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RUNS IN THE FAMILY

New findings about schizophrenia rekindle old questions about genes and identity.

BY SIDDHARTHA MUKHERJEE

The author and his father have seen several relatives succumb to mental illness.

In the winter of 2012, I travelled from New Delhi, where I grew up, to Calcutta to visit my cousin Moni. My father accompanied me as a guide and companion, but he was a sullen and brooding presence, lost in a private anguish. He is the youngest of five brothers, and Moni is his firstborn nephew—the eldest brother's son. Since 2004, Moni, now fifty-two, has been confined to an institution for the mentally ill (a "lunatic home," as my father calls it), with a diagnosis of schizophrenia. He is kept awash in antipsychotics and sedatives, and an attendant watches, bathes, and feeds him through the day.

My father has never accepted Moni's diagnosis. Over the years, he has waged a lonely campaign against the psychiatrists charged with his nephew's care, hoping to convince them that their diagnosis was a colossal error, or that Moni's broken psyche would somehow mend itself. He has visited the institution in Calcutta twice—once without warning, hoping to see a transformed Moni, living a secretly normal life behind the barred gates. But there was more than just avuncular love at stake for him in these visits. Moni is not the only member of the family with mental illness. Two of my father's four brothers suffered from various unravellings of the mind. Madness has been among the Mukherjees for generations, and at least part of my father's reluctance to accept Moni's diagnosis lies in a grim suspicion that something of the illness may be buried, like toxic waste, in himself.

Rajesh, my father's third-born brother, had once been the most promising of the Mukherjee boys—the nimblest, the most charismatic, the most admired. But in the summer of 1946, at the age of twenty-two, he began to behave oddly, as if a wire had been tripped in his brain. The most obvious change in his personality was a volatility: good news triggered uncontained outbursts of joy; bad news plunged him into inconsolable desolation. By that winter, the sine curve of Rajesh's psyche had tightened in its frequency and gained in its amplitude. My father recalls an altered brother: fearful at times, reckless at others, descending and ascending steep slopes of mood, irritable one morning and overjoyed the next. When Rajesh received news of a successful performance on his college exams, he vanished, elated, on a two-night excursion, supposedly "exercising" at a wrestling camp. He was feverish and hallucinating when he returned, and died of pneumonia soon afterward. Only years later, in medical school, did I realize that Rajesh was likely in the throes of an acute manic phase. His mental breakdown was the result of a near-textbook case of bipolar disorder.

Jagu, the fourth-born of my father's siblings, came to live with us in Delhi in 1975, when I was five years old and he was forty-five. His mind, too, was failing. Tall and rail thin, with a slightly feral look in his eyes and a shock of matted, overgrown hair, he resembled a Bengali Jim Morrison. Unlike Rajesh, whose illness had surfaced in his twenties, Jagu had been troubled from his adolescence. Socially awkward, withdrawn from everyone except my grandmother, he was unable to hold a job or live by himself. By 1975, he had visions, phantasms, and voices in his head that told him what to do. He was still capable of extraordinary bursts of tenderness—when I accidentally smashed a beloved Venetian vase at home, he hid me in his bedclothes and informed my mother that he had "mounds of cash" stashed away, enough to buy "a thousand" replacement vases. But this episode was symptomatic: even his love for me extended the fabric of his psychosis and confabulation.

PHOTOGRAPH BY DAYANITA SINGH

Unlike Rajesh, Jagu was formally diagnosed. In the late nineteen-seventies, a physician in Delhi examined him and determined that he had schizophrenia. But no medicines were prescribed. Instead, Jagu continued to live at home, half hidden away in my grandmother's room. (As in many families in India, my grandmother lived with us.) For nearly a decade, she and my father maintained a fragile truce, with Jagu living under her care, eating meals in her room and wearing clothes that she stitched for him. At night, when Jagu was consumed by his fears and fantasies, she put him to bed like a child, with her hand on his forehead. She was his nurse, his housekeeper, his only friend, and, more important, his public defender. When my grandmother died, in 1985, Jagu joined a religious sect in Delhi and disappeared, until his death, a dozen years later.

We lost contact with Moni, too. He shuttled between schools and dropped out of college. The commanders in his head became stronger and more insistent. In 2004, he was beaten up by a group of goons, ostensibly for urinating in a public garden. (An internal voice had instructed him, "Piss here; piss here.") In the winter of that year, after yet another breakdown with hallucinations and hissing internal voices, he was institutionalized in Calcutta.

When my father and I visited Moni in 2012, I had not seen him for nearly two decades. Even so, I expected to recognize him. But the person I met in the visiting room bore such little resemblance to my memory of my cousin that—had his attendant not confirmed the name—I could easily have been meeting a stranger. He had aged beyond his years. His speech, once effusive and rapid, was hesitant and fitful; the words emerged with a sudden, surprising force, as if he were spitting out pips of food that had been put into his mouth.

The most memorable feature of his illness, though, was not the storm within his mind but the lull in his eyes. The word *moni* means "gem" in Bengali, but in common usage it also refers to something ineffably beautiful: the shining pinpricks of light in each eye. But this was precisely what was missing in Moni. The twin points of light in his eyes had dulled and nearly vanished, as if someone with a minute brush had painted them gray.

That schizophrenia runs in families was evident even to the person who first defined the illness. In 1911, Eugen Bleuler, a Swiss-German psychiatrist, published a book describing a series of cases of men and women, typically in their teens and early twenties, whose thoughts had begun to tangle and degenerate. "In this malady, the associations lose their continuity," Bleuler wrote. "The threads between thoughts are torn." Psychotic visions and paranoid thoughts flashed out of nowhere. Some patients "feel themselves weak, their spirit escapes, they will never survive the day. There is a growth in their heads. Their bones have turned liquid; their hearts have turned into stone. . . . The patient's wife must not use eggs in cooking, otherwise he will grow feathers." His patients were often trapped between flickering emotional states, unable to choose between two radically opposed visions, Bleuler noted. "You devil, you angel, you devil, you angel," one woman said to her lover.

Bleuler tried to find an explanation for the mysterious symptoms, but there was only one seemingly common element: schizophrenic patients tended to have first-degree relatives who were also schizophrenic. He had no tools to understand the mechanism behind the heredity. The word "gene" had been coined just two years before Bleuler published his book. The notion that a mental illness could be carried across generations by unitary, indivisible factors—corpuscles of information threading through families—would have struck most of Bleuler's contemporaries as mad in its own right. Still, Bleuler was astonishingly prescient about the complex nature of inheritance. "If one is looking for '*the* heredity,' one can nearly always find it," he wrote. "We will not be able to do anything about it even later on, unless the single factor of heredity can be broken down into many hereditary factors along specific lines."

In the nineteen-sixties, Bleuler's hunch was confirmed by twin studies. Psychiatrists determined that if an identical twin was schizophrenic the other twin had a forty-to-fifty-per-cent chance of developing the disease—fifty-fold higher than the risk in the general population. By the early two-thousands, large population studies had revealed a strong genetic link between schizophrenia and bipolar disorder. Some of the families described in these studies had a crisscrossing history that was achingly similar to my own: one sibling affected with schizophrenia, another with bipolar disorder, and a nephew or niece also schizophrenic.

"The twin studies clarified two important features of schizophrenia and bipolar disorder," Jeffrey Lieberman, a Columbia University psychiatrist who has studied schizophrenia for thirty years, told me. "First, it was clear that there wasn't a single gene, but dozens of genes involved in causing schizophrenia—each perhaps exerting a small effect. And, second, even if you inherited the entire set of risk genes, as identical twins do, you still might not develop the disease. Obviously, there were other triggers or instigators involved in releasing the illness." But while these studies established that schizophrenia had a genetic basis, they revealed nothing about the nature of the genes involved. "For doctors, patients, and families in the schizophrenia community, genetics became the ultimate mystery," Lieberman said. "If we knew the identity of the genes, we would find the causes, and if we found the causes we could find medicines."

In 2006, an international consortium of psychiatric geneticists launched a genomic survey of schizophrenia, hoping to advance the search for the implicated genes. With 3,322 patients and 3,587 controls, this was one of the largest and most rigorous such studies in the history of the disease. Researchers scanned through the nearly seven thousand genomes to find variations in gene segments that were correlated with schizophrenia. This strategy, termed an "association study," does not pinpoint a gene, but it provides a general location where a disease-linked gene may be found, like a treasure map with a large "X" scratched in a corner of the genome.

The results, reported in 2009 (and updated in 2014) in the journal *Nature*,

were a dispiriting validation of Bleuler's hunch about multiple hereditary factors: more than a hundred independent segments of the genome were associated with schizophrenia. "There are lots of small, common genetic effects, scattered across the genome," one researcher said. "There are many different biological processes involved." Some of the putative culprits made biological sense—if dimly. There were genes linked to transmitters that relay messages between neurons, and genes for molecular channels that move electrical signals up and down nerve cells. But by far the most surprising association involved a gene segment on chromosome 6. This region of the genome—termed the MHC region—carries hundreds of genes typically associated with the immune system.

"The MHC-segment finding was so strange and striking that you had to sit up and take notice," Lieberman told me. "Here was the most definitive evidence that something in the immune system might have something to do with schizophrenia. There had been hints about an immunological association before, but this was impossible to argue with. It raised an endlessly fascinating question: what was the link between immune-response genes and schizophrenia?"

Lieberman pulled out a figure from the paper to illustrate the strength of the association. One method of plotting the results of a gene-association study is called a Manhattan plot, in which the height of a bar corresponds to the strength of the risk for the disease. In the schizophrenia plot, the segment on chromosome 6 loomed over all other contenders—about twice the height of most of the other risk-conferring gene segments. The MHC region, the central repository of most of our immune-system genes, was like a lone skyscraper towering over the skyline of a newly built metropolis.

The Delhi of my childhood was a low-rise city. In the nineteen-sixties, my father, having clambered through the ranks of a Japanese multinational company (it was a folie à deux; he spoke incomprehensible English, and his managers didn't understand any), had built himself a sizable two-story house, a far step from the two-room flat in Calcutta that he had shared with his four brothers and his mother after Partition. The house, he believed, would be his ticket to firm middle-class respectability, but a dyslexic neighborhood sign painter, hired on the cheap to paint "MUKHERJEE" by the front door, had, to my father's endless chagrin, reversed the letter "J," so that its tail curled to the right, like the Greek *τ*. The incongruous letter remained there throughout much of my childhood—a discomfiting advertisement to the world that not everything inside the house was quite normally aligned.

A memory: It is 1981 or 1982, and I am eleven or twelve. My father has returned from a business trip. It is one of those blistering afternoons when the ceiling fans seem merely to slosh heat around the room. Two of our neighbors are waiting for him. The air seems tense with anxiety.

My father enters the living room, and the men talk to him for a few minutes. Their voices rise, and their words sharpen. I can make out the jagged contours of most of the sentences, even through the walls of the adjacent room, where I am supposed to be doing homework. Jagu has borrowed money from both of these men—not large sums, but enough to bring them to our house, demanding repayment. He told one of the men that he needed the cash for medicine (he has never been prescribed any), and the other that he needed it to buy a train ticket to Calcutta to visit his other brothers (no such trip had been planned; it would be impossible for Jagu to travel alone). "You should learn to control him," one of the men says.

My father listens silently, but I can feel a meniscus of rage rising in him, coating his throat with bile. He walks to the steel closet, where we keep the household cash, and brings it to the men, making a point of not bothering to count the notes. They should keep the change.

By the time the men leave, I know that there will be a bruising altercation. With the instinctual certainty of animals that run uphill before a tsunami, our cook has left the kitchen to summon my grandmother. The tension between my father and Jagu has been building for a while: Jagu's behavior at home has been particularly disruptive in recent weeks—and this episode seems to have pushed my father over some edge. A fragile varnish of class and normalcy has cracked.

He walks into Jagu's room and yanks him off the bed. Jagu wails desolately, like a child who is being punished for a transgression that he does not understand. My father is livid, glowing with anger, dangerous. He shoves Jagu across the room. It is an inconceivable act of violence for him; he has never raised a hand. My mother is in the kitchen, crying. I watch the scene rise to an ugly crescendo from behind the living-room curtains, as if watching a film in slow motion.

And then my grandmother emerges from her room, glowering like a she-wolf. She is screaming at my father, doubling down on his violence. Her eyes are alight like coals. *Don't you dare touch him*.

"Get out," she hisses to Jagu, who retreats quickly behind her.

I have never seen her more formidable. Her Bengali furls backward toward its village origins. I can make out some words, thick with accent and idiom: *womb, wash, taint*. When I piece the sentence together, its poison is remarkable: *If you hit him, I will wash my womb with water to clean your taint,* she says. *I will wash my womb*.

My father is frothing with tears now. His head hangs heavily. *Wash it,* he says under his breath, pleadingly. *Wash it, clean it, wash it.*

When Beth Stevens began work as a postdoctoral fellow at Stanford University, in 2004, she was not interested in studying schizophrenia or bipolar disorder. She was fascinated by the pinpricks of light in eyes.

The human eye is born restless. Neural connections between the eyes and the brain are formed long before a child is born, establishing the wiring and the circuitry that allow her to begin visualizing the world the minute she emerges from the womb. Long before

the eyelids open, during the early development of the visual system, waves of spontaneous activity ripple from the retina to the brain, like dancers running through their motions before a performance. These waves reconfigure the wiring of the brain—rehearsing its future circuits, strengthening and loosening the connections between neurons. (The neurobiologist Carla Shatz, who discovered these waves of spontaneous activity, wrote, "Cells that fire together, wire together.") This fetal warmup act is crucial to the performance of the visual system: the world has to be dreamed before it is seen.

During this rehearsal period, synapses between nerve cells are generated in great excess, to be pruned back during later development. The elimination of synaptic connections, which results in the constant refinement of neural circuits, like the soldering and resoldering of wires on a circuit board, is not a feature unique to the visual system. Throughout the brain—particularly in the parts involved in cognition, memory, and learning—synapse pruning continues into our first three decades, which suggests that it may be responsible, in part, for the starburst of adaptive learning that characterizes the first decades of human life. We are hardwired not to be hardwired, and this anatomical plasticity may be the key to the plasticity of our minds.

In the winter of 2004, having joined the laboratory of Ben Barres, a neuroscientist at Stanford, Stevens began to study the pruning of synapses in the visual system. "When I began my work in Ben's lab, little was known about how specific synapses are eliminated," she told me. "The pruning phenomenon was thought to be quite general." There was evidence of synapse pruning in the cortex of the brain during learning, cognition, and the formation of memories. But Stevens and Barres focussed their attention on visual neurons, because they were the easiest to study: the eye would be the eye to the brain.

In 2007, they announced a startling discovery. Stevens was trying to identify the proteins that recognized and eliminated neuronal synapses during visual development. "The strangest finding was that a protein that usually tags and removes pieces of dead cells, bacterial remnants, or cellular debris was also being reworked to tag and remove the synapses," she said. Mice designed to lack tagging proteins—called complement proteins—had problems both in clearing cellular debris and in tagging and pruning their synapses.

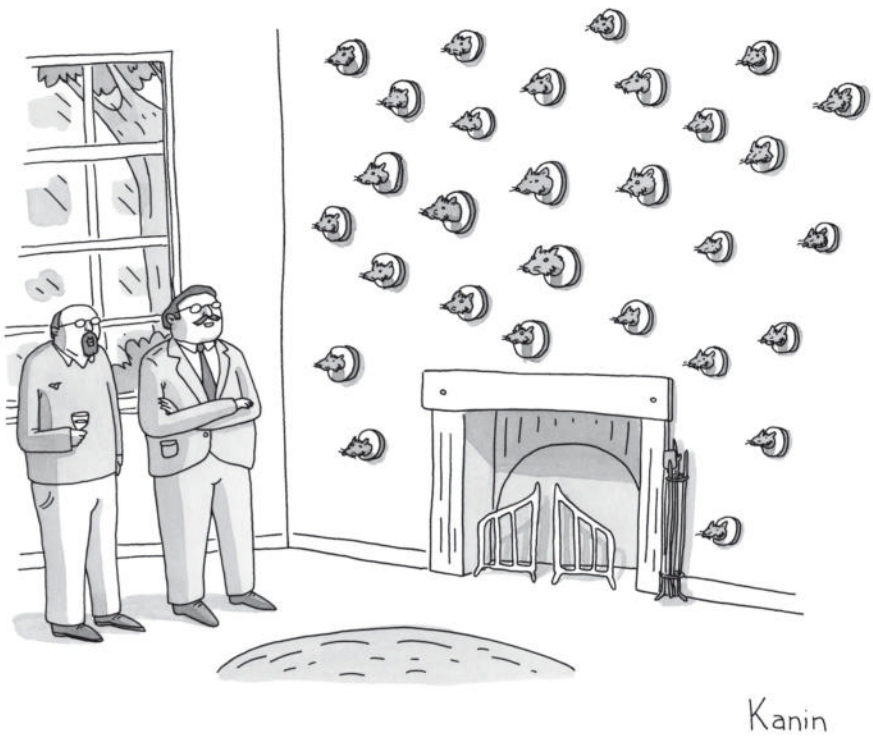
The Stevens and Barres study, published in the journal *Cell* in 2007, documented one of the most arresting instances of repurposing in biology: a protein designed to ticket germs and junk for destruction had been co-opted by the nervous system to ticket synapses for destruction. "It reinforces an old intuition," my psychiatrist friend Hans, in Boston, told me. "The secret of learning is the systematic elimination of excess. We grow, mostly, by dying."

The following year, Stevens moved to Boston Children's Hospital, to set up her own lab. When I visited her on a recent icy March morning, the lab was thrumming. Graduate students were folded over microscopes, like half-open books. One woman sat on her bench determinedly mashing a freshly biopsied fragment of a human brain into individual cells so that she could grow them in a tissue-culture flask.

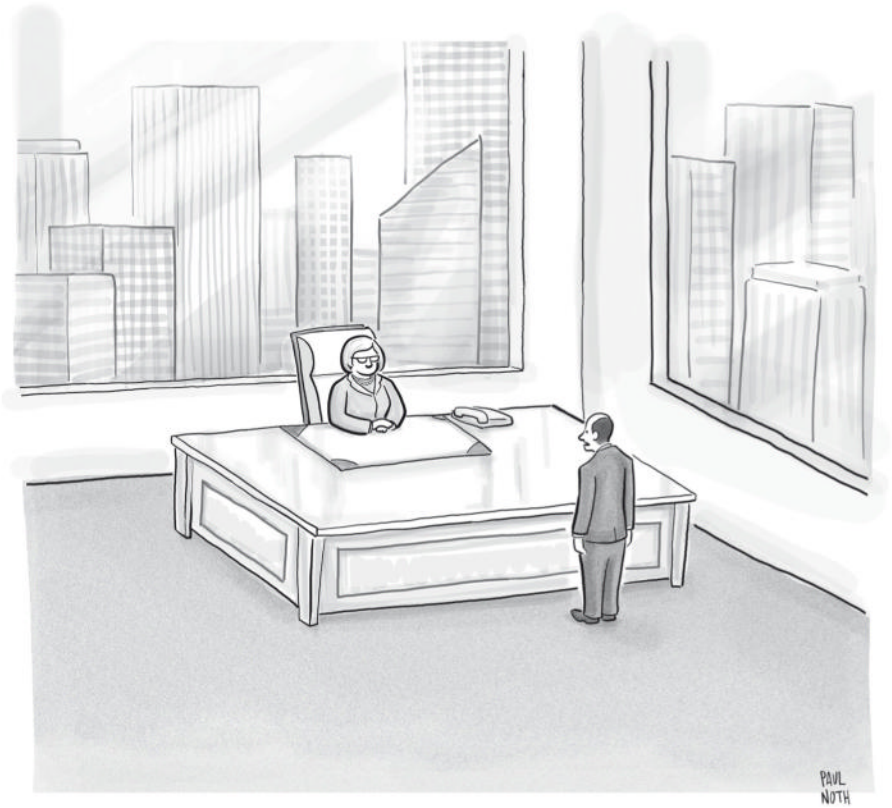
There is something effortlessly kinetic about Stevens: as she speaks, her hands and fingers trace the arcs of ideas, forming and unforming synapses in the air. "The questions we took on in the new lab were direct continuations of the questions that I had at Stanford," she said. "Once we had recognized that immunological proteins can tag and mark synapses for pruning, we asked, What process does the actual pruning? Who does the synapse editing?"

By 2012, Stevens and her students had identified the editor. Specialized cells known as microglia were well established as scavengers of the nervous system: spidery and many-fingered, they had been seen crawling around the brain, scrounging for debris, and their role in eliminating pathogens and cellular waste had been known for decades. But Stevens also found them coiled around synapses that had been marked for elimination. She leaned into her computer screen to show me an image of one: a twelve-limbed microglial cell wrapped around the body of a neuron, eating synapses, presumably, for lunch.

Stevens's data pointed to a new role for these cells: they were the pruners of the brain's maturing circuits—their "constant gardeners," as one report put it. "Once we knew about the involvement of the microglia, all sorts of questions popped



"Pound for pound, I'm the most successful hunter I know."



"But I already asked the other parent company. They told me to ask you."

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up," Stevens said. "How does a microglial cell know which synapses to eliminate? In part, because they are tagged by these immune proteins, yes—but what marks one synapse for elimination and not another? We know that synapses compete against one another, and the strongest synapse wins. But how does the weakest synapse get tagged for pruning? The lab is now working on all these questions. It's opened up a whole new universe."

A WINDBLOWN CORRIDOR—SO frigid in early March that the road turns bone white with ice crystals—separates the glass tower that houses Beth Stevens's laboratory from Harvard Medical School's Department of Genetics. In 2010, largely unaware of Stevens's studies on synapse pruning, Steve McCarroll, a geneticist, became fascinated by the genetic association between schizophrenia and the immune system.

McCarroll, a disarmingly boyish forty-five-year-old, develops tools to understand human genetics. He is the archetypal fox to Stevens's hedgehog: where Stevens has spent a decade gnawing at the roots of a single question—how and why synapses are pruned in the brain—McCarroll roams widely, inventing new techniques for studying genes that can be applied across a range of biological problems. "I study how variations in the human genome can produce the fascinating biological variations that we see among humans every day," McCarroll told me. "The link between the MHC region and schizophrenia was one of the strongest links in psychiatric genetics. But it was also the most puzzling: Why was an immune-response region so potently shaping the risk of a mental illness? What was the connection between the immunity and schizophrenia?" McCarroll assigned the problem to Aswin Sekar, a twenty-four-year-old student in his lab who was working toward an M.D.-Ph.D. at Harvard. "Geneticists considered it an almost intractable problem, but Aswin wanted something substantial—a real puzzle to crack."

I met Sekar for coffee at a cafeteria near McCarroll's lab. Bleary-eyed from an all-night shift in the I.C.U.—having finished his Ph.D. work, Sekar has returned to his medical studies—he apologized for his incoherence, then proceeded to give me the most fiercely coherent tutorial on psychiatric genetics that I have ever received. The MHC region is, perhaps, the most notorious segment of the human genome—"a gene mapper's nightmare," as Sekar described it. Human immunity depends on diversity: the thousands of pathogens that have invaded our bodies in the past have forced us to evolve a vast repertoire of immune-response genes, including some genes with dozens of variants. Sekar's job was to sift through these, trying to identify the gene variants that correlated with the risk of schizophrenia. If the gene-association study of 2009 had provided a broad aerial view of the neighborhood where the schizophrenia gene might be found, Sekar was the dogged gumshoe, travelling door to door with a spiral notebook in an attempt to track down the culprit.

Three years ago, Sekar and McCarroll found a lead. Buried within the MHC segment are two genes called C4A and C4B. The two genes are nearly identical: they likely descended from a common ancestor millions of years ago, and now sit cheek by jowl on the genome; together, they're called C4 genes, and they come in four common variants. Using molecular techniques developed in McCarroll's laboratory, Sekar discovered how the four variants could generate different amounts of the C4A and C4B proteins in the brain. On a December afternoon in 2013, during his winter break, Sekar sprawled on the couch with a laptop computer in his apartment, in Boston, and analyzed data from more than sixty-four thousand schizophrenia patients and controls, gathered by dozens of investigators in twenty-two countries. (The data are stored in a central repository that schizophrenia researchers can access remotely.) He began to map the relationship between the four C4-gene variants and the risk of schizophrenia. The result was striking: the risk of schizophrenia correlated powerfully with the inheritance of the C4 gene variant—particularly C4A. The more C4A protein a gene variant seemed to produce, the more common that variant was among schizophrenic patients.

Sekar e-mailed the data to McCarroll on the evening of December 31st.

"We had friends for New Year's Eve dinner that night, and the doorbell had just rung when the e-mail popped up," McCarroll recalled. "Of course, I barely spoke to the guests. It was an unbelievable result. A kid in his twenties walks into a lab, defines the variations in one of the most complex regions of the human genome, and shows how the variants might underlie the risk of schizophrenia. Data that had puzzled so many people for so many years suddenly seemed to make sense."

By now, the C4A gene had become an obsession for Sekar and McCarroll. What did the gene do? Why were variants in this gene associated with the risk for schizophrenia? The molecular identity of the C4A gene was particularly tantalizing. C4A, they knew, encodes a protein used by the immune system to recognize, tag, and eliminate cellular debris. It was, in short, intimately linked to the same immunological factors that Beth Stevens, across the street, had implicated in synaptic pruning.

Sekar and McCarroll soon launched a series of collaborative experiments with Beth Stevens to determine how C4A might be involved in synapse editing, and how synapse editing, in turn, might be linked to schizophrenia. They were joined by Mike Carroll, an immunologist, who had long studied C4's role in immune diseases. In human-brain tissues and in neurons cultured in flasks, they found that the C4 protein accumulated abundantly at synapses; in mice, this accumulation occurred almost precisely at the time that pruning begins. Mice that lacked the C4 gene underpruned the synapses in parts of their brain, which suggested a direct connection between the gene and pruning. Sekar confirmed that the C4A was more abundant in the brains of schizophrenic patients than in normal brains. The increase in C4A levels in schizophrenic patients was most significant in the parts of the brain involved in cognition, planning, and thinking, the functions that are most impaired in people with schizophrenia, and less noticeable in parts of the brain that control balance, posture, and speech, aspects that remain relatively intact in those with the disease.

A magnificently simple theory began to convulse out of the results. Perhaps C4A, like the other immunological factors that Stevens had identified in synapse pruning, marks neuronal synapses destined to be eliminated during normal brain development. During the maturation of the brain, microglia recognize these factors as tags and engulf the tagged synapses. Variations in the C4A gene cause different amounts of the C4A protein to be expressed in the human brain. The overabundance of C4A protein in some people contributes to an excessively exuberant pruning of synapses—thereby decreasing the number of synapses in the brain, which would explain the well-established fact that schizophrenic patients tended to have fewer neuronal connections. That the symptoms of schizophrenia break loose during the second and third decades of life makes sense, in retrospect: adolescence and early adulthood are periods when synaptic pruning reaches a climax in the regions of the brain that govern planning and thinking.

Schizophrenia, as McCarroll put it, "may be a disease of overpruning." Synapses that should have been preserved get cut, like a garden that has been sheared back too aggressively in the winter. "The C4A paper is one of the most important papers in schizophrenia in our times, because it identifies a pathway and provides a mechanism," Lieberman said. "It opens a black box. Now we have to figure out how overpruned synapses cause all the diffuse symptoms of the disease—the psychosis, the cognitive collapse, the emotional emptiness, and the withdrawal."

When people think of heredity in a colloquial sense, they think about the inheritance of unique features across generations: the peculiar shape of a father's nose or the susceptibility to an unusual illness that runs through a family. But the conundrum that heredity addresses is really much more general: What is the nature of instruction that allows an organism to build a psyche, or a nose—*any* nose—in the first place? The C4-gene variant that contributes to schizophrenia is the same gene that, in all likelihood, is used by the brain to prune synapses and thus enable cognition, the tethering of thoughts to realities, and adaptive learning. Push the activity of the gene beyond some point, and Bleuler's threads of association break; a mind-demolishing illness is unleashed. Swerve too far in the other direction, and we lose our capacity for adaptive learning; the blooming, buzzing confusions of childhood—its naïve, unshorn circuits—are retained. Our unique selves must live in some balanced state between overedited and underedited brain circuits, between overpruned and underpruned synapses.

One night in 1946, Rajesh came home from college with a riddle, a mathematical puzzle. The three younger brothers went at it, passing it back and forth like an arithmetic soccer ball. They were driven by the rivalry of siblings, the fragile pride of adolescence, the terror of failure in an unforgiving city. I imagine the three of them—twenty-two, sixteen, thirteen—each splayed in a corner of the pinched room, each spinning fantastical solutions, each attacking the problem with his distinctive strategy. My father: grim, purposeful, bullheaded, methodical, but lacking inspiration. Jagu: unconventional, oblique, but unfocussed. Rajesh: thorough, inspired, disciplined, often arrogant. Night fell, and the puzzle was still not solved. But, unlike his brothers, Rajesh stayed up all night. He paced the room, scribbling solutions and alternatives. By dawn, he had cracked it. He wrote the solution on four sheets of paper and left it by the feet of one of his brothers.

There is a trope in popular culture of the "crazy genius," a mind split between madness and brilliance, oscillating between the two states at the throw of a single switch. But Rajesh had no switch. There was no split or oscillation, no pendulum. The magic and the mania were perfectly contiguous—bordering kingdoms requiring no passports. They were part of the same whole, indivisible. It is tempting to romanticize psychotic illness, so let me emphasize that the men and women with these mental disorders experience terrifying

cognitive, social, and psychological disturbances that send gashes of devastation through their lives; I know this story as intimately as anyone.

The night of the math puzzle is imprinted in the lore of my family. What happened next is not. Years later, my father told me of the week of terror that followed. Rajesh's sleepless night turned into a second sleepless night, then a third. The all-nighter had tipped him into a burst of fulminant mania. Or perhaps it was the mania that came first and spurred the all-night marathon of problem solving and the solution. In any event, he disappeared and could not be found for some days. My grandmother, hoping to prevent future breakdowns, banned puzzles and games from the house. For Rajesh, it was a portent of the future—the first of many such breakdowns to come.

One inevitable fantasy inspired by the identification of genes for mental illness is that we will someday discover treatments that can reverse their pathologies. "All the current medicines for schizophrenia treat only the symptoms, and that, too, quite poorly," Lieberman says. "Nothing treats the underlying cause." Perhaps there will be a way to arrest the overpruning of synapses in schizophrenia, say, or to prevent instability in neural activity in bipolar disorder. But which symptoms would we seek to abrogate or relieve? What if we needed to treat children long before their symptoms appeared; what if the treatment, in its attempts to normalize the psyche, interrupted the construction of individual selves?

On the evening of my visit to McCarroll's lab, I met my psychiatrist friend Hans for dinner at a restaurant in Boston. He treats a range of psychiatric illnesses, including schizophrenia, personality disorders, and depression. Some of his patients have mild forms of psychosis, some inhabit the borderlands of mania, and some have intense obsessions. Many live highly functional lives—and some parlay their obsessions and psychoses into profoundly creative avenues. Their illness paralyzes and galvanizes them; it is their devil, their angel, their devil.

Our conversation turned to the C4A study. If psychiatry enters an era of neurological landscaping—if we could learn to perm and prune our neural synapses with medicines at will—where would we draw the lines of treatment? "What if a little psychosis is good for you?" Hans asked. "In fact, the words 'good' and 'bad' make no sense here. The psychosis or the obsession *is* you." How much of Rajesh's incandescence and Jagu's tenderness were linked to the unique constructions of their psyches that emanated, ultimately, from the unique constructions of their genomes?

The day after our visit with Moni, my father and I took a walk in Calcutta. We started near Sealdah Station, where my grandmother had stepped off the train in 1946, with five boys and four steel trunks in tow. From the edge of the station, we retraced their path, walking past open-air stalls of fish and vegetables on the left, and a stagnating pond of water hyacinths on the right. As we headed toward the city, the crowd thickened. On both sides of the street, the larger apartments divided into tenements, as if driven by some furious biological process—one room splitting into two, two becoming four, and four, eight. There was the clank of cooking and the mineral smell of coal smoke. At a pharmacist's shop, we turned into the inlet of Hayat Khan Lane and walked toward the house that my father and his family had occupied. The front door of the house opened into a small courtyard. A woman was in the kitchen downstairs, menacing a coconut with a scythe.

"Are you Bibhuti's daughter?" my father asked in Bengali. Bibhuti Mukhopadhyay had owned the house and rented it to my grandmother. He was no longer alive, but my father recalled two children, a son and a daughter.

"No, I'm his brother's daughter-in-law," the woman said warily. "We have lived here since Bibhuti's son died."

A tiny bolt of understanding passed between them. The woman recognized my father: not the actual man, whom she had never met, but the form of the man. In Calcutta—in Berlin, Peshawar, Delhi, Dhaka—men like this seem to turn up every day, appearing off the streets and walking unannounced into houses, stepping casually over thresholds into their past.

Her manner warmed. "Were you the family that lived here once? Weren't there many brothers?" She asked all this matter-of-factly, as if the visit were long overdue.

Her son, about twelve years old, peeked out from a window upstairs with a textbook in his hand. I knew that window. Jagu had parked himself there for days on end, staring into the courtyard.

She turned to my father. "Go upstairs if you'd like. Look around, but leave your shoes on the stairwell."

I removed my sneakers, and the ground felt intimate on my soles, as if I had always lived here. It was smaller than I had expected—as places reconstructed from borrowed memories inevitably are—and also duller and dustier. Memories sharpen the past; it is reality that decays. We climbed a narrow gullet of stairs to a pair of small rooms. The four younger brothers, Nakul, Rajesh, Jagu, and my father, had shared one of the rooms. The eldest boy, Ratan—Moni's father—and my grandmother had shared the adjacent room, but, as Jagu's mind involuted into madness, she had moved Ratan out with his brothers and taken Jagu in.

We climbed up to the balcony on the roof. Dusk was falling so quickly that you could almost sense the curvature of the earth arching away from the sun. My father looked out toward the lights of the station. A train whistled in the distance like a desolate bird. He knew I was writing about heredity.

"Genes," he said, frowning.

"Is there a Bengali word?" I asked.

He searched his inner lexicon. There was no word—but perhaps he could find a substitute.

"*Abhed*," he offered. I had never heard him use the term. It means "indivisible" or "impenetrable," but it is also used loosely to denote "identity." I marvelled at the choice; it was an echo chamber of a word. Gregor Mendel might have relished its many resonances: indivisible, impenetrable, inseparable, identity.

I asked my father what he thought about Moni, Rajesh, and Jagu.

"*Abheder dosh*," he said.

A flaw in identity, a genetic illness, a blemish that cannot be separated from the self—the same phrase served all meanings. He had made some peace with its indivisibility. ♦