JOHNS HOPKINS MEDICINE

GeneticLinks

NEWS FROM THE JOHNS HOPKINS MOOD DISORDERS CENTER FALL 2009

Where We Stand

The past year at the Mood Disorders Center has been rich with discovery. Thanks to the clinical information and DNA you have generously donated, we have many exciting new genetic findings that hold much promise for the treatment of mood disorders. You can learn more about them in these pages.

We are recruiting patients for studies of new medications in a program headed by Jennifer Payne, who directs the Women's Mood Disorders Program. We're also recruiting patients for brain stimulation treatments, including those involving transcranial magnetic stimulation, in a program headed by Irving Reti, who directs our ECT program. And we are planning studies to bring mood disorders into the age of personalized medicine by searching for genes that can predict if, for example, a patient responds better to lithium than to Depakote.

Last fall, we and 15 other psychiatry departments established the National Network of Depression Centers, and we hosted the first meeting of the network's governing board. J. Raymond DePaulo Jr., and Kay Redfield Jamison, who co-direct our center, are leading the way in bringing together the country's best researchers and practitioners to make a difference for people with mood disorders.

James Potash, M.D., M.P.H.
Arlene and Robert Kogod Associate Professor
Research Director, Johns Hopkins Mood Disorders Center

Does Your Family Suffer From Bipolar Disorder and Depression?

If you or a family member has bipolar disorder, and another member has bipolar disorder or depression, your family may qualify to participate in our research study and would be compensated.

Participation involves having an interview with a clinician and giving a small blood sample. You do not have to come to Johns Hopkins to participate. All information gathered will be confidential, and results will be published in a manner to ensure anonymity.

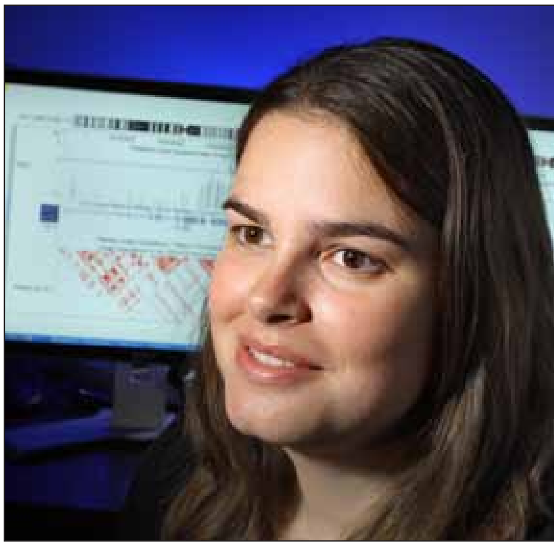
If you and your family might be interested in participating, please contact our research staff at 410-614-1017 or moods@jhu.edu.

Principal Investigator: **James Potash, M.D., M.P.H., RPN #85-01-07-01**

A Genetic Link to Postpartum Depression?

For up to 20 percent of women who give birth, the joy of having a newborn becomes overshadowed by changes in sleep, energy, appetite and concentration, and even thoughts of suicide and harming the baby. Until recently, scientists have known little about the genetics and biochemistry underlying PPD. Now, thanks to recent research conducted by the Johns Hopkins Women's Mood Disorders Center, they know more.

Psychiatrist Jennifer Payne, who heads the center, directed what is only the second study to examine the entire human genome for postpartum disorders. (The first study, conducted in the United Kingdom, focused on postpartum psychosis, a more severe, much rarer condition.) "Our goal," says psychiatric geneticist Pamela Belmonte Mahon, "was to search for chromosomal regions that harbor genetic variants that can lead to susceptibility to postpartum depression symptoms."



Pamela Belmonte Mahon: inching closer to postpartum depression's genetic variants.

The Hopkins team used blood samples from more than 1,000 women who had ever been pregnant and participated in the Genetics of Recurrent Early Onset Depression study or the National Institute of Mental Health's Genetics Initiative on Bipolar Disorder. About 30 percent of the women reported having symptoms of postpartum depression. By comparing that group with the 70 percent of women who didn't have symptoms, Payne and Belmonte Mahon determined which regions of the genome might show genetic changes that predispose women to PPD.

After conducting a linkage study that turned up suspicious regions on chromosome 1 and chromosome 9, they followed up with fine-mapping studies that identified one particular gene, HMCN1, which seems to be associated with postpartum depression symptoms. "It's a good candidate gene," says Belmonte Mahon. "It's expressed in the brain, and it contains estrogen receptor-binding sites."

If replicated in further studies, the results could be used to develop more targeted therapies. Says Payne, "We're trying to make treatments that fix what is actually broken."

At the same time, she adds, research on postpartum depression has broader implications for psychiatric care.

"We don't really know what has gone biochemically wrong in patients with major depression," says Payne. "Postpartum depression is one of the few ways that you can predict that a subgroup of the population will be depressed at a particular time. Understanding the biological basis of that can lead to a better understanding and treatment of depression in general." ■

To learn more about our studies, call 410-614-1017 or e-mail moods@jhu.edu.

Homing In on the Genome

Relentless genome detective James Potash tracks variations that increase risk for a mood disorder.

It's been clear for some time that a person's susceptibility to bipolar disorder varies widely and is largely hereditary. What's been less clear are how many genetic variations it takes—and which ones. And when you're talking about variations within the 25,000 or so genes in the human genome, finding them might seem a lot like finding a few needles in a haystack.

Yet, by conducting genome-wide association studies, that's exactly what psychiatrist James Potash is doing. "Think of it like a manhunt," says the recently named Arlene and Robert Kogod Professor in Mood Disorders. "You question everyone in the United States, and you narrow it down to one county. That's what our old screens were like. But now we have a higher resolution; now we're asking what block the person lives on."

That resolution is owed to a DNA microarray. "It's the same technology as computer chips," Potash explains. "Computer chips can take millions of resistors and cram them into a small space. DNA microarrays take millions of bits of DNA and put them in a tiny space."

Using blood from volunteers who donated their DNA, Potash and his team worked with researchers around the country to study 1 million places (single nucleotides) in the genome where there appears to be a common variation in people with bipolar disorder. The most intriguing result was in a gene known as ANK3, which had been implicated in previous studies. The results, which were published in the journal *Molecular Psychiatry*, showed that the variation in ANK3 corresponded to a roughly 40 percent increase in the risk for illness. "This is something, but not a huge risk," Potash says. "We had thought we would find variations that increase your risk by three- to fivefold. Instead there are probably going to be lots of variations that increase your risk individually, each by a small amount."

Now Potash is conducting a similar genome-wide association study for recurrent early-onset depression using the same high-resolution technology on a broad scale. Working with a publicly available dataset from the Netherlands and researchers at seven universities, he and his group are using DNA from blood donated over the last decade. "It's not the only study, but it's the most comprehensive kind of experiment," says Potash. "With these large-scale meta-analyses, the hope is that when you put the results of thousands of people together, you get results you feel confident about." ■

Of Mice and Moods

Some of the most important work in understanding the genetic underpinnings of mood disorders can be done only in the organ where the illness lives: the brain. To that end, the Mood Disorders Center is studying the actual brain tissue of mice and rats for clues to how certain gene modifications called epigenetic changes might help trigger these disorders. But why use rodent tissue instead of real human brains?

For one thing, human brain tissue can be studied only after death. And researchers can't control or even know what state the brain was in when the tissue was removed. The person may have been in a manic phase. Or on medication. There also can be considerable genetic variation between samples.

"These things cause a lot of background noise during experiments," says Richard Lee, a postdoctoral researcher in psychiatrist James Potash's lab who wrote the protocol to get permission from Hopkins' Animal Care and Use Committee for the studies,. "An animal model allows us to get rid of all that. And we can completely control for medications."

One of the unknowns that Lee is tackling is the question of how, exactly, mood stabilizers such as lithium help people who have bipolar disorder. "We really have no idea how lithium works," he says. "It was discovered by serendipity. I want to give lithium to rats and then look at changes in gene expression and at epigenetic modifications. If we know why it works, then we can design better drugs."

Lee is also using mice to study gene modifications that occur with stress, which can lead to depression and bipolar disorder. This presents its own unique challenges because, as Lee quips, "there's no evidence of any mice showing signs of bipolar disorder or having suicidal thoughts." So, using methods approved and deemed to be humane, Lee creates stressors in the lab by spiking the animals' drinking water with stress hormones or gently restraining them in a tube.

Already, the work has located a region in the genome that responds epigenetically to stress. The results are preliminary, but the data are solid, Lee says. The hope is that the results will translate from mouse to human. ■

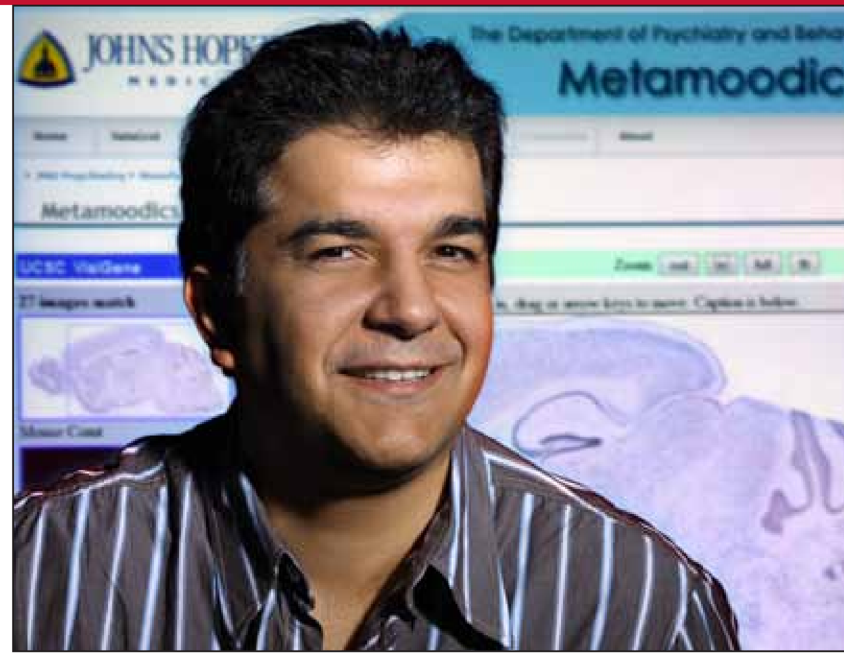
Richard Lee pays close attention to how drugs change gene expression—and behavior.

In the Meta-Mood

You're a scientist researching the genetics of bipolar disorder and you think you've found a particular gene that seems to predispose people to that condition. Before you start to do more research and analysis, you need to know what other researchers have already found. Has it been associated with bipolar disorder in earlier studies? Has it been linked to other mood disorders? What have other scientists learned about the biology of this gene?

Now, thanks to a Web application being developed at the Johns Hopkins Mood Disorders Center, you can go to a single Web site, type the name of that gene, and get all of that information fast, and for free.

This application, dubbed Metamoodics, integrates data from studies published in scientific journals and all over the Internet in a single place. "This information has been collated and curated so researchers don't have to do laborious searches through the literature and other biological databases to find answers," says Peter Zandi, professor of psychiatry, who began the software project nearly two years ago in collaboration with the Mood Disorders Center.



Mehdi Pirooznia considered all the things he, as a researcher, would want from a software program that stores mood disorder data.

The bulk of the data, from genome-wide association studies, is being supplied by collaborative research groups such as the Genetic Association Information Network, a public-private partnership established to investigate the genetic basis of common complex diseases. Data are also culled on specific genes by performing searches in PubMed. And, Metamooodics contains data from gene expression studies on mood disorders.

Eventually, Metamoodics will likely house data for approximately 500 genes, says Mehdi Pirooznia, a postdoctoral researcher working with Zandi who wrote the code for the software. In addition to searching by gene, users will be able to search by polymorphism (a genetic variation), chromosome or study.

The software also allows users to perform meta-analyses on the data they find. The gene set enrichment analysis, for example, lets researchers examine whether a set of genes together provide a better signal in a genome-wide experiment than does each gene individually.

Metamoodics also hosts discussion forums and has a place for a virtual conference to enable researchers to gather and talk about their work. "We hope that it will be a place for psychiatrists and researchers to go to do research and also become a community," says Pirooznia. For a closer look at the software, visit http://psychiatry.igm.jhmi.edu/metamoodics/. ■

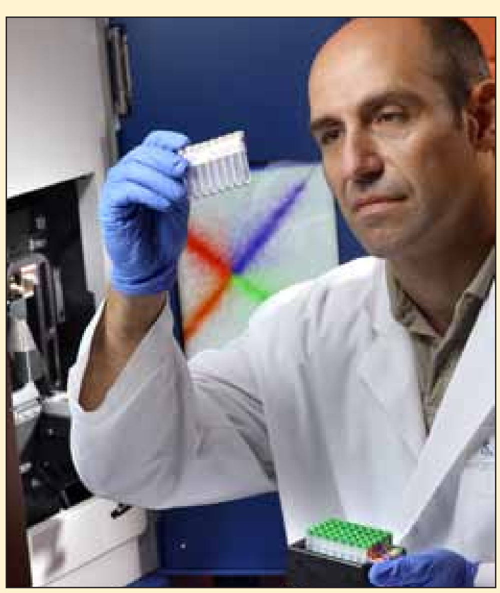
> "This information has been collated and curated so researchers don't have to do laborious searches through the literature and other biological databases to find answers."

The Order Behind the Disorder

Because genetics plays a strong role in the development of bipolar disorder and major depression, researchers at the Mood Disorder Center are working to identify which of the estimated 25,000 genes in the human genome predispose a person to developing these disorders. Now, thanks to a new DNA sequencing machine the Department of Psychiatry purchased at the end of last year, they can find those genes much faster.

Sequencing unlocks the genetic code of any sample of tissue by determining the order of the chemical letters called nucleotide bases—A, G, C and T—that spell out the genes in a molecule of DNA.

"With the old technology," says Sarven Sabunciyan, an assistant professor in Johns Hopkins' Division of Developmental Neurovirology, "we could get about 480,000 bases of sequencing information per week. But in a full run on the new machine, we can get 20 billion bases of sequencing data in the same amount of time and at a fraction of the cost."



Sarven Sabunciyan: Promising therapies begin with sequencing data.

Sabunciyan has been collaborating with psychiatrist James Potash at the Mood Disorders Center and with epigenetics pioneer Andrew Feinberg to discover the epigenetic factors involved in bipolar disorder and depression. Epigenetic modifications, which include everything but changes in the DNA sequence itself, can turn genes off and on and cause disease.

Sabunciyan has worked closely with Richard Lee (see page 2), a postdoctoral research fellow in Potash's lab. Lee is treating cells with mood stabilizers used to manage bipolar disorder, such as lithium and Depakote, to see how and where these drugs affect the genome. They are using the new sequencing machine to identify genes that get turned on or off in response to these medications. "Previous technology," Sabunciyan says, "did not allow us to do this on a genome-wide scale."

What they hope to find are clues that will lead to better therapies for people with bipolar disorder. And, thanks in large part to this new technology, says Lee, "Successful treatments might simply be a matter of turning off genes x, y and z." ■

Toward Cure for Our Great Depression

The data on mood disorders are consistently dire. Depression and bipolar disorder affect one in five Americans. Depression is second only to heart disease in terms of its share of health care costs. Yet there's been no commensurate, organized, large-scale research response to fight these diseases.

J. Raymond DePaulo: Strength in numbers.

Until now.

Taking a cue from what the National Comprehensive Cancer Network has accomplished, the Johns Hopkins Mood Disorders Center joined 15 other university-based psychiatry departments to found the National Network of Depression Centers last fall. "In terms of scientific opportunity," says psychiatrist J. Raymond DePaulo, co-director of the Mood Disorders Center, we believe that depression and psychiatry are at the same place that cancer was in 1971."

When Congress passed the National Cancer Act nearly 40 years ago, scientists were just beginning to unravel some of the mechanisms behind the then-second leading cause of death in the United States. The legislation authorized funding for a national cancer program and the establishment of National Cancer Institute-designated cancer centers. Today, treatment has advanced dramatically: Leukemia, for example, now has an 80 percent cure rate.

"We have a molecular toolkit that we could only have imagined in 1971," DePaulo says. "We have functional brain imaging methods to see the brain operating while a person is making decisions and in different states. And we have a highly prevalent, stigmatizing and often lethal condition to work on."

Just as people once whispered the very word *cancer*, many still consider mood disorder a disgrace. Simply by using the word *depression* in their facility names, the NNDC can make these illnesses part of the health care conversation and, they hope, attract new financial commitment.

Already the 16 centers are joining forces to develop standard clinical care guidelines. They're also discussing ways to collaborate on large-scale genetic studies and on transcranial magnetic stimulation, a noninvasive method to treat major depression by delivering electromagnetic pulses to the brain.

"There is a big need for big studies in terms of genetics and patient care," says DePaulo. "We can now do research with larger populations of patients across all 16 centers. That's the idea here." ■

It Would Be So Cool

In December 1992, after weeks of feeling good about herself, Cheryl Johnson sank into a deep depression. She told her therapist that she needed medication or she might kill herself. Within two days, she saw a psychiatrist, who diagnosed her with bipolar disorder and wrote her a prescription for lithium.

"Lithium saved my life," Johnson says. "Most people have that little thing in their mind that tells them to shut up when they should, but I didn't. Lithium put me in a place that made me feel more normal. It's nice to feel like everyone else."

Johnson, director of training and quality at an organization that provides services to people with disabilities, had to switch medications after 13 years, but through continued treatment and monitoring, she has managed her disease. Then, four years ago, she saw an advertisement calling for bipolar disorder patients to participate in a genetic study at Johns Hopkins. She picked up the telephone and signed up.

Johnson has undergone psychological testing and donated her blood to supply the study with DNA samples. And when she asked her parents to donate their blood, they did, which, she says, had the added benefit of making them more open to talking about her disorder. "It's not different from having a cardiac disease, except that with a cardiac disease, you can do things that make it worse, like consuming too much cholesterol. But with bipolar disorder, it's just there," Johnson says." The only thing I can do to help is to be involved with these studies."

Already, the DNA supplied by Johnson, her parents and other study volunteers has helped uncover evidence for the involvement in bipolar disorder of a gene called ANK3, which plays a role in the excitability of brain cells. "Participating feels so hopeful," says Johnson. "If there is anyone we can help benefit, who could get treatment earlier as a result, that would be so cool." ■

Cheryl Johnson—re-engaged in a favorite pastime.

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