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Jumping genes in the brain

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Genetic elements that jump around the genome can influence brain circuitry, scientists report in this week's Nature. In a study of rat adult hippocampus neural stem cells, US researchers discovered an up to twofold enrichment of the transcripts of retrotransposons known as L1 elements, which can jump around the genome and comprise roughly 20% of mammalian genomes.

"We thought retrotransposition events normally only occurred in germ cells, or in very early development, the first cell stages. This is the first evidence these events might be occurring in developing neurons seen in the adult brain," Haig Kazazian at the University of Pennsylvania in Philadelphia, who did not participate in this study, told *The Scientist*.

To investigate how L1s might retrotranspose, the researchers used a human L1 engineered with an enhanced green fluorescent protein that activated only when the entire construct underwent retransposition. In mice bearing this construct, immunofluorescence microscopy revealed fluorescence only in germ cells and brain tissue. Moreover, fluorescence was only seen in neurons and not in astrocytes or oligodendrocytes.

"It's really surprising how selective this is for neurons," senior author Fred Gage from the Salk Institute for Biological Studies in La Jolla, Calif., told *The Scientist*. "We speculate that this is a mechanism for generating the diversity in the brain analogous to the immune system's ability to generate diversity in antibodies."

Looking for regulators of L1 activity, the researchers found that human L1 contained two binding sites for Sox proteins, which are expressed in brain and testis. RNA interference showed that a 75% decrease in Sox2 in neural stem cells led to a sixfold increase in L1 expression. They also showed that the decrease in Sox2 activity coincided with changes in genomic acetylation and methylation, suggesting L1 activity is regulated by accessibility to open areas of DNA.

Gage and colleagues then used inverse polymerase chain reaction to reveal that L1s can insert within neuronally expressed genes. Rat adult hippocampus neural stem cells harboring detectable retranspositions tended to differentiate into neurons rather than glial cells, revealing L1s can affect cell fate.

"The next big question is what impact this diversity has, if any, on brain function," Gage said. "Whether the host is actually using these retrotransposons for their survival, whether this has evolutionary value, are much broader questions that need more looking into as well," he added.

"If they could verify that L1 transposition events actually effect neural differences between individuals, it would turn both the fields of neurobiology and L1 retrotransposons upside down," the National Institutes of Health's Anthony Furano, who did not participate in this study, told *The Scientist*.

Gage noted that the effects of L1 activity would most likely be neutral or deleterious. "If there was a germline mutation where you increase or decrease the rate this occurs, this could lead to certain genetic abnormalities or diseases that would be very hard to track down," he said.

In the current study, Gage and colleagues used a human construct in rat cells because no comparable rodent construct was as well tested. They are now building mouse and rodent constructs for the future. Furano suggested tagging endogenous L1 elements to confirm whether they naturally insert themselves in neural progenitor cells. "That in itself could very well alter the normal control mechanisms that affect L1 activity," he cautioned.

In future experiments, the researchers will attempt to block or overexpress retrotransposition at various times in development using RNA interference and other techniques to look for any changes in cell or animal behavior, Gage said. "We plan to cross this trait into other transgenic systems to see if we can get regulatable control of this." They also want to collect and test human tissues for L1 activity and conduct comparative genomic studies analyzing retrotransposition across species and individuals.

Kazazian did caution that humans had relatively few active L1s compared to mice. "It's hard to know what effect they'd actually have," he said.

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