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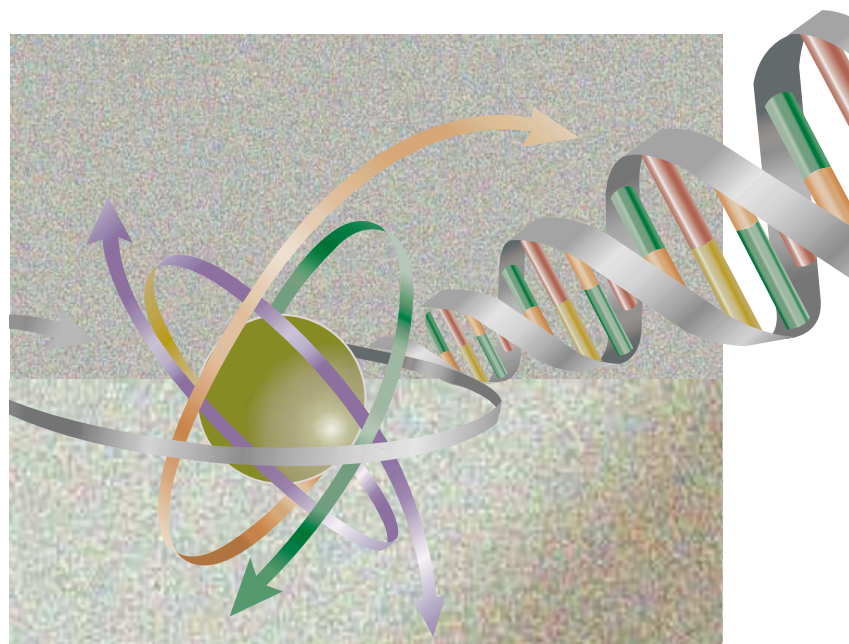
EVOLUTIONARY GENOMICS

Splicing and evolutionary change

With the estimated number of genes in the human genome hovering at a modest 30,000, alternative splicing has received much attention as a potential amplifier of genomic complexity, albeit without direct evidence across an entire genome. In a new study in *Nature Genetics*, Modrek and Lee outline a bioinformatic approach that, for the first time, makes the case that alternative splicing is indeed associated with increased evolutionary change.

The authors used databases of expressed sequence tags (ESTs) to compare exon–intron structure and exon sequence conservation in pairs of orthologues from the human and mouse. As expected, ~90% of the exons had identical boundaries in the two genomes, and there was a high degree of sequence similarity between matching exons. Also, for each exon, they estimated the fraction of total transcripts of a gene that include this particular exon. An alternatively spliced exon was said to be the 'major form' if it was included in the mature mRNA more than 50% of the time.

By relating the frequency of inclusion of a particular exon to the likelihood that it would be conserved between the two genomes, the authors hit on a notable finding. Constitutive exons are almost always conserved, as are alternatively spliced exons that are classified as the major form. 'Minor form' exons, however, were conserved only ~25% of the time. Strikingly, the frequency of inclusion of an exon in human ESTs can predict whether it will be conserved in the mouse.



Modrek and Lee note that the presence of an exon in the orthologue from one genome but not the other, could be explained by exon creation or exon loss, both occurring after the divergence of each lineage from their most recent common ancestor. Constitutive and major-form exons changed little after the divergence of the human and mouse genomes, and most minor-form alternatively spliced exons appeared since then, which indicates that alternative splicing might accompany evolutionary change.

The authors propose a scenario in which a new exon with weak splice signals is added to a gene, and as a result is included in only a small

fraction of the mature transcripts. As the major form is still produced in near-to-normal quantities, initially deleterious effects of adding a new exon would be neutral, leaving the minor-form free to evolve rapidly, possibly serving as an 'internal paralogue' and ultimately acquiring a useful function. The search is now on for alternatively spliced exons that are linked definitively to a specific instance of evolutionary novelty.

Alan Packer, Acting Editor,
Nature Genetics

References and links

ORIGINAL RESEARCH PAPER Modrek, B. & Lee, C. Alternative splicing in the human, mouse and rat genomes is associated with an increased frequency of exon creation and/or loss. *Nature Genet.* 5 May 2003 (10.1038/ng1159)