

POPULATION GENOMICS

Encounters with archaic hominins

The presence of Neanderthal DNA fragments in the genomes of modern humans from Europe and East Asia indicates multiple episodes of interbreeding between Neanderthals and the ancestors of both populations.

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Although modern humans are currently found across the globe, less than 100,000 years ago they were mostly confined to Africa. At that time their hominin cousins, Neanderthals and Denisovans, inhabited western and eastern Eurasia, respectively. When groups of anatomically modern humans started spreading out of Africa, these populations met. The traces of these encounters can be now found in the genomes of the descendants of those humans who migrated out of Africa — their genomes carry 2–6% of Neanderthal and Denisovan DNA fragments. Writing in *Nature Ecology & Evolution*, Villanea and Schraiber¹ report that Neanderthals did not contribute to the modern human gene pool just once; an initial encounter between modern humans migrating out of Africa was followed by additional independent encounters with the ancestors of modern European and East Asian populations.

Recent developments in ancient DNA research and population genetics methods are rapidly increasing our knowledge of the nature of these events yet, at the same time, accumulation of data also complicates the picture (Fig. 1). With the availability of more genomes, a scenario of multiple encounters emerged — in fact, the observation that modern East Asian populations carry ~12–20% more Neanderthal DNA than European populations suggests that the ancestors of East Asians encountered Neanderthals more than once².

Villanea and Schraiber provide further evidence in support of multiple encounters by analysing the distribution of Neanderthal DNA fragments in contemporary Europeans and East Asians. The authors noticed an elusive yet revealing signal: in both populations, the proportion of Neanderthal DNA fragments with a frequency of 2–6% is a bit higher than would be expected if only one encounter had occurred between

Neanderthals and modern humans. An intuitive explanation for this signal is that when Neanderthals and modern humans met, all Neanderthal DNA fragments entered the human gene pool at a similar frequency. Over time, most of these fragments are expected to drift to different frequencies. If only one ancient encounter between Neanderthals and ancient modern humans occurred, a large proportion of Neanderthal DNA fragments would have had sufficient time to drift to allele frequencies lower or higher than 2–6%. If a subsequent encounter occurred after the initial separations of the ancestors of different modern human populations, more Neanderthal DNA fragments would be reintroduced and found at this range of frequencies, which is what we observe in European and East Asian populations today.

However, this signal could, in principle, be confounded by other processes, such as natural selection against Neanderthal

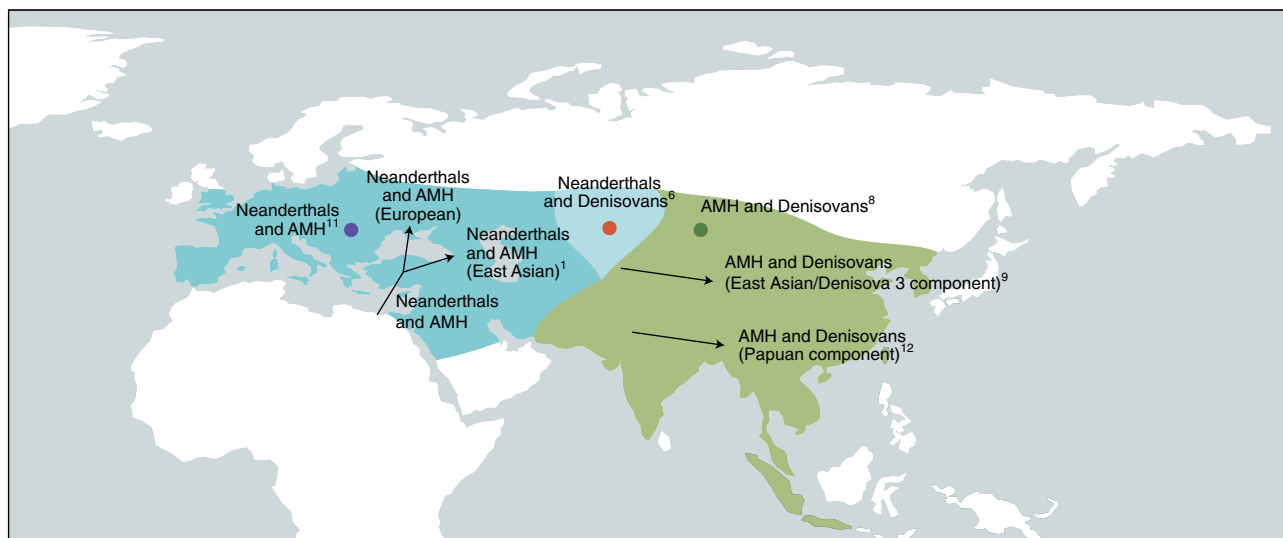


Fig. 1 | Map of the encounters between different archaic hominins and ancient modern humans (AMH). The approximate distribution of Neanderthals is indicated in blue and the approximate distribution of Denisovans is indicated in green. Arrows indicate human migrations and the corresponding encounter. Note that locations are only hypothetical. Evidence for the encounters between Denisovans and Neanderthal was found at Denisova cave⁶ (red dot); between Neanderthals and anatomically modern humans at the Oase cave¹¹ (purple dot); and between AMH and Denisovans at the site of Mal'ta⁸ (green dot). The admixture between a super-archaic hominin and the ancestors of Denisova 3 (ref. 7) is not shown. Denisova 3 indicates the sequenced high-coverage Denisovan¹². Publ. note: Springer Nature is neutral about jurisdictional claims in maps.

variants³, or the contribution of ancient populations devoid of Neanderthal ancestry to modern genomes⁴. The latter scenario is particularly challenging, since a population often defined as ‘basal Eurasian’ was shown to have contributed to about 9% of the gene pool of modern Europeans, and could account for at least part of the 12–20% higher proportion of Neanderthal fragments in present-day East Asians compared with Europeans. In addition, Villanea and Schraiber relied on previously detected Neanderthal fragments⁵. Thus, their analyses could, in theory, be susceptible to errors in the detection of these fragments. For example, some Denisovan fragments in East Asian genomes could have been misidentified as Neanderthal, or there could be biases in identifying Neanderthal fragments at different allele frequencies. The authors explored these potential issues quantitatively, showing that a model with multiple encounters between ancient modern humans and Neanderthals is robust to different sources of errors. To do this, they combined an elegant analytical approach that allows understanding the qualitative features of the model, with deep learning, a powerful machine learning technique to explore complex models with many parameters that is gaining great relevance in genomics.

The scenario of multiple episodes of modern-human–Neanderthal interbreeding fits with the emerging view of complex and frequent interactions between different hominin groups. Direct evidence of interbreeding between Neanderthals and Denisovans has recently been documented⁶, and we now know that Denisovans interbred with other ancient hominins⁷ as well as modern humans on more than one occasion⁸. In fact, Denisovans contributed at least twice to the modern human gene pool, leaving two distinct

genetic components. The first, more abundant component, primarily present in the genomes of Papuan and Australian aboriginal populations, shows little resemblance to the sequenced Denisovan genome; the second, much smaller component, is closer to the sequenced Denisovan genome, and is primarily in East Asian populations⁹. However, while these two Denisovan components are very distinct, the same study could not identify two distinct Neanderthal components in modern human genomes. A probable explanation for the apparent contrast between this observation and the finding of Villanea and Schraiber is that when modern humans spread into Eurasia, Neanderthal populations were extremely homogeneous. This is supported by the weak differentiation between Neanderthal genomes across Western Europe and Siberia^{6,10}. In contrast, Denisovans could have been much more diverse, and distributed across a wider range. Although we do not yet know the past geographical distribution of Denisovans, they could potentially have been present in regions as far as Siberia and the ancient Sunda (now Indonesia), given the presence of Denisovan DNA fragments in human populations today. It is also possible that modern humans encountered Neanderthals in a relatively restricted region. These encounters might have occurred almost continuously in space when modern humans spread across Eurasia, with some additional encounters after ancient European and East Asian populations separated.

It is worth noting that admixture encounters are usually modelled as discrete events, and Villanea and Schraiber do not model space explicitly. This is due to a combination of limitations of the current population genetics approaches and, more importantly, the scarcity of available genomic data. Hence, at present, we cannot

exclude that interbreeding was relatively continuous in time and space. To resolve the complex spatio-temporal dynamics of these encounters, the sequencing of further ancient genomes is necessary. In particular, a clearer picture of the diversity of Neanderthals across Eurasia and the Levant will allow better determination of the contribution of different Neanderthal populations to different human populations. Some of these encounters might not have contributed to the modern human gene pool of Neanderthal fragments, as illustrated by an ancient modern human from Romania¹¹. Thus, efforts in sequencing ancient samples, both human and Neanderthal, will be pivotal in providing the resolution to model and clarify the complex history of encounters between archaic hominins and modern humans. □

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Competing interests

The author declares no competing interests.