

## LINKS FOR WEB HUMAN EVOLUTION

International HapMap Project: <http://www.hapmap.org>

## Following the signposts of selection

Despite our fascination with the evolutionary processes that have led to the unique characteristics of humans, insights into the genetic basis of these changes have been limited. Only a handful of genes have been pinpointed as strong candidates for having undergone adaptive changes in the human lineage, and our knowledge of the underlying mechanisms is also sparse. However, as illustrated by two recent papers that use different strategies to identify regions and genes that have experienced selection during human evolution, the tools are now becoming available to make greater progress in this area.

One theory is that changes in gene regulation have been key to human evolution, a hypothesis that can be tested by examining gene-expression differences between humans and other primates. Gilad and colleagues used a multi-species microarray to assess differences in expression in the liver between over 1,000 human genes and their orthologues from three other primates. They identified 19 genes that are expressed at the same levels in the three non-human primates, but at higher or lower levels in humans compared with these other species. This is strong evidence that changes in the expression of these genes have been selected for specifically in the human lineage.

Notably, the genes that show increased expression in humans were particularly enriched for transcription-factor genes. This is consistent with previous findings that such

genes have evolved rapidly at the level of coding sequence in humans, and ties in with how gene-expression changes might have evolved, with transcription-factor modifications affecting the regulation of their target genes.

In a second study, Voight and colleagues used a different strategy to identify regions containing alleles that have been under very recent selection and have not yet reached fixation in the human genome. They took advantage of SNP data from the **International HapMap Project** for three different populations to locate genomic regions that contain unusual patterns of linkage disequilibrium that are indicative of an ongoing selective sweep — a process that alters linkage disequilibrium patterns and ultimately drives down genomic diversity in the region surrounding a positively selected allele. This analysis revealed many such regions throughout the genome, some of which contain genes that have been shown to have undergone positive selection in previous studies.

The authors also picked out the genes within their regions of interest that are the best candidates for having experienced selection. Several functional categories were enriched

within these genes, including those such as olfaction and reproduction that have previously been highlighted as targets of selection. However, a number of new categories also stood out, including genes that are involved in metabolism. Intriguingly, this might correspond to changes in the human diet during the expansion of agriculture, which fits in with the authors' estimates of the timing of the selection that is captured in their study.

Much remains to be learned from the approaches that were used in both of these studies: for example, the expression-based method has so far been used only for genes that are expressed in the liver, and the authors of the second study stress that much uncertainty remains about the actual genetic targets of selection and the nature of the adaptation. Clearly, exploring the genetic basis of human evolution is a challenge that has only just begun.

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**ORIGINAL RESEARCH PAPERS** Gilad, Y. et al. Expression profiling in primates reveals a rapid evolution of human transcription factors. *Nature* 9 March 2006 (doi:10.1038/nature04559) | Voight, B. F. et al. A map of recent positive selection in the human genome. *PLoS Biol.* 4, e72 (2006)

