NEWS IN FOCUS

CHRISTOPHER RYNN/UNIV. DUNDEE

Denny inherited one set of chromosomes from her Neanderthal ancestors, depicted in this model.

EVOLUTION

First ancient–human hybrid

A direct descendant of two different groups of early humans has been found in Russia.

BY MATTHEW WARREN

A female who died around 90,000 years ago was half Neanderthal and half Denisovan, according to genome analysis of a bone discovered in a Siberian cave. This is the first time that scientists have identified an ancient individual whose parents belonged to distinct human groups. The findings were published on 22 August in *Nature*[1].

"To find a first-generation person of mixed ancestry from these groups is absolutely extraordinary," says population geneticist Pontus Skoglund at the Francis Crick Institute in London. "It's really great science coupled with a little bit of luck."

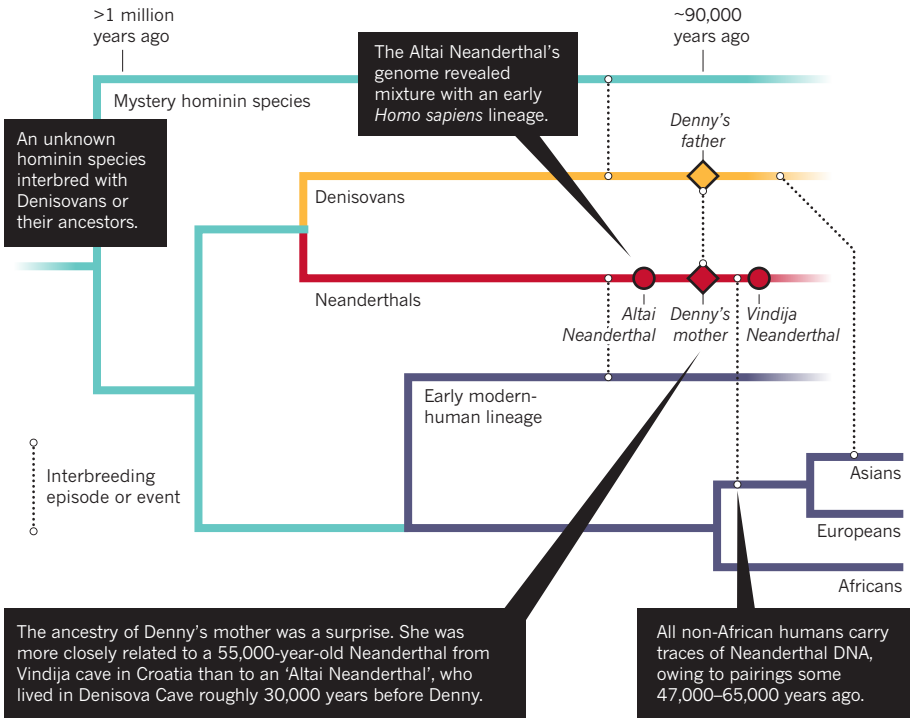
The team, led by palaeogeneticists Viviane Slon and Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, conducted the genome analysis on a single bone fragment recovered from Denisova Cave in the Altai Mountains of Russia. This cave lends its name to the 'Denisovans', a group of extinct humans first identified on the basis of DNA sequences from the tip of a finger bone discovered[2] there in 2008. The Altai region, and the cave specifically, were also home to Neanderthals.

Given the patterns of genetic variation in ancient and modern humans, scientists already knew that Denisovans and Neanderthals must have bred with each other — and with *Homo sapiens* (See 'Tangled tree'). But no one had previously found the first-generation offspring from such pairings, and Pääbo says that he questioned the data when his colleagues first shared them. "I thought they must have screwed up something," he says. Before the discovery of the Neanderthal–Denisovan individual, whom the team has affectionately named Denny, the best evidence for so close an association was found in the DNA of a *Homo sapiens* specimen who had a Neanderthal ancestor within the previous 4–6 generations[3].

Pääbo's team first uncovered Denny's ▶

TANGLED TREE

A female born to a Neanderthal mother and Denisovan father roughly 90,000 years ago — nicknamed Denny — is one of many examples of interbreeding between ancient human groups.



SOURCE: M. KUHLWILM *ET AL. NATURE* **530**, 429–433 (2016)/REF. 1

remains several years ago, by looking through a collection of more than 2,000 unidentified bone fragments for signs of human proteins. In a 2016 paper[4], they used radiocarbon dating to determine that the bone belonged to a hominin who lived more than 50,000 years ago (the upper limit of the dating technique; subsequent genetic analysis has put the specimen at around 90,000 years old, according to Pääbo). They then sequenced the specimen's mitochondrial DNA — the DNA found inside cells' energy converters — and compared that data to sequences from other ancient humans. This analysis showed that the specimen's mitochondrial DNA came from a Neanderthal.

But that was only half of the picture. Mitochondrial DNA is inherited from the mother and represents just a single line of inheritance, leaving the identity of the father and the individual's broader ancestry unknown.

In the latest study, the team sought to get a clearer understanding of the specimen's ancestry by sequencing its genome and comparing the variation in its DNA to that of three other hominins — a Neanderthal and a Denisovan, both found in Denisova Cave, and a modern-day human from Africa. Around 40% of DNA fragments from the specimen matched Neanderthal DNA — but another 40% matched the Denisovan. By sequencing the sex chromosomes, the researchers also determined that the fragment came from a female, and the thickness of the bone suggested that she was at least 13 years old.

With equal amounts of Denisovan and Neanderthal DNA, the specimen seemed to have one parent from each hominin group. But there was another possibility: Denny's parents could have belonged to a population of Denisovan–Neanderthal hybrids.

A FASCINATING GENOME

To work out which of these options was more likely, the researchers examined sites in the genome where Neanderthal and Denisovan genetics differ. At each of these locations, they compared fragments of Denny's DNA to the genomes of the two ancient hominins. In more than 40% of cases, one of the DNA fragments matched the Neanderthal genome, whereas the other matched that of a Denisovan, suggesting that she had acquired one set of chromosomes from a Neanderthal and the other from a Denisovan. That made it clear that Denny was the direct offspring of two distinct humans, says Pääbo. "We'd almost caught these people in the act."

A bone fragment was sequenced for its genome.

THOMAS HIGHAM/UNIV. OXFORD

The results convincingly demonstrate that the specimen is indeed a first-generation hybrid, says Kelley Harris, a population geneticist at the University of Washington in Seattle. Skoglund agrees: "It's a really clear-cut case," he says. "I think it's going to go into the textbooks right away."

Harris says that sexual encounters between Neanderthals and Denisovans might have been quite common. "The number of pure Denisovan bones that have been found I can count on one hand," she says — so the fact that a hybrid has already been discovered suggests that such offspring could have been widespread. This raises another interesting question: if Neanderthals and Denisovans mated frequently, why did the two hominin populations remain genetically distinct for several hundred-thousand years? Harris suggests that Neanderthal–Denisovan offspring could have been infertile or otherwise biologically unfit, preventing the two species from merging.

Neanderthal–Denisovan pairings could also have had some advantages, even if there were other costs, says Chris Stringer, a palaeoanthropologist at the Natural History Museum in London. Neanderthals and Denisovans were less genetically diverse than modern humans, and so interbreeding might have provided a way of "topping up" their genomes with a bit of extra genetic variation, he says.

Pääbo agrees that Neanderthals and Denisovans would have readily bred with each other when they met — but he thinks that those encounters were rare. Most Neanderthal remains have been found across western Eurasia, whereas Denisovans have so far been discovered only in their eponymous Siberian cave. Although the two groups' home turf overlapped in the Altai Mountains, and possibly elsewhere, these areas would have been sparsely populated.

With a Neanderthal mother and a Denisovan father, what should the new specimen be called? "We shy away a little from the word 'hybrid'," says Pääbo. The term implies that the two groups are discrete species of human, whereas in reality the boundaries between them are blurry — as the new study shows. Defining a species in the natural world is not always clear-cut, says Harris, and it's interesting to see that long-running debates about how to categorize organisms are starting to be applied to humans.

Whatever scientists decide to call Denny, Skoglund says he would have loved to be able to meet her. "It's probably the most fascinating person who's ever had their genome sequenced." ■

1. Slon, V. *et al. Nature* https://doi.org/10.1038/s41586-018-0455-x (2018).
2. Krause, J. *et al. Nature* **464**, 894–897 (2010).
3. Fu, Q. *et al. Nature* **524**, 216–219 (2015).
4. Brown, S. *et al. Sci. Rep.* **6**, 23559 (2016).