# Genetics: Unlocking the Future of Mental Illness Research

Experts say our limited understanding of the brain has caught up with us and that psychiatric drug development has hit a wall. The best way forward, according to Huda Zogbhi, MD, from the Howard Hughes Medical Institute in Houston, might lie in our genes.

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Common wisdom says that if you want to cure a disease, you need to understand the underlying causes of that disease. If that's the case, then we are in trouble when it comes to mental illness. There are theories for how depression, bipolar disorder and schizophrenia spring from chemical and structural problems in the brain, but experts say our limited understanding of the process has brought us about as far as we can go in terms of developing new treatments for these disorders. If we want better treatments, they say, then a revolution is in order: a genetic revolution.

On March 30, Thomas Insel, MD, the director of the National Institute of Mental Health (NIMH), stated plainly in a blog post on the NIMH website what a growing number of large studies have been suggesting for some time: "If we are honest with ourselves and our patients, we need to admit that today's treatments, both medications and psychosocial interventions, may be good, but they are not good enough."

Insel goes on to point out some of the deficiencies of current treatments—and the worrisome fact that what he calls the "old model" of drug development for mental illnesses isn't working anymore. The key question therefore is what to do about an imperfect system that probably isn't capable of bringing mental health treatment to the next level. "Who will develop this new generation of medications for people with mental illness?" Insel asked.

In answer to that question, Insel referenced in his blog post a proposal issued by a group of leading neurobiologists and geneticists in the journal *Science*. Huda Zoghbi, MD—a professor at Baylor College of Medicine and an investigator with the Howard Hughes Medical Institute—and her colleagues proposed that we should be spending more on the study of genes in people with mental illness and mapping the neuronal circuits of their brains.

Our genes, along with our environment, shape our brains over the course of a lifetime. Among other things, genes have the capacity to spur the creation of a new cell or to generate proteins that affect the behavior of other cells. Think of a row of dominos that splits in two, and then four,

and ultimately hundreds of different rows. Tip just one domino and it determines the action of a thousand others. Though the example is highly simplified, that first domino is the equivalent of a gene.  Thus a single gene in the brain, a system so complex we still don't fully understand it, can have a profound effect on a person's thinking and mood.

Zoghbi hopes that mapping the influence of specific genes on the brains of people with diseases like schizophrenia or autism will one day lead to better treatments. She acknowledges that this kind of research won't generate quick returns, but it could pay off handsomely in the long run. "Let's do something today, where the technology is ready, and this will increase our likelihood that in maybe 10 to 15 years we might have interventions that will make the lives of patients better," Zoghbi says. "If we do nothing, if we maintain the status quo, it could be 50 years from now before we have something good."

System Failure

In his blog post, Insel spells out the traditional model of developing medicines for psychological disorders. First, the NIMH funds early research to discover how molecules in the brain work, and how they influence diseases, then the pharmaceutical industry steps in. That industry, along with academic scientists, screens millions of chemical compounds to find those that act on the target molecules in the brain. At that point, industry takes over; developing the chemical compounds into drugs and then testing them, first in animals and then humans. If a drug makes it to U.S. Food and Drug Administration approval, the NIMH often compares the new drugs with a host of older ones and determines how much—if any—additional benefit the new drug offers in terms of efficacy or safety.

"This traditional model appears to be in trouble," Insel says. "Over the past year, biotech has gradually moved away from central nervous system (CNS) targets, citing the difficulty of creating new drugs in this area. In the past couple months, two of the major pharmaceutical companies for antidepressants and antipsychotics, GlaxoSmithKline (GSK) and AstraZeneca, have announced termination of their psychiatric medication development programs. There are worrisome indications that other companies may soon follow."

One of the main problems, Insel goes on to recount, is that drug development based on our current understanding of the molecular underpinnings of the brain are no longer resulting in medications that work.

"If industry continues to abandon medication development for those with mental illness," Insel continues, "NIMH, either alone or in a partnership, will need to fill the gap by investing in the next generation of treatments."

That next generation of treatments might depend on expanding our knowledge of how genes influence mental illness.

Enter the Genetic Revolution

The prospects for developing revolutionary new drugs over the next several years are not particularly high. This is due in large part, Zoghbi says, to our lack of knowledge about the basic mechanisms that underlie many major illnesses.

“We know so little,” she asserts. “I mean, think about how common schizophrenia and autism are, and yet we know so little about how many molecules can really cause the neurons to malfunction to give you features of schizophrenia or autism.”

Zogbhi explains the implications of our lack of knowledge. “It’s sort of like wanting to have the most effective transportation system in a city but you have no clue about the number of people who need the transportation: where people live, where people work, where they want to go…. This is really why we thought about writing our article, so that a commitment can be made to identify the building blocks, the molecules and the neuronal types and the circuits that could be affected and lead to any of these diseases. I think the payoff of this kind of work will be big.”

Technology to sequence the entire human genome more quickly and cheaply has come just at the time that investigation into the genetic links to mental illness are most needed. Zogbhi says that identifying the aberrant genes that are common to people with specific diseases can lead to studies that investigate the role of those genes in cells, then in cellular networks, and ultimately in behavior and thinking. This kind of research, in turn, could give rise to the next generation of diagnostic tests and treatment tools for specific illnesses.

Zogbhi acknowledges that understanding the genetic basis for disease is only part of the picture; environment also plays a prominent role. Forty years ago, the “nurturists” held sway—those who believed that a person’s upbringing and environment were at the heart of most illnesses. Then the “naturists” swept in and claimed the field, showing in various experiments how important brain chemistry and function—and the genes affecting them—were to the development of psychological disorders. For much of the last 40 years, those two camps have been in serious conflict. Fortunately, the field has evolved to embrace both views. This pleases Zogbhi.

“If you’re doomed to be born with a gene that makes you susceptible to certain diseases, by understanding the relationship between the gene and the environment, you can actually capitalize on that and manipulate the environment so that you can still be functional,” she says, “and you can still go through college and not succumb to all the features of a disease like schizophrenia. You can then be integrated into society where you’re productive. This is to me one of the most exciting revelations in science in the last decade.”

Exploring this new avenue of science is going to take money, and lots of it. Zoghbi says that the NIHM shouldn’t abandon ongoing research, but she does feel that a significant investment in genetics and neural circuitry is a must to come up with transformative solutions.

“It is more productive for society to spend the money on understanding why something is wrong, how it goes wrong and what you can do about it, than to simply let things go wrong and see how we can put Band-Aids on them and patch them, ” Zogbhi urges. “ We spend a lot more money on

Band-Aids and I just hope we take advantage of this opportunity to really get to the root of the problems and how to prevent them.”

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