

The diverse origins of the human gene pool

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Analyses of the genomes of Neanderthals and Denisovans, the closest evolutionary relatives of present-day humans, suggest that our ancestors were part of a web of now-extinct populations linked by limited, but intermittent or sometimes perhaps even persistent, gene flow.

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For decades, paleontologists intensely debated how ‘modern humans’ — that is, the direct ancestors of all humans alive today — originated. One view was that modern humans emerged recently in Africa from which they spread worldwide and replaced all other forms of humans, or ‘hominins’, without mixing with them — a process that ended some 30–40 thousand years ago. Another view favoured regional continuity under which hominins in different parts of the world evolved more or less independently over hundreds of thousands or millions of years into present-day humans, with some gene flow between them. This debate was so intense because it bears on the fundamental question of when and where modern humans originated, but it is also of importance for guiding how we should think about the genetic variation in the current human gene pool — does it all go back to variation that accumulated exclusively in Africa, or does it have deep roots elsewhere as well?

Gene flow and adaptation in ancient hominins

The sequencing of the Neanderthal genome showed that neither the exclusively African model nor the regional continuity model of modern human origins is completely correct: while most of the human gene pool shows origins in Africa, approximately 1–3% of the genomes of all people outside sub-Saharan Africa show Neanderthal ancestry¹. In addition, up to 5% of the genomes of people in Oceania were contributed by another group, the Denisovans, distant relatives of the Neanderthals who have been identified based on a genome sequence from a bone found in southern Siberia². The analysis of high-quality genomes of a Neanderthal, a Denisovan and present-day humans¹ has yielded evidence for at least three additional instances of gene flow: one from Neanderthals into the ancestors of many present-day groups in Asia, one from Neanderthals into Denisovans, and one into

Denisovans from an unknown hominin that diverged at least a million years ago from the human lineage. In addition, gene flow from Denisovans to people in mainland Asia is likely to have occurred, and unpublished work shows that early modern humans mixed with Neanderthals when they arrived in Europe (Q. Fu, M. Hajdinjak and S.P., unpublished observations). These results show that the ancestral modern human gene pool — and the gene pools of Neanderthals, Denisovans and other extinct hominins — were open systems that allowed exchange of genes among the groups when they met. This may have had advantages for the ability of modern humans to adapt to new environments as they spread across Eurasia.

Adaptation through the acquisition of new mutations is generally a slow process: it is rare for favourable alleles to appear, and these are often lost by chance when they first occur in a single individual or in very few individuals. By contrast, if favourable alleles have emerged in one group, they can spread to other groups relatively rapidly by gene flow. This process, called ‘adaptive introgression’, is well documented in bacteria and plants, and described in some cases in animals³, but it has not previously been considered an important factor in human adaptation. However, because Neanderthals and Denisovans lived in Europe and Asia for hundreds of thousands of years, they presumably carried alleles that were favourable given the conditions where they lived. Through gene flow, modern humans spreading across Eurasia from Africa could then acquire these alleles ‘for free’ at a frequency of a few percent, thus ensuring that they were not lost and could be acted upon by positive selection.

In this issue, Racimo *et al.*⁴ review the methods currently available for detecting such introgression and subsequent positive selection of Neanderthal and Denisovan alleles in the ancestors of present-day humans and summarize the cases where this has been

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doi:10.1038/nrg3954

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documented or proposed. Not surprisingly, genes involved in systems that interact directly with the environment such as the skin, immune system, digestive system and intermediary metabolism are those that are most commonly found to show evidence of positive selection and also those in which adaptive introduction of alleles from now-extinct hominins seems to be the most frequent. Additional such alleles will probably be discovered when researchers start to more systematically examine the Neanderthal and Denisovan genome sequences for the presence of variants associated with diseases or other phenotypes in present-day humans.

The hominin metapopulation

The multiple instances of gene flow now documented among hominin groups show that modern humans were part of what one could term a ‘hominin metapopulation’ — that is, a web of different hominin populations, including Neanderthals, Denisovans and other groups, who were linked by limited, but intermittent or even persistent, gene flow. As Racimo *et al.*⁴ describe, this allowed advantageous alleles to spread into present-day humans. Although no direct evidence has yet been found, alleles presumably also spread in other directions, for example, from modern humans into Neanderthals. Moreover, alleles may have spread indirectly via Neanderthals and Denisovans from other more distantly related groups into present-day humans. It may even be possible that some people today carry alleles from *Homo erectus* if Neanderthals or Denisovans had mixed with members of this group.

In hindsight we know that one population among those making up the hominin metapopulation ended up being very special — the one we now call ‘modern humans’; it went on to develop technology and culture that allowed it to spread from its African homeland across Eurasia and beyond. By force or more subtle

competition it caused every other hominin group to become extinct. A key question is, what biological features made this population special⁵? As the ancestors of modern humans were presumably part of the hominin metapopulation, one can imagine that the multiple genetic variants that set modern humans apart from other hominins originated not in one single African population but in many different African populations and, in rare cases, perhaps even outside Africa. Gene flow in the hominin metapopulation could then have allowed these genetic variants to come together in the explosive constellation that caused the modern human population to expand and replace everyone else, in the process usurping some locally valuable alleles from the less fortunate hominins it encountered.

As more high-quality genome sequences from Neanderthals, Denisovans and other extinct groups, particularly those from Asia and Africa, become available, we are likely to find more examples of adaptive introgression and to gain a better understanding of how the combination of genetic features that set modern humans apart from other hominin groups first arose.

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Competing interests statement

The author declares no competing interests.

FURTHER INFORMATION

Ancient genomes database: <https://bioinf.eva.mpg.de/jbrowse/>

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