

What it takes to be a (hu)man

A statistical comparison of more than 7,000 genes from the chimpanzee with their counterparts in humans and mice has gone a long way to pinpointing the genetic differences that underlie the characteristics that make us human.

Humans and chimps are notoriously similar at the genomic level, to the extent that there is a strong move to put them in the same genus. This overall similarity makes it all the more interesting to try to identify the genes that have allowed humans to become so dominant.

A direct comparison of the two genomes is an obvious way to approach this task but the problem is that the selectively advantageous mutations that got us to the top of the tree (or rather, out of the trees) would be few and far between; most of the genetic differences would be neutral mutations that are fixed by genetic drift.

Luckily, statistical tests are available that allow us to test for genes that are subject to positive selection. These tests are usually applied on a gene-by-gene basis, but now Andrew Clark and colleagues have taken this approach to a whole new level with their genome-wide analysis.

They started with 200,000 chimp exon sequences — essentially covering the orthologues of all human exons — which they aligned with human and mouse sequences. They whittled down the resultant 20,000 gene alignments to a list of 7,645 genes, the orthology and annotation of which they were confident about.

The next step was to identify genes that have undergone adaptive evolution. Having the mouse in the alignments was an important aspect of this analysis: it allowed the authors to identify genes that were evolving faster specifically in the human lineage. The authors used two tests, both of which are based on the comparison between synonymous and non-synonymous mutations, to identify 1,534 human genes that were apparently subject to positive selection.

Perhaps the most interesting results came when Clark and colleagues examined the results of their statistical tests with respect to functional categories of these genes. Genes that are involved in olfaction showed a tendency to be under positive selection, as to a lesser extent did genes that are involved in amino-acid catabolism and Mendelian disease genes. Interestingly, they also identified several genes that are involved in hearing that have undergone adaptive evolution in the human lineage,



leading the authors to speculate that tuning of hearing acuity could have had a role in the development of language in humans.

So, this impressive and comprehensive study has given us some real leads to follow up in our quest to find out what makes us so special. With the first draft of the chimp genome released in December 2003, and the detailed comparisons between it and the human sequence to be published soon, an even more comprehensive list of such genes will shortly be available.

Nick Campbell

References and links

ORIGINAL RESEARCH PAPER Clark, A. *et al.* Inferring nonneutral evolution from human-chimp-mouse orthologous gene trios. *Science* **302**, 1960–1963 (2003)

FURTHER READING Olson, M. & Varki, A. Sequencing the chimpanzee genome: insights into human evolution and disease. *Nature Rev. Genet.* **4**, 20–28 (2003)

WEB SITE

Celera diagnostics:
<http://www.applera.com/celeraiagnostics>