Sex with Neanderthals and Denisovans gave healthy boost to human genome: study

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For a few years now, scientists have known that humans and their evolutionary cousins had some casual flings, but now it appears that these liaisons led to a more meaningful relationship.

Sex with Neanderthals and another close relative — the recently discovered Denisovans — has endowed some human gene pools with beneficial versions of immune system genes, report researchers at the Stanford University School of Medicine in an article to be published online by the journal *Science* at the *Science Express* website on August 25.

Although modern humans, Neanderthals and Denisovans share a common ancestor in Africa, the groups split into separate, distinct populations approximately 400,000 years ago. The Neanderthal lineage migrated northwestward into West Asia and Europe, and the Denisovan lineage moved northeastward into East Asia. The ancestors of modern man stayed in Africa until 65,000 years or so ago, when they expanded into Eurasia and then encountered the other human-like groups. In some cases, the rendezvous were amorous in nature.

Last year, a partial genome sequence of Neanderthals, who died out approximately 30,000 years ago, revealed that these trysts left as much as 4 percent Neanderthal DNA in the genetic blueprint of some present-day humans. Last December, the genome of another human cousin, the extinct Denisovans, made clear that up to 6 percent of some people's genomes are Denisovan in origin.

Now, a team of researchers led by Peter Parham, PhD, professor of structural biology and of microbiology and immunology, has found that these matings had a positive effect on modern human fitness. "The cross breeding wasn't just a random event that happened, it gave something useful to the gene pool of the modern human," said Parham, who is senior author on the study.

The useful gift was the introduction of new variants of immune system genes called the HLA class I genes, which are critical for our body's ability to recognize and destroy pathogens. HLA genes are some of the most variable and adaptable genes in our genome, in part because the rapid evolution of viruses demands flexibility on the part of our immune system.

"The HLA gene system, with its diversity of variants, is like a magnifying glass," said lead author Laurent Abi-Rached, PhD, explaining that it provides a lot more detail about the history of populations than typical gene families. Abi-Rached is a research associate in the Parham lab.

Prior to the sequencing of the Neanderthal and Denisovan genomes, Parham and his group had suspected that at least one HLA variant came from archaic humans. They determined that the variant known as HLA-B*73 is rare in present-day African populations but occurs with significant frequency in West Asian populations. The ethnic distribution of HLA-B*73 and its similarity across populations suggested that it came from a relatively recent co-mingling of modern human and archaic human DNA, which most likely would have happened outside of Africa. Parham's team wanted to discern which archaic humans were the source of the HLA-B*73 gene type. In the last year they have found the answer in the genome sequence of a recently discovered human relative, the Denisovans, whose existence first came to light in 2008 with the discovery of an unfamiliar finger bone and tooth in a cave in Siberia.

By comparing the HLA genes of the archaic humans with modern humans, the researchers were able to show that the HLA-B*73 allele likely came from cross breeding with Denisovans. Little is known about what the Denisovans looked like (the finger bone and the tooth are the only known fossils), but the genome sequence extracted from the finger bone gives insight into where they overlapped with modern humans. Gene flow from the Denisovans into modern humans has left the highest frequency of the HLA-B*73 allele in populations in West Asia, the most likely site for the fortuitous mating to have taken place.

Even in West Asian populations, the HLA-B*73 variant never represents more than 5 percent of all known variants of that gene. However, other human HLA types that arose from ancient matings are found in much greater frequencies. "Certain traits coming from these archaic humans have become the dominant form," said Parham. For example, another HLA gene type, called HLA-A*11, is absent from African populations, but represents up to 64 percent of variants in East Asia and Oceania, with the greatest frequency in people from Papua New Guinea. "The likely interpretation was that these HLA class variants provided an advantage to modern human and so rose to high frequencies," Parham said.

A similar scenario is seen in some HLA gene types found in the Neanderthal genome, which was also sequenced from DNA extracted from ancient bones. These gene variants are common in European and Asian populations but rare in African populations. "We are finding frequencies in Asia and Europe that are far greater than whole genome estimates of archaic DNA in modern human genomes, which is 1 to 6 percent," said Parham. Within one class of HLA gene, the researchers estimate that Europeans owe half of their variants to interbreeding with Neanderthals and Denisovans, Asians owe up to 80 percent and Papua New Guineans, up to 95 percent.

"This is not the pattern seen genome-wide," said Abi-Rached. "The HLA system is unique in its diversity and the strength of natural selection acting on it, but it's possible that other gene systems, particularly the ones under similar pressure for variation, could show a similar pattern."

Provided by Stanford University