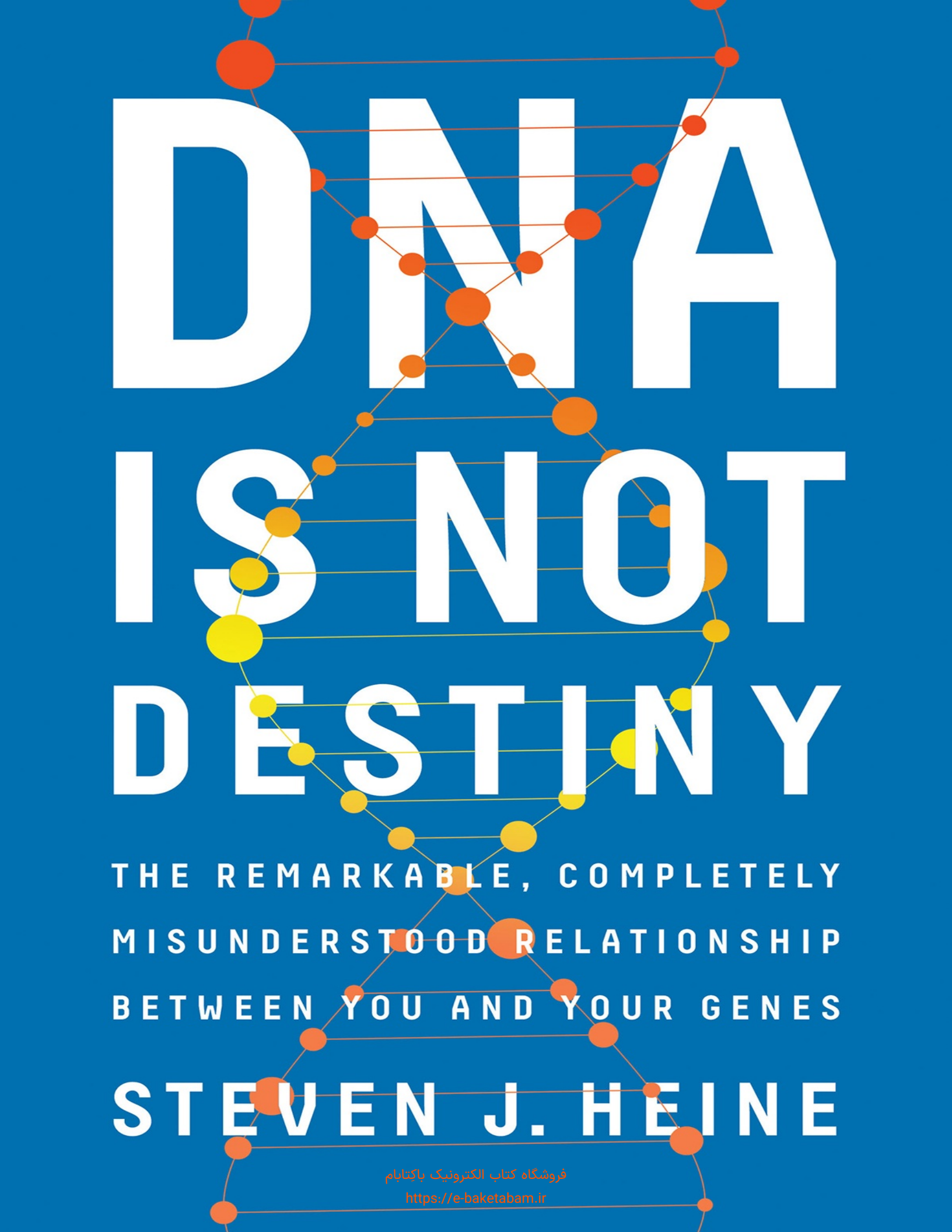

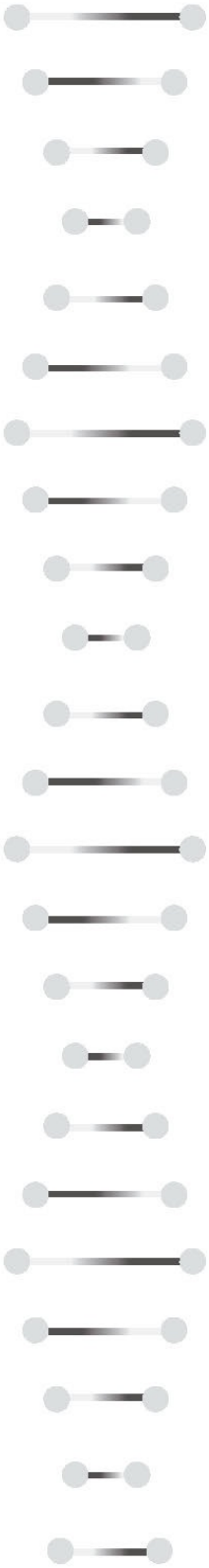

DNA IS NOT DESTINY

The Remarkable, Completely Misunderstood Relationship between You and Your Genes

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W. W. Norton & Company
Independent Publishers Since 1923
New York | London

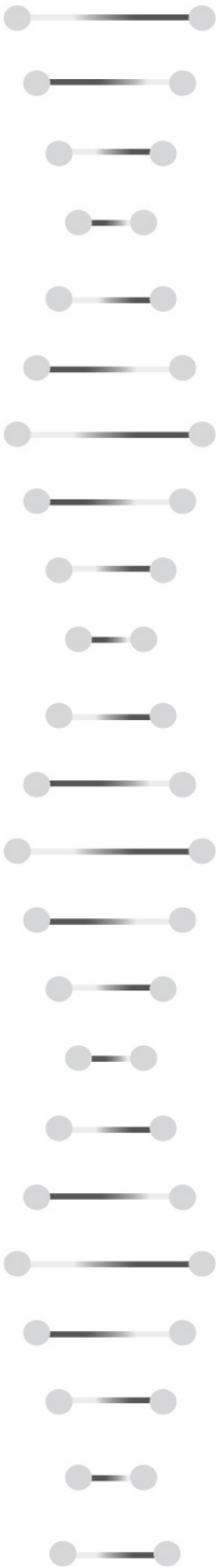
To my parents.

Thanks for the genes and the experiences.

Contents

1.

Introduction



IN THE SECOND WEEK OF APRIL 2003, OUR world changed forever: we sequenced the first complete human genome.

We now have access to information about ourselves that no previous generation has ever had: we can peer directly into our own genetic makeup. We each have a unique string of nucleotides in our cells that contributes to who we are, and since that fateful week in 2003, we are able to unravel this string and read it. It's a 6-billion-letter autobiographical code that seemingly flows straight from the pen of God. Our genome contains deep secrets about us: where our ancestors came from, which diseases we'll likely avoid and which ones might kill us, and what kinds of physical and psychological attributes we're predisposed to have. This remarkable scientific revolution seems to provide us with nothing short of a window into our souls.

It is hard not to be both excited and frightened about the vast potential of this achievement. Our knowledge of the human genome promises a flood of great medical advances. For example, President Bill Clinton foresaw a future in which genetic discoveries made it "conceivable that our children's children will know the term 'cancer' only as a constellation of stars."[1] And we may someday have the potential not only to treat diseases, but also, via genetic engineering, to eliminate hundreds of genetic diseases for good. Many talk breathlessly about a future with designer babies, where prospective generations will not only be born with fewer genetic vulnerabilities to disease, but also with genetic enhancements that make them more fit and more intelligent than ever before.[2]

Moreover, our knowledge of the human genome can be used as a nearly ironclad means to identify individuals. For example, the popular crime drama *CSI: Crime Scene Investigation* was based on the premise that crime scenes were riddled with invisible traces of DNA that unambiguously identified all who were involved. Indeed, this plays out in real court cases that depend on DNA testing to identify the perpetrators. Sometimes this endeavor can get taken to absurd ends, such as the Hong Kong Cleanup Initiative, which promises to collect DNA traces from litter to create a picture of the litterer's face, to publicly identify and shame him or her. The same logic has been exploited by PooPrints DNA testing kits, which promise to identify delinquent dog owners who have failed to clean up after their pet.[3]

Our genes can also tell us long lost tales about who our ancestors were, and where they likely came from, based on similarities between our own genomes and those of people living around the world. And the ability of genome sequencing to identify people's ancestry and personal history has even been extended to those long since gone; for example, scientists have read the genetic

script of a Neanderthal man who lived approximately 38,000 years ago, from DNA in his remains. Our genes seem to stand as a nearly permanent record of our life and the lives of our predecessors.

The genomic revolution promises to completely upend our understanding of the world. And with the advent of direct-to-consumer genetic testing companies, such as 23andMe, you can now affordably get yourself genotyped. What will you do when you learn about the genetic secrets of your own life? My bet is that you're going to respond in all the wrong ways.

This is not because of any specific genes that you might learn about, but because of the psychological machinery in your brain which influences *how you think about genes*. We come equipped with a set of psychological biases that ascribe almost mystical powers to our genes. These biases can lead to racism, sexism, or eugenics, but they can also foster tolerance for others, sympathy, and potential for progress. We're going to explore how these psychological biases work, how they make us vulnerable to the massive hype surrounding the genomic revolution, and how we can corral them into more effective ways of thinking.

The Genomics Revolution and You

If you feel somewhat overwhelmed and anxious about this genomic revolution, you're not alone. Technological innovations can always be challenging to cope with, but the problem is even more daunting when it comes to genomics. One reason we find genomic progress so disturbing is because of its unprecedented blinding speed. Much has been made of the breakneck rate of progress underlying the personal computer revolution: Intel cofounder Gordon Moore's famous "Moore's Law" claimed that the number of transistors on microchips would double every two years. But the pace of the genomic revolution far outstrips this. When the first complete human genome was sequenced in 2003, it cost a few billion dollars and thousands of person-years worth of efforts. Yet barely a decade later, a complete sequence of your own genome was available for about $1,000, and would be ready for you within a matter of days. Genomic sequencing is no longer a special tool for those pursuing research questions in large international scientific consortiums; it is now available to you as a consumer product and could soon be part of your family's routine medical care. In a seeming blink of an eye, the genomic revolution has infiltrated our lives.

Another reason why people find the genomic revolution to be disturbing is

that, unlike other scientific revolutions, this one is personal. Splitting the atom may have changed the world, but discovering your own genome will change how you view yourself. Reading over your unique sequence of DNA can feel as though you are gazing into a crystal ball, discovering secrets that have been passed down to you from your ancestors.

But the main reason we are so anxious about the genomic revolution is that we are psychologically equipped to *misunderstand* it. Unlike, say, the study of subatomic physics, where almost no one outside of the physics community feels that he or she can make heads or tails of it, the notion that we possess genes that make us who we are makes intuitive sense. But it turns out that conclusion is inaccurate, or at least imprecise. Yet we persist in this belief that our genes control our lives. We are *genetic fatalists*.

To see our fatalistic thoughts on genes in action, let's visit the 2014 television series, *Dead Famous DNA*, which was broadcast on Britain's Channel 4. The premise of the show is described by its host, Mark Evans: "I want to hunt down the DNA of the most famous people who ever lived. The aim is to find out who they really are." Evans enters the seedy world of body-part trafficking to obtain and genotype parts of dead celebrities and reveal the secrets of their lives. The show aspires "to understand what made Einstein so intelligent, Marilyn Monroe so attractive, and Adolf Hitler so evil." The answers to these fundamental questions were supposedly all waiting to be read directly from the genomes of these famous people.

My favorite episode was when Evans sought to explain what killed Elvis Presley. He obtained a hair sample, which was purportedly snipped from Elvis's head, and placed in safe-keeping by his barber. (Authentic samples are a key challenge for the show: in this same episode Evans paid $5,000 for what was purported to be a lock of King George's hair, only to have the genotyping lab inform him that he had just bought a piece of a very expensive wig.) Evans was confident this hair sample must have come from Elvis, because genetic testing revealed risk factors for migraines, glaucoma, and obesity; all of which are conditions that Elvis suffered from.[4] And the purported smoking gun was found at the precise genetic address RSID 193922380, which is located on the MYBPC3 gene that sits on chromosome 11. At this location, the sample possessed a G nucleotide (in contrast to a C, like most people have). This particular genetic variant was suspected to be associated with familial hypertrophic cardiomyopathy, a serious kind of heart disease, and Elvis did indeed die of a heart attack. Evans inquired about this variant to geneticist Stephen Kingsmore. "Do you think this is significant enough to tip it towards . . . ?" Kingsmore replied in somewhat guarded terms: "It looks pretty suspicious

that this may indeed have contributed potentially to Elvis's death." This was summarized by Evans as evidence that Elvis's "early death was his genetic destiny," and was further embellished by headlines published around the world, such as that of *The Mirror*, "Shocking DNA results reveal Elvis Presley was always destined to die young." The mystery surrounding Elvis's early death had apparently been solved.

Yet if we look more closely at this claim, it starts to fall apart. The variant of Elvis's that the show discussed, having a G nucleotide at RSID 193922380, has not at all been shown to be a strong predictor of familial hypertrophic cardiomyopathy.[5] To make matters worse, there were no signs from Elvis's autopsy to suggest that he could ever have been diagnosed with familial hypertrophic cardiomyopathy.[6] It's true that, near the end of Elvis's life, he was indeed suffering from migraines and glaucoma, and he had become obese. But did the genetic variants in his alleged DNA cause these? Most certainly not in any direct way. In the case of obesity, there are at least 97 common genetic variants that increase the likelihood of becoming obese.[7] Virtually all of us have several of these variants, and the one obese-relevant variant identified in Elvis's DNA by Dr. Kingsmore is not even one of the stronger predictors. The same goes for Elvis's genetic risks for migraines[8] and glaucoma;[9] neither of the genetic variants identified in Elvis's DNA are strong predictors for these. Saying that these genes caused him to have these conditions is akin to saying that the unusually warm winter was what caused Donald Trump to win the Republican nomination for president in 2016. The weather may influence voter turnout, but it certainly isn't the deciding factor in the outcome. There are just far too many other factors involved.

But the more obvious question that we should be asking is whether the best way to solve the mystery of what caused Elvis's heart attack is to look at his genome in the first place. After all, Elvis was hardly a poster child for a healthy lifestyle. Near the end of his life, he was reportedly addicted to multiple drugs, including Demerol, and had been hospitalized numerous times for overdosing on barbiturates.[10] His autopsy report identified 11 drugs present in his system at the time of his death.[11] Moreover, the excess of Elvis's diet has become the stuff of legend, with his alleged favorite sandwich, the Fool's Gold Loaf, consisting of a whole loaf of French bread, hollowed out and filled with an entire jar of peanut butter, another jar of grape jelly, and a pound of bacon. The BBC documentary series *Arena* estimated that near the end of his life, Elvis's daily caloric intake rivaled that of an Asian elephant![12] If these legends carry any truth, it would

make more sense to inquire about the genetic variants that Elvis possessed that kept him so relatively thin in the face of his obscenely gluttonous diet.

The claim that Elvis's death was telegraphed in his DNA feels like a more satisfying explanation than saying he was done in by an excess of greasy sandwiches, though, doesn't it? But that account, however well it may fit with the fatalistic ways that we tend to think about genes, is a preposterous misreading of the predictive strength of Elvis's genes. The popularity of *Dead Famous DNA* is a perfect example of the way our psychological biases about genes have run amok.

The Psychology of Genetics

Unfortunately, the fatalistic attitude toward genes that is on display in *Dead Famous DNA* is not at all unusual. Why do ideas about genes affect us in this way? To address this question, I launched a series of psychological experiments with the help of my graduate students to explore what happens when people encounter genetic arguments in their lives. Do people ignore this information? Treat it the same as other kinds of information? Or do they give it special attention?

In one of our studies, we wanted to see how people would respond to learning about different causes of obesity.[13] We had Canadian university students come into our lab to read some newspaper articles and answer some questions about them. First they read some distractor articles to throw them off the scent of the true purpose of our study. Then, one group of students who were randomly assigned to a "genetics" condition read an article about scientific research regarding "obesity genes"—genes that affect how much people weigh. Another group assigned to a "social experiences" condition read about scientific research that showed that the weight of people's friends affected how much they weigh. A third group assigned to a "control" condition read an article that was unrelated to obesity—it was about corn production. These were the kinds of news articles that you might encounter with your morning paper, and they were all based on legitimate scientific research. Later on, the students were told they would be participating in a second study that involved food preferences. They were provided with a bowl of cookies and were asked to evaluate the taste of them on various dimensions. This last bit was a ruse, as actually the whole point of our study was to see how many cookies people ate after reading the

newspaper articles. What did we find? Those who read about the existence of obesity genes ate one-third more cookies than those who read either about social causes of obesity or who didn't read anything about obesity. Even though our weight is influenced by both our environments and our genes, it was only the arguments about genes that affected people's behaviors. Learning about the existence of obesity genes led people to act in ways more likely to make them obese!

A key reason why we find genes so compelling is that we have a particular preference for explaining the events that unfold around us. In every society that has been investigated, there is clear evidence to show that we are predisposed to think of the world as emerging from hidden underlying *essences*. We believe families share traits because of their common "blood"; Indian yogis derive their power from some hidden prana energy; traditional Chinese medical practitioners diagnose someone with, for instance, "liver fire," on the basis of having an imbalance between his or her yin and yang; medieval alchemists sought the mystical forces of a philosopher's stone with the hope of changing lead into gold; and Yoda was able to perform his magical Jedi feats because of his command of "the Force." With the advent of genomic science, we now have a new essence: our genes. And when we think of genes, we activate this ancient and universal human tendency to imagine essences, and we are left with an unshakable sense that genes determine life outcomes.

We can see our essence-based conception of genes in everyday discourse. For example, President Obama said that racism is "part of our DNA";[14] Pink sings that her love for partying "is genetic";[15] Brad Pitt argued that "it's in our DNA" as Americans to own a gun;[16] Donald Trump attributes his drive for success to having "a certain gene";[17] and so many corporations claim that innovation is part of their DNA that there's a growing backlash against the clichéd expression.[18] These statements reveal that we not only regularly stud our conversations with genetic concepts, but when we do, we also equate our DNA with some inherent and unchangeable essence that makes us who we are. Our daily conversations about genetic concepts reinforce the idea that our genes are our fate.

And there is a dark side to these so-called essences. Imagined essences underlie why some people think that certain races are inferior to others, that women should be treated differently than men, that gay men and lesbians are ultimately different from heterosexuals, that people with mental illnesses are dangerous, or that criminals won't ever be able to escape a life of crime.

These dangerous associations imbue genetic information with an unusually powerful, almost sinister feel. Reflecting these concerns, when the Human Genome Project was first established as a joint venture between the Department of Energy and the National Institutes of Health in 1990, there was already much discussion about the potential dangers that genetic information entailed. In response to these fears, a special program was established called the Ethical, Legal, and Social Issues Research Program. It was mandated by law that a total of 5 percent of all funding for human genome research would be set aside for this program.[19] Given that the sequencing of the genome ultimately totaled in the billions of dollars, this mandatory budget of 5 percent for research on implications of the genome was an unusually enormous sum for a research program that fell largely within the humanities and social sciences.

The fears we have about genetics are not necessarily misplaced; when we talk about genetics, we can quickly get into some rather treacherous topics. For example, research on human genetics in the first half of the 20th century was deeply connected with the study of eugenics. At that time, if you were a researcher studying human genetics, it's quite likely that you also self-identified as a eugenicist, given how closely the fields were linked back then.[20] Although the scientific study of eugenics was hastily abandoned following the rise of the Nazis and the Holocaust, today there are again new concerns about how genetic innovations may be applied in disturbing ways. For example, in 2013, Senator Rand Paul gave a speech about future genetic nightmares where he described events from the dystopian movie *Gattaca*. Although Paul's speech got more media coverage because it turned out that he had plagiarized it from the movie's Wikipedia page, his speech is also noteworthy for his assumptions that genetic research stands to usher in a society right out of *Brave New World*, where "the state select(s) for perfection." Paul asked, "Will we have the strength of character to resist a world where eugenics is practiced voluntarily? Are we prepared to select out the imperfect among us? In the process will we eliminate some part of our humanness, our specialness, when we seek perfection?"[21]

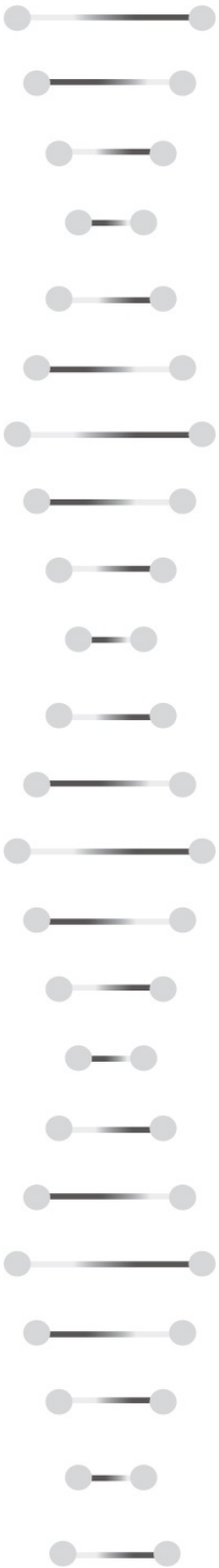
With the advent of new genetic engineering technologies such as CRISPR/Cas9, concerns about the proliferation of designer babies,[22] contentious political debates about the perceived dangers of genetically modified organisms, and the rise of direct-to-consumer genomics companies such as 23andMe, our concerns about dystopian genetic futures will only become more common.

The genomics revolution promises to change our lives in many exciting ways, but along with these genuine scientific advances, the revolution also

comes packaged with an enormous amount of unwarranted hype. Our genomes provide us with a grand vista from which to view ourselves and our world, but as long as we're peering through a set of distorted lenses, we're going to see things that aren't really there. Over the next several chapters, we're going to take a closer look at our mistaken assumptions about our genes, and gain a clearer understanding of how our genes actually influence us. We'll discuss my own experiences getting genotyped, and how my own psychological biases interfered with how I made sense of the feedback I received. We'll see that although discussions about our genes can arouse our darkest fears and prejudices, a closer look reveals in sharp relief that our DNA is not our destiny.

2.

How Genes Make You Who You Are



IT WAS A BAD CASE OF TEST ANXIETY THAT launched the field of genetics. A brilliant young student, Johann Mendel, aspired to become a schoolteacher near the town of Heinzendorf in Silesia (now Hynčice in the Czech Republic), where he had grown up. His family had great faith in his promise as a scholar, and his sister Theresia had loaned him her portion of the family estate to pay for his studies. But despite this support and encouragement, and his obvious brilliance, Mendel suffered an enormous anxiety attack during his oral examinations and failed the certification exam that would have qualified him as a teacher. Six years later, he gave up in the middle of his second attempt at the exam. Humiliated, he resigned himself to life as a monk at St. Thomas's Abbey in the nearby city of Brünn (now Brno), where he took on the name of Gregor. To Mendel's surprise, the monastery turned out to be an ideal place for his scientific studies because he had few distractions, access to the voluminous monastic library, and the support of the monastery's abbot, Cyrill Napp, who recognized that Mendel's skills for scientific study clearly outweighed his talents as a priest. Indeed, Napp was so taken by the passion and discipline of young Gregor that he ordered a new greenhouse be constructed for him to pursue his scientific interests. And it was here, in the gardens and greenhouse of the St. Thomas monastery, that Mendel conducted one of the most famous series of experiments in the history of science. He grew peas.[1]

Mendel sought to provide a quantitative foundation for one of the most poorly understood scientific questions. Why do offspring resemble their parents? It was so clear that they did, but the mechanisms behind this remained unknown. Although Mendel had earlier attempted to address this by breeding mice, the bishop had deemed it inappropriate for a celibate priest to be studying mice having sex, so he turned to breeding plants instead. He worked with a number of different species, but it was his eight-year experiment with peas, *Pisum sativum*, that earned him his later fame. During this period, Mendel would brush the pollen from one variety of pea onto another, about 29,000 times, thereby cross-fertilizing the varieties. He then recorded information about their offspring. The plants differed from each other across seven different traits: seed shape (either wrinkled or round), location of the flowers (at the tip or along the stem), seed color (green or yellow), seed coat (white or gray), shape of ripe pod (either inflated or pinched), unripe pod color (green or yellow), and height (tall or short). Mendel wanted to see what happened when you crossed, for example, a pea with a green pod with one with a yellow pod. You might expect that the colors would blend together to create a pod of intermediate color—say, one that was chartreuse. But he never found this; when he crossed the green peas with

yellow peas, the resulting second generation of peas was all yellow. Mendel then crossed the peas of this second generation with each other: yellow peas with other yellow peas. In doing this, and counting very carefully, he found that the subsequent generation produced peas that were either yellow or green, and with the highly specific proportion of three yellow peas for every one green one. This same ratio emerged for all of the seven different traits that he had studied, and it pointed to something profound that forever altered the way scientists understood heredity.

Mendel's experiments revealed that each plant inherited one "character," as he called them, from each of their two parents. Further, he identified that these characters came in one of two forms; they were either dominant or recessive. Recessive characters (such as the ones that create green pods) were only visible in the next generation if the offspring inherited the same recessive characters from both parents; otherwise, the next generation only displayed the dominant character (such as the ones that create yellow pods). Mendel signified these characters with a capital letter, A, if they were dominant, and a lower case letter, a, if they were recessive. This led to four different combinations in the offspring that Mendel's diligent counting revealed were equally likely: AA, Aa, aA, and aa. This labeling is still used today, and the characters that they refer to are now known as genes. These genes come in different versions (such as whether the gene is associated with a yellow or green pod), which are termed alleles.

It was in the garden of St. Thomas that Mendel had discovered the quantum nature of inheritance. Genes, and their corresponding traits, never blend—our parents' blood does not get mixed together—rather, genes segregate such that we inherit one copy of the gene from each parent. The genes always remain intact from generation to generation, like pearls on a string, and each parent passes down a particular collection of these pearls to their children. The specific combination of these pearls that we receive from our parents (that is, the alleles such as Aa or aa) are termed our genotypes. Although genotypes remain hidden from our view, they specify the kinds of proteins that are created in an organism. The set of observable characteristics of an organism, which are products of the proteins created by genotypes, is called a phenotype (e.g., whether the pea pod is actually green or yellow). This discovery laid the foundation of modern genetics.

Mendel realized from his results that he was onto something big, and he published his findings in 1866 in a 44-page article in the *Proceedings of the Natural History Society of Brünn*, a journal that was carried in the best libraries at the time. He also sent out 40 copies of his article to several leading scientists around the world. But the response that he got was virtual silence; few people read his article at the time, and of those who did, none of them seemed to fully

appreciate what Mendel had found. Charles Darwin was one of the scientists to whom Mendel sent a copy of his article, and he received it at a fortuitous moment. Darwin was being challenged by a Scottish engineer named Fleeming Jenkin, who pointed out that evolution could not possibly occur if traits blended together. A gazelle, say, that could run a little bit faster than the other gazelles would indeed be more likely to survive and pass on its traits to its offspring, but its offspring would inherit a running speed that was a mixture of one fleet parent and one slow one, thereby diluting the advantageous trait until it would no longer carry any selective advantage. Mendel's model of quantum inheritance showed that traits don't dilute over generations, and his findings served as a direct answer to Jenkin's criticism. Alas, it seems that Darwin never read the article that Mendel sent to him.

Mendel lived for another 18 years after the publication of his article, and he continued breeding experiments with a number of other plant species as well as bees, but he never again found the same kind of clear evidence for quantum inheritance that he had found with peas. He later had to give up his research completely when he became abbot of St. Thomas. At the time of his death, Mendel's research remained virtually unknown to science. It wasn't until 16 years after he had died that his work was rediscovered and he was christened the father of genetics. The posthumous rediscovery of Mendel's work, and his promotion to the pantheon of science, has made Mendel's life story a beacon of hope for all scientists who feel that their work is underappreciated.

DNA and the Making of Proteins

Our genes are stored in 23 pairs of chromosomes that reside inside the nuclei of almost all the cells in our bodies. When sperm and egg cells are produced, the 23 pairs of chromosomes are reduced by a process of meiosis into 23 single chromosomes in each sperm or egg cell. Each set of single chromosomes contains a unique shuffling and recombining of the genes that were contained in each original chromosomal pair. Like poker players, sperm and egg cells are basically dealt a unique set of genes from the deck of the complete set of chromosomes in your body. This is why siblings (aside from identical twins) are never duplicates of each other. On average, we inherit approximately half of our genetic code from each parent, yet it's a different combination for each sibling, so that siblings share about half of their unique genetic markers with each other. One of those 23 pairs of chromosomes determines our sex. Typically, women

inherit an X chromosome from each parent, so they have a pair of X chromosomes. Men, in contrast, typically inherit an X chromosome from their mother and a Y chromosome from their father.

Each of our chromosomes is a long unbroken string of deoxyribonucleic acid (DNA), which consists of two long polymer molecules that spiral around each other. Binding these two molecular strings together in a double helix are a series of the basic building blocks of DNA: the nucleotides, which are organic molecules that come in four different flavors (guanine, adenine, thymine, and cytosine), and are identified by the letters, G, A, T, and C. Each nucleotide is matched with its corresponding "spouse" on the other strand of DNA, such that G is always matched with C, and A is always matched with T. There are about 3 billion monogamous pairs of these nucleotides total in each of our cells. Just like the letters of the alphabet, which can be arranged into a nearly infinite set of possible words, these four nucleotides can be arranged into a nearly infinite set of possible combinations, typically several thousands of nucleotides long, which form our genes.

Genes function by leading to the "expression" or creation of proteins. When a gene is expressed, the double helix of DNA will unravel, much like a zipper unzipping, and will replicate a mirror image of itself on a strand of messenger RNA, a similar long polymer molecule that binds to the string of nucleotides of DNA. This messenger RNA then detaches from the DNA molecule and moves to another part of the cell to a ribosome, which is essentially a protein factory. There, the messenger RNA is translated into a unique protein. Amazingly, all the different proteins in our bodies, from the neurochemicals that course through our brains to the enamel in our teeth, come from the four nucleotides that constitute our DNA. It's the particular combination of the letters that determines the nature of the protein. In this way, DNA is very much a molecule of *information*, not unlike a string of computer code that carries instructions for how proteins can be made.

We have approximately 21,000 protein-coding genes lined up along our chromosomes; a number roughly similar to that of other mammals, yet curiously smaller than that of many plants, such as tomatoes, which have more than 30,000 genes.[2] This may not seem like a lot of genes to work with, especially since we share so many of the same genes with other species (we share approximately 98 percent of our genes with chimpanzees, and 92 percent with mice; even the lowly yeast shares about one-quarter of our genes).[3] Before the results of the Human Genome Project were announced in 2003, geneticists had always assumed that the actual number of human genes would be much higher. The