Archaic admixture in human history
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Modern humans evolved in Southern or Eastern Africa, and spread from there across the rest of the world. As they expanded across Africa and Eurasia, they encountered other hominin groups. The extent to which modern and ‘archaic’ human groups interbred is an area of active research, and while we know that modern humans interbred with Neanderthals and Denisovans, there is not yet agreement on how many admixture events there were or on how much Neanderthal or Denisovan DNA can be found in contemporary genomes. Here we review what is known about archaic admixture in human history, with a focus on what has been discovered in the past 2 years.

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Introduction

Two archaic human genomes have been sequenced to high coverage so far: a Neanderthal genome [1,2] and a Denisovan genome [3,4], and both of these genomes represent contributed DNA to present-day humans. Neanderthal ancestry is present in all non-African populations, comprising between 1.5 and 2.1% of their genomes [2]. Conversely, modern human DNA is also found in Neanderthals [5**]. Denisovan ancestry though is mostly restricted to Oceanian populations, which have between 4 and 6% Denisovan DNA [4].

There have been several recent reviews on topics related to archaic admixture [6–8]. Rather than repeat all of the same topics here, we will focus on some issues raised by recent research without trying to be comprehensive.

Neanderthal and Denisovan ancestry in non-African populations

As genomic data on more human populations have become available, we have been able to obtain a more detailed understanding of how Neanderthal and Denisovan ancestry levels vary across populations. For example, it has been shown that East Asians have more Neanderthal ancestry than do Europeans [3,9]. One recent study found evidence that Oceanians (i.e., indigenous Australians and Melanesians) have the highest amount of Neanderthal DNA among all non-African groups [10*]. Interestingly, another study published almost simultaneously concluded that Melanesians have less Neanderthal DNA than other non-African groups [11*], while another performed two separate analyses showing either that Melanesians have less Neanderthal DNA than other non-African groups (S07 [12]), or that they have an amount of Neanderthal DNA intermediate between Europeans and East Asians (S10 [12]). There are a couple different potential explanations for these conflicting results. Vernot et al. [11*] analyzed samples from the Bismarck Archipelago, while Sankararaman et al. [10*] analyzed Papuans, indigenous Australians and Bougainville islanders, and Malaspinas et al. [12] analyzed Papuans and indigenous Australians. While historical differences between various Oceanian populations could in principle explain the different amounts of Neanderthal ancestry found in them, this seems unlikely. Instead, differences in the methodology for identifying archaic human admixture tracts seem to be a more plausible explanation. Two comparisons could help distinguish between these competing claims. First, if all of the genomes contained in the three studies were combined, with identical filtering and variant calling pipelines, then analyses could determine if variability among Oceanian groups explains the published observations. In addition, thorough simulation studies could answer whether any of the inference methods used have particular biases in under or overestimating the amount Neanderthal ancestry in different human populations.

As for Denisovan ancestry outside of Oceanians, small amounts (e.g., <0.2%) have been detected in East Asians [13], Native Americans [2,14] and South Asians [10*]. Further sampling of genomes from around the world, as well as additional analyses, will be needed to understand what is causing this observation.

Explaining patterns of Neanderthal admixture

Several different explanations have been proposed to account for the varying amount of Neanderthal DNA present in different non-African populations (Figure 1). Prüfer et al. [2] suggested that the greater amount of Neanderthal DNA found in East Asian genomes relative to European genomes could be the result of a single pulse of Neanderthal admixture followed by differing levels of
Neanderthal admixture that postdates the split time of European and East Asian populations (i.e., separate admixture events in the ancestors of European populations and the ancestors of East Asian populations), (2) a single pulse of admixture in all non-Africans followed by a separate Neanderthal admixture event (i.e., the ‘multiple admixture model’) in the ancestors of East Asian populations, or (3) a single pulse of admixture in all non-African populations, followed by admixture with a population with less Neanderthal ancestry (i.e., the ‘dilution’ model) in the ancestors of modern day Europeans [9,17,18]. The first explanation is unlikely, given that recent estimates of the time of admixture are earlier than the generally accepted population split times [12,19]. The third explanation is also somewhat unlikely, in that no candidate diluting populations have been proposed. While some European genomes are known to contain a small (2–3%) amount of sub-Saharan African ancestry [20], and sub-Saharan African genomes are known to contain much less Neanderthal DNA, the effect of this admixture is expected to be much less than what would be needed to explain the lesser amount of Neanderthal ancestry found in European populations [15]. Finally, similar multiple admixture and dilution models have been proposed to explain the differing amount of Neanderthal ancestry found in Melanesians [10*,11*].

Archaic ancestry informs models of migration out of Africa

Knowledge about archaic admixture in the genomes of modern humans can shed light on past migratory routes. If two populations shared a past migratory route where admixture with other hominins occurred, they will probably share introgressed archaic DNA.

In the case of the first modern human migration(s) out of Africa, two main routes have been hypothesized: a northern route through Egypt and Sinai, and a southern route from Ethiopia through the Arabian Peninsula. When similar amounts of Neanderthal DNA were found in all non-African populations, it was suggested that interbreeding with Neanderthals occurred in a single population ancestral to all present-day non-Africans [1]. This was seen as support for a single migration out-of-Africa [21]. On the other hand, evidence of modern human introgression into East Asian Neanderthals 100 thousand years ago supports a second, more ancient dispersal out of Africa [5**]. This is in line with the conclusions of a study on modern human populations that found evidence for two waves of migration out of Africa: the first one through the South, followed by a northern migration [22].

Similarly, there is a debate on whether the peopling of Southeast Asia and Oceania was through one or multiple waves. The study of Denisovan ancestry in Asia and Oceania is helping to clarify this debate. Varying amounts of Denisovan DNA were found in populations of Southeast Asia and Oceania, which has been interpreted as

purifying selection in the two populations. However, two simulation-based studies concluded that this model cannot explain the observed patterns of Neanderthal admixture [15,16]. Other proposed explanations include (1)
evidence that humans occupied this part of the planet in at least two waves of migration [12,21].

Recent studies on the amount of Neanderthal ancestry in Oceanian populations (discussed above) are also relevant in this context. Vernot et al. [11*], who found that Melanesians have less Neanderthal ancestry than other non-Africans, argued that this result indicated that Melanesian populations diverged from Eurasians before the split between European and East Asian populations. Malaspina et al. [12] came to a similar conclusion as well, consistent with at least two major migrations of modern humans into Southeast Asia.

Functional consequences of archaic admixture

After admixture between modern and archaic humans occurred, natural selection influenced the amount and the pattern of admixture observed in contemporary genomes. Purifying selection against deleterious archaic alleles generally leads to a reduction in the amount of surviving archaic DNA over time, except in the unusual scenario where most mutations are recessive [23*]. Indirect evidence for widespread purifying selection can be found in the distribution of inferred Neanderthal and Denisovan ancestry tracts across the genome — in particular, researchers found that highly conserved regions contain less archaic human DNA, and observed that many large (e.g., >5 Mb) regions of the genome have no apparent Neanderthal or Denisovan admixture [10*,11*,17,18]. These ‘archaic ancestry deserts’ are incompatible with simple models of neutral introgression, and they probably contain important functional elements. The X chromosome in particular has extremely low levels of Neanderthal and Denisovan introgression, consistent with standard evolutionary models of closely related taxa with partial reproductive isolation. While negative epistatic interactions (e.g., Bateman–Dobzhansky–Müller Incompatibilities) may be present in these deserts [10*,17], simple additive models of selection cannot be ruled out [23*].

More direct evidence for purifying selection can be found in the decrease in Neanderthal ancestry in ancient modern human samples over time [24**], from ~4% roughly 40 thousand years ago to the current 1.5-2%. Further theoretical work will be needed to reconcile these results on the plausibility of purifying selection [23*,24**] with the earlier studies claiming that differential levels of purifying selection could not explain the differing levels of Neanderthal ancestry in non-African populations [15,16].

By contrast, adaptive introgression (i.e., when the archaic allele is advantageous) is expected to lead to an increase in frequency of the introgressed allele; these regions can be identified by finding areas of the genome with extremely high amounts of archaic ancestry, similar to admixture mapping techniques. Adaptive introgression in humans seems to be quite rare (reviewed in [6]), with perhaps the most striking example being the EPAS1 gene in Tibetans, which is involved in adaptation to living at high altitudes and was probably inherited from Denisovans [25].

Once Neanderthal and Denisovan ancestry tracts have been identified from whole-genome sequences, SNPs that tag these tracts can be genotyped in a much larger collection of people. This, combined with medical records, can be used to obtain a more detailed understanding of the phenotypic effects of archaic admixture. Simonti et al. [26] presented the first such study, looking at patterns of Neanderthal admixture across ~28 000 individuals of European ancestry for which electronic health records were available. They found that many SNPs implicated by GWAS were probably inherited from Neanderthals, including a significant number associated with actinic keratosis, mood disorders and depression [26]. The interpretation of these findings is not straightforward, as most of the identified SNPs are at low frequency and probably not strongly selected for or against. They may represent weakly deleterious mutations though, and contribute to the increased genetic load in non-Africans thought to have arisen from Neanderthal admixture [23*].

Admixture with other archaic human groups

Our review has focused on admixture with Neanderthals and Denisovans, in part because the availability of archaic human genomes greatly facilitates the identification and quantification of admixture. However, as modern humans expanded from sub-Saharan Africa to the rest of the world, they encountered other archaic human groups both inside Africa and across Eurasia, so there were many potential opportunities for admixture. For example, there are several fossils with archaic features that date to <50 000 years ago in Africa [27–29], and Homo floresiensis occupied the island of Flores roughly contemporaneously with the earliest evidence of modern humans in East Asia [30,31].

Thus far, studies of admixture with archaic human groups other than Neanderthals and Denisovans have relied on searching for unusual patterns of linkage disequilibrium (LD) in sequence polymorphism data (cf. [32]). Studies of sub-Saharan African populations have consistently found evidence for some archaic admixture, though the amount and the timing of this admixture has been difficult to quantify [32–36]. In practice, patterns of LD caused by ancient admixture are difficult to distinguish from patterns of LD caused by more recent demographic events, such as population structure within modern humans. Because of this, detecting archaic admixture without a reference genome cannot be done accurately without also estimating a demographic model incorporating modern human population history [32,35].

Going forwards, there are several areas of work that could improve our ability to detect archaic admixture. The
studies described above all use an ad hoc statistic $S^*$, and identify $S^*$ outliers as archaic introgression candidates. A more systematic approach that jointly considers recent demographic history and potential archaic admixture, and quantifies the strength of the evidence (e.g., in a Bayesian context) has the potential to provide a more solid framework for analysis. On the data front, there is still a shortage of publicly available whole-genome sequence data from many important regions of the world, including Africa, the Middle East, South Asia and Southeast Asia. While there are ongoing studies that will eventually fill these gaps, it will be important for researchers to make raw data (e.g., fastq or bam files) available to the scientific community, so that genomes from different studies can be accurately compared with each other.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


10. Sankararaman S, Mallick S, Patterson N, Reich D: The combined landscape of denisovan and neandertal ancestry in present-day humans. Curr Biol 2016, 26:1241-1247. This study, along with Ref. [11], developed new methods for identifying specific genomic regions inherited from Neandertals or Denisovans. They concluded that Oceanians have the highest amount of Neandertal ancestry among all Non-Africans, and that South Asians have more Denisovan ancestry than other continental Eurasian groups.

11. Vernot B, Tucci S, Kelso J, Schraiber JG, Wolf AB, Gittleman RM, Dannemann M, Groze S, McCoy RC, Norton H et al.: Excavating Neandertal and Denisovan DNA from the genomes of Melanesian individuals. Science 2016. This study, along with Ref. [10], developed new methods for identifying specific genomic regions inherited from Neandertals or Denisovans. The authors concluded that Melanesians have less Neandertal ancestry than do other non-African groups.


23. Harris K, Nielsen R: The genetic cost of Neandertal introgression. Genetics 2016, 203:881-891. The authors show that purifying selection against Neandertal introgressed sequences in modern humans was a result of the increased mutational load in Neandertals, due to their lower population size.


