

“Housekeeping” Genes Play Important Role in Developmental Pathways of Cells

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Unconventional view of these conventional genes sheds light on development of Lesch Nyhan disease

A study from the Center for Molecular Genetics at the University of California, San Diego School of Medicine shows that a gene called HPRT plays an important role in setting the program by which primitive or precursor cells decide to become normal nerve cells in the human brain. This unconventional view of metabolic genes known as “housekeeping” genes is now online at the journal *Molecular Therapy*.

“Housekeeping” genes are expressed in most cells under most conditions, and scientists usually regard them as having simple metabolic functions that regulate normal metabolism, or that can cause serious disease when the genes don't function properly. But they were not previously thought to be involved with setting developmental pathways that determine how stem cells and other primitive cells decide to become neurons, muscle cells, bone or blood cells.

“We showed that HPRT carries out an important new role by causing mistakes in the ways in which a number of super-regulatory genes called transcription factors genes are expressed – some up, some down, but many incorrectly,” said Theodore Friedmann, MD, professor of pediatrics and director of the Gene Therapy Program at the UC San Diego School of Medicine. The researchers propose that many other housekeeping genes in addition to HPRT may also be found to regulate important developmental pathways.

The study also provides the first direct experimental support for a possible role that HPRT plays in the development of the devastating neurological disorder in Lesch Nyhan disease, a rare, X-linked inherited disorder caused by a deficiency of an enzyme produced by mutations in the HPRT gene. Complications of the disease usually appear in boys during their first year of life, and may result in severe gout and kidney problems, poor muscle control, and neurological problems that cause the boys to injure themselves uncontrollably. The study by the Friedmann group now supports the idea that the HPRT gene defects cause neurological problems by directly interfering with the birth and function of brain neurons, especially the ones that rely on dopamine for nerve transmission.

“This finding is important because a better understanding of the dopamine defect in Lesch Nyhan disease will almost certainly shed light on the similar defect in Parkinson's disease,” said Friedmann. “The major difference in these two diseases is that in Parkinson's disease, the dopaminergic neurons degenerate and disappear. In Lesch Nyhan disease, the dopamine neurons are present in more or less normal numbers and locations, but appear to function improperly. Now we know a little more about why that is.”

A distinct and severely aberrant neurobehavioral symptom of Lesch Nyhan disease is self-mutilation, associated with severe depletion of the neurotransmitter dopamine in the basal ganglia region of the brain, as well as defective dopamine (DA) uptake. This is demonstrated in both humans and the HPRT-deficient mouse model, even though DA neurons are present in relatively normal numbers and with normal distribution patterns.

The UCSD research identified a number of abnormally expressed genes in HPRT-deficient mice and in human HPRT-deficient fibroblasts or stem cells. This discovery led them to the hypothesis that complex, interacting networks and pathways affect many aspect of central nervous system development, possibly including defects in the development of DA neurons themselves.

Contributors to the paper include Ghiabe-Henri Guibinga and Stephen Hsu of the UC San Diego Department of Pediatrics, Center for Molecular Genetics. The research was funded in part by the National Institutes of Health and the Lesch Nyhan Syndrome Children's Research Foundation.

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Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu

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