The Neanderthal Code

WILL AN EXTINCT GENOME REVEAL WHAT MAKES US HUMAN?

BY MICHAEL DUMIAK

AN ARGUMENT THAT BEGAN 150 years ago with a stunning discovery in Germany’s Neander valley may soon come to an end in an ultra-sterile lab at the Max Planck Institute for Evolutionary Anthropology in Leipzig. Genetic anthropologist Svante Pääbo is coolly confident that he has found a way to reassemble the genetic code of a Neanderthal who lived in Croatia 45,000 years ago and who may provide answers to some important questions: Were Neanderthals a separate species from us? Did they interbreed with modern humans? Do their genes survive in modern humans?

“The big picture is that modern humans came out of Africa and replaced Neanderthals,” says Pääbo, a bristly browed Swede with a penchant for wearing sandals and goofy socks. “The really important question is what the mutations are that became fixed in [modern] humans. What are these things that are unique to us with respect to Neanderthals?”

Finding these unique mutations could reveal the biological basis for the way that modern human brains developed, and how we acquired language and art. It may also settle the long-running debate between scientists who believe that anatomically modern humans came from Africa and gradually forced the Neanderthals into extinction, an idea called the Out-of-Africa theory, and those who believe that Neanderthals were among the archaic human species with whom anatomically modern humans interbred as they moved across the globe, an idea called Multi-Regional Evolution.

Nuclear DNA, the prize for genetic sequencing, contains the Neanderthal’s full genetic code. Some of Pääbo’s earlier work focused on retrieving mitochondrial DNA from Neanderthal bones. (Mitochondria are the microscopic organelles that provide energy to our cells.) Those studies supported the Out-of-Africa theory by showing that no strains of Neanderthal mitochondria survive in modern humans. Because each cell has several mitochondria and only one set of nuclear DNA, mitochondrial DNA is much easier to find, but it only contains a small portion of the Neanderthal’s genes. A new sequencing technique is allowing researchers to piece together the elusive nuclear DNA.

Finding Neanderthal nuclear DNA is like alchemy, only better. A small piece of Neanderthal bone is drilled out and dissolved into a test-tube solution. The sample is flown to a company called 454 Life Sciences in Branford, Connecticut. It is then poured into a machine that sifts through every miniscule fragment of DNA, discarding the 95 percent of recovered genetic material that comes from contaminants such as bacteria or people who have handled the bone. The process is like picking millions of needles out of billions of haystacks.

Even so, Pääbo may have the entire Neanderthal genome sequenced in the next 18 months. As the pieces fall into place the biological differences between modern humans and Neanderthals will come into focus. One interesting marker is a gene labeled FOXP2, which researchers suspect plays a role in the development of language. By comparing the Neanderthal FOXP2 gene to the modern human and chimpanzee versions of the gene, Pääbo believes he can determine whether Neanderthals were capable of developing complex

languages, and that could help scientists determine whether language gave modern humans enough of a survival advantage to doom Neanderthals to extinction.

Neanderthals appeared about 230,000 years ago, evolving from a *Homo erectus* population that migrated to Europe from Africa about one million years ago. Starting about 40,000 years ago anatomically modern humans emigrating from Africa began pushing Neanderthals to Europe’s fringes. Twelve thousand years later, the last Neanderthals were clinging to settlements in the Iberian peninsula. Were they killed off, were they starved into extinction, or did they blend into the modern population?

The debate over the Neanderthals’ fate has been as hard-fought as our other culture wars. “If you bring any kind of biology into cultural evolution you are a Nazi. If you say anything bad about Neanderthals you are a racist. I’m oversimplifying, but I think it’s the bottom line,” says Jean-Jacques Hublin (“The New Neandertal,” July/August 2005), director of the Max Planck Institute’s human evolution department. “Some people are desperate to prove that Neanderthals invented, separately, the Upper Paleolithic before modern humans arrived.” Hublin is referring to the period beginning roughly 40,000 years ago in Europe when people started making a wider variety of tools and the first artwork appeared.

Hublin clashes with researchers like João Zilhão at the University of Bristol, who discovered the remains of a child, dated to 24,000 years ago, with both Neanderthal and modern human characteristics that seemed to indicate the two groups interbred. “There is an idea that modern humans emerged out of Africa like the chosen people,” he once told the *London Observer*. “Their arrival is portrayed almost like a Biblical event, these golden ones replacing debased Europeans, the Neanderthals. This is nonsense.”

Sequencing the Neanderthal genome should provide a clearer picture of how much, if any, genetic material Neanderthals passed along to us. This is why Pääbo is constantly asked whether Neanderthals had sex with modern humans. If so, Multi-Regional looks better; if not, and Neanderthal genetics differ widely from that of modern humans, the Multi-Regional Evolution boat has got a hole in it.

Pääbo’s research is already showing differences between Neanderthals and modern humans, and he clearly backs the Out-of-Africa theory. He is tightlipped about the subject, citing pending publications. But a report in the journal *Nature* states his lab has already found substantial differences between the Y-chromosomes in Neanderthals and those in modern humans—another indicator that the groups did not interbreed. Michael Egholm, a chemist and vice president of 454 Life Sciences, acknowledges that the preliminary data backs the Out-of-Africa theory. “We can see a lot about who Neanderthals were, and they do not belong to the same population as any modern humans.”

But some of the grand old sparring partners in this argument are actually pretty sanguine. Chris Stringer of London’s Natural History Museum, a leading Out-of-Africa proponent, figures the DNA record will support the idea that Neanderthals were a different species. “The interbreeding has quite got in the way of a lot of discussions. Milford and I have been talking past each other for 20 years on this one,” Stringer says. “I regard them as a different species, but… that doesn’t say anything about whether they interbred with us or not.”

University of Michigan paleoanthropologist Milford Wolpoff, the top Multi-Regional researcher, doesn’t think the DNA record will show that at all. “You’ve got to think to yourself that Neanderthals were never more than one or two percent of the human population, and we make an awful lot of them,” he says. Wolpoff has high hopes for ancient DNA analysis; he expects it will show at least some Neanderthal genes survive in modern Europeans.

Ancient DNA analysis is having a spillover effect beyond genetics and anthropology. It’s sparking new ways of looking at scientific puzzles and prompting archaeologists to contend with genetics as a potentially vital tool. For a practice that is only 20 years old, that’s remarkable. “If you would have asked me two years ago, I’d have said there is no chance that we would be looking at ancient nuclear DNA,” Wolpoff says. “Here Svante’s doing it. I’m glad I didn’t say anything, because I would have been wrong.”

Cross-disciplinary molecular archaeology departments and research centers are popping up at universities around the world, including an American Association of Anthropological Genetics with 80 members. Migration and domestication patterns are two of the many areas being explored with this new technology.

But there are limits. More recent DNA is too similar to modern DNA. “It’s been very frustrating. I actually started out as an Egyptologist,” Pääbo says. “My aim was to look at the history of Egypt and say, ‘Well, we know Alexander the Great comes
to Egypt. Does that make a genetic difference? Or was it only political? We can’t distinguish these things genetically.”

DNA analysis remains a slow and expensive process, so researchers say the days of measuring fossils with calipers are not going away soon. Egholm, on the other hand, is in the business of optimisms, and he believes the limits can be overcome. “If one can sequence Neanderthal DNA, if one can take a few nanograms of 40,000-year-old DNA and get a meaningful sequence out of that, you can sequence just about anything.”

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