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Could Interbreeding Between Humans and Neanderthals Have Led to an Enhanced Human Brain?

Might mating between an ancient human and a Neanderthal - perhaps occurring in only a single instance - have introduced a gene variant into the human population that enhanced human brain function? That question is at the heart of a new study by researchers at the Howard Hughes Medical Institute and the University of Chicago.

The new research, which was published online during the week of November 6, 2006, in the early edition of the *Proceedings of the National Academy of Sciences (PNAS)*, suggests that human evolution was not just a matter of spontaneous advantageous mutations arising within the human lineage. Human evolution may also have been influenced by interbreeding with other *Homo* species, which introduced gene variants, known as alleles, that are beneficial to human reproductive fitness, said the study's senior author Bruce T. Lahn, a Howard Hughes Medical Institute researcher at the University of Chicago.

The scientists said they have developed the most robust genetic evidence to date that suggests humans and Neanderthals interbred when they existed together thousands of years ago. The interbreeding hypothesis contrasts with at least one prominent theory that posits that no interbreeding occurred when the two species encountered one another.

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- Bruce T. Lahn

Lahn collaborated on the studies with Patrick D. Evans, Nitzan Mekel-Bobrov, Eric J. Vallender and Richard R. Hudson, all of the University of Chicago.

In their studies, Lahn and his colleagues performed a detailed statistical analysis of the DNA sequence structure of the gene *microcephalin*, which is known to play a role in regulating brain size in humans. Mutations in the human gene cause development of a much smaller brain, a condition called microcephaly.

Earlier studies by Lahn's group yielded evidence that the *microcephalin* gene has two distinct classes of alleles. One class, called the D alleles, is comprised of a group of alleles with rather similar DNA sequences. The other class is called the non-D alleles. Lahn and colleagues previously showed that all modern copies of the D alleles arose from a single progenitor copy about 37,000 years ago, which then increased in frequency rapidly and are now present in about 70 percent of the world's population. This rapid rise in frequency indicates that the D alleles underwent positive selection in the recent history of humans. This means that these alleles conferred a fitness advantage on those who possessed one of them such that these people had slightly higher reproductive success than people who didn't possess the alleles, said Lahn.

The estimate that all modern copies of the D alleles descended from a single progenitor copy about 37,000 years ago is based on the measurement of sequence difference between different copies of the D alleles. As a copy of a gene is passed from one generation to the next, mutations are introduced at a steady rate, such that a certain number of generations later, the descendent copies of the gene would on average vary from one another in DNA sequence by a certain amount. The greater the number of the generations, the more DNA sequence difference there would be between two descendent copies, said Lahn. The amount of sequence difference between different copies of a gene can therefore be used to estimate the amount of evolutionary time that has elapsed since the two copies descended from their common progenitor.

In the new studies reported in *PNAS*, the researchers performed detailed sequence comparisons between the D alleles and the non-D alleles of *microcephalin*. The scientists determined that these two classes of alleles have likely evolved in two separate lineages for about 1.1 million years -- with the non-D alleles having evolved in the *Homo sapiens* lineage and the D alleles having evolved in an archaic, and now extinct, *Homo* lineage. Then, about 37,000 years ago, a copy of the D allele crossed from the archaic *Homo* lineage into humans, possibly by interbreeding between members of the two populations. This copy subsequently spread in humans from a single copy when it first crossed into humans to an allele that is now present in an estimated 70 percent of the population worldwide today.

The estimate of 1.1 million years that separates the two lineages is based on the amount of sequence difference between the D and the non-D alleles.

Although the identity of this archaic *Homo* lineage is yet to be determined, the researchers argue that a likely candidate is the Neanderthals. The 1.1 million year separation between humans and this archaic *Homo* species is roughly consistent with previous estimates of the amount of evolutionary time separating the *Homo sapiens* lineage and the Neanderthal lineage, said Lahn. Furthermore, the time of introgression of the D allele into humans -- about 37,000 years ago -- is when humans and Neanderthals coexisted in many parts of the world.

Lahn said the group's data suggest that the interbreeding was unlikely to be a thorough genetic mixing, but rather a rare - and perhaps even a single -- event that introduced the ancestral D allele previously present in this other *Homo* species into the human line.

“By no means do these findings constitute definitive proof that a Neanderthal was the source of the original copy of the D allele,” said Lahn. “However, our evidence shows that it is one of the best candidates. The timeline - including the introgression of the allele into humans 37,000 years ago and its origin in a lineage that separated with the human line 1.1 million years ago -- agrees with the contact between, and the evolutionary history of, Neanderthals and humans.

“And a third line of evidence, albeit weaker, is that the D alleles are much more prevalent in Eurasia and lower in sub-Saharan Africa, which is consistent with an origin in the former area. And we know that Neanderthals evolved outside of Africa,” said Lahn.

Lahn also said that although the disruption of the *microcephalin* gene in humans leads to smaller brains, the role of the D alleles in brain evolution remains unknown. “The D alleles may not even change brain size; they may only make the brain a bit more efficient if it indeed affects brain function,” he said. “For example, someone inheriting the D allele may have only a slightly more efficient brain on average. While that enhancement might confer only a subtle evolutionary advantage on that person, when that effect is propagated over a thousand generations of natural selection, the result will be to drive the D alleles to a very high prevalence.”

Lahn and his colleagues believe that other genes might well show similar telltale signs of an origin in archaic *Homo* lineages such as Neanderthals. They are currently using their analytical tool to search for evidence of that origin for other genes in the human genome.

Such findings may have broader implications for understanding human evolution than just revealing the possibility of human-Neanderthal interbreeding, he said. “In addition to being perhaps the most robust genetic evidence for introgression of genes from archaic *Homo* species into humans, I think this finding demonstrates that the evolution of our species has been profoundly impacted by gene flow from our relative species,” said Lahn.

“Finding evidence of mixing is not all that surprising. But our study demonstrates the possibility that interbreeding contributed advantageous variants into the human gene pool that subsequently spread. This implies that the evolution of human biology has been affected by the contribution of advantageous genetic variants from archaic relatives that we have replaced or even killed off,” he said.

Until now, said Lahn, the scientific debate over genetic exchange between humans and other *Homo* species has led to two prominent competing theories. One holds that anatomically modern humans replaced archaic species, with no interbreeding. And the other states that extensive interbreeding did take place and that modern humans evolved from that interbreeding in many regions of the world.

Genetic and fossil evidence for the latter “multiregional” theory has been inconclusive, said Lahn, so that theory has been largely discredited. However, he said, the newer evidence of gene exchange -- as well as other genetic evidence that might follow -- could give rise to a more moderate version holding that some genetic exchange did take place. Furthermore, it will become increasingly appreciated that such genetic exchange might have made our species much more fit.