas Romanoff II. (Hulton/Archive by Getty Images.)

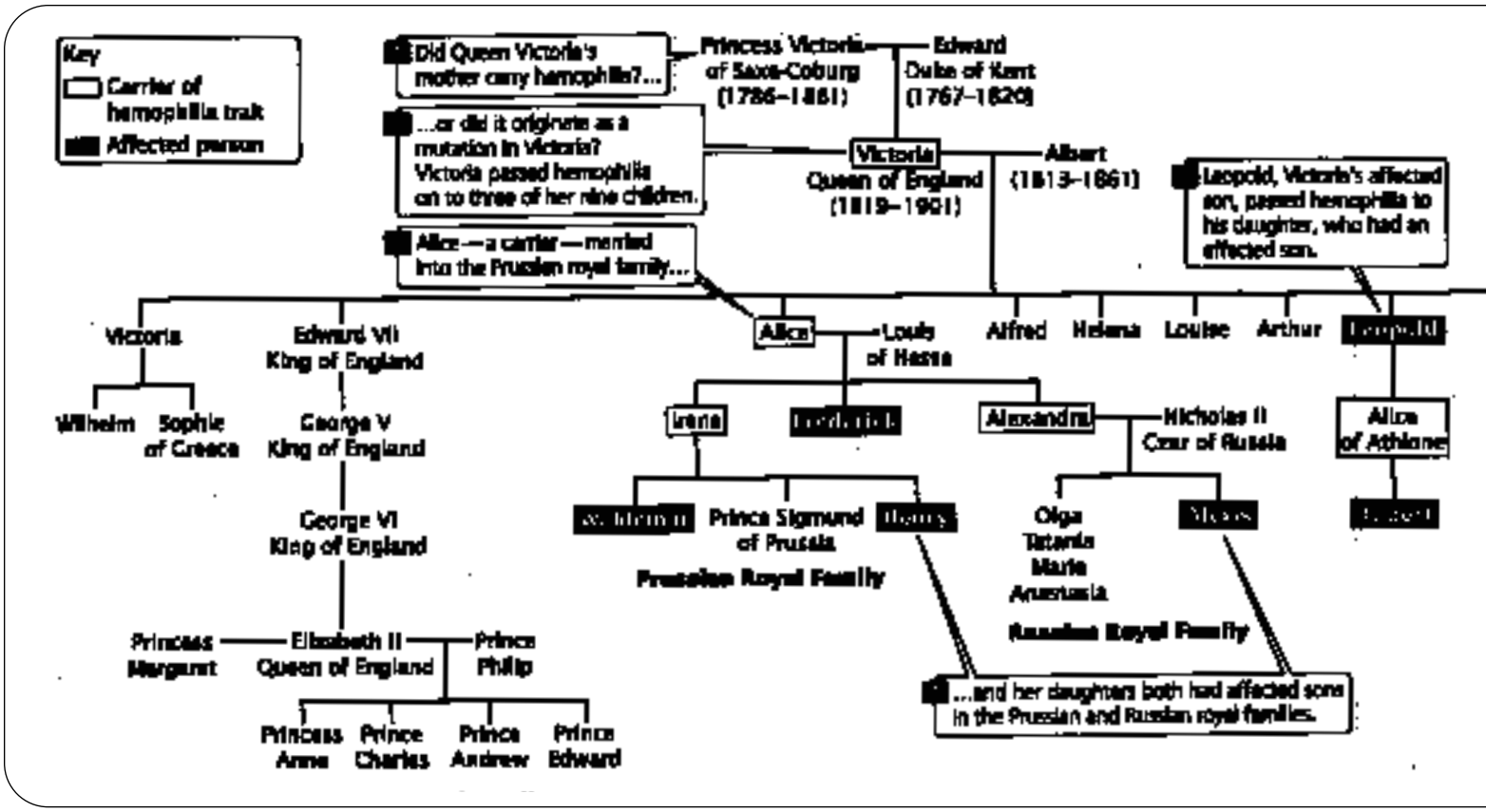
- Royal Hemophilia and Romanov DNA
- The Importance of Genetics
  - The Role of Genetics in Biology
  - Genetic Variation is the Foundation of Evolution
  - Divisions of Genetics
- A Brief History of Genetics
  - Prehistory
  - Early Written Records
  - The Rise of Modern Genetics
  - Twentieth-Century Genetics
  - The Future of Genetics
- Basic Concepts in Genetics

Royal Hemophilia and Romanov DNA

On August 12, 1904, Tsar Nicholas Romanov II of Russia wrote in his diary: "A great never-to-be forgotten day when the mercy of God has visited us so clearly." That day Alexis, Nicholas's first son and heir to the Russian throne, had been born.

At birth, Alexis was a large and vigorous baby with yellow curls and blue eyes, but at 6 weeks of age he began spontaneously hemorrhaging from the navel. The bleeding persisted for several days and caused great alarm. As he grew and began to walk, Alexis often stumbled and fell, as all children do. Even his small scrapes bled profusely, and minor bruises led to significant internal bleeding. It soon became clear that Alexis had hemophilia.

Hemophilia results from a genetic deficiency of blood clotting. When a blood vessel is severed, a complex cascade of reactions swings into action, eventually producing a protein called fibrin. Fibrin molecules stick together to form a clot, which stems the flow of blood. Hemophilia, marked by slow clotting and excessive bleeding, is the result if any one of the factors in the clotting cascade is missing or faulty. In those with hemophilia, life-threatening blood loss can occur with minor injuries, and spontaneous bleeding into joints erodes the bone with crippling consequences.



1.1 Hemophilia was passed down through the royal families of Europe.

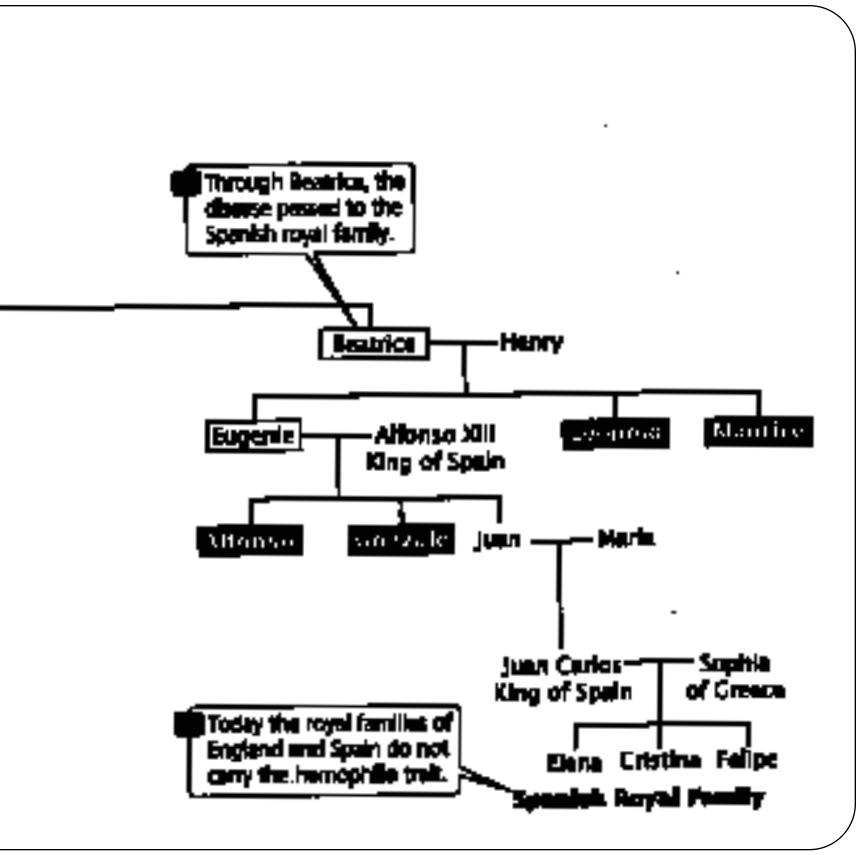
Alexis suffered from classic hemophilia, which is caused by a defective copy of a gene on the X chromosome. Females possess two X chromosomes per cell and may be unaffected carriers of the gene for hemophilia. A carrier has one normal version and one defective version of the gene; the normal version produces enough of the clotting factor to prevent hemophilia. A female exhibits hemophilia only if she inherits two defective copies of the gene, which is rare. Because males have a single X chromosome per cell, if they inherit a defective copy of the gene, they develop hemophilia. Consequently, hemophilia is more common in males than in females.

Alexis inherited the hemophilia gene from his mother, Alexandra, who was a carrier. The gene appears to have originated with Queen Victoria of England (1819–1901), (FIGURE 1.1). One of her sons, Leopold, had hemophilia and died at the age of 31 from brain hemorrhage following a minor fall. At least two of Victoria's daughters were carriers; through marriage, they spread the hemophilia gene to the royal families of Prussia, Spain, and Russia. In all, 10 of Queen Victoria's male descendants suffered from hemophilia. Six female descendants, including her granddaughter Alexandra (Alexis's mother), were carriers.

Nicholas and Alexandra constantly worried about Alexis's health. Although they prohibited his participation in sports and other physical activities, cuts and scrapes were inevitable, and Alexis experienced a number of severe bleeding episodes. The royal physicians were helpless during these crises—they had no treatment that would stop the bleeding. Gregory Rasputin, a monk and self-proclaimed "miracle worker," prayed over Alexis during one bleeding crisis, after which Alexis made a remarkable recovery. Rasputin then gained considerable influence over the royal family.

At this moment in history, the Russian Revolution broke out. Bolsheviks captured the tsar and his family and held them captive in the city of Ekaterinburg. On the night of July 16, 1918, a firing squad executed the royal family and their attendants, including Alexis and his four sisters. Eight days later, a protsarist army fought its way into Ekaterinburg. Although army investigators searched vigorously for the bodies of Nicholas and his family, they found only a few personal effects and a single finger. The Bolsheviks eventually won the revolution and instituted the world's first communist state.

Historians have debated the role that Alexis's illness may have played in the Russian Revolution. Some have argued that the revolution was successful because the tsar and Alexandra were distracted by their son's illness and under the influence of Rasputin. Others point out that many factors contributed to the overthrow of the tsar. It is probably naive to attribute the revolution entirely to one sick boy, but it is



clear that a genetic defect, passed down through the royal family, contributed to the success of the Russian Revolution.

More than 80 years after the tsar and his family were executed, an article in the *Moscow News* reported the discovery of their skeletons outside Ekaterinburg. The remains had first been located in 1979; however, because of secrecy surrounding the tsar's execution, the location of the graves was not made public until the breakup of the Soviet government in 1989. The skeletons were eventually recovered and examined by a team of forensic anthropologists, who concluded that they were indeed the remains of the tsar and his wife, three of their five children, and the family doctor, cook, maid, and footman. The bodies of Alexis and his sister Anastasia are still missing.

To prove that the skeletons were those of the royal family, mitochondrial DNA (which is inherited only from the mother) was extracted from the bones and amplified with a molecular technique called the polymerase chain reaction (PCR). DNA samples from the skeletons thought to belong to Alexandra and the children were compared with DNA taken from Prince Philip of England, also a direct descendant of Queen Victoria. Analysis showed that mitochondrial DNA from Prince Philip was identical with that from these four skeletons.

DNA from the skeleton presumed to be Tsar Nicholas was compared with that of two living descendants of the Romanov line. The samples matched at all but one nucleotide position: the living relatives possessed a cytosine (C) residue at this position, whereas some of the skeletal DNA possessed a thymine (T) residue and some possessed a C. This difference could be due to normal variation in the DNA; so experts concluded that the skeleton was almost certainly that of Tsar Nicholas. The finding remained controversial, however, until July 1994, when the body of Nicholas's younger brother Georgij, who died in 1899, was exhumed. Mitochondrial DNA from Georgij also contained both C and T at the controversial position, proving that the skeleton was indeed that of Tsar Nicholas.

This chapter introduces you to genetics and reviews some concepts that you may have encountered briefly in a preceding biology course. We begin by considering the importance of genetics to each of us, to society at large, and to students of biology. We then turn to the history of genetics, how the field as a whole developed. The final part of the chapter reviews some fundamental terms and principles of genetics that are used throughout the book.

There has never been a more exciting time to undertake the study of genetics than now. Genetics is one of the frontiers of science. Pick up almost any major newspaper or news magazine and chances are that you will see something related to genetics: the discovery of cancer-causing genes; the use of gene therapy to treat diseases; or reports of possible hereditary influences on intelligence, personality, and sexual orientation. These findings often have significant economic and ethical implications, making the study of genetics relevant, timely, and interesting.

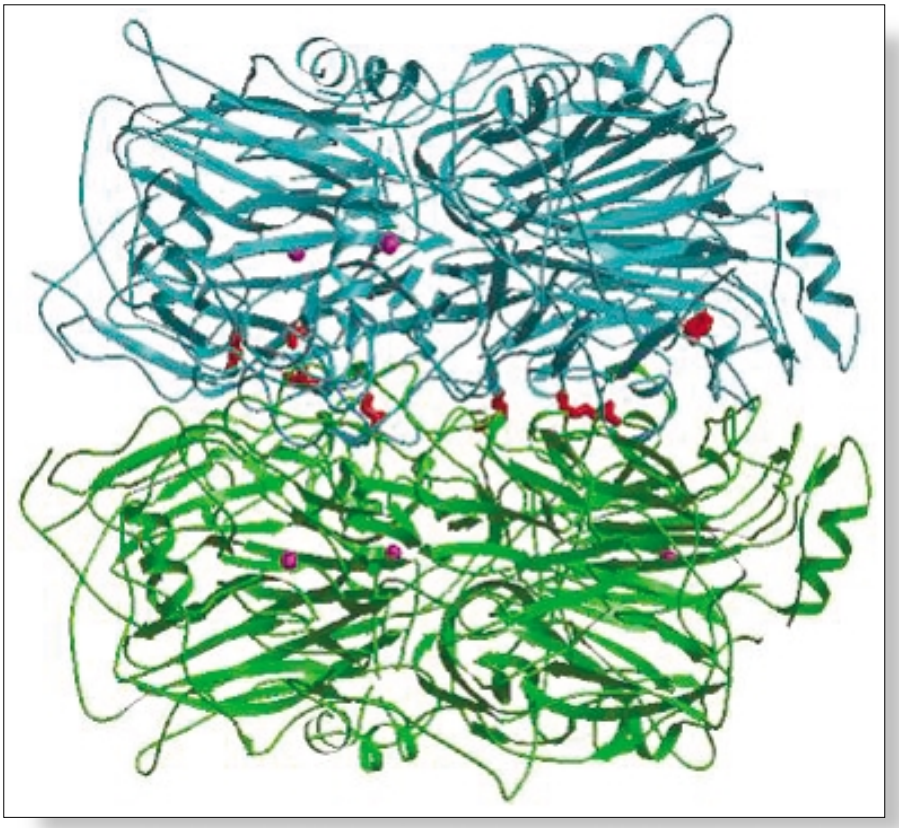
www.whfreeman.com/pierce More information about the history of Nicholas II and other tsars of Russia and about hemophilia

The Importance of Genetics

Alexis's hemophilia illustrates the important role that genetics plays in the life of an individual. A difference in one gene, of the 35,000 or so genes that each human possesses, changed Alexis's life, affected his family, and perhaps even altered history. We all possess genes that influence our lives. They affect our height and weight, our hair color and skin pigmentation. They influence our susceptibility to many diseases and disorders **(FIGURE 1.2)** and even contribute to our intelligence and personality. Genes are fundamental to who and what we are.

Although the science of genetics is relatively new, people have understood the hereditary nature of traits and have "practiced" genetics for thousands of years. The rise of agriculture began when humans started to apply genetic principles to the domestication of plants and animals. Today, the major crops and animals used in agriculture have undergone extensive genetic alterations to greatly increase their yields and provide many desirable traits, such as disease and pest

3 Basic Principles of Heredity



Alkaptonuria results from impaired function of homogentisate dioxygenase (shown here), an enzyme required for catabolism of the amino acids phenylalanine and tyrosine. (Courtesy of David E. Timm, Department of Molecular Biology, Indiana School of Medicine, and Miguel Penalva, Centro de Investigaciones. Biológicas CSIC, Madrid, Spain.)

- Black Urine and First Cousins
- Mendel: The Father of Genetics
  - Mendel's Success
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- Monohybrid Crosses
  - What Monohybrid Crosses Reveal
  - Predicting The Outcomes of Genetic Crosses
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- Multiple-Loci Crosses
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Black Urine and First Cousins

Voiding black urine is a rare and peculiar trait. In 1902, Archibald Garrod discovered the hereditary basis of black urine and, in the process, contributed to our understanding of the nature of genes.

Garrod was an English physician who was more interested in chemical explanations of disease than in the practice of medicine. He became intrigued by several of his patients who produced black urine, a condition known as alkaptonuria. The urine of alkaptonurics contains homogentisic acid, a compound that, on exposure to air, oxidizes and turns the urine black. Garrod observed that alkaptonuria appears at birth and remains for life. He noted that often several children in the same family were affected: of the 32 cases that he knew about, 19 appeared in only seven families. Furthermore, the parents of these alkaptonurics were frequently first cousins. With the assistance of geneticist William Bateson, Garrod recognized that this pattern of inheritance is precisely the pattern produced by the transmission of a rare, recessive gene.

Garrod later proposed that several other human disorders, including albinism and cystinuria, are inherited in the same way as alkaptonuria. He concluded that each gene

encodes an enzyme that controls a biochemical reaction. When there is a flaw in a gene, its enzyme is deficient, resulting in a biochemical disorder. He called these flaws "inborn errors of metabolism." Garrod was the first to apply the basic principles of genetics, which we will learn about in this chapter, to the inheritance of a human disease. His idea—that genes code for enzymes—was revolutionary and correct. Unfortunately, Garrod's ideas were not recognized as being important at the time and were appreciated only after they had been rediscovered 30 years later.

This chapter is about the principles of heredity: how genes are passed from generation to generation. These principles were first put forth by Gregor Mendel, so we begin by examining his scientific achievements. We then turn to simple genetic crosses, those in which a single characteristic is examined. We learn some techniques for predicting the outcome of genetic crosses and then turn to crosses in which two or more characteristics are examined. We will see how the principles applied to simple genetic crosses and the ratios of offspring that they produce serve as the key for understanding more complicated crosses. We end the chapter by considering statistical tests for analyzing crosses and factors that vary their outcome.

Throughout this chapter, a number of concepts are interwoven: Mendel's principles of segregation and independent assortment, probability, and the behavior of chromosomes. These might at first appear to be unrelated, but they are actually different views of the same phenomenon, because the genes that undergo segregation and independent assortment are located on chromosomes. The principle aim of this chapter is to examine these different views and to clarify their relations.

www.whfreeman.com/pierce Archibald Garrod's original paper on the genetics of alkaptonuria

Mendel: The Father of Genetics

In 1902, the basic principles of genetics, which Archibald Garrod successfully applied to the inheritance of alkaptonuria, had just become widely known among biologists. Surprisingly, these principles had been discovered some 35 years earlier by Johann Gregor Mendel (1822–1884).

Mendel was born in what is now part of the Czech Republic. Although his parents were simple farmers with little money, he was able to achieve a sound education and was admitted to the Augustinian monastery in Brno in September 1843. After graduating from seminary, Mendel was ordained a priest and appointed to a teaching position in a local school. He excelled at teaching, and the abbot of the monastery recommended him for further study at the University of Vienna, which he attended from 1851 to 1853. There, Mendel enrolled in the newly opened Physics Institute and took courses in mathematics, chemistry, entomology, paleontology, botany, and plant physiology. It was probably here that Mendel acquired the scientific method, which he later applied so successfully to his genetics experiments. After 2 years of study in Vienna, Mendel returned to Brno, where he taught school and began his experimental work with pea plants. He conducted breeding experiments from 1856 to 1863 and presented his results publicly at meetings of the Brno Natural Science Society in 1865. Mendel's paper from these lectures was published in 1866. In spite of widespread interest in heredity, the effect of his research on the scientific community was minimal. At the time, no one seems to have noticed that Mendel had discovered the basic principles of inheritance.

In 1868, Mendel was elected abbot of his monastery, and increasing administrative duties brought an end to his teaching and eventually to his genetics experiments. He died at the age of 61 on January 6, 1884, unrecognized for his contribution to genetics.

The significance of Mendel's discovery was unappreciated until 1900, when three botanists—Hugo de Vries, Erich von Tschermak, and Carl Correns—began independently conducting similar experiments with plants and arrived at conclusions similar to those of Mendel. Coming across Mendel's paper, they interpreted their results in terms of his principles and drew attention to his pioneering work.

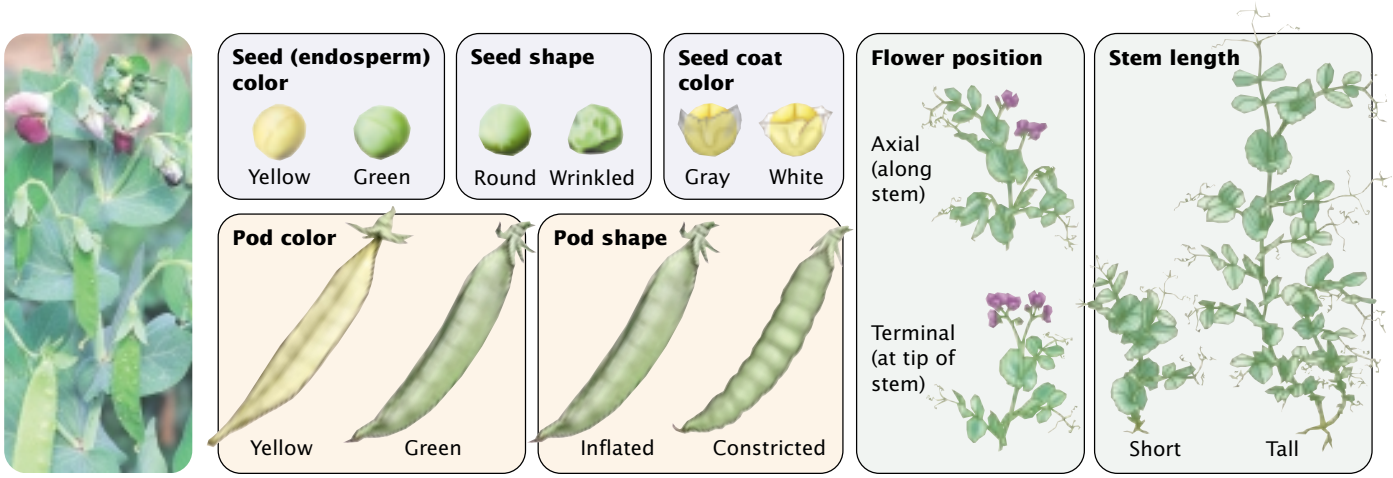
Concepts

Gregor Mendel put forth the basic principles of inheritance, publishing his findings in 1866. The significance of his work did not become widely appreciated until 1900.

Mendel's Success

Mendel's approach to the study of heredity was effective for several reasons. Foremost was his choice of experimental subject, the pea plant *Pisum sativum* (**Figure 3.1**), which offered clear advantages for genetic investigation. It is easy to cultivate, and Mendel had the monastery garden and greenhouse at his disposal. Peas grow relatively rapidly, completing an entire generation in a single growing season. By today's standards, one generation per year seems frightfully slow—fruit flies complete a generation in 2 weeks and bacteria in 20 minutes—but Mendel was under no pressure to publish quickly and was able to follow the inheritance of individual characteristics for several generations. Had he chosen to work on an organism with a longer generation time—horses, for example—he might never have discovered the basis of inheritance. Pea plants also produce many offspring—their seeds—which allowed Mendel to detect meaningful mathematical ratios in the traits that he observed in the progeny.

The large number of varieties of peas that were available to Mendel was also crucial, because these varieties differed in various traits and were genetically pure. Mendel was therefore able to begin with plants of variable, known genetic makeup.



3.1 Mendel used the pea plant *Pisum sativum* in his studies of heredity. He examined seven characteristics that appeared in the seeds and in plants grown from the seeds. (Photo from Wally Eberhart/Visuals Unlimited.)

Much of Mendel's success can be attributed to the seven characteristics that he chose for study (see Figure 3.1). He avoided characteristics that display a range of variation; instead, he focused his attention on those that exist in two easily differentiated forms, such as white versus gray seed coats, round versus wrinkled seeds, and inflated versus constricted pods.

Finally, Mendel was successful because he adopted an experimental approach. Unlike many earlier investigators who just described the *results* of crosses, Mendel formulated *hypotheses* based on his initial observations and then conducted additional crosses to test his hypotheses. He kept careful records of the numbers of progeny possessing each type of trait and computed ratios of the different types. He paid close attention to detail, was adept at seeing patterns in detail, and was patient and thorough, conducting his experiments for 10 years before attempting to write up his results.

www.whfreeman.com/pierce Mendel's original paper (in German, with an English translation), as well as references, essays, and commentaries on Mendel's work

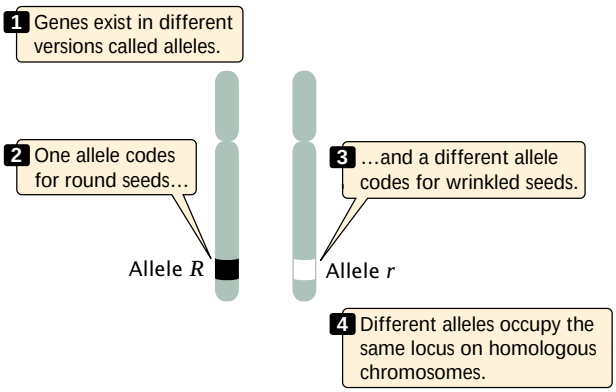
Genetic Terminology

Before we examine Mendel's crosses and the conclusions that he made from them, it will be helpful to review some terms commonly used in genetics (Table 3.1). The term *gene* was a word that Mendel never knew. It was not coined until 1909, when the Danish geneticist Wilhelm Johannsen first used it. The definition of a gene varies with the context of its use, and so its definition will change as we explore different aspects of heredity. For our present use in the context of genetic crosses, we will define a **gene** as an inherited factor that determines a characteristic.

Table 3.1 Summary of important genetic terms

Term	Definition
Gene	A genetic factor (region of DNA) that helps determine a characteristic
Allele	One of two or more alternate forms of a gene
Locus	Specific place on a chromosome occupied by an allele
Genotype	Set of alleles that an individual possesses
Heterozygote	An individual possessing two different alleles at a locus
Homozygote	An individual possessing two of the same alleles at a locus
Phenotype or trait	The appearance or manifestation of a character
Character or characteristic	An attribute or feature

Genes frequently come in different versions called **alleles** (FIGURE 3.2). In Mendel's crosses, seed shape was determined by a gene that exists as two different alleles: one allele codes for round seeds and the other codes for wrinkled seeds. All alleles for any particular gene will be found at a specific place on a chromosome called the **locus** for that gene. (The plural of locus is loci; it's bad form in genetics—and incorrect—to speak of locuses.) Thus, there is a specific place—a locus—on a chromosome in pea plants



3.2 At each locus, a diploid organism possesses two alleles located on different homologous chromosomes.

where the shape of seeds is determined. This locus might be occupied by an allele for round seeds or one for wrinkled seeds. We will use the term *allele* when referring to a specific version of a gene; we will use the term *gene* to refer more generally to any allele at a locus.

The **genotype** is the set of alleles that an individual organism possesses. A diploid organism that possesses two identical alleles is **homozygous** for that locus. One that possesses two different alleles is **heterozygous** for the locus.

Another important term is **phenotype,** which is the manifestation or appearance of a characteristic. A phenotype can refer to any type of characteristic: physical, physiological, biochemical, or behavioral. Thus, the condition of having round seeds is a phenotype, a body weight of 50 kg is a phenotype, and having sickle-cell anemia is a phenotype. In this book, the term *characteristic* or *character* refers to a general feature such as eye color; the term *trait* or *phenotype* refers to specific manifestations of that feature, such as blue or brown eyes.

A given phenotype arises from a genotype that develops within a particular environment. The genotype determines the potential for development; it sets certain limits, or boundaries, on that development. How the phenotype develops within those limits is determined by the effects of other genes and environmental factors, and the balance between these influences varies from character to character. For some characters, the differences between phenotypes are determined largely by differences in genotype; in other words, the genetic limits for that phenotype are narrow. Seed shape in Mendel's peas is a good example of a characteristic for which the genetic limits are narrow and the phenotypic differences are largely genetic. For other characters, environmental differences are more important; in this case, the limits imposed by the genotype are broad. The height that an oak tree reaches at maturity is a phenotype that is strongly influenced by environmental factors, such as the availability of water, sunlight, and nutrients. Nevertheless, the tree's genotype still imposes some limits on its height: an oak tree will never grow to be 300 m tall no matter how much sunlight, water, and fertilizer are provided. Thus, even the height of an oak tree is determined to some degree by genes. For many characteristics, both genes and environment are important in determining phenotypic differences.

An obvious but important concept is that only the genotype is inherited. Although the phenotype is determined, at least to some extent, by genotype, organisms do not transmit their phenotypes to the next generation. The distinction between genotype and phenotype is one of the most important principles of modern genetics. The next section describes Mendel's careful observation of phenotypes through several generations of breeding experiments. These experiments allowed him to deduce not only the genotypes of the individual plants, but also the rules governing their inheritance.

Concepts

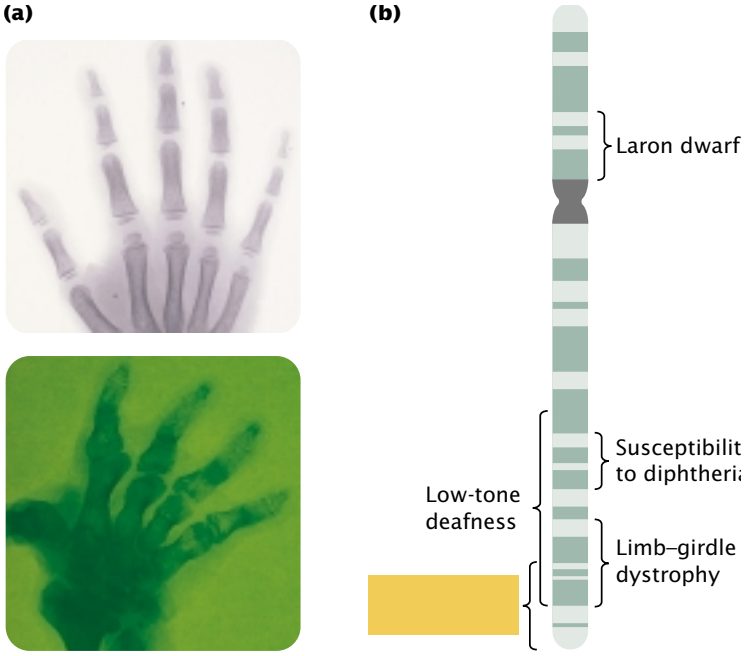
Each phenotype results from a genotype developing within a specific environment. The genotype, not the phenotype, is inherited.

Monohybrid Crosses

Mendel started with 34 varieties of peas and spent 2 years selecting those varieties that he would use in his experiments. He verified that each variety was genetically pure (homozygous for each of the traits that he chose to study) by growing the plants for two generations and confirming that all offspring were the same as their parents. He then carried out a number of crosses between the different varieties. Although peas are normally self-fertilizing (each plant crosses with itself), Mendel conducted crosses between different plants by opening the buds before the anthers were fully developed, removing the anthers, and then dusting the stigma with pollen from a different plant.

Mendel began by studying **monohybrid crosses**—those between parents that differed in a single characteristic. In one experiment, Mendel crossed a pea plant homozygous for round seeds with one that was homozygous for wrinkled seeds (**Figure 3.3**). This first generation of a cross is the **P** (parental) **generation.**

After crossing the two varieties in the P generation, Mendel observed the offspring that resulted from the cross. In regard to seed characteristics, such as seed shape, the phenotype develops as soon as the seed matures, because the seed traits are determined by the newly formed embryo within the seed. For characters associated with the plant itself, such as stem length, the phenotype doesn't develop until the plant grows from the seed; for these characters, Mendel had to wait until the following spring, plant the seeds, and then observe the phenotypes on the plants that germinated.



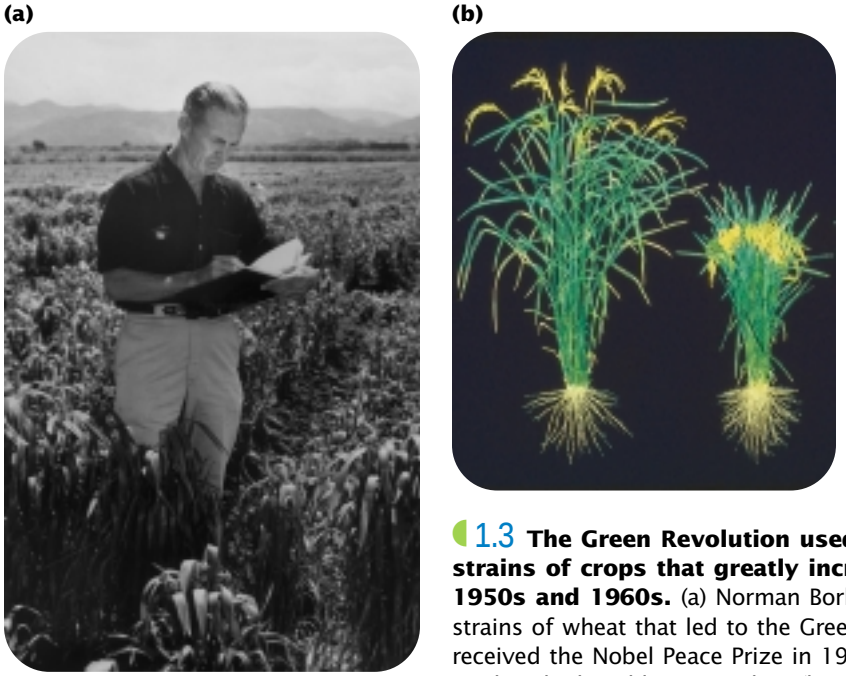
1.2 Genes influence susceptibility to many diseases and disorders. (a) X-ray of the hand of a person suffering from diastrophic dysplasia (bottom), a hereditary growth disorder that results in curved bones, short limbs, and hand deformities, compared with an X-ray of a normal hand (top). (b) This disorder is due to a defect in a gene on chromosome 5. Other genetic disorders encoded by genes on chromosome 5 also are indicated by braces. (Part a: top, Biophoto Associates/Science Source Photo Researchers; bottom, courtesy of Eric Lander, Whitehead Institute, MIT.)

resistance, special nutritional qualities, and characteristics that facilitate harvest. The Green Revolution, which expanded global food production in the 1950s and 1960s, relied heavily on the application of genetics (FIGURE 1.3). Today, genetically engineered corn, soybeans, and other crops constitute a significant proportion of all the food produced worldwide.

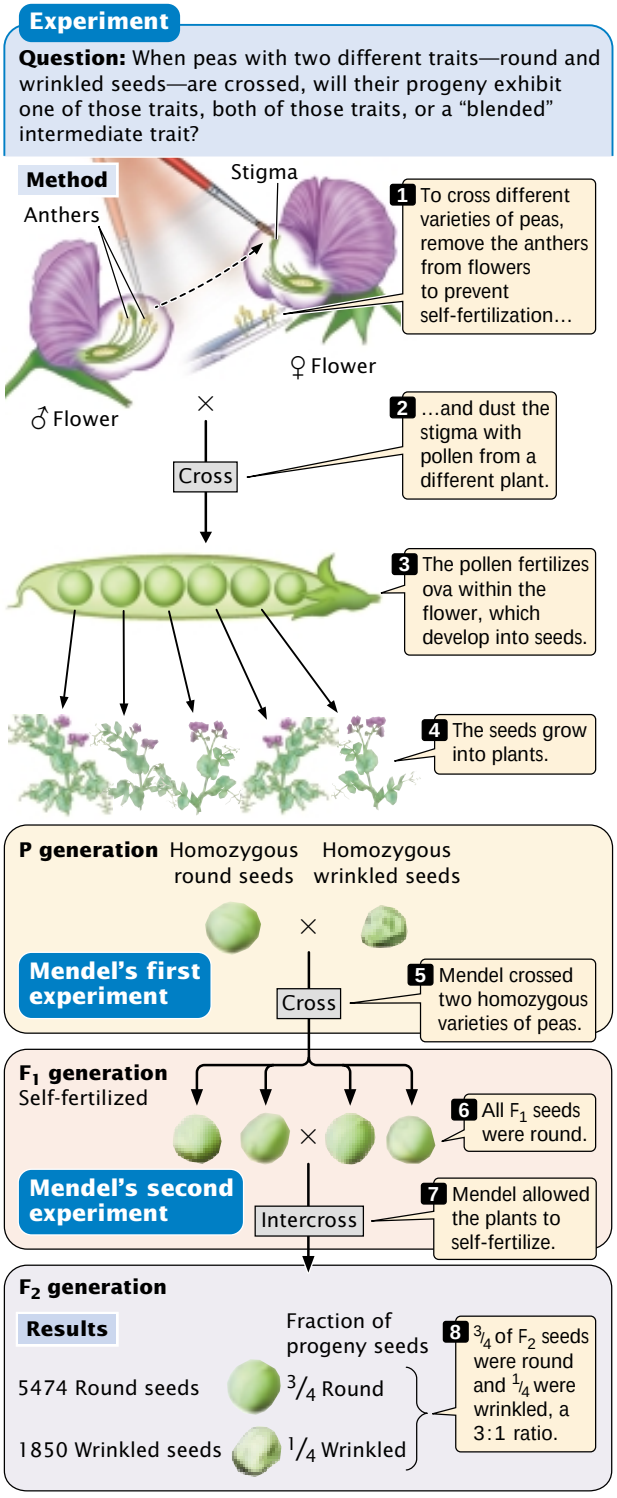
The pharmaceutical industry is another area where genetics plays an important role. Numerous drugs and food additives are synthesized by fungi and bacteria that have been genetically manipulated to make them efficient producers of these substances. The biotechnology industry employs molecular genetic techniques to develop and mass-produce substances of commercial value. Growth hormone, insulin, and clotting factor are now produced commercially by genetically engineered bacteria (FIGURE 1.4). Techniques of molecular genetics have also been used to produce bacteria that remove minerals from ore, break down toxic chemicals, and inhibit damaging frost formation on crop plants.

Genetics also plays a critical role in medicine. Physicians recognize that many diseases and disorders have a hereditary component, including well-known genetic disorders such as sickle-cell anemia and Huntington disease as well as many common diseases such as asthma, diabetes, and hypertension. Advances in molecular genetics have allowed important insights into the nature of cancer and permitted the development of many diagnostic tests. Gene therapy—the direct alteration of genes to treat human diseases—has become a reality.

www.whfreeman.com/pierce Information about biotechnology, including its history and applications



1.3 The Green Revolution used genetic techniques to develop new strains of crops that greatly increased world food production during the 1950s and 1960s. (a) Norman Borlaug, a leader in the development of new strains of wheat that led to the Green Revolution, and a family in Ghana. Borlaug received the Nobel Peace Prize in 1970. (b) Traditional rice plant (top) and modern, high-yielding rice plant (bottom). (Part a, UPI/Corbis-Bettman; part b, IRRI.)



3.3 Mendel conducted monohybrid crosses.

The offspring from the parents in the P generation are the **F_1 (first filial) generation.** When Mendel examined the F_1 of this cross, he found that they expressed only one of the phenotypes present in the parental generation: all the F_1 seeds were round. Mendel carried out 60 such crosses and always obtained this result. He also conducted **reciprocal crosses:** in one cross, pollen (the male gamete) was taken from a plant with round seeds and, in its reciprocal cross, pollen was taken from a plant with wrinkled seeds. Reciprocal crosses gave the same result: all the F_1 were round.

Mendel wasn't content with examining only the seeds arising from these monohybrid crosses. The following spring, he planted the F_1 seeds, cultivated the plants that germinated from them, and allowed the plants to self-fertilize, producing a second generation (the **F_2 generation**). Both of the traits from the P generation emerged in the F_2; Mendel counted 5474 round seeds and 1850 wrinkled seeds in the F_2 (see Figure 3.3). He noticed that the number of the round and wrinkled seeds constituted approximately a 3 to 1 ratio; that is, about $^3/_4$ of the F_2 seeds were round and $^1/_4$ were wrinkled. Mendel conducted monohybrid crosses for all seven of the characteristics that he studied in pea plants, and in all of the crosses he obtained the same result: all of the F_1 resembled only one of the two parents, but both parental traits emerged in the F_2 in approximately a 3:1 ratio.

What Monohybrid Crosses Reveal

Mendel drew several important conclusions from the results of his monohybrid crosses. First, he reasoned that, although the F_1 plants display the phenotype of only one parent, they must inherit genetic factors from both parents because they transmit both phenotypes to the F_2 generation. The presence of both round and wrinkled seeds in the F_2 could be explained only if the F_1 plants possessed both round and wrinkled genetic factors that they had inherited from the P generation. He concluded that each plant must therefore possess two genetic factors coding for a character.

The genetic factors that Mendel discovered (alleles) are, by convention, designated with letters; the allele for round seeds is usually represented by *R*, and the allele for wrinkled seeds by *r*. The plants in the P generation of Mendel's cross possessed two identical alleles: *RR* in the round-seeded parent and *rr* in the wrinkled-seeded parent (◖ FIGURE 3.4a).

A second conclusion that Mendel drew from his monohybrid crosses was that the two alleles in each plant separate when gametes are formed, and one allele goes into each gamete. When two gametes (one from each parent) fuse to produce a zygote, the allele from the male parent unites with the allele from the female parent to produce the genotype of the offspring. Thus, Mendel's F_1 plants inherited an *R* allele from the round-seeded plant and an *r* allele from the wrinkled-seeded plant (◖ FIGURE 3.4b). However, only the trait encoded by round allele (*R*) was *observed* in the F_1—all the F_1 progeny had round seeds. Those traits that appeared unchanged in the F_1 heterozygous offspring

The New Genetics
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Should Genetics Researchers Probe Abraham Lincoln's Genes?

by Art Caplan

Many people agree that no one should be forced to have a genetic test without his or her consent, yet for obvious reasons this ethical principle is difficult to follow when dealing with those who are deceased. There are all sorts of reasons why genetic testing on certain deceased persons might prove important, but one of the primary reasons is for purposes of identification. In anthropology, genetic analysis might help tell us whether we have found the body of a Romanov, Hitler, or Mengele. In cases of war or terrorist attacks, such as those on September 11, 2001, there might be no other way to determine the identify of a deceased person except by matching tissue samples with previously stored biological tissue or with samples from close relatives.

One historically interesting case, which highlights the ethical issues faced when determining genetic facts about the dead, is that which centers on Abraham Lincoln. Medical geneticists and advocates for patients with Marfan syndrome have long wondered whether President Lincoln had this particular genetic disease. After all, Lincoln had the tall gangly build often associated with Marfan's syndrome, which affects the connective tissues and cartilage of the body. Biographers and students of this man, whom many consider to be our greatest president, would like to know whether the depression that Lincoln suffered throughout his life might have been linked to the painful, arthritis-like symptoms of Marfan syndrome.

Lincoln was assassinated on April 14, 1865, and died early the next morning. An autopsy was performed, and samples of his hair, bone, and blood were preserved and stored at the National Museum of Health and Medicine; they are still there. The presence of a recently found genetic marker indicates whether someone has Marfan syndrome. With this advancement, it would be possible to use some of the stored remains of Abe Lincoln to see if he had this condition. However, would it be ethical to perform this test?

We must be careful about genetic testing, because often too much weight is assigned to the results of such tests. There is a temptation to see DNA as the essence, the blueprint, of a person—that the factor that forms who we are and what we do. Given this tendency, should society be cautious about letting people explore the genes of the deceased? And, if we should not test without permission, then how can we obtain permission in cases where the person in question is dead? In Honest Abe's case, the "patient" is deceased and has no immediate survivors; there is no one to consent. But allowing testing without consent sets a dangerous precedent.

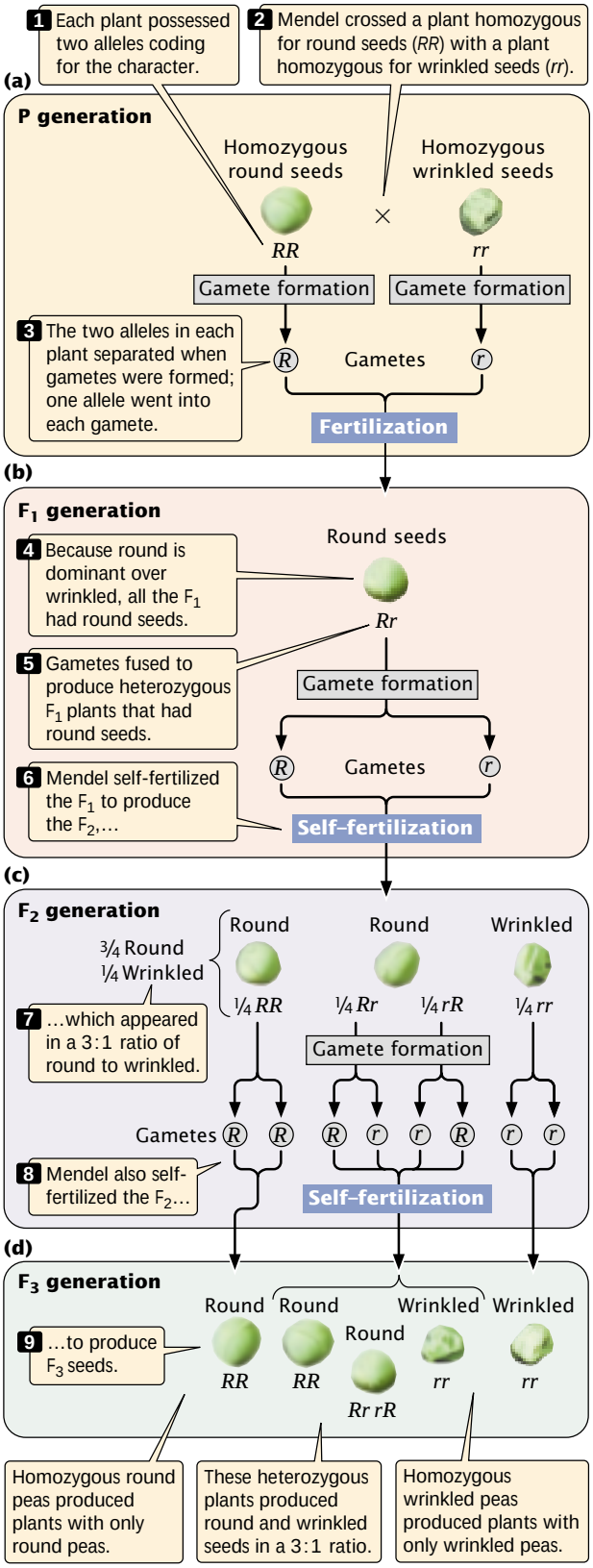
Abraham Lincoln had the tall, gangly build often associated with Marfan syndrome. (Cartoon by Frank Billew, 1864. Bettmann/Corbis.)

It may seem a bit strange to apply the notions of privacy and consent to the deceased. But, considering that most people today agree that consent should be obtained before these tests are administered, do researchers have the right to pry into Lincoln's DNA simply because neither he nor his descendants are around to say that they can't? Are we to say that anyone's body is open to examination whenever a genetic test becomes available that might tell us an interesting fact about that person's biological makeup?

Many prominent people from the past have taken special precautions to restrict access to their diaries, papers and letters; for instance, Sigmund Freud locked away his personal papers for 100 years. Will future Lincolns and Freuds need to embargo their mortal remains for eternity to prevent unwanted genetic snooping by subsequent generations?

And, when it comes right down to it, what is the point of establishing whether Lincoln had Marfan syndrome? After all, we don't need to inspect his genes to determine whether he was presidential timber—Marfan or no Marfan, he obviously was. The real questions to ask are, Do we adequately understand what he did as president and what he believed? How did his actions shape our country, and what can we learn from them that will benefit us today?

In the end, the genetic basis for Lincoln's behavior and leadership might be seen as having no relevance. Some would say that genetic testing might divert our attention from Lincoln's work, writings, thoughts, and deeds and, instead, require that we see him as a jumble of DNA output. Perhaps it makes more sense to encourage efforts to understand and appreciate Lincoln's legacy through his actions rather than through reconstituting and analyzing his DNA.



3.4 Mendel's monohybrid crosses revealed the principle of segregation and the concept of dominance.

Mendel called **dominant,** and those traits that disappeared in the F_1 heterozygous offspring he called **recessive.** When dominant and recessive alleles are present together, the recessive allele is masked, or suppressed. The concept of dominance was a third important conclusion that Mendel derived from his monohybrid crosses.

Mendel's fourth conclusion was that the two alleles of an individual plant separate with equal probability into the gametes. When plants of the F_1 (with genotype *Rr*) produced gametes, half of the gametes received the *R* allele for round seeds and half received the *r* allele for wrinkled seeds. The gametes then paired randomly to produce the following genotypes in equal proportions among the F_2: *RR*, *Rr*, *rR*, *rr* (**Figure 3.4c**). Because round (*R*) is dominant over wrinkled (*r*), there were three round progeny in the F_2 (*RR*, *Rr*, *rR*) for every one wrinkled progeny (*rr*) in the F_2. This 3:1 ratio of round to wrinkled progeny that Mendel observed in the F_2 could occur only if the two alleles of a genotype separated into the gametes with equal probability.

The conclusions that Mendel developed about inheritance from his monohybrid crosses have been further developed and formalized into the principle of segregation and the concept of dominance. The **principle of segregation** (Mendel's first law) states that each individual diploid organism possesses two alleles for any particular characteristic. These two alleles segregate (separate) when gametes are formed, and one allele goes into each gamete. Furthermore, the two alleles segregate into gametes in equal proportions. The **concept of dominance** states that, when two different alleles are present in a genotype, only the trait of the dominant allele is observed in the phenotype.

Mendel confirmed these principles by allowing his F_2 plants to self-fertilize and produce an F_3 generation. He found that the F_2 plants grown from the wrinkled seeds—those displaying the recessive trait (*rr*)—produced an F_3 in which all plants produced wrinkled seeds. Because his wrinkled-seeded plants were homozygous for wrinkled alleles (*rr*) they could pass on only wrinkled alleles to their progeny (**Figure 3.4d**).

The F_2 plants grown from round seeds—the dominant trait—fell into two types (Figure 3.4c). On self-fertilization, about $^2/_3$ of the F_2 plants produced both round and wrinkled seeds in the F_3 generation. These F_2 plants were heterozygous (*Rr*); so they produced $^1/_4$ *RR* (round), $^1/_2$ *Rr* (round), and $^1/_4$ *rr* (wrinkled) seeds, giving a 3:1 ratio of round to wrinkled in the F_3. About $^1/_3$ of the F_2 plants were of the second type; they produced only the dominant round-seeded trait in the F_3. These F_2 plants were homozygous for the round allele (*RR*) and thus could produce only round offspring in the F_3 generation. Mendel planted the seeds obtained in the F_3 and carried these plants through three more rounds of self-fertilization. In each generation, $^2/_3$ of the round-seeded plants produced round and wrinkled offspring, whereas $^1/_3$ produced only round offspring. These results are entirely consistent with the principle of segregation.

Concepts

The principle of segregation states that each individual organism possesses two alleles coding for a characteristic. These alleles segregate when gametes are formed, and one allele goes into each gamete. The concept of dominance states that, when dominant and recessive alleles are present together, only the trait of the dominant allele is observed.

Connecting Concepts

Relating Genetic Crosses to Meiosis

We have now seen how the results of monohybrid crosses are explained by Mendel's principle of segregation. Many students find that they enjoy working genetic crosses but are frustrated by the abstract nature of the symbols. Perhaps you feel the same at this point. You may be asking "What do these symbols really represent? What does the genotype *RR* mean in regard to the biology of the organism?" The answers to these questions lie in relating the abstract symbols of crosses to the structure and behavior of chromosomes, the repositories of genetic information (Chapter 2).

In 1900, when Mendel's work was rediscovered and biologists began to apply his principles of heredity, the relation between genes and chromosomes was still unclear. The theory that genes are located on chromosomes (the **chromosome theory of heredity**) was developed in the early 1900s by Walter Sutton, then a graduate student at Columbia University. Through the careful study of meiosis in insects, Sutton documented the fact that each homologous pair of chromosomes consists of one maternal chromosome and one paternal chromosome. Showing that these pairs segregate independently into gametes in meiosis, he concluded that this process is the biological basis for Mendel's principles of heredity. The German cytologist and embryologist Theodor Boveri came to similar conclusions at about the same time.

Sutton knew that diploid cells have two sets of chromosomes. Each chromosome has a pairing partner, its homologous chromosome. One chromosome of each homologous pair is inherited from the mother and the other is inherited from the father. Similarly, diploid cells possess two alleles at each locus, and these alleles constitute the genotype for that locus. The principle of segregation indicates that one allele of the genotype is inherited from each parent.

This similarity between the number of chromosomes and the number of alleles is not accidental—the two alleles of a genotype are located on homologous chromosomes. The symbols used in genetic crosses, such as *R* and *r*, are just shorthand notations for particular sequences of DNA in the chromosomes that code for particular phenotypes. The two alleles of a genotype are found on different but homologous chromosomes. During the S stage of meiotic interphase, each chromosome replicates, producing two copies of each allele, one on each chromatid (◖ FIGURE 3.5a). The homologous chromosomes segregate during anaphase I, thereby separating the two different alleles (◖ FIGURE 3.5b and c). This chromosome segregation is the basis of the principle of segregation. During anaphase II of meiosis, the two chromatids of each replicated chromosome separate; so each gamete resulting from meiosis carries only a single allele at each locus, as Mendel's principle of segregation predicts.

If crossing over has taken place during prophase I of meiosis, then the two chromatids of each replicated chromosome are no longer identical, and the segregation of different alleles takes place at anaphase I and anaphase II (see Figure 3.5c). Of course, Mendel didn't know anything about chromosomes; he formulated his principles of heredity entirely on the basis of the results of the crosses that he carried out. Nevertheless, we should not forget that these principles work because they are based on the behavior of actual chromosomes during meiosis.

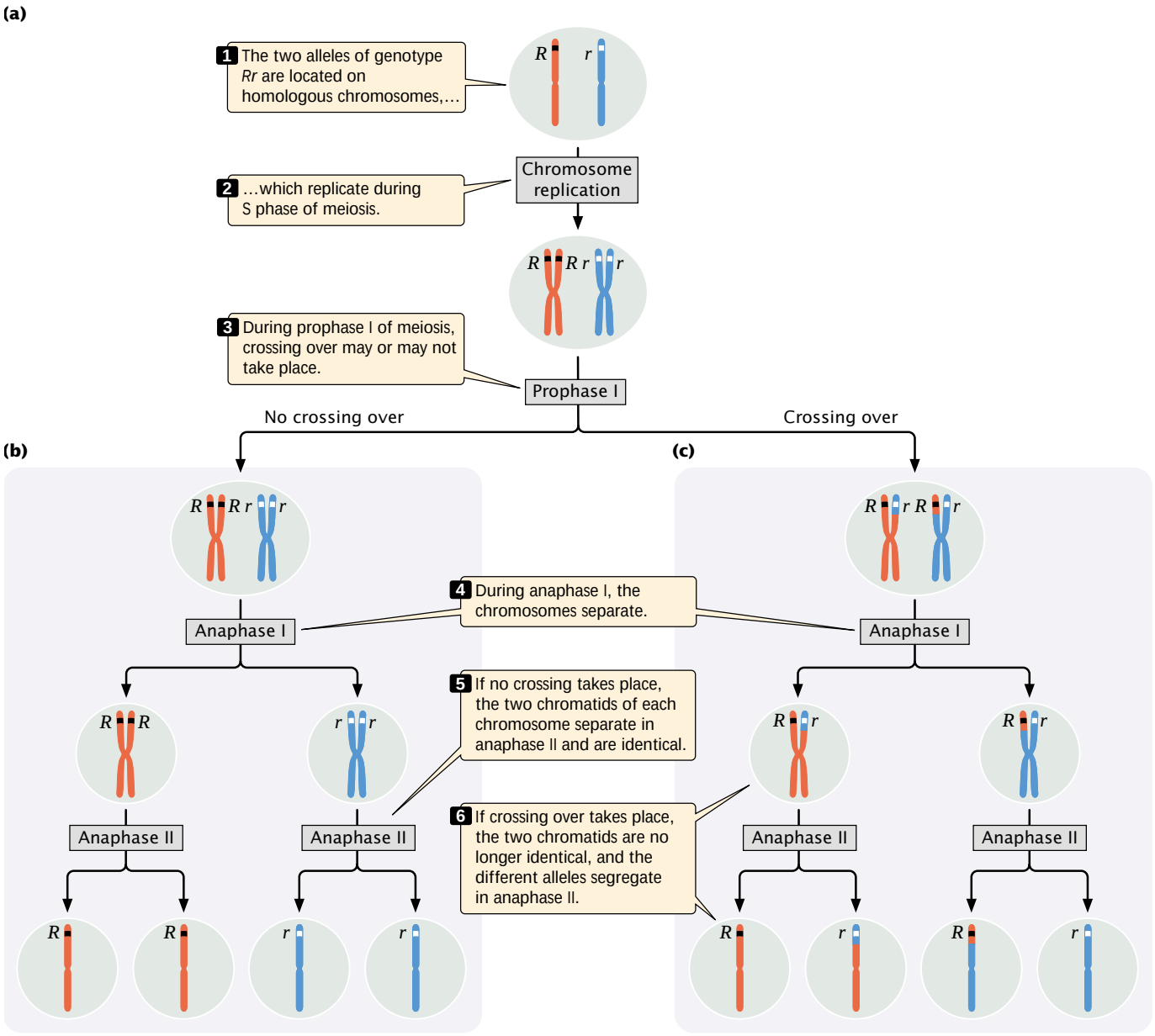
Concepts

The chromosome theory of inheritance states that genes are located on chromosomes. The two alleles of a genotype segregate during anaphase I of meiosis, when homologous chromosomes separate. The alleles may also segregate during anaphase II of meiosis if crossing over has taken place.

Predicting the Outcomes of Genetic Crosses

One of Mendel's goals in conducting his experiments on pea plants was to develop a way to predict the outcome of crosses between plants with different phenotypes. In this section, we will first learn a simple, shorthand method for predicting outcomes of genetic crosses (the Punnett square), and then we will learn how to use probability to predict the results of crosses.

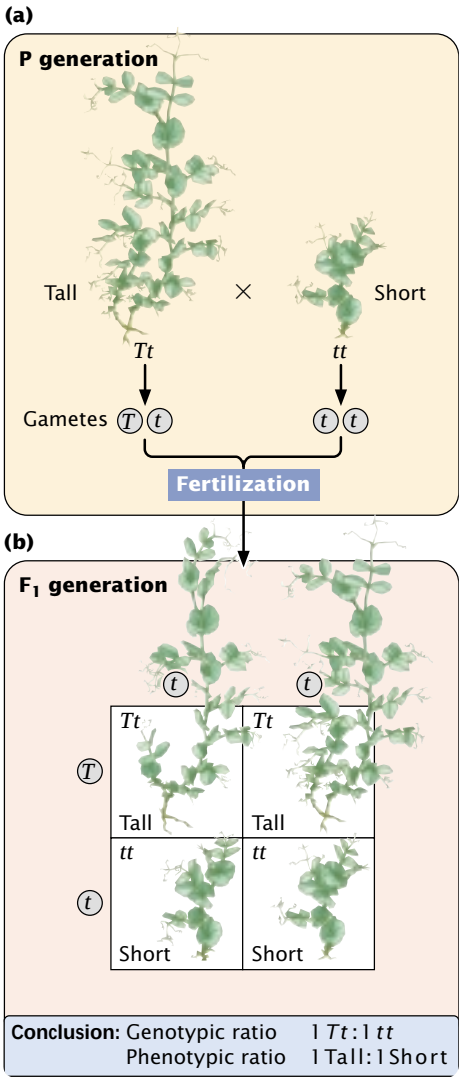
The Punnett square To illustrate the Punnett square, let's examine another cross that Mendel carried out. By crossing two varieties of peas that differed in height, Mendel established that tall (*T*) was dominant over short (*t*). He tested his theory concerning the inheritance of dominant traits by crossing an F_1 tall plant that was heterozygous (*Tt*) with the short homozygous parental variety (*tt*). This type of cross, between an F_1 genotype and either of the parental genotypes, is called a **backcross.**



3.5 Segregation happens because homologous chromosomes separate in meiosis.

To predict the types of offspring that result from this cross, we first determine which gametes will be produced by each parent (FIGURE 3.6a). The principle of segregation tells us that the two alleles in each parent separate, and one allele passes to each gamete. All gametes from the homozygous *tt* short plant will receive a single short (*t*) allele. The tall plant in this cross is heterozygous (*Tt*); so 50% of its gametes will receive a tall allele (*T*) and the other 50% will receive a short allele (*t*).

A **Punnett square** is constructed by drawing a grid, putting the gametes produced by one parent along the upper edge and the gametes produced by the other parent down the left side (FIGURE 3.6b). Each cell (a block within the Punnett square) contains an allele from each of the corresponding gametes, generating the genotype of the progeny produced by fusion of those gametes. In the upper left-hand cell of the Punnett square in Figure 3.6b, a gamete containing *T* from the tall plant unites with a gamete containing *t* from the short plant, giving the genotype of the progeny (*Tt*). It is useful to write the phenotype expressed by each genotype; here the progeny will be tall, because the tall allele is dominant over the short allele.



3.6 The Punnett square can be used for determining the results of a genetic cross.

This process is repeated for all the cells in the Punnett square.

By simply counting, we can determine the types of progeny produced and their ratios. In Figure 3.6b, two cells contain tall (*Tt*) progeny and two cells contain short (*tt*) progeny; so the genotypic ratio expected for this cross is 2 *Tt* to 2 *tt* (a 1:1 ratio). Another way to express this result is to say that we expect $\frac{1}{2}$ of the progeny to have genotype *Tt* (and phenotype tall) and $\frac{1}{2}$ of the progeny to have genotype *tt* (and phenotype short). In this cross, the genotypic ratio and the phenotypic ratio are the same, but this outcome need not be the case. Try completing a Punnett square for the cross in which the F_1 round-seeded plants in Figure 3.4 undergo self-fertilization (you should obtain a phenotypic ratio of 3 round to 1 wrinkled and a genotypic ratio of 1 *RR* to 2 *Rr* to 1 *rr*).

Concepts

The Punnett square is a short-hand method of predicting the genotypic and phenotypic ratios of progeny from a genetic cross.

Probability as a tool in genetics

Another method for determining the outcome of a genetic cross is to use the rules of probability, as Mendel did with his crosses. **Probability** expresses the likelihood of a particular event occurring. It is the number of times that a particular event occurs, divided by the number of all possible outcomes. For example, a deck of 52 cards contains only one king of hearts. The probability of drawing one card from the deck at random and obtaining the king of hearts is $\frac{1}{52}$, because there is only one card that is the king of hearts (one event) and there are 52 cards that can be drawn from the deck (52 possible outcomes). The probability of drawing a card and obtaining an ace is $\frac{4}{52}$, because there are four cards that are aces (four events) and 52 cards (possible outcomes). Probability can be expressed either as a fraction ($\frac{1}{52}$ in this case) or as a decimal number (0.019).

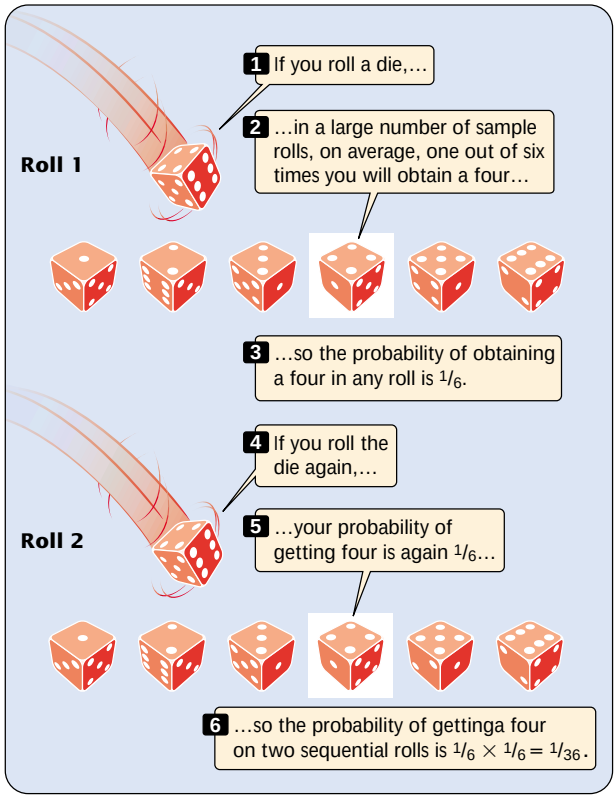
The probability of a particular event may be determined by knowing something about *how* the event occurs or *how often* it occurs. We know, for example, that the probability of rolling a six-sided die (one member of a pair of dice) and getting a four is $\frac{1}{6}$, because the die has six sides and any one side is equally likely to end up on top. So, in this case, understanding the nature of the event—the shape of the thrown die—allows us to determine the probability. In other cases, we determine the probability of an event by making a large number of observations. When a weather forecaster says that there is a 40% chance of rain on a particular day, this probability was obtained by observing a large number of days with similar atmospheric conditions and finding that it rains on 40% of those days. In this case, the probability has been determined empirically (by observation).

The multiplication rule

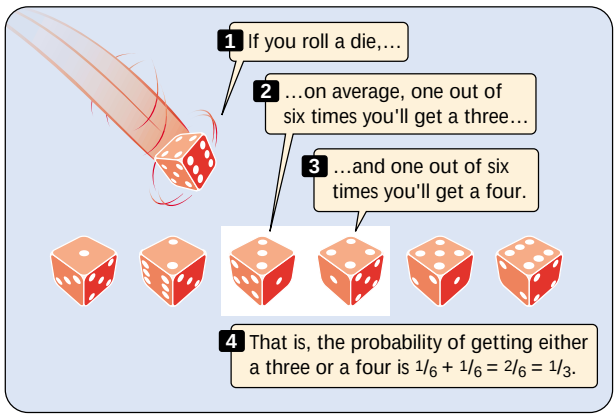
Two rules of probability are useful for predicting the ratios of offspring produced in genetic crosses. The first is the **multiplication rule,** which states that the probability of two or more independent events occurring together is calculated by multiplying their independent probabilities.

To illustrate the use of the multiplication rule, let's again consider the roll of dice. The probability of rolling one die and obtaining a four is $\frac{1}{6}$. To calculate the probability of rolling a die twice and obtaining 2 fours, we can apply the multiplication rule. The probability of obtaining a four on the first roll is $\frac{1}{6}$ and the probability of obtaining a four on the second roll is $\frac{1}{6}$; so the probability of rolling a four on both is $\frac{1}{6} \times \frac{1}{6} = \frac{1}{36}$ (FIGURE 3.7a). The key indicator for applying the multiplication rule is the word *and;*

(a) The multiplication rule



(b) The addition rule



3.7 The multiplication and addition rules can be used to determine the probability of combinations of events.

in the example just considered, we wanted to know the probability of obtaining a four on the first roll *and* a four on the second roll.

For the multiplication rule to be valid, the events whose joint probability is being calculated must be independent—the outcome of one event must not influence the outcome of the other. For example, the number that comes up on one roll of the die has no influence on the number that comes up on the other roll, so these events are independent. However, if we wanted to know the probability of being hit on the head with a hammer and going to the hospital on the same day, we could not simply multiply the probability of being hit on the head with a hammer by the probability of going to the hospital. The multiplication rule cannot be applied here, because the two events are not independent—being hit on the head with a hammer certainly influences the probability of going to the hospital.

The addition rule The second rule of probability frequently used in genetics is the **addition rule,** which states that the probability of any one of two or more mutually exclusive events is calculated by adding the probabilities of these events. Let's look at this rule in concrete terms. To obtain the probability of throwing a die once and rolling *either* a three *or* a four, we would use the addition rule, adding the probability of obtaining a three ($1/6$) to the probability of obtaining a four (again, $1/6$), or $1/6 + 1/6 = 2/6 = 1/3$ (◖ FIGURE 3.7b). The key indicator for applying the addition rule are the words *either* and *or*.

For the addition rule to be valid, the events whose probability is being calculated must be mutually exclusive, meaning that one event excludes the possibility of the other occurring. For example, you cannot throw a single die just once and obtain both a three and a four, because only one side of the die can be on top. These events are mutually exclusive.

Concepts

The multiplication rule states that the probability of two or more independent events occurring together is calculated by multiplying their independent probabilities. The addition rule states that the probability that any one of two or more mutually exclusive events occurring is calculated by adding their probabilities.

The application of probability to genetic crosses The multiplication and addition rules of probability can be used in place of the Punnett square to predict the ratios of progeny expected from a genetic cross. Let's first consider a cross between two pea plants heterozygous for the locus that determines height, $Tt \times Tt$. Half of the gametes produced by each plant have a *T* allele, and the other half have a *t* allele; so the probability for each type of gamete is $1/2$.

The gametes from the two parents can combine in four different ways to produce offspring. Using the multiplication rule, we can determine the probability of each possible type. To calculate the probability of obtaining *TT* progeny, for example, we multiply the probability of receiving a *T* allele from the first parent ($1/2$) times the probability of

receiving a *T* allele from the second parent ($^1/_2$). The multiplication rule should be used here because we need the probability of receiving a *T* allele from the first parent *and* a *T* allele from the second parent—two independent events. The four types of progeny from this cross and their associated probabilities are:

TT	(*T* gamete and *T* gamete)	$^1/_2 \times {}^1/_2 = {}^1/_4$	tall
Tt	(*T* gamete and *t* gamete)	$^1/_2 \times {}^1/_2 = {}^1/_4$	tall
tT	(*t* gamete and *T* gamete)	$^1/_2 \times {}^1/_2 = {}^1/_4$	tall
tt	(*t* gamete and *t* gamete)	$^1/_2 \times {}^1/_2 = {}^1/_4$	short

Notice that there are two ways for heterozygous progeny to be produced: a heterozygote can either receive a *T* allele from the first parent and a *t* allele from the second or receive a *t* allele from the first parent and a *T* allele from the second.

After determining the probabilities of obtaining each type of progeny, we can use the addition rule to determine the overall phenotypic ratios. Because of dominance, a tall plant can have genotype *TT*, *Tt*, or *tT*; so, using the addition rule, we find the probability of tall progeny to be $^1/_4 + {}^1/_4 + {}^1/_4 = {}^3/_4$. Because only one genotype codes for short (*tt*), the probability of short progeny is simply $^1/_4$.

Two methods have now been introduced to solve genetic crosses: the Punnett square and the probability method. At this point, you may be saying "Why bother with probability rules and calculations? The Punnett square is easier to understand and just as quick." For simple monohybrid crosses, the Punnett square is simpler and just as easy to use. However, when tackling more complex crosses concerning genes at two or more loci, the probability method is both clearer and quicker than the Punnett square.

The binomial expansion and probability When probability is used, it is important to recognize that there may be several different ways in which a set of events can occur. Consider two parents who are both heterozygous for albinism, a recessive condition in humans that causes reduced pigmentation in the skin, hair, and eyes (**FIGURE 3.8**). When two parents heterozygous for albinism mate (*Aa* × *Aa*), the probability of their having a child with albinism (*aa*) is $^1/_4$ and the probability of having a child with normal pigmentation (*AA* or *Aa*) is $^3/_4$. Suppose we want to know the probability of this couple having three children with albinism. In this case, there is only one way in which they can have three children with albinism—their first child has albinism *and* their second child has albinism *and* their third child has albinism. Here we simply apply the multiplication rule: $^1/_4 \times {}^1/_4 \times {}^1/_4 = {}^1/_{64}$.

Suppose we now ask, What is the probability of this couple having three children, one with albinism and two with normal pigmentation. This situation is more complicated. The first child might have albinism, whereas the second and third are unaffected; the probability of this sequence of events is $^1/_4 \times {}^3/_4 \times {}^3/_4 = {}^9/_{64}$. Alternatively, the

3.8 Albinism in human beings is usually inherited as a recessive trait. (Richard Dranitzke/SS/Photo Researchers.)`

first and third children might have normal pigmentation, whereas the second has albinism; the probability of this sequence is $^3/_4 \times {}^1/_4 \times {}^3/_4 = {}^9/_{64}$. Finally, the first two children might have normal pigmentation and the third albinism; the probability of this sequence is $^3/_4 \times {}^3/_4 \times {}^1/_4 = {}^9/_{64}$. Because *either* the first sequence *or* the second sequence *or* the third sequence produces one child with albinism and two with normal pigmentation, we apply the addition rule and add the probabilities: $^9/_{64} + {}^9/_{64} + {}^9/_{64} = {}^{27}/_{64}$.

If we want to know the probability of this couple having five children, two with albinism and three with normal pigmentation, figuring out the different combinations of children and their probabilities becomes more difficult. This task is made easier if we apply the binomial expansion.

The binomial takes the form $(a + b)^n$, where *a* equals the probability of one event, *b* equals the probability of the alternative event, and *n* equals the number of times the event occurs. For figuring the probability of two out of five children with albinism:

a = the probability of a child having albinism = $^1/_4$

b = the probability of a child having normal pigmentation = $^3/_4$

The binomial for this situation is $(a + b)^5$ because there are five children in the family ($n = 5$). The expansion is:

$$(a + b)^5 = a^5 + 5a^4b + 10a^3b^2 + 10a^2b^3 + 5ab^4 + b^5$$

The first term in the expansion (a^5) equals the probability of having five children all with albinism, because a is the probability of albinism. The second term ($5a^4b$) equals the probability of having four children with albinism and one with normal pigmentation, the third term ($10a^3b^2$) equals the probability of having three children with albinism and two with normal pigmentation, and so forth.

To obtain the probability of any combination of events, we insert the values of a and b; so the probability of having two out of five children with albinism is:

$$10a^2b^3 = 10(1/4)^2(3/4)^3 = 270/1024 = .26$$

We could easily figure out the probability of any desired combination of albinism and pigmentation among five children by using the other terms in the expansion.

How did we expand the binomial in this example? In general, the expansion of any binomial $(a + b)^n$ consists of a series of $n + 1$ terms. In the preceding example, $n = 5$; so there are $5 + 1 = 6$ terms: a^5, $5a^4b$, $10a^3b^2$, $10a^2b^3$, $5ab^4$, and b^5. To write out the terms, first figure out their exponents. The exponent of a in the first term always begins with the power to which the binomial is raised, or n. In our example, n equals 5, so our first term is a^5. The exponent of a decreases by one in each successive term; so the exponent of a is 4 in the second term (a^4), 3 in the third term (a^3), and so forth. The exponent of b is 0 (no b) in the first term and increases by 1 in each successive term, increasing from 0 to 5 in our example.

Next, determine the coefficient of each term. The coefficient of the first term is always 1; so in our example the first term is $1a^5$, or just a^5. The coefficient of the second term is always the same as the power to which the binomial is raised; in our example this coefficient is 5 and the term is $5a^4b$. For the coefficient of the third term, look back at the preceding term; multiply the coefficient of the preceding term (5 in our example) by the exponent of a in that term (4) and then divide by the number of that term (second term, or 2). So the coefficient of the third term in our example is $(5 \times 4)/2 = 20/2 = 10$ and the term is $10a^3b^2$. Follow this same procedure for each successive term.

Another way to determine the probability of any particular combination of events is to use the following formula:

$$P = \frac{n!}{s!t!}a^s b^t$$

where P equals the overall probability of event X with probability a occurring s times and event Y with probability b occurring t times. For our albinism example, event X would be the occurrence of a child with albinism and event Y the occurrence of a child with normal pigmentation; s would equal the number of children with albinism (2) and t, the number of children with normal pigmentation (3). The ! symbol is termed factorial, and it means the product of all the integers from n to 1. In this example, $n = 5$; so $n! = 5 \times 4 \times 3 \times 2 \times 1$. Applying this formula to obtain the probability of two out of five children having albinism, we obtain:

$$P = \frac{5!}{2!3!}(1/4)^2(3/4)^3$$

$$P = \frac{5 \times 4 \times 3 \times 2 \times 1}{2 \times 1 \times 3 \times 2 \times 1}(1/4)^2(3/4)^3 = .26$$

This value is the same as that obtained with the binomial expansion.

The Testcross

A useful tool for analyzing genetic crosses is the **testcross,** in which one individual of unknown genotype is crossed with another individual with a homozygous recessive genotype for the trait in question. Figure 3.6 illustrates a testcross (as well as a backcross). A testcross tests, or reveals, the genotype of the first individual.

Suppose you were given a tall pea plant with no information about its parents. Because tallness is a dominant trait in peas, your plant could be either homozygous (TT) or heterozygous (Tt), but you would not know which. You could determine its genotype by performing a testcross. If the plant were homozygous (TT), a testcross would produce all tall progeny ($TT \times tt \rightarrow$ all Tt); if the plant were heterozygous (Tt), the testcross would produce half tall progeny and half short progeny ($Tt \times tt \rightarrow 1/2\ Tt$ and $1/2\ tt$). When a testcross is performed, any recessive allele in the unknown genotype is expressed in the progeny, because it will be paired with a recessive allele from the homozygous recessive parent.

Concepts

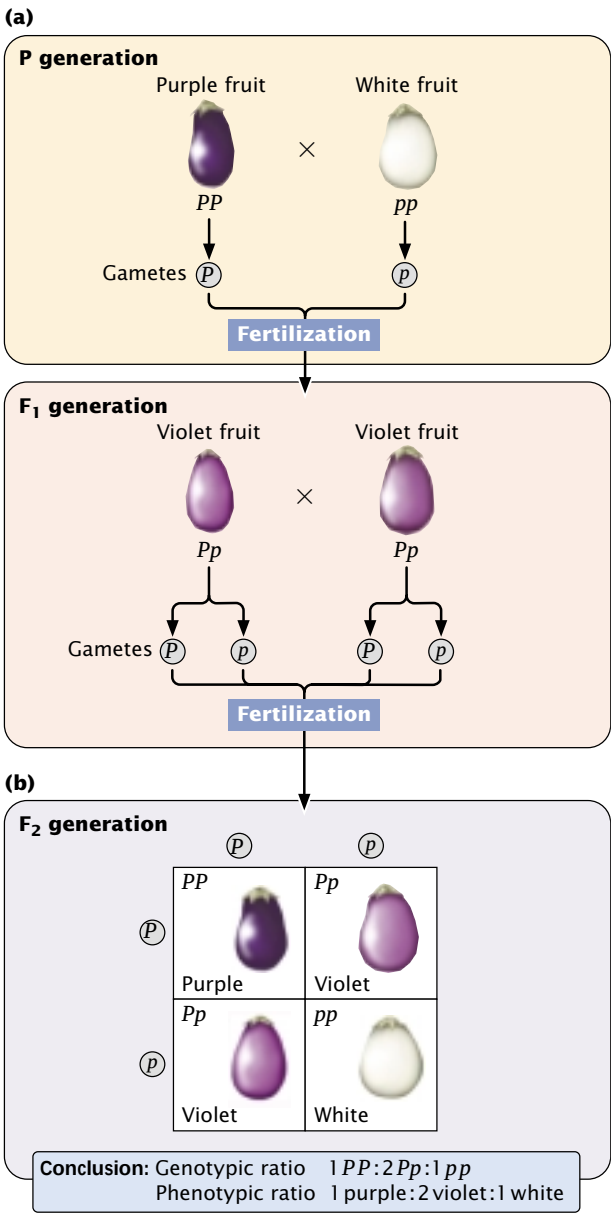
The bionomial expansion may be used to determine the probability of a particular set of of events. A testcross is a cross between an individual with an unknown genotype and one with a homozygous recessive genotype. The outcome of the testcross can reveal the unknown genotype.

Incomplete Dominance

The seven characters in pea plants that Mendel chose to study extensively all exhibited dominance, but Mendel did realize that not all characters have traits that exhibit dominance. He conducted some crosses concerning the length of time that pea plants take to flower. When he crossed two homozygous varieties that differed in their flowering time by an average of 20 days, the length of time taken by the F_1 plants to flower was intermediate between those of

the two parents. When the heterozygote has a phenotype intermediate between the phenotypes of the two homozygotes, the trait is said to display **incomplete dominance.**

Incomplete dominance is also exhibited in the fruit color of eggplants. When a homozygous plant that produces purple fruit (*PP*) is crossed with a homozygous plant that produces white fruit (*pp*), all the heterozygous F_1 (*Pp*) produce violet fruit (FIGURE 3.9a). When the F_1 are crossed with each other, $\frac{1}{4}$ of the F_2 are purple (*PP*), $\frac{1}{2}$ are violet (*Pp*), and $\frac{1}{4}$ are white (*pp*), as shown in FIGURE 3.9b. This 1:2:1 ratio is different from the 3:1 ratio that we would observe if eggplant fruit color exhibited dominance. When a trait displays incomplete dominance, the genotypic ratios and phenotypic ratios of the offspring are the *same*, because each genotype has its own phenotype. It is impossible to obtain eggplants that are pure breeding for violet fruit, because all plants with violet fruit are heterozygous.



3.9 Fruit color in eggplant is inherited as an incompletely dominant trait.

3.10 Leopard spotting in horses exhibits incomplete dominance. (Frank Oberle/Bruce Coleman.)

Another example of incomplete dominance is feather color in chickens. A cross between a homozygous black chicken and a homozygous white chicken produces F_1 chickens that are gray. If these gray F_1 are intercrossed, they produce F_2 birds in a ratio of 1 black: 2 gray: 1 white. Leopard white spotting in horses is incompletely dominant over unspotted horses: *LL* horses are white with numerous dark spots, heterozygous *Ll* horses have fewer spots, and *ll* horses have no spots (FIGURE 3.10). The concept of dominance and some of its variations are discussed further in Chapter 5.

Concepts

Incomplete dominance is exhibited when the heterozygote has a phenotype intermediate between the phenotypes of the two homozygotes. When a trait exhibits incomplete dominance, a cross between two heterozygotes produces a 1:2:1 phenotypic ratio in the progeny.

Genetic Symbols

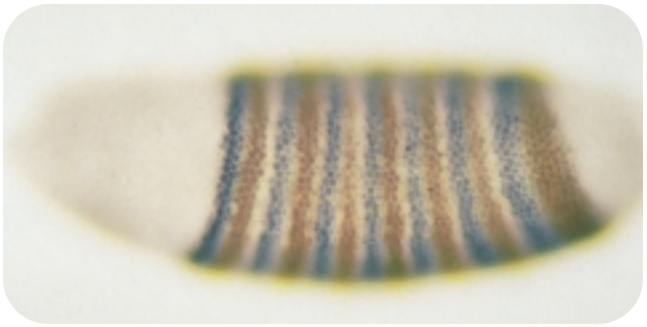
As we have seen, genetic crosses are usually depicted with the use of symbols to designate the different alleles. Lowercase letters are traditionally used to designate recessive alleles, and uppercase letters are for dominant alleles. Two or three letters may be used for a single allele: the recessive allele for heart-shaped leaves in cucumbers is designated *hl*, and the recessive allele for abnormal sperm head shape in mice is designated *azh*.

The normal allele for a character—called the **wild type** because it is the allele most often found in the wild—is of-

1.4 The biotechnology industry uses molecular genetic methods to produce substances of economic value. In the apparatus shown, growth hormone is produced by genetically engineered bacteria. (James Holmes/Celltech Ltd./Science Photo Library/Photo Researchers.)

The Role of Genetics in Biology

Although an understanding of genetics is important to all people, it is critical to the student of biology. Genetics provides one of biology's unifying principles: all organisms use nucleic acids for their genetic material and all encode their genetic information in the same way. Genetics undergirds the study of many other biological disciplines. Evolution, for example, is genetic change taking place through time; so the study of evolution requires an understanding of basic genetics. Developmental biology relies heavily on genetics: tissues and organs form through the regulated expression of genes (**Figure 1.5**). Even such fields as taxonomy, ecology, and animal behavior are making increasing use of genetic methods. The study of almost any field of biology or medicine is incomplete without a thorough understanding of genes and genetic methods.



1.5 The key to development lies in the regulation of gene expression. This early fruit-fly embryo illustrates the localized production of proteins from two genes, *ftz* (stained gray) and *eve* (stained brown), which determine the development of body segments in the adult fly. (Peter Lawrence, 1992. *The Making of a Fly,* Blackwell Scientific Publications.)

Genetic Variation Is the Foundation of Evolution

Life on Earth exists in a tremendous array of forms and features that occupy almost every conceivable environment. All life has a common origin (see Chapter 2); so this diversity has developed during Earth's 4-billion-year history. Life is also characterized by adaptation: many organisms are exquisitely suited to the environment in which they are found. The history of life is a chronicle of new forms of life emerging, old forms disappearing, and existing forms changing.

Life's diversity and adaptation are a product of evolution, which is simply genetic change through time. Evolution is a two-step process: first, genetic variants arise randomly and, then, the proportion of particular variants increases or decreases. Genetic variation is therefore the foundation of all evolutionary change and is ultimately the basis of all life as we know it. Genetics, the study of genetic variation, is critical to understanding the past, present, and future of life.

Concepts

Heredity affects many of our physical features as well as our susceptibility to many diseases and disorders. Genetics contributes to advances in agriculture, pharmaceuticals, and medicine and is fundamental to modern biology. Genetic variation is the foundation of the diversity of all life.

Divisions of Genetics

Traditionally, the study of genetics has been divided into three major subdisciplines: transmission genetics, molecular genetics, and population genetics (**Figure 1.6**). Also known as classical genetics, **transmission genetics** encompasses the basic principles of genetics and how traits are passed from one generation to the next. This area addresses the relation between chromosomes and heredity, the arrangement of genes on chromosomes, and gene mapping. Here the focus is on the individual organism—how an individual organism inherits its genetic makeup and how it passes its genes to the next generation.

Molecular genetics concerns the chemical nature of the gene itself: how genetic information is encoded, replicated, and expressed. It includes the cellular processes of replication, transcription, and translation—by which genetic information is transferred from one molecule to another—and gene

Table 3.2 Phenotypic ratios for simple genetic crosses (crosses for a single locus)

Ratio	Genotypes of Parents	Genotypes of Progeny	Type of Dominance
3:1	*Aa* × *Aa*	¾ *A*__: ¼ *aa*	Dominance
1:2:1	*Aa* × *Aa*	¼ *AA*: ½ *Aa*: ¼ *aa*	Incomplete dominance
1:1	*Aa* × *aa*	½ *Aa*: ½ *aa*	Dominance or incomplete dominance
	Aa × *AA*	½ *Aa*: ½ *AA*	Incomplete dominance
Uniform progency	*AA* × *AA*	All *AA*	Dominance or incomplete dominance
	aa × *aa*	All *aa*	Dominance or incomplete dominance
	AA × *aa*	All *Aa*	Dominance or incomplete dominance
	AA × *Aa*	All *A*__	Dominance

Note: A line in a genotype, such as *A*__, indicates that any allele is possible.

ten symbolized by one or more letters and a plus sign (+). The letter(s) chosen are usually based on the phenotype of the mutant. The first letter is lowercase if the mutant phenotype is recessive, uppercase if the mutant phenotype is dominant. For example, the recessive allele for yellow eyes in the Oriental fruit fly is represented by *ye*, whereas the allele for wild-type eye color is represented by ye^+. At times, the letters for the wild-type allele are dropped and the allele is represented simply by a plus sign. Superscripts and subscripts are sometimes added to distinguish between genes: Lfr_1 and Lfr_2 represent dominant alleles at different loci that produce lacerate leaf margins in opium poppies; El^R represents an allele in goats that restricts the length of the ears.

A slash may be used to distinguish alleles present in an individual genotype. The genotype of a goat that is heterozygous for restricted ears might be written El^+/El^R or simply $+/El^R$. If genotypes at more than one locus are presented together, a space may separate them. A goat heterozygous for a pair of alleles that produce restricted ears and heterozygous for another pair of alleles that produce goiter can be designated by El^+/El^R *G*/*g*.

Connecting Concepts

Ratios in Simple Crosses

Now that we have had some experience with genetic crosses, let's review the ratios that appear in the progeny of simple crosses, in which a single locus is under consideration. Understanding these ratios and the parental genotypes that produce them will allow you to work simple genetic crosses quickly, without resorting to the Punnett square. Later, we will use these ratios to work more complicated crosses entailing several loci.

There are only four phenotypic ratios to understand (Table 3.2). The 3:1 ratio arises in a simple genetic cross when both of the parents are heterozygous for a dominant trait (*Aa* × *Aa*). The second phenotypic ratio is the 1:2:1 ratio, which arises in the progeny of crosses between two parents heterozygous for a character that exhibits incomplete dominance (*Aa* × *Aa*). The third phenotypic ratio is the 1:1 ratio, which results from the mating of a homozygous parent and a heterozygous parent. If the character exhibits dominance, the homozygous parent in this cross must carry two recessive alleles (*Aa* × *aa*) to obtain a 1:1 ratio, because a cross between a homozygous dominant parent and a heterozygous parent (*AA* × *Aa*) produces only offspring displaying the dominant trait. For a character with incomplete dominance, a 1:1 ratio results from a cross between the heterozygote and either homozygote (*Aa* × *aa* or *Aa* × *AA*).

The fourth phenotypic ratio is not really a ratio—all the offspring have the same phenotype. Several combinations of parents can produce this outcome (Table 3.2). A cross between any two homozygous parents—either between two of the same homozygotes (*AA* × *AA* and *aa* × *aa*) or between two different homozygotes (*AA* × *aa*)—produces progeny all having the same phenotype. Progeny of a single phenotype can also result from a cross between a homozygous dominant parent and a heterozygote (*AA* × *Aa*).

If we are interested in the ratios of genotypes instead of phenotypes, there are only three outcomes to remember (Table 3.3): the 1:2:1 ratio, produced by a cross between

Table 3.3 Genotypic ratios for simple genetic crosses (crosses for a single locus)

Ratio	Genotypes of Parents	Genotypes of Progeny
1:2:1	*Aa* × *Aa*	¼ *AA*: ½ *Aa*: ¼ *aa*
1:1	*Aa* × *aa*	½ *Aa*: ½ *aa*
	Aa × *AA*	½ *Aa*: ½ *AA*
Uniform progeny	*AA* × *AA*	All *AA*
	aa × *aa*	All *aa*
	AA × *aa*	All *Aa*

two heterozygotes; the 1:1 ratio, produced by a cross between a heterozygote and a homozygote; and the uniform progeny produced by a cross between two homozygotes. These simple phenotypic and genotypic ratios and the parental genotypes that produce them provide the key to understanding crosses for a single locus and, as you will see in the next section, for multiple loci.

Multiple-Loci Crosses

We will now extend Mendel's principle of segregation to more complex crosses for alleles at multiple loci. Understanding the nature of these crosses will require an additional principle, the principle of independent assortment.

Dihybrid Crosses

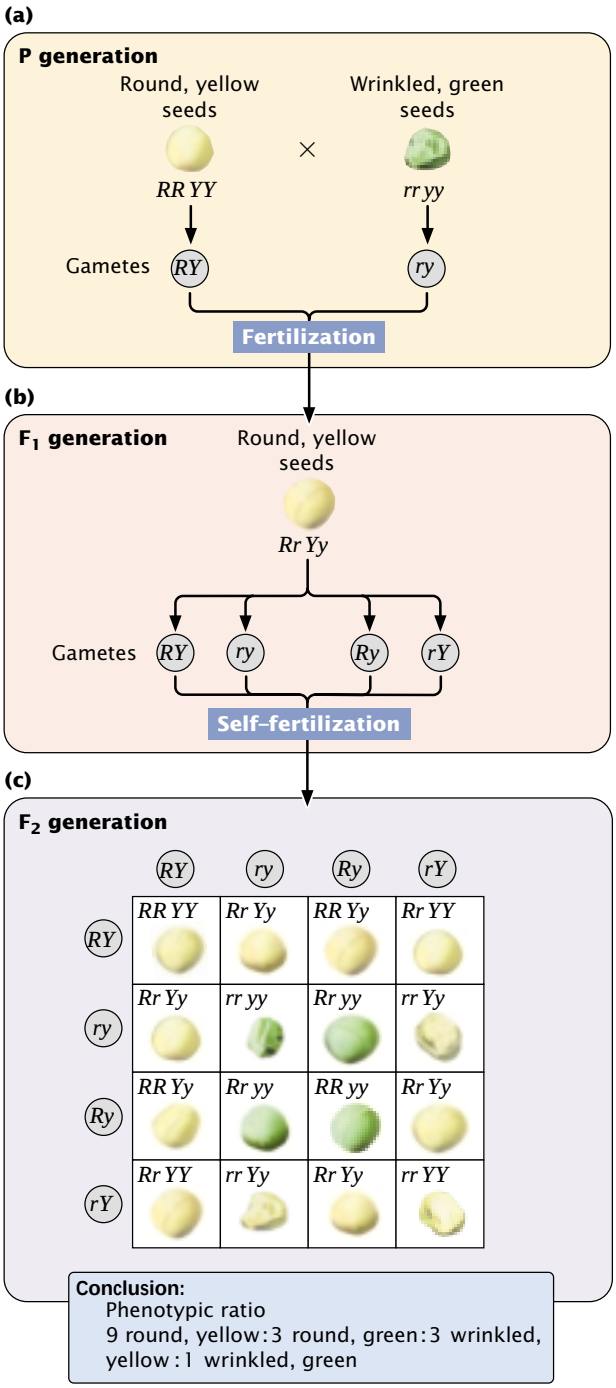
In addition to his work on monohybrid crosses, Mendel also crossed varieties of peas that differed in *two* characteristics **(dihybrid crosses).** For example, he had one homozygous variety of pea that produced round seeds and yellow endosperm; another homozygous variety produced wrinkled seeds and green endosperm. When he crossed the two, all the F_1 progeny had round seeds and yellow endosperm. He then self-fertilized the F_1 and obtained the following progeny in the F_2: 315 round, yellow seeds; 101 wrinkled, yellow seeds; 108 round, green seeds; and 32 wrinkled, green seeds. Mendel recognized that these traits appeared approximately in a 9:3:3:1 ratio; that is, $^9/_{16}$ of the progeny were round and yellow, $^3/_{16}$ were wrinkled and yellow, $^3/_{16}$ were round and green, and $^1/_{16}$ were wrinkled and green.

The Principle of Independent Assortment

Mendel carried out a number of dihybrid crosses for pairs of characteristics and always obtained a 9:3:3:1 ratio in the F_2. This ratio makes perfect sense in regard to segregation and dominance if we add a third principle, which Mendel recognized in his dihybrid crosses: the **principle of independent assortment** (Mendel's second law). This principle states that alleles at different loci separate independently of one another.

A common mistake is to think that the principle of segregation and the principle of independent assortment refer to two different processes. The principle of independent assortment is really an extension of the principle of segregation. The principle of segregation states that the two alleles of a locus separate when gametes are formed; the principle of independent assortment states that, when these two alleles separate, their separation is independent of the separation of alleles at *other* loci.

Let's see how the principle of independent assortment explains the results that Mendel obtained in his dihybrid cross. Each plant possesses two alleles coding for each characteristic, so the parental plants must have had genotypes *RRYY* and *rryy* (FIGURE 3.11a). The principle of segregation indicates that the alleles for each locus separate, and one allele for each locus passes to each gamete. The gametes produced by the round, yellow parent therefore contain alleles *RY*, whereas the gametes produced by the wrinkled, green parent contain alleles *ry*. These two types of gametes unite to produce the F_1, all with genotype *RrYy*. Because



3.11 Mendel conducted dihybrid crosses.

round is dominant over wrinkled and yellow is dominant over green, the phenotype of the F_1 will be round and yellow.

When Mendel self-fertilized the F_1 plants to produce the F_2, the alleles for each locus separated, with one allele going into each gamete. This is where the principle of independent assortment becomes important. Each pair of alleles can separate in two ways: (1) *R* separates with *Y* and *r* separates with *y* to produce gametes *RY* and *ry* or (2) *R* separates with *y* and *r* separates with *Y* to produce gametes *Ry* and *rY*. The principle of independent assortment tells us that the alleles at each locus separate independently; thus, both kinds of separation occur equally and all four type of gametes (*RY, ry, Ry,* and *rY*) are produced in equal proportions (**Figure 3.11b**). When these four types of gametes are combined to produce the F_2 generation, the progeny consist of $^9/_{16}$ round and yellow, $^3/_{16}$ wrinkled and yellow, $^3/_{16}$ round and green, and $^1/_{16}$ wrinkled and green, resulting in a 9:3:3:1 phenotypic ratio (**Figure 3.11c**).

The Relation of the Principle of Independent Assortment to Meiosis

An important qualification of the principle of independent assortment is that it applies to characters encoded by loci located on different chromosomes because, like the principle of segregation, it is based wholly on the behavior of chromosomes during meiosis. Each pair of homologous chromosomes separates independently of all other pairs in anaphase I of meiosis (see Figure 2.18); so genes located on different pairs of homologs will assort independently. Genes that happen to be located on the same chromosome will travel together during anaphase I of meiosis and will arrive at the same destination—within the same gamete (unless crossing over takes place). Genes located on the same chromosome therefore do not assort independently (unless they are located sufficiently far apart that crossing over takes place every meiotic division, as will be discussed fully in Chapter 7).

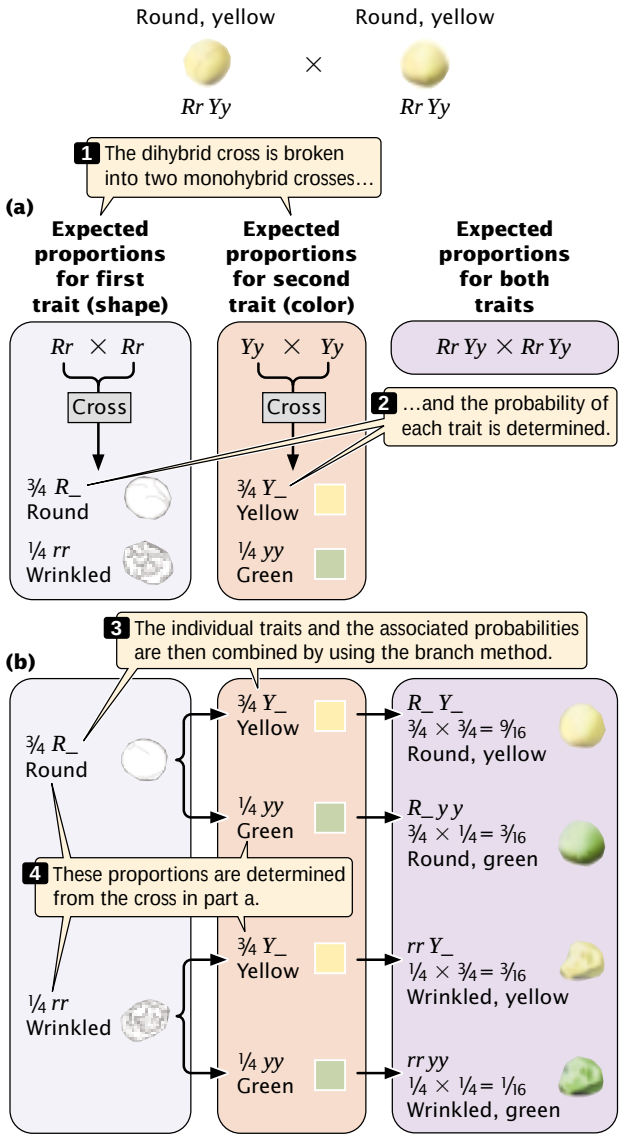
Concepts

The principle of independent assortment states that genes coding for different characteristics separate independently of one another when gametes are formed, owing to independent separation of homologous pairs of chromosomes during meiosis. Genes located close together on the same chromosome do not, however, assort independently.

Applying Probability and the Branch Diagram to Dihybrid Crosses

When the genes at two loci separate independently, a dihybrid cross can be understood as two monohybrid crosses. Let's examine Mendel's dihybrid cross (*RrYy* × *RrYy*) by considering each characteristic separately (**Figure 3.12a**). If we consider only the shape of the seeds, the cross was *Rr* × *Rr*, which yields a 3:1 phenotypic ratio ($^3/_4$ round and $^1/_4$ wrinkled progeny, see Table 3.2). Next consider the other characteristic, the color of the endosperm. The cross was *Yy* × *Yy*, which produces a 3:1 phenotypic ratio ($^3/_4$ yellow and $^1/_4$ green progeny).

We can now combine these monohybrid ratios by using the multiplication rule to obtain the proportion of progeny with different combinations of seed shape and color. The proportion of progeny with round and yellow seeds is $^3/_4$ (the probability of round) × $^3/_4$ (the probability of yellow) = $^9/_{16}$. The proportion of progeny with round and green seeds is $^3/_4 \times ^1/_4 = ^3/_{16}$; the proportion of progeny with wrinkled and yellow seeds is $^1/_4 \times ^3/_4 = ^3/_{16}$; and the



3.12 A branch diagram can be used for determining the phenotypes and expected proportions of offspring from a dihybrid cross (*RrYy* × *RrYy*).

proportion of progeny with wrinkled and green seeds is $\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$.

Branch diagrams are a convenient way of organizing all the combinations of characteristics (FIGURE 3.12b). In the first column, list the proportions of the phenotypes for one character (here, $\frac{3}{4}$ round and $\frac{1}{4}$ wrinkled). In the second column, list the proportions of the phenotypes for the second character ($\frac{3}{4}$ yellow and $\frac{1}{4}$ green) next to each of the phenotypes in the first column: put $\frac{3}{4}$ yellow and $\frac{1}{4}$ green next to the round phenotype and again next to the wrinkled phenotype. Draw lines between the phenotypes in the first column and each of the phenotypes in the second column. Now follow each branch of the diagram, multiplying the probabilities for each trait along that branch. One branch leads from round to yellow, yielding round and yellow progeny. Another branch leads from round to green, yielding round and green progeny, and so on. The probability of progeny with a particular combination of traits is calculated by using the multiplicative rule: the probability of round ($\frac{3}{4}$) and yellow ($\frac{3}{4}$) seeds is $\frac{3}{4} \times \frac{3}{4} = \frac{9}{16}$. The advantage of the branch diagram is that it helps keep track of all the potential combinations of traits that may appear in the progeny. It can be used to determine phenotypic or genotypic ratios for any number of characteristics.

Using probability is much faster than using the Punnett square for crosses that include multiple loci. Genotypic and phenotypic ratios can quickly be worked out by combining, with the multiplication rule, the simple ratios in Tables 3.2 and 3.3. The probability method is particularly efficient if we need the probability of only a *particular* phenotype or genotype among the progeny of a cross. Suppose we needed to know the probability of obtaining the genotype *Rryy* in the F_2 of the dihybrid cross in Figure 3.11. The probability of obtaining the *Rr* genotype in a cross of $Rr \times Rr$ is $\frac{1}{2}$ and that of obtaining *yy* progeny in a cross of $Yy \times Yy$ is $\frac{1}{4}$ (see Table 3.3). Using the multiplication rule, we find the probability of *Rryy* to be $\frac{1}{2} \times \frac{1}{4} = \frac{1}{8}$.

To illustrate the advantage of the probability method, consider the cross *AaBbccDdEe* × *AaBbCcddEe*. Suppose we wanted to know the probability of obtaining offspring with the genotype *aabbccddee*. If we used a Punnett square to determine this probability, we might be working on the solution for months. However, we can quickly figure the probability of obtaining this one genotype by breaking this cross into a series of single-locus crosses:

Cross	Progeny genotype	Probability
$Aa \times Aa$	*aa*	$\frac{1}{4}$
$Bb \times Bb$	*bb*	$\frac{1}{4}$
$cc \times Cc$	*cc*	$\frac{1}{2}$
$Dd \times dd$	*dd*	$\frac{1}{2}$
$Ee \times Ee$	*ee*	$\frac{1}{4}$

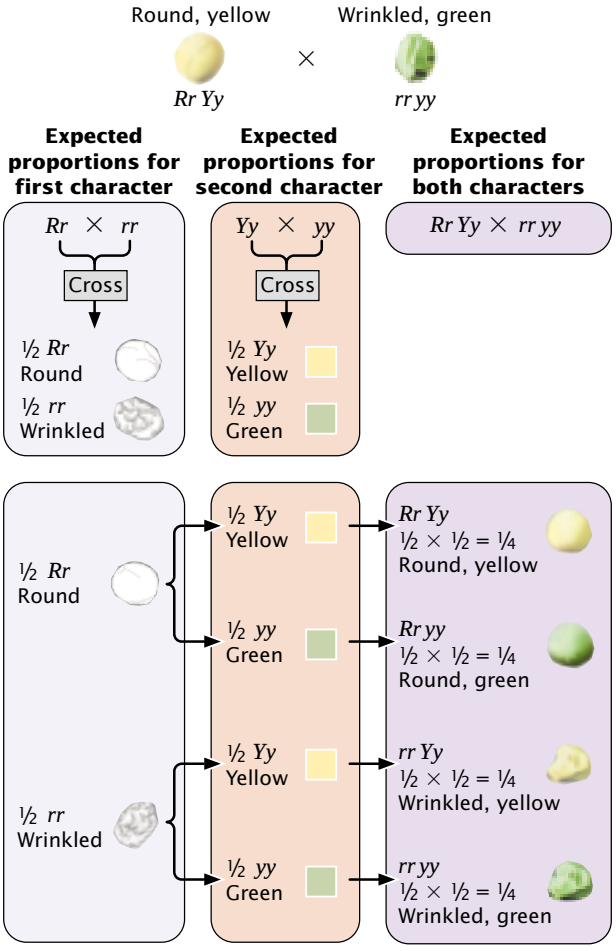
The probability of an offspring from this cross having genotype *aabbccddee* is now easily obtained by using the multiplication rule: $\frac{1}{4} \times \frac{1}{4} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{4} = \frac{1}{256}$. This calculation assumes that genes at these five loci all assort independently.

Concepts

A cross including several characteristics can be worked by breaking the cross down into single-locus crosses and using the multiplication rule to determine the proportions of combinations of characteristics (provided the genes assort independently).

The Dihybrid Testcross

Let's practice using the branch diagram by determining the types and proportions of phenotypes in a dihybrid testcross between the round and yellow F_1 plants (*Rr Yy*) that Mendel obtained in his dihybrid cross and the wrinkled and green plants (*rryy*) (FIGURE 3.13). Break the cross down into a series of single-locus crosses. The cross $Rr \times rr$ yields $\frac{1}{2}$ round (*Rr*) progeny and $\frac{1}{2}$ wrinkled (*rr*) progeny. The cross $Yy \times yy$ yields $\frac{1}{2}$ yellow (*Yy*) progeny and $\frac{1}{2}$ green (*yy*)



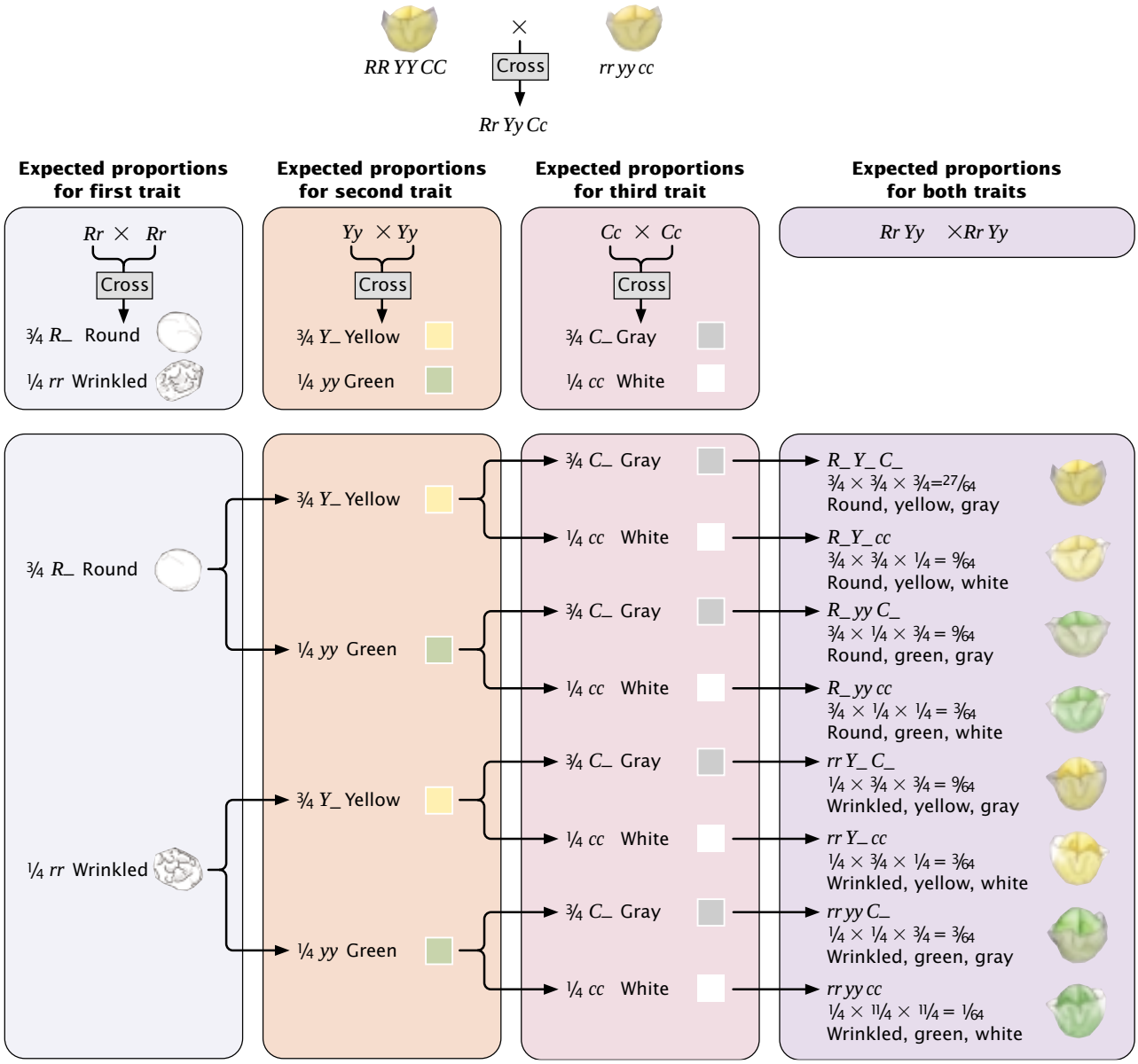
3.13 A branch diagram can be used for determining the phenotypes and expected proportions of offspring from a dihybrid testcross (*RrYy* × *rryy*).

progeny. Using the multiplication rule, we find the proportion of round and yellow progeny to be $\frac{1}{2}$ (the probability of round) $\times$ $\frac{1}{2}$ (the probability of yellow) $= \frac{1}{4}$. Four combinations of traits with the following proportions appear in the offspring: $\frac{1}{4}$ *RrYy*, round yellow; $\frac{1}{4}$ *Rryy*, round green; $\frac{1}{4}$ *rrYy*, wrinkled yellow; and $\frac{1}{4}$ *rryy*, wrinkled green.

Trihybrid Crosses

The branch diagram can also be applied to crosses including three characters (called **trihybrid crosses**). In one trihybrid cross, Mendel crossed a pure-breeding variety that possessed round seeds, yellow endosperm, and gray seed coats with another pure-breeding variety that possessed wrinkled seeds, green endosperm, and white seed coats (FIGURE 3.14). The branch diagram shows that the expected phenotypic ratio in the F_2 is 27:9:9:9:3:3:3:1, and the numbers that Mendel obtained from this cross closely fit these expected ones.

In monohybrid crosses, we have seen that three genotypes (*RR*, *Rr*, and *rr*) are produced in the F_2. In dihybrid crosses, nine genotypes (3 genotypes for the first locus $\times$ 3 genotypes for the second locus $= 9$) are produced in the F_2:



3.14 A branch diagram can be used for determining the phenotypes and expected proportions of offspring from a trihybrid cross (*RrYyCc* × *RrYyCc*).

RRYY, RRYy, RRyy, RrYY, RrYy, Rryy, rrYY, rrYy, and *rryy.* There are three possible genotypes at each locus (when there are two alternative alleles); so the number of *genotypes* produced in the F_2 of a cross between individuals heterozygous for *n* loci will be 3^n. If there is incomplete dominance, the number of *phenotypes* also will be 3^n because, with incomplete dominance, each genotype produces a different phenotype. If the traits exhibit dominance, the number of phenotypes will be 2^n.

Worked Problem

Not only are the principles of segregation and independent assortment important because they explain how heredity works, but they also provide the means for predicting the outcome of genetic crosses. This predictive power has made genetics a powerful tool in agriculture and other fields, and the ability to apply the principles of heredity is an important skill for all students of genetics. Practice with genetic problems is essential for mastering the basic principles of heredity—no amount of reading and memorization can substitute for the experience gained by deriving solutions to specific problems in genetics.

Students may have difficulty with genetics problems when they are unsure where to begin or how to organize the problem and plan a solution. In genetics, every problem is different, so there is no common series of steps that can be applied to all genetics problems. One must use logic and common sense to analyze a problem and arrive at a solution. Nevertheless, certain steps can facilitate the process, and solving the following problem will serve to illustrate these steps.

In mice, black coat color (*B*) is dominant over brown (*b*), and a solid pattern (*S*) is dominant over white spotted (*s*). Color and spotting are controlled by genes that assort independently. A homozygous black, spotted mouse is crossed with a homozygous brown, solid mouse. All the F_1 mice are black and solid. A testcross is then carried out by mating the F_1 mice with brown, spotted mice.

(a) Give the genotypes of the parents and the F_1 mice.

(b) Give the genotypes and phenotypes, along with their expected ratios, of the progeny expected from the testcross.

• Solution

Step 1: Determine the questions to be answered. What question or questions is the problem asking? Is it asking for genotypes, genotypic ratios, or phenotypic ratios? This problem asks you to provide the *genotypes* of the parents and the F_1, the *expected genotypes* and *phenotypes* of the progeny of the testcross, and their *expected proportions.*

Step 2: Write down the basic information given in the problem. This problem provides important information about the dominance relations of the characters and about the mice being crossed. Black is dominant over brown and solid is dominant over white spotted. Furthermore, the genes for the two characters assort independently. In this problem, symbols are provided for the different alleles (*B* for black, *b* for brown, *S* for solid, and *s* for spotted); had these symbols not been provided, you would need to choose symbols to represent these alleles. It is useful to record these symbols at the beginning of the solution:

B—black	*S*—solid
b—brown	*s*—white-spotted

Next, write out the crosses given in the problem.

P	homozygous black, spotted	×	homozygous brown, solid
	↓		
F_1	black, solid		
Testcross	black, solid	×	brown, spotted

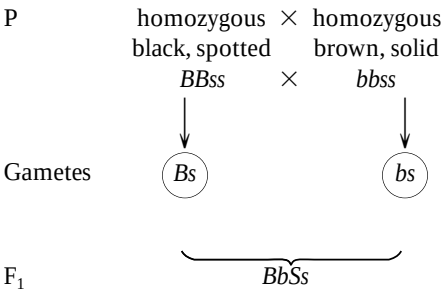
Step 3: Write down any genetic information that can be determined from the phenotypes alone. From the phenotypes and the statement that they are homozygous, you know that the P-generation mice must be *BBss* and *bbSS.* The F_1 mice are black and solid, both dominant traits, so the F_1 mice must possess at least one black allele (*B*) and one spotted allele (*S*). At this point, you cannot be certain about the other alleles, so represent the genotype of the F_1 as *B?S?*. The brown, spotted mice in the testcross must be *bbss,* because both brown and spotted are recessive traits that will be expressed only if two recessive alleles are present. Record these genotypes on the crosses that you wrote out in step 2:

P	homozygous black, spotted	×	homozygous brown, solid
	BBss	×	*bbSS*
	↓		
F_1	black, solid		
	B?S?		
Testcross	black, solid	×	brown, spotted
	B?S?	×	*bbss*

Step 4: Break down the problem into smaller parts. First, determine the genotype of the F_1. After this genotype has been determined, you can predict the results of the testcross and determine the genotypes and phenotypes of the progeny from the testcross. Second, because this cross includes two independently assorting loci, it can be conveniently broken down into two single-locus crosses: one for coat color and another for spotting.

Third, use a branch diagram to determine the proportion of progeny of the testcross with different combinations of the two traits.

Step 5: Work the different parts of problem. Start by determining the genotype of the F_1 progeny. Mendel's first law indicates that the two alleles at a locus separate, one going into each gamete. Thus, the gametes produced by the black, spotted parent contain *Bs* and the gametes produced by the brown, spotted parent contain *bS*, which combine to produce F_1 progeny with the genotype *BbSs:*



Use the F_1 genotype to work the testcross (*BbSs* × *bbss*), breaking it into two single-locus crosses. First, consider the cross for coat color: *Bb* × *bb*. Any cross between a heterozygote and a homozygous recessive genotype produces a 1:1 phenotypic ratio of progeny (see Table 3.2):

BB × *bb*

↓

½ *Bb* black

½ *bb* brown

Next do the cross for spotting: *Ss* × *ss*. This cross also is between a heterozygote and a homozygous recessive genotype and will produce ½ solid (*Ss*) and ½ spotted (*ss*) progeny (see Table 3.2).

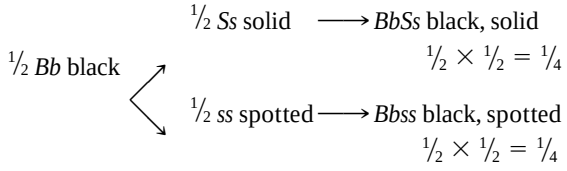
Ss × *ss*

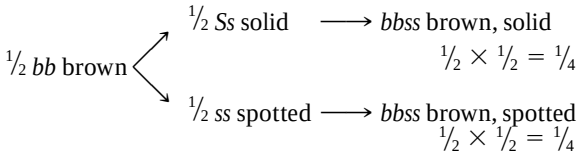
↓

½ *Ss* solid

½ *ss* spotted

Finally, determine the proportions of progeny with combinations of these characters by using the branch diagram.





Step 6: Check all work. As a last step, reread the problem, checking to see if your answers are consistent with the information provided. You have used the genotypes *BBss* and *bbSS* in the P generation. Do these genotypes code for the phenotypes given in the problem? Are the F_1 progeny phenotypes consistent with the genotypes that you assigned? The answers are consistent with the information.

Observed and Expected Ratios

When two individuals of known genotype are crossed, we expect certain ratios of genotypes and phenotypes in the progeny; these expected ratios are based on the Mendelian principles of segregation, independent assortment, and dominance. The ratios of genotypes and phenotypes *actually* observed among the progeny, however, may deviate from these expectations.

For example, in German cockroaches, brown body color (*Y*) is dominant over yellow body color (*y*). If we cross a brown, heterozygous cockroach (*Yy*) with a yellow cockroach (*yy*), we expect a 1:1 ratio of brown (*Yy*) and yellow (*yy*) progeny. Among 40 progeny, we would therefore expect to see 20 brown and 20 yellow offspring. However, the observed numbers might deviate from these expected values; we might in fact see 22 brown and 18 yellow progeny.

Chance plays a critical role in genetic crosses, just as it does in flipping a coin. When you flip a coin, you expect a 1:1 ratio—½ heads and ½ tails. If you flip a coin 1000 times, the proportion of heads and tails obtained would probably be very close to that expected 1:1 ratio. However, if you flip the coin 10 times, the ratio of heads to tails might be quite different from 1:1. You could easily get 6 heads and 4 tails, or 3 and 7 tails, just by chance. It is possible that you might even get 10 heads and 0 tails. The same thing happens in genetic crosses. We may expect 20 brown and 20 yellow cockroaches, but 22 brown and 18 yellow progeny *could* arise as a result of chance.

The Goodness-of-Fit Chi-Square Test

If you expected a 1:1 ratio of brown and yellow cockroaches but the cross produced 22 brown and 18 yellow, you probably wouldn't be too surprised even though it wasn't a perfect 1:1 ratio. In this case, it seems reasonable to assume that chance produced the deviation between the expected and the observed results. But, if you observed 25 brown and 15 yellow, would the ratio still be 1:1? Something other than chance might have caused the deviation. Perhaps the

inheritance of this character is more complicated than was assumed or perhaps some of the yellow progeny died before they were counted. Clearly, we need some means of evaluating how likely it is that chance is responsible for the deviation between the observed and the expected numbers.

To evaluate the role of chance in producing deviations between observed and expected values, a statistical test called the **goodness-of-fit chi-square test** is used. This test provides information about how well observed values fit expected values. Before we learn how to calculate the chi square, it is important to understand what this test does and does not indicate about a genetic cross.

The chi-square test cannot tell us whether a genetic cross has been correctly carried out, whether the results are correct, or whether we have chosen the correct genetic explanation for the results. What it does indicate is the *probability* that the difference between the observed and the expected values is due to chance. In other words, it indicates the likelihood that chance alone could produce the deviation between the expected and the observed values.

If we expected 20 brown and 20 yellow progeny from a genetic cross, the chi-square test gives the probability that we might observe 25 brown and 15 yellow progeny simply owing to chance deviations from the expected 20:20 ratio. When the probability calculated from the chi-square test is high, we assume that chance alone produced the difference. When the probability is low, we assume that some factor other than chance—some significant factor—produced the deviation.

To use the goodness-of-fit chi-square test, we first determine the expected results. The chi-square test must always be applied to numbers of progeny, not to proportions or percentages. Let's consider a locus for coat color in domestic cats, for which black color (*B*) is dominant over gray (*b*). If we crossed two heterozygous black cats (*Bb* × *Bb*), we would expect a 3:1 ratio of black and gray kittens. A series of such crosses yields a total of 50 kittens—30 black and 20 gray. These numbers are our *observed* values. We can obtain the *expected* numbers by multiplying the expected proportions by the total number of observed progeny. In this case, the expected number of black kittens is $\frac{3}{4} \times 50 = 37.5$ and the expected number of gray kittens is $\frac{1}{4} \times 50 = 12.5$. The chi-square ($\chi^2$) value is calculated by using the following formula:

$$\chi^2 = \Sigma \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

where Σ means the sum of all the squared differences between observed and expected divided by the expected values. To calculate the chi-square value for our black and gray kittens, we would first subtract the number of *expected* black kittens from the number of *observed* black kittens ($30 - 37.5 = -7.5$) and square this value: $-7.5^2 = 56.25$. We then divide this result by the expected number of black kittens, 56.25/37.5, $= 1.5$. We repeat the calculations on the number of expected gray kittens: $(20 - 12.5)^2/12.5 = 4.5$. To obtain the overall chi-square value, we sum the (observed − expected)^2/expected values: $1.5 + 4.5 = 6.0$.

Table 3.4 Critical values of the χ^2 distribution

					P				
df	**.995**	**.975**	**.9**	**.5**	**.1**	**.05**	**.025**	**.01**	**.005**
1	.000	.000	0.016	0.455	2.706	3.841	5.024	6.635	7.879
2	0.010	0.051	0.211	1.386	4.605	5.991	7.378	9.210	10.597
3	0.072	0.216	0.584	2.366	6.251	7.815	9.348	11.345	12.838
4	0.207	0.484	1.064	3.357	7.779	9.488	11.143	13.277	14.860
5	0.412	0.831	1.610	4.351	9.236	11.070	12.832	15.086	16.750
6	0.676	1.237	2.204	5.348	10.645	12.592	14.449	16.812	18.548
7	0.989	1.690	2.833	6.346	12.017	14.067	16.013	18.475	20.278
8	1.344	2.180	3.490	7.344	13.362	15.507	17.535	20.090	21.955
9	1.735	2.700	4.168	8.343	14.684	16.919	19.023	21.666	23.589
10	2.156	3.247	4.865	9.342	15.987	18.307	20.483	23.209	25.188
11	2.603	3.816	5.578	10.341	17.275	19.675	21.920	24.725	26.757
12	3.074	4.404	6.304	11.340	18.549	21.026	23.337	26.217	28.300
13	3.565	5.009	7.042	12.340	19.812	22.362	24.736	27.688	29.819
14	4.075	5.629	7.790	13.339	21.064	23.685	26.119	29.141	31.319
15	4.601	6.262	8.547	14.339	22.307	24.996	27.488	30.578	32.801

P, probability; df, degrees of freedom.

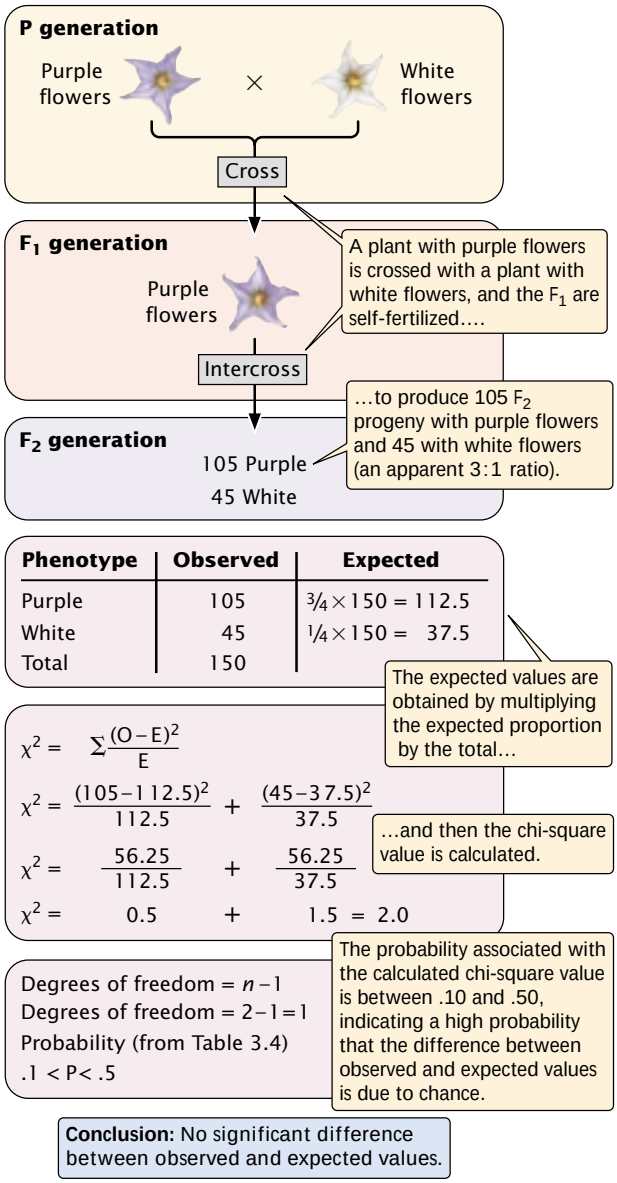
The next step is to determine the probability associated with this calculated chi-square value, which is the probability that the deviation between the observed and the expected results could be due to chance. This step requires us to compare the calculated chi-square value (6.0) with theoretical values that have the same degrees of freedom in a chi-square table. The degrees of freedom represent the number of ways in which the observed classes are free to vary. For a goodness-of-fit chi-square test, the degrees of freedom are equal to $n - 1$, where n is the number of different expected phenotypes. In our example, there are two expected phenotypes (black and gray); so $n = 2$ and the degree of freedom equals $2 - 1 = 1$.

Now that we have our calculated chi-square value and have figured out the associated degrees of freedom, we are ready to obtain the probability from a chi-square table (Table 3.4). The degrees of freedom are given in the left-hand column of the table and the probabilities are given at the top; within the body of the table are chi-square values associated with these probabilities. First, find the row for the appropriate degrees of freedom; for our example with 1 degree of freedom, it is the first row of the table. Find where our calculated chi-square value (6.0) lies among the theoretical values in this row. The theoretical chi-square values increase from left to right and the probabilities decrease from left to right. Our chi-square value of 6.0 falls between the value of 5.024, associated with a probability of .025, and the value of 6.635, associated with a probability of .01.

Thus, the probability associated with our chi-square value is less than .025 and greater than .01. So, there is less than a 2.5% probability that the deviation that we observed between the expected and the observed numbers of black and gray kittens could be due to chance.

Most scientists use the .05 probability level as their cutoff value: if the probability of chance being responsible for the deviation is greater than or equal to .05, they accept that chance may be responsible for the deviation between the observed and the expected values. When the probability is less than .05, scientists assume that chance is not responsible and a significant difference exists. The expression *significant difference* means that some factor other than chance is responsible for the observed values being different from the expected values. In regard to the kittens, perhaps one of the genotypes experienced increased mortality before the progeny were counted or perhaps other genetic factors skewed the observed ratios.

In choosing .05 as the cutoff value, scientists have agreed to assume that chance is responsible for the deviations between observed and expected values unless there is strong evidence to the contrary. It is important to bear in mind that even if we obtain a probability of, say, .01, there is still a 1% probability that the deviation between the observed and expected numbers is due to nothing more than chance. Calculation of the chi-square value is illustrated in (◖FIGURE 3.15).



◖3.15 **A chi-square test is used to determine the probability that the difference between observed and expected values is due to chance.**

Concepts

Differences between observed and expected ratios can arise by chance. The goodness-of-fit chi-square test can be used to evaluate whether deviations between observed and expected numbers are likely to be due to chance or to some other significant factor.

Penetrance and Expressivity

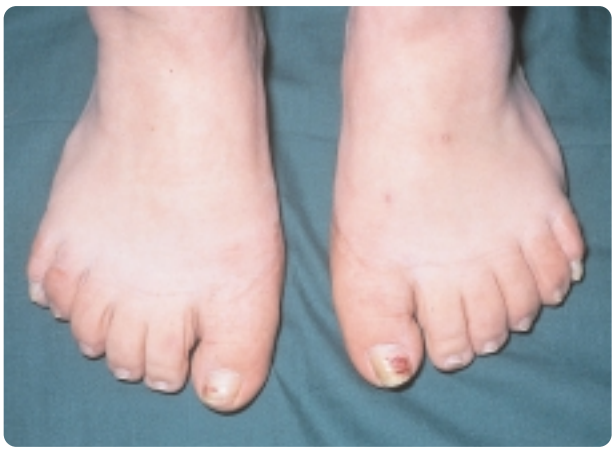
In the genetic crosses considered thus far, we have assumed that every individual with a particular genotype expresses

the expected phenotype. We assumed, for example, that the genotype *Rr* always produces round seeds and that the genotype *rr* always produces wrinkled seeds. For some characters, such an assumption is incorrect: the genotype does not always produce the expected phenotype, a phenomenon termed **incomplete penetrance.**

Incomplete penetrance is seen in human polydactyly, the condition of having extra fingers and toes (FIGURE 3.16). There are several different forms of human polydactyly, but the trait is usually caused by a dominant allele. Occasionally, people possess the allele for polydactyly (as evidenced by the fact that their children inherit the polydactyly) but nevertheless have a normal number of fingers and toes. In these cases, the gene for polydactyly is not fully penetrant. **Penetrance** is defined as the percentage of individuals having a particular genotype that express the expected phenotype. For example, if we examined 42 people having an allele for polydactyly and found that only 38 of them were polydactylous, the penetrance would be 38/42 = 0.90 (90%).

A related concept is that of **expressivity,** the degree to which a character is expressed. In addition to incomplete penetrance, polydactyly exhibits variable expressivity. Some polydactylous persons possess extra fingers and toes that are fully functional, whereas others possess only a small tag of extra skin.

Incomplete penetrance and variable expressivity are due to the effects of other genes and to environmental factors that can alter or completely suppress the effect of a particular gene. A gene might encode an enzyme that produces a particular phenotype only within a limited temperature range. At higher or lower temperatures, the enzyme would not function and the phenotype would not be expressed; the allele encoding such an enzyme is therefore penetrant only within a particular temperature range. Many characters exhibit incomplete penetrance and variable expressivity, emphasizing the fact that the mere presence of a gene does not guarantee its expression.



3.16 Human polydactyly (extra digits) exhibits incomplete penetrance and variable expressivity.
(Biophoto Associates/Science Source/Photo Researchers.)

Concepts

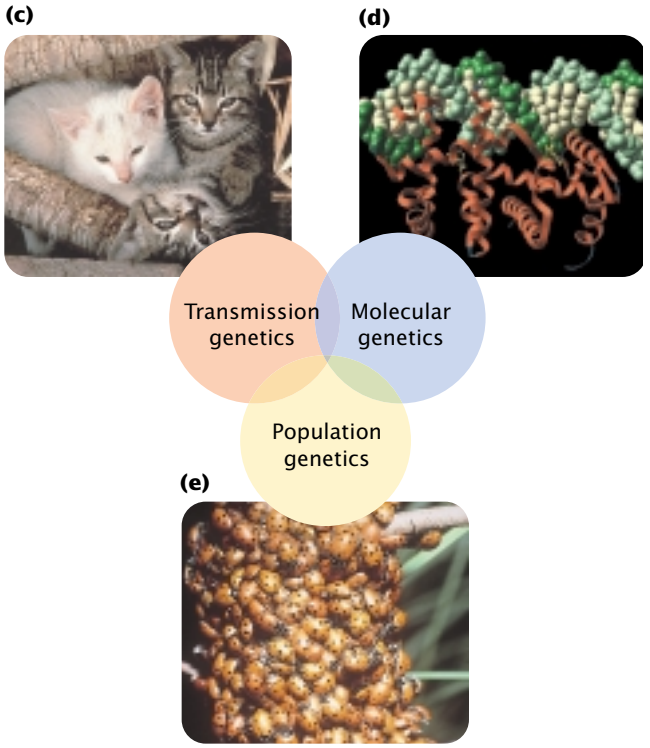
Penetrance is the percentage of individuals having a particular genotype who express the associated phenotype. Expressivity is the degree to which a trait is expressed. Incomplete penetrance and variable expressivity result from the influence of other genes and environmental factors on the phenotype.

Connecting Concepts Across Chapters

This chapter has introduced several important concepts of heredity and presented techniques for making predictions about the types of offspring that parents will produce. Two key principles of inheritance were introduced: the principles of segregation and independent assortment. These principles serve as the foundation for understanding much of heredity. In this chapter, we also learned some essential terminology and techniques for discussing and analyzing genetic crosses. A critical concept is the connection between the behavior of chromosomes during meiosis (Chapter 2) and the seemingly abstract symbols used in genetic crosses.

The principles taught in this chapter provide important links to much of what follows in this book. In Chapters 4 through 7, we will learn about additional factors that affect the outcome of genetic crosses: sex, interactions between genes, linkage between genes, and environment. These factors build on the principles of segregation and independent assortment. In Chapters 10 through 21, where we focus on molecular aspects of heredity, the importance of these basic principles is not so obvious, but most nuclear processes are based on the inheritance of chromosomal genes. In Chapters 22 and 23, we turn to quantitative and population genetics. These chapters build directly on the principles of heredity and can only be understood with a firm grasp of how genes are inherited. The material covered in the present chapter therefore serves as a foundation for almost all of heredity.

Finally, this chapter introduces problem solving, which is at the heart of genetics. Developing hypotheses to explain genetic phenomenon (such as the types and proportions of progeny produced in a genetic cross) and testing these hypotheses by doing genetic crosses and collecting additional data are common to all of genetics. The ability to think analytically and draw logical conclusions from observations are emphasized throughout this book.



1.6 Genetics can be subdivided into three interrelated fields. (Top left, Alan Carey/Photo Researchers; top right, MONA file M0214602 tif; bottom, J. Alcock/Visuals Unlimited.)

regulation—the processes that control the expression of genetic information. The focus in molecular genetics is the gene—its structure, organization, and function.

Population genetics explores the genetic composition of groups of individual members of the same species (populations) and how that composition changes over time and space. Because evolution is genetic change, population genetics is fundamentally the study of evolution. The focus of population genetics is the group of genes found in a population.

It is convenient and traditional to divide the study of genetics into these three groups, but we should recognize that the fields overlap and that each major subdivision can be further divided into a number of more specialized fields, such as chromosomal genetics, biochemical genetics, quantitative genetics, and so forth. Genetics can alternatively be subdivided by organism (fruit fly, corn, or bacterial genetics), and each of these organisms can be studied at the level of transmission, molecular, and population genetics. Modern genetics is an extremely broad field, encompassing many interrelated subdisciplines and specializations.

Concepts

The three major divisions of genetics are transmission genetics, molecular genetics, and population genetics. Transmission genetics examines the principles of heredity; molecular genetics deals with the gene and the cellular processes by which genetic information is transferred and expressed; population genetics concerns the genetic composition of groups of organisms and how that composition changes over time and space.

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A Brief History of Genetics

Although the science of genetics is young—almost entirely a product of the past 100 years—people have been using genetic principles for thousands of years.

Prehistory

The first evidence that humans understood and applied the principles of heredity is found in the domestication of plants and animals, which began between approximately 10,000 and 12,000 years ago. Early nomadic people depended on hunting and gathering for subsistence but, as human populations grew, the availability of wild food resources declined. This decline created pressure to develop new sources of food; so people began to manipulate wild plants and animals, giving rise to early agriculture and the first fixed settlements.

Initially, people simply selected and cultivated wild plants and animals that had desirable traits. Archeological evidence of the speed and direction of the domestication process demonstrates that people quickly learned a simple but crucial rule of heredity: like breeds like. By selecting and breeding individual plants or animals with desirable traits, they could produce these same traits in future generations.

The world's first agriculture is thought to have developed in the Middle East, in what is now Turkey, Iraq, Iran, Syria, Jordan, and Israel, where domesticated plants and animals were major dietary components of many populations by 10,000 years ago. The first domesticated organisms included wheat, peas, lentils, barley, dogs, goats, and sheep. Selective breeding produced woollier and more manageable goats and sheep and seeds of cereal plants that were larger and easier to harvest. By 4000 years ago, sophisticated genetic techniques were already in use in the Middle East. Assyrians and Babylonians developed several hundred varieties of date palms that differed in fruit size, color, taste, and time of ripening. An Assyrian bas-relief from 2880 years ago depicts the use of artificial fertilization to control crosses between date palms (FIGURE 1.7). Other crops and domesticated animals were developed by cultures in Asia, Africa, and the Americas in the same period.

CONCEPTS SUMMARY

- Gregor Mendel, an Austrian monk living in what is now the Czech Republic, first discovered the principles of heredity by conducting experiments on pea plants.
- Mendel's success can be attributed to his choice of the pea plant as an experimental organism, the use of characters with a few, easily distinguishable phenotypes, his experimental approach, and careful attention to detail.
- Genes are inherited factors that determine a character. Alternate forms of a gene are called alleles. The alleles are located at a specific place, a locus, on a chromosome, and the set of genes that an individual possesses is its genotype. Phenotype is the manifestation or appearance of a characteristic and may refer to physical, biochemical, or behavioral characteristics.
- Phenotypes are produced by the combined effects of genes and environmental factors. Only the genotype—not the phenotype—is inherited.
- The principle of segregation states that an individual possesses two alleles coding for a trait and that these two alleles separate in equal proportions when gametes are formed.
- The concept of dominance indicates that, when dominant and recessive alleles are present in a heterozygote, only the trait of the dominant allele is observed in the phenotype.
- The two alleles of a genotype are located on homologous chromosomes, which separate during anaphase I of meiosis. The separation of homologous chromosomes brings about the segregation of alleles.
- The types of progeny produced from a genetic cross can be predicted by applying the Punnett square or probability.
- Probability is the likelihood of a particular event occurring. The multiplication rule of probability states that the probability of two or more independent events occurring together is calculated by multiplying the probabilities of the independent events. The addition rule of probability states that the probability of any of two or more mutually exclusive events occurring is calculated by adding the probabilities of the events.
- The binomial expansion may be used to determine the probability of a particular combination of events.
- A testcross reveals the genotype (homozygote or heterozygote) of an individual having a dominant trait and consists of crossing that individual with one having the homozygous recessive genotype.
- Incomplete dominance occurs when a heterozygote has a phenotype that is intermediate between the phenotypes of the two homozygotes.
- The principle of independent assortment states that genes coding for different characters assort independently when gametes are formed.
- Independent assortment is based on the random separation of homologous pairs of chromosomes during anaphase I of meiosis; it occurs when genes coding for two characters are located on different pairs of chromosomes.
- When genes assort independently, the multiplication rule of probability can be used to obtain the probability of inheriting more than one trait: a cross including more than one trait can be broken down into simple crosses, and the probabilities of obtaining any combination of traits can be obtained by multiplying the probabilities for each trait.
- Observed ratios of progeny from a genetic cross may deviate from the expected ratios owing to chance. The goodness-of-fit chi-square test can be used to determine the probability that a difference between observed and expected numbers is due to chance.
- Penetrance is the percentage of individuals with a particular genotype that exhibit the expected phenotype. Expressivity is the degree to which a character is expressed. Incomplete penetrance and variable expressivity result from the influence of other genes and environmental effects on the phenotype.

IMPORTANT TERMS

gene (p. 47)
allele (p. 47)
locus (p. 47)
genotype (p. 48)
homozygous (p. 48)
heterozygous (p. 48)
phenotype (p. 48)
monohybrid cross (p. 48)
P (parental) generation (p. 48)
F_1 (filial 1) generation (p. 49)
reciprocal crosses (p. 49)
F_2 (filial 2) generation (p. 49)
dominant (p. 51)
recessive (p. 51)
principle of segregation (Mendel's first law) (p. 51)
concept of dominance (p. 51)
chromosome theory of heredity (p. 52)
backcross (p. 52)
Punnett square (p. 53)
probability (p. 54)
multiplication rule (p. 54)
addition rule (p. 55)
testcross (p. 57)
incomplete dominance (p. 58)
wild type (p. 58)
dihybrid cross (p. 59)
principle of independent assortment (Mendel's second law) (p. 60)
trihybrid cross (p. 63)
goodness-of-fit chi-square test (p. 66)
incomplete penetrance (p. 68)
penetrance (p. 68)
expressivity (p. 68)

Worked Problems

1. Short hair in rabbits (*S*) is dominant over long hair (*s*). The following crosses are carried out, producing the progeny shown. Give all possible genotypes of the parents in each cross.

Parents	Progeny
(a) short × short	4 short and 2 long
(b) short × short	8 short
(c) short × long	12 short
(d) short × long	3 short and 1 long
(e) long × long	2 long

• Solution

For this problem, it is useful to first gather as much information about the genotypes of the parents as possible on the basis of their phenotypes. We can then look at the types of progeny produced to provide the missing information. Notice that the problem asks for *all* possible genotypes of the parents.

(a) short × short 4 short and 2 long
Because short hair is dominant over long hair, a rabbit having short hair could be either *SS* or *Ss*. The two long-haired offspring must be homozygous (*ss*) because long hair is recessive and will appear in the phenotype only when both alleles for long hair are present. Because each parent contributes one of the two alleles found in the progeny, each parent must be carrying the *s* allele and must therefore be *Ss*.

(b) short × short 8 short
The short-haired parents could be *SS* or *Ss*. All 8 of the offspring are short (*S*_), and so at least one of the parents is likely to be homozygous (*SS*); if both parents were heterozygous, $\frac{1}{4}$ long-haired (*ss*) progeny would be expected, but we do not observe any long-haired progeny. The other parent could be homozygous (*SS*) or heterozygous (*Ss*); as long as one parent is homozygous, all the offspring will be short haired. It is theoretically possible, although unlikely, that both parents are heterozygous (*Ss* × *Ss*). If this were the case, we would expect 2 of the 8 progeny to be long haired. Although no long-haired progeny are observed, it is possible that just by chance no long-haired rabbits would be produced among the 8 progeny of the cross.

(c) short × long 12 short
The short-haired parent could be *SS* or *Ss*. The long-haired parent must be *ss*. If the short-haired parent were heterozygous (*Ss*), half of the offspring would be expected to be long haired, but we don't see any long-haired progeny. Therefore this parent is most likely homozygous (*SS*). It is theoretically possible, although unlikely, that the parent is heterozygous and just by chance no long-haired progeny were produced.

(d) short × long 3 short and 1 long
On the basis of its phenotype, the short-haired parent could be homozygous (*SS*) or heterozygous (*Ss*), but the presence of one long-haired offspring tells us that the short-haired parent must be heterozygous (*Ss*). The long-haired parent must be homozygous (*ss*).

(e) long × long 2 long
Because long hair is recessive, both parents must be homozygous for a long-hair allele (*ss*).

2. In cats, black coat color is dominant over gray. A female black cat whose mother is gray mates with a gray male. If this female has a litter of six kittens, what is the probability that three will be black and three will be gray?

• Solution

Because black (*G*) is dominant over gray (*g*), a black cat may be homozygous (*GG*) or heterozygous (*gg*). The black female in this problem must be heterozygous (*Bb*) because her mother is gray (*gg*) and she must inherit one of her mother's alleles. The gray male is homozygous (*gg*) because gray is recessive. Thus the cross is:

Gg × *gg*
black female gray male
↓
$\frac{1}{2}$ *Gg* black
$\frac{1}{2}$ *gg* gray

We can use the binomial expansion to determine the probability of obtaining three black and three gray kittens in a litter of six. Let *a* equal the probability of a kitten being black and *b* equal the probability of a kitten being gray. The binomial is $(a + b)^6$, the expansion of which is:

$$(a + b)^6 = a^6 + 6a^5b + 15a^4b^2 + 20a^3b^3 + 15a^2b^4 + 6a^1b^5 + b^6$$

(See text for an explanation of how to expand the binomial.) The probability of obtaining three black and three gray kittens in a litter of six is provided by the term $20a^3b^3$. The probabilities of *a* and *b* are both $\frac{1}{2}$, so the overall probability is $20(\frac{1}{2})^3(\frac{1}{2})^3 = \frac{20}{64} = \frac{5}{16}$.

3. The following genotypes are crossed: *AaBbCdDd* × *AaBbCcDd*. Give the proportion of the progeny of this cross having the following genotypes: **(a)** *AaBbCcDd*, **(b)** *aabbccdd*, **(c)** *AaBbccDd*.

• Solution

This problem is easily worked if the cross is broken down into simple crosses and the multiplication rule is used to find the different combinations of genotypes:

Locus 1 $Aa \times Aa = \frac{1}{4}\,AA, \frac{1}{2}\,Aa, \frac{1}{4}\,aa$
Locus 2 $Bb \times Bb = \frac{1}{4}\,BB, \frac{1}{2}\,Bb, \frac{1}{4}\,bb$

Locus 3 $Cc \times Cc = {}^1/_4\, CC, {}^1/_2\, Cc, {}^1/_4\, cc$
Locus 4 $Dd \times Dd = {}^1/_4\, DD, {}^1/_2\, Dd, {}^1/_4\, dd$

To find the probability of any combination of genotypes, simply multiply the probabilities of the different genotypes:

(a) *AaBbCcDd* ${}^1/_2\,(Aa) \times {}^1/_2\,(Bb) \times {}^1/_2\,(Cc) \times {}^1/_2\,(Dd) = {}^1/_{16}$

(b) *aabbccdd* ${}^1/_4\,(aa) \times {}^1/_4\,(bb) \times {}^1/_4\,(cc) \times {}^1/_4\,(dd) = {}^1/_{256}$

(c) *AaBbccDd* ${}^1/_2\,(Aa) \times {}^1/_2\,(Bb) \times {}^1/_4\,(cc) \times {}^1/_2\,(Dd) = {}^1/_{32}$

4. In corn, purple kernels are dominant over yellow kernels, and full kernels are dominant over shrunken kernels. A corn plant having purple and full kernels is crossed with a plant having yellow and shrunken kernels, and the following progeny are obtained:

purple, full	112
purple, shrunken	103
yellow, full	91
yellow, shrunken	94

What are the most likely genotypes of the parents and progeny? Test your genetic hypothesis with a chi-square test.

• Solution

The best way to begin this problem is by breaking the cross down into simple crosses for a single characteristic (seed color or seed shape):

P	purple × yellow	full × shrunken
F_1	112 + 103 = 215 purple	112 + 91 = 203 full
	91 + 94 = 185 yellow	103 + 94 = 197 shrunken

Purple × yellow produces approximately ${}^1/_2$ purple and ${}^1/_2$ yellow. A 1:1 ratio is usually caused by a cross between a heterozygote and a homozygote. Because purple is dominant, the purple parent must be heterozygous (*Pp*) and the yellow parent must be homozygous (*pp*). The purple progeny produced by this cross will be heterozygous (*Pp*) and the yellow progeny must be homozygous (*pp*).

Now let's examine the other character. Full × shrunken produces ${}^1/_2$ full and ${}^1/_2$ shrunken, or a 1:1 ratio, and so these progeny phenotypes also are produced by a cross between a heterozygote (*Ff*) and a homozygote (*ff*); the full-kernel progeny will be heterozygous (*Ff*) and the shrunken-kernel progeny will be homozygous (*ff*).

Now combine the two crosses and use the multiplication rule to obtain the overall genotypes and the proportions of each genotype:

P	purple, full	×	yellow, shrunken
	PpFf	×	*ppyy*
F_1	*PpFf* = ${}^1/_2$ purple	× ${}^1/_2$ full	= ${}^1/_4$ purple, full
	Ppff = ${}^1/_2$ purple	× ${}^1/_2$ shrunken	= ${}^1/_4$ purple, shrunken
	ppFf = ${}^1/_2$ yellow	× ${}^1/_2$ full	= ${}^1/_4$ yellow, full
	ppff = ${}^1/_2$ yellow	× ${}^1/_2$ shrunken	= ${}^1/_4$ yellow shrunken

Our genetic explanation predicts that, from this cross, we should see ${}^1/_4$ purple, full-kernel progeny; ${}^1/_4$ purple, shrunken-kernel progeny; ${}^1/_4$ yellow, full-kernel progeny; and ${}^1/_4$ yellow, shrunken-kernel progeny. A total of 400 progeny were produced; so ${}^1/_4 \times 400 = 100$ of each phenotype are expected. These observed numbers do not fit the expected numbers exactly. Could the difference between what we observe and what we expect be due to chance? If the probability is high that chance alone is responsible for the difference between observed and expected, we will assume that the progeny have been produced in the 1:1:1:1 ratio predicted by the cross. If the probability that the difference between observed and expected is due to chance is low, the progeny are not really in the predicted ratio and some other, *significant* factor must be responsible for the deviation.

The observed and expected numbers are:

Phenotype	Observed	Expected
purple full	112	${}^1/_4 \times 400 = 100$
purple shrunken	103	${}^1/_4 \times 400 = 100$
yellow full	91	${}^1/_4 \times 400 = 100$
yellow shrunken	94	${}^1/_4 \times 400 = 100$

To determine the probability that the difference between observed and expected is due to chance, we calculate a chi-square value with the formula $\chi^2 = \Sigma[(\text{observed} - \text{expected})^2/\text{expected}]$:

$$\chi^2 = \frac{(112-100)^2}{100} + \frac{(103-100)^2}{100} + \frac{(91-100)^2}{100} + \frac{(94-100)^2}{100}$$
$$= \frac{12^2}{100} + \frac{3^2}{100} + \frac{9^2}{100} + \frac{6^2}{100}$$
$$= \frac{144}{100} + \frac{9}{100} + \frac{81}{100} + \frac{36}{100}$$
$$= 1.44 + 0.09 + 0.81 + 0.36 = 2.70$$

Now that we have the chi-square value, we must determine the probability of this chi-square value being due to chance. To obtain this probability, we first calculate the degrees of freedom, which for a goodness-of-fit chi-square test are $n - 1$, where n equals the number of expected phenotypic classes. In this case, there are four expected phenotypic classes; so the degrees of freedom equal $4 - 1 = 3$. We must now look up the chi-square value in a chi-square table (see Table 3.4). We select the row corresponding to 3 degrees of freedom and look along this row to find our calculated chi-square value. The calculated chi-square value of 2.7 lies between 2.366 (a probability of .5) and 6.251 (a probability of .1). The probability (P) associated with the calculated chi-square value is therefore $.5 < P < .1$. This is the probability that the difference between what we observed and what we expect is due to chance, which in this case is relatively high, and so chance is likely responsible for the deviation. We can conclude that the progeny *do* appear in the 1:1:1:1 ratio predicted by our genetic explanation.

COMPREHENSION QUESTIONS

* 1. Why was Mendel's approach to the study of heredity so successful?

2. What is the relation between the terms *allele*, *locus*, *gene*, and *genotype*?

* 3. What is the principle of segregation? Why is it important?

4. What is the concept of dominance? How does dominance differ from incomplete dominance?

5. Give the phenotypic ratios that may appear among the progeny of simple crosses and the genotypes of the parents that may give rise to each ratio.

6. Give the genotypic ratios that may appear among the progeny of simple crosses and the genotypes of the parents that may give rise to each ratio.

* 7. What is the chromosome theory of inheritance? Why was it important?

8. What is the principle of independent assortment? How is it related to the principle of segregation?

9. How is the principle of independent assortment related to meiosis?

10. How is the goodness-of-fit chi-square test used to analyze genetic crosses? What does the probability associated with a chi-square value indicate about the results of a cross?

11. What is incomplete penetrance and what causes it?

APPLICATION QUESTIONS AND PROBLEMS

*12. In cucumbers, orange fruit color (*R*) is dominant over cream fruit color (*r*). A cucumber plant homozygous for orange fruits is crossed with a plant homozygous for cream fruits. The F_1 are intercrossed to produce the F_2.

(a) Give the genotypes and phenotypes of the parents, the F_1, and the F_2.

(b) Give the genotypes and phenotypes of the offspring of a backcross between the F_1 and the orange parent.

(c) Give the genotypes and phenotypes of a backcross between the F_1 and the cream parent.

*13. In rabbits, coat color is a genetically determined characteristic. Some black females always produce black progeny, whereas other black females produce black progeny and white progeny. Explain how these outcomes occur.

*14. In cats, blood type A results from an allele (I^A) that is dominant over an allele (i^B) that produces blood type B. There is no O blood type. The blood types of male and female cats that were mated and the blood types of their kittens follow. Give the most likely genotypes for the parents of each litter.

	Male parent	Female parent	Kittens
(a)	blood type A	blood type B	4 kittens with blood type A, 3 with blood type B
(b)	blood type B	blood type B	6 kittens with blood type B
(c)	blood type B	blood type A	8 kittens with blood type A
(d)	blood type A	blood type A	7 kittens with blood type A, 2 kittens with blood type B
(e)	blood type A	blood type A	10 kittens with blood type A
(f)	blood type A	blood type B	4 kittens with blood type A, 1 kitten with blood type B

15. In sheep, lustrous fleece (*L*) results from an allele that is dominant over an allele for normal fleece (*l*). A ewe (adult female) with lustrous fleece is mated with a ram (adult male) with normal fleece. The ewe then gives birth to a single lamb with normal fleece. From this single offspring, is it possible to determine the genotypes of the two parents? If so, what are their genotypes? If not, why not?

*16. In humans, alkaptonuria is a metabolic disorder in which affected persons produce black urine (see the introduction to this chapter). Alkaptonuria results from an allele (*a*) that is recessive to the allele for normal metabolism (*A*). Sally has normal metabolism, but her brother has alkaptonuria. Sally's father has alkaptonuria, and her mother has normal metabolism.

(a) Give the genotypes of Sally, her mother, her father, and her brother.

(b) If Sally's parents have another child, what is the probability that this child will have alkaptonuria?

(c) If Sally marries a man with alkaptonuria, what is the probability that their first child will have alkaptonuria?

17. Suppose that you are raising Mongolian gerbils. You notice that some of your gerbils have white spots, whereas others have solid coats. What type of crosses could you carry out to determine whether white spots are due to a recessive or a dominant allele?

*18. Hairlessness in American rat terriers is recessive to the presence of hair. Suppose that you have a rat terrier with hair. How can you determine whether this dog is homozygous or heterozygous for the hairy trait?

19. In snapdragons, red flower color (*R*) is incompletely dominant over white flower color (*r*); the heterozygotes produce pink flowers. A red snapdragon is crossed with a white snapdragon, and the F_1 are intercrossed to produce the F_2.
(a) Give the genotypes and phenotypes of the F_1 and F_2, along with their expected proportions.
(b) If the F_1 are backcrossed to the white parent, what will the genotypes and phenotypes of the offspring be?
(c) If the F_1 are backcrossed to the red parent, what are the genotypes and phenotypes of the offspring?

20. What is the probability of rolling one six-sided die and obtaining the following numbers?
(a) 2
(b) 1 or 2
(c) An even number
(d) Any number but a 6

*21. What is the probability of rolling two six-sided dice and obtaining the following numbers?
(a) 2 and 3
(b) 6 and 6
(c) At least one 6
(d) Two of the same number (two 1s, or two 2s, or two 3s, etc.)
(e) An even number on both dice
(f) An even number on at least one die

*22. In a family of seven children, what is the probability of obtaining the following numbers of boys and girls?
(a) All boys
(b) All children of the same sex
(c) Six girls and one boy
(d) Four boys and three girls
(e) Four girls and three boys

23. Phenylketonuria (PKU) is a disease that results from a recessive gene. Two normal parents produce a child with PKU.
(a) What is the probability that a sperm from the father will contain the PKU allele?
(b) What is the probability that an egg from the mother will contain the PKU allele?
(c) What is the probability that their next child will have PKU?
(d) What is the probability that their next child will be heterozygous for the PKU gene?

*24. In German cockroaches, curved wing (*cv*) is recessive to normal wing (cv^+). A homozygous cockroach having normal wings is crossed with a homozygous cockroach having curved wings. The F_1 are intercrossed to produce the F_2. Assume that the pair of chromosomes containing the locus for wing shape is metacentric. Draw this pair of chromosomes as it would appear in the parents, the F_1, and each class of F_2 progeny at metaphase I of meiosis. Assume that no crossing over takes place. At each stage, label a location for the alleles for wing shape (*cv* and cv^+) on the chromosomes.

*25. In guinea pigs, the allele for black fur (*B*) is dominant over the allele for brown (*b*) fur. A black guinea pig is crossed with a brown guinea pig, producing five F_1 black guinea pigs and six F_1 brown guinea pigs.
(a) How many copies of the black allele (*B*) will be present in *each* cell from an F_1 black guinea pig at the following stages: G_1, G_2, metaphase of mitosis, metaphase I of meiosis, metaphase II of meiosis, and after the second cytokinesis following meiosis? Assume that no crossing over takes place.
(b) How may copies of the brown allele (*b*) will be present in each cell from an F_1 brown guinea pig at the same stages? Assume that no crossing over takes place.

26. In watermelons, bitter fruit (*B*) is dominant over sweet fruit (*b*), and yellow spots (*S*) are dominant over no spots (*s*). The genes for these two characteristics assort independently. A homozygous plant that has bitter fruit and yellow spots is crossed with a homozygous plant that has sweet fruit and no spots. The F_1 are intercrossed to produce the F_2.
(a) What will be the phenotypic ratios in the F_2?
(b) If an F_1 plant is backcrossed with the bitter, yellow spotted parent, what phenotypes and proportions are expected in the offspring?
(c) If an F_1 plant is backcrossed with the sweet, nonspotted parent, what phenotypes and proportions are expected in the offspring?

27. In cats, curled ears (*Cu*) result from an allele that is dominant over an allele for normal ears (*cu*). Black color results from an independently assorting allele (*G*) that is dominant over an allele for gray (*g*). A gray cat homozygous for curled ears is mated with a homozygous black cat with normal ears. All the F_1 cats are black and have curled ears.
(a) If two of the F_1 cats mate, what phenotypes and proportions are expected in the F_2?
(b) An F_1 cat mates with a stray cat that is gray and possesses normal ears. What phenotypes and proportions of progeny are expected from this cross?

*28. The following two genotypes are crossed: *AaBbCcddEe* × *AabbCcDdEe*. What will the proportion of the following genotypes be among the progeny of this cross?
(a) *AaBbCcDdEe*
(b) *AabbCcddee*
(c) *aabbccddee*
(d) *AABBCCDDEE*

29. In mice, an allele for apricot eyes (a) is recessive to an allele for brown eyes (a^+). At an independently assorting locus, an allele for tan (t) coat color is recessive to an allele for black (t^+) coat color. A mouse that is homozygous for brown eyes and black coat color is crossed with a mouse having apricot eyes and a tan coat. The resulting F_1 are intercrossed to produce the F_2. In a litter of eight F_2 mice, what is the probability that two will have apricot eyes and tan coats?

30. In cucumbers, dull fruit (D) is dominant over glossy fruit (d), orange fruit (R) is dominant over cream fruit (r), and bitter cotyledons (B) are dominant over nonbitter cotyledons (b). The three characters are encoded by genes located on different pairs of chromosomes. A plant homozygous for dull, orange fruit and bitter cotyledons is crossed with a plant that has glossy, cream fruit and nonbitter cotyledons. The F_1 are intercrossed to produce the F_2.

    (a) Give the phenotypes and their expected proportions in the F_2.

    (b) An F_1 plant is crossed with a plant that has glossy, cream fruit and nonbitter cotyledons. Give the phenotypes and expected proportions among the progeny of this cross.

* 31. *A* and *a* are alleles located on a pair of metacentric chromosomes. *B* and *b* are alleles located on a pair of acrocentric chromosomes. A cross is made between individuals having the following genotypes: $AaBb \times aabb$.

    (a) Draw the chromosomes as they would appear in each type of gamete produced by the individuals of this cross.

    (b) For each type of progeny resulting from this cross, draw the chromosomes as they would appear in a cell at G_1, G_2, and metaphase of mitosis.

32. Ptosis (droopy eyelid) may be inherited as a dominant human trait. Among 40 people who are heterozygous for the ptosis allele, 13 have ptosis and 27 have normal eyelids.

    (a) What is the penetrance for ptosis?

    (b) If ptosis exhibited variable expressivity, what would it mean?

33. In sailfin mollies (fish), gold color is due to an allele (g) that is recessive to the allele for normal color (G). A gold fish is crossed with a normal fish. Among the offspring, 88 are normal and 82 are gold.

    (a) What are the most likely genotypes of the parents in this cross?

    (b) Assess the plausibility of your hypothesis by performing a chi-square test.

34. In guinea pigs, the allele for black coat color (B) is dominant over the allele for white coat color (b). At an independently assorting locus, an allele for rough coat (R) is dominant over an allele for smooth coat (r). A guinea pig that is homozygous for black color and rough coat is crossed with a guinea pig that has a white and smooth coat. In a series of matings, the F_1 are crossed with guinea pigs having white, smooth coats. From these matings, the following phenotypes appear in the offspring: 24 black, rough guinea pigs; 26 black, smooth guinea pigs; 23 white, rough guinea pigs; and 5 white, smooth guinea pigs.

    (a) Using a chi-square test, compare the observed numbers of progeny with those expected from the cross.

    (b) What conclusions can you draw from the results of the chi-square test?

    (c) Suggest an explanation for these results.

CHALLENGE QUESTIONS

35. Dwarfism is a recessive trait in Hereford cattle. A rancher in western Texas discovers that several of the calves in his herd are dwarfs, and he wants to eliminate this undesirable trait from the herd as rapidly as possible. Suppose that the rancher hires you as a genetic consultant to advise him on how to breed the dwarfism trait out of the herd. What crosses would you advise the rancher to conduct to ensure that the allele causing dwarfism is eliminated from the herd?

36. A geneticist discovers an obese mouse in his laboratory colony. He breeds this obese mouse with a normal mouse. All the F_1 mice from this cross are normal in size. When he interbreeds two F_1 mice, eight of the F_2 mice are normal in size and two are obese. The geneticist then intercrosses two of his obese mice, and he finds that all of the progeny from this cross are obese. These results lead the geneticist to conclude that obesity in mice results from a recessive allele.

    A second geneticist at a different university also discovers an obese mouse in her laboratory colony. She carries out the same crosses as the first geneticist did and obtains the same results. She also concludes that obesity in mice results from a recessive allele. One day the two geneticists meet at a genetics conference, learn of each other's experiments, and decide to exchange mice. They both find that, when they cross two obese mice from the different laboratories, all the offspring are normal; however, when they cross two obese mice from the same laboratory, all the offspring are obese. Explain their results.

37. Albinism is a recessive trait in humans. A geneticist studies a series of families in which both parents are normal and at least one child has albinism. The geneticist reasons that both parents in these families must be heterozygotes and that albinism should appear in $\frac{1}{4}$ of the children of these families. To his surprise, the geneticist finds that the

frequency of albinism among the children of these families is considerably greater than 1/4. There is no evidence that normal pigmentation exhibits incomplete penetrance. Can you think of an explanation for the higher-than-expected frequency of albinism among these families?

38. Two distinct phenotypes are found in the salamander *Plethodon cinereus*: a red form and a black form. Some biologists have speculated that the red phenotype is due to an autosomal allele that is dominant over an allele for black. Unfortunately, these salamanders will not mate in captivity; so the hypothesis that red is dominant over black has never been tested.

One day a genetics student is hiking through the forest and finds 30 female salamanders, some red and some black, laying eggs. The student places each female and her eggs (about 20–30 eggs per female) in separate plastic bags and takes them back to the lab. There, the student successfully raises the eggs until they hatch. After the eggs have hatched, the student records the phenotypes of the juvenile salamanders, along with the phenotypes of their mothers. Thus, the student has the phenotypes for 30 females and their progeny, but no information is available about the phenotypes of the fathers.

Explain how the student can determine whether red is dominant over black with this information on the phenotypes of the females and their offspring.

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A fascinating account that contains much recent research on Mendel's life as a scientist.

4 Sex Determination and Sex-Linked Characteristics

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- The Toothless, Hairless Men of Sind
- Sex Determination
  - Chromosomal Sex-Determining Systems
  - Genic Sex-Determining Systems
  - Environmental Sex Determination
  - Sex Determination in *Drosophila*
  - Sex Determination in Humans
- Sex-Linked Characteristics
  - X-linked White Eyes in *Drosophila*
  - Nondisjunction and the Chromosome Theory of Inheritance
  - X-linked Color Blindness in Humans
  - Symbols for X-linked Genes
  - Dosage Compensation
  - Z-linked Characteristics
  - Y-linked Characteristics

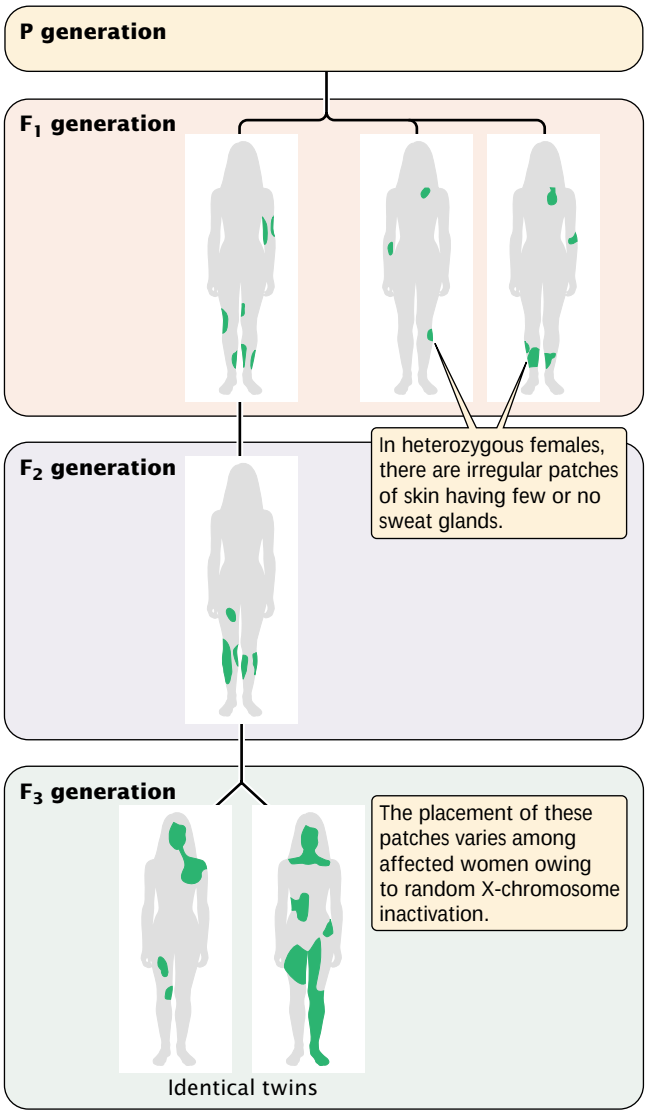
The Toothless, Hairless Men of Sind

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

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

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

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



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

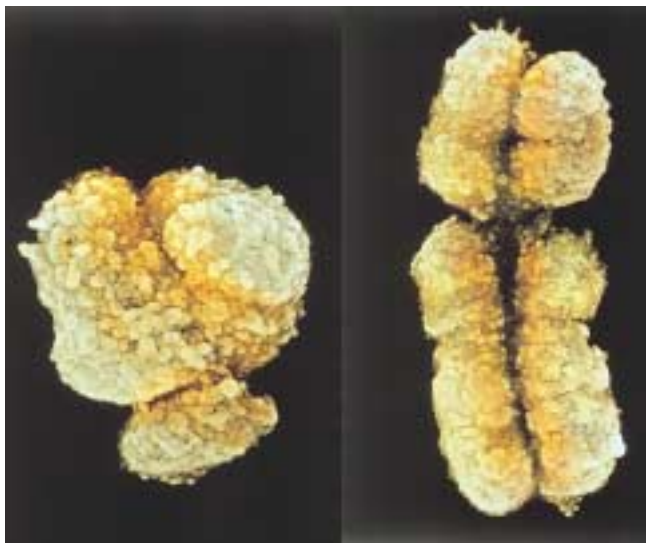
glands; the placement of these patches varies among affected women (FIGURE 4.1). The patchy occurrence of these features is explained by the fact that the gene for anhidrotic ectodermal dysplasia is located on a sex chromosome.

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

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

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

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



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

Sex Determination

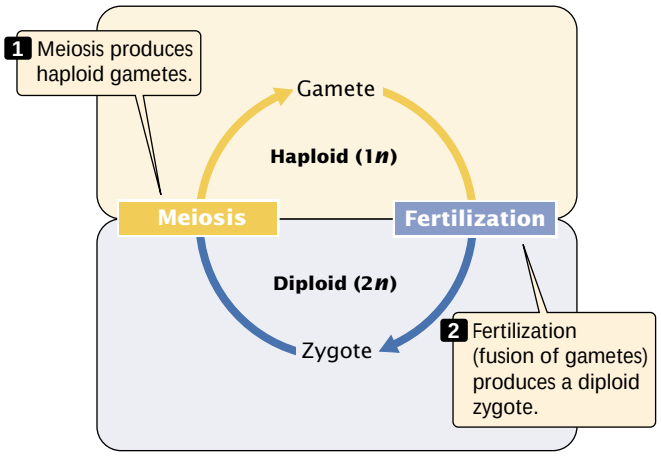
Sexual reproduction is the formation of offspring that are genetically distinct from their parents; most often, two parents contribute genes to their offspring. Among most eukaryotes, sexual reproduction consists of two processes that lead to an alternation of haploid and diploid cells: meiosis produces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

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

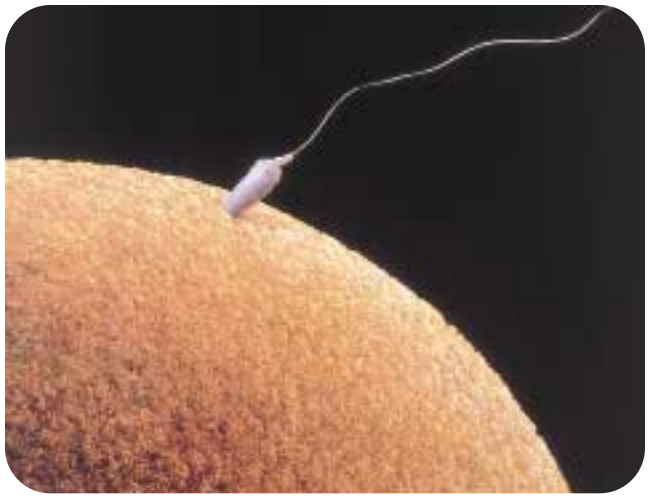
The mechanism by which sex is established is termed **sex determination.** We define the sex of an individual in terms of the individual's phenotype—ultimately, the type of gametes that it produces. Sometimes an individual has chromosomes or genes that are normally associated with one sex but a morphology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

Concepts

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



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



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

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

Chromosomal Sex-Determining Systems

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

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

1.7 Ancient peoples practiced genetic techniques in agriculture. (Top) Comparison of ancient (left) and modern (right) wheat. (Bottom) Assyrian bas-relief sculpture showing artificial pollination of date palms at the time of King Assurnasirpalli II, who reigned from 883–859 B.C. (Top left and right, IRRI; bottom, Metropolitan Museum of Art, gift of John D. Rockefeller Jr., 1932.

Concepts

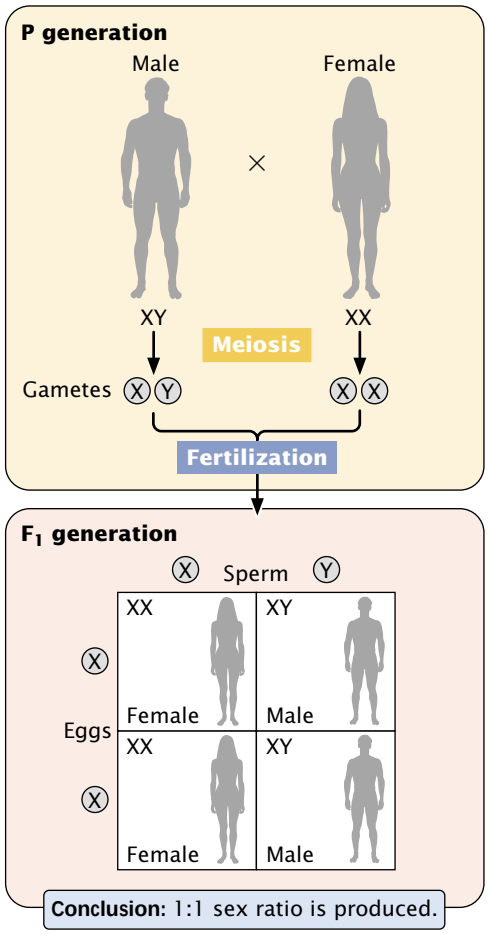
Humans first applied genetics to the domestication of plants and animals between approximately 10,000 and 12,000 years ago. This domestication led to the development of agriculture and fixed human settlements.

Early Written Records

Ancient writings demonstrate that early humans were aware of their own heredity. Hindu sacred writings dating to 2000 years ago attribute many traits to the father and suggest that differences between siblings can be accounted for by effects from the mother. These same writings advise that one should avoid potential spouses having undesirable traits that might be passed on to one's children. The Talmud, the Jewish book of religious laws based on oral traditions dating back thousands of years, presents an uncannily accurate understanding of the inheritance of hemophilia. It directs that, if a woman bears two sons who die of bleeding after circumcision, any additional sons that she bears should not be circumcised; nor should the sons of her sisters be circumcised, although the sons of her brothers should. This advice accurately depicts the X-linked pattern of inheritance of hemophilia (discussed further in Chapter 6).

The ancient Greeks gave careful consideration to human reproduction and heredity. The Greek physician Alcmaeon (circa 520 B.C.) conducted dissections of animals and proposed that the brain was not only the principle site of perception, but also the origin of semen. This proposal sparked a long philosophical debate about where semen was produced and its role in heredity. The debate culminated in the concept of **pangenesis,** which proposed that specific particles, later called gemmules, carry information from various parts of the body to the reproductive organs, from where they are passed to the embryo at the moment of conception **(Figure 1.8a)**. Although incorrect, the concept of pangenesis was highly influential and persisted until the late 1800s.

Pangenesis led the ancient Greeks to propose the notion of the **inheritance of acquired characteristics,** in which traits acquired during one's lifetime become incorporated into one's hereditary information and are passed on to



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

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

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

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

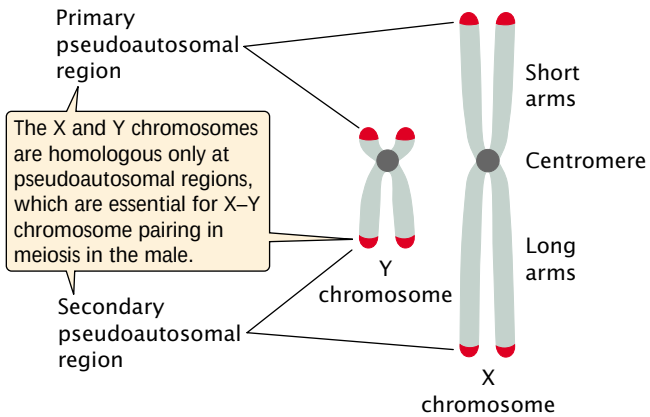
XX-XO sex determination

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

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

XX-XY sex determination

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



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

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

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

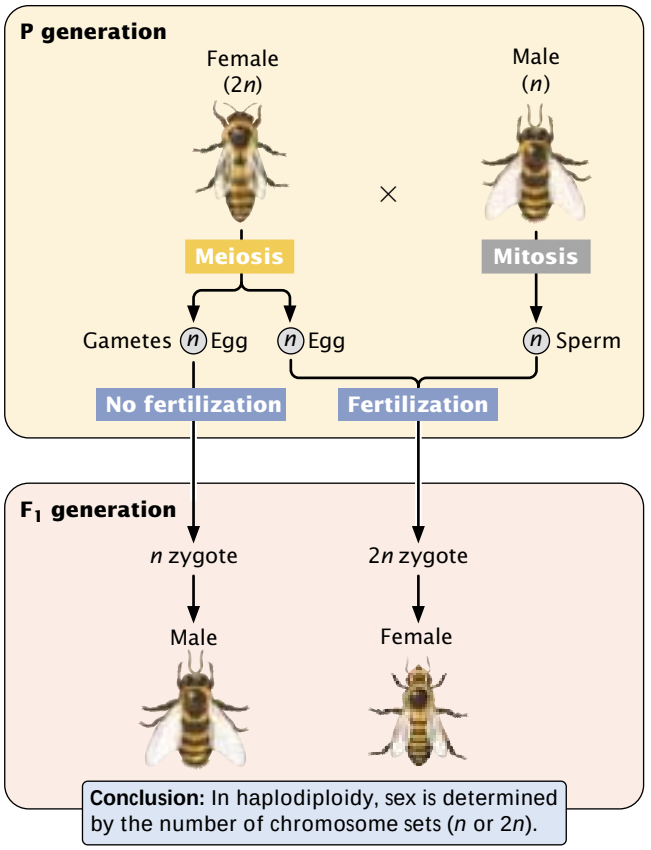
ZZ-ZW sex determination In this system, the female is heterogametic and the male is homogametic. To prevent confusion with the XX-XY system, the sex chromosomes in this system are labeled Z and W, but the chromosomes do not resemble Zs and Ws. Females in this system are ZW; after meiosis, half of the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

Concepts

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

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

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



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

Concepts

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

Genic Sex-Determining Systems

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

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

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

Environmental Sex Determination

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

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

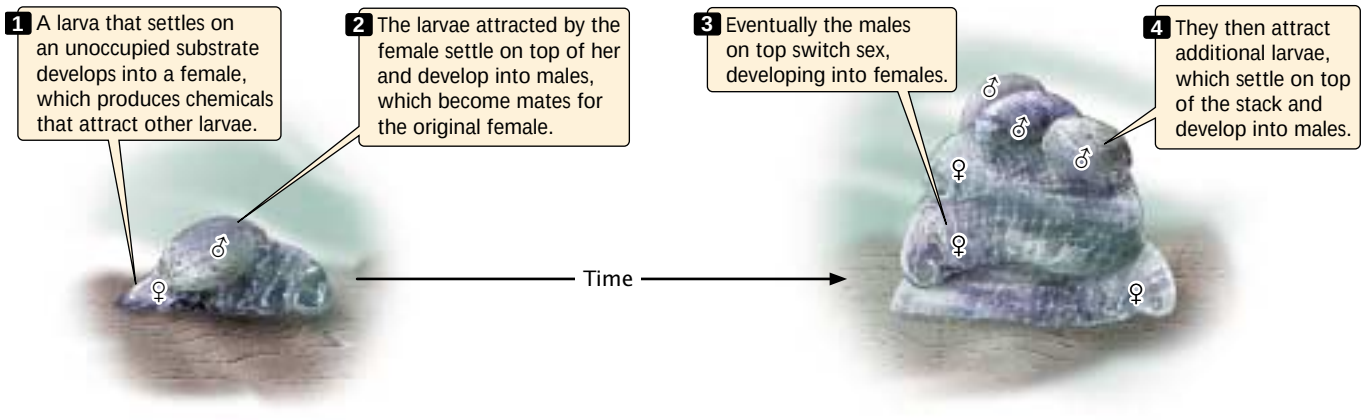
Environmental factors are also important in determining sex in many reptiles. Although most snakes and lizards have sex chromosomes, in many turtles, crocodiles, and alligators, temperature during embryonic development determines sexual phenotype. In turtles, for example, warm temperatures produce females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

Concepts

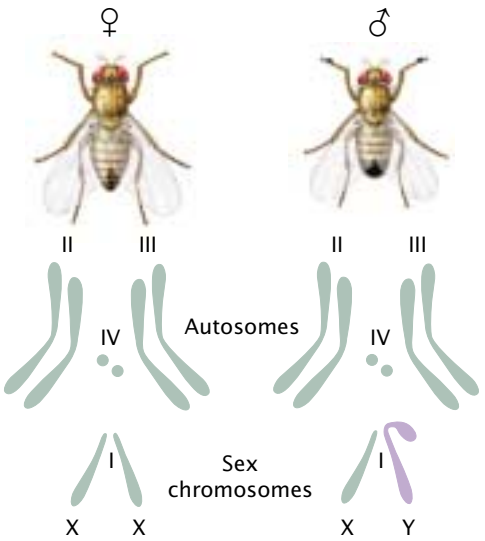
In genic sex determination, sex is determined by genes at one or more loci, but there are no obvious differences in the chromosomes of males and females. In environmental sex determination, sex is determined fully or in part by environmental factors.

Sex Determination in *Drosophila*

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



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



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

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

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

Concepts

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

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

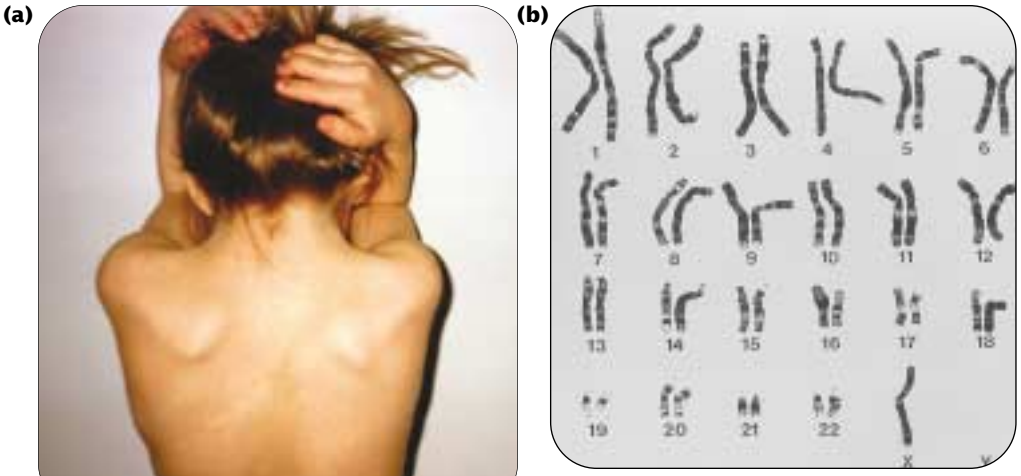
Sex Determination in Humans

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

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

Table 4.1 Chromosome complements and sexual phenotypes in *Drosophila*

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



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

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

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

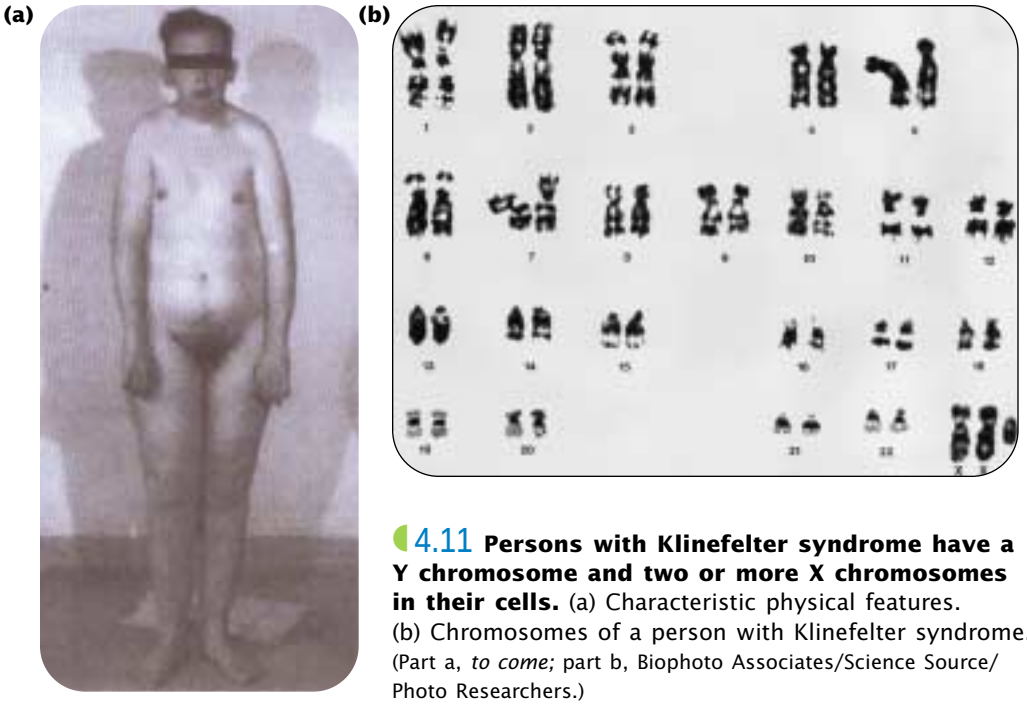
Klinefelter syndrome Persons who have **Klinefelter syndrome,** which occurs with a frequency of about 1 in 1000 male births, have cells with one or more Y chromosomes and multiple X chromosomes. The cells of most males having this condition are XXY, but cells of a few Klinefelter males are XXXY, XXXXY,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

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

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

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

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



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

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

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

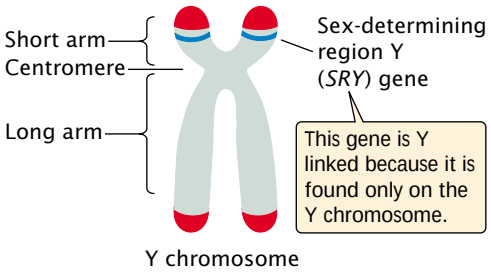
In 1987, David Page and his colleagues at the Massachusetts Institute of Technology located what appeared to be the male-determining gene near the tip of the short arm of the Y chromosome. They had examined the DNA of several XX males and XY females. The cells of one XX male that they studied possessed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

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

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

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

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



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

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

Concepts

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

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

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

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

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

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

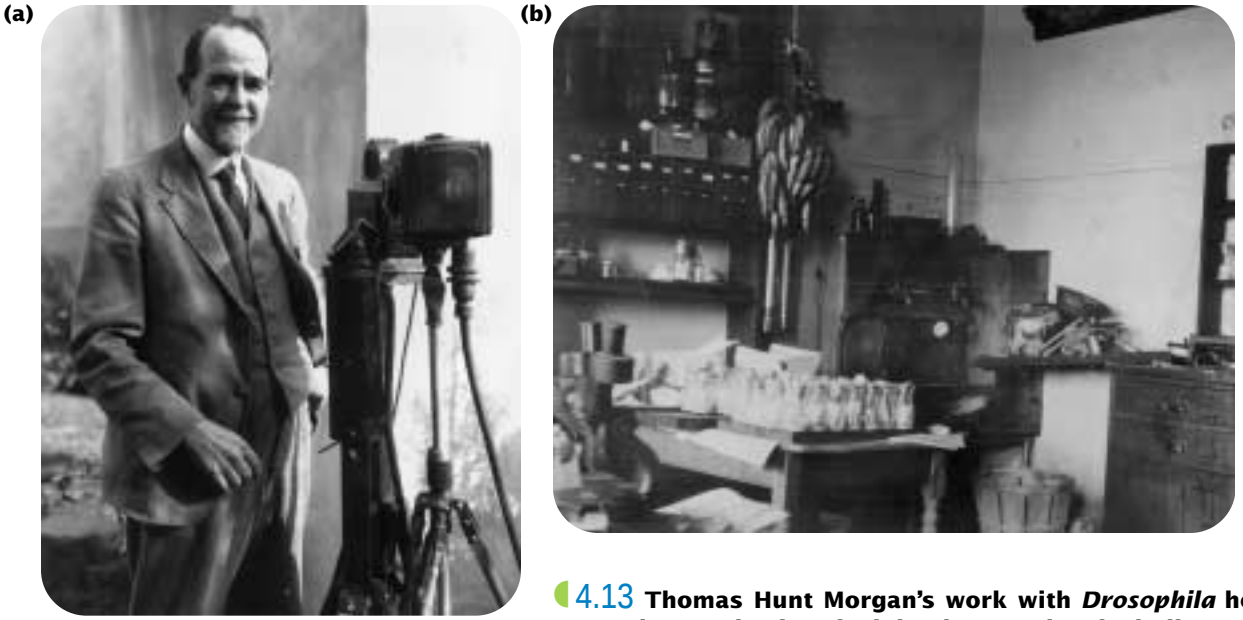
Sex-Linked Characteristics

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

X-Linked White Eyes in *Drosophila*

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

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



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

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

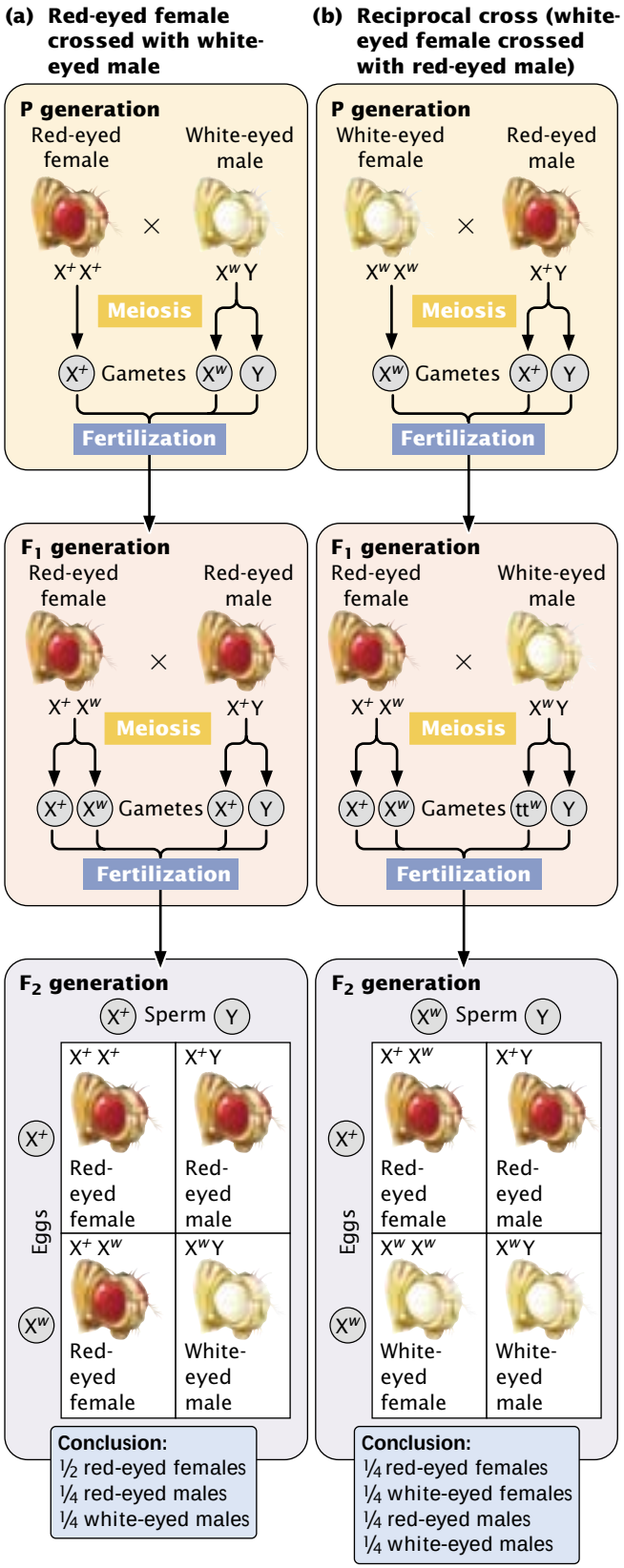
In spite of its physical limitations, the Fly Room was the source of some of the most important research in the history of biology. There was daily excitement among the students, some of whom initially came to the laboratory as undergraduates. The close quarters facilitated informality and the free flow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

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

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

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

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



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

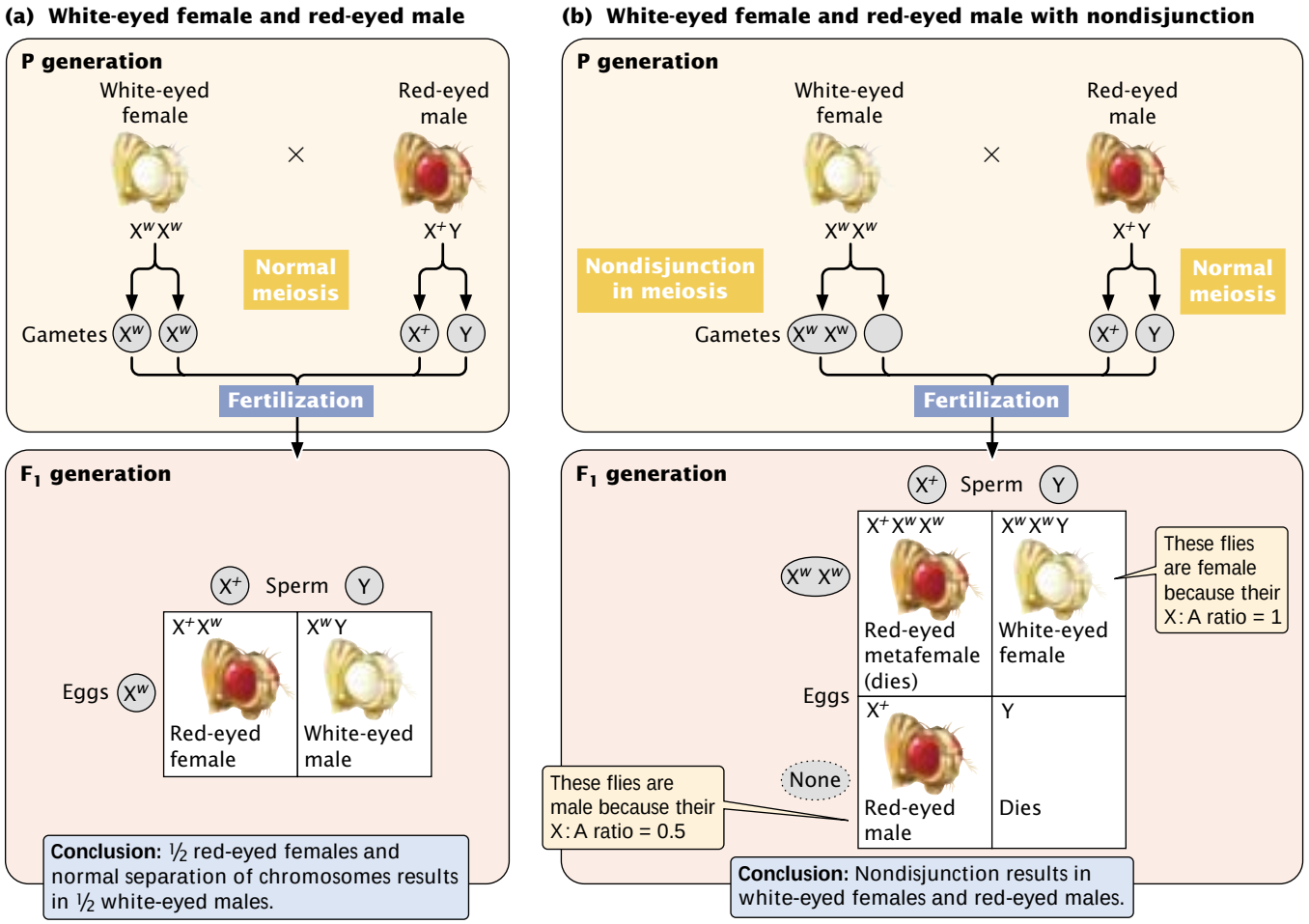
Nondisjunction and the Chromosome Theory of Inheritance

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

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

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

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



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

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

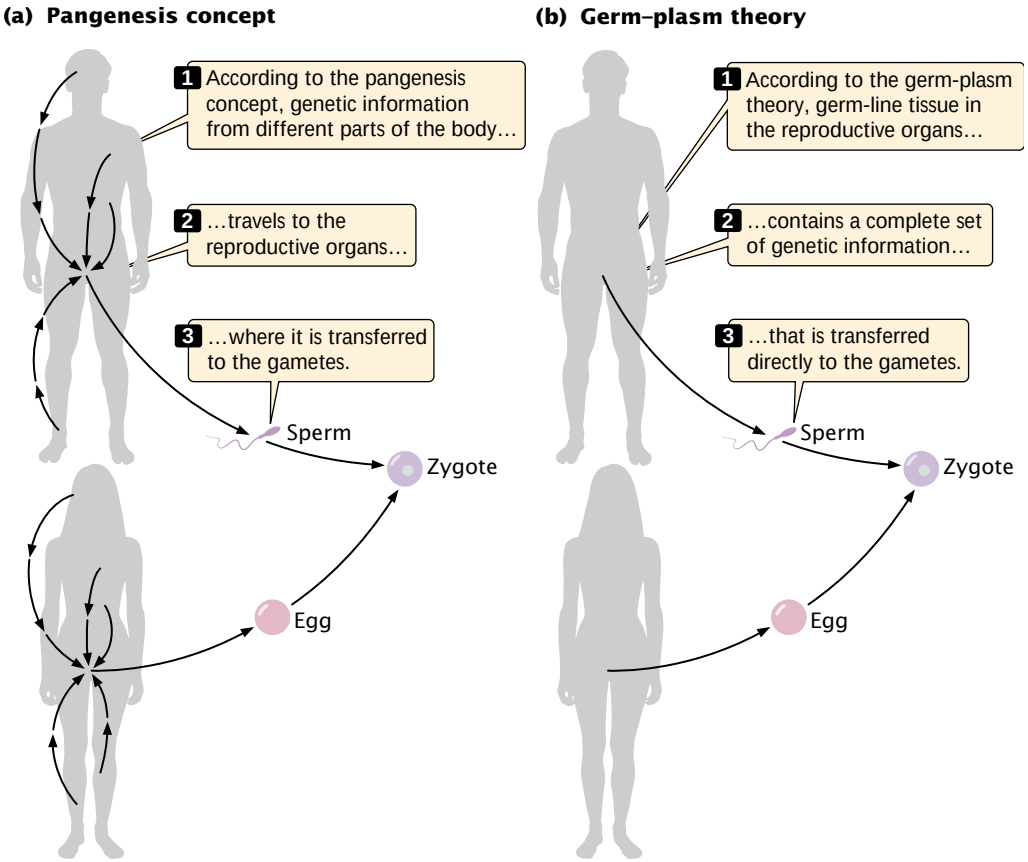
Concepts

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

X-Linked Color Blindness in Humans

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

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



1.8 Pangenesis, an early concept of inheritance, compared with the modern germ-plasm theory.

offspring; for example, people who developed musical ability through diligent study would produce children who are innately endowed with musical ability. The notion of the inheritance of acquired characteristics also is no longer accepted, but it remained popular through the twentieth century.

The Greek philosopher Aristotle (384–322 B.C.) was keenly interested in heredity. He rejected the concepts of both pangenesis and the inheritance of acquired characteristics, pointing out that people sometimes resemble past ancestors more than their parents and that acquired characteristics such as mutilated body parts are not passed on. Aristotle believed that both males and females made contributions to the offspring and that there was a struggle of sorts between male and female contributions.

Although the ancient Romans contributed little to the understanding of human heredity, they successfully developed a number of techniques for animal and plant breeding; the techniques were based on trial and error rather than any general concept of heredity. Little new was added to the understanding of genetics in the next 1000 years. The ancient ideas of pangenesis and the inheritance of acquired characteristics, along with techniques of plant and animal breeding, persisted until the rise of modern science in the seventeenth and eighteenth centuries.

The Rise of Modern Genetics

Dutch spectacle makers began to put together simple microscopes in the late 1500s, enabling Robert Hooke (1653–1703) to discover cells in 1665. Microscopes provided naturalists with new and exciting vistas on life, and perhaps it was excessive enthusiasm for this new world of the very small that gave rise to the idea of **preformationism.** According to preformationism, inside the egg or sperm existed a tiny miniature adult, a *homunculus*, which simply enlarged during development. Ovists argued that the homunculus resided in the egg, whereas spermists insisted that it was in the sperm (◖ FIGURE 1.9). Preformationism meant that all traits would be inherited from only one parent—from the father if the homunculus was in the sperm or from the mother if it was in the egg. Although many observations suggested that offspring possess a mixture of traits from both parents, preformationism remained a popular concept throughout much of the seventeenth and eighteenth centuries.

Another early notion of heredity was **blending inheritance,** which proposed that offspring are a blend, or mixture,

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

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

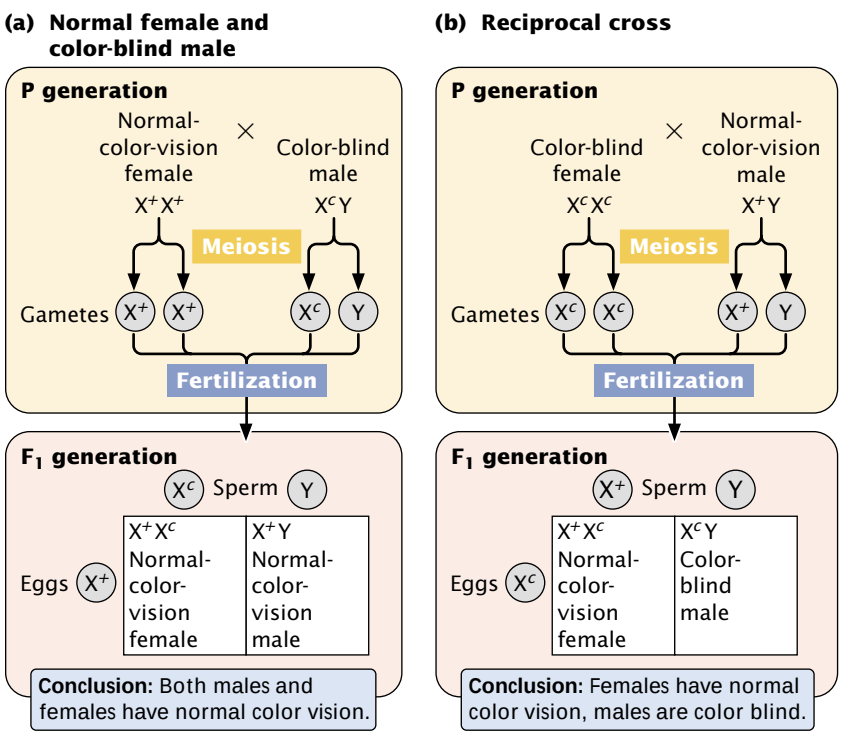
If a color-blind man mates with a woman homozygous for normal color vision (**Figure 4.16a**), all of the gametes produced by the woman will contain an allele for normal color vision. Half of the man's gametes will receive the X chromosome with the color-blind allele, and the other half will receive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

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

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

Concepts

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



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

Symbols for X-Linked Genes

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

Dosage Compensation

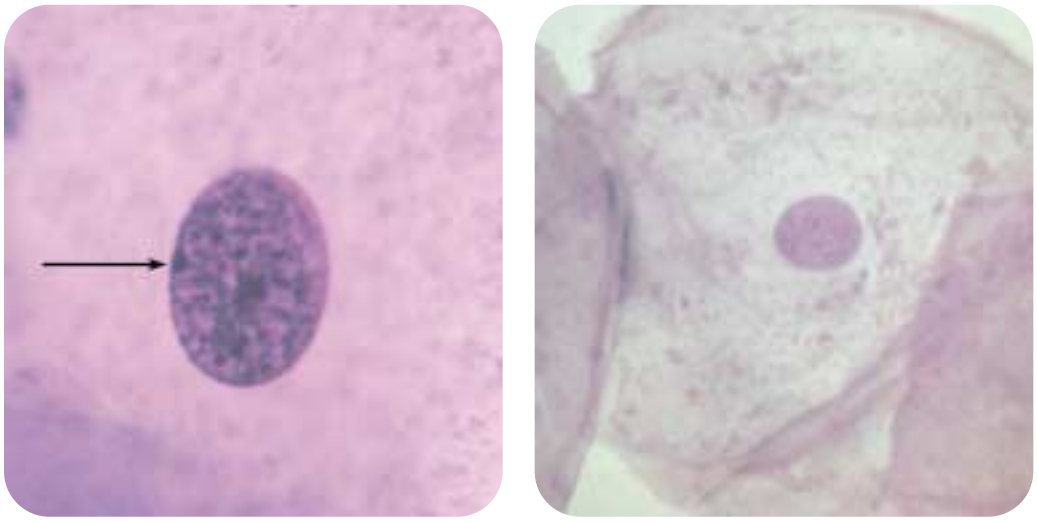
The presence of different numbers of X chromosomes in males and females presents a special problem in development. Because females have two copies of every X-linked gene and males possess one copy, the amount of gene product (protein) from X-linked genes would normally differ in the two sexes—females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

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

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

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

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



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

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

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

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

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

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

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

Concepts

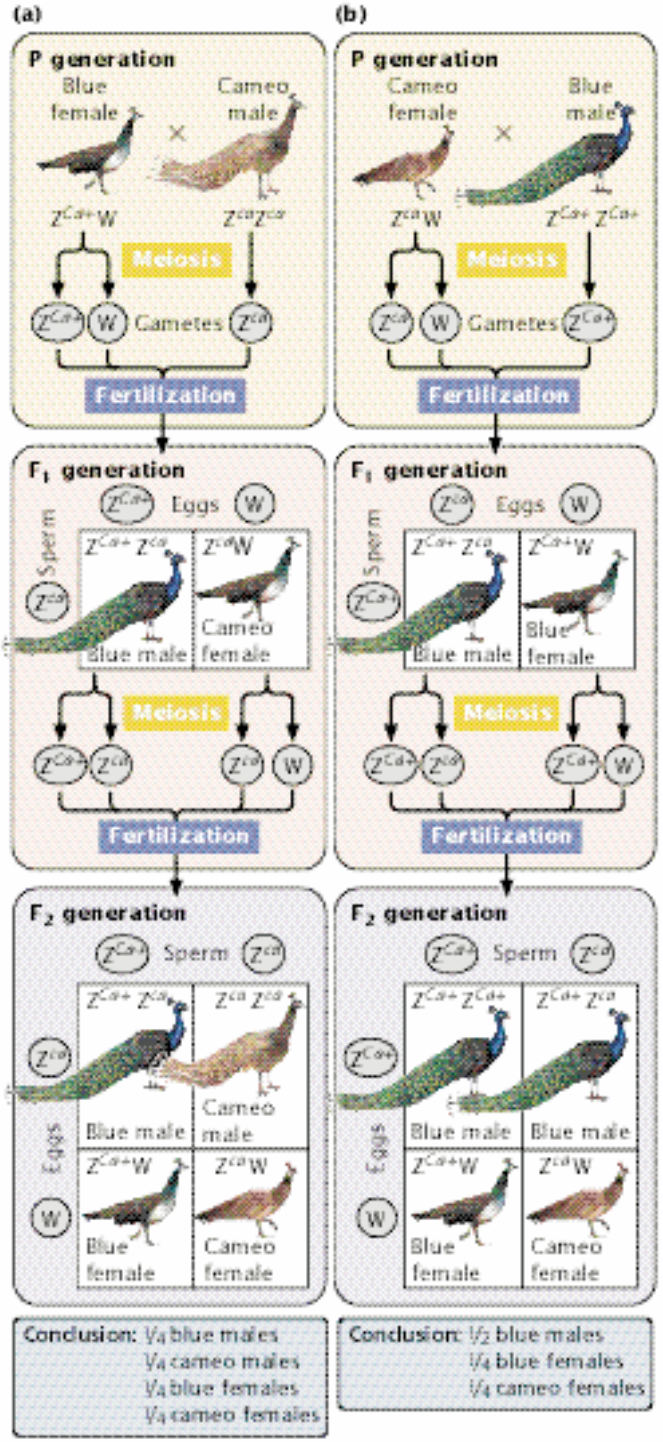
In mammals, dosage compensation ensures that the same amount of X-linked gene product will be produced in the cells of both males and females. All but one X chromosome is randomly inactivated in each cell; which X chromosome is inactivated is random and varies from cell to cell.

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

Z-Linked Characteristics

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

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



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

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

Y-Linked Characteristics

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

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

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

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

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

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

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

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

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

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

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

Concepts

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

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

Connecting Concepts

Recognizing Sex-linked Inheritance

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

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

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

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

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

Connecting Concepts Across Chapters

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

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

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

CONCEPTS SUMMARY

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

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

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

IMPORTANT TERMS

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

Worked Problems

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

• Solution

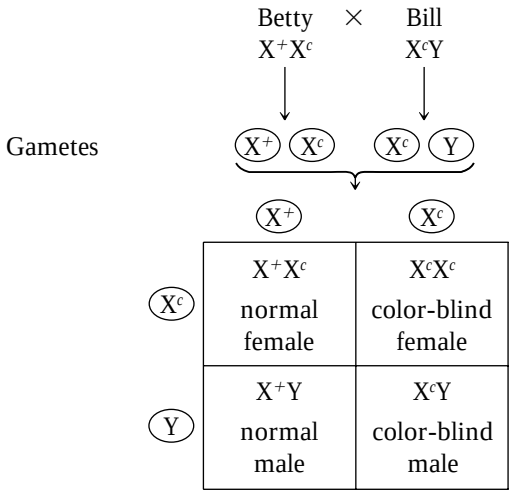
Sex in fruit flies is determined by the X:A ratio—the ratio of the number of X chromosomes to the number of haploid autosomal sets. An X:A ratio of 1.0 produces a female fly; an X:A ratio of 0.5 produces a male. If the X:A ratio is greater than 1.0, the fly is a metafemale; if it is less than 0.5, the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

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

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

• Solution

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

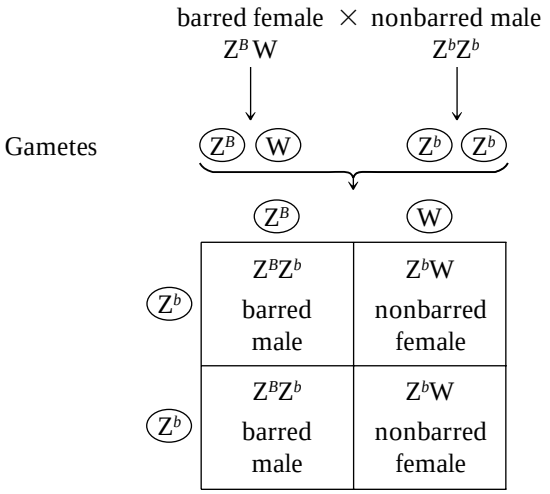


Thus, $\frac{1}{4}$ of the children are expected to be female with normal color vision, $\frac{1}{4}$ female with color blindness, $\frac{1}{4}$ male with normal color vision, and $\frac{1}{4}$ male with color blindness.

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

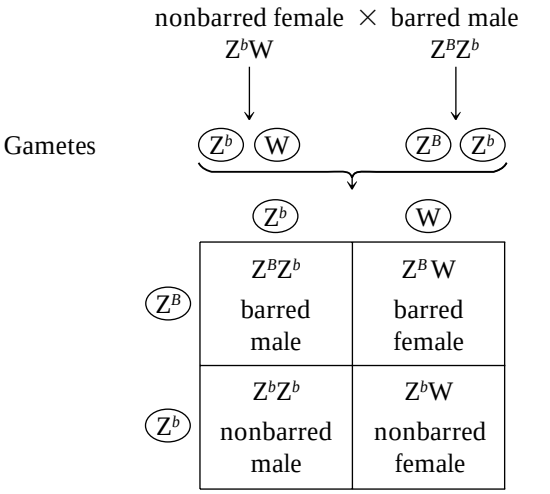
• Solution

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



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

The F_1 are now crossed to produce the F_2:



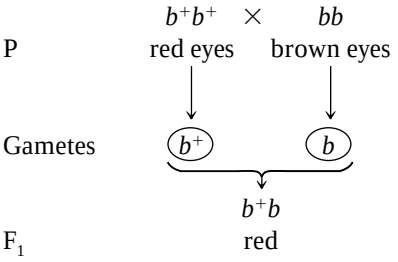
So, ¼ of the F_2 are barred males, ¼ are nonbarred males, ¼ are barred females, and ¼ are nonbarred females.

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

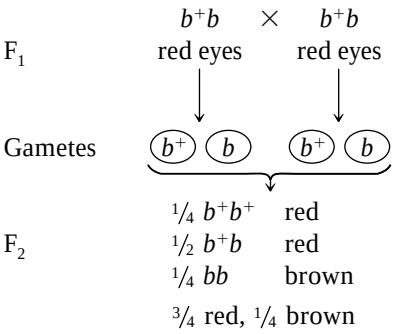
• Solution

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

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

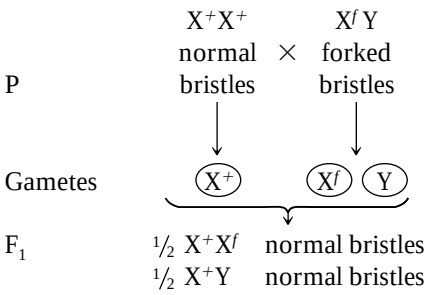


The F_1 are then intercrossed to produce the F_2. Whenever two individuals heterozygous for an autosomal recessive characteristic are crossed, ¾ of the offspring will have the dominant trait and ¼ will have the recessive trait; thus, ¾ of the F_2 flies will have red eyes and ¼ will have brown eyes:

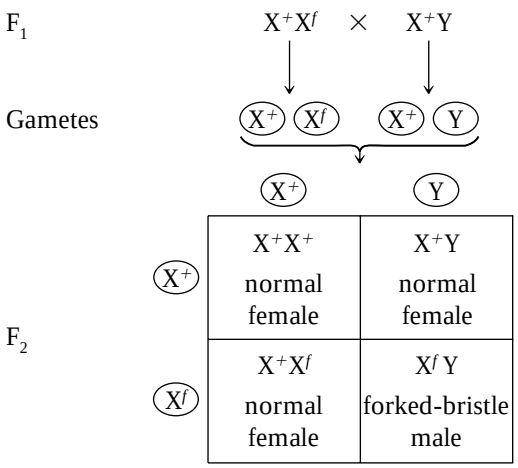


Next, we work out the results for the X-linked characteristic. A female that is homozygous for normal bristles (X^+X^+) is crossed with a male that has forked bristles (X^fY). The female F_1 from this cross are heterozygous (X^+X^f), receiving an X chromosome with a normal-bristle allele from their mother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

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

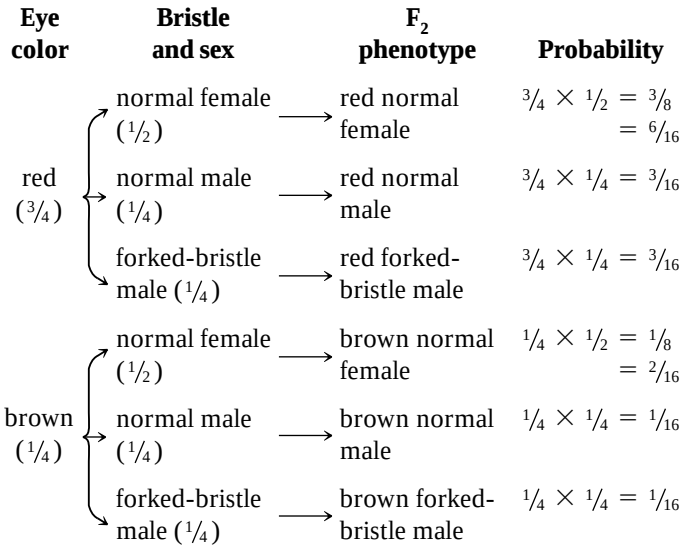


When these F_1 are intercrossed, ½ of the F_2 will be normal-bristle females, ¼ will be normal-bristle males, and ¼ will be forked-bristle males:



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

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



COMPREHENSION QUESTIONS

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

2. How do monoecious organisms differ from dioecious organisms?

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

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

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

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

7. What is meant by genic sex determination?

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

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

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

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

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

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

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

APPLICATION QUESTIONS AND PROBLEMS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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