# Are We Hardwired?

## The Role of Genes in Human Behavior

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# *Prologue*

Why are human beings so different from one another? Why are some people tall, some short; some brown-eyed, some blue-eyed? The fact that daughters and sons tend to look like their mothers and fathers suggests that physical features are heritable and therefore due in large part to genes. But what about behavior? Why, in the very same family, are some children assertive, others shy? Why are some people confident, others uncertain? Why are some highly emotional, others more reserved and "logical?" Are these traits heritable, too? Do differences in these traits among individuals also have a genetic basis?

The idea that at least some of the variability we see in human behavior and personality is heritable, and therefore genetically determined, would certainly come as no surprise to most animal breeders. For at least half a millennium or more, animals have been bred specifically to reinforce certain behavioral or personality traits. Some dogs, ranging in size from tiny terriers to massive pit bulls or Dobermans, have been bred for their aggressive nature. Others, such as collies or spaniels, faithfully transmit a docile, loving nature from generation to generation. Still others have been bred to carry out specific tasks related to hunting or managing flocks of animals. In the laboratory, rats and mice have been selectively bred for many generations to create strains that are fearful or aggressive. These strains pass on their personality differences each time they breed. No one seriously questions the role of genes in the development of animal behavior, or of inheritance in passing these traits from one generation to the next. Yet we are reluctant to acknowledge a similar role of genes in guiding human behavior.

At a deeper level, we know that the lives of cells are closely governed by genes, whether those cells are individual, free-living organisms such

as yeast and amoebas, or the interactive cells that make up our own bodies. Single-cell organisms show definite signs of behavior. Within ourselves, the cells charged with managing how we react, how we behave, are all located within our nervous systems. And it is precisely when we come to the cellularly more complex nervous system that the issue of genes and behavior becomes complicated. The major complication arises because, more than in any other organ or system in the body, the behavior of cells in the nervous system is affected not only by genes but by the external environment. Nerve cells are our window onto the world around us. We use the various images impressed onto our nerve cells to formulate responses to our environment, and this experience of our environment—and our responses to it—are remembered. Nerve cells are altered by contact with the environment, in ways that are still only crudely understood but which alter the way we respond to the same information when it appears in the environment again.

The role of genes in governing behavior remains one of the most controversial topics in all of human biology. Early in this century, overeager promotion of a genetic basis for behavior led to the initial silly excesses but ultimately to the stunning horrors of eugenics. Subsequent reactions to these excesses, within both the scientific community and society as a whole, led to a nearly complete dismissal of a role for genes in human behavior for many decades. We are slowly coming back to a more balanced view. A detailed study of the biological basis of behavior in animals, from the simplest single-celled creatures through the most complex mammals, shows that genes play a very important role in guiding behavior. Inheritance studies in humans, especially those involving twins reared together or apart, indicate clearly that humans are no exception. The variability we see around us in the way humans respond in a given situation is to a large extent influenced by the variability in their genetic makeup.

Part of our concern about the role of genes in determining human behavior surely lies in our concerns about free will and personal responsibility. All legal and moral systems assume that individuals are free to choose among alternative courses of behavior; individual responsibility has no meaning in the absence of unimpeded choice. But if our every behavior can be predicted from what is written into our genes before we are born, what does that say about our freedom to

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# *About Genes and Behavior*

In the preceding chapters we have presented a good deal of evidence, both direct and indirect, for a role of genes in explaining a substantial portion of the variability we see in the behavior of both animals and humans. But we have said very little about *how* genes might do this. In part, that is because we do not yet know all the details of how genes influence behavior. As we see below, there is good evidence that most behaviors, especially in humans, are genetically complex; that is, they are influenced by not just one gene, but by many. But until we know what the individual genes influencing a behavior are, it is difficult to say anything about how they may act as a group, and we are still at the stage of identifying the individual genes.

It is easy for mutations in a single gene to disrupt a behavior, as we saw in the case of the *lrn-1* and *-2* genes in *C. elegans*. There are also numerous examples of individual defective genes disrupting human behavior, such as the genes underlying Huntington's disease and the heritable forms of Alzheimer's disease. But that does not mean that

the behavior in question is controlled by a single gene. Any behavior is always an outward expression—a phenotype—reflecting the operation of biological systems regulated by many different genes, interacting with each other and with the environment. The numbers of genes involved in most behaviors would certainly be in the range of dozens, and perhaps even hundreds. That mutation of a single gene can often disrupt an entire behavior simply reflects the fact that the biological systems underlying that behavior are tightly regulated; breakdown of a single component can often shut down an entire pathway. Think of all the individual parts in a computer required to store and retrieve a document from memory. If one of the components involved should break down, memory function is lost. But that certainly does not mean that memory in the computer can be accounted for by the single part that broke. So it is with genes involved in determining complex human traits.

The underlying issue of complexity in the genetic regulation of behavior will be very much tied up with the types of genes we believe will be involved in that regulation. What kinds of genes will we be looking for as we begin to dissect the genetic basis of behavior? When we think of a particular human behavioral trait—boldness versus shyness, for example, or curiosity versus indifference—should we expect to find unique genes whose alleles directly and specifically cause the varying phenotypes we see in these traits in the individuals around us?

In thinking about the kinds of genes we might expect to see influencing various human behaviors, it might be useful to take a brief look at two other areas of human biology where scientists have gained important mechanistic insights by ferreting out the genes involved: cancer and aging.

For most of its clinical history, cancer was viewed as a thousand or more different diseases—at least as many different cancers as there were different cell types in the body, each requiring different treatment, each with its own outcome. Although there were hints that at least some kinds of cancer might have a genetic basis, no one knew where to begin. It seemed that if cancer was indeed caused by genes, then there would have to be an enormous number of different cancer genes—at least one gene for each different cancer type. For many years that possibility inhibited scientists from trying to unravel the genetic basis of cancer.

Fortunately, it didn't discourage all scientists from pursuing this question. And those who stayed in the game ultimately found out that there really are no "cancer genes" per se. In fact, there are relatively few genes involved in causing cancer, and we find the very same genes—or at least the same classes of genes—underlying each cancer, regardless of tissue origin. Cancer turns out to be caused by allelic variants of the genes responsible for regulating normal cell division. Cancer cells, at least when they first arise in the body, are no different from their noncancerous neighbors, with the exception that they have somehow acquired allelic variants of cell division genes that result in cell division when there should be none. Otherwise, the cells are perfectly normal. Different cancers are different because the cells in which they arise are different, but the genes responsible are largely the same. This new mind-set about what cancer represents has revolutionized strategies for both the detection and the treatment of cancer, strategies that are already finding their way to the clinic.

A similar shift in thinking has occurred in the study of aging. When we add up all of the outward manifestations of aging, and combine them with all of the internal age-related changes detectable by laboratory tests, we end up with a staggeringly long list of degenerative alterations associated with age. It seemed to some researchers that an enormous number of different processes must be taking place during aging in the various tissues and cells of the body to explain such a diversity of measurable events. And again there was the assumption that to the extent that aging is genetically controlled, there must be enormous numbers of genes involved—at least as many different genes as there are different aging phenotypes.

Yet this turns out not to be the case. A degenerative process involving alterations in the activity of a single gene, expressed in all cells in the body, can compromise the function of many different cells in the body, but each in a different way. For example, in Werner's syndrome, a mutation in a single gene causes accelerated aging in many different tissues. Beginning at age twenty or so, individuals with Werner's syndrome develop gray hair, aged skin, bone loss, muscle wasting, cataracts, and cardiovascular disease, among other things. And all because of an alteration in a single gene, in this case a gene involved in unwinding DNA—perhaps in preparation for repair of the DNA damage that is thought to be a major contributor to aging. The

Werner's gene is by no means the only gene involved in aging—we surely will find others—but the rather startling range of phenotypes caused by this single gene, across such a large number of cell types, suggests the possibility that a relatively small number of genes could account for a large proportion of aging phenotypes.

Cancer and aging are not behaviors, but a study of their underlying genetics has important implications as we think about behavioral genetics. First, as we have seen, just because a particular biological phenomenon is complex does not mean a priori that large numbers of genes are involved. Certainly, cancer and aging involve more than single genes. But each type of cancer, or each aging phenotype, does not necessarily involve separate and distinct sets of genes. Second, the genes involved in modulating a particular phenotype may or may not have an obvious connection with the phenotype. Although in retrospect we might have made the connection several decades ago between genes controlling cell division and cancer, we might never have connected cataracts in the elderly with a DNA repair enzyme, if someone had not discovered the gene first and shown its involvement in Werner's syndrome.

### *DNA and the Language of Genes*

There are an estimated 50,000 to 100,000 genes spread out among the twenty-four chromosomes that make up the human genome: twenty-two "autosomes," present in each cell as pairs, plus the X and Y sex chromosomes. The genes are contained in long, linear strands of DNA stored in the nucleus of each cell in the body. Humans have an enormous amount of DNA—about a meter of it per cell. If all of the DNA in an adult human being ($10^{14}$ cells, give or take a few trillion) were strung out end-to-end, it would reach from the earth to the moon and back many thousands of times.

DNA is made from small chemical units called nucleotides (Fig. 5.1). There are just four of these units, called by their abbreviations A, C, G, and T. They are linked side by side into individual DNA strands, with no restrictions on linear sequence; any nucleotide can lie next to, and hook up with, any other nucleotide along the same strand. In cells, DNA always occurs in the form of the well-known "double-helix"—two individual strands wound about one another to form a helix. The

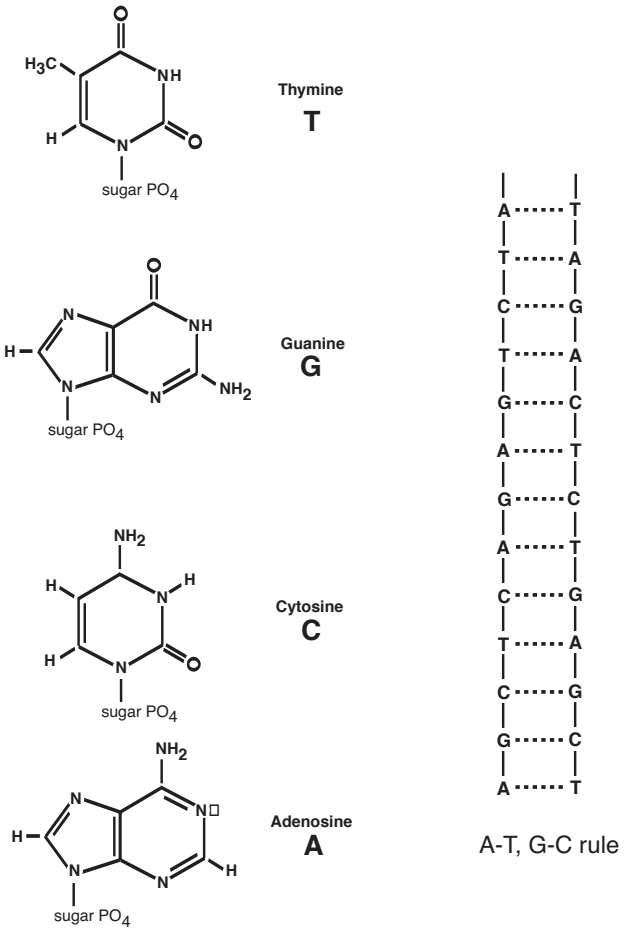


**Figure 5.1** The four nucleotide subunits used to make DNA.

nucleotides facing each other across the two strands of the double helix form a sort of bond with one another to stabilize the helix, and here there are restrictions on who can shake hands with whom. An "A" can face only a "T" across a double helix, and a "C" can lie across from only a "G" (Fig. 5.2).

This restriction on pairing between nucleotides in opposing strands is the secret to faithful DNA replication. When a cell divides, the two strands must each replicate, so that an identical DNA double helix can be transmitted to each of the new daughter cells. As can be seen in Figure 5.2, when two DNA strands pull apart, each serves as a template for assembly of a new strand; new copies of individual nucleotides

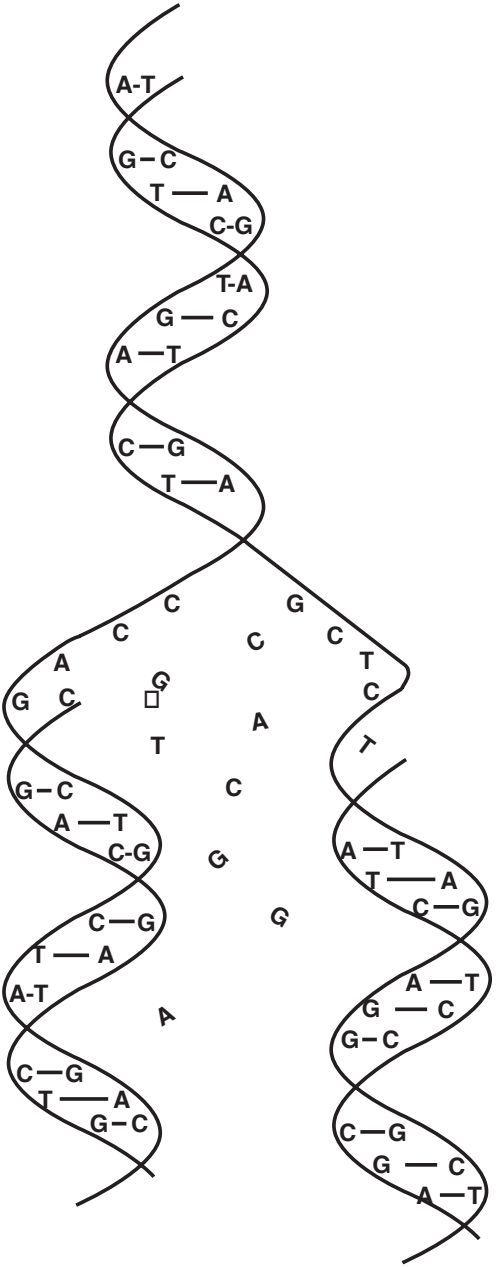


**Figure 5.2** Detailed structure of replicating DNA. New strands are generated from free-floating nucleotides, using the unwound strands as a template.

are brought in and lined up along the template strand according to the pairing rules, A with T, and G with C. Once the new set of nucleotides is lined up along the template, and locked into place with each other and with the template strand, voila! We have two new double helices that are exact replicas of the original helix. This insight, among others, earned a Nobel prize for James Watson, Francis Crick, and Maurice Wilkins in 1962.

Genes are defined stretches of nucleotides lying along one or the other of the two strands of DNA (both are used), marked by a starting point and a stopping point. The nucleotides between these two points are read in groups of three, with each such triplet specifying a particular amino acid; the gene as a whole thus defines a particular protein. Alleles of a given gene represent slight variations between individuals in the nucleotide sequence of that gene, which results in minor amino acid variations in the corresponding protein. Alleles arise because the DNA copying process is not always perfect; when DNA is replicated at the time of cell division, so-called copy errors creep into genes from time to time. If the new variant is kept, it becomes an allele of the gene from which it arose.

The way in which genes give rise to proteins within a cell is shown in Figure 5.3. A given gene is first copied into a form called "messenger RNA." RNA is very similar to DNA. The advantage of making separate RNA forms of genes is that individual gene copies can be moved out of the nucleus and into the portion of the cell where proteins are made, without disturbing the rest of the genome. Once at this site, the messenger copy of the gene is attached to a small structure called a ribosome, where its sequence is read off, triplet by triplet, and converted into the amino acid sequence of a protein.

Each gene consists on average of about a thousand nucleotides. Even at the upper limit of 100,000 genes in the human genome, it is obvious that genes account for only a very small portion of all the DNA we carry around in our cells. It turns out that actual genes are scattered rather widely throughout the genome, separated by vast stretches of DNA that do not code for anything (Fig. 5.4). Even within genes there are stretches of nucleotides, called "introns," that don't code for anything. What does all of this extra DNA do? Some of it surely represents genes we once used, far back in evolutionary time, and no longer need. Some of it probably serves as raw material for gen-

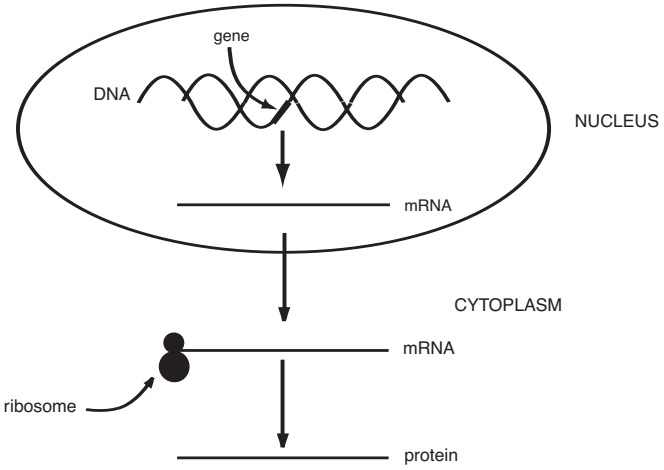


**Figure 5.3** Information flow: DNA RNA protein.

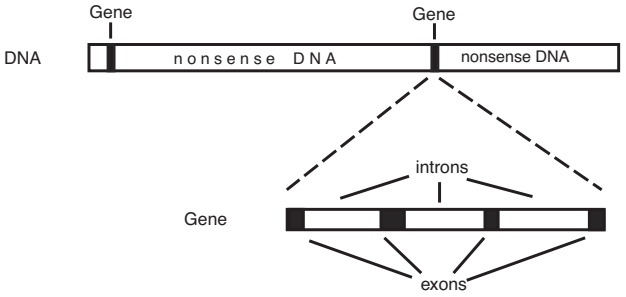


**Figure 5.4** Sense and nonsense DNA. In the expanded gene, only the portions in black (exons) actually code for the protein corresponding to the gene.

erating new genes. The bottom line is we simply do not know. It is often called "junk" DNA, or "nonsense" DNA. But as discussed in later chapters and in Appendix I, below, some of this DNA has properties that make it very useful for "tagging" selected regions of DNA, and following them around from one generation to the next.

### *The One and the Many: Single-Gene versus Multigene Traits*

Most of the genetics that was done in the twentieth century, both classical transmission genetics and even the more recent molec-

ular genetics, has involved the study of single genes—how they are inherited and which properties of the individual organism they affect (transmission genetics), and the structure, function, and regulation of the underlying gene (molecular genetics). Mendel, for example, studied inheritance in peas. He proved that certain traits, such as the texture or color of peas, or the height of plants, were controlled by individual "units of inheritance" that eventually came to be known as genes. Heredity had previously been viewed as some sort of "blending" of the overall characteristics of each parent. The idea that individuals are composed of a large number of individual traits that can be passed forward separately and distinctly from one another was a major revolution in the way we view heredity.

Mendel was also the first to describe alleles of genes. Alleles are slightly different forms of the same gene present within a given population. These differences arise through the various processes of mutation, which result in nucleotide changes in the sequence of a gene. The resulting changes in the protein encoded by the altered gene (the allele) can be harmful, neutral, or favorable with respect to the function of that protein. Harmful mutations generally do not survive the winnowing processes of natural selection. Neutral or favorable changes are usually kept. Favorable alleles, over time, can increase their frequency substantially within a population if they result in improved reproductive efficiency. Mutations can arise because of physical damage, such as that caused by radiation and certain chemicals that damage DNA. But perhaps the major source of mutations that alter genes within a population is the introduction of copy errors during the normal reproduction of DNA in dividing germ cells. Radiation and chemical damage is fairly easy to detect and repair, but copy errors are much more subtle, and often result in uncorrected changes in genes, thus giving rise to new alleles for natural selection to act upon.

A majority of the genes making up the genomes of most species have allelic forms; such genes are referred to as "polymorphic," or having many forms. In terms of the genetic basis of variable behaviors, we are concerned primarily with polymorphic genes. The question behavioral geneticists ask is to what extent the variability we observe in behavior within a population can be ascribed to genetic differences. Genetically based differences arise principally through the inheritance of different alleles of polymorphic genes. So throughout the remain-

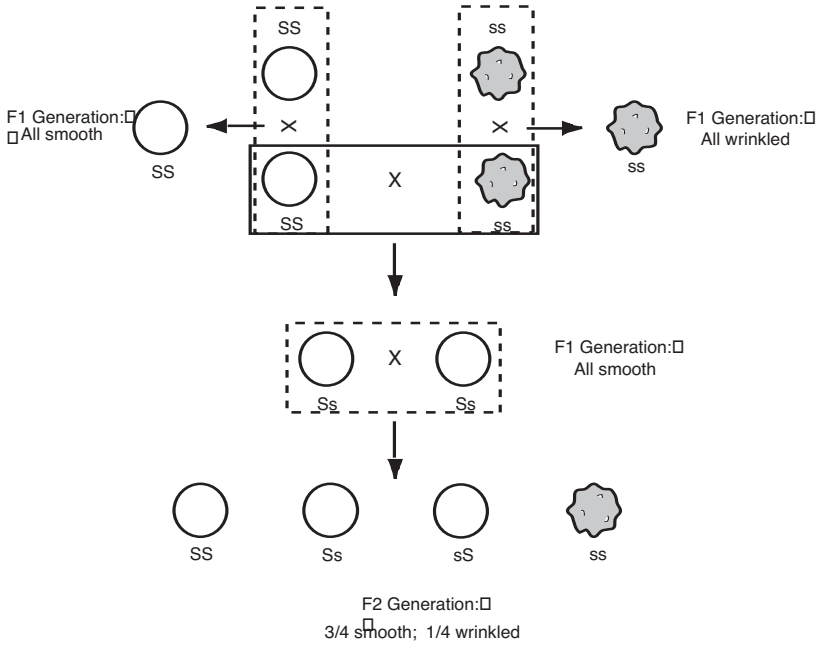


**Figure 5.5** Mendel's results from a pea breeding experiment. Breeding pairs are enclosed within boxes.

der of this book, we are not talking so much about genes that regulate behavior, but rather different alleles of individual genes that contribute to differences in behavior.

Mendel also defined the important concept of dominant and recessive alleles. Each individual has two copies of each gene, one inherited from each parent. If there is more than one allele of a given gene within the population, an individual may have two different alleles for a given gene, in which case that individual is said to be heterozygous for that gene. The protein each allele encodes usually has slightly different properties. For example, Mendel identified a gene governing the quality of the skin covering individual peas (Fig. 5.5). One allele of this gene (S) results in smooth skin, and the other allele (s) codes for wrinkled skin. Mendel showed in his breeding experiments that if an individual plant had two "smooth" alleles (in genetic terms, *homozygous* for the smooth allele, i.e., SS), the peas of that plant would be smooth. If the individual had two "wrinkled" alleles (homozygous wrinkled, ss),

its peas would be wrinkled. If a plant had one wrinkled and one smooth allele (*heterozygous*, i.e., Ss), the resulting peas were not halfway between wrinkled and smooth; the traits did not blend. The peas in such a plant were all perfectly smooth. The smooth allele is therefore said to be dominant over wrinkled. The important thing to recognize is that there is no observable (phenotypic) difference between the peas of plants that are homozygous smooth (SS) and heterozygous (Ss).

A major question confronting behavioral geneticists is to what extent classical Mendelian (single-gene) inheritance is useful in explaining the influence of genes on behavior. There are a few examples of single genes governing a behavior, even in humans. For example, there is a single gene that determines whether individuals can taste the chemical phenylthiocarbamide (PTC). Genes that affect the ability to taste definitely affect behavior, in the sense that they are involved in an organism's response to the environment. The PTC taste gene in humans has two alleles, one conferring the ability to taste PTC, and one that results in an inability to taste PTC. The allele conferring the ability to taste is dominant: If an individual has one copy of each allele, he/she can taste PTC. In humans, we can see that this trait is governed by a single gene by looking at inheritance patterns in families. Roughly 25 percent of the population cannot taste PTC, which indicates that the recessive allele of this gene is present in about half the population.*

In animals, where we can do controlled breeding experiments, the difference in inheritance patterns can be determined in a slightly different way. Imagine that a *ptc* gene exists in mice, with the same dominant/recessive pattern as in humans. (For simplicity's sake, we assume the existence of only a single dominant allele and a single recessive allele.) Imagine further that we begin randomly breeding mice, and testing the offspring for the ability to taste PTC. We then begin selectively breeding together those offspring who, on the one hand, cannot taste PTC, and separately those offspring who can taste PTC in their food.

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* We do not know the significance of the ability to taste PTC, or the reason for the existence of two distinct alleles controlling its taste in humans. PTC is not found in food; our ability to taste it presumably reflects a random cross-reactivity of PTC with some standard taste receptor. The alleles we are discussing here would be alleles of that receptor.

Possible results of such a breeding experiment are presented in Figure 5.6. Within essentially a single generation, we would have a subline of mice all of whom were unable to taste the chemical (curve A). We would be selecting for mice with two defective (recessive) copies of the *ptc* gene; two such mice mated together would have no good copies of the gene to pass on. They would thus transmit this deficiency to 100 percent of their offspring each time they mate. It would take a somewhat longer number of generations to derive mice all of whom were able to taste PTC (curve B in Fig. 5.6). This reflects the fact that phenotypically, there is no difference between a heterozygote carrying one dominant and one recessive gene, and two dominant genes; both can taste PTC. The recessive gene will disappear only gradually from the population, whenever two copies show up in the same individual (who is then eliminated from the breeding pool). If the ability to taste PTC were controlled by multiple genes, each with dominant and negative alleles, the ability to generate either type of subline would look like curve C.

Let's look at the breeding and selection pattern for a genetically complex personality phenotype in mice—fearfulness versus adventure

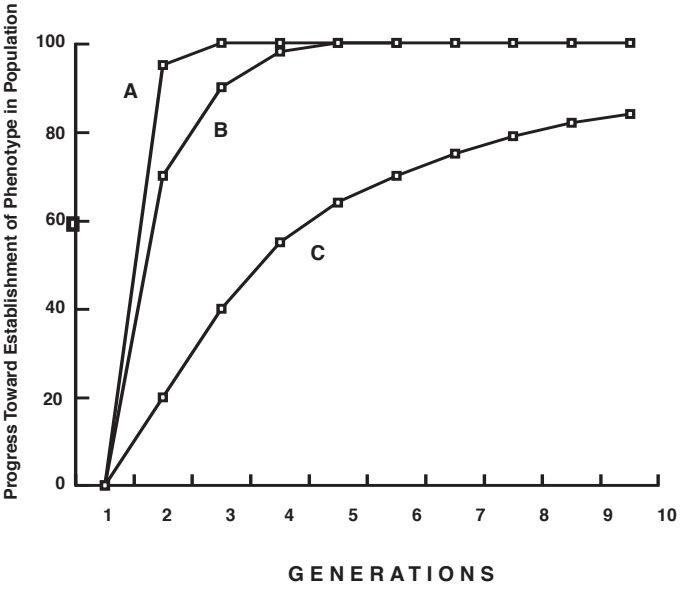


**Figure 5.6** Selective breeding for the ability to taste PTC.

seeking. If individual field mice are placed in a large, open box, under full light, we see a range of behaviors displayed by individuals in an unselected population. Some mice will become almost catatonically fearful; they will cringe in one corner, and not move. They will urinate and defecate. The majority of mice will show a little more curiosity, and explore their surroundings somewhat, some more boldly than others, but generally hugging the walls as they move about. A few mice will roam around the entire floor surface of the box, exploring, seemingly unconcerned about anything at all.

There could well be implications of this range of behaviors in a population of mice for survival in an open field. In a time of plentiful food, we can imagine that fearful mice will have a survival advantage because they are less likely to be eaten by a predator than are their more adventurous relatives. Caution would be a good thing in that case. But when food is scarce, the fearful mice may be at a disadvantage because they will be too timid to seek out resources aggressively. They might also be less successful in finding mates. So having a range of behavioral traits related to fearfulness could be advantageous for the species as a whole.

When we try to develop sublines of fearful mice and bold mice, starting with a normal, unselected population showing all of the variants just described, the result is very different from what we saw with the ability to taste PTC, which is controlled by a single gene. With video cameras and electronic detectors, mice placed in an "open-field box" of the type described above can be monitored precisely for the extent to which they move about and explore their surroundings. The mice are allowed to breed, and the offspring are scored in an open-field box and segregated into most fearful and least fearful subgroups. The procedure is then repeated, but with subsequent breedings allowed only within each subgroup. After each mating, the offspring are again sorted into most fearful and most adventurous subgroups, and the inbreeding continues.

The results of such a breeding program do in fact look like curve C in Figure 5.6. After perhaps a dozen generations of breeding and selection for the desired traits, sublines of mice will have been generated that differ by a factor of a hundred or more in fearfulness. Mice from the fearful subline freeze up almost completely when placed in an open-field box; the bold mice move about and explore almost without fear. It is important that they do this whether they were reared by their

own mothers, or were transferred immediately after birth to a surrogate mother of the opposite behavioral phenotype for nursing and rearing. When newborns from each strain are mixed and placed with a surrogate mother, each will go on to express its own genetic predisposition, rather than that of its surrogate littermates or its surrogate mother. This experiment tells us several important things. First, since these traits are passed on faithfully to offspring independently of contact with others of their species, we can conclude that they are inherited and not learned. But the degree to which the genetic predisposition to fearfulness or fearlessness is expressed continues to change across a large number of selective breeding generations. The most likely interpretation of this is that there are many different genes involved in regulating these behaviors, and that a large portion of these genes have multiple alleles affecting the degree to which each of them contributes to the overall phenotype. It is unlikely that we will find a single gene that we can call "*frfl*" (for "fearful") that completely dominates this phenotype.

From the fact that boldness as opposed to fearfulness is heritable and not learned, we know it is largely a genetic trait. But it is not the case that all individuals in a natural (unselected) population are either fearful or fearless. If scores for individuals are plotted on a common graph, there is a continuous range of phenotypes from extremely fearful to very bold, with most individuals lying somewhere in between in a classical bell-shaped curve (Fig. 5.7). The individuals at either end of the curve approximate the members of the two sublines we generated by selective breeding: very fearful or extremely fearless. This range of genetically controlled phenotypes within an unselected population is the definition of what is called a "quantitative genetic trait." A number of different genes control the trait, and the position of any member of an unselected population on this curve is a reflection of that individual's particular collection of alleles for the various genes underlying the fearfulness-versus-bold trait. Virtually every behavior that has been analyzed in human populations generates a curve such as that shown in Figure 5.7.

While behavior in an open-field test is clearly a quantitative trait, we can discern the effects of individual genes in the overall behavioral pattern. Albinism in mice is known to be controlled by a single recessive gene. There are mice that are genetically identical except for hav-

ing different alleles of the albinism gene. The albino mice are much more tentative than their nonalbino littermates. This is mostly because the albino mice are much more sensitive to bright, full-spectrum light. In a field test carried out with red light, to which the albino mice are much less sensitive, they score about the same as non-albino mice in terms of moving about in an open field. These kinds of subtle interactions involving many different types of genes underscores the complexity of sorting out the genetic contribution to many behaviors.

Essentially all of the animal and human behaviors we discuss in the remainder of this book are quantitative traits. One of the major goals of molecular biology and molecular medicine in the coming decades is to identify as many genes associated with quantitative traits as we possibly can, whether these be traits for behavior, disease, or any other complex aspect of human biology. It might seem to make sense that the genes associated with any given quantitative trait should all be clustered next to each other on a single chromosome, where they could interact with one another. That is not the way it works, however; the genes involved with a single trait are usually spread more or less randomly throughout the entire genome. The chromosomal locations of the various genes associated with a given quantitative trait, like the albinism gene that affects mouse behavior in an open-field test, are

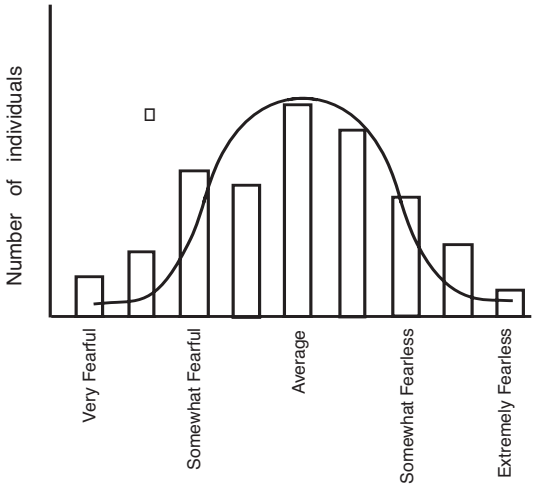


**Figure 5.7** The distribution of fearful/fearless types in a wild mouse population forms a typical bell-shaped curve.

called "quantitative trait loci," or QTLs. Whereas some of the genes at these QTLs may interact with one another in a highly interdependent fashion in creating the ultimate phenotype characterizing a particular behavior, other genes may affect that behavior relatively independently of one another. Most important, not all QTLs will affect a given trait equally; some will be "heavy hitters," accounting for a quarter or a third of the genetic component of that trait. Others will make relatively minor (but, by definition, detectable) contributions to that trait. Molecular biologists tend to be interested in all of the identifiable QTLs underlying a trait; molecular medicine is generally concerned with the heavy hitters.

But genes cannot explain all of the variability in quantitative traits; environment, too, has a role to play. This is a point often overlooked when interpreting the results of studies in behavioral genetics. Most data consistently show an effect of the environment ranging from 30 to 70 percent for different behaviors. There are two important points to bear in mind about the role of environment in determining behaviors. First, when we measure behavior we are not measuring genotype, we are measuring phenotype. Phenotype is determined *only* by the interaction of a particular genotype with the environment. The second point is that two identical genotypes, placed in two different environments, may produce two quite different phenotypes with respect to any particular characteristic, behavioral or otherwise. In many of the studies we discuss in this book, involving monozygotic twins with identical genotypes, the impact of the environment on many behaviors often seems rather minimal. That is largely because the different environments we are talking about are not always that different, and the twins involved can manipulate and extract from their respective environments quite similar things, in the end.

The impact of environment on behavior can be shown quite clearly in a variation of the open-field test just discussed. Newborn rabbits are somewhat unique in that the mother spends very little time with them. She is away from the nest almost the entire day, and nurses them only once per day, usually in the evening after she returns from foraging. Even rabbits maintained in a laboratory environment follow this pattern of minimal contact with newborn young. When recently weaned rabbits are placed in an open-field test box, they exhibit the same range of responses seen in rats and mice: Some huddle, almost immobilized,

against the walls, while others explore the field box with varying degrees of fearlessness.

Researchers found that by subjecting young rabbits to a variety of sensory experiences during the preweaning period—handling them or exposing them to mild shocks or higher or lower than normal temperatures—they could greatly increase the tendency of these animals to explore their surroundings in an open-field test later on. Increases in the degree of adventurousness as adults correlated directly with the amount of preweaning handling. But unlike the degree of gene-biased fearlessness produced in selectively bred mice, the fearlessness developing as a result of early life environmental experience is not passed from one generation to the next. The offspring of two "environmentally generated" fearless parents will show the same random assortment of fearful/fearless phenotypes as the offspring of two timid parents.

Environmental effects can also be seen in standard inbred strains of mice. These strains are created by starting with a single pair of mice, and repeatedly breeding only brother and sister descendants in each generation. The object here is not to select for a particular trait, but just to achieve strains of mice in which all members are in effect the equivalent of human identical twins, which is achieved after about thirty generations. These kinds of strains have proved invaluable for studying cancer, organ transplantation, and other physiological phenomena where precise genetic definition is critical.

All of the members of a given inbred strain are genetically identical, but each inbred strain is different from every other strain. Differences between strains for phenotypes such as fearfulness/boldness, although not selected for, do show up, and are presumed to be largely genetic. But differences among members of the same strain cannot be genetic, by definition, and we do see modest differences in such traits among members of the same strain. These differences cannot be enhanced by selective breeding, because they are not transmitted from one generation to the next. How such differences arise in mice is not entirely clear. While most colonies are managed in a highly uniform manner, differences may occur in the way individual mice are handled by animal care technicians. Different degrees of crowding during the early part of life, different ratios of males to females in the same cage, different experiences with viral or bacterial pathogens could well affect behavior. It is never possible to control environmental factors com-

pletely, and the variabilities we see within inbred mouse strains makes it absolutely clear that these factors can affect behavior. That such differences are not learned is shown by experiments wherein, for example, newborn pups from a fearful mother are transferred at birth to an aggressive foster mother. As adults, the variability among these mice in fearfulness is not significantly different from mice reared by fearful mothers.

A clear example of the interaction of genes with the environment in humans is the drastic increase in obesity among individuals in industrialized countries in the past hundred years. Most studies suggest that the frequency of individuals who are overweight has almost quadrupled since the end of the nineteenth century. There is no way that the genetic composition—the distribution of alleles affecting body weight—of any population breeding as slowly as humans could have changed in so short a time. The change must be primarily environmental: Changes in diet and much less expenditure of energy in the daily tasks of living are almost certainly the culprits. These environmental changes have interacted with the existing pool of individual genotypes in different ways, and many of the underlying changes in body weight are purely behavioral in nature. We look at this question in more detail in Chapter 10.

### *Going for the Genes*

One of the goals of behavioral genetics is to find and identify the genes in which allelic variation could be responsible for the variability we observe among individuals for a given behavior. We are thus looking only for polymorphic genes, genes present in multiple forms among the members of a given population of animals or people. Since behavior is for all practical purposes controlled by the brain and nervous system, with help from certain hormone-producing tissues, we will be looking at genes expressed in those systems. But how do we go about finding those genes?

The most important tool in the isolation and identification of any gene is a good genome map. A genome map consists of physical pictures of the individual chromosomes making up the genome, with the location of what are called DNA markers clearly indicated. In the early days of genome mapping, DNA markers were simply genes whose

location had been very laboriously traced to specific chromosomal locations. In research animals such as *C. elegans* or fruit flies, the presence of individual genes is usually first detected by mutations giving rise to observable phenotypes. Once it has been established that a given gene is physically associated with a particular chromosome (the first one is always the hardest!), that gene can serve as a "marker" for that chromosome. When a new mutation appears, we can ask whether or not this mutation is inherited along with alleles of the marker gene. If it is, then it must be on the same chromosome as the marker gene. Additional genes traced to this same chromosome can then be mapped even more precisely.* Starting early in this century, researchers have gradually identified the chromosomal locations of a large number of genes that are polymorphic within fruit fly populations.

It has been much more difficult and painstaking to establish the locations of genes in the human genome. In fact the first gene was not mapped with a specific chromosome until 1968. Humans have twenty-three chromosomal pairs, compared to four for fruit flies, and considerably more genes. Nevertheless, by the 1980s fairly precise chromosomal locations for a thousand or so human genes had been established. Today, as part of the Human Genome Project, markers are being established on each and every chromosome to aid in gene mapping.

The locations of genes already mapped serve as ready markers, but molecular geneticists have moved well beyond that. They have established DNA markers that have nothing to do with genes per se. True genes are not lined up end-to-end continuously along a chromosome; they are separated by stretches of DNA that do not code for anything, or "nonsense" DNA. Nevertheless, scientists have found that some portions of this DNA are remarkably well conserved from generation to generation, and are even present in the population (and inherited faithfully) in allelic forms. These nonsense DNA markers can be used in the same way as allelic genes to pinpoint the chromosomal location of new genes. The section of the DNA containing that marker can then be isolated and systematically searched for the new gene. Once the gene is isolated, it can be sequenced, and the nature of the protein

* The way in which DNA markers are used to determine the location of a new gene is described in more detail in Appendix I.

it encodes can be inferred from the DNA sequence. And of course, that gene itself now becomes a marker on the map of the chromosome on which it was found.

The availability of a detailed set of DNA markers for the human genome (the first sets have become available only in the past few years, and are still being refined) provides molecular geneticists with an alternate approach to identifying the multiple genes associated with complex, quantitative genetic traits. This extraordinarily powerful new tool is called a "genome scan." For a given quantitative trait, one can correlate inheritance of that trait with inheritance of the full range, or with selected subsets, of human genome DNA markers. This requires large numbers of individuals, preferably representing at least three generations. This technique can tell us which DNA markers are inherited along with a given trait, thus revealing the approximate chromosomal location of the underlying genes. The sections surrounding the DNA marker can then be examined for the presence of candidate genes. The great advantage of a genome scan is that it provides a systematic means of uncovering trait-associated genes whose existence was previously unsuspected.*

From what we have discussed in this chapter, there are several things to carry with us as we continue to explore the genetic basis of behavior. It is true that most behaviors are quantitative genetic traits—they are almost certainly not going to be governed by one or even a small number of genes. And the effects of these genes will, to varying degrees, be subject to modification by the environment. But from what we understand of other phenomena, such as cancer and aging, it may well be the case that the genes influencing behavior will not be very different among different behaviors. So should we set out to look for "fearful" genes? Should we expect to find genes dedicated only to mental functioning? Will special genes guide us to become artists, or engineers? A few decades ago, many scientists might have said yes. Today, they are hedging their bets, but now they have powerful new tools to reshape their answers. In the next few chapters we examine some of the experiments that are causing researchers to take a more cautious, yet hopeful, approach to understanding genes and behavior.

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* Details of how a genome scan is used to detect previously unsuspected genes are given in Appendix I.