Field of Genes

Unlocking the Future of Mental Illness Research.

March 1, 2011 By David Evans

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—a professor at Baylor College of Medicine in Houston and an investigator with the Howard Hughes Medical Institute—might lie in our genes.

Common wisdom says that if you want to cure a disease, you need to understand the underlying causes of that disease. There are theories for how depression, bipolar disorder and schizophrenia spring from chemical and structural problems in the brain, but 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, then we may need a genetic revolution.

Thomas Insel, MD, the director of the National Institute of Mental Health (NIMH), says what a growing number of 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.”

He points out some of the deficiencies of current treatments—and the worrisome fact that the “old model” of drug development for mental illnesses isn’t working anymore. The key question is what to do about an imperfect system that probably isn’t capable of bringing mental health treatment to the next level.

To answer that question, Insel referenced a proposal issued by a group of leading neurobiologists and geneticists in the journal Science. In short, Zoghbi and her colleagues proposed we spend more on studying 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. "[By doing research] today, it 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.

System Failure

In a controversial blog post on this topic, Insel spelled 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 influence diseases. Then the pharmaceutical 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 2010], two major pharmaceutical companies for antidepressants and antipsychotics, GlaxoSmithKline (GSK) and AstraZeneca, have announced termination of their psychiatric medication development programs. There are worrisome indications other companies may soon follow."

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

The next generation of treatments might require 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. According to Zoghbi, this is due in large part to our lack of knowledge about the basic mechanisms that underlie many major mental illnesses.

"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 [those conditions]."

She continues, “It’s 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…. [We need] 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. The payoff of this kind of work will be big.”

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 could give rise to the next generation of diagnostic tests and treatment tools for specific illnesses.

Understanding the genetic basis for disease is only part of the picture; environment also plays a prominent role. Forty years ago, the “nurturists”—those who believed that a person’s upbringing and environment were at the heart of most illnesses—held sway. Then the “naturists” swept in and showed 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 past 40 years, those two camps have been in serious conflict. Fortunately, the field has evolved to embrace both views.

“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,” Zoghbi says.

Exploring this new avenue of science is going to take money, and lots of it. She believes that the NIMH shouldn’t abandon ongoing research, but feels 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 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, ” she says. “ We spend a lot more money on [proverbial] 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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