

in humans is Huntington's disease, in which the nervous system gradually wastes away ([Figure 12.14](#)). People who are heterozygous for the dominant Huntington allele (Hh) will inevitably develop the fatal disease. However, the onset of Huntington's disease may not occur until age 40, at which point the afflicted persons may have already passed the allele to 50 percent of their offspring.

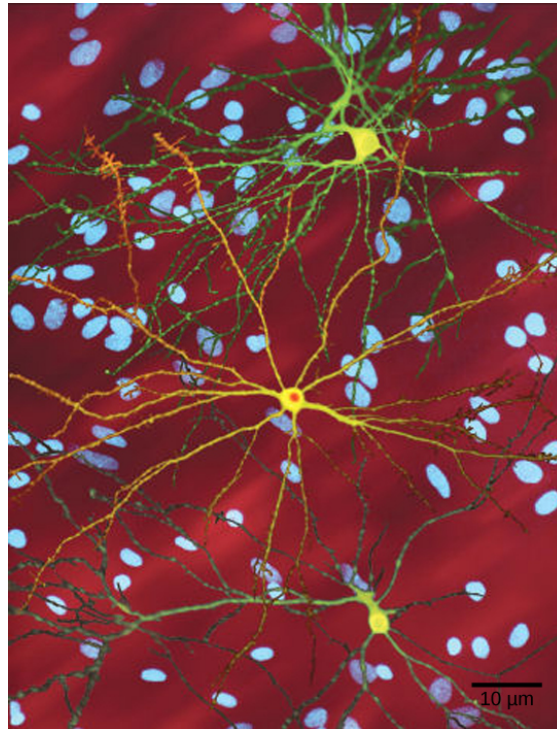


Figure 12.14 The neuron in the center of this micrograph (yellow) has nuclear inclusions characteristic of Huntington's disease (orange area in the center of the neuron). Huntington's disease occurs when an abnormal dominant allele for the Huntington gene is present. (credit: Dr. Steven Finkbeiner, Gladstone Institute of Neurological Disease, The Taube-Koret Center for Huntington's Disease Research, and the University of California San Francisco/Wikimedia)

12.3 Laws of Inheritance

By the end of this section, you will be able to do the following:

- Explain Mendel's law of segregation and independent assortment in terms of genetics and the events of meiosis
- Use the forked-line method and the probability rules to calculate the probability of genotypes and phenotypes from multiple gene crosses
- Explain the effect of linkage and recombination on gamete genotypes
- Explain the phenotypic outcomes of epistatic effects between genes

Mendel generalized the results of his pea-plant experiments into four postulates, some of which are sometimes called “laws,” that describe the basis of dominant and recessive inheritance in diploid organisms. As you have learned, more complex extensions of Mendelism exist that do not exhibit the same F_2 phenotypic ratios (3:1). Nevertheless, these laws summarize the basics of classical genetics.

Pairs of Unit Factors, or Genes

Mendel proposed first that paired unit factors of heredity were transmitted faithfully from generation to generation by the dissociation and reassociation of paired factors during gametogenesis and fertilization, respectively. After he crossed peas with contrasting traits and found that the recessive trait resurfaced in the F_2 generation, Mendel deduced that hereditary factors must be inherited as discrete units. This finding contradicted the belief at that time that parental traits were blended in the offspring.

Alleles Can Be Dominant or Recessive

Mendel's **law of dominance** states that in a heterozygote, one trait will conceal the presence of another trait for the same characteristic. Rather than both alleles contributing to a phenotype, the dominant allele will be expressed exclusively. The recessive allele will remain “latent” but will be transmitted to offspring by the same manner in which the dominant allele is transmitted. The recessive trait will only be expressed by offspring that have two copies of this allele ([Figure 12.15](#)), and these offspring will breed true when self-crossed.

Since Mendel's experiments with pea plants, researchers have found that the law of dominance does not always hold true. Instead, several different patterns of inheritance have been found to exist.



Figure 12.15 The child in the photo expresses albinism, a recessive trait.

Equal Segregation of Alleles

Observing that true-breeding pea plants with contrasting traits gave rise to F_1 generations that all expressed the dominant trait and F_2 generations that expressed the dominant and recessive traits in a 3:1 ratio, Mendel proposed the **law of segregation**. This law states that paired unit factors (genes) must segregate equally into gametes such that offspring have an equal likelihood of inheriting either factor. For the F_2 generation of a monohybrid cross, the following three possible combinations of genotypes could result: homozygous dominant, heterozygous, or homozygous recessive. Because heterozygotes could arise from two different pathways (receiving one dominant and one recessive allele from either parent), and because heterozygotes and homozygous dominant individuals are phenotypically identical, the law supports Mendel's observed 3:1 phenotypic ratio. The equal segregation of alleles is the reason we can apply the Punnett square to accurately predict the offspring of parents with known genotypes. The physical basis of Mendel's law of segregation is the first division of meiosis, in which the homologous chromosomes with their different versions of each gene are segregated into daughter nuclei. The role of the meiotic segregation of chromosomes in sexual reproduction was not understood by the scientific community during Mendel's lifetime.

Independent Assortment

Mendel's **law of independent assortment** states that genes do not influence each other with regard to the sorting of alleles into gametes, and every possible combination of alleles for every gene is equally likely to occur. The independent assortment of genes can be illustrated by the **dihybrid** cross, a cross between two true-breeding parents that express different traits for two characteristics. Consider the characteristics of seed color and seed texture for two pea plants, one that has green, wrinkled seeds ($yyrr$) and another that has yellow, round seeds ($YYRR$). Because each parent is homozygous, the law of segregation indicates that the gametes for the green/wrinkled plant all are yr , and the gametes for the yellow/round plant are all YR . Therefore, the F_1 generation of offspring all are $YyRr$ ([Figure 12.16](#)).

VISUAL CONNECTION

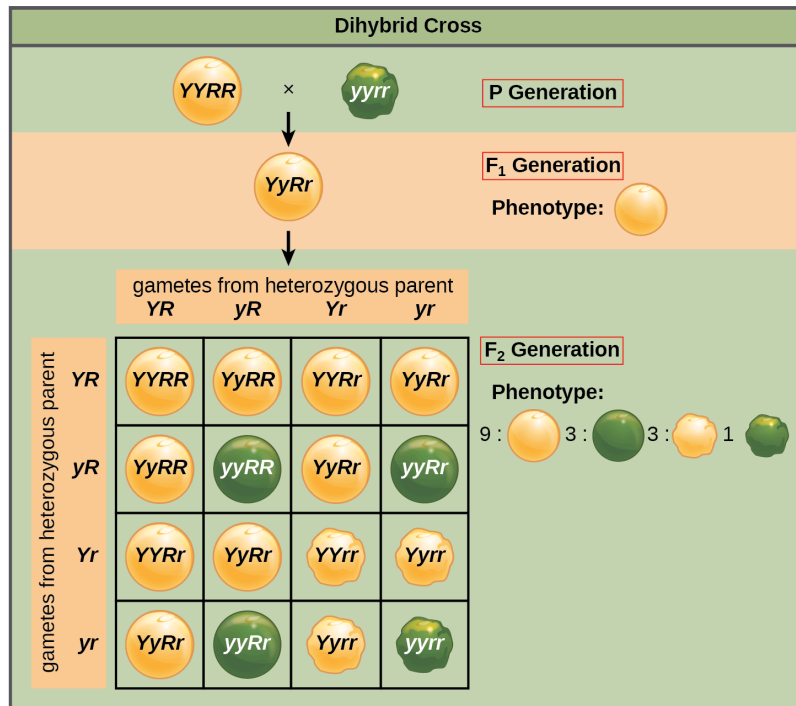


Figure 12.16 This dihybrid cross of pea plants involves the genes for seed color and texture.

In pea plants, purple flowers (P) are dominant to white flowers (p) and yellow peas (Y) are dominant to green peas (y). What are the possible genotypes and phenotypes for a cross between PpYY and ppYy pea plants? How many squares do you need to do a Punnett square analysis of this cross?

For the F₂ generation, the law of segregation requires that each gamete receive either an R allele or an r allele along with either a Y allele or a y allele. The law of independent assortment states that a gamete into which an r allele sorted would be equally likely to contain either a Y allele or a y allele. Thus, there are four equally likely gametes that can be formed when the YyRr heterozygote is self-crossed, as follows: YR, Yr, yR, and yr. Arranging these gametes along the top and left of a 4 × 4 Punnett square (Figure 12.16) gives us 16 equally likely genotypic combinations. From these genotypes, we infer a phenotypic ratio of 9 round/yellow:3 round/green:3 wrinkled/yellow:1 wrinkled/green (Figure 12.16). These are the offspring ratios we would expect, assuming we performed the crosses with a large enough sample size.

Because of independent assortment and dominance, the 9:3:3:1 dihybrid phenotypic ratio can be collapsed into two 3:1 ratios, characteristic of any monohybrid cross that follows a dominant and recessive pattern. Ignoring seed color and considering only seed texture in the above dihybrid cross, we would expect that three quarters of the F₂ generation offspring would be round, and one quarter would be wrinkled. Similarly, isolating only seed color, we would assume that three quarters of the F₂ offspring would be yellow and one quarter would be green. The sorting of alleles for texture and color are independent events, so we can apply the product rule. Therefore, the proportion of round and yellow F₂ offspring is expected to be $(3/4) \times (3/4) = 9/16$, and the proportion of wrinkled and green offspring is expected to be $(1/4) \times (1/4) = 1/16$. These proportions are identical to those obtained using a Punnett square. Round, green and wrinkled, yellow offspring can also be calculated using the product rule, as each of these genotypes includes one dominant and one recessive phenotype. Therefore, the proportion of each is calculated as $(3/4) \times (1/4) = 3/16$.

The law of independent assortment also indicates that a cross between yellow, wrinkled (YYrr) and green, round (yyRR) parents would yield the same F₁ and F₂ offspring as in the YYRR × yyrr cross.

The physical basis for the law of independent assortment also lies in meiosis I, in which the different homologous pairs line up in random orientations. Each gamete can contain any combination of paternal and maternal chromosomes (and therefore the genes on them) because the orientation of tetrads on the metaphase plane is random.

Forked-Line Method

When more than two genes are being considered, the Punnett-square method becomes unwieldy. For instance, examining a cross involving four genes would require a 16×16 grid containing 256 boxes. It would be extremely cumbersome to manually enter each genotype. For more complex crosses, the forked-line and probability methods are preferred.

To prepare a forked-line diagram for a cross between F_1 heterozygotes resulting from a cross between $AABBCC$ and $aabbcc$ parents, we first create rows equal to the number of genes being considered, and then segregate the alleles in each row on forked lines according to the probabilities for individual monohybrid crosses (Figure 12.17). We then multiply the values along each forked path to obtain the F_2 offspring probabilities. Note that this process is a diagrammatic version of the product rule. The values along each forked pathway can be multiplied because each gene assorts independently. For a trihybrid cross, the F_2 phenotypic ratio is 27:9:9:3:3:3:1.

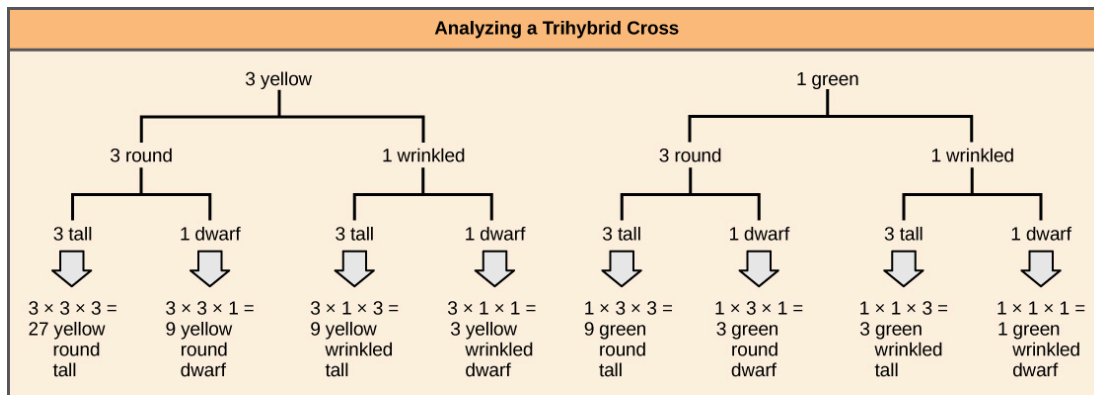


Figure 12.17 The forked-line method can be used to analyze a trihybrid cross. Here, the probability for color in the F_2 generation occupies the top row (3 yellow:1 green). The probability for shape occupies the second row (3 round: 1 wrinkled), and the probability for height occupies the third row (3 tall:1 dwarf). The probability for each possible combination of traits is calculated by multiplying the probability for each individual trait. Thus, the probability of F_2 offspring having yellow, round, and tall traits is $3 \times 3 \times 3$, or 27.

Probability Method

While the forked-line method is a diagrammatic approach to keeping track of probabilities in a cross, the probability method gives the proportions of offspring expected to exhibit each phenotype (or genotype) without the added visual assistance. Both methods make use of the product rule and consider the alleles for each gene separately. Earlier, we examined the phenotypic proportions for a trihybrid cross using the forked-line method; now we will use the probability method to examine the genotypic proportions for a cross with even more genes.

For a trihybrid cross, writing out the forked-line method is tedious, albeit not as tedious as using the Punnett-square method. To fully demonstrate the power of the probability method, however, we can consider specific genetic calculations. For instance, for a tetrahybrid cross between individuals that are heterozygotes for all four genes, and in which all four genes are sorting independently and in a dominant and recessive pattern, what proportion of the offspring will be expected to be homozygous recessive for all four alleles? Rather than writing out every possible genotype, we can use the probability method. We know that for each gene, the fraction of homozygous recessive offspring will be $1/4$. Therefore, multiplying this fraction for each of the four genes, $(1/4) \times (1/4) \times (1/4) \times (1/4)$, we determine that $1/256$ of the offspring will be quadruply homozygous recessive.

For the same tetrahybrid cross, what is the expected proportion of offspring that have the dominant phenotype at all four loci? We can answer this question using phenotypic proportions, but let's do it the hard way—using genotypic proportions. The question asks for the proportion of offspring that are 1) homozygous dominant at A or heterozygous at A, and 2) homozygous at B or heterozygous at B, and so on. Noting the “or” and “and” in each circumstance makes clear where to apply the sum and product rules. The probability of a homozygous dominant at A is $1/4$ and the probability of a heterozygote at A is $1/2$. The probability of the homozygote or the heterozygote is $1/4 + 1/2 = 3/4$ using the sum rule. The same probability can be obtained in the same way for each of the other genes, so that the probability of a dominant phenotype at A and B and C and D is, using the product rule, equal to $3/4 \times 3/4 \times 3/4 \times 3/4$, or $81/256$. If you are ever unsure about how to combine probabilities, returning to the forked-line method should make it clear.

Rules for Multihybrid Fertilization

Predicting the genotypes and phenotypes of offspring from given crosses is the best way to test your knowledge of Mendelian

genetics. Given a multihybrid cross that obeys independent assortment and follows a dominant and recessive pattern, several generalized rules exist; you can use these rules to check your results as you work through genetics calculations (Table 12.5). To apply these rules, first you must determine n , the number of heterozygous gene pairs (the number of genes segregating two alleles each). For example, a cross between $AaBb$ and $AaBb$ heterozygotes has an n of 2. In contrast, a cross between $AABb$ and $AABb$ has an n of 1 because A is not heterozygous.

General Rules for Multihybrid Crosses

General Rule	Number of Heterozygous Gene Pairs
Number of different F_1 gametes	2^n
Number of different F_2 genotypes	3^n
Given dominant and recessive inheritance, the number of different F_2 phenotypes	2^n

Table 12.5

Linked Genes Violate the Law of Independent Assortment

Although all of Mendel's pea characteristics behaved according to the law of independent assortment, we now know that some allele combinations are not inherited independently of each other. Genes that are located on separate non-homologous chromosomes will always sort independently. However, each chromosome contains hundreds or thousands of genes, organized linearly on chromosomes like beads on a string. The segregation of alleles into gametes can be influenced by **linkage**, in which genes that are located physically close to each other on the same chromosome are more likely to be inherited as a pair. However, because of the process of recombination, or "crossover," it is possible for two genes on the same chromosome to behave independently, or as if they are not linked. To understand this, let's consider the biological basis of gene linkage and recombination.

Homologous chromosomes possess the same genes in the same linear order. The alleles may differ on homologous chromosome pairs, but the genes to which they correspond do not. In preparation for the first division of meiosis, homologous chromosomes replicate and synapse. Like genes on the homologs align with each other. At this stage, segments of homologous chromosomes exchange linear segments of genetic material (Figure 12.18). This process is called *recombination*, or crossover, and it is a common genetic process. Because the genes are aligned during recombination, the gene order is not altered. Instead, the result of recombination is that maternal and paternal alleles are combined onto the same chromosome. Across a given chromosome, several recombination events may occur, causing extensive shuffling of alleles.

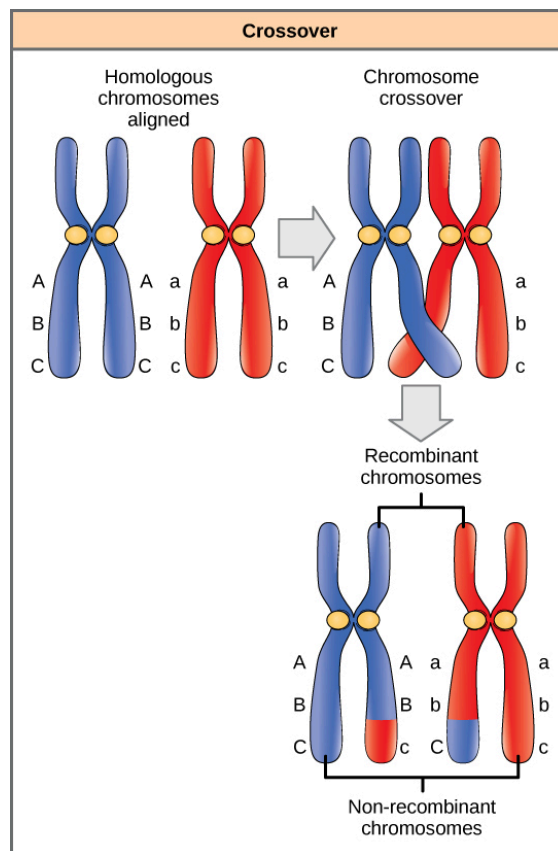


Figure 12.18 The process of crossover, or recombination, occurs when two homologous chromosomes align during meiosis and exchange a segment of genetic material. Here, the alleles for gene C were exchanged. The result is two recombinant and two non-recombinant chromosomes.

When two genes are located in close proximity on the same chromosome, they are considered linked, and their alleles tend to be transmitted through meiosis together. To exemplify this, imagine a dihybrid cross involving flower color and plant height in which the genes are next to each other on the chromosome. If one homologous chromosome has alleles for tall plants and red flowers, and the other chromosome has genes for short plants and yellow flowers, then when the gametes are formed, the tall and red alleles will go together into a gamete and the short and yellow alleles will go into other gametes. These are called the parental genotypes because they have been inherited intact from the parents of the individual producing gametes. But unlike if the genes were on different chromosomes, there will be no gametes with tall and yellow alleles and no gametes with short and red alleles. If you create the Punnett square with these gametes, you will see that the classical Mendelian prediction of a 9:3:3:1 outcome of a dihybrid cross would not apply. As the distance between two genes increases, the probability of one or more crossovers between them increases, and the genes behave more like they are on separate chromosomes. Geneticists have used the proportion of recombinant gametes (the ones not like the parents) as a measure of how far apart genes are on a chromosome. Using this information, they have constructed elaborate maps of genes on chromosomes for well-studied organisms, including humans.

Mendel's seminal publication makes no mention of linkage, and many researchers have questioned whether he encountered linkage but chose not to publish those crosses out of concern that they would invalidate his independent assortment postulate. The garden pea has seven chromosomes, and some have suggested that his choice of seven characteristics was not a coincidence. However, even if the genes he examined were not located on separate chromosomes, it is possible that he simply did not observe linkage because of the extensive shuffling effects of recombination.



SCIENTIFIC METHOD CONNECTION

Testing the Hypothesis of Independent Assortment

To better appreciate the amount of labor and ingenuity that went into Mendel's experiments, proceed through one of Mendel's

dihybrid crosses.

Question: What will be the offspring of a dihybrid cross?

Background: Consider that pea plants mature in one growing season, and you have access to a large garden in which you can cultivate thousands of pea plants. There are several true-breeding plants with the following pairs of traits: tall plants with inflated pods, and dwarf plants with constricted pods. Before the plants have matured, you remove the pollen-producing organs from the tall/inflated plants in your crosses to prevent self-fertilization. Upon plant maturation, the plants are manually crossed by transferring pollen from the dwarf/constricted plants to the stigma of the tall/inflated plants.

Hypothesis: Both trait pairs will sort independently according to Mendelian laws. When the true-breeding parents are crossed, all of the F_1 offspring are tall and have inflated pods, which indicates that the tall and inflated traits are dominant over the dwarf and constricted traits, respectively. A self-cross of the F_1 heterozygotes results in 2,000 F_2 progeny.

Test the hypothesis: Because each trait pair sorts independently, the ratios of tall:dwarf and inflated:constricted are each expected to be 3:1. The tall/dwarf trait pair is called T/t , and the inflated/constricted trait pair is designated I/i . Each member of the F_1 generation therefore has a genotype of $TtIi$. Construct a grid analogous to Figure 12.16, in which you cross two $TtIi$ individuals. Each individual can donate four combinations of two traits: TI , Ti , tI , or ti , meaning that there are 16 possibilities of offspring genotypes. Because the T and I alleles are dominant, any individual having one or two of those alleles will express the tall or inflated phenotypes, respectively, regardless if they also have a t or i allele. Only individuals that are tt or ii will express the dwarf and constricted alleles, respectively. As shown in Figure 12.19, you predict that you will observe the following offspring proportions: tall/inflated:tall/constricted:dwarf/inflated:dwarf/constricted in a 9:3:3:1 ratio. Notice from the grid that when considering the tall/dwarf and inflated/constricted trait pairs in isolation, they are each inherited in 3:1 ratios.

		$TtIi$			
		TI	Ti	tI	ti
$TtIi$	TI	$TTII$	$TTIi$	$TtII$	$TtIi$
	Ti	$TTIi$	$TTii$	$TtIi$	$Ttii$
	tI	$TtII$	$TtIi$	$ttII$	$ttIi$
	ti	$TtIi$	$Ttii$	$ttIi$	$ttii$

Figure 12.19 This figure shows all possible combinations of offspring resulting from a dihybrid cross of pea plants that are heterozygous for the tall/dwarf and inflated/constricted alleles.

Test the hypothesis: You cross the dwarf and tall plants and then self-cross the offspring. For best results, this is repeated with hundreds or even thousands of pea plants. What special precautions should be taken in the crosses and in growing the plants?

Analyze your data: You observe the following plant phenotypes in the F_2 generation: 2706 tall/inflated, 930 tall/constricted, 888 dwarf/inflated, and 300 dwarf/constricted. Reduce these findings to a ratio and determine if they are consistent with Mendelian laws.

Form a conclusion: Were the results close to the expected 9:3:3:1 phenotypic ratio? Do the results support the prediction? What might be observed if far fewer plants were used, given that alleles segregate randomly into gametes? Try to imagine growing that many pea plants, and consider the potential for experimental error. For instance, what would happen if it was extremely windy one day?

Epistasis

Mendel's studies in pea plants implied that the sum of an individual's phenotype was controlled by genes (or as he called them, unit factors), such that every characteristic was distinctly and completely controlled by a single gene. In fact, single observable characteristics are almost always under the influence of multiple genes (each with two or more alleles) acting in unison. For example, at least eight genes contribute to eye color in humans.

LINK TO LEARNING

Eye color in humans is determined by multiple genes. Use the [Eye Color Calculator \(http://openstax.org/l/eye_color_calc\)](http://openstax.org/l/eye_color_calc) to predict the eye color of children from parental eye color.

In some cases, several genes can contribute to aspects of a common phenotype without their gene products ever directly interacting. In the case of organ development, for instance, genes may be expressed sequentially, with each gene adding to the complexity and specificity of the organ. Genes may function in complementary or synergistic fashions, such that two or more genes need to be expressed simultaneously to affect a phenotype. Genes may also oppose each other, with one gene modifying the expression of another.

In **epistasis**, the interaction between genes is antagonistic, such that one gene masks or interferes with the expression of another. “Epistasis” is a word composed of Greek roots that mean “standing upon.” The alleles that are being masked or silenced are said to be hypostatic to the epistatic alleles that are doing the masking. Often the biochemical basis of epistasis is a gene pathway in which the expression of one gene is dependent on the function of a gene that precedes or follows it in the pathway.

An example of epistasis is pigmentation in mice. The wild-type coat color, agouti (AA), is dominant to solid-colored fur (aa). However, a separate gene (C) is necessary for pigment production. A mouse with a recessive c allele at this locus is unable to produce pigment and is albino regardless of the allele present at locus A ([Figure 12.20](#)). Therefore, the genotypes $AAcc$, $Aacc$, and $aacc$ all produce the same albino phenotype. A cross between heterozygotes for both genes ($AaCc \times AaCc$) would generate offspring with a phenotypic ratio of 9 agouti:3 solid color:4 albino ([Figure 12.20](#)). In this case, the C gene is epistatic to the A gene.

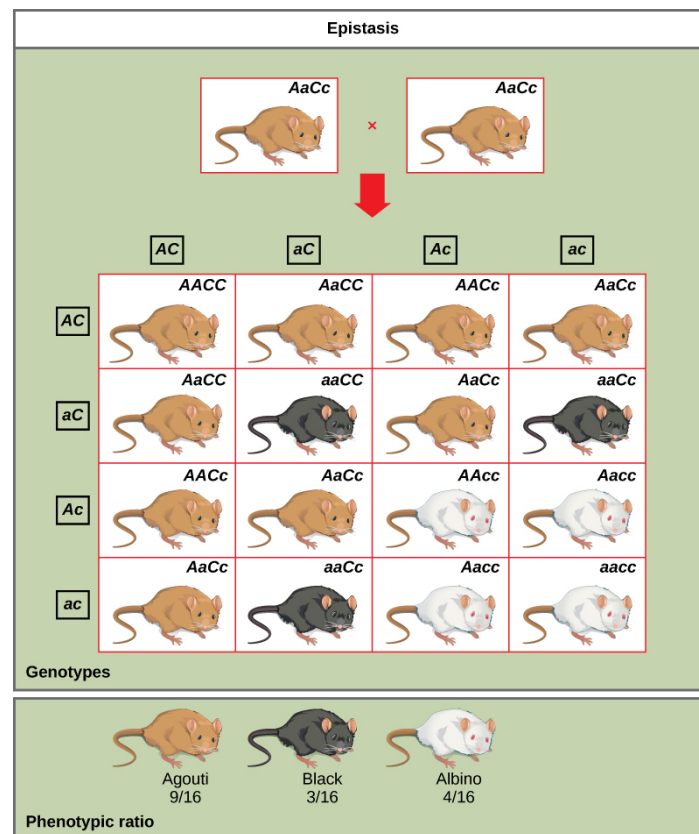


Figure 12.20 In mice, the mottled agouti coat color (*A*) is dominant to a solid coloration, such as black or gray. A gene at a separate locus (*C*) is responsible for pigment production. The recessive *c* allele does not produce pigment, and a mouse with the homozygous recessive *cc* genotype is albino regardless of the allele present at the *A* locus. Thus, the *C* gene is epistatic to the *A* gene.

Epistasis can also occur when a dominant allele masks expression at a separate gene. Fruit color in summer squash is expressed in this way. Homozygous recessive expression of the *W* gene (*ww*) coupled with homozygous dominant or heterozygous expression of the *Y* gene (*YY* or *Yy*) generates yellow fruit, and the *wwyy* genotype produces green fruit. However, if a dominant copy of the *W* gene is present in the homozygous or heterozygous form, the summer squash will produce white fruit regardless of the *Y* alleles. A cross between white heterozygotes for both genes (*WwYy* × *WwYy*) would produce offspring with a phenotypic ratio of 12 white:3 yellow:1 green.

Finally, epistasis can be reciprocal such that either gene, when present in the dominant (or recessive) form, expresses the same phenotype. In the shepherd's purse plant (*Capsella bursa-pastoris*), the characteristic of seed shape is controlled by two genes in a dominant epistatic relationship. When the genes *A* and *B* are both homozygous recessive (*aabb*), the seeds are ovoid. If the dominant allele for either of these genes is present, the result is triangular seeds. That is, every possible genotype other than *aabb* results in triangular seeds, and a cross between heterozygotes for both genes (*AaBb* × *AaBb*) would yield offspring with a phenotypic ratio of 15 triangular:1 ovoid.

As you work through genetics problems, keep in mind that any single characteristic that results in a phenotypic ratio that totals 16 is typical of a two-gene interaction. Recall the phenotypic inheritance pattern for Mendel's dihybrid cross, which considered two noninteracting genes—9:3:3:1. Similarly, we would expect interacting gene pairs to also exhibit ratios expressed as 16 parts. Note that we are assuming the interacting genes are not linked; they are still assorting independently into gametes.

LINK TO LEARNING

For an excellent review of Mendel's experiments and to perform your own crosses and identify patterns of inheritance, visit the [Mendel's Peas](http://openstax.org/l/mendels_peas) (http://openstax.org/l/mendels_peas) web lab.