

Genome Tea Leaves

By Sheldon Krimsky

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GENETICS IS INCREASINGLY ENTANGLED with popular culture. Individuals are charting their genetic horoscopes and have been captivated by their genetic roots. Along with our DNA, our genes have become the ultimate “preexisting condition” — which can now allegedly be “read” via ancestry testing, prenatal screening, and medical genome scans. Even forensics has been transformed. In purporting to read what preexists — what is indelible — these gene-reading technologies have also at times been billed as the ultimate prognosticators of everything from health to wealth to likely time of death. The depth of our belief in genes has reached the ears of policy

The Age of Genomes

Tales from the Front Lines of Genetic Medicine

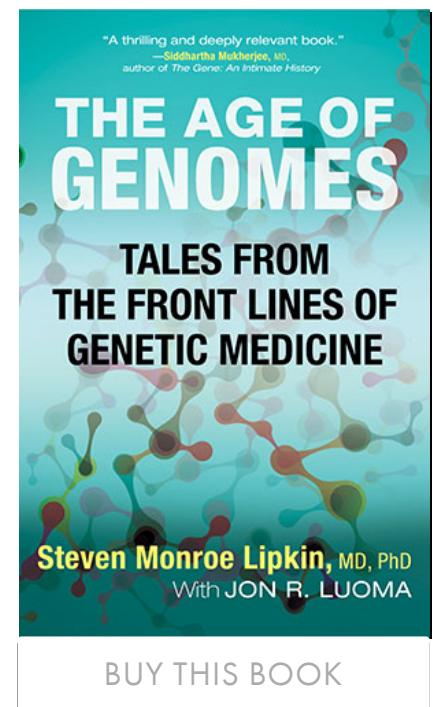
By Steven Monroe Lipkin and Jon R. Luoma

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makers, exemplified by adoption of a recent law forbidding genetic discrimination in health care and the work place. Significantly, this law drew support from across the political spectrum and passed in 2008 by a resounding vote of 414-1 in the House and 95-0 in the Senate.

Two recent books — Siddhartha Mukherjee's *The Gene: An Intimate History* and Steven Monroe Lipkin's *The Age of Genomes: Tales from the Front Lines of Genetic Medicine* — distill genetic knowledge for a general audience and explore what is at stake in genetic research. A professor at the Columbia University School of Medicine, Mukherjee mesmerized readers with his 2010 Pulitzer Prize-winning book *The Emperor of All Maladies: A Biography of Cancer*. That same unique style — personal, empathic, historical, and metaphorical, likened to that of a nonfiction novel — is on display here. In *The Age of Genomes*, Steven Monroe Lipkin, a clinical geneticist in New York, draws from his years in practice to bring a different kind of nuance to discussions of medical genetics.

Nuance is precisely what we need in order to move away from the naïve assumption that straightforward links exist between genes and complex diseases, and between genes and animal cognition or behavioral traits, such as intelligence and personality. Not only do these texts provide that subtlety, they ably demonstrate how, in most cases, far more



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The Gene

An Intimate History

By Siddhartha
Mukherjee

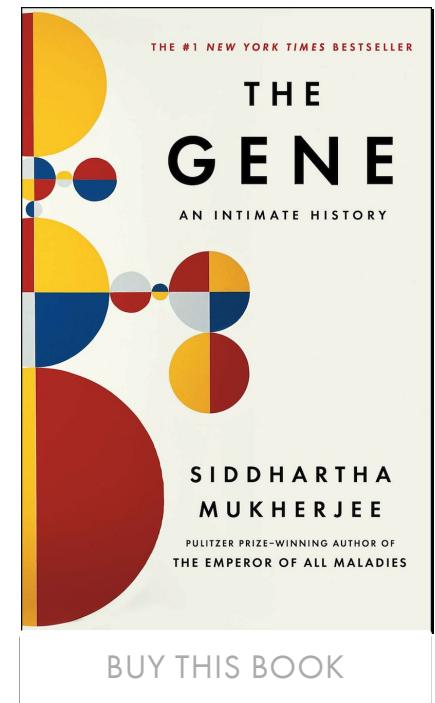
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complex multilevel interactions — that include but aren't limited to genes — are at play in disease and in behavior.

Taken together, these books also clarify the nature of the challenges the field of medicine faces in keeping up with, and embracing, the deluge of new research findings in genetics. Toward the end of this review, I'll probe the state of their relationship using the fight to treat cancer as an example.

Our contemporary landscape is rife with promises as we move from the era of the Human Genome Project to its many progeny, like the Precision Medicine Initiative and private ventures like 23andMe. The challenge for researchers and society at large is to walk a thin line; it is to capitalize on those promises while fully understanding the ethical challenges and limitations of the research — including the high costs inherent in personalized medicine, the specter of designer babies, and the always incomplete nature of causal explanations.

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In *The Gene*, Mukherjee's Bengali family life sets the stage for his focusing questions: where does the mental illness of three members of his extended family come from and why did his mother and her identical twin differ in so many

respects? This backdrop enables Mukherjee to viscerally and intimately ground his main topic: the science of heredity — and to take his readers through the evolution of the science.

The first half of the book represents a consensus history of the gene, taking us through Gregor Mendel's pea experiments and early views about the transmission of traits, the history of eugenics, the discovery of the structure of the DNA molecule, and the race to sequence the human genome. It ends with a rather bold declaration of genes as the master molecule: "If experimental biology was the 'new music,' then the gene was its conductor, its orchestra, its assonant refrain, its principal instrument, its score." The rest of the book presents the gene in less reductionist and more realistic terms as it functions in medicine and human behavior — including in gender, sexuality, intelligence, and illness. For instance, general intelligence, often represented as IQ, pretends to be a biological quality that is measurable and heritable, when in reality, Mukherjee notes, "it is [...] a meme masquerading as a gene." In other words, however we measure it, a test for general intelligence necessitates the use of cultural priorities in laying the foundation for the measurement — it is, thus, a meme, a cultural symbol or idea that is passed through generations, rather than a measurable genetic entity. This is not to say that certain aspects of

intelligence are uninfluenced by genes. Mental illness is similarly intertwined with culture. How and why it appears and reappears across generations in Mukherjee's family is, as noted above, one of his core questions. Multiple genes and complex interactions are at work, but with very low predictive value. Culture matters for their expression, and sometimes these illnesses yield unanticipated benefits: "the very genes that cause these illnesses can also, albeit in rare circumstances, potentiate a mystical form of creative urgency that is fundamentally linked to the illness itself." The same genes, in other words, can be correlated with disability and creativity depending on context.

By bringing the reader up to speed in this way on current understandings of genetics, Mukherjee attacks an outdated view of nature versus nurture, a dualism that continues to shape public attitudes about the causes of disease or behavior. "Nature" is considered to be the genes that you inherit, and "nurture" is everything else (upbringing, environment, nutrition, education, etc.). The first problem with this dualism is that it leaves out the womb. Exposure to toxins or to infinitesimal changes in natural or synthetic hormones in the womb can affect the health or gender identity of the offspring. The point is that genes are always interacting with the environment in the womb and beyond. "Nature versus nurture" represents a false dichotomy. We can all cite an

example of a heavy smoker who was not afflicted with lung cancer (in fact only about 15 percent of them are). Perhaps she had a more efficient genomically grounded ability to repair mutations than most do. Then again, that ability isn't fixed over time and can be affected by environmental factors. The environment isn't all-determining, and neither are genes. Not all women with the breast cancer genetic mutation will get breast cancer. Why? Again, the answer may be found in other protective genes or in a host of environmental exposures, or, most likely, a combination of both.

Mukherjee offers a nuanced approach for understanding and studying these multilayered interactions — one influenced by what's called a "complex systems interpretation of genetic causality." Consider twins like Mukherjee's mother and aunt who "share families, live in the same homes, typically attend the same school, often read the same books, are immersed in the same culture, and share similar circles of friends," and yet exhibit unmistakable differences. He attributes their differences to "unsystematic, idiosyncratic, serendipitous events." Even conjoined identical twins, like Abby and Brittany Hensel, have distinctly different personalities — Abby is considered the feisty, stubborn twin, who chooses orange juice for breakfast, while Brittany is the joker of the family who only drinks milk. It takes billions of genetic events

for a fertilized egg to form into a human being. For two separated twins, those events will create all the cells in their bodies, including brain cells, as well as the proteins that direct the development of the fetus. Why would we expect these billions of cell divisions and protein syntheses of two closely spaced fetuses to be absolutely identical? Not even their fingerprints are identical. And even for conjoined twins, distinct local events will create their two brains and the neural circuits that may then go on to impact personality.

This is where systems theory is evoked: “Genes can describe the form or fate of a complex organism in likelihoods and possibilities — but they cannot accurately describe the form or fate itself.” When Mukherjee is pushed to the limits of explanation, he appeals to metaphor to cultivate the reader’s intuition: “Genes form the threads of the web; the detritus that adheres to it transforms every web into a singular being.” In other words, our genes do not act alone — they are not self-actualizing. They provide a framework in conjunction with other processes that determine our physical characteristics or phenotypes. Whatever happened to the Central Dogma of molecular biology: genes encode RNA to build proteins? Mukherjee recasts it as: Genes encode RNAs to build proteins to sense environments that influence epigenomes that regulate genes (epigenomes are all the proteins and molecular pathways that affect the

expression of genes external to the DNA sequence).

For those readers with a modicum of genetics knowledge gleaned in high school or college, Mukherjee's book may contain some surprises. Consider, for instance, the rare but theoretically significant condition of children born anatomically and physiologically female while having the XY male chromosome in every cell of their body. This condition, called Androgen Insensitivity Syndrome, is caused by genetic mutations in the X chromosome, which prevent their bodies from processing the testosterone they produce. The result: A genetic male with female sex characteristics. Mukherjee also explains how your grandparents' environmental exposures can affect how your genes function. From historical events such as the much-studied Dutch Hunger Winter (1944–1945), we now know that our DNA only tells us part of the story of the human condition. In this example, not only were the starving, pregnant women and their fetuses affected, but depending on the fetus's period of gestation — the first three months of development being the most fragile — future grandchildren had an increased likelihood of heart disease and obesity. Proteins called histones are a likely mediating factor. Three billion base pairs of DNA are wrapped around these proteins and they can act as "switches" turning genes on and off. The point is that these switches — whether

they're in the on or off position — can be passed down to us from the DNA we inherit from our parents and grandparents. A person with type 1 diabetes might not make enough insulin because of a mutation in his pancreatic islet cells or because the switches that turn the cells' DNA on are defective. In either case, the patient is insulin deficient. The "causes" are different, but the end result is the same disease.

Mukherjee's gift for explaining science stands up to that of George Gamow, Stephen Jay Gould, or Lewis Thomas. He cuts through the technical complexity and lays bare fundamental ideas. However, even for someone as talented as Mukherjee, the pitfalls inherent in science communication are very real. A recent *New Yorker* excerpt (May 2, 2016) from his book elicited a strong reaction from a number of prominent scientists who claimed Mukherjee oversimplified the mechanisms of gene regulation. He failed to mention proteins (transcription factors) and RNA encoded by DNA, which are central to gene expression, although they are not part of the discussion of epigenetics, which was Mukherjee's goal in the article. In addition, he allegedly placed too much weight on histones as "genetic switches" that can be both inherited and affected by environmental exposures. His book may attract some of the same criticism. The fact is that providing intuitive understanding for the lay reader is often at odds with the nuances of the

actual science-in-the-making, but this doesn't mean that the attempt should not be made to illuminate the core principles.

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Steven Monroe Lipkin discusses genetics through a more focused lens, demonstrating the medical realities and applicability of the research Mukherjee examines. Exploring genetic diseases from the perspective of a clinical geneticist, he takes the reader through a Grand Rounds of clinical genetic abnormalities, and he frames his book by dividing these up into six "classes" of genetic disease — from those that can't be treated at all (Alzheimer's), to those that could be if we just knew a little more (late-onset diabetes), to those that affect other members of your family but not you (bipolar), to those that can be cured (like single-gene Gaucher disease). The two remaining classes he addresses: Genetic diseases that are not the effect of disease genes, but still might affect development (like inherited epigenetic tags); and genetic mutations found on tumors.

Beginning with simple monogenic abnormalities like Gaucher disease, which can be treated, he proceeds to more complex diseases involving more than one genetic mutation and probable multiple gene-gene interactions. Invoking an analogy of his own, Lipkin writes: "complex traits are a different

type of beast. They are more like a swarm of bees. Shooting bullets at a swarm of bees no matter how high precision the rifle, isn't going to do much good." It's a safe analogy and hard to dispute.

Alzheimer's is an example of precisely such a complex genetic disease, where identified mutations, or what are called genetic markers, indicate a risk but not a cause. The stakes in finding a treatment or at least delaying the symptoms are huge — the societal cost of caring for the current 5.4 million US Alzheimer's patients is estimated to be \$325 billion a year, and the cost is expected to reach over half a trillion dollars by 2025. How many diseases are like Alzheimer's? Lots.

With the development of prenatal genetic diagnosis (also known as preimplantation genetic diagnosis, or PGD, because it is linked to in vitro fertilization), which can now be done by extracting fetal cells from a pregnant mother's blood, women (and their families) are the locus or agents of choice: they have to choose whether they wish to carry to term a severely genetically damaged fetus, or indeed one who may have a certain probability of disease. As we gain more knowledge of how the genes we inherit can affect our health, the question regarding how far we push for PGD to eliminate probabilistic risks, including those for adult onset diseases like Alzheimer's, becomes

ever more clinically real and morally pressing. And while PGD has not met with societal disapproval thus far, new methods of gene editing could cross an ethical boundary: human germline gene therapy, for instance, could open the door to “designer babies” — which will begin innocently enough with “gene disease-free” babies, but then fall into slippery slope terrain.

Lipkin brings a personal face to these issues by discussing the anguish of parents who will do almost anything to avoid a genetically diseased child. The British have already officially approved a technique for preventing mitochondrial abnormalities in the mother’s egg from reaching her newborn. This involves replacing the mitochondrial cells of a prospective mother with those of a donor, resulting in a so-called three-genome baby. It sounds straightforward, but once PGD in conjunction with in vitro fertilization and gene editing become available for preventing genetic diseases, then genetic enhancement or personalized eugenics may be unstoppable. GenePeeks is a company that matches donor egg or sperm with that of a prospective parent to avoid more than a thousand serious conditions that could arise when two recessive genes meet. As they claim on their website, “we are all silent carriers of disease-causing mutations.” It is estimated that humans carry about 400 disease-causing recessive mutations,

but only on average two that are lethal to a child.

For me, the most compelling chapter in Lipkin's book discusses a cancer patient whose tumors were exhibiting proteins encoded by genes with "spelling errors" — another way of saying that the genes have mutations. It is here that we begin to learn how medical education is failing to keep up with research. To understand illness, according to Lipkin, students and doctors must grasp the interacting systems of anatomy, cell biology, and genetics. They must understand the technology that makes the latest developments possible — and also understand the results and limitations of the data it produces. As some of his fellow clinical geneticists have put it in a recent publication:

The complexity of clinical sequencing reports might be prone to misinterpretation by nongeneticist physicians, leading to over- or underestimation of the disease risk associated with a given variant. Such results might prompt physicians to order an expensive cascade of follow-up diagnostic tests, each with its own potential complications, risks to the patient, and costs.

However, even Lipkin — a clinical geneticist at the cutting edge of his field — shows himself to be at risk of falling behind. When discussing

cancer research, he embeds himself in the orthodoxy from which Mukherjee, for instance, is slowly departing. This is clear when he writes: “Since we now know that cancer is fundamentally a disease of damaged DNA, this knowledge is changing the paradigm that physicians and scientists use to approach the diagnosis and treatment of cancer.” But this approach to understanding cancer is currently disputed. Robert Weinberg, professor of cancer research at MIT, and world authority on the causes of cancer, acknowledges that the somatic mutation theory of cancer — “DNA mutations in a single cell cause cancer” — is far too simplistic and that a more realistic approach lies in a systems biology paradigm that involves understanding “intercellular signaling channels.” Other biologists even question whether mutations are a necessary condition for cancer. According to one view, cancer is a disease of cells gone awry; in another, it is a breakdown of tissue organization. The latter view is supported by evidence that tumor cells isolated from an animal with cancer, when transplanted to an animal without cancer, become normalized, suggesting tissue interactions (such as a breakdown of cell to cell communication across layers of tissue), and not mutagenic cells, are the cause. As scientists move away from the magic bullet approach to attacking cancer cells, the challenge is to find new therapies based on tumor ecology — the microenvironment surrounding the tumor —

rather than to find oncogenes (genes that have the potential to cause cancer).

But for clinical geneticists, mutations are the fundamental markers for understanding disease. In terms of tackling cancer, this focus on mutations — fueled by the rapid growth and promise of sequencing technology — has hindered progress in systems biology. At a 2012 meeting of cancer specialists at the World Oncology Forum in Lugano, Switzerland, the general consensus was that, even after 40 years, we are not winning the war against cancer. Lipkin provides an insider's look at how personalized gene sequencing is increasingly driving cancer therapy to its detriment. Personalized gene sequencing has indeed proven successful for single gene diseases like Gaucher disease or cystic fibrosis. But for complex diseases like cancer and autism, causal explanation, much less for prediction, remains a pipe dream.

Though Lipkin does not embrace the path Weinberg and Mukherjee promote with systems theory and systems biology, he leans in the right direction by taking us through a tapestry of actual cases in clinical genetics and arguing for skepticism. He makes clear that unless you are carrying a monogenic mutation, don't count on predictive genetic sequences — or, as he puts it: "if a doctor or genetic professional tells you he or she knows what is going to happen

[from your genome tea leaves,] find another health-care provider."



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