Eight

Back to When You Were Just a Fertilized Egg

I'm reminded of a cartoon where one lab-coated scientist is telling the other, "You know how you're on the phone, and the other person wants to get off but won't say it, so they say, 'Well, you probably need to get going,' like *you're* the one who wants to get off, when it's really *them*? I think I found the gene for that."

This chapter is about progress in finding "the gene for that."

Our prototypical behavior has occurred. How was it influenced by events when the egg and sperm that formed that person joined, creating their genome—the chromosomes, the sequences of DNA—destined to be duplicated in every cell in that future person's body? What role did those genes play in causing that behavior?

Genes are relevant to, say, aggression, which is why we're less alarmed if a toddler pulls at the ears of a basset hound rather than a pit bull. Genes are relevant to everything in this book. Many neurotransmitters and hormones are coded for by genes. As are molecules that construct or degrade those messengers, as are their receptors. Ditto for growth factors guiding brain plasticity. Genes typically come in different versions; we each consist of an individuated orchestration of the different versions of our approximately twenty thousand genes.

This topic carries two burdens. The first reflects many people being troubled by linking genes with behavior—in one incident from my academic youth, a

federally funded conference was canceled for suggesting that genes were pertinent to violence. This suspicion of gene/behavior links exists because of the pseudoscientific genetics used to justify various "isms," prejudice, and discrimination. Such pseudoscience has fostered racism and sexism, birthed eugenics and forced sterilizations, allowed scientifically meaningless versions of words like "innate" to justify the neglect of have-nots. And monstrous distortions of genetics have fueled those who lynch, ethnically cleanse, or march children into gas chambers.*[1]

But studying the genetics of behavior also carries the opposite burden of people who are overly enthusiastic about the subject. After all, this is the genomics era, with personalized genomic medicine, people getting their genomes sequenced, and popular writing about genomics giddy with terms like "the holy grail" and "the code of codes." In a reductionist view, understanding something complex requires breaking it down into its components; understand those parts, add them together, and you'll understand the big picture. And in this reductionist world, to understand cells, organs, bodies, and behavior, the best constituent part to study is genes.

Overenthusiasm for genes can reflect a sense that people possess an immutable, distinctive essence (although essentialism predates genomics). Consider a study concerning "moral spillover" based on kinship.[2] Suppose a person harmed people two generations ago; are this person's grandchildren obliged to help his victims' grandchildren? Subjects viewed a biological grandchild as more obligated than one adopted into the family at birth; the biological relationship carried a taint. Moreover, subjects were more willing to jail two long-lost identical twins for a crime committed by one of them than to jail two unrelated but perfect look-alikes—the former, raised in different environments, share a moral taint because of their identical genes. People see essentialism embedded in bloodlines—i.e., genes.*

This chapter threads between these two extremes, concluding that while genes are important to this book's concerns, they're far less so than often thought. The chapter first introduces gene function and regulation, showing the limits of genes' power. Next it examines genetic influences on behavior in general. Finally we'll examine genetic influences on our best and worst behaviors.

PART I: GENES FROM THE BOTTOM UP

We start by considering the limited power of genes. If you are shaky about topics such as the central dogma (DNA codes for RNA, which codes for protein sequence), protein structure determining function, the three-nucleotide codon code, or the basics of point, insertion, and deletion mutations, first read the primer in appendix 3.

Do Genes Know What They Are Doing? The Triumph of the Environment

So genes specify protein structure, shape, and function. And since proteins do virtually everything, this makes DNA the holy grail of life. But no—genes don't "decide" when a new protein is made.

Dogma was that there'd be a stretch of DNA in a chromosome, constituting a single gene, followed by a stop codon, followed immediately by the next gene, and then the next. . . . But genes don't actually come one after another—not all DNA constitutes genes. Instead there are stretches of DNA between genes that are noncoding, that are not "transcribed."* And now a flabbergasting number—95 percent of DNA is noncoding. *Ninety-five percent.*

What is that 95 percent? Some is junk—remnants of pseudogenes inactivated by evolution.*[3] But buried in that are the keys to the kingdom, the instruction manual for *when* to transcribe particular genes, the on/off switches for gene transcription. A gene doesn't "decide" when to be photocopied into RNA, to generate its protein. Instead, before the start of the stretch of DNA coding for that gene is a short stretch called a promoter*—the "on" switch. What turns the promoter switch on? Something called a transcription factor (TF) binds to the promoter. This causes the recruitment of enzymes that transcribe the gene into RNA. Meanwhile, other transcription factors deactivate genes.

This is huge. Saying that a gene "decides" when it is transcribed* is like saying that a recipe decides when a cake is baked.

Thus transcription factors regulate genes. What regulates transcription factors? The answer devastates the concept of genetic determinism: the

environment.

To start unexcitingly, “environment” can mean intracellular environment. Suppose a hardworking neuron is low on energy. This state activates a particular transcription factor, which binds to a specific promoter, which activates the next gene in line (the “downstream” gene). This gene codes for a glucose transporter; more glucose transporter proteins are made and inserted into the cell membrane, improving the neuron’s ability to access circulating glucose.

Next consider “environment,” including the neuron next door, which releases serotonin onto the neuron in question. Suppose less serotonin has been released lately. Sentinel transcription factors in dendritic spines sense this, travel to the DNA, and bind to the promoter upstream of the serotonin receptor gene. More receptor is made and placed in the dendritic spines, and they become more sensitive to the faint serotonin signal.

Sometimes “environment” can be far-flung within an organism. A male secretes testosterone, which travels through the bloodstream and binds to androgen receptors in muscle cells. This activates a transcription-factor cascade that results in more intracellular scaffolding proteins, enlarging the cell (i.e., muscle mass increases).

Finally, and most important, there is “environment,” meaning the outside world. A female smells her newborn, meaning that odorant molecules that floated off the baby bind to receptors in her nose. The receptors activate and (many steps later in the hypothalamus) a transcription factor activates, leading to the production of more oxytocin. Once secreted, the oxytocin causes milk letdown. Genes are not the deterministic holy grail if they can be regulated by the smell of a baby’s tushy. Genes are regulated by all the incarnations of environment.

In other words, *genes don’t make sense outside the context of environment*. Promoters and transcription factor introduce if/then clauses: “If you smell your baby, then activate the oxytocin gene.”

Now the plot thickens.

There are multiple types of transcription factors in a cell, each binding to a particular DNA sequence constituting a particular promoter.

Consider a genome containing one gene. In that imaginary organism there is only a single profile of transcription (i.e., the gene is transcribed), requiring only one transcription factor.

Now consider a genome consisting of genes A and B, meaning three different transcription profiles—A is transcribed, B is transcribed, A and B are transcribed

—requiring three different TFs (assuming you activate only one at a time).

Three genes, seven transcription profiles: A, B, C, A + B, A + C, B + C, A + B + C. Seven different TFs.

Four genes, fifteen profiles. Five genes, thirty-one profiles.*

As the number of genes in a genome increases, the number of possible expression profiles increases exponentially. As does the number of TFs needed to produce those profiles.

Now another wrinkle that, in the lingo of an ancient generation, will blow your mind.

TFs are usually proteins, coded for by genes. Back to genes A and B. To fully exploit them, you need the TF that activates gene A, and the TF that activates gene B, and the TF that activates genes A and B. Thus there must exist three more genes, each coding for one of those TFs. Requiring TFs that activate *those* genes. And TFs for the genes coding for those TFs . . .

Whoa. Genomes aren't infinite; instead TFs regulate one another's transcription, solving that pesky infinity problem. Importantly, across the species whose genomes have been sequenced, the longer the genome (i.e., roughly the more genes there are), the greater the percentage of genes coding for TFs. In other words, *the more genomically complex the organism, the larger the percentage of the genome devoted to gene regulation by the environment*.

Back to mutations. Can there be mutations in DNA stretches constituting promoters? Yes, and more often than in genes themselves. In the 1970s Allan Wilson and Mary-Claire King at Berkeley correctly theorized that the evolution of genes is less important than the evolution of regulatory sequences upstream of genes (and thus how the environment regulates genes). Reflecting that, a disproportionate share of genetic differences between chimps and humans are in genes for TFs.

Time for more complexity. Suppose you have genes 1–10, and transcription factors A, B, and C. TF-A induces the transcription of genes 1, 3, 5, 7, and 9. TF-B induces genes 1, 2, 5, and 6. TF-C induces 1, 5, and 10. Thus, upstream of gene 1 are separate promoters responding to TFs A, B, and C—thus genes can be regulated by multiple TFs. Conversely, each TF usually activates more than one gene, meaning that multiple genes are typically activated in *networks* (for example, cell injury causes a TF called NF-κB to activate a network of inflammation genes). Suppose the promoter upstream of gene 3 that responds to promoter TF-A has a mutation making it responsive to TF-B. Result? Gene 3 is now activated as part of a different network. Same networkwide outcome if there

is a mutation in a gene for a TF, producing a protein that binds to a different promoter type.[4]

Consider this: the human genome codes for about 1,500 different TFs, contains 4,000,000 TF-binding sites, and the average cell uses about 200,000 such sites to generate its distinctive gene-expression profile.[5] This is boggling.

Epigenetics

The last chapter introduced the phenomenon of environmental influences freezing genetic on/off in one position. Such "epigenetic" changes* were relevant to events, particularly in childhood, causing persistent effects on the brain and behavior. For example, recall those pair-bonding prairie voles; when females and males first mate, there are epigenetic changes in regulation of oxytocin and vasopressin receptor genes in the nucleus accumbens, that target of mesolimbic dopamine projection.[6]

Let's translate the last chapter's imagery of "freezing on/off switches" into molecular biology.[7] What mechanisms underlie epigenetic changes in gene regulation? An environmental input results in a chemical being attached tightly to a promoter, or to some nearby structural proteins surrounding DNA. The result of either is that TFs can no longer access or properly bind to the promoter, thus silencing the gene.

As emphasized in the last chapter, epigenetic changes can be multigenerational.[8] Dogma was that all the epigenetic marks (i.e., changes in the DNA or surrounding proteins) were erased in eggs and sperm. But it turns out that epigenetic marks can be passed on by both (e.g., make male mice diabetic, and they pass the trait to their offspring via epigenetic changes in sperm).

Recall one of the great punching bags of science history, the eighteenth-century French biologist Jean-Baptiste Lamarck.[9] All anybody knows about the guy now is that he was wrong about heredity. Suppose a giraffe habitually stretches her neck to reach leaves high in a tree; this lengthens her neck. According to Lamarck, when she has babies, they will have longer necks because of "acquired inheritance."* Lunatic! Buffoon! Epigenetically mediated mechanisms of inheritance—now often called "neo-Lamarckian inheritance"—prove Lamarck right in this narrow domain. Centuries late, the guy's getting some acclaim.

Thus, not only does environment regulate genes, but it can do so with effects that last days to lifetimes.

The Modular Construction of Genes: Exons and Introns

Time to do in another dogma about DNA. It turns out that most genes are not coded for by a continuous stretch of DNA. Instead there might be a stretch of noncoding DNA in the middle. In that case, the two separate stretches of coding DNA are called “exons,” separated by an “intron.” Many genes are broken into numerous exons (with, logically, one less intron than the number of exons).

How do you produce a protein from an “exonic” gene? The RNA photocopy of the gene initially contains the exons and introns; an enzyme removes the intronic parts and splices together the exons. Clunky, but with big implications.

Back to each particular gene coding for a particular protein.[10] Introns and exons destroy this simplicity. Imagine a gene consisting of exons 1, 2, and 3, separated by introns A and B. In one part of the body a splicing enzyme exists that splices out the introns and also trashes exon 3, producing a protein coded for by exons 1 and 2. Meanwhile, elsewhere in the body, a different splicing enzyme jettisons exon 2 along with the introns, producing a protein derived from exons 1 and 3. In another cell type a protein is made solely from exon 1. . . . Thus “alternative splicing” can generate multiple unique proteins from a single stretch of DNA; so much for “one gene specifies one protein”—this gene specifies seven (A, B, C, A-B, A-C, B-C, and A-B-C). Remarkably, 90 percent of human genes with exons are alternatively spliced. Moreover, when a gene is regulated by multiple TFs, each can direct the transcription of a different combination of exons. Oh, and splicing enzymes are proteins, meaning that each is coded for by a gene. Loops and loops.

Transposable Genetic Elements, the Stability of the Genome, and Neurogenesis

Time to unmoor another cherished idea, namely that genes inherited from your parents (i.e., what you started with as a fertilized egg) are immutable. This calls up a great chapter of science history. In the 1940s an accomplished plant geneticist named Barbara McClintock observed something impossible. She was studying the inheritance of kernel color in maize (a frequent tool of geneticists)

and found patterns of mutations unexplained by any known mechanism. The only possibility, she concluded, was that stretches of DNA had been copied, with the copy then randomly inserted into another stretch of DNA.

Yeah, right.

Clearly McClintock, with her (derisively named) "jumping genes," had gone mad, and so she was ignored (not exactly true, but this detracts from the drama). She soldiered on in epic isolation. And finally, with the molecular revolution of the 1970s, she was vindicated about her (now termed) transposable genetic elements, or transposons. She was lionized, canonized, Nobel Prized (and was wonderfully inspirational, as disinterested in acclaim as in her ostracism, working until her nineties).

Transpositional events rarely produce great outcomes. Consider a hypothetical stretch of DNA coding for "The fertilized egg is implanted in the uterus."

There has been a transpositional event, where the underlined stretch of message was copied and randomly plunked down elsewhere: "The fertilized eggterus is implanted in the uterus."

Gibberish.

But sometimes "The fertilized egg is implanted in the uterus" becomes "The fertilized eggplant is implanted in the uterus."

Now, that's not an everyday occurrence.

Plants utilize transposons. Suppose there is a drought; plants can't move to wetter pastures like animals can. Plant "stress" such as drought induces transpositions in particular cells, where the plant metaphorically shuffles its DNA deck, hoping to generate some novel savior of a protein.

Mammals have fewer transposons than plants. The immune system is one transposon hot spot, in the enormous stretches of DNA coding for antibodies. A novel virus invades; shuffling the DNA increases the odds of coming up with an antibody that will target the invader.*

The main point here is that transposons occur in the brain.[11] In humans transpositional events occur in stem cells in the brain when they are becoming neurons, making the brain a mosaic of neurons with different DNA sequences. In other words, when you make neurons, that boring DNA sequence you inherited isn't good enough. Remarkably, transpositional events occur in neurons that

form memories in *fruit flies*. Even flies evolved such that their neurons are freed from the strict genetic marching orders they inherit.

Chance

Finally, chance lessens genes as the Code of Codes. Chance, driven by Brownian motion—the random movement of particles in a fluid—has big effects on tiny things like molecules floating in cells, including molecules regulating gene transcription.[12] This influences how quickly an activated TF reaches the DNA, splicing enzymes bump into target stretches of RNA, and an enzyme synthesizing something grabs the two precursor molecules needed for the synthesis. I'll stop here; otherwise, I'll go on for hours.

Some Key Points, Completing This Part of the Chapter

a. Genes are not autonomous agents commanding biological events.
b. Instead, genes are regulated by the environment, with "environment" consisting of everything from events inside the cell to the universe.
c. Much of your DNA turns environmental influences into gene transcription, rather than coding for genes themselves; moreover, evolution is heavily about changing regulation of gene transcription, rather than genes themselves.
d. Epigenetics can allow environmental effects to be lifelong, or even multigenerational.
e. And thanks to transposons, neurons contain a mosaic of different genomes.

In other words, genes don't *determine* much. This theme continues as we focus on the effects of genes on behavior.

PART 2: GENES FROM THE TOP DOWN—BEHAVIOR GENETICS

Long before anything was known about promoters, exons, or transcription factors, it became clear that you study genetics top down, by observing traits shared by relatives. Early in the last century, this emerged as the science of "behavior genetics." As we'll see, the field has often been mired in controversy, typically because of disagreements over the magnitude of genetic effects on things like IQ or sexual orientation.

First Attempts

The field began with the primitive idea that, if everyone in a family does it, it must be genetic. This was confounded by environment running in families as well.

The next approach depended on closer relatives having more genes in common than distant ones. Thus, if a trait runs in a family and is more common among closer relatives, it's genetic. But obviously, closer relatives share more environment as well—think of a child and parent versus a child and grandparent.

Research grew subtler. Consider someone's biological aunt (i.e., the sister of a parent), and the uncle who married the aunt. The uncle shares some degree of environment with the individual, while the aunt shares the same, plus genes. Therefore, the extent to which the aunt is more similar to the individual than the uncle reflects the genetic influence. But as we'll see, this approach has problems.

More sophistication was needed.

Twins, Adoptees, and Adopted Twins

A major advance came with "twin studies." Initially, examining twins helped rule out the possibility of genetic determination of a behavior. Consider pairs of identical twins, sharing 100 percent of their genes. Suppose one of each pair has schizophrenia; does the twin as well? If there are any cases where the other twin

doesn't (i.e., where the "concordance rate" is less than 100 percent), you've shown that the genome and epigenetic profile inherited at birth do not solely determine the incidence of schizophrenia (in fact the concordance rate is about 50 percent).

But then a more elegant twin approach emerged, involving the key distinction between identical (monozygotic, or MZ) twins, who share 100 percent of their genes, and fraternal, nonidentical (dizygotic, or DZ) twins, who, like all other sibling pairs, share 50 percent of their genes. Compare pairs of MZ twins with same-sex DZ twins. Each pair is the same age, was raised in the same environment, and shared a fetal environment; the only difference is the percentage of genes shared. Examine a trait occurring in one member of the twin pair; is it there in the other? The logic ran that, if a trait is shared more among MZ than among DZ twins, that increased degree of sharing reflects the genetic contribution to the trait.

Another major advance came in the 1960s. Identify individuals adopted soon after birth. All they share with their biological parents is genes; all they share with their adoptive parents is environment. Thus, if adopted individuals share a trait more with their biological than with their adoptive parents, you've uncovered a genetic influence. This replicates a classic tool in animal studies, namely "cross-fostering"—switching newborn rat pups between two mothers. The approach was pioneered in revealing a strong genetic component to schizophrenia.[13]

Then came the most wonderful, amazing, like, totally awesome thing ever in behavior genetics, started by Thomas Bouchard of the University of Minnesota. In 1979 Bouchard found a pair of identical twins who were—get this—separated at birth and adopted into different homes, with no knowledge of each other's existence until being reunited as adults.[14] Identical twins separated at birth are so spectacular and rare that behavior geneticists swoon over them, want to collect them all. Bouchard eventually studied more than a hundred such pairs.

The attraction was obvious—same genes, different environments (and the more different the better); thus, similarities in behavior probably reflect genetic influences. Here's an imaginary twin pair that would be God's gift to behavior geneticists—identical twin boys separated at birth. One, Shmuel, is raised as an Orthodox Jew in the Amazon; the other, Wolfie, is raised as a Nazi in the Sahara. Reunite them as adults and see if they do similar quirky things like, say, flushing the toilet before using it. Flabbergastingly, one twin pair came close to that. They were born in 1933 in Trinidad to a German Catholic mother and a Jewish father;

when the boys were six months of age, the parents separated; the mother returned to Germany with one son, and the other remained in Trinidad with the father. The latter was raised there and in Israel as Jack Yufe, an observant Jew whose first language was Yiddish. The other, Oskar Stohr, was raised in Germany as a Hitler Youth zealot. Reunited and studied by Bouchard, they warily got to know each other, discovering numerous shared behavioral and personality traits including . . . flushing the toilet before use. (As we'll see, studies were more systematic than just documenting bathroom quirks. The flushing detail, however, always comes up in accounts of the pair.)

Behavior geneticists, wielding adoption and twin approaches, generated scads of studies, filling specialized journals like *Genes, Brain and Behavior* and *Twin Research and Human Genetics*. Collectively, the research consistently showed that genetics plays a major role in a gamut of domains of behavior, including IQ and its subcomponents (i.e., verbal ability, and spatial ability),*[15] schizophrenia, depression, bipolar disorder, autism, attention-deficit disorder, compulsive gambling, and alcoholism.

Nearly as strong genetic influences were shown for personality measures related to extroversion, agreeableness, conscientiousness, neuroticism, and openness to experience (known as the "Big Five" personality traits).[16] Likewise with genetic influences on degree of religiosity, attitude toward authority, attitude toward homosexuality,* and propensities toward cooperation and risk taking in games.

Other twin studies showed genetic influences on the likelihood of risky sexual behavior and on people's degree of attraction to secondary sexual characteristics (e.g., musculature in men, breast size in women).[17]

Meanwhile, some social scientists report genetic influences on the extent of political involvement and sophistication (independent of political orientation); there are behavior genetics papers in the *American Journal of Political Science*.[18]

Genes, genes, everywhere. Large genetic contributions have even been uncovered for everything from the frequency with which teenagers text to the occurrence of dental phobias.[19]

So does this mean there is a gene "for" finding chest hair on guys to be hot, for likelihood of voting, for feelings about dentists? Vanishingly unlikely. Instead, gene and behavior are often connected by tortuous routes.[20] Consider the genetic influence on voter participation; the mediating factor between the two turns out to be sense of control and efficacy. People who vote regularly feel

that their actions matter, and this central locus of control reflects some genetically influenced personality traits (e.g., high optimism, low neuroticism). Or how about the link between genes and self-confidence? Some studies show that the intervening variable is genetic effects on height; taller people are considered more attractive and treated better, boosting their self-confidence, dammit.*

In other words, genetic influences on behavior often work through very indirect routes, something rarely emphasized when news broadcasts toss out behavior genetics sound bites—"Scientists report genetic influence on strategy when playing Candyland."

The Debates About Twin and Adoption Studies

Many scientists have heavily criticized the assumptions in twin and adoption studies, showing that they generally lead to overestimates of the importance of genes.* Most behavior geneticists recognize these problems but argue that the overestimates are tiny.[21] A summary of this technical but important debate:

Criticism #1: Twin studies are premised on MZ and same-sex DZ twin pairs sharing environment equally (while sharing genes to very different extents). This "equal environment assumption" (EEA) is simply wrong; starting with parents, MZ twins are treated more similarly than DZ twins, creating more similar environments for them. If this isn't recognized, greater similarity between MZs will be misattributed to genes.[22]

Scientists such as Kenneth Kendler of Virginia Commonwealth University, a dean of the field, have tried to control for this by (a) quantifying just how similar childhoods were for twins (with respect to variables like sharing rooms, clothing, friends, teachers, and adversity); (b) examining cases of "mistaken zygosity," where parents were wrong about their twins' MZ/DZ status (thus, for example, raising their DZ twins as if they were MZ); and (c) comparing full-, half-, and step-siblings who were reared together for differing lengths of time. Most of these studies show that controlling for the assumption of MZs sharing more environment than do DZs doesn't significantly reduce the size of genetic influences.*[23] Hold that thought.

Criticism #2: MZ twins experience life more similarly starting as fetuses. DZ twins are "dichorionic," meaning that they have separate placentas. In contrast, 75 percent of MZ twins share one placenta (i.e., are "monochorionic").* Thus

most MZ twin fetuses share maternal blood flow more than do DZ twins, and thus are exposed to more similar levels of maternal hormones and nutrients. If that isn't recognized, greater similarity in MZs will be misattributed to genes.

Various studies have determined what the chorionic status was in different MZ pairs and then examined end points related to cognition, personality, and psychiatric disease. By a small margin, most studies show that chorionic status does make a difference, leading to overestimates of genetic influence. How big of an overestimation? As stated in one review, "small but not negligible."[24]

Criticism #3: Recall that adoption studies assume that if a child is adopted soon after birth, she shares genes but no environment with her biological parents. But what about prenatal environmental effects? A newborn just spent nine months sharing the circulatory environment with Mom. Moreover, eggs and sperm can carry epigenetic changes into the next generation. If these various effects are ignored, an environmentally based similarity between mother and child would be misattributed to genes.

Epigenetic transmission via sperm seems of small significance. But prenatal and epigenetic effects from the mother can be huge—for example, the Dutch Hunger Winter phenomenon showed that third-trimester malnutrition increased the risk of some adult diseases more than *tenfold*.

This confound can be controlled for. Roughly half your genes come from each parent, but prenatal environment comes from Mom. Thus, traits shared more with biological mothers than with fathers argue against a genetic influence.* The few tests of this, concerning the genetic influence on schizophrenia demonstrated in twin studies, suggest that prenatal effects aren't big.

Criticism #4: Adoption studies assume that a child and adoptive parents share environment but not genes.[25] That might approach being true if adoption involved choosing adoptive parents randomly among everyone on earth. Instead, adoption agencies prefer to place children with families of similar racial or ethnic background as the biological parents (a policy advocated by the National Association of Black Social Workers and the Child Welfare League).* Thus, kids and adoptive parents typically share genes at a higher-than-chance level; if this isn't recognized, a similarity between them will be misattributed to environment.

Researchers admit there is selective placement but argue over whether it's consequential. This remains unsettled. Bouchard, with his twins separated at birth, controlled for cultural, material, and technological similarities between the separate homes of twin pairs, concluding that shared similarity of home

environments due to selective placement was a negligible factor. A similar conclusion was reached in a larger study carried out by both Kendler and another dean of the field, Robert Plomin of King's College London.

These conclusions have been challenged. The most fire-breathing critic has been Princeton psychologist Leon Kamin, who argues that concluding that selective placement isn't important is wrong because of misinterpretation of results, use of wimpy analytical tests, and overreliance on questionable retrospective data. He wrote: "We suggest that no scientific purpose is served by the flood of heritability estimates generated by these studies."[26]

Here's where I give up—if super smart people who think about this issue all the time can't agree, I sure don't know how seriously selective placement distorts the literature.

Criticism #5: Adoptive parents tend to be more educated, wealthier, and more psychiatrically healthy than biological parents.[27] Thus, adoptive households show "range restriction," being more homogeneous than biological ones, which decreases the ability to detect environmental effects on behavior. Predictably, attempts to control for this satisfy only some critics.

So what do we know after this slog through the criticisms and countercriticisms about adoption and twin studies?

- Everyone agrees that confounds from prenatal environment, epigenetics, selective placement, range restriction, and assumptions about equal environment are unavoidable.
- Most of these confounds inflate the perceived importance of genes.
- Efforts have been made to control for these confounds and generally have shown that they are of less magnitude than charged by many critics.
- Crucially, these studies have mostly been about psychiatric disorders, which, while plenty interesting, aren't terribly relevant to the concerns of this book. In other words, no one has studied whether these confounds matter when considering genetic influences on, say, people's tendency to endorse their culture's moral rules yet rationalize why those rules don't apply

to them today, because they're stressed and it's their birthday. Lots more work to be done.

The Fragile Nature of Heritability Estimates

Now starts a bruising, difficult, immensely important subject. I review its logic every time I teach it, because it's so unintuitive, and I'm still always just words away from getting it wrong when I open my mouth in class.

Behavior genetics studies usually produce a number called a heritability score.[28] For example, studies have reported heritability scores in the 40 to 60 percent range for traits related to prosocial behavior, resilience after psychosocial stress, social responsiveness, political attitudes, aggression, and leadership potential.

What's a heritability score? "What does a gene do?" is at least two questions. How does a gene influence average levels of a trait? How does a gene influence *variation* among people in levels of that trait?

These are crucially different. For example, how much do genes have to do with people's scores averaging 100 on this thing called an IQ test? Then how much do genes have to do with one person scoring higher than another?

Or how much do genes help in explaining why humans usually enjoy ice cream? How much in explaining why people like different flavors?

These issues utilize two terms with similar sounds but different meanings. If genes strongly influence average levels of a trait, that trait is strongly inherited. If genes strongly influence the extent of variability around that average level, that trait has high heritability.* It is a population measure, where a heritability score indicates the percentage of total variation attributable to genetics.

The difference between an inherited trait and heritability generates at least two problems that inflate the putative influence of genes. First, people confuse the two terms (things would be easier if heritability were called something like "gene tendency"), and in a consistent direction. People often mistakenly believe that if a trait is strongly inherited, it's thus highly heritable. And it's particularly bad that confusion is typically in that direction, because people are usually more interested in variability of traits among humans than in average levels of traits. For example, it's more interesting to consider why some people are smarter than others than why humans are smarter than turnips.

The second problem is that research consistently inflates heritability measures, leading people to conclude that genes influence individual differences more than they do.

Let's slowly work through this, because it's really important.

The Difference Between a Trait Being Inherited and Having a High Degree of Heritability

You can appreciate the difference by considering cases where they dissociate.

First, an example of a trait that is highly inherited but has low heritability, offered by the philosopher Ned Block:[29] What do genes have to do with humans averaging five fingers per hand? Tons; it's an inherited trait. What do genes have to do with variation around that average? Not much—cases of other than five fingers on a hand are mostly due to accidents. While average finger number is an inherited trait, the heritability of finger number is low—genes don't explain individual differences much. Or stated differently: Say you want to guess whether some organism's limb has five fingers or a hoof. Knowing their genetic makeup will help by identifying their species. Alternatively, you're trying to guess whether a particular person is likely to have five or four fingers on his hand. Knowing whether he uses buzz saws while blindfolded is more useful than knowing the sequence of his genome.

Next consider the opposite—a trait that is not highly inherited but which has high heritability. What do genes directly have to do with humans being more likely than chimps to wear earrings? Not much. Now consider individual differences among humans—how much do genes help predict which individuals are wearing earrings at a high school dance in 1958? Tons. Basically, if you had two X chromosomes, you probably wore earrings, but if you had a Y chromosome, you wouldn't have been caught dead doing so. Thus, while genes had little to do with the prevalence of earrings among Americans in 1958 being around 50 percent, they had lots to do with determining *which* Americans wore them. Thus, in that time and place, wearing earrings, while not a strongly inherited trait, had high heritability.

The Reliability of Heritability Measures

We're now clear on the difference between inherited traits and their degree of heritability and recognize that people are usually more interested in the latter—you versus your neighbor—than the former—you versus a wildebeest. As we saw, scads of behavioral and personality traits have heritability scores of 40 to 60 percent, meaning that genetics explains about half the variability in the trait. The point of this section is that the nature of research typically inflates such scores.*[30]

Say a plant geneticist sits in the desert, studying a particular species of plant. In this imaginary scenario a single gene, gene 3127, regulates the plant's growth. Gene 3127 comes in versions, A, B, and C. Plants with version A always grow to be one inch tall; version B, two inches; C, three inches.* What single fact gives you the most power in predicting a plant's height? Obviously, whether it has version A, B, or C—that explains all the variation in height between plants, meaning 100 percent heritability.

Meanwhile, twelve thousand miles away in a rain forest, a second plant geneticist is studying a clone of that same plant. And in that environment plants with version A, B, or C are 101, 102, or 103 inches tall, respectively. This geneticist also concludes that plant height in this case shows 100 percent heritability.

Then, as required by the plot line, the two stand side by side at a conference, one brandishing 1/2/3 inch data, the other 101/102/103. They combine data sets. Now you want to predict the height of one example of that plant, taken from anywhere on the planet. You can either know which version of gene 3127 it possesses or what environment it is growing in. Which is more useful? Knowing which environment. When you study this plant species in two environments, you discover that heritability of height is miniscule.

Neon lights! This is crucial: Study a gene in only one environment and, by definition, you've eliminated the ability to see if it works differently in other environments (in other words, if other environments regulate the gene differently). And thus you've artificially inflated the importance of the genetic contribution. The more environments in which you study a genetic trait, the more novel environmental effects will be revealed, decreasing the heritability score.

Scientists study things in controlled settings to minimize variation in extraneous factors and thus get cleaner, more interpretable results—for example, making sure that the plants all have their height measured around the same time of year. This inflates heritability scores, because you've prevented yourself from

ever discovering that some extraneous environmental factor isn't actually extraneous.* Thus a heritability score tells how much variation in a trait is explained by genes *in the environment(s) in which it's been studied*. As you study the trait in more environments, the heritability score will decrease. This is recognized by Bouchard: "These conclusions [derived from a behavior genetics study] can be generalized, of course only to new populations exposed to a range of environments similar to those studied."[31]

Okay, that was slick on my part, inventing a plant that grows in both desert and rain forest, just to trash heritability scores. Real plants rarely occur in both of those environments. Instead, in one rain forest the three gene versions might produce plants of heights 1, 2, and 3 inches, while in another they are 1.1, 2.1, and 3.1, producing a heritability score that, while less than 100 percent, is still extremely high.

Genes typically still play hefty roles in explaining individual variability, given that any given species lives in a limited range of environments—capybaras stick to the tropics, polar bears to the Arctic. This business about heterogeneous environments driving down heritability scores is important only in considering some hypothetical species that, say, lives in both tundra and desert, in various population densities, in nomadic bands, sedentary farming communities, and urban apartment buildings.

Oh, that's right, humans. Of all species, heritability scores in humans plummet the most when shifting from a controlled experimental setting to considering the species' full range of habitats. Just consider how much the heritability score for wearing earrings, with its gender split, has declined since 1958.

Now to consider an extremely important complication.

Gene/Environment Interactions

Back to our plant. Imagine a growth pattern in environment A of 1, 1, and 1 for the three gene variants, while in environment B it's 10, 10, and 10. When considering the combined data from both environments, heritability is zero—variation is entirely explained by which environment the plant grew in.

Now, instead, in environment A it's 1, 2, and 3, while in environment B it's also 1, 2, and 3. Heritability is 100 percent, with all variability in height explained by genetic variation.

Now say environment A is 1, 2, and 3, and environment B is 1.5, 2.5, 3.5. Heritability is somewhere between 0 percent and 100 percent.

Now for something different: Environment A: 1, 2, 3. Environment B: *3*, *2*, *1*. In this case even talking about a heritability score is problematic, because different gene variants have diametrically opposite effects in different environments. We have an example of a central concept in genetics, a *gene/environment interaction*, where qualitative, rather than just quantitative, effects of a gene differ by environment. Here's a rule of thumb for recognizing gene/environment interactions, translated into English: You are studying the behavioral effects of a gene in two environments. Someone asks, "What are the effects of the gene on some behavior?" You answer, "It depends on the environment." Then they ask, "What are the effects of environment on this behavior?" And you answer, "It depends on the version of the gene." "It depends" = a gene/environment interaction.

Here are some classic examples concerning behavior:[32]

The disease phenylketonuria arises from a single gene mutation; skipping over details, the mutation disables an enzyme that converts a potentially neurotoxic dietary constituent, phenylalanine, into something safe. Thus, if you eat a normal diet, phenylalanine accumulates, damaging the brain. But eat a phenylalanine-free diet from birth, and there is no damage. What are the effects of this mutation on brain development? *It depends* on your diet. What's the effect of diet on brain development? *It depends* on whether you have this (rare) mutation.

Another gene/environment interaction pertains to depression, a disease involving serotonin abnormalities.[33] A gene called 5HTT codes for a transporter that removes serotonin from the synapse; having a particular 5HTT variant increases the risk of depression . . . but only when coupled with childhood trauma.* What's the effect of 5HTT variant on depression risk? It depends on childhood trauma exposure. What's the effect of childhood trauma exposure on depression risk? It depends on 5HTT variant (plus loads of other genes, but you get the point).

Another example concerns FADS2, a gene involved in fat metabolism.[34] One variant is associated with higher IQ, but only in breast-fed children. Same pair of "what's the effect" questions, same "it depends" answers.

One final gene/environment interaction was revealed in an important 1999 *Science* paper. The study was a collaboration among three behavioral geneticists—one at Oregon Health Sciences University, one at the University of Alberta, and one at the State University of New York in Albany.[35] They studied mouse strains known to have genetic variants relevant to particular behaviors (e.g., addiction or anxiety). First they ensured that the mice from a particular strain were essentially genetically identical in all three labs. Then the scientists did cartwheels to test the animals in identical conditions in the labs.

They standardized everything. Because some mice were born in the lab but others came from breeders, homegrowns were given bouncy van rides to simulate the jostling that commercially bred mice undergo during shipping, just in case that was important. Animals were tested at the same day of age on the same date at the same local time. Animals had been weaned at the same age and lived in the same brand of cage with the same brand and thickness of sawdust bedding, changed on the same day of the week. They were handled the same number of times by humans wearing the same brand of surgical gloves. They were fed the same food and kept in the same lighting environment at the same temperature. The environments of these animals could hardly have been more similar if the three scientists had been identical triplets separated at birth.

What did they observe? Some gene variants showed massive gene/environment interactions, with variants having radically different effects in different labs.

Here's the sort of data they got: Take a strain called 129/SvEvTac and a test measuring the effects of cocaine on activity. In Oregon cocaine increased activity in these mice by 667 centimeters of movement per fifteen minutes. In Albany, an increase of 701. Those are pretty similar numbers; good. And in Alberta? More than 5,000. That's like identical triplets pole-vaulting, each in a different location; they've all had the same training, equipment, running surface, night's rest, breakfast, and brand of underwear. The first two vault 18 feet and 18 feet one inch, and the third vaults 108 feet.

Maybe the scientists didn't know what they were doing; maybe the labs were chaotic. But variability was small within each lab, showing stable environmental conditions. And crucially, a few variants didn't show a gene/environment interaction, producing similar effects in the three labs.

What does this mean? That most of the gene variants were so sensitive to environment that gene/environment interactions occurred even in these

obsessively similar lab settings, where incredibly subtle (and still unidentified) environmental differences made huge differences in what the gene did.

Citing "gene/environment interactions" is a time-honored genetics cliché.[36] My students roll their eyes when I mention them. *I* roll my eyes when I mention them. Eat your vegetables, floss your teeth, remember to say, "It's difficult to quantitatively assess the relative contributions of genes and environment to a particular trait when they interact." This suggests a radical conclusion: *it's not meaningful to ask what a gene does, just what it does in a particular environment*. This is summarized wonderfully by the neurobiologist Donald Hebb: "It is no more appropriate to say things like characteristic A is more influenced by nature than nurture than . . . to say that the area of a rectangle is more influenced by its length than its width." It's appropriate to figure out if lengths or widths explain more of the variability in a population of rectangles. But not in individual ones.

As we conclude part 2 of this chapter, some key points:

a. A gene's influence on the average value of a trait (i.e., whether it is inherited) differs from its influence on variability of that trait across individuals (its heritability).
b. Even in the realm of inherited traits—say, the inheritance of five fingers as the human average—you can't really say that there is genetic determination in the classically hard-assed sense of the word. This is because the inheritance of a gene's effect requires not just passing on the gene but also the context that regulates the gene in that manner.
c. Heritability scores are relevant only to the environments in which the traits have been studied. The more environments you study a trait in, the lower the heritability is likely to be.
d. Gene/environment interactions are ubiquitous and can be dramatic. Thus, you can't really say what a gene "does," only what it does in the environments in which it's been studied.

Current research actively explores gene/environment interactions.[37] How's this for fascinating: Heritability of various aspects of cognitive development is

very high (e.g., around 70 percent for IQ) in kids from high–socioeconomic status (SES) families but is only around 10 percent in low-SES kids. Thus, higher SES allows the full range of genetic influences on cognition to flourish, whereas lower-SES settings restrict them. In other words, genes are nearly irrelevant to cognitive development if you're growing up in awful poverty—poverty's adverse effects trump the genetics.* Similarly, heritability of alcohol use is lower among religious than nonreligious subjects—i.e., your genes don't matter much if you're in a religious environment that condemns drinking. Domains like these showcase the potential power of classical behavior genetics.

PART 3: SO WHAT DO GENES ACTUALLY HAVE TO DO WITH BEHAVIORS WE'RE INTERESTED IN?

The Marriage of Behavior Genetics and Molecular Genetics

Behavior genetics has gotten a huge boost by incorporating molecular approaches—after examining similarities and differences between twins or adoptees, find the actual genes that underlie those similarities and differences. This powerful approach has identified various genes relevant to our interests. But first, our usual caveats: (a) not all of these findings consistently replicate; (b) effect sizes are typically small (in other words, some gene may be involved, but not in a major way); and (c) the most interesting findings show gene/environment interactions.

Studying Candidate Genes

Gene searches can take a "candidate" approach or a genomewide association approach (stay tuned). The former requires a list of plausible suspects—genes already known to be related to some behavior. For example, if you're interested in a behavior that involves serotonin, obvious candidate genes would include those coding for enzymes that make or degrade serotonin, pumps that remove it from the synapse, or serotonin receptors. Pick one that interests you, and study it in animals using molecular tools to generate "knockout" mice (where you've eliminated that gene) or "transgenic" mice (with an extra copy of the gene). Make manipulations like these only in certain brain regions or at certain times. Then examine what's different about behavior. Once you're convinced of an effect, ask whether variants of that gene help explain individual differences in human versions of the behavior. I start with the topic that has gotten the most attention, for better or worse, mostly "worse."

The Serotonin System

What do genes related to serotonin have to do with our best and worst behaviors? Plenty.

Chapter 2 presented a fairly clear picture of low levels of serotonin fostering impulsive antisocial behavior. There are lower-than-average levels of serotonin breakdown products in the bloodstreams of people with that profile, and of serotonin itself in the frontal cortex of such animals. Even more convincingly, drugs that decrease "serotonergic tone" (i.e., decreasing serotonin levels or sensitivity to serotonin) increase impulsive aggression; raising the tone does the opposite.

This generates some simple predictions—all of the following should be associated with impulsive aggression, as they will produce low serotonin signaling:

a. Low-activity variants of the gene for tryptophan hydroxylase (TH), which makes serotonin
b. High-activity variants of the gene for monoamine oxidase-A (MAO-A), which degrades serotonin
c. High-activity variants of the gene for the serotonin transporter (5HTT), which removes serotonin from the synapse
d. Variants of genes for serotonin receptors that are less sensitive to serotonin

An extensive literature shows that for each of those genes the results are inconsistent and generally go in the *opposite* direction from "low serotonin = aggression" dogma. Ugh.

Studies of genes for TH and serotonin receptors are inconsistent messes.[38] In contrast, the picture of 5HTT, the serotonin transporter gene, is consistently in the opposite direction from what's expected. Two variants exist, with one producing less transporter protein, meaning less serotonin removed from the synapse.* And counter to expectations, this variant, producing more serotonin in the synapse, is associated with more impulsive aggression, not less. Thus, according to these findings, "high serotonin = aggression" (recognizing this as simplified shorthand).

The clearest and most counterintuitive studies concern MAO-A. It burst on the scene in a hugely influential 1993 *Science* paper reporting a Dutch family with an MAO-A gene mutation that eliminated the protein.[39] Thus serotonin isn't broken down and accumulates in the synapse. And counter to chapter 2's predictions, the family was characterized by varied antisocial and aggressive behaviors.

Mouse studies in which the MAO-A gene was "knocked out" (producing the equivalent of the Dutch family's mutation) produced the same—elevated serotonin levels in the synapse and hyperaggressive animals with enhanced fear responses.[40]

This finding, of course, concerned a *mutation* in MAO-A resulting in the complete absence of the protein. Research soon focused on low-activity MAO-A variants that produced elevated serotonin levels.[*41] People with that variant averaged higher levels of aggression and impulsivity and, when looking at angry or fearful faces, more activation of the amygdala and insula and less activation of the prefrontal cortex. This suggests a scenario of more fear reactivity and less frontal capacity to restrain such fear, a perfect storm for reactive aggression. Related studies showed decreased activation of frontal cortical regions during various attentional tasks and enhanced anterior cingulate activity in response to social rejection in such individuals.

So studies where serotonin breakdown products are measured in the body, or where serotonin levels are manipulated with drugs, say that low serotonin = aggression.[42] And the genetic studies, particularly of MAO-A, say high serotonin = aggression. What explains this discrepancy? The key probably is that a drug manipulation lasts for a few hours or days, while genetic variants have their effects on serotonin for a lifetime. Possible explanations: (a) The low-activity MAO-A variants don't produce higher synaptic levels of serotonin all that consistently because the 5HTT serotonin reuptake pump works harder at removing serotonin from the synapse, compensating, and maybe even *over*compensating. There is evidence for this, just to make life really complicated. (b) Those variants do produce chronically elevated serotonin levels in the synapse, but the postsynaptic neurons compensate or overcompensate by decreasing serotonin receptor numbers, thereby reducing sensitivity to all that serotonin; there is evidence for that too. (c) The lifelong consequences of differences in serotonin signaling due to gene variants (versus transient differences due to drugs) produce structural changes in the developing brain. There is evidence there as well, and in accordance with that, while temporarily

inhibiting MAO-A activity with a drug in an adult rodent decreases impulsive aggression, doing the same in fetal rodents produces adults with increased impulsive aggression.

Yikes, this is complicated. Why go through the agony of all these explanatory twists and turns? Because this obscure corner of neurogenetics has caught the public's fancy, with—I kid you not—the low-activity MAO-A variant being referred to as the "warrior gene" by both scientists and in the media.*[43] And that warrior hoo-hah is worsened by the MAO-A gene being X linked and its variants being more consequential in males than females. Amazingly, prison sentences for murderers have now been lessened in at least two cases because it was argued that the criminal, having the "warrior gene" variant of MAO-A, was inevitably fated to be uncontrollably violent. OMG.

Responsible people in the field have recoiled in horror at this sort of unfounded genetic determinism seeping into the courtroom. The effects of MAO-A variants are tiny. There is nonspecificity in the sense that MAO-A degrades not only serotonin but norepinephrine as well. Most of all, there is nonspecificity in the behavioral effects of the variants. For example, while nearly everyone seems to remember that the landmark MAO-A paper that started all the excitement was about aggression (one authoritative review referred to the Dutch family with the mutation as "notorious for the persistent and extreme reactive aggression demonstrated by some of its males"), in actuality members of the family with the mutation had borderline mental retardation. Moreover, while some individuals with the mutation were quite violent, the antisocial behavior of others consisted of arson and exhibitionism. So maybe the gene has something to do with the extreme reactive aggression of some family members. But it is just as responsible for explaining why other family members, rather than being aggressive, were flashers. In other words, there is as much rationale for going on about the "drop your pants gene" as the "warrior gene."

Probably the biggest reason to reject warrior-gene determinism nonsense is something that should be utterly predictable by now: MAO-A effects on behavior show strong gene/environment interactions.

This brings us to a hugely important 2002 study, one of my favorites, by Avshalom Caspi and colleagues at Duke University.[44] The authors followed a large cohort of children from birth to age twenty-six, studying their genetics, upbringing, and adult behavior. Did MAO-A variant status predict antisocial behavior in twenty-six-year-olds (as measured by a composite of standard psychological assessments and convictions for violent crimes)? No. But MAO-A

status coupled with something else powerfully did. Having the low-activity version of MAO-A tripled the likelihood . . . but only in people with a history of severe childhood abuse. And if there was no such history, the variant was not predictive of anything. This is the essence of gene/environment interaction. What does having a particular variant of the MAO-A gene have to do with antisocial behavior? It depends on the environment. “Warrior gene” my ass.

This study is important not just for its demonstration of a powerful gene/environment interaction but for what the interaction is, namely the ability of an abusive childhood environment to collaborate with a particular genetic constitution. To quote a major review on the subject, “In a healthy environment, increased threat sensitivity, poor emotion control and enhanced fear memory in MAOA-L [i.e., the “warrior” variant] men might only manifest as variation in temperament within a ‘normal’ or subclinical range. However, these same characteristics in an abusive childhood environment—one typified by persistent uncertainty, unpredictable threat, poor behavioral modeling and social referencing, and inconsistent reinforcement for prosocial decision making—might predispose toward frank aggression and impulsive violence in the adult.” In a similar vein, the low-activity variant of the serotonin transporter gene was reported to be associated with adult aggressiveness . . . but only when coupled with childhood adversity.[45] This is straight out of the lessons of the previous chapter.

Since then, this MAO-A variant/childhood abuse interaction has been frequently replicated, and even demonstrated with respect to aggressive behavior in rhesus monkeys.[46] There have also been hints as to how this interaction works—the MAO-A gene promoter is regulated by stress and glucocorticoids.

MAO-A variants show other important gene/environment interactions. For example, in one study the low-activity MAO-A variant predicts criminality, but only if coupled with high testosterone levels (consistent with that, the MAO-A gene also has a promoter responsive to androgens). In another study low-activity MAO-A participants in an economic game were more likely than high-activity ones to retaliate aggressively when exploited by the other player—but only if that exploitation produced a large economic loss; if the loss was small, there was no difference. In another study low-activity individuals were more aggressive than others—but only in circumstances of social exclusion. Thus the effects of this genetic variant can be understood only by considering other, nongenetic factors in individuals’ lives, such as childhood adversity and adult provocation.[47]

The Dopamine System

Chapter 2 introduced the role of dopamine in the anticipation of reward and in goal-directed behavior. Lots of work has examined the genes involved, most broadly showing that variants that produce lowered dopamine signaling (less dopamine in the synapse, fewer dopamine receptors, or lower responsiveness of these receptors) are associated with sensation seeking, risk taking, attentional problems, and extroversion. Such individuals have to seek experiences of greater intensity to compensate for the blunted dopamine signaling.

Much of the research has focused on one particular dopamine receptor; there are at least five kinds (found in different parts of the brain, binding dopamine with differing strengths and duration), each coded for by a gene.[48] Work has focused on the gene for the D4 dopamine receptor (the gene is called DRD4), which mostly occurs in the neurons in the cortex and nucleus accumbens. The DRD4 gene is super variable, coming in at least ten different flavors in humans. One stretch of the gene is repeated a variable number of times, and the version with seven repeats (the "7R" form) produces a receptor protein that is sparse in the cortex and relatively unresponsive to dopamine. This is the variant associated with a host of related traits—sensation and novelty seeking, extroversion, alcoholism, promiscuity, less sensitive parenting, financial risk taking, impulsivity, and, probably most consistently, ADHD (attention-deficit/hyperactivity disorder).

The implications cut both ways—the 7R could make you more likely to impulsively steal the old lady's kidney dialysis machine, or to impulsively give the deed of your house to a homeless family. In come gene/environment interactions. For example, kids with the 7R variant are less generous than average. But only if they show insecure attachment to their parents. Secure-attachment 7Rs show *more* generosity than average. Thus 7R has something to do with generosity—but its effect is entirely context dependent. In another study 7R students expressed the least interest in organizations advocating prosocial causes, unless they were given a religious prime,* in which case they were the *most* prosocial. One more—7Rs are worse at gratification-postponement tasks, but only if they grew up poor. Repeat the mantra: don't ask what a gene does; ask what it does in a particular context.[49]

Interestingly, the next chapter considers the extremely varied frequency of the 7R variant in different populations. As we'll see, it tells you a lot about the

history of human migration, as well as about differences between collectivist and individualist cultures.[50]

We shift now to other parts of the dopamine system. As introduced in chapter 2, after dopamine binds to receptors, it floats off and must be removed from the synapse.[51] One route involves its being degraded by the enzyme catechol-O-methyltransferase (COMT). Among the variants of the COMT gene is one associated with a more efficient enzyme. "More efficient" = better at degrading dopamine = less dopamine in the synapse = less dopamine signaling. The highly efficient COMT variant is associated with higher rates of extroversion, aggression, criminality, and conduct disorder. Moreover, in a gene/environment interaction straight out of the MAO-A playbook, that COMT variant is associated with anger traits, but only when coupled with childhood sexual abuse. Intriguingly, the variants seem pertinent to frontal regulation of behavior and cognition, especially during stress.

In addition to degradation, neurotransmitters can be removed from the synapse by being taken back up into the axon terminal for recycling.[52] Dopamine reuptake is accomplished by the dopamine transporter (DAT). Naturally, the DAT gene comes in different variants, and those that produce higher levels of synaptic dopamine (i.e., transporter variants that are less efficient) in the striatum are associated with people who are more oriented toward social signaling—they're drawn more than average to happy faces, are more repelled by angry faces, and have more positive parenting styles. How these findings merge with the findings from the DRD4 and COMT studies (i.e., fitting risk taking with a preference for happy faces) is not immediately apparent.

Cool people with certain versions of these dopamine-related genes are more likely to engage in all sorts of interesting behaviors, ranging from the healthy to the pathological. But not so fast:

- These findings are not consistent, no doubt reflecting unrecognized gene/environment interactions.
- Again, why should the COMT world be related to sensation seeking, while there are the DAT people and their happy faces? Both genes are about ending dopamine signaling. This is probably related to different parts of the brain differing as to whether DAT or COMT plays a bigger role.[53]

- The COMT literature is majorly messy, for the inconvenient reason that the enzyme also degrades norepinephrine. So COMT variants are pertinent to two totally different neurotransmitter systems.
- These effects are tiny. For example, knowing which DRD4 variant someone has explains only 3 to 4 percent of the variation in novelty-seeking behavior.
- The final piece of confusion seems most important but is least considered in the literature (probably because it would be premature). Suppose that every study shows with whopping clarity and consistency that a DRD4 variant is highly predictive of novelty seeking. That still doesn't tell us why for some people novelty seeking means frequently switching their openings in chess games, while for others it means looking for a new locale because it's getting stale being a mercenary in the Congo. No gene or handful of genes that we are aware of will tell us much about that.

The Neuropeptides Oxytocin and Vasopressin

Time for a quick recap from chapter 4. Oxytocin and vasopressin are involved in prosociality, ranging from parent/offspring bonds to monogamous bonds to trust, empathy, generosity, and social intelligence. Recall the caveats: (a) sometimes these neuropeptides are more about sociality than prosociality (in other words, boosting social information gathering, rather than acting prosocially with that information); (b) they most consistently boost prosociality in people who already lean in that direction (e.g., making generous people more generous, while having no effect on ungenerous people); and (c) the prosocial effects are within groups, and these neuropeptides can make people crappier to outsiders—more xenophobic and preemptively aggressive.

Chapter 4 also touched on oxytocin and vasopressin genetics, showing that individuals with genetic variants that result in higher levels of either the hormones or their receptors tend toward more stable monogamous relationships, more actively engaged parenting, better skill at perspective taking, more empathy, and stronger fusiform cortex responses to faces. These are fairly consistent effects of moderate magnitude.

Meanwhile, there are studies showing that one oxytocin receptor gene variant is associated with extreme aggression in kids, as well as a callous, unemotional style that foreshadows adult psychopathy.[54] Moreover, another variant is associated with social disconnection in kids and unstable adult relationships. But unfortunately these findings are uninterpretable because no one knows if these variants produce more, less, or the usual amount of oxytocin signaling.

Of course, there are cool gene/environment interactions. For example, having a particular oxytocin receptor gene variant predicts less sensitive mothering—but only when coupled with childhood adversity. Another variant is associated with aggression—but only when people have been drinking. Yet another variant is associated with greater seeking of emotional support during times of stress—among Americans (including first generation Korean Americans) but not Koreans (stay tuned for more in the next chapter).

Genes Related to Steroid Hormones

We start with testosterone. The hormone is not a protein (none of the steroid hormones are), meaning there isn't a testosterone gene. However, there are genes for the enzymes that construct testosterone, for the enzyme that converts it to estrogen, and for the testosterone (androgen) receptor. The most work has focused on the gene for the receptor, which comes in variants that differ in their responsiveness to testosterone.*

Intriguingly, a few studies have shown that among criminals, having the more potent variant is associated with violent crimes.[55] A related finding concerns sex differences in structure of the cortex, and adolescent boys with the more potent variant show more dramatic "masculinization" of the cortex. An interaction between receptor variant and testosterone levels occurs. High basal testosterone levels do not predict elevated levels of aggressive mood or of amygdaloid reactivity to threatening faces in males—except in those with that variant. Interestingly, the equivalent variant predicts aggressiveness in Akita dogs.

How important are these findings? A key theme in chapter 4 was how little individual differences in testosterone levels in the normal range predict individual differences in behavior. How much more predictability is there when combining knowledge of testosterone levels *and* of receptor sensitivity? Not

much. How about hormone levels *and* receptor sensitivity *and* number of receptors? Still not much. But definitely an improvement in predictive power.

Similar themes concern the genetics of the estrogen receptor.[56] For example, different receptor variants are associated with higher rates of anxiety among women, but not men, and higher rates of antisocial behavior and conduct disorder in men, but not women. Meanwhile, in genetically manipulated mice, the presence or absence of the receptor gene influences aggression in females . . . depending on how many brothers there were in the litter in utero—gene/environment again. Once again, the magnitude of these genetic influences is tiny.

Finally, there is work on genes related to glucocorticoids, particularly regarding gene/environment interactions.[57] For example, there is an interaction between one variant of the gene for a type of receptor for glucocorticoids (for mavens: it's the MR receptor) and childhood abuse in producing an amygdala that is hyperreactive to threat. Then there is a protein called FKBP5, which modifies the activity of another type of receptor for glucocorticoids (the GR receptor); one FKBP5 variant is associated with aggression, hostility, PTSD, and hyperreactivity of the amygdala to threat—but only when coupled with childhood abuse.

Buoyed by these findings, some researchers have examined two candidate genes simultaneously. For example, having both "risk" variants of 5HTT and DRD4 synergistically increases the risk of disruptive behavior in kids—an effect exacerbated by low socioeconomic status.[58]

Phew; all these pages and we've only gotten to thinking about two genes and one environmental variable simultaneously. And despite this, things still aren't great:

- The usual—results aren't terribly consistent from one study to the next.
- The usual—effect sizes are small. Knowing what variant of a candidate gene someone has (or even what variants of a collection of genes) doesn't help much in predicting their behavior.
- A major reason is that, after getting a handle on 5HTT and DRD4 interactions, there are still roughly 19,998 more human genes and a gazillion more environments to study. Time to

switch to the other main approach—looking at all those 20,000 genes at once.

Fishing Expeditions, Instead of Looking Where the Light Is

The small effect sizes reflect a limitation in the candidate gene approach; in scientific lingo, the problem is that one is only looking where the light is. The cliché harks back to a joke: You discover someone at night, searching the ground under a street lamp. "What's wrong?" "I dropped my ring; I'm looking for it." Trying to be helpful, you ask, "Were you standing on this side or that side of the lamp when you dropped it?" "Oh, no, I was over by those trees when I dropped it." "Then why are you searching here?" "This is where the light is." With candidate gene approaches, you look only where the light is, examine only genes that you already know are involved. And with twenty thousand or so genes, it's pretty safe to assume there are still some interesting genes that you don't know about yet. The challenge is to find them.

The most common way of trying to find them all is with genomewide association studies (GWAS).[59] Examine, say, the gene for hemoglobin and look at the eleventh nucleotide in the sequence; everyone will pretty much have the same DNA letter in that spot. However, there are little hot spots of variability, single nucleotides where, say, two different DNA letters occur, each in about 50 percent of the population (and where this typically doesn't change the amino acid being specified, because of DNA redundancy). There are more than a million of such "SNPs" (single-nucleotide polymorphisms) scattered throughout the genome—in stretches of DNA coding for genes, for promoters, for mysterious DNA junk. Collect DNA from a huge number of people, and examine whether particular SNPs associate with particular traits. If an SNP that's implicated occurs in a gene, you've just gotten a hint that the gene may be involved in that trait.*

A GWAS study might implicate scads of genes as being associated with a trait. Hopefully, some will be candidate genes already known to be related to the trait. But other identified genes may be mysterious. Now go check out what they do.

In a related approach, suppose you have two populations, one with and one without a degenerative muscle disease. Take a muscle biopsy from everyone, and

see which of the ~20,000 genes are transcriptionally active in the muscle cells. With this "microarray" or "gene chip" approach, you look for genes that are transcriptionally active only in diseased or in healthy muscle, not in both. Identify them, and you have some new candidate genes to explore.*

These fishing expeditions* show why we're so ignorant about the genetics of behavior.[60] Consider a classic GWAS that looked for genes related to height. This was a crazy difficult study involving examining the genomes of 183,727 people. *183,727*. It must have taken an army of scientists just to label the test tubes. And reflecting that, the paper reporting the findings in *Nature* had approximately 280 authors.

And the results? *Hundreds* of genetic variants were implicated in regulating height. A handful of genes identified were known to be involved in skeletal growth, but the rest was terra incognita. The single genetic variant identified that most powerfully predicted height explained all of 0.4 percent—four tenths of one percent—of the variation in height, and all those hundreds of variants put together explained only about 10 percent of the variation.

Meanwhile, an equally acclaimed study did a GWAS regarding body mass index (BMI). Similar amazingness—almost a quarter million genomes examined, even more authors than the height study. And in this case the single most explanatory genetic variant identified accounted for only 0.3 percent of the variation in BMI. Thus both height and BMI are highly "polygenic" traits. Same for age of menarche (when girls menstruate for the first time). Moreover, additional genes are being missed because their variants are too rare to be picked up by current GWAS techniques. Thus these traits are probably influenced by hundreds of genes.[61]

What about behavior? A superb 2013 GWAS study examined the genetic variants associated with educational attainment.[62] The usual over-the-top numbers—126,559 study subjects, about 180 authors. And the most predictive genetic variant accounted for 0.02 percent—two hundredths of one percent—of the variation. All the identified variants together accounted for about 2 percent of the variation. A commentary accompanying the paper contained this landmark of understatement: "In short, educational attainment looks to be a very polygenic trait."

Educational attainment—how many years of high school or college one completes—is relatively easy to measure. How about the subtler, messier behaviors that fill this book's pages? A handful of studies have tackled that, and the findings are much the same—at the end, you have a list of scores of genes

implicated and can then go figure out what they do (logically, starting with the ones that showed the strongest statistical associations). Hard, hard approaches that are still in their infancy. Made worse by a GWAS missing more subtly variable spots,* meaning even more genes are likely involved.[63]

As we conclude this section, some key points:[64]

a. This review of candidate genes barely scratches even the surface of the surface. Go on PubMed (a major search engine of the biomedical literature) and search "MAO gene/behavior"—up come more than 500 research papers. "Serotonin transporter gene/behavior"—1,250 papers. "Dopamine receptor gene/behavior"—nearly 2,000.
b. The candidate gene approaches show that the effect of a single gene on a behavior is typically tiny. In other words, having the "warrior gene" variant of MAO probably has less effect on your behavior than does believing that you have it.
c. Genomewide survey approaches show that these behaviors are influenced by huge numbers of genes, each one playing only a tiny role.
d. What this translates into is nonspecificity. For example, serotonin transporter gene variants have been linked to risk of depression, but also anxiety, obsessive-compulsive disorder, schizophrenia, bipolar disorder, Tourette's syndrome, and borderline personality disorder. In other words, that gene is part of a network of hundreds of genes pertinent to depression, but also part of another equally large and partially overlapping network relevant to anxiety, another relevant to OCD, and so on. And meanwhile, we're plugging away, trying to understand interactions of two genes at a time.
e. And, of course, gene and environment, gene and environment.

CONCLUSIONS

At long last, you (and I!) have gotten to the end of this excruciatingly but necessarily long chapter. Amid all these tiny effects and technical limitations, it's important to not throw out the genetic baby with the bathwater, as has been an agitated sociopolitical goal at times (during my intellectual youth in the 1970s, sandwiched between the geologic periods of Cranberry Bell-bottoms and of John Travolta White Suits was the Genes-Have-Nothing-to-Do-with-Behavior Ice Age).

Genes have plenty to do with behavior. Even more appropriately, all behavioral traits are affected to some degree by genetic variability.[65] They have to be, given that they specify the structure of all the proteins pertinent to every neurotransmitter, hormone, receptor, etc. that there is. And they have plenty to do with individual differences in behavior, given the large percentage of genes that are polymorphic, coming in different flavors. But their effects are supremely context dependent. Ask not what a gene does. Ask what it does in a particular environment and when expressed in a particular network of other genes (i.e., gene/gene/gene/gene . . . /environment).

Thus, for our purposes, genes aren't about inevitability. Instead they're about context-dependent tendencies, propensities, potentials, and vulnerabilities. All embedded in the fabric of the other factors, biological and otherwise, that fill these pages.

Now that this chapter's done, why don't we all take a bathroom break and then see what's in the refrigerator.