Mice, showing genetic variation in coat color.

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Study Plan

12.1 The Beginnings of Genetics: Mendel's Garden Peas

Mendel chose true-breeding garden peas for his experiments

Mendel first worked with single-character crosses

Mendel's single-character crosses led him to propose the principle of segregation

Mendel could predict both classes and proportions of offspring from his hypotheses

Mendel used a testcross to check the validity of his hypotheses

Mendel tested the independence of different genes in crosses

Mendel's research founded the field of genetics

Sutton's chromosome theory of inheritance related Mendel's genes to chromosomes

12.2 Later Modifications and Additions to Mendel's Hypotheses

In incomplete dominance, dominant alleles do not completely mask recessive alleles

In codominance, the effects of different alleles are equally detectable in heterozygotes

In multiple alleles, more than two alleles of a gene are present in a population

In epistasis, genes interact, with the activity of one gene influencing the activity of another gene

In polygenic inheritance, a character is controlled by the common effects of several genes

In pleiotropy, two or more characters are affected by a single gene

12 Mendel, Genes, and Inheritance

Why It Matters

Parties and champagne were among the last things on Ernest Irons's mind on New Year's Eve, 1904. Irons, a medical intern, was examining a blood specimen from a new patient and was sketching what he saw through his microscope—peculiarly elongated red blood cells **(Figure 12.1).** He and his supervisor, James Herrick, had never seen anything like them. The shape of the cells was reminiscent of a sickle, a cutting tool with a crescent-shaped blade.

The patient had complained of weakness, dizziness, shortness of breath, and pain. His father and two sisters had died from mysterious ailments that had damaged their lungs or kidneys. Did those deceased family members also have sickle-shaped red cells in their blood? Was there a connection between the abnormal cells and the ailments? How did the cells become sickled?

The medical problems that baffled Irons and Herrick killed their patient when he was only 32 years old. The patient's symptoms were characteristic of a genetic disorder now called *sickle-cell disease*. This disease develops when a person has received two copies of a gene (one from each parent) that codes for an altered subunit of hemoglobin, the oxygen-transporting protein in red blood cells. When oxygen sup-

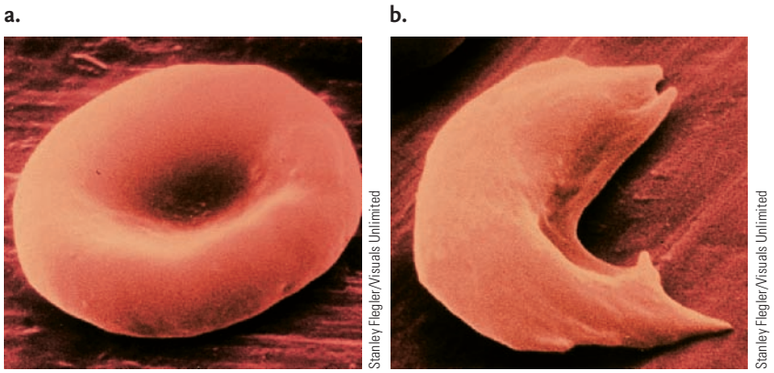


Figure 12.1
Red blood cell shape in sickle-cell disease. **(a)** A normal red blood cell. **(b)** A sickled red blood cell.

plies are low, the altered hemoglobin forms long, fibrous, crystal-like structures that push red blood cells into the sickle shape. The altered protein differs from the normal protein by just a single amino acid.

The sickled red blood cells are too elongated and inflexible to pass through the capillaries, the smallest vessels in the circulatory system. As a result, the cells block the capillaries. The surrounding tissues become starved for oxygen and saturated with metabolic wastes, causing the symptoms experienced by Irons and Herrick's patient. The problem worsens as oxygen concentration falls in tissues and more red blood cells are pushed into the sickled form. (You will learn more about sickle-cell disease in this chapter and in Chapter 13.)

Researchers have studied sickle-cell disease in great detail at both the molecular and the clinical levels. You may find it curious, though, that our understanding of sickle-cell disease—and all other heritable traits—actually began with studies of pea plants in a monastery garden.

Fifty years before Ernest Irons sketched sickled red blood cells, a scholarly monk named Gregor Mendel **(Figure 12.2)** used garden peas to study patterns of inheritance. To test his hypotheses about inheritance, Mendel bred generation after generation of pea plants and carefully observed the patterns by which parents transmit traits to their offspring. Through his experiments and observations, Mendel discovered the fundamental rules that govern inheritance. His discoveries and conclusions founded the science of genetics and still have the power to explain many of the puzzling and sometimes devastating aspects of inheritance that continue to occupy our attention.

Figure 12.2
Gregor Mendel (1822–1884), the founder of genetics.

12.1 The Beginnings of Genetics: Mendel's Garden Peas

Until about 1900, scientists and the general public believed in the **blending theory of inheritance**, which suggested that hereditary traits blend evenly in offspring through mixing of the parents' blood, much like the effect of mixing coffee and cream. Even today, many people assume that parental characteristics such as skin color, body size, and facial features blend evenly in their offspring, with the traits of the children appearing about halfway between those of their parents. Yet if blending takes place, why don't extremes, such as very tall and very short individuals, gradually disappear over generations as repeated blending takes place? Also, why do children with blue eyes keep turning up among the offspring of brown-eyed parents?

Gregor Mendel's experiments with garden peas, performed in the 1860s, provided the first answers to these questions and many more. Mendel was an Augustinian monk who lived in a monastery in Brünn, now part of the Czech Republic. But he had an unusual education for a monk in the mid-nineteenth century. He had studied mathematics, chemistry, zoology, and botany at the University of Vienna under some of the foremost scientists of his day. He had also been reared on a farm and was well aware of agricultural principles and their application. He kept abreast of breeding experiments published in scientific journals. Mendel also won several awards for developing improved varieties of fruits and vegetables.

In his work with peas, Mendel studied a variety of heritable characteristics called **characters**, such as flower color or seed shape. A variation in a character, such as purple or white flower color, is called a **trait.** Mendel established that characters are passed to offspring in the form of discrete hereditary factors, which now are known as genes. Mendel observed that, rather than blending evenly, many parental traits appear unchanged in offspring, whereas others disappear in one generation to reappear unchanged in the next. Although Mendel did not know it, the inheritance patterns he observed are the result of the segregation of chromosomes, on which the genes are located, to gametes in meiosis (see Chapter 11). Mendel's methods illustrate, perhaps as well as any experiments in the

history of science, how rigorous scientific work is conducted: through observation, making hypotheses, and testing the hypotheses with experiments.

Mendel Chose True-Breeding Garden Peas for His Experiments

Mendel chose the garden pea (*Pisum sativum;* **Figure 12.3**) for his research because the plant could be grown easily in the monastery garden, without elaborate equipment. As in other flowering plants, gametes are produced in structures of the flowers (see Figure 12.3). The male gametes are sperm nuclei contained in the pollen, which is produced in the *anthers* of the flower. The female gametes are egg cells, produced in the *carpel* of the flowers. Normally, pea plants **self-fertilize** (also known as **self-pollinate**, or more simply, *self*): sperm nuclei in pollen produced by anthers fertilize egg cells housed in the carpel of the same flower. However, for his experiments, Mendel prevented self-fertilization simply by cutting off the anthers. Pollen to fertilize these flowers must then come from a different plant. This technique is called **cross-pollination**, or more simply, a *cross*. This technique allowed Mendel to test the effects of mating pea plants of different parental types.

To begin his experiments, Mendel chose pea plants that were known to be **true-breeding** (also called *pure-breeding*); that is, when self-fertilized, or more simply, *selfed,* they passed traits without change from one generation to the next.

Mendel First Worked with Single-Character Crosses

Flower color was among the seven characters Mendel selected for study; one true-breeding variety of peas had purple flowers, and the other true-breeding variety had white flowers (see Figure 12.3). Would these traits blend evenly if plants with purple flowers were cross-pollinated with plants with white flowers?

To answer this question, Mendel took pollen from the anthers of plants with purple flowers and placed it in the flowers of white-flowered plants. He placed the pollen on the *stigma,* the part of the carpel that receives pollen in flowers (see Figure 12.3). He also performed the reciprocal experiment by placing pollen from white-flowered plants on the stigmas of purple-flowered plants. Seeds were the result of the crosses; each seed contains a zygote, or embryo, that will develop into a new pea plant. The plants that develop from the seeds produced by the cross—the first generation of offspring from the cross—are the **F_1 generation** (F stands for *filial; filius* = son). The plants used in the initial cross are called the parental or **P generation.** The plants that grew from the F_1 seeds all formed purple flowers, as if the trait for white flowers had disappeared. The flowers showed no evidence of blending.

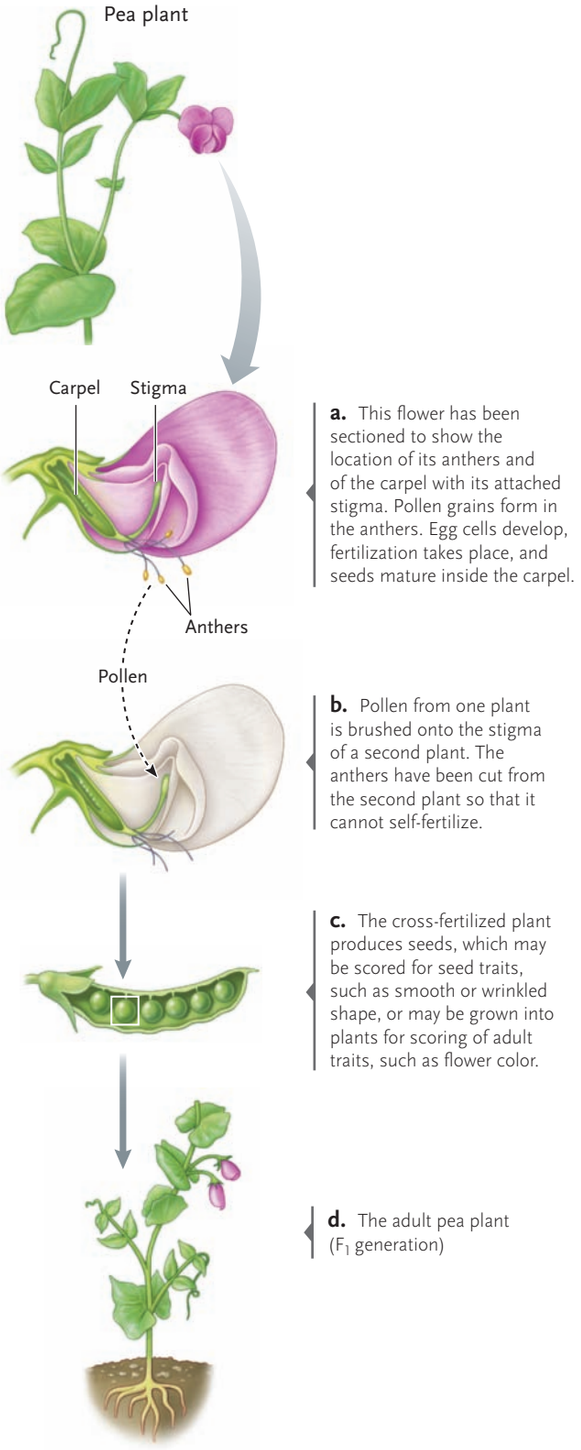


Figure 12.3
The garden pea *(Pisum sativum)*, the focus of Mendel's experiments.

Mendel then allowed the purple-flowered F_1 plants to self, producing seeds that represented the **F_2 generation.** When he planted the F_2 seeds produced by this cross, the white-flowered trait reappeared: both purple-flowered and white-flowered plants were produced. Mendel counted 705 plants with purple flowers and 224 with white flowers, in a ratio that he noted was

close to 3 : 1, or about 75% purple-flowered plants and 25% white-flowered plants.

Mendel made similar crosses that involved six other characters with pairs of traits **(Figure 12.4);** for example, the character of seed color has the traits yellow and green. In all cases, he observed a uniform F_1 generation, in which only one of the two traits was present. In the F_2 generation, the missing trait reappeared, and both traits were present among the offspring. Moreover, the trait present in the F_1 generation was present in a definite, predictable proportion among the offspring.

Mendel's Single-Character Crosses Led Him to Propose the Principle of Segregation

Using his knowledge of mathematics, Mendel developed a set of hypotheses to explain the results of his crosses. His first hypothesis was: *The adult plants carry a* pair *of factors that govern the inheritance of each character.* He correctly deduced that for each character, an organism inherits one factor from each parent.

In modern terminology, Mendel's factors are called *genes,* which are located on chromosomes; the different versions of a gene, producing different traits of a character, are **alleles** of the gene (see Section 11.1). Although Mendel did not use the modern terms *genes* and *alleles,* we use them in this chapter in our description of Mendel's work. Thus, there are two alleles of the gene that govern flower color in garden peas: one allele for purple flower color and the other allele for white flower color. Organisms with two copies of each gene are now known as diploids (see Section 11.1); the two alleles of a gene in a diploid individual may be identical or different.

How can the disappearance of one of the traits, such as white flowers, in the F_1 generation and its reappearance in the F_2 generation be explained? Mendel deduced that the trait that had seemed to "disappear" in the F_1 generation actually was present but was masked in some way by the "stronger" allele. Mendel called the masking effect **dominance.** Accordingly, Mendel's second hypothesis stated: *If an individual's pair of genes consists of different alleles, one allele is dominant over the other.* This hypothesis assumes that one allele is **dominant** and the other allele is **recessive.** When a dominant allele for a trait is paired with a recessive allele for the same trait, the dominant allele is

Figure 12.4
Mendel's crosses with seven different characters in peas, including his results and the calculated ratios of offspring.

Character	Traits crossed	F_1	F_2		Ratio
Seed shape	round × wrinkled	All round	5474 round	1850 wrinkled	2.96:1
Seed color	yellow × green	All yellow	6022 yellow	2001 green	3.01:1
Pod shape	inflated × constricted	All inflated	882 inflated	299 constricted	2.95:1
Pod color	green × yellow	All green	428 green	152 yellow	2.82:1
Flower color	purple × white	All purple	705 purple	224 white	3.15:1
Flower position	axial (along stems) × terminal (at tips)	All axial	651 axial	207 terminal	3.14:1
Stem length	tall × dwarf	All tall	787 tall	277 dwarf	2.84:1

expressed. By contrast, a recessive allele is expressed only when two copies of the allele are present. For example, for flower color in Mendel's experiments, the allele for purple flowers was dominant and the allele for white flowers was recessive.

As a third hypothesis, Mendel proposed: *The pairs of alleles that control a character* ***segregate*** *(separate) as gametes are formed; half the gametes carry one allele, and the other half carry the other allele.* This hypothesis is now known as Mendel's **Principle of Segregation.** During fertilization, fusion of the haploid maternal and paternal gametes produces a diploid nucleus called the *zygote nucleus*. The zygote nucleus receives one allele for the character from the male gamete and one allele for the same character from the female gamete, reuniting the pairs.

Mendel's three hypotheses explained the results of the crosses **(Figure 12.5).** Both alleles of the gene that governs flower color in the original, true-breeding parent plant with purple flowers are the same. The symbol *P* is used here to designate this allele, with the capital letter indicating that it is dominant, which gives this true-breeding parent the *PP* combination of alleles. Such an individual is called a **homozygote** (*homo* = same) and is said to be **homozygous** for the *P* allele. In other words, the individual has two copies of the same allele of the flower color gene. Therefore, when the individual produces gametes and the paired alleles separate, all the gametes of this individual will receive a *P* allele (see the left side heading in Figure 12.5a).

In the original true-breeding parent with white flowers, both alleles of the gene are also the same. The symbol *p* is used here to designate this allele, with the lowercase letter indicating that it is recessive, which gives this true-breeding plant the homozygous *pp* combination of alleles. These alleles also separate during gamete formation, producing gametes with one *p* allele (see the top heading in Figure 12.5a). (Mendel originated the practice of using uppercase and lowercase letters to designate dominant and recessive alleles.)

All the F_1 plants produced by crossing purple-flowered and white-flowered plants—the cross *PP* × *pp*—receive the same combination of alleles, *Pp* (see the cell in Figure 12.5a). An individual of this type, with two different alleles of a gene, is called a **heterozygote** (*hetero* = different) and is said to be **heterozygous** for the trait. Because *P* is dominant over *p,* all the *Pp* plants have purple flowers, even though they also carry the allele for white flowers. An F_1 heterozygote produced from a cross that involves a single character is called a **monohybrid** (*mono* = one; *hybrid* = an offspring of parents with different traits).

According to Mendel's hypotheses, all the *Pp* plants in the F_1 generation produce two kinds of gametes. Because the heterozygous *Pp* pair separates during gamete formation, half of the gametes receive the *P* allele and half receive the *p* allele. Figure 12.5b shows how these gametes can combine during selfing of F_1 plants. Generally, a cross between two individuals that are each heterozygous for the same pair of alleles—*Pp* × *Pp* here—is called a **monohybrid cross.** The gametes are entered in both the rows and columns in Figure 12.5b; the cells show the possible combinations. Combining two gametes that both carry the *P* allele produces a *PP* F_2 plant; combining *P* from one parent and *p* from the other produces a *Pp* plant; and combining *p* from both F_1 parents produces a *pp* F_2 plant. The homozygous *PP* and heterozygous *Pp* plants in the F_2 generation have purple flowers, the dominant trait; the homozygous *pp* offspring have white flowers, the recessive trait.

Mendel's hypotheses explain how individuals may differ genetically but still look the same. The *PP* and *Pp* plants, although genetically different, both have purple flowers. In modern terminology, **genotype** refers to the *genetic constitution of an organism,* and **phenotype** (Greek *phainein* = to show) refers to its *outward appearance*. In this case, the two different genotypes *PP* and *Pp* produce the same purple-flower phenotype.

Thus, the results of Mendel's crosses support his three hypotheses:

1. The genes that govern genetic characters occur in pairs in individuals.
2. If different alleles are present in an individual's pair of genes, one allele is dominant over the other.
3. The two alleles of a gene segregate and enter gametes singly.

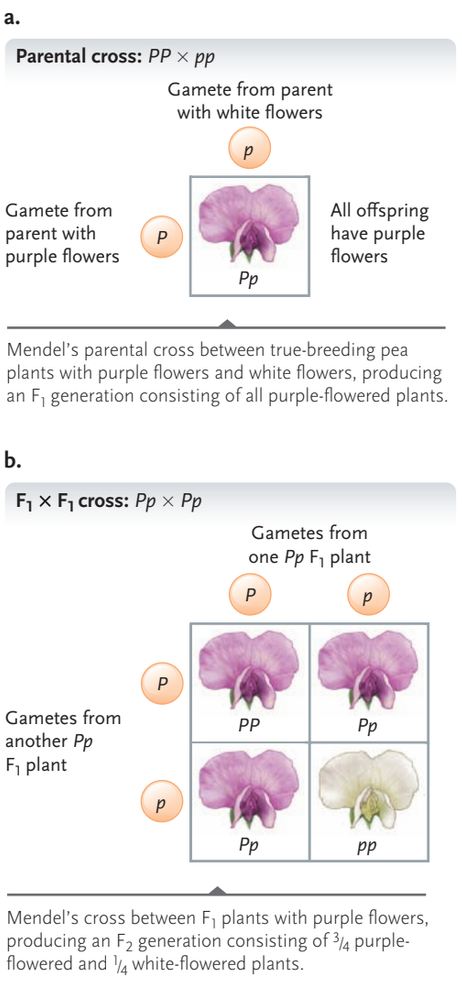


Figure 12.5
The principle of segregation in Mendel's crosses studying the inheritance of flower color in garden peas.

Mendel Could Predict Both Classes and Proportions of Offspring from His Hypotheses

Mendel could predict both classes and proportions of offspring from his hypotheses. To understand how Mendel's hypotheses allowed him to predict the proportions of offspring resulting from a genetic cross,

let's review the mathematical rules that govern **probability**—that is, the possibility that an outcome will occur if it is a matter of chance, as in the random fertilization of an egg by a sperm cell that contains one allele or another.

In the mathematics of probability, the likelihood of an outcome is predicted on a scale of 0 to 1. An outcome that is certain to occur has a probability of 1, and an outcome that cannot possibly happen has a probability of 0. If two different outcomes are equally likely, as in getting heads or tails in flipping a coin, we determine the probability of one of the outcomes by dividing that outcome by the total number of possible outcomes. For obtaining heads in flipping a coin, the probability is 1 divided by 2, or 1/2. The probabilities of all the possible outcomes, when added together, must equal 1. Thus, a coin flip has only two possible outcomes, heads or tails, each with a probability of 1/2; the sum of these probabilities is: $1/2 + 1/2 = 1$.

The Product Rule in Probability. What is the chance of flipping two heads in succession? Because the outcome of one flip has no effect on the next one, the two successive flips are independent. When two or more events are independent, the probability that they will occur in succession is calculated using the **product rule**—their individual probabilities are multiplied. That is, the probability that events A and B *both* will occur equals the probability of event A *multiplied* by the probability of event B. For example, the probability of getting heads on the first flip is 1/2; the probability of heads on the second flip is also 1/2 **(Figure 12.6).** Because the events are independent, the probability of getting two heads in a row is $1/2 \times 1/2 = 1/4$.

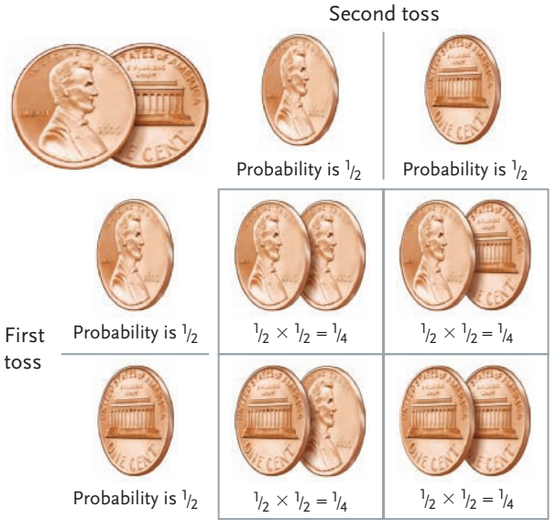


Figure 12.6
Rules of probability. For each coin toss, the probability of a head is 1/2; the probability of a tail is also 1/2. Because the outcome of the first toss is independent of the outcome of the second, the combined probabilities of the outcomes of successive tosses are calculated by multiplying their individual probabilities according to the product rule.

Applying the same principles, the probability of getting two tails is also $1/2 \times 1/2 = 1/4$ (see Figure 12.6). Similarly, because the sex of one child has no effect on the sex of the next child in a family, the probability of having four girls in a row is the product of their individual probabilities (very close to 1/2 for each birth): $1/2 \times 1/2 \times 1/2 \times 1/2 = 1/16$.

The Sum Rule in Probability. Another relationship, the **sum rule**, applies when there are two or more different ways of obtaining the same outcome; that is, the probability that *either* event A *or* event B will occur equals the probability of event A *plus* the probability of event B. Returning to the coin toss example, the probability of getting a head and a tail in two tosses can be determined. We could toss the coin twice and get a head, then a tail. The probability that this will occur is 1/2 for the head $\times$ 1/2 for the tail = 1/4 (see Figure 12.6). However, we could toss the coin twice and get first a tail, then a head. The probability that this will occur is also 1/4 (see Figure 12.6). Both of these outcomes must be considered together, because both give a head and a tail. That is, there are two ways of obtaining the same outcome. Therefore, for the probability of tossing and head and a tail, we sum the individual probabilities to get the final probability: here, $1/4 + 1/4 = 1/2$.

Probability in Mendel's Crosses. The same rules of probability just discussed apply to Mendel's crosses. For example, in the crosses that involve the purple-flowered and white-flowered traits, half of the gametes of the F_1 generation contain the *P* allele of the gene and half contain the *p* allele (see Figure 12.5b). To produce a *PP* zygote, two *P* gametes must combine. The probability of selecting a *P* gamete from one F_1 parent is 1/2, and the probability of selecting a *P* gamete from the other F_1 parent is also 1/2. Therefore, the probability of producing a *PP* zygote from this monohybrid cross is $1/2 \times 1/2 = 1/4$. That is, by the product rule, one-fourth of the offspring of the F_1 cross $Pp \times Pp$ are expected to be *PP,* which have purple flowers **(Figure 12.7a).** By the same line of reasoning, one-fourth of the F_2 offspring are expected to be *pp,* which have white flowers **(Figure 12.7b).**

What about the production of *Pp* offspring? The cross $Pp \times Pp$ can produce *Pp* in two different ways. A *P* gamete from the first parent can combine with a *p* gamete from the second parent *(Pp),* or a *p* gamete from the first parent can combine with a *P* gamete from the second parent *(pP)* **(Figure 12.7c).** Because there are two different ways to get the same outcome, we apply the sum rule to obtain the combined probability. Each of the ways to get *Pp* has an individual probability of 1/4; when we add these individual probabilities, we have $1/4 + 1/4 = 1/2$. Therefore, half of the offspring are expected to be *Pp,* which have purple flowers. We could get the same result from the requirement that all of the individual probabilities must

add up to 1. If the probability of *PP* is 1/4 and the probability of *pp* is 1/4, then the probability of the remaining possibility, *Pp*, must be 1/2, because the total of the individual probabilities must add up to 1: 1/4 + 1/4 + 1/2 = 1.

What if we want to know the probability of obtaining purple flowers in the cross *Pp* × *Pp*? In this case, the rule of addition applies, because there are two ways to get purple flowers: genotypes *PP* and *Pp*. Adding the individual probabilities of these combinations, 1/4 *PP* + 1/2 *Pp*, gives a total of 3/4, indicating that three-fourths of the F_2 offspring are expected to have purple flowers. Because the total probabilities must add up to 1, the remaining one-fourth of the offspring are expected to have white flowers (1/4 *pp*). These proportions give the ratio 3:1, which is close to the ratio Mendel obtained in his cross.

What we have just stepped through in describing Figure 12.7 is the **Punnett square** method for determining the genotypes of offspring and their expected proportions. To use the Punnett square, write the probability of obtaining gametes with each type of allele from one parent at the top of the diagram and write the chance of obtaining each type of allele from the other parent on the left side. Then fill in the cells by combining the alleles from the top and from the left and multiply their individual probabilities.

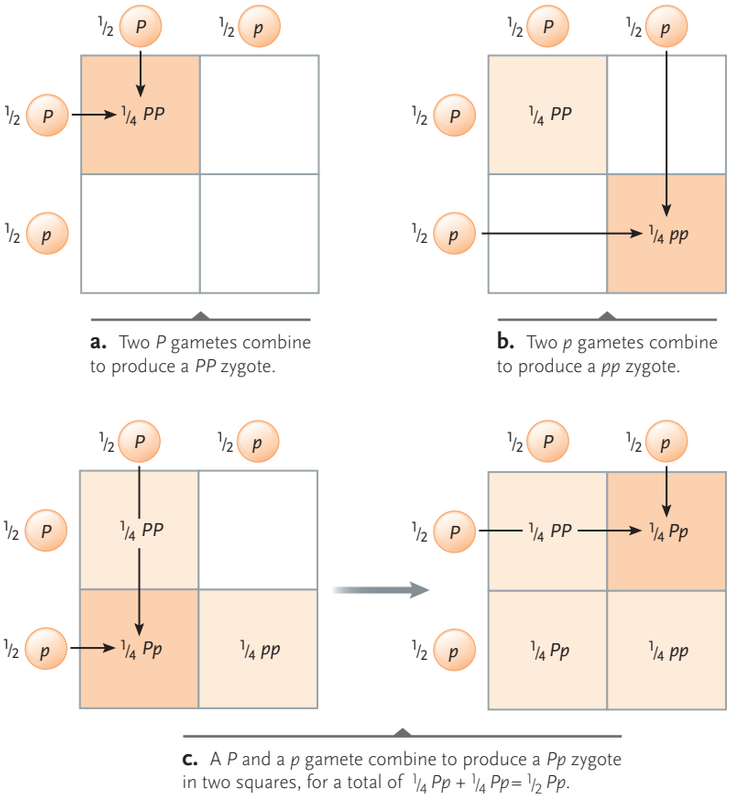


Figure 12.7
Punnett square method for predicting offspring and their ratios in genetic crosses. The example is the $F_1 \times F_1$ cross of purple-flowered plants from Figure 12.5. Each cell shows the genotype and proportion of one type of zygote.

Mendel Used a Testcross to Check the Validity of His Hypotheses

Mendel realized that he could assess the validity of his hypotheses by determining whether they could be used successfully to *predict* the outcome of a cross of a different type than he had tried so far. Accordingly, he crossed an F_1 plant with purple flowers, assumed to have the heterozygous genotype *Pp*, with a true-breeding white-flowered plant, with the homozygous genotype *pp*. In this cross, *Pp* × *pp*, all the gametes of the *pp* plant contain a single *p* allele. Therefore, the probability that a gamete from this parent contains *p* is 1. The gamete and its probability of 1 are entered as the row heading of the Punnett square in **Figure 12.8.** The *Pp* parent produces two types of gametes, half that contain the *P* allele and half that contain the *p* allele. These values, 1/2 *P* and 1/2 *p*, are entered as the column headings. Filling in the possible combinations in the cells gives the two expected classes, *Pp* and *pp*, both with a probability of 1/2. Thus, half the offspring of this cross are expected to have purple flowers and half are expected to have white flowers; the ratio is 1:1. Mendel's actual results in this cross were 85 purple-flowered plants and 81 white-flowered plants, which closely approach the expected 1:1 ratio. Mendel also made the same type of cross with all the other traits used in his study, including those traits affecting seed shape, seed color, and plant height, and found the same 1:1 ratio.

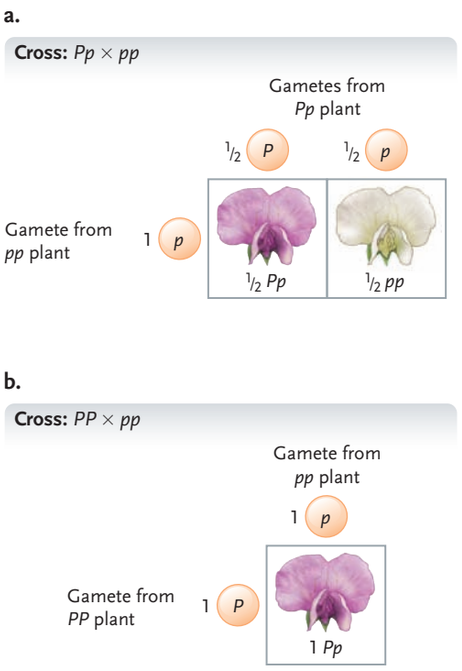


Figure 12.8
Method of predicting the outcome of genetic crosses.

A cross between an individual with the dominant phenotype and a homozygous recessive individual, such as the one described, is called a **testcross.** Geneticists use a testcross as a standard test to determine whether an individual with a dominant trait is a heterozygote or a homozygote, because these cannot be distinguished phenotypically. If the offspring of the testcross are of two types, with half displaying the dominant trait and half the recessive trait, then the individual in question must be a heterozygote (see Figure 12.8). If all the offspring display the dominant trait, the individual in question must be a homozygote. For example, the cross $PP \times pp$ gives all Pp progeny, which show the dominant purple phenotype (see Figure 12.8).

Obviously, the testcross method cannot be used for humans. However, it can be used in reverse, by noting the traits present in families over several generations and working backward to deduce whether a parent must have been a homozygote or a heterozygote (see also Chapter 13).

Mendel Tested the Independence of Different Genes in Crosses

Mendel next asked what happens in crosses when more than one character is involved. Would the alleles of different characters be inherited independently, or would they interact to alter their expected proportions in offspring?

To answer these questions, Mendel crossed parental stocks that had differences in two of the hereditary characters he was studying: seed shape and seed color. His single-character crosses had shown each was controlled by a pair of alleles. For seed shape, the *RR* or *Rr* genotypes produce round seeds and the *rr* genotype produces wrinkled seeds. For seed color, yellow is dominant. The homozygous *YY* or heterozygous *Yy* genotypes produce yellow seeds; the homozygous *yy* genotype produces green seeds.

Mendel crossed plants that bred true for the production of round and yellow seeds *(RR YY)* with plants that bred true for the production of wrinkled and green seeds *(rr yy)* **(Figure 12.9).** The cross, *RR YY* × *rr yy*, yielded an F_1 generation that consisted of all round yellow seeds, with the genotype *Rr Yy*. A zygote produced from a cross that involves two characters is called a **dihybrid** (*di* = two).

Mendel then planted the F_1 seeds, grew the plants to maturity, and selfed them; that is, he crossed the F_1 plants to themselves. A cross between two individuals that are heterozygous for two pairs of alleles—here, *Rr Yy* × *Rr Yy*—is called a **dihybrid cross** (see Figure 12.9). The seeds produced by these plants, representing the F_2 generation, included 315 round yellow seeds, 101 wrinkled yellow seeds, 103 round green seeds, and 32 wrinkled green seeds. Mendel noted that these numbers were close to a 9:3:3:1 ratio (3:1 for round:wrinkled, and 3:1 for yellow:green).

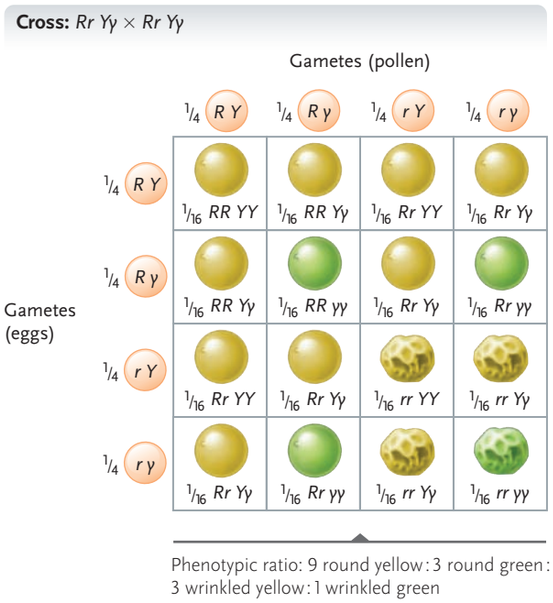


Figure 12.9
The principle of independent assortment in Mendel's crosses involving two hereditary characters in garden peas, seed shape, and seed color.

This 9:3:3:1 ratio was consistent with Mendel's previous findings if he added one further hypothesis: *The alleles of the genes that govern the two characters segregate independently during formation of gametes.* That is, the allele for seed shape that the gamete receives (*R* or *r*) has no influence on which allele for seed color it receives (*Y* or *y*) and vice versa. The two events are completely independent. Mendel termed this assumption **independent assortment;** it is now known as Mendel's **Principle of Independent Assortment.**

To understand the effect of independent assortment in the cross, assume that the *RR YY* parent produces only *R Y* gametes and the *rr yy* parent produces only *r y* gametes. In the F_1 generation, all possible combinations of these gametes produce only one genotype, *Rr Yy*, in the offspring. As observed, all the F_1 will be round yellow seeds.

If the alleles that control seed shape and seed color assort independently in gamete formation, each F_1 plant grown from the seeds would produce four types of gametes. The *R* allele for seed shape can be delivered independently to a gamete with either the *Y* or *y* allele for seed color, and similarly, the *r* allele can be delivered to a gamete with either the *Y* or *y* allele. Thus, the independent assortment of genes from the *Rr Yy* parents is expected to produce four types of gametes with equal probability: 1/4 *R Y*, 1/4 *R y*, 1/4 *r Y*, and 1/4 *r y*. These gametes and their probabilities are entered as the row and column headings of the Punnett square in Figure 12.9.

Filling in the cells of the diagram (see Figure 12.9) gives 16 combinations of alleles, all with an equal prob-

ability of 1 in every 16 offspring. Of these, the genotypes *RR YY, RR Yy, Rr YY,* and *Rr Yy* all have the same phenotype: round yellow seeds. These combinations occur in 9 of the 16 cells in the diagram, giving a total probability of 9/16. The genotypes *rr YY* and *rr Yy,* which produce the wrinkled yellow seeds, are found in three cells, giving a probability of 3/16 for this phenotype. Similarly, the genotypes *RR yy* and *Rr yy,* which yield round green seeds, occur in three cells, giving a probability of 3/16. Finally, the genotype *rr yy,* which produces wrinkled green seeds, is found in only one cell and therefore has a probability of 1/16.

These probabilities of round yellow seeds, wrinkled yellow seeds, round green seeds, and wrinkled green seeds, in a 9 : 3 : 3 : 1 ratio, closely approximate the actual results of 315 : 101 : 108 : 32 obtained by Mendel. Thus, Mendel's first three hypotheses, with the added hypothesis of independent assortment, explain the observed results of his dihybrid cross. Mendel's testcrosses completely confirmed his hypotheses; for example, the testcross *Rr Yy* × *rr yy* produced 55 round yellow seeds, 51 round green seeds, 49 wrinkled yellow seeds, and 53 wrinkled green seeds. This distribution corresponds well with the expected 1 : 1 : 1 : 1 ratio in the offspring. (Try to set up a Punnett square for this cross and predict the expected classes of offspring and their frequencies.)

Mendel's first three hypotheses provided a coherent explanation of the pattern of inheritance for alternate traits of the same character, such as purple and white for flower color. His fourth hypothesis, independent assortment, addressed the inheritance of traits for different characters, such as seed shape, seed color, and flower color, and showed that, instead of being inherited together, the traits of different characters were distributed independently to offspring.

Mendel's Research Founded the Field of Genetics

Mendel's techniques and conclusions were so advanced for his time that their significance was not immediately appreciated. Mendel's success was based partly on a good choice of experimental organism. He was also lucky. The characters he chose all segregate independently; that is, none of them is physically near each other on the chromosomes, a condition that would have given ratios other than 9 : 3 : 3 : 1, showing that they do not assort independently. Mendel's findings anticipated in detail the patterns by which genes and chromosomes determine inheritance. Yet, when Mendel first reported his findings, during the nineteenth century, the structure and function of chromosomes and the patterns by which they are separated and distributed to gametes were unknown; meiosis remained to be discovered. In addition, his use of mathematical analysis was a new and radical departure from the usual biological techniques of his day.

Mendel reported his results to a small group of fellow intellectuals in Brünn and presented his results in 1866 in a natural history journal published in the city. His article received little notice outside of Brünn, and those who read it were unable to appreciate the significance of his findings. His work was overlooked until the early 1900s, when three investigators—Hugo de Vries in Holland, Carl Correns in Germany, and Erich von Tschermak in Austria—independently performed a series of breeding experiments similar to Mendel's and reached the same conclusions. These investigators, in searching through previously published scientific articles, discovered to their surprise Mendel's article about his experiments conducted 34 years earlier. Each gave credit to Mendel's discoveries, and the quality and far-reaching implications of his work were at last realized. Mendel died in 1884, 16 years before the rediscovery of his experiments and conclusions, and thus he never received the recognition that he so richly deserved during his lifetime.

Mendel was unable to relate the behavior of his "factors" (genes) to cell structures because the critical information he required was not obtained until later, through the discovery of meiosis during the 1890s. The next section describes how a genetics student familiar with meiosis was able to make the connection between Mendel's factors and chromosomes.

Sutton's Chromosome Theory of Inheritance Related Mendel's Genes to Chromosomes

By the time Mendel's results were rediscovered in the early 1900s, critical information from studies of meiosis was available. It was not long before a genetics student, Walter Sutton, recognized the similarities between the inheritance of the genes discovered by Mendel and the behavior of chromosomes in meiosis and fertilization **(Figure 12.10).**

In a historic article published in 1903, Sutton, then a graduate student at Columbia University in New York, drew all the necessary parallels between genes and chromosomes:

- Chromosomes occur in pairs in sexually reproducing, diploid organisms, as do the alleles of each gene.
- The chromosomes of each pair are separated and delivered singly to gametes, as are the alleles of a gene.
- The separation of any pair of chromosomes in meiosis and gamete formation is independent of the separation of other pairs (see Figure 12.10), as in the independent assortment of the alleles of different genes in Mendel's dihybrid crosses.
- Finally, one member of each chromosome pair is derived in fertilization from the male parent, and the other member is derived from the female parent, in an exact parallel with the two alleles of a gene.

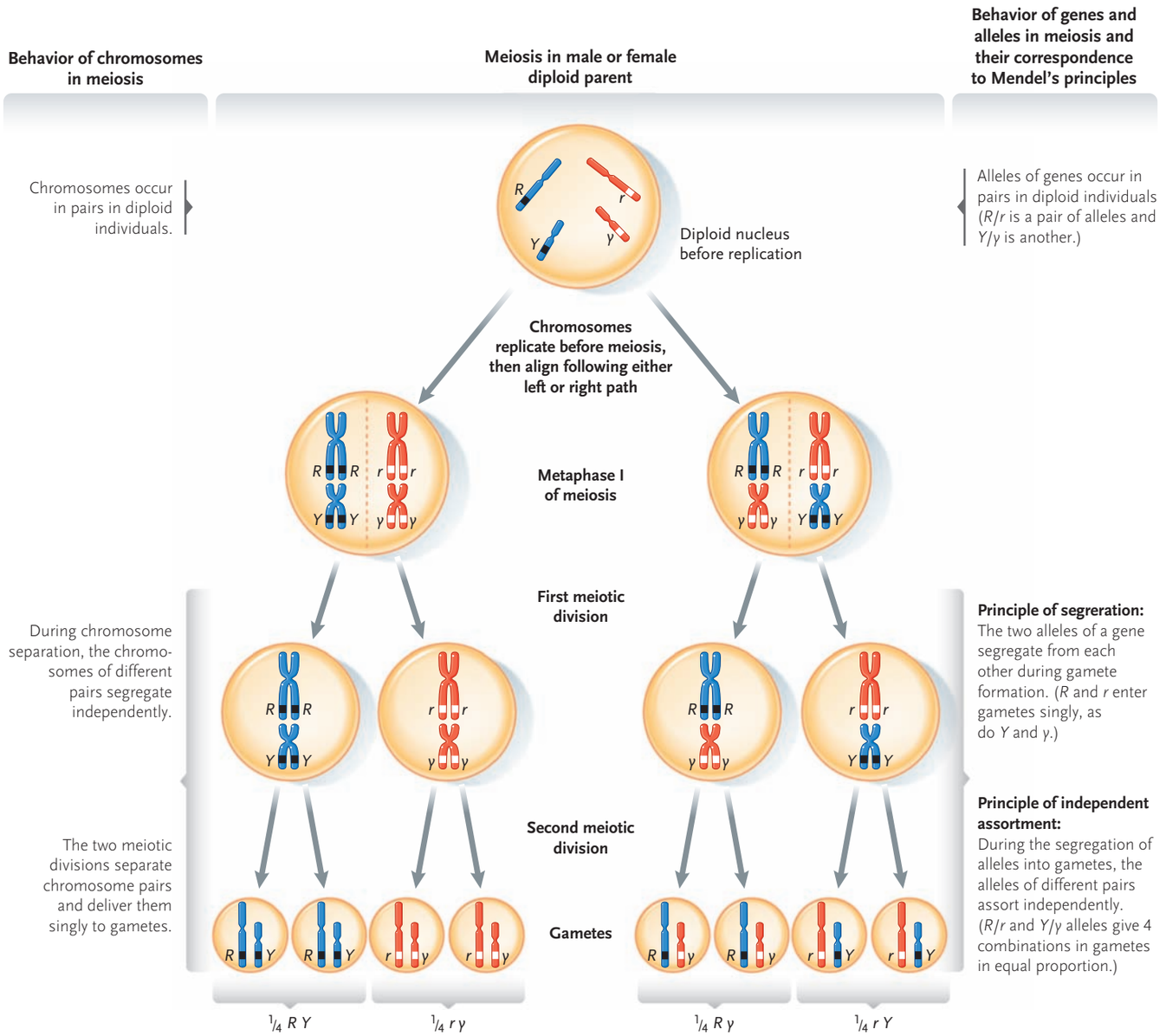


Figure 12.10
The parallels between the behavior of chromosomes and genes and alleles in meiosis. The gametes show four different combinations of alleles produced by independent segregation of chromosome pairs.

From this total coincidence in behavior, Sutton correctly concluded that genes and their alleles are carried on the chromosomes, a conclusion known today as the **chromosome theory of inheritance.**

The exact parallel between the principles set forth by Mendel, and the behavior of chromosomes and genes during meiosis, is shown in Figure 12.10 for an *Rr Yy* diploid. For a cross of *Rr Yy* × *Rr Yy,* when the gametes fuse randomly, the progeny will show a phenotypic ratio of 9:3:3:1. This mechanism explains the same ratio of gametes and progeny as the *Rr Yy* × *Ry Yy* cross in Figure 12.9.

The particular site on a chromosome at which a gene is located is called the **locus** (plural, *loci*) of the gene. The locus is a particular DNA sequence that encodes (typically) a protein responsible for the phenotype controlled by the gene. A locus for a gene with two alleles, *A* and *a,* on a homologous pair of chromosomes is shown in **Figure 12.11.** At the molecular level, different alleles consist of small differences in the DNA sequence of a gene, which may result in functional differences in the protein encoded by the gene. These differences are detected as distinct phenotypes in the offspring of a cross. *Insights from the Molecular Revolution* describes a molecular study that uncovered the mechanisms that control height in pea plants, one of the seven characteristics originally examined by Mendel.

All the genetics research conducted since the early 1900s has confirmed Mendel's basic hypotheses about inheritance. This research has shown that Mendel's conclusions apply to all types of organisms, from yeast and fruit flies to humans, and has led to the rapidly growing field of human genetics. In humans, a number of easily seen traits show inheritance patterns that

Insights from the Molecular Revolution

Why Mendel's Dwarf Pea Plants Were So Short

Two independent research teams worked out the molecular basis for one of the seven characters Mendel studied—dwarfing, which is governed by stem length in garden peas. The investigators, including Diane Lester and her colleagues at the University of Tasmania in Australia and David Martin and his coworkers at Oregon State University, were interested in learning the molecular differences in the alleles of the gene that produced tall or dwarf plants. The dominant *T* allele (*T* = tall) of the gene produces plants of normal height; the recessive *t* allele produces dwarf plants with short stems. How can a single gene control the overall height of a plant?

Lester's team discovered that the gene codes for an enzyme that carries out a preliminary step in the synthesis of the plant hormone gibberellin, which, among other effects, causes the stems of plants to elongate. Martin's group cloned the gene and determined its complete DNA sequence. (Cloning techniques and DNA sequencing are described in Sections 18.1 and 18.3.) The sequence showed that the *T* and *t* alleles of the gene encode two versions of the enzyme that catalyzes gibberellin synthesis, which differ by only a single amino acid. Lester's group found that the faulty enzyme encoded by the *t* allele carries out its step (addition of a hydroxyl group to a precursor) much more slowly than the enzyme encoded by the normal *T* allele. As a result, plants with the *t* allele have only about 5% as much gibberellin in their stems as *T* plants. The reduced gibberellin levels limit stem elongation, producing the dwarf plants.

Thus, the methods of molecular biology allowed contemporary researchers to study a gene first discovered in the mid-nineteenth century. The findings leave little doubt that a change in a single amino acid leads to the dwarf phenotype Mendel observed in his monastery garden.

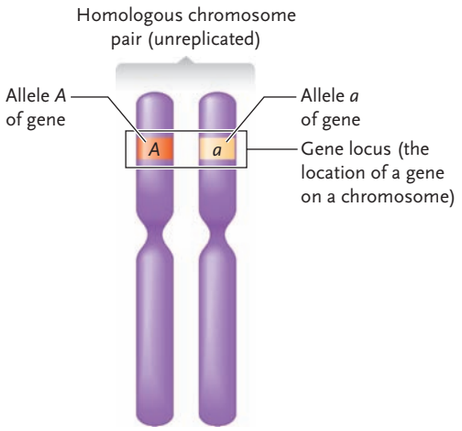


Figure 12.11
A locus, the site occupied by a gene on a pair of homologous chromosomes. Two alleles, *A* and *a*, of the gene are present at this locus in the homologous pair. These alleles have differences in the DNA sequence of the gene.

follow Mendelian principles **(Figure 12.12);** for example, albinism, the lack of normal skin color, is recessive to normal skin color, and normally separated fingers are recessive to fingers with webs between them. Similarly, achondroplasia, the most frequent form of short-limb dwarfism, is a dominant trait that involves abnormal bone growth. Many human disorders that cannot be seen easily also show simple inheritance patterns. For instance, cystic fibrosis, in which a defect in the membrane transport of chloride ions leads to pulmonary and digestive dysfunctions and eventually death, is a recessive trait.

The post-Mendel research has demonstrated additional patterns of inheritance (see the next section) that were not anticipated by Mendel and, in some circumstances, require modifications or additions to his hypotheses.

Study Break

1. Two pairs of traits are segregating in a cross. Two parents produce 156 progeny that fall into 4 phenotypes. The numbers of offspring in the 4 phenotypes are 89, 31, 28, and 8. What are the genotypes of the two parents?
2. If instead, the four phenotypes in question 1 occur in approximately equal numbers, what are the genotypes of the parents? What is this kind of cross called?

12.2 Later Modifications and Additions to Mendel's Hypotheses

The rediscovery of Mendel's research in the early 1900s produced an immediate burst of interest in genetics. The research that followed greatly expanded our understanding of genes and their inheritance. The discovery that the alleles of many genes are neither fully dominant nor fully recessive was among these new findings. Some alleles show incomplete dominance, in which recessive alleles do have some effect on the phenotype of heterozygotes. Other alleles are codominant; that is, they have different and approximately equal effects in heterozygotes.

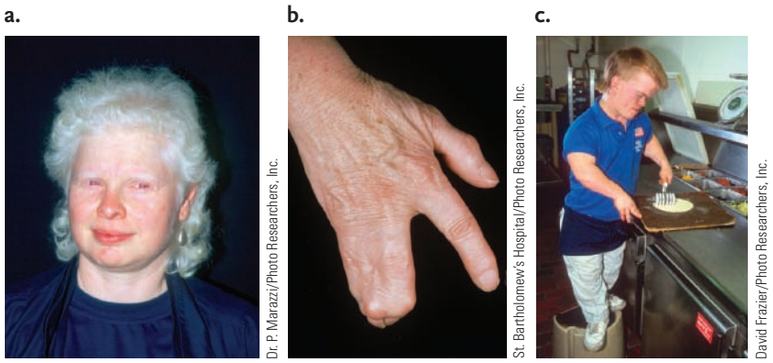


Figure 12.12
Human traits showing inheritance patterns that follow Mendelian principles. **(a)** Lack of normal skin color (albinism). **(b)** Webbed fingers. **(c)** Achondroplasia, or short-limbed dwarfism.

Further research also demonstrated that more than two alleles of a gene may be present among all the members of a population. This condition, called multiple alleles, is still consistent with Mendel's conclusions because each sexually reproducing, diploid individual in a population has only two alleles of each gene—a pair—which are inherited and passed on according to Mendel's principles.

Geneticists also found that the activity of one gene can influence the activity of a different gene, a phenomenon called epistasis. Furthermore, some characters are explained by polygenic inheritance, in which several different genes each contribute to the phenotype. In addition, alterations in a single gene sometimes affect more than one phenotype in an organism; this phenomenon is called pleiotropy. The following sections discuss each of these so-called extensions of Mendel's fundamental principles.

In Incomplete Dominance, Dominant Alleles Do Not Completely Mask Recessive Alleles

Incomplete dominance occurs when the effects of recessive alleles can be detected to some extent in heterozygotes. Flower color in snapdragons shows incomplete dominance **(Figure 12.13).** If true-breeding, red-flowered and white-flowered snapdragon plants are crossed, all the F_1 offspring have pink flowers (see Figure 12.13). The pink color might make it appear that the pure red and white colors have blended out and disappeared—mixing red and white makes pink—until two F_1 plants are crossed. The cross demonstrates that the red and white traits both reappear in the F_2 generation, which has red, pink, and white flowers in numbers approximating a 1 : 2 : 1 ratio.

This outcome can be explained by incomplete dominance between a C^R allele for red color and a C^W allele for white color. When one allele is not completely dominant to the other, we use a superscript to signify the character. In this case, *C* signifies the character for flower color and the superscripts indicate the alleles (R for red and W for white). Therefore, the initial cross is C^RC^R (red) $\times$ C^WC^W (white), which produces C^RC^W F_1 (pink) plants. The C^R allele encodes an enzyme that produces a red pigment, but two alleles (C^RC^R) are necessary to produce enough of the active form of the enzyme to produce fully red flowers. The enzyme is completely inactive in C^WC^W plants, which produce colorless flowers that appear white because of the scattering of light by cell walls and other structures. With their single C^R allele, the C^RC^W heterozygotes of the F_1 generation can produce only enough pigment to give the flowers a pink color. When the pink C^RC^W F_1 plants are crossed, the fully red and white colors reappear, together with the pink color, in the F_2 generation, in a ratio of 1/4 C^RC^R (red), 1/2 C^RC^W (pink), and 1/4 C^WC^W (white). This ratio is exactly the same as the ratio of genotypes produced from a cross of two heterozygotes in Mendel's experiments (for example, see Figure 12.7).

Some human disorders show incomplete dominance. For example, sickle-cell disease (see the introduction to this chapter) is characterized by an alteration in the hemoglobin molecule that changes the shape of red blood cells when oxygen levels are low. An individual with sickle-cell disease is homozygous for a recessive allele that encodes a defective form of one of the polypeptides of the hemoglobin molecule. Individuals heterozygous for that recessive allele and the normal allele have a condition known as *sickle-cell trait,* which is a milder form of the disease because the individuals still produce normal polypeptides from the normal allele.

Familial hypercholesterolemia is another example of incomplete dominance. The gene involved encodes the low-density lipoprotein (LDL) receptor, a cell membrane protein responsible for removing excess cholesterol from the blood (see Section 6.5). Individuals with familial hypercholesterolemia are homozygous for a defective LDL receptor gene, produce no LDL receptors, and have a severe form of the disease. These individuals have six times the normal level of cholesterol in the blood and therefore are very prone to atherosclerosis (hardening of the arteries). Many individuals with familial hypercholesterolemia have heart attacks as children. Heterozygous individuals have half the normal number of receptors, which results in a milder form of the disease. Their symptoms are twice the normal blood cholesterol level, an unusually high risk of atherosclerosis, and a high risk of heart attacks before age 35.

Many alleles that appear to be completely dominant are actually incomplete in their effects when analyzed at the biochemical or molecular level. For exam-

ple, for pigments that produce fur or flower colors, biochemical studies often show that even though heterozygotes may produce enough pigment to make them look the same externally as homozygous dominants, a difference in the amount of pigment is measurable at the biochemical level. Thus, whether dominance between alleles is complete or incomplete often depends on the level at which the effects of the alleles are examined.

A similar situation occurs in humans who carry the recessive allele that causes Tay–Sachs disease. Children who are homozygous for the recessive allele do not have a functional version of an enzyme that breaks down gangliosides, a type of membrane lipid. As a result, gangliosides accumulate in the brain, leading to mental impairment and eventually to death. Heterozygotes are without symptoms of the disease, even though they have one copy of the recessive allele. However, at the biochemical level, reduced breakdown of gangliosides can be detected in heterozygotes, evidently due to a reduced quantity of the active enzyme.

In Codominance, the Effects of Different Alleles Are Equally Detectable in Heterozygotes

Codominance occurs when alleles have approximately equal effects in individuals, making the alleles equally detectable in heterozygotes. The inheritance of the human blood types, M, MN, and N, is an example of codominance. These are different blood types from the familiar blood types of the ABO blood group. The L^M and L^N alleles of the MN blood group gene that control this character encode different forms of a glycoprotein molecule located on the surface of red blood cells. If the genotype is L^ML^M, only the M form of the glycoprotein is present and the blood type is M; if it is L^NL^N, only the N form is present and the blood type is N. In heterozygotes with the L^ML^N genotype, both glycoprotein types are present and can be detected, producing the blood type MN. Because each genotype has a different phenotype, the inheritance pattern for the MN blood group alleles is generally the same as for incompletely dominant alleles.

The MN blood types do not affect blood transfusions and have relatively little medical importance. However, they have been invaluable in tracing human evolution and prehistoric migrations, and they are frequently used in initial tests to determine the paternity of a child. Among their primary advantages in research and paternity determination is that the genotype of all individuals, including heterozygotes, can be detected directly—and inexpensively—from their phenotype, with no requirement for further genetic tests or analysis.

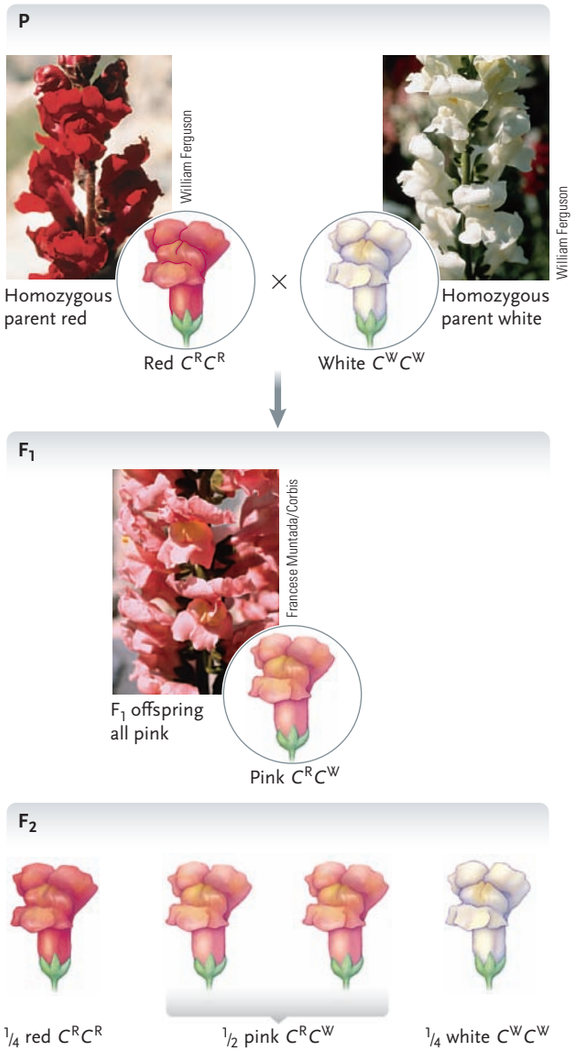


Figure 12.13 Incomplete dominance in the inheritance of flower color in snapdragons.

In Multiple Alleles, More Than Two Alleles of a Gene Are Present in a Population

One of Mendel's major and most fundamental assumptions was that alleles occur in pairs in individuals; in the pairs, the alleles may be the same or different. After the rediscovery of Mendel's principles, it soon became apparent that although alleles do indeed occur in pairs in individuals, **multiple alleles** (more than two different alleles of a gene) may be present if all the individuals of a population are taken into account. For example, for a gene *B*, there could be the normal allele, *B*, and several alleles with alterations in the gene named, for example, b_1, b_2, b_3, and so on. Some individuals in a population may have the *B* and b_1 alleles of a gene; others, the b_2 and b_3 alleles; still others, the b_3 and b_5 alleles; and so on, for all possible combinations. Thus, although any one individual can

Figure 12.14
Multiple alleles. Multiple alleles consist of small differences in the DNA sequence of a gene at one or more points, which result in detectable differences in the structure of the protein encoded by the gene. The *B* allele is the normal allele, which encodes a protein with normal function. The three *b* alleles each have alterations of the normal protein-coding DNA sequence that may adversely affect the function of that protein.

have only two alleles of the gene, there are more than two alleles in the population as a whole. Genes may certainly occur in many more than the four alleles of the example; for instance, one of the genes that plays a part in the acceptance or rejection of organ transplants in humans has more than 200 different alleles.

The multiple alleles of a gene each contain differences at one or more points in their DNA sequences **(Figure 12.14),** which cause detectable alterations in the structure and function of proteins encoded by the alleles. Multiple alleles present no real difficulty in genetic analysis because each diploid individual still has only two of the alleles, allowing gametes to be predicted and traced through crosses by the usual methods.

Human ABO Blood Group. The human *ABO* blood group provides another interesting example of multiple alleles, in a system that also exhibits both dominance and codominance. The ABO blood group was discovered in 1901 by Karl Landsteiner, an Austrian biochemist who was investigating the sometimes fatal outcome of attempts to transfer whole blood from one person to another. Landsteiner found that only certain combinations of four blood types, designated A, B, AB, and O, can be mixed safely in transfusions **(Table 12.1).**

Landsteiner determined that, in the wrong combinations, red blood cells from one blood type are agglutinated or clumped by an agent in the serum of another type (the serum is the fluid in which the blood cells are suspended). The clumping was later found to depend on the action of an antibody in the blood serum. (Antibodies, protein molecules that interact with specific substances called antigens, are discussed in Chapter 43.)

Table 12.1 **Blood Types of the Human ABO Blood Group**

Blood Type	Antigens	Antibodies	Blood Types Accepted in a Transfusion
A	A	Anti-B	A or O
B	B	Anti-A	B or O
AB	A and B	None	A, B, AB, or O
O	None	Anti-A, anti-B	O

The antigens responsible for the blood types of the ABO blood group are the carbohydrate parts of glycoproteins located on the surfaces of red blood cells (unrelated to the glycoprotein carbohydrates responsible for the blood types of the MN blood group). People with type A blood have *antigen A* on their red blood cells, and people with type B blood have *antigen B* on their red blood cells. At the same time, people with type A blood have antibodies against antigen B, and people with type B blood have antibodies against antigen A. People with type O blood have neither antigen A nor antigen B on their red blood cells, but they have antibodies against both of these antigens. People with type AB blood have neither anti-A nor anti-B antibodies, but they have both the A and B antigens, and their red blood cells are clumped by antibodies in the blood of all the other groups.

The four blood types—A, B, AB, and O—are produced by different combinations of multiple (three) alleles of a single gene *I* **(Figure 12.15).** The three alleles, designated I^A, I^B, and i, produce the following blood types:

I^AI^A = type A blood
I^Ai = type A blood
I^AI^B = type AB blood
I^BI^B = type B blood
I^Bi = type B blood
ii = type O blood

In addition, I^A and I^B are codominant alleles that are each dominant to the i allele.

In Epistasis, Genes Interact, with the Activity of One Gene Influencing the Activity of Another Gene

The genetic characters discussed so far in this chapter, such as flower color, seed shape, and the blood types of the ABO group, are all produced by the alleles of single genes, with each gene functioning on its own. This is not the case for every gene. In **epistasis** (*epi* = on or over; *stasis* = standing or stopping), genes interact, with one or more alleles of a gene at one locus inhibiting or masking the effects of one or more alleles of a gene at a different locus. The result of epistasis is that some expected phenotypes do not appear among offspring.

Labrador retrievers (Labs) may have black, chocolate brown, or yellow fur **(Figure 12.16).** The different colors result from variations in the amount and distribution in hairs of a brownish black pigment called melanin. One gene, coding for an enzyme involved in melanin production, determines how much melanin is produced. The dominant *B* allele of this gene produces black fur color in *BB* or *Bb* Labs; less pigment is produced in *bb* dogs, which are chocolate brown. How-

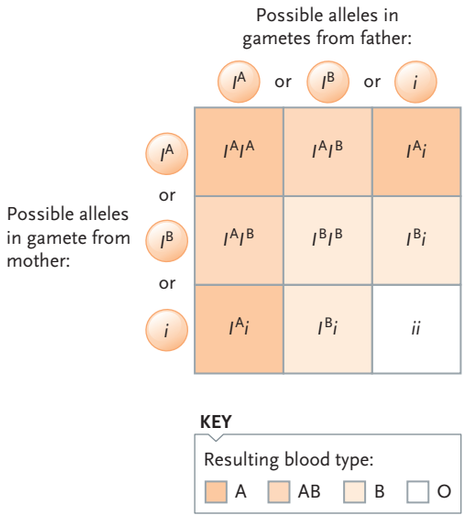
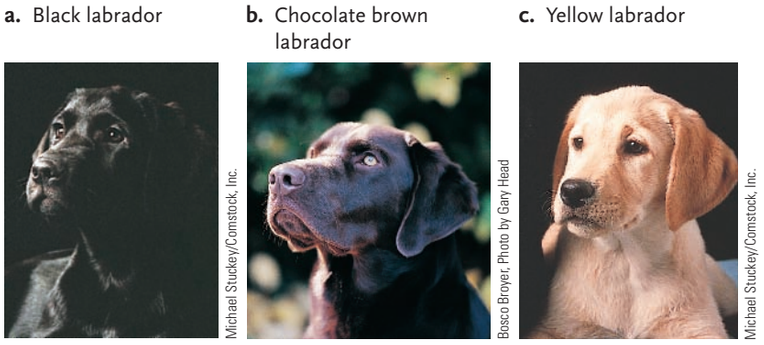


Figure 12.15
Inheritance of the blood types of the human ABO blood group.



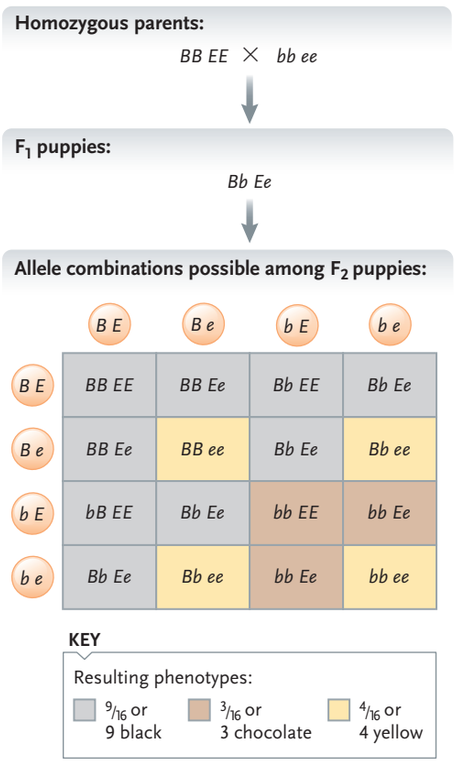


Figure 12.16
An example of epistasis: the inheritance of coat color in Labrador retrievers.

ever, another gene at a different locus determines whether the black or chocolate color appears at all, by controlling the deposition of pigment in hairs. A dominant allele *E* of this second gene permits pigment deposition, so that the black color in *BB* or *Bb* individuals, or the chocolate color in *bb* individuals, actually appears in the fur. Pigment deposition is almost completely blocked in homozygous recessive *ee* individuals, so the fur lacks melanin and has a yellow color whether the genotype for the *B* gene is *BB*, *Bb*, or *bb*. Thus, the *E* gene is epistatic to the *B* gene (that is, *E* and *B* interact).

Epistasis by the *E* gene eliminates some of the expected classes from crosses among Labs. Rather than two separate classes, as would be expected from a dihybrid cross without epistasis, the *BB ee*, *Bb ee*, *bB ee*, and *bb ee* genotypes produce a single yellow phenotype, giving the distribution: 9/16 black, 3/16 chocolate, and 4/16 yellow. That is, the ratio is 9:3:4 instead of the expected 9:3:3:1 ratio. Many other dihybrid crosses that involve epistatic interactions produce distributions that differ from the expected 9:3:3:1 ratio.

In human biology, researchers believe that gene interactions and epistasis are common. Current thinking is that epistasis is an important factor in determining an individual's susceptibility to common human diseases. That is, the different degrees of susceptibility are the result of different gene interactions in the individuals. A specific example is insulin resistance, a disorder in which muscle, fat, and liver cells do not use insulin correctly, with the result that glucose and insulin levels become high in the blood. This disorder is believed to be determined by several genes often interacting with one another.

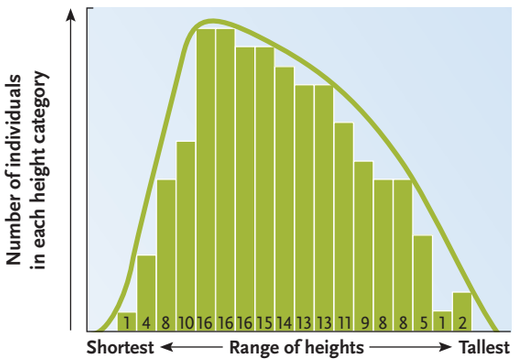
In Polygenic Inheritance, a Character Is Controlled by the Common Effects of Several Genes

Some characters follow a pattern of inheritance in which there is a more or less even gradation of types, forming a continuous distribution, rather than "on" or "off" (discontinuous) effects such as the production of purple or white flowers in pea plants. For example, in the human population, people range from short to tall, in a continuous distribution of gradations in height between limits of about 4 and 7 feet. Typically, a continuous distribution of this type is the result of **polygenic inheritance**, in which several to many differ-

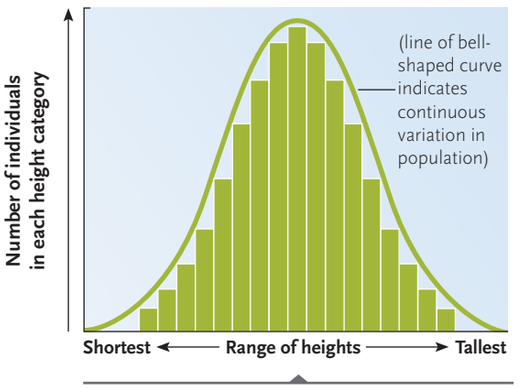
a. Students at Brigham Young University, arranged according to height

Dan Fairbanks/Brigham Young University

b. Actual distribution of individuals in the photo according to height



c. Idealized bell-shaped curve for a population that displays continuous variation in a trait



If the sample in the photo included more individuals, the distribution would more closely approach this ideal.

Figure 12.17
Continuous variation in height due to polygenic inheritance.

ent genes contribute to the same character. Other characters that undertake a similar continuous distribution include skin color and body weight in humans, ear length in corn, seed color in wheat, and color spotting in mice. These characters are also known as *quantitative traits*.

Polygenic inheritance can be detected by defining classes of a variation, such as human body height of 60 inches in one class, 61 inches in the next class, 62 inches in the next class, and so on. The number of individuals in each class is then plotted as a graph. If the plot produces a bell-shaped curve, with fewer individuals at the extremes and the greatest numbers clustered around the midpoint, it is a good indication that the trait is quantitative **(Figure 12.17).**

Polygenic inheritance is often modified by the environment. For example, height in humans is not the result of genetics alone. Poor nutrition during infancy and childhood is one environmental factor that can limit growth and prevent individuals from reaching the height expected from genetic inheritance; good nutrition can have the opposite effect. Thus, the average young adult in Japan today is several inches taller than the average adult in the 1930s, when nutrition was poorer. Similarly, individuals who live in cloudy, northern or southern climates usually have lighter skin color than individuals with the same genotype who live in sunny climates.

At first glance, the effects of polygenic inheritance might appear to support the idea that characteristics of parents are blended in their offspring. Commonly, people believe that the children in a family with one tall and one short parent will be of intermediate height. Although the children of such parents are most likely to be of intermediate height, careful genetic analysis of many such families shows that their offspring actually range over a continuum from short to tall, forming a typical bell-shaped curve. Careful analysis of the inheritance of skin color produces the same result: Although the skin color of children is most often intermediate between that of the parents, a typical bell-shaped distribution is obtained in which some children at the extremes are lighter or darker than either parent. Thus, genetic analysis does not support the idea of blending or even mixing of parental traits in polygenic characteristics such as body size or skin color.

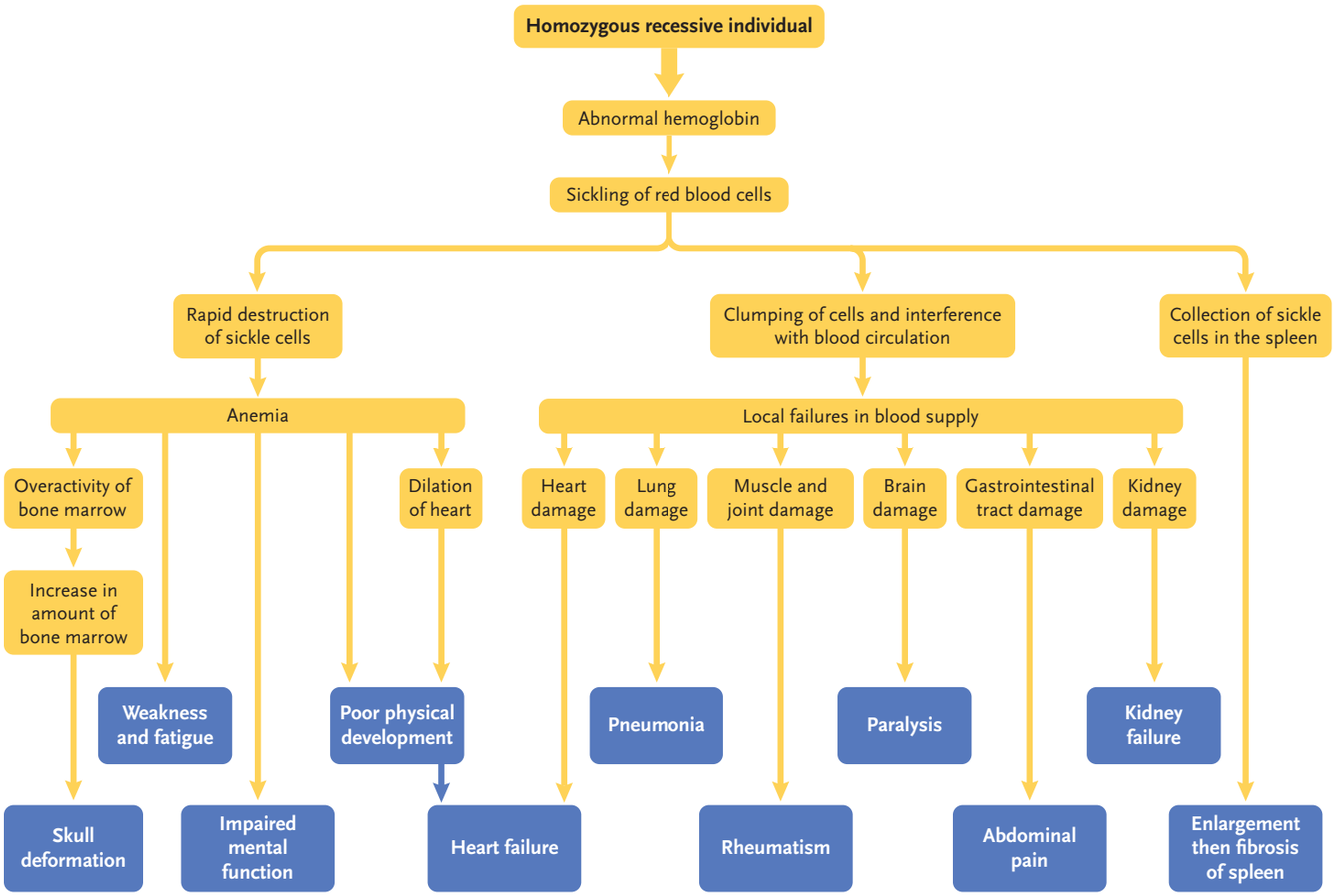


Figure 12.18
Pleiotropy, as demonstrated by the wide-ranging, multiple effects of the single mutant allele responsible for sickle-cell disease.

In Pleiotropy, Two or More Characters Are Affected by a Single Gene

In **pleiotropy**, single genes affect more than one character of an organism. For example, sickle-cell disease (see earlier discussion) is caused by a recessive allele of a single gene that affects hemoglobin structure and function. However, the altered hemoglobin, the primary phenotypic change of the sickle-cell mutation, leads to blood vessel blockage, which can damage many tissues and organs in the body and affect many body functions, producing such wide-ranging symptoms as fatigue, abdominal pain, heart failure, paralysis, and pneumonia **(Figure 12.18).** Physicians recognize these wide-ranging pleiotropic effects as symptoms of sickle-cell disease.

The next chapter describes additional patterns of inheritance that were not anticipated by Mendel, including the effects of recombination during meiosis. These additional patterns also extend, rather than contradict, Mendel's fundamental principles.

Study Break

1. Palomino horses have a golden coat color, with a white mane and tail. Palominos do not breed true. Instead, there is a 50% chance that a foal will be a Palomino. What is the explanation?
2. A true-breeding rabbit with *agouti* (mottled, grayish brown) fur crossed with a true-breeding rabbit with *chinchilla* (silver) fur produces all agouti offspring. A true-breeding *chinchilla* rabbit crossed with a true-breeding *Himalayan* rabbit (white fur with pigmented nose, ears, tail, and legs) produces all *chinchilla* offspring. A true-breeding *Himalayan* rabbit crossed with a true-breeding *albino* rabbit produces all *Himalayan* offspring. Explain the inheritance of the fur colors.

Unanswered Questions

The determination of genetic principles by Mendel and later geneticists involved crosses of plants and animals with visible traits, that is, phenotypes that could be seen by visual examination. Examples are smooth and wrinkled seeds of garden peas and red and white eyes of fruit flies. Until recently, it was impossible to determine the biochemical or molecular basis for traits. Even now, we do not know the molecular basis for most of the traits mentioned in this chapter, or for many others. For example, the molecular reason for the dwarf (short stem) phenotype of Mendel's peas was determined only as recently as the 1990s. Similar research is ongoing to determine the molecular bases for other visible genetic traits in a wide variety of organisms, including humans.

Is epistasis involved in human diseases?

Current research involves molecular investigations into epistasis, which is increasingly being recognized as an important phenomenon in common human diseases. Consequently, research is focused on identifying and understanding key epistatic relationships to help in the treatment and cure of such diseases.

For example, Nicholas Katsanis's research group at Johns Hopkins University is studying Bardet–Biedl syndrome, a genetic disorder characterized by obesity and learning defects. The severity of the symptoms varies dramatically among patients. Katsanis's group has shown that epistasis is involved in the development of Bardet–Biedl syndrome. These researchers have identified a DNA sequence that interacts with other molecules known to be altered in patients with Bardet–Biedl syndrome. For example, they showed in particular families that a more severe form of the disease occurs in individuals who have both a mutation in the DNA sequence and mutations in known Bardet–Biedl syndrome genes. However, mutations in the DNA sequence alone do not cause the illness. Experiments with zebrafish as a model organism have provided more evidence that the DNA sequence has an epistatic effect on other Bardet–Biedl syndrome mutations. This research opens the way to developing a better understanding of disorders that involve gene interactions.

Is polygenic inheritance involved in human disorders?

Polygenic inheritance involves a number of genes contributing to the same phenotypic traits, such as height of an individual or weight of a pumpkin. The traits are known as quantitative traits, and the genes responsible are called quantitative trait loci, or QTLs. Researchers are making great strides in identifying and characterizing the QTL genes involved with the goal of obtaining a molecular understanding of the traits. Such traits include a number of genetic disorders in humans, such as alcoholism, arthritis, behavioral and psychiatric disorders, cancer, diabetes, obesity, hypertension, and sensitivity to drugs.

For example, Xiasong Wang of The Jackson Laboratory is studying the genetics of atherosclerosis, the basis for coronary artery disease. The major risk factors for atherosclerosis are mainly genetically determined, notably high blood levels of low-density lipoproteins (LDLs), and low levels of high-density lipoproteins (HDLs). The level of the HDL is the more important of the two, because high levels of HDLs are known to be protective against cardiovascular disease. Wang's group has identified 21 mouse and 27 human atherosclerosis QTLs, and 37 mouse and 30 human HDL-regulating QTLs. Currently, these researchers are using genomic and bioinformatics approaches to determine the nature of the QTL genes that are common to both organisms.

Peter J. Russell

Review

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12.1 The Beginnings of Genetics: Mendel's Garden Peas

- Mendel was successful in his research because of his good choice of experimental organism, which had clearly defined characters, such as flower color or seed shape, and because he analyzed his results quantitatively (Figures 12.3 and 12.4).
- Mendel showed that traits are passed from parents to offspring as hereditary factors (now called genes and alleles) in predictable ratios and combinations, disproving the notion of blended inheritance (Figure 12.5).
- Mendel realized that his results with crosses that involve single characters (monohybrid crosses) could be explained if three hypotheses were true: (1) The genes that govern genetic characters occur in pairs in individuals. (2) If different alleles of a gene are present in the pair of an individual, one allele is dominant over the other. (3) The two alleles of a gene segregate and enter gametes singly (Figures 12.5 and 12.7).
- Mendel confirmed his hypotheses by a testcross between an F_1 heterozygote with a homozygous recessive parent. This type of testcross is still used to determine whether an individual is homozygous or heterozygous for a dominant allele (Figure 12.8).
- To explain the results of his crosses with individuals showing differences in two characters—dihybrid crosses—Mendel added a fourth hypothesis: The alleles of the genes that govern the two characters segregate independently during formation of gametes (Figure 12.9).
- Walter Sutton was the first person to note the similarities between the inheritance of genes and the behavior of chromosomes in meiosis and fertilization. These parallels made it obvious that genes and alleles are carried on the chromosomes. Sutton's parallels are called the chromosome theory of inheritance (Figure 12.10).
- A locus is the site occupied by a gene on a chromosome (Figure 12.11).

Animation: Crossing garden pea plants

Animation: Genetic terms

Animation: Monohybrid cross

Animation: F_2 ratios interaction

Practice: Testcross

Animation: Dihybrid cross

Animation: Crossover review

12.2 Later Modifications and Additions to Mendel's Hypotheses

- In incomplete dominance, some or all alleles of a gene are neither completely dominant nor recessive. In such cases, the phenotype of heterozygotes with different alleles of the gene can be distinguished from that of either homozygote (Figure 12.13).
- In codominance, different alleles of a gene have approximately equal effects in heterozygotes, also allowing heterozygotes to be distinguished from either homozygote.
- Many genes may have multiple alleles if all the individuals in a population are taken into account. However, any diploid individual in a population has only two alleles of these genes, which are inherited and passed on according to Mendel's principles (Figures 12.14 and 12.15).
- In epistasis, genes interact, with one or more alleles of one locus inhibiting or masking the effects of one or more alleles at a different locus. The result is that some expected phenotypes do not appear among offspring (Figure 12.16).
- In polygenic inheritance, genes at several to many different loci interact to control the same character, producing a more or less continuous variation in the character from one extreme to another. Plotting the distribution of such characters among individuals typically produces a bell-shaped curve (Figure 12.17).
- In pleiotropy, one gene affects more than one character of an organism (Figure 12.18).

Animation: Comb shape in chickens

Animation: Codominance: ABO blood types

Animation: Incomplete dominance

Animation: Coat color in Labrador retrievers

Animation: Pleiotropic effects of Marfan syndrome

Animation: Coat color in the Himalayan rabbit

Interaction: Continuous variation in height

Questions

Self-Test Questions

1. The dominant *C* allele of a gene that controls color in corn produces kernels with color; plants homozygous for a recessive *c* allele of this gene have colorless or white kernels. What kinds of gametes, and in what proportions, would be produced by the plants in the following crosses? What seed color, and in what proportions, would be expected in the offspring of the crosses?
   a. $CC \times Cc$ b. $Cc \times Cc$ c. $Cc \times cc$
2. In peas, the allele *T* produces tall plants and the allele *t* produces dwarf plants. The *T* allele is dominant to *t*. If a tall plant is crossed with a dwarf, the offspring are distributed about equally between tall and dwarf plants. What are the genotypes of the parents?
3. The ability of humans to taste the bitter chemical phenylthiocarbamide (PTC) is a genetic trait. People with at least one copy of the normal, dominant allele of the *PTC* gene can taste PTC; those who are homozygous for a mutant, recessive allele cannot taste it. Could two parents able to taste PTC have a nontaster child? Could nontaster parents have a child able to taste PTC? A pair of taster parents, both of whom had one parent able to taste PTC and one nontaster parent, are expecting their first child. What is the chance that the child will be able to taste PTC? Unable to taste PTC? Suppose the first child is a nontaster. What is the chance that their second child will also be unable to taste PTC?
4. One gene has the alleles *A* and *a*; another gene has the alleles *B* and *b*. For each of the following genotypes, what types of gametes will be produced, and in what proportions, if the two gene pairs assort independently?
   a. *AA BB* c. *Aa bb*
   b. *Aa BB* d. *Aa Bb*
5. What genotypes, and in what frequencies, will be present in the offspring from the following matings?
   a. $AA\ BB \times aa\ BB$ c. $Aa\ Bb \times aa\ bb$
   b. $Aa\ BB \times AA\ Bb$ d. $Aa\ Bb \times Aa\ Bb$
6. In addition to the two genes in problem 4, assume you now study a third independently assorting gene that has the alleles *C* and *c*. For each of the following genotypes, indicate what types of gametes will be produced:
   a. *AA BB CC* c. *Aa BB Cc*
   b. *Aa BB cc* d. *Aa Bb Cc*
7. A man is homozygous dominant for alleles at 10 different genes that assort independently. How many genotypically different types of sperm cells can he produce? A woman is homozygous recessive for the alleles of 8 of these 10 genes, but she is heterozygous for the other 2 genes. How many genotypically different types of eggs can she produce? What hypothesis can you suggest to describe the relationship between the number of different possible gametes and the number of heterozygous and homozygous genes that are present?
8. In guinea pigs, an allele for rough fur *(R)* is dominant over an allele for smooth fur *(r);* an allele for black coat *(B)* is dominant over that for white *(b)*. You have an animal with rough, black fur. What cross would you use to determine whether the animal is homozygous for these traits? What phenotype would you expect in the offspring if the animal is homozygous?
9. You cross a lima bean plant from a variety that breeds true for green pods with another lima bean from a variety that breeds true for yellow pods. You note that all the F_1 plants have green pods. These green-pod F_1 plants, when crossed, yield 675 plants with green pods and 217 with yellow pods. How many genes probably control pod color in this experiment? Give the alleles letter designations. Which is dominant?
10. Some recessive alleles have such a detrimental effect that they are lethal when present in both chromosomes of a pair. Homozygous recessives cannot survive and die at some point during embryonic development. Suppose that the allele *r* is lethal in the homozygous *rr* condition. What genotypic ratios would you expect among the living offspring of the following crosses?
    a. $RR \times Rr$
    b. $Rr \times Rr$
11. In garden peas, the genotypes *GG* or *Gg* produce green pods and *gg* produces yellow pods; *TT* or *Tt* plants are tall and *tt* plants are dwarfed; *RR* or *Rr* produce round seeds and *rr* produces wrinkled seeds. If a plant of a true-breeding, tall variety with green pods and round seeds is crossed with a plant of a true-breeding, dwarf variety with yellow pods and wrinkled seeds, what phenotypes are expected, and in what ratios, in the F_1 generation? What phenotypes, and in what ratios, are expected if F_1 individuals are crossed?

12. In chickens, feathered legs are produced by a dominant allele *F*. Another allele *f* of the same gene produces featherless legs. The dominant allele *P* of a gene at a different locus produces pea combs; a recessive allele *p* of this gene causes single combs. A breeder makes the following crosses with birds 1, 2, 3, and 4; all parents have feathered legs and pea combs:

Cross	Offspring
1 × 2	all feathered, pea comb
1 × 3	3/4 feathered; 1/4 featherless, all pea comb
1 × 4	9/16 feathered, pea comb; 3/16 featherless, pea comb; 3/16 feathered, single comb; 1/16 featherless, single comb

What are the genotypes of the four birds?

13. A mixup in a hospital ward caused a mother with O and MN blood types to think that a baby given to her really belonged to someone else. Tests in the hospital showed that the doubting mother was able to taste PTC (see problem 3). The baby given to her had O and MN blood types and had no reaction when the bitter PTC chemical was placed on its tongue. The mother had four other children with the following blood types and tasting abilities for PTC:
    a. Type A and MN blood, taster
    b. Type B and N blood, nontaster
    c. Type A and M blood, taster
    d. Type A and N blood, taster

    Without knowing the father's blood types and tasting ability, can you determine whether the child is really hers? (Assume that all her children have the same father.)

14. In cats, the genotype *AA* produces tabby fur color; *Aa* is also a tabby, and *aa* is black. Another gene at a different locus is epistatic to the gene for fur color. When present in its dominant *W* form (*WW* or *Ww*), this gene blocks the formation of fur color and all the offspring are white; *ww* individuals develop normal fur color. What fur colors, and in what proportions, would you expect from the cross *Aa Ww* × *Aa Ww*?

15. Having malformed hands with shortened fingers is a dominant trait controlled by a single gene; people who are homozygous for the recessive allele have normal hands and fingers. Having woolly hair is a dominant trait controlled by a different gene; homozygous recessive individuals have normal, nonwoolly hair. Suppose a woman with normal hands and nonwoolly hair marries a man who has malformed hands and woolly hair. Their first child has normal hands and nonwoolly hair. What are the genotypes of the mother, the father, and the child? If this couple has a second child, what is the probability that it will have normal hands and woolly hair?

Questions for Discussion

1. The eyes of brown-eyed people are not alike, but rather vary considerably in shade and pattern. What do you think causes these differences?
2. Explain how individuals of an organism that are phenotypically alike can produce different ratios of progeny phenotypes.
3. ABO blood type tests can be used to exclude paternity. Suppose a defendant who is the alleged father of a child takes a blood type test and the results do not exclude him as the father. Do the results indicate that he is the father? What arguments could a lawyer make based on the test results to exclude the defendant from being the father? (Assume the tests were performed correctly.)

Experimental Analysis

Imagine that you are a breeder of Labrador retriever dogs. Labs can be black, chocolate brown, or yellow. Suppose that a yellow Lab is donated to you and you need to know its genotype. You have a range of dogs with known genotypes. What cross would you make to determine the genotype of the donated dog? Explain how the resulting puppies show you the Lab's genotype.

Evolution Link

How could an epistatic interaction shelter a harmful allele from the action of natural selection?