# Obsession's Unlikely Origins

*A shortage of certain immune cells might prompt obsessive-compulsive disorder.*

A BONE MARROW TRANSPLANT SEEMS AN UNLIKELY PRESCRIPTION FOR obsessive-compulsive disorder (OCD), an anxiety condition that drives people to repetitively wash their hands, for example, or continually check door locks. Surprisingly, a transplant stopped obsessive grooming in mice with a disorder that resembles OCD, according to HHMI investigator Mario Capecchi of the University of Utah and colleagues.

The researchers don't recommend the procedure for OCD patients. Bone marrow transplant is usually reserved for people whose bone marrow doesn't work properly or has been destroyed by chemotherapy or radiation treatment. But they do think the discovery could spark new treatments for a disorder that affects more than 2 million adults in the United States alone.

The most recent study isn't the first to implicate a faulty gene in obsessive behavior (see Web Extra, "Is OCD in the Blood?"). But it provides the first experimental evidence that defects in the immune system help trigger OCD, Capecchi says. Researchers had long suspected a connection, but the data remained circumstantial.

It's not surprising that grooming and immune defenses are tightly linked, he adds. Both have the same goal—protecting against diseases.

Capecchi and his colleagues didn't set out to find an OCD-immune link. Capecchi helped develop gene targeting, a technique that allows researchers to rewrite the DNA instructions of any gene—work for which he shared the 2007 Nobel Prize in Physiology or Medicine. For more than a decade, his team has used gene targeting to tease out the functions of *Hox* genes, a family of 39 genes that help shape the developing embryo and perform other jobs in the body. They disabled, or knocked out, the genes one by one in mice and documented the impact on the animals' health.

When Capecchi and his then graduate student Joy Greer got around to the gene *Hoxb8*, however, they found that the knockout mice showed no obvious physical flaws. So the pair put the nocturnal rodents under surveillance with infrared cameras. "We were looking for behaviors because we weren't seeing anything else that was wrong," says Capecchi. By tallying how the rodents spent their time, the researchers found that the animals devoted an hour each day to washing themselves, twice that of normal mice.

The mice weren't just getting squeaky clean. They groomed so intently that they ripped out clumps of fur, leaving large bald patches, and often licked their skin raw, the researchers reported in 2002. Capecchi and Greer likened the behavior to a disorder that's similar to OCD called trichotillomania, in which patients repeatedly pull or twist their hair until it falls out.

Capecchi's group decided to trace the source of the abnormal grooming by determining which brain cells made Hoxb8 protein. Nerve cells that control behavior were the likely candidates. However, the only brain cells cranking out Hoxb8 were

microglia, immune cells that scoop up and destroy cellular rubbish and invading pathogens. "That was a complete surprise," says Capecchi.

When the researchers returned to their knockout mice, they found that animals lacking *Hoxb8* carried 15 percent fewer microglia in their brains, suggesting that the cells are somehow necessary for normal neural wiring.

Capecchi and colleagues tested the idea by giving the mice bone marrow transplants. The brain harbors two kinds of microglia. About 60 percent of the cells are present in the brain from early in life. But the others descend from cells that originate in the bone marrow and then migrate into position. A bone marrow transplant can replace these cells.

When mice missing *Hoxb8* received bone marrow from normal animals, most of them groomed less. Their fur filled in, and their skin sores healed. And when Capecchi and colleagues introduced bone marrow from mice lacking *Hoxb8* into normal animals, the recipients began cleaning themselves excessively. The team reported its findings May 28, 2010, in *Cell*.

"People thought of microglia as scavengers," Capecchi says. "But we say they are monitoring what's going on in the brain and having an influence on the output." In other words, they change behavior. The cells could modify how the brain works in several ways, he notes. They could release chemical messengers called cytokines that trigger brain cells to fire more or less often. Microglia also send out tendrils that cozy up to synapses, the junctions between nerve cells, and thus they might be able to alter the activity between neurons.

Capecchi and colleagues are extending the work to patients, testing people with trichotillomania to determine whether they carry defects in their *Hoxb8* genes. He'd also like to study bone marrow recipients—around 300,000 of the procedures have been performed—to determine whether their behavior changed after the transplant.

Current OCD treatments include psychotherapy and drugs like Prozac (fluoxetine). But focusing on microglia could lead to alternatives that might work better than tricky therapies that try to fine-tune the nervous system, says Capecchi. "Treating the immune system, which we know more about, might have an influence on the disease." ■ –MITCH LESLIE

**WEB EXTRA**: To read about Shahin Rafii's work in the sidebar, "Is OCD in the Blood?" go to www.hhmi.org/bulletin/nov2010.

*VSA Partners*