CHAPTER 1

GENES: HOW THEY ARE INHERITED

Like begets like: dogs have puppies, cats have kittens, and humans have baby humans. Moreover, you tend to look more like your parents or other relatives than people you are not related to. The mechanics behind these simple statements—the laws of heredity—were first worked out by Gregor Mendel in the 1860s, who studied how variation in garden peas was transmitted from parents to offspring (Mendel 1865). But peas aren't so terribly interesting—and after all, this is an anthropology textbook—so we will use variation in humans to illustrate the mechanics of inheritance. The variation we will use is the ABO blood group system, but before explaining how the ABO blood groups are inherited, you first need to know something about blood.

■ BLOOD AND ABO BLOOD GROUPS

Suppose you stick a needle with a syringe into a vein, withdraw a few ccs (cubic centimeters—a cc is about 20 drops or so) of blood, squirt the blood into a test tube, and let it sit. After 30 minutes or so, the blood will have spontaneously formed a clot—all it takes is exposure of the blood to air to initiate clotting. Remove the clot and what is left behind is a clear, yellowish fluid called **serum**. If you instead add a chemical to the test tube that inhibits clotting and spin the blood at high speed in a centrifuge, you will find that the blood has separated into different components (Figure 1.1). At the bottom are the red blood cells (RBCs, also known as **erythrocytes**), which transport oxygen around the body. Immediately on top of the RBCs is a ghostly white layer, sometimes referred to as the buffy coat, that consists of white blood cells (also known as **lymphocytes**), which are important for protecting the body from invading cells. And on top of the white blood cells is a clear, yellowish fluid called **plasma**. Plasma is like serum, except plasma also contains the various factors that are involved in blood clot formation.

Suppose now we take serum from one person and mix it with RBCs from another person and do this for many different people. Sometimes nothing will happen, but sometimes the RBCs will clump together (**agglutinate**). Agglutination is entirely different from clotting (Figure 1.2). You may think that mixing blood components from different people is a strange thing to do, but in fact Karl Landsteiner won a Nobel Prize for doing just that. During the nineteenth century, physicians began giving blood transfusions to people who had lost life-threatening quantities of blood through injury or illness. Seems reasonable enough—someone needs more blood, so give them blood from somebody else—and indeed, sometimes the blood transfusion recipients recovered spectacularly. But sometimes they actually got much sicker from the transfusion, to the point of even dying, and nobody knew why this would happen. Landsteiner, an Austrian physician, took it upon himself to figure out why such adverse reactions to blood transfusions occurred. Through his mixing experiments, he discovered that people's blood could be classified into four groups (Landsteiner 1900), corresponding to what are now known as blood groups A, B, AB, and O. Mix together blood from people with the same blood group and nothing happens. But mix together blood from a group A person with blood from a group B person and you get agglutination—and if you do this in a blood transfusion, clumps of agglutinated cells will form in the veins, blocking small capillaries and leading to tissue death, which is bad news indeed.

So what causes agglutination? It turns out that RBCs carry on their surface substances called **antigens**, and
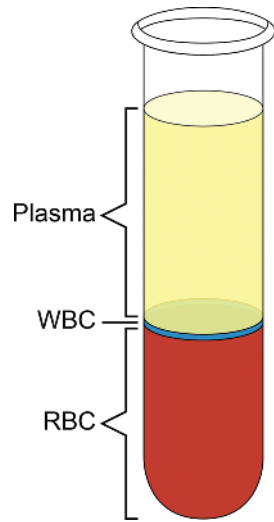
FIGURE 1.1

The components of blood, after adding an anticoagulant, followed by centrifugation. RBC, red blood cells; WBC, white blood cells.

these antigens cause the formation of substances in the serum called **antibodies**, which bind to antigens. Each antibody has two binding sites for its particular antigen, and there are many copies of each antigen on each RBC. So, mix together RBCs with serum containing antibodies against an antigen on those RBCs, and you get lots of antibodies binding to lots of RBCs, resulting in agglutination. But if the serum does not contain antibodies against the antigens on the RBCs, then there is no agglutination.

Table 1.1 lists the antigens present on the RBCs and the antibodies present in the serum of the A, B,

TABLE 1.1 ■ **Antigens and antibodies for the ABO blood groups**

Blood group	Antigens on RBCs	Antibodies
A	A	anti-B
B	B	anti-A
AB	A,B	none
O	None	anti-A, anti-B

RBCs, red blood cells.

AB, and O blood groups (for those of you who have seen blood groups with + or −, such as A+ or B−, don't worry, we'll get to that later in the chapter). The O blood group can be thought of as a "null" blood group, in that there are no O antigens or anti-O antibodies. Note that if you have a particular antigen on your RBCs, you don't have antibodies against that antigen—otherwise you would be agglutinating your own blood cells, which would be very bad news indeed (however, there are diseases known in which the body starts making antibodies against its own antigens; such diseases are known as **autoimmune diseases** and examples include lupus and some types of arthritis). Note that people with blood type O are known as "universal donors," because their RBCs lack A or B antigens and hence can be safely transfused into people of any blood type—that's why you often hear emergency room physicians on TV shows shouting for type O blood when a patient comes in who needs blood immediately. Conversely, people of blood type AB are known as "universal recipients," because they can receive RBCs of any blood type in a transfusion, as they lack anti-A and anti-B antibodies.
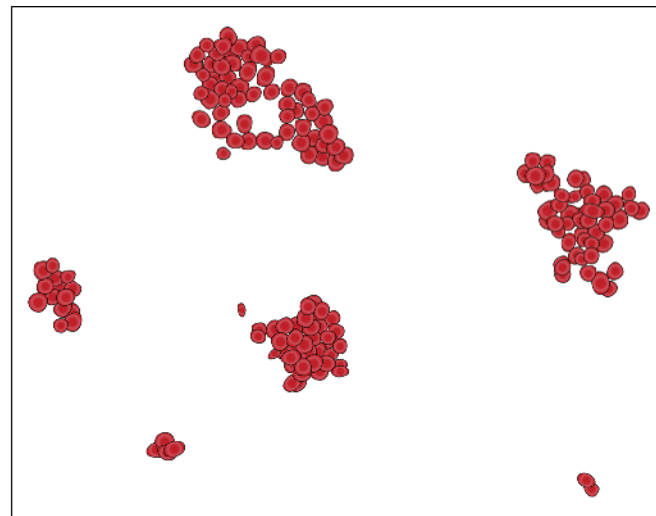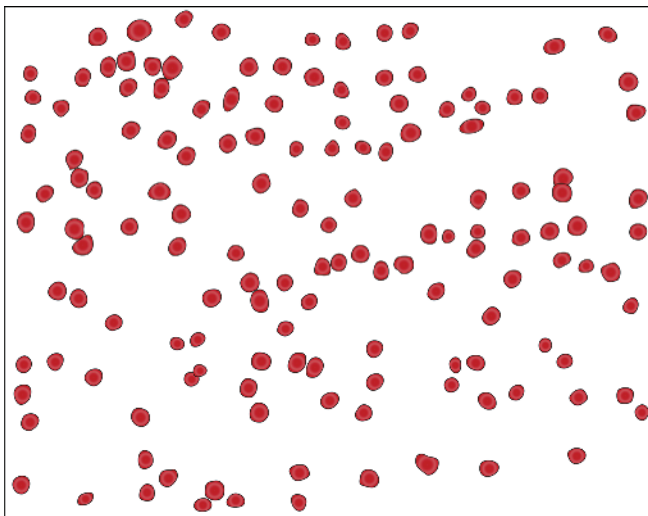

FIGURE 1.2

Left, a version of red blood cells that have not agglutinated. Right, a version of red blood cells that have agglutinated.

■ INHERITANCE OF ABO BLOOD GROUPS

Now that you know something about ABO blood groups, we can go into how they are inherited. First, some facts and terminology. Humans are **diploid**, meaning that each **gene** is present in two copies (for now, just think of a gene as the instructions for doing something, as in "the gene for the ABO blood groups"; in the next chapter, we'll see what genes actually are). One copy is inherited from the mother, through the egg, and one copy is inherited from the father, through the sperm. Any particular gene can come in different forms, or variants, and these are called **alleles**. For the ABO blood group gene, there are three alleles, namely, the A allele, the B allele, and the O allele. And since everyone has two alleles, there are six possible combinations of alleles; the pair of alleles that you have is your **genotype**. For three genotypes, the two alleles are the same (namely, AA, BB, and OO), and these are called **homozygous genotypes** or **homozygotes**. For the other three genotypes, the two alleles are different (namely, AB, AO, and BO), and these are called **heterozygous genotypes** or **heterozygotes**. The astute reader may wonder how it is that six different genotypes result in just four different blood groups. The actual blood group, or **phenotype**, associated with each genotype is shown in Table 1.2. Note that both the AA genotype and the AO genotype result in blood type A, and both the BB genotype and the BO genotype result in blood type B, thereby explaining how six different genotypes result in just four different blood groups.

The ABO blood groups also nicely illustrate the concept of **dominant** versus **recessive** alleles. If the heterozygote for two alleles exhibits exactly the same phenotype as the homozygote for one of the alleles, then that allele is said to be dominant, and the allele that does not exhibit a phenotype in the heterozygote is said to be recessive. Thus, since the AO genotype results in exactly the same phenotype (blood group) as the AA genotype, the A allele is dominant with respect to the O allele, and the O allele is recessive with respect to the A allele. Similarly, the B allele is dominant with respect to the O allele, and the O allele is recessive with

respect to the B allele, because the phenotype of the BO heterozygote is exactly the same as that of the BB homozygote. What about the A and B alleles—which is dominant and which is recessive with respect to each other? To figure this out, look at the phenotype (blood group) associated with AB heterozygotes. It turns out that AB heterozygotes have a different phenotype than either AA or BB homozygotes—they are type AB. We therefore say that the A and B alleles are **codominant** with respect to each other (other terms you may come across, such as **partial dominance** or **incomplete dominance,** mean basically the same thing as codominance: the heterozygote has a different phenotype than either homozygote).

Note that the dominance relationship is a property of a pair of alleles, not of a single allele, and, therefore, can vary depending on which pair of alleles are considered. For example, it would be incorrect to simply say that the A allele is dominant, because even though it is dominant with respect to the O allele, it is codominant with respect to the B allele. Determining the dominance relationships of a pair of alleles simply involves comparing the phenotype of the heterozygote to the phenotype of each homozygote. If the heterozygous phenotype matches one of the homozygotes, then that allele is dominant and the other is recessive. If the heterozygous phenotype differs from both homozygotes, then the alleles are codominant.

A lot of terminology was introduced in the previous paragraphs—but if you want to walk the walk, you've got to be able to talk the talk. So, the sooner you become conversant with the terminology—at the very least, know what is meant by gene versus allele, genotype versus phenotype, homozygote versus heterozygote, and dominant versus recessive versus codominant—the better. Now, how are ABO blood groups transmitted from parents to offspring? Recall that humans are diploid, with two ABO blood group alleles, one inherited from the mother and one inherited from the father. This means that the mother's egg and the father's sperm are **haploid**, carrying one allele each instead of the usual two alleles. If the parent is homozygous, then all of the **gametes** (eggs for women, sperm for men) produced by that parent will carry the same allele. But if the parent is heterozygous, then on average half of the gametes will carry one allele, and half will carry the other allele. Knowing the genotypes of the mother and the father, we can then predict the genotypes of the offspring. For example, suppose one parent has the AA genotype and the other parent has the AB genotype. The AA parent will produce only A gametes, while the AB parent will produce 50% A gametes and 50% B gametes. Thus, we expect that any child of these parents has a 50% chance of being genotype AA and a 50% chance of being genotype AB. Moreover, if we look at lots and

TABLE 1.2 ■ **ABO blood group genotypes and corresponding phenotypes**

Genotype	Phenotype (blood type)
AA	A
AO	A
BB	B
BO	B
AB	AB
OO	O

Father

		A	O
	A	AA	AO
Mother	O	AO	OO

FIGURE 1.3

Punnett square illustrating the ABO blood group genotypes expected among the children when both parents have the AO genotype.

lots of children where one parent is AA and the other is AB, we expect about half the children to have genotype AA and half to have genotype AB.

In this example, the children end up having the same genotypes and blood groups as the parents. However, this need not always be the case. A convenient way of diagramming the expected outcome of any type of mating is the **Punnett square**, imaginatively named after its inventor, the geneticist Reginald Punnett. An example of a Punnett square is shown in Figure 1.3 for the case when both parents are of genotype AO (hence blood type A). In this situation, 25% of the children are expected to be genotype OO, and hence blood type O. So, having a child of blood type O when the parents are both type A (or both type B, or one is type A and one is type B) need not be a cause for concern on the part of the father, as genetics shows how this can arise. However, genetics cannot so easily explain a child of blood type A or B when both parents are blood type O (do the Punnett square if this is not immediately obvious to you), so in such cases, the mother would have some explaining to do to the father!

The idea that gametes carry only one allele, and that a heterozygous parent produces gametes carrying either allele in equal frequency, is the basis of Mendel's First Law of Segregation (i.e., alleles **segregate** into gametes). There are two important consequences. First, offspring are produced by the random union of gametes, hence the outcome of one mating has no influence on the outcome of subsequent matings. Suppose a genotype AA parent and a genotype AB parent have an AA child. The chance that the next child is genotype AB is still 50%. Suppose these same parents have 10 children, all of genotype AA. We may now wonder if perhaps we haven't made a mistake in our genotyping of the parents, but assuming the genotypes are correct, then the chance that the eleventh child is genotype AB is still just 50%. There is no "memory" to the system, no compensating for prior events—predicting the genotype of a child is subject to the same laws of chance as flipping a coin.

The second important consequence of Mendel's First Law of Segregation is that inheritance is

particulate. That is, whatever genes are (and remember, all the mechanics of how genes are inherited were worked out long before anybody knew what genes actually are), they behave as discrete particles. Prior to the rediscovery of Mendel's work, it was generally assumed that inheritance was **blending**: genes were thought to behave like blood (thus, all the emphasis on people's bloodlines), so the characteristics of the genes in the parents would become mixed in the children. And the children would in turn transmit these mixed characteristics to their children, and so forth.

Blending inheritance may sound reasonable, but it posed a big problem for Darwin's theory of evolution. Darwin proposed that individuals with characteristics that enhanced their survival or fertility would transmit those characteristics to their offspring, thereby increasing the frequency of such advantageous characteristics in subsequent generations. But if in each generation the advantageous characteristics are blending with the less-advantageous characteristics, then it is hard to see how advantageous characteristics can increase in frequency. It's like mixing paint—mix red and white paint together and you will get pink paint, and no matter how much more red or white paint you add, you still end up with various shades of pink. Indeed, Darwin spent a long time grappling with this issue and never came up with a satisfactory answer.

However, the idea that genes behave as particles neatly solves the problem. Suppose an individual of ABO blood group genotype AA (hence, blood type A) has a child with an individual of genotype OO (hence, blood type O). The child (genotype AO, blood type A) grows up and then marries an AA individual (blood type A) and has one child who is genotype AO (blood type A). Imagine that this continues for 10 generations, with each generation producing an AO individual who marries an AA individual and has an AO child. Now, after 10 generations of only blood type A in this family, suppose in the eleventh generation the AO individual marries an individual with genotype OO (blood type O) and they have a child with genotype OO. This child will have the O blood type—the fact that the O allele came from a long line of individuals of genotype AO, who were all blood type A, does not change what that O allele does when it is now paired with another O allele. It's as if we mixed red with white paint to get pink paint, but then we can get pure red or pure white paint back out of the mixture.

▌ INHERITANCE OF MORE THAN ONE GENE: ABO AND RHESUS BLOOD GROUPS

To illustrate the mechanics of inheritance for more than one gene, we will use the second blood group

to be discovered, so first you need to know something about this blood group. Although blood transfusion success increased markedly with the recognition of the importance of the ABO blood groups, serious reactions after a blood transfusion still happened, even when the donor and the recipient were matched for ABO blood type. Moreover, it became apparent that a disease called **hemolytic disease of the newborn** (HDN) was due to antibodies from the mother crossing the placenta and attacking an antigen on fetal RBCs. Hemolytic disease of the newborn is quite serious as it can result in severe anemia, jaundice, and even death of the newborn—and again, HDN was observed even when there was no ABO blood group incompatibility between mother and child. These observations lead to the discovery of the second human blood group, namely, the **rhesus** (Rh) blood group—so named because it was initially thought that the factor causing blood transfusion reactions and HDN was identical to an antigen identified first on rhesus monkey RBCs and then shown to also occur on human RBCs (Landsteiner and Wiener 1940). Actually, we now know that the HDN-causing factor and the antigen on rhesus monkey RBCs are not the same, but the name stuck.

The rhesus blood group is a very complex system but can be simplified into two major alleles, Rh+ and Rh−. The Rh+ allele is dominant to the Rh− allele, so there are two blood types (phenotypes): Rh positive (corresponding to genotypes Rh+/Rh+ and Rh+/Rh−) and Rh negative (corresponding to genotype Rh−/Rh−). These are the source of the + and − that is added on to the ABO blood type, for example, A+ means that person is ABO blood type A and Rh blood type positive, while O− means that the person is ABO blood type O and Rh blood type negative.

People who are Rh positive have Rh+ antigens on their RBCs but no Rh antibodies; people who are Rh negative do not have Rh antigens on their RBCs and hence can make anti-Rh+ antibodies if exposed to Rh+ RBCs. Note that this is the usual way that antibodies work: you only make the antibodies after you are exposed to the antigen. If you are Rh negative, you won't make anti-Rh+ antibodies until you are exposed to RBCs with the Rh+ antigen. So, an Rh− person could be transfused with Rh+ blood without suffering any ill effects—by the time any anti-Rh+ antibodies are made, the transfused Rh+ RBCs will no longer be present. A second such transfusion of Rh+ blood, however, would be bad news, because now anti-Rh+ antibodies will already be present from the first transfusion and they can agglutinate the transfused Rh+ RBCs. Note also that the ABO antibodies are an apparent exception to the rule that you make antibodies only after you are exposed to antigens, since you are born with antibodies to the ABO antigens that you do not possess. What seems to happen is that chemical
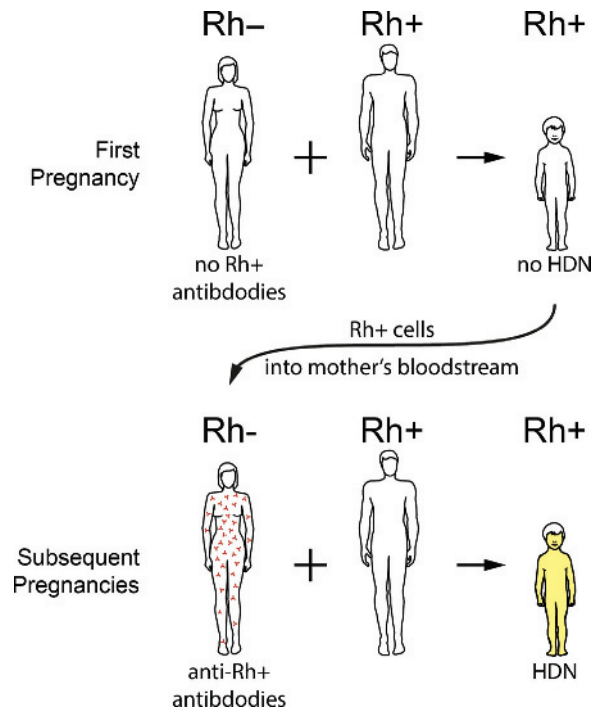

FIGURE 1.4

The circumstances leading to HDN. See text for details. HDN, hemolytic disease of the newborn.

substances that are similar to the ABO antigens are so widespread in nature (they are simple sugars that are commonly found in the environment) that exposure occurs somehow in the womb, resulting in production of the antibodies even before birth.

So, how does HDN arise? Hemolytic disease of the newborn occurs under the following circumstances (Figure 1.4): when an Rh− mother has an Rh+ child (which can happen when the father is Rh+), ordinarily nothing happens to the first such child. However, fetal cells typically do cross the placenta and get into the mother's bloodstream. If the mother is Rh+, nothing will happen, as she will not develop anti-Rh+ antibodies, but an Rh− mother will react against the Rh+ antigens on the fetal RBCs and develop anti-Rh+ antibodies. If the Rh− mother then subsequently becomes pregnant with another Rh+ child, the mother's anti-Rh+ antibodies can cross the placenta and attack the fetal RBCs that carry the Rh+ antigens, resulting in HDN. Untreated HDN results in death in about one-third of the cases, so this is a serious matter; affected infants usually need blood transfusions and treatment for jaundice (caused by excess levels of hemoglobin due to the destruction of fetal blood cells) immediately.

Fortunately, there is a simple and effective means of preventing HDN, and that is to give the mother an injection of concentrated anti-Rh+ antibodies shortly after the birth of the first child (and after any

subsequent children). These antibodies coat any Rh+ fetal RBCs that make it into the mother's bloodstream, thereby preventing the mother's immune system from making her own Rh+ antibodies. This injection usually goes by the name "Rhogam," so those of you who have experienced pregnancy either directly or via a pregnant partner and wondered about this Rhogam injection, now you know.

Incidentally, there are more than 30 different blood group systems known. However, the ABO and Rh blood groups are by far the most important because of their role in blood transfusions and HDN. That's why most of you probably know your ABO/Rh blood type but not your Lewis, Kell, or any other blood type. Still, these other blood groups sometimes pop up in cases involving adverse reactions to blood transfusions or HDN. In such cases, the first course of action is to check the ABO/Rh blood type, and if these cannot explain what is going on (e.g., a case of HDN where the mother is Rh+), then some other blood group must be involved, and in fact this is how most of these other blood groups were discovered.

The inheritance of the Rh blood type alone is quite simple, as Rh+ is dominant to Rh−. But what about the inheritance of both ABO and Rh blood type? Consider the following example, shown in Figure 1.5, where one parent is type AB− and the other parent is type O+, and we want to know what to expect for the children. The first step is to figure out the genotypes of the parents. The AB− parent can have only the A/B, Rh−/Rh− genotype, but the O+ parent can have one of two possible genotypes: O/O, Rh+/Rh+ or O/O, Rh+/Rh−. Without any further information, we don't know which genotype this person has, but suppose we know that one of this person's parents was O+ and the other was O−. Then we know that this person must have inherited an Rh− allele from the O− parent; hence, the genotype must be O/O, Rh+/Rh−. As shown in Figure 1.5, we then expect four blood types among the children: A+, A−, B+, and B−. And, we expect these to occur in equal frequency, so there is a 25% chance of any one child having any one of these blood types.

We have just demonstrated **Mendel's Second Law of Independent Assortment**: alleles from different genes assort independently into gametes. That is, if you go back to the example in Figure 1.5, you see that for just the ABO gene, from Mendel's First Law, there is a 50% chance of a child with blood type A and a 50% chance of a child with blood type B. And, by the same reasoning, if you consider only the Rh gene, there is a 50% chance of an Rh+ child and a 50% chance of an Rh− child. To get the probability for both the ABO and Rh blood types, multiply the separate probabilities: the chance of an A+ child, for example, is 50% of 50%, or 25%. Independent genes behave independently, so the probability of having a child of a particular genotype for two (or more) genes is obtained by multiplying the probabilities for each genotype—just as you would do if you wanted to know the probability of getting both a head by flipping a coin and a six on a roll of a die (which would be 1/2 times 1/6, or 1/12).

Let's look at another example of Mendel's Second Law, this time using some (slightly modified) actual data. Table 1.3 shows some data from families with **elliptocytosis**, a hereditary blood disorder in which a large fraction of the RBCs have an elliptical shape rather than the usual disc shape. In severe cases, the afflicted individuals suffer from anemia, as the abnormal RBCs break down prematurely. Elliptocytosis is a partially dominant disease, meaning that heterozygotes show some of the symptoms, while homozygotes are even more strongly afflicted. Table 1.3 also includes the Rh blood type information, and for reasons that will become clear in just a minute, the data in Table 1.3 are specifically chosen from families where one parent is heterozygous for both Rh and for elliptocytosis (i.e., Rh+/Rh−, Ep+/Ep−, using Ep+ to designate the disease-associated allele and Ep− to designate the

TABLE 1.3 ■ **Observed number of offspring who are Rh+ or Rh− and either afflicted with elliptocytosis (Ep+) or not (Ep−) in families as discussed in the text**[a]

Phenotype	Observed number
Rh+, Ep+	34
Rh+, Ep−	3
Rh−, Ep+	4
Rh−, Ep−	32

[a]Data are taken from Lawler, S.D., and Sandler, M., *Annals of Eugenics* 18:328–334 (1954); as the data come from a variety of families with a variety of genotypes, I have taken the liberty of tabulating the data as if they all came from families with the same parental genotypes, in order to make things simple. The key observations (66 offspring of the "major" or parental types and seven offspring of the "minor," or recombinant types) are as reported by Lawler and Sandler and led to the conclusion of linkage between the rhesus blood group and elliptocytosis loci.

Father

		O+	O−
Mother	A−	AO, +/−	AO, −/−
	B−	BO, +/−	BO, −/−

FIGURE 1.5

Punnett square illustrating the ABO and Rh blood group genotypes expected among the children of a mother with the AB, Rh−/Rh− genotype and a father with the OO, Rh+/Rh− genotype. The genotypes at the ABO and Rh genes assort independently.

"normal" allele) while the other parent is homozygous for the recessive alleles at both genes (i.e., Rh−/Rh−, Ep−/Ep−). Note that in such families, according to Mendel's Second Law, we expect four possible genotype combinations that should occur in equal frequencies, with the associated phenotypes as follows:

25% Rh+/Rh−, Ep+/Ep−, which are Rh positive and affected with elliptocytosis

25% Rh+/Rh−, Ep−/Ep−, which are Rh positive and not affected with elliptocytosis

25% Rh−/Rh−, Ep+/Ep−, which are Rh negative and affected with elliptocytosis

25% Rh−/Rh−, Ep−/Ep−, which are Rh negative and not affected with elliptocytosis

(Do the Punnett square if this isn't obvious to you). And the results? As you can see in Table 1.3, the observed results are quite different from those expected by Mendel's Second Law of Independent Assortment.

So, what is going on here? One possibility is that nothing of any significance is going on, and what we have observed is simply a chance deviation from the expected frequencies. After all, we don't expect to get exactly 25% of each phenotype, just as if we flip a coin 10 times, we don't expect to get exactly five heads and

five tails. But how likely are we to get the results in Table 1.3, if we actually expect 25% of each combination? This is a question for statistics, and rather than run the risk of scaring off readers now, we'll put off the discussion of statistical tests to Chapter 4. For now, just take it on faith that it is extremely unlikely that we would obtain the data in Table 1.3 if the true frequencies really were 25% of each phenotype.

If the data don't fit our expectations, then either there is something wrong with the data or there is something wrong with our expectations. In this case, the problem is with the expectations, because it turns out that the elliptocytosis and rhesus blood group genes are an example of a very important and well-known exception to Mendel's Second Law of Independent Assortment. This exception involves genes that are located close to one another on the same **chromosome**. We'll learn more about chromosomes in the next chapter; for now, all you need to know is that chromosomes are the physical structures within cells that contain genes. Chromosomes come in pairs, with one member of each pair inherited from the mother and the other inherited from the father. Humans have 23 pairs of chromosomes in each cell (Figure 1.6). So, genes have specific, physical locations on chromosomes, which is where the term **locus** comes from, as a synonym for a gene—we can talk about the ABO blood group gene, or the ABO blood group locus. And
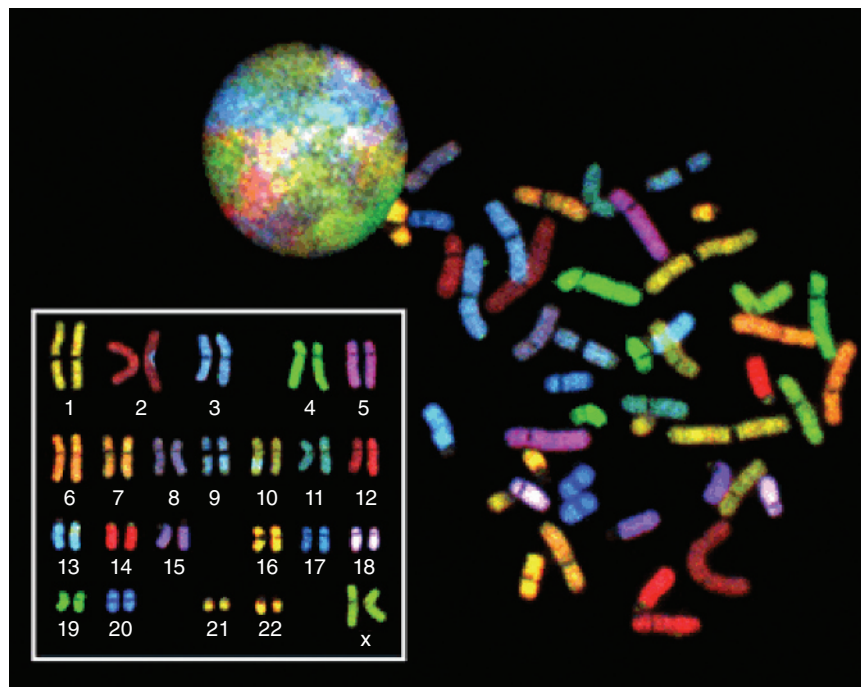

FIGURE 1.6

Example of a human karyotype, showing the 23 pairs of chromosomes. In this example, from a female, each chromosome has been stained with a different fluorescent dye; this is known as a spectral karyotype. Reprinted with permission from Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Sky_spectral_karyotype.png).
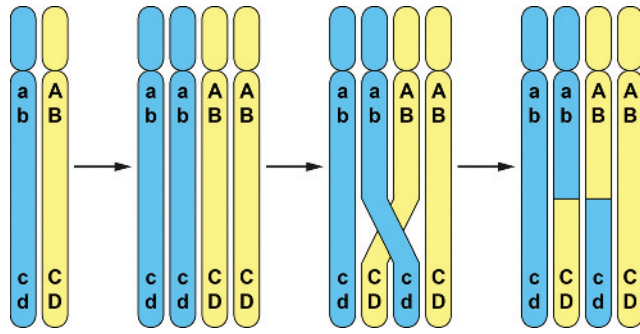
FIGURE 1.7

Recombination between chromosomes during meiosis, resulting in the exchange of chromosome segments. In this example consisting of 4 genes, each with two alleles, the individual inherited one chromosome with alleles abcd from one parent, and another chromosome with alleles ABCD from the other parent. These chromosomes duplicate and then two of them undergo recombination, with the result that there are two parental chromosomes (abcd and ABCD) and two nonparental or recombinant chromosomes (abCD and ABcd).

the key point is that genes located near one another on the same chromosome are **linked**, and the alleles that are on the same chromosome will be inherited together more often than predicted by chance. You might think that alleles on the same chromosome will always be inherited together, but such is not the case: during **meiosis** (the process of forming gametes—eggs and sperm), there is exchange (**recombination**) of segments between the two copies of each chromosome (Figure 1.7). In other words, you have two copies of each of your chromosomes, one you inherited from your mother and one you inherited from your father. But as shown in Figure 1.7, when you have children, the set of haploid chromosomes that you transmit to them will not be intact copies of either your maternal or paternal chromosomes. Instead, each chromosome you transmit to your children will contain some segments from your paternal copy and some from your maternal copy of that chromosome. However, each chromosome that you transmit will be a faithful copy in that all genes will be present and in the correct order (barring the rare chromosomal change that results in duplications of segments, loss of segments, or a different order of segments—these sorts of events will be discussed later). The results in Table 1.3 (which depart from the expected 25% of each combination of Rh and elliptocytosis alleles) are most simply explained if the genes for elliptocytosis and the Rh blood group are linked (located close together on the same chromosome)—which indeed they are.

The concept of **linkage** is extremely important, as we'll see in a minute, but first some technical points about detecting linkage. Note that in Table 1.3 we focused on families where one parent was known to be heterozygous for both Rh and Ep, and that is a general requirement: in order to detect whether two loci are linked or not, at least one parent must be heterozygous for both loci (i.e., doubly heterozygous). This is so we can distinguish between **parental** and **nonparental** (or more accurately, **recombinant**) gametes produced by the heterozygous parent, as shown in Figure 1.7. When an individual is homozygous for one (or more) of the loci in question, then parental and recombinant types cannot be distinguished from one another (if this is not obvious, make the genotypes in Figure 1.7 homozygous instead of heterozygous and see whether you can distinguish parental from recombinant gametes). The parent who is doubly heterozygous is said to be the **informative** parent, because then we can tell whether or not recombination has occurred in the gametes produced by this parent. Note that in principle, there are two possible associations between the alleles at the two loci in the informative parent (assuming that the loci are indeed linked): in the case of the Rh and Ep loci, the informative parent could have the Rh+ and Ep+ alleles on one chromosome and the Rh− and Ep− alleles on the other chromosome, or the informative parent could have the Rh+ and Ep− alleles on one chromosome and the Rh− and Ep+ alleles on the other chromosome. The particular combination of associated alleles is known as the **phase**; note that the phase can be different in different individuals, so you have to be careful when combining data from different families. The phase can sometimes be determined if you have data from the parents of the informative parent. For example, if the father of the informative parent is Rh−/Rh−, Ep+/Ep−, and the mother is Rh+/Rh−, Ep−/Ep−, then the informative parent has one Rh−/Ep+ chromosome and one Rh+/Ep− chromosome. If this isn't immediately obvious, note that the Ep+ allele had to come from the father, who is Rh−/Rh−, and so the father contributed an Rh−/Ep+ chromosome. Similarly, the Rh+ allele had to come from the mother, and so the mother contributed an Rh+/Ep− chromosome. Otherwise, you can compute how likely you are to observe the number of offspring of each parental/recombinant type, assuming each of the possible phases for the informative parent—but I ask you to take this on faith, as the details of this sort of computation are beyond the scope of this book. Determining the phase has other applications when it comes to making inferences about the demographic history of populations, and we will return to this topic in Chapter 9.

Recombination is a remarkable process that generates new genetic variation, in terms of shuffling

around maternal and paternal segments of chromosomes to create new combinations of alleles. Moreover, the amount of recombination is roughly proportional to the physical distance between linked genes: the alleles for genes that are located very close together on the same chromosome will tend to be inherited together, while for genes that are far apart on the same chromosome, there is so much recombination that their alleles will be inherited independently, as if they were on different chromosomes. Hopefully, this makes sense: the greater the distance between two genes, the more opportunity there is for one (or more) recombination events to occur between them. Think of it as placing two marks on a piece of string, then cutting the string at some random location. If the two marks are close together, only rarely will you cut the string in between them, but if the two marks are near the opposite ends of the string, then you'll almost always cut between them.

Linkage is of particular importance because it allows disease genes to be **mapped** (located on a chromosome) and ultimately identified by looking in families for the cosegregation of **marker genes** (genes whose chromosomal location are known) with the disease. Even just knowing about the linkage relationships of a disease gene can provide some useful information. For example, in the case of elliptocytosis, extensive family studies showed that some cases of elliptocytosis showed linkage to the Rh blood group locus (as in the example in Table 1.3) but others did not (Morton 1956). So, there must be more than one gene which, when mutated, can cause elliptocytosis—linkage studies thus provided some of the first evidence that what appears to be the same genetic disease can have different underlying causes. Linkage is also an important concept behind some strategies for identifying genes that have been subject to recent positive selection, as will be discussed in more detail in Chapter 18.

▌ SEX CHROMOSOMES

There is an important extension to Mendel's First Law, which applies to genes found on the **sex chromosomes**. The members of each pair of chromosomes are physically indistinguishable for 22 of the 23 pairs of chromosomes in humans (Figure 1.6), and these are the **autosomes**, numbered from 1 to 22. The remaining pair are the sex chromosomes, dubbed X and Y, which are quite different; females have two X chromosomes while males have one X chromosome and one Y chromosome. Females thus produce gametes (eggs) carrying an X chromosome, while for males, 50% of the gametes (sperm) carry an X chromosome and 50% carry a Y chromosome. This accounts for the expected

50:50 male:female sex ratio and moreover makes clear that the responsibility for the determination of the sex of a child lies with the father, not with the mother—somebody should have informed Henry VIII before he lopped off the heads of various wives for failing to deliver a son!

The X and Y chromosomes differ greatly in size (Figure 1.6) and gene content; the X chromosome is much larger than the Y chromosome and has on the order of a thousand genes, while the Y chromosome has only about a dozen genes, mostly involved in male fertility. Importantly, the genes on the X chromosome thus do not have a corresponding copy on the Y chromosome, so males, with just one X chromosome, are said to be **hemizygous** for genes on the X chromosome. This means that the phenotype associated with a recessive allele at an **X-linked gene** (on the X chromosome) will always be manifested in males with that allele. For example, there are X-linked, recessive alleles that cause red–green colorblindness. A female who is heterozygous, having one normal color vision allele and one color blindness allele, will herself have normal color vision, because color blindness is recessive. However, if she has children with a male with normal color vision, there is a 50% chance that a son will be color-blind, but none of the daughters will be color-blind (as shown in Figure 1.8). Such X-linked recessive traits will, therefore, occur more often in males than in females. In fact, in order for a female to manifest a sex-linked recessive trait, she must inherit an X chromosome from her father who carries the recessive allele (do the Punnett square if this isn't obvious), so her father must also manifest the trait. Some X-linked traits are so debilitating that males with the trait hardly ever reproduce, and so these traits tend to occur only in males. Examples of such traits include hemophilia (which, until recently, was invariably lethal before affected men reached reproductive age) and some forms of mental retardation.

	Father	
	X^N	Y
Mother X^N	$X^N X^N$	$X^N Y$
X^c	$X^N X^c$	$X^c Y$

FIGURE 1.8

Punnett square illustrating the genotypes expected in the children where the mother is heterozygous for the colorblindness gene (X^N/X^c, where X^N is the allele for normal color vision and X^c is the colorblindness allele) and the father has normal color vision (X^N/Y). In such families, half of the male children are expected to have color blindness.

▌ DETERMINING HOW TRAITS ARE INHERITED: PEDIGREE ANALYSIS

Given a particular trait of interest, how do we figure out how it is inherited? If we were interested in garden peas (or fruit flies or mice or other commonly used experimental organisms), then it would be simple: select individuals who differ in the trait, have them mate, and see what happens in the offspring and subsequent generations. With humans it's more complicated: it isn't ethical (or practical) to select people and have them mate, so we have to rely on what nature provides, namely, we analyze families where at least one individual has the trait of interest. This type of analysis is called **pedigree analysis**. Consider the example in Figure 1.9, which is a diagram of three generations of a family. To figure out how the trait is inherited, focus on the following questions: (1) do people with the trait have at least one parent with the trait; and (2) are there equal numbers of males and females with the trait? In the example in Figure 1.9, all people with the trait have parents with the trait, and there are roughly equal numbers of males and females with the trait. These are the hallmarks of **autosomal dominant** inheritance, where autosomal means that the gene is on one of the 22 pairs of physically identical chromosomes (autosomes) and dominant means that people with the trait can be either heterozygous or homozygous for the responsible allele (as, e.g., people with ABO blood type A can have either the AO or the AA genotype). Hopefully, it is clear by now why people with an autosomal dominant trait have a parent with the trait: if you have the autosomal dominant trait, you have at least one allele for the trait, which you must have inherited from one of your parents, who then must also have the trait. Armed with this knowledge,
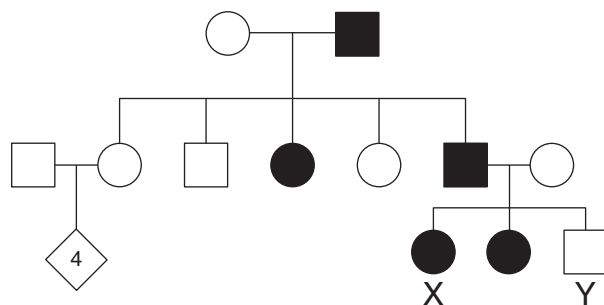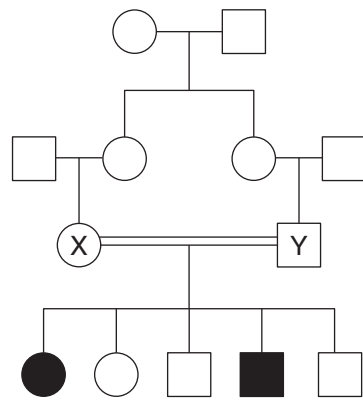

FIGURE 1.9

Pedigree illustrating autosomal dominant inheritance. Squares are males, circles are females, horizontal lines between a square and a circle indicate matings, and vertical lines indicate offspring. Solid symbols indicate individuals with the trait. The diamond with a 4 indicates four children of unknown sex without the trait.

we can assign genotypes to the individuals as shown in Figure 1.9: if we designate the (dominant) allele for the trait **A** and the (recessive) allele for the absence of the trait **a**, then all of the individuals with solid symbols have the **Aa** genotype and everyone else has the **aa** genotype. Moreover, we can predict that if individual X in the figure (who has the trait) has a child, then there is a 50% chance that the child will have the trait. And, if individual Y (who lacks the trait) has a child with someone who also doesn't have the trait, then there is a 0% chance that their child will have the trait— even though individual Y has two sisters, a father, and aunt, and a grandfather with the trait (if either of these statements isn't immediately obvious, do the Punnett square!).

However, there are important exceptions to these general statements about autosomal dominant inheritance. For example, achondroplastic dwarfism (a type of dwarfism characterized by a long, narrow trunk and short arms and legs) is an autosomal dominant trait in humans, and yet about 80% of achondroplastic dwarfs are born to parents of normal stature. But a hallmark of autosomal dominant inheritance is that people with the trait have a parent with the trait, so how can this be? It turns out that most cases of achondroplastic dwarfism are due to new **mutations**, not to inheritance of the allele for dwarfism from a dwarf parent. In Chapter 2, we will discuss how mutations occur. For now, just realize that most mutations are very rare, but for traits that are extremely harmful or otherwise greatly reduce a person's chances of having children, most cases of children with such traits do indeed reflect new mutations (for achondroplastic dwarfs, there is reduced fertility and often complications with pregnancy, which tends to limit the number of children they have).

Now let's consider the pedigree in Figure 1.10 and ask the same questions: do people with the trait have a parent with the trait; and are there roughly equal numbers of males and females with the trait? Here we see that both males and females have the trait, but people with the trait do not have a parent with the trait. These are the characteristics of **autosomal recessive** inheritance. The idea is that in order to exhibit an autosomal recessive trait, by definition a person must be homozygous for the relevant allele. And the most likely way for that to happen is for two heterozygotes to have a child—because the trait is recessive, they will not exhibit the trait, but there is a 25% chance that they will have a child with the homozygous recessive genotype. To be sure, there are other ways of having such a child: a heterozygote can mate with an individual who is homozygous for the recessive allele (and then have a 50% chance of a child with the homozygous recessive genotype), or two homozygotes for the recessive allele can mate (and then have a

FIGURE 1.10

Pedigree illustrating autosomal recessive inheritance. The double horizontal lines indicate mating between people who are related (in this case, first cousins); the other symbols are explained in the legend to Figure 1.9.

FIGURE 1.11

Pedigree illustrating sex-linked recessive inheritance. The symbols are explained in the legend to Figure 1.9.

100% chance of a child with the homozygous recessive genotype). For common traits, especially those which don't have any impact on reproduction, such matings are also common (as, e.g., with the O allele of the ABO blood groups). But if a trait is very rare, or very debilitating, then virtually all matings that produce children with the homozygous recessive genotype involve two heterozygotes, who thus do not exhibit the trait. For example, until very recently people afflicted with cystic fibrosis, which is an autosomal recessive disease, invariably died from the disease before having children. Thus, all children born with cystic fibrosis were born to people without the disease but who, therefore, are heterozygous for the allele causing the disease (barring new mutations). And what is the chance that a couple with one child with cystic fibrosis will have another child with cystic fibrosis? Hopefully, the answer is obvious to you by now: 25% (if not, do the Punnett square!).

Also note that a new symbol appears in the pedigree in Figure 1.10, and that is a double horizontal line between individuals X and Y. Further inspection reveals that individuals X and Y are related: they are first cousins, having one set of grandparents in common. The double horizontal line thus indicates a **consanguineous** marriage (one involving related individuals), which results in consanguinity or **inbreeding** in the children. Inbreeding will be discussed in more detail in Chapter 5; just realize for now that inbreeding results in an increase in homozygosity in the children. This happens because the same allele can be transmitted from one of the grandparents to both parents and then to both of their children (the first cousins). There is then a 25% chance that this same allele gets transmitted from both of the first cousins to their
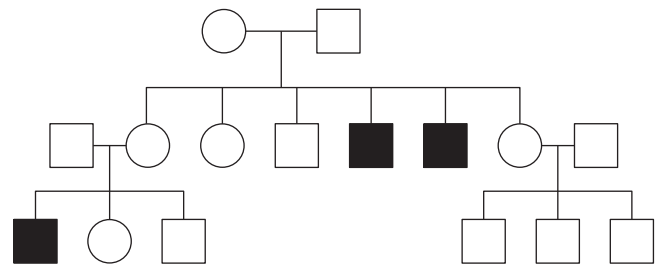
child. Overall, a child of first cousins has a 1/16 (or, about 6%) chance of being homozygous for an allele that was present in one of the grandparents of the first cousins. For a rare trait, this can be much higher than the chance of a homozygous recessive child from two unrelated parents. In fact, some extremely rare traits are known only from children of related parents, and in general, an increase in the frequency of related parents among children with a particular trait is an indication that the trait exhibits autosomal recessive inheritance.

Finally, consider the pedigree shown in Figure 1.11. Here, we see that individuals with the trait have parents who do not have the trait, which suggests recessive inheritance. However, only males have the trait. These are the hallmarks of an **X-linked recessive** trait, where the responsible gene is located on the X chromosome. A female who is heterozygous for an X-linked recessive trait will not exhibit the trait and is sometimes said to be a **carrier** for the trait. However, 50% of her sons will inherit an X chromosome with the recessive allele and hence will exhibit the trait. And, there is a 50% chance that her daughters will inherit an X chromosome with the recessive allele from her and hence also have a 50% chance of having a son with the trait. A famous example involving an X-linked recessive trait is that of Queen Victoria (1837–1901) of England, who bore three daughters who turned out to be carriers of hemophilia as well as a son with the disease. Several of her descendants married into various European royal families, resulting in numerous hemophiliacs among these royal families in succeeding generations.

Autosomal dominant, autosomal recessive, and X-linked recessive are the most common modes of inheritance of human traits. The other possible types of inheritance (X-linked dominant and Y-linked) are relatively rare and are left as exercises for you to work out (there is also **mitochondrial DNA**, which is maternally inherited, as discussed in Chapter 9). In working out how a trait is inherited from pedigrees, it is important to keep in mind that lots of families

(ideally, with lots of children) are needed to establish the mode of inheritance. Any individual family, especially if there are only a few children, may not be informative enough. For example, if two parents without a trait have a son with the trait and a daughter without the trait, this could be X-linked recessive inheritance, but it could also be autosomal recessive inheritance. If the trait is observed to occur only in male children in many families, then there would be conclusive evidence for X-linked inheritance.

▌ WHAT IS—AND ISN'T—INHERITED

Take a look sometime at the unfortunately named Online Mendelian Inheritance in Man Web site (unfortunately named because Mendelian inheritance also applies to women!) accessible at http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim. This is a catalog of traits that exhibit, as the name suggests, Mendelian inheritance—that is, these are traits for which the variation is inherited in an autosomal/X-linked, dominant/recessive fashion. The variety of traits that exhibit Mendelian inheritance is truly staggering. The ability to roll one's tongue, attached versus free earlobes, wet versus dry ear wax, widow's peak (a pointed front hairline)—these are just a few of the traits that have been suggested to exhibit Mendelian inheritance. My own favorite is #108390, urinary excretion of the odoriferous component of asparagus, which simply means that after eating asparagus, some people have smelly urine and some people don't. Smelly urine is inherited as an autosomal dominant trait, although recent work suggests that in fact everyone has smelly urine after eating asparagus, and rather it is the ability to smell the smelly urine that varies among people and is inherited (you can look it up for the details).

Moreover, these are not the only traits that are inherited. Many traits have a more complex genetic basis and/or are influenced by both genes and the environment. Such traits include many that are of anthropological interest (such as variation in skin pigmentation, discussed in Chapter 20), as well as many common diseases (such as susceptibility to adult-onset diabetes or heart disease). These traits are generally known as **quantitative traits**, because the variation is continuous, meaning that the only limit on the values that the phenotype can take is the precision of the instrument used to make the measurement. For example, measure someone's height with a meterstick and you might get a value such as 183 cm (for the metrically challenged, this is about 6 ft). Use a laser and you might get a value like 183.241 cm. Another way to think about quantitative traits is that no matter how similar two phenotypes are, in theory it is always possible for someone to come along with a phenotype that

is in between them (e.g., two people may be 183.241 and 183.242 cm in height but then a third person may be 183.2415 cm). In contrast to quantitative traits are **discrete traits**, which are usually either present or absent or exist in a few discrete categories that are counted as whole numbers (i.e., there are just four possible ABO blood group types). Quantitative traits are also influenced by the environment, whereas discrete traits generally depend only on the genotype (e.g., your ABO blood group genotype completely determines your ABO blood group type regardless of the environment, whereas your height is influenced by your genes, your diet, your overall health, etc.).

A simple example as to how the environment and the genotype interact to determine the phenotype is provided by a very rare type of deafness that is caused by both a particular mutation and an exposure to an antibiotic during childhood. If you have the "normal" genotype at this gene, you will have normal hearing. And, if you have the "deafness" genotype, but never take antibiotics, you will also have normal hearing. But, if you have the "deafness" genotype and you take an antibiotic during childhood (typically because you have some infectious disease, most commonly an ear infection), you will become deaf. It takes both the deafness genotype and the environmental exposure to an antibiotic to produce the deafness phenotype. For those of you who are parents, I hasten to add that this particular deafness mutation is *extremely* rare—it has only been found in a few families around the world—so you should not be concerned that you risk making your child deaf by administering antibiotics in case of an illness!

The analysis of quantitative traits gets very complicated very quickly and is beyond the scope of this book. But, since quantitative traits are also of great interest to people, it is important to know how to think about them. Let's take weight as an example. Suppose my weight is somewhat heavier than average, and I would then like to know how much of my excess weight is due to my genotype, and how much is due to what I eat and my level of physical activity (this would be my environment). If it turns out that my genotype is mostly responsible, good, then I can blame my parents for my excess weight, but if it turns out that my diet/exercise is mostly responsible, then I have only myself to blame. To figure this out, let's carry out the following thought experiments: create identical copies of me (i.e., clones with the exact same genotype at all genes as me) and put them on all possible diets and exercise regimens, and then see how often these clones have excess weight. At the same time, take everyone else, have them eat what I eat and exercise as much as I do, and see whether they also end up with excess weight or not. In the first experiment, we get an idea as to how my genotype "performs" in different

environments, while in the second experiment, we get an idea as to how much of an impact my own environment has when many different genotypes are exposed to it. If my clones tend to always have excess weight no matter the diet, then good, my genotype is to blame and I can eat whatever I want without feeling guilty. But if many different genotypes tend to have excess weight with my diet and level of exercise, then that would indicate that my environment is to blame for my excess weight (in which case, I will blame advertisers for enticing me to eat a poor diet!).

Obviously, we can't actually carry out such an experiment with humans but we can with other organisms. In particular, we can take cuttings from plants, thereby creating many different individual plants with identical genotypes and then raise the cuttings in different environments. An example where this was actually done is shown in Figure 1.12, where seven different cuttings (representing seven different genotypes) of a weed called *Achillea* were raised in three different environments (low, medium, and high altitude). Now, let's suppose I have bad news and good

FIGURE 1.12

Image of cuttings from seven different *Achillea* plants grown at three different altitudes. The plants in each column are cuttings from the same plant and hence genetically identical. Modified with permission from Clausen, J., Keck, D.D., and Hiesey, W.H., "Experimental studies on the nature of species," *Environmental Responses of Climatic Races of Achillea*, *Volume 3: Carnegie Institute of Washington*, Washington, DC, 1948.

news for you. The bad news is that you have been very bad in this life, and so in your next life you will be reincarnated as an *Achillea* weed. The good news is that I will let you choose which genotype you can come back as. Look at Figure 1.12—which genotype would you choose? Your answer should be, well, it depends on which environment you end up in—the "best" genotype depends on whether you are planted at low, middle, or high altitude. Suppose I instead let you choose your environment—at which altitude would you like to be planted? Again, your answer should be that your choice of altitude depends on which genotype you come back as. The important take-home message: *there is no one genotype that performs best across all environments, and there is no one environment that is best for all genotypes*. To the extent that these sorts of experiments have been done, this is the usual result. Therefore, in order to understand how genes and environments interact to produce phenotypes, it is necessary to understand the **norm of reaction**—how phenotypes vary across different environments for different genotypes (as is shown in Figure 1.12 for a very limited number of genotypes and environments). Individuals who have a particular talent—academic, artistic, musical, athletic, and so forth—are often assumed to be innately talented, that is, that they would be talented regardless of the environment. Or, you may think that anyone raised in the same environment as a talented individual—given the same training, opportunities, circumstances, encouragement, experiences, and so forth—would develop a similarly exceptional talent. But the norm of reaction shows that both views are unfounded and most likely wrong: individuals who have an exceptional phenotype probably owe this to the combination of their particular genotype and their particular environment. Put the same genotype in a different environment, or expose a different genotype to the same environment, and you most likely won't get the same exceptional phenotype.

Finally, we have been concerned in this section with what sorts of traits are inherited, but it is also important to keep in mind that many human traits are *not* inherited. It is often thought that if a trait "runs in families," then it must be inherited. This is what I call the "fallacy of familiality"; there are many traits that tend to run in families but are not inherited. For example, family members tend to share political viewpoints and religious beliefs more often than people chosen at random, hence political viewpoints and religious beliefs are familial but they are not inherited. A particularly sobering example is pellagra, a disease due to vitamin deficiency that increased significantly in prevalence in the southern United States in the early 1900s. The actual cause for the increase in pellagra was poor nutrition associated with poverty, but a commission appointed to study the disease concluded
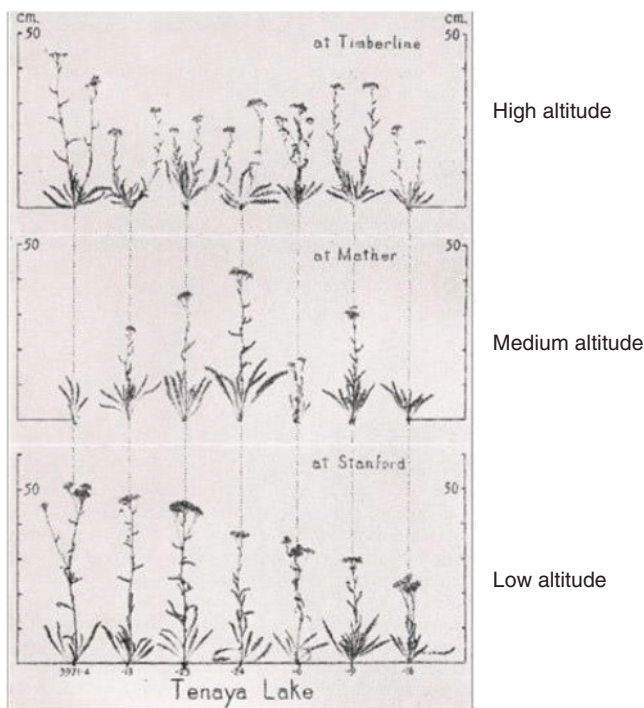
that it was instead inherited because it tended to run in families. Apparently, the commission did not realize that poverty also tends to run in families, and it took a long time before it was realized that simply improving the quality of the diet was sufficient to eliminate the disease.

CONCLUDING REMARKS

In this first chapter, we've covered the basics of how human traits are inherited. We've seen that genes are particulate and that alleles are not influenced by phenotypes—an O allele inherited from an AO parent behaves exactly the same as an O allele inherited from an OO parent. We've also seen that alleles at different genes are inherited independently—unless the genes in question are linked, that is, located close to one another on the same chromosome. We've gone through the properties of autosomal recessive, autosomal dominant, and sex-linked recessive inheritance, and how the mode of inheritance of a trait can be inferred from studying families. We've also briefly touched upon quantitative traits and distinguished what is inherited (passed on by genes) from what is merely familial. You now know (more or less) as much about genes as scientists did before they figured out what genes actually are, what they do, and how they do it, which is what we shall turn to next.