PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Signs of selection in our genes

ArticleInfo		
ArticleID	:	5084
ArticleDOI	:	10.1186/gb-spotlight-20050506-01
ArticleCitationID	:	spotlight-20050506-01
ArticleSequenceNumber	:	60
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2005–5–6 OnlineDate : 2005–5–6
ArticleCopyright	:	BioMed Central Ltd2005
ArticleGrants	:	
ArticleContext	:	130596611

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Humans and chimpanzees have been diverging for around 5 million years, during which time they've acquired major anatomical and cognitive differences, but New York–based researchers report this week in PLoS Biology that some of the strongest evidence of positive selection since divergence is seen in genes that relate to immunological defense and apoptosis.

Building on an earlier study, Cornell University's Rasmus Nielsen and colleagues compared over 13,000 annotated human genes and their chimp equivalents, using the ratio of synonymous to nonsynonymous mutations as evidence of positive selection. Their aim, Nielsen said, was to determine "which genes have been changing as humans and chimpanzees have evolved into their modern forms."

The team subjected orthologous human–chimp gene pairs from published human data and polymerase chain reaction data obtained from a single male chimpanzee to likelihood analysis, which revealed any differences in mutation type ratio. They excluded genes with fewer than three nucleotide differences.

Nielsen's team made several surprising discoveries, including increased positive selection on the X chromosome and a relative lack of positive selection on genes expressed in the brain. Many genes that showed signs of positive selection were involved in sensory perception or immune defenses, they report, and some of the strongest evidence for selection was seen in genes involved in apoptosis. The latter finding offers "a possible link between selfish mutations during spermatogenesis and cancer prevalence," Nielsen told *The Scientist*.

Apoptosis kills a large proportion of cells during spermatogenesis. A mutation allowing a cell to avoid such a fate should spread in the population because it would confer a selective advantage. However, cancer cells are also eliminated by apoptosis, so any positive selection would be balanced against an increased risk of cancer. "Much of the same molecular machinery is used to destroy cancer cells," Nielsen explained.

Justin Fay, a geneticist at Washington University's School of Medicine, said Nielsen's team has done "a great job of squeezing out any evidence for positive selection on protein coding sequences." However, he pointed to the limitations of their statistical modeling technique, which is only able to detect positive selection on a gene when it has multiple selected substitutions.

"It is entirely possible that every gene has had a single positively selected change between human and chimp," said Fay, who was not involved in the study. The sequences of many genes responsible for crucial differences between the two species could differ by only a single base, but would have been missed by Nielsen's method, he said.

However, these are early days in understanding the differences between humans and chimpanzees. The "highly preliminary analysis" is limited by two facts, according to Christopher Wills, from the University of California, San Diego. "First, [Nielsen et al. did not use a mouse outgroup, even though that should have been possible, and second they were unable to look at possible regulatory changes in the genes," he told *The Scientist*.

"What the paper is really looking at is the subset of genetic changes that have undergone selection-driven functional and conformational changes in the proteins that they code for," said Wills, who was not involved in the study. He too highlighted the pitfall of only identifying genes that have undergone many changes. "A change as small as a single base can have a profound effect on gene function and expression," he continued, "and their search will of course have missed these."

Nielsen acknowledged the limitations. "Humans and chimpanzees are so similar that we sometimes cannot detect enough differences to make meaningful scientific statements," he said. "However, I think many people in the scientific community were surprised to see, after all, how much you could determine regarding the evolution of these two closely related species."

Wills is more cautious, pointing out that although genes for immune defense are important, they do not contribute to the morphological and behavioral differences that exist between humans and chimpanzees. "The authors are just looking at the tip of the iceberg," he said.

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