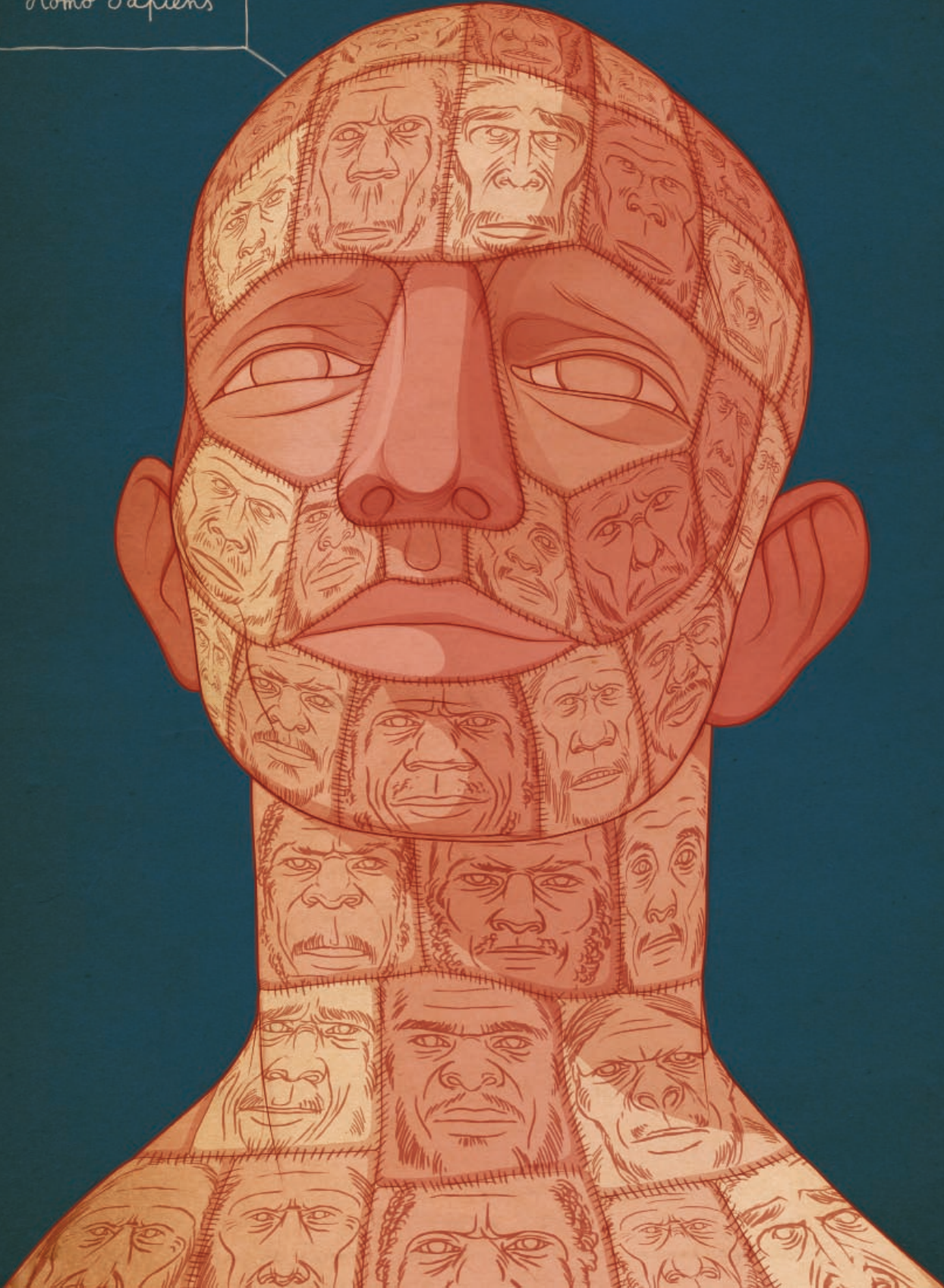


Homo Sapiens



RICHARD WILKINSON

We thought we had just about nailed human evolution, now everything is up for grabs again. Ed Yong reports

Our hybrid origins

ONCE upon a time the human story seemed so simple. Between 5 and 7 million years ago, our ancestors split from those of chimpanzees. Since then, numerous human-like species have roamed the Earth, but we out-competed them all. Today we are the sole survivors.

Then came the news that these other hominins live on inside many of us. In a groundbreaking study of ancient DNA, a team led by Svante Pääbo at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, revealed that many people carry the genetic legacy of Neanderthals. Everyone of non-African descent can trace between 1 and 4 per cent of their genes directly back to our Homo cousins. These genes even turn up in people living in areas where no Neanderthal fossils have ever been found, such as China and Papua New Guinea. The implication is clear: at some point in human history, populations that left Africa interbred with other ancient people. Homo sapiens is a hybrid (Science, vol 328, p 710).

That bombshell was dropped in May 2010. Seven months later, the team was at it again. This time they had sequenced DNA from a lone pinky finger bone, excavated from the

Denisova cave in Siberia and dated to between 30,000 and 50,000 years old. Once again, they were able to unpick the full genome, revealing it to belong to a young woman from a previously unrecognised group of ancient hominins, which they named the Denisovans. And, once again, comparisons with modern humans showed that some of the ancient DNA lives on, comprising between 5 and 7 per cent of the genes of people from Melanesia, which includes Papua New Guinea, Fiji and nearby islands (Nature, vol 468, p 1053).

These two studies look set to spark a revolution. Pääbo and colleagues are the first to decipher entire genomes of ancient hominins. In doing so they bring a new approach to understanding human origins – one that has the potential to upend much of what we thought we knew about human evolution. Already, the results have settled a long-standing argument about whether early modern humans bred with other hominins as they spread around the world.

They also raise an intriguing possibility. The percentage of genes involved may be small, but with two positive results from two studies, it seems likely that further research will show genes from other extinct groups of

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REBUILDING ANCIENT GENOMES

The sequencing of ancient DNA has been a massive technical achievement. That's because DNA degrades with age, especially in hot and humid conditions. Even when it is present, it is usually swamped by genetic material from bacteria and fungi that have infiltrated the sample while it lay in the ground.

Working in a clean room to avoid contamination from their own DNA, researchers remove these unwanted sequences using enzymes. They then isolate the tiny fragments of ancient DNA, amplify them and use a computer to pinpoint overlapping segments so that they can stitch the genome

back together. In this way, a team led by Svante Pääbo from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, was able to sequence 40,000-year-old DNA to get rough drafts of both the Neanderthal and Denisovan genomes.

To find out whether these two early hominins interbred with early modern humans, their genomes were compared with those of modern humans. Because of our common ancestry we share the vast majority of our genes with these groups, but the differences are telling. Pääbo's team focused on "single nucleotide polymorphisms," or

SNPs, which are sites on the genome that vary from person to person by a single DNA "letter". Neanderthals share as many SNPs with Europeans as they do with Asians, but they share fewer with Africans. That makes them genetically closer to those living outside of Africa than those living in the continent.

The team also found that Denisovans share the same number of SNPs with almost all non-Africans, but they share even more with Melanesians. These small differences showed that Neanderthal DNA entered the modern human genome after Homo sapiens left Africa,

and that Denisovan DNA came in after the Melanesians split from the rest of Asia.

The next step is to discover what these ancient genes do. "It's possible that early modern humans could have used the Neanderthal or Denisovan genetic material to adapt to their environment," says David Reich from Harvard Medical School in Boston. Indeed, the most recent studies indicate that interbreeding allowed early humans to acquire genes that helped protect them against local diseases as they migrated across the globe (New Scientist, 18 June 2011, p 11).

hominins in modern humans too. In other words, it looks like we have a mosaic genome. Researchers are itching to get their hands on more hominin DNA to explore this possibility as well as other key questions about human origins. "Once, we just had fossils and we'd argue about what they really show," says John Hawks from the University of Wisconsin, Madison. "With DNA, you know when things are the same. It changes everything."

For a start, DNA analysis gives us a new way to identify the various groups of early human. Before now, they have always been defined on the basis of their bones, but the Denisovans are the first to reveal themselves by their genes alone. Analysis of their genome places

where, but the most likely scenario is that when the ancestors of modern humans left Africa they bred with Neanderthals in the Middle East, around 60,000 years ago, picking up a small proportion of their genes before spreading throughout Europe and Asia. Then, in east Asia, they encountered Denisovans and repeated the same cycle of interbreeding and genetic acquisition, before colonising Melanesia 45,000 years ago. "Population mixture is not an exception in human evolution. It's perhaps the rule and it has been going on for a long period of human history," says geneticist David Reich at Harvard Medical School in Boston, who was involved in the studies.

across Eurasia, as all part of a single evolving species that met and mated extensively over tens of thousands of years, ultimately giving rise to modern humans.

Neither fossils nor modern genomes could settle the debate, and for decades the same evidence would often be used to support both sides. "It was pretty polarised and personal at times," recalls Chris Stringer at the Natural History Museum in London, who championed the then-dominant Out of Africa model.

Breeding controversy

The ancient genome studies have reopened the debate. "It's nice to be on the right side of this," says Wolpoff, multiregionalism's fiercest champion. "The DNA we have shows three lineages of humans in the Pleistocene that can interbreed with each other. It's very much what we interpreted the fossils to mean." Stringer disagrees. "The implication [from the multiregional model] was that we would see Neanderthals gradually changing into modern humans," he says. "Instead, we see Neanderthals going up to around 30,000 or 40,000 years ago and then disappearing. They've passed some DNA on but that didn't change their evolutionary history."

Stringer also points out that only the most extreme versions of the Out of Africa model ruled out the possibility of sex between different groups. "I've never said there couldn't be interbreeding but I argued that it

"One study estimated that up to 14 per cent of Eurasian genomes could be heirlooms from ancient hominin groups"

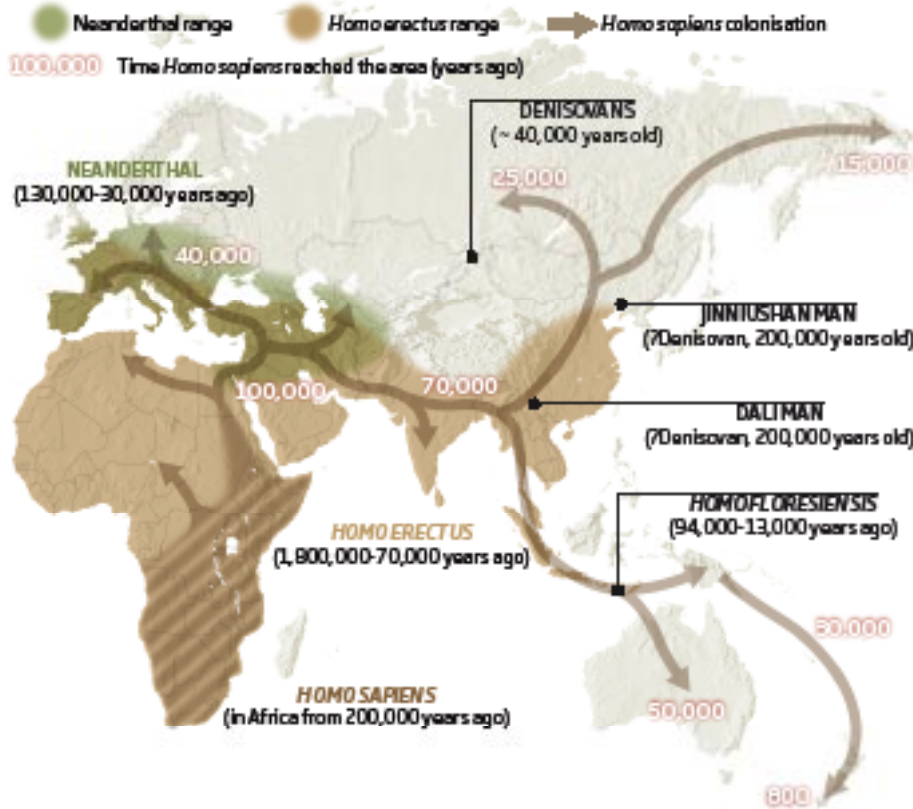
them as cousins of the Neanderthals – their common ancestor split from our own ancestral line around 800,000 years ago, before dividing again around 640,000 years ago. But the paths of these three would cross again. "As populations increased in size and came into contact with one another, they started to interbreed," says Milford Wolpoff at the University of Michigan in Ann Arbor.

This interbreeding happened at least twice. DNA cannot show exactly when or

These findings have catapulted geneticists into a controversial battle between two groups, each espousing a different story of human evolution. The first, supporters of the Out of Africa model, believe that all living humans trace their ancestry to a small African population that swept the world, replacing other species of early humans and consigning their genes to history. Their rivals, supporters of the so-called "multiregional model", see these prehistoric groups, scattered

All mixed up

Genome analysis suggests that after early modern humans left Africa they interbred with Neanderthals in the Middle East around 60,000 years ago and with Denisovans some time before 45,000 years ago



was trivial." He could still be right – it doesn't necessarily take a lot of sex for genes from a resident population to infiltrate the genomes of colonisers. When an incoming group mates with an established one, the genes they pick up quickly rise to prominence as their population grows. The truth is, we still don't know whether interbreeding was the norm for ancient hominins or something of a fringe activity. Reich and Pääbo are actively pursuing the problem by studying the genomes of modern people who carry Neanderthal DNA, but for now we have no answers.

Meanwhile, the sequencing of ancient DNA has also triggered a new wave of excitement among fossil hunters. The Denisovans are a particular source of inspiration because so far they are known only by one finger bone and a tooth found in the Denisova cave. Yet as their genes turn up in modern Melanesians, they must have spread across Asia. "We're starting to find fossils in southern China and south-east Asia that could

well be connected to Denisovans," says Alan Cooper from the University of Adelaide in South Australia. "Things are afoot, and the ancient DNA provoked that."

In fact, both Stringer and Wolpoff believe it is likely that Denisovan fossils have already been found. Several skulls unearthed in China, for example, don't look like Neanderthals or modern humans, and could be Denisovans hidden in plain sight. They include remains like the Dali man found in central China, and Jinniushan man from the country's north-east. Analysis of DNA from fossils like these could help us work out when and where the Denisovans lived, and how this overlapped with the habitat of early modern humans.

While others concentrate on learning more about the Denisovans, Pääbo and Cooper have their sights set on the so-called "hobbit", a small hominin that lived on the Indonesian island of Flores from about 90,000 years ago. Since its discovery in 2004, there has been heated debate about how Homo floresiensis,

as it is officially known, fits into our family tree. What makes it particularly intriguing is that despite it having a brain just a third the size of ours, it made tools, controlled fire and lived in much the same way as our direct ancestors, from whom it was geographically isolated. The hobbit genome doubtless has some stories to tell, but ancient DNA is easily degraded and contaminated and, so far, Pääbo and Cooper have been unable to obtain any from the fossils available. "We didn't get at the samples until every physical anthropologist in south-east Asia had handled the things," says Cooper. But he remains hopeful.

"Given that the hobbits survived until 12,000 years ago, it's just a question of finding the right specimen, one that has been preserved in clay or something similar." A single tooth was found more recently, and Cooper is keen to get his hands on it.

Back to our roots

Others would dearly love to sequence DNA from ancient African hominins. As the continent where humans evolved, Africa has a long history of diverse populations with lots of regional differences. "I think anything found in Africa has a chance of making things a lot more complicated," says Hawks. Until now, the various groups have been distinguished from one another by the morphology of fossils alone, but DNA analysis offers a new and more probing way of sorting out the relationships between them. That will be easier said than done, though. The problem is Africa's largely hot and humid climate – the worst conditions for preserving DNA.

Luckily there is another approach. "DNA can be dug up in a 40,000-year-old cave but it can also be passed down from parent to child," says Reich. Even without ancient genomes to hand, geneticists can look for signatures of interbreeding in the DNA of living people. They can hunt for parts of the genome that travel down the generations as a unit even though they are far apart; these could be heirlooms from other ancient hominins. They can also search for regions of the genome that seem older than their neighbours, which would hint at an origin that pre-dates the rise of modern humans.

Another approach is to identify parts of the genome that are considerably more diverse in people living in one part of the world than another. Rasmus Nielson at the University of California, Berkeley, did exactly that, comparing the DNA of people living in

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BENCE VOLKAMP/REVA

Ancient DNA found in a Siberian cave lives on in modern Melanesians

Africa with those living elsewhere and, without any ancient DNA, identified 13 sections of DNA in humans of non-African descent that could have come from Neanderthals. Sequencing of the Neanderthal genome confirmed that 10 of these predictions were right.

“The trick is to sequence the genomes of a diverse range of people from all across the world,” says Reich. This work is already under way. An international consortium called the 1000 Genomes Project is currently sequencing genomes from populations that have been ignored by previous studies, including some in Africa, the Americas and

the Indian subcontinent. These diverse genomes could be a source of important details about our history.

The prospects look promising. Tantalising hints that other extinct hominins have left echoes in many of our genomes have already been found. For example, many European and Asian people have a version of a gene called *microcephalin*, involved in brain development, which was thought to be inherited from Neanderthals. However, none of the three female Neanderthals that Pääbo and Reich analysed carried this variant, so either it was rare among Neanderthals or we acquired it from another

hominin. Then there is the study by Jeffrey Wall from the University of Southern California, Los Angeles, which estimated that up to 14 per cent of Eurasian genomes could be heirlooms from ancient hominin groups. Neanderthals only contributed between 1 and 4 per cent, so who did the rest come from?

These approaches can tell us a lot about how much interbreeding early humans got up to, but they have limits. They rely on mathematical models that make several assumptions about how genes change over time. If these assumptions are wrong, the studies could detect phantom signs of mixed DNA, where none exists. “In this context, it is very useful to have an ancient genome to directly test these predictions,” says Reich. The ancient DNA acts like a cheat-sheet, allowing scientists to run their models, check their “answers”, and refine their methods.

Ultimately, it was DNA that sealed the case that early humans interbred with other hominins, and we need more of it to really understand the mosaic nature of human evolution.

It must only be a matter of time. Fossil hunters are starting to handle their finds with the care of crime-scene analysts. “Everyone now treats new material as if it had DNA in it,” says Wolpoff. “There are a lot of people who would like to have the next specimen that we get ancient DNA out of. Everybody knows the payoff is good. I think we’re at the very beginning of the information explosion.” ■

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JUST ANOTHER PROMISCUOUS PRIMATE?

The animal world is rife with examples of incoming migrants replacing resident populations. Mammoths, cave bears, bison and others all show a similar pattern of migration and replacement to the one that characterises the spread of early modern humans across Eurasia. Whether these other animals inbred with resident populations or simply out-competed them is another matter – one that will only be resolved when

their genomes are scrutinised.

However, we do know that hybridisation is fairly common in the natural world. For example, the surprising lack of genetic diversity among Old World monkeys suggests that as they evolved, many subspecies and species mated with one another to produce a complex tangle of hybrid lineages. “When species meet, they do have sex with each other,” says Svante Pääbo of the Max

Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

So perhaps we should not be surprised to find that early humans mated with individuals from other hominin groups that they came across, including Neanderthals and Denisovans.

Nevertheless, studies of ancient genomes may still reveal that early humans were more inclined to hybridise than other species. One underlying reason might be

that human behaviour is driven by culture as well as biology. “Most cultures require you to seek mates someplace else: get your mates from another village, get your mates from the guys across the river,” says Milford Wolpoff at the University of Michigan in Ann Arbor. “And that leads to a level of mixture that other species may not have. It remains to be seen whether we’re one of many cases or whether we’re special.”