MARK KINSINGER (*left*) and his younger sister, Ruth (*right, not their real names*), were born with the same genetic disorder. Mark, not diagnosed until age four, suffered irreversible brain damage. Since then, a pilot screening program and early intervention have fully prevented disability in other children with the condition, including Ruth.

MEDICINE

GENOMICS FOR THE PEOPLE

A children's clinic raised and supported by Amish and Mennonites proves that high-tech genetics research can be harnessed right now to prevent disease

By Kevin A. Strauss

Levi and Emma Kinsinger operate a small greenhouse in southern Pennsylvania. On November 6, 2002, they traveled 450 miles round-trip by taxi, at a rate of a dollar per mile, to bring their eldest son—Mark—to the Clinic for Special Children in Strasburg, Pa. At age four, Mark was frail and socially detached. He lay on the floor in constant, restless motion. His eyes roamed but did not fix, and he was unmoved by sound. From time to time, a guttural noise escaped his throat as he shook violently. The Kinsingers' question, one I've heard countless times in my work as a pediatrician, gave voice to their quiet desperation:

"What can we do to help our child?"

Photographs by Grant Delin

Kevin A. Strauss, who earned his M.D. from Harvard Medical School, is medical director of the Clinic for Special Children in Strasburg, Pa.

Our clinic is a medical home for children like Mark. (For privacy, I have changed the names of all patients and their families.) Its sturdy timber frame, erected by Amish and Mennonite hands, encloses a modern pediatric office equipped with an arsenal of high-tech gene-sequencing tools. We serve the North American "Plain" communities descended from European Anabaptists who fled to the New World in the 1600s to 1800s seeking religious asylum. Today's Plain people live in small, isolated Christian settlements throughout North America and eschew modern ways. Electricity and telephones are commonly forbidden in the home, codes of dress and conduct emphasize group cohesion, private and government insurance are rejected, and members distrust technologies that erode social interdependence.

The Plain people choose to live differently in the modern world, but every parent knows what it means to fear for a sick child: "Will my daughter ever walk?" "Can you stop the seizures?" "Is it autism?" Such are the questions that move us to translate the complex language of modern biochemistry and genetics into meaningful answers for children and families. To date, our laboratory has identified more than 170 different disease-causing gene mutations disproportionately represented among the Plain people. Nearly half endanger the developing brain and, left untreated, cause death or disability in children. Rapid, affordable, on-site molecular testing opens a precious window; it allows us to expose future health threats, craft more precise therapies and preempt disease before it strikes.

Our collaborative relationship with the Plain people also provides a glimpse into how genomics research will transform understanding of more common diseases. With the cooperation of a few dedicated Amish families, we recently discovered a specific genetic variation that appears to be linked to bipolar (manic-depressive) disorder, which affects between 2 and 4 percent of people worldwide and remains woefully underdiagnosed and undertreated. Linking a genetic variation to bipolar disorder moves genomics one step closer to the medical mainstream; it challenges the medical research community to close the gap between what we know about the causes of human suffering and what we can do for the people who need our help.

PROGRESS, ONE CHILD AT A TIME

WHAT THE KINSINGERS NEEDED was clarity. Within a few days we detected a constellation of chemical abnormalities in Mark's blood that implicated deficiency of an enzyme—5,10-methylenetetrahydrofolate reductase (MTHFR)—as the cause of his disabilities. Our lab director, Erik Puffenberger, worked quickly to discover an error in both of Mark's MTHFR-coding genes. This knowledge allowed us to diagnose three more affected children from the Kinsingers' home settlement.

I searched the medical literature and found the first description of MTHFR deficiency, published 30 years earlier by S. Harvey Mudd and his colleagues. Mudd was a legend in the small world of research devoted to intermediary metabolism, the collective processes that convert food into the energy and building blocks of cells. He elucidated what came to be known as the transsulfuration pathway—a complex network of chemical reactions that recycles an essential amino acid, methionine, while simultaneously supplying methyl groups (CH_3) to molecules throughout the body. Methionine is indispensable for the growth of the brain and other tissues, and methyl tags profoundly affect how these tissues function. MTHFR is a vital link in the chemical supply chain; lacking this enzyme, Mark had suffered the devastating neurological consequences of cerebral methionine and CH_3 deprivation.

I called Mudd, then age 75 and emeritus researcher at the National Institute of Mental Health. He generously guided me through the complexities of transsulfuration and suggested a treatment: an over-the-counter compound called betaine, which supplies the brain with methionine and CH_3 via an alternative metabolic pathway and can be administered as a dietary powder for just 60 cents a day. In the months that followed, I frequently made the four-hour trip to the Kinsingers' settlement with clinic nurse Christine Hendrickson. We traveled from farm to farm, carefully assessing the effects of betaine on our young patients. Armed with a cooler of dry ice, a portable centrifuge and a power inverter in my car's cigarette lighter, we spun and froze blood samples in the field. We shipped them to Mudd, who called on his network of colleagues to analyze methionine, betaine and a host of other chemicals in the transsulfuration pathway. This partnership allowed us to correlate the dose of betaine to its specific therapeutic actions and thereby establish a treatment protocol that we published together in 2007.

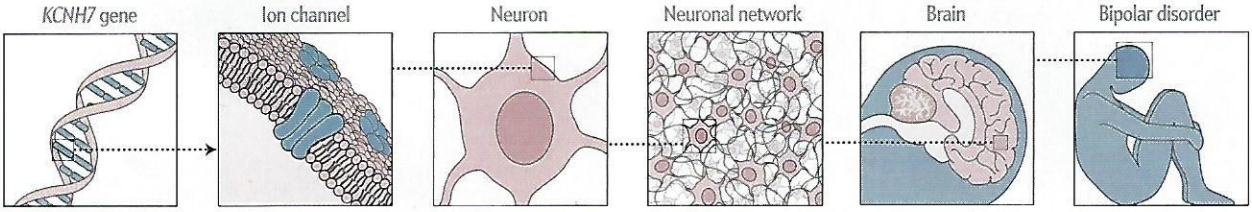
Weeks after starting betaine, Mark took his first steps and awoke to light and sound. Other patients also made quick and decisive progress, but we learned a poignant lesson about the arrow of biological time. Mark and other children who started betaine later in life were left with permanent disabilities traced to stagnant brain growth during infancy. The dense matrix of neural connections that form within this narrow window becomes an enduring substrate for our mental life. Once that window closes, the damage is done. Mark's case brought the tragedy of an entire community into sharp relief. During the three decades after Mudd's

IN BRIEF

The Clinic for Special Children in Strasburg, Pa., in collaboration with the Amish and Mennonite families it serves, has closed the gap between growing scientific knowledge of human genetics and its translation into effective medical care. **Genetic information**—gathered with high-tech, low-cost approaches—enables the nonprofit clinic to efficiently diagnose and treat dozens of potentially crippling or fatal genetic conditions. **The clinic's practice** is a model for improving medical care in underserved communities throughout the world. **A recent study** spearheaded by the clinic links a gene mutation to bipolar disorder and shows how research in isolated communities might enrich understanding and treatment of common human afflictions.

How Genetic Mutations Lead to Disease

Gene mutations can disrupt biology at multiple levels (molecules, cells, tissues and organs) to cause disease. Certain mutations are particularly prevalent in Amish and Mennonite populations. For each patient the clinic sees, it applies advanced technologies to identify the individual's genetic variants, understand their causal links to disease, and devise ways to alleviate or prevent the mutations' harmful effects. In related work, the clinic and its collaborators recently identified a gene mutation linked to bipolar disorder among the Amish, and they are now constructing a picture of how it might impair emotional regulation (*below*). This knowledge could lead to a deeper understanding of bipolar disorder in the general population and to new strategies for prevention and treatment.



Gene
A gene consists of a sequence of DNA "letters" that spell out the amino acids needed to make a protein. Proteins are the main workhorses of cells. A mutation in a gene can alter the functioning of the encoded protein. The bipolar study pinpointed a mutation in a gene called *KCNH7*.

Protein
To function properly, proteins must have the right structure, location and abundance in each cell. *KCNH7* encodes a protein that spans the cell membrane, forming a channel that regulates the flow of potassium ions. The mutant is altered at just a single amino acid, but this subtle change affects potassium movement across the membrane.

Cell
All cells contain the same genes, but many genes are expressed (that is, give rise to proteins) only in select cell types. The ion channel encoded by *KCNH7* is used by neurons throughout the brain. Potassium currents critically shape each neuron's electrical behavior, and the mutant alters the cells' firing patterns.

Tissue
Tissues can contain a mixture of cell types. Brain tissue, for instance, includes neurons and supporting cells called glia. The mutant *KCNH7* gene would be expected to disrupt the operation, not only of individual nerve cells, but of whole neuronal circuits, such as those regulating emotions and behavior.

Organ
Nerve cells throughout the brain make the ion channel encoded by the *KCNH7* gene, but the channel is most abundant in brain regions underlying emotions and cognition. Consistent with that finding, mutation of the gene has been tied to mania observed in laboratory animals.

Behavior
Bipolar disorder is marked by a spectrum of behaviors that can include depression, mania and psychosis. New insight into how the *KCNH7* mutation affects each level of biology—from misspelled protein to perturbed brain function—could lead to fresh ideas for interrupting the chain of events underlying the disorder.

publication about MTHFR deficiency, children like Mark lived and died in obscurity, shrouded in confusion and sorrow.

While working out the details of therapy, we developed a test to screen young couples for the genetic defect and were alarmed to find that 30 percent of healthy Amish from the Kinsingers' settlement carried one mutant copy of MTHFR. From this figure, we could infer that one in 50 of their babies would be born with the disease. In 2003, recognizing the critical role of preemptive therapy, we reached out to biochemist Edwin Naylor at his pioneering newborn screening lab in Pittsburgh. Together we were able to develop and implement a method for detecting the MTHFR mutation from the dried filter-paper blood spots collected on every newborn as part of mandatory state screening for various hereditary disorders.

Remarkably, the first child diagnosed by this novel filter-paper method was Mark's sister Ruth, born September 2003, just 10 months after the Kinsingers first brought Mark to our clinic. Ruth started betaine therapy during her second week of life and has flourished during 12 years of follow-up. Today she is an accomplished student, affectionate daughter and formidable stickball player.

In 2009 Mudd and his wife had the opportunity to meet the Kinsingers at a Clinic for Special Children 20th anniversary celebration. As the Mudds spoke with Ruth's parents, Ruth quietly climbed into Mudd's lap. He told me later that it was the finest moment of his scientific career.

Mudd died in January 2014 at age 86. Several weeks later his widow received a handmade card that read: "Dear Mrs. Mudd, Greetings of love are being sent your way. How are you today? I'm fine. It is a foggy morning, and looks as if it would be sunny. I am looking forward to going barefoot. Love, Ruth."

GRASSROOTS GENOMIC MEDICINE

THE UNUSUALLY HIGH INCIDENCE of MTHFR deficiency and other genetic disorders among the Plain people is rooted in their unique social and cultural history. Small bands of Anabaptists who survived the trans-Atlantic migration composed a meager gene pool. Like all of us, these individuals unknowingly harbored damaging sequence variants (more commonly called mutations) in their genetic code. In isolated populations, such gene variants can propagate silently through carriers over generations, randomly drifting up or down in prevalence, until a child inherits two copies of the damaging genetic change from parents who share a common ancestry. This recessive pattern of inheritance is an important mechanism of genetic disease in isolated communities across the world. Among modern Anabaptists, the ancestral constellation of gene variants causes much individual and communal suffering, a problem compounded by limited science

Illustration by Amanda Montañez

MENNONITE BOY on the left has maple syrup urine disease [*see box on opposite page*] and lives 23 miles from the clinic. The boy on the right has glutaric aciduria type 1. His family relocated so that he could be cared for at the clinic.

education and poor access to the U.S. health care system.

In the early 1960s the late Victor McKusick, a pioneer of modern medical genetics, first recognized the potential for studying hereditary disease patterns among the Amish and launched a comprehensive field study to this end. Though wary of technology's power to undermine social relationships, Plain people opened their homes to McKusick and his collaborators in the hope that future generations might benefit. This work culminated in the 1978 publication of *Medical Genetic Studies of the Amish,* which catalogued 18 previously recognized and 16 newly diagnosed genetic disorders among the Amish of North America. These early research efforts established many key principles about human genetic disorders but did little to help the population under study. Many Amish grew weary of doctors who were interested in investigating their patterns of disease but unable or unwilling to care for them.

A decade later a young physician by the name of D. Holmes Morton would take a different approach. In 1988, while Morton was a fellow in biochemical genetics at Children's Hospital of Philadelphia, a colleague asked him to analyze a urine sample from a six-year-old Amish boy named Danny (his real name) who had suffered an abrupt and unexplained regression of motor skills at 14 months of age. Local doctors called it cerebral palsy, but Morton, using a technique called gas chromatography/mass spectrometry, detected a substance called 3-hydroxyglutaric acid in the boy's urine. This distinctive chemical footprint implicated a rare genetic disorder called glutaric aciduria type 1 (GA1)—not cerebral palsy—as the cause of Danny's brain injury.

Morton visited Danny at his home in Lancaster County, where he learned of the many families who communicated in letters about their children with so-called Amish cerebral palsy. In 1991 he and his colleagues published a report of 10 definite cases of GA1 among the Amish, doubling the number of published cases worldwide. He listened to harrowing stories from parents who had fallen into a kind of learned helplessness; generation after generation, they watched their children struck down by a mysterious brain disease only then to be vexed by a medical system too remote, too fragmented and too expensive to help them. This wheel of anguish convinced Holmes and his wife, Caroline, of the need for a local clinic—a medical home—where uninsured Plain families could bring their special children for affordable and compassionate care.

Thus began a health care experiment fundamentally different from the profit-driven U.S. health system: a grassroots collaboration between the Mortons and a handful of committed parents who knew firsthand the pains inflicted by genetic disease. An Amish farmer who had two grandchildren with GA1 offered two and a half acres of his field to site the clinic. Other Plain community members provided timber and labor to raise its mortise-and-tenon frame. From then until now, the Plain communities have continued to support the project as a valuable investment in their children. Nearly 75 percent of the current annual operating budget of $2.6 million comes from charitable sources, including more than $850,000 raised by Plain people at benefit auctions that offer quilts, furniture, plants, ponies, barbecued chicken, handmade pretzels, whoopie pies, and more. This support limits out-of-pocket clinical and lab fees to between $50 and $150 per visit, 70 to 90 percent below the cost of comparable services at academic health centers.

The Mortons recognized from the outset that the most effective approach for treating GA1 and other disorders was to start with healthy newborns, detect genetic risks before disease onset and provide informed, local services across the arc of youth. Yet preemptive strategies are easier to conceptualize than to implement. And the details matter: an accurate genetic diagnosis is meaningless if it comes too late, and a clever molecular therapy is useless if it costs too much. The clinic is a place where science is harnessed to practical ends, empowering communities to better care for their own while shielded from medical bankruptcy.

Our ground floor is equipped with an array of advanced gene-sequencing tools. The on-site lab team, led by Puffenberg-

The Economics of Prevention

The Clinic for Special Children's progress in managing a disorder called maple syrup urine disease (MSUD) illustrates the practical economic benefits of integrating biochemical and genetic science with the everyday practice of medicine. MSUD is rare worldwide but common among Mennonite settlements of Pennsylvania, where it affects about one in 380 newborns. It is a dangerous disorder; before the clinic opened its doors in 1989, 39 percent of MSUD victims died during childhood, and most survivors were left with severe mental and physical disabilities.

Children with MSUD lack an enzyme necessary for degrading three dietary amino acids. Consequently, certain chemicals reach concentrations that poison the brain. In excess, these chemicals spill into the urine, giving it the characteristic odor of maple syrup. Affected children appear normal at birth, but within three to five days become inconsolable and then develop forceful, involuntary muscle spasms. Left untreated, accumulating toxins cause brain swelling, coma and death.

Before the clinic's inception, health services for children who had rare and complex genetic disorders were woefully inadequate in rural communities. Those with conditions such as MSUD had medical care that was fragmented, costly and ineffective. During each medical crisis, families were forced to travel 100 miles or more to reach the nearest academic medical center, where they remained for weeks and paid cash rates of $50,000 to $100,000 for emergency services. This reactionary cycle encumbered the Mennonite people with medical debt but did not alleviate the burden of disease.

Since 1989 our clinic has managed 80 Mennonite MSUD patients from the time they were newborns. Half were diagnosed on-site between 12 and 24 hours of life and transitioned safely at home. The remainder were diagnosed by mandatory state newborn screening and discharged safely to home after an average five-day hospital stay. Over 25 years we have made incremental improvements in the monitoring and treatment of MSUD that include inexpensive filter paper–based chemical testing from home, sophisticated intravenous nutritional mixtures used to reduce toxin levels, and new dietary formulas designed to optimize the chemical environment of the brain. These innovations have decreased hospitalizations from 7.0 to 0.1 days per patient per year. A 98 percent decrease in hospital costs applied to all the MSUD patients under our care saves the community at least $4.8 million annually—nearly twice the clinic's operating budget.

Advanced technologies have the reputation of being prohibitively expensive, but the cost depends in large part on how they are deployed. Investing resources in preemptive diagnosis and disease prevention can be instrumental in reducing unnecessary and wasteful medical spending. —*K.A.S.*

er, has worked closely with clinic physicians to discover between five and 15 population-specific damaging gene variants each year since 1998. Focused molecular strategies allow the team to accurately diagnose most genetic disorders within fewer than 24 hours for a cost of $50. Precise genetic knowledge allows us to look into the future, understand when and how disease is likely to unfold, and take actions to keep children safe.

In the instance of GA1, Morton worked closely with Naylor to implement elective statewide newborn screening in 1994. A few years later Stephen I. Goodman of the University of Colorado School of Medicine deciphered the specific genetic change underlying "Amish" GA1, which enabled Puffenberger to perform rapid, inexpensive molecular testing. By identifying affected children before disease onset and intensifying their medical care, we were able to reduce the risk of disability from 94 to 36 percent, but we still agonized each time an affected infant succumbed to brain injury.

Then, in 2006, I collaborated with Richard Finkel, a founder of the nutrition-supplement company Applied Nutrition, to design what we call a "medical formula"—a prescription diet—for infants and children with GA1. We knew that the mutation responsible for GA1 caused glutaric acid and other toxins—produced from the amino acid lysine—to accumulate in the brain and that the presence of a different amino acid, arginine, could limit lysine's entry into the brain. By judiciously manipulating the relative dietary proportions of these two amino acids (with the help of computer modeling), we thought we could reduce cerebral lysine uptake and thereby limit neurotoxin production by the brain.

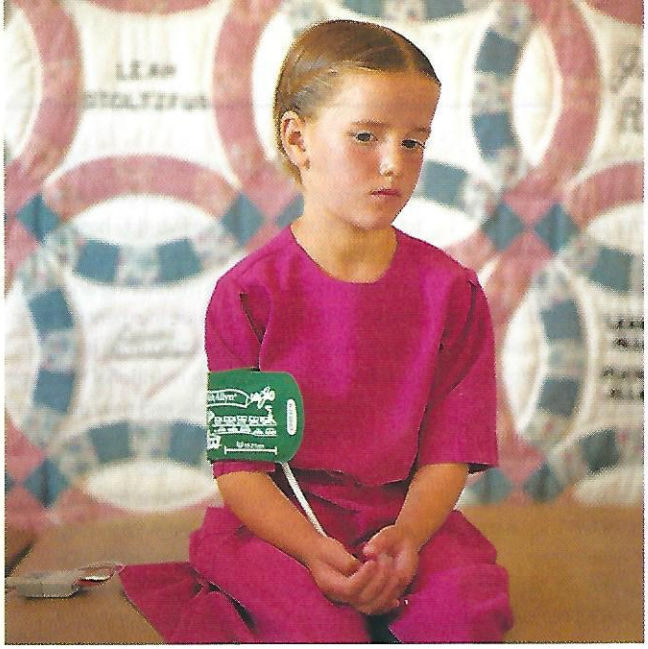
I tested the new approach on 12 affected infants in a clinical trial conducted between 2006 and 2011. Treated infants had half the toxin excretion, a third of the hospitalizations and complete protection from brain injury. We published our findings in 2011 and to date have treated a total of 25 consecutive newborns with the customized medical formula. The results have been durable; the brain injury rate remains less than 5 percent, and nearly all children born today with GA1 grow up healthy. For many other genetic disorders we treat, similar stepwise innovations in diagnosis and treatment have enabled us to reduce rates of disability, hospitalization and death by between 50 and 95 percent—a powerful testament to the idea that science guided by conscience can do much to prevent human misery.

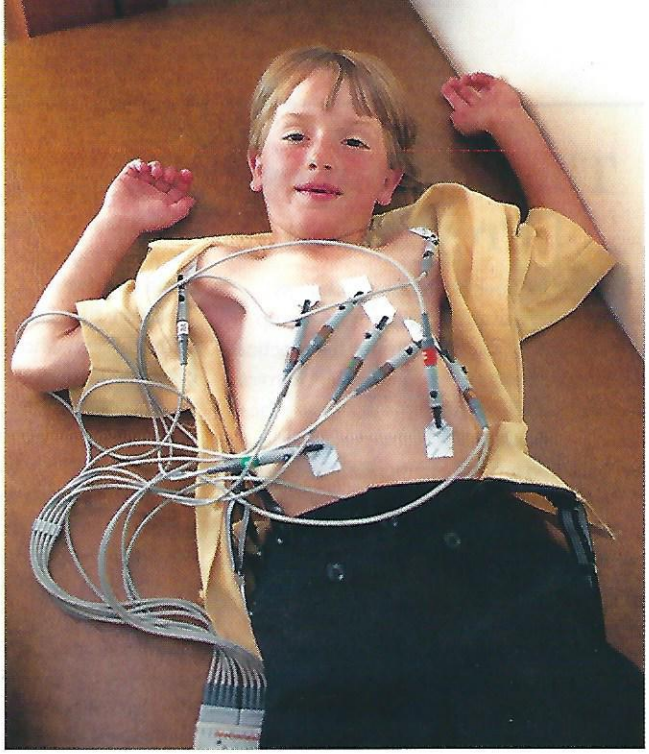
MANY POPULATIONS, ONE BIOLOGY

THE STUDY OF RARE GENETIC DISORDERS has a special role to play in the growth of biological science. Only by carefully observing the medical consequences of a gene mutation can we fully appreciate how the normal gene contributes to human biology. William Harvey foresaw this in 1657, when he suggested that investigation of rare disorders is the best way to reveal nature's "secret mysteries" and thereby advance mainstream medical practice. Three and a half centuries later we understand Harvey's axiom in modern terms. By attending closely to the dynamic interplay between a rare gene variant and mental health, we recently gained key insight into one of the most common human afflictions.

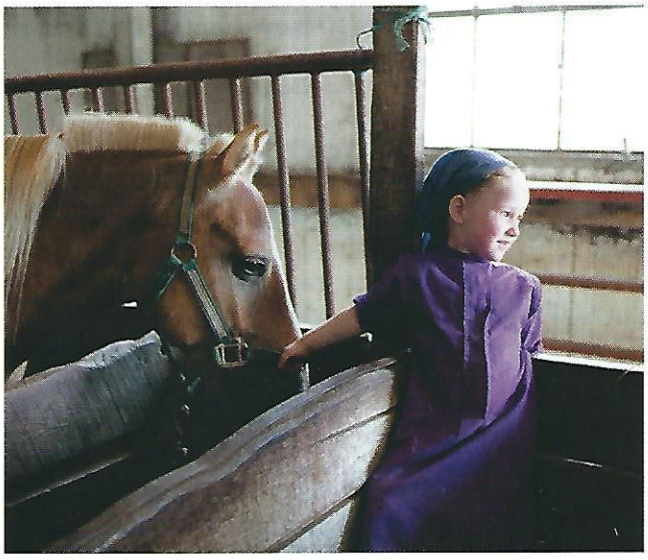
It was a crisp autumn morning when I first met Katie, a woman of about 40 who had agreed to participate in our research study of bipolar disorder among the Pennsylvania Amish. She preferred we meet in the barn where her husband, David, repaired small engines. Machine parts were strewn about carelessly in a manner unexpected for an Amish shop. Most days David did the work of two—Katie's bipolar disease had dominated their shared life for more than a decade, and David often struggled in isolation to raise their five children.

Bipolar disorder first exacted its toll on Katie after the birth





CHILDREN treated at the clinic have many serious health issues, such as heart arrhythmias (*top panels*), brain malformations (*bottom left*), and hereditary attention deficit disorder (*all three, bottom right*).



of her second child. She began to speak fast, sometimes very fast, and often followed random trains of thought into obliquity. At intervals she stayed up nights on end, cleaning and recleaning the house. "These floors are filthy. Filthy. Filthy." During the dark periods that followed, Katie lay in bed ruminating, hopeless and racked with guilt. Familiar voices—her husband, children, and parents—incessantly whispered to her from behind: "You're worthless." But her biggest concern, conveyed repeatedly when we first met, was a mass that filled her abdomen and tormented her relentlessly, a chronic perceptual hallucination that she called her "miserableness."

Mental disorders—including bipolar disorder—are common worldwide, affecting 12 to 47 percent of different populations. In the U.S., psychiatric disease accounts for 40 percent of medical disability among young adults, and suicides outnumber homicides two to one. Isolated groups such as the Amish provide distinct advantages for investigating the heritability of psychiatric illness and other common medical conditions. One such effort, the Amish Study of Major Affective Disorders, began in 1976 and tracks several large, multigeneration Amish pedigrees with a high prevalence of bipolar disorder. Over three decades the cohort swelled to include more than 400 subjects and remains one of the most intensively studied in the history of medical genetics.

On October 31, 2011, Puffenberger and I attended a Family Meeting hosted by Alan Shuldiner and the University of Maryland's Amish Research Clinic. Leading psychiatric investigators addressed a gathering of Plain people concerned about mental illness within their families and communities. As the meeting drew to a close, researchers summarized 35 years of Amish bipolar research with a dispiriting message: "There is not a lot new to tell you." On the way to the parking lot, I was stopped by three Amish sisters whose family had participated in familial bipolar research for more than two decades. Nine of 11 siblings from their generation had spent much of adult life debilitated

SCIENTIFIC AMERICAN ONLINE Read more about the clinic's work at ScientificAmerican.com/dec2015/clinic

by mania or depression. They wondered if our clinic, which had a reputation for taking on intractable problems, might help them better understand if "some gene was involved."

The timing was right. We had recently begun collaborating with the Broad Institute in Cambridge, Mass., to explore the utility of whole exome sequencing for investigating rare genetic disorders in children. The exome consists of all coding letters, or nucleotides, that are "read" to construct the body's 19,000 proteins.

Although the exome represents only about 1 percent of the human genome, it contains the vast majority of genetic changes that can cause disease, and whole exome sequencing is at present the most efficient and lowest-cost method for disease-gene discovery.

Although our clinic has historically focused on pediatric health, psychiatric disorders pervade every aspect of family and community life, and our collaborators in Cambridge allowed us to reserve seven exome samples for Amish adults with bipolar disorder. Remarkably, all seven people shared an exceedingly rare variation in a gene that encodes the KCNH7 protein. This single-letter substitution, called a missense change, alters the structure of KCNH7 at an amino acid conserved across the evolution of many different animal species; changes in such conserved regions often critically alter the way a protein functions.

Over the next two years, Sander Markx and Michael First of Columbia University's department of psychiatry helped us expand the study to more individuals and implement a method to rigorously categorize their symptoms. Ultimately we were privileged to collaborate with investigators at Weill Cornell Medical College, the University of Pennsylvania, Franklin & Marshall College and the McKusick-Nathans Institute of Genetic Medicine. This team approach also allowed us to track the movement of KCNH7 protein in cells, demonstrate how its mutant form alters electrical firing in neurons and establish a statistical foundation for our discovery. For the first time, we identified a specific genetic change that signals a strong predisposition to bipolar disease among the Amish. We published our findings in 2014; they now allow investigators worldwide to explore the connection between KCNH7 and mental illness in other populations.

KCNH7 is especially abundant in brain regions that affect mood and cognition, where it forms channels that mediate potassium movement across cell membranes. These ephemeral waves of ions, moving in and out of membranes too thin to see, are directly linked to what we think and feel. Our everyday experience belies this fact; it is difficult to imagine electrochemical signals at the root of violence, addiction, psychosis and suicide. But our research suggests that a subtle change in the threshold and timing of ion currents can cast a person into repeated cycles of madness and despair.

To realize at the genetic level that the mind is embodied in this way allows us to understand mental suffering in concrete terms. Discovery of the KCNH7 variant is important because it provides a foothold for rational discussions among scientists and patients and helps to strip away the layers of guilt and shame that surround mental illness. In the near term, knowledge that connects genetic variation to bipolar disease can lead to more timely and effective medical care for people such as Katie. On a longer time scale, it might be possible to design drugs that modulate the KCNH7 ion channel—a form of precision medicine that could open up a whole new class of therapeutics for the treatment of bipolar disorder in all populations.

TIME AND OPPORTUNITY

THE STUDY OF BIPOLAR GENETICS in the Amish is a parable about the future of medicine—about how genetic information might be used to predict *your* future. At the clinic, we now have a simple and inexpensive blood test that can be collected from umbilical cord blood at birth to inform us about a child's risk for bipolar disorder 30 years hence. Because adult-onset psychiatric disorders are often preceded by erratic thought and behavior in youth, early detection of a genetic risk factor could enable more timely and effective mental health care across a lifetime. But should we begin screening Amish newborns for the damaging KCNH7 variant?

Such questions are accruing quickly and pertain to all of us. Peer into your exome, and you will find between 20,000 and 40,000 deviations from the so-called normal human sequence of nucleotide letters. Twenty percent of the variants in your DNA code have the potential to alter protein function, and about 1,000 are exceedingly rare, possibly even unique to you. How many of these changes can predict your future? And if so, what can or should be done about it? The answer depends, in part, on what knowledge we deem actionable for any particular person at a specific time. That is perhaps one key to our clinic's success: cumulative population knowledge—painstakingly acquired over the past 25 years—works like a Rosetta Stone. It allows us to decipher the meaning of genomic data within a specific social context and thereby tailor medical care to the individual: the right treatment for the right person at the right time.

In all populations, this kind of deep knowledge about gene action will allow scientists to visualize cellular machinery in exquisite detail and understand how the various molecular parts interact in health and disease. But it is people—not their component parts—who suffer. Clinicians and molecular biologists who work side by side at an appropriate scale, one patient at a time, can weave genomics into the physician's craft, yielding strategies that are preemptive rather than reactive.

Pediatric practice is a good place to put this idea to the test. At our clinic, knowledge and treatment grow in lockstep as we explore the complex interactions between gene variation and environment that play out over the formative stage of life. Caring for children challenges us to leverage the predictive power of genetic knowledge, focusing on outcomes that matter most. One child at a time, we continue to close the gap between genomic research and the day-to-day practice of medicine, which at our clinic is a practical endeavor, driven by what this child needs, right now. SA

MORE TO EXPLORE

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