

May 3, 2010

Contact: Tim Stephens, (831) 459-2495, stephens@ucsc.edu

Neanderthal genome yields insights into human evolution and evidence of interbreeding

EMBARGOED: Not for release until 2 p.m. U.S. Eastern Time on Thursday, May 6.

SANTA CRUZ, CA--After extracting ancient DNA from the 40,000-year-old bones of Neanderthals, scientists have obtained a draft sequence of the Neanderthal genome, yielding important new insights into the evolution of modern humans.

Among the findings, published in the May 7 issue of *Science*, is evidence that shortly after early modern humans migrated out of Africa, some of them interbred with Neanderthals, leaving bits of Neanderthal DNA sequences scattered through the genomes of present-day non-Africans.

"We can now say that, in all probability, there was gene flow from Neanderthals to modern humans," said the paper's first author, Richard E. (Ed) Green of the University of California, Santa Cruz.

Green, now an assistant professor of biomolecular engineering in the Baskin School of Engineering at UC Santa Cruz, began working on the Neanderthal genome as a postdoctoral researcher at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. Svante Pääbo, director of the institute's genetics department, leads the Neanderthal Genome Project, which involves an international consortium of researchers. David Reich, a population geneticist at the Broad Institute of MIT and Harvard, also played a leading role in the new study and the ongoing investigation of the Neanderthal genome.

"The Neanderthal genome sequence allows us to begin to define all those features in our genome where we differ from all other organisms on the planet, including our closest evolutionary relative, the Neanderthals," Pääbo said.

The researchers identified a catalog of genetic features unique to modern humans by comparing the Neanderthal, human, and chimpanzee genomes. Genes involved in cognitive development, skull structure, energy metabolism, and skin morphology and physiology are among those highlighted in the study as likely to have undergone important changes in recent human evolution.

"With this paper, we are just scratching the surface," Green said. "The Neanderthal genome is a goldmine of information about recent human evolution, and it will be put to use for years to come."

Neanderthals lived in much of Europe and western Asia before dying out 30,000 years ago. They coexisted with humans in Europe for thousands of years, and fossil evidence led some scientists to speculate that interbreeding may have occurred there. But the Neanderthal DNA signal shows up not only in the genomes of Europeans, but also in people from East Asia and Papua New Guinea, where Neanderthals never lived.

"The scenario is not what most people had envisioned," Green said. "We found the genetic signal of Neanderthals in all the non-African genomes, meaning that the admixture occurred early on, probably in the Middle East, and is shared with all descendants of the early humans who migrated out of Africa."

The study did not address the functional significance of the finding that between 1 and 4 percent of the genomes of non-Africans is derived from Neanderthals. But Green said there is no evidence that anything genetically important came over from Neanderthals. "The signal is sparsely distributed across the genome, just a 'bread crumbs' clue of what happened in the past," he said. "If there was something that conferred a fitness advantage, we probably would have found it already by comparing human genomes."

The draft sequence of the Neanderthal genome is composed of more than 3 billion nucleotides--the "letters" of the genetic code (A, C, T, and G) that are strung together in DNA. The sequence was derived from DNA extracted from three Neanderthal bones found in the Vindiga Cave in Croatia; smaller amounts of sequence data were also obtained from three bones from other sites. Two of the Vindiga bones could be dated by carbon-dating of collagen and were found to be about 38,000 and 44,000 years old.

Deriving a genome sequence--representing the genetic code on all of an organism's chromosomes--from such ancient DNA is a remarkable technological feat. The Neanderthal bones were not well preserved, and more than 95 percent of the DNA extracted from them came from bacteria and other organisms that had colonized the bone. The DNA itself was degraded into small fragments and had been chemically modified in many places.

The researchers had to develop special methods to extract the Neanderthal DNA and ensure that it was not contaminated with human DNA. They used new sequencing technology to obtain sequence data directly from the extracted DNA without amplifying it first. Although genome scientists like to sequence a genome at least four or five times to ensure accuracy, most of the Neanderthal genome has been covered only one to two times so far.

The draft Neanderthal sequence is probably riddled with errors, Green said, but having the human and chimpanzee genomes for comparison makes it extremely useful despite its limitations. Places where humans differ from chimps, while Neanderthals still have the ancestral chimp sequence, may represent uniquely human genetic traits. Such comparisons enabled the researchers to catalog the genetic changes that have become fixed or have risen to high frequency in modern humans during the past few hundred thousand years.

"It sheds light on a critical time in human evolution since we diverged from Neanderthals," Green said. "What adaptive changes occurred in the past 300,000 years as we were becoming fully modern humans? That's what I find most exciting. Right now we are still in the realm of identifying candidates for further study."

The ancestral lineages of humans and chimpanzees are thought to have diverged about 5 or 6 million years ago. By analyzing the Neanderthal genome and genomes of present-day humans, Green and his colleagues estimated that the ancestral populations of Neanderthals and modern humans separated between 270,000 and 440,000 years ago.

The evidence for more recent gene flow between Neanderthals and humans came from an analysis showing that Neanderthals are more closely related to some present-day humans than to others. The researchers looked at places where the DNA sequence is known to vary among individuals by a single "letter." Comparing different individuals with Neanderthals, they asked how frequently the Neanderthal sequence matches that of different humans.

The frequency of Neanderthal matches would be the same for all human populations if gene flow between Neanderthals and humans stopped before human populations began to develop genetic differences. But that's not what the study found. Looking at a diverse set of modern humans--including individuals from Southern Africa, West Africa, Papua New Guinea, China, and Western Europe--the researchers found that the frequency of Neanderthal matches is higher for non-Africans than for Africans.

According to Green, even a very small number of instances of interbreeding could account for these results. The researchers estimated that the gene flow from Neanderthals to humans occurred between 50,000 and 80,000 years ago. The best explanation is that the admixture occurred when early humans left Africa and encountered Neanderthals for the first time.

"How these peoples would have interacted culturally is not something we can speculate on in any meaningful way. But knowing there was gene flow is important, and it is fascinating to think about how that may have happened," Green said.

The researchers were not able to rule out one possible alternative explanation for their findings. In that scenario, the signal they detected could represent an ancient genetic substructure that existed within Africa, such that the ancestral population of present-day

non-Africans was more closely related to Neanderthals than was the ancestral population of present-day Africans. "We think that's not the case, but we can't rule it out," Green said.

The researchers expect many new findings to emerge from ongoing investigations of the Neanderthal genome and other ancient genetic sequences. Pääbo's group recently found evidence of a previously unknown type of hominid after analyzing DNA extracted from what they had thought was a Neanderthal finger bone found in Siberia. Green is also taking part in that continuing investigation.

The Neanderthal genome sequence has been posted on the UCSC Genome Browser (genome.ucsc.edu), which contains a large collection of genomes and provides a convenient framework for genome comparisons and tools for genome analysis.

The *Science* paper on the Neanderthal genome involved 56 coauthors from 22 different institutions. An accompanying paper by the same team, with Hernán Burbano of the Max Planck Institute as first author, describes a particular method used to investigate the genome. Support for the project includes funding from the Max Planck Society of Germany, the Ministry of Science and Innovation (MICINN) of Spain, and the National Human Genome Research Institute of the U.S. National Institutes of Health.

#####

Notes to reporters: You may contact Green at (831) 502-7394 or ed@soe.ucsc.edu.

An embargoed *Science* **teleconference** for reporters only will be held on Wednesday, May 5, at 10:30 a.m. U.S. Eastern Time. For dialing instructions, contact Natasha Pinol in the *Science* press office at npinol@aaas.org.

For more UCSC news, visit www.ucsc.edu/news_events.