

JOHNS HOPKINS
MEDICINE

MoodMatters

NEWS FROM THE JOHNS HOPKINS MOOD DISORDERS CENTER

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Looking for genetic 'typos'

The story of someone's susceptibility to bipolar disorder, or any illness with a genetic component, is all there in the DNA, just waiting to be figured out. Also written there are answers to questions like *Will this particular medicine help me, or is it a waste of time?* and *Did I inherit this problem?*

Psychiatrist **James Potash**, the Arlene and Robert Kogod Professor, has spent years looking at the genetics of mood disorders. He has studied the genome, the entire genetic blueprint—the chemical owner's manual that spells out how our cells make specific use of the endless strings of proteins—looking for landmarks, variations, red flags. The DNA he's pored over has come from Johns Hopkins Mood Disorder Center patients and their families, volunteers who have donated their blood with the hope that knowledge will come from any genetic secrets that Potash and colleagues can wrest from a very long tickertape—millions of bits of information that would be impossible to make sense of without computers.

Now, Potash believes, a new way of asking questions will yield answers that can be matched with what he has already learned to refine his search for better, more personalized ways to treat bipolar disorder. He is working to decipher the synaptome—basically, a circuit map of communication made from studying chemical messages that are sent by nerve cells in the brain. A synapse is a tiny gap between one nerve fiber and the next; every time a nerve impulse is passed along, a neurotransmitter crosses this gap and sparks an electrical impulse in the next neuron. Potash and



James Potash believes that asking new questions in new ways holds the key to finding better treatments.

colleagues know which proteins are in the synapses, and which genes—they are looking at 1,500—express these brain synaptic proteins.

In a study of DNA from blood samples of 800 people with bipolar disorder and of 400 people who do not have it, they're looking for mutations that interfere with the function of these synaptic proteins. "The key answers," says Potash, "will be found in changes in the DNA that result in severe 'typos' in the genes that vastly change their meaning or render them meaningless, as if *well* were misspelled as *hell* or *welq*." ■



"It's not one simple gene," says Peter Zandi, "where if you have a certain mutation, you're going to develop bipolar disorder."

Action potential

Scientists are convinced that genetic factors are important in determining who develops bipolar disorder. "But it's not one simple gene," says scientist **Peter Zandi**. "There's something very complicated going on in the genetic architecture of the disease."

Zandi has been doing genome-wide association studies, looking at DNA from thousands of people who have bipolar disorder and thousands who don't, seeking genetic markers related to who gets the disease and who doesn't. But this is like looking through thousands of mug shots at the police station to find a single criminal when there's actually a whole gang at large.

Now Zandi is focusing on a gene called ANK3, which many recent studies have pointed to as a likely culprit in bipolar disorder. "It's clearly not the only gene, but it's a leading candidate," he says. "The question is, how is it involved?" Zandi and colleagues decided to look at two other genes that ANK3 interacts with: KCNQ2 and KCNQ3.

"These are ion channel genes," says Zandi. "That's interesting to us because ANK3 is a scaffolding protein responsible for forming these ion channels and locating them in certain parts of the membranes of neurons." When ANK3 interacts with KCNQ2 and KCNQ3, it forms a potassium ion channel that somehow affects the neuron's "action potential," a tiny flash of electricity as a nerve impulse is transmitted. Think of ANK3 as the utility pole and KCNQ2/3 as the transformers routing the electricity.

Zandi suspects that susceptibility to bipolar disorder may be connected to the disruption of the normal interaction between ANK3 and the two potassium ion channel genes, and that this, in turn, disrupts the ability of neurons to do their job. "That's pretty exciting," he says. "If we find a whole new pathway that's important, that would lead us to new targets to develop drugs that might help inhibit disruption of this pathway." ■



Greetings all! We are very pleased to have the chance to update you on the exciting new developments in our Mood Disorders Center. First, you may have noticed that we have changed our newsletter name from *Genetic Links* to *Mood Matters*. This change reflects the broadening of the scope of our efforts. Although genetics remains central to the research that we do, we have also put into place new programs designed to attack the illness on other fronts. These include work aimed at looking at brain structure in mood disorders, at developing new brain stimulation treatments, and at finding genetic variations that predict who will respond to particular medications. We want to thank all of you who have so generously given of your time and energy to help move the process of discovery forward. It is because of your contributions that gene discovery in mood disorders is now truly advancing. Together we will keep the momentum going and make a difference for those who are suffering.

Jimmy Potash
Arlene and Robert Kogod
Associate Professor
Director, Mood Disorders
Research



Frank Mondimore

Will lithium work? One day, a blood test may give the answer.

Imagine that you're diagnosed with a bipolar disorder, and the next step is a blood test—so your doctor can check your genetic profile and determine which drug is most likely to help you. “The idea has tremendous potential to help patients,” says scientist **Peter Zandi**, who with psychiatrist **Frank Mondimore** and colleagues, has embarked on an ambitious project to determine the “pharmacogenetics” of lithium. They hope to find genetic markers that will identify who is likely to respond well to lithium and who should try a different drug.

The study, involving eight hospitals in the United States and two overseas, will follow 700 people with bipolar disorder who are taking lithium. “We will enroll patients who are stable on just lithium,” says Mondimore, in order to isolate genetic factors that are specific to response to lithium alone. “If someone isn't doing well or relapses, we will cross them over to Depakote,” another mood-stabilizing drug, which has a different chemical action. “We'll follow them all for

two years to see how they do.” Each visit will include a physical exam and various rating scales to measure progress and make sure the patient is getting better and staying well.

Then comes the intensive, genome-wide association study of the patients' DNA as the scientists look for markers in people who responded well to lithium

The genome is the body's chemical recipe book; each of our cells uses it to make specific building blocks—actually, strings of chemicals, identified with letters.

or to Depakote. The genome is the body's chemical recipe book; each of our cells uses it to make specific building blocks—actually, strings of chemicals, identified with letters. The run of letters is impenetrable; it helps that there are landmarks, called SNPs (pronounced “snips”).

These are characteristic fluctuations, like misspelled words, that can help scientists home in on particular neighborhoods of the genome, out of a million “street addresses.”

Over time, Zandi hopes to expand the search to include markers that show which patients are more likely to have significant side effects that, he says, “can often be very troubling and can discourage adherence to the medication—one of the leading reasons why patients relapse. Any genetic factors that can help predict who's going to have problematic side effects would be incredibly important clinically.”

This research marks a sea-change from genetic studies done in the past, notes Mondimore. “Instead of looking for markers for susceptibility to disease, we are looking for markers that will be of direct help to patients,” he says. “This is personalized medicine, helping us tailor the right treatment to the individual patient.” The project is supported by both the NIH and “Project Match,” led by Hopkins' friend Gil Lamphere. ■

Buoyed by entrepreneurial philanthropy

Gil Lamphere thinks a lot about the people who are where he used to be, trapped in the rock-bottom bleakness of depression. He knows what they're going through, and also knows how lucky he is to have found the right doctors, whose perseverance and creativity in testing, combining and fine-tuning medications brought him back, so that he feels better today than ever.



Gil Lamphere: "This was what I call a very high return on philanthropic investment."

Lamphere, a financier, even testified before a Congressional subcommittee to raise awareness that depression is a physical illness that takes time and understanding to treat. His remarkable story—for more than two years he endured a depression so severe that it defied 27 medicines and 42 electroconvulsive therapy treatments; then he came to Johns Hopkins, where psychiatrists Paul McHugh and Ray DePaulo had him feeling dramatically better within a few days—inspired people all over the country.

He began receiving calls from families of people "stuck at 50 percent, 40 percent of their normal personality," he says. "They were despondent, their families were breaking apart, they had no hope. I realized that nearly 16 million Americans are suffering from depression, and depression is going to surpass cancer very soon as the number one illness in the U.S."

Lamphere soon found a way he could use his own business expertise to help these people. At a meeting, James Potash, research director of the Mood Disorders Center, mentioned a project that might ease one of the most agonizing aspects of depression—the time-consuming process to find an effective drug. Potash hoped to develop a set of markers that could be used in a routine lab test to predict whether someone is genetically more likely to respond to the drugs lithium or Depakote. Lamphere immediately recognized the potential here; along with two friends, whom he describes as fellow "entrepreneurial philanthropists," he provided funding to move the research forward. "For not a lot of money, and in a very short period of time," he says, "you could affect millions of people."

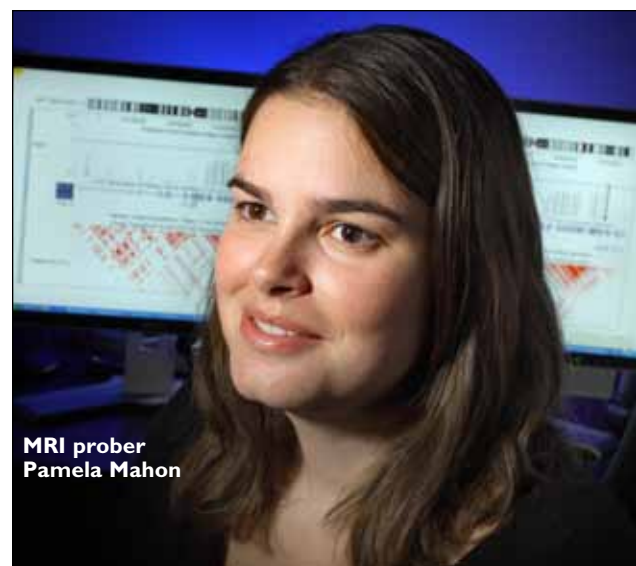
Now that the search for markers to identify whether lithium and Depakote will work is under way, the next step is to undertake the search for markers for other, chemically different drugs, he says, to end this "hit-and-miss game" for good. ■

Lithium and changes to the brain

The amygdala is hit hard in bipolar disorder. This little almond-shaped structure that nestles in each temporal lobe of the brain (there's one on either side of the head) plays a huge role in quality of life. It's a vital center where emotions, perception and experience are processed together. But in bipolar disorder, the amygdala's ability to do these tasks is impaired. There are changes in blood flow, and on an MRI, the amygdala looks very different from the way it ought to; there's less "gray matter" and a marked loss of volume, among other changes.

But then there's lithium. Although it doesn't help everyone with bipolar disorder, for those it does, the results are remarkable: Lithium helps restore amygdala function and stabilizes and protects its delicate cells and interactions.

Can lithium actually reverse the structural damage to the amygdala? **Pamela Mahon**, who specializes in neuroimaging genetics, is very interested in finding out. As part of Project Match, a multifaceted project designed to help people with bipolar disorder find the best medication as quickly



MRI prober Pamela Mahon

as possible, Mahon will obtain MRI brain images from each new patient who joins the study. As scientists scrutinize DNA samples from these patients, looking for genetic clues to help determine who will respond better to lithium or another drug, Depakote, Mahon will be looking for differences in the MRIs.

"We will be comparing the brain images of those who respond well to lithium and those who do not," she says. "We believe that in people who respond well, we will see an increase in the size of the amygdala."

The next step, she says, will be to connect the genetic variations with variations in the amygdala, "so that we can connect the genes to the brain images and ultimately to our knowledge of the disease itself." ■

A window into the brain

What's up your nose? Believe it or not, it's the next best thing to living brain tissue—plain old cells from the olfactory epithelium, the tissue lining the nasal cavity, which contains neurons from the central nervous system. "These neurons have many of the properties of brain nerve cells," says psychiatrist **Fernando Goes**, "which gives us a



For Fernando Goes, the nasal lining offers a great stand-in for brain neurons.

window into the brain." Goes and neuroscientist **Akira Sawa** are teaming up in a project to study these neurons in people with bipolar disorder.

Now, Goes is looking for volunteers, people with bipolar disorder, who are willing to donate a few cells. "It's a minor outpatient procedure, done by a specialized surgeon, that takes just a few

minutes," he explains. The majority of laboratory work to study bipolar disorder comes from blood samples. This chance to study living tissue, which can then be cultured in the lab, allows Goes to explore the biological pathways of these nerve cells. "This could reveal important insights about bipolar disorder," he says, "and allow us to test the effects of various new drugs."

If you have bipolar disorder, are between the ages of 18 and 65, and are interested in donating a few cells, Goes would love to talk to you. He can be reached at 443-287-6382 or fgoes1@jhmi.edu.

This study was made possible with private support from families of people with bipolar disorder. ■

Bigger is better

Decades ago, several top medical institutions joined forces to form national centers of excellence for treating cancer and heart disease. As soon as they did, breakthroughs in research and treatment started coming faster.

Three years ago, after years of trying to make it happen, we formed the National Network of Depression Centers to help people all over the country find the best treatment for depression and bipolar disorder. Johns Hopkins and 15 other centers began to integrate our clinical expertise and share what we're learning in our laboratories: It's easier to notice a genetic "red flag" in a group of thousands of people than it is in dozens or even a few hundred. Our ultimate goal is to establish more comprehensive depression centers throughout the country so that all Americans are no more than 250 miles away from specialized help, standardized assessments and personalized care.

You can learn more about this network at <http://www.nndc.org/>.

J. Raymond DePaulo Jr., M.D.
Director, Department of Psychiatry and Behavioral Sciences



Virginia Willour seeks clues to a deadly behavior.

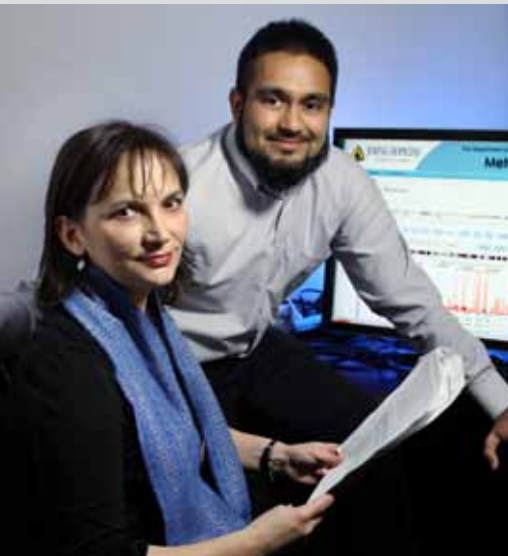
The genetics of attempted suicide

Is there something different in the genetic makeup of someone with bipolar disorder who attempts suicide? Research by geneticist **Virginia Willour** strongly suggests that there is.

Willour has been studying the genetic data of about 6,000 people from the United States and Europe who have bipolar disorder. These people have been divided into those who have attempted suicide and those who haven't. Otherwise, the two groups are as closely matched as possible by age, sex, health and other factors because, says Willour, "we want to make sure that the genetic differences we identify are related to suicidal behavior and not to something else."

One of the genes Willour has found may be involved in the same biological pathways that are regulated by lithium, "which may give us an idea of why lithium works to decrease suicide risk," she notes. A better understanding of how this gene and pathway work will dovetail nicely with other important work on lithium being done at the Mood Disorders Center; also, it might provide additional tools to help identify who might benefit most from lithium as well as an alternative to it.

Willour is encouraged by the progress, and the pace, of her findings thus far. "We're really fortunate," she says, "that suicidal behavior is taken so seriously by both the research community and the public. Because of that, we're able to get cooperation across universities and continents for our genetic studies." ■



Dunya Jancic and Fayez Seifuddin: the "Nerve Center"

Their work is rigorous, time-consuming, sometimes tedious and, increasingly, exciting. Meet **Dunya Jancic** and **Fayez Seifuddin**, the clinical genetic data managers of the Mood Disorders Center, where scientists are conducting research involving thousands of patients. For each patient, a single blood sample turns into "genotyped" DNA, collected on special SNP panels (each SNP represents a genetic landmark). Among a million SNPs across the genome for each person, scientists look for genetic markers for susceptibility to disease or response to treatment. Jancic, who has a Ph.D. in physics, and Seifuddin, who's working toward a Ph.D., say the vastness of the data they manage is good news for patients. "We're seeing progress much faster than I expected," Seifuddin says, "because we have so many samples." Research Director James Potash says the two are the operation's nerve center: "What they do is vital to our mission."

MoodMatters

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