NATIONAL ACADEMIES OF SCIENCES,
ENGINEERING, AND MEDICINE
THE UNIVERSITY OF TEXAS AT DALLAS
ARIZONA STATE UNIVERSITY
WINTER 2016

ISSUES
IN SCIENCE AND TECHNOLOGY

Climate and Energy: The Outliers

The wisdom of experience

In defense of democracy

The nuclear option

Venture investment in fusion

Better mental health data

A schizophrenia gene?

Citizen engineers

Rep. Lamar Smith on research accountability

Global R&D for Latin America

How safe are e-cigarettes?

USA $12.00 / CAN $13.00
6 4>
0 56698 57433 0

JONATHAN LEO

The Search for Schizophrenia Genes

Larger and larger samples are showing smaller and smaller effect sizes. What does this mean for drug development, clinical practice, and our view of mental illness?

To gain insight into the biological basis of disease, President Obama launched the Precision Medicine Initiative in January 2015. A major aspiration of the program is to identify the genetic underpinnings of disease. Some commentators have questioned whether this research agenda has more to do with science or politics. In a *New York Times* op-ed, Dr. Michael Joyner, an anesthesiologist and physiologist at the Mayo Clinic, pointed out some reasons to be skeptical. In Joyner's words, "no clear genetic story has emerged for a vast majority of cases." The title of his piece summed up his conclusion: "'Moonshot' Medicine Will Let Us Down." In other words, we are spending a lot of money on something with questionable utility, and even when we do find genetic variants that contribute to risk, their predictive power is based on environment, culture, and behavior.

The idea that mental illness is the result of a genetic predisposition is the foundation for modern-day psychiatry, and has been the driving force for how research money is allocated, how patients are treated, and how society views people diagnosed with conditions identified in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V). Schizophrenia holds a unique spot in the annals of mental health research because of its perceived anatomical underpinnings, and is often cited as evidence in favor of a genetic predisposition to other conditions. The logic at work is that if schizophrenia is genetic, then depression, obsessive compulsive disorder, attention deficit hyperactivity disorder (ADHD), and a host of other DSM-V conditions must also have their roots in dysfunctional genes.

During the pre-molecular era—from about 1970 to 1990—a series of family, twin, and adoption studies were used to estimate the heritability of schizophrenia from 42 percent to 87 percent. Although the technology at that time was not advanced enough to identify the specific genes, it was assumed that technological advances would eventually catch up and pinpoint the genetic culprits. Once the genes were discovered, biological markers would be identified, which, in turn, would lead to the development of precision drugs. After the biological roots of schizophrenia were discovered, the other DSM-V conditions would shortly reveal their secrets—so the story went.

The technology has now caught up, and we are firmly entrenched in the molecular era of behavioral research. Yet, in spite of the fact that molecular geneticists have spent countless hours and millions of dollars, a specific gene has never been found. In the 1990s, several scientists reported finding a "schizophrenia gene" only to eventually retract their findings. Decades of research have confirmed that the influence of genetics on psychiatric conditions is relatively minor, and that those earlier studies misjudged

heritability estimates.

Even for many common physical conditions, such as cancer, cardiovascular disease, and diabetes, all with clear biological pathology, the Human Genome Project has shown that there are hundreds of genetic risk variants, each with a very small effect. As geneticists implicate more and more genes, and the importance of each individual gene decreases, it becomes hard to see how this information can be used in a clinical setting. Compared to these physical conditions, the debate about genetic risk factors for psychological conditions such as schizophrenia, depression, and ADHD, which all lack distinct biological markers, is even more heated.

Genes of small effect and lowered expectations

The current trend in psychiatric genetics is to use enormous samples to find genes of miniscule effects. In May 2014, the Schizophrenia Working Group published "Biological Insights from 108 Schizophrenia-Associated Genetic Loci." The study, a genome-wide association study (GWAS), looked at 36,989 patients and 113,075 controls and identified 108 loci with genome-wide associations. The risk scores explain up to 4 percent of the variance in the diagnosis of schizophrenia. Some might label this a success, but it's reasonable to ask, "Only four percent?" Is the other 96 percent explained by the environment or more hidden genes? To complicate matters, these same genes have been implicated in other conditions, such as ADHD and autism. In his book *Misbehaving Science*, Aaron Panofsky, an associate professor in public policy at the University of California, Los Angeles (UCLA), discusses the strategies that behavior geneticists use to cope with the failure of molecular genetics. In his words: "One of the most basic strategies for dealing with the disappointment of molecular genetics has been to lower expectations."

These lowered expectations were evident in the news articles about the study. In general, there was a disconnect between what the study actually showed—*that nature plays a minor role*—compared to the news headlines—*that nature has won the race*. An article in *Scientific American* stated, "This finding lays to rest any argument that genetics plays *no role*" (italics added). But the author could have stated, "With genetics explaining only 4 percent of the cause, this study lays to rest any argument that genetics plays a *major* role." Taking the study's results at face value, one could conclude that genetics plays a role—but not much of one. It was only in the realm of speculation that the genetic view won.

As another example, an enthusiastic article by a psychiatric geneticist in *The Lancet Psychiatry* referred to the 108 schizophrenia-variant study as a "game changer" and a "remarkable success." He declared: "The importance of showing at least some biological validity of the clinical concept that is schizophrenia cannot be overstated." But he is, in fact, overstating the usefulness of these results, as indicated by the rest of *The Lancet* article, which concluded that genetics cannot be used to make clinical predictions. Going beyond the actual results, some behavioral geneticists suggest that in the future, researchers may discover more than 8,000 variants for schizophrenia. In *USA Today*, Steve Hyman, director of the Stanley Center for Psychiatric Research, commented: "Now we have 108 pieces, but maybe it's a 1,000-piece puzzle…" As more and more variants are implicated, the results become even more watered down. For instance, a recent algorithm to examine the polygenic risk of schizophrenia estimated that there are 20,000 single nucleotide polymorphisms (SNPs), or differences in single DNA components, implicated in schizophrenia. Commenting on these results, Alkes Price from the Harvard School of Public Health noted that because so many regions are implicated, there is the concern that "GWAS will ultimately implicate the entire genome, becoming uninformative." A clinically useful signal appears impossible to distinguish from the noise.

Even if you completely agree with the 108 loci study's methodology and all its inherent assumptions, there is no way to conclude that the researchers have discovered "schizophrenia genes." In fact, they have disproved their existence. For each of the 108 loci there is a very small difference between the percent found in those diagnosed with schizophrenia and the control sample. Take the very first one: it's found in 86.4 percent of the patients, and in 85 percent of the control group. This is a minor difference, and whether or not you have the variant tells you nothing about your risk of being diagnosed with schizophrenia. These genes are neither unique nor specific for people diagnosed with schizophrenia; many of the genes are scattered far and wide, and most of us carry at least some of them. As Kenneth Kendler, a psychiatry professor and geneticist at Virginia Commonwealth University, concluded in a recent paper, "All of us carry schizophrenia risk variants, and the vast majority of us carry quite a lot of them." It is only by combining all the genetic markers into a single polygenic risk score that researchers can say that an individual has an increased risk of developing schizophrenia. However, even those individuals with

a supposedly increased risk were more likely to *not* develop schizophrenia.

Behavioral geneticists are having an even harder time for other psychological conditions. For major depressive disorder (MDD), the results are much more sobering. A 2013 mega-analysis of genome-wide association studies, published in *Molecular Psychiatry*, concluded that "we were unable to identify robust and replicable findings." Even though it is the largest genome-wide analysis yet conducted for MDD, the authors still mention the "missing heritability" theme, and attribute their failure to find the supposed risk genes to the sample being "underpowered to detect genetic effects typical for complex traits." To explain the failure of finding predictive genes, researchers often refer to the idea of "missing heritability." The thinking is that just because we cannot find the genes this doesn't mean that they are not there—they're just hiding. We need more time and more money to find them.

Implications for psychiatry

It is impossible to separate genetic theories from the medicalization of psychological stress. The widespread use of psychiatric medications is based on the idea that schizophrenia and other psychological conditions arise, in part, from genetic defects that result in biological alterations such as reduced levels of neurotransmitters, or deficits in neuronal circuits, that need to be fine-tuned with medications. In general, higher genetic contributions to a disease equate to a stronger case for pharmacological treatment, while diseases with a higher environmental component are seen as better candidates for lifestyle changes and therapy. In 1996, in regards to ADHD, Stephen Faraone, a leading psychiatric genetic researcher, stated: "Many parents are reluctant for their children to take psychotropic medication and others find it difficult to maintain prescribed regimes. These problems are mitigated by discussing the genetic etiology of ADHD…" If parents really believe that their child has a measurable chemical imbalance, then just as they would treat their diabetic child, they would surely treat their child diagnosed with ADHD.

In January 2001, *Time* magazine declared: "Drugs of the Future: Amazing new medicines will be based on DNA." Although a tremendous amount of money has been spent on the idea that medications can be designed to fit specific genetic profiles, the results have not been as promising. Writing in a 2013 *Medscape* article titled "Testing of Patients with Schizophrenia and their Families," Lynn DeLisi, editor-in-chief of *Schizophrenia Research*, stated that "there is still no currently proven risk factor, consistently replicated in independent studies, that confers risk for schizophrenia, and, even if there were, the risk is likely to be so low that a test using it would not be at all useful. It also is a misuse of the concept of risk to assume that it is synonymous with 'prediction,' and thus it is able to determine who will become ill. Risk factors only elevate one's chances of becoming ill."

In addition, these studies cost an enormous amount of money. In the debate about how to spend our health care dollars, the general public should be very skeptical about the economics of this research. Although some geneticists have enthusiastically speculated about what genetic research might mean for treatment of DSM-V conditions, it is hard to imagine how to plan a therapeutic program based on genes which are not distinct for the condition in question. The geneticists suggest that the myriad of genes involved are all pointing toward specific systems that drug developers can focus on. However, another interpretation is that the discovery of genes-of-small-effect suggests that finding a specific drug with strong efficacy and few side effects is becoming less likely. In contrast to speculations about the development of magic bullets, Richard Bentall, a professor of clinical psychology at the University of Liverpool, has summed up the current state of psychiatric genetic research in very frank terms: "No effective treatments have so far been devised on the basis of genetic information and, given what we now know, it seems very unlikely that further research into the genetics of psychosis will lead to important therapeutic advances in the future. Indeed, from the point of view of patients, there can be few other areas of medical research that have yielded such a dismal return for effort expended."

Genetics as destiny?

Even if genetics are implicated in a disease, development of the disease is not inevitable. Given the right environment, the disease will not necessarily develop. Diabetes can be prevented by changes in diet, and lung cancer deaths can be drastically reduced by no-smoking campaigns. Psychological conditions are even more dependent on the environment. Post-traumatic stress disorder (PTSD) is seen in veterans and abused children, for instance. Even if there is a genetic component to PTSD, it is still entirely preventable by removing the environmental stressor—not going to war or not growing up in an abusive household. With no biological markers that can be used to identify mental illness, even the diagnosis of these conditions is subject to society's vagaries of what is considered abnormal. In America, 9 percent of school-aged

children are diagnosed with ADHD, while in France it is less than 0.5 percent. It is unlikely that this is the result of a genetic difference between American and French children.

For most biologists, the nature-versus-nurture debate is not an either/or debate, but is about the relative contributions of each. A growing number of studies have shown that various environmental insults during childhood, such as sexual, physical, or emotional abuse, peer victimization, and parental loss, are risk factors for schizophrenia. A recent study, "Accumulated Environmental Risk Determining Age at Schizophrenia Onset," looked at both the genetic and the environmental risk factors in a group of 750 male patients. The researchers found that the environmental factors, but not genetic factors, were a major risk factor for schizophrenia onset. They discovered "robust effects of accumulated environmental risk on age-at-onset of schizophrenia" but "non-detectable effect of accumulated genome-wide association study-derived risk variants on lead phenotypes of schizophrenia." Because early cannabis use—an avoidable risk factor—was an environmental predictor, the authors suggest the need for increased public awareness. At least in terms of prevention, it appears that the focus should be on the environment. Some authors expressed surprise at the fact that the polygenetic risk scores had no significant effect on the phenotypes. However, we know these genes play only a small role in the development of schizophrenia, that they are implicated in several other DSM-V diagnoses, and that they are spread far and wide in the general population.

It is ironic that the very body of research that was supposed to validate the most important theory of biological psychiatry is now calling this theory into question. There is nothing wrong, per se, with looking for genes of very small effect, but with no single gene emerging as a culprit, the justification for this research is weak. We now know that biomarkers or specific genes for psychological conditions do not exist, that this research will *not* lead to magic pharmacological bullets, and that many of our assumptions about mental illness were wrong. If the message for the general public is to be skeptical of how our health care dollars are spent, the message for the psychiatry community is to rethink how it treats patients, how it allocates research money, and its emphasis on the biological treatments of psychological conditions.

But this is wishful thinking. UCLA just announced the investment of $250 million into the "Depression Grand Challenge." In a statement, reminiscent more of a marketing program than an accurate scientific appraisal of the field, Dr. Nelson Frelmer, professor of psychiatry and biobehavioral science and director of the Center for Neurobehavioral Genetics at UCLA, claimed that "advances in technology for genetic research have now made it possible for us to discover the causes of depression. We know a genetics-based strategy will be successful, just as it has been with heart disease, diabetes, and cancer." Continuing with the familiar "Success is right around the corner, we just need more money" logic, the press release declared that this investment will make it possible for researchers to first discover the causes of depression through the largest-ever genetic study for a single disorder, and to then use these findings to "examine the molecular mechanisms and brain circuitry through which genetic and environmental factors lead to depression." Can all the scientists involved with this research stand by these statements as accurate portrayals of the science of mental health? What happens ten years and $250 million from now, when we have explained 3 percent of the cause of depression and we don't have a magic pharmacological bullet? The reality is that it hasn't worked for schizophrenia, or any other psychological condition, so there is little reason to believe that it will work for clinical depression.

Further Reading

L. DeLisi, "Ethical issues in the use of genetic testing of patients with schizophrenia and their families," *Medscape* 27, no. 3 (2014): 191-196.

Jay Joseph, *The Missing Gene* (New York: Algora Publishing, 2006).

S. Lawrie, "Clinical risk prediction in schizophrenia," *The Lancet Psychiatry* 1, no. 6 (2014): 406-408.

Aaron Panofsky, *Misbehaving Science: Controversy and the Development of Behavior Genetics* (Chicago, IL: University of Chicago Press, 2014).

Schizophrenia Working Group, "Biological Insights from 108 Schizophrenia-Associated Genetic Loci," *Nature* 511 (2014): 421-427.

Filippo Varese, Feikje Smeets, Marjan Drukker, Ritsaert Lieverse, Tineke Lataster, Wolfgang Viechtbauer, John Read, Jim van Os, and Richard P. Bentall, "Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies," *Schizophrenia Bulletin* 38, no. 4 (2012): 661-671.

Jonathan Leo (Jonathan.leo@lmunet.edu) is a professor of neuroanatomy at Lincoln Memorial University in Harrogate, Tennessee.