



# *chapter four*

# HOW IS GENETIC RESEARCH ON BEHAVIOR CONDUCTED?

## 4

### ■ ■ ■ Anja, an identical twin

Anja has an identical twin sister, Anke, who looks so much like her that they have trouble telling who's who in childhood photographs. Anja and her twin have the same curly brown hair, the same charming grin, and the same lanky bodies. Both are left-handed, nearsighted, and allergic to cats. In many such ways the twins are physically alike.



Yet if you stand the twins side by side, you can find physical distinctions. Anja has a light-brown birthmark near her left ear that Anke does not, and she is a half inch shorter than her sister.

There are non-physical differences, too. Anja is a professional writer while her twin works in graphic design. Anja likes her cup of coffee in the morning while her sister starts the day with diet cola. Anja likes to run for her exercise, and Anke prefers to swim. Anja dresses more conservatively than her sister, but is politically more liberal. Anja has a dry sense of humor, yet her twin is the one who tells outrageously funny stories.

Sometime when Anja is talking with her twin and they both start to say the same thing at the same moment, she wonders what makes them think so much alike. Other times, such as when Anke shows up wearing a new tattoo or puts another pro-gun bumper sticker on her truck, Anja wonders why they think so differently. She knows that their identical genes make them look almost identical. But why don't those identical genes make their minds identical, too?



The fruit fly *Drosophila melanogaster* is tiny (about 3 mm long) and short-lived (about 2 weeks). However, its petite size and quick life cycle, plus its non-fussy eating habits, make it the ideal study organism for behavioral geneticists.

## Animal studies

The “teacher’s pet” of behavioral genetic research is the common fruit fly, *Drosophila melanogaster*, and some 2,000 related species. The fruit fly is a favorite of researchers for simple reasons. Fruit flies are easy to collect and keep: just bait a jar with overripe fruit and trap them. They reproduce rapidly and copiously; the time span from egg to adult is less than two weeks and one female produces hundreds of offspring. Fruit flies willingly cooperate in researchers’ efforts to selectively breed them and to run them through all sorts of experiments. What’s more, fruit flies do not bite and do not transmit disease to humans, and researchers do not need to obtain government approval to ensure that the research protects the flies’ rights and privacy.

Basic genetic research on fruit flies started more than 100 years ago, but the classic study on behavior dates to the 1950s. Researchers noticed that if you put fruit flies in a tilting maze, some would crawl upward and others would crawl downward. This tendency to move with or against gravity is called **geotaxis**.

The researchers selected fruit flies that preferred to move uphill and bred them together and did the same for fruit flies that preferred to move downhill. When after many generations they had created strains of fruit flies that consistently responded to gravity in the same way, the researchers were able to conclude that there was a genetic basis to geotaxis. This

selective breeding experiment contributed early evidence to the claim that heredity plays a role in behavioral traits.

The mice and rabbit studies described in Chapter 2 and many others like them were all modeled after this original fruit fly experiment. Bacteria, yeast, shrimp, moths, spiders, mosquitoes, ants, snails, cats, and dogs are just a few of the many other species that have served as subjects for behavioral genetic research.

When they study animals, genetic researchers frame questions in terms of *variations* in behavior among individuals within a species. They explore such questions as:

- How do bacteria vary in their use of the little whips, called flagellae, by which they propel themselves?
- How do worms vary in their response to stimuli such as touch, taste, smell, and temperature?
- How do variations in the trilling calls of male crickets affect their attractiveness to female crickets?
- How do bee species differ in the ratio of pollen to nectar they collect?
- How do fish vary in their use of specific courtship rituals such as swinging, sidling, nibbling, pecking, and thrusting?
- How does the variation in feather color, plumage, and body outline of male chickens affect their attractiveness to females?
- How do rats differ in play, how do pigs differ in responses to stress, and how do chimpanzees differ in personality?



As this partial list suggests, questions about behavior are endless. One way such questions are researched is through breeding experiments already described, in which researchers create distinct lines that consistently and reliably diverge in behavior on a particular trait despite minimal environmental variation.

Another method is to create **inbred strains**. These are whole populations of genetically near-identical animals that have been created by mating brothers to sisters for a number of generations. (In recent years researchers have learned how to make inbred strains through **cloning**.) Researchers look for variations in behavior between different inbred strains reared in identical environments, as evidence of genetic components to behavior. They also look for variations in

behavior *within* inbred strains. Since members of an in-bred strain are genetically alike, observed differences in behavior can be attributed to pre- or post-natal environmental causes.

Animals make excellent research studies not merely because they can be bred at will and kept in controlled environments. Another reason they are so suitable is that, as mentioned in Chapter 2, their genomes are related to ours. When researchers discover the function and location of genes associated with behavioral traits in animals, they have clues as to the function and location of genes associated with related behavioral traits in humans. Such research requires species-specific genome maps and knowledge of which regions correspond across species.

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**Cloned animals allow researchers to observe how organisms with identical genes develop differently. This provides clues as to the interactive effects of the environment on genes.**



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Scientists refer to identical twins as MZ twins (for monozygotic, meaning developing from a single fertilized egg), because they are not truly identical, not even genetically. Developmental and epigenetic factors cause each twin's genes to be slightly unique and to operate in unique fashion.

## Family Studies

A fundamental experimental method involving humans is the **family study**. This starts with one person, called the **proband**, and the focus is on one particular trait possessed by that person. The proband's family tree (**pedigree**) is drawn up to include **first-degree relatives** (parents, siblings, and children) and sometimes also **second-degree relatives** (aunts, uncles, grandchildren, grandparents, and nephews or nieces), plus even more distant family members. The members of the family tree are looked at to see who, if anyone, has the trait identified in the proband or related traits.



This type of study can reveal whether the trait runs in the family. It does not explain *why*. Both genes and environment are implicated because the members of a biological family are similar genetically and also tend to live in similar environments. However, it is sometimes possible to get a clue about cause from a family study. For example, if a proband has a trait in common with first-degree relatives and also with more distant relatives, the possibility is raised that the cause comes from the environment shared by the family rather than shared genes.

## Twin Studies

In **twin studies**, researchers actively recruit living twins. They observe the twins' behaviors, give them personality tests, interview them, and ask them to fill out surveys. Researchers also extract data on twins from existing databanks, such as records on hospital patients or members of the armed forces.

Twin studies rely on the fact that identical (**MZ** or **monozygotic**) twins have essentially the same set of genes while fraternal (**DZ** or **dizygotic**) twins have, on average, a half-identical set. A basic assumption in these studies is that since pairs of both types are raised alongside each other, both types are affected by their environments to an equal degree. In other words, the environment of an identical twin pair is not working to make

those two alike to any greater degree than the environment of a fraternal twin pair makes those two alike. The single factor making identical twins more alike compared to fraternal twins is their greater genetic similarity. This is called the **equal environments assumption**.

Given this assumption, twin pairs may be examined for a particular trait such as autism, scores on a personality test, or educational attainment. Data from many twin pairs are collected and the rates of similarity for identical and fraternal pairs are then compared.

If the trait under study is discrete — either present or absent, such as a disease — **concordance rates** are calculated. This is the proportion of the twin pairs that both have the trait under study. If the trait under study is continuous — appearing to different degrees in individuals, such as height or I.Q. — then a **correlation coefficient** is calculated. This number reflects the extent to which the measurement or score for one twin predicts the measurement or score for the second twin.

Here's how twin study findings are analyzed:

- Genetic influence is indicated when the concordance rate or correlation coefficient for identical twins exceeds that for fraternal twins;
- Shared environmental influences are indicated when the similarity for both types of twins are quite close (and significantly more than zero); and
- Non-shared environmental influences



are indicated when identical twins are dissimilar for a trait.

In the typical twin study, all three sources of influence are operating simultaneously, but can be teased apart and given “weights” by combining data from family strategies.

Here are two examples. A study on male homosexuality and bisexuality produced a concordance rate of .52 for identical twins and .22 for fraternal twins (it can help to read a correlation of .52 as “52 percent”).<sup>1</sup> It has been found that identical twins have a correlation of .96 for the ridge pattern in their fingerprints while fraternal twins have a correlation of .47.<sup>2</sup>

Note that in the first example, the concordance rate for identical twins was not

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**Fraternal or DZ (dizygotic) twins typically are born at the same time and are raised very similarly, just like identical twins, but they are only about half alike genetically. Scientists look at how a particular behavior trait varies between pairs of identical twins and pairs of fraternal twins to mathematically estimate how genes (and by inference, environments) affect that behavior.**

1.0 and the concordance rate for fraternal twins was not .5. This suggests that homosexuality and bisexuality are not purely determined by genetics. Note in the second example how much closer the correlation rates are to 1.0 percent and .5, respectively. This suggests that the physical features of a fingerprint are very highly determined by one's genetic make-up.

Heritability estimates also are derived from twin studies. As explained in Chapter 3, such estimates are based on ratios: the relationship between the phenotypic (observable) variation of the trait in twin pairs and the genetic variation for those twin pairs. Ratios for identical twins and fraternal twins are compared to calculate heritability.

In the sexuality study quoted above, the researchers estimated heritability for male homosexuality and bisexuality of between .31 and .74. Notice how broad that range is. It suggests that the variation

in sexual orientation in the male population is anywhere from under one-third to just about two-thirds a factor of heredity. This leaves ample room for influential environmental effects.

## Adoption Studies

Adoption studies look at biologically related people who have been reared apart. One method is to compare identical twins adopted into separate homes, that is, into measurably dissimilar environments. The disparate environments are assumed to shape them differently so that similarities in traits are attributed, at least in part, to genetic effects.

Another method compares adopted children to both their biological and adoptive parents. Evidence for partial genetic influence on a trait is found when adoptees are more similar for the trait to their biological parents than to their adoptive parents. Evidence for some environmental influence is found when the adoptee is more like his or her adoptive parents than the biological parents.

Yet another adoption method is to compare adopted children to other children in the family who are biological offspring of the parents. Similarity found here would suggest environmental effects for the trait under investigation, while dissimilarity would suggest genetic effects.

Adoption studies are not as numerous as family or twin studies because subjects are hard to find, especially given the

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Scientists learn about the genetic influence on behavior (and by inference, the environmental influence on behavior) by comparing the traits of biologically related siblings, non-biologically related siblings, parents and their children (related biologically and not), adoptive and biological parents and their children, and other combinations.



decline in within-nation adoption over the past several decades. Also, in countries such as the United States where adoption records are confidential, it can be difficult for researchers to get accurate information about the biological parents.

### Combined studies

We have described family, twin, and adoption studies as distinct types of research, but in practice they can overlap. As just noted, an adoption study might look at pairs of twins that had been adopted away into different families. Some studies have unusual permutations, for example, a family study might include stepchildren who are related to one but not both parents.

Furthermore, data from all three kinds of studies can be pooled together. This kind of undertaking, called **meta-analysis**, attempts to extract more meaning out of data that have been generated by multiple studies of the same trait. In a mathematical exercise called **model fitting**, several plausible explanations, in the form of mathematical formulas, are proposed that express the relative contributions of genetics and environment to the variance for a trait. The combined data are plugged into each model to see which one best explains the variance.

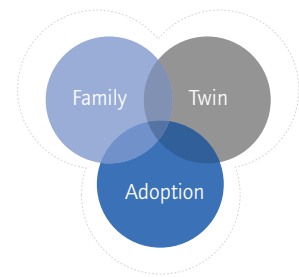
One of the problems confronted by model fitters is that different studies might use different diagnostic measures to identify those who have or do not have

the trait under study. For example, a subject who is gauged as “highly religious” in one study might not be so categorized in another. Therefore, researchers must assume degrees of error and hope that the signal outweighs the noise.

Today, researchers attempt to be consistent with each other in their data collection methods. They collaborate on diagnostic measures and study designs with the intention of eventually pooling their data for meta-analysis. Several such projects are underway involving teams across the country and around the world. These studies are investigating schizophrenia and other mental illnesses, alcoholism, autism, and many other behavioral disorders.

### Linkage analysis

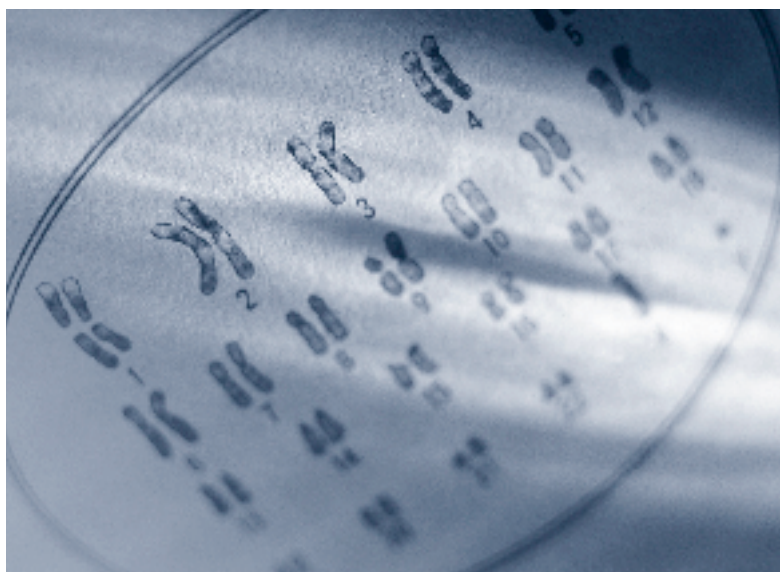
The traditional way that behavior has been studied by geneticists using twin, family, and adoption studies is referred to as **quantitative research**, because the objective is to identify how behavioral traits vary by degree (quantitatively) in individuals in a population. Molecular research, which probes at the DNA level, complements this classical approach. Such research makes use of the tremendous computing power that has come about in recent years. It also takes advantage of the completed drafts of human, animal, and insect DNA sequences achieved through the Human Genome Project and related ventures.



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**In a meta-analysis study, data from family, twin, and adoption studies on the same trait are pooled together and analyzed, in an attempt to extract more meaning.**





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Through increasingly sophisticated techniques, researchers have been able to find the locations of genes within chromosomes and to identify the effects those genes have when activated.

Before the advent of modern molecular genetics, researchers did not have any efficient means for pinpointing the genes that underlie a trait. Their main resource was an approach called **linkage analysis** that helped them close in on the neighborhood along a chromosome where a gene for a trait might be located.

Linkage analysis relies on the fact that chromosomes are paired. In germ cells, the two chromosomes in a pair commonly exchange genetic material before the full complement of chromosomes splits in half to create the sperm and egg cells of reproduction. This exchange is called **recombination** or **crossing over**. Recombination is a normal exchange process, unrelated to mutation, that enhances genetic diversity. It creates new combinations of alleles on each chromosome.

The frequency with which the alleles for two different genes get separated by

recombination depends on the distance between the genes. If the two alleles on one chromosome are far apart, one of them is likely to end up on the other chromosome from the pair after recombination. If the two alleles are close together, they are likely to remain on the same chromosome from the pair after recombination. Remember that the two chromosomes of each pair peel off into separate germ cells. The alleles that remain together on one chromosome after recombination will be inherited together. The alleles that end up on different chromosomes will not be inherited together.

In classical linkage analysis, researchers collect data on two variables from family groups. The first variable is the trait being researched. The second variable is called a **genetic marker**. This is a gene whose precise location on a chromosome is already known. For each family member, researchers record whether and to what extent the trait is present and which allele for the marker gene is present. They note how often the trait and any particular allele for the marker gene are inherited together. Where a pattern of frequency occurs, this suggests that the gene for the trait is near the marker gene (“linked”) because the combination of alleles for the two genes (**haplotypes**) is *not* being broken apart in recombination. Researchers make statistical calculations from their data to come up with a **lod score** (“lod” stands for “logarithmic

odds” or “likelihood of odds”). The higher the lod score, the higher the probability that the two genes are close by on the same chromosome.

Researchers do this type of analysis with several families. They also look for linkage between the gene for the trait under study and several different marker genes. The first tactic helps them confirm linkage and the latter tactic helps them better target the approximate location along the chromosome of the trait-related gene.

Linkage analysis has shortcomings. It does not reveal the precise locations of genes. Furthermore, it is suitable only for one type of gene – what researchers refer to as a **major gene**. This term describes genes for which an allele, acting by itself, is sufficient to trigger significant and easily observable phenotypic differences in a trait. In humans such genes are primarily associated with health disorders, and so linkage analysis has mainly been applied in the search for the responsible gene in rare single-gene disorders that heavily affect some families, such as Huntington’s disease. Classical linkage analysis has much less practical value for researchers studying behavior. This is because in almost all cases, behavior is affected by **multiple locus genes** — by many genes whose alleles, operating in synchrony, each contribute in some small way to observable differences in a trait.

By 1980, advances in technology had enabled researchers to develop a method for tracking the co-inheritance of a trait

with a discrete sequence of DNA in the genome that varies in the population, rather than with an entire gene. (Many such variable DNA sequences exist in the genome of humans and other organisms.) Subsequently, researchers learned how to track the co-inheritance of a trait with single bits of DNA in the genome that vary in a population (these are called **SNPs** or single nucleotide polymorphisms). This refined search capability of modern linkage analysis has been used to reveal the actual location of many genes along the chromosomes.

Also thanks to technological advances, researchers no longer have to bother with tracking the co-inheritance of a trait with a single marker or SNP at a time. Instead they do **whole genome scans**. DNA samples are simultaneously read at dozens or more markers or SNPs located along the chromosomes to see if any particular DNA sequence shows up more than randomly in individuals who have the trait. The noun *genotype* is turned into a verb to describe this activity. Genotyping makes it technically feasible to find the location of multiple genes that play minor roles in traits. This kind of research is called **QTL analysis**. As you may recall, QTL stands for quantitative trait loci. Through QTL analysis, researchers seek the location of the many genes whose alleles, in their many different forms, affect a variable trait.

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**Microarray analysis allows researchers to visually observe expressed genes. This technique is providing important clues about the mysterious relationship between genes and behavior.**



## Association studies

Another molecular research route is the **association study**. This focuses on a single gene that has already been isolated, the **candidate gene**. Through the association study, researchers seek to identify whether the variation in this gene's alleles might be statistically associated with variation in a particular trait.

DNA samples are taken from subjects who have the trait and a similar number of subjects (a **control group**) without the trait. Each subject's DNA is genotyped to see which allele is present at the genetic locus under study. A statistical test is then conducted to see if any allele shows up more frequently in subjects with the trait compared to subjects without the trait.

Association studies have two advantages over linkage analysis. First, they require a smaller number of subjects who do not have to be related. Second, they can help identify specific genes, not just chromosomal regions. This moves researchers that much closer to the next step, which is to figure out how specific genes correlated with a trait contribute to the biological processes underlying that trait.

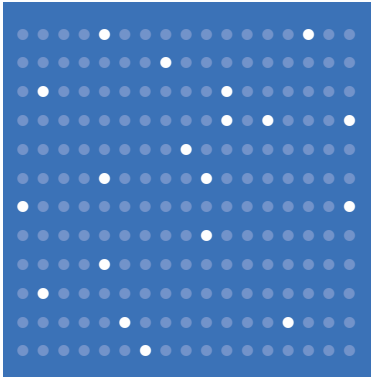
The complete mapping of the human genome has helped researchers find candidate genes on which to focus their research using the association method. Animal studies also have helped identify good targets for association studies using human subjects. The quantity of association studies churning out from research

labs in recent years has been described as a “veritable cascade.”<sup>3</sup> These studies cover a broad spectrum of diseases and traits — Parkinson's disease, multiple sclerosis, restless leg syndrome, smoking behavior, and migraines, to name just a few.

## Microarray analysis

Recall the quantitative experiments in behavioral genetics involving fruit flies and gravity, described earlier in this chapter. From these experiments researchers knew that genetics was involved in geotaxis, but they could not show how. In 2002 — fifty years after that initial research — scientists were finally able to identify several of the many genes involved in this trait. The molecular technology that allowed them to do this is **microarray analysis**. This technique is revolutionary because it allows scientists to examine thousands of genes simultaneously.

Here is a simplistic explanation of this complex procedure: an organism's genome is extracted and placed in segments on a chip. The chip is soaked in a solution containing RNA that has been expressed by a particular cell. The solution also contains a fluorescent dye. If a particular gene is expressed in the cell, the RNA from the solution will bind to it. This will cause that particular segment to light up. The more the gene is expressed, the stronger the fluorescence. In the recent fruit fly investigation,



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**In microarray analysis, genomic material from a cell is placed on a slide soaked in an RNA solution. Genes that are expressed in the cell bind to the RNA, causing a fluorescent reaction.**

microarray analysis helped scientists find genes that were expressed in the flies that like to crawl up and in those that like to crawl down.<sup>4</sup>

Researchers also use microarray techniques on humans. For example, they take tissue samples from subjects with and without a mental disorder or some other observable trait. They then compare results from the two types of subjects to learn which genes are involved and their expression patterns. With the increasing popularity of microarray experiments, huge amounts of data are being produced that eventually should lead to a better understanding of how specific genotypes relate to phenotypes.

## Knockout studies

One final molecular research method used in behavioral genetics will be described here. This technique has been applied to mice but not to humans, for reasons that will be obvious once you learn about it. It is the [knockout study](#). Researchers use modern laboratory techniques to deactivate a gene in [stem cells](#) (undifferentiated cells that can turn into specialized cells). These cells are inserted into an embryo that is then implanted into the womb of a female. After the offspring is born and has matured, its germ cells (sperm or eggs) are examined to see if any evolved from the altered stem cells. Those germ cells are used for breeding to create a line of knockout mice, all missing the target gene.

The knockout mice are studied to see whether their behavior differs from untreated mice. If a behavior is altered when the gene is knocked out, then the gene is implicated. Similar techniques are used to knock in genes. It also is possible through these techniques to add or deactivate even a small segment of DNA in order to determine the function of a gene's component parts. Researchers also can move a gene from one spot in the genome to another to see how location affects expression.

Mice behavior traits that have been studied using this kind of genetic manipulation include movement patterns, willingness to explore, weight retention, learning and memory, social interaction,





**Variations in nutrition, education, upbringing, and other aspects of environment help make each human personality unique. Even genetically identical twins have distinct personalities, resulting in large part from environmental effects.**

and stress response, among many others. Since mice and humans have similar genomes, researchers hope to obtain from the mice studies clues about corresponding genes in humans.

### Anja's Question

Research in behavioral genetics has provided an answer to the question posed by Anja. She is the woman who wonders why her appearance is so very similar to her identical twin's but her behavior is not so much alike.

The answer has two parts. First, the role of genes in physical development is far more direct than it is in behavior. Second, non-shared environmental influences (including chance occurrences) are so great that they cause even closely attached twins to develop personalities as different from each other as those of any ordinary pair of non-twin siblings.

Here's a more detailed explanation. The twins' similar height is a product of skeletal structure (among other things). Scores of genes encode for the amino acids that engender proteins that influence bone length. The work of these genes is affected by their interactions with other genes, their interactions with the environment, developmental noise, and the epigenetic factors that control gene expression.

All sorts of small environmental variables surrounding two genetically equivalent females who are raised similarly

would cause them to end up with slightly different heights. Anja is a little shorter than her sister perhaps because she received a slightly less copious supply of nutrients through her umbilical cord during fetal development, compared to her twin. Perhaps her sister crowded her in the uterus. After birth, she might have had an illness her twin did not have that ever so slightly retarded her growth. Perhaps she did not like milk as a child, and so her body had less calcium with which to build bones in the formative years.

The twins' nearsightedness is a product of their genetic endowment operating in an environment where people spend long hours staring at electronic screens and reading small type. Slight differences in these conditions might cause the twins' eyesights to differ slightly. If there are major environmental differences, such as if one twin contracts a virus that triggers a serious eye infection or if one twin is hit in the eye with a BB gun pellet, there could be a larger difference in their visual abilities.

Anja has a birthmark that her sister does not, and this is explained by developmental noise operating on genetics. Random chance resulted in extra pigment cells clustering near her ear, resulting in the light-brown mark.

A multitude of genes encode for the amino acids that, in chains linked together as proteins, build and maintain the various parts of the brain and their

connections and that move nerve impulses throughout the body. These genes, too, are influenced by interactions with other genes, interactions with environmental factors, developmental noise, and epigenetic effects. As a result, the twins have brains that differ in structure and in the neuronal connections through which impulses are processed.

But behavior is a *product* of the brain. Anke's predilection for decorating her body with tattoos, to take one example of a behavioral trait, is mediated in the brain but it is not a *part* of the brain. This magnifies the differences in behavior, because no matter how close any twins are, they uniquely experience the world — their genotype is differently affected by non-shared environmental factors. Each twin's brain is wired somewhat differently, impulses move through their nervous systems somewhat differently, and



different memories are saved and stored. Differences build upon differences to create two unique personalities.

It should be noted that behavior is not exclusively a product of the brain. Other organs play their part, too. For example, your kidneys affect how you handle alcohol and your lungs affect your ability to run. So in parallel to this description of the brain, the many other organs in the respective bodies of Anja and Anke follow unique developmental pathways and thus have different mediating effects on the behavior of each twin.

### Concerns about non-molecular research

It would be nice to be able to explain to Anja which specific genetic and environmental variables cause her to either resemble or be distinct from her twin sister. And it would be nice to explain how genes and environments work together to have those effects. But any sort of detailed explanation must wait until the research is much further along. We cannot expect answers, one textbook on behavioral genetics says, “when such research is at the stage of placing one’s toes into the pond to test the temperature of the water.”<sup>5</sup>

In addition to the large questions of which and how, the field also struggles with basic questions over methodology. Here are some of the questions that have confronted researchers:

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**Is a tattoo a beautiful adornment or a disfiguring scar? Identical twins may differ in their opinions on the matter, because each has a unique personality shaped by a unique experience of the world.**



The twin relationship is sufficiently unusual that some critics question whether conclusions from behavior studies of twins can be applied to the general population. Twin researchers respond that their work often yields results similar to those obtained through other kinds of studies.

■ *How do researchers know that they have correctly categorized identical and fraternal twins?* In the past, researchers categorized twins based on visual checks (do they look alike?), physical tests (do they have the same blood type?), and self-reports (do they think they are identical or fraternal?). Today, researchers can use DNA testing to confirm whether twins developed from one or two eggs. Many of the field's original studies do not stand on this level of certainty. Yet they are probably fairly accurate: by conducting DNA checks on twins categorized as identical or fraternal by non-DNA methods, researchers have learned that the latter are correct about 95 percent of the time.

■ *Is the equal environments assumption valid?* As we explained earlier, twin studies assume that identical and fraternal twin pairs all experience the same degree of shared environment. But this may not be wholly true. The close resemblance of identical twins may cause them to think of themselves as alike and other people to act towards them as though they were alike. In addition, all identical twin pairs are same-sex (there are very rare exceptions), but a third of all fraternal twin pairs are opposite-sex. These factors could make the environments of identical twins more similar compared to the environments of fraternal twins. Many scientists assert that the equal environments assumption is valid, based on studies conducted specifically to test it, but others remain unconvinced.

■ *Is it valid to generalize from twin studies?* Some people say that the twin experience is not typical. Twins have a greater incidence of premature birth and therefore of developmental problems. Also, people tend to treat twins as special and many twins perceive themselves as having a special closeness to each other. These kinds of subtle differences between twins and non-twins suggest that conclusions from studies on the former may not apply to the latter. A point in defense of twin studies is that the data they produce, on many traits, converge with the data produced through other kinds of studies.

■ *Is it valid to generalize from adoption studies?* The people involved in adoptions — the children, the biological parents, and the adoptive families — may not be typical of the broader population because they have experienced an unusual family drama. This could limit the relevance of data from adoption studies — but again, the convergence of findings from adoption studies and other forms of research argues against this being an important concern.

■ *Are shared environmental effects adequately controlled for in adoption studies?* An assumption underlying many adoption studies is that adoptees are randomly assigned into dissimilar environments and not selectively placed. Based on this assumption, any correlations found between adopted-away identical

twins would be due entirely to genetics.

But the fact is that many children are adopted by relatives or into families that are similar in many respects to their biological families. For example, adoption agencies have been known to place a child born to Irish Catholics into an Irish Catholic family in the same city. Some adopted-away twins do not part company until they are a few months or years old; they may experience important stages of their development in a shared environment. All twins, even those adopted away at birth, are together in the womb that at least in part operates as a shared environment. These are three examples of how adopted-away twins may experience environments that are more similar than assumed.

■ *Are non-shared environmental effects adequately controlled for in twin studies?* Although twins develop together in one womb, they experience it differently as they compete for resources. All fraternal twins develop in separate chorionic sacs, and so do some identical twins. These are two examples of how even the prenatal environment can operate as an unaccounted-for non-shared environmental influence.

Obviously it is very difficult to observe and identify all the non-shared environmental factors at work shaping a trait, and yet they may have a much stronger effect than factors of shared environment. As a pair of scientists wrote, “Because these

non-shared differences are nonsystematic and largely accidental or random, they are and will continue to be very difficult to study.” The scientists called this a “gloomy prospect.”<sup>6</sup>

■ *What about non-additive genetic effects?* How do studies on quantitative traits take these into account? Genes do not work simply in an additive way, with each gene contributing to an effect in a separate and measurable way. Genes also have non-additive effects that, as we explained in Chapter 3, fall into two main categories: genotype-environment correlation and genotype-environment interaction. In the past, quantitative studies did not take these into consideration; modern research designs have been better at incorporating measurements of the former than the latter.

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**An underlying assumption of adoption studies is that children are randomly placed with families. In practice, children may be placed in families that are similar in important ways to their biological family, making it more difficult to determine the degree to which genetic or environmental effects work to influence a trait. Twins researchers say they now recognize non-random placement and take it into account when making their estimations.**





## Concerns about molecular research

Gene discoveries for all sorts of traits, from grooming to obsessive hand-washing, have been heralded by molecular researchers. Yet most of these claims have not stood up over time. From literally hundreds of molecular studies, only a handful of genes have been solidly identified with a quantitative trait. And none of these confirmed genes has more than a very small effect of the relevant trait's total variation.

Scientists think that the reason there are so few confirmed QTLs is that molecular studies are very difficult to replicate. This is not necessarily because the original studies are faulty — though some claims for allelic associations have been based on low statistical correlations. Replication problems stem mainly from the fact that for statistical reasons a larger pool of subjects is needed to make confir-

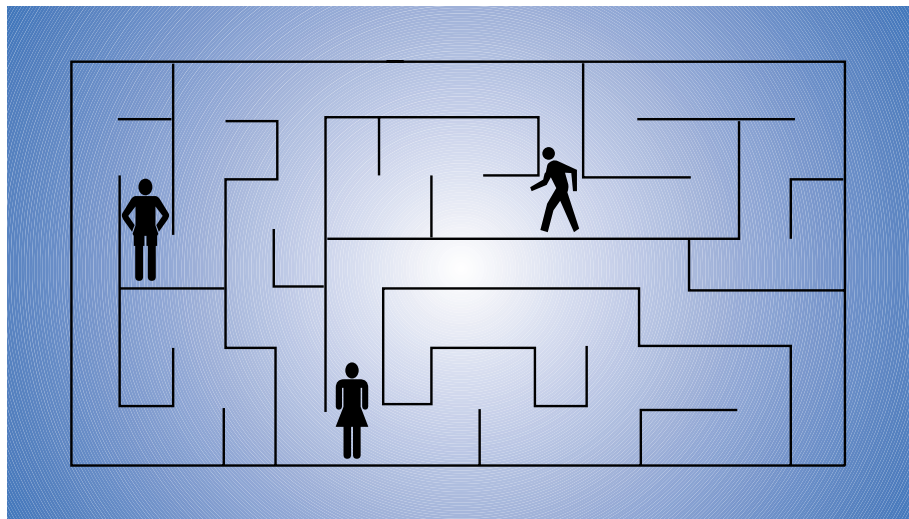
mations, and these studies are harder to do. Another important reason is that, as we stated before, most genes are of very small effect, and so are simply difficult to identify through molecular means.

The lack of success in confirming QTL claims is one concern that has been raised about molecular research into behavior, but there are other concerns, too. Here are some of the questions that have been raised:

■ *How much insight about human behavior can you get from behavior observed in animals?* Knockout studies provide tempting opportunities to speculate about the role of particular genes in human behavior, but it is a temptation that must be avoided. Suppose, for example, that a knockout study creates mice that run a maze faster. Does this mean similarly affected humans would also run a maze faster? Maze running is not a typical human activity, so what is

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**What genes affect the ability of humans to run a maze?** Researchers cannot look for the answer to that question by conducting knockout studies on human subjects, because that would be unethical. Yet they cannot speculate about human maze-running behavior based on results from studies of knock-out mice, either. This is because the genes shared by humans and other animals express themselves differently and in very different contexts.



the analogous behavior?

The reason it is risky to speculate about such questions is because there are significant differences in how and when genes express themselves in different species. Species also differ in terms of gene-gene and gene-environment interactions. Analogous genetic mutations in animals and humans could have very different effects on protein process, and thus indirectly on behavior.

■ *Do the molecular studies find false positives?* When researchers use genome scans to look for any correlations between a trait and tens of thousands of genes, the possibility always exists of random hits. There also is the possibility of finding a correlation that exists in one population but not in others. The reason for this is that certain alleles appear more frequently in some populations than in others; such numerical counts are called gene frequencies. If researchers designing an association study do not carefully control for population, it may produce false data. Two molecular geneticists in a 1994 article nicely explain this risk; they call it the “chopsticks problem”:

*Suppose that a would-be geneticist set out to study the ‘trait’ of ability to eat with chopsticks in the San Francisco population by performing an association study with the HLA complex [a set of immune response genes that frequently vary between ethnic groups]. The allele*



*HLA-A1 would turn out to be positively associated with ability to use chopsticks – not because immunological determinants play any role in manual dexterity, but simply because the allele HLA-A1 is more common among Asians than Caucasians.*<sup>7</sup>

## Overcoming the research concerns

Behavioral geneticists have worked tremendously hard to improve their research methods and so improve the quality of the data generated. On the quantitative front, researchers have tried many different techniques to capture the environmental influences that act in concert with genes to influence behaviors. Some researchers have tried counting the number of books in each subject’s household, assessing parents’ vocabulary,

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Gene studies conducted on non-random populations may lead to false conclusions. This is called the “chopsticks problem,” after this well-known example: If you conduct a gene study of residents in San Francisco, you might find a gene that correlates with using chopsticks. However, that gene might not have anything remotely to do with utensil habits. It might be related to the fact that most of those studied are of Asian heritage.



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**Scientists are grappling with the problem of how to identify and measure the environmental variables that influence behavior. Does the presence or absence of certain objects in the home have an effect? Or are environmental effects not so easily quantified?**

noting the availability of such household objects as power tools and dictionaries, or measuring other variables deemed relevant.

Another approach has been to use questionnaires and/or interviews to determine whether identical twins are treated more similarly compared to fraternal twins. Researchers also have studied fraternal twins who look a lot alike to see if they are more concordant than fraternal twins who do not resemble each other. Piece by piece these efforts are resulting in better and more useful data, but they also serve to underline the difficulty of accounting for all the truly pertinent environmental factors.

On the molecular front, researchers are increasing sample sizes and improving statistical methods. The astounding advances in microarray technology have allowed researchers to target ever-smaller regions of DNA while scanning ever-larger segments of the genome simultaneously; over time this should improve the

yield for “gene hunters” while reducing the number of false positives. Meanwhile, scientists as a whole have become more cautious about issuing speculative claims about genes based on unreplicated work.

Another exciting development has come about with the introduction into the behavioral genetics lab of sophisticated brain imaging tools. These tools allow researchers to observe the brain activity that occurs in organisms when specific genes are expressed in controlled environments.

Yet the increasing sophistication of molecular research serves to underscore the truly monumental tasks of behavioral genetics. As one scientist has summed up the state of affairs: “Researchers have been creative in developing new theories, measuring tools, statistical programs, etc. But the constant retooling of approaches points to the extraordinary complexity of trying to dissect out the environmental, genetic, stochastic and personal parameters in the development of behaviors in human beings.”<sup>8</sup>

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#### Notes

- 1 See Bailey, J. M. and Pillard, R. C. (1991).
- 2 Falconer, D. S. and T. F. C. Mackay (1996, p. 173).
- 3 Bird, T. D. *et al.* (2001, p. 1153).
- 4 See Toma, D. P. *et al.* (2002).
- 5 See Carey, G. (2002, pg. 6).
- 6 Plomin, R. and D. David (1987, pg. 8).
- 7 See Lander, E. S. and N. J. Schork (1994, p. 2041). Also cited in Schaffner, K. (forthcoming).
- 8 Beckwith, J. (forthcoming).

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