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Gene gives clues to self-injurious behavior in rare disorder

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In humans, inherited mutations in a gene called HPRT1 lead to very specific self-destructive behavior. Boys with Lesch-Nyhan disease experience uncontrollable urges to bite their fingers, slam their arms into doorways and otherwise harm themselves.

Puzzlingly, mice with mutations in the same gene don't behave differently than normal mice. Researchers at Emory University School of Medicine have identified a gene related to HPRT1, present in humans but not in mice that helps explain this discrepancy.

The results were published this week by the journal *PLoS One*.

Mice missing HPRT1 and engineered with a copy of the related human gene, called PRTFDC1, are more aggressive and, under the influence of amphetamines, display repetitive behavior resembling nail biting.

"Other strains of mice don't do this, even under the influence of amphetamines," says first author Alaine Keebaugh, an Emory postdoctoral fellow. "It's not exactly the same as the finger-biting seen in Lesch-Nyhan patients, but they're close enough that we think it provides some insight into the biology. It suggests that PRTFDC1 could be a target for treating the disease."

Keebaugh began researching HPRT1 and PRTFDC1 while a graduate student in the laboratory of James Thomas, PhD, former assistant professor of human genetics at Emory University School of Medicine.

The co-first author is Emory postdoctoral fellow Heather Mitchell.

HPRT1 was the first gene to be "knocked out" when scientists were first developing the technique in the 1980s, an accomplishment that earned Mario Capecchi and Oliver Smithies the Nobel Prize in Medicine.

"HPRT1 has a special place in the history of genetics because of this," Keebaugh says. "It also shows that knockout mice don't always exactly parallel human disease."

The HPRT1 gene is located on the X chromosome. Males are vulnerable to Lesch-Nyhan disease (and other X-linked disorders) because they have only one X chromosome. HPRT1 encodes an enzyme that recycles purines, which are building blocks of DNA.

The PRTFDC1 gene looks like HPRT1, and apparently comes from a duplication of an ancestor gene millions of years ago. All mammals Keebaugh examined except mice have working copies of PRTFDC1. It's not clear whether the protein encoded by PRTFDC1 also recycles purines, she says.

"In mice, the presence of PRTFDC1 seems to enhance the effects of not having HPRT1," she says. "This suggests the two proteins are not just doing the same things. One may be regulating the other, which is something we want to investigate further."

In humans, the absence of HPRT1 leads to overabundant purines, which appears to perturb development of certain parts of the brain. In addition, the building blocks are broken down into uric acid, which accumulates in the body and can cause painful swelling of the joints.

These gout-like symptoms can be treated with medication, but the striking behavior and other neurological problems don't go away. Lesch-

Nyhan patients tend to have delayed development and stiff movements and are sometimes unable to walk. They have a deficiency of the chemical messenger dopamine in the basal ganglia, the same part of the brain affected by Parkinson's disease.

Mice without HPRT1 do have reduced dopamine in the basal ganglia and are more sensitive to amphetamines, which work by enhancing dopamine's effects in the brain. This link with dopamine is what led Keebaugh to test the effects of amphetamines on the mice.

Mice missing HPRT1 and with added PRTFDC1 displayed a unique behavior: they had a "distinctive hunched posture," bobbing their heads and appearing to bite their nails. However, they did not actually damage their paws.

Keebaugh says she is continuing to study the function of PRTFDC1 with the aim of understanding how Lesch-Nyhan disease develops and identifying potential treatments.

More information: A.C. Keebaugh, H.A. Mitchell, M. Gaval-Cruz, K.G. Freeman, G.L. Edwards, D. Weinshenker, and J.W. Thomas. PRTFDC1 is a genetic modifier of HPRT-deficiency in the mouse. *PLOS One* (2011).

Provided by Emory University