13

Patterns of Inheritance

FIGURE 13.1
Human beings are extremely diverse in appearance. The differences between us are partly inherited and partly the result of environmental factors we encounter in our lives.

Every living creature is a product of the long evolutionary history of life on earth. While all organisms share this history, only humans wonder about the processes that led to their origin. We are still far from understanding everything about our origins, but we have learned a great deal. Like a partially completed jigsaw puzzle, the boundaries have fallen into place, and much of the internal structure is becoming apparent. In this chapter, we will discuss one piece of the puzzle—the enigma of heredity. Why do groups of people from different parts of the world often differ in appearance (figure 13.1)? Why do the members of a family tend to resemble one another more than they resemble members of other families?

Concept Outline

13.1 Mendel solved the mystery of heredity.

Early Ideas about Heredity: The Road to Mendel

As far back as written records go, patterns of resemblance among the members of particular families have been noted and commented on (figure 13.2). Some familial features are unusual, such as the protruding lower lip of the European royal family Hapsburg, evident in pictures and descriptions of family members from the thirteenth century onward. Other characteristics, like the occurrence of redheaded children within families of redheaded parents, are more common (figure 13.3). Inherited features, the building blocks of evolution, will be our concern in this chapter.

Classical Assumption 1: Constancy of Species

Two concepts provided the basis for most of the thinking about heredity before the twentieth century. The first is that *heredity occurs within species.* For a very long time people believed that it was possible to obtain bizarre composite animals by breeding (crossing) widely different species. The minotaur of Cretan mythology, a creature with the body of a bull and the torso and head of a man, is one example. The giraffe was thought to be another; its scientific name, *Giraffa camelopardalis*, suggests the belief that it was the result of a cross between a camel and a leopard. From the Middle Ages onward, however, people discovered that such extreme crosses were not possible and that variation and heredity occur mainly within the boundaries of a particular species. Species were thought to have been maintained without significant change from the time of their creation.

Classical Assumption 2: Direct Transmission of Traits

The second early concept related to heredity is that *traits are transmitted directly.* When variation is inherited by offspring from their parents, *what* is transmitted? The ancient Greeks suggested that the parents' body parts were transmitted directly to their offspring. Hippocrates called this type of reproductive material *gonos*, meaning "seed." Hence, a characteristic such as a misshapen limb was the result of material that came from the misshapen limb of a parent. Information from each part of the body was supposedly passed along independently of the information from the other parts, and the child was formed after the hereditary material from all parts of the parents' bodies had come together.

This idea was predominant until fairly recently. For example, in 1868, Charles Darwin proposed that all cells and tissues excrete microscopic granules, or "gemmules," that

FIGURE 13.2
Heredity is responsible for family resemblance. Family resemblances are often strong—a visual manifestation of the mechanism of heredity. This is the Johnson family, the wife and daughters of one of the authors. While each daughter is different, all clearly resemble their mother.

FIGURE 13.3
Red hair is inherited. Many different traits are inherited in human families. This redhead is exhibiting one of these traits.

are passed to offspring, guiding the growth of the corresponding part in the developing embryo. Most similar theories of the direct transmission of hereditary material assumed that the male and female contributions *blend* in the offspring. Thus, parents with red and brown hair would produce children with reddish brown hair, and tall and short parents would produce children of intermediate height.

Koelreuter Demonstrates Hybridization between Species

Taken together, however, these two concepts lead to a paradox. If no variation enters a species from outside, and if the variation within each species blends in every generation, then all members of a species should soon have the same appearance. Obviously, this does not happen. Individuals within most species differ widely from each other, and they differ in characteristics that are transmitted from generation to generation.

How could this paradox be resolved? Actually, the resolution had been provided long before Darwin, in the work of the German botanist Josef Koelreuter. In 1760, Koelreuter carried out successful **hybridizations** of plant species, crossing different strains of tobacco and obtaining fertile offspring. The hybrids differed in appearance from both parent strains. When individuals within the hybrid generation were crossed, their offspring were highly variable. Some of these offspring resembled plants of the hybrid generation (their parents), but a few resembled the original strains (their grandparents).

The Classical Assumptions Fail

Koelreuter's work represents the beginning of modern genetics, the first clues pointing to the modern theory of heredity. Koelreuter's experiments provided an important clue about how heredity works: the traits he was studying could be masked in one generation, only to reappear in the next. This pattern contradicts the theory of direct transmission. How could a trait that is transmitted directly disappear and then reappear? Nor were the traits of Koelreuter's plants blended. A contemporary account stated that the traits reappeared in the third generation "fully restored to all their original powers and properties."

It is worth repeating that the offspring in Koelreuter's crosses were not identical to one another. Some resembled the hybrid generation, while others did not. The alternative forms of the characters Koelreuter was studying were distributed among the offspring. Referring to a heritable feature as a **character,** a modern geneticist would say the alternative forms of each character were **segregating** among the progeny of a mating, meaning that some offspring exhibited one alternative form of a character (for example, hairy leaves), while other offspring from the same mating exhibited a different alternative (smooth leaves). This segregation of alternative forms of a character, or **traits,** provided the clue that led Gregor Mendel to his understanding of the nature of heredity.

FIGURE 13.4
The garden pea, *Pisum sativum*. Easy to cultivate and able to produce many distinctive varieties, the garden pea was a popular experimental subject in investigations of heredity as long as a century before Gregor Mendel's experiments.

Knight Studies Heredity in Peas

Over the next hundred years, other investigators elaborated on Koelreuter's work. Prominent among them were English gentleman farmers trying to improve varieties of agricultural plants. In one such series of experiments, carried out in the 1790s, T. A. Knight crossed two true-breeding varieties (varieties that remain uniform from one generation to the next) of the garden pea, *Pisum sativum* (figure 13.4). One of these varieties had purple flowers, and the other had white flowers. All of the progeny of the cross had purple flowers. Among the offspring of these hybrids, however, were some plants with purple flowers and others, less common, with white flowers. Just as in Koelreuter's earlier studies, a trait from one of the parents disappeared in one generation only to reappear in the next.

In these deceptively simple results were the makings of a scientific revolution. Nevertheless, another century passed before the process of gene segregation was fully appreciated. Why did it take so long? One reason was that early workers did not quantify their results. A numerical record of results proved to be crucial to understanding the process. Knight and later experimenters who carried out other crosses with pea plants noted that some traits had a "stronger tendency" to appear than others, but they did not record the numbers of the different classes of progeny. Science was young then, and it was not obvious that the numbers were important.

Early geneticists demonstrated that some forms of an inherited character (1) can disappear in one generation only to reappear unchanged in future generations; (2) segregate among the offspring of a cross; and (3) are more likely to be represented than their alternatives.

Mendel and the Garden Pea

The first quantitative studies of inheritance were carried out by Gregor Mendel, an Austrian monk (figure 13.5). Born in 1822 to peasant parents, Mendel was educated in a monastery and went on to study science and mathematics at the University of Vienna, where he failed his examinations for a teaching certificate. He returned to the monastery and spent the rest of his life there, eventually becoming abbot. In the garden of the monastery (figure 13.6), Mendel initiated a series of experiments on plant hybridization. The results of these experiments would ultimately change our views of heredity irrevocably.

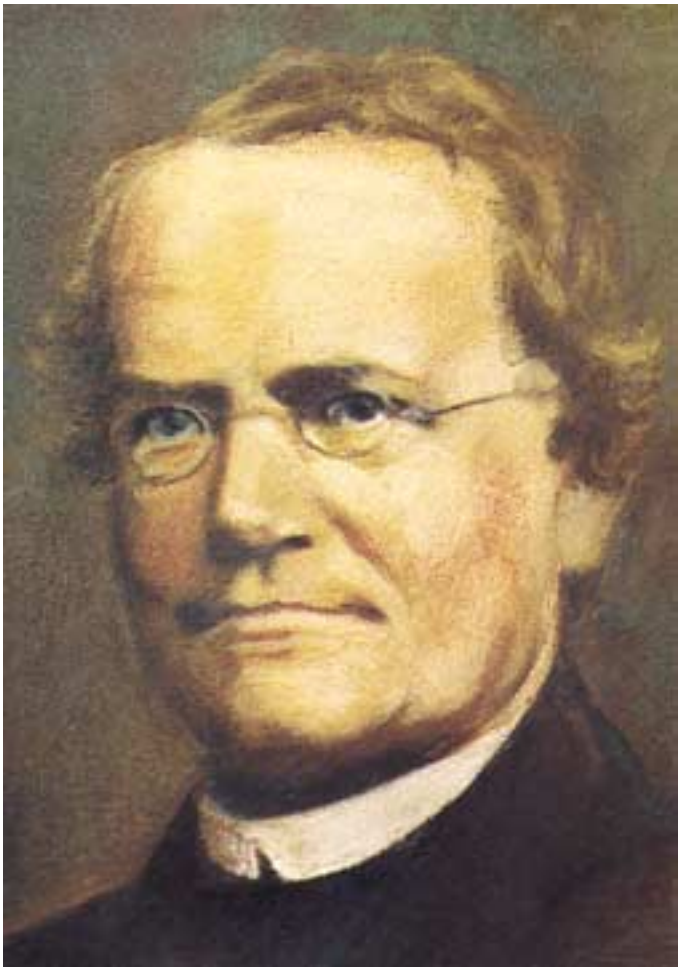


FIGURE 13.5
Gregor Johann Mendel. Cultivating his plants in the garden of a monastery in Brunn, Austria (now Brno, Czech Republic), Mendel studied how differences among varieties of peas were inherited when the varieties were crossed. Similar experiments had been done before, but Mendel was the first to quantify the results and appreciate their significance.

Why Mendel Chose the Garden Pea

For his experiments, Mendel chose the garden pea, the same plant Knight and many others had studied earlier. The choice was a good one for several reasons. First, many earlier investigators had produced hybrid peas by crossing different varieties. Mendel knew that he could expect to observe segregation of traits among the offspring. Second, a large number of true-breeding varieties of peas were available. Mendel initially examined 32. Then, for further study, he selected lines that differed with respect to seven easily distinguishable traits, such as round versus wrinkled seeds and purple versus white flowers, a character that Knight had studied. Third, pea plants are small and easy to grow, and they have a relatively short generation time. Thus, one can conduct experiments involving numerous plants, grow several generations in a single year, and obtain results relatively quickly.

A fourth advantage of studying peas is that the sexual organs of the pea are enclosed within the flower (figure 13.7). The flowers of peas, like those of many flowering plants, contain both male and female sex organs. Furthermore, the gametes produced by the male and female parts of the same flower, unlike those of many flowering plants, can fuse to form viable offspring. Fertilization takes place automatically within an individual flower if it is not disturbed, resulting in offspring that are the progeny from a single individual. Therefore, one can either let individual flowers engage in **self-fertilization,** or remove the flower's male parts before fertilization and introduce pollen from a strain with a different trait, thus performing *cross-pollination* which results in **cross-fertilization.**

FIGURE 13.6
The garden where Mendel carried out his plant-breeding experiments. Gregor Mendel did his key scientific experiments in this small garden in a monastery.

Mendel's Experimental Design

Mendel was careful to focus on only a few specific differences between the plants he was using and to ignore the countless other differences he must have seen. He also had the insight to realize that the differences he selected to analyze must be comparable. For example, he appreciated that trying to study the inheritance of round seeds versus tall height would be useless.

Mendel usually conducted his experiments in three stages:

1. First, he allowed pea plants of a given variety to produce progeny by self-fertilization for several generations. Mendel thus was able to assure himself that the traits he was studying were indeed constant, transmitted unchanged from generation to generation. Pea plants with white flowers, for example, when crossed with each other, produced only offspring with white flowers, regardless of the number of generations.
2. Mendel then performed crosses between varieties exhibiting alternative forms of characters. For example, he removed the male parts from the flower of a plant that produced white flowers and fertilized it with pollen from a purple-flowered plant. He also carried out the reciprocal cross, using pollen from a white-flowered individual to fertilize a flower on a pea plant that produced purple flowers (figure 13.8).
3. Finally, Mendel permitted the hybrid offspring produced by these crosses to self-pollinate for several generations. By doing so, he allowed the alternative forms of a character to segregate among the progeny. This was the same experimental design that Knight and others had used much earlier. But Mendel went an important step farther: he counted the numbers of offspring exhibiting each trait in each succeeding generation. No one had ever done that before. The quantitative results Mendel obtained proved to be of supreme importance in revealing the process of heredity.

Mendel's experiments with the garden pea involved crosses between true-breeding varieties, followed by a generation or more of inbreeding.

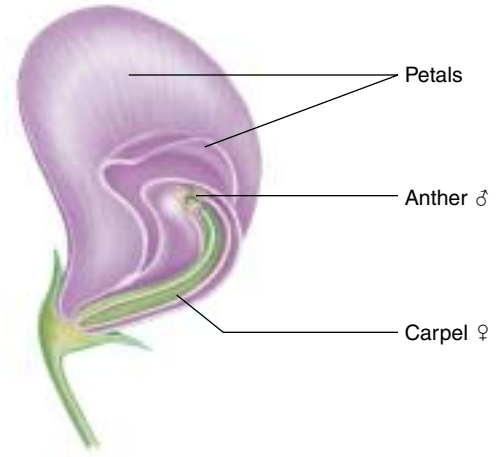


FIGURE 13.7
Structure of the pea flower (longitudinal section). In a pea plant flower, the petals enclose the male anther (containing pollen grains, which give rise to haploid sperm) and the female carpel (containing ovules, which give rise to haploid eggs). This ensures that self-fertilization will take place unless the flower is disturbed.

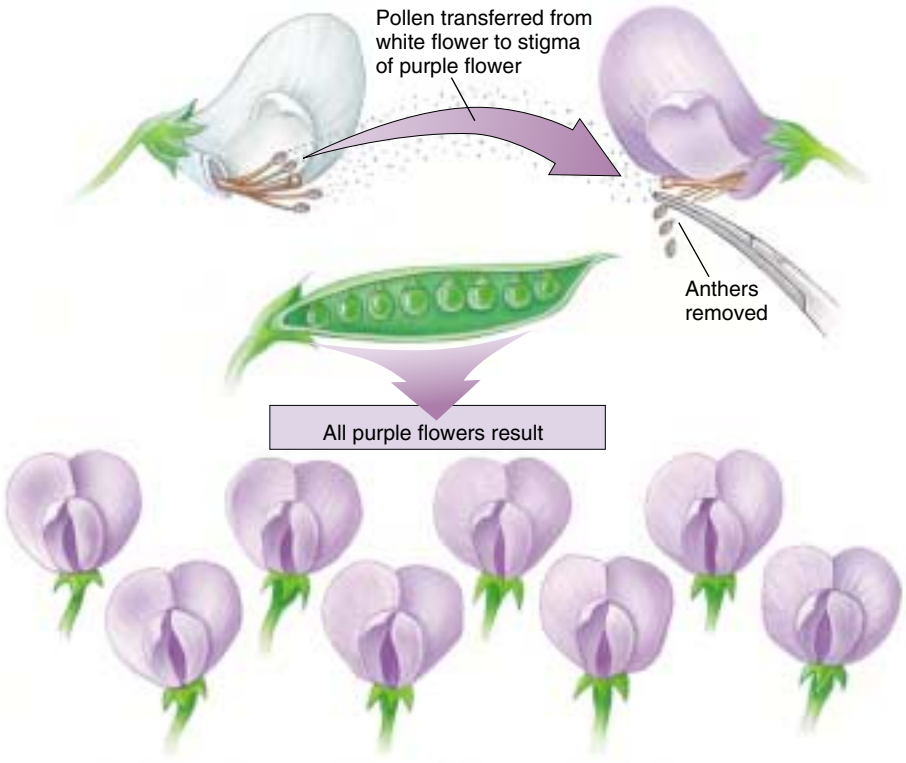


FIGURE 13.8
How Mendel conducted his experiments. Mendel pushed aside the petals of a white flower and collected pollen from the anthers. He then placed that pollen onto the stigma (part of the carpel) of a purple flower whose anthers had been removed, causing cross-fertilization to take place. All the seeds in the pod that resulted from this pollination were hybrids of the white-flowered male parent and the purple-flowered female parent. After planting these seeds, Mendel observed the pea plants they produced. All of the progeny of this cross had purple flowers.

What Mendel Found

The seven characters Mendel studied in his experiments possessed several variants that differed from one another in ways that were easy to recognize and score (figure 13.9). We will examine in detail Mendel's crosses with flower color. His experiments with other characters were similar, and they produced similar results.

The F_1 Generation

When Mendel crossed two contrasting varieties of peas, such as white-flowered and purple-flowered plants, the hybrid offspring he obtained did not have flowers of intermediate color, as the theory of blending inheritance would predict. Instead, in every case the flower color of the offspring resembled one of their parents. It is customary to refer to these offspring as the **first filial** (*filius* is

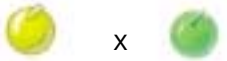
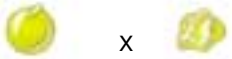
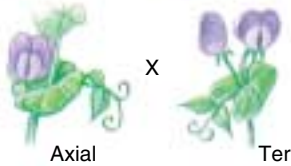
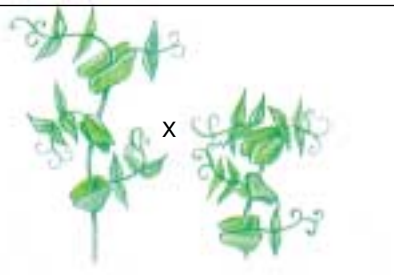
Character	Dominant vs. recessive trait	F_2 generation		Ratio
		Dominant form	Recessive form	
Flower color	 Purple X White	705	224	3.15:1
Seed color	 Yellow X Green	6022	2001	3.01:1
Seed shape	 Round X Wrinkled	5474	1850	2.96:1
Pod color	 Green X Yellow	428	152	2.82:1
Pod shape	 Inflated X Constricted	882	299	2.95:1
Flower position	 Axial X Terminal	651	207	3.14:1
Plant height	 Tall X Dwarf	787	277	2.84:1

FIGURE 13.9
Mendel's experimental results. This table illustrates the seven characters Mendel studied in his crosses of the garden pea and presents the data he obtained from these crosses. Each pair of traits appeared in the F_2 generation in very close to a 3:1 ratio.

Latin for "son"), or **F_1,** generation. Thus, in a cross of white-flowered with purple-flowered plants, the F_1 offspring all had purple flowers, just as Knight and others had reported earlier.

Mendel referred to the trait expressed in the F_1 plants as **dominant** and to the alternative form that was not expressed in the F_1 plants as **recessive.** For each of the seven pairs of contrasting traits that Mendel examined, one of the pair proved to be dominant and the other recessive.

The F_2 Generation

After allowing individual F_1 plants to mature and self-pollinate, Mendel collected and planted the seeds from each plant to see what the offspring in the **second filial,** or **F_2,** generation would look like. He found, just as Knight had earlier, that some F_2 plants exhibited white flowers, the recessive trait. Hidden in the F_1 generation, the recessive form reappeared among some F_2 individuals.

Believing the proportions of the F_2 types would provide some clue about the mechanism of heredity, Mendel counted the numbers of each type among the F_2 progeny (figure 13.10). In the cross between the purple-flowered F_1 plants, he counted a total of 929 F_2 individuals (see figure 13.9). Of these, 705 (75.9%) had purple flowers and 224 (24.1%) had white flowers. Approximately ¼ of the F_2 individuals exhibited the recessive form of the character. Mendel obtained the same numerical result with the other six characters he examined: ¾ of the F_2 individuals exhibited the dominant trait, and ¼ displayed the recessive trait. In other words, the dominant:recessive ratio among the F_2 plants was always close to 3:1. Mendel carried out similar experiments with other traits, such as wrinkled versus round seeds (figure 13.11), and obtained the same result.

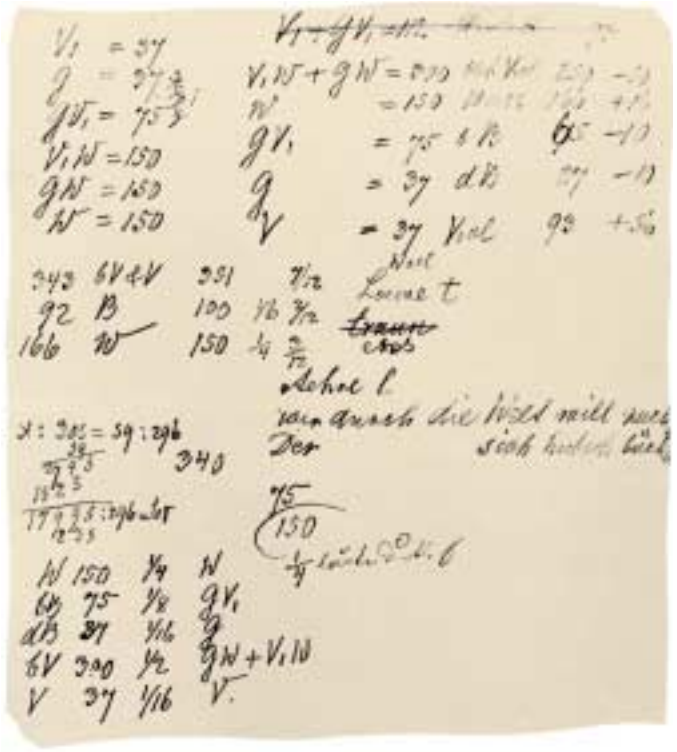


FIGURE 13.10
A page from Mendel's notebook.

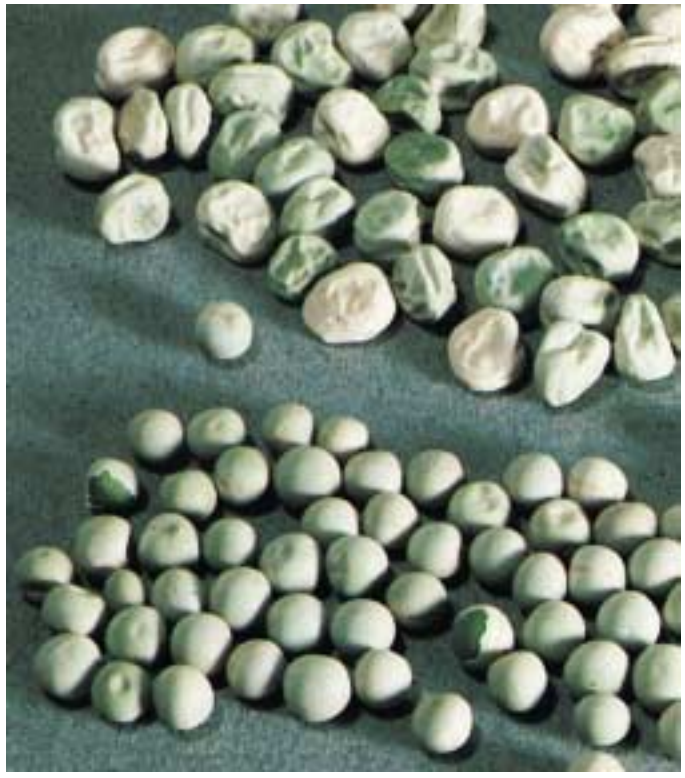


FIGURE 13.11
Seed shape: a Mendelian character. One of the differences Mendel studied affected the shape of pea plant seeds. In some varieties, the seeds were round, while in others, they were wrinkled.

A Disguised 1:2:1 Ratio

Mendel went on to examine how the F_2 plants passed traits on to subsequent generations. He found that the recessive ¼ were always true-breeding. In the cross of white-flowered with purple-flowered plants, for example, the white-flowered F_2 individuals reliably produced white-flowered offspring when they were allowed to self-fertilize. By contrast, only ⅓ of the dominant purple-flowered F_2 individuals (¼ of all F_2 offspring) proved true-breeding, while ⅔ were not. This last class of plants produced dominant and recessive individuals in the third filial (F_3) generation in a 3:1 ratio. This result suggested that, for the entire sample, the 3:1 ratio that Mendel observed in the F_2 generation was really a disguised 1:2:1 ratio: ¼ pure-breeding dominant individuals, ½ not-pure-breeding dominant individuals, and ¼ pure-breeding recessive individuals (figure 13.12).

Mendel's Model of Heredity

From his experiments, Mendel was able to understand four things about the nature of heredity. *First*, the plants he crossed did not produce progeny of intermediate appearance, as a theory of blending inheritance would have predicted. Instead, different plants inherited each alternative intact, as a discrete characteristic that either was or was not visible in a particular generation. *Second*, Mendel learned that for each pair of alternative forms of a character, one alternative was not expressed in the F_1 hybrids, although it reappeared in some F_2 individuals. ***The trait that "disappeared" must therefore be latent (present but not expressed) in the F_1 individuals.*** *Third*, the pairs of alternative traits examined segregated among the progeny of a particular cross, some individuals exhibiting one trait, some the other. *Fourth*, these alternative traits were expressed in the F_2 generation in the ratio of ¾ dominant to ¼ recessive. This characteristic 3:1 segregation is often referred to as the **Mendelian ratio.**

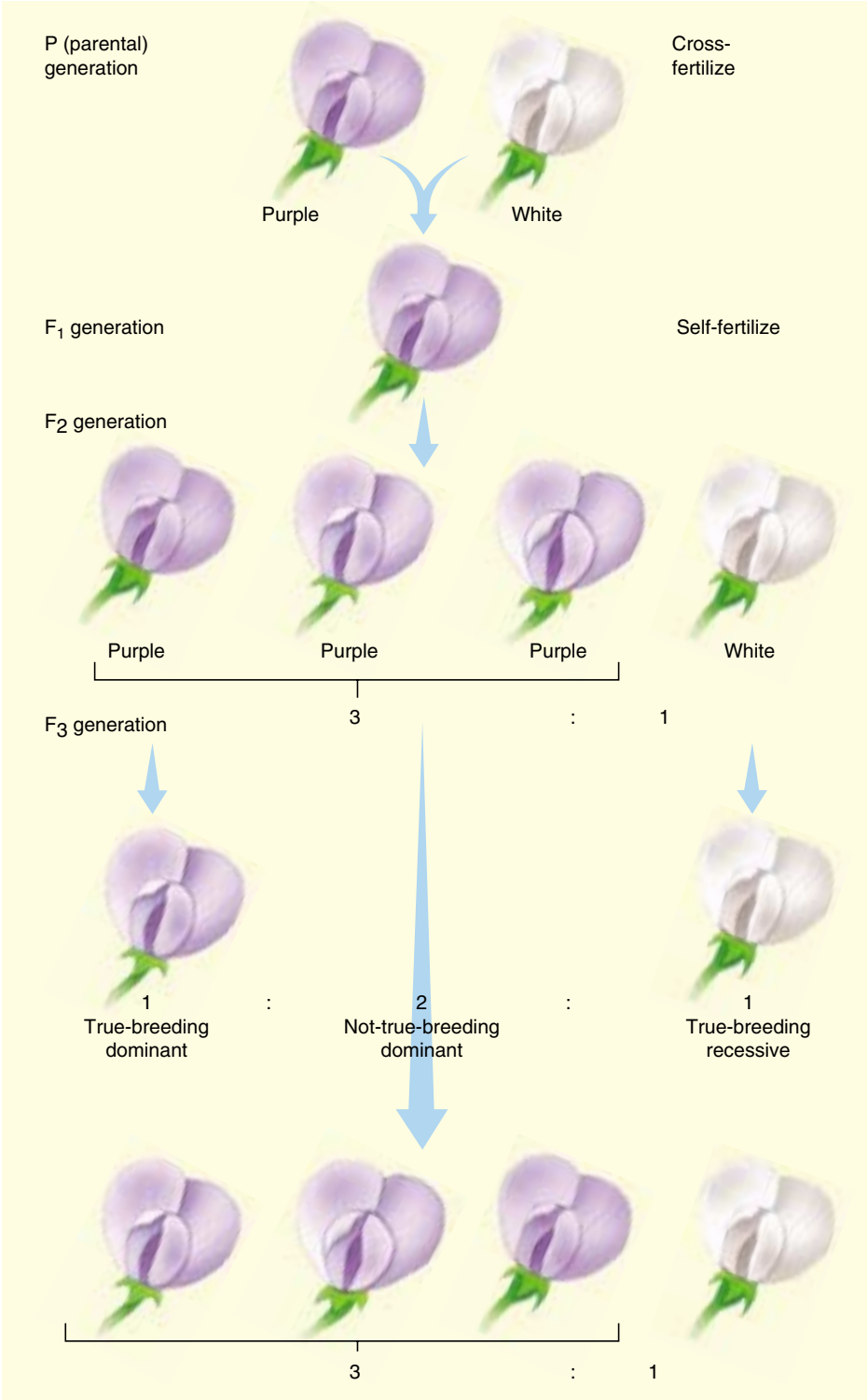


FIGURE 13.12
The F_2 generation is a disguised 1:2:1 ratio. By allowing the F_2 generation to self-fertilize, Mendel found from the offspring (F_3) that the ratio of F_2 plants was one true-breeding dominant, two not-true-breeding dominant, and one true-breeding recessive.

Table 13.1 Some Dominant and Recessive Traits in Humans

Recessive Traits	Phenotypes	Dominant Traits	Phenotypes
Albinism	Lack of melanin pigmentation	Middigital hair	Presence of hair on middle segment of fingers
Alkaptonuria	Inability to metabolize homogenistic acid	Brachydactyly	Short fingers
Red-green color blindness	Inability to distinguish red or green wavelengths of light	Huntington's disease	Degeneration of nervous system, starting in middle age
Cystic fibrosis	Abnormal gland secretion, leading to liver degeneration and lung failure	Phenylthiocarbamide (PTC) sensitivity	Ability to taste PTC as bitter
Duchenne muscular dystrophy	Wasting away of muscles during childhood	Camptodactyly	Inability to straighten the little finger
Hemophilia	Inability to form blood clots	Hypercholesterolemia (the most common human Mendelian disorder—1 in 500)	Elevated levels of blood cholesterol and risk of heart attack
Sickle cell anemia	Defective hemoglobin that causes red blood cells to curve and stick together	Polydactyly	Extra fingers and toes

To explain these results, Mendel proposed a simple model. It has become one of the most famous models in the history of science, containing simple assumptions and making clear predictions. The model has five elements:

1. Parents do not transmit physiological traits directly to their offspring. Rather, they transmit discrete information about the traits, what Mendel called "factors." These factors later act in the offspring to produce the trait. In modern terms, we would say that information about the alternative forms of characters that an individual expresses is *encoded* by the factors that it receives from its parents.
2. Each individual receives two factors that may code for the same trait or for two alternative traits for a character. We now know that there are two factors for each character present in each individual because these factors are carried on chromosomes, and each adult individual is *diploid.* When the individual forms gametes (eggs or sperm), they contain only one of each kind of chromosome (see chapter 12); the gametes are *haploid.* Therefore, only one factor for each character of the adult organism is contained in the gamete. Which of the two factors ends up in a particular gamete is randomly determined.
3. Not all copies of a factor are identical. In modern terms, the alternative forms of a factor, leading to alternative forms of a character, are called **alleles.** When two haploid gametes containing exactly the same allele of a factor fuse during fertilization to form a zygote, the offspring that develops from that zygote is said to be **homozygous;** when the two haploid gametes contain different alleles, the individual offspring is **heterozygous.**

   In modern terminology, Mendel's factors are called **genes.** We now know that each gene is composed of a particular DNA nucleotide sequence (see chapter 3). The particular location of a gene on a chromosome is referred to as the gene's **locus** (plural, loci).
4. The two alleles, one contributed by the male gamete and one by the female, do not influence each other in any way. In the cells that develop within the new individual, these alleles remain discrete. They neither blend with nor alter each other. (Mendel referred to them as "uncontaminated.") Thus, when the individual matures and produces its own gametes, the alleles for each gene segregate randomly into these gametes, as described in element 2.
5. The presence of a particular allele does not ensure that the trait encoded by it will be expressed in an individual carrying that allele. In heterozygous individuals, only one allele (the dominant one) is expressed, while the other (recessive) allele is present but unexpressed. To distinguish between the presence of an allele and its expression, modern geneticists refer to the totality of alleles that an individual contains as the individual's **genotype** and to the physical appearance of that individual as its **phenotype.** The phenotype of an individual is the observable outward manifestation of its genotype, the result of the functioning of the enzymes and proteins encoded by the genes it carries. In other words, the genotype is the blueprint, and the phenotype is the visible outcome.

These five elements, taken together, constitute Mendel's model of the hereditary process. Many traits in humans also exhibit dominant or recessive inheritance, similar to the traits Mendel studied in peas (table 13.1).

When Mendel crossed two contrasting varieties, he found all of the offspring in the first generation exhibited one (dominant) trait, and none exhibited the other (recessive) trait. In the following generation, 25% were pure-breeding for the dominant trait, 50% were hybrid for the two traits and exhibited the dominant trait, and 25% were pure-breeding for the recessive trait.

How Mendel Interpreted His Results

Does Mendel's model predict the results he actually obtained? To test his model, Mendel first expressed it in terms of a simple set of symbols, and then used the symbols to interpret his results. It is very instructive to do the same. Consider again Mendel's cross of purple-flowered with white-flowered plants. We will assign the symbol *P* to the dominant allele, associated with the production of purple flowers, and the symbol *p* to the recessive allele, associated with the production of white flowers. By convention, genetic traits are usually assigned a letter symbol referring to their more common forms, in this case "P" for purple flower color. The dominant allele is written in upper case, as *P;* the recessive allele (white flower color) is assigned the same symbol in lower case, *p*.

In this system, the genotype of an individual that is true-breeding for the recessive white-flowered trait would be designated *pp*. In such an individual, both copies of the allele specify the white-flowered phenotype. Similarly, the genotype of a true-breeding purple-flowered individual would be designated *PP*, and a heterozygote would be designated *Pp* (dominant allele first). Using these conventions, and denoting a cross between two strains with ×, we can symbolize Mendel's original cross as *pp* × *PP*.

The F_1 Generation

Using these simple symbols, we can now go back and reexamine the crosses Mendel carried out. Because a white-flowered parent (*pp*) can produce only *p* gametes, and a pure purple-flowered (homozygous dominant) parent (*PP*) can produce only *P* gametes, the union of an egg and a sperm from these parents can produce only heterozygous *Pp* offspring in the F_1 generation. Because the *P* allele is dominant, all of these F_1 individuals are expected to have purple flowers. The *p* allele is present in these heterozygous individuals, but it is not phenotypically expressed. This is the basis for the latency Mendel saw in recessive traits.

The F_2 Generation

When F_1 individuals are allowed to self-fertilize, the *P* and *p* alleles segregate randomly during gamete formation. Their subsequent union at fertilization to form F_2 individuals is also random, not being influenced by which alternative alleles the individual gametes carry. What will the F_2 individuals look like? The possibilities may be visualized in a simple diagram called a **Punnett square,** named after its originator, the English geneticist Reginald Crundall Punnett (figure 13.13). Mendel's model, ana-

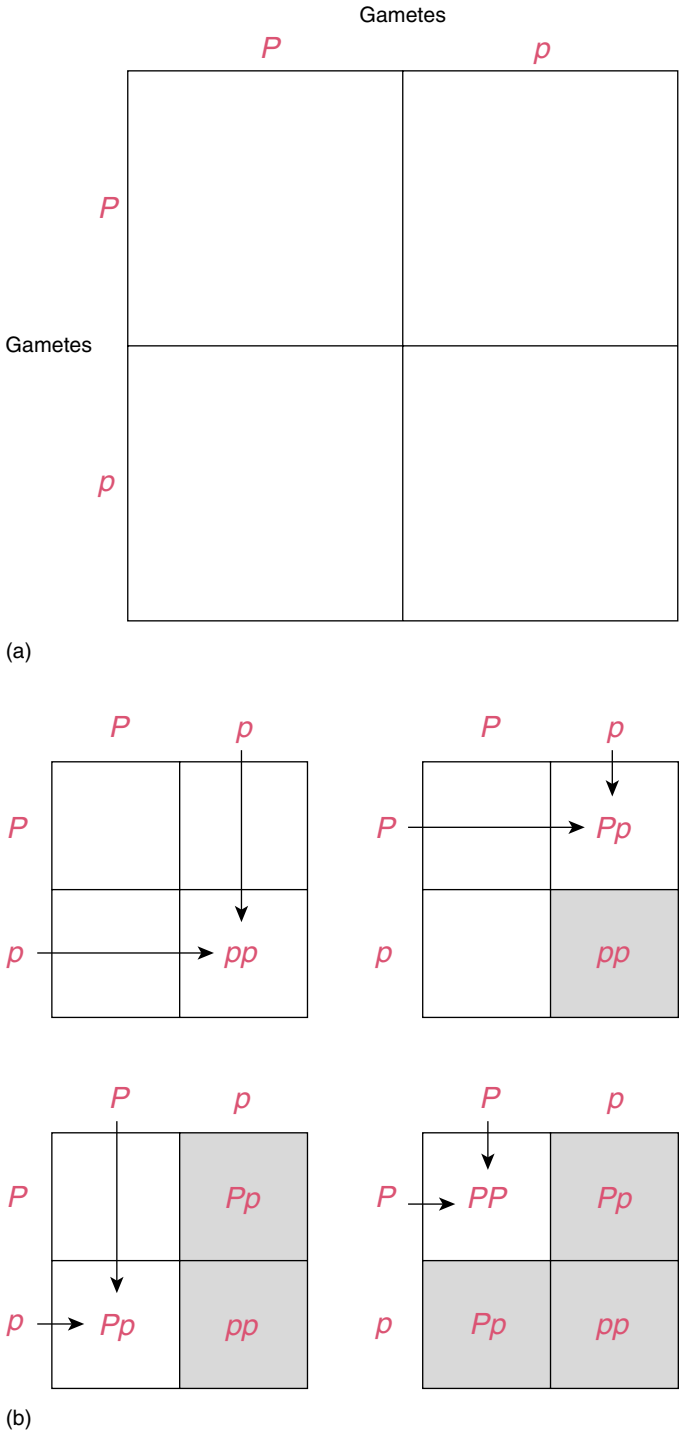


FIGURE 13.13
A Punnett square. (*a*) To make a Punnett square, place the different possible types of female gametes along one side of a square and the different possible types of male gametes along the other. (*b*) Each potential zygote can then be represented as the intersection of a vertical line and a horizontal line.

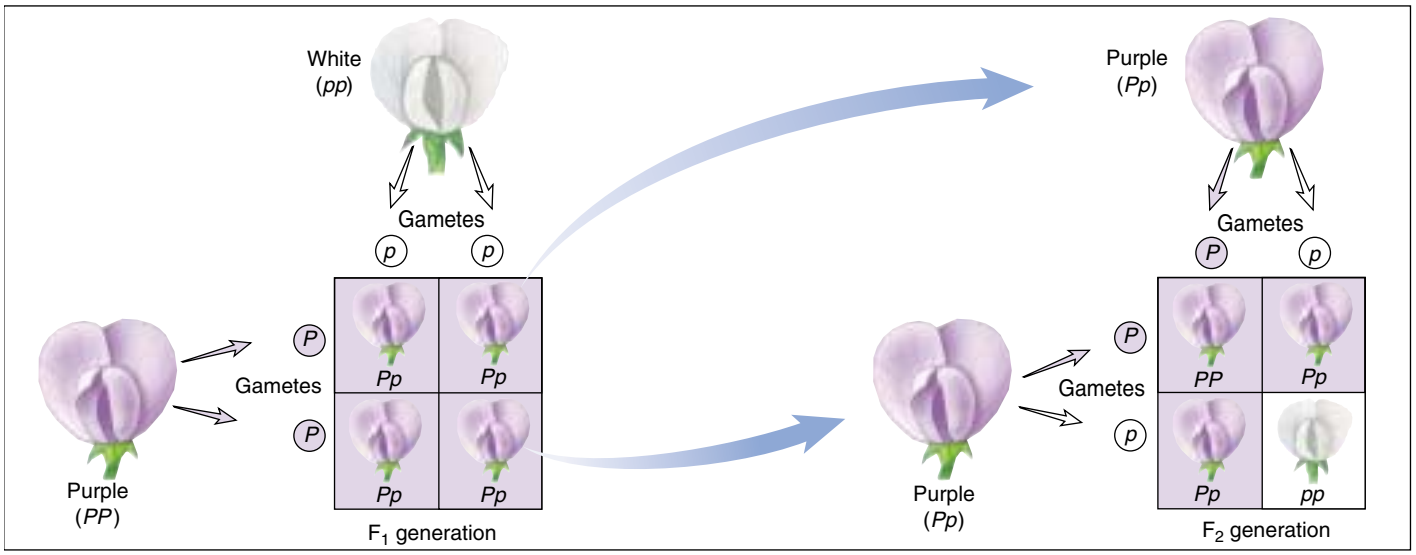


FIGURE 13.14
Mendel's cross of pea plants differing in flower color. All of the offspring of the first cross (the F_1 generation) are *Pp* heterozygotes with purple flowers. When two heterozygous F_1 individuals are crossed, three kinds of F_2 offspring are possible: *PP* homozygotes (purple flowers); *Pp* heterozygotes (also purple flowers); and *pp* homozygotes (white flowers). Therefore, in the F_2 generation, the ratio of dominant to recessive phenotypes is 3:1. However, the ratio of genotypes is 1:2:1 (1 *PP*: 2 *Pp*: 1 *pp*).

lyzed in terms of a Punnett square, clearly predicts that the F_2 generation should consist of ¾ purple-flowered plants and ¼ white-flowered plants, a phenotypic ratio of 3:1 (figure 13.14).

The Laws of Probability Can Predict Mendel's Results

A different way to express Mendel's result is to say that there are three chances in four (¾) that any particular F_2 individual will exhibit the dominant trait, and one chance in four (¼) that an F_2 individual will express the recessive trait. Stating the results in terms of probabilities allows simple predictions to be made about the outcomes of crosses. If both F_1 parents are *Pp* (heterozygotes), the probability that a particular F_2 individual will be *pp* (homozygous recessive) is the probability of receiving a *p* gamete from the male (½) times the probability of receiving a *p* gamete from the female (½), or ¼. This is the same operation we perform in the Punnett square illustrated in figure 13.13. The ways probability theory can be used to analyze Mendel's results is discussed in detail on page 251.

Further Generations

As you can see in figure 13.14, there are really three kinds of F_2 individuals: ¼ are pure-breeding, white-flowered individuals (*pp*); ½ are heterozygous, purple-flowered individuals (*Pp*); and ¼ are pure-breeding, purple-flowered individuals (*PP*). The 3:1 phenotypic ratio is really a disguised 1:2:1 genotypic ratio.

Mendel's First Law of Heredity: Segregation

Mendel's model thus accounts in a neat and satisfying way for the segregation ratios he observed. Its central assumption—that alternative alleles of a character segregate from each other in heterozygous individuals and remain distinct—has since been verified in many other organisms. It is commonly referred to as **Mendel's First Law of Heredity,** or the **Law of Segregation.** As you saw in chapter 12, the segregational behavior of alternative alleles has a simple physical basis, the alignment of chromosomes at random on the metaphase plate during meiosis I. It is a tribute to the intellect of Mendel's analysis that he arrived at the correct scheme with no knowledge of the cellular mechanisms of inheritance; neither chromosomes nor meiosis had yet been described.

The Testcross

To test his model further, Mendel devised a simple and powerful procedure called the **testcross.** Consider a purple-flowered plant. It is impossible to tell whether such a plant is homozygous or heterozygous simply by looking at its phenotype. To learn its genotype, you must cross it with some other plant. What kind of cross would provide the answer? If you cross it with a homozygous dominant individual, all of the progeny will show the dominant phenotype whether the test plant is homozygous or heterozygous. It is also difficult (but not impossible) to distinguish between the two possible test plant genotypes by crossing with a heterozygous individual. However, if you cross the test plant with a homozygous recessive individual, the two possible test plant genotypes will give totally different results (figure 13.15):

Alternative 1: unknown individual homozygous dominant (*PP*). *PP* × *pp:* all offspring have purple flowers (*Pp*)

Alternative 2: unknown individual heterozygous (*Pp*). *Pp* × *pp:* ½ of offspring have white flowers (*pp*) and ½ have purple flowers (*Pp*)

To perform his testcross, Mendel crossed heterozygous F_1 individuals back to the parent homozygous for the recessive trait. He predicted that the dominant and recessive traits would appear in a 1:1 ratio, and that is what he observed. For each pair of alleles he investigated, Mendel observed phenotypic F_2 ratios of 3:1 (see figure 13.14) and testcross ratios very close to 1:1, just as his model predicted.

Testcrosses can also be used to determine the genotype of an individual when two genes are involved. Mendel carried out many two-gene crosses, some of which we will discuss. He often used testcrosses to verify the genotypes of particular dominant-appearing F_2 individuals. Thus, an F_2 individual showing both dominant traits (*A_ B_*) might have any of the following genotypes: *AABB*, *AaBB*, *AABb*, or *AaBb*. By crossing dominant-appearing F_2 individuals with homozygous recessive individuals (that is, *A_ B_* × *aabb*), Mendel was able to determine if either or both of the traits bred true among the progeny, and so to determine the genotype of the F_2 parent:

AABB	trait A breeds true	trait B breeds true
AaBB	_____	trait B breeds true
AABb	trait A breeds true	_____
AaBb	_____	_____

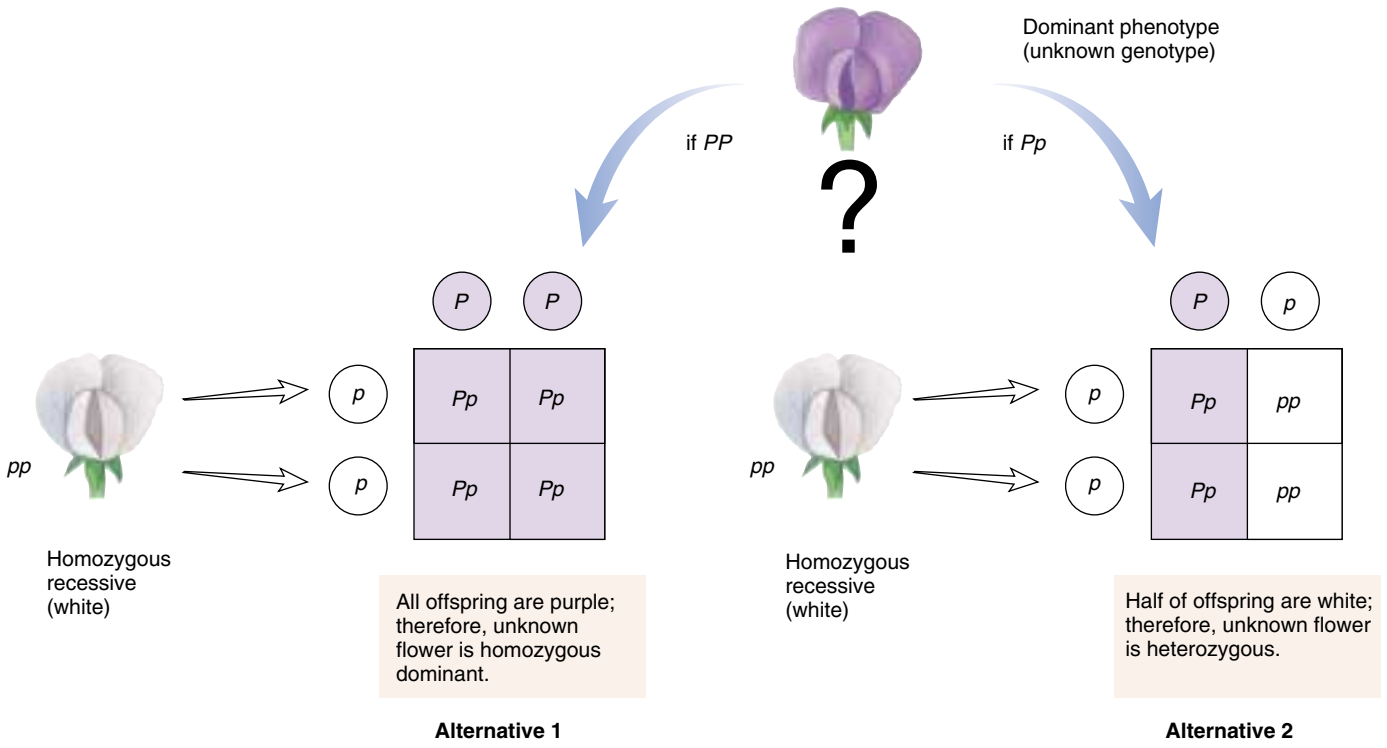


FIGURE 13.15
A testcross. To determine whether an individual exhibiting a dominant phenotype, such as purple flowers, is homozygous or heterozygous for the dominant allele, Mendel crossed the individual in question with a plant that he knew to be homozygous recessive, in this case a plant with white flowers.

Probability and Allele Distribution

Many, although not all, alternative alleles produce discretely different phenotypes. Mendel's pea plants were tall or dwarf, had purple or white flowers, and produced round or wrinkled seeds. The eye color of a fruit fly may be red or white, and the skin color of a human may be pigmented or albino. When only two alternative alleles exist for a given character, the distribution of phenotypes among the offspring of a cross is referred to as a **binomial distribution.**

As an example, consider the distribution of sexes in humans. Imagine that a couple has chosen to have three children. How likely is it that two of the children will be boys and one will be a girl? The frequency of any particular possibility is referred to as its **probability** of occurrence. Let p symbolize the probability of having a boy at any given birth and q symbolize the probability of having a girl. Since any birth is equally likely to produce a girl or boy:

$$p = q = ½$$

Table 13.A shows eight possible gender combinations among the three children. The sum of the probabilities of the eight possible combinations must equal one. Thus:

$$p^3 + 3p^2q + 3pq^2 + q^3 = 1$$

The probability that the three children will be two boys and one girl is:

$$3p^2q = 3 \times (½)^2 \times (½) = ⅜$$

To test your understanding, try to estimate the probability that two parents heterozygous for the recessive allele producing albinism (a) will have one albino child in a family of three. First, set up a Punnett square:

		Father's Gametes	
		A	***a***
Mother's Gametes	***A***	*AA*	*Aa*
	a	*Aa*	*aa*

You can see that one-fourth of the children are expected to be albino (aa). Thus, for any given birth the probability of an albino child is ¼. This probability can be symbolized by q. The probability of a nonalbino child is ¾, symbolized by p. Therefore, the probability that there will be one albino child among the three children is:

$$3p^2q = 3 \times (¾)^2 \times (¼) = {}^{27}⁄_{64}, \text{ or } 42\%$$

This means that the chance of having one albino child in the three is 42%.

Table 13.A Binomial Distribution of the Sexes of Children in Human Families

Composition of Family	Order of Birth	Calculation	Probability	
3 boys	bbb	$p \times p \times p$	p^3	
2 boys and 1 girl	bbg	$p \times p \times q$	p^2q	$3p^2q$
	bgb	$p \times q \times p$	p^2q	
	gbb	$q \times p \times p$	p^2q	
1 boy and 2 girls	ggb	$q \times q \times p$	pq^2	$3pq^2$
	gbg	$q \times p \times q$	pq^2	
	bgg	$p \times q \times q$	pq^2	
3 girls	ggg	$q \times q \times q$	q^3	

Vocabulary of Genetics

allele One of two or more alternative forms of a gene.

diploid Having two sets of chromosomes, which are referred to as *homologues.* Animals and plants are diploid in the dominant phase of their life cycles as are some protists.

dominant allele An allele that dictates the appearance of heterozygotes. One allele is said to be dominant over another if a heterozygous individual with one copy of that allele has the same appearance as a homozygous individual with two copies of it.

gene The basic unit of heredity; a sequence of DNA nucleotides on a chromosome that encodes a polypeptide or RNA molecule and so determines the nature of an individual's inherited traits.

genotype The total set of genes present in the cells of an organism. This term is often also used to refer to the set of alleles at a single gene.

haploid Having only one set of chromosomes. Gametes, certain animals, protists and fungi, and certain stages in the life cycle of plants are haploid.

heterozygote A diploid individual carrying two different alleles of a gene on two homologous chromosomes. Most human beings are heterozygous for many genes.

homozygote A diploid individual carrying identical alleles of a gene on both homologous chromosomes.

locus The location of a gene on a chromosome.

phenotype The realized expression of the genotype; the observable manifestation of a trait (affecting an individual's structure, physiology, or behavior) that results from the biological activity of the DNA molecules.

recessive allele An allele whose phenotypic effect is masked in heterozygotes by the presence of a dominant allele.

Mendel's Second Law of Heredity: Independent Assortment

After Mendel had demonstrated that different traits of a given character (alleles of a given gene) segregate independently of each other in crosses, he asked whether different genes also segregate independently. Mendel set out to answer this question in a straightforward way. He first established a series of pure-breeding lines of peas that differed in just two of the seven characters he had studied. He then crossed contrasting pairs of the pure-breeding lines to create heterozygotes. In a cross involving different seed shape alleles (round, *R*, and wrinkled, *r*) and different seed color alleles (yellow, *Y*, and green, *y*), all the F_1 individuals were identical, each one heterozygous for both seed shape (*Rr*) and seed color (*Yy*). The F_1 individuals of such a cross are **dihybrids,** individuals heterozygous for both genes.

The third step in Mendel's analysis was to allow the dihybrids to self-fertilize. If the alleles affecting seed shape and seed color were segregating independently, then the probability that a particular pair of seed shape alleles would occur together with a particular pair of seed color alleles would be simply the product of the individual probabilities that each pair would occur separately. Thus, the probability that an individual with wrinkled green seeds (*rryy*) would appear in the F_2 generation would be equal to the probability of observing an individual with wrinkled seeds (¼) times the probability of observing one with green seeds (¼), or 1/16.

Because the gene controlling seed shape and the gene controlling seed color are each represented by a pair of alternative alleles in the dihybrid individuals, four types of gametes are expected: *RY*, *Ry*, *rY*, and *ry*. Therefore, in the F_2 generation there are 16 possible combinations of alleles, each of them equally probable (figure 13.16). Of these, 9 possess at least one dominant allele for each gene (signified *R__Y__*, where the dash indicates the presence of either allele) and, thus, should have round, yellow seeds. Of the rest, 3 possess at least one dominant *R* allele but are homozygous recessive for color (*R__yy*); 3 others possess at least one dominant *Y* allele but are homozygous recessive for shape (*rrY__*); and 1 combination among the 16 is homozygous recessive for both genes (*rryy*). The hypothesis that color and shape genes assort independently thus predicts that the F_2 generation will display a 9:3:3:1 phenotypic ratio: nine individuals with round, yellow seeds, three with round, green seeds, three with wrinkled, yellow seeds, and one with wrinkled, green seeds (see figure 13.16).

What did Mendel actually observe? From a total of 556 seeds from dihybrid plants he had allowed to self-fertilize, he observed: 315 round yellow (*R__Y__*), 108 round green (*R__yy*), 101 wrinkled yellow (*rrY__*), and 32 wrinkled green (*rryy*). These results are very close to a 9:3:3:1 ratio (which would be 313:104:104:35). Consequently, the two genes appeared to assort completely independently of each other.

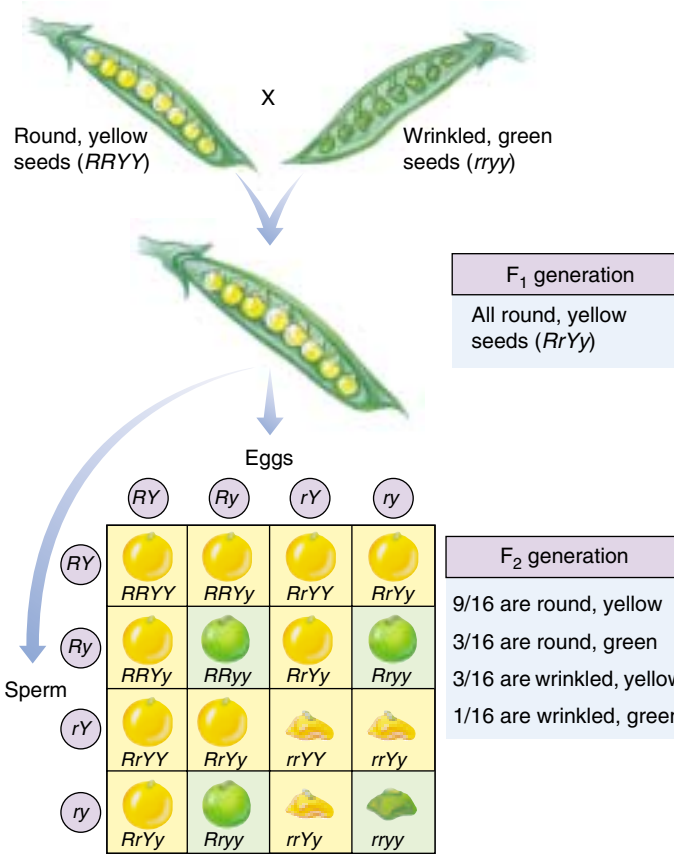


FIGURE 13.16
Analyzing a dihybrid cross. This Punnett square shows the results of Mendel's dihybrid cross between plants with round yellow seeds and plants with wrinkled green seeds. The ratio of the four possible combinations of phenotypes is predicted to be 9:3:3:1, the ratio that Mendel found.

Note that this independent assortment of different genes in no way alters the independent segregation of individual pairs of alleles. Round versus wrinkled seeds occur in a ratio of approximately 3:1 (423:133); so do yellow versus green seeds (416:140). Mendel obtained similar results for other pairs of traits.

Mendel's discovery is often referred to as **Mendel's Second Law of Heredity,** or the **Law of Independent Assortment.** Genes that assort independently of one another, like the seven genes Mendel studied, usually do so because they are located on different chromosomes, which segregate independently during the meiotic process of gamete formation. A modern restatement of Mendel's Second Law would be that *genes that are located on different chromosomes assort independently during meiosis.*

Mendel summed up his discoveries about heredity in two laws. Mendel's First Law of Heredity states that alternative alleles of a trait segregate independently; his Second Law of Heredity states that genes located on different chromosomes assort independently.

Mendelian Inheritance Is Not Always Easy to Analyze

Although Mendel's results did not receive much notice during his lifetime, three different investigators independently rediscovered his pioneering paper in 1900, 16 years after his death. They came across it while searching the literature in preparation for publishing their own findings, which closely resembled those Mendel had presented more than three decades earlier. In the decades following the rediscovery of Mendel, many investigators set out to test Mendel's ideas. However, scientists attempting to confirm Mendel's theory often had trouble obtaining the same simple ratios he had reported. Often, the expression of the genotype is not straightforward. Most phenotypes reflect the action of many genes that act sequentially or jointly, and the phenotype can be affected by alleles that lack complete dominance and the environment.

Continuous Variation

Few phenotypes are the result of the action of only one gene. Instead, most characters reflect the action of **polygenes,** many genes that act sequentially or jointly. When multiple genes act jointly to influence a character such as height or weight, the character often shows a range of small differences. Because all of the genes that play a role in determining phenotypes such as height or weight segregate independently of one another, one sees a gradation in the degree of difference when many individuals are examined (figure 13.17). We call this gradation **continuous variation.** The greater the number of genes that influence a character, the more continuous the expected distribution of the versions of that character.

How can one describe the variation in a character such as the height of the individuals in figure 13.17? Individuals range from quite short to very tall, with average heights more common than either extreme. What one often does is to group the variation into categories—in this case, by measuring the heights of the individuals in inches, rounding fractions of an inch to the nearest whole number. Each height, in inches, is a separate phenotypic category. Plotting the numbers in each height category produces a histogram, such as that in figure 13.17. The histogram approximates an idealized bell-shaped curve, and the variation can be characterized by the mean and spread of that curve.

Pleiotropic Effects

Often, an individual allele will have more than one effect on the phenotype. Such an allele is said to be **pleiotropic.** When the pioneering French geneticist Lucien Cuenot studied yellow fur in mice, a dominant trait, he was unable to obtain a true-breeding yellow strain by crossing individual yellow mice with each other. Individuals homozygous for the yellow allele died, because the yellow allele was

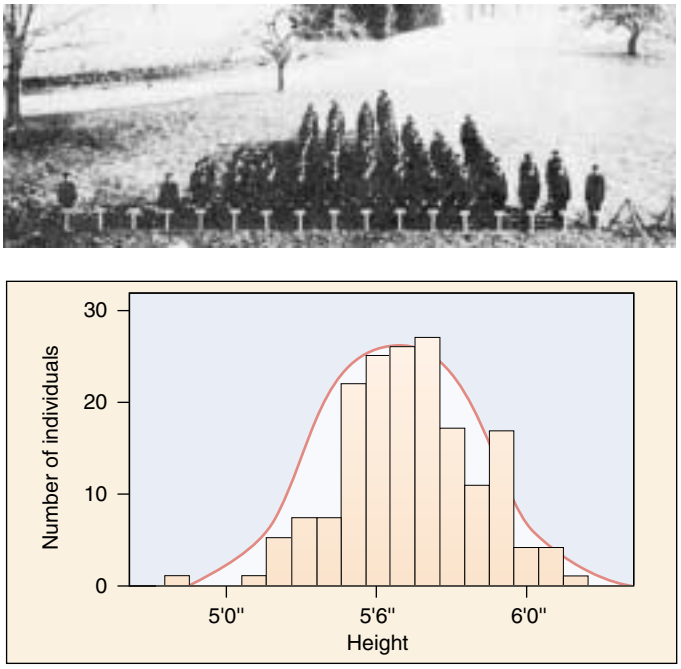


FIGURE 13.17
Height is a continuously varying trait. The photo shows variation in height among students of the 1914 class of the Connecticut Agricultural College. Because many genes contribute to height and tend to segregate independently of one another, the cumulative contribution of different combinations of alleles to height forms a *continuous* distribution of possible height, in which the extremes are much rarer than the intermediate values.

pleiotropic: one effect was yellow coat color, but another was a lethal developmental defect. A pleiotropic allele may be dominant with respect to one phenotypic consequence (yellow fur) and recessive with respect to another (lethal developmental defect). In pleiotropy, one gene affects many traits, in marked contrast to polygeny, where many genes affect one trait. Pleiotropic effects are difficult to predict, because the genes that affect a trait often perform other functions we may know nothing about.

Pleiotropic effects are characteristic of many inherited disorders, such as cystic fibrosis and sickle cell anemia, both discussed later in this chapter. In these disorders, multiple symptoms can be traced back to a single gene defect. In cystic fibrosis, patients exhibit clogged blood vessels, overly sticky mucus, salty sweat, liver and pancreas failure, and a battery of other symptoms. All are pleiotropic effects of a single defect, a mutation in a gene that encodes a chloride ion transmembrane channel. In sickle cell anemia, a defect in the oxygen-carrying hemoglobin molecule causes anemia, heart failure, increased susceptibility to pneumonia, kidney failure, enlargement of the spleen, and many other symptoms. It is usually difficult to deduce the nature of the primary defect from the range of a gene's pleiotropic effects.

Lack of Complete Dominance

Not all alternative alleles are fully dominant or fully recessive in heterozygotes. Some pairs of alleles instead produce a heterozygous phenotype that is either intermediate between those of the parents (incomplete dominance), or representative of both parental phenotypes (codominance). For example, in the cross of red and white flowering Japanese four o'clocks described in figure 13.18, all the F_1 offspring had pink flowers—indicating that neither red nor white flower color was dominant. Does this example of incomplete dominance argue that Mendel was wrong? Not at all. When two of the F_1 pink flowers were crossed, they produced red-, pink-, and white-flowered plants in a 1:2:1 ratio. Heterozygotes are simply intermediate in color.

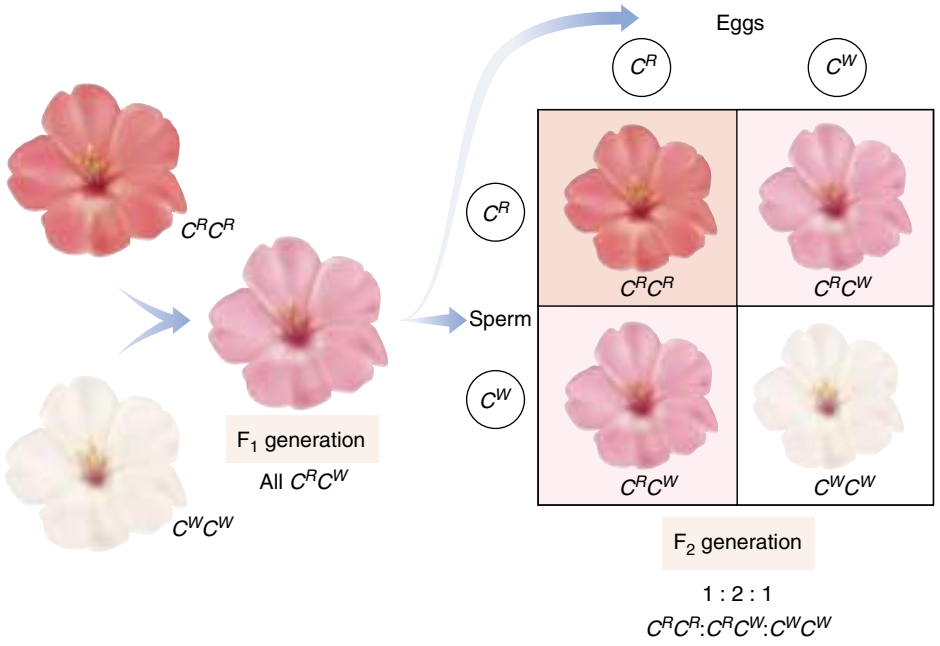


FIGURE 13.18
Incomplete dominance. In a cross between a red-flowered Japanese four o'clock, genotype C^RC^R, and a white-flowered one (C^WC^W), neither allele is dominant. The heterozygous progeny have pink flowers and the genotype C^RC^W. If two of these heterozygotes are crossed, the phenotypes of their progeny occur in a ratio of 1:2:1 (red:pink:white).

Environmental Effects

The degree to which an allele is expressed may depend on the environment. Some alleles are heat-sensitive, for example. Traits influenced by such alleles are more sensitive to temperature or light than are the products of other alleles. The arctic foxes in figure 13.19, for example, make fur pigment only when the weather is warm. Similarly, the *ch* allele in Himalayan rabbits and Siamese cats encodes a heat-sensitive version of tyrosinase, one of the enzymes mediating the production of melanin, a dark pigment. The ch version of the enzyme is inactivated at temperatures above about 33°C. At the surface of the body and head, the temperature is above 33°C and the tyrosinase enzyme is inactive, while it is more active at body extremities such as the tips of the ears and tail, where the temperature is below 33°C. The dark melanin pigment this enzyme produces causes the ears, snout, feet, and tail of Himalayan rabbits and Siamese cats to be black.

(a)

(b)

FIGURE 13.19
Environmental effects on an allele. (*a*) An arctic fox in winter has a coat that is almost white, so it is difficult to see the fox against a snowy background. (*b*) In summer, the same fox's fur darkens to a reddish brown, so that it resembles the color of the surrounding tundra. Heat-sensitive alleles control this color change.

Epistasis

In the tests of Mendel's ideas that followed the rediscovery of his work, scientists had trouble obtaining Mendel's simple ratios particularly with dihybrid crosses. Recall that when individuals heterozygous for two different genes mate (a dihybrid cross), four different phenotypes are possible among the progeny: offspring may display the dominant phenotype for both genes, either one of the genes, or for neither gene. Sometimes, however, it is not possible for an investigator to identify successfully each of the four phenotypic classes, because two or more of the classes look alike. Such situations proved confusing to investigators following Mendel.

One example of such difficulty in identification is seen in the analysis of particular varieties of corn, *Zea mays*. Some commercial varieties exhibit a purple pigment called anthocyanin in their seed coats, while others do not. In 1918, geneticist R. A. Emerson crossed two pure-breeding corn varieties, neither exhibiting anthocyanin pigment. Surprisingly, all of the F_1 plants produced purple seeds.

When two of these pigment-producing F_1 plants were crossed to produce an F_2 generation, 56% were pigment producers and 44% were not. What was happening? Emerson correctly deduced that two genes were involved in producing pigment, and that the second cross had thus been a dihybrid cross. Mendel had predicted 16 equally possible ways gametes could combine. How many of these were in each of the two types Emerson obtained? He multiplied the fraction that were pigment producers (0.56) by 16 to obtain 9, and multiplied the fraction that were not (0.44) by 16 to obtain 7. Thus, Emerson had a **modified ratio** of 9:7 instead of the usual 9:3:3:1 ratio.

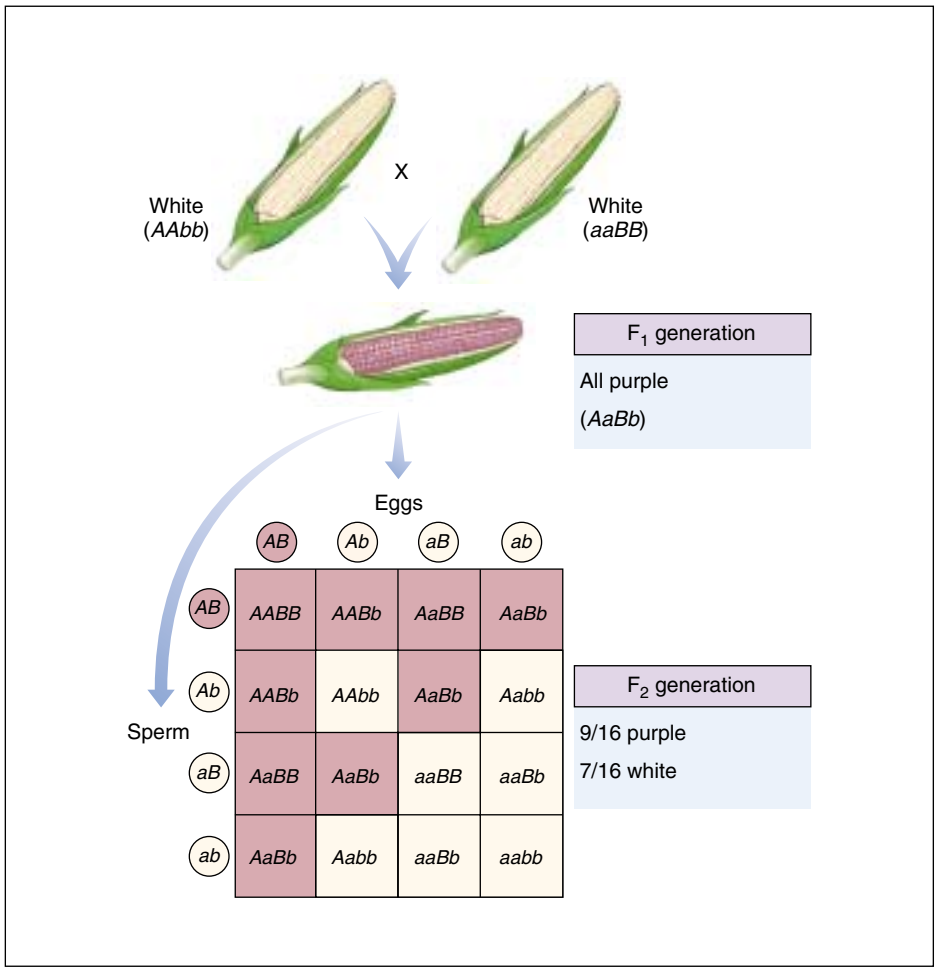


FIGURE 13.20
How epistasis affects grain color. The purple pigment found in some varieties of corn is the product of a two-step biochemical pathway. Unless both enzymes are active (the plant has a dominant allele for each of the two genes, *A* and *B*), no pigment is expressed.

Why Was Emerson's Ratio Modified? When genes act sequentially, as in a biochemical pathway, an allele expressed as a defective enzyme early in the pathway blocks the flow of material through the rest of the pathway. This makes it impossible to judge whether the later steps of the pathway are functioning properly. Such gene interaction, where one gene can interfere with the expression of another gene, is the basis of the phenomenon called **epistasis.**

The pigment anthocyanin is the product of a two-step biochemical pathway:

$$\text{Starting molecule} \xrightarrow[\text{(Colorless)}]{\text{Enzyme 1}} \text{Intermediate} \xrightarrow[\text{(Colorless)}]{\text{Enzyme 2}} \text{Anthocyanin (Purple)}$$

To produce pigment, a plant must possess at least one functional copy of each enzyme gene (figure 13.20). The dominant alleles encode functional enzymes, but the recessive alleles encode nonfunctional enzymes. Of the 16 genotypes predicted by random assortment, 9 contain at least one dominant allele of both genes; they produce purple progeny. The remaining 7 genotypes lack dominant alleles at either or both loci (3 + 3 + 1 = 7) and so are phenotypically the same (nonpigmented), giving the phenotypic ratio of 9:7 that Emerson observed. The inability to see the effect of enzyme 2 when enzyme 1 is nonfunctional is an example of epistasis.

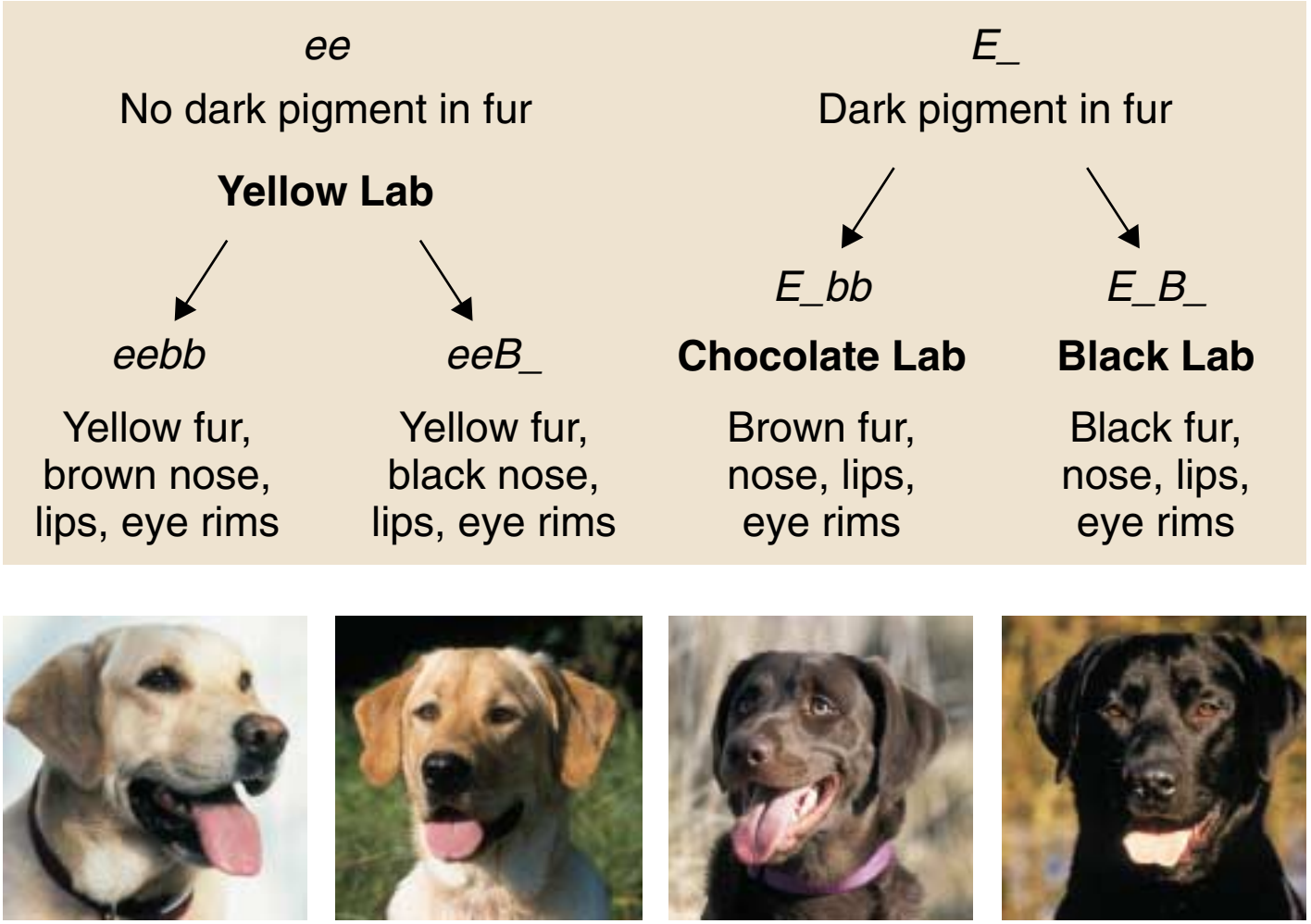


FIGURE 13.21
The effect of epistatic interactions on coat color in dogs. The coat color seen in Labrador retrievers is an example of the interaction of two genes, each with two alleles. The *E* gene determines if the pigment will be deposited in the fur, and the *B* gene determines how dark the pigment will be.

Other Examples of Epistasis

In many animals, coat color is the result of epistatic interactions among genes. Coat color in Labrador retrievers, a breed of dog, is due primarily to the interaction of two genes. The *E* gene determines if dark pigment (eumelanin) will be deposited in the fur or not. If a dog has the genotype *ee*, no pigment will be deposited in the fur, and it will be yellow. If a dog has the genotype *EE* or *Ee* (*E_*), pigment will be deposited in the fur.

A second gene, the *B* gene, determines how dark the pigment will be. This gene controls the distribution of melanosomes in a hair. Dogs with the genotype *E_bb* will have brown fur and are called chocolate labs. Dogs with the genotype *E_B_* will have black fur. But, even in yellow dogs, the *B* gene does have some effect. Yellow dogs with the genotype *eebb* will have brown pigment on their nose, lips, and eye rims, while yellow dogs with the genotype *eeB_* will have black pigment in these areas. The interaction among these alleles is illustrated in figure 13.21. The genes for coat color in this breed have been found, and a genetic test is available to determine the coat colors in a litter of puppies.

A variety of factors can disguise the Mendelian segregation of alleles. Among them are the continuous variation that results when many genes contribute to a trait, incomplete dominance and codominance that produce heterozygotes unlike either parent, environmental influences on the expression of phenotypes, and gene interactions that produce epistasis.

13.2 Human genetics follows Mendelian principles.

Random changes in genes, called mutations, occur in any population. These changes rarely improve the functioning of the proteins those genes encode, just as randomly changing a wire in a computer rarely improves the computer's functioning. Mutant alleles are usually recessive to other alleles. When two seemingly normal individuals who are heterozygous for such an allele produce offspring homozygous for the allele, the offspring suffer the detrimental effects of the mutant allele. When a detrimental allele occurs at a significant frequency in a population, the harmful effect it produces is called a **gene disorder.**

Most Gene Disorders Are Rare

Tay-Sachs disease is an incurable hereditary disorder in which the nervous system deteriorates. Affected children appear normal at birth and usually do not develop symptoms until about the eighth month, when signs of mental deterioration appear. The children are blind within a year after birth, and they rarely live past five years of age.

Tay-Sachs disease is rare in most human populations, occurring in only 1 of 300,000 births in the United States. However, the disease has a high incidence among Jews of Eastern and Central Europe (Ashkenazi), and among American Jews, 90% of whom trace their ancestry to Eastern and Central Europe. In these populations, it is estimated that 1 in 28 individuals is a heterozygous carrier of the disease, and approximately 1 in 3500 infants has the disease. Because the disease is caused by a recessive allele, most of the people who carry the defective allele do not themselves develop symptoms of the disease.

The Tay-Sachs allele produces the disease by encoding a nonfunctional form of the enzyme hexosaminidase A. This enzyme breaks down *gangliosides*, a class of lipids occurring within the lysosomes of brain cells (figure 13.22). As a result, the lysosomes fill with gangliosides, swell, and eventually burst, releasing oxidative enzymes that kill the cells. There is no known cure for this disorder.

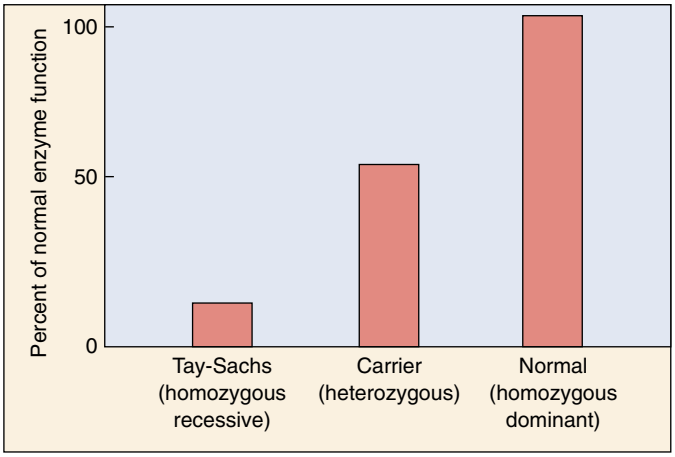


FIGURE 13.22
Tay-Sachs disease. Homozygous individuals (*left bar*) typically have less than 10% of the normal level of hexosaminidase A (*right bar*), while heterozygous individuals (*middle bar*) have about 50% of the normal level—enough to prevent deterioration of the central nervous system.

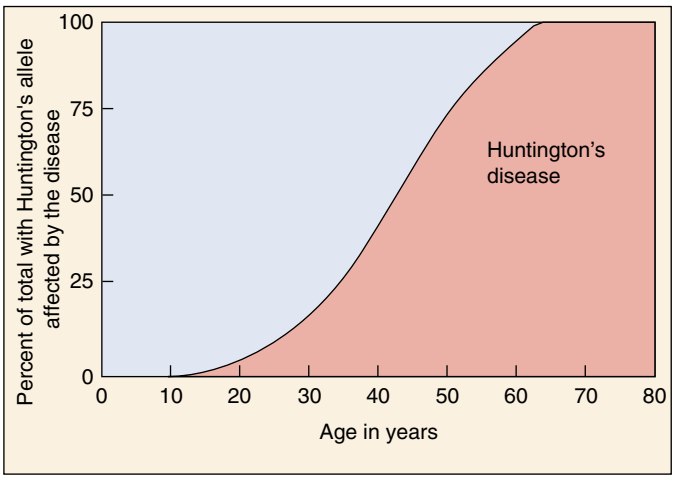


FIGURE 13.23
Huntington's disease is a dominant genetic disorder. It is because of the late age of onset of this disease that it persists despite the fact that it is dominant and fatal.

Not All Gene Defects Are Recessive

Not all hereditary disorders are recessive. **Huntington's disease** is a hereditary condition caused by a dominant allele that leads to the progressive deterioration of brain cells (figure 13.23). Perhaps 1 in 24,000 individuals develops the disorder. Because the allele is dominant, every individual that carries the allele expresses the disorder. Nevertheless, the disorder persists in human populations because its symptoms usually do not develop until the affected individuals are more than 30 years old, and by that time most of those individuals have already had children. Consequently, the allele is often transmitted before the lethal condition develops. A person who is heterozygous for Huntington's disease has a 50% chance of passing the *disease* to his or her children (even though the other parent does not have the disorder). In contrast, the carrier of a recessive disorder such as cystic fibrosis has a 50% chance of passing the *allele* to offspring and must mate with another carrier to risk bearing a child with the disease.

Most gene defects are rare recessives, although some are dominant.

Multiple Alleles: The ABO Blood Groups

A gene may have more than two alleles in a population, and most genes possess several different alleles. Often, no single allele is dominant; instead, each allele has its own effect, and the alleles are considered **codominant.**

A human gene with more than one codominant allele is the gene that determines ABO blood type. This gene encodes an enzyme that adds sugar molecules to lipids on the surface of red blood cells. These sugars act as recognition markers for the immune system. The gene that encodes the enzyme, designated *I*, has three common alleles: I^B, whose product adds galactose; I^A, whose product adds galactosamine; and *i*, which codes for a protein that does not add a sugar.

Different combinations of the three *I* gene alleles occur in different individuals because each person possesses two copies of the chromosome bearing the *I* gene and may be homozygous for any allele or heterozygous for any two. An individual heterozygous for the I^A and I^B alleles produces both forms of the enzyme and adds both galactose and galactosamine to the surfaces of red blood cells. Because both alleles are expressed simultaneously in heterozygotes, the I^A and I^B alleles are codominant. Both I^A and I^B are dominant over the *i* allele because both I^A or I^B alleles lead to sugar addition and the *i* allele does not. The different combinations of the three alleles produce four different phenotypes (figure 13.24):

1. Type A individuals add only galactosamine. They are either I^AI^A homozygotes or I^Ai heterozygotes.
2. Type B individuals add only galactose. They are either I^BI^B homozygotes or I^Bi heterozygotes.
3. Type AB individuals add both sugars and are I^AI^B heterozygotes.
4. Type O individuals add neither sugar and are *ii* homozygotes.

These four different cell surface phenotypes are called the **ABO blood groups** or, less commonly, the Landsteiner blood groups, after the man who first described them. As Landsteiner noted, a person's immune system can distinguish between these four phenotypes. If a type A individual receives a transfusion of type B blood, the recipient's immune system recognizes that the type B blood cells possess a "foreign" antigen (galactose) and attacks the donated blood cells, causing the cells to clump, or agglutinate. This also happens if the donated blood is type AB. However, if the donated blood is type O, no immune attack will occur, as there are no galactose antigens on the surfaces of blood cells produced by the type O donor. In general, any individual's immune system will tolerate a transfusion of type O blood. Because neither galactose nor galactosamine is foreign to type AB individuals (whose red blood cells have both sugars), those individuals may receive any type of blood.

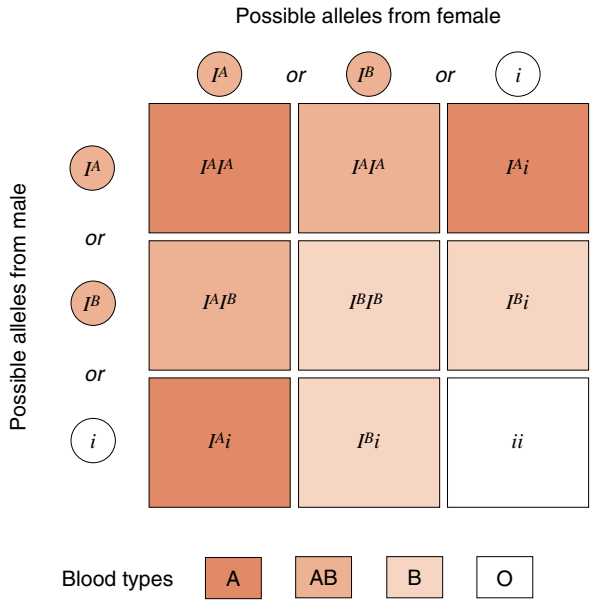


FIGURE 13.24
Multiple alleles control the ABO blood groups. Different combinations of the three *I* gene alleles result in four different blood type phenotypes: type A (either I^AI^A homozygotes or I^Ai heterozygotes), type B (either I^BI^B homozygotes or I^Bi heterozygotes), type AB (I^AI^B heterozygotes), and type O (*ii* homozygotes).

The Rh Blood Group

Another set of cell surface markers on human red blood cells are the **Rh blood group** antigens, named for the rhesus monkey in which they were first described. About 85% of adult humans have the Rh cell surface marker on their red blood cells, and are called Rh-positive. Rh-negative persons lack this cell surface marker because they are homozygous for the recessive gene encoding it.

If an Rh-negative person is exposed to Rh-positive blood, the Rh surface antigens of that blood are treated like foreign invaders by the Rh-negative person's immune system, which proceeds to make antibodies directed against the Rh antigens. This most commonly happens when an Rh-negative woman gives birth to an Rh-positive child (whose father is Rh-positive). At birth, some fetal red blood cells cross the placental barrier and enter the mother's bloodstream, where they induce the production of "anti-Rh" antibodies. In subsequent pregnancies, the mother's antibodies can cross back to the new fetus and cause its red blood cells to clump, leading to a potentially fatal condition called erythroblastosis fetalis.

Many blood group genes possess multiple alleles, several of which may be common.

Patterns of Inheritance Can Be Deduced from Pedigrees

When a blood vessel ruptures, the blood in the immediate area of the rupture forms a solid gel called a clot. The clot forms as a result of the polymerization of protein fibers circulating in the blood. A dozen proteins are involved in this process, and all must function properly for a blood clot to form. A mutation causing any of these proteins to lose their activity leads to a form of **hemophilia,** a hereditary condition in which the blood is slow to clot or does not clot at all.

Hemophilias are recessive disorders, expressed only when an individual does not possess any copy of the normal allele and so cannot produce one of the proteins necessary for clotting. Most of the genes that encode the blood-clotting proteins are on autosomes, but two (designated VIII and IX) are on the X chromosome. These two genes are sex-linked: any male who inherits a mutant allele of either of the two genes will develop hemophilia because his other sex chromosome is a Y chromosome that lacks any alleles of those genes.

The most famous instance of hemophilia, often called the Royal hemophilia, is a sex-linked form that arose in one of the parents of Queen Victoria of England (1819–1901; figure 13.25). In the five generations since Queen Victoria, 10 of her male descendants have had hemophilia. The present British royal family has escaped the disorder because Queen Victoria's son, King Edward VII, did not inherit the defective allele, and all the subsequent rulers of England are his descendants. Three of Victoria's nine children did receive the defective allele, however, and they carried it by marriage into many of the other royal families of Europe (figure 13.26), where it is still being passed to future generations—except in Russia, where all of the five children of Victoria's granddaughter Alexandra were killed soon after the Russian revolution in 1917. (Speculation that one daughter, Anastasia, survived ended in 1999 when DNA analysis confirmed the identity of her remains.)

Family pedigrees can reveal the mode of inheritance of a hereditary trait.

FIGURE 13.25
Queen Victoria of England, surrounded by some of her descendants in 1894. Of Victoria's four daughters who lived to bear children, two, Alice and Beatrice, were carriers of Royal hemophilia. Two of Alice's daughters are standing behind Victoria (wearing feathered boas): Princess Irene of Prussia (right), and Alexandra (left), who would soon become Czarina of Russia. Both Irene and Alexandra were also carriers of hemophilia.

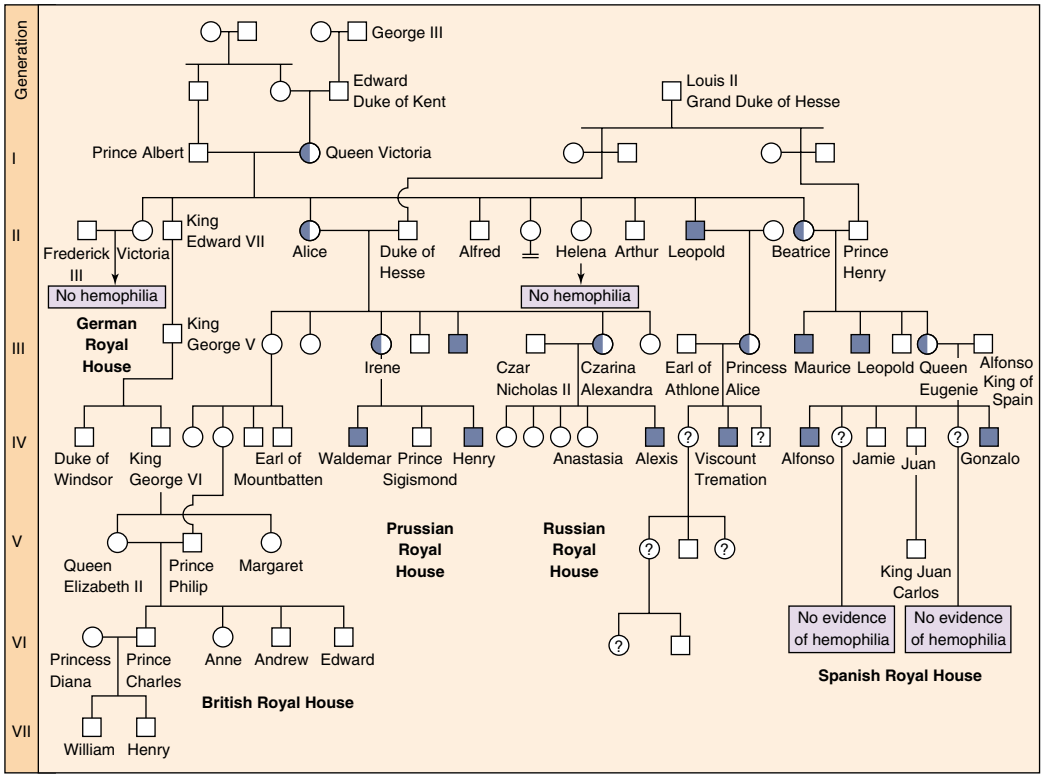


FIGURE 13.26
The Royal hemophilia pedigree. Queen Victoria's daughter Alice introduced hemophilia into the Russian and Austrian royal houses, and Victoria's daughter Beatrice introduced it into the Spanish royal house. Victoria's son Leopold, himself a victim, also transmitted the disorder in a third line of descent. Half-shaded symbols represent carriers with one normal allele and one defective allele; fully shaded symbols represent affected individuals.

Gene Disorders Can Be Due to Simple Alterations of Proteins

Sickle cell anemia is a heritable disorder first noted in Chicago in 1904. Afflicted individuals have defective molecules of hemoglobin, the protein within red blood cells that carries oxygen. Consequently, these individuals are unable to properly transport oxygen to their tissues. The defective hemoglobin molecules stick to one another, forming stiff, rod-like structures and resulting in the formation of sickle-shaped red blood cells (figure 13.27). As a result of their stiffness and irregular shape, these cells have difficulty moving through the smallest blood vessels; they tend to accumulate in those vessels and form clots. People who have large proportions of sickle-shaped red blood cells tend to have intermittent illness and a shortened life span.

FIGURE 13.27
Sickle cell anemia. In individuals homozygous for the sickle cell trait, many of the red blood cells have sickle or irregular shapes, such as the cell on the far right.

The hemoglobin in the defective red blood cells differs from that in normal red blood cells in only one of hemoglobin's 574 amino acid subunits. In the defective hemoglobin, the amino acid valine replaces a glutamic acid at a single position in the protein. Interestingly, the position of the change is far from the active site of hemoglobin where the iron-bearing heme group binds oxygen. Instead, the change occurs on the outer edge of the protein. Why then is the result so catastrophic? The sickle cell mutation puts a very nonpolar amino acid on the surface of the hemoglobin protein, creating a "sticky patch" that sticks to other such patches—nonpolar amino acids tend to associate with one another in polar environments like water. As one hemoglobin adheres to another, ever-longer chains of hemoglobin molecules form.

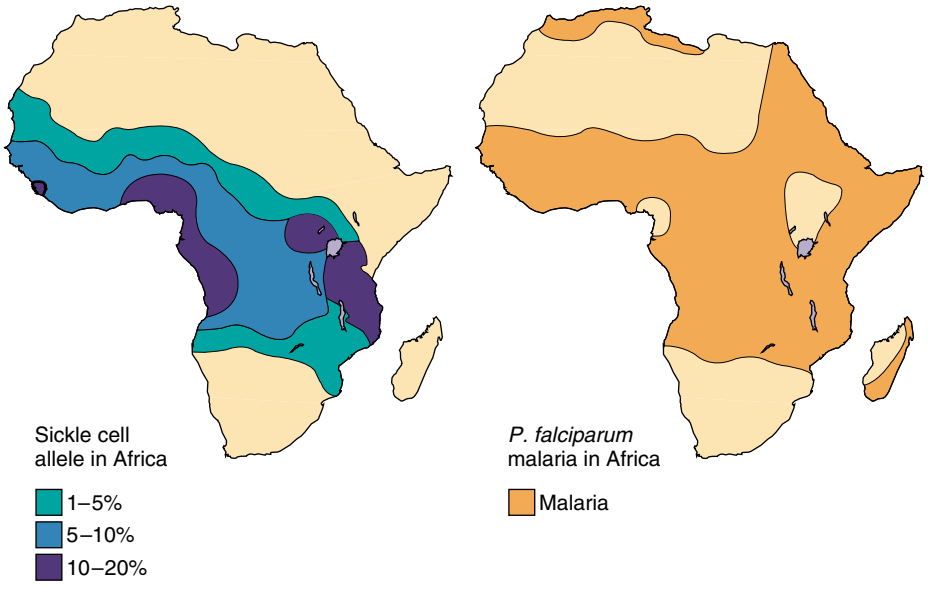


FIGURE 13.28
The sickle cell allele increases resistance to malaria. The distribution of sickle cell anemia closely matches the occurrence of malaria in central Africa. This is not a coincidence. The sickle cell allele, when heterozygous, increases resistance to malaria, a very serious disease.

Individuals heterozygous for the sickle cell allele are generally indistinguishable from normal persons. However, some of their red blood cells show the sickling characteristic when they are exposed to low levels of oxygen. The allele responsible for sickle cell anemia is particularly common among people of African descent; about 9% of African Americans are heterozygous for this allele, and about 0.2% are homozygous and therefore have the disorder. In some groups of people in Africa, up to 45% of all individuals are heterozygous for this allele, and 6% are homozygous. What factors determine the high frequency of sickle cell anemia in Africa? It turns out that heterozygosity for the sickle cell anemia allele increases resistance to malaria, a common and serious disease in central Africa (figure 13.28). We will discuss this situation in detail in chapter 21.

Sickle cell anemia is caused by a single-nucleotide change in the gene for hemoglobin, producing a protein with a nonpolar amino acid on its surface that tends to make the molecules clump together.

Table 13.2 Some Important Genetic Disorders

Disorder	Symptom	Defect	Dominant/ Recessive	Frequency among Human Births
Cystic fibrosis	Mucus clogs lungs, liver, and pancreas	Failure of chloride ion transport mechanism	Recessive	1/2500 (Caucasians)
Sickle cell anemia	Poor blood circulation	Abnormal hemoglobin molecules	Recessive	1/625 (African Americans)
Tay-Sachs disease	Deterioration of central nervous system in infancy	Defective enzyme (hexosaminidase A)	Recessive	1/3500 (Ashkenazi Jews)
Phenylketonuria	Brain fails to develop in infancy	Defective enzyme (phenylalanine hydroxylase)	Recessive	1/12,000
Hemophilia	Blood fails to clot	Defective blood clotting factor VIII	Sex-linked recessive	1/10,000 (Caucasian males)
Huntington's disease	Brain tissue gradually deteriorates in middle age	Production of an inhibitor of brain cell metabolism	Dominant	1/24,000
Muscular dystrophy (Duchenne)	Muscles waste away	Degradation of myelin coating of nerves stimulating muscles	Sex-linked recessive	1/3700 (males)
Hypercholesterolemia	Excessive cholesterol levels in blood, leading to heart disease	Abnormal form of cholesterol cell surface receptor	Dominant	1/500

Some Defects May Soon Be Curable

Some of the most common and serious gene defects result from single recessive mutations, including many of the defects listed in table 13.2. Recent developments in gene technology have raised the hope that this class of disorders may be curable. Perhaps the best example is **cystic fibrosis (CF),** the most common fatal genetic disorder among Caucasians.

Cystic fibrosis is a fatal disease in which the body cells of affected individuals secrete a thick mucus that clogs the airways of the lungs. These same secretions block the ducts of the pancreas and liver so that the few patients who do not die of lung disease die of liver failure. There is no known cure.

Cystic fibrosis results from a defect in a single gene, called *cf*, that is passed down from parent to child. One in 20 individuals possesses at least one copy of the defective gene. Most carriers are not afflicted with the disease; only those children who inherit a copy of the defective gene from each parent succumb to cystic fibrosis—about 1 in 2500 infants.

The function of the *cf* gene has proven difficult to study. In 1985 the first clear clue was obtained. An investigator, Paul Quinton, seized on a commonly observed characteristic of cystic fibrosis patients, that their sweat is abnormally salty, and performed the following experiment. He isolated a sweat duct from a small piece of skin and placed it in a solution of salt (NaCl) that was three times as concentrated as the NaCl inside the duct. He then monitored the movement of ions. Diffusion tends to drive both the sodium (Na^+) and the chloride (Cl^-) ions into the duct because of the higher outer ion concentrations. In skin isolated from normal individuals, Na^+ and Cl^- ions both entered the duct, as expected. In skin isolated from cystic fibrosis individuals, however, only Na^+ ions entered the duct—no Cl^- ions entered. For the first time, the molecular nature of cystic fibrosis became clear. Cystic fibrosis is a defect in a plasma membrane protein called CFTR (cystic fibrosis transmembrane conductance regulator) that normally regulates passage of Cl^- ions into and out of the body's cells. CFTR does not function properly in cystic fibrosis patients (see figure 4.8).

The defective *cf* gene was isolated in 1987, and its position on a particular human chromosome (chromosome 7) was pinpointed in 1989. In 1990 a working *cf* gene was successfully transferred via adenovirus into human lung cells growing in tissue culture. The defective cells were "cured," becoming able to transport chloride ions across their plasma membranes. Then in 1991, a team of researchers successfully transferred a normal human *cf* gene into the lung cells of a living animal—a rat. The *cf* gene was first inserted into a cold virus that easily infects lung cells, and the virus was inhaled by the rat. Carried piggyback, the *cf* gene entered the rat lung cells and began producing the normal human CFTR protein within these cells! Tests of gene transfer into CF patients were begun in 1993, and while a great deal of work remains to be done (the initial experiments were not successful), the future for cystic fibrosis patients for the first time seems bright.

Cystic fibrosis, and other genetic disorders, are potentially curable if ways can be found to successfully introduce normal alleles of the genes into affected individuals.

13.3 Genes are on chromosomes.

Chromosomes: The Vehicles of Mendelian Inheritance

Chromosomes are not the only kinds of structures that segregate regularly when eukaryotic cells divide. Centrioles also divide and segregate in a regular fashion, as do the mitochondria and chloroplasts (when present) in the cytoplasm. Therefore, in the early twentieth century it was by no means obvious that chromosomes were the vehicles of hereditary information.

The Chromosomal Theory of Inheritance

A central role for chromosomes in heredity was first suggested in 1900 by the German geneticist Karl Correns, in one of the papers announcing the rediscovery of Mendel's work. Soon after, observations that similar chromosomes paired with one another during meiosis led directly to the **chromosomal theory of inheritance,** first formulated by the American Walter Sutton in 1902.

Several pieces of evidence supported Sutton's theory. One was that reproduction involves the initial union of only two cells, egg and sperm. If Mendel's model were correct, then these two gametes must make equal hereditary contributions. Sperm, however, contain little cytoplasm, suggesting that the hereditary material must reside within the nuclei of the gametes. Furthermore, while diploid individuals have two copies of each pair of homologous chromosomes, gametes have only one. This observation was consistent with Mendel's model, in which diploid individuals have two copies of each heritable gene and gametes have one. Finally, chromosomes segregate during meiosis, and each pair of homologues orients on the metaphase plate independently of every other pair. Segregation and independent assortment were two characteristics of the genes in Mendel's model.

A Problem with the Chromosomal Theory

However, investigators soon pointed out one problem with this theory. If Mendelian characters are determined by genes located on the chromosomes, and if the independent assortment of Mendelian traits reflects the independent assortment of chromosomes in meiosis, why does the number of characters that assort independently in a given kind of organism often greatly exceed the number of chromosome pairs the organism possesses? This seemed a fatal objection, and it led many early researchers to have serious reservations about Sutton's theory.

Morgan's White-Eyed Fly

The essential correctness of the chromosomal theory of heredity was demonstrated long before this paradox was resolved. A single small fly provided the proof. In 1910 Thomas Hunt Morgan, studying the fruit fly *Drosophila melanogaster*, detected a **mutant** male fly, one that differed strikingly from normal flies of the same species: its eyes were white instead of red (figure 13.29).

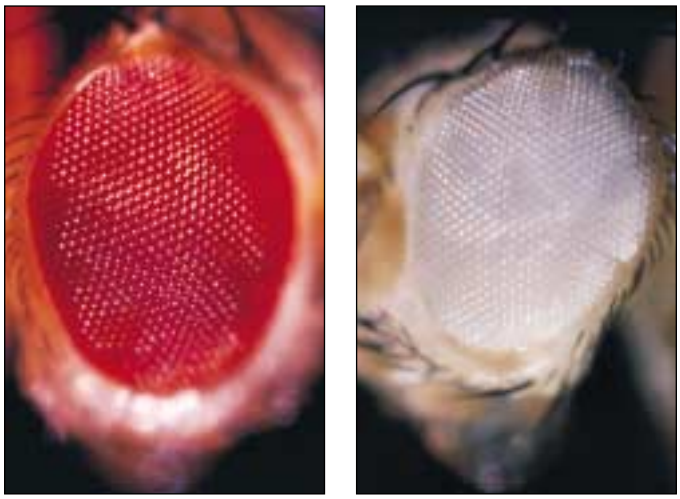


FIGURE 13.29
Red-eyed (normal) and white-eyed (mutant) *Drosophila*. The white-eyed defect is hereditary, the result of a mutation in a gene located on the X chromosome. By studying this mutation, Morgan first demonstrated that genes are on chromosomes.

Morgan immediately set out to determine if this new trait would be inherited in a Mendelian fashion. He first crossed the mutant male to a normal female to see if red or white eyes were dominant. All of the F_1 progeny had red eyes, so Morgan concluded that red eye color was dominant over white. Following the experimental procedure that Mendel had established long ago, Morgan then crossed the red-eyed flies from the F_1 generation with each other. Of the 4252 F_2 progeny Morgan examined, 782 (18%) had white eyes. Although the ratio of red eyes to white eyes in the F_2 progeny was greater than 3:1, the results of the cross nevertheless provided clear evidence that eye color segregates. However, there was something about the outcome that was strange and totally unpredicted by Mendel's theory—*all of the white-eyed F_2 flies were males!*

How could this result be explained? Perhaps it was impossible for a white-eyed female fly to exist; such individuals might not be viable for some unknown reason. To test this idea, Morgan testcrossed the female F_1 progeny with the original white-eyed male. He obtained both white-eyed and red-eyed males and females in a 1:1:1:1 ratio, just as Mendelian theory predicted. Hence, a female could have white eyes. Why, then, were there no white-eyed females among the progeny of the original cross?

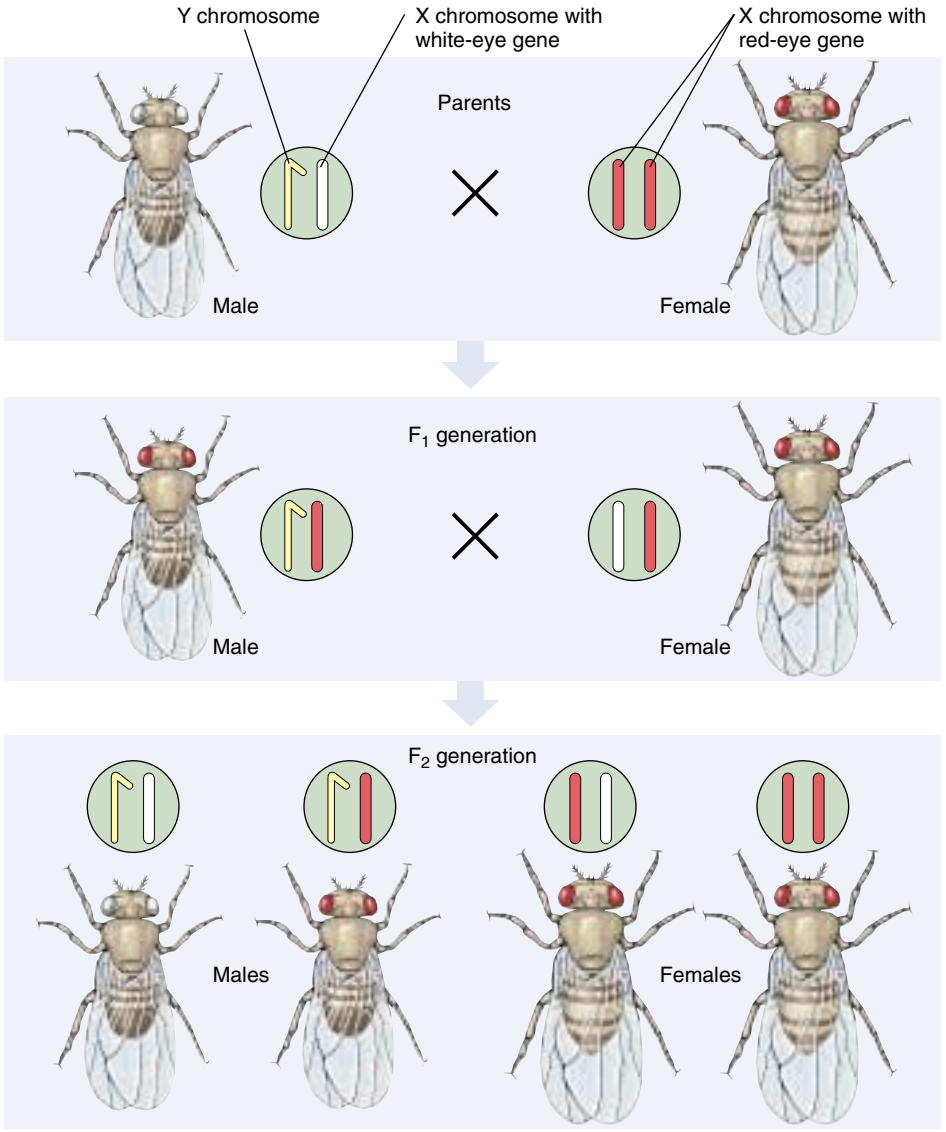


FIGURE 13.30
Morgan's experiment demonstrating the chromosomal basis of sex linkage in *Drosophila*. The white-eyed mutant male fly was crossed with a normal female. The F_1 generation flies all exhibited red eyes, as expected for flies heterozygous for a recessive white-eye allele. In the F_2 generation, all of the white-eyed flies were male.

Sex Linkage

The solution to this puzzle involved sex. In *Drosophila*, the sex of an individual is determined by the number of copies of a particular chromosome, the **X chromosome,** that an individual possesses. A fly with two X chromosomes is a female, and a fly with only one X chromosome is a male. In males, the single X chromosome pairs in meiosis with a dissimilar partner called the **Y chromosome.** The female thus produces only X gametes, while the male produces both X and Y gametes. When fertilization involves an X sperm, the result is an XX zygote, which develops into a female; when fertilization involves a Y sperm, the result is an XY zygote, which develops into a male.

The solution to Morgan's puzzle is that the gene causing the white-eye trait in *Drosophila* resides only on the X chromosome—it is absent from the Y chromosome. (We now know that the Y chromosome in flies carries almost no functional genes.) A trait determined by a gene on the X chromosome is said to be **sex-linked.** Knowing the white-eye trait is recessive to the red-eye trait, we can now see that Morgan's result was a natural consequence of the Mendelian assortment of chromosomes (figure 13.30).

Morgan's experiment was one of the most important in the history of genetics because it presented the first clear evidence that the genes determining Mendelian traits do indeed reside on the chromosomes, as Sutton had proposed. The segregation of the white-eye trait has a one-to-one correspondence with the segregation of the X chromosome. In other words, Mendelian traits such as eye color in *Drosophila* assort independently because chromosomes do. When Mendel observed the segregation of alternative traits in pea plants, he was observing a reflection of the meiotic segregation of chromosomes.

Mendelian traits assort independently because they are determined by genes located on chromosomes that assort independently in meiosis.

Genetic Recombination

Morgan's experiments led to the general acceptance of Sutton's chromosomal theory of inheritance. Scientists then attempted to resolve the paradox that there are many more independently assorting Mendelian genes than chromosomes. In 1903 the Dutch geneticist Hugo de Vries suggested that this paradox could be resolved only by assuming that homologous chromosomes exchange elements during meiosis. In 1909, French cytologist F. A. Janssens provided evidence to support this suggestion. Investigating chiasmata produced during amphibian meiosis, Janssens noticed that of the four chromatids involved in each chiasma, two crossed each other and two did not. He suggested that this crossing of chromatids reflected a switch in chromosomal arms between the paternal and maternal homologues, involving one chromatid in each homologue. His suggestion was not accepted widely, primarily because it was difficult to see how two chromatids could break and rejoin at exactly the same position.

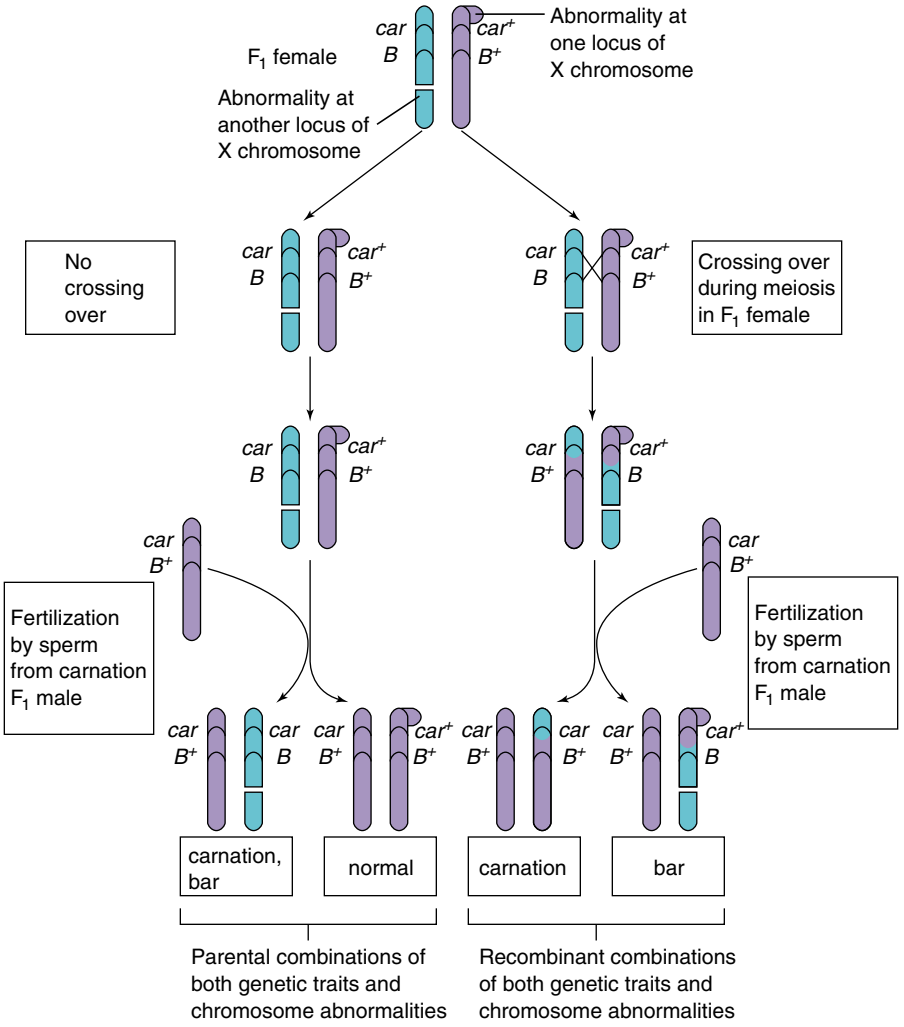


FIGURE 13.31
Stern's experiment demonstrating the physical exchange of chromosomal arms during crossing over. Stern monitored crossing over between two genes, the recessive carnation eye color (*car*) and the dominant bar-shaped eye (*B*), on chromosomes with physical peculiarities visible under a microscope. Whenever these genes recombined through crossing over, the chromosomes recombined as well. Therefore, the recombination of genes reflects a physical exchange of chromosome arms. The "+" notation on the alleles refers to the wild-type allele, the most common allele at a particular gene.

Crossing Over

Later experiments clearly established that Janssens was indeed correct. One of these experiments, performed in 1931 by American geneticist Curt Stern, is described in figure 13.31. Stern studied two sex-linked eye characters in *Drosophila* strains whose X chromosomes were visibly abnormal at both ends. He first examined many flies and identified those in which an exchange had occurred with respect to the two eye characters. He then studied the chromosomes of those flies to see if their X chromosomes had exchanged arms. Stern found that all of the individuals that had exchanged eye traits also possessed chromosomes that had exchanged abnormal ends. The conclusion was inescapable: genetic exchanges of characters such as eye color involve the physical exchange of chromosome arms, a phenomenon called **crossing over.** Crossing over creates new combinations of genes, and is thus a form of **genetic recombination.**

The chromosomal exchanges Stern demonstrated provide the solution to the paradox, because crossing over can occur between homologues anywhere along the length of the chromosome, in locations that seem to be randomly determined. Thus, if two different genes are located relatively far apart on a chromosome, crossing over is more likely to occur somewhere between them than if they are located close together. Two genes can be on the same chromosome and still show independent assortment if they are located so far apart on the chromosome that crossing over occurs regularly between them (figure 13.32).

Using Recombination to Make Genetic Maps

Because crossing over is more frequent between two genes that are relatively far apart than between two that are close together, the frequency of crossing over can be used to map the relative positions of genes on chromosomes. In a cross, the proportion of progeny exhibiting an exchange between two genes is a measure of the frequency of crossover events between them, and thus indicates the relative distance separating them. The results of such crosses can be used to construct a **genetic map** that measures distance between genes in terms of the frequency of recombination. One "map unit" is defined as the distance within which a crossover event is expected to occur in an average of 1% of gametes. A map unit is now called a **centimorgan,** after Thomas Hunt Morgan.

In recent times new technologies have allowed geneticists to create gene maps based on the relative positions of specific gene sequences called *restriction sites* because they are recognized by DNA-cleaving enzymes called restriction endonucleases. Restriction maps, discussed in chapter 19, have largely supplanted genetic recombination maps for detailed gene analysis because they are far easier to produce. Recombination maps remain the method of choice for genes widely separated on a chromosome.

The Three-Point Cross. In constructing a genetic map, one simultaneously monitors recombination among three or more genes located on the same chromosome, referred to as **syntenic** genes. When genes are close enough together on a chromosome that they do not assort independently, they are said to be **linked** to one another. A cross involving three linked genes is called a **three-point cross.** Data obtained by Morgan on traits encoded by genes on the X chromosome of *Drosophila* were used by his student A. H. Sturtevant, to draw the first genetic map (figure 13.33). By convention, the most common allele of a gene is often denoted with the symbol "+" and is designated as **wild type.** All other alleles are denoted with just the specific letters.

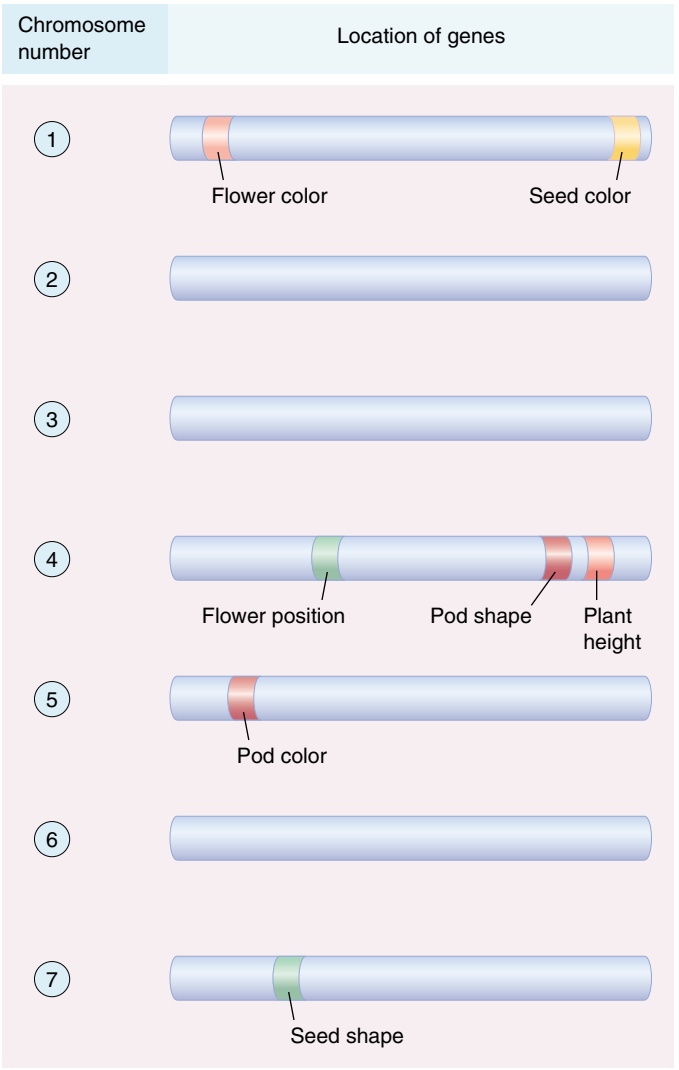


FIGURE 13.32
The chromosomal locations of the seven genes studied by Mendel in the garden pea. The genes for plant height and pod shape are very close to each other and rarely recombine. Plant height and pod shape were not among the characters Mendel examined in dihybrid crosses. One wonders what he would have made of the linkage he surely would have detected had he tested these characters.

FIGURE 13.33
The first genetic map. This map of the X chromosome of *Drosophila* was prepared in 1913 by A. H. Sturtevant, a student of Morgan. On it he located the relative positions of five recessive traits that exhibited sex linkage by estimating their relative recombination frequencies in genetic crosses. Sturtevant arbitrarily chose the position of the *yellow* gene as zero on his map to provide a frame of reference. The higher the recombination frequency, the farther apart the two genes.

Five traits		Recombination frequencies		Genetic map
y	Yellow body color	*y* and *w*	0.010	.58 *r*
w	White eye color	*v* and *m*	0.030	
v	Vermilion eye color	*v* and *r*	0.269	
m	Miniature wing	*v* and *w*	0.300	.34 *m*
r	Rudimentary wing	*v* and *y*	0.322	.31 *v*
		w and *m*	0.327	
		y and *m*	0.355	.01 *w*
		w and *r*	0.450	0 *y*

Analyzing a Three-Point Cross. The first genetic map was constructed by A. H. Sturtevant, a student of Morgan's in 1913. He studied several traits of *Drosophila*, all of which exhibited sex linkage and thus were encoded by genes residing on the same chromosome (the X chromosome). Here we will describe his study of three traits: *y*, yellow body color (the normal body color is gray), *w*, white eye color (the normal eye color is red), and *m*, miniature wing (the normal wing is 50% longer).

Sturtevant carried out the mapping cross by crossing a female fly homozygous for the three recessive alleles with a normal male fly that carried none of them. All of the progeny were heterozygotes. Such a cross is conventionally represented by a diagram like the one that follows, in which the lines represent gene locations and + indicates the normal, or "wild-type" allele. Each female fly participating in a cross possesses two homologous copies of the chromosome being mapped, and both chromosomes are represented in the diagram. Crossing over occurs between these two copies in meiosis.

P generation $\frac{y\ w\ m}{y\ w\ m} \times \frac{y^+\ w^+\ m^+}{\quad}$ (Y chromosome)

$\downarrow$

F_1 generation females $\frac{y\ w\ m}{y^+\ w^+\ m^+}$

These heterozygous females, the F_1 generation, are the key to the mapping procedure. Because they are heterozygous, any crossing over that occurs during meiosis will, if it occurs between where these genes are located, produce gametes with different combinations of alleles for these genes—in other words, recombinant chromosomes. Thus, a crossover between the homologous X chromosomes of such a female in the interval between the *y* and *w* genes will yield recombinant [$y\ w^+$] and [$y^+\ w$] chromosomes, which are different combinations than we started with. In the diagram below, the crossed lines between the chromosomes indicate where the crossover occurs. (In the parental chromosomes of this cross, *w* is always linked with *y* and y^+ linked with w^+.)

$$\frac{y\ \ w\ m}{y^+\ w^+\ m^+} \rightarrow \frac{y\ \ w^+\ m^+}{y^+\ w\ \ m}$$

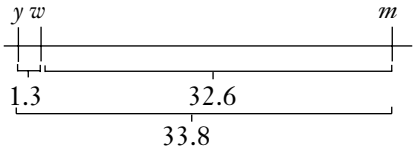
In order to see all the recombinant types that might be present among the gametes of these heterozygous flies, Sturtevant conducted a testcross. He crossed female heterozygous flies to males recessive for all three traits and examined the progeny. Because males contribute either a Y chromosome with no genes on it or an X chromosome with recessive alleles at all three loci, the male contribution does not disguise the potentially recombinant female chromosomes.

Table 13.3 summarizes the results Sturtevant obtained. The parentals are represented by the highest number of progeny and the double crossovers (progeny in which two crossovers occurred) by the lowest number. To analyze his data, Sturtevant considered the traits in pairs and determined which involved a crossover event.

1. For the body trait (*y*) and the eye trait (*w*), the first two classes, [$y^+\ w^+$] and [$y\ w$], involve no crossovers (they are parental combinations). In table 13.3, no progeny numbers are tabulated for these two classes on the "body-eye" column (a dash appears instead).
2. The next two classes have the same body-eye combination as the parents, [$y^+\ w^+$] and [$y\ w$], so again no numbers are entered as recombinants under body-eye crossover type.
3. The next two classes, [$y^+\ w$] and [$y\ w^+$], do *not* have the same body-eye combinations as the parent chromosomes, so the observed numbers of progeny are recorded, 16 and 12, respectively.
4. The last two classes also differ from parental chromosomes in body-eye combination, so again the observed numbers of each class are recorded, 1 and 0.
5. The sum of the numbers of observed progeny that are recombinant for body (*y*) and eye (*w*) is 16 + 12 + 1, or 29. Because the total number of progeny is 2205, this represents 29/2205, or 0.01315. The percentage of recombination between *y* and *w* is thus 1.315%, or 1.3 centimorgans.

To estimate the percentage of recombination between eye (*w*) and wing (*m*), one proceeds in the same manner, obtaining a value of 32.608%, or 32.6 centimorgans. Similarly, body (*y*) and wing (*m*) are separated by a recombination distance of 33.832%, or 33.8 centimorgans.

From this, then, we can construct our genetic map. The biggest distance, 33.8 centimorgans, separates the two outside genes, which are evidently *y* and *m*. The gene *w* is between them, near *y*.



The two distances 1.3 and 32.6 do not add up to 33.8 but rather to 33.9. The difference, 0.1, represents chromosomes in which two crossovers occurred, one between *y* and *w* and another between *w* and *m*. These chromosomes do not exhibit recombination between *y* and *m*.

Genetic maps such as this are key tools in genetic analysis, permitting an investigator reliably to predict how a newly discovered trait, once it has been located on the chromosome map, will recombine with many others.

Table 13.3 Sturtevant's Results

	Phenotypes				Crossover Types		
	Body	Eye	Wing	Number of Progeny	Body-Eye	Eye-Wing	Body-Wing
Parental	y^+	w^+	m^+	758	—	—	—
	y	w	m	700	—	—	—
Single crossover	y^+	w^+	m	401	—	401	401
	y	w	m^+	317	—	317	317
	y^+	w	m	16	16	—	16
	y	w^+	m^+	12	12	—	12
Double crossover	y^+	w	m^+	1	1	1	—
	y	w^+	m	0	0	0	—
TOTAL				2205	29	719	746
Recombination frequency (%)					1.315	32.608	33.832

The Human Genetic Map

Genetic maps of human chromosomes (figure 13.34) are of great importance. Knowing where particular genes are located on human chromosomes can often be used to tell whether a fetus at risk of inheriting a genetic disorder actually has the disorder. The genetic-engineering techniques described in chapter 19 have begun to permit investigators to isolate specific genes and determine their nucleotide sequences. It is hoped that knowledge of differences at the gene level may suggest successful therapies for particular genetic disorders and that knowledge of a gene's location on a chromosome will soon permit the substitution of normal alleles for dysfunctional ones. Because of the great potential of this approach, investigators are working hard to assemble a detailed map of the entire human genome, the **Human Genome Project,** described in chapter 19. Initially, this map will consist of a "library" of thousands of small fragments of DNA whose relative positions are known. Investigators wishing to study a particular gene will first use techniques described in chapter 19 to screen this library and determine which fragment carries the gene of interest. They will then be able to analyze that fragment in detail. In parallel with this mammoth undertaking, the other, smaller genomes have already been sequenced, including those of yeasts and several bacteria. Progress on the human genome is rapid, and the full map is expected within the next 10 years.

Gene maps locate the relative positions of different genes on the chromosomes of an organism. Traditionally produced by analyzing the relative amounts of recombination in genetic crosses, gene maps are increasingly being made by analyzing the sizes of fragments made by restriction enzymes.

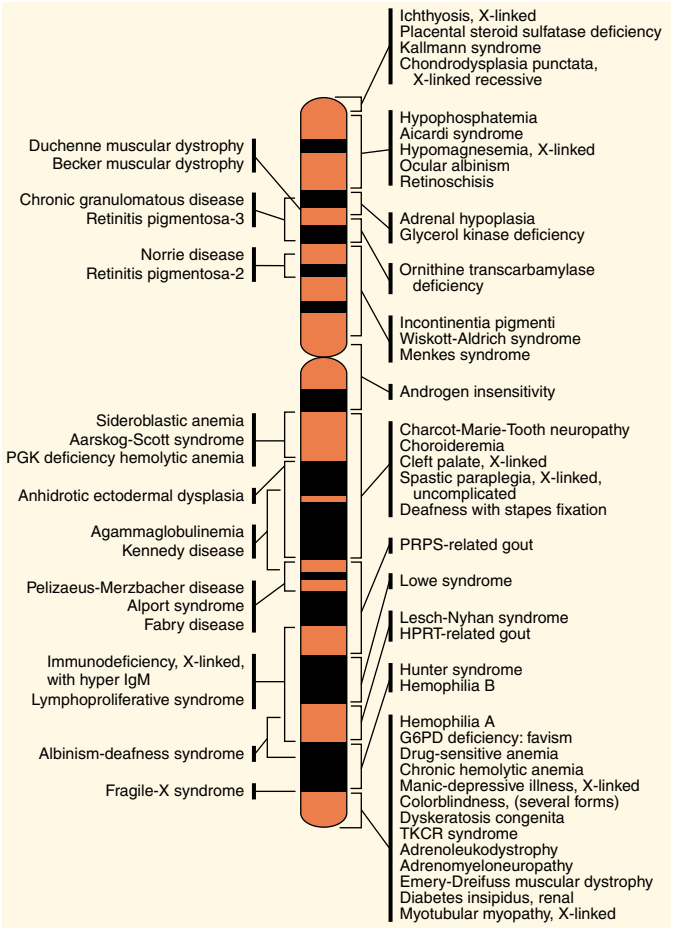


FIGURE 13.34
The human X chromosome gene map. Over 59 diseases have been traced to specific segments of the X chromosome. Many of these disorders are also influenced by genes on other chromosomes.

Human Chromosomes

Each human somatic cell normally has 46 chromosomes, which in meiosis form 23 pairs. By convention, the chromosomes are divided into seven groups (designated A through G), each characterized by a different size, shape, and appearance. The differences among the chromosomes are most clearly visible when the chromosomes are arranged in order in a karyotype (figure 13.35). Techniques that stain individual segments of chromosomes with different-colored dyes make the identification of chromosomes unambiguous. Like a fingerprint, each chromosome always exhibits the same pattern of colored bands.

Human Sex Chromosomes

Of the 23 pairs of human chromosomes, 22 are perfectly matched in both males and females and are called **autosomes.** The remaining pair, the **sex chromosomes,** consist of two similar chromosomes in females and two dissimilar chromosomes in males. In humans, females are designated XX and males XY. One of the sex chromosomes in the male (the Y chromosome) is highly condensed and bears few functional genes. Because few genes on the Y chromosome are expressed, recessive alleles on a male's single X chromosome have no *active* counterpart on the Y chromosome. Some of the active genes the Y chromosome does possess are responsible for the features associated with "maleness" in humans. Consequently, any individual with *at least* one Y chromosome is a male.

Sex Chromosomes in Other Organisms

The structure and number of sex chromosomes vary in different organisms (table 13.4). In the fruit fly D*rosophila*, females are XX and males XY, as in humans and most other vertebrates. However, in birds, the male has two Z chromosomes, and the female has a Z and a W chromosome. In some insects, such as grasshoppers, there is no Y chromosome—females are XX and males are characterized as XO (the O indicates the absence of a chromosome).

Sex Determination

In humans a specific gene located on the Y chromosome known as *SRY* plays a key role in development of male sexual characteristics. This gene is expressed early in development, and acts to masculinize genitalia and secondary sexual organs that would otherwise be female. Lacking a Y chromosome, females fail to undergo these changes.

Among fishes and in some species of reptiles, environmental changes can cause changes in the expression of this sex-determining gene, and thus of the sex of the adult individual.

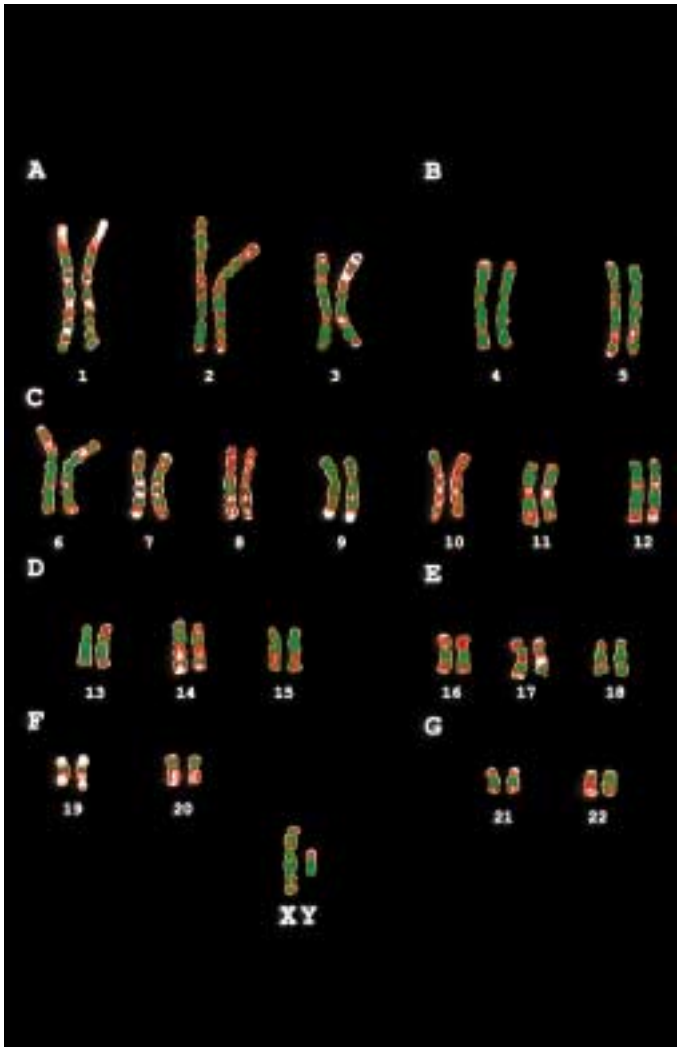


FIGURE 13.35
A human karyotype. This karyotype shows the colored banding patterns, arranged by class A–G.

Table 13.4 Sex Determination in Some Organisms

	Female	Male
Humans, *Drosophila*	XX	XY
Birds	ZW	ZZ
Grasshoppers	XX	XO
Honeybees	Diploid	Haploid

Barr Bodies

Although males have only one copy of the X chromosome and females have two, female cells do not produce twice as much of the proteins encoded by genes on the X chromosome. Instead, one of the X chromosomes in females is inactivated early in embryonic development, shortly after the embryo's sex is determined. Which X chromosome is inactivated varies randomly from cell to cell. If a woman is heterozygous for a sex-linked trait, some of her cells will express one allele and some the other. The inactivated and highly condensed X chromosome is visible as a darkly staining **Barr body** attached to the nuclear membrane (figure 13.36).

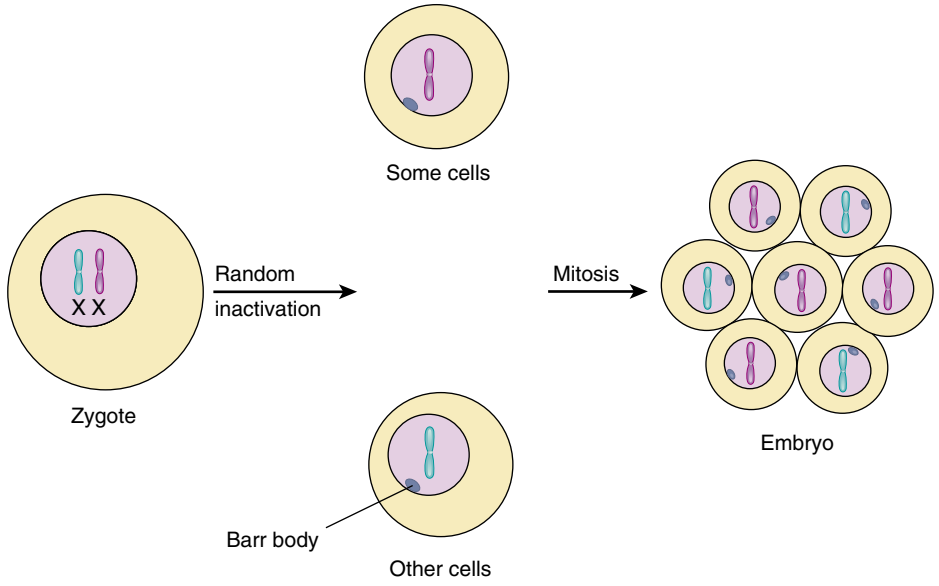


FIGURE 13.36
Barr bodies. In the developing female embryo, one of the X chromosomes (determined randomly) condenses and becomes inactivated. These condensed X chromosomes, called Barr bodies, then attach to the nuclear membrane.

X-inactivation is not restricted to humans. The patches of color on tortoiseshell and calico cats are a familiar result of this process. The gene for orange coat color is located on the X chromosome. The *O* allele specifies orange fur, and the *o* allele specifies black fur. Early in development, one X chromosome is inactivated in the cells that will become skin cells. If the remaining active X carries the *O* allele, then the patch of skin that results from that cell will have orange fur. If it carries the *o* allele, then the fur will be black. Because X-inactivation is a random process, the orange and black patches appear randomly in the cat's coat. Because only females have two copies of the X chromosome, only they can be heterozygous at the *O* gene, so almost all calico cats are females (figure 13.37). The exception is male cats that have the genotype XXY; the XXY genotype is discussed in the next section. The white on a calico cat is due to the action of an allele at another gene, the white spotting gene.

One of the 23 pairs of human chromosomes carries the genes that determine sex. The gene determining maleness is located on a version of the sex chromosome called Y, which has few other transcribed genes.

FIGURE 13.37
A calico cat. The coat coloration of this cat is due to the random inactivation of her X chromosome during early development. The female is heterozygous for orange coat color, but because only one coat color allele is expressed, she exhibits patches of orange and black fur.

Human Abnormalities Due to Alterations in Chromosome Number

Occasionally, homologues or sister chromatids fail to separate properly in meiosis, leading to the acquisition or loss of a chromosome in a gamete. This condition, called **primary nondisjunction,** can result in individuals with severe abnormalities if the affected gamete forms a zygote.

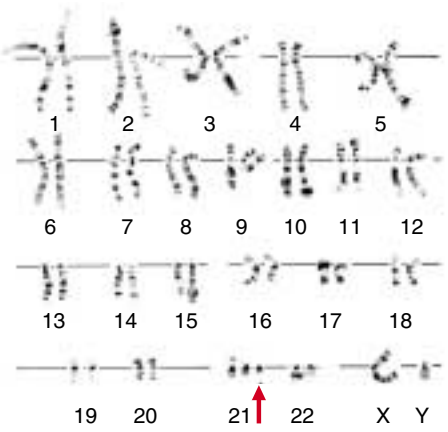


FIGURE 13.38
Down syndrome. As shown in this male karyotype, Down syndrome is associated with trisomy of chromosome 21. A child with Down syndrome sitting on his father's knee.

Nondisjunction Involving Autosomes

Almost all humans of the same sex have the same karyotype, for the same reason that all automobiles have engines, transmissions, and wheels: other arrangements don't work well. Humans who have lost even one copy of an autosome (called **monosomics**) do not survive development. In all but a few cases, humans who have gained an extra autosome (called **trisomics**) also do not survive. However, five of the smallest autosomes—those numbered 13, 15, 18, 21, and 22—can be present in humans as three copies and still allow the individual to survive for a time. The presence of an extra chromosome 13, 15, or 18 causes severe developmental defects, and infants with such a genetic makeup die within a few months. In contrast, individuals who have an extra copy of chromosome 21 or, more rarely, chromosome 22, usually survive to adulthood. In such individuals, the maturation of the skeletal system is delayed, so they generally are short and have poor muscle tone. Their mental development is also affected, and children with trisomy 21 or trisomy 22 are always mentally retarded.

Down Syndrome. The developmental defect produced by trisomy 21 (figure 13.38) was first described in 1866 by J. Langdon Down; for this reason, it is called **Down syndrome** (formerly "Down's syndrome"). About 1 in every 750 children exhibits Down syndrome, and the frequency is similar in all racial groups. Similar conditions also occur in chimpanzees and other related primates. In humans, the defect is associated with a particular small portion of chromosome 21. When this chromosomal segment is present in three copies instead of two, Down syndrome results. In 97% of the human cases examined, all of chromosome 21 is present in three copies. In the other 3%, a small portion of chromosome 21 containing the critical segment has been added to another chromosome by a process called *translocation* (see chapter 18); it exists along with the normal two copies of chromosome 21. This condition is known as *translocation Down syndrome.*

Not much is known about the developmental role of the genes whose extra copies produces Down syndrome, although clues are beginning to emerge from current research. Some researchers suspect that the gene or genes that produce Down syndrome are similar or identical to some of the genes associated with cancer and with Alzheimer's disease. The reason for this suspicion is that one of the human cancer-causing genes (to be described in chapter 18) and the gene causing Alzheimer's disease are located on the segment of chromosome 21 associated with Down syndrome. Moreover, cancer is more common in children with Down syndrome. The incidence of leukemia, for example, is 11 times higher in children with Down syndrome than in unaffected children of the same age.

How does Down syndrome arise? In humans, it comes about almost exclusively as a result of primary nondisjunction of chromosome 21 during egg formation. The cause of these primary nondisjunctions is not known, but their incidence, like that of cancer, increases with age (figure 13.39). In mothers younger than 20 years of age, the risk of giving birth to a child with Down syndrome is about 1 in 1700; in mothers 20 to 30 years old, the risk is only about 1 in 1400. In mothers 30 to 35 years old, however, the risk rises to 1 in 750, and by age 45, the risk is as high as 1 in 16!

Primary nondisjunctions are far more common in women than in men because all of the eggs a woman will ever produce have developed to the point of prophase in meiosis I by the time she is born. By the time she has children, her eggs are as old as she is. In contrast, men produce new sperm daily. Therefore, there is a much greater chance for problems of various kinds, including those that cause primary nondisjunction, to accumulate over time in the gametes of women than in those of men. For this reason, the age of the mother is more critical than that of the father in couples contemplating childbearing.

Nondisjunction Involving the Sex Chromosomes

Individuals that gain or lose a sex chromosome do not generally experience the severe developmental abnormalities caused by similar changes in autosomes. Such individuals may reach maturity, but they have somewhat abnormal features.

The X Chromosome. When X chromosomes fail to separate during meiosis, some of the gametes that are produced possess both X chromosomes and so are XX gametes; the other gametes that result from such an event have no sex chromosome and are designated "O" (figure 13.40).

If an XX gamete combines with an X gamete, the resulting XXX zygote develops into a female with one functional X chromosome and two Barr bodies. She is sterile but usually normal in other respects. If an XX gamete instead combines with a Y gamete, the effects are more serious. The resulting XXY zygote develops into a sterile male who has many female body characteristics and, in some cases, diminished mental capacity. This condition, called *Klinefelter syndrome*, occurs in about 1 out of every 500 male births.

If an O gamete fuses with a Y gamete, the resulting OY zygote is nonviable and fails to develop further because humans cannot survive when they lack the genes on the X chromosome. If, on the other hand, an O gamete fuses with an X gamete, the XO zygote develops into a sterile female of short stature, with a webbed neck and immature sex organs that do not undergo changes during puberty. The mental abilities of an XO individual are in the low-normal range. This condition, called *Turner syndrome*, occurs roughly once in every 5000 female births.

The Y Chromosome. The Y chromosome can also fail to separate in meiosis, leading to the formation of YY gametes. When these gametes combine with X gametes, the XYY zygotes develop into fertile males of normal appearance. The frequency of the XYY genotype (Jacob's syndrome) is about 1 per 1000 newborn males, but it is approximately 20 times higher among males in penal and mental institutions. This observation has led to the highly controversial suggestion that XYY males are inherently antisocial, a suggestion supported by some studies but not by others. In any case, most XYY males do not develop patterns of antisocial behavior.

Gene dosage plays a crucial role in development, so humans do not tolerate the loss or addition of chromosomes well. Autosome loss is always lethal, and an extra autosome is with few exceptions lethal too. Additional sex chromosomes have less serious consequences, although they can lead to sterility.

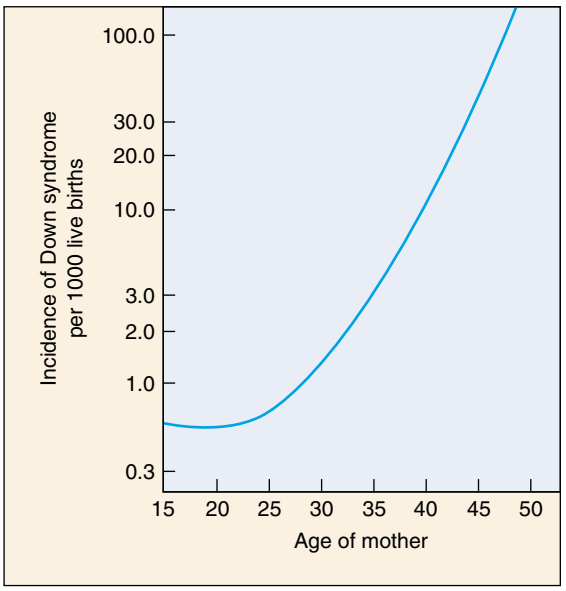


FIGURE 13.39
Correlation between maternal age and the incidence of Down syndrome. As women age, the chances they will bear a child with Down syndrome increase. After a woman reaches 35, the frequency of Down syndrome increases rapidly.

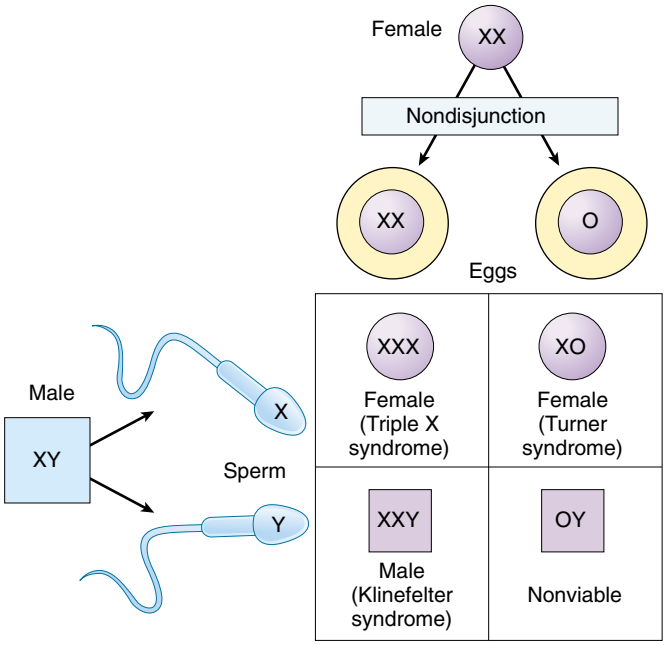


FIGURE 13.40
How nondisjunction can produce abnormalities in the number of sex chromosomes. When nondisjunction occurs in the production of female gametes, the gamete with two X chromosomes (XX) produces Klinefelter males (XXY) and XXX females. The gamete with no X chromosome (O) produces Turner females (XO) and nonviable OY males lacking any X chromosome.

Genetic Counseling

Although most genetic disorders cannot yet be cured, we are learning a great deal about them, and progress toward successful therapy is being made in many cases. In the absence of a cure, however, the only recourse is to try to avoid producing children with these conditions. The process of identifying parents at risk of producing children with genetic defects and of assessing the genetic state of early embryos is called *genetic counseling*.

If a genetic defect is caused by a recessive allele, how can potential parents determine the likelihood that they carry the allele? One way is through pedigree analysis, often employed as an aid in genetic counseling. By analyzing a person's pedigree, it is sometimes possible to estimate the likelihood that the person is a carrier for certain disorders. For example, if one of your relatives has been afflicted with a recessive genetic disorder such as cystic fibrosis, it is possible that you are a heterozygous carrier of the recessive allele for that disorder. When a couple is expecting a child, and pedigree analysis indicates that both of them have a significant probability of being heterozygous carriers of a recessive allele responsible for a serious genetic disorder, the pregnancy is said to be a **high-risk pregnancy.** In such cases, there is a significant probability that the child will exhibit the clinical disorder.

Another class of high-risk pregnancies is that in which the mothers are more than 35 years old. As we have seen, the frequency of birth of infants with Down syndrome increases dramatically in the pregnancies of older women (see figure 13.39).

When a pregnancy is diagnosed as being high-risk, many women elect to undergo *amniocentesis*, a procedure that permits the prenatal diagnosis of many genetic disorders. In the fourth month of pregnancy, a sterile hypodermic needle is inserted into the expanded uterus of the mother, removing a small sample of the amniotic fluid bathing the fetus (figure 13.41). Within the fluid are free-floating cells derived from the fetus; once removed, these cells can be grown in cultures in the laboratory. During amniocentesis, the position of the needle and that of the fetus are usually observed by means of *ultrasound.* The sound waves used in ultrasound are not harmful to mother or fetus, and they permit the person withdrawing the amniotic fluid to do so without damaging the fetus. In addition, ultrasound can be used to examine the fetus for signs of major abnormalities.

In recent years, physicians have increasingly turned to a new, less invasive procedure for genetic screening called **chorionic villi sampling.** In this procedure, the physician removes cells from the chorion, a membranous part of the placenta that nourishes the fetus. This procedure can be used earlier in pregnancy (by the eighth week) and yields results much more rapidly than does amniocentesis.

To test for certain genetic disorders, genetic counselors can look for three things in the cultures of cells obtained from amniocentesis or chorionic villi sampling. First, analysis of the karyotype can reveal aneuploidy (extra or missing chromosomes) and gross chromosomal alterations. Second, in many cases it is possible to test directly for the *proper functioning of enzymes* involved in genetic disorders. The lack of normal enzymatic activity signals the presence of the disorder. Thus, the lack of the enzyme responsible for breaking down phenylalanine signals PKU (phenylke-

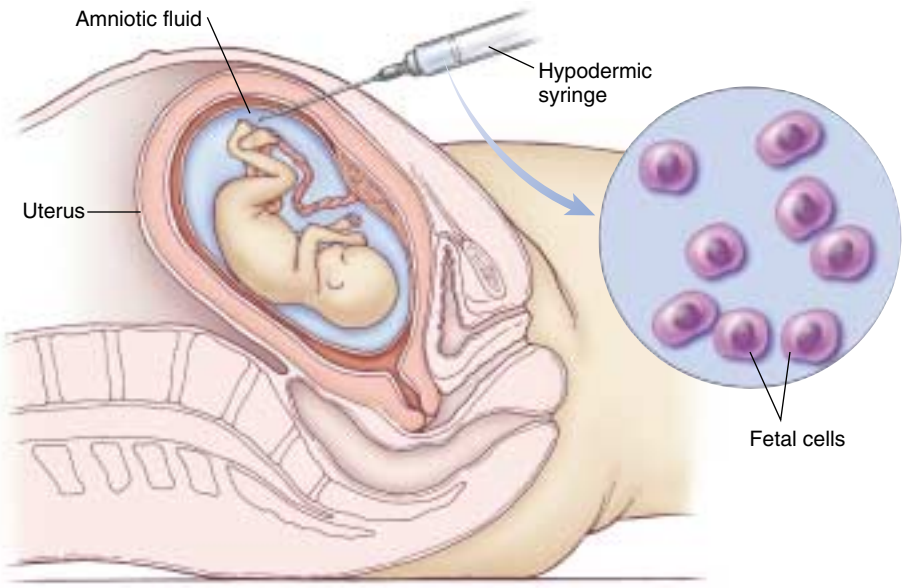


FIGURE 13.41
Amniocentesis. A needle is inserted into the amniotic cavity, and a sample of amniotic fluid, containing some free cells derived from the fetus, is withdrawn into a syringe. The fetal cells are then grown in culture and their karyotype and many of their metabolic functions are examined.

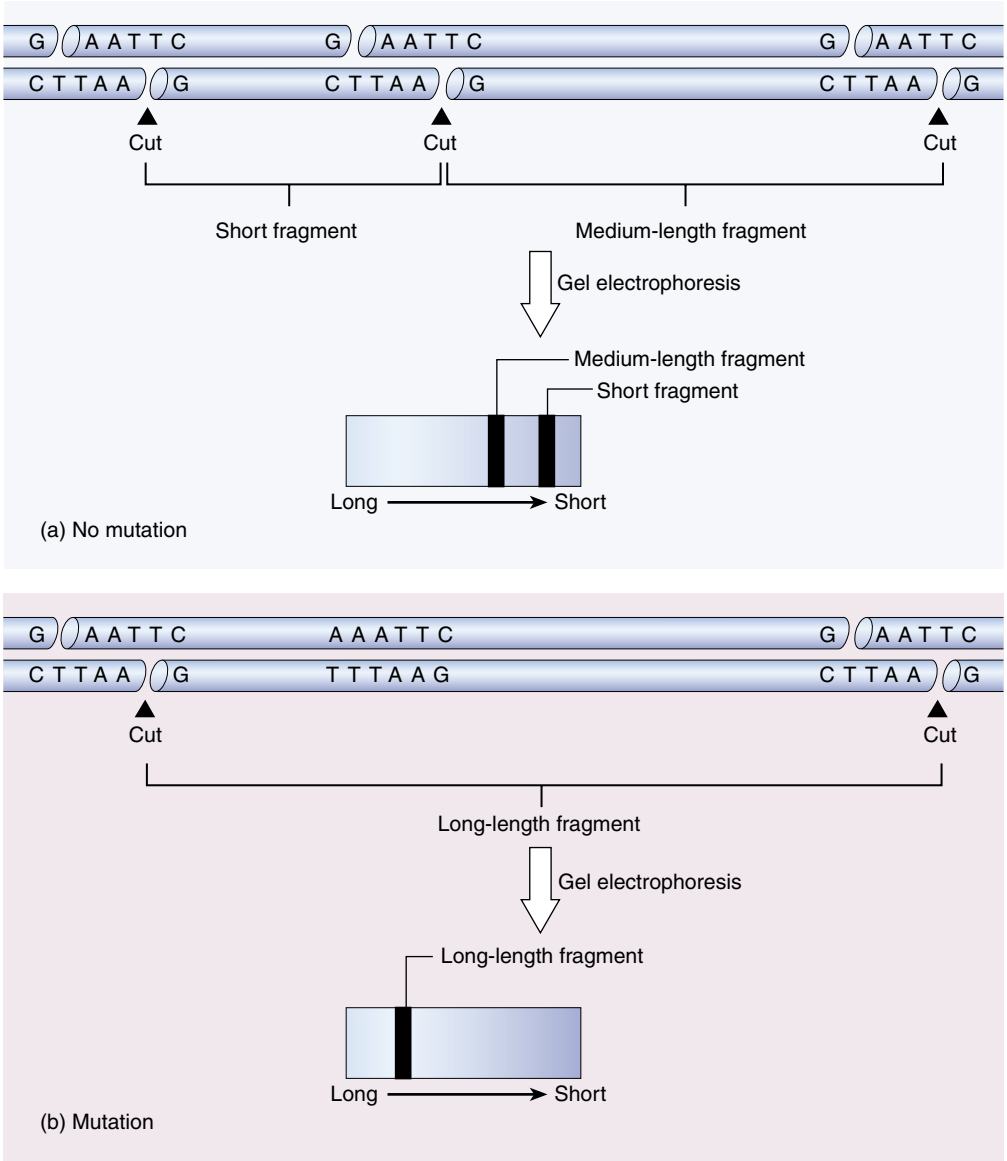


FIGURE 13.42
RFLPs. Restriction fragment length polymorphisms (RFLPs) are playing an increasingly important role in genetic identification. In (*a*), the restriction endonuclease cuts the DNA molecule in three places, producing two fragments. In (*b*), the mutation of a single nucleotide from G to A (see top fragment) alters a restriction endonuclease cutting site. Now the enzyme no longer cuts the DNA molecule at that site. As a result, a single long fragment is obtained, rather than two shorter ones. Such a change is easy to detect when the fragments are subjected to a technique called gel electrophoresis.

tonuria), the absence of the enzyme responsible for the breakdown of gangliosides indicates Tay-Sachs disease, and so forth.

Third, genetic counselors can look for an *association with known genetic markers.* For sickle cell anemia, Huntington's disease, and one form of muscular dystrophy (a genetic disorder characterized by weakened muscles), investigators have found other mutations on the same chromosomes that, by chance, occur at about the same place as the mutations that cause those disorders. By testing for the presence of these other mutations, a genetic counselor can identify individuals with a high probability of possessing the disorder-causing mutations. Finding such mutations in the first place is a little like searching for a needle in a haystack, but persistent efforts have proved successful in these three disorders. The associated mutations are detectable because they alter the length of the DNA segments that restriction enzymes produce when they cut strands of DNA at particular places (see chapter 18). Therefore, these mutations produce what are called **restriction fragment length polymorphisms,** or **RFLPs** (figure 13.42).

Many gene defects can be detected early in pregnancy, allowing for appropriate planning by the prospective parents.

Summary

Questions

Media Resources

13.1 Mendel solved the mystery of heredity.

- Koelreuter noted the basic facts of heredity a century before Mendel. He found that alternative traits segregate in crosses and may mask each other's appearance. Mendel, however, was the first to quantify his data, counting the numbers of each alternative type among the progeny of crosses.
- By counting progeny types, Mendel learned that the alternatives that were masked in hybrids (the F_1 generation) appeared only 25% of the time in the F_2 generation. This finding, which led directly to Mendel's model of heredity, is usually referred to as the Mendelian ratio of 3:1 dominant-to-recessive traits.
- When two genes are located on different chromosomes, the alleles assort independently.
- Because phenotypes are often influenced by more than one gene, the ratios of alternative phenotypes observed in crosses sometimes deviate from the simple ratios predicted by Mendel.

1. Why weren't the implications of Koelreuter's results recognized for a century?

2. What characteristics of the garden pea made this organism a good choice for Mendel's experiments on heredity?

3. To determine whether a purple-flowered pea plant of unknown genotype is homozygous or heterozygous, what type of plant should it be crossed with?

4. In a dihybrid cross between two heterozygotes, what fraction of the offspring should be homozygous recessive for both traits?

- Exploration: Heredity in families
- Introduction to Classic Genetics
- Monohybrid Cross
- Dihybrid Cross
- Experiments: Probability and Hypothesis Testing in Biology

13.2 Human genetics follows Mendelian principles.

- Some genetic disorders are relatively common in human populations; others are rare. Many of the most important genetic disorders are associated with recessive alleles, which are not eliminated from the human population, even though their effects in homozygotes may be lethal.

5. Why is Huntington's disease maintained at its current frequency in human populations?

- Beyond Mendel
- On Science Article: Advances in Gene Therapy
- Experiment: Muller-Lethal Mutations in Populations

13.3 Genes are on chromosomes.

- The first clear evidence that genes reside on chromosomes was provided by Thomas Hunt Morgan, who demonstrated that the segregation of the white-eye trait in *Drosophila* is associated with the segregation of the X chromosome, which is involved in sex determination.
- The first genetic evidence that crossing over occurs between chromosomes was provided by Curt Stern, who showed that when two Mendelian traits exchange during a cross, so do visible abnormalities on the ends of the chromosomes bearing those traits.
- The frequency of crossing over between genes can be used to construct genetic maps.
- Primary nondisjunction results when chromosomes do not separate during meiosis, leading to gametes with missing or extra chromosomes. In humans, the loss of an autosome is invariably fatal.

6. When Morgan crossed a white-eyed male fly with a normal red-eyed female, and then crossed two of the red-eyed progeny, about ¼ of the offspring were white-eyed—but they were ALL male! Why?

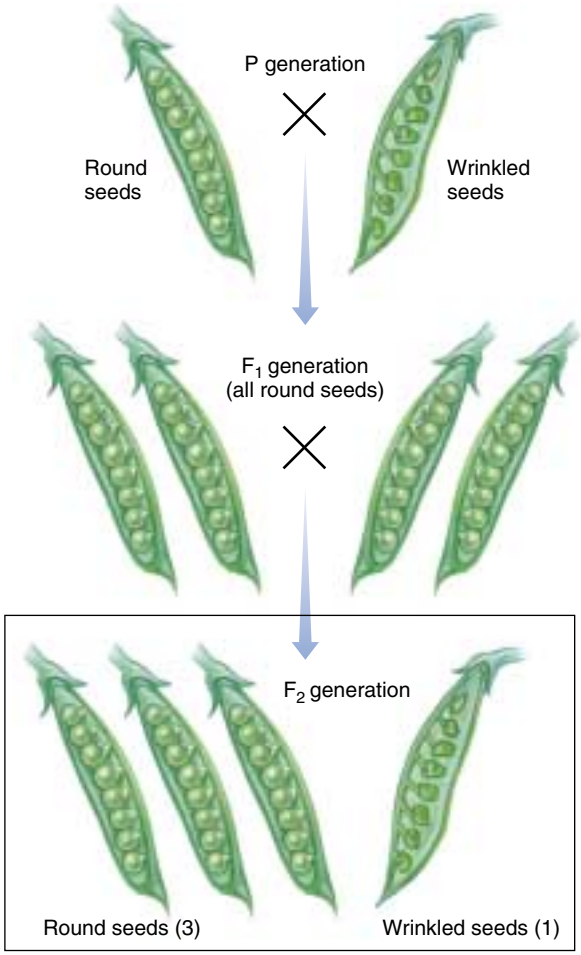
7. What is primary nondisjunction? How is it related to Down syndrome?

8. Is an individual with Klinefelter syndrome genetically male or female? Why?

- Exploration: Down Syndrome
- Exploration: Constructing a Genetic Map
- Exploration: Gene Segregation within families
- Exploration: Making a Restriction Map
- Exploration: Cystic Fibrosis
- Recombination
- Introduction to Chromosomes Sex Chromosomes
- Abnormal Chromosomes

Mendelian Genetics Problems

1. The illustration below describes Mendel's cross of *wrinkled* and *round* seed characters. (Hint: Do you expect all the seeds in a pod to be the same?) What is wrong with this diagram?



2. The annual plant *Haplopappus gracilis* has two pairs of chromosomes (1 and 2). In this species, the probability that two characters *a* and *b* selected at random will be on the same chromosome is equal to the probability that they will both be on chromosome 1 (½ × ½ = ¼, or 0.25), plus the probability that they will both be on chromosome 2 (also ½ × ½ = ¼, or 0.25), for an overall probability of ½, or 0.5. In general, the probability that two randomly selected characters will be on the same chromosome is equal to $1/n$ where n is the number of chromosome pairs. Humans have 23 pairs of chromosomes. What is the probability that any two human characters selected at random will be on the same chromosome?

3. Among Hereford cattle there is a dominant allele called *polled;* the individuals that have this allele lack horns. Suppose you acquire a herd consisting entirely of polled cattle, and you carefully determine that no cow in the herd has horns. Some of the calves born that year, however, grow horns. You remove them from the herd and make certain that no horned adult has gotten into your pasture. Despite your efforts, more horned calves are born the next year. What is the reason for the appearance of the horned calves? If your goal is to maintain a herd consisting entirely of polled cattle, what should you do?

4. An inherited trait among humans in Norway causes affected individuals to have very wavy hair, not unlike that of a sheep. The trait, called *woolly*, is very evident when it occurs in families; no child possesses woolly hair unless at least one parent does. Imagine you are a Norwegian judge, and you have before you a woolly-haired man suing his normal-haired wife for divorce because their first child has woolly hair but their second child has normal hair. The husband claims this constitutes evidence of his wife's infidelity. Do you accept his claim? Justify your decision.

5. In human beings, Down syndrome, a serious developmental abnormality, results from the presence of three copies of chromosome 21 rather than the usual two copies. If a female exhibiting Down syndrome mates with a normal male, what proportion of her offspring would you expect to be affected?

6. Many animals and plants bear recessive alleles for *albinism*, a condition in which homozygous individuals lack certain pigments. An albino plant, for example, lacks chlorophyll and is white, and an albino human lacks melanin. If two normally pigmented persons heterozygous for the same albinism allele marry, what proportion of their children would you expect to be albino?

7. You inherit a racehorse and decide to put him out to stud. In looking over the stud book, however, you discover that the horse's grandfather exhibited a rare disorder that causes brittle bones. The disorder is hereditary and results from homozygosity for a recessive allele. If your horse is heterozygous for the allele, it will not be possible to use him for stud because the genetic defect may be passed on. How would you determine whether your horse carries this allele?

8. In the fly *Drosophila*, the allele for dumpy wings (*d*) is recessive to the normal long-wing allele (d^+), and the allele for white eye (*w*) is recessive to the normal red-eye allele (w^+). In a cross of $d^+d^+w^+w \times d^+dww$, what proportion of the offspring are expected to be "normal" (long wings, red eyes)? What proportion are expected to have dumpy wings and white eyes?

9. Your instructor presents you with a *Drosophila* with red eyes, as well as a stock of white-eyed flies and another stock of flies homozygous for the red-eye allele. You know that the presence of white eyes in *Drosophila* is caused by homozygosity for a recessive allele. How would you determine whether the single red-eyed fly was heterozygous for the white-eye allele?

10. Some children are born with recessive traits (and, therefore, must be homozygous for the recessive allele specifying the trait), even though neither of the parents exhibits the trait. What can account for this?
11. You collect two individuals of *Drosophila*, one a young male and the other a young, unmated female. Both are normal in appearance, with the red eyes typical of *Drosophila*. You keep the two flies in the same bottle, where they mate. Two weeks later, the offspring they have produced all have red eyes. From among the offspring, you select 100 individuals, some male and some female. You cross each individually with a fly you know to be homozygous for the recessive allele *sepia*, which produces black eyes when homozygous. Examining the results of your 100 crosses, you observe that in about half of the crosses, only red-eyed flies were produced. In the other half, however, the progeny of each cross consists of about 50% red-eyed flies and 50% black-eyed flies. What were the genotypes of your original two flies?
12. Hemophilia is a recessive sex-linked human blood disease that leads to failure of blood to clot normally. One form of hemophilia has been traced to the royal family of England, from which it spread throughout the royal families of Europe. For the purposes of this problem, assume that it originated as a mutation either in Prince Albert or in his wife, Queen Victoria.
    a. Prince Albert did not have hemophilia. If the disease is a sex-linked recessive abnormality, how could it have originated in Prince Albert, a male, who would have been expected to exhibit sex-linked recessive traits?
    b. Alexis, the son of Czar Nicholas II of Russia and Empress Alexandra (a granddaughter of Victoria), had hemophilia, but their daughter Anastasia did not. Anastasia died, a victim of the Russian revolution, before she had any children. Can we assume that Anastasia would have been a carrier of the disease? Would your answer be different if the disease had been present in Nicholas II or in Alexandra?
13. In 1986, *National Geographic* magazine conducted a survey of its readers' abilities to detect odors. About 7% of Caucasians in the United States could not smell the odor of musk. If neither parent could smell musk, none of their children were able to smell it. On the other hand, if the two parents could smell musk, their children generally could smell it, too, but a few of the children in those families were unable to smell it. Assuming that a single pair of alleles governs this trait, is the ability to smell musk best explained as an example of dominant or recessive inheritance?
14. A couple with a newborn baby is troubled that the child does not resemble either of them. Suspecting that a mix-up occurred at the hospital, they check the blood type of the infant. It is type O. As the father is type A and the mother type B, they conclude a mix-up must have occurred. Are they correct?
15. Mabel's sister died of cystic fibrosis as a child. Mabel does not have the disease, and neither do her parents. Mabel is pregnant with her first child. If you were a genetic counselor, what would you tell her about the probability that her child will have cystic fibrosis?
16. How many chromosomes would you expect to find in the karyotype of a person with Turner syndrome?
17. A woman is married for the second time. Her first husband has blood type A and her child by that marriage has type O. Her new husband has type B blood, and when they have a child its blood type is AB. What is the woman's blood genotype and blood type?
18. Two intensely freckled parents have five children. Three eventually become intensely freckled and two do not. Assuming this trait is governed by a single pair of alleles, is the expression of intense freckles best explained as an example of dominant or recessive inheritance?
19. Total color blindness is a rare hereditary disorder among humans. Affected individuals can see no colors, only shades of gray. It occurs in individuals homozygous for a recessive allele, and it is not sex-linked. A man whose father is totally color blind intends to marry a woman whose mother is totally color blind. What are the chances they will produce offspring who are totally color blind?
20. A normally pigmented man marries an albino woman. They have three children, one of whom is an albino. What is the genotype of the father?
21. Four babies are born in a hospital, and each has a different blood type: A, B, AB, and O. The parents of these babies have the following pairs of blood groups: A and B, O and O, AB and O, and B and B. Which baby belongs to which parents?
22. A couple both work in an atomic energy plant, and both are exposed daily to low-level background radiation. After several years, they have a child who has Duchenne muscular dystrophy, a recessive genetic defect caused by a mutation on the X chromosome. Neither the parents nor the grandparents have the disease. The couple sue the plant, claiming that the abnormality in their child is the direct result of radiation-induced mutation of their gametes, and that the company should have protected them from this radiation. Before reaching a decision, the judge hearing the case insists on knowing the sex of the child. Which sex would be more likely to result in an award of damages, and why?