CHAPTER 7

Multifactorial Traits

7.1 Genes and the Environment Mold Most Traits

Environmental influences mold many human traits. Fingerprint pattern, skin color, disease susceptibilities, and even intelligence and behavior are molded by both genes and the environment.

7.2 Methods Used to Investigate Multifactorial Traits

Separating genetic from environmental influences on phenotype is enormously difficult. Observations on how common a trait is in a population, combined with theoretical predictions of the percentage of genes that certain relatives should share, enable us to calculate heritability. This is an estimate of genetic contribution to variations among individuals in a trait. Twins are important in studying multifactorial traits.

7.3 Some Multifactorial Traits

Cardiovascular health and body weight are two common characteristics that are influenced by the interactions of specific predisposing genes and environmental factors.

A woman who is a prolific writer has a daughter who becomes a successful novelist. An overweight man and woman have obese children. A man whose father suffers from alcoholism has the same problem. Are these characteristics—writing talent, obesity, and alcoholism—inherited or imitated? Or are they a combination of nature (genetics) and nurture (the environment)?

Most of the traits and medical conditions mentioned so far in this book are single-gene characteristics, inherited according to Mendel's laws, or linked on the same chromosome. Many single gene disorders are very rare, each affecting one in hundreds or even thousands of individuals. Using Mendel's laws, geneticists can predict the probability that certain family members will inherit single gene conditions. Most more common traits and diseases, though, can seem to "run in families" with no apparent pattern, or they occur sporadically, with just one case in a family. Genes rarely act completely alone. Even single gene disorders are modified by environmental factors or other genes. This chapter discusses the nature of non-Mendelian characteristics, and the tools used to study them. Chapter 8 focuses on the most difficult traits to assess for their inherited components—behaviors.

7.1 Genes and the Environment Mold Most Traits

On the first page of the first chapter of *On the Origin of Species,* Charles Darwin noted that two factors are responsible for variation among organisms—"the nature of the organism and the nature of the conditions." Darwin's thoughts were a 19th-century musing on "heredity versus the environment." Though this phrase might seem to indicate otherwise, genes and the environment are not adversaries. They are two forces that interact, and they do so in ways that mold many of our characteristics.

A trait can be described as either Mendelian or **polygenic.** A single gene is responsible for a Mendelian trait. A polygenic trait, as its name implies, reflects the activities of more than one gene, and the effect of these multiple inputs is often additive, although not necessarily equal. Both Mendelian and polygenic traits can also be **multifactorial,** which means they are influenced by the environment (multifactorial traits are also called complex traits). Pure polygenic traits—those not influenced by the environment—are very rare. Multifactorial traits include common characteristics such as height and skin color, illnesses, and behavioral conditions and tendencies. Behavioral traits are not inherently different from other types of traits; they simply involve the functioning of the brain, rather than another organ. Figure 7.1 depicts the comparative contributions of genes and the environment to several disorders and events.

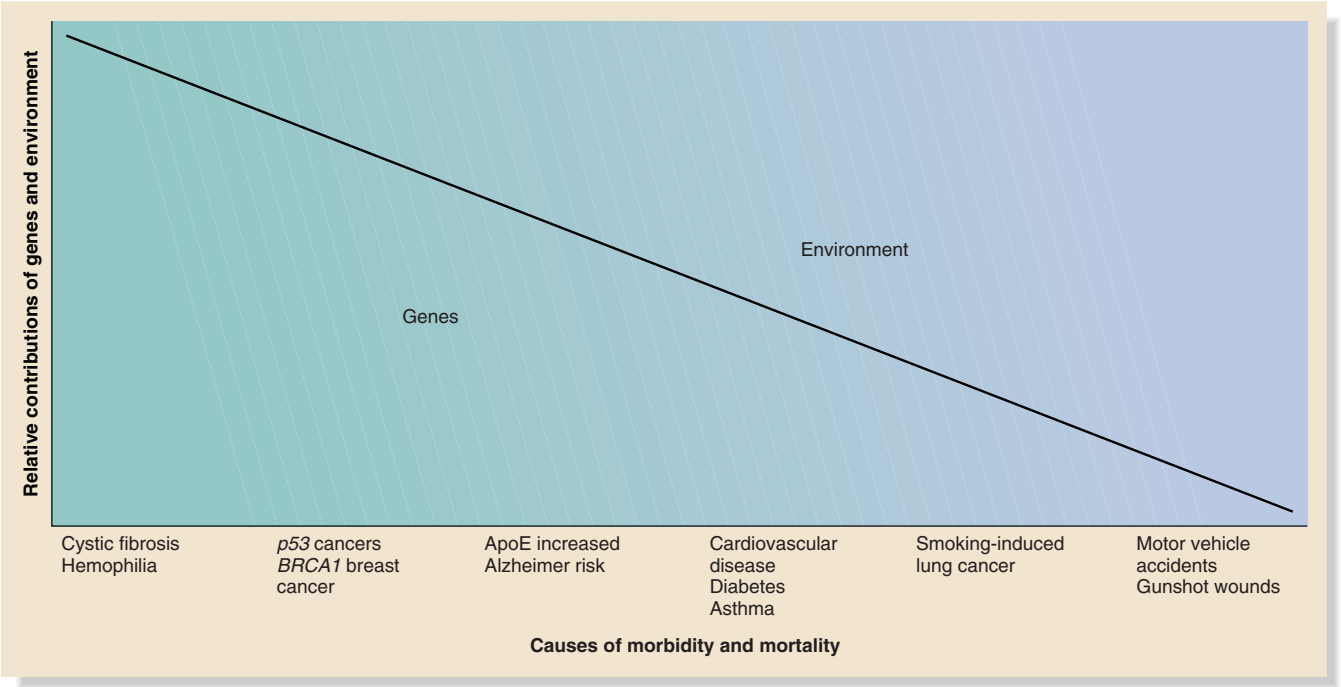


figure 7.1

Genes and environment. The comparative contributions of genes and the environment in causing traits and disorders form a continuum. In this schematic representation, the examples toward the left are caused predominantly by genes, and those to the right, more by environmental effects. The classic multifactorial conditions are in the middle—these are polygenic and influenced by the environment.

In contrast to a single gene disorder, a complex multifactorial condition may be caused by the additive contributions of several genes, each of which confers susceptibility. For example, we know that multiple sclerosis (MS) has a genetic component, because siblings of an affected individual are 25 times as likely to develop MS as siblings of people who do not have MS. One model of MS origin is that five susceptibility genes have alleles, each of which increases the risk of developing the condition. Those risks add up, and, in the presence of an appropriate (and unknown) environmental trigger, the disease begins.

Polygenic Traits Are Continuously Varying

For a polygenic trait, the combined action of many genes often produces a continuum of the phenotype, which is called a continuously varying or quantitative trait. The parts of chromosomes that contribute to polygenic traits are therefore called quantitative trait loci, or QTLs. A multifactorial trait is continuously varying only if it is also polygenic. That is, it is the genetic component of the trait that contributes the continuing variation of the phenotype. The individual genes that confer a polygenic trait follow Mendel's laws (if they are unlinked), but together they do not produce Mendelian ratios. They all contribute to the phenotype, without showing dominance or recessiveness with respect to each other. For example, the multiple genes that regulate height and skin color result in continuously varying traits that exhibit a range of possible phenotypes. Mendelian traits are instead discrete or qualitative, often providing an all-or-none phenotype such as "affected" versus "normal."

A polygenic trait is variable in populations, such as the many nuances of hair color, body weight, and cholesterol levels. Some genes contribute more to a polygenic trait than others, and within genes, certain alleles have differing impacts that depend upon exactly how they influence or contribute to a trait, as well as by how common they are in a particular population. For example, a mutation in the gene that encodes the receptor that takes low-density lipoproteins (LDL cholesterol) into cells drastically raises a person's blood serum cholesterol level. But because fewer than 1 percent of the individuals in most populations have this mutation, it contributes very little to the variation in cholesterol level seen at the population level.

Although the expression of a polygenic trait is continuous, we can categorize individuals into classes and calculate the frequencies of the classes. When we do this and plot the frequency for each phenotype class, a bell-shaped curve results. This curve indicating continuous variation of a polygenic trait is strikingly similar for any trait. Even when different numbers of genes affect the trait, the curve is the same shape, as is evident in the following examples.

Fingerprint Patterns, Height, and Eye Color

The skin on the fingertips folds into patterns of raised skin called dermal ridges that in turn align to form loops, whorls, and arches. A technique called dermatoglyphics ("skin writing") compares the number of ridges that comprise these patterns to identify and distinguish individuals (figure 7.2). Dermatoglyphics is part of genetics, because certain disorders (such as Down syndrome) are characterized by unusual ridge patterns, and of course it is also part of forensics, used for fingerprint analysis. Fingerprint pattern is a multifactorial trait.

The number of ridges in a fingerprint pattern is largely determined by genes, but also responds to the environment. During weeks 6 through 13 of prenatal development, the ridge pattern can be altered as the fetus touches the finger and toe pads to the wall of the amniotic sac. This early environmental effect explains why the fingerprints of identical twins, who share all genes, are not exactly alike.

We can quantify a fingerprint with a measurement called a total ridge count, which tallies the number of ridges comprising a whorl, loop, or arch part of the pattern for each finger. The average total ridge count in a male is 145, and in a female, 126. Plotting total ridge count reveals the bell curve characteristic of a continuously varying trait.

The effect of the environment on height is more obvious than that on fingerprint pattern—people who do not have enough to eat do not reach their genetic potential for height. Students lined up according to height vividly reveal the effects of genes and the environment on this continuously varying trait.

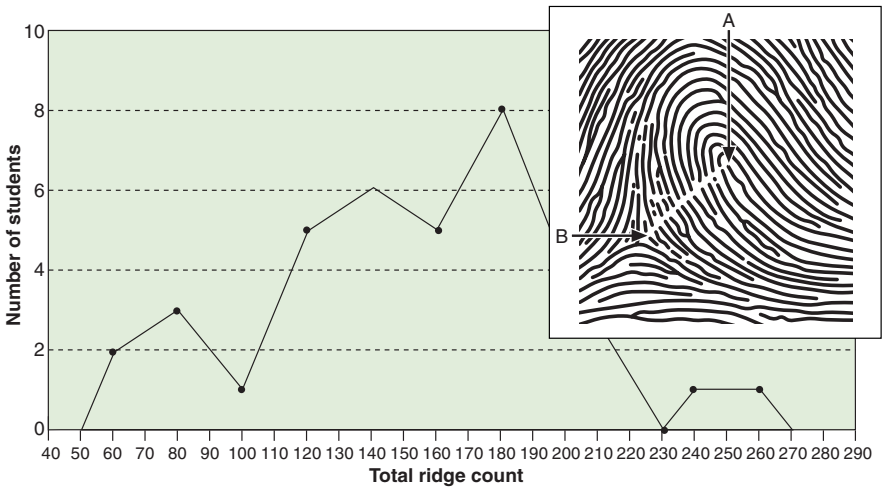


figure 7.2

Anatomy of a fingerprint. Total ridge counts of a number of individuals, plotted on a bar graph, form an approximate bell-shaped curve. This signals a multifactorial trait. The number of ridges between landmark points A and B on this loop pattern is 12. Total ridge count includes the number of ridges on all fingers.

The top part of figure 7.3 depicts students from 1920, and the bottom part, students from 1997. The similarity of the bell curve reflects the inherited component of the trait. But also note that the tallest people in the old photograph are 5′9″, whereas the tallest people in the more recent photograph are 6′5″. The difference is attributed to such factors as improved diet and better overall health.

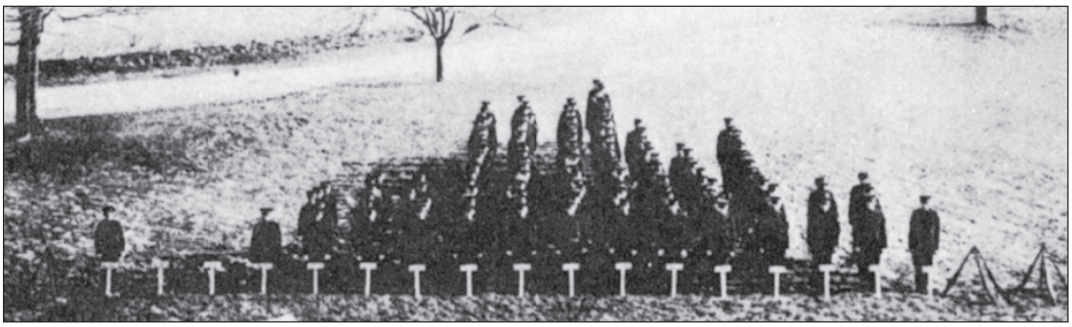
We usually do not know exactly how many genes contribute to multifactorial traits that are also polygenic. However, geneticists can suggest models for different expressions of a trait based on a certain number of genes acting in an additive manner. Figure 7.4 shows this approach for eye color, as figure 7.5 does for skin color.

The colored part of the eye, the iris, is colored by the pigment melanin, which cells called melanocytes produce. Blue eyes have just enough melanin to make the color opaque. People with dark blue or green, brown, or black eyes make increasingly more melanin in the iris. Unlike melanin in skin melanocytes, the pigment in the eye tends to stay in the cell that produces it. If there is such a thing as a purely polygenic trait—that is, one caused by genes but not the environment—then eye color might be a candidate.

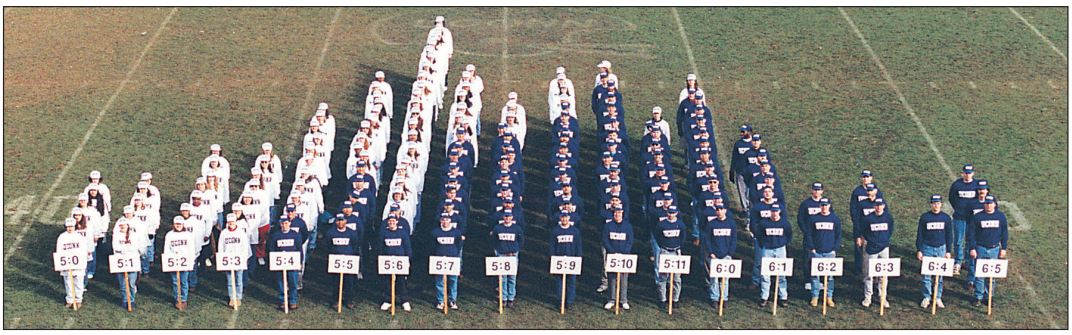
One model of how different eye colors arise considers two genes with two alleles each, that interact additively to produce five eye colors—light blue, deep blue or green, light brown, medium brown, and dark brown/black. (It seems that manufacturers of mascara follow this two-gene scheme.) If each allele contributes a certain amount of pigment, then the greater the number of such alleles, the darker the eye color. If eye color is controlled by two genes, *A* and *B*, each of which comes in two allelic forms—*A* and *a* and *B* and *b*—then the lightest color would be genotype *aabb;* the darkest, *AABB*. The bell curve arises because there are more ways to inherit light brown eyes, the midrange color, with any two contributing dominant alleles, than there are ways to inherit the other colors. Eye color may actually be more complex than a two-gene explanation.

A Closer Look at Skin Color

Skin color is also due to melanin production. Melanocytes in skin have long extensions that snake between the other, tile-like skin cells, distributing pigment granules through the skin layers. Some melanin exits the melanocytes and enters the hardened, or keratinized, cells in the skin's upper layers. Here the melanin breaks into pieces, and as the skin cells are pushed up towards the skin's surface, the melanin bits provide color. The pigment protects against DNA damage from ultraviolet radiation, and exposure to the sun increases melanin synthe-



a.



b.

figure 7.3

The inheritance of height. Previous editions of this (and other) textbooks have used the photograph in (*a*) to illustrate the continuously varying nature of height. In the photo, taken around 1920, 175 cadets at the Connecticut Agricultural College lined up by height. In 1997, Professor Linda Strausbaugh asked her genetics students at the school, today the University of Connecticut at Storrs, to recreate the scene (*b*). They did, and confirmed the continuously varying nature of human height. But they also elegantly demonstrated how height has increased during the 20th century. Improved nutrition has definitely played a role in expressing genetic potential for height. The tallest people in the old photograph (*a*) are 5′9″ tall, whereas the tallest people in the more recent photograph (*b*) are 6′5″ tall.

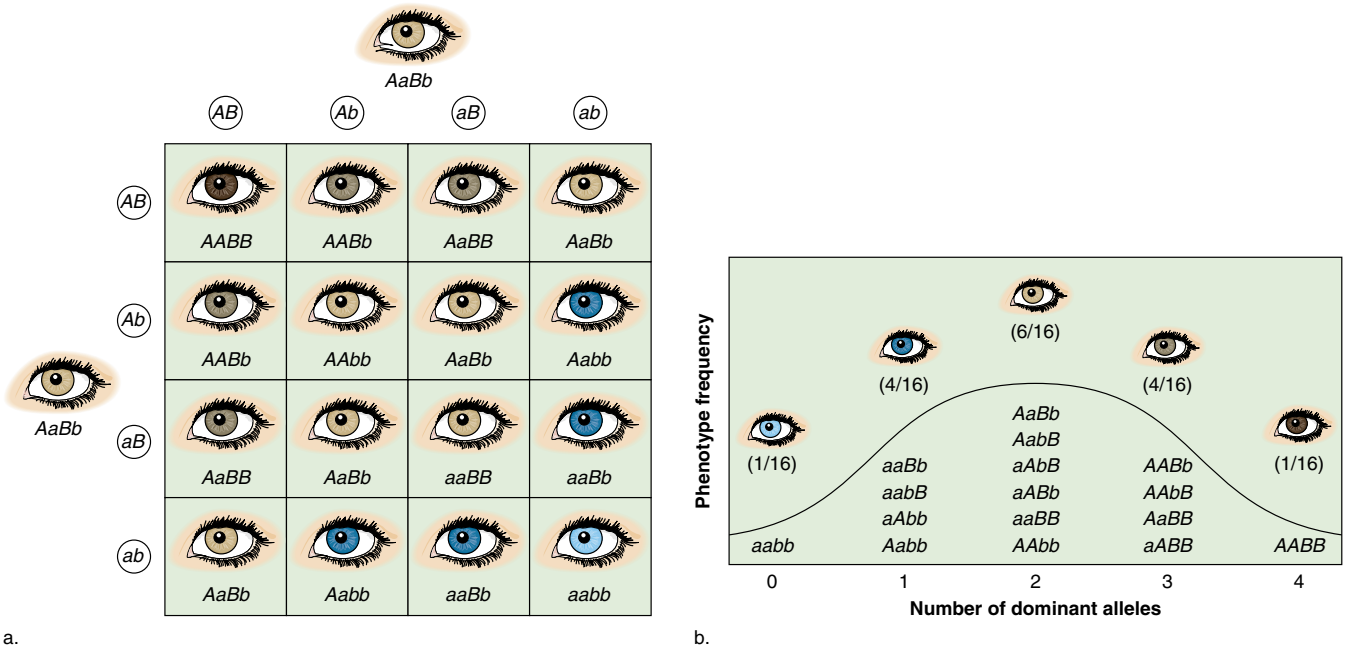


figure 7.4

Variations in eye color. (*a*) A model of two genes, with two alleles each, can explain existence of five eye colors in humans. (*b*) The frequency distribution of eye colors forms the characteristic bell-shaped curve for a polygenic trait.

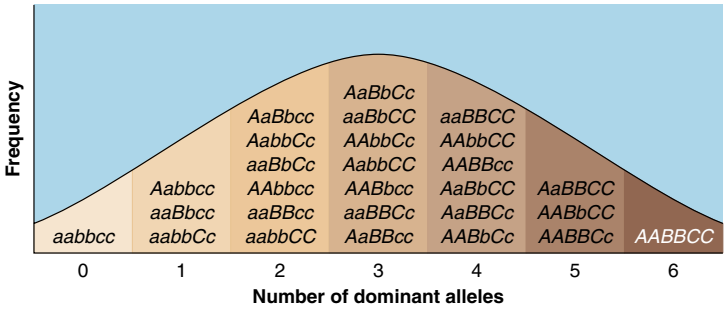


figure 7.5

Variations in skin color. A model of three genes, with two alleles each, can explain some of the hues of human skin. In actuality, this trait likely involves many more than three genes.

sis. Although people come in a wide variety of hues, we all have about the same number of melanocytes per unit area of skin. Differences in skin color arise from the number and distribution of melanin pieces in the skin cells in the uppermost layers. People with albinism cannot manufacture melanin (see figure 4.15).

The definition of race based on skin color is more a social construct than a biological concept. From a genetic perspective, races are groups within species that are distinguished by different allele frequencies. Although we tend to classify people by skin color because it is an obvious visible way to distinguish individuals, skin color is not a reliable indicator of heritage. Golfer Tiger Woods, for example, is African American, Caucasian, Asian, and Native American. He illustrates that skin color alone hardly indicates a person's ethnic and genetic background (figure 7.6). The case of Thomas Jefferson and his dark-skinned descendants described in chapter 1 also illustrates how the

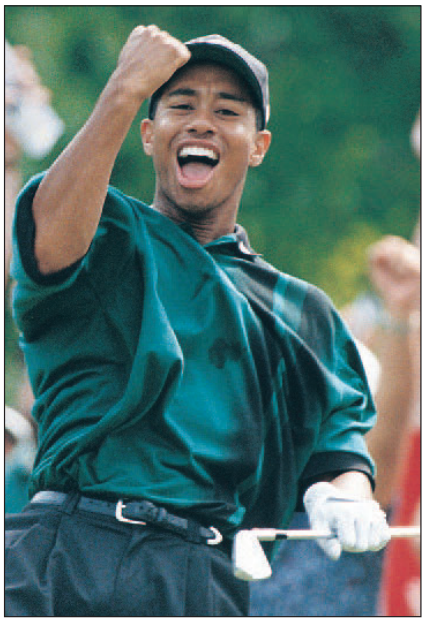


figure 7.6

Skin color is only one way humans differ from each other. Golfer Tiger Woods objected to being called black; he is actually part African American, Caucasian, Asian, and Native American.

traditional definition of race considers only one trait—the distribution of melanin. When many genes are examined, two people with black skin may be less alike than either is to another person with white skin. On a population level, sub-Saharan Africans and Australian aborigines have dark skin, but they are very dissimilar in other inherited characteristics. Their dark skins may reflect the same adaptation (persistence of a valuable genetic trait) to life in a sunny, tropical climate.

Even as racial distinctions based on skin color continue to cause social problems, people are beginning to rethink accepted definitions of race, if only to recognize more variations of skin color. The U.S. Census expanded racial classifications to include multiracial groups, but this led to confusion. In 2000, nearly 7 million people checked more than one box for race. About 800,000 people claimed to be both black and white, presumably because they have one parent of each race. An editorial on the census results in a prominent medical journal concluded that this self-identification in more than one racial group "underscores the heterogeneity of the U.S. population and the futility of using race as a biologic marker."

The American College of Physicians advises its members not to indicate race on medical records, because it does not provide any valuable medical information. In fact, recent studies show that screening for variants of genes that control response to a particular drug is a better predictor of efficacy than prescribing a drug based on consideration of skin color. This study was published shortly after two others that showed that of two drugs used to treat heart failure, one worked equally well in blacks and whites, and the other was more effective in whites. Some physicians criticized the implication to not give blacks the second drug, because some people with darker skin might indeed be best helped with that drug. Human genome information, perhaps in the form of SNP patterns, will help physicians select the drugs that will treat individual patients, based on genotypes that directly relate to a drug's mechanism of action. Overall, 93 percent of inherited traits that vary are no more common in people of one skin color than any other.

Fingerprint pattern, height, eye color, and skin color are "normal" polygenic, multifactorial traits. Illnesses, too, may result from the interplay of a gene or genes with environmental influences. Reading 7.1 presents three interesting examples of environmental influences on illness.

KEY CONCEPTS

Polygenic traits are determined by more than one gene and vary continuously in expression. Multifactorial traits are determined by a combination of a gene or genes and the environment. • A bell curve describes the distribution of phenotypic classes of a polygenic trait, such as fingerprint pattern, height, eye color, and skin color.

7.2 Methods Used to Investigate Multifactorial Traits

It is much more challenging to predict recurrence risks for polygenic traits and disorders than it is for Mendelian traits. Geneticists evaluate the input of genes, using information from population and family studies.

Empiric Risk

Using Mendel's laws, it is possible to predict the risk that a single gene trait will recur in a family if one knows the mode of inheritance—such as autosomal dominant or recessive. To predict the risk that a multifactorial trait will recur, geneticists use **empiric risks,** which are predictions of recurrence based on the trait's incidence in a specific population. Incidence is the rate at which a certain event occurs, such as the number of new cases of a particular disorder diagnosed per year in a population of known size.

Empiric risk is not a calculation, but an observation, a population statistic. The population might be broad, such as an ethnic group or residents of a geographical area, or genetically more well-defined, such as families that have a particular disease. In general, empiric risk for an individual increases with the severity of the disorder, the number of affected family members, and how closely related the person is to affected individuals.

Empiric risk may be used to predict the likelihood that a neural tube defect (NTD) will recur. In the United States, the overall population's risk of carrying a fetus with an NTD is about 1 in 1,000 (0.1 percent). For people of English, Irish, or Scottish ancestry, the risk is about 3 in 1,000. However, if a sibling has an NTD, no matter what the ethnic group, the risk of recurrence increases to 3 percent, and if two siblings are affected, the risk to a third child is even greater. By determining whether a fetus has any siblings with NTDs, a genetic counselor can predict the risk to that fetus, using the known empiric risk.

If a trait has an inherited component, then it makes sense that the closer the relationship between two individuals, one of whom has the trait, the greater the probability that the second individual has the trait, too. Studies of empiric risk support this logic. Table 7.1 summarizes the empiric risk

table 7.1

Empiric Risk of Recurrence for Cleft Lip

Relationship to Affected Person	Empiric Risk of Recurrence
Identical twin	40.0%
Sibling	4.1%
Child	3.5%
Niece/nephew	0.8%
First cousin	0.3%
General population risk (no affected relatives)	0.1%

Reading 7.1

Disentangling Genetic from Environmental Effects

Sometimes it is difficult to determine whether differences among individuals for a trait are caused by genes, the environment, or both. The following examples illustrate how important it can be to understand effects on gene expression. Even a Mendelian (single gene) disorder can be influenced by the actions of other genes or environmental factors.

Cystic Fibrosis

When researchers realized that cystic fibrosis (CF) was caused by several allele combinations that produce varying degrees of symptom severity, they attempted to see if genotypes correlated to specific phenotypes. Such information would inform people of how sick they would become. Unfortunately, researchers could not establish a direct correlation. Apparently, other genes influence the expression of the cystic fibrosis alleles.

CF held another surprise. In many cases, an environmental input influences the course of an inherited illness; in CF, it was the other way around. The thick mucus that builds up along airway linings provides a very attractive environment for bacteria, most notably a highly transmissible and quick-killing species called *Burkholderia cepacia.* Bacterial infection is familiar to people with CF, but in the past, they have usually been infected by *Pseudomonas aeruginosa.* Unlike a *Pseudomonas* infection, which can be present, on and off, for two decades before it kills, *B. cepacia* can do so in weeks. *B. cepacia* have appendages called cable pili that enable them to anchor tenaciously to the mucus-covered cells lining the airway. They are resistant to most antibiotic drugs.

Epidemics of *B. cepacia* were first reported a few years ago from Toronto and Edinburgh, under tragic circumstances. Because the infection is transferred so easily from person to person, it swept through summer camps for children with CF. Patients and their families were not prepared for such deadly bacterial infections. The camps and other support services are vitally important to affected families, but suddenly any patient with a *B. cepacia* diagnosis was isolated to avoid spread of the infection to others with CF.

Genetics has helped these patients a little. But rather than determining genotypes for the underlying CF, researchers are typing the DNA of the bacteria. Only patients with the more virulent strains of *B. cepacia* need be isolated. The task now is to correlate all of the information: Which CF genotypes attract which genetic variants of which bacteria?

Type I Diabetes Mellitus

Type I or juvenile diabetes mellitus runs in families, but in no particular pattern of recurrence. The reason for the unpredictability may be environmental. In this inborn error in glucose (sugar) metabolism, the immune system attacks the pancreas. As a result, the pancreas does not produce the insulin required to route blood glucose into cells for use.

When studying the pancreases of young people who died suddenly just weeks after being diagnosed with diabetes, researchers observed severe infection of the pancreas plus an unusually strong immune response to the infection. They concluded that certain individuals may inherit a susceptibility to that type of infection or a strong immune response to it, but not develop diabetes unless such an infection occurs.

Neural Tube Defects

Sometimes what appears to be an environmental influence is actually genetic. This may be the case for neural tube defects (NTDs), which are openings in the brain or spinal cord that occur at the end of the first month of prenatal development.

An NTD is an example of a "threshold" birth defect, in which no particular gene is implicated, but the effects of several genes and environmental influences sum, expressing the phenotype after a certain point is reached. Such a condition has a high population frequency compared to a Mendelian trait (1/1,000 for NTDs), and recurrence risk in an affected family is low (2 to 5 percent for NTDs).

Researchers have long attributed NTDs to a combination of genes and the environment, based on two observations.

1. A woman who has one affected child is at increased risk of having another affected child (implicating heredity).
2. Recurrence risk diminishes by 70 percent if a woman takes folic acid supplements shortly before and during pregnancy (implicating a vitamin deficiency).

An inherited enzyme deficiency may explain why vitamin supplementation prevents some NTDs. A large group of Irish women whose children have NTDs were found to be deficient in both folic acid and vitamin B_{12}. Only one biochemical reaction in the human body requires both of these vitamins; an abnormality in the enzyme that catalyzes that reaction could cause the double vitamin deficiency. Researchers are now trying to determine how disruption of this reaction causes an NTD. Meanwhile, pregnant women routinely take folic acid supplements to reduce the incidence of these birth defects. In the future, genetic tests will be able to identify women whose embryos are most likely to benefit from folic acid supplementation.

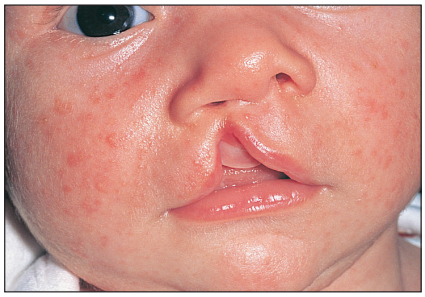


figure 7.7

Cleft lip. Cleft lip is more likely to occur in a person who has an affected relative.

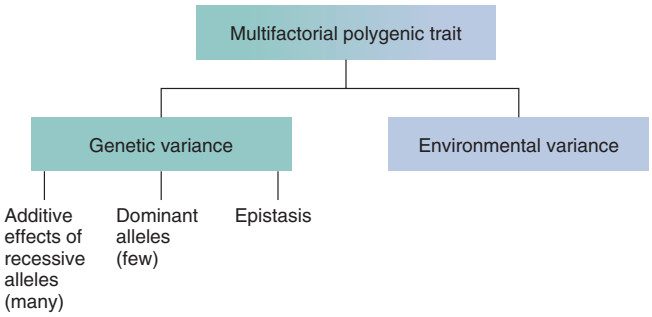


figure 7.8

Heritability estimates the genetic contribution to a trait. Observed variance in a polygenic, multifactorial trait or illness reflects genetic and environmental contributions. Genetic variants are mostly determined by additive effects of recessive alleles of different genes, but can also be influenced by effects of a few dominant alleles and by epistasis (interactions between alleles of different genes).

for cleft lip (figure 7.7) among groups of identical twins, siblings, parent-child pairs, nieces and nephews to uncles and aunts, cousins, and the general population.

Because empiric risk is based solely on observation, we can use it to derive risks of recurrence for disorders with poorly understood transmission patterns. For example, certain multifactorial disorders affect one sex more often than the other. Pyloric stenosis is an overgrowth of muscle at the juncture between the stomach and the small intestine. It is five times more common among males than females. The condition must be corrected surgically shortly after birth, or the newborn will be unable to digest foods. Empiric data show that the risk of recurrence for the brother of an affected brother is 3.8 percent, but for the brother of an affected sister, the risk is 9.2 percent.

Heritability—The Genetic Contribution to a Multifactorial Trait

As Charles Darwin observed, some of the variation of a trait is due to heredity, and some to environmental influences. A measurement called **heritability,** designated H, estimates the percentage of the phenotypic variation for a particular trait that is due to genes in a certain population at a certain time. Figure 7.8 outlines the factors that contribute to observed variation in a trait. Heritability equals 1.0 for a trait that is completely the result of gene action, and 0 if it is entirely caused by an environmental influence. Most traits lie in between. For example, height has a heritability of 0.8, and body mass index, which is a measure of weight taking height into account, has a heritability of 0.55. Table 7.2 lists some traits and their heritabilities.

Heritability changes as the environment changes. For example, the heritability of skin color would be higher in the winter months, when sun exposure is less likely to increase melanin synthesis.

Heritability can be estimated in several ways using statistical methods. One way is to compare the actual proportion of pairs of people related in a certain manner who share a particular trait, to the expected proportion of pairs that would share it if it were inherited in a Mendelian fashion. The expected proportion is derived by knowing the blood relationships of the individuals, and using a measurement called the **correlation coefficient,** which is the proportion of genes that two people related in a certain way share (table 7.3). (It is also called the coefficient of relatedness.) A parent and child, for example, share 50 percent of their genes, because of the mechanism of meiosis. Siblings share on average 50 percent of their genes, because they have a 50 percent chance of inheriting each allele for a gene from each parent. (The designations of primary (1°), secondary (2°), and tertiary (3°) relatives are useful in genetic counseling when empiric risks are consulted.)

If the heritability of a trait is very high, then of a group of 100 sibling pairs, nearly 50 would be expected to have it, because siblings share on average 50 percent of their genes. Height is a trait for which heritability reflects the environmental influence of nutrition. Of 100 sibling pairs in a population, for example, 40 are the same number of inches tall. Heritability for height among this group of sibling pairs is .40/.50, or 80 percent, which is the observed phenotypic variation divided by the expected phenotypic variation if environment had no influence.

Genetic variance for a polygenic trait is mostly due to the additive effects of recessive alleles of different genes. For some traits, a few dominant alleles can greatly influence phenotype, but because they are

table 7.2

Heritabilities for Some Human Traits

Trait	Heritability
Clubfoot	0.8
Height	0.8
Blood pressure	0.6
Body mass index	0.5
Verbal aptitude	0.7
Mathematical aptitude	0.3
Spelling aptitude	0.5
Total fingerprint ridge count	0.9
Intelligence	0.5–0.8
Total serum cholesterol	0.6

table 7.3

Correlation Coefficients for Pairs of Relatives

Relationship	Degree of Relationship	Percent Shared Genes (Correlation Coefficients)
Sibling to sibling	1°	50% (1/2)
Parent to child	1°	50% (1/2)
Uncle/aunt to niece/nephew	2°	25% (1/4)
Grandparent to grandchild	2°	25% (1/4)
First cousin to first cousin	3°	12 1/2% (1/8)

rare, they do not contribute greatly to heritability. Heart disease caused by a faulty LDL (low density lipoprotein cholesterol) receptor is an example of a condition caused by a rare dominant allele, but that is also influenced by many other genes. Epistasis (interaction between alleles of different genes) can also influence heritability. Some geneticists calculate a "narrow" heritability that considers only additive recessive effects, and a "broad" heritability that also considers the effects of rare dominant alleles and epistasis. For LDL cholesterol level, for example, the narrow heritability is 0.36, but the broad heritability is 0.96, reflecting the fact that a rare dominant allele can have a large impact on LDL level.

Multifactorial inheritance has many applications in agriculture, where a breeder needs to know whether such traits as birth weight, milk yield, length of wool fiber, and egg hatchability are determined largely by heredity or the environment. The breeder can control the environmental input by adjusting the conditions under which animals are raised, and the inherited input by setting up matings between particular individuals. Studying multifactorial traits in humans is difficult, because information must be obtained from many families. Two special types of people, however, can help geneticists to tease apart the genetic and environmental components of multifactorial traits—adopted individuals and twins.

Adopted Individuals

A person adopted by people who are not blood relatives shares environmental influences, but typically not many genes, with his or her adoptive family. Conversely, adopted individuals share genes, but not the exact environment, with their biological parents. Therefore, biologists assume that similarities between adopted people and adoptive parents reflect mostly environmental influences, whereas similarities between adoptees and their biological parents reflect mostly genetic influences. Information on both sets of parents can reveal how heredity and the environment each contribute to the development of a trait.

Many early adoption studies used the Danish Adoption Register, a compendium of all adopted Danish children and their families from 1924 to 1947. One study examined correlations between causes of death among biological and adoptive parents and adopted children. If a biological parent died of infection before age 50, the adopted child was five times more likely to die of infection at a young age than a similar person in the general population. This may be because inherited variants in immune system genes increase susceptibility to certain infections. In support of this hypothesis, the risk that an adopted individual would die young from infection did not correlate with adoptive parents' death from infection before age 50.

Although researchers concluded that length of life is mostly determined by heredity, they did find evidence of environmental influences. For example, if adoptive parents died before age 50 of cardiovascular disease, their adopted children were three times as likely to die of heart and blood vessel disease as a person in the general population. What environmental factor might account for this correlation?

Twins

Studies that use twins to separate the genetic from the environmental contribution to a phenotype provide more meaningful information than studying adopted individuals. In fact, twin studies have largely replaced adoption methods.

Using twins to study genetic influence on traits dates to 1924, when German dermatologist Hermann Siemens compared school transcripts of identical versus fraternal twins. Noticing that grades and teachers' comments were much more alike for identical twins than for fraternal twins, he proposed that genes contribute to intelligence.

A trait that occurs more frequently in both members of identical (MZ) twin pairs than in both members of fraternal (DZ) twin pairs is at least partly controlled by heredity. Geneticists calculate the **concordance** of a trait as the percentage of pairs in which both twins express the trait.

In one study, 142 MZ twin pairs and 142 DZ twin pairs took a "distorted tunes test," in which 26 familiar songs were played, each with at least one note altered. A person was considered to be "tune deaf" if he or she failed to detect three or more of the mistakes. Concordance for "tune deafness" was 0.67 for MZ twins, but only 0.44 for DZ twins, indicating a considerable inherited component in the ability to perceive musical pitch accurately. Figure 7.9 compares twin types for a variety of hard-to-measure traits. Figure 3.16 shows how DZ and MZ twins arise.

Diseases caused by single genes that are 100 percent penetrant, whether dominant or recessive, are 100 percent concordant in MZ twins. If one twin has the disease, so does the other. However, among DZ twins, concordance generally is 50 percent for a dominant trait and 25 percent for a recessive trait. These are the Mendelian values that apply to any two siblings. For a polygenic trait with little environmental input, concordance values for MZ twins are significantly greater than for DZ twins. A trait molded mostly by the environment exhibits similar concordance values for both types of twins.

An ongoing investigation called the Twins Early Development Study shows how concordance values indicate the degree to which heredity contributes to a trait. Headed by Robert Plomin of the Institute of

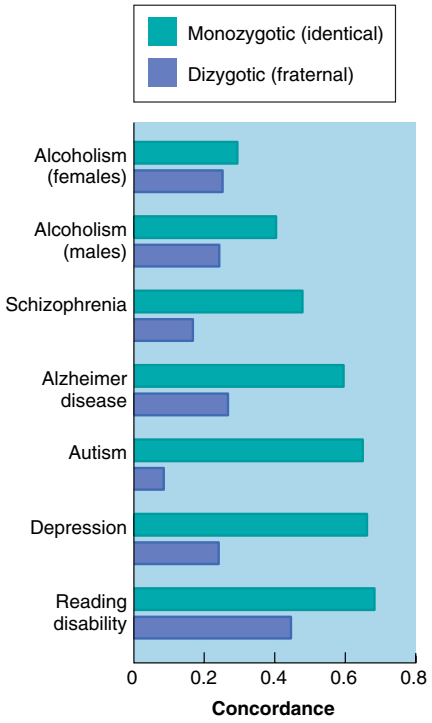


figure 7.9

Twin studies. A trait more often present in both members of MZ twin pairs than in both members of DZ twin pairs is presumed to have a significant inherited component.

Source: Robert Plomin, et al., "The Genetic Basis of Complex Human Behaviors," *Science* 17 June 1994, vol. 264, pp. 1733–39. Copyright 1994 American Association for the Advancement of Science.

Psychiatry in London, this project is following 7,756 pairs of twins born in England and Wales in 1994. One experiment looked at 2-year-olds whose language skills place them in the lowest 5 percent of children that age. With the parents' help, researchers recorded the number of words in the vocabularies of 1,044 pairs of identical twins, 1,006 pairs of same-sex fraternal twins, and 989 pairs of opposite-sex twins. The results clearly indicated a large genetic influence for children lagging behind in language skills—the concordance for the identical twins was 81 percent, but it was 42 percent for the fraternal twins. Put another way, if an identical twin fell into the lowest 5 percent of 2-year-olds for language acquisition, the chance that her identical twin would, too, was 81 percent. But if a fraternal twin was in this category, the chance that her twin would also be was only 42 percent. When similar assessments were done on twin pairs of all abilities, the differences between the concordance values was not nearly as great. This indicates that the environment plays a larger role in most children's adeptness at learning vocabulary than it does for the 5 percent who struggle to do so.

Comparing twin types has a limitation—the technique assumes that both types of twins share similar experiences. In fact, identical twins are often closer than fraternal twins. This discrepancy between how close the two types of twins are led to misleading results in twin studies conducted in the 1940s. One study concluded that tuberculosis is inherited because concordance among identical twins was higher than among fraternal twins. Actually, part of the reason for the difference in concordance was that the infectious disease was more readily passed between identical twins because their parents kept them in close physical contact.

A more informative way to use twins to assess the genetic component of a multifactorial trait is to study identical twins who were separated at birth, then raised in very different environments. Hermann Siemens suggested this in 1924, but much of the work using this "twins reared apart" approach has taken place at the University of Minnesota. Here, since 1979, hundreds of sets of identical/fraternal twins and triplets who were separated at birth have visited the laboratories of Thomas Bouchard. For a week or more, the twins and triplets undergo tests that measure physical and behavioral traits, including 24 different blood types, handedness, direction of hair growth, fingerprint pattern, height, weight, functioning of all organ systems, intelligence, allergies, and dental patterns. Researchers videotape facial expressions and body movements in different circumstances and probe participants' fears, vocational interests, and superstitions.

Twins and triplets separated at birth provide natural experiments for distinguishing nature from nurture. Many of their common traits can be attributed to genetics, especially if their environments have been very different (figure 7.10). By con-

Separated at birth, the Mallifert twins meet accidentally.

figure 7.10

trast, their differences tend to reflect differences in their upbringing, since their genes are identical (MZ twins and triplets) or similar (DZ twins and triplets).

The researchers have found that identical twins and triplets separated at birth and reunited later are remarkably similar, even when they grow up in very different adoptive families. Idiosyncrasies are particularly striking. For example, twins who met for the first time when they were in their thirties responded identically to questions; each paused for 30 seconds, rotated a gold necklace she was wearing three times, and then answered the question. Coincidence, or genetics?

The "twins reared apart" approach is not a perfectly controlled way to separate nature from nurture. Identical twins and other multiples share an environment in the uterus and possibly in early infancy that may affect later development. Siblings, whether adoptive or biological, do not always share identical home environments. Differences in sex, general health, school and peer experiences, temperament, and personality affect each individual's perception of such environmental influences as parental affection and discipline.

Adoption studies, likewise, are not perfectly controlled experiments. Adoption agencies often search for adoptive families with ethnic, socioeconomic, or religious backgrounds similar to those of the biological parents. Thus, even when different families adopt and raise separated twins, their environments might not be as different as they might be for two unrelated adoptees. However, twins and triplets reared apart are still providing intriguing insights into the number of body movements, psychological quirks, interests, and other personality traits that seem to be rooted in our genes.

Association Studies

Empiric risk, heritability, and adoptee and twin studies are traditional ways of estimating the degree to which genes contribute to the variability of a trait or illness. Until recently, geneticists had to be satisfied with these limited measures of inheritance. With genomics, however, powerful tools are emerging that can help to identify the specific genes that contribute directly to pathogenesis, or confer susceptibility to, disease.

Identifying the single genes behind Mendelian traits and disorders has largely relied on linkage analysis, discussed in chapters 5 and 22. Researchers compiled data on families with more than one affected member, determining whether a section of chromosome (a marker) was inherited along with a disease-causing gene by inferring whether alleles of the two genes were in coupling or repulsion (see figure 5.13). Such linkage analysis in humans is extremely difficult to do because the rarity of single gene disorders makes it hard to find enough families and individuals to compare. Because detecting linkage to one gene is so difficult, using the approach to identify the several genes that contribute to a polygenic trait is even more daunting. Fortunately, another, related method is coming to the forefront of genetic research and can more powerfully detect the several genes that contribute to a polygenic trait—**SNP mapping.** Because SNP mapping tracks large populations rather than families, it is somewhat easier to find participants, although the sheer volume of data can seem overwhelming—at least to a human. (Computers can handle it!)

Recall from chapter 1 that a SNP, or single nucleotide polymorphism, is a site within a DNA sequence that varies in at least 1 percent of a population. The human genome has about 12 to 16 million SNPs among the 3 billion bases. Researchers have identified more than 3 million SNPs. The number comes from an analysis of linkage disequilibrium (LD), which is the tendency for certain SNPs to be inherited together. Linkage disequilibrium generally occurs over areas that are 5,000 to 50,000 bases long. Three million SNPs, spread out over the genome, will enable researchers to pair specific SNPs with specific genes that cause or contribute to a particular disease or trait, because the distance between the SNPs will be less than the average length of a DNA sequence that is in linkage disequilibrium. Several SNPs that are transmitted together constitute a haplotype, which is short for "haploid genotype."

SNPs are useful in **association studies,** in which researchers compare SNP patterns between a group of individuals who have a particular disorder and a group that does not. An association study uses a case-control design, which means that each individual in one group is matched to an individual in the other group so that as many characteristics as possible are shared, such as age, sex, activity level, and environmental exposures. In this way, SNP differences can be contrasted to presence or absence of the particular medical condition. Variables are limited. When many SNPs are considered, many susceptibility genes can be tracked, and patterns may emerge that can then be used to predict the course of the illness.

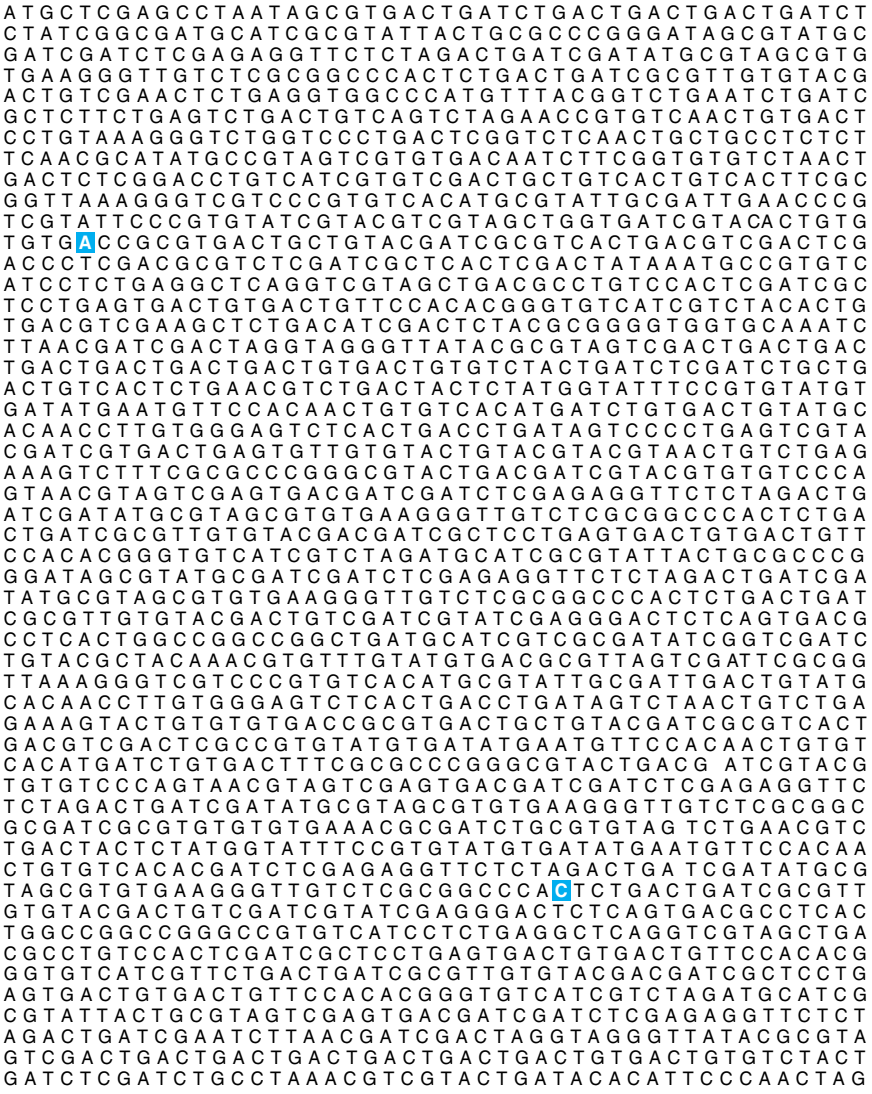
It will take a great deal of research to test whether SNP patterns are actually meaningful. For example, if a certain SNP pattern in a population is associated with breast cancer, then the next step might be for researchers to see if these tumors are different, at a cell and tissue level, from other cases of breast cancer. Software can compare SNP and histological data to see if the SNP pattern accurately reflects a physically distinct subtype of the disease. Then, eventually, a simple SNP scan might replace or augment microscopic analysis of the tumor. Figure 7.11 shows how SNP patterns are generated and compared in association studies.

SNP association studies, which are well under way in many biotech and pharmaceutical companies as well as academic laboratories, promise many practical benefits. Obtaining SNP maps is a much faster way to identify DNA sequence differences among individuals than sequencing everyone's genome. The correlations between SNP patterns and elevated disease risks may be able to guide medical care, including the ability to make more meaningful prognoses, and to predict an individual's likely response to a particular drug. Identifying the SNPs that travel with genes of interest will enable researchers to then search through human genome data to identify nearby genes whose protein products suggest that they could be implicated in the pathogenesis of the disorder. This was the case, for example, in Crohn disease, in which the intestines become severely inflamed in response to the presence of certain bacteria.

Two different research groups identified a gene that increases risk for developing Crohn disease. One group consulted older linkage data that indicated a causative gene on chromosome 16 in some families. These researchers considered all the genes identified so far in that region, and pursued one, called NOD2, that encodes a protein that takes part

figure 7.11

Association studies. Association studies are correlations that use SNP profiles. By considering many individuals and many SNPs, researchers correlate SNP patterns with genes that affect health. Such correlations identify parts of chromosomes that are associated with increased risk of developing the particular condition. (*a*) This illustration is a schematic view of how frequently SNPs occur—about one per 1,200 bases, although they are not evenly distributed. (*b*) An individual SNP may be correlated to one gene that contributes to a particular phenotype. For polygenic traits, SNP patterns on several chromosomes might be considered.



in the inflammatory response. Then they examined DNA from patients and controls and found that patients were more likely to have mutations in this gene than the healthy comparisons. The second research group looked at 11 SNPs in 235 families with affected members. They found a certain pattern that was more likely than chance to be present in the affected individuals, and found that these people also had mutations in the NOD2 gene.

The Crohn disease research reveals a limitation of association studies—they are just correlations, not proofs of causation. It is rare to find a DNA sequence that contributes to a polygenic trait that is found exclusively in affected individuals. The NOD2 allele that elevates risk of developing Crohn disease, for example, is found in 5 percent of the general population, but in 15 percent of individuals with the condition. Clearly, more than one gene contributes to Crohn disease. Further studies will expand the number of SNPs and search for associations on other chromosomes.

The more complex a SNP association study, the more individuals are required to achieve statistical significance. Consider an investigation that examines 20 genes, each with 4 SNPs, that contribute to development of a particular polygenic disease. A screen would look for 80 data points per individual. With so many possible genotypes (3,160), it's clear that many thousands of individuals would have to be examined to note any correlations between the SNP pattern and disease.

Table 7.4 reviews the measures of multifactorial traits.

table 7.4

Terms Used in Evaluating Multifactorial Traits

Association Study Detecting correlation between SNP (or other marker) patterns and increased risk of developing a particular medical condition.

Empiric Risk The risk of recurrence of a trait or illness based on known incidence in a particular population.

Heritability The percentage of phenotypic variation for a trait that is attributable to genetic differences. It equals the ratio of the observed phenotypic variation to the expected phenotypic variation for a population of individuals who are related in a particular way.

Correlation Coefficient The proportion of genes that two people related in a particular way share. Used to calculate heritability.

Concordance The percentage of twin pairs in which both twins express a trait.

Association studies that correlate SNP patterns to increased disease risk are replacing linkage studies based on families. Association studies are suited for polygenic disorders because they can track correlations to several genes.

KEY CONCEPTS

Empiric risk applies population incidence data to predict risk of recurrence for a multifactorial trait or disorder. • Heritability measures the genetic contribution to a multifactorial trait; it is specific to a particular population at a particular time. A correlation coefficient is the proportion of genes that individuals related in a certain way are expected to share, and is used to calculate heritability. • Researchers compare traits in adopted individuals to those in their adoptive and biological parents to assess the genetic contribution to a trait. • Concordance is the percentage of twin pairs in which both express a trait. For a trait largely determined by genes, concordance is higher for MZ than DZ twins.

7.3 Some Multifactorial Traits

Multifactorial traits include such common conditions as heart and blood vessel (cardiovascular) disease and obesity, as well as harder-to-define traits such as intelligence and aspects of personality, mood, and behavior.

Heart Health

Arthur Ashe was a professional tennis player who suffered a severe heart attack in his early thirties. He was in top physical shape and followed a low-fat diet, but an inherited tendency to deposit lipids (fats) on the insides of his coronary arteries led to a heart attack. He eventually died of AIDS, which he acquired from a blood transfusion during heart surgery.

In contrast to Arthur Ashe was the case of an 88-year-old man reported in a medical journal. He ate 25 eggs a day, yet had a very healthy heart and low serum cholesterol level. The lucky egg eater didn't have a sky-high cholesterol level or plaque-clogged coronary arteries because his particular metabolism, orchestrated by genes, could handle the large load of dietary lipids. The vastly different health status of Arthur Ashe and the elderly egg lover demonstrates the powerful influence of genes—Ashe followed all preventative measures and suffered a heart attack; the 88-year-old ate a diet oozing with cholesterol and enjoyed good cardiovascular health.

Genes control how well the body handles levels of lipids in the blood; how readily the blood clots; blood pressure; and the stickiness of white blood cells to the walls of blood vessels, a property controlled by cellular adhesion factors (see figure 2.21). Fats are insoluble in the fluid environment of the blood, but when bound to proteins to form large molecules called lipoproteins, fats can travel in the circulation. Several genes encode the protein parts of lipoproteins, called apolipoproteins. Some types of lipoproteins ferry lipids in the blood to tissues, where they are utilized, and other types of lipoproteins take lipids to the liver, where they are dismantled or converted to biochemicals that the body can excrete more easily. One allele of a gene that encodes apolipoprotein E, called E4, increases the risk of a heart attack threefold in people who smoke. This is clear evidence that genes and environmental factors can interact in ways that cause illness.

Maintaining a healthy cardiovascular system requires a balance: cells require sufficient lipid levels inside but cannot allow too much accumulation on the outside. Several dozen genes control lipid levels in the blood and tissues by specifying other proteins. These include enzymes that process lipids; that transport lipids; and proteins that function as receptors that admit lipids into cells.

Much of what we know about genetic control of cardiovascular health comes from studying rare inherited conditions. Identifying and understanding a genetic cause of a disease can help the larger number of people who suffer from noninherited forms of the illness. For example, the cholesterol-lowering drugs that millions of people take today, called statins, grew out of research on people with familial hypercholesterolemia, described in figure 5.2. In another example, inborn errors of metabolism that affect several types of liver enzymes led to the discovery that high blood levels of an amino acid, homocysteine, elevate the risk of developing arteriosclerosis. This is the hardening and narrowing of arteries that precede cholesterol deposition. Getting enough dietary folic acid can keep homocysteine levels within a healthy range.

As many as 20 to 50 genes regulate blood pressure. One gene encodes angiotensinogen, a protein that is elevated in the blood of people with hypertension. This

protein controls blood vessel tone and fluid balance in the body. Certain alleles are found much more frequently among people with hypertension than chance would explain. Even though environmental factors, such as emotional stress, can raise blood pressure, knowing who is genetically susceptible to dangerously high blood pressure can alert doctors to monitor high-risk individuals.

An enzyme, lipoprotein lipase, specified by a gene on chromosome 8, is important in lipid metabolism. It lines the walls of the smallest blood vessels, where it breaks down fat packets released from the small intestine and liver. Lipoprotein lipase is activated by high-density lipoproteins (HDLs), and it breaks down low-density lipoproteins (LDLs). High HDL levels and low LDL levels are associated with a healthy cardiovascular system.

A group of autosomal recessive inborn errors of metabolism called type I hyperlipoproteinemias cause a deficiency of lipoprotein lipase, which in turn causes triglycerides (a type of fat) to build to dangerously high levels in the blood. Lipoprotein lipase also regulates fat cell size; fat cells usually contribute to obesity by enlarging, rather than by dividing to form more fat cells.

The fluidity of the blood is also critical to cardiovascular health. Overly active clotting factors, overly sticky white blood cells, or disregulation of homocysteine can induce formation of clots that block blood flow, usually in blood vessels in the heart or in the legs.

Genetic research into cardiovascular function is leading the way in the analysis of multifactorial disease. One pharmaceutical company offers a genetic test panel that detects either of two alleles at 35 sites within 15 genes (figure 7.12). A patient's DNA is applied to a nylon strip containing the test genes, and a dark line forms where the sample matches the test, revealing which genes predisposing to cardiovascular disease are present. DNA microarrays will test for many more characteristics that affect the heart and blood vessels.

The premise behind "multilocus genotype information" is that people have composite genetic risks that are based on the small contributions of several genes—the essence of polygenic inheritance. Computer analysis of the multigene tests account for environmental factors, such as those outlined in table 7.5. The test panels can also be used to predict how individuals will respond to certain drugs, such as those that lower cholesterol level or blood pressure. Many companies are now conducting association tests to establish disease-specific SNP profiles.

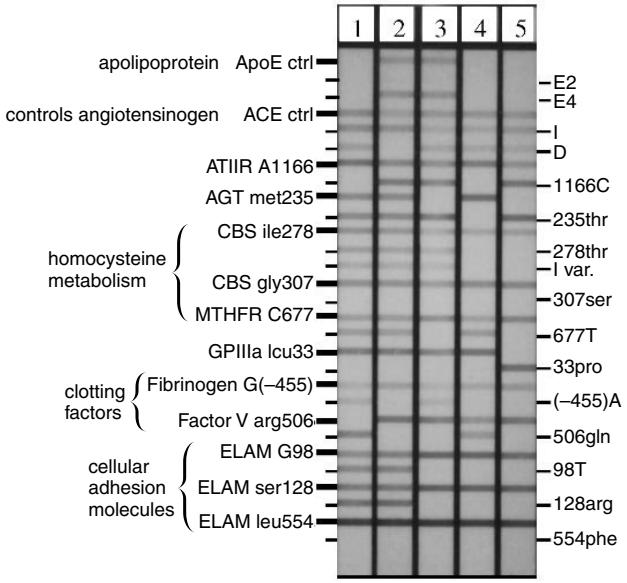


figure 7.12

Assessing a complex genotype for cardiovascular disease risk. Each strip represents an individual whose DNA is being probed for specific alleles that predispose to development of disease. The notations on the left indicate the gene, and the notations on the right indicate rare alleles. Apolipoproteins transport cholesterol. Angiotensinogen controls blood pressure. Homocysteine, in excess, may cause arteriosclerosis, which may trigger other disorders. Abnormal clotting factors or cellular adhesion molecules may lead to blockage of blood vessels.

table 7.5

Risk Factors for Cardiovascular Disease

Uncontrollable	Controllable or Treatable
Age	Fatty diet
Male sex	Hypertension
Genes	Smoking
Lipid metabolism	High serum cholesterol
Apolipoproteins	Low serum HDL
Lipoprotein lipase	High serum LDL
Blood clotting	Stress
Fibrinogen	Insufficient exercise
Clotting factors	Obesity
Homocysteine metabolism	Diabetes
Leukocyte adhesion	

Body Weight

One half of all adults in the United States are obese—defined as 20 percent or more above ideal weight. Obesity raises the risk of developing hypertension, diabetes, stroke, gallstones, sleep apnea, some cancers, and psychological problems. The reason that losing weight can be difficult may reside in the genes—at least 17 genes interact to control body weight, and it is likely that subtle abnormalities or variants in many genes add up to create the tendency to gain. Still, the environment plays a significant role in body weight. Recall that heritability for body mass index, a measure of weight that accounts for height, is 0.55. Research approaches designed to tease out the genetic contributions to body weight range from the molecular level, to comparing body weights, to population studies that highlight environmental inputs.

Leptin and Associated Proteins

In 1994, Jeffrey Friedman at Rockefeller University discovered a gene that encodes a protein hormone called **leptin** in mice and in humans. Normally, eating stimulates fat cells (adipocytes) to secrete the hormone. Leptin travels in the bloodstream to the brain's hypothalamus, where it binds to receptors on cells and signals them to suppress appetite and increase metabolism to digest the food already eaten. The leptin gene is one of several so-called thrifty genes that probably conserved energy in times past when periodic famine was a way of life. Low levels of leptin signal starvation, which triggers hunger and lowers metabolic rate.

When Friedman gave mice extra leptin, they ate less and lost weight. Headlines proclaimed the new magic weight loss elixir but research soon revealed that very few people could blame their obesity on low leptin levels. Figure 7.13 depicts two such rare cases—cousins who are extremely obese due to lack of leptin. Consanguinity (relatives marrying relatives) in the pedigree accounts for the transmission of the condition. Treating one of the cousins with leptin has had excellent results—he no longer overeats, has lost weight, and has shown signs of puberty. A more common situation explaining obesity, although still rare, is defective leptin receptors on cells in the hypothalamus. The receptors do not recognize the hormone signal to cease eating.

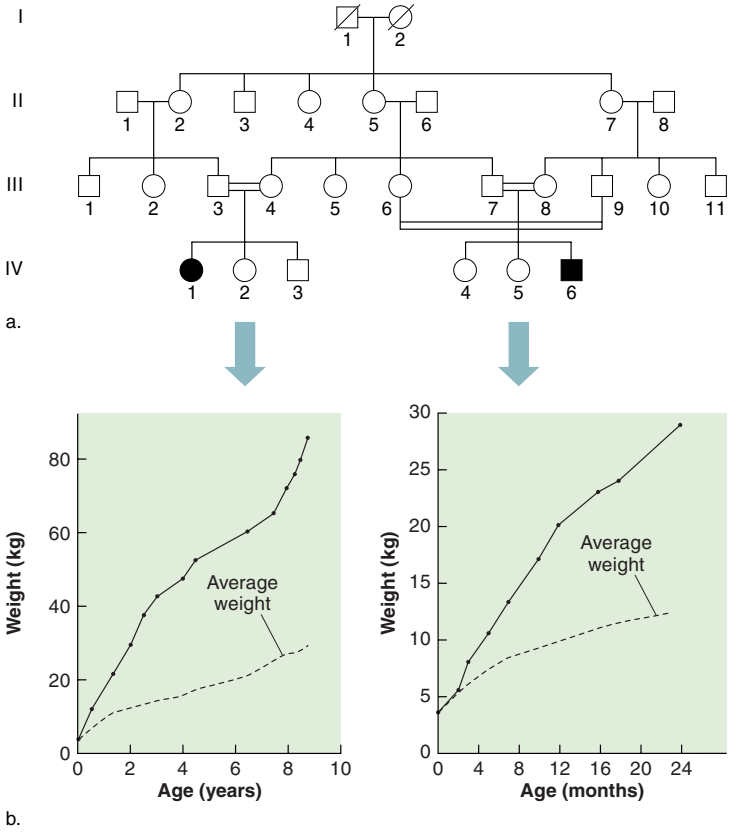


figure 7.13

Leptin deficiency is rare. The two affected cousins depicted in the pedigree (individuals IV-1 and IV-6) inherited the same recessive allele from shared ancestors (*a*). Their obesity is extreme (*b*).

Genes whose protein products are involved in other aspects of leptin function may explain more cases of obesity. Some proteins escort leptin from the circulation to the brain. A pair of specific proteins have opposite functions, one acting as an accelerator of weight gain and the other as a brake. **Neuropeptide Y** is produced in the hypothalamus in response to low leptin levels. Sensing starvation, it increases appetite. The "brake," the **melanocortin-4 receptor,** is activated when weight is gained, and it suppresses appetite. Some of these proteins may be involved in eating disorders, discussed in the next chapter. Drug companies are exploring all of these leptin-related proteins in the never-ending search for drugs that can control body weight (table 7.6).

Environmental Influences on Obesity

Many studies on adopted individuals and twins suggest that obesity has a heritability of 75 percent. Although the environment contributes only about 25 percent to variability in body weight, that component can be striking when eating and exercise habits change suddenly in a population. Natural experiments illustrate this phenomenon.

On the tiny island of Naura, in Western Samoa, the residents' lifestyles changed drastically when they found a market for the tons of bird droppings on their island as commercial fertilizer. The influx of money translated into inactivity and a high-fat diet, replacing an agricultural lifestyle and a diet of fish and vegetables. Within just a generation, two-thirds of the population had become obese, and a third suffered from diabetes.

table 7.6

Sites of Possible Genetic Control of Body Weight Related to Leptin

Protein	Function
Leptin	Stimulates cells in hypothalamus to decrease appetite and metabolize nutrients.
Leptin transporter	Enables leptin to cross from bloodstream into brain.
Leptin receptor	Binds leptin on surfaces of hypothalamus cells, triggering hormone's effects.
Neuropeptide Y	Produced in hypothalamus when leptin levels are low and individual loses weight, stimulating appetite and lowering rate of energy use. An appetite "accelerator" that responds to starvation.
Melanocortin-4 receptor	Activated when leptin levels are high and the individual gains weight, dampening appetite and increasing rate of energy use. Appetite "brake" that responds to weight gain.

The Pima Indians offer another example of environmental effects on body weight. These people separated into two populations during the Middle Ages, one group settling in the Sierra Madre mountains of Mexico, the other in southern Arizona. By the 1970s, the Arizona Indians no longer farmed nor ate a low-fat diet, now consuming 40 percent of their calories from fat. With this drastic change in lifestyle, they developed the highest prevalence of obesity of any population on earth. (Prevalence is the total number of individuals with a certain condition in a particular population at a given time.) Half of the Arizona group had diabetes by age 35, weighing, on average, 57 pounds (26 kilograms) more than their southern relatives, who still eat a low fat diet and are very active.

The Pima Indians demonstrate that the tendency to gain weight is not sealed in the genes dealt at conception, but instead is more a tendency to gain weight if the environment provides fatty foods. Study of an aboriginal group called the Nunavut Inuit brings the research full circle, applying a molecular analysis to a specific population.

The Inuit, also known as Canadian Eskimos, account for 35 percent of the 52,000 people who live in the Northwest Territories. Like the western Samoans and Pima Indians, lifestyle changes have recently increased their average body weight. Researchers zeroed in on an inherited predisposing factor to their weight gain—a variant of a protein that is part of the signal transduction pathway depicted in figure 2.20. This particular protein enables adipocytes to swell with fat. A mutation in this gene packs too much fat into fat cells everywhere, causing an overall roundness to the physique. Researchers typed 213 healthy Inuits for this gene, finding that those with the mutation had the highest weight, waist and hip measurements, and other measures of obesity.

Interactions and contributions of genes and the environment provide some of the greatest challenges in studying human genetics. Why does one heavy smoker develop lung cancer, but another does not? Why can one person consistently overeat and never gain weight, while another does so easily? Because we exist in an environment, no gene functions in a vacuum. Subtle interactions of nature and nurture profoundly affect our lives and make us all—even identical twins—unique individuals.

Key Concepts

Genes that affect lipid metabolism, blood clotting, leukocyte adhesion, and blood pressure influence cardiovascular health.

- Genes that encode leptin, the leptin receptor, and proteins that transmit leptin's signals affect body weight. Studies on adopted individuals and twins indicate a heritability of 75 percent for obesity. Populations that suddenly became sedentary and switched to a fatty diet reflect environmental influences on body weight.

Summary

7.1 Genes and the Environment Mold Most Traits

1. **Multifactorial traits** are attributable to both the environment and genes. A **polygenic trait** is determined by more than one gene and varies continuously in its expression. The frequency distribution of phenotypes for a polygenic trait is a bell curve.

7.2 Methods Used to Investigate Multifactorial Traits

2. **Empiric risk** measures the likelihood that a multifactorial trait will recur based on its prevalence in a population. The risk rises as genetic closeness to an affected individual increases, as the severity of the phenotype increases, and as the number of affected relatives rises.
3. **Heritability** estimates the proportion of variation in a multifactorial trait that is attributable to genetics. It describes a trait in a particular population at a particular time. Heritability is estimated by comparing the actual incidence of a shared trait among people related in a certain way to the expected incidence (**correlation coefficient**). In some cases rare dominant alleles can contribute to heritability.
4. Characteristics shared by adopted people and their biological parents are mostly inherited, whereas similarities between adopted people and their adoptive parents reflect environmental influences.
5. **Concordance** measures the frequency of expression of a trait in both members of MZ or DZ twin pairs. The more influence genes exert over a trait, the higher the concordance value.
6. **Association studies** correlate SNP patterns to increased risk of developing a particular disorder.

7.3 Some Multifactorial Traits

7. Genes that control lipid metabolism and blood clotting contribute to cardiovascular health.
8. **Leptin,** its receptor, its transporter, **neuropeptide Y,** and the **melanocortin-4 receptor** are proteins that affect body weight. Fat cells secrete leptin in response to starvation, and the protein acts in the hypothalamus. Populations that switch to a fatty diet and a less-active lifestyle reveal the effects of the environment on weight.

Review Questions

1. What is the difference between a Mendelian multifactorial trait and a polygenic multifactorial trait?
2. Which has a greater heritability—eye color or height? State a reason for your answer.
3. How can skin color have a different heritability at different times of the year, or in genetically similar populations that live in different areas?
4. How can the environment influence the course of cystic fibrosis, which is a Mendelian (single gene) disorder?
5. Describe the type of information provided by
   a. empiric calculation
   b. twin studies
   c. adoption studies
   d. association studies
6. Why does SNP mapping require enormous amounts of data?
7. Name three types of proteins that affect cardiovascular functioning, and three that affect body weight.
8. In a large, diverse population, why are medium brown skin colors more common than very white or very black skin?

Applied Questions

1. Why is the recurrence risk for a single gene disorder so much higher than for a polygenic disorder?
2. State two ways that the study of a multifactorial trait involves statistical analysis.
3. According to table 7.2, would taking a preparatory course better help a student improve the verbal part of the SAT exam, or the math part? Provide a reason for your answer.
4. One way to calculate heritability is to double the difference between the concordance values for MZ versus DZ twins. For multiple sclerosis, concordance for MZ twins is 30 percent, and for DZ twins, 3 percent. What is the heritability? What does the heritability suggest about the relative contributions of genes and the environment in causing MS?
5. Why is a case-control experimental design valuable in an association study?
6. How can an association study be clinically valuable, if it does not lead immediately to identification of the disease-causing gene?
7. Studies among Caucasians in the United States revealed the following heritabilities for traits associated with cardiovascular health:

HDL cholesterol level	0.63
triglyceride level	0.37
diastolic blood pressure	0.21
lipoprotein A activity	0.77
body mass index	0.55

   List the traits in order, from most affected by genes to least.
8. In a given population at a particular time, a researcher examines 200 parent-child pairs for bushy eyebrows. In 50 pairs, both parent and child have the trait. Another researcher examines 100 sibling pairs for the trait of selfishness, as assessed by the parents. In 10 of the sibling pairs, the parents rate both children as selfish.
   a. What is the heritability of bushy eyebrows for this population?
   b. What is the heritability of selfishness?
   c. What are some problems with calculating the heritability for selfishness?
9. A G protein mutation studied in Canadian Inuits "accounted for between 1.6 percent and 3.3 percent of the total variation of the obesity-related trait." Does this statement, taken from the research paper reporting the results of experiments, mean that the mutation is the sole determinant of the obesity, or that there are other influences?
10. Would a treatment for obesity seek to increase production of neuropeptide Y and decrease the production of the melanocortin-4 receptor, or the opposite?

Suggested Readings

Graves, Joseph L. Jr. *The Emperor's New Clothes: Biological Theories of Race at the Millennium.* 2001. Piscataway, NJ: Rutgers University Press. An examination of definitions of race, and the consequences of seeing people as black or white.

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