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Abstract: The article discusses the research of Harvard University geneticist David Reich regarding the interbreeding of homo sapiens and related hominin species such as Neanderthals and Denisovans throughout history. Topics include methods of tracking genetic patterns through mitochondrial DNA, the prevalence of non-human DNA in modern European and Asian genomes, and whether interbreeding of human-like species with homo sapiens may have affected the evolutionary health and traits of modern humans through natural selection.

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INTERBREEDING With Neanderthals

Telltale evidence of ancient liaisons with Neanderthals and other extinct human relatives can be found in the DNA of billions of people

David Reich, a geneticist at the Harvard Medical School, has redrawn our species' family tree. And today, in his office overlooking Avenue Louis Pasteur in Boston, he picks up a blue marker, walks up to a blank white wall, and shows the result to me. He starts with a pair of lines-one for humans and one for Neanderthals-that split off from a common ancestor no more than 700,000 years ago. The human branch divides into lineages of Africans, Asians, and Europeans, and then into twigs for smaller groups like the people of New Guinea or the residents of the remote Andaman Islands in the Indian Ocean. Reich also creates a branch off the Neanderthal line for the Denisovans, a paleolithic lineage geneticists discovered only a few years ago.

All well and good. This is the sort of picture you'd expect if we and our humanlike relatives diverged neatly through evolution. It looks a lot like the tree of life that Darwin included in The Origin of Species. But then Reich violates his tree. Instead of making new branches, he starts linking branches together. He inscribes a line that links the Neanderthal lineage to the Europeans and Asians. He joins the Denisovan line and the one leading to the people of New Guinea. He crisscrosses the tree again and again, joining the branches into a thicket of grafts.

Reich steps back and looks over his creation. He has a high forehead, a peregrine profile, and a very soft voice. "So," he says quietly, "it's a little bit complicated."

That's putting it mildly. Over the past 15 years, Reich has developed a toolbox of sophisticated statistical methods to extract history out of our DNA. And with those methods he has revealed scandalous liaisons dating back tens of thousands of years. Some 200,000 years ago, our ancestors evolved in East Africa. They spread throughout the rest of the continent and then moved out into Asia and Europe. As they journeyed along coastlines and over mountains, they encountered Neanderthals and other human relatives. And at least once in a while, they had sex.

We don't know the prurient details of those encounters, although it is possible that someday Reich and other scientists will be able to fill in a few of them. But the work Reich has done already leaves no doubt that interbreeding was a major feature of human evolution. Billions of people carry sizable chunks of DNA from Neanderthals and other archaic human relatives. Some of those genes may play important roles in our health today.

"We've been mixing quite often with distant relatives in our history," Reich says. In fact, he expects much more evidence of interbreeding to surface. There may be other, undiscovered humanlike beings lurking in our genomes.

Reich's wall, in other words, is about to get a lot messier.

New Revelations From DNA

When Reich entered college, in 1992, most of what scientists knew about human evolution came from fossils. The emerging consensus was that Homo sapiens evolved only in Africa. Humans then migrated to the other continents, where they lived for a time alongside humanlike relatives known as hominins.

Paleoanthropologists who supported this "out-of-Africa" model argued that Neanderthals, although they ranged over much of Europe, did not give rise to today's Europeans. Instead, they evolved separately from an ancient hominin and then, about 30,000 years ago, disappeared. Today's Europeans are not latter-day Neanderthals but African immigrants.

A new way to dig up human history emerged and bolstered this perspective. Geneticists learned how to sequence small fragments of DNA and compare the versions of those fragments from different individuals. In the mid-1980s, the late geneticist Allan Wilson and molecular geneticist Rebecca Cann gathered samples of genes from people belonging to a wide range of ethnic groups. They zeroed in on the DNA found in sausage-shaped structures in the cell, known as mitochondria.

Mitochondrial DNA is unusual in that it is passed down virtually unchanged from mothers to their children. When a woman's mitochondrial DNA mutates, all of her children will inherit the change, creating a genetic marker in her descendants.

The results of the new genetic studies strongly supported the out-of-Africa model. Cann and Wilson took advantage of the fact that mitochondrial DNA mutates at a relatively steady rate over the centuries. By tallying up the mutations in the mitochondrial DNA in various human populations, therefore, they could estimate how long they had been diverging from each other. They found that all the different mitochondrial DNA in living humans descended from a common ancestor who lived in Africa about 200,000 years ago, a woman who was nicknamed "mitochondrial Eve."

"I was very much a part of that tradition," says Reich, who arrived at the University of Oxford to earn his Ph.D. in genetics several years after Cann and Wilson published their results. Reich began learning how to analyze human DNA to learn more about how humans emerged from Africa. The research was interesting, but he wasn't sure yet that he wanted to be a scientist.

In the summer of 1997, he took a break from the lab bench to try his hand at journalism, writing a short article for The Economist about the findings of Svante Pääbo, a geneticist in Leipzig, Germany, at the Max Planck Institute for Evolutionary Anthropology. Pääbo's team had just extracted DNA from a 40,000-year-old Neanderthal fossil. "That was the only story I ever wrote," Reich says. He chose a good subject. It was one of the most important achievements in the study of human evolution.

The researchers had ground up a peppercorn-size chip of bone from a Neanderthal humerus. They doused it in chemicals that drew away all the molecules except any DNA it might hold. It did hold a lot of DNA, and most of that genetic material belonged to the bacteria that had inhabited its pores. After setting aside the microbial DNA, the Max Planck researchers were left with 379 base pairs of mitochondrial Neanderthal DNA. "I thought it was totally the most amazing stuff in the world," Reich says.

Pääbo and his colleagues compared the Neanderthal DNA to the same stretch of DNA from human mitochondria, as well as to equivalent chimpanzee DNA. The Neanderthal DNA was more similar to human than to chimp. But it was still quite different from the gene fragments of Asian, African, and European humans, which were all very similar to one another.

This result seemed to confirm the out-of-Africa model. If Neanderthals were the ancestors of living humans, then you'd expect their mitochondrial DNA to be more like that of Europeans. As Reich wrote in his article, Pääbo's study suggested that no Neanderthal DNA was present in living humans.

But Pääbo was examining just a minuscule portion of the Neanderthal genome. Reich would later help Pääbo study its entirety, and the full story would turn out to be far more complicated. "I guess not only Svante turned out to be wrong, but I did, too," Reich reflects.

Detecting Ancient Relations

After his try at writing, Reich decided that he preferred science after all and went back to the bench. And it was then that his research made a decisive shift. At the time, most geneticists were looking for ways to reconstruct the history of distinct populations. They wanted to trace the expansion of Celts into Great Britain, for example, or track Native Americans back to their closest relatives in Siberia. But Reich was curious about what happened when these groups came into contact with each other. Even though they would probably remain mostly separate, some individuals might interbreed. Reich wondered if he could look at the genomes of living humans and find evidence of those ancient liaisons.

Detecting these signs is not easy. Imagine that two people from very distant parts of the world -- a woman from Spain, say, and a man from Polynesia -- get married and have a girl. She is born with 23 pairs of chromosomes: one set from her mother and one from her father. Her mother's chromosomes are loaded with genetic markers that pinpoint her Spanish heritage. Likewise, her father's DNA is unmistakably Polynesian. But as the girl's own eggs develop, her DNA gets mixed up. In the cells that give rise to an egg, a Spanish chromosome will pair up with its Polynesian counterpart. Segments of the chromosomes switch places. Each egg ends up with a new, hybrid chromosome. Now imagine that the girl grows up and marries a Spanish man. The DNA of her children will be only one quarter Polynesian, and the Polynesian DNA will be chopped up into even smaller segments. As the generations pass, the signs of interbreeding get even fainter.

Despite the challenge, Reich thought that detecting interbreeding could be important. It could expose some of humanity's hidden history, or even shed light on why people are susceptible to certain diseases. When Reich arrived at Harvard Medical School, he began a study on prostate cancer that proved the value of this type of analysis by revealing the genes that make certain men more likely to develop such cancers. "Prostate cancer occurs 1.5 to 2 times more often in African American men than in European men," Reich says. "We were able to find the reason why"

To do so, Reich had to reconstruct the genetic history of African Americans, who came to the United States as slaves beginning in the 17th century. White owners sometimes had sex with their slaves and fathered children, thereby introducing European genes into the African American population. Freed slaves also had children with Native Americans and Latinos. As a result, African Americans today may have up to 80 percent European DNA.

Reich and his colleagues inspected the DNA of 1,597 African American men with prostate cancer. They surveyed around 1,300 short segments scattered through the men's genomes and compared them with the same locations in the genomes of men from Europe, Asia, and Africa. They were able to determine which continent each segment in each African American man's genome had come from.

Reich and his colleagues found seven genetic risk factors, which together constituted a hot spot of cancer risk. African American men who had the European version of all seven of the markers were no more likely to get prostate cancer than Europeans were; the African versions, though, were associated with elevated risk. The seven sites appear to control a gene involved in cell division. Mutations to those sites lead to cells' multiplying too quickly.

Interbreeding in the United States took place over just the past few centuries. For his next project, Reich took on a much bigger challenge: the entire ethnic history of India. Today 1.21 billion people live in India. Their cultural variety is staggering: The country is home to 2,000 ethnic groups, and every Indian banknote has to have its value printed in 15 languages.

Reich wanted to see if the DNA of Indians contained clues about their origins as a people. Did they all descend from the same founding population, or could he tease apart DNA passed down from different ancestral groups?

He collaborated with scientists from the Centre for Cellular and Molecular Biology in Hyderabad to analyze the DNA of 132 Indians. Their subjects represented 25 ethnic groups, ranging from the Kashmiri Pandit, who live near the base of the Himalayas, to the Kurumba, who inhabit the southern tip of India. In each person's DNA, the scientists surveyed 560,000 sites, comparing each site in each Indian. The researchers also compared the data with that of groups of people outside India, including Europeans and Africans.

Reich and his colleagues programmed a computer to carry out a thorough analysis of these tens of millions of data points. The computer then created a range of possible genealogical trees and measured how well each tree could explain the genetic variations found across India. In 2009 the scientists reported that Indians can trace much of their DNA to just two ancestral populations.

"It's a mixture between populations that are as different from each other as East Asians are from Europeans," Reich says.

One population came from the same stock as the people of the Andaman Islands in the Indian Ocean. They arrived on the Indian subcontinent perhaps 40,000 years ago, and their descendants made up most of the population of India until maybe a few thousand years ago. Then a second group, closely related to the ancestors of Europeans, appeared on the subcontinent. When the two groups made contact, they began to intermarry, mixing their genes together. In some ethnic groups, their DNA is now almost entirely blended. But in the far north and south of the subcontinent, the genes have mixed far less.

This discovery impressed Reich with the importance of interbreeding in human history. "You might think we're living in special times now," he says. "But we've been mixing quite often with distant relatives in our history." And the statistical methods that Reich and his colleagues designed to probe the history of India proved crucial for his project deciphering the far earlier relationship of humans and Neanderthals.

Ever since Reich wrote his article about Neanderthal DNA back in 1997, Pääbo had been pushing to get more of their genes. By 2010 he and his colleagues had created a rough draft of the entire Neanderthal genome, comprising over 60 percent of its more than 3 billion base pairs. Pääbo could now return to the question of how Neanderthals and humans were related, with thousands of times more data. But in order to make sense of the huge amount of DNA he had, he needed to work with people who were experts on how the relationships between populations can be gleaned from DNA -- people like Reich.

"For our community it was always the great question, what the history of Neanderthal and modern human interactions was," Reich says. "And the data Pääbo was gathering was a great way to get into it."

The Neaderthal With in Us

Reich and his colleagues began analyzing Pääbo's Neanderthal genome in 2007. They worked their way through the DNA in much the same way they had looked at the genes of Indians. They compared each site in the Neanderthal genome to the corresponding site in the genomes of humans, as well as the genome of a chimpanzee. Once more, they tried to work out the most likely evolutionary history that would explain the evidence.

"We were assuming Neanderthals and humans had not mixed," Reich says. After all, that's what Pääbo had initially found in 1997, looking at a tiny snip of mitochondrial DNA. And when he was able to look at larger pieces of mitochondrial DNA, he got the same result.

Most of the Neanderthal genes Reich and his colleagues looked at again supported Pääbo's earlier research. In other words, all the human versions resembled each other more than any of them resembled the Neanderthal version. But then their computers began to spit out some strange results. Chunks of Neanderthal DNA turned out to be more similar to the corresponding chunks of Europeans and Asians than they were to African DNA. On the other hand, in no case did Africans and Neanderthals share similar versions of a gene, to the exclusion of other humans. Was it possible that Europeans and Asians had a little Neanderthal DNA after all?

"We were suspicious of the result," Reich says. "We found signals of mixture and then worked very hard to make them go away."

He tried for a year, to no avail. Finally, Reich and his colleagues had no choice but to conclude that Neanderthals had mated with humans. They estimated that the DNA of living Asians and Europeans was (on average) 2.5 percent Neanderthal. They had to reject a pure version of the out-of-Africa model. Instead, their model was closer to out-of-Africa-and-get-to-know-some-Nean-derthals-very-well.

The patterns Reich and his colleagues identified can help narrow down when and where the interbreeding took place. Since Africans do not carry Neanderthal DNA, it would appear Neanderthals bred only with the ancestors of Europeans and Asians. One possibility is that when humans emerged out of Africa some 50,000 or more years ago, they encountered Neanderthals in the Near East. Once humans and Neanderthals mated, the humans continued to expand into Europe and Asia, taking Neanderthal genes with them. Another possibility is that the interbreeding came later. Neanderthals lived across a vast range, from Spain to Russia. As humans came into contact with Neanderthals, they might have mated in several places.

Humans and Neanderthals did not merge into a single people, however; the 2.5 percent of Neanderthal DNA found in Asians and Europeans is a very small fraction. Mathias Currat and Laurent Excoffier, two Swiss geneticists, studied how much interbreeding would be necessary to end up with so little Neanderthal DNA in humans today. All it would take, they concluded, would be for a Neanderthal and a human to create a child once every 30 years. "It's not surprising to me," Reich says of that finding. "Humans don't mix easily across group boundaries. People tend to mix with people who look like them, who speak their language."

Beyond these rough outlines, the story quickly gets foggy. Clearly the hybrid children from these interbreedings had to have been accepted into human cultures. But we can't say whether these couplings happened as rapes during violent battles between humans and Neanderthals or when individual Neanderthals were welcomed into human society.

Reich hopes to find more clues to bring the story into better focus. One question he wants to address is how genes flowed from Neanderthals into humans. Were human males mating with Neanderthal females, or vice versa?

"There is actually a real chance of studying the directionality of gene flow," Reich says. Females have two X chromosomes, while males have one X and one Y. If Neanderthal females mated with male humans, he notes, they would provide an X chromosome to all of their children. If Neanderthal males were involved, they would be able to provide an X to their daughters but none to their sons. If Reich were to find an unusually low amount of Neanderthal DNA on the X chromosome compared with the other chromosomes, it might be a clue that Nean-derthal males impregnated human females. A high ratio would point the other way, to Neanderthal great-great-grandmothers. "We are looking hard at this," he says.

Other Distant Relatives

One evening in 2010, Reich was having dinner with Pääabo and some colleagues in a Leipzig beer garden. They were finishing up their work on the Neanderthal genome. Now Pääbo had more news for Reich. He believed he had found DNA in another extinct hominin.

Pääbo had been collaborating with Russian paleoanthropologists who were excavating fossils in a cave in Siberia called Den-isova. The cavern was loaded with petrified remains that had been laid down over thousands of years. Some appeared to be Neanderthal. Some seemed human. The Russians shipped bone samples to Germany, where Pääbo's postdoc, Johannes Krause, began grinding them to search for DNA. Most held nothing but bacterial genes. But then Krause looked at the tip of a pinkie bone that belonged to a girl who died more than 50,000 years ago, and everything changed.

The specimen was packed with DNA. When Krause sequenced a small sample, he could immediately see it was not quite human and not quite Neanderthal. It belonged to some other hominin unknown to science. Pääbo and his colleagues dubbed the long-gone girl the Denisovan.

Reich immediately jumped into the project. He and his colleagues applied the same methods to the new genome as they had to Neanderthal DNA. Overall, the Denisovan genes were closest to the Neanderthals, but the genome had many mutations not found in either humans or Neanderthals. Denisovan ancestors apparently had diverged from the ancestors of Neanderthals somewhat more recently than the split between Neanderthals and modern human beings.

It is possible that their common ancestor emigrated from Africa many hundreds of thousands of years ago, leaving our own ancestors behind on that continent. The ancestors of Neanderthals headed north and as far west as Europe. The Denisovans' ancestors, meanwhile, headed east and survived long enough to at least leave that pinkie bone in the Siberian cave. The Denisovan girl's genes give us a few clues to what she might have looked like. She had gene variants that would have given her dark skin, brown eyes, and brown hair, for example. At some point after 50,000 years ago, the Denisovans vanished, just like their Neanderthal cousins.

Knowing that Neanderthals and humans had interbred, Reich and his colleagues looked carefully for Denisovan DNA in the genomes of living humans. They found it in genomes from two populations, one from New Guinea and another from the nearby island of Bougainville. As much as 5 percent of their DNA came from the vanished Denisovans.

This result was dramatically different from the findings in their Neanderthal study. It prompted Reich and his colleagues to make a much broader survey of human DNA. They could not find a trace of Denisovan DNA in Africans. Nor could they find it in Europeans, nor in mainland Asians. But they did find vestiges in the genomes of Australian Aborigines. In the Philippines they also found it in people called Mamanwa. These short, dark-skinned tribespeople have long intrigued anthropologists, since they seem so unlike most residents of the western Pacific.

"It was so striking that we thought it must be a mistake at first. But it's a really distinct, consistent, overwhelming pattern. The only way to explain this is by gene exchange," Reich says. "The Denisovan group probably was spread out over thousands and thousands of miles," extending from the tundra of Siberia in the north all the way down to the steamy jungles of southeast Asia -- a bigger range than Neanderthals'.

Ancient DNA, Modern Health'

By the time the Neanderthals and Denisovans encountered modern humans, their genes had been evolving separately for hundreds of thousands of years. Yet it's possible their DNA is still influencing the health of billions of people today. It's possible that some of their genes caused harm when they were combined with human DNA, raising the risk of certain diseases or reducing a person's fertility.

On the other hand, some of the foreign DNA may have benefited us. In August 2011, Peter Parham of Stanford University and his colleagues found that the Neanderthal and Denisovan versions of some immune system genes are now remarkably widespread. They can be found in Europe, Asia, and even the Pacific islands. Their prevalence suggests that they may have provided some disease-fighting advantage.

Reich is not ready to take a firm stand on how our Neanderthal or Denisovan DNA is affecting our health. The draft genomes of Neanderthals and Denisovans still have too many gaps and errors to allow for that sort of certainty. But he is open to the possibility that some of their genes were favored by natural selection in humans. "These were people coming out of Africa, and they had to cope with environments to which Neanderthals and Denisovans were already adapted."

Fortunately, Reich says, we can do more than just speculate about why a particular piece of Neanderthal or Denisovan DNA is still in our genomes. "You could associate it to people's traits," he says. Are people with a particular chunk of Neanderthal DNA faster runners than people without it? Are people with a particular chunk of Denisovan DNA better at logic puzzles? "It's an experiment you can actually do."

For Reich, the revelations from the Neanderthal and Denisovan genomes are probably just the beginning of a new understanding of our evolution. He would not be surprised if the genome of yet another ancient hominin comes to light in our DNA. "Why not? It doesn't seem unlikely at this point," he says.

One place where such evidence might turn up is in Africa. Michael Hammer, a geneticist at the University of Arizona, and his colleagues have found hints of a new hominin by looking at the DNA of Africans. They found snippets, about 2 percent of the genome in total, that seem out of place in human DNA. The best explanation is that this is the result of another archaic human who interbred with Africans about 35,000 years ago, Hammer argues.

To confirm such findings, scientists will need to find more ancient genomes, and Reich thinks they will. "I'm optimistic," he says. "The world is full of things like Denisova Cave. There must be thousands of other bones out there."

DNA of living Asians and Europeans was [on average] 2.5 percent Neanderthal.

Neanderthal genes could explain why some people today can resist certain diseases.

A reconstructed Neanderthal skeleton (foreground) and modern human.

ANCIENT RELATIONS Geneticist David Reich (above) and his colleagues estimate that the DNA of living Asians and Europeans is, on average, 2.5 percent Neanderthal. The interactions probably happened across the area inhabited by Neanderthals.

OTHER MATCHES Certain Oceanic populations have up to 5 percent Denisovan DNA.

Red pins show areas of possible Neanderthal-human interaction; yellow, Denisovan-human interbreeding.

100 PERCENT NEADERTHAL

Did Neanderthal males, like the one reconstructed here, mate with human females or vice versa? David Reich hopes to find more clues in the DNA. "There is actually a real chance of studying the directionality of the gene flow," he says.

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By CARL ZIMMER

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