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Complete Neanderthal Genome Sequenced

DNA Signatures Found in Present-Day Europeans and Asians, but Not in Africans

Researchers have produced the first whole genome sequence of the 3 billion letters in the Neanderthal genome, and the initial analysis suggests that up to 2 percent of the DNA in the genome of present-day humans outside of Africa originated in Neanderthals or in Neanderthals' ancestors.

The international research team, which includes researchers from the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health, reports its findings in the May 7, 2010, issue of Science.

The current fossil record suggests that Neanderthals, or Homo neanderthalensis, diverged from the primate line that led to present-day humans, or Homo sapiens, some 400,000 years ago in Africa. Neanderthals migrated north into Eurasia, where they became a geographically isolated group that evolved independently from the line that became modern humans in Africa. They lived in Europe and western Asia, as far east as southern Siberia and as far south as the Middle East.

Approximately 30,000 years ago, Neanderthals disappeared. That makes them the most recent, extinct relative of modern humans, as both Neanderthals and humans share a common ancestor from about 800,000 years ago. Chimpanzees diverged from the same primate line some 5 million to 7 million years ago

The researchers compared DNA samples from the bones of three female Neanderthals who lived some 40,000 years ago in Europe to samples from five present-day humans from China, France, Papua New Guinea, southern Africa and western Africa. This provided the first genome-wide look at the similarities and differences of the closest evolutionary relative to humans, and maybe even identifying, for the first time, genetic variations that gave rise to modern humans.

"This sequencing project is a technological tour de force," said NHGRI Director Eric D. Green, M.D., Ph.D. "You must appreciate that this international team has produced a draft sequence of a genome that existed 400 centuries ago. Their analysis shows the power of comparative genomics and brings new insights to our understanding of human evolution."

The Neanderthal DNA was removed from bones discovered at Vindija Cave in Croatia and prepared in the clean room facility of the Max Planck Institute for Evolutionary Anthropology (http://www.eva.mpg.de/english/index.htm) in Leipzig, Germany, to prevent contamination with contemporary DNA. The Max Planck group is led by their Department of Evolutionary Genetics Director Svante Pääbo, Ph.D., a well-known pioneer in Neanderthal genome research. The team deposited the Neanderthal genome sequence in the publicly available NIH genetic sequence database GenBank (http://www.ncbi.nlm.nih.gov/genbank/).

To understand the genomic differences between present-day humans and Neanderthals, the researchers compared subtle differences in the Neanderthal genome to the genomes found in DNA from the five people, as well as to chimpanzee DNA. An analysis of the genetic variation showed that Neanderthal DNA is 99.7 percent identical to present-day human DNA, and 98.8 percent identical to chimpanzee DNA. Present-day human DNA is also 98.8 percent identical to chimpanzee.

"The genomic calculations showed good correlation with the fossil record," said coauthor Jim Mullikin, Ph.D., an NHGRI computational geneticist and acting director of the NIH Intramural Sequencing Center (http://www.nisc.nih.gov/). "According to our results, the ancestors of Neanderthals and modern humans went their separate ways about 400,000 years ago."

The comparison between Neanderthal and present-day human genomes has produced a catalog of genetic differences that allow the researchers to identify features that are unique to present-day humans. For example, the catalog includes differences in genes that code for functional elements, such as proteins, in which the Neanderthal versions are more like those of the chimpanzee than present-day humans. Some evolutionary changes were found in known genes involved in cognitive development, skull structure, energy metabolism, skin morphology and wound healing.

Anthropologists have used the fossil record to construct tree-shaped diagrams that show how the different branches of hominins, which includes humans and human ancestors, split off from one another. These diagrams tend to proceed in a straight line, from the tree-trunk base of a common ancestor through progressively smaller branches until the species of interest is reached. The Neanderthal data suggests evolution did not proceed in a straight line. Rather, evolution appears to be a messier process, with emerging species merging back into the lines from which they diverged.

Now the view emerging from the genomic data suggests that Neanderthals – who migrated out of Africa a few hundred thousand years ago – re-encountered anatomically modern humans, who began migrating out of Africa some 80,000 years ago. Humans migrating out of Africa were likely to be small pioneering groups and appear to have encountered Neanderthals living in the Fertile Crescent of the Middle East about 60,000 years ago.

"It was a very unique series of events, with a founding population of modern humans of greatly reduced size -- tens to hundreds of individuals," Dr. Mullikin said. Geneticists can detect a population constriction or bottleneck where certain genetic markers are concentrated; that only occurs when the population is small.

"At that time," Dr. Mullikin continued, "where the population was greatly reduced, the modern humans migrating out of Africa encountered Neanderthals and inter-breeding occurred between the two groups, leaving an additional, but subtle, genetic signature in the out-of-Africa group of modern humans."

As modern humans migrated out of the Middle East after encountering Neanderthals, and dispersed across the globe, they carried Neanderthal DNA with them. The research team concluded that 2 percent of the genomes of present-day humans living from Europe to Asia — and as far into the Pacific Ocean as Papua New Guinea — was inherited from Neanderthals. The team did not find traces of Neanderthal DNA in the two present-day humans from Africa. It is not known, however, whether a more systematic sampling of African populations will reveal the presence of Neanderthal DNA in some indigenous Africans.

"The data suggests that the genes flowed from Neanderthal to modern humans," Dr. Mullikin said. "That had to have occurred at least once during the 20,000 to 30,000 years, in which modern humans and Neanderthal both lived on the Eurasian continent." The researchers have not yet detected any signs that DNA from modern humans can be found in the Neanderthal genome.

Previous studies, such as the International HapMap Project, which created a comprehensive catalog of human genetic variation, examined common genetic variation in populations across the globe, and concluded that average genetic variation between a person in Asia, Europe or Africa was essentially identical. The current study raises the possibility that Europeans and Asians, who include Neanderthal DNA, may be slightly more distinct from Africans than previously appreciated – a difference at the DNA sequence level that could not be seen with the resolution of the HapMap.

"These are preliminary data based on a very limited number of samples, so it is not clear how widely applicable these findings are to all populations," said Vence L. Bonham, Jr., J.D., senior advisor to the NHGRI Director on Societal Implications of Genomics. "The findings do not change our basic understanding that humans originated in Africa and dispersed around the world in a migration out of that continent."

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NHGRI is one of the 27 institutes and centers at the NIH, an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases. Additional information about NHGRI can be found at its website, www.genome.gov.

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