Researchers capture jumping genes

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An ambitious hunt by Johns Hopkins scientists for actively "jumping genes" in humans has yielded compelling new evidence that the genome, anything but static, contains numerous pesky mobile elements that may help to explain why people have such a variety of physical traits and disease risks.

Using bioinformatics to compare the standard assembly of genetic elements as outlined in the reference human genome to raw whole-genome data from 310 individuals recently made available by the 1000 Genomes Project, the team revealed 1,016 new insertions of RIPs, or retrotransposon insertion polymorphisms, thereby expanding the catalog of insertions that are present in some individuals and absent in others. Their results appeared online October 27 in *Genome Research*.

Retrotransposons are travelling bits of DNA that replicate by copying and pasting themselves at new locations in the genome. Having duplicated themselves and accumulated over evolutionary history, transposable elements now make up about half of the human genome. However, only a tiny subfamily of these insertions known as LINE-1 (L1) is still active in humans. Line 1 insertions are able to mobilize not only themselves but also other pieces of DNA.

"In any individual, only between 80 to 100 retrotransposons are actively copying and inserting into new sites," says Haig Kazazian, M.D., professor of human genetics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. "We're not only discovering where they are and who has which ones, but also

finding out that they insert with a remarkable frequency: On the order of one in every 50 individuals has a brand-new insertion that wasn't in their parents."

The researchers recognized L1 retrotransposons - distinguishing them from the vast amount of fixed "fossil" transposable elements that litter the genome - because these actively jumping genes are human specific and almost exactly the same in sequence from one person to another.

"Our genome contains around half a million interspersed L1 sequences that have accumulated over evolutionary history, along with over a million more repeats, most of which were mobilized by L1 elements," explains Adam D. Ewing, Ph.D., a postdoctoral fellow in Kazazian's lab. "Since the vast majority of these are ancestral and therefore common to all humans and even some of our primate relatives, we can ignore them and focus on L1s that contain human-specific characters in their sequences. Those are the actively mobilized elements responsible for considerable genomic diversity among human individuals."

The high frequency of these L1 insertions gives us a better idea about the extent of human diversity, according to Kazazian, whose 22-year focus on retrotransposons seeks to reveal how they alter the expression of human genes.

Just as the structural variants known as single nucleotide polymorphisms (or SNPs, pronounced "snips") serve as markers for various diseases, the hope is that RIPs - which are up to 6,000 times bigger than SNPs, and therefore may have a stronger effect on gene expression - will correlate with disease phenotypes.

"In that same way that someone had to go out and find the SNPs, this study was about finding RIPs that remain active and continue to produce new insertions," Kazazian says. "Now we have the background necessary

to begin studies that may correlate these L1 insertions with everything from autism to cancer."

More information: *Genome Research*: genome.cshlp.org/

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