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New gene expression modulator

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A novel gene regulatory mechanism with profound implications for the evolutionary biology of mammalian genomes is described in May 20 Nature by a group at the Johns Hopkins School of Medicine, Baltimore, led by Jef D. Boeke.

Open reading frames of Line-1 (L1) elements - the most abundant autonomous retrotransposons in the human genome - have the ability 'quash' to gene expression when inserted into RNA transcripts, according to Boeke.

Boeke's team fused the L1 sequence encoding the open reading frame endonuclease/reverse transcriptase (ORF2) in the sense orientation downstream of a reporter promoter. This led to "a potent transcriptional elongation block that was shown to be dependent on length and the high A content of the open reading frame," Boeke told us.

When the sequence was fused in the antisense orientation, there were some RNA polymerases that made it all the way through, "but about 85% of the time, what we saw was a much shorter transcript," Boeke said. Characterization of the sequence revealed a premature polyadenylation occurring on the antisense strand of the transposon.

To test the hypothesis that insertion of ORF2 into a human gene, whether in the sense or antisense orientation, would have a similar effect, the authors performed bioinformatic analyses on gene expression data from Biogen. "There was about five times more L1 in the poorly expressed than in the highly expressed sequences," said Boeke. Correcting for the extra length of introns already known to correlate with poor gene expression, Boeke said, "the effect [is still] highly statistically significant."

The hypothesis predicts that no matter the region in which they reside, highly expressed genes should have low L1 content and poorly expressed genes should have high L1 content. "And that's exactly what we found," said Boeke.

"The effect has significant potential for evolution," said Haig H. Kazazian, professor and chair at the Department of Genetics at the University of Pennsylvania School of Medicine. However, "I still am left with a little caveat that I'd like to see the effect *in vivo*," he told us.

Disruption of transcription through L1 elements in the sense orientation and causing truncation of transcripts in the antisense orientation mean a real modulation of transcription of a lot of genes, Kazazian, who was not involved in the study, said.

Many of these transposon copies are polymorphic - meaning that some alleles have them and some alleles don't, Boeke said. "We think those polymorphisms could very well underlie subtle differences in human phenotypes like susceptibility to complex diseases that are caused by mutations at many loci - like cancer susceptibility, heart disease - all the common diseases that are thought to have a genetic component," he said.

Kazazian said he felt that some of the polymorphisms might have an effect in terms of susceptibility, "but I wouldn't suspect that a large fraction of the susceptibility differences in individuals might be due to this effect," he said. "I think he's getting a little carried away."

"I'm not sure whether the elongation defect that they observed in their transient expression assay is relevant to the transcription of any given single nuclear gene in its normal context," said Anthony Furano, genomic structure and function section chief in the Laboratory of Molecular and Cellular Biology at the National Institutes of Health, Bethesda, Md. He said that all of the factors that normally ensure faithful elongation of nuclear genes may be bypassed or overwhelmed in a transient expression assay.

In addition, Furano said, "they do not indicate whether the difference between Line-1 concentration of low and high expression genes is statistically significant." He said that it was not clear whether the L1 sequences were of sufficient length or base composition to exert the transcriptional effect that they attribute to the difference in L1 concentration.

"The biochemistry is beautiful - but what it means in terms of their hypothesis I'm not at all sure about," Furano, who was not involved in the study, said.

References

1. *Nature*, [http://www.nature.com/]

2. Jef D. Boeke, [http://www.bs.jhmi.edu/MBG/boekelab/index.html]

3. Haig H. Kazazian, Jr., [http://www.med.upenn.edu/camb/faculty/ggr/kazazian.html]

4. Anthony V. Furano, [http://www.niddk.nih.gov/intram/people/afurano.htm]