Lou Gehrig was the finest first baseman ever to play major league baseball. A left-handed power hitter who grew up in New York City, Gehrig played for the New York Yankees from 1923 to 1939. Throughout his career, he lived in the shadow of his teammates Babe Ruth and Joe DiMaggio, but Gehrig was a great hitter in his own right: he compiled a lifetime batting average of .340 and drove in more than 100 runs every season for 13 years. Gehrig’s greatest baseball record, which stood for more than 50 years and has been broken only once by Cal Ripkin, Jr., in 1995, is his record of playing 2130 consecutive games.

In the 1938 baseball season, Gehrig fell into a strange slump. For the first time since his rookie year, his batting average dropped below .300 and, in the World Series that year, he managed only four hits—all singles. Nevertheless, he finished the season convinced that he was undergoing a temporary slump that he would overcome in the next season. He returned to training camp in 1939 with high spirits. When the season began, however, it was clear to everyone that something was terribly wrong. Gehrig had no power in his swing; he was awkward and clumsy at first base. His condition worsened and, on May 2, he voluntarily removed himself from the lineup. The Yankees sent Gehrig to the Mayo Clinic for diagnosis and, on June 20, his medical report was made public: Lou Gehrig was suffering from a rare, progressive disease known as amyotrophic lateral sclerosis (ALS). Within two years, he was dead. Since then, ALS has commonly been known as Lou Gehrig disease.

Gehrig experienced symptoms typical of ALS: progressive weakness and wasting of skeletal muscles due to...
degeneration of the motor neurons. Most cases of ALS are sporadic, appearing in people with no family history of the disease. However, about 10% of cases run in families, and in these cases the disease is inherited as an autosomal dominant trait. In 1993, geneticists discovered that some familial cases of ALS are caused by a defect in a gene that encodes an enzyme called superoxide dismutase 1 (SOD1). This enzyme helps the cell to break down superoxide free radicals, which are highly reactive and extremely toxic. In families studied by the researchers, people with ALS had a defective allele for SOD1 (Figure 6.1) that produced an altered form of the enzyme. How the altered enzyme causes the symptoms of the disease has not been firmly established.

Amyotrophic lateral sclerosis is just one of a large number of human diseases that are currently the focus of intensive genetic research. This chapter will discuss human genetic characteristics and some of the techniques used to study human inheritance. A number of human characteristics have already been mentioned in discussions of general hereditary principles (Chapters 3 through 5), so by now you know that they follow the same rules of inheritance as those of characteristics in other organisms. So why do we have a separate chapter on human heredity? The answer is that the study of human inheritance requires special techniques—primarily because human biology and culture impose certain constraints on the geneticist. In this chapter, we'll consider these constraints and examine three important techniques that human geneticists use to overcome them: pedigrees, twin studies, and adoption studies. At the end of the chapter, we will see how the information garnered with these techniques can be used in genetic counseling and prenatal diagnosis.

Keep in mind as you go through this chapter that many important characteristics are influenced by both genes and environment, and separating these factors is always difficult in humans. Studies of twins and adopted persons are designed to distinguish the effects of genes and environment, but such studies are based on assumptions that may be difficult to meet for some human characteristics, particularly behavioral ones. Therefore, it's always prudent to interpret the results of such studies with caution.

Information on amyotrophic lateral sclerosis, and more about Lou Gehrig, his outstanding career in baseball, and his fight with amyotrophic lateral sclerosis

The Study of Human Genetic Characteristics

Humans are the best and the worst of all organisms for genetic study. On the one hand, we know more about human anatomy, physiology, and biochemistry than we know about most other organisms; for many families, we have detailed records extending back many generations; and the medical implications of genetic knowledge of humans provide tremendous incentive for genetic studies. On the other hand, the study of human genetic characteristics presents some major obstacles.

First, controlled matings are not possible. With other organisms, geneticists carry out specific crosses to test their hypotheses about inheritance. We have seen, for example, how the testcross provides a convenient way to determine if an individual with a dominant trait is homozygous or heterozygous. Unfortunately (for the geneticist at least), matings between humans are more frequently determined by romance, family expectations, and—occasionally—accident than they are by the requirements of the geneticist.

Another obstacle is that humans have a long generation time. Human reproductive age is not normally reached until 10 to 14 years after birth, and most humans do not reproduce until they are 18 years of age or older; thus, generation time in humans is usually about 20 years. This long generation time means that, even if geneticists could control human crosses, they would have to wait on average 40 years just to observe the F2 progeny. In contrast, generation time in Drosophila is 2 weeks; in bacteria, it's a mere 20 minutes.

Finally, human family size is generally small. Observation of even the simple genetic ratios that we learned in
Chapter 3 would require a substantial number of progeny in each family. When parents produce only 2 children, it's impossible to detect a 3:1 ratio. Even an extremely large family with 10 to 15 children would not permit the recognition of a dihybrid 9:3:3:1 ratio.

Although these special constraints make genetic studies of humans more complex, understanding human heredity is tremendously important. So geneticists have been forced to develop techniques that are uniquely suited to human biology and culture.

**Concepts**

Although the principles of heredity are the same in humans and other organisms, the study of human inheritance is constrained by the inability to control genetic crosses, the long generation time, and the small number of offspring.

---

### Analyzing Pedigrees

An important technique used by geneticists to study human inheritance is the pedigree. A *pedigree* is a pictorial representation of a family history, essentially a family tree that outlines the inheritance of one or more characteristics. The symbols commonly used in pedigrees are summarized in [FIGURE 6.2](#). The pedigree shown in [FIGURE 6.3a](#) illustrates a family with Waardenburg syndrome, an autosomal dominant type of deafness that may be accompanied by fair skin, a white forelock, and visual problems ([FIGURE 6.3b](#)). Males in a pedigree are represented by squares, females by circles. A horizontal line drawn between two symbols representing a man and a woman indicates a mating; children are connected to their parents by vertical lines extending below the parents. Persons who exhibit the trait of interest are represented by filled circles and squares; in the pedigree of Figure 6.3a, the filled symbols represent members of the family who have Waardenburg syndrome. Unaffected persons are represented by open circles and squares.

Let's look closely at Figure 6.3 and consider some additional features of a pedigree. Each generation in a pedigree is identified by a Roman numeral; within each generation, family members are assigned Arabic numerals, and children in each family are listed in birth order from left to right. Person II-4, a man with Waardenburg syndrome, mated with II-5, an unaffected woman, and they produced five children. The oldest of their children is III-8, a male with Waardenburg syndrome, and the youngest is III-14, an unaffected female. Deceased family members are indicated by a slash through the circle or square, as shown for I-1 and II-1 in Figure 6.3a. Twins are represented by diagonal lines.

---

6.2 *Standard symbols are used in pedigrees.*
extending from a common point (IV-14 and IV-15; non-identical twins).

When a particular characteristic or disease is observed in a person, a geneticist studies the family of this affected person and draws a pedigree. The person from whom the pedigree is initiated is called the **proband** and is usually designated by an arrow (IV-1 in Figure 6.3a).

The limited number of offspring in most human families means that it is usually impossible to discern clear Mendelian ratios in a single pedigree. Pedigree analysis requires a certain amount of genetic sleuthing, based on recognizing patterns associated with different modes of inheritance. For example, autosomal dominant traits should appear with equal frequency in both sexes and should not skip generations, provided that the trait is fully penetrant (see p. 000 in Chapter 3) and not sex influenced (see p. 000 in Chapter 5).

Certain patterns may exclude the possibility of a particular mode of inheritance. For instance, a son inherits his X chromosome from his mother. If we observe that a trait is passed from father to son, we can exclude the possibility of X-linked inheritance. In the following sections, the traits discussed are assumed to be fully penetrant and rare.

**Autosomal Recessive Traits**

Autosomal recessive traits normally appear with equal frequency in both sexes (unless penetrance differs in males and females), and appear only when a person inherits two alleles for the trait, one from each parent. If the trait is uncommon, most parents carrying the allele are heterozygous and unaffected; consequently, the trait appears to skip generations (Figure 6.4). Frequently, a recessive allele may be passed for a number of generations without the trait appearing in a pedigree. Whenever both parents are heterozygous, approximately 1/4 of the offspring are expected to express the trait, but this ratio will not be obvious unless the family is large. In the rare event that both parents are affected by an autosomal recessive trait, all the offspring will be affected.

---

**Figure 6.3** Waardenburg syndrome is an autosomal dominant disease characterized by deafness, fair skin, visual problems, and a white forelock. (Photograph courtesy of Guy Rowland.)

---

**Figure 6.4** Autosomal recessive traits normally appear with equal frequency in both sexes and seem to skip generations.
When a recessive trait is rare, persons from outside the family are usually homozygous for the normal allele. Thus, when an affected person mates with someone outside the family (aa × AA), usually none of the children will display the trait, although all will be carriers (i.e., heterozygous). A recessive trait is more likely to appear in a pedigree when two people within the same family mate, because there is a greater chance of both parents carrying the same recessive allele. Mating between closely related people is called consanguinity. In the pedigree shown in Figure 6.4, persons III-3 and III-4 are first cousins, and both are heterozygous for the recessive allele; when they mate, 1/4 of their children are expected to have the recessive trait.

A number of human metabolic diseases are inherited as autosomal recessive traits. One of them is Tay-Sachs disease. Children with Tay-Sachs disease appear healthy at birth but become listless and weak at about 6 months of age. Gradually, their physical and neurological conditions worsen, leading to blindness, deafness, and eventually death at 2 to 3 years of age. The disease results from the accumulation of a lipid called \( G_{M2} \) ganglioside in the brain. A normal component of brain cells, \( G_{M2} \) ganglioside is usually broken down by an enzyme called hexosaminidase A, but children with Tay-Sachs disease lack this enzyme. Excessive \( G_{M2} \) ganglioside accumulates in the brain, causing swelling and, ultimately, neurological symptoms. Heterozygotes have only one normal copy of the hexosaminidase A allele and produce only about half the normal amount of the enzyme, but this amount is enough to ensure that \( G_{M2} \) ganglioside is broken down normally, and heterozygotes are usually healthy.

**Autosomal Dominant Traits**

Autosomal dominant traits appear in both sexes with equal frequency, and both sexes are capable of transmitting these traits to their offspring. Every person with a dominant trait must inherit the allele from at least one parent; autosomal dominant traits therefore do not skip generations (Figure 6.5). Exceptions to this rule arise when people acquire the trait as a result of a new mutation or when the trait has reduced penetrance.

If an autosomal dominant allele is rare, most people displaying the trait are heterozygous. When one parent is affected and heterozygous and the other parent is unaffected, approximately 1/2 of the offspring will be affected. If both parents have the trait and are heterozygous, approximately 3/4 of the children will be affected. Provided the trait is fully penetrant, unaffected people do not transmit the trait to their descendants. In Figure 6.5, we see that none of the descendants of II-4 (who is unaffected) have the trait.
in cholesterol transport. Cholesterol is an essential component of cell membranes and is used in the synthesis of bile salts and several hormones. Most of our cholesterol is obtained through foods, primarily those high in saturated fats. Because cholesterol is a lipid (a nonpolar, or uncharged, compound), it is not readily soluble in the blood (a polar, or charged, solution). Cholesterol must therefore be transported throughout the body in small soluble particles called lipoproteins (Figure 6.6); a lipoprotein consists of a core of lipid surrounded by a shell of charged phospholipids and proteins that dissolve easily in blood. One of the principle lipoproteins in the transport of cholesterol is low-density lipoprotein (LDL). When an LDL molecule reaches a cell, it attaches to an LDL receptor, which then moves the LDL through the cell membrane into the cytoplasm, where it is broken down and its cholesterol is released for use by the cell.

Familial hypercholesterolemia is due to a defect in the gene (located on human chromosome 19) that normally codes for the LDL receptor. The disease is usually considered an autosomal dominant disorder because heterozygotes are deficient in LDL receptors. In these people, too little cholesterol is removed from the blood, leading to elevated blood levels of cholesterol and increased risk of coronary artery disease. Persons heterozygous for familial hypercholesterolemia have blood LDL levels that are twice normal and usually have heart attacks by the age of 35. About 1 in 500 people is heterozygous for familial hypercholesterolemia and is predisposed to early coronary artery disease.

Very rarely, a person inherits two defective LDL receptor alleles. Such persons don’t make any functional LDL receptors; their blood cholesterol levels are more than six times normal and they may suffer a heart attack as early as age 2 and almost inevitably by age 20. Because homozygotes are more severely affected than heterozygotes, familial hypercholesterolemia is said to be incompletely dominant. However, homozygotes are rarely seen (occurring with a frequency of only about 1 in 1 million people), and the
common heterozygous form of the disease appears as a simple dominant trait in most pedigrees.

**X-Linked Recessive Traits**

X-linked recessive traits have a distinctive pattern of inheritance (Figure 6.7). First, these traits appear more frequently in males, because males need inherit only a single copy of the allele to display the trait, whereas females must inherit two copies of the allele, one from each parent, to be affected. Second, because a male inherits his X chromosome from his mother, affected males are usually born to unaffected mothers who carry an allele for the trait. Because the trait is passed from unaffected female to affected male to unaffected female, it tends to skip generations (see Figure 6.7). When a woman is heterozygous, approximately 1/2 of her sons will be affected and 1/2 of her daughters will be unaffected carriers. For example, we know that females I-2, II-2, and III-7 in Figure 6.7 are all carriers because they transmit the trait to approximately half of their sons.

A third important characteristic of X-linked recessive traits is that they are not passed from father to son, because a son inherits his father’s Y chromosome, not his X. In Figure 6.7, there is no case of a father and son who are both affected. All daughters of an affected man, however, will be carriers (if their mother is homozygous for the normal allele). When a woman displays an X-linked trait, she must be homozygous for the trait, and all of her sons will also display the trait.

**Concepts**

Rare X-linked recessive traits appear more often in males than in females and are not passed from father to son. Affected sons are usually born to unaffected mothers; thus X-linked recessive traits tend to skip generations.

An example of an X-linked recessive trait in humans is hemophilia A, also called classical hemophilia (Figure 6.8). This disease results from the absence of a protein necessary for blood to clot. The complex process of blood clotting consists of a cascade of reactions that includes more than 13 different factors. For this reason, there are several types of clotting disorders, each due to a glitch in a different step of the clotting pathway.

Hemophilia A results from abnormal or missing factor VIII, one of the proteins in the clotting cascade. The gene for factor VIII is located on the tip of the long arm of the X chromosome; so hemophilia A is an X-linked recessive disorder. People with hemophilia A bleed excessively; even small cuts and bruises can be life threatening. Spontaneous bleeding occurs in joints such as elbows, knees, and ankles, which produces pain, swelling, and erosion of the bone. Fortunately, bleeding in people with hemophilia A can be now controlled by administering concentrated doses of factor VIII.

**X-Linked Dominant Traits**

X-linked dominant traits appear in males and females, although they often affect more females than males. As with X-linked recessive traits, a male inherits an X-linked dominant trait only from his mother—the trait is not passed from father to son. A female, on the other hand, inherits an X chromosome from both her mother and father; so females can receive an X-linked trait from either parent. Each child with an X-linked dominant trait must have an affected parent (unless the child possesses a new mutation or the trait has reduced penetrance). X-linked dominant traits do not skip generations (Figure 6.9); affected men pass the trait on to all their daughters and none of their sons, as is seen in the children of I-1 in Figure 6.9. In contrast, affected women (if heterozygous) pass the trait on to 1/2 of their sons and 1/2 of their daughters, as seen in the children of II-5 in the pedigree.

**Concepts**

X-linked dominant traits affect both males and females. Affected males must have affected mothers (unless they possess a new mutation), and they pass the trait on to all their daughters.

An example of an X-linked dominant trait in humans is hypophosphatemia, also called familial vitamin D-resistant rickets. People with this trait have features that superficially resemble those produced by rickets: bone deformi-
ties, stiff spines and joints, bowed legs, and mild growth deficiencies. This disorder, however, is resistant to treatment with vitamin D, which normally cures rickets. X-linked hypophosphatemia results from the defective transport of phosphate, especially in cells of the kidneys. People with this disorder excrete large amounts of phosphate in their urine, resulting in low levels of phosphate in the blood and reduced deposition of minerals in the bone. As is common with X-linked dominant traits, males with hypophosphatemia are often more severely affected than females.

Y-Linked Traits

Y-linked traits exhibit a specific, easily recognized pattern of inheritance. Only males are affected, and the trait is passed from father to son. If a man is affected, all his male offspring should also be affected, as is the case for I-1, II-4, II-6, III-6, and III-10 of the pedigree in Figure 6.10. Y-linked traits do not skip generations. As discussed in Chapter 4, comparatively few genes reside on the human Y chromosome, and so few human traits are Y linked.

6.8 Classic hemophilia is inherited as an X-linked recessive trait. This pedigree is of hemophilia in the royal families of Europe.

6.9 X-linked dominant traits affect both males and females. An affected male must have an affected mother.
TheOnlineMendelianInheritanceinMan,a comprehensive database of human genes and genetic disorders

**6.10** Y-linked traits appear only in males and are passed from a father to all his sons.

**Concepts**

Y-linked traits appear only in males and are passed from a father to all his sons.

The major characteristics of autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, and Y-linked traits are summarized in Table 6.1.

**Table 6.1** Pedigree characteristics of autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, and Y-linked traits

<table>
<thead>
<tr>
<th><strong>Autosomal recessive trait</strong></th>
<th><strong>Autosomal dominant trait</strong></th>
<th><strong>X-linked recessive trait</strong></th>
<th><strong>X-linked dominant trait</strong></th>
<th><strong>Y-linked trait</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Appears in both sexes with equal frequency.</td>
<td>1. Appears in both sexes with equal frequency.</td>
<td>1. More males than females are affected.</td>
<td>1. Both males and females are affected; often more females than males are affected.</td>
<td>1. Only males are affected.</td>
</tr>
<tr>
<td>2. Trait tends to skip generations.</td>
<td>2. Both sexes transmit the trait to their offspring.</td>
<td>2. Affected sons are usually born to unaffected mothers; thus, the trait skips generations.</td>
<td>2. Does not skip generations.</td>
<td>2. Is passed from father to all sons.</td>
</tr>
<tr>
<td>3. Affected offspring are usually born to unaffected parents.</td>
<td>3. Does not skip generations.</td>
<td>3. A carrier (heterozygous) mother produces approximately 1/2 affected sons.</td>
<td>3. Affected sons must have an affected mother; affected daughters must have either an affected mother or an affected father.</td>
<td>3. Does not skip generations.</td>
</tr>
<tr>
<td>4. When both parents are heterozygous, approximately 1/4 of the offspring will be affected.</td>
<td>4. Affected offspring must have an affected parent, unless they possess a new mutation.</td>
<td>4. Is never passed from father to son.</td>
<td>4. Affected mothers (if heterozygous) will pass the trait on to 1/2 of their sons and 1/2 of their daughters.</td>
<td></td>
</tr>
<tr>
<td>5. Appears more frequently among the children of consanguine marriages.</td>
<td>5. When one parent is affected (heterozygous) and the other parent is unaffected, approximately 1/2 of the offspring will be affected.</td>
<td>5. All daughters of affected fathers are carriers.</td>
<td><strong>Worked Problem</strong></td>
<td></td>
</tr>
</tbody>
</table>

The following pedigree represents the inheritance of a rare disorder in an extended family. What is the most likely mode of inheritance for this disease? (Assume that the trait is fully penetrant.)

- **Solution**

To answer this question, we should consider each mode of inheritance and determine which, if any, we can
Another method that geneticists use to analyze the genetics of human characteristics is twin studies. Twins come in two types: dizygotic (nonidentical) twins arise when two separate eggs are fertilized by two different sperm, producing genetically distinct zygotes; monozygotic (identical) twins result when a single egg, fertilized by a single sperm, splits early in development into two separate embryos.

Because monozygotic twins arise from a single egg and sperm (a single, “mono,” zygote), except for rare somatic mutations, they’re genetically identical, having 100% of their genes in common (Figure 6.11a). Dizygotic twins (Figure 6.11b), on the other hand, have on average only 50% of their genes in common (the same percentage that any pair of siblings has in common). Like other siblings, dizygotic twins may be of the same or different sexes. The only difference between dizygotic twins and other siblings is that dizygotic twins are the same age and shared a common uterine environment.

The frequency with which dizygotic twins are born varies among populations. Among North American Caucasians, about 7 dizygotic twin pairs are born per 1000 births but, among Japanese, the rate is only about 3 pairs per 1000 births; among Nigerians, about 40 dizygotic twin pairs are born per 1000 births. The rate of dizygotic twinning also varies with maternal age (Figure 6.12), and dizygotic twinning tends to run in families. In contrast, monozygotic twinning is relatively constant. The frequency of monozygotic twinning in most ethnic groups is about 4 twin pairs per 1000 births, and there is relatively little tendency for monozygotic twins to run in families.
Concordance

Comparisons of dizygotic and monozygotic twins can be used to estimate the importance of genetic and environmental factors in producing differences in a characteristic. This is often done by calculating the concordance for a trait. If both members of a twin pair have a trait, the twins are said to be concordant; if only one member of the pair has the trait, the twins are said to be discordant. Concordance is the percentage of twin pairs that are concordant for a trait.

Because identical twins have 100% of their genes in common and dizygotic twins have on average only 50% in common, genetically influenced traits should exhibit higher concordance in monozygotic twins. For instance, when one member of a monozygotic twin pair has asthma, the other twin of the pair has asthma about 48% of the time, so the monozygotic concordance for asthma is 48%. However, when a dizygotic twin has asthma, the other twin has asthma only 19% of the time (19% dizygotic concordance). The higher concordance in the monozygotic twins suggests that genes influence asthma, a finding supported by other family studies of this disease. Concordance values for several human traits and diseases are listed in Table 6.2.

The hallmark of a genetic influence on a particular characteristic is higher concordance in monozygotic twins compared with concordance in dizygotic twins. High concordance in monozygotic twins by itself does not signal a genetic influence. Twins normally share the same environment—they are raised in the same home, have the same friends, attend the same school—so high concordance may be due to common genes or to common environment. If the high concordance is due to environmental factors, then dizygotic twins, who also share the same environment, should have just as high a concordance as that of monozygotic twins. When genes influence the characteristic, however, monozygotic twin pairs should exhibit higher concordance than dizygotic twin pairs, because monozygotic twins have a greater percentage of genes in common.

It is important to note that any discordance among monozygotic twins must be due to environmental factors, because monozygotic twins are genetically identical. The use of twins in genetic research rests on the important assumption that, when there is greater concordance in monozygotic twins than in dizygotic twins, it is because monozygotic twins are more similar in their genes and not because they have experienced a more similar environment.

### Table 6.2

Concordance of monozygotic and dizygotic twins for several traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>Monozygotic Concordance (%)</th>
<th>Dizygotic Concordance (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack (males)</td>
<td>39</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Heart attack (females)</td>
<td>44</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>47</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Cancer (all sites)</td>
<td>12</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>59</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>32</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>28</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

The degree of environmental similarity between monozygotic twins and dizygotic twins is assumed to be the same. This assumption may not always be correct, particularly for human behaviors. Because they look alike, identical twins may be treated more similarly by parents, teachers, and peers than are nonidentical twins. Evidence of this similar treatment is seen in the past tendency of parents to dress identical twins alike. In spite of this potential complication, twin studies have played a pivotal role in the study of human genetics.

### Twin Studies and Obesity

To illustrate the use of twins in genetic research, let’s consider a genetic study of obesity. Obesity is a serious public health problem. About 50% of adults in affluent societies are overweight and from 15% to 25% are obese. Obesity increases the risk of a number of medical conditions, including diabetes, gallbladder disease, high blood pressure, some cancers, and heart disease. Obesity is clearly familial: when both parents are obese, 80% of their children will also become obese; when both parents are not overweight, only 15% of their children will eventually become obese. The familial nature of obesity could result from genes that influence body weight; alternatively, it could be entirely environmental, resulting from the fact that family members usually have similar diets and exercise habits.

A number of genetic studies have examined twins in an effort to untangle the genetic and environmental contributions to obesity. The largest twin study of obesity was conducted on more than 4000 pairs of twins taken from the National Academy of Sciences National Research Council twin registry. This registry is a database of almost 16,000 male twin pairs, born between 1917 and 1927, who served in the U.S. armed forces during World War II or the Korean War. Albert Stunkard and his colleagues obtained weight and height for each of the twins from medical records compiled at the time of their induction into the armed forces. Equivalent data were again collected in 1967, when the men were 40 to 50 years old. The researchers then computed how overweight each man was at induction and at middle age in 1967. Concordance values for monozygotic twins (MZ) and dizygotic twins (DZ) at induction and at follow-up are shown in Table 6.3.

<table>
<thead>
<tr>
<th>Percent Overweight</th>
<th>At Induction</th>
<th>At Follow-up in 1967</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>31</td>
</tr>
<tr>
<td>20</td>
<td>57</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>30</td>
<td>51</td>
<td>19</td>
</tr>
<tr>
<td>35</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>44</td>
<td>0</td>
</tr>
</tbody>
</table>

*Percent overweight was determined by comparing each man’s actual weight with a standard recommended weight for his height.


This study shows that genes influence variation in body weight, yet genes alone do not cause obesity. In less affluent societies, obesity is rare, and no one can become overweight unless caloric intake exceeds energy expenditure. One does not inherit obesity; rather, one inherits a predisposition toward a particular body weight; geneticists say that some people are genetically more at risk for obesity than others. How genes affect the risk of obesity is not yet completely understood. In 1994, scientists at Rockefeller University isolated a gene that causes an inherited form of obesity in mice (Figure 6.13). This gene encodes a protein called leptin, named after the Greek word for “thin.” Leptin is produced by fat tissue and decreases appetite by affecting

![Image 6.13](Obesity in some mice is due to a defect in the gene that encodes the protein leptin. Obese mouse on the left compared with normal-sized mouse on the right. (Remi Banali/Liason.)
the hypothalamus, a part of the brain. A decrease in body fat leads to decreased leptin, which stimulates appetite; an increase in body fat leads to increased levels of leptin, which reduces appetite. Obese mice possess two mutated copies of the leptin gene and produce no functional leptin; giving leptin to these mice promotes weight loss.

The discovery of the leptin gene raised hopes that obesity in humans might be influenced by defects in the same gene and that the administration of leptin might be an effective treatment for obesity. Unfortunately, most overweight people are not deficient in leptin. Most, in fact, have elevated levels of leptin and appear to be somewhat resistant to its effects. Only a few rare cases of human obesity have been linked to genetic defects in leptin. The results of further studies have revealed that the genetic and hormonal control of body weight is quite complex; several other genes have been identified that also cause obesity in mice, and the molecular underpinnings of weight control are still being elucidated.

Comparisons of adopted persons with their adoptive parents and with their biological parents can therefore help to define the roles of genetic and environmental factors in the determination of human variation.

Adoption studies assume that the environments of biological and adoptive families are independent (i.e., not more alike than would be expected by chance). This assumption may not always be correct, because adoption agencies carefully choose adoptive parents and may select a family that resembles the biological family. Offspring and their biological mother also share a common environment during prenatal development. Some of the similarity between adopted persons and their biological parents may be due to these similar environments and not due to common genetic factors.

**Concepts**

- Similarities between adopted persons and their genetically unrelated adoptive parents indicate that environmental factors affect the characteristic; similarities between adopted persons and their biological parents indicate that genetic factors influence the characteristic.

**Adoption Studies and Obesity**

Like twin studies, adoption studies have played an important role in demonstrating that obesity has a genetic influence. In 1986, geneticists published the results of a study of 540 people who had been adopted in Denmark between 1924 and 1947. The geneticists obtained information concerning the adult body weight and height of the adopted persons, along with the adult weight and height of their biological parents and their unrelated adoptive parents.

Geneticists used a measurement called the body-mass index to analyze the relation between the weight of the adopted persons and that of their parents. (The body-mass index, which is a measure of weight divided by height, provides a measure of weight that is independent of height.) On the basis of body-mass index, sex, and age, the adopted persons were divided into four weight classes: thin, median weight, overweight, and obese. A strong relation was found between the weight classification of the adopted persons and the body-mass index of their biological parents: obese adoptees tended to have heavier biological parents, whereas thin adoptees tended to have lighter biological parents (Figure 6.14). Because the only connection between the adoptees and their biological parents was the genes that they have in common, the investigators concluded that genetic factors influence adult body weight. There was no clear relation between the weight classification of adoptees and the body-mass index of their adoptive parents (see Figure 6.14), suggesting that the rearing environment has little effect on adult body weight.
Adoption Studies and Alcoholism

Adoption studies have also been successfully used to assess the importance of genetic factors on alcoholism. Although frequently considered a moral weakness in the past, today alcoholism is more often treated as a disease or as a psychiatric condition. An estimated 10 million people in the United States are problem drinkers, and as many as 6 million are severely addicted to alcohol. Of the U.S. population, 11% are heavy drinkers and consume as much as 50% of all alcohol sold.

A large study of alcoholism was carried out on 1775 Swedish adoptees who had been separated from their mothers at an early age and raised by biologically unrelated adoptive parents. The results of this study, along with those of others, suggest that there are at least two distinct groups of alcoholics. Type I alcoholics include men and women who typically develop problems with alcohol after the age of 25 (usually in middle age). These alcoholics lose control of the ability to drink in moderation—they drink in binges—and tend to be nonaggressive during drinking bouts. Type II alcoholics consist largely of men who begin drinking before the age of 25 (often in adolescence); they actively seek out alcohol, but do not binge, and tend to be impulsive, thrill-seeking, and aggressive while drinking.

The Swedish adoption study also found that alcohol abuse among biological parents was associated with increased alcoholism in adopted persons. Type I alcoholism usually required both a genetic predisposition and exposure to a rearing environment in which alcohol was consumed. Type II alcoholism appeared to be highly hereditary; it developed primarily among males whose biological fathers also were Type II alcoholics, regardless of whether the adoptive parents drank. A male adoptee whose biological father was a Type II alcoholic was nine times as likely to become an alcoholic as was an adoptee whose biological father was not an alcoholic.

The results of the Swedish adoption study have been corroborated by other investigations, suggesting that some people are genetically predisposed to alcoholism. However, alcoholism is a complex behavioral characteristic that is undoubtedly influenced by many factors. It would be wrong to conclude that alcoholism is strictly a genetic characteristic. Although some people may be genetically predisposed to alcohol abuse, no gene forces a person to drink, and no one becomes alcoholic without the presence of a specific environmental factor—namely, alcohol.

Genetic Counseling and Genetic Testing

Our knowledge of human genetic diseases and disorders has expanded rapidly in the past 20 years. Victor McKusick’s Mendelian Inheritance in Man now lists more than 13,000 human genetic diseases, disorders, and traits that have a simple genetic basis. Research has provided a great deal of information about the inheritance, chromosomal location, biochemical basis, and symptoms of many of these genetic traits. This information is often useful to people who have a genetic condition.

Genetic Counseling

Genetic counseling is a new field that provides information to patients and others who are concerned about hereditary conditions. It is also an educational process that helps patients and family members deal with many aspects of a
genetic condition. Genetic counseling often includes interpreting a diagnosis of the condition; providing information about symptoms, treatment, and prognosis; helping the patient and family understand the mode of inheritance; and calculating probabilities that family members might transmit the condition to future generations. Good genetic counseling also provides information about the reproductive options that are available to those at risk for the disease. Finally, genetic counseling tries to help the patient and family cope with the psychological and physical stress that may be associated with their disorder. Clearly, all of these considerations cannot be handled by a single person; so most genetic counseling is done by a team that can include counselors, physicians, medical geneticists, and laboratory personnel. Table 6.4 lists some common reasons for seeking genetic counseling.

Genetic counseling usually begins with a diagnosis of the condition. On the bases of a physical examination, biochemical tests, chromosome analysis, family history, and other information, a physician determines the cause of the condition. An accurate diagnosis is critical, because treatment and the probability of passing on the condition may vary, depending on the diagnosis. For example, there are a number of different types of dwarfism, which may be caused by chromosome abnormalities, single-gene mutations, hormonal imbalances, or environmental factors. People who have dwarfism resulting from an autosomal dominant gene have a 50% chance of passing the condition to their children, whereas people with dwarfism caused by a rare recessive gene have a low likelihood of passing the trait to their children.

When the nature of the condition is known, a genetic counselor sits down with the patient and other family members and explains the diagnosis. A family pedigree may be constructed, and the probability of transmitting the condition to future generations can be calculated for different family members. The counselor helps the family interpret the genetic risks and explains various reproductive options that are available, including prenatal diagnosis, artificial insemination, and in vitro fertilization. A family’s decision about future pregnancies frequently depends on the magnitude of the genetic risk, the severity and effects of the condition, the importance of having children, and religious and cultural views. The genetic counselor helps the family sort through these factors and facilitates their decision making. Throughout the process, a good genetic counselor uses nondirected counseling, which means that he or she provides information and facilitates discussion but does not bring his or her own opinion and values into the discussion. The goal of nondirected counseling is for the family to reach its own decision on the basis of the best available information.

Genetic conditions are often perceived differently from other diseases and medical problems, because genetic conditions are intrinsic to the individual person and can be passed on to children. Such perceptions may produce feelings of guilt about past reproductive choices and intense personal dilemmas about future choices. Genetic counselors are trained to help patients and family members recognize and cope with these feelings.

<table>
<thead>
<tr>
<th>Table 6.3</th>
<th>Common reasons for seeking genetic counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A person knows of a genetic disease in the family.</td>
<td></td>
</tr>
<tr>
<td>2. A couple has given birth to a child with a genetic disease, birth defect, or chromosomal abnormality.</td>
<td></td>
</tr>
<tr>
<td>3. A couple has a child who is mentally retarded or a close relative is mentally retarded.</td>
<td></td>
</tr>
<tr>
<td>4. An older woman becomes pregnant or wants to become pregnant. There is disagreement about the age at which a prospective mother who has no other risk factor should seek genetic counseling; many experts suggest that any prospective mother age 35 or older should seek genetic counseling.</td>
<td></td>
</tr>
<tr>
<td>5. Husband and wife are closely related (e.g., first cousins).</td>
<td></td>
</tr>
<tr>
<td>6. A couple experiences difficulties achieving a successful pregnancy.</td>
<td></td>
</tr>
<tr>
<td>7. A pregnant woman is concerned about exposure to an environmental substance (drug, chemical, or virus) that causes birth defects.</td>
<td></td>
</tr>
<tr>
<td>8. A couple needs assistance in interpreting the results of a prenatal or other test.</td>
<td></td>
</tr>
<tr>
<td>9. Both parents are known carriers for a regressive genetic disease.</td>
<td></td>
</tr>
</tbody>
</table>
Information on genetic counseling and human genetic diseases, as well as a list of genetic counseling training programs accredited by the American Board of Genetic Counseling

**Genetic Testing**

Improvements in our understanding of human heredity and the identification of numerous disease-causing genes have led to the development of hundreds of tests for genetic conditions. The ultimate goal of genetic testing is to recognize the potential for a genetic condition at an early stage. In some cases, genetic testing allows early intervention that may lessen or even prevent the development of the condition. In other cases, genetic testing allows people to make informed choices about reproduction. For those who know that they are at risk for a genetic condition, genetic testing may help alleviate anxiety associated with the uncertainty of their situation. Genetic testing includes newborn screening, heterozygote screening, presymptomatic diagnosis, and prenatal testing.

**Newborn screening** Testing for genetic disorders in newborn infants is called **newborn screening**. Most states in the United States and many other countries require that newborn infants be tested for phenylketonuria and galactosemia. These metabolic diseases are caused by autosomal recessive alleles; if not treated at an early age, they can result in mental retardation, but early intervention — through the administration of a modified diet — prevents retardation (see p. 000 in Chapter 5). Testing is done by analyzing a drop of the infant’s blood collected soon after birth. Because of widespread screening, the frequency of mental retardation due to these genetic conditions has dropped tremendously. Screening newborns for additional genetic diseases that benefit from treatment, such as sickle-cell anemia and hypothyroidism, also is common.

**Heterozygote screening** Testing members of a population to identify heterozygous carriers of recessive disease-causing alleles, who are healthy but have the potential to produce children with the particular disease, is termed **heterozygote screening**.

Testing for Tay-Sachs disease is a successful example of heterozygote screening. In the general population of North America, the frequency of Tay-Sachs disease is only about 1 person in 360,000. Among Ashkenazi Jews (descendants of Jewish people who settled in eastern and central Europe), the frequency is 100 times as great. A simple blood test is used to detect Ashkenazi Jews who carry the Tay-Sachs allele. If a man and woman are both heterozygotes, approximately one in four of their children is expected to have Tay-Sachs disease. A prenatal test for the Tay-Sachs allele also is available. Screening programs have led to a significant decline in the number of children of Ashkenazi ancestry born with Tay-Sachs disease (now fewer than 10 children per year in the United States).

**Presymptomatic testing** Evaluating healthy people to determine whether they have inherited a disease-causing allele gene is known as **presymptomatic genetic testing**. For example, presymptomatic testing is available for members of families that have an autosomal dominant form of breast cancer. In this case, early identification of the disease-causing allele allows for closer surveillance and the early detection of tumors. Presymptomatic testing is also available for some genetic diseases for which no treatment is available, such as Huntington disease, an autosomal dominant disease that leads to slow physical and mental deterioration in middle age (see introduction to Chapter 5). Presymptomatic testing for untreatable conditions raises a number of social and ethical questions (Chapter 18).

Several hundred genetic diseases and disorders can now be diagnosed prenataly. The major purpose of prenatal tests is to provide families with the information that they need to make choices during pregnancies and, in some cases, to prepare for the birth of a child with a genetic condition. A number of approaches to prenatal diagnosis are described in the following sections.

**Ultrasoundography** Some genetic conditions can be detected through direct visualization of the fetus. Such visualization is most commonly done with **ultrasonography** — usually referred to as ultrasound. In this technique, high-frequency sound is beamed into the uterus; when the sound waves encounter dense tissue, they bounce back and are transformed into a picture (Figure 6.15). The size of the fetus can be determined, as can genetic conditions such as neural tube defects (defects in the development of the spinal column and the skull) and skeletal abnormalities.

**Amniocentesis** Most prenatal testing requires fetal tissue, which can be obtained in several ways. The most widely used method is **amniocentesis**, a procedure for obtaining a
A couple are seeking help at a clinic that offers preimplantation genetic diagnosis (PGD), which combines in vitro fertilization with molecular analysis of the DNA from a single cell of the developing embryo, and permits the selection and transfer to the uterus of embryos free of a genetic disease. Before PGD, the only alternative for those wishing to prevent the birth of a child with a serious genetic disorder was early chorionic villus sampling or amniocentesis, followed by abortion if the fetus had a disorder.

Consider a couple at risk of having a second child with severe combined immune deficiency (SCID). A child born with this condition has a seriously impaired immune system. As recently as 20 years ago, those affected died early in life, but the use of bone-marrow transplantation, which can provide the child with a supply of healthy blood stem cells, has greatly extended survival. In general, the earlier the transplantation and the closer the tissue match of the marrow donor, the better a recipient child's chances.

The couple tell the medical geneticist that they are seeking his help in identifying and transferring only embryos free of the SCID mutation so that they can begin their pregnancy knowing that it will be healthy. Some weeks later they reveal another reason for their interest in this technology: the health of their six-year-old daughter, who is affected with SCID, is on a downward course despite one partly matched bone-marrow transplant earlier in her life. Their child's best hope of survival is another bone-marrow transplant, using tissue from a compatible donor, preferably a sibling. Is it possible, they ask, to test the healthy embryos for tissue compatibility and transfer only those that match their daughter's type?

The geneticist responds that it is indeed technically possible to do so but he wonders whether helping the couple in this way is ethically appro-
Sample of amniotic fluid from a pregnant woman (Figure 6.16). Amniotic fluid—the substance that fills the amniotic sac and surrounds the developing fetus—contains fetal cells that can be used for genetic testing.

Amniocentesis is routinely performed as an outpatient procedure with the use of a local or no anesthetic. First, ultrasonography is used to locate the position of the fetus in the uterus. Next, a long, sterile needle is inserted through the abdominal wall into the amniotic sac (see Figure 6.16), and a small amount of amniotic fluid is withdrawn through the needle. Fetal cells are separated from the amniotic fluid and placed in a culture medium that stimulates them to grow and divide. Genetic tests are then performed on the cultured cells. Complications with amniocentesis (mostly miscarriage) are rare, arising in only about 1 in 400 procedures.

Chorionic villus sampling A major disadvantage with amniocentesis is that it is routinely performed in about the 16th week of a pregnancy, (although many obstetricians now successfully perform amniocentesis several weeks earlier). The cells obtained with amniocentesis must then be cultured before genetic tests can be performed, requiring yet more time. For these reasons, genetic information about the fetus may not be available until the 17th or 18th week of pregnancy. By this stage, abortion carries a risk of complications and may be stressful for the parents. Chorionic villus sampling (CVS) can be performed earlier (between the 10th and 11th weeks of pregnancy) and collects more fetal tissue, which eliminates the necessity of culturing the cells. Complications with amniocentesis (mostly miscarriage) are rare, arising in only about 1 in 400 procedures.

In CVS, a catheter—a soft plastic tube—is inserted into the vagina (Figure 6.17) and, with the use of ultrasound for guidance, is pushed through the cervix into the uterus. The tip of the tube is placed into contact with the chorion, the outer layer of the placenta. Suction is then applied, and a small piece of the chorion is removed. Although the chorion is composed of fetal cells, it is a part of the placenta that is expelled from the uterus after birth; so the removal of a small sample does not endanger the fetus. The tissue that is removed contains millions of actively dividing cells that can be used directly in many genetic tests. Chorionic villus sampling has a somewhat higher risk of complication than that of amniocentesis; the results of several studies suggest that this procedure may increase the incidence of limb defects in the fetus when performed earlier than 10 weeks of gestation.

Fetal cells obtained by amniocentesis or by CVS can be used to prepare a karyotype, which is a picture of a complete set of metaphase chromosomes. Karyotypes can be studied for chromosome abnormalities (Chapter 9). Biochemical analyses can be conducted on fetal cells to determine the presence of particular metabolic products of genes. For genetic diseases in which the DNA sequence of the causative gene has been determined, the DNA sequence (DNA testing; Chapter 18) can be examined for defective alleles.

Maternal blood tests Some genetic conditions can be detected by performing a blood test on the mother (maternal blood testing). For instance, α-fetoprotein is normally produced by the fetus during development and is present in the fetal blood, the amniotic fluid, and the mother’s blood during pregnancy. The level of α-fetoprotein is significantly higher than normal when the fetus has a neural-tube or one of several other disorders. Some chromosome
abnormalities produce lower-than-normal levels of α-fetoprotein. Measuring the amount of α-fetoprotein in the mother’s blood gives an indication of these conditions. However, because other factors affect the amount of α-fetoprotein in maternal blood, a high or low level by itself does not necessarily indicate a problem. Thus, when a blood test indicates that the amount of α-fetoprotein is abnormal, follow-up tests (additional α-fetoprotein determinations, ultrasound, amniocentesis, or all three) are usually performed.

Fetal cell sorting Prenatal tests that utilize only maternal blood are highly desirable because they are noninvasive and pose no risk to the fetus. During pregnancy, a few fetal cells are released into the mother’s circulatory system, where they mix and circulate with her blood. Recent advances have made it possible to separate fetal cells from a maternal blood sample (a procedure called fetal cell sorting). With the use of lasers and automated cell-sorting machines, fetal cells can be detected and separated from maternal blood cells. The fetal cells obtained can be cultured for chromosome analysis or used as a source of fetal DNA for molecular testing (see p. 000 in Chapter 18).

A large number of genetic diseases can now be detected prenatally (Table 6.5), and the number is growing rapidly as new disease-causing genes are isolated. The Human Genome Project (Chapter 18) has accelerated the rate at which new genes are being isolated and new genetic tests are being developed. In spite of these advances, prenatal tests are still not available for many common genetic diseases, and no test can guarantee that a “perfect” child will be born.

Preimplantation genetic diagnosis Prenatal genetic tests provide today’s couples with increasing amounts of information about the health of their future children. New reproductive technologies also provide couples with options for using this information. One of these technologies is in vitro fertilization. In this procedure, hormones are used to induce ovulation. The ovulated eggs are surgically removed from the surface of the ovary, placed in a laboratory dish, and fertilized with sperm. The resulting embryo is then implanted into the uterus. Thousands of babies resulting from in vitro fertilization have now been born.

Genetic testing can be combined with in vitro fertilization to allow implantation of embryos that are free of a specific genetic defect. Called preimplantation genetic diagnosis (PGD), this technique allows people who carry a genetic defect to avoid producing a child with the disorder. For example, when a woman is a carrier of an X-linked recessive disease, approximately half of her sons are expected to have the disease. Through in vitro fertilization and preimplantation testing, it is possible to select an embryo without the disorder for implantation in her uterus.

The procedure begins with the production of several single-celled embryos through in vitro fertilization. The embryos are allowed to divide several times until they reach the 8 or 16-cell stage. At this point, one cell is removed from each embryo and tested for the genetic abnormality. Removing a single cell at this early stage does not harm the embryo. After determination of which embryos are free of
the disorder, a healthy embryo is selected and implanted in the woman’s uterus.

Preimplantation genetic diagnosis requires the ability to conduct a genetic test on a single cell. Such testing is possible with the use of the polymerase chain reaction through which minute quantities of DNA can be amplified (replicated) quickly (Chapter 18). After amplification of the cell’s DNA, the DNA sequence is examined. Preimplantation diagnosis is still experimental and is available at only a few research centers. Its use raises a number of ethical concerns, because it provides a means of actively selecting for or against certain genetic traits.

**Table 6.5** Examples of genetic diseases and disorders that can be detected prenatally and the techniques used in their detection

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Method of Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome abnormalities</td>
<td>Examination of a karyotype from cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Cleft lip and palate</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>DNA analysis of cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Dwarfism</td>
<td>Ultrasound or X-ray; some forms can be detected by DNA analysis of cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Fetal blood sampling or DNA analysis of cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome (deficiency of purine metabolism leading to spasms, seizures, and compulsory self-mutilation)</td>
<td>Biochemical tests on cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Neural-tube defects</td>
<td>Initial screening with maternal blood test, followed by biochemical tests on amniotic fluid obtained by amniocentesis and ultrasound</td>
</tr>
<tr>
<td>Osteogenesis imperfecta (brittle bones)</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>DNA analysis of cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>Fetal blood sampling or DNA analysis of cells obtained by amniocentesis or CVS</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Biochemical tests on cells obtained by amniocentesis or CVS</td>
</tr>
</tbody>
</table>

* A sample of fetal blood is obtained by inserting needle into the umbilical cord.

Genetic testing is used to screen newborns for genetic diseases, detect persons who are heterozygous for recessive diseases, detect disease-causing alleles in those who have not yet developed symptoms of the disease, and detect defective alleles in unborn babies. Preimplantation genetic diagnosis combined with in vitro fertilization allows for selection of embryos that are free from specific genetic diseases.

**Connecting Concepts Across Chapters**
This chapter builds on the basic principles of heredity that were introduced in Chapters 1 through 5, extending them to human genetic characteristics. A dominant theme of the chapter is that human inheritance is not fundamentally different from inheritance in other organisms, but the unique biological and cultural characteristics of humans require special techniques for the study of human characteristics.

Several topics introduced in this chapter are explored further in later chapters. Molecular techniques used in genetic testing and some of the ethical implications of modern genetic testing are presented in Chapter 18. Chromosome mutations and karyotypes are studied in Chapter 9. In Chapter 22, we examine additional techniques for separating genetic and environmental contributions to characteristics in humans and other organisms.
There are several difficulties in applying traditional genetic techniques to the study of human traits, including the inability to conduct controlled crosses, long generation time, small family size, and the difficulty of separating genetic and environmental influences.

A pedi-ure is a pictorial representation of a family history that displays the inheritance of one or more traits through several generations.

Autosomal recessive traits typically appear with equal frequency in both sexes. If a trait is uncommon, the parents of a child with an autosomal recessive trait are usually heterozygous and unaffected, so the trait tends to skip generations. When both parents are heterozygous, approximately 1/4 of the offspring will have the trait. Recessive traits are more likely to appear in families with consanguinity (mating between closely related persons).

Autosomal dominant traits usually appear equally in both sexes and do not skip generations. When one parent is affected and heterozygous, approximately 1/2 of the offspring will have the trait. When both parents are affected and heterozygous, approximately 3/4 of the offspring will be affected. Unaffected people do not normally transmit an autosomal dominant trait to their offspring.

X-linked recessive traits appear more frequently in males than in females. Affected males are usually born to females who are unaffected carriers. When a woman is a heterozygous carrier and a man is unaffected, approximately 1/2 of their sons will have the trait and 1/2 of their daughters will be unaffected carriers. X-linked traits are not passed from father to son.

X-linked dominant traits appear in males and females, but more frequently in males. They do not skip generations. Affected men pass an X-linked dominant trait to all of their daughters but none of their sons. Heterozygous women pass the trait to 1/2 of their sons and 1/2 of their daughters.

Y-linked traits appear only in males and are passed from father to all sons.

Analysis of twins is an important technique for the study of human genetic characteristics. Dizygotic twins arise from two separate eggs fertilized by two separate sperm; monozygotic twins arise from a single egg, fertilized by a single sperm, that splits into two separate embryos early in development.

Concordance is the percentage of twin pairs in which both members of the pair express a trait. Higher concordance in monozygotic than in dizygotic twins indicates a genetic influence on the trait; less than 100% concordance in monozygotic twins indicates environmental influences on the trait.

Adoption studies are used to analyze the inheritance of human characteristics. Similarities between adopted children and their biological parents indicate the importance of genetic factors in the expression of a trait; similarities between adopted children and their genetically unrelated adoptive parents indicate the influence of environmental factors.

Genetic counseling provides information and support to people concerned about hereditary conditions in their families.

Genetic testing includes screening for disease-causing alleles in newborns, the detection of people heterozygous for recessive alleles, presymptomatic testing for the presence of a disease-causing allele in at-risk people, and prenatal diagnosis.

Common techniques used for prenatal diagnosis include ultrasound, amniocentesis, chorionic villus sampling, and maternal blood sampling. Preimplantation genetic diagnosis can be used to select for embryos that are free of a genetic disease.
marries Tom, who has normal fingers; they adopt a son named Bill who has normal fingers. Bill’s biological parents both have normal fingers. After adopting Bill, Joanna and Tom produce two children: an older daughter with short fingers and a younger son with normal fingers.

(a) Using correct symbols and labels, draw a pedigree illustrating the inheritance of short fingers in Joanna’s family.

(b) What is the most likely mode of inheritance for short fingers in this family?

(c) If Joanna and Tom have another biological child, what is the probability (based on your answer to part b) that this child will have short fingers?

• Solution

(a) In the pedigree for the family, note that persons with the trait (short fingers) are indicated by filled circles (females) and filled squares (males). Joanna’s identical twin brothers are connected to the line above with diagonal lines that have a horizontal line between them. The adopted child of Joanna and Tom is enclosed in brackets and is connected to the biological parents by a dashed diagonal line.

(b) The most likely mode of inheritance for short fingers in this family is autosomal dominant. The trait appears equally in males and females and does not skip generations. When one parent has the trait, it appears in approximately half of that parent’s sons and daughters, although the number of children in the families is small. We can eliminate Y-linked inheritance because the trait is found in females. If short fingers were X-linked recessive, females with the trait would be expected to pass the trait to all their sons, but Joanna (III-6), who has short fingers, produced a son with normal fingers. For X-linked dominant traits, affected men should pass the trait to all their daughters; because male II-1 has short fingers and produced two daughters without short fingers (III-7 and III-8), we know that the trait cannot be X-linked dominant. It is unlikely that the trait is autosomal recessive because it does not skip generations and approximately half of the children of affected parents have the trait.

(c) If having short fingers is autosomal dominant, Tom must be homozygous (bb) because he has normal fingers. Joanna must be heterozygous (Bb) because she and Tom have produced both short- and normal-fingered offspring. In a cross between a heterozygote and homozygote, half of the progeny are expected to be heterozygous and half homozygous (Bb × bb → ½ Bb, ½ bb); so the probability that Joanna’s and Tom’s next biological child will have short fingers is ½.

2. Concordance values for a series of traits were measured in monozygotic twins and dizygotic twins; the results are shown in the following table. For each trait, indicate whether the rates of concordance suggest genetic influences, environmental influences, or both. Explain your reasoning.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Monozygotic Concordance (%)</th>
<th>Dizygotic Concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) ABO blood type</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>(b) Diabetes</td>
<td>85</td>
<td>36</td>
</tr>
<tr>
<td>(c) Coffee drinking</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>(d) Smoking</td>
<td>75</td>
<td>42</td>
</tr>
<tr>
<td>(e) Schizophrenia</td>
<td>53</td>
<td>16</td>
</tr>
</tbody>
</table>

• Solution

(a) The concordance of ABO blood type in the monozygotic twins is 100%. This high concordance in monozygotic twins does not, by itself, indicate a genetic basis for the trait. An important indicator of a genetic influence on the trait is lower concordance in dizygotic twins. Because concordance for ABO blood type is substantially lower in the dizygotic twins, we would be safe in concluding that genes play a role in determining differences in ABO blood types.

(b) The concordance for diabetes is substantially higher in monozygotic twins than in dizygotic twins; therefore, we can conclude that genetic factors play some role in susceptibility to diabetes. The fact that monozygotic twins show a concordance less than 100% suggests that environmental factors also play a role.

(c) Both monozygotic and dizygotic twins exhibit the same high concordance for coffee drinking; so we can conclude that there is little genetic influence on coffee drinking. The fact that monozygotic twins show a concordance less than 100% suggests that environmental factors play a role.

(d) There is lower concordance of smoking in dizygotic twins than in monozygotic twins, so genetic factors appear to influence the tendency to smoke. The fact that monozygotic twins show a concordance less than 100% suggests that environmental factors also play a role.

(e) Monozygotic twins exhibit substantially higher concordance for schizophrenia than do dizygotic twins; so we can conclude that genetic factors influence this psychiatric disorder. Because the concordance of monozygotic twins is substantially less than 100%, we can also conclude that environmental factors play a role in the disorder as well.
**COMPREHENSION QUESTIONS**

1. What three factors complicate the task of studying the inheritance of human characteristics?
2. Describe the features that will be exhibited in a pedigree in which a trait is segregating with each of the following modes of inheritance: autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, and Y-linked inheritance.
3. What are the two types of twins and how do they arise?
4. Explain how a comparison of concordance in monozygotic and dizygotic twins can be used to determine the extent to which the expression of a trait is influenced by genes or by environmental factors.
5. How are adoption studies used to separate the effects of genes and environment in the study of human characteristics?
6. What is genetic counseling?
7. Briefly define newborn screening, heterozygote screening, presymptomatic testing, and prenatal diagnosis.
8. What are the differences between amniocentesis and chorionic villus sampling? What is the purpose of these two techniques?
9. What is preimplantation genetic diagnosis?

**APPLICATION QUESTIONS AND PROBLEMS**

10. Joe is color-blind. His mother and father both have normal vision, but his mother’s father (Joe’s maternal grandfather) is color-blind. All Joe’s other grandparents have normal color vision. Joe has three sisters—Patty, Betsy, and Lora—all with normal color vision. Joe’s oldest sister, Patty, is married to a man with normal color vision; they have two children, a 9-year-old color-blind boy and a 4-year-old girl with normal color vision.

   (a) Using correct symbols and labels, draw a pedigree of Joe’s family.
   (b) What is the most likely mode of inheritance for color blindness in Joe’s family?
   (c) If Joe marries a woman who has no family history of color blindness, what is the probability that their first child will be a color-blind boy?
   (d) If Joe marries a woman who is a carrier of the color-blind allele, what is the probability that their first child will be a color-blind boy?
   (e) If Patty and her husband have another child, what is the probability that the child will be a color-blind boy?

11. A man with a specific unusual genetic trait marries an unaffected woman and they have four children. Pedigrees of this family are shown in parts a through e, but the presence or absence of the trait in the children is not indicated. For each type of inheritance, indicate how many children of each sex are expected to express the trait by filling in the appropriate circles and squares. Assume that the trait is rare and fully penetrant.

   (a) Autosomal recessive trait
   (b) Autosomal dominant trait
   (c) X-linked recessive trait
For each of the following pedigrees, give the most likely mode of inheritance, assuming that the trait is rare. Carefully explain your reasoning.

(a) * X-linked dominant trait
(b) Y-linked trait
(c) X-linked dominant trait
(d) Y-linked trait
(e) X-linked dominant trait
13. The trait represented in the following pedigree is expressed only in the males of the family. Is the trait Y linked? Why or why not? If you believe the trait is not Y linked, propose an alternate explanation for its inheritance.

*14. A geneticist studies a series of characteristics in monozygotic twins and dizygotic twins, obtaining the following concordances. For each characteristic, indicate whether the rates of concordance suggest genetic influences, environmental influences, or both. Explain your reasoning.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Monozygotic concordance (%)</th>
<th>Dizygotic concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine headaches</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Eye color</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Measles</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Clubfoot</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>Handedness</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

15. In a study of schizophrenia (a mental disorder including disorganization of thought and withdrawal from reality), researchers looked at the prevalence of the disorder in the biological and adoptive parents of people who were adopted as children; they found the following results:

<table>
<thead>
<tr>
<th>Adopted persons</th>
<th>Prevalence of schizophrenia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With schizophrenia</td>
<td>Biological parents</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Without schizophrenia</td>
<td>6</td>
</tr>
</tbody>
</table>


16. The following pedigree illustrates the inheritance of Nance-Horan syndrome, a rare genetic condition in which affected persons have cataracts and abnormally shaped teeth.

(a) On the basis of this pedigree, what do you think is the most likely mode of inheritance for Nance-Horan syndrome?
(b) If couple III-7 and III-8 have another child, what is the probability that the child will have Nance-Horan syndrome?
(c) If III-2 and III-7 mated, what is the probability that one of their children would have Nance-Horan syndrome?

17. The following pedigree illustrates the inheritance of ringed hair, a condition in which each hair is differentiated into light and dark zones. What mode or modes of inheritance are possible for the ringed-hair trait in this family?
*18. Ectodactyly is a rare condition in which the fingers are absent and the hand is split. This condition is usually inherited as an autosomal dominant trait. Ademar Freire-Maia reported the appearance of ectodactyly in a family in Sao Paulo, Brazil, whose pedigree is shown here. Is this pedigree consistent with autosomal dominant inheritance? If not, what mode of inheritance is most likely? Explain your reasoning. (Pedigree adapted from A. Freire-Maia, Journal of Heredity 62(1971):53.)

**CHALLENGE QUESTIONS**

19. Draw a pedigree that represents an autosomal dominant trait, sex-limited to males, and that excludes the possibility that the trait is Y linked.

20. Androgen insensitivity syndrome is a rare disorder of sexual development, in which people with an XY karyotype, genetically male, develop external female features. All persons with androgen insensitivity syndrome are infertile. In the past, some researchers proposed that androgen insensitivity syndrome is inherited as a sex-limited, autosomal dominant trait. (It is sex-limited because females cannot express the trait.) Other investigators suggested that this disorder is inherited as a X-linked recessive trait. Draw a pedigree that would show conclusively that androgen insensitivity syndrome is inherited as an X-linked recessive trait and that excludes the possibility that it is sex-limited, autosomal dominant. If you believe that no pedigree can conclusively differentiate between the two choices (sex-limited, X-linked recessive and sex-limited, autosomal dominant), explain why. Remember that all affected persons are infertile.

**SUGGESTED READINGS**

An excellent review of the genetics of body weight in humans. This issue of Nature has a section on obesity, with additional review articles on obesity as a medical problem, on the molecular basis of thermogenesis, on nervous-system control of food intake, and medical strategies for treatment of obesity.

Contains recommendations for standardized symbols used in pedigree construction.

Excellent review of the genetics of atherosclerosis by two scientists who received the Nobel Prize for their research on atherosclerosis.

A good review of how genes influence alcoholism in humans.

Reports new evidence that mutated SOD1 may be implicated in apoptosis (programmed cell death) in people with amyotrophic lateral sclerosis.

A classic textbook on genetic counseling.

A textbook on medical aspects of human genetics.

A well-written review of the history of pedigree analysis and recent changes in symbols that have been necessitated by changing life styles and new reproductive technologies.
A well-written textbook on human genetics.

A discussion of new methods for using twins in the study of genes.

A review of genetic counseling in light of the Human Genome Project, with special consideration of the role of nondirected counseling.

A comprehensive catalog of all known simple human genetic disorders and the genes responsible for them.

A book on human genetics written for the layperson; contains a catalog of more than 100 human genetic traits.

Describes the Danish adoption study of obesity.