From the Lab to the Couch: Personalized Psychiatry in the Genomic Era

By Karen Brown on Wed, 04 Dec 2013

http://www.pbs.org/wgbh/nova/next/body/personalized-psychiatry/

Last spring, my half-sister Michele called me concerned about her 21-year-old daughter's mental health, as she'd had several bouts of depression and it appeared another one was coming on. This time, Michele was eager to get in touch with her daughter's therapist before their next meeting. She had some new—and potentially treatment-altering—information.

"Her tests came back," Michele told me. "Turns out she's got a MTHFR-gene mutation. We're waiting to find out which kind." This was not a conversation anyone would have had 10 years ago, and it's not one that many are having now. But if personalized, gene-based medicine keeps expanding into the brain sciences, it might be.

Michele, who works as a medical researcher in Australia, may know more than the average parent about the potential of genetics in treating psychiatric conditions. She had read studies that a mutation in the MTHFR gene may increase the risk of psychiatric disorders. Depending on the variation of the mutation, it could also signify which medications are most useful—with some studies recommending folate supplements instead of, or in addition to, antidepressants.

She wasn't expecting the information to translate directly into a cure for her daughter's depression, the way she might expect penicillin to work on strep throat. But she was hoping for a treatment plan a few steps above educated guessing, which—unlike infectious disease or cancer medicine—is still the primary approach in psychiatry. "You basically have this bind—that we have very effective treatments," says Helen Mayberg, professor of psychiatry, neurology, and radiology at Emory University in Atlanta. "The problem is that it's trial and error for any one person."

Even the most skilled psychiatrists tend to choose medications or therapy based on population-wide statistics, not individual profiles. As a result, a great many patients get cycled through myriad medications and therapies before they come across something that works well—and without side effects. Each false start could waste months of time, during which jobs are lost, relationships end, and misery endures. Could the new era of personalized medicine offer a way to shorten their suffering?

"We are very much at the precipice of starting to think and do these studies," says Dr. Madhukar Trivedi, a psychiatric researcher at University of Texas Southwestern Medical School in Dallas, "but were are still early in the course of this, compared to some of our medical brethren."

Nevertheless, the number of researchers like Trivedi, who are searching for biological clues to psychiatric treatment, is multiplying, buoyed by support from federal agencies, including the National Institutes of Mental Health. They call the field "personalized psychiatry."

"We are very committed to taking genetics as far it will go," says Tom Insel, director of the NIMH. Granted, he says, the field of personalized psychiatry is still "more of a promise than a reality, and that sets it apart from genetics of different tumors or cancers. But it's exactly where we need to be going."

The latest research into the psychiatric genome fits with NIMH's newest priorities. Last spring, when the fifth edition of the Diagnostic Standards Manual (DSM5) came out, Insel lamented the degree to which mental health

providers remain dependent on symptoms to diagnose disease, rather than underlying biology. He announced NIMH funding would be shifting towards the search for psychiatric biomarkers—a practice he calls "precision psychiatry."

"What makes this especially interesting," Insel says, "is that when you look at scores of genes, they don't look like they've been picked at random. They look like they tell a story."

Search for Biomarkers

Genetic variation is thought to help explain why some people in similar environments get psychiatric illness and others don't—though the messiness of mental illness has made it difficult to match specific genes with complex disorders.

Large-scale epidemiological research into family histories of mental illness, known as genome-wide association studies, have suggested links between heredity and disease. But psychiatric researchers have remained stymied when it comes to using genetic profiles to predict who will develop major disorders such as schizophrenia, depression, or bipolar disorder. Finding a genetic biomarker that can actually direct treatment is harder still.

When personalized, genomic medicine was getting off the ground a decade ago, the hope was "there would be some biomarker of some high reliability, reproducibility for psychiatric disorders, to personalize it, or give us greater precision," says Dr. Francis Lee, who runs a psychiatric research lab at Weill Cornell Medical College, "and that hasn't happened yet."

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Genes direct production of proteins, which in turn can affect how medications are metabolized, whether they find their targeted receptors, and which neurotransmitters are most accessible. Early on, Lee was expecting to link a single gene mutation to a psychiatric disorder the way gene mutations have been linked to sickle cell anemia or cystic fibrosis. "I was naive 10 years ago," he says. "There's not going to be one single gene. There's probably going to be an ensemble of genes."

In recent years, however, researchers have begun to find significant genetic clues to mental illness, thanks in part to the NIMH-funded study "Sequenced Treatment Alternatives to Relieve Depression," known as Star-D, data from which were released in 2006. The six-year, $35-million study followed 2,876 participants. The goal was to help narrow down treatment options for the 60-70% of depression patients for whom the first medication does not work. "We have 30 different depression medications, many types of psychotherapy, exercise, ECT [electroshock therapy]," says Trivedi, who was principal investigator on the study. "No one treatment is good for everyone."

Subsequent researchers have mined the database of genetic data from the Star-D trial. For example, one study compared the genetic profiles of the participants who responded well to the drug Celexa (citalopram) with those who didn't. People with a variation in the HTR2A gene and the GRIK4 gene were found most likely to respond well to the drug. These findings are promising, Trivedi says, "and yet there's a hole. And the hole is, we currently do not have a lab test that helps me either diagnose or decide which treatment is better than another for a given patient."

Filling that hole became the impetus for Trivedi's latest NIMH-funded study, called Embarc. Researchers are halfway through a four-year study, in which they take blood tests and brain scans on subjects in four cities across the country, divide them up into genetic subgroups, test different medications on each, and compare the results against a placebo and each other.

Trivedi is not ready to disclose early results—having just completed the first phase—other than to call them "encouraging." Researchers are planning to match up genetic biomarkers to structural markers in the brain such as cortical thickness and functional markers such as brain circuitry and connectivity. During treatment, they will look at epigenetic changes, or ways in which gene expression adapts to medication and "shows changes in the patient's

biology that can be a harbinger or preventer of eventual outcomes," Trivedi says. "So you don't have to wait 8 to 12 weeks to decide if this treatment is good or not for that patient."

Anxious Mice

One problem in psychiatric research is knowing what to measure and how to measure it. In studies of obesity or hypertension, scientists can measure weight gain or blood pressure. In psychiatry, Lee says, it's hard to measure how sad you are, how suicidal, or how anxious. "We're still using self-report and psychiatric interviews for many of these types of studies."

So Lee and his colleagues started their research at the molecular level. They focused on a particular genetic variant, one connected to a growth factor called brain-derived neurotrophic factor, or BDNF. The BDNF gene variant occurs in 30% percent of Caucasians and 50% of Asians, according to the Human Genome Project. "While many studies have shown it's not going to be predictive of who gets, for example, a certain form of anxiety disorder," says Lee, "it might actually turn out to be something that would predict who will respond better or worse to a variety of treatments."

His group started by placing the BDNF gene variant—found almost exclusively in humans—into mice. After seven years, Lee and co-author B.J. Casey found that mice injected with the altered gene exhibited what's called "fear extinction," a form of learning that diminishes a particular fear. The results suggested that people with the BDNF polymorphism might have a harder time using cognitive behavioral therapy, known as CBT, against anxiety disorders since the treatment relies on unlearning fearful associations. For instance, in humans, that might mean uncoupling loud bangs from the memory of gunshots, or divorcing the sight of a neighborhood intersection from a past car accident.

After Lee and Casey's mouse study, another research group based at the University of Puerto Rico looked at whether BDNF levels in humans correlates with how well CBT reduces a person's symptoms of post-traumatic stress disorder—and found they did. "With CBT, you basically have to train your brain," says Lee. "And that's what BDNF fits very well. It's a plasticity gene."

Now, Lee is in the middle of another BNDF study with Dr. JoAnn Difede, one funded by the Department of Defense, involving veterans returning from Iraq and Afghanistan who have a PTSD diagnosis. "You have 50% of the people who have PTSD don't respond to CBT or to drugs, and no one knows why," Lee says. "You can imagine this genetic variant might explain a portion of that."

Since his working hypothesis suggests that the BDNF gene variant makes cognitive behavioral therapy less effective, Lee and colleagues are testing a drug that could bypass the BDNF mechanism. They're giving D-Cycloserine—an antibiotic that also works as a short-acting cognitive enhancer—to veterans who carry the BDNF gene variant. If Lee is right, the drug could make the therapy more effective in veterans who show the same "deficit in fear extinction" that his mice did.

"This is what I think the future of how personalized psychiatry will work," Lee says. "You will find there are patients who, for example, have a [gene] variant that won't let them respond to traditional cognitive behavioral therapy, for a variety of reasons, but then you can find a drug that will actually help you get around the problem."

This could be game-changing for soldiers, in particular. An estimated 15-30% of those who go into combat are expected to come home with PTSD, and many of them appear resistant to the traditional treatments. Since most soldiers already have to give the military biological samples when they sign up, Lee proposes comparing their genetic profiles against a panel of PTSD or anxiety-disorder related genes and identifying those who have a variant that does not do well on CBT. They would be candidates for the cognitive enhancer or a longer and more intensive regimen of CBT.

“We probably can’t explain why you’re the one out of five subjects who actually got PTSD,” Lee says. But, he continues, “what we will be able to tell them is that, ‘we are going to go down a very methodical treatment course for you, and the genetic information might help us accelerate the time to help treat you faster.’ ”

“We just have to be smarter than we were 10 years ago,” he added. “It’s not just going to be a be-all diagnostic marker, but it could be something that would inform what we now call pharmacogenetics,” or the use of genetic information in determining which drugs to prescribe.

Peering into the Brain

Dr. Mayberg, the Emory psychiatry professor, thinks she may be even closer to finding a treatment-changing biomarker, not through genetic tests but through brain scans. For decades, she has been trying to map circuits in the brain using evolving methods in neuroimaging, from CT scanning to functional MRI. Early on, she started by looking at the brains of people with diseases such as Parkinson’s, Huntington’s, and Alzeimer’s before moving onto depression. She was motivated by the discouraging statistic that 40% of the depressed population does not respond to the traditional regimen of antidepressant drugs and psychotherapy. “So why doesn’t everybody get well?” she says. “It isn’t that the treatment is bad. It just may not be good for *you*.”

In the same way that some diabetics respond to pills and others to injected insulin, Mayberg says, depressed patients need to find a match between their brain type and their treatment. In her latest research, she wanted to know how the brain’s metabolism and circuitry looks when a treatment is working—be it medication or talk therapy—versus when it’s not.

“We want to not only match a patient to a treatment that is most likely to get them well,” Mayberg says, “but we also want to know in advance that a treatment is unlikely to work.”

The resulting study, published just this past June, measured glucose metabolism in the brain using a specialized PET scan. First the researchers looked at resting brain scans, when the subject isn’t doing anything. Then one half received 12 weeks of cognitive behavioral therapy from expert therapists; the other received 12 weeks of the antidepressant escitalopram oxalate.

Researchers observed who responded to which treatment and who responded to none, matching those results to the brain scans. They focused on six regions of the brain. The one region that seemed to predict success was the right interior insula, which is considered a key area for sensory and emotional processing. If someone had high activity in the insula, they did great on drugs but not therapy, Mayberg says. If they had low activity in the insula, they did great on therapy but drugs were ineffective.

To Mayberg, this is the very definition of a biomarker. But to confirm the finding, she’s planning a new study that would follow a more prospective method. Researchers would recruit patients according to their insula activity, try out the treatment they think matches an individual’s brain structure, and see if it works. They’ll know if they’re right if the remission rate is greater than 40%—the traditional rate of success when doctors use trial and error along with a patient’s symptoms and family history. “If something is going to actually be useful, you need to know that, if I treated by the biomarker, I did better than the usual way we do it,” Mayberg says.

Increasingly, other researchers are also looking for clues in brain structure. In one recent study, researchers found that patients with psychosis who had more cortical gyrification—folding of the cerebral cortex—responded better to antipsychotic drugs than those with less gyrification. But with rising skepticism in the general public over the promise of neuroimaging, and neuroscience in general, (take the recent book, “Brainwashed: The Seductive Appeal of Mindless Neuroscience”), will clinicians be likely to order expensive brain scans for their patients—and will insurance companies pay?

They certainly ought to, Mayberg says. “Nobody questions when you have chest pain and you end up on an angiogram table,” she says. So why should fMRIs be off limits when it comes to treating a potentially lethal disease like depression?

“If this is a test that actually is reliable and valid and sensitive and specific, and works as a biomarker,” she says, “why shouldn’t we be scanning people to make management decisions when we can’t do it any other way?”

From Lab to Practice

Private industry is paying close attention. Some companies are already advertising genetic testing kits or consumer brain scans for psychiatric treatment, and the Mayo Clinic recently won a patent for a clinical decision-making tool based on psychiatric genetics. But many experts in the field caution against letting either commercial or clinical interests outpace solid research.

Dr. Trivedi of the University of Texas says he wants to see more investment in the science—using larger sample sizes—before clinicians use blood tests, genetic profiles, or brain scans to address a complex set of behavioral and emotional factors. “If they are using it as one more tool in their decision making,” he says, “then it is OK.” Dr. Lee of Weill Cornell, while excited by his research into neurotrophic gene variants, believes any clinical application is “still years away,” after his and others’ studies have been peer-reviewed and replicated.

The good news, he says, is that by then, genetic sequencing for the general population is likely to be quite affordable. Consumers can already hire companies like 23andMe to produce a panel of gene variants for $99, although they don’t currently include ones implicated in psychiatric disorders.

As for my niece in Australia, after she tested positive for the MTHFR gene variant, her doctor recommended she try a specialized diet, plus folate supplements, to address her depression. But after a few months, she couldn’t take the restrictions and decided to try a more traditional route: medications, exercise, and keeping busy. With no concrete scientific proof—trial and error is still the go-to approach.