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## Many Jumping Genes Still Hopping Around the Human Genome

The sequencing of the human genome spelled out for scientists the three billion DNA letters that encode the genetic instructions for human life. But due to natural genetic variation, the genetic code in any one person may not perfectly match up to the “reference” genome sequence produced by the Human Genome Project. New research indicates that jumping genes – previously thought to have settled down over millions of years of evolution – may be an ongoing source of this genetic variation between individuals.

Our chromosomes are notorious hoarders of junk – ancient, mostly inactive DNA sequences that comprise the bulk of the human genome. About 45 percent of it is the burned-out hulks of “jumping genes” or transposons, genetic elements that can crash randomly into functional genes causing mutations – some good, some harmful, most neutral.

Over time, such mutational events have helped shape plant and animal genomes and create diversity up and down the tree of life. The human genome has an abundance of what are called LINE-1 retrotransposons, which copy their own RNA and insert it at other chromosomal locations in a “copy-and-paste” manner. Until now, it was believed that all but a very few of them are molecular fossils whose jumping days are long over. A report published June 25, 2010, in the journal *Cell*, however, suggests that there's more life in LINE-1s than had been thought.

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HHMI investigator John V. Moran and first author Christine Beck say that by looking at the genomes of just six individuals, they have identified 68 new full-length LINE-1s that are present in some people, but don't show up in the

DNA analyzed by the Human Genome Project. They found the majority of these LINE-1s to be “hot for retrotransposition” – capable of efficiently pasting copies of their own DNA sequences into different places in the genome. The number of hot LINE-1s they have discovered so far is approximately four times the number identified in previous studies.

“These results suggest that the diversity and number of active LINE-1s is under-represented in the reference DNA sequence generated by the Human Genome Project,” said Moran, who is at the University of Michigan Medical School. “Our work re-opens the question that there may be more active LINE-1s in today’s populations and that retrotransposition is more common than we had previously thought.”

If so, the movement of still-hot LINE-1s in our genome could be an ongoing source of genetic variation among individuals, said the researchers. However, Moran cautioned that these newly detected ‘jumping genes’ have not been linked to any specific phenotypic differences among people.

“LINE-1 (long interspersed element-1) retrotransposons account for about 17 percent of human DNA. Although they have been instrumental in shaping the human genome, the vast majority of LINE-1s in our genetic endowment – an estimated half-million copies – are incomplete sequences that were “dead on arrival” when they jumped,” said Moran.

Since 1988, scientists have traced some cases of rare diseases such as hemophilia, muscular dystrophy, and X-linked retinitis pigmentosa to mutations caused by LINE-1 insertions into genes. As with mutations caused by other agents, it would be expected that most LINE-1 insertions are neither helpful nor harmful, that a small number are harmful, and that some might have beneficial effects.

In the 1990’s, Moran developed a method for detecting “hot,” or highly active, LINE-1 elements in cultured cells. When the decoded sequence of the human genome was published in 2001, Moran and his former post-doctoral fellow Richard Badge, a co-author on the new report, collaborated with researchers at the University of Pennsylvania to search for active LINE-1s in the “reference” DNA genome. The DNA for this government-funded project was obtained from an anonymous donor in Buffalo, NY, with smaller samples from a handful of other unidentified individuals. The search turned up only six LINE-1 elements that, when tested in cultured cells, showed high potential for jumping around the genome.

Nevertheless, there was reason to believe that the genomes of many people might contain hot LINE-1 elements not found in the reference sequence, Moran said. So Beck and Moran teamed up with Badge – presently at the University of Leicester in the UK – and HHMI investigator Evan Eichler at the University of Washington to test this notion using the DNA of six females from diverse backgrounds: one each from Japan, China, and Northern

Europe; two from Africa; and one from an anonymous donor. Each person's DNA previously had been collected and analyzed as part of a government funded project to study human genetic diversity.

The search netted 68 full-length LINE-1 elements. The scientists tested 67 and found that 37 of them were "hot" for copying and pasting their DNA into other genome locations. Many of the active LINE-1s are uncommon in the population. Four were deemed "rare" and three of them appear restricted to individuals of African heritage.

These results confirmed Moran's hypothesis that active LINE-1 elements are under-represented in the standard DNA sequences used for genomic studies. Moreover, some of the hot LINE-1s, in addition to moving their own DNA around, may also facilitate the movement of other retrotransposon-like entities.

One question to be pursued is whether the new LINE-1s might alter gene expression as a way of creating diversity. "We don't know much about the impact of these elements on phenotypes," said Moran. "We now know that these specific events have happened, but we have no idea, as yet, whether they functionally impact the human genome."