SEPARATING THEM FROM US

Some genes that differ between modern humans and Neandertals

Gene	Significance
RPTN	Encodes the protein repetin, expressed in skin, sweat glands, hair roots, and tongue papilli
TRPMI	Encodes melastatin, a protein that helps maintain skin pigmentation
THADA	Associated with type 2 diabetes in humans; evolutionary changes may have affected energy metabolism
DYRK1A	Found in an area critical for causing Down syndrome
NRG3	Mutations associated with schizophrenia
CADPS2,AUTS2	Mutations implicated in autism
RUNX2 (CBRA1)	Causes cleidocranial dysplasia, characterized by delayed closure of cranial sutures, malformed clavicles, bell-shaped rib cage, and dental abnormalities
SPAG17	Protein important for the beating of the sperm flagellum

Different paths. A partial list of genes that differ between Neandertals (*left*, reconstruction from Amud Cave, Israel) and early modern humans (*right*, reconstruction from Qafzeh Cave, Israel).

variants that Neandertals and some modern humans inherited from a common ancestor they shared before Neandertals split off. Although all early modern populations, including in Africa, interbred, that gene flow was not complete enough to pass these Neandertal motifs to all Africans. Human populations that were more closely related to the ancestors of Neandertals carry those motifs while Africans do not, says Reich.

To date, the genomic data don't support interbreeding in the time and place when everyone most expected it: between 45,000 and about 30,000 years ago in Europe. Neandertals and moderns lived in such proximity in France, for example, that some researchers think Neandertals imitated modern stone-tool and beadmaking technologies. But such late European mixing cannot explain the current findings, in which Asians and Europeans are equally similar to Neandertals. It's still possible that Neandertals and modern humans in Europe interbred rarely and that the Neandertal genes were swamped out in a large population of modern humans, says Slatkin.

In some ways, it is surprising that there isn't more evidence of interbreeding, now that researchers know it was biologically possible. "For some reason, they didn't interbreed a lot—something was preventing them," says evolutionary geneticist Sarah Tishkoff of the University of Pennsylvania. "Was it a cultural barrier?"

Modern motifs

The Neandertal genome also gives researchers a powerful new tool to fish for genes that have evolved recently in our lineage, after we split from Neandertals. The team compared the Neandertal genome with the genomes of five diverse modern humans. They found 78 new nucleotide substitutions that change the protein-coding capacity of genes and that are present in most humans today; just five genes had more than one such substitution. That's a tiny fraction of the 3 billion bases in each genome. "Only 78 substitutions in the last 300,000 years!" says Poinar. "The fact that so few changes have become fixed on the human lineage is amazing."

But the mutations they've found so far "are all very interesting, precisely because there are so few," says Pääbo, whose team is trying to identify their function. The catalog includes changes in genes that encode proteins important for wound healing, the beating of sperm flagellum, and gene transcription (see table, above). Several of these newly evolved modern human genes encode proteins expressed in the skin, sweat glands, and inner sheaths of hair roots, as well as skin pigmentation. "The fact that three of six genes carrying multiple substitutions are in skin is fascinating," says Poinar. Pääbo speculates that these changes "reflect that skin physiology has changed but how, of course, we don't know yet."

Some of those changes are likely to be neutral changes that accumulated through genetic drift, but the team also used the Neandertal data to find other evolutionary changes that were beneficial to modern humans and so rose to high frequencies in some populations. Specifically, they have identified 15 regions containing between one and 12 genes. The widest region is located on chromosome 2 and contains the gene *THADA*, a region that varies in modern humans and that has been associated with type 2 diabetes. Changes in this gene may have affected energy metabolism in modern humans.

Other mutations appear to be in genes important in cognitive development and that, when mutated in living people, contribute to diseases such as Down syndrome, schizophrenia, and autism. One gene, *RUNX2*, is associated with a disease that leads a spectrum of developmental abnormalities, including misshapen clavicles and a bell-shaped rib cage. Suggestively, Neandertals had bell-shaped rib cages and possibly peculiar clavicles. But precisely how all these genetic differences are expressed physiologically is the next frontier. "We need to follow up. Are there regions that are functionally significant?" says Tishkoff. By 7 May, the Neandertal data should be posted on Ensembl and the UC Santa Cruz browser, so other teams can do just that, says Pääbo.

His own group is already working on such functional studies. Postdoctoral researcher Matthias Gralle is analyzing the way these recently evolved genetic differences change the way proteins are expressed. Such studies may eventually offer clues about why Neandertals went extinct—and our ancestors didn't. "The mystery isn't just why they disappeared," says paleoanthropologist Jean-Jacques Hublin of the Max Planck Institute for Evolutionary Anthropology. "It is why we were so successful that we replaced all the others." For now, researchers are delighted that this "groundbreaking" genomic work has made it possible to ask such interesting questions, says Poinar. "This is the real appeal of this project: What will the genome of the Neandertal tell us about functional differences between the two [species]," says Poinar.

–ANN GIBBONS

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