Gene Interaction

4

Several genes interact to produce readily observable traits of tomatoes such as color, size, and shape. Multiple genes and environmental factors contribute to tomato characteristics such as taste.

CHAPTER OUTLINE

ESSENTIAL IDEAS

- Dominance relationships between alleles have a molecular basis. The biological effect of gene products determines what type of dominance is observed.
- Gene expression can be affected by nongenetic (environmental) factors and also as a consequence of factors related to sex.
- Gene expression can be affected by interactions with other genes, causing characteristic changes in Mendelian ratios.
- Mutation of different genes can produce the same effect on phenotype. The number of genes causing mutation of a phenotype is discovered by genetic complementation analysis.

Mendel's laws of segregation and independent assortment encapsulate the basic rules of genetic transmission in diploid organisms. We see the results of these rules through the analysis of the relative proportions of progeny with different phenotypes from crosses. We can also glimpse the hereditary transmission of DNA, RNA, and protein variation through analyses of Southern, northern, and western blots. On a mechanical level, we portray the physical basis of these rules through the movement and segregation of homologous chromosomes and sister chromatids during meiosis.

Mendel's success in identifying and describing these two hereditary laws was partly due to his use of traits whose

phenotypic characteristics are determined exclusively by inheritance of alleles for single genes. In interpreting the inheritance of these traits, he did not have to contend with phenotypic variation introduced by other genes or by environmental (nongenetic) factors. In Mendel's experiments, each trait was decided by a single pair of alleles, one fully dominant and one fully recessive, at each of seven genes. The simple case in which just two alleles influence a trait is, however, quite rare in nature. Although a diploid organism can have no more than two alleles at a locus (because such individuals have just two copies of each chromosome), there may be many alleles for a single locus within a population. Rarely do geneticists observe just two alleles segregating at a locus, with one allele completely dominant to the other, with only the alleles at a single locus controlling the phenotype, and with environmental factors playing a minimal role in determining the phenotypic character. In most cases, phenotype determination is more complicated because one or more additional circumstances affect the outcome. Collectively, these circumstances are identified as *gene interactions;* this phrase refers to any of several ways different genes can collaborate or interact with one another or with nongenetic (environmental) factors to influence the expression of a phenotypic character. Among the most important of these interactions are the following:

- There may be more than two alleles for a given locus within the population.
- Dominance of one allele over another may not be complete.
- Two or more genes may affect a single trait.
- The expression of a trait may be dependent on the interaction of two or more genes, on the interaction of genes with nongenetic factors, or both.

In this chapter, we examine patterns of phenotypic variation that result from the occurrence of each of these circumstances. Our discussions demonstrate that while traits arising through gene interactions do not always exhibit the classic Mendelian ratios (described in Chapter 2), the observed ratios can nevertheless be explained by Mendelian principles.

4.1 Interactions between Alleles Produce Dominance Relationships

Mendel wisely chose to examine traits presenting in one of two alternative forms. One form of each trait he studied displays complete dominance over the other form. Complete dominance makes the phenotype of a heterozygous organism indistinguishable from that of an organism homozygous for the dominant allele; thus, only organisms homozygous for the recessive allele display the recessive phenotype. The complete dominance of one allele also results in the exclusive expression of the dominant phenotype among the heterozygous F_1 progeny of a cross between pure-breeding homozygous parents, while the F_2 progeny display a 3:1 ratio of dominant to recessive phenotypes. We now know that the phenotypes of the seven traits that Mendel studied are controlled by two alternative alleles at seven different genes. In the cases that have been examined at the molecular level, the dominant alleles reflect the wild-type function of the gene, while the recessive alleles encode gene products with reduced or no functional activity.

Questions concerning the molecular basis of dominant and recessive alleles drove genetic research in the early and mid-20th century, including questions of how dominance of an allele could be ascertained, why certain mutations are recessive whereas others are dominant, and whether mutations always cause genes to lose function or whether mutations can impart new or additional functions to alleles.

The Molecular Basis of Dominance

A character is called dominant if it is seen in the homozygous and heterozygous genotypes, and it is called recessive if it is observed only in a single homozygous genotype. In this sense, dominance and recessiveness have a phenotypic basis. The phenotypes are, however, a consequence of the activities of proteins produced by the alleles of a gene. In this sense, dominance and recessiveness have a molecular basis. The dominance of one allele over another is determined by the activity of the protein products of the allele—by the manner in which the protein products of alleles work to produce the phenotype.

Let's compare two examples to illustrate the molecular basis of dominance and recessiveness. In both examples, a wild-type allele produces an active enzyme and a mutant allele produces either very little enzyme or none at all. In the first example the mutant allele is recessive,

but in the second example the mutant allele is dominant. In the first example, gene *R* has a dominant wild-type allele R^+ and a recessive mutant allele *r*. Gene *R* produces an enzyme that must generate 40 or more units of catalytic activity to drive a critical reaction step. Successful completion of this step produces the wild-type phenotype, whereas failure to complete the step generates a mutant phenotype. Each copy of allele R^+ produces 50 units of enzyme activity. The mutant allele *r* produces no functional enzyme and has 0 units of activity. Homozygous R^+R^+ organisms produce 100 units of enzyme activity (50 units from each copy of R^+), far exceeding the minimum required to achieve the wild-type phenotype. Heterozygous organisms (R^+r) produce a total of 50 units of enzyme activity, which is sufficient to produce the wild-type phenotype. Homozygous *rr* organisms produce no enzymatic action, however, and display the mutant phenotype. Based on its ability to catalyze the critical reaction step and produce the wild-type phenotype in either a homozygous (R^+R^+) and heterozygous (R^+r) genotype, R^+ is dominant over *r*. Dominant wild-type alleles of this kind are identified as **haplosufficient** since one (haplo) copy is sufficient to produce the wild-type phenotype.

The second example involves gene *T*, for which the wild-type allele is recessive to a mutant allele. Gene *T* produces an enzyme required to catalyze a critical reaction step that produces a wild-type phenotype if it is completed. The inability to complete the reaction step results in a mutant phenotype. For the reaction step in question, 18 units of enzyme activity are required. The wild-type allele T_1 produces 10 units of activity. A mutant allele, T_2, generates 5 units of enzyme activity. Homozygous T_1T_1 organisms generate 20 units of catalytic enzyme activity, enough to catalyze the critical reaction step and produce the wild-type phenotype. Heterozygous organisms, on the other hand, produce only 15 units of enzymatic activity and have the mutant phenotype because they fall short of the 18 units required to catalyze the reaction step. Similarly, homozygous T_2T_2 organisms, which produce 10 units of enzyme activity, also have a mutant phenotype. In this case, the mutant allele T_2 is dominant over the wild-type allele T_1 since both the heterozygous (T_1T_2) and homozygous (T_2T_2) organisms have a mutant phenotype. In cases like this, the wild-type allele is identified as **haploinsufficient** because a single copy is not sufficient to produce the wild-type phenotype.

Effects of Mutation

Genetic analysis often focuses on rare mutations and other infrequent phenomena. In many instances, the study of these rare events provides clues to the underlying causes of commonly occurring events that are not yet understood. In the case of any genetic mutation, a central question concerns the precise mechanism through which the mutation disrupts normal gene function.

From a functional perspective, the wild-type phenotype is produced in organisms with two copies of the wild-type allele (Figure 4.1a). In comparison to the level of activity of the protein products of the wild-type allele, mutant alleles can often be placed into either a *loss-of-function* or a *gain-of-function* category. A **loss-of-function mutation** results in a significant decrease or in the complete loss of the functional activity of a gene product. This common mutational category contains mutations like those described in the *R* gene example above. Loss-of-function mutant alleles are usually recessive, but under certain circumstances, they may be dominant.

Gain-of-function mutations identify alleles that have acquired a new function or are altered to express substantially more activity than the wild-type allele. Gain-of-function mutations are almost always dominant and usually produce dominant mutant phenotypes in heterozygous organisms. As a consequence of their newly acquired functions, certain gain-of-function mutations are lethal in a homozygous state.

Loss-of-Function Mutations As the previous discussion suggests, mutations resulting in a loss of function vary in the extent of loss of normal activity of the gene product. A loss-of-function mutation that results in a complete loss of gene function in comparison to the wild-type gene product is identified as a **null mutation,** also known as an **amorphic mutation** (Figure 4.1b). The word *null* means "zero" or "nothing," and the word *amorphic* means "without form." These mutant alleles produce no functional gene product and are often lethal in a homozygous genotype. The elimination of functional gene products can result from various types of mutational events, including those that block transcription, produce a gene product that lacks activity, or result in deletion of all or part of the gene.

Alternatively, a mutation resulting in partial loss of gene function may be identified as a **leaky mutation,** also known as a **hypomorphic mutation** (Figure 4.1c). *Hypomorphic* means "reduced form"; like the term *leaky*, it implies that a small percentage of normal functional capability is retained by the mutant allele but at a lower level than is found for the wild-type allele. The severity of the phenotypic abnormality depends on the residual level of activity from the leaky mutant allele. A greater percentage of activity from a leaky allele results in a less severely affected phenotype than when the mutation incurs a more substantial loss of function. Both null and hypomorphic loss-of-function mutations are often recessive and homozygous lethal. Dominant loss-of-function mutations are also known to occur.

Certain loss-of-function mutations produce dominant mutant phenotypes through alterations in the function of a multimeric protein of which the mutant polypeptide forms a part (Figure 4.1d). Multimeric proteins, composed of two or more polypeptides that join together to form a

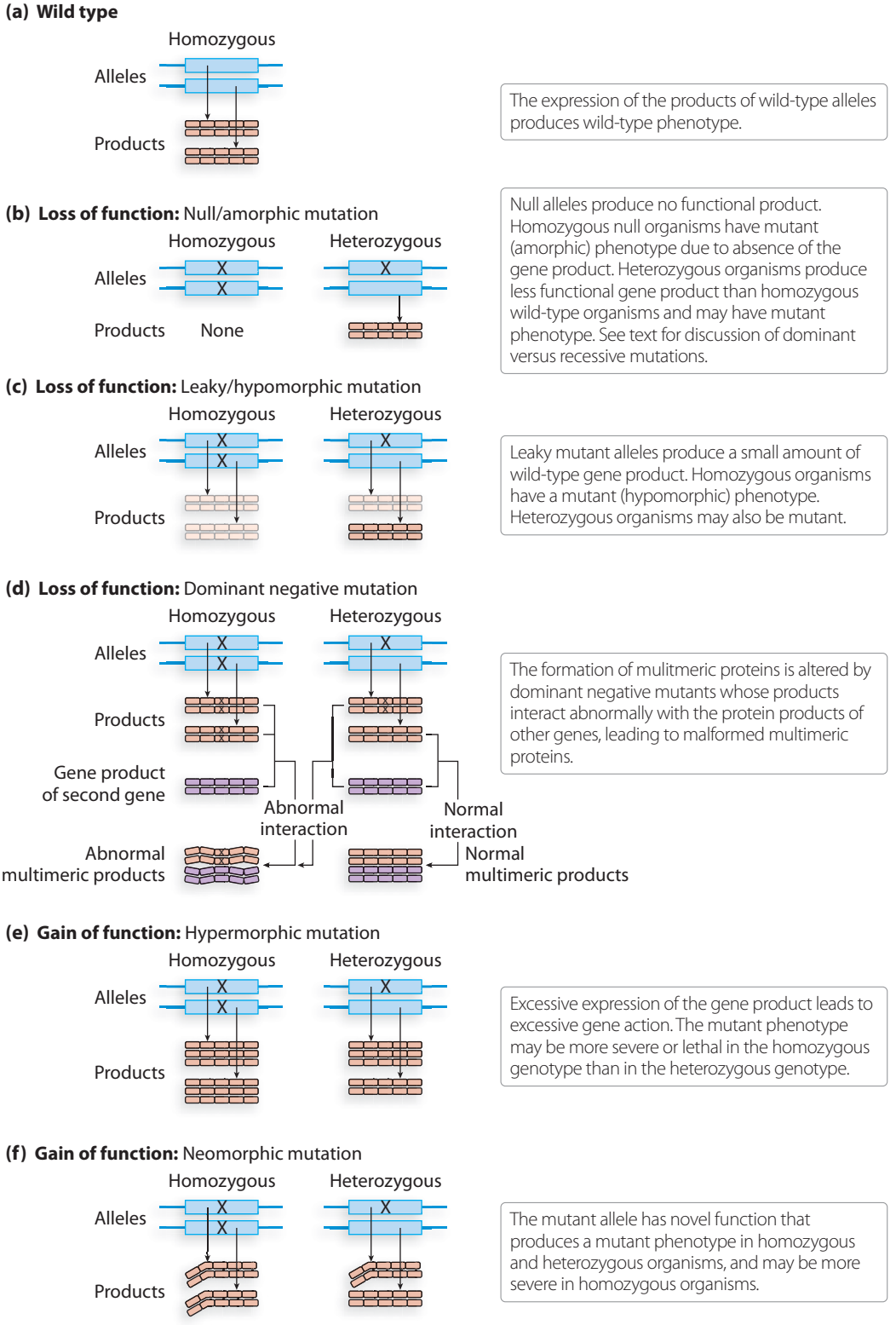


Figure 4.1 **The functional consequences of mutation.** **(a)** Wild-type. **(b)**, **(c)**, and **(d)** Loss-of-function mutations. **(e)** and **(f)** Gain-of-function mutations.

functional protein, are particularly subject to **dominant negative mutations** as a consequence of some change that prevents the polypeptides from interacting normally to produce a functional protein. A multimeric protein that contains an abnormal polypeptide may suffer a reduction or total loss of functional capacity. Mutations of this kind are dominant due to the substantial loss of function of the multimeric protein. These mutations are characterized as "negative" due to the spoiler effect of the abnormal polypeptide on the multimeric protein.

An example of dominant negative mutation is seen in the human hereditary disorder osteogenesis imperfecta (OMIM 116200, 116210, and 116220), which is caused by defects in the bone protein collagen and has multiple forms with different severity. Collagen protein is composed of three interwoven polypeptide strands—two polypeptides from the *COL1A1* gene and one polypeptide from the *COL1A2* gene. The trimeric collagen protein is subject to dominant negative mutation as a consequence of *COL1A1* mutations that produce a defective polypeptide. The trimeric structure of collagen and the 2:1 ratio of incorporation of COL1A1 polypeptide over COL1A2 polypeptide means that in individuals who are homozygous wild type for *COL1A2* and heterozygous for *COL1A1* mutation, most collagen protein contains one or two mutant COL1A1 proteins. As a result, most collagen protein is defective, and osteogenesis imperfecta develops.

Gain-of-Function Mutations Mutations resulting in a gain of function fall into two categories that depend on the functional behavior of the new mutation. **Hypermorphic** ("greater than wild-type form") **mutations** produce more gene activity per allele than the wild type (**Figure 4.1e**) and are usually dominant. The gene product of a hypermorphic allele is indistinguishable from that of the wild-type allele, but it is present in a greater amount and thus induces a higher level of activity. The excess concentration is the functional equivalent of overdrive, pushing processes forward more rapidly, at the wrong time, in the wrong place, or for a longer time than normal. Hypermorphic mutants often result from regulatory mutations that increase gene transcription, block the normal response to regulatory signals that silence transcription, or increase the number of gene copies by gene duplication. The severity of phenotypic effect may coincide with the genotype such that mutation homozygotes display a more severely affected phenotype than is observed in heterozygotes.

Gain-of-function mutations resulting from **neomorphic** ("new form") **mutations** acquire novel gene activities not found in the wild type (**Figure 4.1f**) and are usually dominant. The gene products of neomorphic mutants are functional, but have structures that differ from the wild-type gene product. The altered structures lead the mutant protein to function differently than the wild-type protein. Homozygotes for a neomorphic allele may exhibit a more severely affected phenotype than do heterozygotes.

Our description of the molecular basis of dominance and of loss-of-function and gain-of-function mutations provides a conceptual basis for understanding how different patterns of dominance relationships can develop among alleles of a gene. These concepts apply to all diploid organisms, but the notational systems that identify genes and alleles are variable among species. These different notational systems developed in the early years of genetics research when genetic experiments were carried out on distinct taxonomic groups. Geneticists studying fruit flies developed one notation system for identifying wild-type and mutant alleles, geneticists studying yeast developed another, and geneticists studying plants developed another. As the table inside the front cover illustrates, each model organism has its own unique style of gene description and nomenclature. The different notation systems cause confusion for students of genetics because they follow different rules for naming and identifying genes and alleles. The table inside the front cover contains the rule systems we follow throughout this book.

Genetic Insight Dominance relationships between alleles are determined by actions or effectiveness of the gene products in producing phenotypes. Activity levels of loss-of-function mutations and gain-of-function mutations are determined by comparisons to the activity level of the products of the corresponding wild-type allele.

Incomplete Dominance

Mendel's description of inheritance of traits controlled by a dominant and a recessive allele of single genes is a simple hereditary process that is relatively rare in nature. Commonly, however, the dominance of one allele over another is not complete. **Incomplete dominance,** also known as **partial dominance,** identifies such circumstances. When incomplete dominance exists among alleles, the phenotype of the heterozygous organism is distinctive; it falls between the phenotypes of the homozygotes on a continuum of some kind and is typically more similar to one homozygous phenotype than the other. When traits display incomplete dominance, two pure-breeding parents with different phenotypes produce F_1 heterozygotes having a phenotype different from that of either parent. The F_1 phenotype is intermediate between the parental forms, although it may more closely resemble one parental phenotype than the other.

In previous discussions we used a notational system in which an uppercase letter—for example, *A* indicates a dominant allele, and the same letter in lowercase—*a*—designates a recessive allele. In incomplete dominance systems, the relationship between alleles is different, so a different notational system—one that avoids implying

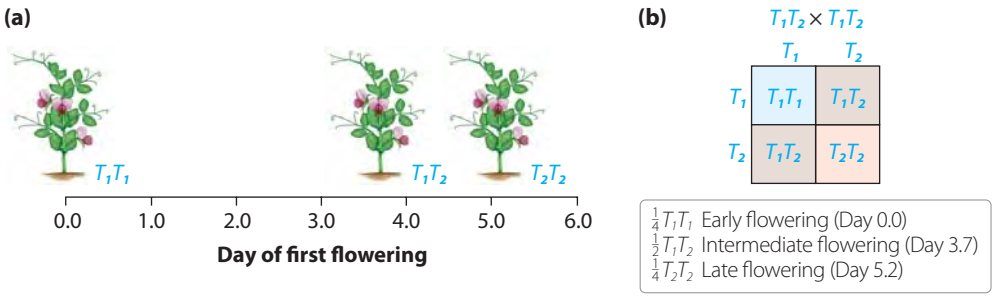


Figure 4.2 Incomplete dominance in flowering time of pea plants. **(a)** Allele T_2 is incompletely dominant over allele T_1 as indicated by the late flowering time of T_1T_2 plants. **(b)** Segregation of alleles T_1 and T_2.

dominance or recessiveness—is used. In the nomenclature system for incomplete dominance, alleles are symbolized with either upper- or lowercase letters plus a suffix that may be a number or a letter. For example, pairs of alleles with incomplete dominance can be designated *A1* and *A2*, B^1 and B^2, d_1 and d_2, and w^a and w^b.

Genetic research has identified innumerable examples of incomplete dominance in animals and plants; one example is the trait described as flowering time in Mendel's pea plants (*Pisum sativum*). In peas, the first appearance of flowers is under the genetic control of a locus that we will call *T* (for flowering *t*ime). The earliest-flowering strain of pea plants has the homozygous genotype T_1T_1; the flowering time of this strain is described as day 0.0. The latest-flowering strain is homozygous T_2T_2, and it flowers 5.2 days later on average than T_1T_1 plants. A cross of pure-breeding, early-flowering and late-flowering strains produces T_1T_2 heterozygous progeny that begin to flower 3.7 days later on average than the earliest-flowering strain (**Figure 4.2a**).

Geneticists can tell that, in this case, flowering time is controlled by a single locus because self-fertilization of T_1T_2 plants produces a 1:2:1 ratio of early-, intermediate-, and late-flowering progeny (**Figure 4.2b**). We say the T_2 allele is partially dominant, but not completely dominant, to T_1 because the heterozygous phenotype is distinct from either homozygous phenotype but more closely resembles the late-flowering strain.

Genetic Insight Incomplete dominance between alleles produces an F_1 hybrid phenotype that is intermediate between the parent phenotypes but is typically more similar to one parent than to the other.

Codominance

Codominance, like incomplete dominance, leads to a heterozygous phenotype different from the phenotype of either homozygous parent. Unlike incomplete dominance, however, codominance is characterized by the detectable expression of both alleles in heterozygotes. Codominance is most clearly identified when the protein products of both alleles are detectable in heterozygous organisms, typically by means of some sort of molecular analysis such as gel electrophoresis or a biochemical assay that can distinguish between the different proteins. We explore the details of these types of molecular analysis in a later discussion (see Chapter 10).

More than one pattern of dominance between the alleles of a gene can occur under certain circumstances. In the following section, we examine the codominance of two alleles and the recessiveness of a third allele of the gene determining human blood type.

Dominance Relationships of ABO Alleles One physiological attribute many of us know about ourselves is our blood type, which is type A, type B, type AB, or type O. All of us have one of these four common blood types that result from alleles at the ABO blood group gene located on chromosome 9 (OMIM 110300). There are three alleles in all human populations, and combinations of the alleles can occur. Most combinations of different ABO alleles result in complete dominance of one allele, but one combination results in codominance.

The three alleles of the ABO gene are identified as I^A, I^B, and *i*, and the four blood groups are phenotypes produced by different combinations of these alleles. On the basis of genotype–phenotype (i.e., blood type) correlation, geneticists have concluded that I^A and I^B have complete dominance over *i*, and that I^A and I^B are codominant to one another. The complete dominance of I^A and I^B to *i* is indicated by the identification of blood type A in individuals whose genotype is I^AI^A or I^Ai, and of blood type B in individuals whose genotype is I^BI^B or I^Bi. The completely recessive nature of the *i* allele is confirmed by the observation that only *ii* homozygotes have blood type O. Lastly, codominance of I^A and I^B to one another is confirmed by the observation that blood type AB occurs only in individuals who have the heterozygous genotype I^AI^B.

ABO blood type is identified by a reaction between an ABO antigen—a sugar moiety embedded on the surface of red blood cells—and an antibody—a molecule produced by the immune system that binds to a specific antigen protein. Blood typing makes use of an antigen–antibody reaction to determine if a specific antigen is present on red blood cells. A positive reaction occurs when the antibody detects its antigen target. The antibody binds the antigen and also attaches to other antigen-bound antibodies, causing red

blood cells to form visible clumps. Clumping indicates that the antibody has detected its antigen target, whereas an absence of clumping indicates that blood does not contain the antigen target of the antibody.

To test for ABO blood type, two antisera—one called "anti-A antiserum" and containing purified anti-A antibody, the other called "anti-B antiserum" and containing purified anti-B antibody—are placed in separate depressions on a microscope slide, and a drop of the blood to be typed is added to each depression. A person with blood type A shows clumping with anti-A antiserum but not with anti-B (**Figure 4.3**). Conversely, blood type B is identified when clumping occurs with anti-B but not with anti-A. If clumping occurs with both antisera, the blood type is AB. Clumping with neither antiserum identifies blood type O.

Proper cross-matching of blood type is essential for safe blood transfusion. In reality, several antigens produced by different genes determine the suitability of donor and recipient blood for transfusion, and hospitals and clinics must carefully compare donor and recipient blood to identify the possibility of adverse reactions before transfusion takes place. The general rule for safe blood transfusion is that the recipient blood must not contain an antibody that reacts with an antigen in the donated blood. When such a reaction occurs, hemolysis can occur and blood clots produced by clumping blood cells form at the site of transfusion. These adverse reactions can potentially cause life-threatening complications.

The antibodies anti-A and anti-B develop in humans from birth, but people do not carry an antibody if they also carry the corresponding antigen. Thus people with blood type A, who have the A antigen, also carry the anti-B antibody. People with blood type B have the B antigen and the anti-A antibody. Those with blood type AB have both antigens and neither anti-A nor anti-B antibody. Finally, people with blood type O have neither A nor B antigen and have both anti-A and anti-B antibody.

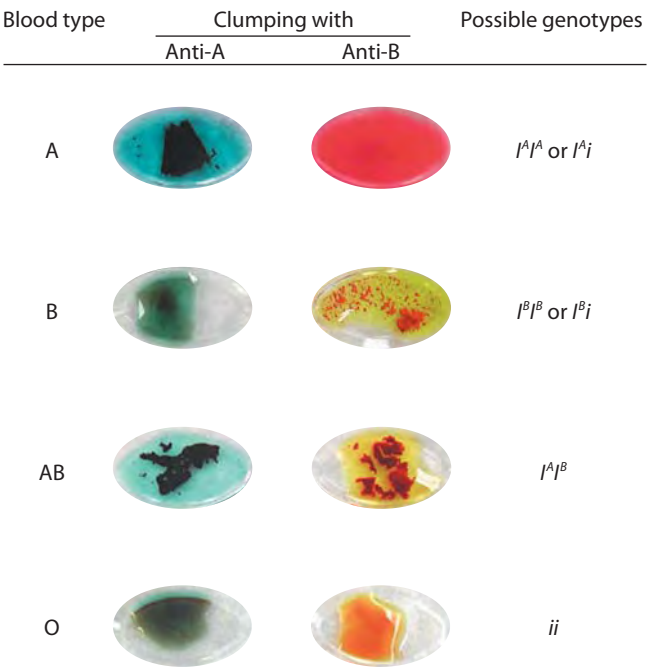


Figure 4.3 ABO blood type. Blood type is determined by mixing a drop of blood with a drop of anti-A or anti-B antiserum.

The Molecular Basis of Dominance and Codominance of ABO Alleles The two ABO blood group antigens on the surfaces of red blood cells each have a slightly different molecular structure. The antigens are glycolipids that contain a lipid component and an oligosaccharide component. The lipid portion of the antigen is anchored in the red blood cell membrane, and the segment protruding outside the cell contains the oligosaccharide. Initially, the oligosaccharide is composed of five sugar molecules and is called the H antigen. It results from the activity of an enzyme produced by the *H* gene (**Figure 4.4**). The H antigen is present on the surfaces of all red blood cells, and it can be further modified, in two alternative ways, by the addition of a sixth sugar; or it can be left unmodified. The final modification of the H antigen depends on the enzymatic activity of the protein product of the ABO blood group locus.

Two alternative sugars can be added to the H antigen by the gene products of the I^A or I^B alleles, respectively. If the I^A allele is present in the genotype, it produces the gene product α-3-N-acetyl-D-galactosaminyltransferase, or simply, "A-transferase." A-transferase catalyzes the addition of the sugar N-acetylgalactosamine to the H antigen, producing a six-sugar oligosaccharide known as the A antigen. The I^Ballele, on the other hand, produces α-3-D-galactosyltransferase, commonly called "B-transferase," which catalyzes the addition of a different sugar, galactose, and produces a six-sugar oligosaccharide known as the B antigen. The molecular basis of the differences between the A and B alleles are several nucleotide differences that change four amino acids of the resulting transferase enzymes and alter enzymatic activity. In contrast, the *i* allele is due to a single base-pair deletion and is a null allele that does not produce a functional gene product capable of adding a sixth sugar to the H antigen.

At the cellular level, anti-A antibody recognizes the N-acetylgalactosamine addition mediated by I^A, and anti-B antibody identifies the galactose addition produced by the action of I^B. Neither of these antibodies has any reactivity with the unmodified H antigen; so unmodified H antigen, present in individuals with blood type O, is not recognized by either antibody. Either one or two copies of the I^A or the I^B allele in a genotype is sufficient to produce an ABO antigen detectable by anti-A or anti-B antibodies. Both I^A and I^B are dominant to *i,* since I^A and I^B produce enzymes that modify the H antigen but *i* does not. On the other hand, the I^AI^B genotype leads to production of both A-transferase and B-transferase, resulting in the addition of N-acetylgalactosamine to some H antigens and the addition of galactose to other H antigens. In the I^AI^B

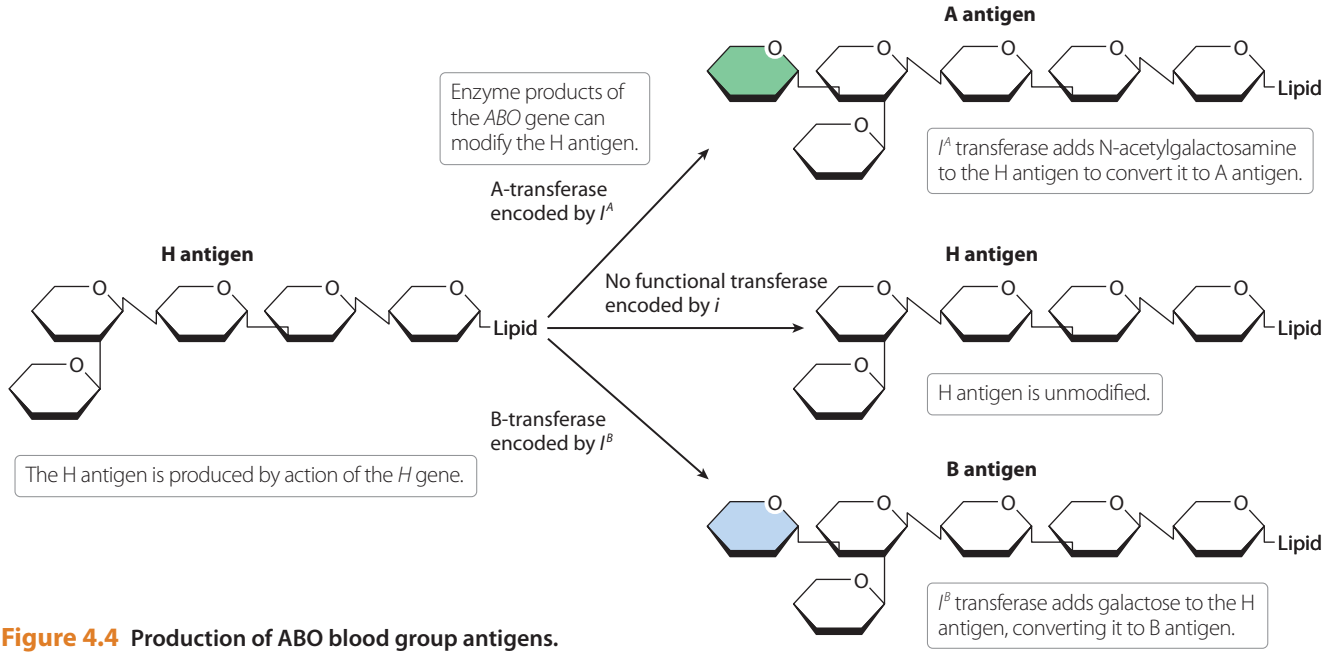


Figure 4.4 Production of ABO blood group antigens.

genotype, all red blood cells carry both types of H-antigen modifications; about half of the red cell-surface antigens are A antigens, and the rest are B antigens. In the heterozygous I^AI^B genotype, therefore, the action of both alleles is detected in the phenotype, leading to the conclusion that I^A and I^B are codominant to one another.

Many nonhuman primates have a blood group system that is essentially identical to the human ABO blood group system. ABO blood groups have been identified in the great apes (chimpanzee, gorilla, and orangutan) as well as in numerous Old World monkey species, including macaques (genus *Macaca*) and baboons (genus *Papio*). Two important evolutionary observations derive from this finding. First, the ABO blood group is a long-standing feature of the immune system genetics in primates, one that evolved early in the ancestral history of primates and was retained over tens of millions of years as primates diversified. Second, the retention of the ABO blood group system in primates demonstrates the importance of this immune system response in protecting primates from infectious and foreign antigens. Natural selection has played a preeminent role in maintaining this system. The ABO blood group genes are one example of the shared evolutionary history that can be identified through the examination of the taxonomic distribution of genes in lineages. **Genetic Analysis 4.1** examines the inheritance of blood group phenotypes where alleles have a variety of dominance relationships.

Genetic Insight Codominance between alleles occurs when the expression of both alleles is detected in heterozygous organisms that have a phenotype distinguishable from either homozygote.

Allelic Series

Diploid genomes contain pairs of homologous chromosomes; thus, each individual organism can possess at most two alleles at a locus. In populations, however, the number of alleles is theoretically unlimited, and some genes have scores of alleles. At the population level, a locus possessing three or more alleles is said to have multiple alleles. The ABO blood group locus, with its three alleles, is one example of multiple alleles. Like the *ABO* gene, other multiple-allelic loci display a variety of dominance relationships among the alleles. Commonly, an order of dominance emerges among the alleles, based on the activity of each allele's protein product, forming a sequential series known as an **allelic series.** Alleles in an allelic series can be completely dominant or completely recessive, or they can display various forms of incomplete dominance or codominance.

The *C*-Gene System for Mammalian Coat Color Genetic analysis of coat color in mammals reveals that many genes are required to produce and distribute pigment to the hair follicles or skin cells, where they are displayed as coat color or skin color. While various interactions among these genes can modify color expression, we focus here on just one gene, the *C* (color) gene that is responsible for coat color in mammals such as cats, rabbits, and mice. This gene has dozens of alleles that have been identified in more than 80 years of genetic analysis, but we limit our discussion to just four alleles that form an allelic series. The *C* gene produces the enzyme tyrosinase, which is active in the first two steps of a multistep biochemical pathway that synthesizes the pigment melanin, which imparts coat color in furred mammals and skin color in humans. In the initial melanin pathway steps, tyrosinase is responsible for the breakdown (catabolism) of the amino acid tyrosine.

GENETIC ANALYSIS 4.1

The MN blood group in humans is an autosomal codominant system with two alleles, *M* and *N*. Its three blood group phenotypes, M, MN, and N, correspond to the genotypes *MM, MN,* and *NN*. The ABO blood group assorts independently of the MN blood group.

A male with blood type O and blood type MN has a female partner with blood type AB and blood type N. Identify the blood types that might be found in their children, and state the proportion for each type.

Solution Strategies	Solution Steps
Evaluate	
1. Identify the topic this problem addresses and describe the nature of the required answer.	1. The problem concerns the inheritance of two blood types. The gene determining ABO blood type carries three alleles: I^A and I^B are codominant to one another and dominant to *i*. The MN blood group gene carries two alleles that are codominant. The answer requires finding the possible blood types, and their expected proportions, of the children of parents whose blood types are given.
2. Identify the critical information given in the problem.	2. The blood types of the parents are given.
Deduce	
3. Deduce the blood group genotypes of the male parent.	3. The male has blood types O and MN. Type O results from homozygosity for the recessive *i* allele, whereas MN is produced in heterozygotes carrying both alleles. The male genotype is *ii MN*.
4. Deduce the blood group genotypes of the female parent.	4. The female has blood groups AB and N. The AB blood type is found in heterozygotes, and blood type N in homozygotes. The female blood group genotype is I^AI^B *NN*.
Solve	
5. Identify the gamete genotypes and their frequencies for the male.	5. Independent assortment predicts two gamete genotypes for the male: All gametes contain *i*, half carry *M*, and half carry *N*.
6. Identify the female gamete genotypes and their frequencies.	6. Independent assortment predicts two gamete genotypes for the female: All gametes contain *N*, half contain I^A, and half contain I^B.
7. Predict the progeny genotypes and phenotypes.	7.

TIP: Use a Punnett square to evaluate this cross.

♀ \ ♂	***Mi***	***Ni***
NI^A	***MNI^{A}i*** Blood types: ***MN*** and ***A***	***NNI^{A}i*** Blood types: ***N*** and ***A***
NI^B	***MNI^{B}i*** Blood types: ***MN*** and ***B***	***NNI^{B}i*** Blood types: ***N*** and ***B***

For more practice, see Problems 6, 9, and 21.

The *C*-gene alleles form an allelic series that is determined by the phenotypes of offspring of various matings. Allele *C* is dominant to all other alleles of the gene, and any genotype with at least one copy of *C* produces wild-type coat color. These genotypes are written as *C*– to indicate that regardless of the second allele in the genotype, the phenotype is dominant. Three other alleles producing tyrosinase enzymes with reduced or no tyrosinase activity form an allelic series with *C* (**Figure 4.5**). The allele c^{ch} produces a phenotype called chinchilla, a diluted coat color. The c^h allele produces the Himalayan phenotype, characterized by fully pigmented extremities (paws, tail, nose, and ears) but virtually absent pigmentation on other parts of the body. The Himalayan phenotype is the "Siamese" coat-color pattern often seen in cats, rabbits, and mice. Finally, the *c* allele produces a protein product with no enzymatic activity. This is a fully recessive null allele, and homozygosity for it produces an albino phenotype.

Crosses between animals with different genotypes at the *C* gene reveal the dominance relations of the alleles. For example, in crosses A, B, and C in **Figure 4.6**, complete dominance of *C* over other alleles in the series is demonstrated by the finding that all of the progeny of an animal with the genotype *CC* have full color, regardless of the genotype of the mate. The dominance order of alleles in the series is revealed by the pattern of 3:1 ratios obtained from crosses of various heterozygous genotypes shown in Figure 4.6. In cross D, chinchilla is shown to be partially dominant over Himalayan. Most of the coat of these animals has diluted (chinchilla) color, and the Himalayan

Full color
CC, *C*–

Chinchilla
$c^{ch}c^{ch}$, $c^{ch}c$

Himalayan
$c^{h}c^{h}$, $c^{h}c$

Albino
cc

Figure 4.5 **Allelic series for coat-color determination in mammals.**

pattern has darker color of paws, face, and tail. Cross E shows that chinchilla is completely dominant over albino. Himalayan is completely dominant over albino (cross F). The dominance relationships within this allelic series locus can be expressed as $C > c^{ch} > c^{h} > c$.

The Molecular Basis of the *C*-Gene Allelic Series

Tyrosinase enzymes produced by different *C*-gene alleles have distinctive levels of catabolic activity that are the basis for the dominance relationships between the alleles. The allele *C* is a dominant wild-type allele producing fully active tyrosinase that is defined as 100% activity. The percentage of wild-type tyrosinase activity produced by each allele explains the order observed for the allelic series. Biochemical examination reveals that the enzyme produced by the c^{ch} hypomorphic allele has less than 20% of the active than the wild-type enzyme. In the homozygous $c^{ch}c^{ch}$ genotype or heterozygous genotypes $c^{ch}c^{h}$ or $c^{ch}c$, only a small amount of melanin is synthesized. This leads to a decreased amount of pigment, and it has the effect of muting the coat color.

The tyrosinase enzyme produced by the hypomorphic c^{h} (Himalayan) allele is unstable and is inactivated at a temperature very near the normal body temperature of most mammals. This type of gene product is an example of a **temperature-sensitive allele.** Cats with the Siamese coat-color pattern are familiar examples of the action of this temperature-sensitive allele. The parts of cats that are farthest away from the core of the body (the paws, ears, tail, and tip of the nose) at most times tend to be slightly cooler than the trunk. At these cooler extremities, the temperature-sensitive tyrosinase produced by the c^{h} allele remains active, producing pigment in the hairs there. However, in the warmer central portion of the body, the slightly higher temperature is enough to cause the tyrosinase produced by the c^{h} allele to denature, or unravel. This inactivates the enzyme and leads to an absence of pigment in the central portion of the body. Animals that are $c^{h}c^{h}$ or $c^{h}c$ have the Himalayan phenotype. The final allele in the series, *c*, is a null allele that does not produce functional tyrosinase. Homozygotes for this allele are unable to initiate the catabolism of tyrosine. This leads to an absence of melanin and produces the condition known as albinism.

Genetic Insight Phenotypes produced by the interactions of multiple alleles in an allelic series reveal hierarchical relationships that depend on the biological action of allelic products. Dominance is associated with the allele producing the most active gene product, and the placement of other alleles in the series is dependent on the relative activity of their respective gene products.

Lethal Mutations

Certain single-gene mutations are so detrimental that they cause death early in life or terminate gestational development. These life-ending mutations are categorized as lethal and are caused by a **lethal mutation.** Lethal alleles are often inherited as recessive mutants, recessive lethal alleles that kill only homozygotes. As a rule, recessive lethal alleles have variable frequencies in populations, and they may persist in some populations over a long period of time. Natural selection can eliminate copies of the allele when they occur in homozygous genotypes; however, recessive lethal alleles are "hidden" by dominant wild-type alleles in heterozygous genotypes, thus evading natural selection. Under certain circumstances, heterozygous carriers of a recessive lethal allele have a natural selection advantage (see Chapter 10).

Lethal alleles are often detected as distortions in segregation ratios, where one or more classes of expected progeny are missing. For example, in plant and animal crosses between two organisms heterozygous for a recessive lethal allele, the phenotype of the progeny is 3:1 (viable : dead). The dead offspring are homozygous for a recessive lethal mutation. These progeny might not be seen at all, due to embryonic lethality, or they may be stillborn or die very young. Of the viable offspring, two-thirds are expected to be heterozygous for the lethal allele and one-third are expected to be homozygous for the dominant wild-type allele (**Figure 4.7**).

In flowering plants, the effects of lethal alleles can be observed directly. For example, mutation of the *RPN1a* gene that encodes a subunit of the 26S proteosome, a multi-protein complex involved in protein degradation, is an example of a loss-of-function null mutation (*rpn1a*) that

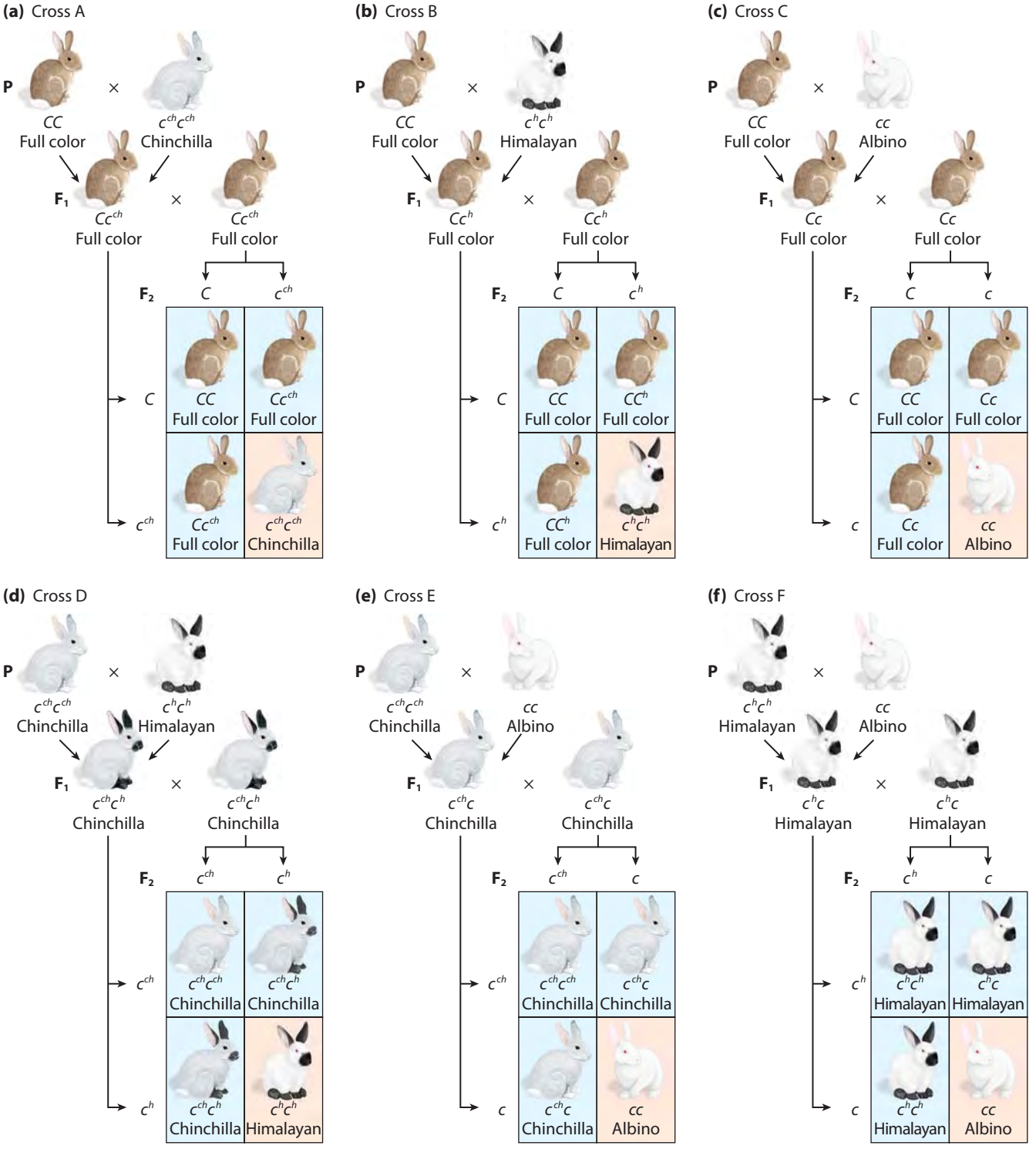


Figure 4.6 The genetics of *C*-gene dominance. **(a)–(f)** Crosses A to F illustrate the complete dominance of *C* and the complete recessiveness of *c*, and establish the allelic series as $C > c^{ch} > c^h > c$.

results in embryonic lethality in *Arabidopsis thaliana* and other plant species. In an *RPN1a/rpn1a* × *RPN1a/rpn1a* cross, a 3:1 segregation ratio of living seeds (*RPN1a*) to dead seeds (*rpn1a/rpn1a*) can be observed in the fruit. When the living seeds are planted, approximately two-thirds are heterozygous for the lethal allele (*RPN1a/rpn1a*) and one-third are homozygous for the wild-type allele (*RPN1a/RPN1a*).

Lethal mutations that result in female gametophytic lethality are also detectable in flowering plants. Consider

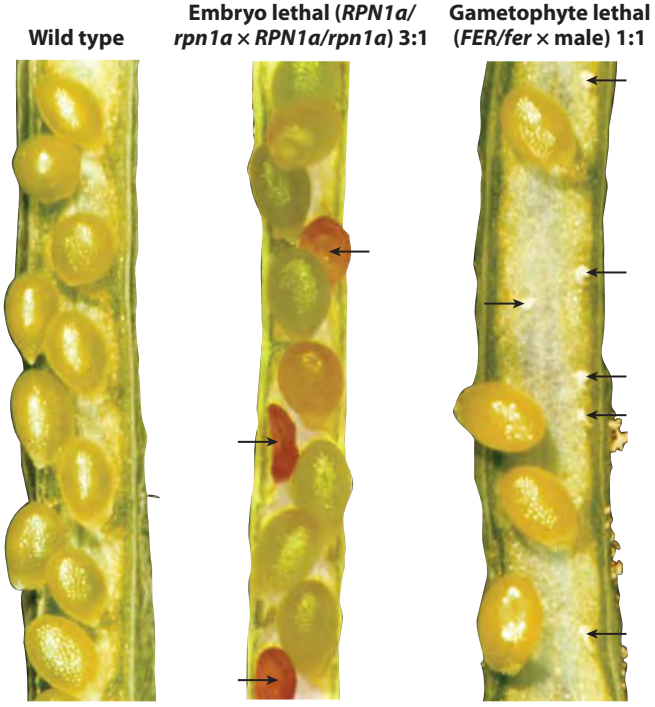


Figure 4.7 Evidence of lethal mutations in plants. Gametophytic lethality is detected by observing a 1:1 ratio of living to dead seeds. Arrows indicate undeveloped seeds.

a plant heterozygous for a female gametophytic allele, *FER/fer*, in which the wild-type *FER* allele was derived from its mother, and the mutant *fer* allele came from its father. During megasporogenesis, half of all megaspores will inherit the *FER* allele and the other half will inherit the *fer* allele. Embryo sacs derived from megaspores inheriting the *fer* allele will die, so that only half of all ovules develop into seeds. The alleles segregate in a 1:1 ratio that is observed among the developing seeds in a fruit. Note that the 1:1 ratio is a direct observation of Mendelian ratios in the gametes of a heterozygous organism. Thus a 1:1 ratio distinguishes female gametophytic lethality from embryonic lethality, which results in a 3:1 ratio among seeds. Plants usually produce pollen in excess, similar to the excess of sperm production relative to egg production in animals; thus, male gametophytic lethality is not observable by looking at developing seeds in the fruit. It can be detected, however, by looking for plants in which half of all the pollen grains are dead.

In contrast, lethal alleles in animals are usually detected by a distortion in segregation ratios. The first case of a lethal allele was identified in 1905 by Lucien Cuenot, who studied a lethal mutation in mice carrying a dominant mutation for yellow coat color. In mice, wild-type coat color is a brown color, called "agouti" (*a-GOO-tee*), produced by the presence of yellow and black pigments in each hair shaft (Figure 4.8a). Agouti hairs are black at the base and tip, with yellow pigment in the central portion of the shaft. Yellow coat color is seen when yellow pigment is deposited along the entire length of the hair shaft, not just in the middle portion as it is in agouti (Figure 4.8b). The *Agouti* gene produces the yellow pigment found in hairs. The wild-type allele for agouti coat color is designated *A*, and its normal activity leads to the production of a moderate amount of yellow pigment. The mutant allele, designated A^Y, is a gain-of-function dominant mutation that produced substantially more yellow pigment than did the wild-type allele.

The A^Y mutation is dominant, but true-breeding yellow mice cannot be produced. From a genetic perspective, this means that mice with yellow coat color are heterozygous (AA^Y) and that the A^YA^Y genotype is lethal in embryonic development. From this information, two important observations about the genetics of the yellow allele can be made. First, mating an agouti mouse and a yellow mouse will *always* result in a 1:1 ratio of agouti and yellow among progeny (Figure 4.9a). Second, crosses between two yellow mice (both of which are necessarily heterozygous) produce evidence of the recessive lethal nature of the A^Y allele (Figure 4.9b). The outcome of these crosses is a 2:1 ratio of yellow to agouti, rather than the 3:1 ratio that is anticipated when heterozygotes expressing a dominant allele are crossed. The genetic interpretation of this observation is that alleles of heterozygous yellow mice segregate normally in gamete formation and unite at random

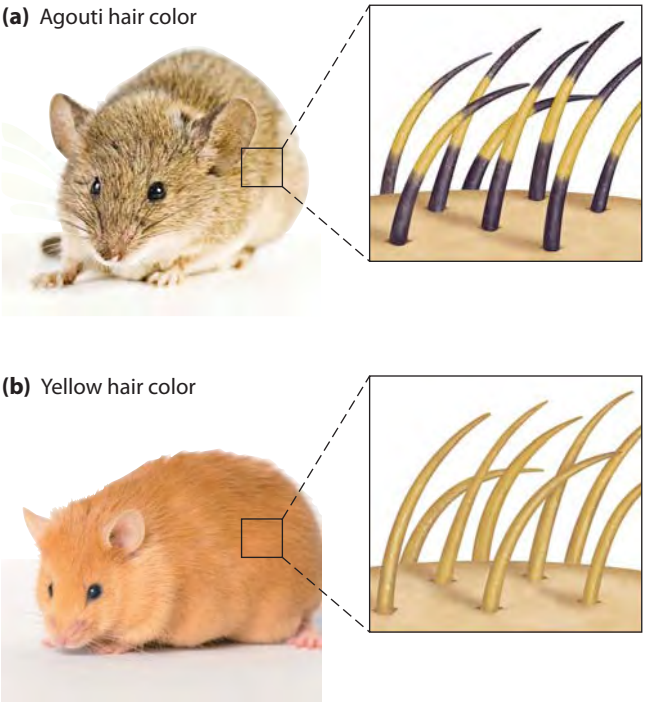


Figure 4.8 Coat color in mice. **(a)** Wild-type agouti coat color is a mixture of black and yellow pigment in hair shafts. **(b)** Yellow coat occurs when yellow pigment produced by the overly active mutant allele A^Y displaces black pigment.

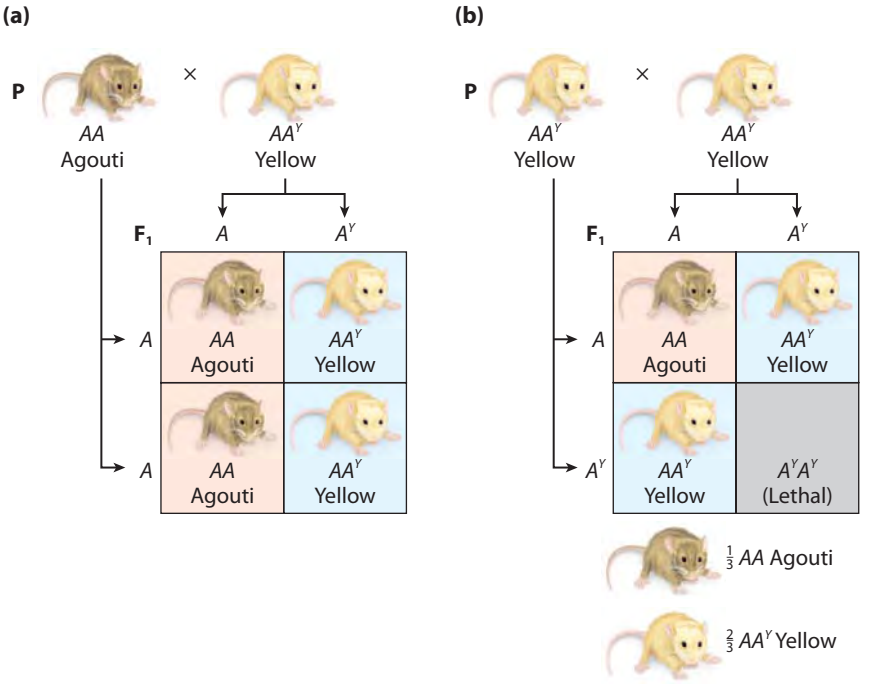


Figure 4.9 Dominance and lethality of A^Y. **(a)** A 1:1 ratio identified A^Y as a dominant mutant allele. **(b)** The lethality of A^Y in the homozygous genotype results in a 2:1 ratio of yellow to agouti in the cross of yellow-coated heterozygous mice.

to produce a 1:2:1 ratio at conception, but that A^YA^Y zygotes do not survive gestation. Recessive lethality of A^Y prevents embryonic development of homozygotes, eliminating that class among progeny and resulting in the 2:1 ratio seen among progeny of heterozygous parents.

Nearly a century after Cuenot first identified homozygous lethality of the mutant A^Y allele, the molecular basis of the lethality was identified. Much to the surprise of geneticists, the lethality had little to do with yellow coat color itself; instead, yellow coat was an almost inadvertent consequence of a mutation that deleted part of a gene near the coat-color gene. The mutation producing the A^Y allele results from a deletion that affects two genes, the *Agouti* gene and a neighboring gene identified as *Raly*. *Raly* produces a protein that is essential for mouse embryo development. Each gene has its own promoter. The wild-type *Raly* promoter drives a high level of transcription, whereas the *Agouti* gene promoter is considerably less actively transcribed (**Figure 4.10**). The dominant mutation producing yellow coat color comes about by a deletion of approximately 120,000 bp that deletes the entire *Raly* gene and the *Agouti* gene promoter, thus bringing the *Agouti* gene under the control of the *Raly* promoter. The *Raly* promoter drives a high level of *Agouti* gene transcription that results in excess yellow pigment that displaces black pigment in hair shafts and leads to the mutant yellow phenotype. Heterozygotes with the AA^Y genotype have yellow coats and survive due to haplosufficiency of the single copy of *Raly*. Homozygous A^YA^Y mice are unable to produce the essential protein product from the *Raly* gene and fail to develop, resulting in the skewed 2:1 Mendelian ratio that characterizes the progeny of two heterozygous yellow-coated mice.

Sex-Limited Traits

The sex of an organism can exert an influence on its gene expression. One consequence of such influence is the potential limitation of gene expression to one sex but not the other in a pattern called **sex-limited gene expression.** Differences in gene expression between the sexes can result in the appearance of these **sex-limited traits.** Both sexes typically carry the genes for sex-limited traits, but the genes are expressed in just one sex.

In mammals, for example, the development of breasts and the ability to produce milk are traits limited to females. Horn development is a trait limited to males in some species of sheep, cows, and other hoofed animals.

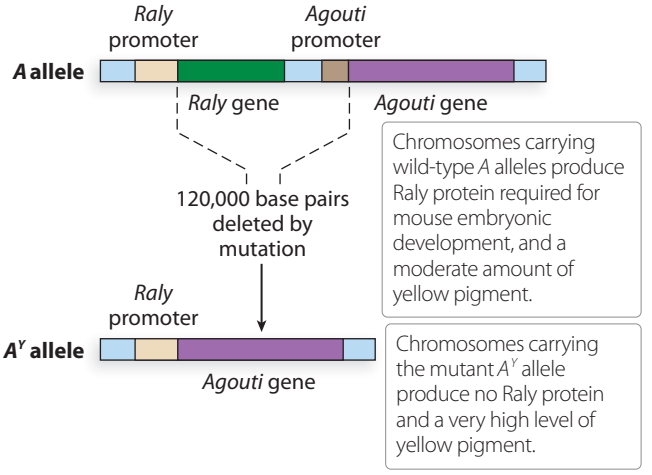


Figure 4.10 Mutation of *Raly* and *Agouti* producing yellow coat.

Behavioral traits in some species, particularly traits related to mating, are also strongly influenced by sex. For example, the courtship behavior of crowned cranes includes an elaborate display of body positioning, neck intertwining, and vocalization that is performed differently by males and females of the species.

The mechanism that limits the expression of a trait to just one sex is most often the differential influence of hormones acting as intercellular regulators of gene expression. In the case of male canary vocalization, for example, changes in male singing patterns are initiated in late winter by an increase in male hormones released by the brain in response to increased day length and warmer temperatures. These hormones stimulate enlargement of the testes and increased production of testosterone, which in turn stimulates the development of neurons in the brain that elaborate the song center, induce the development of muscles in the vocalization area of the throat, and allow males to produce sex-limited vocalization to attract mates.

Sex-Influenced Traits

Sex-influenced traits are those in which the phenotype corresponding to a particular genotype differs depending on the sex of the organism carrying the genotype. Among many possible examples, human sex-influenced pattern baldness, the common form of baldness involving hair loss on top of the head in men, is a familiar condition.

Male pattern baldness is inherited as an autosomal trait determined by two alleles, *B* and *b*, which are present in three genotypes in each sex. In both sexes, *BB* homozygotes have full hair. Homozygotes of either sex with the *bb* genotype experience hair loss, but male hormones are a principal factor influencing substantial male hair loss. In *bb* males, the hair loss produces the horseshoe-shaped pattern baldness phenotype. In *bb* females, on the other hand, the hair thins on top of the head but is not completely lost as it is in males. Males with the heterozygous genotype (*Bb*) express pattern baldness in the same form as that seen in *bb* males. In contrast, *Bb* heterozygous females have full hair (Figure 4.11). Thus, the *B* allele is dominant to the *b* allele in females, while the opposite is true in males.

Delayed Age of Onset

From an evolutionary perspective, it is easy to understand that a dominant lethal allele can be efficiently eliminated by the action of natural selection. Even so, there are numerous examples of dominant lethal hereditary conditions, and a pertinent evolutionary genetic question concerns how these mutations persist in populations. One answer is that some dominant lethal alleles sidestep natural selection by having a **delayed age of onset;** the abnormalities they produce do not appear until after affected organisms have had an opportunity to reproduce and transmit the mutation to the next generation.

One prominent example of delayed age of onset of a dominant lethal allele in humans is the condition called Huntington disease (HD). This progressive neuromuscular disorder, usually fatal within 10 to 15 years of diagnosis, is caused by mutation of a gene near one end of chromosome 4. (We have much more to say about the symptoms and progression of HD in Chapter 5, where we also discuss the mapping of the HD gene, and in Chapter 16, where we discuss the cloning of the HD gene). The HD mutant allele persists in the population because symptoms do not begin in about half of all cases until the person's late thirties or early forties, well after most people have begun having children (Figure 4.12).

Genetic Insight Lethal alleles cause the death of organisms and may be either dominant or recessive. Death may occur early or late in life. When death occurs during gestation, the presence of a lethal allele is often detected by the absence of an expected class of progeny or by the alteration of seed or seedling ratios.

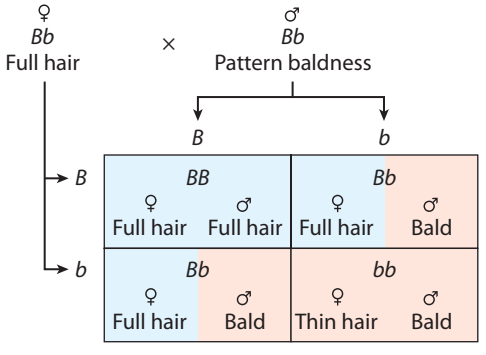


Figure 4.11 Sex-influenced inheritance of pattern baldness. The baldness allele (*b*) is expressed differently in males and females.

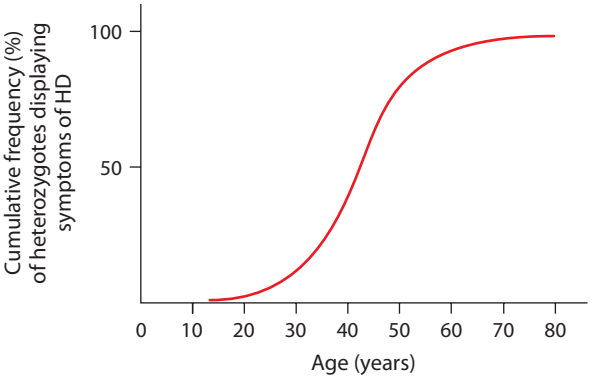


Figure 4.12 The age-of-onset curve for Huntington disease (HD).

4.2 Some Genes Produce Variable Phenotypes

To interpret phenotype ratios and identify the distribution of genotypes among phenotypic classes, geneticists make the assumption that phenotypes differ because their underlying genotypes differ. This assumption is valid only to the extent that a particular genotype always produces the same phenotype. If the strict correlation between genotype and phenotype does not consistently hold true—if instead the same genotype can produce different phenotypes—the usual reasons are gene–environment interaction or interactions with alleles of other genes in the genome.

In this section, we describe two phenomena, referred to as *incomplete penetrance* and *variable expressivity*, in which phenotypic variation occurs among organisms with the same genotype. In addition, we look at specific instances of environmental influence on gene expression that is often associated with incomplete penetrance or variable expressivity.

Incomplete Penetrance

When the phenotype of an organism is consistent with the organism's genotype, the organism is said to be **penetrant** for the trait. In such a case, if the organism carries a dominant allele for the trait in question, the dominant phenotype is displayed. Sometimes an organism with a particular genotype fails to produce the corresponding phenotype, in which case the organism is **nonpenetrant** for the trait.

Traits for which nonpenetrant individuals occasionally or routinely occur are identified as displaying **incomplete penetrance.** The human condition known as polydactyly ("many digits") is an autosomal dominant condition that displays incomplete penetrance. Individuals with polydactyly have more than five fingers and toes—the most common alternative number is six (**Figure 4.13**). Polydactyly occurs in hundreds of families around the world, and in these families the dominant allele is nonpenetrant in about 25–30% of individuals who carry it. Most people who carry the dominant mutant polydactyly allele have extra digits; but at least one in four people with the mutant allele do not have extra digits and instead express the normal five digits. The gene mutated to produce polydactyly was recently identified (see Chapter 20).

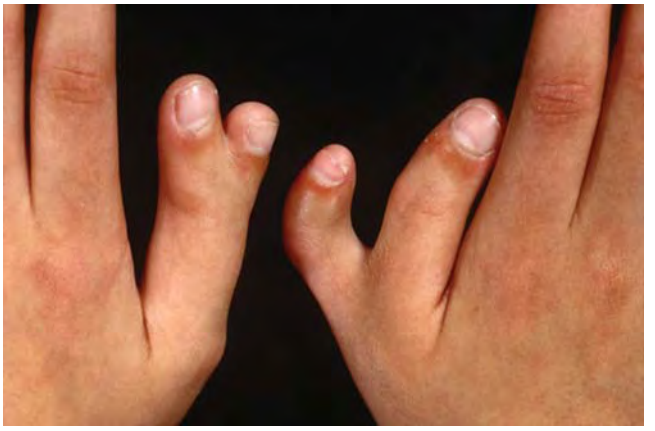


Figure 4.13 **Polydactyly, an autosomal dominant trait with incomplete penetrance.**

Figure 4.14 shows a family in which polydactyly segregates as a dominant mutation. Nine individuals in the family carry a copy of the polydactyly allele. Six of them are penetrant for the phenotype (meaning that they express the phenotype), but at least three family members—II-6, II-10, and III-10—are nonpenetrant. Each of these individuals has a child or grandchild with polydactyly; thus, each carries the dominant allele for polydactyly but is nonpenetrant for the condition. When nonpenetrant individuals are relatively common, the magnitude of frequency of penetrance can be quantified. Penetrance values vary among different families; but for the family shown in Figure 4.14, the penetrance of polydactyly is $\frac{6}{9}$, or 66.7%, which is about the average seen worldwide among hundreds of families with polydactyly.

Variable Expressivity

Sometimes the discrepancy between genotype and phenotype is a matter of degree rather than presence or absence.

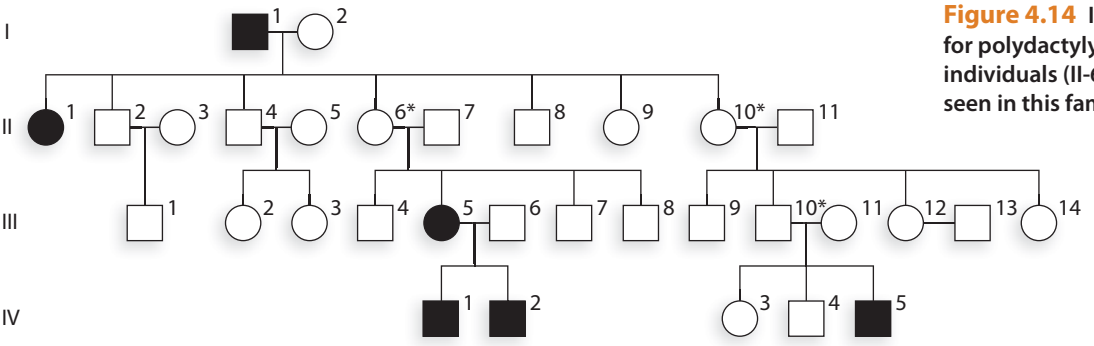


Figure 4.14 **Incomplete penetrance for polydactyly. Three nonpenetrant individuals (II-6, II-10, and III-10) are seen in this family.**

In the phenomenon of **variable expressivity,** the same genotype produces phenotypes that vary in the degree or magnitude of expression of the allele of interest.

Waardenburg syndrome is a human autosomal dominant disorder displaying variable expressivity. Individuals with Waardenburg syndrome may have any or all of four principal features of the syndrome: (1) hearing loss, (2) differently colored eyes, (3) a white forelock of hair, and (4) premature graying of hair. In the Waardenburg pedigree shown in **Figure 4.15**, notice that the circles and squares representing family members with Waardenburg syndrome may be entirely or only partly colored. Each quadrant of the symbols represents one of the principal features of the syndrome. The diversity of symbol darkening demonstrates the variation in expressivity of Waardenburg syndrome in this family. Molecular genetic analysis tells us that each family member with Waardenburg syndrome carries exactly the same dominant allele, yet among the eight affected members of the family, there are six different patterns of phenotypic expression.

It is often difficult to pinpoint the cause of incomplete penetrance or variable expressivity. Three kinds of interactions may be responsible: (1) other genes that act in ways that modify the expression of the mutant allele, (2) environmental or developmental (i.e., nongenetic) factors that interact with the mutant allele to modify its expression, and (3) some combination of other genes and environmental factors interacting to modify expression of the mutation. In inbred laboratory strains of model genetic organisms, variation in genetic factors can be eliminated experimentally to allow separation of gene–gene and gene–environment variability, something that cannot be done in organisms such as humans.

Gene–Environment Interactions

Genes control virtually all of the differences observed between species. The genome of an organism lays out the body plan and biochemical pathways of the organism, and it controls the progress of development from conception to death. But genes alone are not responsible for all the variation seen between organisms. The environment, the myriad of physical substances and conditions an organism encounters at different stages of life, is the other essential contributor to observable variation between organisms. **Gene–environment interaction** is the result of the influence of environmental factors (i.e., nongenetic factors) on the expression of genes and on the phenotypes of organisms.

> Genetic Insight In incomplete penetrance, a genotype is not expressed by every organism in which it is present. In variable expressivity, the organisms that share a genotype express the corresponding phenotype to different degrees. Both are explained by genetic and/or nongenetic interactions that modify or prevent the consistent expression of a genotype.

As an example, consider the tall and short pure-breeding lines of pea plants studied by Mendel. Inherited genetic variation dictates that one line will produce tall plants and the other line will produce short plants, but the environment in which the individual plants are grown also has a significant influence on plant height. Environmental factors such as variations in water, light, soil nutrients, and temperature each influence plant growth. It is not hard to imagine that genetically identical plants of a type adapted to temperate zones might grow to different heights if one plant has an ideal growth environment while the other faces a hot, arid environment with poor soil.

Phenotypic expression of genotypes can also depend on the interaction of genetically controlled developmental programs and external factors operating on organisms. For example, the seasonal change in coat color observed in arctic mammals that are nearly white in winter but have darker coats in spring and summer results from an interaction between numerous genes and external environmental cues such as day length and temperature. Similarly, environmental cues that induce plants to bloom in the spring trigger changes in gene expression that stimulate the growth and development of multiple plant structures, including flowers and reproductive structures.

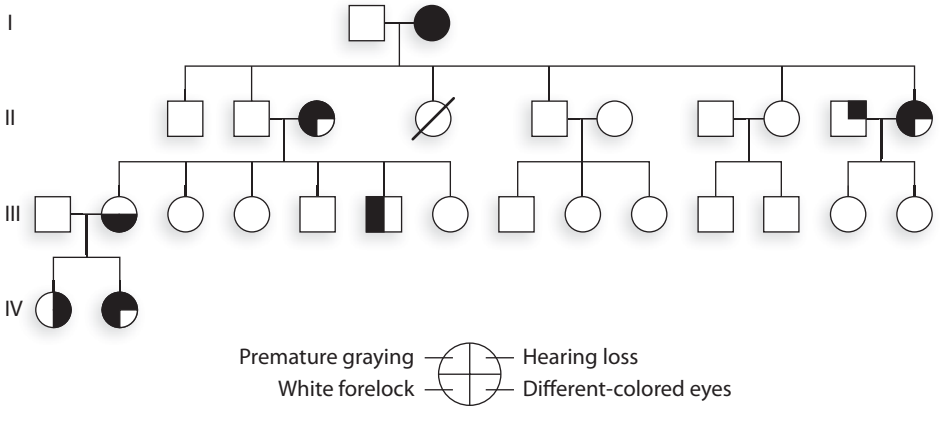


Figure 4.15 **Variable expressivity of Waardenburg syndrome.**

Such capacities to make seasonal changes evolved by aiding the survival of these organisms, and they suggest that gene–environment interaction is pivotal in understanding and interpreting phenotypic variation.

Environmental Modification to Prevent Hereditary Disease A prime example of gene–environment interaction in humans is actually a case of environmental intervention that is commonly practiced to prevent the development of the human autosomal recessive condition known as phenylketonuria (PKU). This case illustrates that the same alleles may produce different phenotypes in different environments. PKU is caused by the absence of the enzyme phenylalanine hydroxylase, which catalyzes the first step of the pathway that breaks down the amino acid phenylalanine, a common component of dietary protein.

At one time, PKU accounted for thousands of cases of severe mental retardation every year. PKU occurred in 1 out of 10,000 to 1 out of 20,000 newborns in most populations around the world. Infants with PKU are normal at birth, but over the first several months of life the body's inability to break down phenylalanine becomes toxic to developing neurons. As neurons die, mental and motor capacities are irretrievably lost, making full manifestation of PKU inevitable. In the 1960s, a simple blood test became available to detect PKU in the first days of life. The test identifies the disease before the disease has had a chance to manifest itself and begin to damage the body. PKU is one of dozens of rare hereditary disorders that newborn infants are routinely screened for in U.S. hospitals.

The key to preventing PKU, following early detection of the disease in newborns, is the severe restriction of phenylalanine in the diet. Because phenylalanine is an amino acid and is a component of many proteins, babies with PKU are given a diet consisting of specially selected and processed proteins that have had phenylalanine removed. An infant who is started on the phenylalanine-free diet soon after birth and kept on it through adolescence avoids the complications of PKU and will develop and function normally despite having PKU. Thousands of people with PKU are living fully normal and productive lives today, thanks to this simple environmental modification that prevents the expression of the devastating PKU phenotype. In this case, people who are homozygous recessive for the mutant PKU allele do not express the trait if they are raised in a largely phenylalanine-free environment.

Dietary hazards abound for children and young adults with PKU, particularly in the form of the artificial sweetener known as aspartame. This sweetener is made by a chemical reaction that fuses the amino acids phenylalanine and aspartic acid to form a compound we perceive to taste sweet. Once consumed, aspartame is quickly broken down into its two constituent amino acids, and phenylalanine is released. Regular intake of aspartame is dangerous for those with PKU; for this reason, a dietary caution reading "Phenylketonurics: Contains phenylalanine" appears on the packaging of food products containing aspartame. Look for it on the next artificially sweetened product you pick up!

Pleiotropic Genes

Pleiotropy is the alteration of multiple, distinct traits of an organism by a mutation in a single gene. Most mutations displaying pleiotropy do so either by altering the development of phenotypic features through the direct action of the mutant protein or as a secondary result of a cascade of problems stemming from the mutation. Mendel unknowingly encountered a case of pleiotropy. Two of the traits he considered for his studies were the inheritance of purple versus white flower color (see Figure 2.1) and the inheritance of a gray versus a white seed coat. Upon noticing that plants with white flowers invariably also have white seed coats, whereas purple-flowered plants always have gray seed coats, he correctly surmised that the inheritance of these traits had the same genetic basis. Today we know that flower color, seed-coat color, and the appearance of color at leaf axils (where the leaf attaches to the stem) result from the production of the purple pigment anthocyanin. Mutations that block anthocyanin production are pleiotropic because they leave several plant structures without color and produce mutant white phenotypes for multiple traits.

Pleiotropy through the direct action of a mutant protein product is frequently encountered in studies of development. One example is the activity of the *Drosophila* hormone called juvenile hormone (JH), which is active throughout the *Drosophila* life cycle and influences numerous attributes of development and reproduction. Increased production or increased activity of JH has been shown to prolong developmental time, decrease adult body size, promote early sexual maturity, raise fecundity (the ability to produce offspring), and decrease life span. An evolutionary tradeoff is associated with changes in JH level or activity. On the one hand, producing more JH can lead to production of more offspring through earlier sexual maturity and higher fecundity. On the other hand, body size decreases and life span is shortened by increased JH activity.

Pleiotropy in sickle cell disease (SCD) is an example of the phenotypically diverse secondary effects that can occur due to a mutant allele. SCD (OMIM 603903) is an autosomal recessive condition caused by mutation of the β-globin gene that, in turn, affects the structure and function of hemoglobin, the main oxygen-carrying molecule in red blood cells (see Chapter 10). Many of the red blood cells of people with SCD take on a sickle shape and cause numerous physical problems and complications. (**Figure 4.16**).

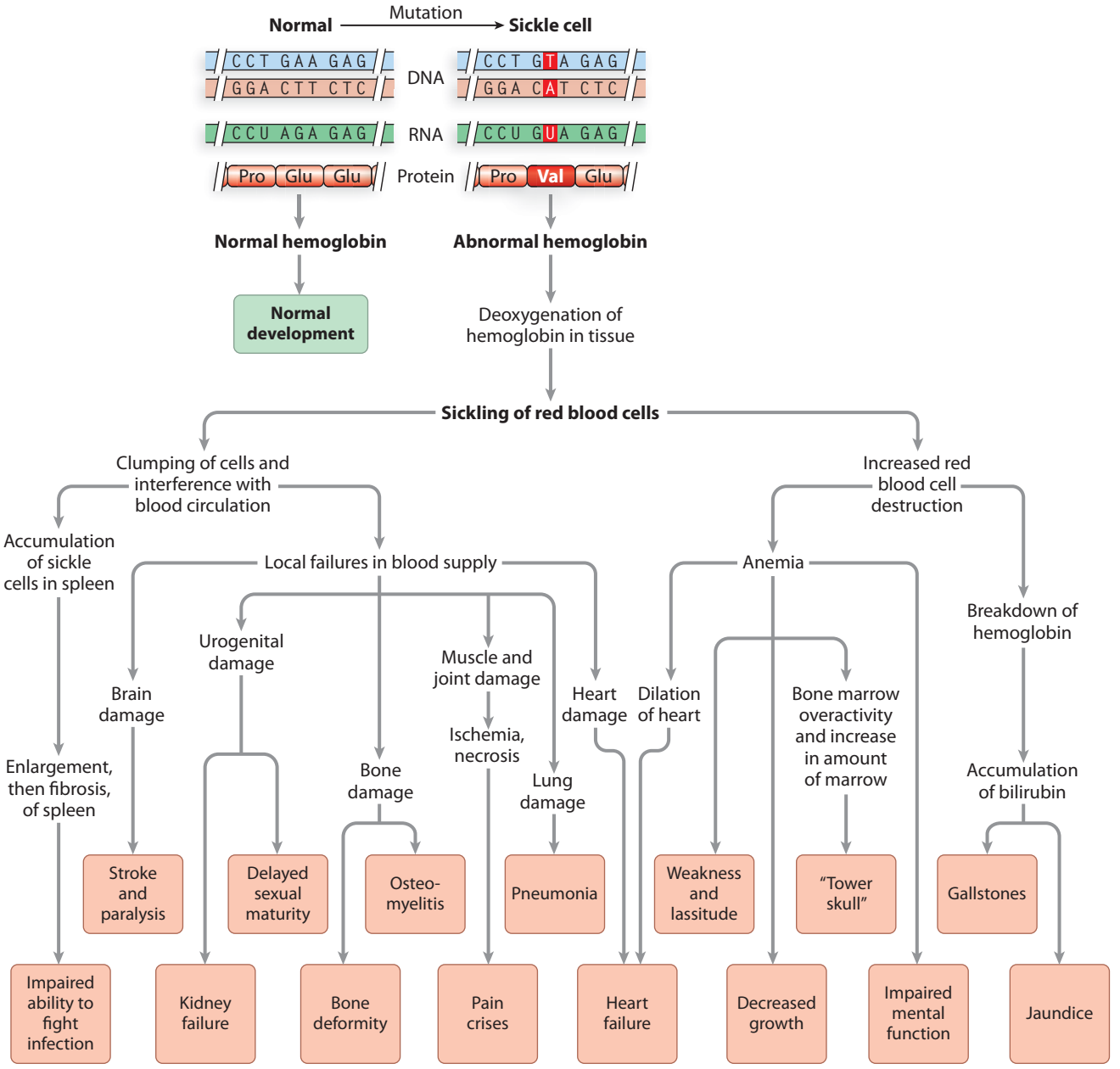


Figure 4.16 Pleiotropy in sickle cell disease. The sickling of red blood cells has a range of phenotypic consequences.

Genetic Insight A pleiotropic allele is one that affects many phenotypic traits. Pleiotropic alleles can work either directly, by influencing the development of multiple processes, or indirectly, by damaging organs and body structures.

4.3 Gene Interaction Modifies Mendelian Ratios

No gene operates alone to produce a phenotypic trait. Rather, genes work together to build the complex structures and organ systems of plants and animals. What we see as a phenotype is the physical manifestation of the action of many genes that have each played a role and have worked in complex but coordinated ways to produce a trait or structure. At the cellular and molecular levels, the mutual reliance of genes on one another requires each gene to carry out its activity in the right place, at the right time, and at the appropriate level. For example, the products of several genes interact to produce flower color. Similarly, a complex phenotypic attribute like the ability to hear requires many genes to produce the various structures that convert acoustical vibrations into the electrical impulses we perceive as sound. In this section, we look in detail at **gene interaction,** the collaboration of multiple genes in the production of a single phenotypic character or a group of related characteristics. First, however, let's

examine the genetic control of phenotypes from a perspective we have not yet explored.

Gene Interaction in Pathways

It is common for biologists to describe phenotypic characters as single-gene traits. This designation means that different forms of a trait can be transmitted to offspring by the segregation of alleles of a single gene. Phenotypic characteristics such as pea flower color and pea shape are examples of single-gene traits inherited as the result of allelic variation at single loci.

The term *single-gene trait* conveniently summarizes the observation that inherited variation for one gene can produce a mutant phenotype rather than a wild-type phenotype. The term is not an accurate depiction of genetic reality, however, as the following example of *Drosophila* eye color makes clear. Numerous genes contribute to production of the wild-type red eye color of *Drosophila*. Geneticists know this to be the case because many distinct mutant eye-color phenotypes have been mapped to different genes. We will consider just three of these genes. Two of the genes produce different eye-color pigments, and the third gene transports pigments to eye cells. The *brown* gene produces an enzyme that operates in a pathway synthesizing a vermilion-colored (bright red) pigment. The gene carries a dominant wild-type allele b^+ and a recessive null mutant allele *b*, and flies that are *bb* have brown-colored eyes. The gene is named after the mutant phenotype it is associated with. The *vermilion* gene produces an enzyme that is active in a pathway synthesizing a brown pigment. The wild-type allele v^+ is dominant over the null mutant allele *v*. Flies that are *vv* have vermilion-colored eyes. The *white* gene produces a pigment-transporting protein from the dominant allele w^+ that carries pigments to the eye. A mutant protein from the *w* allele is incapable of pigment transportation, and flies that do not produce the protein have white eyes.

Production of wild-type proteins from all three genes is necessary to produce wild-type eye color, and hereditary eye color mutations result from the mutation of one or more of the genes (Figure 4.17). Wild-type eye color is the result of synthesis of brown and vermilion pigments and the transportation of both pigments to eye cells, where they are blended. Mutation of any one or more of these genes results in a mutant phenotype. This example demonstrates that multiple genes are active in pathways determining different biological properties. Inherited variation of one gene can block a segment of a pathway and produce a mutation attributable to a single gene, but such a finding does not negate the importance of the action of multiple genes affecting each trait.

Three distinct types of genetic pathways can be identified. The eye-color example just described illustrates a **biosynthetic pathway.** Biosynthetic pathways are networks of interacting genes that produce a molecule or compound as their end product. Compounds such as pigments, amino acids, nucleotides, hormones, and so on are examples of the products of biosynthetic pathways.

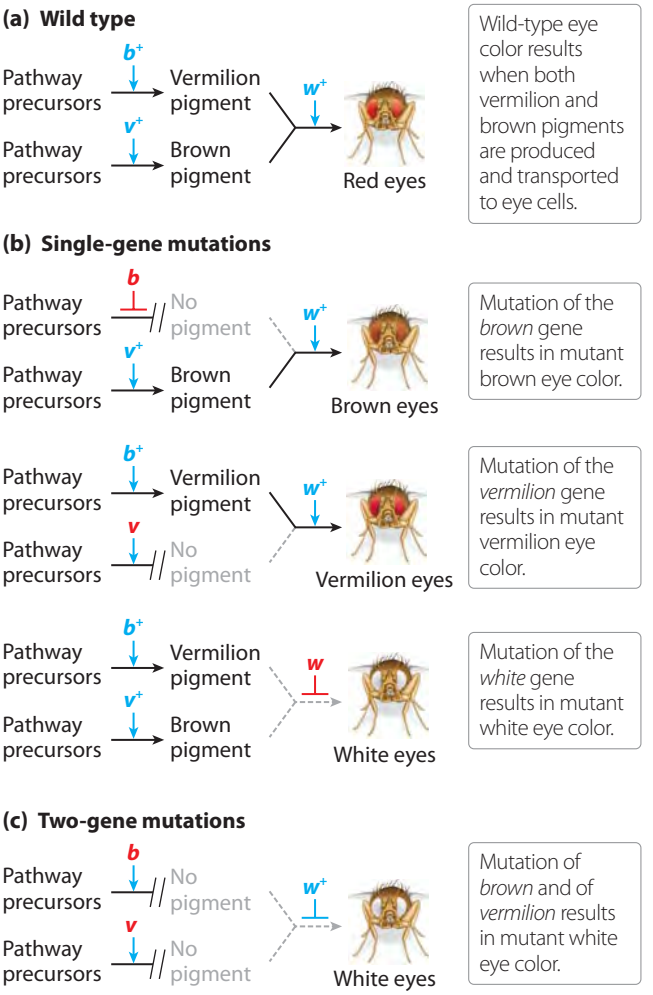


Figure 4.17 Interacting genes control eye color in *Drosophila*. **(a)** Wild-type (red) eye color requires activity of three genes. **(b)** Mutation of any gene produces a distinctive mutant phenotype. **(c)** Double mutation of *brown* and *vermilion* produces white eyes.

Signal transduction pathways are a second type of multiple-gene pathway. These pathways are responsible for reception of chemical signals, such as hormones, that are generated outside a cell and initiate a response inside a cell. Signal transduction operates through the release of a signaling molecule that is part of a sequence of steps culminating in the activation or repression of gene expression in response to an intracellular or extracellular signal.

Finally, *developmental pathways* consist of genes that direct the growth, development, and differentiation of body parts and structures. Numerous developmental pathways have been identified in organisms, and the functions of their genes have been determined by experimental analyses of mutant phenotypes. Geneticists use this analytic approach, known as *genetic dissection*, to identify the step-by-step events making up a genetic pathway. The use of genetic dissection to analyze a biosynthetic pathway is explored in the next section. Examples of signal transduction and developmental pathways are presented in later discussions (see Chapter 20).

Genetic Insight Gene interaction is the rule, not the exception, for phenotype production: No gene operates alone to produce a phenotype, even though hereditary variation at one locus may lead to segregation patterns consistent with single-gene traits. Networks of collaborating genes make up biosynthetic, signal transduction, or developmental pathways.

The One Gene–One Enzyme Hypothesis

The concept of biosynthetic pathways originated with Archibald Garrod's suggestion in 1908 that the inability to produce the enzyme homogentisic acid oxidase is the cause of the human hereditary condition known as alkaptonuria. It was not until the middle of the 20th century, however, that the details of specific biosynthetic pathways began to emerge. George Beadle and Edward Tatum were among the first to investigate biosynthetic pathways, in research that laid the groundwork for the later definition and examination of signal transduction and developmental pathways.

Beadle and Tatum's experiment studied growth variants of the fungus *Neurospora crassa,* and its details are described in **Experimental Insight 4.1**. The idea behind their experiments was simple—to generate single-gene mutations in *Neurospora* and interpret the normal function of genes by observing the phenotypic consequences of their mutation. The famous hereditary proposal known as the **one gene–one enzyme hypothesis** came out of these experiments. It says that each gene produces an enzyme, and each enzyme has a specific functional role in a biosynthetic pathway that produces a phenotype. Beadle and Tatum observed that single-gene mutations block the completion of biosynthetic pathways and lead to the production of mutant phenotypes. Their hypothesis proposed that each mutant phenotype was attributable to the loss or defective function of a specific enzyme. Since each enzyme defect was inherited as a single-gene defect, the one gene–one enzyme hypothesis identifies the direct connection between genes, proteins, and phenotypes.

The one gene–one enzyme concept has undergone adjustments since its proposal to account for three

Experimental Insight 4.1

The One Gene–One Enzyme Hypothesis

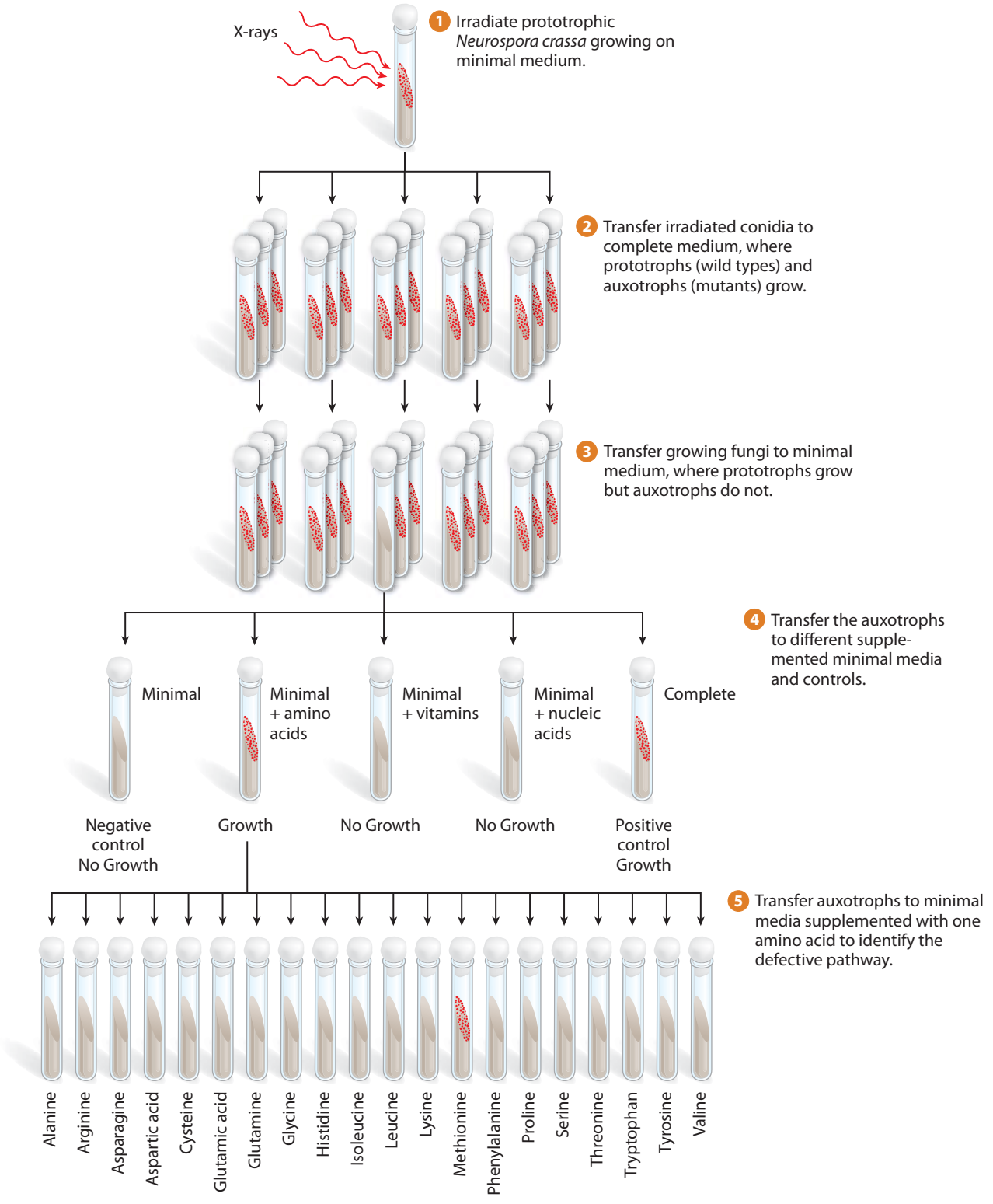
George Beadle and Edward Tatum's experiments had the goal of describing gene function. Their work took place at about the time DNA was being identified as the hereditary molecule, and more than a decade before DNA structure was identified. To provide information for analysis, Beadle and Tatum devised an experiment that would induce single-gene mutations in the filamentous fungus *Neurospora crassa* and then studied the mutants to determine how mutations altered *Neurospora* growth. Recall that *Neurospora* can grow as a haploid, or two haploid cells can fuse to form and grow as diploids that undergo meiosis (see Chapter 2).

In the first step of their experiments, Beadle and Tatum grew numerous genetically identical cultures of haploid wild-type fungi that were irradiated to induce random mutations ❶. The irradiated conidia (asexually produced fungal spores) were mated with wild-type haploids. The resulting diploids underwent meiosis to produce haploid spores that were grown in a two-step process to identify mutants. The diploids could also be tested to confirm the presence of a single-gene mutation by observation of a 3:1 ratio in their progeny. Irradiated haploid spores were grown first on a *complete growth medium* that contains a rich mixture of nutrients and supplements and is capable of supporting the growth of wild-type and mutant fungi ❷. In the second step, growing fungi were picked from colonies on the complete medium and transferred to a *minimal growth medium* that supplies only the minimal constituents needed to support the growth of wild-type fungi ❸. Mutant fungi are identified because they grow on complete medium, but they are unable to grow on a minimal growth medium.

With numerous mutants in hand, Beadle and Tatum were able to address questions of which genes were mutated by another two-part process. They identified the chemical category of the compound that cannot be produced and then determined the specific missing compound. An example of this analysis is illustrated in steps ❹ and ❺, where growth analysis tests a mutant for its ability to grow on various kinds of *supplemented minimal media*. These are growth media that have had one or more compounds added to them to support the growth of specific kinds of mutants. Step 4 shows one mutant that grows only on medium that has been supplemented with all 20 of the common amino acids; this result indicates that the strain lacks the ability to synthesize one or more amino acids. The specific defect in this mutant strain is tested in step ❺ using 20 different supplemented minimal media, each supplemented with one amino acid. One mutant grows on minimal medium supplemented with methionine (met), thus identifying the strain as one that is unable to synthesize methionine. This strain is described as being *Met*– ("Met minus" or "methionine minus"), to identify the defective pathway. The wild type is able to synthesize methionine and is identified as *Met*+ ("Met plus" or "methionine plus").

By testing hundreds of independent mutants in this way, Beadle and Tatum discovered that most mutants carried single mutations that could be overcome by supplementing minimal growth media with one particular compound. This finding led them to propose that single mutations prevented mutants from completing a specific step of a biochemical pathway. Based on this outcome, they proposed that single-gene mutations altered the ability of mutants to produce one enzyme critical in a particular biosynthetic pathway. The correlation between single-gene mutations and single defects in biosynthetic pathways is the basis of the one gene–one enzyme hypothesis.

Experimental Insight 4.1 Continued



observations: (1) Some protein-producing genes do not produce enzymes, but produce transport proteins, structural proteins, and regulatory proteins; (2) some genes produce RNAs rather than proteins; and (3) some proteins (e.g., β-globin) must join with other proteins to acquire a function. Despite these modifications, Beadle and Tatum's fundamental conclusion linking each gene to a particular product is valid and forms the basis for understanding of gene function.

Genetic Dissection to Investigate Gene Action

Beadle and Tatum's experiments opened the way to investigation of the roles of individual-gene mutations in biosynthetic pathways. These investigations began with three assumptions about biosynthetic pathways that have proven to be correct: (1) Biosynthetic pathways consist of sequential steps, (2) completion of one step generates the substrate for the next step in the pathway, and (3) completion of every step is necessary for production of the end product of the pathway. These assumptions support the conclusion that wild-type strains are able to complete each pathway step, and that mutant strains are unable to complete a pathway because one or more pathway steps are blocked by mutation.

Genetic dissection in this context is an experimental approach that tests the ability of a mutant to execute each step of a biosynthetic pathway and assembles the steps of a pathway by determining the point at which the pathway is blocked in each mutant. The strategy of genetic dissection is illustrated for a *met*− strain in **Figure 4.18** using experimental data collected in 1947 by Norman Horowitz on four independently isolated *Neurospora crassa met*− mutants.

The goals of Horowitz's genetic dissection analysis were to (1) determine the number of intermediate steps within the methionine biosynthetic pathway, (2) determine the order of steps in the pathway, and (3) identify the step affected by each mutation. In designing his experiment, Horowitz relied on previous biochemical work identifying homoserine as the first compound in the methionine biosynthetic pathway and identifying cysteine, homocysteine, and cystathionine as later intermediates in the pathway. Horowitz tested the control prototroph (met+) and four methionine-requiring auxotrophs (Met 1 to Met 4) for their ability to grow on (1) minimal medium, (2) minimal medium plus cysteine only, (3) minimal medium plus cystathionine only, (4) minimal medium plus homocysteine only, and (5) minimal medium plus methionine only. Figure 4.18a shows growth (+) or no growth (−) of the four *met*− mutants and the wild-type strain (*met*+) on each of the experimental media. The wild-type strain grows on all media, since supplementation of minimal medium with any of the intermediates has no effect on its growth. Each methionine mutant grows on minimal medium plus methionine, the end product of the biosynthetic pathway, but they show different growth patterns with other supplemented media. The following is an analysis of each mutant:

1. Met 1 grows only on minimal medium plus methionine, thus indicating that a mutation in the last step of the pathway prevents conversion of the final intermediate product to methionine. Only the addition of methionine to minimal medium bypasses the pathway block.
2. Met 2 exhibits growth with supplementation by either methionine or homocysteine, thus indicating a block at the step that produces homocysteine. This result also tells us that homocysteine is the substrate converted to methionine in the biosynthetic pathway.
3. Met 3 grows on minimal medium supplemented with either methionine, homocysteine, or cystathionine, but not on minimal medium plus cysteine. This tells us that *Met 3* is blocked at the step that produces cystathionine and that cystathionine precedes homocysteine in the pathway.
4. Met 4 grows with any supplementation of minimal medium. This tells us that *Met 4* is defective at a step that precedes the production of cysteine.

Figure 4.18b shows the steps of the biosynthetic pathway for methionine as determined by analysis of these mutants. The pathway step that is blocked in the mutant is identified based on the logic that supplementation by a compound needed *after* the blockage will permit growth,

(a) Experimental data

Mutant strain	Growth Medium: Minimal medium	Minimal + cysteine	Minimal + cystathionine	Minimal + homocysteine	Minimal + methionine	Compound accumulating in mutant
Control prototroph	+	+	+	+	+	None
Met 1	−	−	−	−	+	Homocysteine
Met 2	−	−	−	+	+	Cystathionine
Met 3	−	−	+	+	+	Cysteine
Met 4	−	+	+	+	+	Homoserine

(b) Order of intermediates in pathway

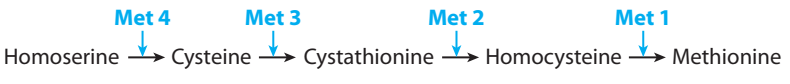


Figure 4.18 Genetic dissection of methionine biosynthesis pathway. **(a)** Growth of a wild-type strain and four independent *met*− mutant strains on minimal medium and various supplemented minimal media. For each mutant, the compound that accumulates is the one that immediately precedes the point of blockage. **(b)** The order of intermediate compounds in the methionine biosynthesis pathway and the step blocked in each *met*− mutant strain.

whereas adding a compound used *before* the blockage will not aid growth. The blocked step is also identified by the substance that accumulates in the auxotroph: In each mutant, a different intermediate substance builds up because the step that would convert it to the next intermediate in the pathway is defective. Accumulation of cysteine by *met 3*, cystathionine by *met 2*, and homocysteine by *met 1* supports the assignment of these mutants to specific steps in the pathway. **Genetic Analysis 4.2** illustrates genetic dissection of a biosynthetic pathway by assessment of the growth habits of auxotrophs.

Genetic Insight Mutant genes encode defective proteins that block individual steps of a biosynthetic pathway. Genetic dissection analyzes nutrient requirements of mutants to determine the order of steps in a biosynthetic pathway and identify the step blocked in each mutant.

Epistasis and Its Results

Genes contributing to different steps of a multistep pathway work together to produce the end product of the pathway. Because of this interaction, mutation of one gene may prevent completion of the pathway and production of the end product. In other words, gene interaction can result in one gene influencing whether and how other pathway genes are expressed or how they function.

Gene interactions occur in various forms, and most produce distinctive progeny phenotype ratios as a result of the specific interaction mechanisms. These altered ratios of wild-type and mutant phenotypes are caused by **epistasis,** the name given to gene interactions—called **epistatic interactions**—in which an allele of one gene modifies or prevents the expression of alleles at another gene. A minimum of two genes are required for epistasis. The genes that interact by epistasis are involved in producing a particular phenotypic characteristic, and they usually participate in the same pathway. Epistasis is most readily detected among progeny of dihybrid crosses where both genes carry dominant and recessive alleles. In these cases, independent assortment predicts a 9:3:3:1 ratio of four phenotypes in the F_2 progeny, but epistasis results in fewer than four phenotypes. This reduction in the number of F_2 phenotype classes occurs because different genotype classes have the same phenotype. In other words, the hallmark of epistatic interaction in a dihybrid cross is modification of the 9:3:3:1 ratio due to the combining of two or more genotype classes into a single phenotypic class.

Epistasis results from mutation in pathways that require a specific activity from every gene in the pathway for the wild-type phenotype to be produced. Given the possible outcomes of dihybrid crosses, there are six ways the F_2 phenotype proportions can be rearranged by epistasis. All six altered ratios have been seen in plants or animals. **Figure 4.19** gives an overview of these patterns, showing the modification of dihybrid ratios that characterizes each form of epistasis. The remainder of this discussion provides a brief description and example of each of the epistatic patterns. First, however, we describe a dihybrid cross involving genes contributing to eye color in the fruit fly *Drosophila melanogaster* in which there is *no interaction* between the genes to alter the resulting 9:3:3:1 phenotypic ratio.

No Interaction (9:3:3:1 ratio) Epistasis is most easily identified through specific deviations from the expected 9:3:3:1 ratio among the F_2 progeny of a dihybrid cross involving dominant and recessive alleles. This expected F_2 ratio results from the action of two independently assorting genes *in the absence of epistasis*—that is, when the genes do not interact to change the expression of one or the other. The contributions of the *brown, vermilion,* and *white* genes to wild-type (red) *Drosophila* eye color are illustrated in Figure 4.17. In this example, we limit our consideration to variation of the *brown* gene and the *vermilion* gene to show the outcome expected from independent assortment of two genes contributing to a specific phenotypic character.

Gene interaction:	None	Complementary	Duplicate	Dominant	Recessive epistasis	Dominant epistasis	Dominant supression
Phenotype ratio:	**9:3:3:1**	**9:7**	**15:1**	**9:6:1**	**9:3:4**	**12:3:1**	**13:3**
Genotype ratio	$\frac{1}{16}$ *AABB* $\frac{2}{16}$ *AaBB* $\frac{2}{16}$ *AABb* $\frac{4}{16}$ *AaBb*	$\frac{9}{16}$ *A–B–*	$\frac{9}{16}$ *A–B–*	*A–B–*	$\frac{9}{16}$ *A–B–*	*A–B–*	$\frac{9}{16}$ *A–B–*
	$\frac{1}{16}$ *AAbb* $\frac{2}{16}$ *Aabb*	$\frac{3}{16}$ *A–bb*	*A–bb*	$\frac{15}{16}$ *A–bb*	*A–bb*	$\frac{3}{16}$ *A–bb*	*A–bb*	$\frac{3}{16}$ *A–bb*
	$\frac{1}{16}$ *aaBB* $\frac{2}{16}$ *aaBb*	$\frac{3}{16}$ *aaB–*	$\frac{7}{16}$ *aaB–*	*aaB–*	$\frac{6}{16}$ *aaB–*	$\frac{4}{16}$ *aaB–*	$\frac{3}{16}$ *aaB–*	$\frac{4}{16}$ *aaB–*
	$\frac{1}{16}$ *aabb*	$\frac{1}{16}$ *aabb*	*aabb*	$\frac{1}{16}$ *aabb*	$\frac{1}{16}$ *aabb*	*aabb*	$\frac{1}{16}$ *aabb*	*aabb*

Figure 4.19 Patterns resulting from epistatic gene interaction.

Four *zmt*$^-$ bacterial mutants (*zmt-1* to *zmt-4*), each with a single-gene mutation, are available for study. Five intermediates in the zmt synthesis pathway have been identified (D, F, M, R, and S), but their order in the pathway is not known. Each mutant is tested for its ability to grow on minimal medium supplemented with one of the intermediate compounds. All mutants grow when zmt is added to minimal medium, and the wild-type strain grows under all growth conditions tested. Find the order of intermediates in the zmt-synthesis pathway, and identify the step that is blocked in each mutant strain. In the growth table at right, "+" indicates growth and "–" indicates no growth.

Mutant Strain	Added to Minimal Medium						
	D	F	M	R	S	Nothing	zmt
Wild type	+	+	+	+	+	+	+
zmt-1	–	–	–	–	+	–	+
zmt-2	–	+	+	+	+	–	+
zmt-3	–	+	–	–	+	–	+
zmt-4	–	+	+	–	+	–	+

Solution Strategies

Evaluate

1. Identify the topic this problem addresses and describe the nature of the required answer.
2. Identify the critical information given in the problem.

Deduce

3. Compare and evaluate the patterns of growth supported by the supplements.

TIP: zmt is the final product of the pathway, and it supports growth of all *zmt*$^-$ mutants.

4. Identify the final product of the pathway and next-latest pathway intermediate compound.

Solve

5. Identify the first compound synthesized in the pathway.
6. Identify the second, third, and fourth compounds synthesized in the pathway.

TIP: Medium supplemented with an intermediate compound that occurs after the pathway step that is blocked by a mutant will support growth.

TIP: To confirm this solution, verify that growth of each mutant is supported by supplementation with compounds that follow the blockage but not by supplementation with compounds that precede the blockage.

7. Assemble the zmt-synthesis pathway, and identify the mutants at each pathway step.

Solution Steps

1. This problem deals with mutants of the zmt-synthesis pathway and requires an analysis of the defect in each mutant as well as ordering of the intermediates in the zmt-synthesis pathway.
2. The problem provides growth information for wild-type *zmt*$^+$ bacteria as well as four *zmt*$^-$ mutant strains when plated on minimal medium and media individually supplemented with zmt or one of five intermediates in the zmt-synthesis pathway.
3. All mutants grow with zmt supplementation and with supplementation by compound S. None grows without any supplementation, and none obtains growth support from compound D. Compounds F, M, and R each support growth of one or more mutants.
4. zmt is the last compound synthesized. Compound S also supports the growth of all mutants and is likely the immediate precursor of zmt.
5. Compound D does not support growth of any of the *zmt*$^-$ mutants and likely occurs before any of the synthesis steps affected by mutations. Compound D is the first compound in the pathway.
6. Compound R supports the growth of mutant *zmt-2*, indicating the compound bypasses the step blocked in *zmt-2*. Compound R likely follows compound D in the pathway, and *zmt-2* is defective in its ability to convert D to R. *zmt-2* grows on intermediate compounds that occur after its point of pathway blockage, but not on compound D that comes before the *zmt*-2 blockage.

   Compound M supports growth of *zmt-2* and *zmt-4*, and bypasses the blockage in both mutants. Growth of *zmt-4* is not supported by compounds D or R that occur before the conversion step blocked in *zmt-4*. The conclusion is that compound M follows R and that *zmt-4* is unable to convert R to M. Compounds F, M, and S each support growth of *zmt-4*, and each bypasses the blockage.

   Compound F supports growth of *zmt-3* and follows compound M in the pathway. *zmt-3* is unable to convert M to F. Compound S supports new growth of *zmt-1*, indicating that it follows compound F in the pathway and that *zmt-1* fails to convert compound F to S.
7. *zmt-2* *zmt-4* *zmt-3* *zmt-1*

   D ⟶ R ⟶ M ⟶ F ⟶ S ⟶ zmt

For more practice, see Problems 4, 16 , 17, and 27.

In other words, there is no interaction between the genes and the outcome is predicted by chance.

The analysis begins with the mating of a pure-breeding brown-eyed fly (b/b; v^+/v^+) to a pure-breeding vermilion-eyed fly (b^+/b^+; v/v). Writing the genotypes in the forms shown separates the alleles on homologous chromosomes by a slash (/) and separates the genes on different chromosomes by the semicolon. In this example, parental flies are assumed to have wild-type function of the w^+ allele, although the genotype for this and other wild-type genes is not shown. The F_1 progeny have wild-type eye color and are dihybrid (b^+/b; v^+/v) (**Figure 4.20**). Progeny in the F_2 generation have four eye-color phenotypes, as predicted by independent assortment. Red eye color (wild type) is observed in $\frac{9}{16}$ of the progeny, brown and vermilion eyes are each seen in $\frac{3}{16}$ of the F_2, and the white-eyed phenotype appears in $\frac{1}{16}$ of the F_2 progeny. These latter progeny are double mutants that are unable to synthesize any colored pigment. The eye color phenotype is white, but the mutational basis of white eye in this case is different from that of flies with mutation of the white gene that transports pigment to the eye (see Figure 4.17). The 9:3:3:1 phenotypic ratio provides evidence that two independently assorting genes contribute to the eye-color phenotype. This ratio indicates that the genes *are not* undergoing epistatic interaction with one another.

The simplest examples of epistasis are interactions between two genes, each with a dominant and a recessive allele. **Foundation Figure 4.21** illustrates six patterns of epistasis for the interaction of two genes. As we describe these patterns here, and as you examine Figure 4.21, notice that the phenotypic ratios observed for each trait result from the combining of the 9:3:3:1 genotype categories. (Refer to Figure 4.19 for an overview of these epistatic patterns.)

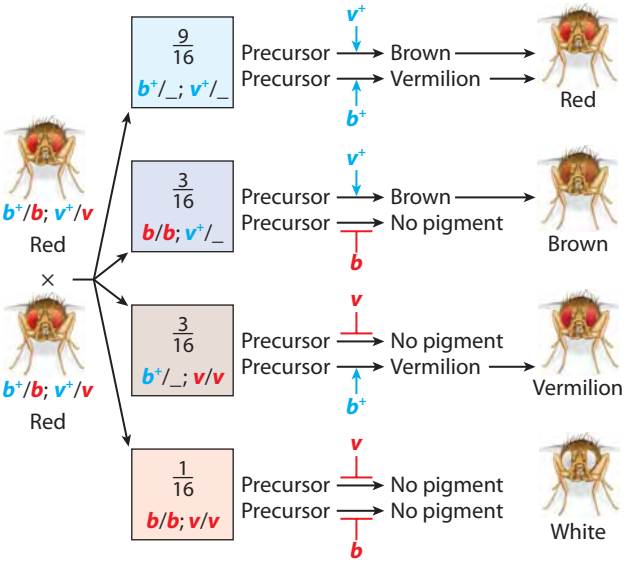


Figure 4.20 No gene interaction in the production of eye color in *Drosophila*. A 9:3:3:1 ratio results from the independent assortment of alleles in a dihybrid cross of red-eyed flies with the genotype b^+/b; v^+/v.

Complementary Gene Interaction (9:7 ratio) William Bateson and Reginald Punnett (of Punnett square fame) were the first biologists to document a deviation from the expected 9:3:3:1 F_2 progeny ratio of a dihybrid cross resulting from the epistatic interaction of two genes. In experiments conducted on sweet peas (*Lathyrus odoratus*), an ornamental plant different from Mendel's edible pea (*Pisum sativum*), Bateson and Punnett began by crossing two pure-breeding white-flowered lines. The F_1 generation yielded a surprise—all of the progeny plants had purple flowers. When Bateson and Punnett crossed F_1 plants, the F_2 produced a ratio of $\frac{9}{16}$ purple-flowered plants to $\frac{7}{16}$ white-flowered plants.

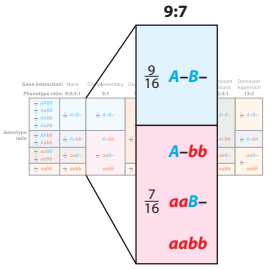
Bateson and Punnett recognized that their results could be explained if two genes interacted with one another to produce sweet pea flower color. Assuming two genes are responsible for a single pigment that gives the sweet pea flower its purple color, each parental line—represented by the genotypes *ccPP* and *CCpp*—is pure-breeding for white flowers as a result of homozygosity for recessive alleles at one of the genes. The cross of these two lines of pure-breeding white parents produces dihybrid purple-flowered F_1 plants—genotype *CcPp*—because the dominant allele at each locus enables completion of each step of the pathway leading to the synthesis of purple pigment. Independent assortment of alleles results in four genotypic classes, *C–P–*, *ccP–*, *C–pp*, and *ccpp*, produced in the 9:3:3:1 ratio that is expected from a dihybrid cross. Among the F_2, however, only the $\frac{9}{16}$ carry the *C–P–* genotype that confers the ability to produce purple pigment. The remaining $\frac{7}{16}$ of the F_2 are homozygous either for one of the recessive alleles *c* and *p* or for both sets of alleles. None of these plants are able to synthesize pigment, due to the absence of functional gene products from one or both loci, and they all have the same mutant phenotype.

A 9:7 phenotypic ratio results from **complementary gene interaction** that requires genes to work in tandem to produce a single product. Figure 4.21 ❶ shows that at the molecular level, purple flower color in sweet peas is produced when the pigment anthocyanin is deposited in petals. The production of the purple-flowered F_1 progeny and the 9:7 F_2 ratio is explained by the independent assortment of two genes, *C* and *P*, that produce gene products controlling different steps of the anthocyanin-synthesis pathway. Since anthocyanin production requires the action of the product of *C* as well as the product of *P*, both steps must be successfully completed for anthocyanin production and deposition in flower petals. On the other hand, any recessive homozygous genotype at the *C* locus, the *P* locus, or both loci results in blockage of the pathway and production of white flowers containing no pigment.

The ability of two mutants with the same mutant phenotype to produce progeny with the wild-type phenotype is called *genetic complementation*, and it indicates that more than one gene is involved in determining the phenotype. We discuss the details of genetic complementation in the last section of this chapter.

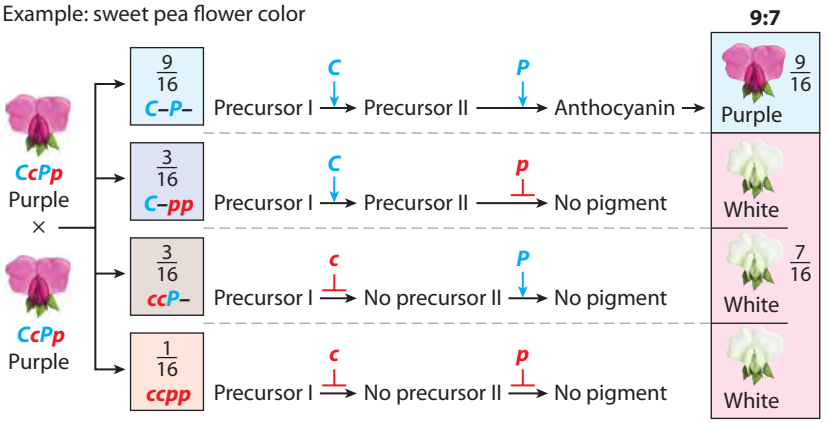
Epistatic Ratios

1 Complementary gene interaction

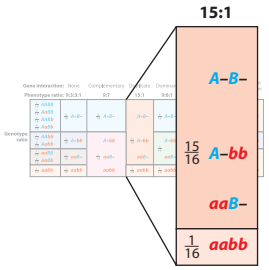


Complementary gene interaction occurs when genes must act in tandem to produce a phenotype. The wild-type action from both genes is required to produce the wild-type phenotype. Mutation of one or both genes produce a mutant phenotype.

Example: sweet pea flower color

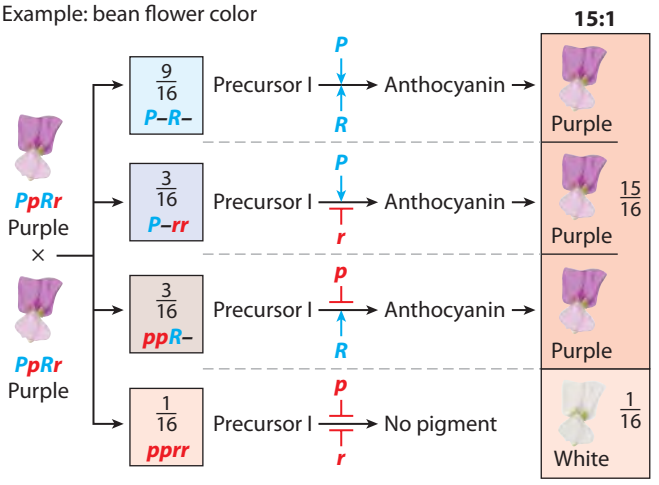


2 Duplicate gene interaction

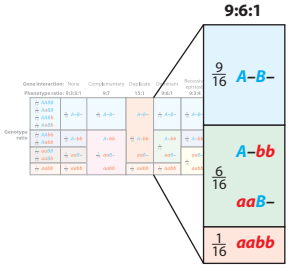


Duplicate gene interaction allows dominant alleles of either duplicate gene to produce the wild-type phenotype. Only organisms with homozygous mutations of both genes have a mutant phenotype.

Example: bean flower color

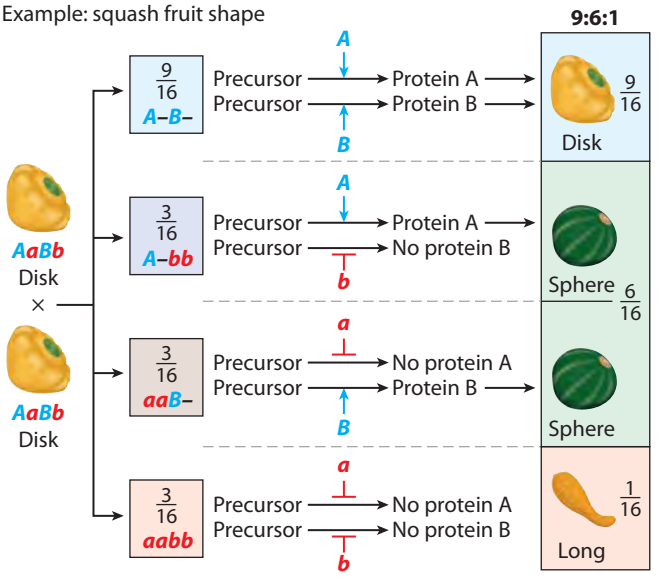


3 Dominant gene interaction

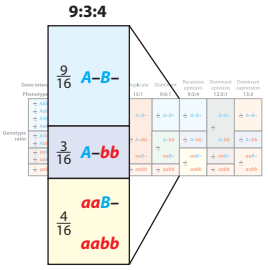


Dominant gene interaction occurs between genes that each contribute to a phenotype producing one. One phenotype if dominant alleles are present at each gene, a second phenotype if recessive alleles are homozygous for either gene, and a third phenotype if recessive homozygosity occurs at both genes.

Example: squash fruit shape

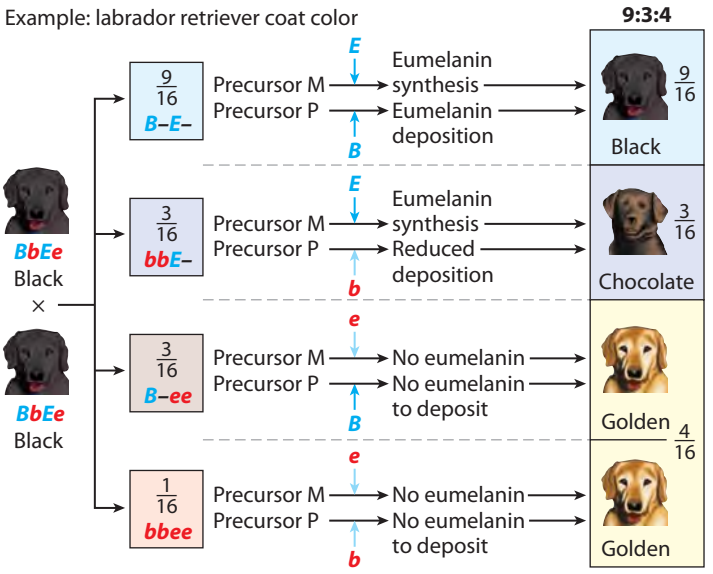


4 Recessive epistasis

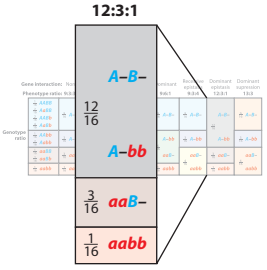


Recessive epistasis occurs when recessive alleles at one gene mask or reduce the expression of alleles at the interacting locus.

Example: labrador retriever coat color

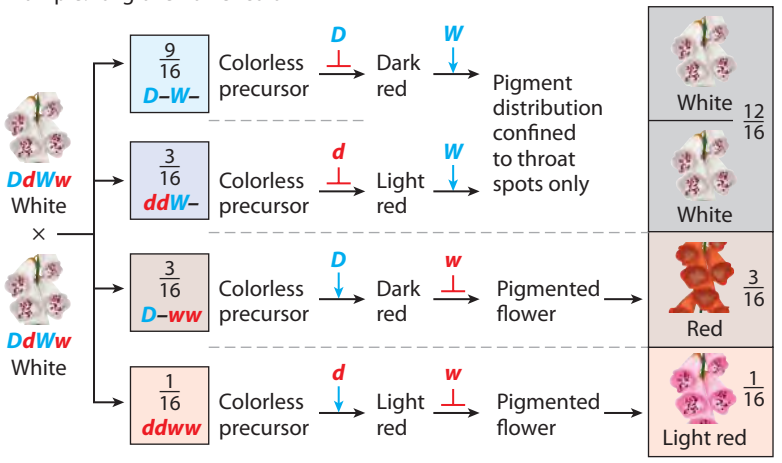


5 Dominant epistasis

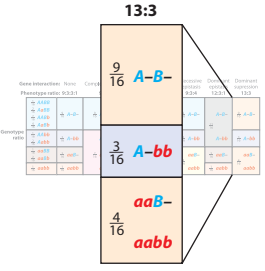


In dominant epistasis, a dominant allele of one gene masks or reduces the expression of alleles of a second gene.

Example: foxglove flower color

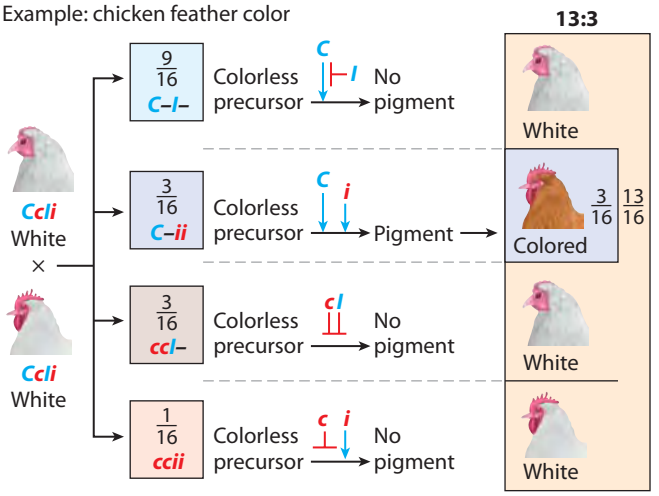


6 Dominant supression



Dominant suppression occurs when the dominant allele of one gene suppresses the expression of a dominant allele of a second gene.

Example: chicken feather color



Duplicate Gene Action (15:1 ratio) Two genes that duplicate one another's activity constitute a redundant genetic system in which any genotype possessing at least one copy of a dominant allele at *either* locus will produce the dominant phenotype. Only when homozygous recessive mutant alleles are present at both loci does the recessive phenotype appear. The genes in a redundant system are said to have **duplicate gene action;** they either encode the same gene product, or they encode gene products that have the same effect in a single pathway or compensatory pathways.

Figure 4.21 ❷ provides an illustration and explanation of duplicate gene action identified inadvertently by Gregor Mendel in an experiment involving flower color in bean plants. Near the end of his famous 1866 paper describing inheritance in peas, Mendel described an experiment with beans that began with the cross of a pure-breeding purple-flowered bean plant to a pure-breeding white-flowered bean plant. The F_1 plants all had purple flowers, and Mendel probably assumed that flower color determination in beans would follow the same pattern as in peas. Among the 32 F_2 plants Mendel produced, however, 31 had purple flowers and only 1 had white flowers. Among the F_2 plants, $\frac{15}{16}$ have a genotype containing at least one copy of either *P* or *R,* and only $\frac{1}{16}$ have the genotype *pprr* and the white-flowered phenotype.

Figure 4.21 ❷ shows that a dominant allele at either locus is capable of catalyzing the conversion of a precursor to anthocyanin and producing the dominant phenotype. Conversely, if homozygous recessive alleles are present at both loci, no functional gene product is produced, and the synthesis pathway is not completed. White flowers result from the absence of pigment in the $\frac{1}{16}$ of the F_2 progeny that are homozygous recessive for alleles of both genes.

Dominant Gene Interaction (9:6:1 ratio) Fruit shape in summer squash is classified as either long, spherical, or disk shaped. Plants that bear long fruit are consistently pure-breeding, indicating that these plants are homozygous for genes controlling fruit shape. On the other hand, plants producing disk-shaped fruit or spherical fruit are sometimes pure-breeding and sometimes not, indicating that plants producing disk-shaped or spherical fruit can be either homozygous or heterozygous for the genes controlling the trait. Figure 4.21 ❸ illustrates and describes **dominant interaction** between two genes controlling squash fruit shape. Dominant interaction is characterized by a 9:6:1 ratio of phenotypes in the progeny of a dihybrid cross.

A cross of two pure-breeding plants producing spherical fruit can generate F_1 that have disk-shaped fruit. This result indicates an interaction between genes controlling fruit shape and suggests that the F_1 disk-shape–producing plants are dihybrid. The F_2 progeny, which display the phenotypic proportions $\frac{9}{16}$ disk, $\frac{6}{16}$ spherical, and $\frac{1}{16}$ long, confirm that hypothesis. Which of the three phenotypes occurs depends on whether a dominant allele is present for both genes, one gene, or neither gene. In the F_2 generation, plants with at least one dominant allele at each locus (*A–B–*) have disk-shaped fruit, plants with recessive alleles at each locus (*aabb*) produce long fruit, and plants that are homozygous recessive at either of the loci (*A–bb* or *aaB–*) produce spherical fruit.

The molecular model of the events underlying dominant interaction assumes that each gene produces a different protein that contributes to fruit shape. When dominant allelic action produces both proteins, disk-shaped fruit is generated. If only one of the proteins is produced, spherical fruit results, as for the genotypic classes *aaB–* and *A–bb*. Plants that are homozygous for recessive alleles of both genes (*aabb*) produce neither protein, and long fruit is the result.

Recessive Epistasis (9:3:4 ratio) Black, chocolate, and yellow coat colors in Labrador retrievers result from the interaction of two genes, one that produces pigment and another that distributes the pigment to hair follicles. This form of gene interaction, in which homozygosity for a recessive allele at one locus can mask the phenotypic expression of a second gene, is called **recessive epistasis** and has the characteristic 9:3:4 ratio of phenotypes illustrated by Figure 4.21 ❹.

Crossing pure-breeding chocolate parents to pure-breeding yellow ones produces F_1 progeny with black coats. That the F_1 progeny are dihybrid is revealed by the F_2 generation, in which $\frac{9}{16}$ of the progeny carry the genotypes in the *B–E–* class and have black coats, $\frac{3}{16}$ have a genotype that is *bbE–*, resulting in chocolate-colored coats, and $\frac{4}{16}$ carry genotypes that are either *B–ee* or *bbee* and have yellow coats.

The molecular explanation for this genetic system is tied to production of the hair pigment melanin. Dogs can produce eumelanin that gives hair a black or brown color and pheomelanin that gives hair a reddish or yellowish tone. The *B* gene is *TYRP1* that controls melanin distribution. The wild-type allele *B* produces full melanin distribution, the mutant allele *b* has reduced distribution. Gene *E* is *MC1R* that controls eumelanin synthesis. Allele *E* permits synthesis; the mutant allele *e* does not. Dogs that are *B_E_* produce and deposit large amounts of eumelanin and have black coats. Dogs that are *bbE_* produce eumelanin but deposit less due to their *bb* genotype. These dogs have chocolate (brown) coat. Dogs that are homozygous ee are unable to produce eumelanin and instead produce only pheomelanin. These dogs have yellow coat color.

Dominant Epistasis (12:3:1 ratio) Determination of flower color in foxgloves provides an example of **dominant epistasis,** where a dominant allele at one locus masks the expression of alleles at a second locus described in Figure 4.21 ❺. In foxgloves, a wild-type allele *d* produces a light red pigment seen in flowers, and a mutant allele *D* produces a dark red flower pigment. At another gene, allele *w* is a wild-type allele that distributes pigment throughout the flower. A mutant allele *W* restricts

pigment to the throat of the flower. Dihybrid F_1 plants (*DdWw*) have white flowers with dark red spots in the flower throat. Dominant epistasis is revealed in the F_2 by a 12:3:1 ratio of white-flowered plants with throat spots (*D–W–* and *ddW–*), dark-red–flowered plants (*D–ww*), and light-red–flowered plants (*ddww*). In foxgloves, allele *W* exerts an epistatic effect by preventing the distribution of flower color outside the throat.

Dominant Suppression (13:3 ratio) Our final example of epistatic gene interaction is **dominant suppression,** illustrated in Figure 4.21 6. Dominant suppression is similar to dominant epistasis but occurs when a dominant allele of one gene completely suppresses the phenotypic expression of alleles of another gene. In chickens, for example, feather color requires a dominant allele *C*. Chickens that are homozygous for a recessive allele *c* have white feathers. The *C* allele can have its color-producing action suppressed by a dominant suppressor allele, *I*. The recessive allele *i* does not exert suppression. Crosses between pure-breeding colored chickens (*CCii*) and pure-breeding white chickens (*ccII*) produce white-feathered F_1 that are dihybrid (*CcIi*). Production of the F_2 results in a 13:3 ratio that is characteristic of dominant suppression. Chickens carrying a *cc* genotype are unable to produce feather color, and those carrying *C–* along with *I–* have feather color production suppressed. Only chickens with the *C–ii* genotype are able to produce colored feathers.

Figure 4.21 6 shows that the product of allele *C* converts a colorless precursor into pigment, whereas the allele *c* product is inactive and fails to convert the precursor, resulting in white feather color for *cc* genotypes. Dominant suppression of *C* by the product of *I* prevents pigment production in chickens with the *C–I–* genotype. The homozygous genotype *ii* is unable to suppress color in the *C–*. **Genetic Analysis 4.3** tests your ability to analyze crosses involving epistatic gene interaction.

4.4 Complementation Analysis Distinguishes Mutations in the Same Gene from Mutations in Different Genes

Suppose you are a geneticist working in California, and you have identified a recessive mutation causing petunia flowers to be white rather than the wild-type purple color. A friend of yours, also a geneticist, is working on petunias in the Netherlands and contacts you because she has also identified a recessive mutation resulting in white-flowered petunias. Since there has been no contact between California petunias and Netherland petunias, the mutations have arisen independently. When geneticists encounter organisms with the same mutant phenotype, two initial questions are (1) do these organisms have mutations of the same gene or of different genes, and (2) how many genes are responsible for the mutations observed?

We have already seen that mutations of different genes can produce the same, or very similar, abnormal phenotypes. This phenomenon is known as **genetic heterogeneity.** We have also seen that a mating of two organisms with the same or a similar abnormal phenotype can sometimes produce offspring with the wild-type phenotype. This phenomenon is called **genetic complementation,** and it occurs when mutant organisms carry mutations of different genes that produce the same abnormal phenotype. In contrast, if the two mutations are in the same gene, offspring of a cross between the two mutants will have a mutant phenotype; this situation is known as a failure of genetic complementation. In this section, we describe how to distinguish whether two independent mutations are in the same gene or in different genes.

An analytic approach called genetic complementation testing examines the relation between two or more recessive mutations affecting one phenotypic attribute. Researchers use it to determine whether two recessive mutations are in the same gene or in different genes. It also provides information on the number of different genes that can produce the mutant phenotype. Here we limit our discussion to testing eukaryotic genomes, using eye color in *Drosophila* as an example. Strategies for complementation testing in bacteria and bacterial viruses (bacteriophage) differ somewhat from those used in plants and animals (Chapter 7).

Genetic complementation testing crosses pure-breeding mutants for a recessive mutation and examines the phenotype of cross progeny. The heterozygous F_1 progeny of these crosses are then examined for the wild-type or mutant phenotypes. If wild-type progeny are produced, genetic complementation has occurred, and the conclusion is that the mutant alleles are of different genes. On the other hand, if the mutant alleles are of the same gene, the progeny of two pure-breeding mutants will have a mutant phenotype. This result indicates that no genetic complementation has taken place.

As an example, we examine genetic complementation testing using two genes affecting *Drosophila* eye color, both of which we have discussed previously: the *vermilion* gene, whose product produces eye-color pigment, and the *white* gene, whose product produces the eye-color pigment transport protein. Both genes are located on the X chromosome in *Drosophila*. The sequential action of the gene products in eye-color production is illustrated in **Figure 4.22a**. Genetic complementation is illustrated by the production of wild-type (red) female progeny from the cross of a pure-breeding female with vermilion eyes to a pure-breeding male with white eyes. No genetic complementation occurs when a pure-breeding apricot female and a pure-breeding buff male are crossed. All progeny have mutant eye colors.

Genetic complementation analysis utilizes numerous crosses of different pure-breeding mutants to one another to determine if the progeny are mutant (no genetic complementation) or wild type (genetic complementation). A

GENETIC ANALYSIS 4.3

Dr. Ara B. Dopsis, a famous plant geneticist, decides to try his hand at iris propagation. He selects two pure-breeding irises, one red and the other blue, and crosses them. To his surprise, all F_1 plants have purple flowers. He decides to create more purple irises by self-fertilizing the F_1 irises. Dr. Dopsis produces 320 F_2 plants consisting of 182 with purple flowers, 59 with blue flowers, and 79 with red flowers.

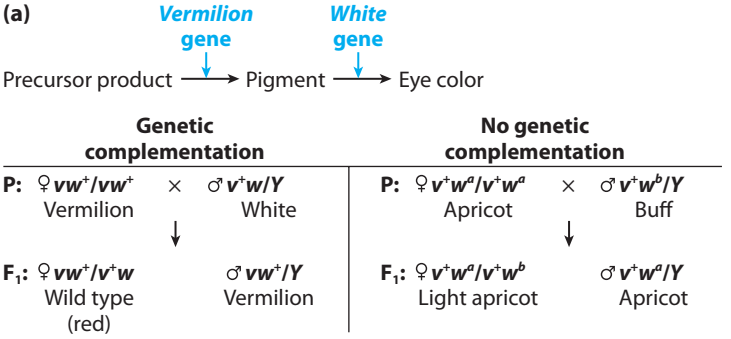
a. From the information available, describe the genetic phenomenon that produces the phenotypic ratio observed in the F_2 plants. Identify the number of genes that are involved in this trait.

b. Using clearly defined symbols of your own choosing, identify the genotypes of parental and F_1 plants.

Solution Strategies	Solution Steps
Evaluate	
1. Identify the topic this problem addresses and state what is required in the answer.	1. This problem concerns an interpretation of F_1 and F_2 results, the identification of the genetic mechanism responsible for the observation, and the assignment of genotypes to parental and F_1 plants in a manner consistent with the genetic mechanism.
2. Identify the critical information given in the problem.	2. The problem states that the blue- and red-flowered parents are pure-breeding and that their F_1 are exclusively purple flowered. Among the F_2 purple is predominant, but red and, to a lesser extent, blue are also observed.
Deduce	
3. Deduce the potential genetic mechanisms that could account for producing purple-flowered F_1 plants from the pure-breeding red and blue parental plants.	3. Two potential mechanisms are suggested by these data. First, a single gene with incomplete dominance might generate a phenotype in F_1 heterozygous plants that is different from that of either homozygous parent. Second, two genes displaying an epistatic interaction might account for a phenotype in an F_1 dihybrid that is distinct from either pure-breeding parent.
4. Determine the relative phenotype proportions predicted by the possible genetic mechanisms and evaluate the observed phenotype ratio. **TIP:** Compare the relative percentages of each phenotype to see which genetic model most closely predicts the observed percentages.	4. A single-gene model predicts that the self-fertilization of an F_1 heterozygote will result in a 1:2:1 (25%:50%:25%) in the F_2. A two-gene epistasis model producing three F_2 phenotypes could be dominant gene interaction (9:6:1 ratio), dominant epistasis (12:3:1 ratio), or recessive epistasis (9:4:3 ratio). Recessive epistasis predictions are a closer match to observations than dominant epistasis predictions. Recessive epistasis predicts phenotype percentages of approximately 56%:25%: 19%. The observed ratio of F_2 phenotypes is $\frac{182}{320} = 56.8\%$ purple, $\frac{79}{320} = 24.7\%$ red, and $\frac{59}{320} = 18.4\%$ blue.
Solve	Answer a
5. Identify the genetic mechanism most likely to account for the outcomes of these crosses.	5. Comparison of the F_2 predictions of the single-gene incomplete dominance model and the two-gene recessive epistasis model determines that recessive epistasis is a better predictor of relative progeny proportions. The likely genetic model explaining these data is recessive epistasis. (Note that the number of F_2 observed in each category can be compared to the number expected by chi-square analysis.)
6. Assign genotypes to parental and F_1 plants.	6. Using symbols *A* and *a* for one gene and *B* and *b* for the second gene, the genotypes of plants are Parents: *aaBB* (red) and *AAbb* (blue) F_1: *AaBb* (purple)

For more practice, see Problems 5, 10 , 22, and 31.

(a)



(b)

Mutation	Apricot	Brown	Buff	Carnation	Cherry	Claret	Coral	Vermilion	White
Apricot	–	+	–	+	–	+	–	+	–
Brown		–	+	+	+	+	+	+	+
Buff			–	+	–	+	–	+	–
Carnation				–	+	+	+	+	+
Cherry					–	+	–	+	–
Claret						–	+	+	+
Coral							–	+	–
Vermilion								–	+
White									–

Complementation

Group	Mutant (allele)
I	Apricot (***w**^a^*), buff (***w**^b^*), cherry (***w**^ch^*), coral (***w**^co^*), white (***w***)
II	Carnation (***c***)
III	Claret (***cl***)
IV	Brown (***b***)
V	Vermilion (***v***)

Figure 4.22 Genetic complementation and no genetic complementation involving the *Drosophila* eye color genes *vermilion* and *white*. **(a)** The cross of pure-breeding vermilion to pure-breeding white shows genetic complementation by production of wild-type eye color in the F_1. The cross between pure-breeding apricot and pure-breeding buff produces no genetic complementation in the F_1 that have mutant eye color. **(b)** Genetic complementation testing among nine distinct *Drosophila* eye color mutants reveals five complementation groups corresponding to five genes. Five mutant alleles of *white* mutually fail to complement and are assigned to the same gene. The other four mutants each complement one another, and the *white* gene mutants and are assigned to their own gene.

table of genetic complementation testing data shown in Figure 4.22b indicates whether the cross of parental mutant phenotypes produces wild-type progeny (indicated in the table by plus symbols: +), or mutant progeny (indicated in the table by minus symbols: −). Any given pair of mutants that *complement* one another by producing wild-type progeny are mutations of *different genes*. (Recall the results of complementary gene action illustrated in Figure 4.21 ❶.) In contrast, the cross of mutant parents produces only the mutant phenotype in progeny when the mutations *fail to complement* one another and are mutations of the *same gene*.

Complementation analysis of the *Drosophila* eye-color mutation results displayed in Figure 4.22b focuses on crosses that *fail to complement* as these are the result of mutations that are in the same gene. Mutations that mutually fail to complement one another are identified as a **complementation group,** consisting of one or more mutant alleles of a single gene. A complementation group consists of mutants whose phenotypes consistently fail to complement one another and that complement mutants in other complementation groups. In the genetic context, a "complementation group" is synonymous with a "gene," because the mutant alleles of each complementation group all affect the same phenotypic characteristic. Thus, in genetic complementation analysis, the number of complementation groups equals the number of genes.

In the complementation testing data in Figure 4.22b, apricot, buff, cherry, coral, and white all exhibit a mutual failure to complement. This result identifies the five mutants as occurring in the same gene. (Historically, white was the first mutation identified and is the name the gene has become known by.) Geneticists conclude that apricot, buff, cherry, coral, and white are mutant alleles of the *white* (*w*) gene in *Drosophila*. These mutations form complementation group I. In contrast, the mutations brown, carnation, claret, and vermilion each complement all other mutants. This observation tells investigators that they are not alleles of another mutant, but that instead each mutant represents a separate gene. Each of these mutants forms its own complementation group (i.e., complementation groups II through V). Among the nine *Drosophila* eye-color mutants examined, five genes (five complementation groups) are identified. One gene is represented by five mutants, and the other four genes are represented by one mutation each.

Genetic Insight Complementation occurs when two mutants produce wild-type progeny, indicating that parental organisms carry mutations of different genes. By contrast, failure to complement occurs when two organisms carry mutations in the same gene.

CASE STUDY

Identification of Xeroderma Pigmentosum Complementation Groups

In this case study, we examine the use of genetic complementation analysis to identify the number of genes involved in a rare but genetically heterogeneous human condition called xeroderma pigmentosum (XP). XP is characterized by severe sensitivity to ultraviolet (UV) irradiation from sunlight and by up to a thousandfold increase in the rate of sun-induced skin cancer. While the experimental approaches to complementation testing in humans are necessarily different from those employed for laboratory organisms, the interpretations of "crosses" follow the same processes.

People with XP are deficient in a type of DNA repair called nucleotide excision repair (NER) that would otherwise protect their skin from the UV-induced damage that leads to cancer. In NER, a short section of DNA containing a UV-induced lesion is removed, and the gap is filled by new DNA (see Chapter 12).

Research work that began in the late 1970s identified seven complementation groups representing seven different genes that are mutated in different forms of XP. Two approaches identify the existence of the seven complementation groups. Anthony Andrews and his colleagues obtained cultured skin cells from XP patients and from normal controls and tested the ability of the cells to grow after exposure to measured doses of UV irradiation (**Figure 4.23**). The cells were exposed to UV light at a wavelength of 254 nm for different amounts of time, and their growth was measured as the percentage of original cells able to form colonies after UV exposure. These researchers identified five distinct patterns of response to UV exposure that are designated as complementation groups A to E.

Other researchers measured the response of cultured XP cells to UV exposure by determining the level of NER taking place in XP cell cultures taken from different XP individuals in comparison to normal cells. The results showed that XP cell lines vary in their levels of NER from less than 5% of normal to about 50% of normal. These results could be due to the mutations being in different genes or, alternatively, to different hypomorphic alleles of the same gene.

Genetic complementation analysis was used in the study of XP cell cultures with low NER to identify cell lineages carrying different XP gene mutations. To do this, two cells from lineages with low NER were fused to form a heterokaryon, a hybrid cell with two nuclei. A heterokaryon contains all the genetic information from both contributing cells. The experimental rationale is that if the two cells contain mutations of *different* genes, the heterokaryon will experience genetic complementation that would be detected as normal or near normal levels of NER; but if the mutations are in the same gene, NER will be about the same in the heterokaryon as in the individual cell lines. This analysis of NER levels in XP heterokaryons ultimately indicated seven complementation groups of XP genes.

Each of the seven XP-associated genes has had its function identified and its position mapped in the human genome in the last decade or so. Four of the genes produce proteins that are required to remove a segment of the strand of DNA damaged by UV irradiation as part of the DNA repair process. Proteins from two other XP-associated genes are required to recognize UV-induced DNA damage and the seventh gene produces a protein that binds to the DNA lesion once it is located. The knowledge of the identity of the seven XP-associated genes has led to the finding that other cancer-associated hereditary diseases also involve mutations of one or another of the XP-associated genes. (see Chapter 12).

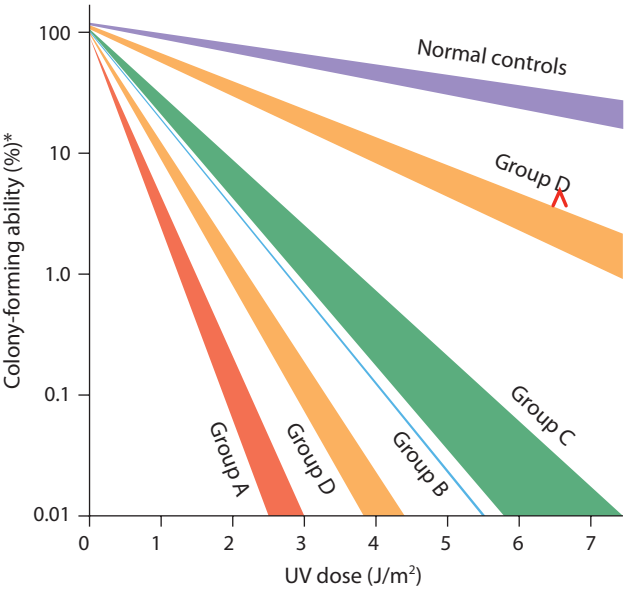


Figure 5.23 Growth of cultured cells from patients with xeroderma pigmentosum (XP). Five XP complementation groups are identified based on growth ability.

SUMMARY

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4.1 Interactions between Alleles Produce Dominance Relationships

- Loss-of-function mutations decrease or eliminate gene activity. Gain-of-function mutations can cause over-expression or result in new functions.
- Incomplete dominance produces heterozygotes with phenotypes that differ from those of either homozygote but are closer to one homozygous phenotype than the other.
- Codominant alleles are both equally detected in the heterozygous phenotype.

- The interaction of allelic products determines the dominance relationship between alleles.
- ABO blood types are produced by alleles whose protein products produce dominance or codominance depending on the genotype.
- Multiple alleles of a single gene can display a variety of dominance relationships that establish an allelic series.
- Lethal alleles can kill gametes, can prevent the gestational development of certain classes of progeny, or can have their lethal effect later in life.
- In sex-limited and sex-influenced traits, alleles are manifested differently in each sex.

4.2 Some Genes Produce Variable Phenotypes

- In incomplete penetrance, an allele does not always have the expected effect on the phenotype.
- In variable expressivity, organisms with the same genotype have different degrees of phenotypic expression.
- Pleiotropic mutations affect two or more distinct and seemingly independent attributes of the phenotype.

4.3 Gene Interaction Modifies Mendelian Ratios

- Epistasis is revealed by six alternative ratios that modify the 9:3:3:1 ratio expected among the progeny of a dihybrid cross.
- Epistasis types and ratios are complementary gene interaction (9:7), duplicate gene interaction (15:1), dominant gene interaction (9:6:1), recessive epistasis (9:3:4), dominant epistasis (12:3:1), and dominant suppression (13:3).

4.4 Complementation Analysis Distinguishes Mutations in the Same Gene from Mutations in Different Genes

- In genetic heterogeneity, mutations in different genes can produce the same phenotype.
- Genetic complementation produces progeny with the wild-type phenotype from parents that are pure-breeding for similar mutant phenotypes. The detection of genetic complementation means the mutations occur in different genes.
- The failure to detect genetic complementation from the cross of two similar mutant organisms identifies the mutant alleles as being carried by the same gene.

KEYWORDS

allelic series *(p. 112)*
biosynthetic pathway *(p. 123)*
codominance *(p. 110)*
complementation group *(p. 135)*
delayed age of onset *(p. 118)*
dominant negative mutation *(p. 109)*
epistatic interaction (epistasis) *(p. 127)*
  complementary gene interaction (9:7 ratio) *(p. 129)*
  dominant interaction (9:6:1 ratio) *(p. 132)*
  dominant epistasis (12:3:1 ratio) *(p. 132)*
  dominant suppression (13:3 ratio) *(p. 134)*
  duplicate gene action (15:1 ratio) *(p. 132)*
  recessive epistasis (9:3:4 ratio) *(p. 132)*
gain-of-function mutation *(p. 107)*
gene–environment interaction *(p. 120)*
gene interaction *(p. 122)*
genetic complementation *(p. 134)*
genetic dissection *(p. 126)*
genetic heterogeneity *(p. 134)*
haploinsufficient *(p. 107)*
haplosufficient *(p. 107)*
hypermorphic mutation *(p. 109)*
incomplete dominance (partial dominance) *(p. 109)*
incomplete penetrance (nonpenetrant, penetrant) *(p. 119)*
leaky mutation (hypomorphic mutation) *(p. 107)*
lethal mutation (lethal allele) *(p. 114)*
loss-of-function mutation *(p. 107)*
neomorphic mutation *(p. 109)*
null mutation (amorphic mutation) *(p. 107)*
one gene–one enzyme hypothesis *(p. 124)*
pleiotropy *(p. 121)*
sex-influenced trait (sex-influenced expression) *(p. 118)*
sex-limited trait (sex-limited gene expression) *(p. 117)*
temperature-sensitive allele *(p. 114)*
variable expressivity *(p. 120)*

PROBLEMS

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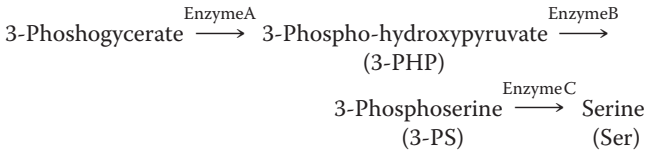
Chapter Concepts

For answers to even-numbred problems, see Appendix: Answers.

1. Define and distinguish *incomplete penetrance* and *variable expressivity*.
2. Define and distinguish *epistasis* and *pleiotropy*.
3. When working on barley plants, two researchers independently identify a short-plant mutation and develop homozygous recessive lines of short plants. Careful measurements of the height of mutant short plants versus normal tall plants indicate that the two mutant lines have the same height. How would you determine if these two mutant lines carry mutation of the same gene or of different genes?
4. Fifteen bacterial colonies growing on a complete medium are replica-plated to a minimal medium. Twelve of the colonies grow on minimal medium.
   a. Using terminology from the chapter, characterize the 12 colonies that grow on minimal medium and the 3 colonies that do not.
   b. The three colonies that do not grow on minimal medium are replica-plated to minimal medium plus the amino acid serine (min + Ser), and all three colonies grow. Characterize these three colonies.

c. The serine biosynthetic pathway is a three-step pathway in which each step is catalyzed by the enzyme product of a different gene, identified as enzymes A, B, and C in the diagram below.



Mutant 1 grows only on min + Ser. In addition to growth on min + Ser, mutant 2 also grows on min + 3-PHP and min + 3-PS. Mutant 3 grows on min + 3-PS and min + Ser. Identify the step of the serine biosynthesis pathway at which each mutant is defective.

5. In a type of parakeet known as a "budgie," feather color is controlled by two genes. A yellow pigment is synthesized under the control of a dominant allele *Y*. Budgies that are homozygous for the recessive *y* allele do not synthesize yellow pigment. At an independently assorting gene, the dominant allele *B* directs synthesis of a blue pigment. Recessive homozygotes with the *bb* genotype do not produce blue pigment. Budgies that produce both yellow and blue pigments have green feathers; those that produce only yellow pigment or only blue pigment have yellow or blue feathers, respectively; and budgies that produce neither pigment are white (albino).
   a. List the genotypes for green, yellow, blue, and albino budgies.
   b. A cross is made between a pure-breeding green budgie and a pure-breeding albino budgie. What are the genotypes of the parent birds?
   c. What are the genotype(s) and phenotype(s) of the F_1 progeny of the cross described in part (b)?
   d. If F_1 males and females are mated, what phenotypes are expected in the F_2, and in what proportions?
   e. The cross of a green budgie and a yellow budgie produces offspring that are 12 green, 4 blue, 13 yellow, and 3 albino. What are the genotypes of the parents?

6. The ABO and MN blood groups are given below for four sets of parents (1 to 4) and four children (a to d). Recall that the ABO blood group has three alleles, I^A, I^B, and *i*. The MN blood group has two codominant alleles, *M* and *N*. Using your knowledge of these genetic systems, match each child with every set of parents who might have conceived the child, and exclude any parental set that could not have conceived the child.

	Mother		Father	
	ABO	MN	ABO	MN
1	O	M	B	M
2	B	N	B	N
3	AB	MN	B	MN
4	A	N	B	MN

	Children	
	ABO	MN
a	B	M
b	O	M
c	AB	MN
d	B	N

7. The wild-type color of horned beetles is black, although other colors are known. A black horned beetle from a pure-breeding strain is crossed to a pure-breeding green female beetle. All of their F_1 progeny are black. These F_1 are allowed to mate at random with one another, and 320 F_2 beetles are produced. The F_2 consists of 179 black, 81 green, and 60 brown. Use these data to explain the genetics of horned beetle color.

8. Two genes interact to produce various phenotypic ratios among F_2 progeny of a dihybrid cross. Design a different pathway explaining each of the F_2 ratios below, using hypothetical genes *R* and *T* and assuming that the dominant allele at each locus catalyzes a different reaction or performs an action leading to pigment production. The recessive allele at each locus is null (loss-of-function). Begin each pathway with a colorless precursor that produces a white or albino phenotype if it is unmodified. The ratios are for F_2 progeny produced by crossing wild-type F_1 organisms with the genotype *RrTt*.
   a. $\frac{9}{16}$ dark blue : $\frac{6}{16}$ light blue : $\frac{1}{16}$ white
   b. $\frac{12}{16}$ white : $\frac{3}{16}$ green : $\frac{1}{16}$ yellow
   c. $\frac{9}{16}$ green : $\frac{3}{16}$ yellow : $\frac{3}{16}$ blue : $\frac{1}{16}$ white
   d. $\frac{9}{16}$ red : $\frac{7}{16}$ white
   e. $\frac{15}{16}$ black : $\frac{1}{16}$ white
   f. $\frac{9}{16}$ black : $\frac{3}{16}$ gray : $\frac{4}{16}$ albino
   g. $\frac{13}{16}$ white : $\frac{3}{16}$ green

9. The ABO blood group assorts independently of the Rhesus (Rh) blood group and the MN blood group. Three alleles, I^A, I^B, and *i*, occur at the *ABO* locus. Two alleles, *R*, a dominant allele producing Rh+, and *r*, a recessive allele for Rh−, are found at the *Rh* locus, and codominant alleles *M* and *N* occur at the *MN* locus. Each gene is autosomal.
   a. A child with blood types A, Rh−, and M is born to a woman who has blood types O, Rh−, and MN and a man who has blood types A, Rh+, and M. Determine the genotypes of each parent.
   b. What proportion of children born to a man with genotype I^AI^B *Rr MN* and a woman who is I^Ai *Rr NN* will have blood types B, Rh−, and MN? Show your work.
   c. A man with blood types B, Rh+, and N says he could not be the father of a child with blood types O, Rh−, and MN. The mother of the child has blood types A, Rh+, and MN. Is the man correct? Explain.

10. In rats, gene B produces black coat color if the genotype is *B*–, but black pigment is not produced if the genotype is *bb*. At an independent locus, gene D produces yellow pigment if the genotype is *D*–, but no pigment is produced when the genotype is *dd*. Production of both pigments results in brown coat color. If neither pigment is produced, coat color is cream. Determine the genotypes of parents of litters with the following phenotype distributions.
    a. 4 brown, 4 black, 4 yellow, 4 cream
    b. 3 brown, 3 yellow, 1 black, 1 cream
    c. 9 black, 7 brown

11. In the rats identified in problem 10, a third independently assorting gene involved in determination of coat color in rats is the *C* gene. At this locus, the genotype *C*– permits expression of pigment from genes *B* and *D*. The *cc* genotype, however, prevents expression of coat color and

results in albino rats. For each of the following crosses, determine the expected phenotype ratio of progeny.

a. *BbDDCc* × *BbDdCc*
b. *BBDdcc* × *BbddCc*
c. *bbDDCc* × *BBddCc*
d. *BbDdCC* × *BbDdCC*

12. Using the information provided in Problems 10 and 11, determine the genotype and phenotype of parents that produce the following progeny:
a. $\frac{9}{16}$ brown : $\frac{3}{16}$ black : $\frac{4}{16}$ albino
b. $\frac{3}{8}$ black : $\frac{3}{8}$ cream : $\frac{2}{8}$ albino
c. $\frac{27}{64}$ brown : $\frac{16}{64}$ albino : $\frac{9}{64}$ yellow : $\frac{9}{64}$ black : $\frac{3}{64}$ cream
d. $\frac{3}{4}$ brown : $\frac{1}{4}$ yellow

13. Total cholesterol in blood is reported as the number of milligrams (mg) of cholesterol per 100 milliliters (mL) of blood. The normal range is 180–220 mg/100 mL. A gene mutation altering the function of cell-surface cholesterol receptors restricts the ability of cells to collect cholesterol from blood and draw it into cells. This defect results in elevated blood cholesterol levels. Individuals who are heterozygous for a mutant allele and a wild-type allele have levels of 300–600 mg/100 mL, and those who are homozygous for the mutation have levels of 800–1000 mg/100 mL. Identify the genetic term that best describes the inheritance of this form of elevated cholesterol level, and justify your choice.

14. Flower color in snapdragons results from the amount of the pigment anthocyanin in the petals. Red flowers are produced by plants that have full anthocyanin production, and ivory-colored flowers are produced by plants that lack the ability to produce anthocyanin. The allele *An1* has full activity in anthocyanin production, and the allele *An2* is a null allele. Dr. Ara B. Dopsis, a famous genetic researcher, crosses pure-breeding red snapdragons to pure-breeding ivory snapdragons and produces F_1 progeny plants that have pink flowers. He proposes that this outcome is the result of incomplete dominance, and he crosses the F_1 to test his hypothesis. What phenotypes does Dr. Dopsis predict will be found in the F_2, and in what proportions?

15. A plant line with reduced fertility comes to the attention of a plant breeder who observes that seed pods often contain a mixture of viable seeds that can be planted to produce new plants, and withered seeds that cannot be sprouted. The breeder examines numerous seed pods in the reduced fertility line and counts 622 viable seeds and 204 nonviable seeds.
a. What single-gene mechanism best explains the breeder's observation?
b. Propose an additional experiment to test the genetic mechanism you propose. If your hypothesis is correct, what experimental outcome do you predict?

16. In cattle, an autosomal mutation called *Dexter* produces calves with short stature and short limbs. Embryos that are homozygous for the *Dexter* mutation have severely stunted development and either spontaneously abort or are stillborn. What progeny phenotypes do you expect from the cross of two *Dexter* cows? What are the expected proportions of the expected phenotypes?

Application and Integration

For answers to even-numbered problems, see Appendix: Answers.

17. The coat color in mink is controlled by two codominant alleles at a single locus. Red coat color is produced by the genotype R_1R_1, silver coat by the genotype R_1R_2, and platinum color by R_2R_2. White spotting of the coat is a recessive trait found with the genotype *ss*. Solid coat color is found with the *S*– genotype.
a. What are the expected progeny phenotypes and proportions for the cross $SsR_1R_2 \times ssR_2R_2$?
b. If the cross $SsR_1R_2 \times SsR_1R_1$is made, what are the progeny phenotypes, and in what proportions are they expected to occur?
c. Two crosses are made between mink. Cross 1 is the cross of a solid, silver mink to one that is solid, platinum. Cross 2 is between a spotted, silver mink and one that is solid, silver. The progeny are described in the table below. Use these data to determine the genotypes of the parents in each cross.

Cross	Offspring					
	Spotted, platinum	Spotted, silver	Spotted, red	Solid, platinum	Solid, silver	Solid, red
1	2	3	0	6	5	0
2	3	7	2	4	5	3

18. Strains of petunias come in four pure-breeding colors: white, blue, red, and purple. White petunias are produced when plants synthesize no flower pigment. Blue petunias and red petunias are produced when plants synthesize blue or red pigment only. Purple petunias are produced in plants that synthesize both red *and* blue pigment. The mixture of red and blue makes purple. Flower-color pigments are synthesized by gene action in two separate pigment-producing biochemical pathways. Pathway I contains gene *A* that produces an enzyme to catalyze conversion of a colorless pigment designated $white_1$ to blue pigment. In Pathway II, the enzymatic product of gene *B* converts the colorless pigment designated $white_2$ to red pigment. The two genes assort independently.

$$\text{Pathway I: } \text{White}_1 \xrightarrow{\text{gene A}} \text{Blue}$$
$$+ \quad = \quad \text{Purple}$$
$$\text{Pathway II: } \text{White}_2 \xrightarrow{\text{gene B}} \text{Red}$$

a. What are the possible genotype(s) for pure-breeding red petunias?
b. What are the possible genotype(s) for true-breeding blue petunias?

c. True-breeding red petunias are crossed to pure-breeding blue petunias, and all the F_1 progeny have purple flowers. If the F_1 are allowed to self-fertilize and produce the F_2, what is the expected phenotypic distribution of the F_2 progeny? Show your work.

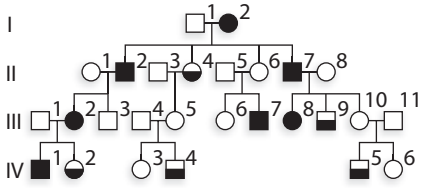
19. Feather color in parakeets is produced by the blending of pigments produced from two biosynthetic pathways shown below. Four independently assorting genes (*A, B, C,* and *D*) produce enzymes that catalyze separate steps of the pathways. For the questions below, use an uppercase letter to indicate a dominant allele producing full enzymatic activity and a lowercase letter to indicate a recessive allele producing no functional enzyme. Feather colors produced by mixing pigments are green (yellow + blue) and purple (red + blue). Red, yellow, and blue feathers result from production of one colored pigment, and white results from absence of pigment production.

Pathway I: Compound I (colorless) —Enzyme A→ Compound II (red) —Enzyme B→ Compound III (yellow)

Pathway II: Compound X (colorless) —Enzyme C→ Compound Y (colorless) —Enzyme D→ Compound Z (blue)

a. What is the genotype of a pure-breeding purple parakeet strain?
b. What is the genotype of a pure-breeding yellow strain of parakeet?
c. If a pure-breeding blue strain of parakeet (*aa BB CC DD*) is crossed to one that is pure-breeding purple, predict the genotype(s) and phenotype(s) of the F_1. Show your work.
d. If F_1 birds identified in part c are mated at random, what phenotypes do you expect in the F_2 generation? What are the ratios among phenotypes? Show your work.

20. Brachydactyly type D is a human autosomal dominant condition in which the thumbs are abnormally short and broad. In most cases, both thumbs are affected, but occasionally just one thumb is involved. The accompanying pedigree shows a family in which brachydactyly type D is segregating. Filled circles and squares represent females and males who have involvement of both thumbs. Half-filled symbols represent family members with just one thumb affected.



a. Is there any evidence of variable expressivity in this family? Explain.
b. Is there evidence of incomplete penetrance in this family? Explain.

21. A male and a female mouse are each from pure-breeding albino strains. They have a litter of 10 pups, all of which have normal pigmentation. The F_1 pups are crossed to one another to produce 56 F_2 mice, of which 31 are normally pigmented and 25 are albino.
a. Using clearly defined allele symbols of your own choosing, give the genotypes of parental and F_1 mice. What genetic phenomenon explains these parental and F_1 phenotypes?
b. What genetic phenomenon explains the F_2 results? Use your allelic symbols to explain the F_2 results.

22. Xeroderma pigmentosum (XP) is an autosomal recessive condition characterized by moderate to severe sensitivity to ultraviolet (UV) light. Patients develop multiple skin lesions on UV-exposed skin, and skin cancers often develop as a result. XP is caused by deficient repair of DNA damage from UV exposure.
a. Many genes are known to be involved in repair of UV-induced DNA damage, and several of these genes are implicated in XP. What genetic phenomenon is illustrated by XP?
b. A series of 10 skin-cell lines was grown from different XP patients. Cells from these lines were fused, and the heterokaryons were tested for genetic complementation by assaying their ability to repair DNA damage caused by a moderate amount of UV exposure. In the table below, + indicates that the fusion cell line performs normal DNA damage mutation repair, and 0 indicates defective DNA repair. Use this information to determine how many DNA-repair genes are mutated in the 10 cell lines, and identify which cell lines share the same mutated genes.

Mutant	1	2	3	4	5	6	7	8	9	10
1	–									
2	+	–								
3	–	+	–							
4	+	+	+	–						
5	+	+	+	+	–					
6	+	–	+	+	–	–				
7	–	+	–	+	+	+	–			
8	+	+	+	–	+	+	+	–		
9	–	–	–	–	–	–	–	–	–	
10	+	+	+	+	–	–	+	+	–	–

Mutant

23. Three strains of green-seeded lentil plants appear to have the same phenotype. The strains are designated G_1, G_2, and G_3. Each green-seeded strain is crossed to a pure-breeding yellow-seeded strain designated Y. The F_1 of each cross are yellow; however, self-fertilization of F_1 plants produces F_2 with different proportions of yellow- and green-seeded plants as shown below.

Parental Strain		F_1 Phenotype	F_2 Phenotype	
Green	Yellow		Green	Yellow
G_1	Y	All yellow	$\frac{1}{4}$	$\frac{3}{4}$
G_2	Y	All yellow	$\frac{7}{16}$	$\frac{9}{16}$
G_3	Y	All yellow	$\frac{37}{64}$	$\frac{27}{64}$

a. For what number of genes are variable alleles segregating in the $G_1 \times Y$ cross? The $G_2 \times Y$ cross? In the $G_3 \times Y$ cross? Explain your rationale for each answer.
b. Using the allele symbols *A* and *a*, *B* and *b*, and *D* and *d* to represent alleles at segregating genes, give the genotypes of parental and F_1 plants in each cross.
c. For each set of F_2 progeny, provide a genetic explanation for the yellow : green ratio. What are the genotypes of yellow and green F_2 lentil plants in the $G_2 \times Y$ cross?

d. If green-seeded strains G_1 and G_3 are crossed, what is the phenotype and the genotype of F_1 progeny?
e. What proportion of the F_2 are expected to be green? Show your work.
f. If strains G_2 and G_3 are crossed, what will be the phenotype of the F_1?
g. What proportion of the F_2 will have yellow seeds? Show your work.

24. Blue flower color is produced in a species of morning glories when dominant alleles are present at two gene loci, *A* and *B*. (Plants with the genotype *A*–*B*– have blue flowers.) Purple flowers result when a dominant allele is present at only one of the two gene loci, *A* or *B*. (Plants with the genotypes *A*–*bb* and *aaB*– are purple.) Flowers are red when the plant is homozygous recessive for each gene (i.e., *aabb*).
a. Two pure-breeding purple strains are crossed, and all the F_1 plants have blue flowers. What are the genotypes of the parental plants?
b. If two F_1 plants are crossed, what are the expected phenotypes and frequencies in the F_2?
c. If an F_1 plant is backcrossed to one of the pure-breeding parental plants, what is the expected ratio of phenotypes among progeny? Why is the phenotype ratio the same regardless of which parental strain is selected for the backcross?

25. The following crosses are performed between morning glories whose flower color is determined as described in Problem 23. Use the segregation data to determine the genotype of each parental plant.

Parental Phenotypes	Offspring Phenotypes
a. blue × blue	$\frac{3}{4}$ blue : $\frac{1}{4}$ purple
b. purple × purple	$\frac{1}{4}$ blue : $\frac{1}{2}$ purple : $\frac{1}{4}$ red
c. blue × red	$\frac{1}{4}$ blue : $\frac{1}{2}$ purple : $\frac{1}{4}$ red
d. purple × red	$\frac{1}{2}$ purple : $\frac{1}{2}$ red
e. blue × purple	$\frac{3}{8}$ blue : $\frac{1}{2}$ purple : $\frac{1}{8}$ red

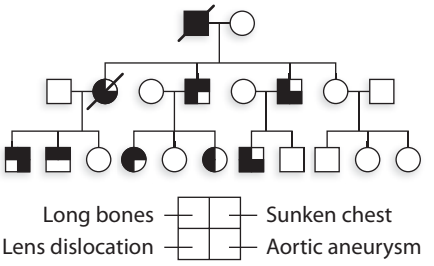
26. Two pure-breeding strains of summer squash producing yellow fruit, Y_1 and Y_2, are each crossed to a pure-breeding strain of summer squash producing green fruit, G_1, and to one another. The following results are obtained:

Cross	P	F_1	F_2
I	Y_1 (yellow) × G_1 (green)	All yellow	$\frac{3}{4}$ yellow : $\frac{1}{4}$ green
II	Y_2 (yellow) × G_1 (green)	All green	$\frac{3}{4}$ green : $\frac{1}{4}$ yellow
III	Y_1 (yellow) × Y_2 (yellow)	All yellow	$\frac{13}{16}$ yellow : $\frac{3}{16}$ green

a. Examine the results of each cross and predict how many genes are responsible for fruit-color determination in summer squash. Justify your answer.
b. Using clearly defined symbols of your choice, give the genotypes of parental, F_1, and F_2 plants in each cross.
c. If the F_1 of crosses I and II are mated, predict the phenotype ratio of the progeny.

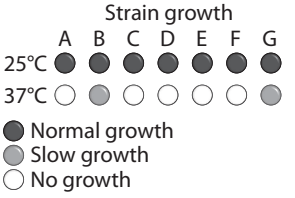
27. Marfan syndrome is an autosomal dominant disorder in humans. It results from mutation of the gene on chromosome 15, which produces the connective tissue protein fibrillin. In its wild-type form, fibrillin gives connective tissues, such as cartilage, elasticity. When mutated, however, fibrillin is rigid and produces a range of phenotypic complications, including excessive growth of the long bones of the leg and arm, sunken chest, dislocation of the lens of the eye, and susceptibility to aortic aneurysm, which can lead to sudden death in some cases.

Different sets of symptoms are seen among various family members, as shown in the pedigree below. Each quadrant of the circles and squares represents a different symptom, as the key indicates.



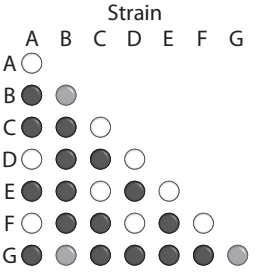
Since all cases of Marfan syndrome are caused by mutation of the fibrillin gene, and all family members with Marfan syndrome carry the same mutant allele, how do you explain the differences shown in the pedigree?

28. Yeast are single-celled eukaryotic organisms that grow in culture as either haploids or diploids. Diploid yeast are generated when two haploid strains fuse together. Seven haploid strains of yeast exhibit similar growth habit: at 25°C, each strain grows normally; but at 37°C, they show different growth capabilities. The table below displays the growth pattern.



a. Describe the nature of the mutation affecting each of these mutant yeast strains. Explain why strains B and G display different growth habit at 37°C than the other strains.
b. Each of the mutant pairs of haploid yeast is fused, and the resulting diploids are tested for their ability to grow at 37°C. The results of the growth experiment are shown below.

37°C growth data



How many different genes are mutated among these seven yeast strains? Identify the strains that represent each gene mutation.

29. During your work as a laboratory assistant in the research facilities of Dr. O. Sophila, a world-famous geneticist, you come across an unusual bottle of fruit flies. All the flies in the bottle appear normal when they are in an incubator set at 22°C. When they are moved to a 30°C incubator, however, a few of the flies slowly become paralyzed; and after about 20 to 30 minutes, they are unable to move. Returning the flies to 22°C restores their ability to move after about 30 to 45 minutes.

With Dr. Sophila's encouragement, you set up 10 individual crosses between single male and female flies that exhibit the unusual behavior. Among 812 progeny, 598 exhibit the unusual behavior and 214 do not. When you leave one of the test bottles in the 30°C incubator too long, you discover that more than 2 hours at high temperature kills the paralyzed flies. When you tell this to Dr. Sophila, he says, "Ah ha! I know the genetic explanation for this condition." What is his explanation?

30. Dr. Ara B. Dopsis and Dr. C. Ellie Gans are performing genetic crosses on daisy plants. They self-fertilize a blue-flowered daisy and grow 100 progeny plants that consist of 55 blue-flowered plants, 22 purple-flowered plants, and 23 white-flowered plants. Dr. Dopsis believes this is the result of segregation of two alleles at one locus and that the progeny ratio is 1:2:1. Dr. Gans thinks the progeny phenotypes are the result of two epistatic genes and that the ratio is 9:3:4.

The two scientists ask you to resolve their conflict by performing chi-square analysis on the data for *both* proposed genetic mechanisms. For each proposed mechanism, fill in the values requested on the form the researchers have provided for your analysis.

a. Use the form below to calculate chi square for the 1:2:1 hypothesis of Dr. Sophila.

Phenotype	Observed	Expected
Blue	55	_____
Purple	22	_____
White	23	_____

Chi-square value: _____ df: _____ *p* value > _____

b. Use the form below to calculate chi square for the 9:3:4 hypothesis of Dr. Gans.

Phenotype	Observed	Expected
Blue	55	_____
Purple	22	_____
White	23	_____

Chi-square value: _____ df: _____ *p* value > _____

c. What is your conclusion regarding these two genetic hypotheses?

d. Using any of the 100 progeny plants, propose a cross that will verify the conclusion you proposed in part (c). Plants may be self-fertilized, or one plant can be crossed to another. What result will be consistent with the 1:2:1 hypothesis? What result will be consistent with the 9:3:4 hypothesis?

31. Human ABO blood type is determined by three alleles (I^A, I^B, and i) whose gene products modify the H antigen produced by protein activity of an independently assorting *H* gene. A rare abnormality known as the "Bombay phenotype" is the result of epistatic interaction between the gene for the ABO blood group and the *H* gene. Individuals with the Bombay phenotype appear to have blood type O based on the inability of both anti-A antibody and anti-B antibody to detect an antigen. The apparent blood type O in Bombay phenotype is due to the absence of H antigen as a result of homozygous recessive mutations of the *H* gene. Individuals with the Bombay phenotype have the *hh* genotype. Use the information above to make predictions about the outcome of the cross shown below.

$$I^A I^B\ Hh \times I^A I^B\ Hh$$

32. In rabbits, albinism is an autosomal recessive condition caused by the absence of the pigment melanin from skin and fur. Pigmentation is a dominant wild-type trait. Three pure-breeding strains of albino rabbits, identified as strains 1, 2, and 3, are crossed to one another. In the table below, F_1 and F_2 progeny are shown for each cross. Based on the available data, propose a genetic explanation for the results. As part of your answer, create genotypes for each albino strain using clearly defined symbols of your own choosing. Use your symbols to diagram each cross, giving the F_1 and F_2 genotypes.

	Cross	F_1 Progeny	F_2 Progeny
Cross A	strain 1 × strain 2	56 albino	192 albino
Cross B	strain 1 × strain 3	72 pigmented	181 pigmented, 139 albino
Cross C	strain 2 × strain 3	34 pigmented	89 pigmented, 72 albino

33. Dr. O. Sophila, a close friend of Dr. Ara B. Dopsis, reviews the F_2 results Dr. Dopsis obtained in his experiment with iris plants described in Genetic Analysis 4.3. Dr. Sophila thinks the F_2 progeny demonstrate that a single gene with incomplete dominance has produced a 1:2:1 ratio. Dr. Dopsis insists his proposal of recessive epistasis producing a 9:4:3 ratio in the F_2 is correct. To test his proposal, Dr. Dopsis examines the F_2 data under the assumptions of the single-gene incomplete dominance model using chi-square analysis. Calculate and interpret this chi-square value. Can Dr. Dopsis reject the single-gene incomplete dominance model on the basis of this analysis? Explain why or why not.