

New DNA analysis shows ancient humans interbred with Denisovans

A new high-coverage DNA sequencing method reconstructs the full genome of Denisovans — relatives to both Neandertals and humans — from genetic fragments in a single finger bone.

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Tens of thousands of years ago modern humans crossed paths with the group of hominins known as the Neandertals. Researchers now think they also met another, less-known group called the Denisovans. The only trace that we have found, however, is a single finger bone and two teeth, but those fragments have been enough to cradle wisps of Denisovan DNA across thousands of years inside a Siberian cave. Now a team of scientists has been able to reconstruct their entire genome from these meager fragments. The analysis adds new twists to prevailing notions about archaic human history.

"Denisova is a big surprise," says John Hawks, a biological anthropologist at the University of Wisconsin–Madison who was not involved in the new research. On its own, a simple finger bone in a cave would have been assumed to belong to a human, Neandertal or other hominin. But when researchers first sequenced a small section of DNA in 2010—a section that covered about 1.9 percent of the genome—they were able to tell that the specimen was neither. "It was the first time a new group of distinct humans was discovered" via genetic analysis rather than by anatomical description, said Svante Pääbo, a researcher at the Max Planck Institute (M.P.I.) for Evolutionary Anthropology in Germany, in a conference call with reporters.

Now Pääbo and his colleagues have devised a new method of genetic analysis that allowed them to reconstruct the entire Denisovan genome with nearly all of the genome sequenced approximately 30 times over akin to what we can do for modern humans. Within this genome, researchers have found clues into not only this group of mysterious hominins, but also our own evolutionary past. Denisovans appear to have been more closely related to Neandertals than to humans, but the evidence also suggests that Denisovans and humans interbred. The new analysis also suggests new ways that early humans may have spread across the globe. The findings were published online August 30 in *Science*¹.

Who were the Denisovans?

Unfortunately, the Denisovan genome doesn't provide many more clues about what this hominin looked like than a pinky bone does. The researchers will only conclude that Denisovans likely had dark skin. They also note that there are alleles



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Denisova cave in Siberia was once home to a unique species of hominins.

"consistent" with those known to call for brown hair and brown eyes. Other than that, they cannot say.

Yet the new genetic analysis does support the hypothesis that Neandertals and Denisovans were more closely related to one another than either was to modern humans. The analysis suggests that the modern human line diverged from what would become the Denisovan line as long as 700,000 years ago—but possibly as recently as 170,000 years ago.

Denisovans also interbred with ancient modern humans, according to Pääbo and his team. Even though the sole fossil specimen was found in the mountains of Siberia, contemporary humans from Melanesia (a region in the South Pacific) seem to be the most likely to harbor Denisovan DNA. The researchers estimate that some 6 percent of contemporary Papuans' genomes come from Denisovans. Australian aborigines and those from Southeast Asian islands also have traces of Denisovan DNA. This suggests that the two groups might have crossed paths in central Asia and then the modern humans continued on to colonize the islands of Oceania.

Yet contemporary residents of mainland Asia do not seem to possess Denisovian traces in their DNA, a "very curious" fact, Hawks says. "We're looking at a very interesting population scenario"—one that does not jibe entirely with what we thought we knew about how waves of modern human populations migrated into and through Asia and out to Oceania's islands. This new genetic evidence might indicate that perhaps an early wave of humans moved through Asia, mixed with Denisovans and then relocated to the islands—to be replaced in Asia by later waves of human migrants from Africa. "It's not totally obvious that that works really well with what we know about the diversity of Asians and Australians," Hawks says. But further genetic analysis and study should help to clarify these early migrations.

Just as with modern *Homo sapiens*, the genome of a single individual cannot tell us exactly what genes and traits are specific to all Denisovans. Yet, just one genome can reveal the genetic diversity of an entire population. Each of our genomes contains information about generations far beyond those of our parents and grandparents, said David Reich, a researcher at the Massachusetts Institute of Technology–Harvard University Broad Institute and a co-author on the paper. Scientists can compare and contrast the set of genes on each chromosome—passed down from each parent—and extrapolate this process back through the generations. "You contain a multitude of ancestors within you," Reich said, borrowing from Walt Whitman.

The new research reveals that the Denisovans had low genetic diversity—just 26 to 33 percent of the genetic diversity of contemporary European or Asian populations. And for the Denisovans, the population on the whole seems to have been very small for hundreds of thousands of years, with relatively little genetic diversity throughout their history.

Curiously, the researchers noted in their paper, the Denisovan population shows "a drastic decline in size at the time when the modern human population began to expand."

Why were modern humans so successful whereas Denisovans (and Neandertals) went extinct? Pääbo and his co-authors could not resist looking into the genetic factors that might be at work. Some of the key differences, they note, center around brain development and synaptic connectivity. "It makes sense that what pops up is connectivity in the brain," Pääbo noted. Neandertals had a similar brain size-to-body ratio as we do, so rather than cranial capacity, it might have been underlying neurological differences that could explain why we flourished while they died out, he said.



Hawks counters that it might be a little early to begin drawing conclusions about human brain evolution from genetic comparisons with archaic relatives. Decoding the genetic map of the brain and cognition from a genome is still a long way off, he notes—unraveling skin color is still difficult enough given our current technologies and knowledge.

New sequencing for old DNA

The Denisovan results rely on a new method of genetic analysis developed by paper co-author Matthias Meyer, also of M.P.I. The procedure allows the researchers to sequence the full genome by using single strands of genetic material rather than the typical double strands required. The technique, which they are calling a single-stranded library preparation, involves stripping the genetic material down to individual strands to copy and avoids a purification step, which can lose precious genetic material.

The finger bone—just one distal phalanx—is so small that it does not contain enough usable carbon for dating, the researchers note. But by counting the number of genetic mutations in a genome and comparing them with other living relatives, such as modern humans and chimpanzees, given assumed rates of mutations since breaking with a last common ancestor, "for the first time you can try to estimate this number into a date and provide molecular dating of the fossil," Meyer said. With the new resolution, the researchers estimate the age of the bone to 74,000 to 82,000 years ago. But that is a wide window, and previous archaeological estimates for the bone are a bit younger, ranging from 30,000 to 50,000 years old. These genetic estimations are also still in limbo because of ongoing debate about the average rate of genetic mutations over time, which could skew the age. "Nevertheless," the researchers noted in their paper, "the results suggest that in

the future it will be possible to determine dates of fossils based on genome sequences."

This new sequencing approach can be used for any DNA that is too fragmented to be read well through more traditional methods. Meyer noted that it could come in handy for analysis of both ancient DNA and contemporary forensic evidence, which also often contains only fragments of genetic material.

Hawks is excited about the new sequencing technology. It is also helpful to have a technology developed specifically for the evolutionary field, he notes. "We're always using the new techniques from other fields, and this is a case where the new technique is developed just for this."

Hawks himself has heard from the researchers that have worked with the Denisovan samples that "the Denisovan pinky is just extraordinary" in terms of the amount of DNA preserved in it. Most bone fragments would be expected to contain less than 5 percent of the individual's endogenous DNA, but this fortuitous finger had a surprising 70 percent, the researchers noted in the study. And many Neandertal fragments have been preserved in vastly different states—many are far worse off than this Denisovan finger bone.

The new sequencing approach could also improve our understanding of known specimens and the evolutionary landscape as a whole. "It's going to increase the yield from other fossils," Hawks notes. Many of the Neandertal specimens, for example, have only a small fraction of their genome sequenced. "If we can go from 2 percent to the whole genome, that opens up a lot more," Hawks says. "Going back further in time will be exciting," he notes, and this new technique should allow us to do that. "There's a huge race on—it's exciting."

The Denisovans might be the first non-Neandertal archaic human to be sequenced, but they are likely not going to be the last. The researchers behind this new study are already at work using the new single-strand sequencing technique to reexamine older specimens. (Meyer said they were working on reassessing old samples but would not specify which specimens they were studying—the mysterious "hobbit" *H. floresiensis* would be a worthy candidate.) Pääbo suggests Asia as a particularly promising location to look for other Denisovan-like groups. "I would be surprised if there were not other groups to be found there in the future," he said.

Taking this technique to specimens from Africa is also likely to yield some exciting results, Hawks says. Africa, with its rich human evolutionary history, holds the greatest genetic diversity. The genomes of contemporary pygmy and hunter-gatherer tribes in Africa, for example, have roughly as many differences as do those of European modern humans and Neandertals. So "any ancient specimen that we find in Africa might be as different from us as Neandertals," Hawks says. "Anything we find from the right place might be another Denisovan."

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References

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