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Something old, something borrowed: admixture and adaptation in human evolution

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The sequencing of ancient DNA from archaic humans — Neanderthals and Denisovans — has revealed that modern and archaic humans interbred at least twice during the Pleistocene. The field of human paleogenomics has now turned its attention towards understanding the nature of this genetic legacy in the gene pool of present-day humans. What exactly did modern humans obtain from interbreeding with Neanderthals and Denisovans? Was the introgressed genetic material beneficial, neutral or maladaptive? Can differences in phenotypes among present-day human populations be explained by archaic human introgression? These questions are of prime importance for our understanding of recent human evolution, but will require careful computational modeling and extensive functional assays before they can be answered in full. Here, we review the recent literature characterizing introgressed DNA and the likely biological consequences for their modern human carriers. We focus particularly on archaic human haplotypes that were beneficial to modern humans as they expanded across the globe, and on ways to understand how populations harboring these haplotypes evolved over time.

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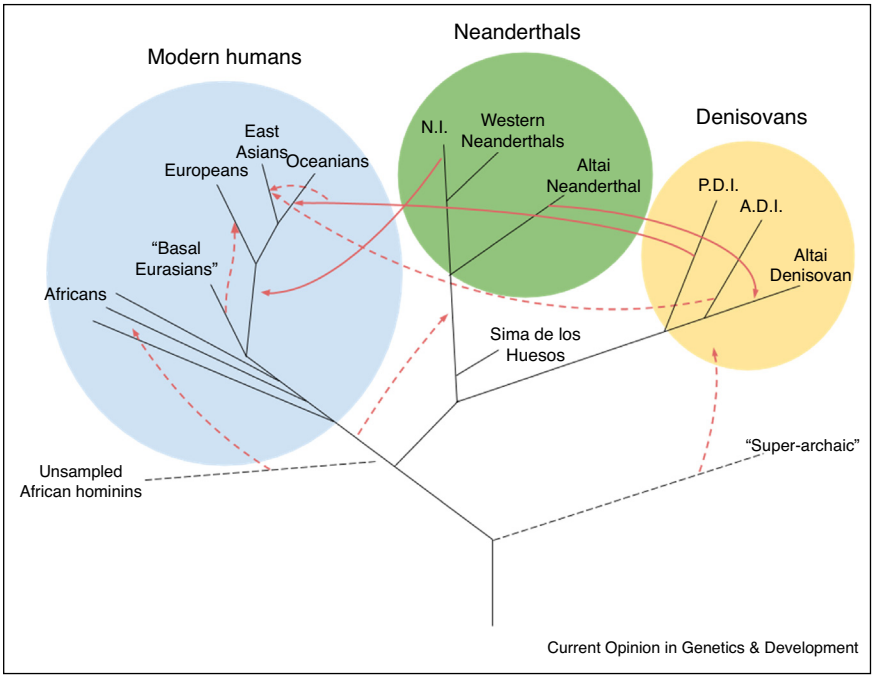
Genome-wide patterns of archaic admixture

In 2010, the first sequenced Neanderthal genome provided evidence for gene flow from Neanderthals into the ancestors of present-day non-Africans, around 50 000–60 000 years ago [1–3]. Since then, archaic human genomes have yielded ever more insightful discoveries. A few years later, a high coverage genome sequence from a Neanderthal found in the Altai mountains allowed researchers to pin down the proportion of Neanderthal ancestry in non-Africans to be ~2% [4]. In 2017, a second high coverage genome sequence from a Neanderthal in Croatia showed that this individual was more closely related to the introgressing Neanderthal population than the Altai Neanderthal, allowing researchers to detect even slightly higher levels of Neanderthal DNA [5]. In 2018, low-coverage genomes of five additional Neanderthals living between 39 000 and 47 000 years ago allowed a first glimpse at population structure in Neanderthals and showed indications of population turnover in late Neanderthal history [6•]. But admixture between different human groups has not been limited to modern humans and Neanderthals. The genome sequence of a previously unknown group, the Denisovans (a sister group to Neanderthals), also contributed to the genomes of present-day people in Oceania, and, to a lower extent, to mainland East and South Asians [7–9,10••,11,12]. Further admixture episodes have also been suggested, including gene flow from an unsampled 'super-archaic' human group into Denisovans [4], from eastern Neanderthals into Denisovans [4], from modern humans into Neanderthals [13,14] and between archaic and modern human groups in Africa [15–17] (Figure 1).

Although the signals of shared ancestry between modern and archaic human groups are quite evident, the exact processes by which introgression occurred remain unclear. For example, higher levels of Neanderthal ancestry have been observed in East Asians compared to Europeans [18]. Recent work has proposed that this difference resulted from a dilution of Neanderthal ancestry in Europeans after admixture with an unsampled modern human population ('basal Eurasians') that had little or no Neanderthal admixture [19] (Figure 1). Others have instead suggested that the higher Neanderthal ancestry observed in East Asians is a result of additional waves of Neanderthal admixture [20–22]. Analysis of an ancient European genome has shown that at least one additional pulse of Neanderthal admixture occurred in Europe, although this modern human population does not seem to have left present-day descendants [23]. Additionally, a recent study suggests that part of the Denisovan-like ancestry found in present-day East Asians is due to an archaic group more closely related to the sequenced Denisovan genome than the Denisovan-like ancestry in South Asians and Oceanians, providing support for a two-pulse model for Denisovan-like admixture [10••] (Figure 1). In the future, more archaic human genomes may

Figure 1



Admixture events between populations of archaic and modern humans. The black tree is a highly simplified representation of the history of population splits among modern and archaic humans, including a Middle Pleistocene hominin from Sima de los Huesos, Spain, for which only limited nuclear DNA is available [77]. For the sake of simplicity, we do not include South Asians, Siberians, Native Americans and ancient modern humans — like Oase or ancient northern Eurasians — in this tree. Red arrows represent major introgression events discussed in the main text. Dashed arrows represent introgression events with only preliminary or suggestive evidence at the time of writing. N.I.: Introgressing Neanderthal population — responsible for introducing Neanderthal DNA into the ancestors of Eurasians. P.D.I.: Papuan-Introgressing Denisovan population — responsible for introducing Denisovan-like DNA into the ancestors of Oceanians (and East Asians in smaller proportions). A.D.I.: Asian-Introgressing Denisovan population — responsible for introducing Denisovan-like DNA into the ancestors of East Asians only.
Figure inspired by Prüfer *et al*. 2014 [4].

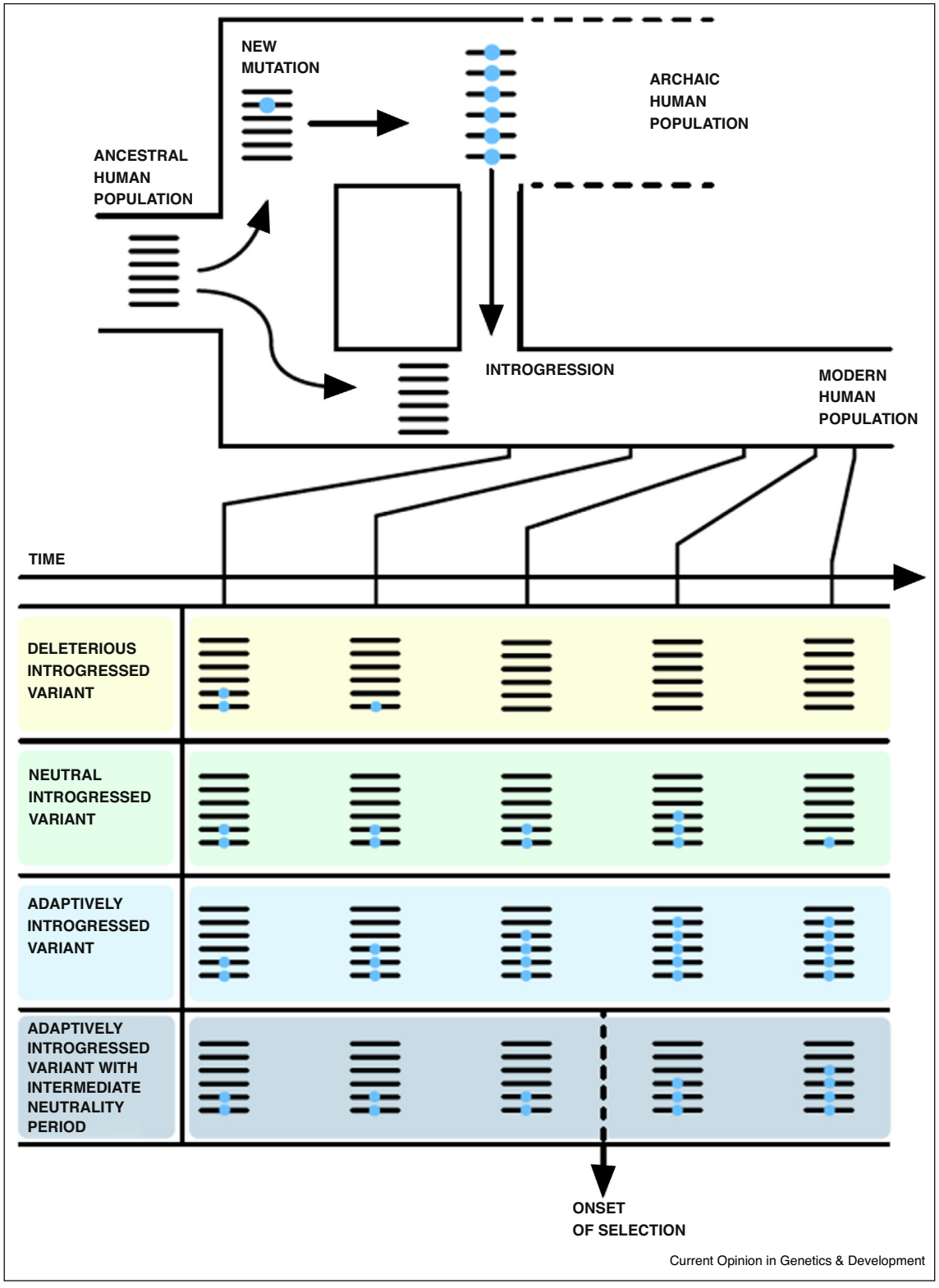
help to improve our understanding of the exact complex dynamics of admixture.

Although most recent studies of modern and archaic human genomes have focused on uncovering the general history of admixture, several works have aimed to localize and characterize specific archaic human DNA tracts in present-day human genomes [22,24–28]. For example, researchers have used the genome sequence of the Altai Neanderthal to detect Neanderthal DNA in present-day non-Africans. They were thereby able to reconstruct up to 40% of the introgressing Neanderthal's genome from the tracts remaining in present-day individuals, even though any one individual has no more than 4% Neanderthal ancestry [25–27]. They also showed that Neanderthal tracts are not uniformly distributed along the genome: large regions appear almost completely devoid of Neanderthal ancestry [25,26]. Recent work has also provided insight into the distribution of Denisovan DNA in the genomes of Oceanians [22,27], which has a similar non-uniform distribution. These 'deserts' — containing almost no Neanderthal or Denisovan DNA — partially overlap, and have been interpreted as evidence for potential incompatibilities between archaic and modern human alleles. The field is now shifting its focus from finding Neanderthal and Denisovan tracts in present-day humans towards functionally characterizing them, and towards modeling their present-day distribution under different modes of natural selection in the past, with the aim of understanding the consequences of this introgression on our evolutionary history.

Admixture and purifying selection

Multiple lines of evidence suggest that negative or purifying selection against archaic human DNA has been the dominant selective force affecting the distribution of archaic human DNA in modern human genomes (Figure 2). Under a model of pure genetic drift, the average proportion of Neanderthal ancestry in modern humans should remain roughly the same over time. However, a study of late Paleolithic modern human genomes in Europe showed a progressive decrease of genome-wide archaic human ancestry with time, suggesting that archaic human haplotypes were being selectively pruned from the human gene pool over thousands of years after the introgression event [29••].

Figure 2



Possible fates of an introduced mutation into a modern human population via introgression from an archaic hominin group. The lines depict chromosomes in a population and the blue dot represents a mutation that first appeared and rose to high frequencies in the archaic human population, before being introgressed into the modern human population.

Two biological scenarios have been proposed to explain the dynamics of purifying selection on archaic human tracts. Two studies [26,30] found enrichments for testis-expressed and meiotic genes in regions of low Neanderthal ancestry, as well as significantly lower Neanderthal ancestry in the X-chromosome than in the autosomes. Similar observations have been reported for regions of low Denisovan ancestry as well [27]. These studies argued that both of these patterns could perhaps be explained by Dobzhansky–Müller incompatibilities [31,32]: mutations that arose in each of the two lineages after the Neanderthal–modern human split and that were mutually incompatible in Neanderthal-modern human hybrids. These incompatibilities could lead to male hybrid sterility or reduced fertility, as genes associated with low male fertility in hybrids are preferentially located on the X-chromosome. Indeed, incompatibilities of this type have been previously observed in other species, for example, fruit flies [33,34]. Later work provided evidence that the abundance of archaic human ancestry deserts in the X-chromosome could be due to repeated selective sweeps driven by meiotic drive, thereby producing post-split incompatibilities [35].

However, two other studies have advanced the idea that purifying selection on Neanderthal tracts was instead due to a higher deleterious load in Neanderthals than in modern humans. They posited that, as Neanderthals had smaller effective population sizes than modern humans, selection was less efficient at pruning away mildly deleterious alleles in Neanderthals. These alleles were then negatively selected when they introgressed into modern humans, which caused a reduction in their frequency [36•,37•]. An increased deleterious load in Neanderthals does not provide an explanation for the previously detected enrichment of testis-expressed genes in regions of reduced Neanderthal ancestry. However, this enrichment has not been detected in a recent model-based approach by Steinrücken *et al.* [28].

Admixture and positive selection

Despite the evidence for widespread negative selection acting against archaic human DNA in modern humans, some archaic human haplotypes have reached very high frequencies in modern human populations, indicating that they may have been targets of positive selection (Figure 2). Specifically, a number of studies have identified introgressed archaic human alleles at high frequencies near genes linked to immunity, metabolism and the response to environmental conditions, like temperature, sunlight and altitude [4,25,26,38–42,43•,44,45•,61] (reviewed in Ref. [46]). Since Neanderthals and Denisovans inhabited Eurasia for at least 300 000 years before modern humans arrived, they were likely well-adapted to the local nutrients, pathogens and conditions that modern humans later faced as they expanded across the globe. For example, a variant in the *EPAS1* gene that confers tolerance to hypoxia at high altitude was introduced into modern humans via admixture with an archaic human population, before undergoing a strong selective sweep in modern Tibetans [42]. A recent work has stressed that introgressed variants need not have been adaptive right after their introduction into the modern human gene pool. The onset of selection in modern humans may have actually occurred several generations after the archaic human alleles were first introduced [47] (Figure 2).

These observations invite speculation about how introgressed archaic human DNA influences phenotypes, many of which are known to be highly polygenic. A first attempt to investigate the effects of Neanderthal DNA on polygenic traits used electronic health records from ~28 000 individuals and found associations between Neanderthal alleles and several neurological, psychiatric, immunological, and dermatological diseases [48]. A more recent study correlated the presence of Neanderthal alleles with several non-disease phenotypes, and showed that Neanderthal DNA contributed to variation in skin tone and hair color, sleeping patterns, mood and smoking status [49•]. This, however, does not imply that these trait-associated Neanderthal alleles were under positive selection. Indeed, for most traits, the contribution of archaic human alleles to present-day human phenotypic variation is not significantly larger than those of randomly drawn non-introgressed alleles occurring at the same frequency in modern humans. Interestingly, in both studies, neurological and behavioral phenotypes are an exception, with Neanderthal alleles contributing more to variation in these traits than frequency-matched modern human alleles.

Prospects for the future

The dynamics of admixture

So far, the detection of adaptive introgression in humans has largely relied on two approaches: (a) inferring archaic human tracts via a method that assumes a neutral model of admixture, and then looking for tracts with significantly higher frequencies than expected under such a model [22,25–27]; or (b) by computing summary statistics that have been found to be sensitive to adaptive introgression in simulations [43•,45•,47,50]. Neither of these approaches relies on an analytical model that explicitly accounts for introgression and selection jointly, and their reliance on simulations or neutral admixture models tailored to human demographic history makes them difficult to apply to the study of adaptive introgression in other species with different histories.

More theoretical work is needed to further our understanding of the dynamics of selected variants after an introgression event, and of the signatures expected in population genomic data under different admixture rates and selection modes. Steps in this direction have been undertaken by Uecker *et al.* [51], who derived analytical

expressions for the probability that a beneficial allele fixes in a population after an introgression event, and that deleterious (incompatible) variants hitchhike along with it. In turn, Aeschbacher *et al.* [52] developed a model to understand the relationship between the per-site selection coefficients against introgressed variants and various summary statistics that can be computed on genome-wide data. More recently, Sachdeva and Barton [53] built a model to study the evolutionary dynamics of an introgressed tract from one population to another, under a scenario of polygenic adaptation operating on variants inside the tract. As a complement to these theoretical approaches, it will also be key to study empirical patterns of introgression in non-human populations that admixed after being separated for some time. These 'natural experiments', in which certain historical or biological parameters may already be known *a priori*, can be compared and contrasted with hypothesized human evolutionary scenarios [54].

Additionally, the first empirical results from studies of archaic human introgression have led to an increasing interest in developing methods for the spatio-temporal localization of adaptive events. This is especially important when studying complex evolutionary histories involving many populations, as these often include multiple divergence and admixture processes. For example, a recently developed program — *Twisst* [55] — can scan a genomic dataset containing numerous individuals from several populations or species, and quantify how evolutionary relationships in a tree relating them differ across the genome. This allows for the identification of loci with strong evidence for adaptive introgression or barriers to introgression. Another recent method — *PolyGraph* — can take as input a previously inferred history of population splits and admixture events (in the form of an admixture graph [56]), and detect episodes of polygenic adaptation, that result in a systematic increase or decrease of the frequency of trait-associated alleles [57•].

Understanding the phenotypic consequences of admixture

There is accumulating evidence that modifications in gene regulation have been an important contribution of Neanderthal introgressed alleles on modern human biology. For example, the contribution of introgressed alleles to gene expression variation is larger than that of non-introgressed alleles of similar frequency [43•,58•]. Additionally, Neanderthal alleles have been shown to be associated with down-regulation of gene expression in brain and testes [59•]. Neanderthal alleles also show a significant contribution to expression changes in immune cells exposed to viral stimuli, highlighting the importance of archaic human variants on present-day immunity [60]. By contrast, the surviving Neanderthal-introgressed structural and amino acid-changing variants appear to be less deleterious than their non-introgressed counterparts [58•,62], suggesting that negative selection has acted on these classes of introgressed variants.

Further phenotypic characterization of introgressed variants — for instance, by using genome editing approaches on stem cells or model organisms — may help us to obtain a more refined understanding of the phenotypic legacy of archaic human introgression, and of the phenotypic differences and commonalities between modern and archaic human groups. Lastly, computational approaches could also be used to estimate how archaic DNA influences expression patterns and methylation [63–68]. These efforts might at some point allow us to predict Neanderthal phenotypes with high precision.

Other admixture events in human evolution

To date, most studies that investigated the phenotypic consequences of archaic human DNA in present-day humans were conducted in individuals with predominantly European ancestry. However, some Neanderthal DNA is also found in other non-African populations, and Denisovan DNA is largely present in Oceanians and — to a lesser extent — in South and East Asians. Fully determining how archaic human DNA impacted the phenotypes of modern humans will require genetic and phenotypic data from individuals from Asia, Oceania and other parts of the world, which may have undergone independent episodes of archaic human introgression.

Additionally, while studies of human adaptive introgression have focused on admixture between modern and archaic humans, the vast numbers of ancient genomes from the Neolithic, the Bronze Age and the Iron Age that are now published or in production [29••,69–71] might allow studying more recent episodes of adaptive introgression, as a consequence of admixture between two or more modern human populations. For example, there is some evidence to suggest that the lactase persistence allele located in a regulatory region of the *LCT* gene — one of the best-known examples of positive selection in humans [72,73] — was perhaps introduced into Western Eurasia via eastward migrations by steppe herder populations [69,74]. However, the evidence for this hypothesis is still scant, and more ancient sequences will be needed to determine with certainty exactly how this occurred, if it occurred at all [72].

The increasing availability of ancient and present-day human genomes from Africa will also make it easier to study admixture patterns between modern African populations [75,76], or between modern and archaic human groups in Africa [15–17] (Figure 1). As the bulk of human evolution happened in this continent, it will not be surprising to find cases of introgression — and adaptive introgression — between different African human groups, once ancient DNA from Africa becomes more readily available.

The detection of archaic human introgression has given us unprecedented insights into human evolution. Researchers have found evidence for multiple admixture events between modern and archaic humans, and are beginning to understand the selective pressures that operated on introgressed material. But it is still unclear how introgression affected phenotypic differences among present-day populations, including differences in disease risk: a research area with potentially fruitful biomedical implications. New genomic and phenotypic data from both present-day and ancient hominins will certainly help to address some of these questions, but it will also be necessary to develop new theory that can properly model both selection and admixture in a joint framework. We still have a long way to go before we can truly say we understand the genetic legacy of our hominin cousins.

Conflict of interest statement

Nothing declared.

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