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Mice Missing Gene Become Anxious and Obsessed

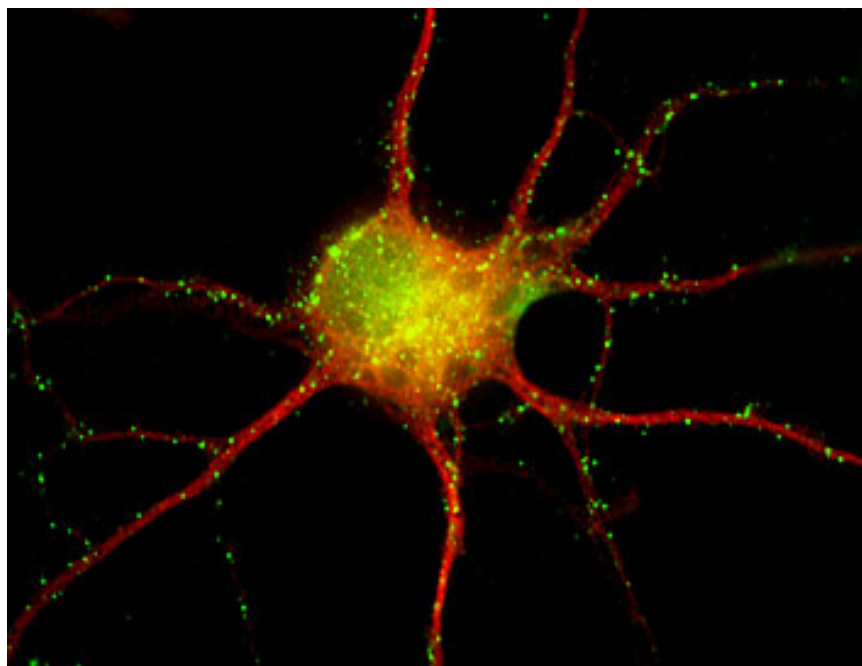


Image Title: An OCD-linked protein slitrk5 (green) in the dendrites (red) of a cortical neuron - Shahin Rafii

By switching off a single gene in mice, Howard Hughes Medical Institute (HHMI) researchers have created rodents that behave anxiously and fixate on grooming. The genetically altered mice, which behave much like people with obsessive-compulsive disorder, could help scientists design new therapies for this debilitating condition.

Obsessive-compulsive disorder (OCD) is associated with repetitive functions, such as handwashing or counting and organizing things over and over again. Whereas an unaffected person might lock a door and know it is locked, a person with OCD is never sure and keeps checking. The repetitive behavior can briefly eliminate the anxiety associated with OCD, but it doesn't stop the obsessive behavior. OCD can interfere with normal life and those with severe OCD can't hold down jobs. Scientists are eager to understand the causes of

OCD and to develop new treatments.

The development of the new animal model of OCD, which is described in an online publication of the journal *Nature Medicine* published April 25, 2010, was a surprising outcome of studies that began with a very different focus. While searching for genes that help regulate the cross-talk between blood stem cells and vascular cells, HHMI investigator Shahin Rafii of Weill Cornell Medical College in New York City and his colleagues Francis Lee and Sergey Shmelkov came across a gene called *slitrk5*. The gene is turned on in blood stem, leukemic, and vascular cells, they found, but it is most active in the brain.

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- **Shahin Rafii**

To see if they could find out more about *slitrk5*'s function, the researchers developed mice that completely lacked the gene. Given the gene's importance in stem cells, Rafii admits to being surprised when he saw that newborn mice lacking *slitrk5* seemed relatively normal. But when the mice reached about three months of age, the scientists began to notice that they seemed extremely anxious. They spent less time in open spaces or in high places and preferred corners or enclosed places more than mice typically do. "If you just touch them, they jump like crazy," says Shmelkov, who is the lead author on the study.

They also noticed wounds and bald patches on the animals' faces, which they soon discovered were caused by the animals' intense and persistent grooming. The mice groomed themselves longer and more frequently than normal mice -- to the point that they lost fur and developed sores. The behavior recalls that of people with trichotillomania, a disease related to OCD in which people obsessively tug on their hair to the point that they pull it out. Rafii and his colleagues found that treating the afflicted mice with Prozac (fluoxetine), which is commonly prescribed to alleviate the symptoms of OCD in patients, ameliorated the excessive grooming. Rafii says the new mouse line could be useful in searching for new drugs that have fewer side effects or are more effective at treating the symptoms of OCD than Prozac.

Rafii's team then collaborated with Lee and Adilia Hormigo of Weill Cornell, experts in molecular neuropsychiatry, on experiments that revealed patterns of activity in the animals' brains that were strikingly similar to those in people with OCD. The orbitofrontal cortex, which sits in the front of the brain, behind the eyes, and contributes to decision-making, was unusually active in the mice. Functional imaging studies have shown that this area is hyperactive in patients with OCD, too, but previous animal models of OCD didn't demonstrate the same kind of overactivation.

In addition, Rafii and his team found that in mice without *slitrk5*, a region deep in the brain called the striatum is smaller, forms less complex neural structures, and harbors fewer glutamate receptors than in normal mice. As a result, information does not appear to transmit well between the cortex and the striatum.

Rafii isn't certain yet what *slitrk5*'s function is, but based on the evidence his lab has observed so far, he suspects it may maintain the balance between signals that amplify and suppress neural activity. "Without the gene, the 'did I lock this door?' question keeps firing," says Rafii.

Rafii now wants to know whether humans with OCD have mutations in the *slitrk5* gene. His team has already begun searching for such mutations in the DNA of affected patients. If they are present, Rafii says that gene therapy to restore *slitrk5* function might be a promising avenue for treatment. He adds that manipulating the vascular and blood cells in which the team originally discovered the *slitrk5* gene might also lead to potential therapies for the difficult-to-manage disorder.