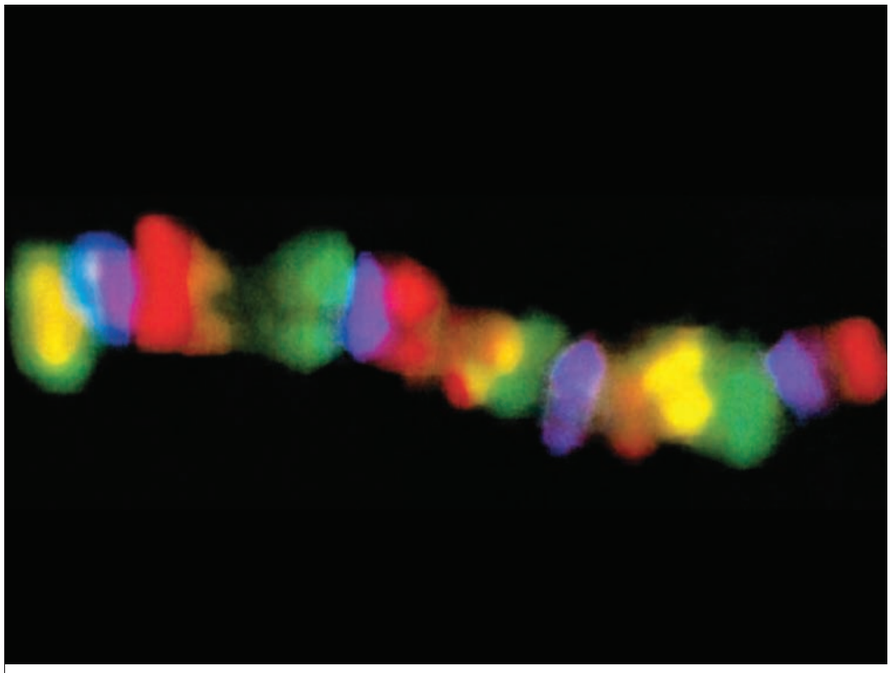
Fluorescent probes bound to specific sequences along human chromosome 10 (light micrograph). New ways of mapping chromosome structure yield insights into the inheritance of normal and abnormal traits.



Study Plan

13 Genes, Chromosomes, and Human Genetics

Why It Matters

Imagine being 10 years old and trapped in a body that each day becomes more shriveled, frail, and old. You are just tall enough to peer over the top of the kitchen counter, and you weigh less than 35 pounds. Already you are bald, and you probably have only a few more years to live. But if you are like Mickey Hayes or Fransie Geringer **(Figure 13.1),** you still have not lost your courage or your childlike curiosity about life. Like them, you still play, laugh, and celebrate birthdays.

Progeria, the premature aging that afflicts Mickey and Fransie, is caused by a genetic error that occurs in only 1 of every 8 million human births. The error is perpetuated each time cells of the embryo—then of the child—duplicate their chromosomes and divide. The outcome of that rare mistake is an acceleration of aging and a greatly reduced life expectancy.

Progeria affects both boys and girls. Usually, symptoms begin to appear before the age of 2 years. The rate of body growth declines to abnormally low levels. Skin becomes thinner, muscles become flaccid, and limb bones start to degenerate. Children with progeria never reach puberty, and most die in their early teens from a stroke or heart

Eddie Adams/AP Wide World Photos

Figure 13.1
Two boys, both younger than 10, who have progeria, a genetic disorder characterized by accelerated aging and extremely reduced life expectancy.

attack brought on by hardening of the arteries, a condition typical of advanced age.

The plight of Mickey and Fransie provides a telling and tragic example of the dramatic effects that gene defects can have on living organisms. We are the products of our genes, and the characteristics of each individual, from humans to pine trees to protozoa, depend on the combination of genes, alleles, and chromosomes inherited from its parents, as well as on environmental effects. This chapter delves deeply into genes and the role of chromosomes in inheritance.

13.1 Genetic Linkage and Recombination

In his historic experiments, Gregor Mendel carried out crosses with seven different characters in garden peas, controlled by seven different genes. He found that each of the genes assorted independently of the others in the formation of gametes. If Mendel had extended his study to additional characters, he would have found exceptions to this principle. This should not be surprising, because an organism has far more genes than chromosomes. Conceptually, then, chromosomes contain many genes, with each gene at a particular locus. Genes located on different chromosomes assort independently in gamete formation because the two chromosomes behave independently of one another during meiosis. Genes located on the same chromosome may be inherited together in genetic crosses—that is, not assort independently—because the chromosome is inherited as a single physical entity in meiosis. Genes on the same chromosome are known as **linked genes**, and the phenomenon is called **linkage.**

The Principles of Linkage and Recombination Were Determined with *Drosophila*

In the early part of the twentieth century, Thomas Hunt Morgan and his coworkers at Columbia University were using the fruit fly, *Drosophila melanogaster,* as a model organism to investigate Mendel's principles in animals. (*Focus on Research* describes the development and use of *Drosophila* in research.) In 1911, Morgan crossed a true-breeding fruit fly with normal red eyes and normal wing length, genotype pr^+pr^+ vg^+vg^+, with a true-breeding fly with the recessive traits of purple eyes and vestigial (that is, short and crumpled) wings, genotype *prpr vgvg,* to analyze the segregation of the two traits (**Figure 13.2,** step 1).

This gene symbolism is new to us. Morgan devised this symbolism, and it is commonly used, much more so than the *A/a* system we have used until now. In this system, the plus (+) symbol indicates a wild-type—normal—allele of a gene. Typically, but not always, a wild-type allele is the most common allele found in a population. In most instances, the wild-type allele is dominant to mutant alleles, but there are exceptions. The letter is chosen based on the phenotype of the organism that expresses the mutant allele, for example, *pr* for *purple* eyes. Thus, we refer to the gene as the *purple* or *pr* gene; the dominant wild-type allele of the gene, pr^+, gives the wild-type red eye color.

The F_1 (first-generation) offspring of Morgan's cross were all pr^+pr vg^+vg, and because of the dominance of the wild-type alleles, they had red eyes and normal wings (see Figure 13.2, step 2). Next, Morgan testcrossed F_1 females to males with purple eyes and vestigial wings, genotype *prpr vgvg*. The testcross was used here because you can follow the meiotic events in just one parent; that is, all of the gametes from the other parent carry recessive alleles for the genes in the cross (see Section 12.1). Based on Mendel's principle of independent assortment (see Section 12.1), there should be four classes of phenotypes in the offspring, in the approximate 1 : 1 : 1 : 1 ratio of red eyes, normal wings : purple, vestigial : red, vestigial : purple, normal. But Morgan did not observe this result (step 3); instead, of the 2839 progeny flies, 1339 were red-normal and 1195 were purple-vestigial. These phenotypes are identical to the two original parental flies (the parents of the female parent used in the testcross); therefore, they are called **parental** phenotypes. The remaining progeny flies consisted of 151 red-vestigial and 154 purple-normal. Because these two classes have phenotypes with different combinations of traits from those of the original parents, they are called **recombinant** phenotypes. If the genes had shown independent assortment, there would have been 25% of each of the four classes, or 50% parental and 50% recombinant phenotypes. In numbers, there would have been 710 (approximately) of each of the 4 classes.

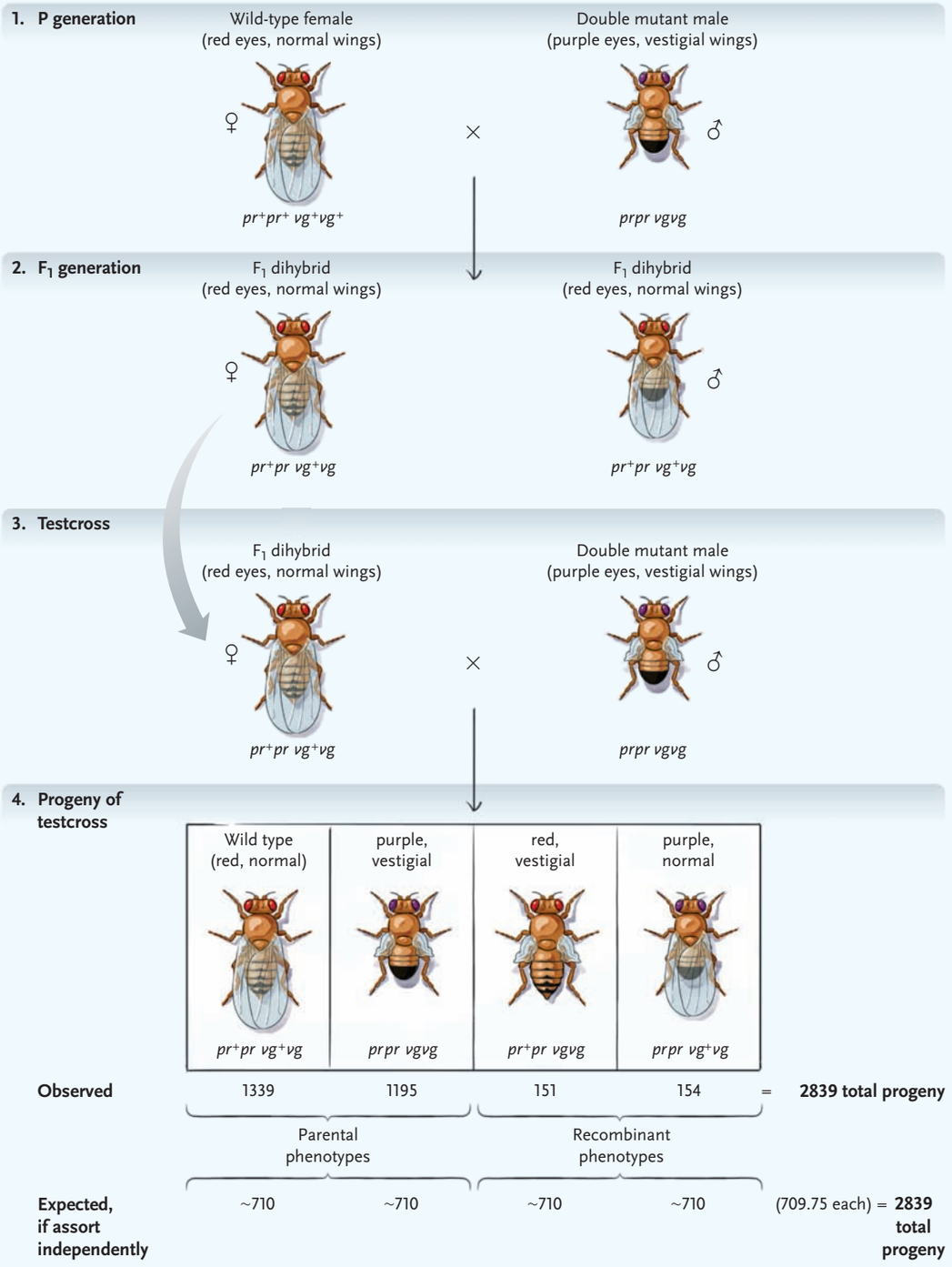
How could the low frequency of recombinant phenotypes be explained? Morgan hypothesized that the two genes are linked genetically—physically associated on the same chromosome. That is, *pr* and *vg* are linked genes. He further hypothesized that the behavior of these linked genes in the testcross is explained by what he called *chromosome recombination,* a process in which

Figure 13.2 Experimental Research

Evidence for Gene Linkage

QUESTION: Do the purple-eye vestigial-wing genes of *Drosophila* assort independently?

EXPERIMENT: Morgan crossed true-breeding wild-type flies with red eyes and normal wings with purple-eyed, vestigial-winged flies. The F_1 dihybrids were all wild-type in phenotype. Next he crossed the F_1 dihybrid flies with purple-eyed, vestigial-winged flies (this is a testcross) and analyzed the phenotypes of the progeny.



RESULTS: 2534 of the testcross progeny flies had parental phenotypes, wild-type and purple, vestigial, while 305 of the progeny had recombinant phenotypes of red, vestigial and purple, normal. If the genes assorted independently, the expectation is a 1:1:1:1 ratio for testcross progeny: approximately 1420 of both parental and recombinant progeny.

CONCLUSION: The purple-eye and vestigial-wing genes do not assort independently. The simplest alternative is that the two genes are linked on the same chromosome.

Focus on Research

Model Research Organisms: The Marvelous Fruit Fly, *Drosophila melanogaster*

Herman Eisenbeiss/Photo Researchers, Inc.

The unobtrusive little fruit fly that appears seemingly from nowhere when rotting fruit or a fermented beverage is around is one of the mainstays of genetic research. It was first described in 1830 by C. F. Fallén, who named it *Drosophila,* meaning "dew lover." The species identifier became *melanogaster,* which means "black belly."

The great geneticist Thomas Hunt Morgan began to culture *D. melanogaster* in 1909 in the famous "Fly Room" at Columbia University. Many important discoveries in genetics were made in the Fly Room, including sex-linked genes and sex linkage and the first chromosome map. The subsequent development of methods to induce mutations in *Drosophila* led, through studies of the mutants produced, to many other discoveries that collectively established or confirmed essentially all the major principles and conclusions of eukaryotic genetics.

One reason for the success of *D. melanogaster* as a subject for genetics research is the ease of culturing it. It is grown usually at 25°C in small milk bottles stopped with a cotton or plastic foam wad and filled about one-third of the way with a fermenting medium that contains water, corn meal, agar, molasses, and yeast. The several hundred eggs laid by each adult female hatch rapidly and progress through larval and pupal stages to produce adult flies in about 10 days, which are ready to breed within 10 to 12 hours.

Males and females can be identified easily with the unaided eye. Many types of mutations produce morphologic differences, such as changes in eye color, wing shape, or the numbers and shapes of bristles, that can be seen with the unaided eye or under a low-power binocular microscope. The salivary gland cells of the fly larvae also have giant chromosomes. The chromosomes are so large that differences can be observed directly with the light microscope.

The availability of a wide range of mutants, comprehensive linkage maps of each of its chromosomes, and the ability to manipulate genes readily by molecular techniques made the fruit fly one of the model organisms for genome sequencing in the Human Genome Project. The sequencing of *Drosophila*'s genome was completed in 2001; there are approximately 14,000 genes in its 165 million base-pair genome. (A database of the *Drosophila* genome is available at http://flybase.bio.indiana.edu). Importantly, the relationship between fruit fly and human genes is close, to the point that many human disease genes have counterparts in the fruit fly genome. This similarity enables the fly genes to be studied as models of human disease genes in efforts to understand better the functions of those genes and how alterations in them lead to disease.

The analysis of fruit fly embryonic development has also contributed significantly to the understanding of development in humans. For example, experiments on mutants that affect fly development have provided insights into the genetic basis of many human birth defects.

Lastly, *Drosophila* molecular biologists are known for their sense of humor in naming genes based on the mutant phenotypes they identify. Their names contrast markedly from the serious naming of yeast and human genes. For instance, the *tinman* mutant of fruit flies lacks a heart in the embryo, *cheap date* mutants are especially sensitive to alcohol, and *indy* (*I*'m *n*ot *d*ead yet) mutants have a doubled life span (named after a character in *Monty Python and the Holy Grail* who, when being taken to be buried, protests "I'm not dead yet.").

two homologous chromosomes exchange segments (crossover) with each other during meiosis (see Figure 11.6). Furthermore, he proposed that the frequency of this recombination is a function of the distance between linked genes. The nearer two genes are, the greater the chance they will be inherited together (resulting in parental phenotypes) and the lower the chance that recombinant phenotypes will be produced. The farther apart two genes are, the lower the chance that they will be inherited together and the greater the chance that recombinant phenotypes will be produced. These brilliant and far-reaching hypotheses were typical of Morgan, who founded genetics research in the United States, developed *Drosophila* as a research organism, and made discoveries that were almost as significant to the development of genetics as those of Mendel.

We show how this applies to the purple-vestigial cross in **Figure 13.3,** which presents the alleles of the genes with cartoons of the chromosomes themselves. This figure allows us to follow pictorially the consequences of crossing-over during meiosis in the production of gametes.

The pr^+pr vg^+vg F_1 dihybrid parent produces four types of gametes (see Figure 13.3). The two parental gametes, pr^+ vg^+ and pr vg, are generated by simple segregation of the chromosomes during meiosis without any crossing-over (recombination) between the genes. The two recombinant gametes, pr^+ vg and pr vg^+, result from crossing-over between the homologous chromatids when they are paired in prophase I of meiosis (see Section 11.1 and Figure 11.4). The offspring of the cross are produced by fusion of each of these four gametes with a pr vg gamete produced by the *prpr vgvg* male parent. The parental or recombinant phenotypes of the offspring directly reflect the genotypes of the gametes of the

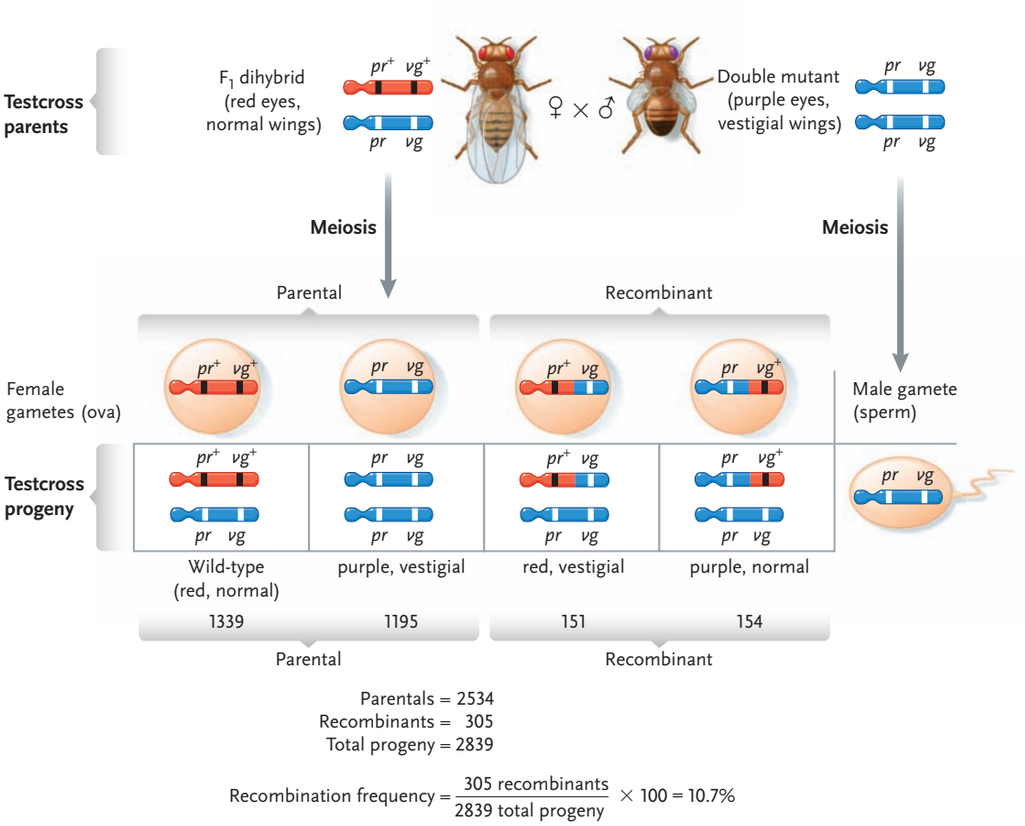


Figure 13.3
Recombination, the result of crossing-over between homologous chromosomes. The testcross of Figure 13.2 is redrawn here showing the two linked genes on chromosomes. The two parental homologs are colored differently to allow us to follow them during the cross. The parental phenotypes in the testcross progeny are generated by segregation of the parental chromosomes, whereas the recombinant phenotypes are generated by crossing-over between the two linked genes.

dihybrid parent. **Genetic recombination** is the process by which the combinations of alleles for different genes in two parental individuals become shuffled into new combinations in offspring individuals.

To determine the distance between the two genes on the chromosome, we calculate the **recombination frequency**, the percentage of testcross progeny that are recombinants. For this testcross, the recombination frequency is 10.7% (see Figure 13.3).

Recombination Frequency Can Be Used to Map Chromosomes

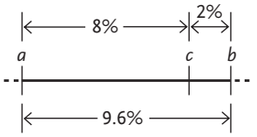
The recombination frequency of 10.7% for the *pr* and *vg* genes of *Drosophila* means that 10.7% of the gametes originating from the pr^+pr vg^+vg parent contained recombined chromosomes. That recombination frequency is characteristic for those two genes. In other crosses that involve linked genes, Morgan found that the recombination frequency was characteristic of the two genes involved, varying from less than 1% to 50% (see the next section).

From these observations, Alfred Sturtevant, then an undergraduate at Columbia University working with Morgan, realized that the variations in recombination frequencies could be used as a means of mapping genes on chromosomes. Sturtevant himself later recalled his lightbulb moment:

> I suddenly realized that the variations in the strength of linkage already attributed by Morgan to difference in the spatial separation of the gene offered the possibility of determining sequence in the linear dimensions of a chromosome. I went home and spent most of the night (to the neglect of my undergraduate homework) in producing the first chromosome map.

Sturtevant's revelation was that the recombination frequency observed between any two linked genes reflects the distance between them on their chromosome. The greater this distance, the greater the chance that a crossover can form between the genes and the greater the recombination frequency.

Therefore, recombination frequencies can be used to make a **linkage map** of a chromosome showing the relative locations of genes. For example, assume that the three genes *a, b,* and *c* are carried together on the same chromosome. Crosses reveal a 9.6% recombination frequency for *a* and *b,* an 8% recombination frequency for *a* and *c,* and a 2% recombination frequency for *b* and *c*. These frequencies allow the genes to be arranged in only one sequence on the chromosomes as follows:



You will note that the *a-b* recombination frequency does not exactly equal the sum of the *a-c* and *c-b* recombination frequencies. This is because genes farther

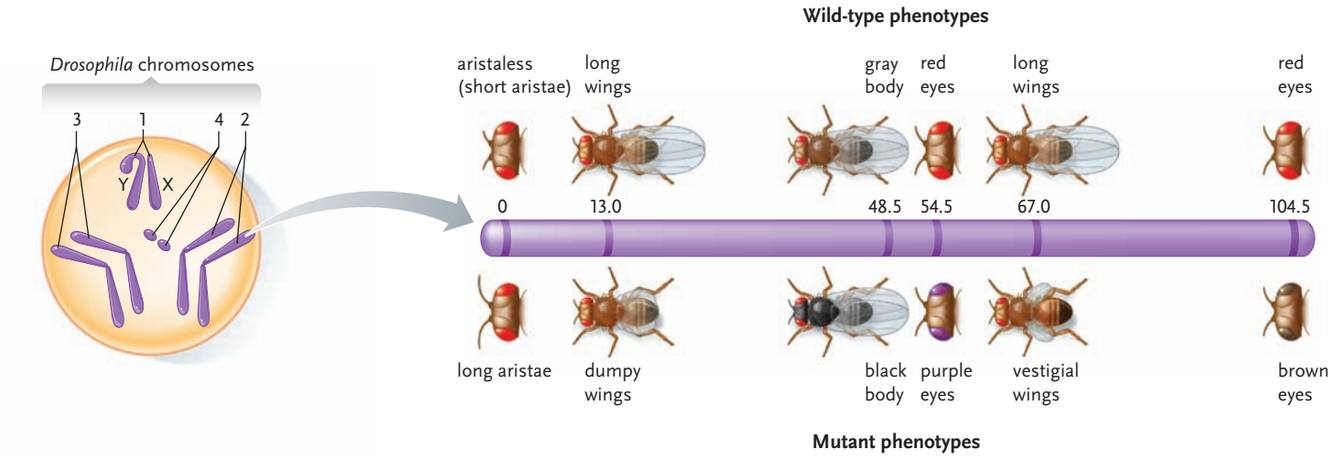


Figure 13.4
Relative map locations of several genes on chromosome 2 of *Drosophila*, as determined by recombination frequencies. For each gene, the diagram shows the normal or "wild-type" phenotype on the top and the mutant phenotype on the bottom. Mutant alleles at two different locations alter wing structure, one producing the dumpy wing and the other the vestigial wing phenotypes; the normal allele at these locations results in normal long-wing structure. Mutant alleles at two different locations also alter eye color.

apart on a chromosome are more likely to have more than one crossover occur between them. Whereas a single crossover between two genes gives recombinants, a double crossover (two single crossovers occurring in the same meiosis) between two genes gives parentals. You can see this simply by drawing single and double crossovers between two genes on a piece of paper. In our example, double crossovers that occur between *a* and *b* have slightly decreased the recombination frequency between these two genes.

Using this method, Sturtevant created the first linkage map showing the arrangement of six genes on the *Drosophila* X chromosome. (A partial linkage map of a *Drosophila* chromosome is shown in **Figure 13.4.**)

Since the time of Morgan, many *Drosophila* genes and those of other eukaryotic organisms widely used for genetic research, including *Neurospora* (a fungus), yeast, maize (corn), and the mouse, have been mapped using the same approach. Recombination frequencies, together with the results of other techniques, have also been used to create linkage maps of the locations of genes in the DNA of prokaryotes such as the human intestinal bacterium *Escherichia coli* (see Chapter 17).

The unit of a linkage map, called a **map unit** (abbreviated mu), is equivalent to a recombination frequency of 1%. The map unit is also called the **centimorgan** in honor of Morgan's discoveries of linkage and recombination. Map units are not absolute physical distances in micrometers or nanometers; rather, they are *relative*, showing the positions of genes with respect to each other. One of the reasons that the units are relative and not absolute distances is that the frequency of crossing-over varies to some extent from one position to another on chromosomes.

In recent years, the linkage maps of a number of species have been supplemented by DNA sequencing of whole genomes, which shows the precise physical locations of genes in the chromosomes.

Widely Separated Linked Genes Assort Independently

Genes can be so widely separated on a chromosome that recombination is likely to occur at some point between them in every cell undergoing meiosis. When this is the case, no linkage is detected and the genes assort independently. In other words, even though the alleles of the genes are carried on the same chromosome, the approximate 1 : 1 : 1 : 1 ratio of phenotypes is seen in the offspring of a dihybrid × double mutant testcross. That is, 50% of the progeny are parentals and 50% are recombinants. Linkage between such widely separated genes can still be detected, however, by testing their linkage to one or more genes that lie between them. For example, the genes *a* and *c* in **Figure 13.5** are located so far apart that they assort independently and show no linkage. However, crosses show that *a* and *b* are 23 map units apart (recombination frequency of 23%), and crosses that show *b* and *c* are 34 map units apart. Therefore, *a* and *c* must also be linked and carried on the same chromosome at 23 + 34 = 57 map units apart. Obviously, we could not see a recombination frequency of 57% in testcross progeny because the maximum frequency of recombinants is 50%.

We now know that some of the genes Mendel studied assort independently even though they are on the same chromosome. For example, the genes for flower color and seed color are located on the same chromosome pair, but they are so far apart that the frequent

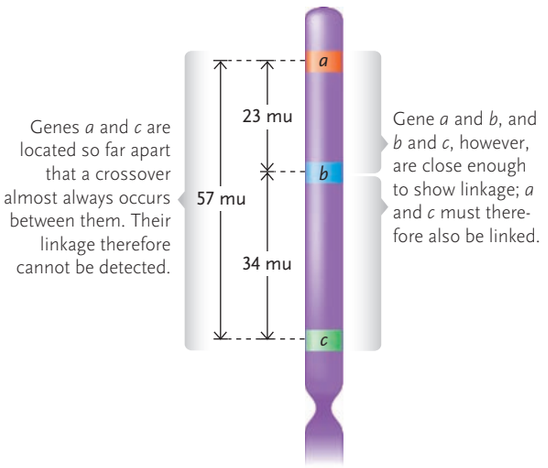


Figure 13.5
Genes far apart on the same chromosome. Genes *a* and *c* are far apart and will not show linkage, suggesting they are on different chromosomes. However, linkage between such genes can be established by noting their linkage to another gene or genes located between them—gene *b* here.

recombination between them makes them appear to be unlinked.

Study Break

You want to determine whether genes *a* and *b* are linked. What cross would you use and why? How would this cross tell you if they are linked?

13.2 Sex-Linked Genes

In many organisms, one or more pairs of chromosomes are different in males and females (see Section 11.1). Genes located on these chromosomes, the *sex chromosomes,* are called **sex-linked genes;** they are inherited differently in males and females. (Note that the word *linked* in *sex-linked gene* means that the gene is on a sex chromosome, whereas the use of the term *linked* when considering two or more genes means that the genes are on the same chromosome, not necessarily a sex chromosome.) Chromosomes other than the sex chromosomes are called **autosomes;** genes on these chromosomes have the same patterns of inheritance in both sexes. In humans, chromosomes 1 to 22 are the autosomes.

Females Are XX and Males Are XY in Both Humans and Fruit Flies

In most species with sex chromosomes, females have two copies of a chromosome known as the **X chromosome,** forming a homologous XX pair, whereas males have only one X chromosome. Another chromosome, the **Y chromosome,** occurs in males but not in females, giving males an XY combination; the XX-XY human chromosome complement is shown in Figure 10.7.

Each normal gamete produced by an XX female carries an X chromosome. Half the gametes produced by an XY male carry an X chromosome and half carry a Y. When a sperm cell carrying an X chromosome fertilizes an X-bearing egg cell, the new individual develops into an XX female. Conversely, when a sperm cell carrying a Y chromosome fertilizes an X-bearing egg cell, the combination produces an XY male **(Figure 13.6).** The Punnett square shows that fertilization is expected to produce females and males with an equal frequency of 1/2. This expectation is closely matched in the human and *Drosophila* populations.

Other sex chromosome arrangements occur, as in some insects with XX females and XO males (the O means there is no Y chromosome). In birds, butterflies, and some reptiles, the situation is reversed: males have a homologous pair of sex chromosomes (ZZ instead of XX), and females have the equivalent of an XY combination (ZW).

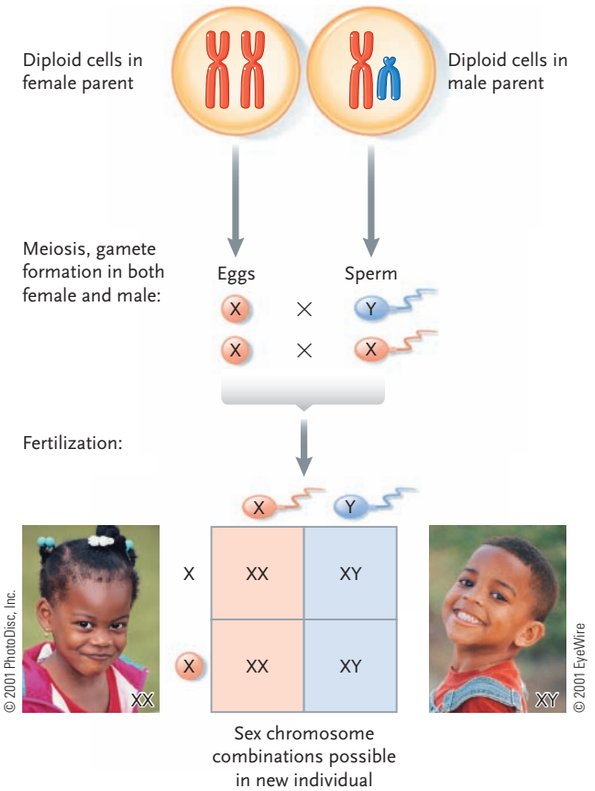


Figure 13.6
Sex chromosomes and the chromosomal basis of sex determination in humans. Females have two X chromosomes and produce gametes (eggs), all of which have the X sex chromosome. Males have one X and one Y chromosome and produce gametes, half with an X and half with a Y chromosome. Males transmit their Y chromosome to their sons, but not to their daughters. Males receive their X chromosome only from their mother.

Human Sex Determination Depends on the Y Chromosome

The human X chromosome carries about 2350 genes. Although some of these genes are associated with sexual traits, such as differing distributions of body fat in males and females, most are concerned with nonsexual traits such as the ability to perceive color, metabolize certain sugars, or form blood clots when tissues are injured. Human sex determination depends on the Y chromosome, which contains the *SRY* gene (for *s*ex-determining *r*egion of the *Y*) that switches development toward maleness at an early point in embryonic development.

For the first month or so of embryonic development in humans and other mammals, the rudimentary structures that give rise to reproductive organs and tissues are the same in XX or XY embryos. After 6 to 8 weeks, the *SRY* gene becomes active in XY embryos, producing a protein that regulates the expression of other genes, thereby stimulating part of these structures to develop as testes. As a part of stimulation by hormones secreted in the developing testes and elsewhere, tissues degenerate that would otherwise develop into female structures such as the vagina and oviducts. The remaining structures develop into the penis and scrotum. In XX embryos, which do not have a copy of the *SRY* gene, development proceeds toward female reproductive structures. The rudimentary male structures degenerate in XX embryos because the hormones released by the developing testes in XY embryos are not present. Further details of the *SRY* gene and its role in human sex determination are presented in Chapter 48 (specifically, see *Insights from the Molecular Revolution* in that chapter).

Sex-Linked Genes Were First Discovered in *Drosophila*

The different sets of sex chromosomes in males and females affect the inheritance of the alleles on these chromosomes in a distinct pattern known as *sex linkage*.

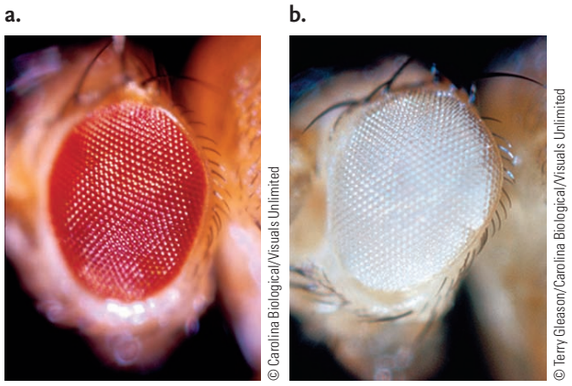


Figure 13.7
Eye color phenotypes in *Drosophila*. **(a)** Normal, red wild-type eye color. **(b)** Mutant white eye color caused by a recessive allele of a sex-linked gene carried on the X chromosome.

Two features of the XX-XY arrangement cause sex linkage. One is that alleles carried on the X chromosome occur in two copies in females but in only one copy in males. The second feature is that alleles carried on the Y chromosome are present in males but not females.

Morgan discovered sex-linked genes and their pattern of sex linkage in 1910. It started when he found a male fly in his stocks with white eyes instead of the normal red eyes **(Figure 13.7).** He crossed the white-eyed male with a true-breeding female with red eyes and observed that all the F_1 flies had red eyes **(Figure 13.8a).** He concluded that the white-eye trait was recessive. Next, he allowed the F_1 flies to interbreed. Based on Mendel's principles, he expected that both male and female F_2 flies would show a 3 : 1 ratio of red-eyed flies to white-eyed flies. Morgan was surprised to find that all the F_2 females had red eyes, and half of the F_2 males had red eyes and half had white eyes **(Figure 13.8b).**

Morgan hypothesized that the alleles segregating in the cross were of a gene located on the X chromosome—now termed a sex-linked gene. The white-eyed male parent in the cross had the genotype X^wY: an X chromosome with a white (X^w) allele, and no other allele of that gene on the Y. The red-eyed female parent in the cross had the genotype $X^{w^+}X^{w^+}$: each X chromosome carries the dominant normal allele for red eyes, X^{w^+}.

We can follow the alleles in this cross (see Figure 13.8a). The F_1 flies of a cross $X^{w^+}X^{w^+} \times X^wY$ are produced as follows. The X chromosome of the males comes from their mother; therefore, their genotype is $X^{w^+}Y$, and their phenotype is red eyes. The females receive one X from each parent; therefore, their genotype is $X^{w^+}X^w$, and their phenotype is red eyes due to the dominance of the X^{w^+} allele.

In the F_2 generation, the females receive an X^{w^+} allele from the male F_1 parent and either an X^{w^+} or X^w allele from the female F_1 parent; these genotypes result in red eyes (see Figure 13.8a). The males receive their one X chromosome from the female F_1 parent, which has the genotype $X^{w^+}X^w$. Therefore, F_2 males are half $X^{w^+}Y$ (red eyes) and half X^wY (white eyes).

Morgan also made a *reciprocal cross* of the one just described; that is, the phenotypes were switched between the sexes. The reciprocal cross here was a white-eyed female (X^wX^w) with a red-eyed male ($X^{w^+}Y$) (see Figure 13.8b). The F_1 males all had white eyes because they received the X^w-bearing chromosome from the female parent; thus, their genotype is X^wY. The F_1 females have red eyes; therefore, they are all heterozygous $X^{w^+}X^w$. This result is clearly different from the cross in Figure 13.8a.

In the F_2 generation of this second cross, both male and female flies showed a 1 : 1 ratio of red eyes to white eyes (see Figure 13.8b). Again, this result differs markedly from that of the cross in Figure 13.8a.

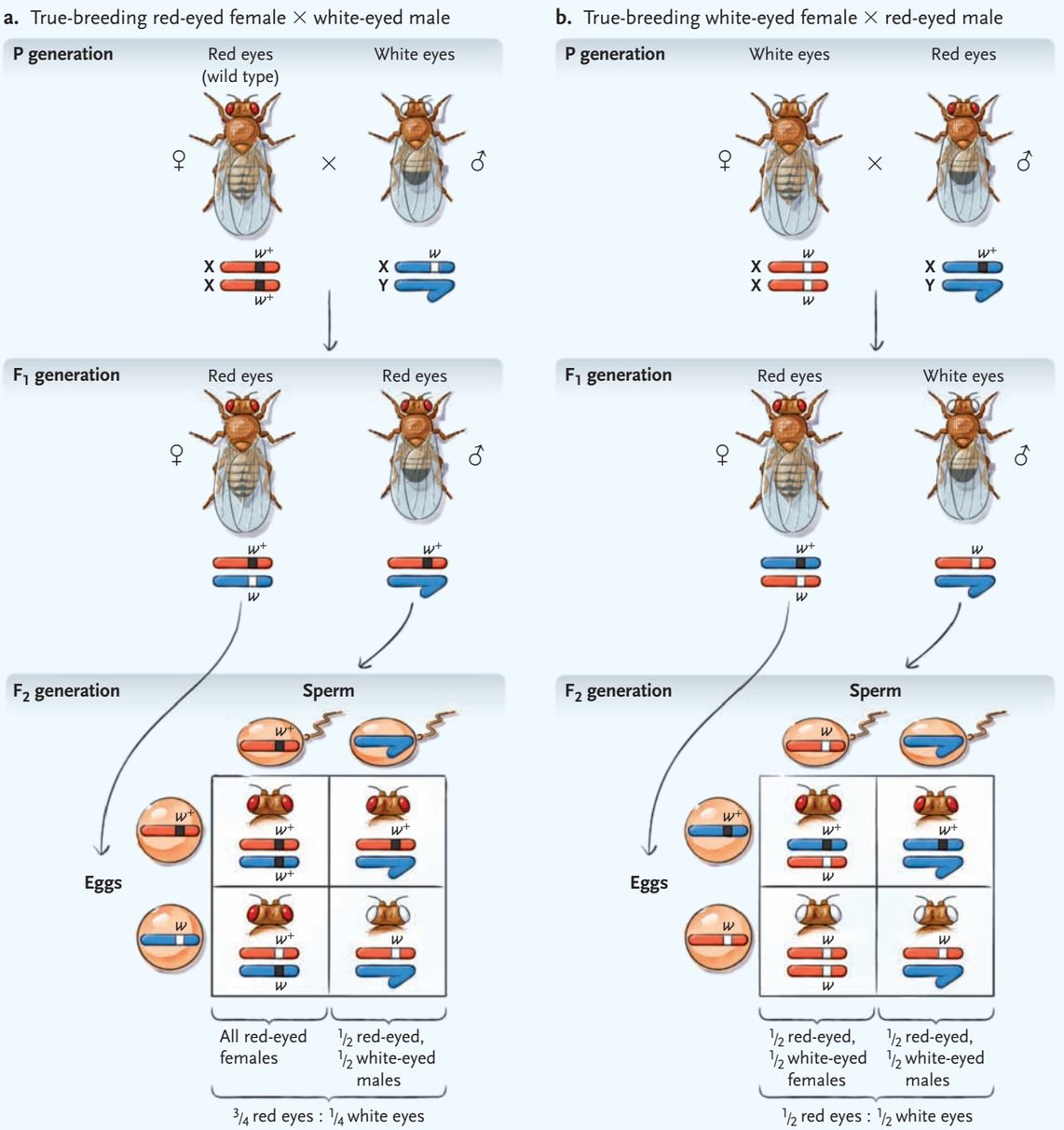
In summary, Morgan's work showed that there is a distinctive pattern in the phenotypic ratios for recip-

Figure 13.8 Experimental Research

Evidence for Sex-Linked Genes

QUESTION: How is the white-eye gene of *Drosophila* inherited?

EXPERIMENT: Morgan crossed a white-eyed male *Drosophila* with a true-breeding female with red eyes and then crossed the F_1 flies to produce the F_2 generation. He also performed the reciprocal cross in which the phenotypes were switched in the parental flies—true-breeding white-eyed female × red-eyed male.



RESULTS: Differences were seen in both the F_1 and F_2 generations for the red ♀ × white ♂ and white ♀ × red ♂ crosses.

CONCLUSION: The segregation pattern for the white-eye trait showed that the white-eye gene is a sex-linked gene located on the X chromosome.

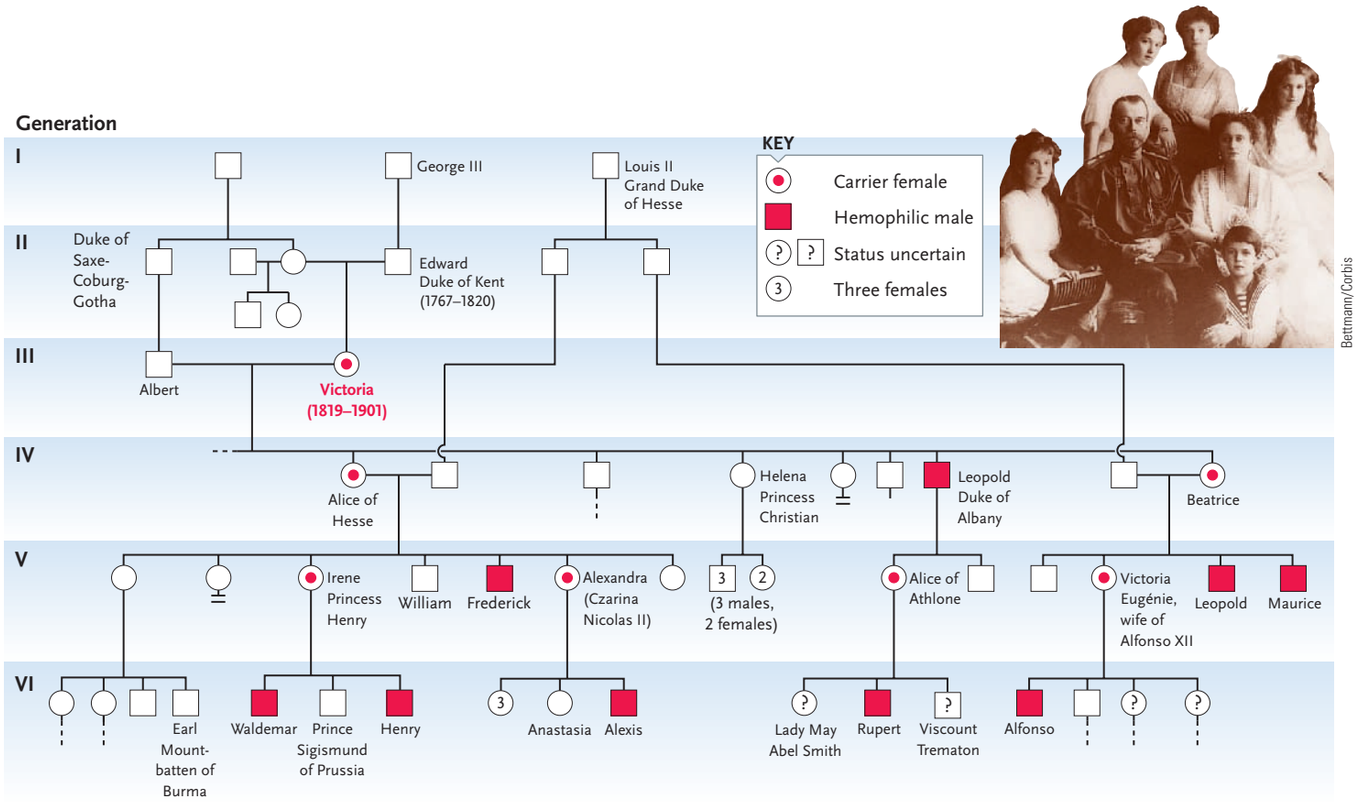


Figure 13.9
Inheritance of hemophilia in descendants of Queen Victoria of England. The photograph shows the Russian royal family in which the son, Crown Prince Alexis, had hemophilia. His mother was a carrier of the mutated gene.

rocal crosses in which the gene involved is on the X chromosome. A key indicator of this sex linkage is when all male offspring of a cross between a true-breeding mutant female and a wild-type male have the mutant phenotype. As we have seen, this occurs because a male receives his X chromosome from his female parent.

Sex-Linked Genes in Humans Are Inherited as They Are in *Drosophila*

For obvious reasons, experimental genetic crosses cannot be conducted with humans. However, a similar analysis can be made by interviewing and testing living members of a family and reconstructing the genotypes and phenotypes of past generations from family records. The results are summarized in a chart called a **pedigree**, which shows all parents and offspring for as many generations as possible, the sex of individuals in the different generations, and the presence or absence of the trait of interest. Females are designated by a circle and males by a square; a solid circle or square indicates the presence of the trait.

In humans, as in fruit flies, sex-linked recessive traits appear more frequently among males than females because males need to receive only one copy of the allele on the X chromosome inherited from their mothers to develop the trait. Females must receive two copies of the recessive allele, one from each parent, to develop the trait. Two examples of human sex-linked traits are red–green color blindness, a recessive trait in which the affected individual is unable to distinguish between the colors red and green because of a defect in light-sensing cells in the retina, and hemophilia, a recessive trait in which affected individuals have a defect in blood clotting.

Hemophiliacs—people with hemophilia—are "bleeders"; that is, if they are injured, they bleed uncontrollably because a protein required for forming blood clots is not produced in functional form. Males are bleeders if they receive an X chromosome that carries the recessive allele. The disease also develops in females with the recessive allele on both of their X chromosomes—a rare combination. Although affected persons, with luck and good care, can reach maturity, their lives are tightly circumscribed by the necessity to avoid injury of any kind. Even internal bleeding from slight bruises can be fatal. The disease, which affects about 1 in 7000 males, can be treated by injection of the required clotting molecules.

Hemophilia has had effects reaching far beyond individuals who inherit the disease. The most famous cases occurred in the royal families of Europe descended from Queen Victoria of England **(Figure 13.9).** The disease was not recorded in Queen Victoria's ancestors, so the recessive allele for the trait probably

appeared as a spontaneous mutation in the queen or one of her parents. Queen Victoria was heterozygous for the recessive hemophilia allele; that is, she was a **carrier**, meaning that she carried the mutant allele and could pass it on to her offspring but she did not have symptoms of the disease. A carrier is indicated in a pedigree by a male or female symbol with a central dot.

Note in Queen Victoria's pedigree in Figure 13.9 that Leopold, Duke of Albany, had hemophilia, as did his grandson, Rupert, Viscount Trematon. The trait alternates from generation to generation in males because a father does not pass his X chromosome to his sons; the X chromosome received by a male always comes from his mother. The appearance of a trait in the males of alternate generations therefore indicates that the allele under study is recessive and carried on the X chromosome.

At one time, 18 of Queen Victoria's 69 descendants were affected males or female carriers. Because so many sons of European royalty were affected, the trait influenced the course of history. In Russia, Crown Prince Alexis was one of Victoria's hemophiliac descendants. His affliction drew together his parents, Czar Nicholas II and Czarina Alexandra (a granddaughter of Victoria and a carrier), and the hypnotic monk Rasputin, who manipulated the family to his advantage by convincing them that only he could control the boy's bleeding. The situation helped trigger the Russian Revolution of 1917, which ended the Russian monarchy and led to the establishment of a Communist government in the former Soviet Union, a significant event in twentieth century history.

Hemophilia affected only sons in the royal lines but could have affected daughters if a hemophiliac son had married a carrier female. Because the disease is rare in the human population as a whole, the chance of such a mating is so low that only a few unions of this type have been recorded.

Inactivation of One X Chromosome Evens out Gene Effects in Mammalian Females

Although mammalian females have twice as many X chromosomes as males, the effects of most genes carried on the X chromosome in females is equalized in the male and female offspring of placental mammals by a *dosage compensation mechanism* that inactivates one of the two X chromosomes in most body cells of female mammals.

As a result of the equalizing mechanism, the activity of most genes carried on the X chromosome is essentially the same in males and females. The inactivation occurs by a condensation process that folds and packs the chromatin of one of the two X chromosomes into a tightly coiled state similar to the condensed state of chromosomes during cell division. The inactive, condensed X chromosome can be seen at one side of the nucleus in cells of females as a dense mass of chromatin called the **Barr body.**

The inactivation occurs during embryonic development. Which of the two X chromosomes becomes inactive in a particular embryonic cell line is a random event. But once one of the X chromosomes is inactivated in a cell, that same X is inactivated in all descendants of the cell. Thus, within one female, one of the X chromosomes is active in particular cells and inactive in others and vice versa.

If the two X chromosomes carry different alleles of a gene, one allele will be active in cell lines in which one X chromosome is active, and the other allele will be active in cell lines in which the other X chromosome is active. For many sex-linked alleles, such as the recessive allele that causes hemophilia, random inactivation of either X chromosome has little overall whole-body effect in heterozygous females because the dominant allele is active in enough of the critical cells to produce a normal phenotype. However, for some genes, the inactivation of either X chromosome in heterozygotes produces recognizably different effects in distinct regions of the body.

For example, the orange and black patches of fur in calico cats result from inactivation of one of the two X chromosomes in regions of the skin of heterozygous females **(Figure 13.10).** Males, which get only one of the two alleles, normally have either black or orange fur. Similarly, in humans, females who are heterozygous for an allele on the X chromosome that blocks development of sweat glands may have a patchy distribution

Ulrike Schanz/Animals, Animals

Figure 13.10
A female cat with the calico color pattern in which patches of orange and black fur are produced by random inactivation of one of the two X chromosomes. Two genes control the black and orange colors: the *O* gene on the X chromosome is for orange fur color, and the *B* gene on an autosome is for black fur color. A calico cat has the genotype *Oo BB* (or *Oo Bb*). An orange patch results when the X chromosome carrying the mutant *o* allele is inactivated. In this case, the *O* gene masks the expression of the *B* gene and orange fur is produced. (This example is of epistasis; see Section 12.2.) A black patch results when the X chromosome carrying the *O* allele is inactivated. In this case, the mutant *o* allele cannot mask *B* gene expression and black fur results. The white patches result from interactions with a different, autosomal gene that entirely blocks pigment deposition in the fur.

of skin areas with and without the glands. Females with the patchy distribution are not seriously affected and may be unaware of the condition.

As we have seen, the discovery of genetic linkage, recombination, and sex-linked genes led to the elaboration and expansion of Mendel's principles of inheritance. Next, we examine what happens when patterns of inheritance are modified by changes in the chromosomes.

Study Break

You have a true-breeding strain of miniature-winged fruit flies, where this wing trait is recessive to the normal long wings. How would you show whether the miniature wing trait is sex-linked or autosomal?

13.3 Chromosomal Alterations That Affect Inheritance

Although chromosomes are relatively stable structures, they are sometimes altered by breaks in the DNA, which can be generated by agents such as radiation or certain chemicals or by enzymes encoded in some infecting viruses. The broken chromosome fragments may be lost, or they may reattach to the same or different chromosomes. The resulting changes in chromosome structure may have genetic consequences if alleles are eliminated, mixed in new combinations, duplicated, or placed in new locations by the alterations in cell lines that lead to the formation of gametes.

Genetic changes may also occur through changes in chromosome number, including addition or loss of one or more chromosomes or even entire sets of chromosomes. Both chromosomal alterations and changes in chromosome number can be a source of disease and disability, as well as a source of variability during evolution.

Deletions, Duplications, Translocations, and Inversions Are the Most Common Chromosomal Alterations

Chromosomal alterations after breakages occur in four major forms **(Figure 13.11):**

- A **deletion** occurs if a broken segment is lost from a chromosome.
- A **duplication** occurs if a segment is broken from one chromosome and inserted into its homolog. In the receiving homolog, the alleles in the inserted fragment are added to the ones already there.
- A **translocation** occurs if a broken segment is attached to a different, nonhomologous chromosome.
- An **inversion** occurs if a broken segment reattaches to the same chromosome from which it was lost, but in reversed orientation, so that the order of genes is reversed.

To be inherited, chromosomal alterations must occur or be included in cells of the germ line leading to development of eggs or sperm.

Deletions and Duplications. A deletion (see Figure 13.11a) may cause severe problems if the missing segment contains genes that are essential for normal development or cellular functions. For example, one deletion from human chromosome 5 typically leads to severe mental retardation and a malformed larynx. The cries of an affected infant sound more like a meow than a human cry. Hence the name of the disorder, *cri-du-chat* (meaning "cat's cry").

A duplication (see Figure 13.11b) may have effects that vary from harmful to beneficial, depending on the genes and alleles contained in the duplicated region. Although most duplications are likely to be detrimental, some have been important sources of evolutionary change. That is, because there are duplicate genes, one copy can mutate into new forms without seriously affecting the basic functions of the organism. For example, mammals have genes that encode several types of

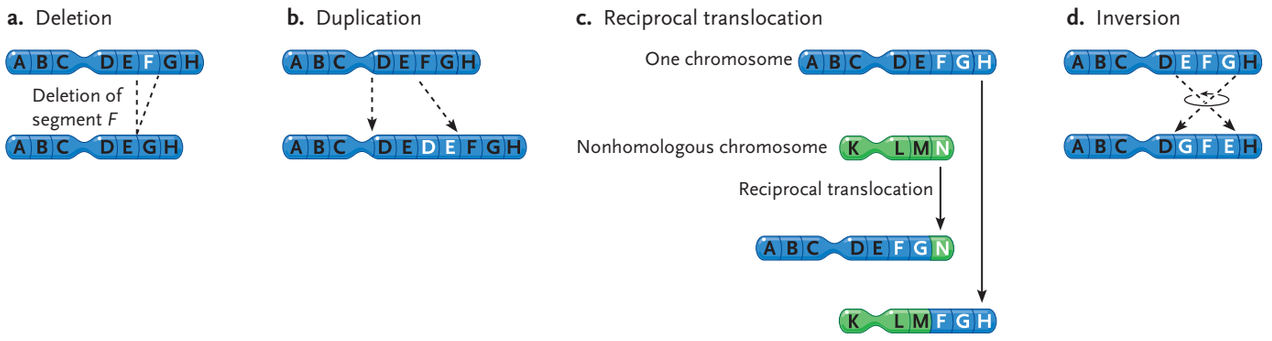


Figure 13.11 Chromosome deletion, duplication, translocation (a reciprocal translocation is shown), and inversion.

hemoglobin that are not present in vertebrates, such as sharks, which evolved earlier; the additional hemoglobin genes of mammals are believed to have appeared through duplications, followed by mutations in the duplicates that created new and beneficial forms of hemoglobin as further evolution took place. Duplications sometimes arise during recombination in meiosis, if crossing-over occurs unequally, so that a segment is deleted from one chromosome of a homologous pair and inserted in the other.

Translocations and Inversions. In a translocation, a segment breaks from one chromosome and attaches to another, nonhomologous chromosome. In many cases, a translocation is reciprocal, meaning that two nonhomologous chromosomes exchange segments (see Figure 13.11c). Reciprocal translocations resemble genetic recombination, except that the two chromosomes involved in the exchange do not contain the same genes.

For example, a particular cancer of the human immune system, Burkitt lymphoma, is caused by a translocation that moves a segment of human chromosome 8 to the end of chromosome 14. The break does not interrupt any genes required for normal cell function. The translocated segment contains genes that control cell division. These genes are precisely regulated at their normal location but are near the control regions of highly active genes in the new location, causing them to be overactive and leading to uncontrolled cell division and the development of a cancer.

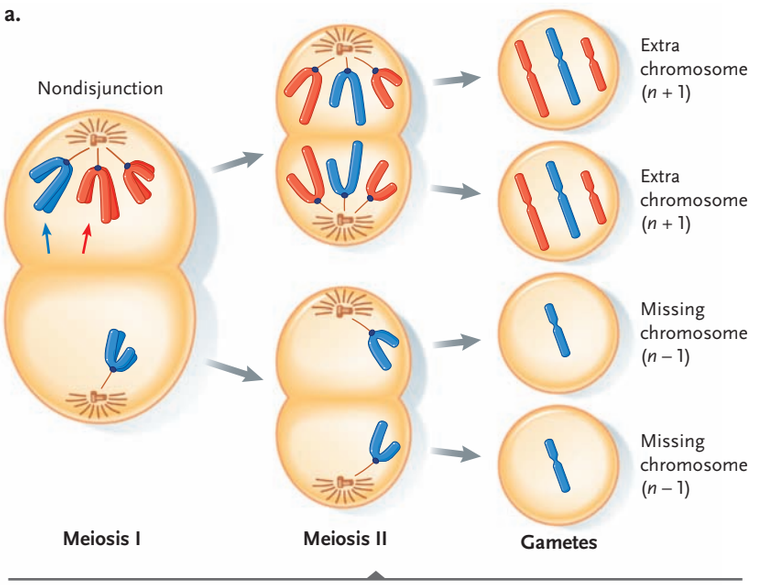
In an inversion, a chromosome segment breaks and then reattaches to the same chromosome, but in reverse order (see Figure 13.11d). Inversions have essentially the same effects as translocations—genes may be broken internally by the inversion, with loss of function, or they may be transferred intact to a new location within the same chromosome, producing effects that range from beneficial to harmful.

Inversions and translocations have been important factors in the evolution of plants and some animals, including insects and primates. For example, five of the chromosome pairs of humans show evidence of translocations and inversions that are not present in one of our nearest primate relatives, gorillas, and therefore must have occurred after the gorilla and human evolutionary lineages split.

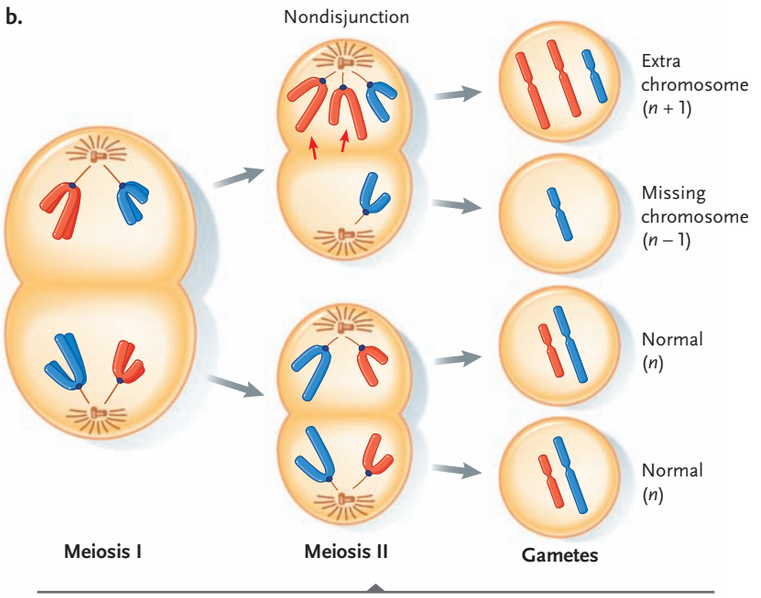
The Number of Entire Chromosomes May Also Change

At times, whole, single chromosomes are lost or gained from cells entering or undergoing meiosis, resulting in a change of chromosome number. Most often, these changes occur through **nondisjunction**—the failure of homologous pairs to separate during the first meiotic division or of chromatids to separate during the second meiotic division **(Figure 13.12).** As a result, gametes are produced that lack one or more chromosomes or contain extra copies of the chromosomes. Fertilization by these gametes produces an individual with extra or missing chromosomes. Such individuals are called **aneuploids**, whereas individuals with a normal set of chromosomes are called **euploids.**

Changes in chromosome number can also occur through duplication of entire sets, meaning individuals may receive one or more extra copies of the entire



Nondisjunction during the first meiotic division causes both chromosomes of one pair to be delivered to the same pole of the spindle. The nondisjunction produces two gametes with an extra chromosome and two with a missing chromosome.



Nondisjunction during the second meiotic division produces two normal gametes, one gamete with an extra chromosome and one gamete with a missing chromosome.

Figure 13.12 Nondisjunction during **(a)** the first meiotic division and **(b)** the second meiotic division.

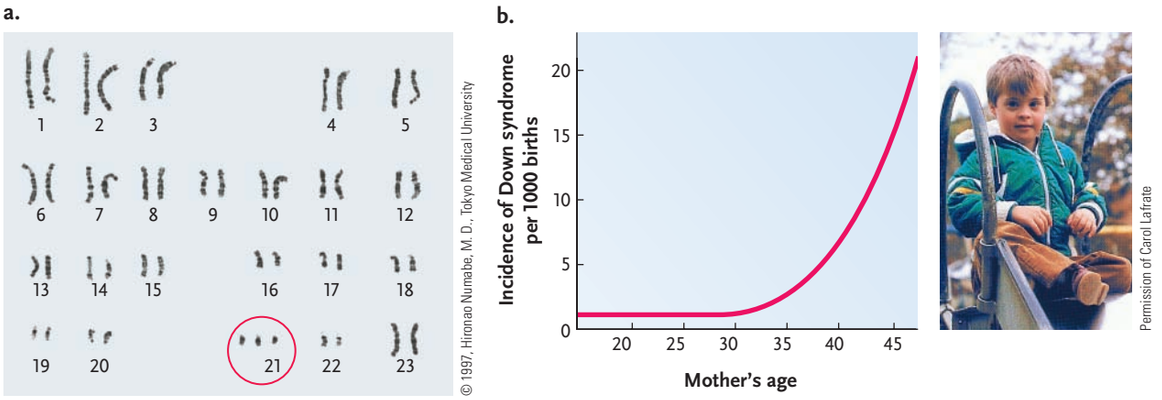


Figure 13.13
Down syndrome. **(a)** The chromosomes of a human female with Down syndrome showing three copies of chromosome 21 (circled in red). **(b)** The increase in the incidence of Down syndrome with increasing age of the mother, from a study conducted in Victoria, Australia, between 1942 and 1957.

haploid complement of chromosomes. Such individuals are called **polyploids.** *Triploids* have three copies of each chromosome instead of two; *tetraploids* have four copies of each chromosome. Multiples higher than tetraploids also occur.

Aneuploids. The effects of addition or loss of whole chromosomes vary depending on the chromosome and the species. In animals, aneuploidy of autosomes usually produces debilitating or lethal developmental abnormalities. These abnormalities also occur in humans; addition or loss of an autosomal chromosome causes embryos to develop so abnormally that they are aborted naturally. For reasons that are not understood, aneuploidy is as much as 10 times more frequent in humans than in other mammals. Of human embryos that have been miscarried and examined, about 70% are aneuploids.

In some cases, autosomal aneuploids survive. This is the case with humans who receive an extra copy of chromosome 21—one of the smallest chromosomes **(Figure 13.13a).** Many of these individuals survive until young adulthood. The condition produced by the extra chromosome, called *Down syndrome* or *trisomy 21,* is characterized by short stature and moderate to severe mental retardation. About 40% of individuals with Down syndrome have heart defects, and skeletal development is slower than normal. Most do not mature sexually and remain sterile. However, with attentive care and special training, individuals with Down syndrome can participate with reasonable success in many activities.

Down syndrome arises from nondisjunction of chromosome 21 during the meiotic divisions, primarily in women (about 5% of nondisjunctions that lead to Down syndrome occur in men). The nondisjunction occurs more frequently as women age, increasing the chance that a child may be born with the syndrome **(Figure 13.13b).** In all, 1 in every 1000 children is born with Down syndrome in the United States, making it one of the most common serious human genetic defects.

Aneuploidy of sex chromosomes can also arise by nondisjunction during meiosis (**Figure 13.14** and **Table 13.1).** Unlike autosomal aneuploidy, which usually has drastic effects on survival, altered numbers of X and Y chromosomes are often tolerated, producing indi-

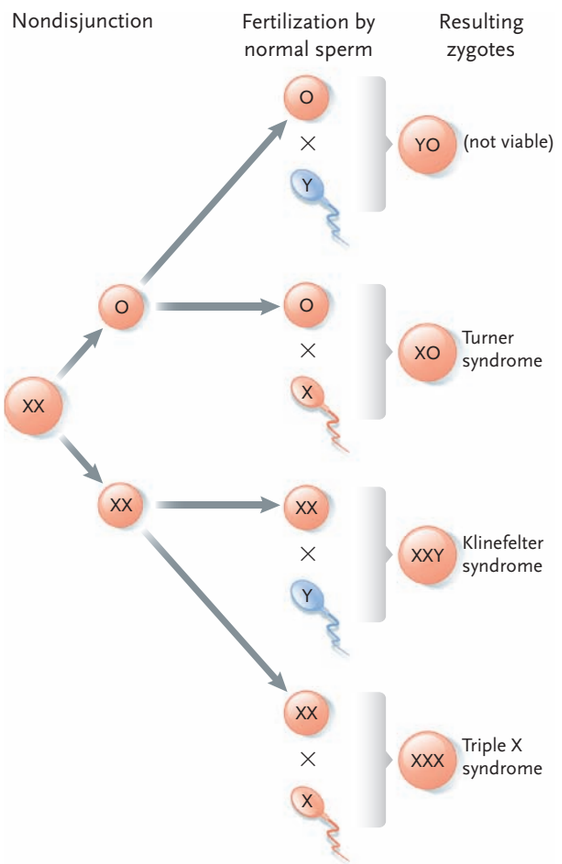


Figure 13.14
Some abnormal combinations of sex chromosomes resulting from nondisjunction of X chromosomes in females.

viduals who progress through embryonic development and grow to adulthood. In the case of multiple X chromosomes, the X-chromosome inactivation mechanism converts all but one of the X chromosomes to a Barr body, so the dosage of active X-chromosome genes is the same as in normal XX females and XY males. However, X chromosomes are not inactivated until about 15 to 16 days after fertilization. Expression of the extra X chromosome genes early in development results in some deterious effects.

Because sexual development in humans is pushed toward male or female reproductive organs primarily by the presence or absence of the Y chromosome, people with a Y chromosome are externally malelike, no matter how many X chromosomes are present. If no Y chromosome is present, X chromosomes in various numbers give rise to femalelike individuals. (Table 13.1 lists the effects of some alterations in sex chromosome number.) Similar abnormal combinations of sex chromosomes also occur in other animals, including *Drosophila,* with varying effects on viability.

Polyploids. Polyploidy often originates from failure of the spindle to function normally during mitosis in cell lines leading to germ-line cells. In these divisions, the spindle fails to separate the duplicated chromosomes, which are incorporated into a single nucleus with twice the usual number of chromosomes. Eventually, meiosis takes place and produces gametes with two copies of each chromosome instead of one. Fusion of one such gamete with a normal haploid gamete produces a triploid, and fusion of two such gametes produces a tetraploid.

The effects of polyploidy vary widely between plants and animals. In plants, polyploids are often hardier and more successful in growth and reproduction than the diploid plants from which they were derived. As a result, polyploidy is common and has been an important source of variability in plant evolution. About half of all flowering plant species are polyploids, including important crop plants such as wheat and other cereals, cotton, strawberries, and bananas.

By contrast, among animals, polyploidy is uncommon because it usually has lethal effects during embryonic development. For example, in humans, all but about 1% of polyploids die before birth, and the few who are born die within a month. The lethality is probably due to disturbance of animal developmental pathways, which are typically much more complex than those of plants.

We now turn to a description of the effects of altered alleles on human health and development.

Study Break

What mechanisms are responsible for (a) duplication of a chromosome segment, (b) generation of a Down syndrome individual, (c) a chromosome translocation, and (d) polyploidy?

Table 13.1 Effects of Unusual Combinations of Sex Chromosomes in Humans

Combination of Sex Chromosomes	Approximate Frequency	Effects
XO	1 in 5000 births	Turner syndrome: females with underdeveloped ovaries; sterile; intelligence and external genitalia are normal; typically, individuals are short in stature with underdeveloped breasts
XXY	1 in 2000 births	Klinefelter syndrome: male external genitalia with very small and underdeveloped testes; sterile; intelligence usually normal; sparse body hair and some development of the breasts; similar characteristics in XXXY and XXXXY individuals
XYY	1in 1000 births	XYY syndrome: apparently normal males but often taller than average
XXX	1 in 1000 births	Triple-X syndrome: apparently normal female with normal or slightly retarded mental function

13.4 Human Genetics and Genetic Counseling

We have already noted a number of human genetic traits and conditions caused by mutant alleles or chromosomal alterations (see **Table 13.2** for a more detailed list). All these traits are of interest as examples of patterns of inheritance that amplify and extend Mendel's basic principles. Those with harmful effects are also important because of their impact on human life and society.

In Autosomal Recessive Inheritance, Heterozygotes Are Carriers and Homozygous Recessives Are Affected by the Trait

Sickle-cell anemia and cystic fibrosis are examples of human traits caused by recessive alleles on autosomes. Many other human genetic traits follow a similar pattern of inheritance (see Table 13.2). These traits are passed on according to the pattern known as **autosomal recessive inheritance**, in which individuals who are homozygous for the dominant allele are free of symptoms and are not carriers; heterozygotes are usually symptom free but are carriers. People who are homozygous for the recessive allele show the trait.

For sickle-cell anemia, between 10% and 15% of African Americans in the United States are carriers—that is, they have sickle-cell trait (see Section 12.2). Although carriers make enough normal hemoglobin through the activity of the dominant allele to be essentially unaffected, the mutant, sickle-cell form of the hemoglobin molecule is also present in their red blood

Table 13.2 Examples of Human Genetic Traits

Trait	Adverse Health Effects
Autosomal Recessive Inheritance	
Albinism	Absence of pigmentation (melanin)
Attached ear lobes	None
Cystic fibrosis	Excess mucus in lungs and digestive cavities
Sickle-cell disease	Severe tissue and organ damage
Galactosemia	Brain, liver, and eye damage
Phenylketonuria	Mental retardation
Tay–Sachs disease	Mental retardation, death
Autosomal Dominant Inheritance	
Free ear lobes	None
Achondroplasia	Defective cartilage formation that causes dwarfism
Early balding in males	None
Campodactyly	Rigid, bent little fingers
Curly hair	None
Huntington disease	Progressive, irreversible degeneration of nervous system
Syndactyly	Webbing between fingers
Polydactyly	Extra digits
Brachydactyly	Short digits
Progeria	Premature aging
X-Linked Inheritance	
Hemophilia A	Deficient blood-clotting
Red–green color blindness	Inability to distinguish red from green
Testicular feminizing syndrome	Absence of male organs, sterility
Changes in Chromosome Structure	
Cri-du-chat	Mental retardation, malformed larynx
Changes in Chromosome Number	
Down syndrome	Mental retardation, heart defects

cells. Carriers can be identified by a simple test for the mutant hemoglobin. In countries where malaria is common, including several countries in Africa, carriers are less susceptible to contraction of the disease, which helps explain the increased proportions of the recessive allele among races that originated in malarial areas.

Cystic fibrosis (CF), one of the most common genetic disorders among persons of Northern European descent, is another autosomal recessive trait **(Figure 13.15).** About 1 in every 25 people from this line of descent is an unaffected carrier with one copy of the recessive allele, and about 1 in 2500 is homozygous for the

Figure 13.15
A child affected by cystic fibrosis. Daily chest thumps, back thumps, and repositioning dislodge thick mucus that collects in airways to the lungs.

recessive allele. The homozygous recessives have an altered membrane transport protein that results in excess Cl^- (chloride ions) to the extracellular fluids. Through pathways that are not completely understood, the alteration in chloride transport causes thick, sticky mucus to collect in airways of the lungs, in the ducts of glands such as the pancreas, and in the digestive tract. The accumulated mucus impairs body functions and, in the lungs, promotes pneumonia and other infections. With current management procedures, the life expectancy for a person with cystic fibrosis is about 40 years.

Another autosomal recessive disease, *phenylketonuria* (PKU), appears in about 1 of every 15,000 births. Affected individuals cannot produce an enzyme that converts the amino acid phenylalanine to another amino acid, tyrosine. As a result, phenylalanine builds up in the blood and is converted in the body into other products, including phenylpyruvate. Elevations in both phenylalanine and phenylpyruvate damage brain tissue and can lead to mental retardation. If diagnosed early enough, an affected infant can be placed on a phenylalanine-restricted diet, which can prevent the PKU symptoms. Most U.S. hospitals routinely test newborn infants to detect the disorder.

In Autosomal Dominant Inheritance, Only Homozygous Recessives Are Unaffected

Some human traits follow a pattern of **autosomal dominant inheritance** (see Table 13.2). In this case, the allele that causes the trait is dominant, and people who

Insights from the Molecular Revolution

Achondroplastic Dwarfing by a Single Amino Acid Change

Researchers recently found that the gene responsible for achondroplastic dwarfing is on chromosome 4. The same chromosome is known to carry a gene encoding a receptor that binds human growth hormone (receptors are proteins in the plasma membrane; when they bind a hormone, they undergo a change in their three-dimensional structure that triggers a response inside the cell). An intriguing question was whether the achondroplastic gene is a mutant form of the gene that encodes the growth hormone receptor. Arnold Munnich and his colleagues at the Hospital of Children's Diseases in Paris, France, performed molecular experiments designed to answer this question.

The receptor binds the *fibroblast growth factor (FGF),* a growth hormone that stimulates a wide range of mammalian cells to grow and divide. The many receptors that bind this hormone form a family called the *fibroblast growth factor receptors (FGFRs).* The gene that encodes the FGFR on chromosome 4 is active in chondrocytes—cells that form cartilage and bone.

Munnich and his colleagues isolated the gene that encodes the FGFR and obtained its DNA sequence. They found two versions of the gene's sequence with a single difference—one version had an adenine-thymine (A-T) base pair and the other had a guanine-cytosine (G-C) base pair at the same position in the DNA sequence. The change substitutes arginine for glycine at one position in the amino acid sequence of the encoded protein. These amino acids have very different chemical properties. The substitution occurs in a segment of the protein that extends across the membrane, connecting a hormone-binding site outside the cell with a site inside the cell that triggers the internal response.

The investigators then looked for the A-T–to–G-C substitution in the mutant form of the gene on chromosome 4 that causes achondroplastic dwarfing. The substitution was present in copies of the gene isolated from 6 families of achondroplastic dwarfs, but absent in 120 people who lack the trait. This result supported the hypothesis that a mutation in the gene that codes for FGFR protein is responsible for achondroplastic dwarfing.

How does the single amino acid substitution cause dwarfing? The cause is not known exactly. The change may inhibit the transmission of the signal triggered by a hormone binding to the receptor on the outer membrane. Evidently, if the signal is not transmitted, the chondrocyte cells fail to respond to the hormone by growing and dividing, interfering with elongation of the limb bones and producing the short arms and legs characteristic of achondroplastic dwarfs.

Identification of the gene responsible for achondroplastic dwarfing opens the future to finding a cure for the condition, possibly through genetic engineering of infants or young children who carry the mutation.

are either homozygous or heterozygous for the dominant allele are affected. Individuals homozygous for the recessive normal allele are unaffected.

Achondroplasia, a type of dwarfing that occurs in about 1 in 10,000 people, is caused by an autosomal dominant allele of a gene on chromosome 4. Of individuals with the dominant allele, only heterozygotes survive embryonic development; homozygous dominants are usually stillborn. When limb bones develop in heterozygous children, cartilage formation is defective, leading to disproportionately short arms and legs. The trunk and head, however, are of normal size. Affected adults are usually not much more than 4 feet tall. Achondroplastic dwarfs are of normal intelligence, are fertile, and can have children. The gene responsible for this trait has been identified (see *Insights from the Molecular Revolution*).

Males Are More Likely to Be Affected by X-Linked Recessive Traits

Red–green color blindness and hemophilia have already been presented as examples of human traits that demonstrate **X-linked recessive inheritance**, that is, traits due to inheritance of recessive alleles carried on the X chromosome. Another X-linked recessive human disease trait is Duchenne muscular dystrophy. In affected individuals, muscle tissue begins to degenerate late in childhood; by the onset of puberty, most individuals with this disease are unable to walk. Muscular weakness progresses, with later involvement of the heart muscle; the average life expectancy for individuals with Duchenne muscular dystrophy is 25 years. (*Insights from the Molecular Revolution* in Chapter 41 discusses molecular research that could lead to a cure for the disease.)

Human Genetic Disorders Can Be Predicted, and Many Can Be Treated

Of all newborns, between 1% and 3% have mutant alleles that encode defective forms of proteins required for normal functions. Possibly 1% have pronounced difficulties due to a chromosomal rearrangement or other aberration. Of all patients in children's hospitals, 10% to 25% are treated for problems arising from inherited disorders. Several approaches, which include genetic counseling, prenatal diagnosis, and genetic screening, can reduce the number of children born with genetic diseases.

Genetic counseling allows prospective parents to assess the possibility that they might have an affected

child. For example, parents may seek counseling if they, a close relative, or one of their existing children has a genetic disorder. Genetic counseling begins with identification of parental genotypes through family pedigrees or direct testing for an altered protein or DNA sequence. With this information in hand, counselors can often predict the chances of having a child with the trait in question. Couples can then make an informed decision about whether to have a child.

Genetic counseling is often combined with techniques of **prenatal diagnosis**, in which cells derived from a developing embryo or its surrounding tissues or fluids are tested for the presence of mutant alleles or chromosomal alterations. In **amniocentesis**, cells are obtained from the amniotic fluid—the watery fluid surrounding the embryo in the mother's uterus. In **chorionic villus sampling**, cells are obtained from portions of the placenta that develop from tissues of the embryo. More than 100 genetic disorders can now be detected by these tests. If prenatal diagnosis detects a serious genetic defect, the prospective parents can reach an informed decision about whether to continue the pregnancy, including religious and moral considerations, as well as genetic and medical advice.

Once a child is born, inherited disorders are identified by **genetic screening**, in which biochemical or molecular tests for disorders are routinely applied to children and adults or to newborn infants in hospitals. The tests can detect inherited disorders early enough to start any available preventive measures before symptoms develop. We have noted that most hospitals in the United States now test all newborns for PKU, making it possible to use dietary restrictions to prevent symptoms of the disorder from developing. As a result, it is becoming less common to see individuals debilitated by PKU.

In addition to the characters and traits described so far in this chapter, some patterns of inheritance depend on genes located not in the cell nucleus, but in mitochondria or chloroplasts in the cytoplasm, as discussed in the following section.

Study Break

1. A man has Simpson syndrome, an addiction to a certain television show. His wife does not have this syndrome. This couple has four children, two boys and two girls. One of the boys and one of the girls has this syndrome; the other children are normal. Can Simpson syndrome be an autosomal recessive trait? A sex-linked recessive trait?
2. In another family, a female child has wiggly ears, whereas her brother does not. Both parents are normal. Can the wiggly ear trait be an autosomal recessive trait? A sex-linked recessive trait?

13.5 Nontraditional Patterns of Inheritance

We consider two examples of nontraditional patterns of inheritance in this section. In **cytoplasmic inheritance**, the pattern of inheritance follows that of genes in the cytoplasmic organelles, mitochondria or chloroplasts. In **genomic imprinting**, the expression of a nuclear gene is based on whether an individual organism inherits the gene from the male or female parent.

Cytoplasmic Inheritance Follows the Pattern of Inheritance of Mitochondria or Chloroplasts

Chapter 5 noted that both chloroplasts and mitochondria contain DNA. Organelle DNA contains genes and alleles that, like nuclear genes, are also subject to being mutated. Mutant genes in some cases result in altered phenotypes, but the inheritance pattern of these mutant genes is fundamentally different from that of mutant genes carried on chromosomes in the nucleus. The two major differences are as follows: (1) ratios typical of Mendelian segregation are not found because genes are not segregating by meiosis, and (2) genes usually show uniparental inheritance from generation to generation. In *uniparental inheritance,* all progeny (both males and females) have the phenotype of only one of the parents. For most multicellular eukaryotes, the mother's phenotype is expressed, a phenomenon called *maternal inheritance*. Maternal inheritance occurs because the amount of cytoplasm in the female gamete usually far exceeds that in the male gamete. Hence, a zygote receives most of its cytoplasm, including mitochondria and (in plants) chloroplasts, from the female parent and little from the male parent.

The first example of cytoplasmic inheritance of a mutant trait was found in 1909 by the German scientist Carl Correns, one of the geneticists who rediscovered Mendel's principles. Correns made his discovery through his genetic studies of a plant, *Mirabilis* (the four-o'clock), using mutant plants that had a variegated pattern of green and white **(Figure 13.16).** In the white segments, chloroplasts are colorless instead of green. Correns fertilized flowers in a green region of the plant with pollen from a white region and vice versa. He discovered that the phenotype of the progeny seedlings showed maternal inheritance. That is, it was always that of the female segment the pollen fertilized: white for the white ♀ × green ♂ cross, and green for the green ♀ × white ♂ cross.

Many examples of maternal inheritance of mutant traits involving the chloroplast are now known. In each case, the trait results from a mutation of one of the genes in the chloroplast genome. Mutant traits that show maternal inheritance have also been character-

Figure 13.16
A four-o'clock *(Mirabilis)* plant with a variegated (patchy) distribution of green and white segments.

ized in many eukaryotic species, including in plants, animals, protists, and fungi. Similar to the mutant traits of chloroplasts, each mutant trait results from an alteration of a gene in the mitochondrial genome.

In humans, several inherited diseases have been traced to mutations in mitochondrial genes **(Table 13.3).** Recall that the mitochondrion plays a critical role in synthesizing ATP, the energy source for many cellular reactions. The mutations producing the diseases in Table 13.3 are in mitochondrial genes that encode components of the ATP-generating system of the organelle. The resulting mitochondrial defects are especially destructive to the organ systems most dependent on mitochondrial reactions for energy: the central nervous system, skeletal and cardiac muscle, the liver, and the kidneys. These inherited diseases show maternal inheritance.

In Genomic Imprinting, the Allele Inherited from One of the Parents Is Expressed While the Other Allele Is Silent

Genomic imprinting is a phenomenon in which the expression of an allele of a gene is determined by the parent that contributed it. In some cases, the paternally derived allele is expressed; in others, the maternally derived allele is expressed. The silent allele—that which is not expressed—is called the *imprinted allele*. The imprinted allele is not inactivated by mutation. Rather, it is silenced by chemical modification (methylation) of certain bases in its sequence.

As an example, Prader-Willi syndrome (PWS) and Angelman syndrome (AS) in humans are each caused by genomic imprinting of a particular gene on a chromosome inherited from one parent, coincident with deletion of the same gene on the homologous chromosome inherited from the other parent. The syndromes differ with respect to the gene imprinted. Both PWS and AS occur in about 1 in 15,000 births and are characterized by serious developmental, mental, and behavioral problems. PWS individuals are compulsive overeaters (leading to obesity), have short stature, have small hands and feet, and show mild to moderate mental retardation. AS individuals are hyperactive, are unable to speak, have seizures, show severe mental retardation, and display a happy disposition with bursts of laughter.

How is genomic imprinting responsible for these two syndromes? PWS is caused when an individual has a normal maternally derived chromosome 15 and a paternally derived chromosome 15 with a deletion of a small region of several genes that includes the PWS gene. The PWS gene is imprinted, and therefore silenced, on maternally derived chromosomes. As a result, when there is no PWS gene on the paternally derived chromosome, there is no PWS gene activity and PWS results. Similarly, AS is caused when an individual has a normal paternally derived chromosome 15 and a maternally derived chromosome 15 with a deletion of the same region; that region also includes the AS gene, the normal function of which is also required for normal development. In this case, genomic imprinting silences the AS gene on the paternally derived chromosome, and because there is no AS gene on the maternally derived chromosome, there is no AS gene activity and AS syndrome develops.

The mechanism of imprinting involves the modification of the DNA in the region that controls the expression of a gene by the addition of methyl (—CH_3) groups to cytosine nucleotides. The methylation of the control region of a gene prevents it from being expressed. (Note that there are a few instances of methylation-activating genes.) The regulation of gene expression by methylation of DNA is discussed further in Chapter 16. Genomic imprinting occurs in the

Table 13.3 **Some Human Diseases Caused by Mutations in Mitochondrial Genes**

Disease	Symptoms
Kearns–Sayre syndrome	May include muscle weakness, mental deficiencies, abnormal heartbeat, short stature
Leber hereditary optic neuropathy	Vision loss from degeneration of the optic nerve, abnormal heartbeat
Mitochondrial myopathy and encephalomyopathy	May include seizures, strokelike episodes, hearing loss, progressive dementia, abnormal heartbeat, short stature
Myoclonic epilepsy	Vision and hearing loss, uncoordinated movement, jerking of limbs, progressive dementia, heart defects

gametes where the allele destined to be inactive in the new embryo after fertilization—either the father's or the mother's depending on the gene—is methylated. That methylated (silenced) state of the gene is passed on as the cells grow and divide to produce the somatic (body) cells of the organism.

A number of cancers are associated with the failure to imprint genes. For instance, the mammalian *Igf2* (insulin growth factor 2) gene encodes a growth factor, a molecule that stimulates cells to grow and divide. *Igf2* is an imprinted gene, with the paternally derived allele on and the maternally derived allele off. In some cases, the imprinting mechanism for this gene does not work, resulting in both alleles of *Igf2* being active, a phenomenon known as **loss of imprinting.** The resulting double dose of the growth factor disrupts the cell division cycle, contributing to uncontrolled growth and cancer.

In this chapter, you have learned about genes and the role of chromosomes in inheritance. In the next chapter, you will learn about the molecular structure and function of the genetic material and about the molecular mechanism by which DNA is replicated.

Study Break

What key feature or features would suggest to you that a mutant trait shows cytoplasmic inheritance?

Unanswered Questions

Does recombination protect against cancer?

In this chapter, we learned that genetic recombination during meiosis in germ-line cells is a mechanism for the exchange of genetic information between chromosomes. Researchers have discovered that genetic recombination also occurs in somatic cells and is a vital mechanism for the repair of damaged or broken chromosomes. If recombination is defective, unrepaired chromosome breaks or gene translocations can have serious consequences to the cell and even lead to cancer. For instance, the *BRCA1* and *BRCA2* genes, which predispose patients to breast cancer, have recombination and repair defects that lead to genome instability. Researchers are using tissue culture cells derived from patients with these genes to find out exactly what goes wrong when recombination is inadequate and how recombination may act to maintain genome stability and provide protection against cancer and other diseases.

How did the *SRY* gene on the Y chromosome evolve?

The key gene on the Y chromosome, which determines the sex of a mammal, is the *SRY* gene. How did this gene evolve? Research is turning up information that it probably evolved from a brain-determining gene on the X chromosome. How did that occur? What other genes are involved in the sex-determining pathway, and how do they interact to coordinate the important developmental events in sex determination? And what genes on the Y chromosome affect male fertility? Researchers are attempting to answer these questions.

How are X chromosomes counted in the mammalian X-chromosome inactivation system?

There is a difference in the number of X chromosomes in female and male mammals. The extra dosage of genes in females is compensated for by the X-chromosome inactivation mechanism (see earlier discussion). Remarkably, this mechanism operates no matter how many X chromosomes are present. That is, in an XXXY cell, all but one of the X chromosomes will be inactivated. How does the cell count the number of X chromosomes? Some information about this exists, but the full molecular details need to be unraveled. Jeannie Lee, a Howard Hughes Medical Institute (HHMI) investigator at Harvard Medical School, is conducting research toward this end.

Peter J. Russell

Review

Go to ThomsonNOW™ at www.thomsonedu.com/login to access quizzing, animations, exercises, articles, and personalized homework help.

13.1 Genetic Linkage and Recombination

- Genes, consisting of sequences of nucleotides in DNA, are arranged linearly in chromosomes.
- Genes carried on the same chromosome are linked together in their transmission from parent to offspring. Linked genes are inherited in patterns similar to those of single genes, except for changes in the linkage due to recombination (Figure 13.2).
- In recombination, alleles linked on the same chromosome are mixed into new combinations by exchange of segments between the chromosomes of a homologous pair. The exchanges occur while homologous chromosomes during prophase I of meiosis.
- The amount of recombination between any two genes located on the same chromosome pair reflects the distance between them on the chromosome. The greater this distance, the greater the chance that chromatids will exchange segments at points between the genes and the greater the recombination frequency.
- The relationship between separation and recombination frequencies is used to produce chromosome maps in which genes are assigned relative locations with respect to each other (Figure 13.4).

13.2 Sex-Linked Genes

- Sex linkage is a pattern of inheritance produced by genes carried on sex chromosomes: chromosomes that differ in males and females. In humans and fruit flies, which have XX females and XY males, most sex-linked genes are carried on the X chromosome.
- Since males have only one X chromosome, they need to receive only one copy of a recessive allele from their mothers to develop the trait. Females must receive two copies of the recessive allele, one from each parent, to develop the trait (Figures 13.6–13.8).
- In mammals, inactivation of one of the two X chromosomes in cells of the female makes the dosage of X-linked genes the same in males and females (Figure 13.10).

Animation: Human sex determination

Animation: Morgan's reciprocal crosses

13.3 Chromosomal Alterations That Affect Inheritance

- Inheritance is influenced by processes that delete, duplicate, or invert segments within chromosomes, or translocate segments between chromosomes (Figure 13.11).
- Chromosomes also change in number by addition or removal of individual chromosomes or entire sets. Changes in single chromosomes usually occur through nondisjunction, in which homologous pairs fail to separate during meiosis I, or sister chromatids fail to separate during meiosis II. As a result, one set of gametes receives an extra copy of a chromosome and the other set is deprived of the chromosome.
- Polyploids have one or more extra copies of the entire chromosome set. Polyploids usually arise when the spindle fails to function during mitosis in cell lines leading to gamete formation, producing gametes that contain double the number of chromosomes typical for the species (Figures 13.12–13.14).

Animation: Karyotype preparation

Animation: Duplication

Animation: Deletion

Animation: Inversion

Animation: Translocation

13.4 Human Genetics and Genetic Counseling

- Three modes of inheritance are most significant in human heredity: autosomal recessive, autosomal dominant, and X-linked recessive inheritance.
- In autosomal recessive inheritance, males or females carry a recessive allele on an autosome. Heterozygotes are carriers that are usually unaffected, but homozygous individuals show symptoms of the trait.
- In autosomal dominant inheritance, a dominant gene is carried on an autosome. Individuals that are homozygous or heterozygous for the trait show symptoms of the trait; homozygous recessives are normal.
- In X-linked recessive inheritance, a recessive allele for the trait is carried on the X chromosome. Male individuals with the recessive allele on their X chromosome or female individuals with the recessive allele on both X chromosomes show symptoms of the trait. Heterozygous females are carriers but usually show no symptoms of the trait.
- Genetic counseling, based on identification of parental genotypes by constructing family pedigrees and prenatal diagnosis, allow prospective parents to reach an informed decision about whether to have a child or continue a pregnancy.

Animation: Autosomal dominant inheritance

Animation: Autosomal recessive inheritance

Animation: X-linked inheritance

Animation: Pedigree diagrams

Animation: Amniocentesis

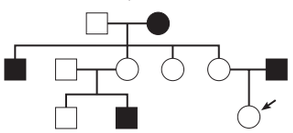
13.5 Nontraditional Patterns of Inheritance

- Cytoplasmic inheritance depends on genes carried on DNA in mitochondria or chloroplasts. Cytoplasmic inheritance follows the maternal line: it parallels the inheritance of the cytoplasm in fertilization, in which most or all of the cytoplasm of the zygote originates from the egg cell (Figure 13.16).
- Genomic imprinting is a phenomenon in which the expression of an allele of a gene is determined by the parent that contributed it. In some cases, the allele inherited from the father is expressed; in others, the allele from the mother is expressed. Commonly, the silencing of the other allele is the result of methylation of the region adjacent to the gene that is responsible for controlling the expression of that gene.

Questions

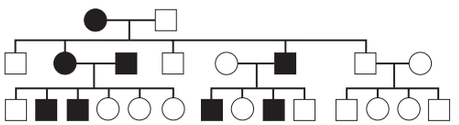
Problems

1. In humans, red–green color blindness is an X-linked recessive trait. If a man with normal vision and a color-blind woman have a son, what is the chance that the son will be color-blind? What is the chance that a daughter will be color-blind?
2. The following pedigree shows the pattern of inheritance of red–green color blindness in a family. Females are shown as circles and males as squares; the squares or circles of individuals affected by the trait are filled in black.



What is the chance that a son of the third-generation female indicated by the arrow will be color-blind if the father is a normal man? If the father is color-blind?

3. Individuals affected by a condition known as polydactyly have extra fingers or toes. The following pedigree shows the pattern of inheritance of this trait in one family:



From the pedigree, can you tell if polydactyly comes from a dominant or recessive allele? Is the trait sex-linked? As far as you can determine, what is the genotype of each person in the pedigree with respect to the trait?

4. A number of genes carried on the same chromosome are tested and show the following crossover frequencies. What is their sequence in the map of the chromosome?

Genes	Crossover Frequencies between Them
C and *A*	7%
B and *D*	3%
B and *A*	4%
C and *D*	6%
C and *B*	3%

5. In *Drosophila*, two genes, one for body color and one for eye color, are carried on the same chromosome. The wild-type gray body color is dominant to black body color, and wild-type red eyes are dominant to purple eyes. You make a cross between a fly with gray body and red eyes and a fly with black body and purple eyes. Among the offspring, about half have gray bodies and red eyes and half have black bodies and purple eyes. A small percentage have (a) black bodies and red eyes or (b) gray bodies and purple eyes. What alleles are carried together on the chromosomes in each of the flies used in the cross? What alleles are carried together on the chromosomes of the F_1 flies with black bodies and red eyes, and those with gray bodies and purple eyes?

6. Another gene in *Drosophila* determines wing length. The dominant wild-type allele of this gene produces long wings; a recessive allele produces vestigial (short) wings. A female that is true-breeding for red eyes and long wings is mated with a male that has purple eyes and vestigial wings. F_1 females are then crossed with purple-eyed, vestigial-winged males. From this second cross, a total of 600 offspring are obtained with the following combinations of traits:

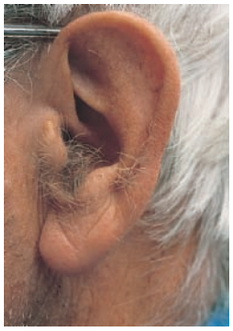
   252 with red eyes and long wings
   276 with purple eyes and vestigial wings
   42 with red eyes and vestigial wings
   30 with purple eyes and long wings

   Are the genes linked, unlinked, or sex-linked? If they are linked, how many map units separate them on the chromosome?

Carolina Biological/Visuals Unlimited

Drosophila with vestigial wings

7. One human gene, which is suspected to be carried on the Y chromosome, controls the length of hair on men's ears. One allele produces nonhairy ears, and another produces hairy ears. If a man with hairy ears has sons, what percentage will also have hairy ears? What percentage of his daughters will have hairy ears?



Bonnie Kamin/Stuart Kenter Associates

Male with hairy ears

8. You conduct a cross in *Drosophila* that produces only half as many male as female offspring. What might you suspect as a cause?

Questions for Discussion

1. Can a linkage map be made for a haploid organism that reproduces sexually?
2. Crossing-over does not occur between any pair of homologous chromosomes during meiosis in male *Drosophila*. From what you have learned about meiosis and crossing-over, propose one hypothesis for why this might be the case.
3. Even though X inactivation occurs in XXY (Klinefelter syndrome) humans, they do not have the same phenotype as normal XY males. Similarly, even though X inactivation occurs in XX individuals, they do not have the same phenotype as XO (Turner syndrome) humans. Why might this be the case?
4. All mammals have evolved from a common ancestor. However, the chromosome number varies among mammals. By what mechanism might this have occurred?

Experimental Analysis

Assume that genes *a*, *b*, *c*, *d*, *e*, and *f* are linked. Explain how you would construct a linkage map that shows the order of these six genes and the map units between them.

Evolution Link

How would the effects of natural selection differ on alleles that cause diseases fatal in childhood (such as progeria) and those that cause diseases that shorten life expectancy to 40 or 50 years (such as cystic fibrosis)?

How Would You Vote?

Advances in genetics have led to our ability to detect mutant genes that cause medical disorders in human embryos and fetuses. Should society encourage women to give birth only if their child will not develop severe medical problems? How severe? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.