

The Scarlet Gene

■ BY CHARLES W. SCHMIDT // ILLUSTRATION BY MARTIN O'NEILL

In December 1979, Faith Reidenbach, a Smith College sophomore, appeared at the student infirmary during exam week. Rambling and delusional, she was diagnosed with mania and sent home to Ohio to recuperate. The college physician recommended further psychiatric evaluation, but Reidenbach's parents sent her instead to their family physician. She had recovered somewhat by then, and the doctor supported her parents' decision not to send her to a psychiatrist. Back at Smith a year later, Reidenbach suffered a second, much worse bout of psychosis. The clinicians who saw her were confronted with an incoherent, hostile and delusional woman who couldn't keep still.

Reidenbach's behavior was consistent with bipolar I disorder, which is characterized by cycling mood changes that include severe psychotic highs, and a psychiatrist diagnosed that condition. At first Reidenbach accepted treatment, but when friends and a therapist suggested she might simply have been overreacting to the stress of college life, she stopped taking medication. Only several years later, when she had another psychotic episode, did she accept that there might be something physically wrong or that both physical and psychological factors might be at work.

Even now, a quarter century after the onset of Reidenbach's symptoms, clear answers about the underpinnings of mental illness are hard to come by. There are no diagnostic blood tests, no CAT scan that can pin down the problem. Instead, diagnoses

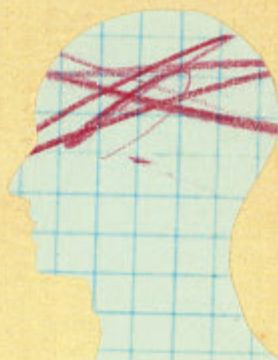
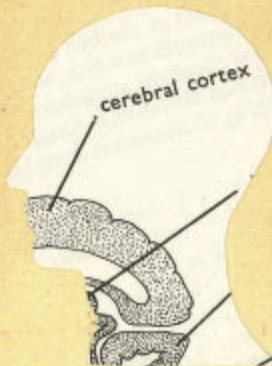
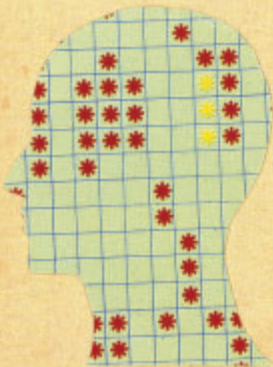
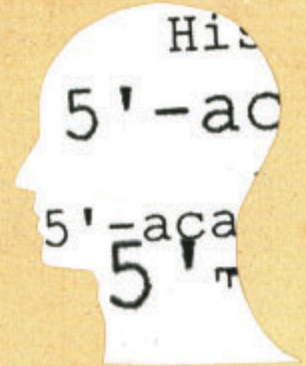
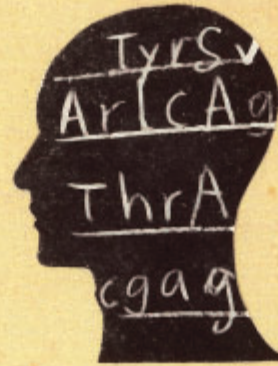
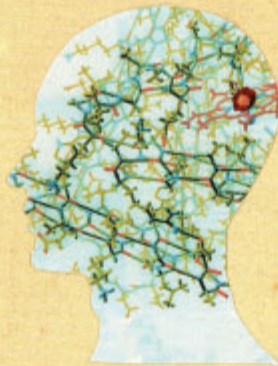
continue to be made by artful observation. Physicians match patient behaviors with those described in the *Diagnostic and Statistical Manual of Mental Disorders*, or *DSM*—first published in 1952 and now in its fourth edition. Though many doctors consider *DSM-IV* to be a highly reliable tool for diagnosis and research, others say that it still requires subjective judgments. What's more, the behavior of some patients either doesn't fit into any *DSM* category or falls into the cracks among several.

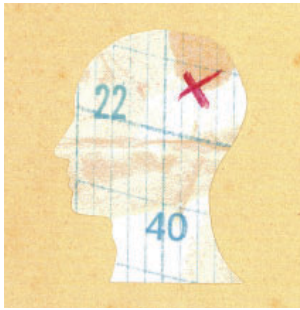
Assessments of behavior and symptoms may not be the only way to diagnose mental illness, however. Working from the inside out, researchers have slowly begun to identify genetic variations that, by distorting the brain's information-processing abilities, seem to nudge some individuals toward disease. This is still new science, and practical applications—including more precise diagnosis and better treatment—may be decades away. Yet progress in understanding the connections between a growing number of genes and conditions such as depression, bipolar I disorder and schizophrenia hint at what may eventually come.

Almost every one of the estimated 20,000 to 25,000 genes in every human produces at least one protein, and those proteins give rise to the activities of the cell. But small changes in the DNA sequences of genes occur regularly. While most variations are harmless, some cause disease by altering the protein or its abundance. What's more, inherited diseases can arise from a problem with one gene (a simple example is



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SCIENTISTS ASSUME THAT BECAUSE MENTAL ILLNESSES ARE COMPLEX, MANY GENES ARE RESPONSIBLE. BUT WHAT IF ONLY SOME ARE INVOLVED?

34

sickle-cell anemia, a condition caused by defects in a single gene that makes the hemoglobin protein), or from interactions among a range of genetic variations as well as, frequently, environmental stresses. Scientists think mental illnesses fall into that second category. Reidenbach, for instance, is convinced her mania was triggered by stress, although scientists still can't explain how genes and stress interact in the onset of bipolar disorder.

A tantalizing picture of how genes and environmental factors interact to produce mental illness comes from studies of major depressive disorder, a condition that affects 16.2% of Americans, according to one recent national survey. One attention-getting study was conducted by Avshalom Caspi and Terrie Moffitt, who hold joint appointments as psychology professors at King's College London and the University of Wisconsin–Madison.

Caspi and Moffitt built on earlier research focusing on a variation in a gene called the serotonin transporter, which normally helps information flow between nerve cells in the brain. The information is stored in chemical messengers called neurotransmitters, of which serotonin is but one. The specific job of the serotonin transporter gene is to make a protein that keeps excess serotonin out of the intercellular gap, or synapse.

Caspi and Moffitt showed that people in their twenties who went through stressful situations, such as losing a job or a romantic partner—and who had also inherited a “short” variant of the transporter gene—seemed less able to cope and were more likely to develop major depression than those who suffered stress but lacked the variant transporter.

Trouble Spots

A GROWING NUMBER OF GENE VARIANTS HAVE BEEN IMPLICATED AS RISK FACTORS FOR MENTAL ILLNESS. HERE ARE 10 THAT SEEM TO PLAY A ROLE IN DEPRESSION AND SCHIZOPHRENIA.

DISORDER	VARIANT	SUSPECTED ROLE
DEPRESSION	Serotonin transporter	May exacerbate lifelong tendency toward anxiety and vulnerability to stress.
	Brain-derived neurotrophic factor (BDNF)	May interfere with development, survival and plasticity of neurons in brain regions related to mood.
	Tryptophan hydroxylase 2	Seems to produce sharply lower levels of serotonin, a neurotransmitter, but that finding has yet to be replicated.
SCHIZOPHRENIA	Catechol-O-methyl transferase (COMT)	Possibly interferes with the normal function of dopamine, a neurotransmitter involved in cognition and reward.
	Dysbindin	Reduced expression may compromise normal functioning of synapses. (Many experts believe schizophrenia is at least in part a synaptic signaling disorder.)
	Neuregulin 1	May cause malformed synapses and may interfere with function of neurotransmitters such as glutamate.
	RGS4	Expression of this gene, which normally helps to reduce the activity of several neurotransmitters, may be lower in the brains of schizophrenics.
	DISC1	Linkage and association studies have implicated this gene, which may be related to hippocampal development and function.
	GRM3	May interfere with normal function of glutamate.
	G72	Studies in German, Han Chinese and other populations report associations between schizophrenia and this gene, which may disrupt synaptic function.

As a neuroscientist, geneticist and clinical psychiatrist, Pamela Sklar has approached the mystery of mental illness from many angles.

“This finding corresponds to what clinicians have thought for centuries,” says Patrick Sullivan, professor of psychiatry at the University of North Carolina at Chapel Hill School of Medicine. “It suggests depression isn’t caused by bad events per se, but rather by an interaction between genes and environment.” Sullivan cautions, however, that the data are not yet complete. What Caspi and Moffitt didn’t explain was how the genetic variation induces this effect. That piece of the puzzle had come a year earlier, from Daniel Weinberger, who directs the Genes, Cognition, and Psychosis Program at the National Institute of Mental Health (NIMH).

Weinberger suspected that those who inherit the variant transporter, and who were associated with more anxiety and fearfulness in earlier studies, would exhibit greater neural activity in the amygdala, the part of the brain that processes fear. So he and colleague Ahmad Hariri divided volunteers into two groups—one with the “short” variant and one without—and compared (using functional magnetic resonance imaging, which generates snapshots of the brain in action) how their amygdala responses differed when they were shown pictures of fearful faces, a common method for triggering an amygdala response.

Sure enough, Weinberger and his colleagues discovered that viewing the pictures produced especially pronounced amygdala activity in subjects with the variant transporter. They then deduced that the variant’s effect on the amygdala makes people more likely to view the world as menacing. Life stresses, they reasoned, may be amplified to the point of inducing depression.

Weinberger’s research group followed up with findings published in the June 8, 2005, issue of *Nature Neuroscience*. They scrutinized circuits connecting the amygdala to the cingulate, an emotion-dampening center near the front of the brain. Subjects with the “short” transporter variant had a smaller amygdala and cingulate, both critical for processing negative emotion. They also had weaker brain circuits, and that apparently interferes with the cingulate’s ability to stop fear triggered by the amygdala.

“All this is a focus of intense research,” says Andreas Meyer-Lindenberg, chief of the Unit for Systems Neuroscience in Psychiatry at the NIMH and an author of the *Nature Neuroscience* article. “Studies show that if you alter serotonin



transmission in newborn mice, you can make them anxious for life. And though we can’t verify it from our data, we also think there’s a highly causal relationship between changes in serotonin metabolism and the smaller size of both the amygdala and the cingulate and a weaker connection between them.”

Serotonin pathways, targeted by many drugs that treat depression, and the genes that control them have a long history in research. But what of the many other genes that may also bear on mental illness? The hunt is on, spurred by recent advances in genomics, which draws biological insights from studies of gene sequences and their variations.

Scientists often start by looking for genetic inheritance patterns among family members with a history of a particular illness. If successful, such analyses point to DNA regions that may correlate with a given disorder. For instance, if several relatives suffer from depression, researchers can sort through their DNA hoping to find regions they all share—in higher proportions than would be expected given their relatedness—where a variant disease gene might lie. Then they try to isolate variations in the gene (or genes) that appear to promote disease susceptibility.

Consider neuregulin 1, one of several genes suspected of playing a role in schizophrenia. Neuregulin 1 is an enormous gene,

more than a million base pairs long, that produces at least 15 “signaling proteins,” which facilitate cell-to-cell communication in various tissues, including the brain. In 2002, deCODE Genetics, a biopharmaceutical company in Reykjavik, Iceland, reported evidence of a connection between neuregulin 1 and schizophrenia. The evidence emerged from a linkage study of Icelandic families that showed that schizophrenia correlated with an area on the eighth of the 23 pairs of human chromosomes. More refined studies pointed to neuregulin 1 as a potential risk factor.

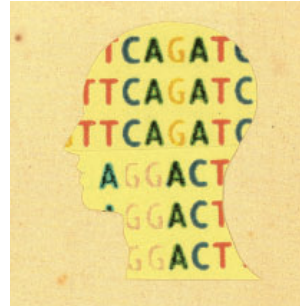
Further studies by Pamela Sklar, associate director of the Psychiatric and Neurodevelopmental Genetics Unit in the Center for Human Genetic Research at the Massachusetts General Hospital, have suggested that other parts of the gene might also be involved. A neuroscientist, geneticist and clinical psychiatrist, Sklar plans to break the huge neuregulin 1 gene into individual chunks for careful study. “We don’t know yet where the actual defect is,” she says. “If we can narrow our search to one part of the gene, then we can really focus attention on that area to see if something there is linked to the disease.”

Because mental illnesses are complex, often inherited disorders, scientists have assumed that multiple genes are involved in their cause, each contributing a tiny portion to the total risk. But what if some genes are found to contribute more of the risk? Sklar thinks it’s possible, and points to recent discoveries in another complex disorder, age-related macular degeneration (AMD), to bolster her case.

Scientists have found that a large amount of the inherited risk for AMD, the leading cause of blindness in the elderly, depends on a variation in a gene that codes for a protein called complement factor H. One hypothesis is that complement factor H, part of the immune system, may help clear cellular debris from the back of the eye. The theory is that the variation slows this activity, thus contributing to blindness.

→ DOSSIER

1. “Genetics of Psychiatric Disorders,” *Nature Neuroscience*, June 2005. Editorial describing how new genetic research methods are being applied to studies of mental illness.
2. “Gene Hunting,” 2001, www.nimh.nih.gov/publicat/huntgene.cfm Brief overview, for a lay audience, of methods used to identify genes associated with mental illness.
3. “Meta-Analysis in Psychiatric Genetics,” by Douglas F. Levinson, *Current Psychiatry Reports*, April 2005. Describes gene-identification methods—emphasizing linkage and association studies—used in research on bipolar disorder and schizophrenia.
4. “Support for Involvement of Neuregulin 1 in Schizophrenia Pathophysiology,” by Pamela Sklar et al, *Molecular Psychiatry*, April 2005. Research supporting neuregulin 1’s suspected role in schizophrenia.



In a new study, Sklar and her colleagues are scanning 500,000 gene variants, known as single nucleotide polymorphisms, obtained from a sampling of patients with bipolar disorder. Ideally, the scan will identify critical risk genes that may also offer treatment opportunities. “People used to

think all the risk genes had such tiny effects that it would be hopeless to find any with large contributions to the total risk,” she says. “The AMD finding shows you can’t rule out the possibility that important risk genes do exist. If we can find them, it’s likely they’ll make more opportune drug targets than genes that contribute comparably smaller risk.”

Many other genes are attracting intense scientific scrutiny. There is brain-derived neurotrophic factor (BDNF): Some researchers suspect a variant BDNF gene might prevent hippocampal cells in the brain from functioning normally and possibly increase the risk of depression. Problems with another gene, which codes for catechol-O-methyl transferase (COMT), could interfere with the metabolism of dopamine, increase the risk of schizophrenia and affect the frequency of manic cycles in bipolar disease. And dysbindin, which has been linked to schizophrenia, appears to affect brain synapses related to overall intellectual abilities.

Yet progress is incremental, and conclusive data linking any risk gene to disease is elusive. More research is needed to identify new genes, to replicate existing evidence in larger population samples and to tie implicated genes into broad disease processes, says Douglas Levinson, professor of psychiatry at the University of Pennsylvania School of Medicine. And as the research moves forward, however slowly, the tentative links between genes and mental illness could solidify into more definitive diagnostic tools that might give the physicians of future Faith Reidenbachs a better understanding of exactly what ails their patients. ■