Rett syndrome mobilizes jumping genes in the brain

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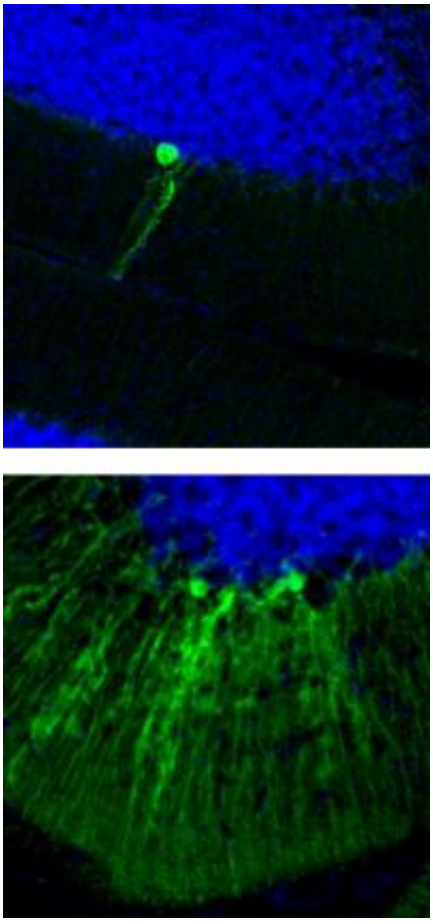

L1 retrotransposons are particularly active in the cerebellum, which plays an important role in motor control. Green cells represent neurons with new L1 insertions. Credit: Courtesy of Dr. Carol Marchetto, Salk Institute for Biological Studies

With few exceptions, jumping genes-restless bits of DNA that can move freely about the genome-are forced to stay put. In patients with Rett syndrome, however, a mutation in the MeCP2 gene mobilizes so-called L1 retrotransposons in brain cells, reshuffling their genomes and possibly contributing to the symptoms of the disease when they find their way into active genes, report researchers at the Salk Institute for Biological Studies.

Their findings, published in the November 18, 2010 issue of the journal *Nature*, could not only explain how a single mutation can cause the baffling variability of symptoms typical of Rett syndrome but also shed new light on the complexity of molecular events that underlie psychiatric disorders such as autism and schizophrenia.

"This is the first time that we can show a connection between genomic stability and a mental disorder," says lead author Fred Gage, Ph.D., a professor in the Salk's Laboratory of Genetics and holder of the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases. "In general genomic mosaicism, generated by L1 retrotransposition, likely requires tight regulation. Epigenetic mechanisms like methlyation are ideally suited for controlling L1 activity."

"There is certainly a genetic component to Rett syndrome and other psychiatric disorders but it may not be the only thing that's relevant," says first author Alysson Muotri, Ph.D., who started the study as a postdoctoral researcher in the Gage lab and now holds an appointment as an assistant professor in the Department of Pediatrics/Cellular and Molecular Medicine at the University of California, San Diego School of Medicine. "Somatic insertions and alterations caused by L1 elements could play a significant but underestimated role because they are hard to detect," he adds.

Rett syndrome, a rare neurodevelopmental disease, affects mostly girls and is considered one of the autism spectrum disorders. Most babies seems to grow and develop normally at first, but over time, children with Rett syndrome have increasing problems with movement, coordination and communication.

Typical features include loss of speech, stereotypic movements, mental retardation and social-behavioral problems. Although almost all cases are caused by a mutation in the MeCP2 gene, how severely people are affected by the symptoms of Rett syndrome varies widely.

Gage and his team found the startling connection between Rett syndrome and overly active L1 retrotransposons, when they asked how their activity is regulated in the brain. In earlier work, they had already shown that L1 retrotransposons, via a "copy and paste" mechanism, add hundreds of extra copies to the genome of neurons, randomly changing the information in single brain cells. Yet, they were only active during a short window of time: the early stages of the development of nerve cells. Once neuronal precursor cells had committed to a neuronal fate, L1 elements were once again marooned at their spot.

"We wanted to know how this process is controlled in the brain and what happens when the process goes awry," explains post-doctoral researcher and co-author Carol Marchetto, Ph.D. They were particularly interested in MeCP2, which plays a role in the regulation of gene activity and which they had found at the regulatory region of LINE-1 elements.

Initial experiments found that MeCP2 interferes with the ability of an artificial L1 element to plug extra copies of itself into the genome of cultured neural stem cells. The artificial element had been genetically engineered to make cells glow green after it had spread to a new spot.

When the Salk researchers tracked the same reporter element in the

brains of mice lacking the gene for MeCP2, its activity increased up to sixfold compared to normal mice (see movie). "The increased activity was specific to certain brain regions," says Marchetto, "and correlated with brain regions that show physiological differences when you delete the MeCP2 gene in mice."

Intrigued, they wanted to know whether Rett syndrome, which is caused by mutations in the MeCP gene, leads to an increased mobility of L1 transposons. Marchetto generated induced pluripotent stem (iPS) cells from a Rett patient's fibroblasts and from a non-affected individual, introduced the reporter element and differentiated them into neuronal precursor cells. "The mobility in cells derived from the Rett patient was almost twice as high compared to normal cells," says Marchetto.

To confirm that not only their artificial L1 element was on the move but also endogenous elements, Muotri and his colleagues developed a new technique that allowed them to detect the subtle increase in DNA content caused by additional L1 copies inserted into the genome. Using this method, they could show that the number of L1 elements in the brains of RTT patients was significantly higher than in the brains of controls.

"The high rates of neuronal transpositions in MeCP2 knock-out mice and Rett patients may be a consequence, rather than a cause, of the disease process," says Gage. "Nonetheless, new somatic insertions, especially during early developmental stages, may play role at later stages of the disease and could explain the wide variability of symptoms observed in Rett syndrome patients."

Provided by Salk Institute