Scientists Hope to Unravel Neanderthal DNA

Jan Woitas/European Pressphoto Agency

From left, Michael Egholm, Svante Paabo and Ralf W. Schmitz showing an original cast of a Neanderthal bone.

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Researchers in Germany said Thursday that they planned to collaborate with an American company in an effort to reconstruct the genome of Neanderthals, the archaic human species that occupied Europe from 300,000 years ago to 30,000 years ago until being displaced by modern humans.

Long a forlorn hope, the sequencing, or decoding, of Neanderthal DNA suddenly seems possible because of a combination of analytic work on ancient DNA by Svante Paabo, of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and a new method of DNA sequencing developed by a Connecticut company, 454 Life Sciences.

The initial genome to be decoded comes from 45,000-year-old Neanderthal bones found in Croatia, though bones from other sites may be analyzed later. Because the genome must be kept in constant repair and starts to break up immediately after the death of the cell, the material surviving in Neanderthal bones exists in tiny fragments 100 or so DNA units in length. As it happens, this is just the length that works best with the 454 machine, which is also able to decode vast amounts of DNA at low cost.

Recovery of the Neanderthal genome, in whole or in part, would be invaluable for reconstructing many events in human prehistory and evolution. It would help address such questions as whether Neanderthals and humans interbred, whether the archaic humans had an articulate form of language, how the Neanderthal brain was constructed, if they had light or dark skin, and the total size of the Neanderthal population.

The project is still at an early stage, but much groundwork has been laid. Most Neanderthal bones contain no Neanderthal DNA at all, but almost all are heavily contaminated with the DNA of the many people who have handled the bones. Dr. Paabo has developed stringent methods to address this contamination problem.

Even with the DNA that is known to be ancient, some 95 percent of that in the Neanderthal bones belongs to ancient bacteria, said Michael Egholm, a vice president of 454 Life Sciences. But bacterial sequences can be recognized and discarded, he said.

Because Neanderthal DNA is so scarce, Dr. Paabo and the 454 Life Science researchers developed their methods on ancient DNA from cave bears and mammoth.

Turning to Neanderthal bones, they have already recovered considerable amounts of DNA sequence, which are derived from every chromosome in the Neanderthal cell, as judged by matching the Neanderthal DNA to the human genome sequence that was first fully decoded in 2003.

The first goal of the project will be to sequence three billion units of Neanderthal DNA, corresponding to the full length of the Neanderthal genome. This will require decoding 20 times as much DNA, because so much of the DNA in the Neanderthal bones belongs to bacteria.

Genomes usually must be decoded several times over to get a complete and accurate sequence, but the first three billion bases of Neanderthal should "hit all the essential differences," Dr. Egholm said.

The researchers' hope is to recover the entire sequence of the Neanderthal genome, but that will depend on whether they can recover enough DNA. From sampling so far, no particular gaps in the sequence are apparent. "We are hitting all the chromosomes and getting good coverage," Dr. Egholm said. If no single specimen yields a full sequence, the genome might be recovered by combining DNA from several individuals.

One of the most important results that researchers are hoping for is to discover, from a three-way comparison of chimp, human and Neanderthal DNA, which genes have made humans human. The chimp and human genomes differ at just 1 percent of the sites on their DNA. At this 1 percent, Neanderthals resemble humans at 96 percent of the sites, to judge from the preliminary work, and chimps at 4 percent. Analysis of these DNA sites, at which humans differ from the two other species, will help understand the evolution of specifically human traits "and perhaps even aspects of cognitive function," Dr. Paabo said.

The degree of resemblance between humans and Neanderthals is fiercely debated by archaeologists, and even issues like whether Neanderthals had language have not been resolved. Dr. Paabo believes that genetic analysis is the best hope of doing so. He has paid particular attention to a gene known as FOXP2, which from its mutated forms in people seems to be involved in several advanced aspects of language.

A longstanding dispute among archaeologists is whether the modern humans who first entered Europe 45,000 years ago, ultimately from Africa, interbred with the Neanderthals or forced them into extinction. Interbreeding could have been genetically advantageous to the incoming humans, says Bruce Lahn, a geneticist at the University of Chicago, because the Neanderthals were well adapted to the cold European climate — the last ice age had another 35,000 years to run — and to local diseases.

Evidence from the human genome suggests some interbreeding with an archaic species, Dr. Lahn said, which could have been Neanderthals or other early humans.

So far no specific evidence of human-Neanderthal interbreeding has been found, Dr. Egholm said. But it may require analysis of almost the full Neanderthal genome to rule out all possibility of genetic interchange.

Dr. Stephen O'Brien, a geneticist at the National Cancer Institute, said that having the Neanderthal genome would be "a very exciting prospect" because it would serve as a reference point for deciding which genes had been selected for in recent human evolution.

The chimpanzee, with which humans shared an ancestor who lived some five million years ago, is one such reference point but the Neanderthals, who split from the modern human lineage some 500,000 years ago, would provide a much more helpful signpost to recent evolutionary events, Dr. O'Brien said, like adaptations as modern humans dispersed from their African homeland and the genetic differences between the three major human ethnic groups of Africans, Asians and Europeans.

Analyzing ancient DNA raises huge problems, Dr. O'Brien said, but "if there is anyone who can solve them, it's Svante Paabo."

If Dr. Paabo and 454 Life Sciences should succeed in reconstructing the entire Neanderthal genome, it might in theory be possible to bring the species back from extinction by inserting the Neanderthal genome into a human egg and having volunteers bear Neanderthal infants. This might be the best possible way of finding out what each Neanderthal gene does, but there would be daunting ethical problems in bringing a Neanderthal child into the world again.

Dr. Paabo said that he could not even imagine how such a project could be accomplished and that in any case ethical concerns "would totally preclude such an experiment."

Dr. Lahn described the idea as "certainly possible but futuristic."

The most serious technical problem would be creating functional chromosomes from Neanderthal DNA. But ethical questions may be less surmountable. "My first consideration would be for a child born alone in the world with no relatives," said Ronald M. Green, an ethicist at Dartmouth College. The risk would be greater if, following the plot line of Mary Shelley's "Frankenstein," a mate were created as a companion for the lonely Neanderthal. "This was a species we competed with," Dr. Green said. "We would not want to recreate a situation of two competing advanced hominid species."

But Dr. Green said there could be arguments in the future for resurrecting the Neanderthals. "If we learn this is a species that was wrongly pushed off the stage of history, there is something of a moral argument for bringing it back," he said. "But the status quo is not without merit. Curiosity alone could not justify what could be a disaster for both species."

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