Researchers find that single gene responsible for OCD-like behaviors in mice

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Researchers at the Ansary Stem Cell Institute and the Department of Psychiatry at Weill Cornell Medical College discovered that mice missing a single gene developed repetitive obsessive-compulsive-like behaviors. The genetically altered mice, which behaved much like people with a certain type of obsessive-compulsive disorder (OCD), could help scientists design new therapies for this debilitating condition.

The researchers made this serendipitous discovery while looking at the role of a gene, called Slitrk5, which they had earlier linked to blood stem cells and vascular cells. In the April 25 online edition of Nature Medicine they report how, in follow-up studies, mice in which the gene was disabled ("knocked-out") demonstrated obsessive self-grooming and extreme anxiety. Further study showed that the frontal lobe-to-striatum circuitry of the brains of these mice were altered in the same ways that are implicated in OCD in humans.

This discovery links Slitrk5 to development of OCD-like behaviors, and offers scientists a new mouse model of the disorder, say the study's senior co-investigators, Dr. Shahin Rafii and Dr. Francis S.Y. Lee. Dr. Rafii is director of the Ansary Stem Cell Institute and professor in genetic medicine Weill Cornell Medical College and and an HHMI investigator. Dr. Lee is associate professor of psychiatry and pharmacology at the Medical College.

"Overall, our data suggest that Slitrk5 may have a central role in the development of the core symptoms of OCD -- self-injurious, repetitive

behavior and increased anxiety," Dr. Rafii says. "Very few psychiatric disorders have been linked to a single gene, and it will be important to find out if patients with the disorder have an alteration of Slitrk5."

The findings may help scientists better understand both development and treatment for one or more of the several different types of human OCD behaviors, say Drs. Sergey Shmelkov and Adília Hormigo, the study's co-lead authors and members of the Ansary Stem Cell Institute. Dr. Shmelkov is an assistant research professor of genetic medicine, and Dr. Hormigo is an assistant professor of neurology at Weill Cornell Medical College and a neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"We can't draw direct parallels between mice and humans, because OCD behavior in mice shows up as excessive self-grooming, and in humans there is a broad spectrum of behaviors, from hand-washing to other compulsive actions as well as obsessive thoughts," says Dr. Lee. "But our finding of altered brain functioning suggests a very strong link at this point to some of the issues seen in humans."

The research team cannot say why a gene found in blood stem cells and vascular cells could be implicated in a behavioral brain disorder, but they speculate that "cross-talk" between the vascular system in the brain and neurons in brain tissue may be the link.

Dr. Rafii and his colleagues had previously identified Slitrk5 in the progenitor stem cells that create blood, and they subsequently demonstrated that the protein created by this gene is expressed in leukemia, embryonic stem cells, and in subsets of endothelial cells, which are the basic building blocks for the circulatory system.

In this study, the researchers were looking at the effects created when the Slitrk5 gene was "knocked out" in laboratory mice and replaced with

a "reporter" gene. "We did this because we wanted to look at the effect on the blood system, which is what we are primarily interested in," says Dr. Shmelkov. "But we didn't find anything, which was frustrating."

But then Dr. Shmelkov and Dr. Hormigo noticed that some of the knockout mice began to develop facial lesions, and over time, all of the mice without Slitrk5 eventually developed the same skin issues. They also noticed that the mice were hyperactive and seemed to groom themselves a lot. The researchers videotaped this behavior and quantified it, and found that the knockout mice groomed themselves significantly more than did wild-type mice, which served as the experimental control. A set of follow-up experiments with scientists from Dr. Lee's laboratory, Dr. Kevin Bath and Iva Dincheva, concluded that the mice were also considerably more anxious compared with control mice.

The scientists gave Prozac, a standard drug used in the treatment for patients with OCD, to both sets of mice, and found that excessive grooming stopped completely in the experimental animals. "Now that we have this mouse model, we can test new therapies for OCD that can ultimately be applied to humans," says Dr. Hormigo. "We know Prozac works to ameliorate some OCD symptoms in humans -- the drug also worked for our OCD mice -- but the effect can be temporary and more targeted treatments are needed."

The researchers then looked at brain function in the mice. By examining activity of the reporter gene that was substituted for Slitrk5 in knockout mice, they found that the gene was active throughout the brain, but excessively active in one part of the frontal cortex. Dr. Francis Lee's group, which included co-lead authors Dr. Deqiang Jing and Catia Proenca, then performed sophisticated analyses and discovered structural abnormalities in a related brain region, the striatum, an area of the brain involved in reward and decision-making. Neurons within the striatum

were less complex than in normal brain tissue, which is an issue because these neurons act like a hub that receives and transmits input to and from the cortex, says Dr. Jing. Further investigation demonstrated that the level of glutamate receptors in these particular neurons was decreased, compared with control mice. "These molecular findings suggest that this gene plays a unique, unexpected role in modifying glutamate neurotransmission in this particular circuit," says Ms. Proenca.

Other researchers have created mouse models of other types of OCD as recently as 2007. However, for the first time, the findings involving Slitrk5 by Drs. Rafii, Lee and their teams are consistent with imaging studies in humans with OCD that implicate dysregulation of corticostriatal circuitry in the disorder.

"This work is an unexpected off-shoot from stem cell science into the realm of psychiatry, and could potentially have major application for treatment of neuropsychiatric diseases," says Dr. Rafii.

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