

EVOLUTION

HUMAN HYBRIDS

DNA analyses find that early *Homo sapiens* mated with other human species and hint that such interbreeding played a key role in the triumph of our kind

By Michael F. Hammer

It is hard to imagine today, but for most of humankind's evolutionary history, multiple humanlike species shared the earth. As recently as 40,000 years ago, *Homo sapiens* lived alongside several kindred forms, including the Neanderthals and tiny *Homo floresiensis*. For decades scientists have debated exactly how *H. sapiens* originated and came to be the last human species standing. Thanks in large part to genetic studies in the 1980s, one theory emerged as the clear front-runner. In this view, anatomically modern humans arose in Africa and spread out across the rest of the Old World, completely replacing the existing archaic groups. Exactly how this novel form became the last human species on the earth is mysterious. Perhaps the invaders killed off the natives they encountered, or outcompeted the strangers on their own turf, or simply reproduced at a higher rate. However it happened, the newcomers seemed to have eliminated their competitors without interbreeding with them.

This recent African Replacement model, as it is known, has essentially served as the modern human origins paradigm for the past 25 years. Yet mounting evidence indicates that it is wrong. Recent advances in

IN BRIEF

A long-reigning theory of the origin of *Homo sapiens* holds that our species arose in a single locale—sub-Saharan Africa—and replaced archaic human species, such as the Neanderthals, without interbreeding with them.

But recent studies of modern and ancient DNA indicate that these modern humans from Africa did mate with archaic humans and hint that this interbreeding helped *H. sapiens* thrive as it colonized new lands.





DNA-sequencing technology have enabled researchers to dramatically scale up data collection from living people as well as from extinct species. Analyses of these data with increasingly sophisticated computational tools indicate that the story of our family history is not as simple as most experts thought. It turns out that people today carry DNA inherited from Neandertals and other archaic humans, revealing that early *H. sapiens* mated with these other species and produced fertile offspring who were able to hand this genetic legacy down through thousands of generations. In addition to upsetting the conventional wisdom about our origins, the discoveries are driving new inquiries into how extensive the interbreeding was, which geographical areas it occurred in and whether modern humans show signs of benefiting from any of the genetic contributions from our prehistoric cousins.

MYSTERIOUS ORIGINS

TO FULLY APPRECIATE the effect of these recent genetic findings on scientists' understanding of human evolution, we must look back to the 1980s, when the debate over the rise of *H. sapiens* was heating up. Examining the fossil data, paleoanthropologists agreed that an earlier member of our genus, *Homo erectus*, arose in Africa some two million years ago and began spreading out of that continent and into other regions of the Old World shortly thereafter. Yet they disagreed over how the ancestors of *H. sapiens* transitioned from that archaic form to our modern one, with its rounded braincase and delicately built skeleton—features that appear in the fossil record at around 195,000 years ago.

Proponents of the so-called Multiregional Evolution model, developed by Milford H. Wolpoff of the University of Michigan and his colleagues, argued that the transformation occurred gradually among archaic populations wherever they lived throughout Africa, Eurasia and Oceania because of a combination of migration and mating that allowed beneficial modern traits to spread among all these populations. In this scenario, although all modern humans shared particular physical features by the end of this transition, some regionally distinctive features inherited from archaic ancestors persisted, perhaps because these traits helped populations to adapt to their local environments. A variant of Multiregional Evolution put forward by Fred Smith, now at Illinois State University, called the Assimilation model, acknowledges a greater contribution of modern traits by populations from Africa.

In contrast, champions of the Replacement model (also known as the Out of Africa model, among other names), including Christopher Stringer of the Natural History Museum in London, contended that anatomically modern humans arose as a distinct species in a single place—sub-Saharan Africa—and went on to completely replace all archaic humans everywhere without interbreeding with them. A looser version of this theory—the Hybridization model proposed by Günter Bräuer of the University of Hamburg in Germany—allows for the occasional production of hybrids between these modern humans and the archaic groups they met up with as they pushed into new lands.

With only the fossil evidence to go on, the debate seemed locked in a stalemate. Genetics changed that situation. With the advent of DNA technology, scientists developed methods for piecing together the past by analyzing genetic variation in contemporary human populations and using it to reconstruct evolutionary trees for individual genes. By studying a gene tree, researchers could infer when and where the last common ancestor of all the

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variants of a given gene existed, thus yielding insights into the population of origin for the ancestral sequence.

In a landmark study published in 1987, Allan C. Wilson of the University of California, Berkeley, and his colleagues reported that the evolutionary tree for the DNA found in mitochondria—the energy-producing components of cells—traced back to a female ancestor who lived in an African population around 200,000 years ago. (Mitochondrial DNA, or mtDNA, is passed down from mother to child and treated as a single gene in ancestry studies.) These findings fit the expectations of the Replacement model, as did subsequent studies of small sections of nuclear DNA, including the paternally inherited Y chromosome.

Further genetic support for the Replacement model came a decade later, when Svante Pääbo, now at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and his colleagues succeeded in extracting and analyzing a fragment of mtDNA from Neandertal bones. The study found that the Neandertal mtDNA sequences were distinct from those of contemporary humans and that there was no sign of interbreeding between them—a result that subsequent studies of mtDNA from additional Neandertal specimens confirmed.

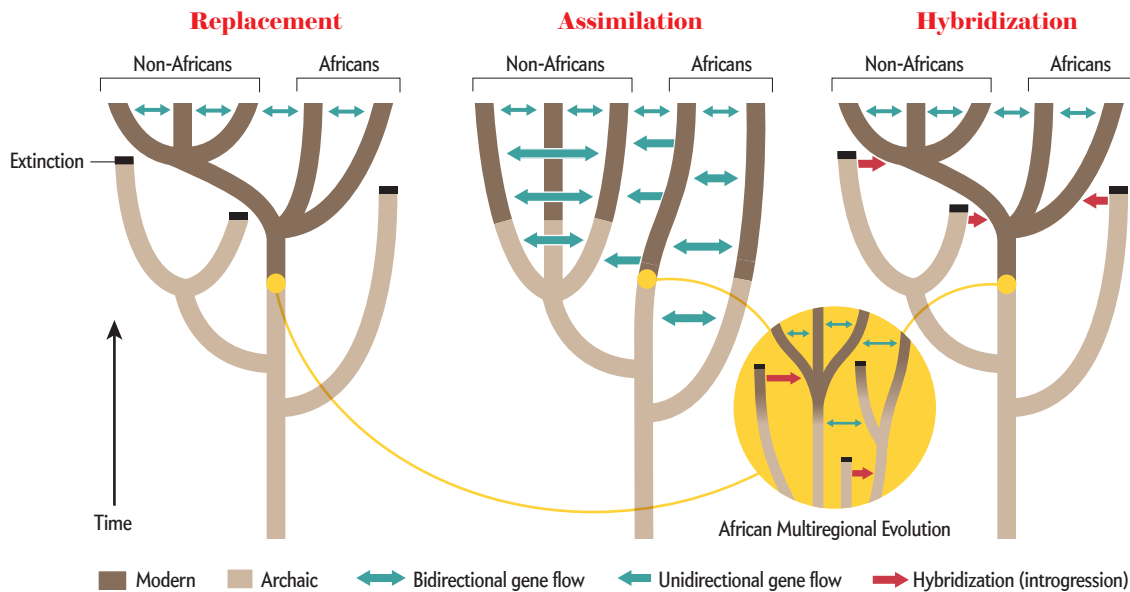
To many researchers, these ancient mtDNA findings put the nail in the coffin of the Multiregional Evolution and Assimilation models. Others, however, maintained that their reasoning suffered from a fundamental problem. The absence of a signal for interbreeding in any single independent region of the genome, such as in mtDNA, does not necessarily mean that other regions of the genome also lack signs of interbreeding. Further, any particular region of the genome that is tested could lack signs of interbreeding even if interbreeding did occur because DNA from other species (introgressed DNA) that provided no survival advantage to *H. sapiens* would tend to disappear from the gene pool over time by chance.

The best way to approach the question of whether *H. sapiens* interbred with archaic species, such as the Neandertals, is thus to compare many regions of their genomes or, ideally, their entire genomes. Yet even before such data became available for archaic humans, some early genetic studies of modern human DNA bucked the majority trend and found data contrary to the Replacement model. One clear example came from a 2005 study led by Daniel Garrigan, then a postdoctoral researcher in my laboratory. Garrigan looked at DNA sequences from a nonfunctional region of the X chromosome known as RRM2P4. Analyses of its reconstructed tree pointed to an origin for the sequence, not in Africa but in East Asia around 1.5 million years ago, implying that the DNA came from an archaic Asian species that intermixed with the *H. sapiens* originally from Africa. Similarly, that same year our lab discovered variation in another nonfunctional region of the X chromosome, Xp21.1, with a gene tree showing two divergent branches that had probably been evolving in complete isola-

Sourcing *Homo sapiens*

Scientists have long debated how anatomically modern humans (dark brown lines) evolved from their archaic predecessors (light brown lines). In the theories depicted here, modern humans originated in Africa. According to the Replacement model, they then replaced archaic human species throughout the Old World without interbreeding with them. The Assimilation model, in contrast, holds that beneficial modern features from Africa spread among these archaic groups by means of a combination of steady migra-

tion and mating known as gene flow (green arrows). The Hybridization model, for its part, posits that modern humans mated only rarely, or hybridized (red arrows), with archaic species as they replaced them. The African Multiregional Evolution model focuses exclusively on the archaic-to-modern transition period in Africa and argues for gene flow and hybridization between distinctive archaic groups there. Such a scenario could theoretically have preceded Replacement, Assimilation or Hybridization.



tion from one another for around a million years. One of these branches was presumably introduced into anatomically modern populations by an archaic African species. The RRM2P4 and Xp21.1 evidence thus hinted that anatomically modern humans mated with archaic humans from Asia and Africa, respectively, rather than simply replacing them without interbreeding.

OUR ARCHAIC DNA

MORE RECENTLY, advances in sequencing technology have enabled scientists to quickly sequence entire nuclear genomes—including those of extinct humans, such as Neandertals. In 2010 Pääbo's group reported that it had reconstructed the better part of a Neandertal genome, based on DNA from several Neandertal fossils from Croatia. Contrary to the team's expectations, the work revealed that Neandertals made a small but significant contribution to the modern human gene pool: non-Africans today exhibit a 1 to 4 percent Neandertal contribution to their genomes on average. To explain this result, the researchers proposed that interbreeding between Neandertals and the ancestors of all non-Africans probably occurred during the limited period when these two groups overlapped in the Middle East, perhaps 80,000 to 50,000 years ago.

Hot on the heels of the Neandertal genome announcement, Pääbo's team revealed an even more startling discovery. The

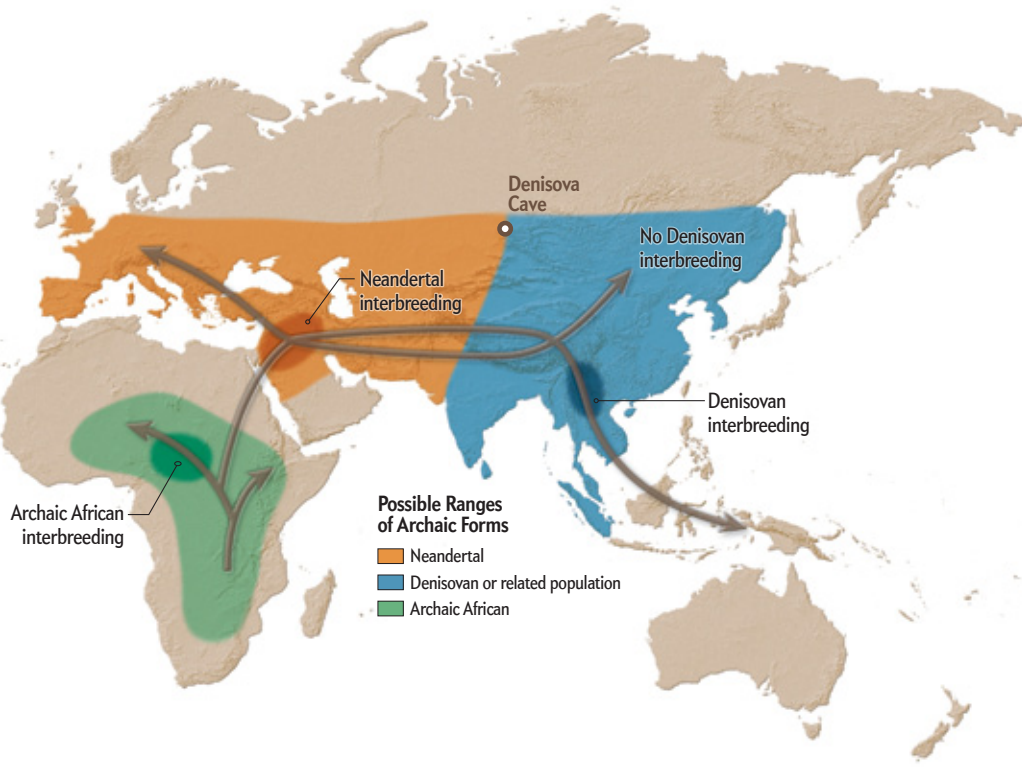
researchers had obtained an mtDNA sequence from a piece of an approximately 40,000-year-old finger bone found in Denisova Cave in the Altai Mountains in Siberia. Although researchers could not determine from the anatomy of the bone what species it represented, the genome sequence showed that this individual belonged to a population that was slightly more closely related to Neandertals than it or Neandertals were to our species. Further, after comparing the Denisovan sequence with its counterpart in modern populations, the team found a significant amount of DNA from a Denisovan-like population—a contribution of 1 to 6 percent—in Melanesians, Aboriginal Australians, Polynesians, and some related groups in the western Pacific but not in Africans or Eurasians.

To explain this increasingly complex pattern of DNA sharing, the researchers proposed that interbreeding with various archaic forms had occurred at two different times: first, when anatomically modern humans initially migrated out of Africa and mated with Neandertals and, later, when the descendants of these initial migrants made their way to Southeast Asia and encountered Denisovan-like humans. The doubly mixed ancestors of present-day groups such as Melanesians then reached Oceania around 45,000 years ago, and a second wave of anatomically modern humans migrated to East Asia without interbreeding with Denisovan-like ancestors.

Evidence for Interbreeding

The fossil record indicates that *Homo sapiens* originated in Africa by around 200,000 years ago. Recent DNA studies suggest that these anatomically modern humans mated with the archaic humans they happened on as they migrated within Africa and out into the rest of the Old World (gray arrows). The map below

shows ranges of archaic species—including a species recently identified on the basis of DNA from a fossilized finger bone from Denisova Cave in Siberia—and regions where interbreeding with moderns may have occurred (ellipses), based on the available DNA evidence.



Although discussion of interbreeding in human evolution typically focuses on mating between anatomically modern humans and Neandertals in Europe or other archaic forms in Asia, the greatest opportunity for interspecies coupling would have been in Africa, where anatomically modern humans and various archaic forms coexisted for much longer than they did anywhere else. Unfortunately, the tropical environments of the African rain forest do not favor the preservation of DNA in ancient remains. Without an African ancient DNA sequence to reference, geneticists are currently limited to scouring the genomes of modern-day Africans for signs of archaic admixture.

To that end, my team at the University of Arizona, in collaboration with Jeffrey D. Wall of the University of California, San Francisco, gathered sequence data from 61 regions of the genome in a sample of three sub-Saharan African populations. Using computer-based simulations to test various evolutionary scenarios, we concluded in a 2011 report that these populations received a 2 percent contribution of genetic material from an extinct human population. This group would have split off from the ancestors of anatomically modern humans some 700,000 years ago and interbred with moderns around 35,000 years ago in Central Africa.

Another genetic hint of archaic admixture in Africa has come

from a study of an unusual Y chromosome sequence obtained from an African-American man living in South Carolina whose DNA was submitted to a direct-to-consumer genetic testing company for analysis. His particular variant had never been seen before. Comparing his Y sequence against those of other humans, as well as chimpanzees, my team determined that his sequence represents a previously unknown Y chromosome lineage that branched off the Y chromosome tree more than 300,000 years ago. We then searched a database of nearly 6,000 African Y chromosomes and identified 11 matches—all of which came from men who lived in a very small area of western Cameroon. The finding, published in March in the *American Journal of Human Genetics*, indicates that the last common ancestor of all modern Y chromosome variants is 70 percent older than previously thought. The presence of this very ancient lineage in contemporary people is a possible sign of interbreeding between *H. sapiens* and an unknown archaic species in western Central Africa.

Recently the fossil record, too, has yielded support for the possibility of interbreeding within Africa. Just after the publication of our results in 2011, a group of paleontologists working at the Iwo Eleru site in Nigeria reanalyzed remains that exhibit cranial features intermediate between those of archaic and modern

SOURCE: "GENOMIC DATA REVEAL A COMPLEX MAKING OF HUMANS," BY ISABEL ALVES ET AL., IN *PLoS GENETICS*, VOL. 8, NO. 7, JULY 19, 2012

humans and determined that they date to just 13,000 years ago—long after anatomically modern *H. sapiens* had debuted. These results, along with similar findings from the Ishango site in the Democratic Republic of the Congo, suggest that the evolution of anatomical modernity in Africa may have been more complicated than any of the leading models for modern human origins have envisioned. Either archaic humans lived alongside modern ones in the recent past, or populations with both modern and archaic features interbred over millennia.

BENEFICIAL CONTRIBUTIONS?

ALTHOUGH THE ANALYSES of Neandertal and Denisovan DNA provide increasing evidence that archaic humans contributed to our genetic heritage, many aspects of this interbreeding remain unresolved. Current estimates of the percentage of our genome that was contributed by Neandertals and Denisovan-like humans are based on a method that does not provide much information about how and when mixing occurred. To learn more, researchers need to improve their understanding of exactly which stretches of the genome came from archaic humans and which archaic species contributed what. During his dissertation work in my lab, Fernando L. Mendez took steps toward doing exactly that. He found strong evidence that some contemporary non-Africans carry a stretch of chromosome 12 containing the gene *STAT2* (which is involved in the body's first line of defense against viral pathogens) that came from Neandertals.

Detailed studies of DNA regions inherited from archaic ancestors will also help tackle the question of whether acquiring these genetic variants conferred an adaptive advantage to early *H. sapiens*. Indeed, *STAT2* provides a fascinating example of an apparently advantageous archaic variant entering the modern human gene pool. Approximately 10 percent of people from Eurasia and Oceania carry the Neandertal-like variant of *STAT2*. Interestingly, it occurs at a roughly 10-fold higher frequency in Melanesia than in East Asia. Analysis suggests that this DNA segment rose to high frequency through positive natural selection (that is, because it aided reproductive success or survival) rather than merely by chance, implying that it benefited the anatomically modern populations of Melanesia.

Similarly, a Neandertal-like section of the so-called human leukocyte antigen (HLA) region of the genome appears to have risen to relatively high frequency in Eurasian populations as a result of positive natural selection related to its role in fighting pathogens. Perhaps we should not be surprised to find archaic contributions containing genes that function to increase immunity. It is easy to imagine that the acquisition of a gene variant that is adapted to fending off pathogens in non-African environments would immediately benefit human ancestors as they expanded from Africa into new habitats.

In light of the accumulating evidence for interbreeding between anatomically modern *H. sapiens* and archaic humans both inside Africa and beyond its confines, the Replacement model is no longer tenable. Modern and archaic species of *Homo* were

able to produce viable hybrid offspring. Thus, archaic forms could go extinct while still leaving behind their genetic footprints in the modern human genome. That said, the genomes of people today seem to derive mostly from African ancestors—contributions from archaic Eurasians are smaller than either the Multiregional Evolution or Assimilation models predict.

A number of researchers now favor Bräuer's Hybridization model, which holds that mating between *H. sapiens* and archaic species was limited to a few isolated instances. I agree that such interbreeding appears to have been rare after modern humans began spreading out of Africa, but I think there is more to the story than that. Given the complexity of the African fossil record, which indicates that a variety of transitional human groups, with a mosaic of archaic and modern features, lived over an extensive geographic area from Morocco to South Africa between roughly 200,000 and 35,000 years ago, I favor a model that involves inter-species mating during the archaic-to-modern transition. Sometimes called African Multiregional Evolution, this scenario allows

for the possibility that some of the traits that make us anatomically modern were inherited from transitional forms before they went extinct. To my mind, African Multiregional Evolution, in combination with Bräuer's Hybridization model, best explains genetic and fossil data to date.

Before scientists can assess this model for modern human origins fully, we will need to better understand which genes code for anatomically modern traits and decipher their evolutionary history. Further analysis of both archaic and modern genomes should aid researchers in pinpointing when and where mixing occurred—and whether the archaic genes that entered the mod-

ern human gene pool benefited the populations that acquired them. This information will help us evaluate the hypothesis that interbreeding with archaic populations that were well adapted to their local environments lent traits to *H. sapiens* that spurred its rise to global preeminence. The sharing of genes through occasional interspecies mating is one way that evolutionary novelties arise in many species of animals and plants, so it should not be surprising if the same process occurred in our own past.

Many loose ends remain. Yet one thing is clear: the roots of modern humans trace back to not just a single ancestral population in Africa but to populations throughout the Old World. Although archaic humans have often been seen as rivals of modern humans, scientists now must seriously consider the possibility that they were the secret of *H. sapiens*' success. ■

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MORE TO EXPLORE

A High-Coverage Genome Sequence from an Archaic Denisovan Individual. Matthias Meyer et al. in *Science*, Vol. 338, pages 222–226; October 12, 2012.

An African American Paternal Lineage Adds an Extremely Ancient Root to the Human Y Chromosome Phylogenetic Tree. Fernando L. Mendez et al. in *American Journal of Human Genetics*, Vol. 92, No. 3, pages 454–459; February 28, 2013.

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