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GENOMICS

The puzzling side of the human genome

The human genome continues to throw surprises at us. Conservation of a sequence among species has traditionally been considered to be a hallmark of an open reading frame or a nearby regulatory element, but it is becoming increasingly clear that this need not always be true. Bejerano *et al.* now provide another nail in that coffin — they show that vertebrate genomes contain ultra-conserved stretches of 200–800 bp that do not have any coding function and are often far from genes.

By comparing human, mouse and rat genomic sequences, the authors found almost 500 sequences, of at least 200 bp long, that are absolutely conserved among these species. Such conservation is unprecedented — not only are there no substitutions in these sequences, but there are no deletions or insertions either, and the longest of them is almost 800 bp. The level of conservation only falls off slightly, to 96%, when the human sequence is compared with that of the chicken, and about two-thirds of the elements are still 76.8% identical between human and *Fugu rubripes* sequences. Such conservation implies that the elements have been under very strong negative selection for more than 400 million years.

Although their function remains mysterious, the authors might have found some clues. Approximately one-quarter of these elements overlap with known genes, many of which are involved in RNA binding and splicing. Some elements lie near genes that

have been implicated in regulating transcription and DNA binding. Often, these reside in intergenic regions that are flanked by genes that are predominantly involved in early development, indicating that these elements might function as distal enhancers in key developmental processes.

Because they cannot be traced to species more distant than fish, the ultra-conserved elements might be a chordate or vertebrate innovation. Moreover, sequence comparisons within vertebrates indicate that these elements might have initially evolved relatively rapidly, but that their evolution has since slowed down; in fact, Bejerano *et al.* have evidence to indicate that the evolution and the 'freezing' of the elements is still going on today. If the 'specialization' of the elements is lineage-specific, the authors suggest that it might have implications for the ontology and physiology of a clade.

Mechanisms that underlie the evolution of ultra-conserved elements are another conundrum. Might they arise as a result of negative selection? But what process would impose such strict conservation criteria — neither protein nor RNA interactions require such perfect conservation. Or might they result from a greatly reduced mutation rate or much more efficient repair? But we know of no mechanisms for this. If

we thought that life would get easier in the genomic era, we might have to think again...

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Bejerano, G. *et al.* Ultraconserved elements in the human genome. *Science* **304**, 1321–1325 (2004)

FURTHER READING Boffelli *et al.* Comparative genomics at the vertebrate extremes. *Nature Rev. Genet.* **5**, 456–465 (2004)

WEB SITE

Ultraconserved elements in the human genome; electronic supplement:
<http://www.cse.ucsc.edu/~jill/ultra.html>