Research team finds key to childhood brain disease lies in genetic junk

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(Medical Xpress) -- As researchers come to understand better how the human genome is put together, they quite often stumble across what appear to be puzzles. One example of this is bits of the genome that appear to no longer serve a useful purpose. Such bits are referred to as junk genes. Some of the junk is dead genes while others are hopping genes that can move themselves to other parts of the genome, and some are what's left of hopping genes after they can no longer hop. New research is indicating that some of this junk isn't as useless as it first appeared, and now a new study by large group of scientists has discovered, as they write in their paper in the *Proceedings of the National Academy of Sciences*, that an anomaly in one such bit of junk, surrounded by other junk genes, appears to be the cause of Ravine encephalopathy, a rare type of brain disorder that kills infants.

The researchers found the anomaly after studying people that live on Réunion Island in the Indian ocean; considered to be part of France, a quarter of the people that live there are white descendants of early settlers. But because the island is so remote, a lot of inbreeding has occurred, resulting in a variety of genetic diseases. One that was not expected was the disease now known as Ravine encephalopathy, named for a region on the island where it is most prevalent. Babies born with it lose white matter in their brain and soon die.

To find out what was going on, the researchers began testing the DNA of several families that showed a proclivity for harboring the disease. Some actually had it, while some did not. Comparing the two allowed the team

to track down which differences in their genes might be accounting for the presence of the disease. Much to their surprise, they found it lay within gene SLC7A2, which is known to be used by the brain during its development stage. But what was most remarkable was the fact that it was a single letter change, from an A to a G, found inside an intron, which was in turn embedded in a LINE jumping gene, which was itself inside of a dead jumping gene called a SINE element, all three of which were up to now, considered junk genes. The researchers found that if a child got the G marker from just one parent, it was safe. One from each however, meant developing Ravine encephalopathy.

The research team isn't clear on why supposed junk genes appear to be serving a purpose, but intend to continue their research to see if they can find answers to this new puzzle in genetic research.

More information: Mutation in a primate-conserved retrotransposon reveals a noncoding RNA as a mediator of infantile encephalopathy, *PNAS*, Published online before print March 12, 2012, doi: 10.1073/pnas.1111596109

Abstract

The human genome is densely populated with transposons and transposon-like repetitive elements. Although the impact of these transposons and elements on human genome evolution is recognized, the significance of subtle variations in their sequence remains mostly unexplored. Here we report homozygosity mapping of an infantile neurodegenerative disease locus in a genetic isolate. Complete DNA sequencing of the 400-kb linkage locus revealed a point mutation in a primate-specific retrotransposon that was transcribed as part of a unique noncoding RNA, which was expressed in the brain. In vitro knockdown of this RNA increased neuronal apoptosis, consistent with the inappropriate dosage of this RNA in vivo and with the phenotype. Moreover, structural analysis of the sequence revealed a small RNA-like

hairpin that was consistent with the putative gain of a functional site when mutated. We show here that a mutation in a unique transposable element-containing RNA is associated with lethal encephalopathy, and we suggest that RNAs that harbor evolutionarily recent repetitive elements may play important roles in human brain development.

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