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NEWS AND COMMENTARY

Human Genome

Which proteins contribute to human-chimpanzee differences?

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Very few of the functional DNA sequence changes that distinguish us from our closest relative have been identified. A recent study by Bustamante *et al*[1] have made significant progress towards this goal by identifying genes that have undergone positive selection for a new or modified function since humans and chimpanzees split.

With the human and chimpanzee genome sequence now available, the list of DNA sequence changes that separate us from our closest living relative can be enumerated. The challenge, however, lies in identifying which of these changes are functional and contribute to the many biological differences that have accumulated. The null hypothesis, as formulated by the neutral theory of molecular evolution,[2] is that the vast majority of sequence changes are not functional. Recently, application of statistical tests of neutrality to a large collection of *Drosophila* polymorphism and divergence data has indicated that positive selection on protein coding sequences may be quite common.[3–5] Bustamante *et al*[1] have extended this line of work to humans by comparing polymorphism to divergence in 11 624 genes.

To identify genes under positive selection, Bustamante *et al*[1] used a likelihood ratio test. The test compares the likelihood of observing any given number of nonsynonymous polymorphic sites and nonsynonymous substitutions between species under a neutral model, that is mutation and genetic drift in a finite population, to the likelihood under a model where all nonsynonymous changes have been under selection, that is have fitness consequences. One consequence of this method is that the estimated selection coefficients may well be underestimates since positive selection may not have acted on all substitutions or may have been episodic.

The likelihood ratio test identified 304 genes as having an excess of nonsynonymous substitutions between species, due to positive selection, and 813 genes as having an excess of amino-acid polymorphism, due to weak negative selection or balancing selection. The positive selected genes are enriched for a number of molecular functions including transcription, immunity, gametogenesis, apoptosis and sensory perception. The genes under weak negative selection are enriched for functional classes including actin binding, cytoskeletal formation and ectoderm development. A 95% confidence interval was used to detect these genes since no gene is individually significant. As a consequence, a fraction of the genes may be false positives. However, a group of genes as a whole are not random and thus provide a comprehensive look into adaptive protein evolution an excellent list of candidates with which to begin understanding the functional consequences of the amino acid changes in these genes■

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