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Researchers Sift Modern Human Genes to Find Evidence of Natural Selection

Researchers have employed a powerful new technique to analyze the genes of modern humans, uncovering evidence of natural selection that occurred approximately 10,000 years ago. The studies indicate that eight genes, including two involved in calcium absorption and a candidate gene for prostate cancer, were altered by selective pressure.

The findings suggest that changes in diet, climate, and culture exerted a selective pressure on the genes of people migrating to Europe from the cradle of human origin in Africa, according to Howard Hughes Medical Institute investigator Leonid Kruglyak at the Fred Hutchinson Cancer Research Center. Kruglyak and colleagues from the University of Washington, Seattle and Pennsylvania State University, published their findings in the October 2004 issue of the *Public Library of Science Biology*.

“There has been a major debate in evolutionary theory over whether selective forces played much of a role in our evolution, or whether a lot of variation is the result of random mutation,” Kruglyak said. But the challenge in detecting evidence of natural selection has been in distinguishing its effects from the massive amount of random variability in genes.

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- Leonid Kruglyak

“There are additional complicating factors, in that real populations change in size, migrate from one geographic area into another, experience bottlenecks, and have non-random mating within populations,” Kruglyak said. “So, if you look at a single gene in isolation and see something unusual, you don't really know whether that gene has been the subject of natural selection, or whether the genome as a whole has additional sources of variability from some of these other events.”

To tease out genetic changes resulting from natural selection, the researchers analyzed variations in a set of 132 genes distributed throughout the genomes of a select group of individuals. The genes, which they compared in 24 African-Americans and 23 European-Americans, are primarily involved in inflammation, blood clotting and blood-pressure regulation.

“By assuming that most of the genomic changes are neutral and not subject to strong selection, you can get a sense of the background distribution of genetic changes,” said Kruglyak. “Then you can look for genetic changes that are unusual against that background. And that background incorporates any of the forces that affect the genome as a whole and not individual genes.”

The scientists' analysis revealed evidence of selection in eight genes in the European-Americans, but none in the African-Americans. “This makes it quite likely that after modern humans originated in Africa hundreds of thousands of years ago, those who migrated out were exposed to new pathogens, new climates, and new diets,” said Kruglyak. “And those pressures caused a recent selection pressure for those populations.”

In addition, the researcher found evidence of natural selection among European-Americans in a chromosome segment that encompasses four genes. This region appears to be the largest “footprint” of selection that has been found in the human genome, said the scientists.

One of the genes in this region, *TRPV6*, is suspected to be involved in prostate-cancer susceptibility and/or tumor aggressiveness. The incidence of prostate cancer is higher in African-Americans than any other ethnic group; in 1996-2000, the incidence among this group was 1.6 times that of whites and nearly double that of Hispanics and Latinos. “So our evidence of natural selection for different versions of the gene between these two populations makes it a stronger candidate for investigation into whether it really plays a role in the disease,” Kruglyak said.

TRPV6 and another of the genes in the footprint, *TRPV5*, are important in regulating calcium absorption. Natural selection for these genes may have influenced the ability of Northern Europeans to digest lactose as adults, which would have had the greatest nutritional advantage in those who were best able to absorb the calcium from milk.

“I think this is a harbinger of what's to come in genomic analysis,” Kruglyak said of the analytic technique. “We now have one sequence of the human genome, but efforts are expanding to generate sequences of large numbers of genes - and eventually those of entire genomes - from many individuals. Our kind of analytic approach allows for figuring out what the background noise looks like to then detect medically and scientifically important signatures of selection against that background.”