

A genetic legacy from archaic Homo

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The roles of fossil human populations in the origin of modern humans have been enigmatic. Earlier (archaic) human populations were biologically similar and were in recurrent temporal and geographic contact, making interbreeding between ancient populations likely. Regardless of the taxonomic status of these populations, adaptive alleles may have introgressed from archaic populations into modern humans. When an introgressed archaic allele has a selective advantage, even rare interbreeding can lead to its spread or fixation in later human populations. Several genetic loci are candidates for such introgression, including microcephalin, a gene influencing brain development. This example may suggest that the evolution of human cognition depended in part on the genetic legacy of archaic groups such as the Neanderthals.

Modern human origins

'Modern' humans include all living people and some fossil specimens identified by their anatomy or associated archaeological evidence [1]. The evolution of modern humans was a process involving both anatomic and behavioral changes, not always linked in space or time. In anatomic terms, modern humans tend to have a high, rounded cranial vault, vertical cranial walls, a small face tucked under the vault, slight supraorbital development, small jaw and tooth size and a chin [2]. These features appeared late in the Pleistocene, including some African fossil specimens between 200 000 and 150 000 years ago [3,4]. Starting ~50 000 years ago, the archaeological record indicates cultural complexification and symbolic expression in Europe [5], Africa [6] and Australasia [7].

There is substantial disagreement about the relationship of these early modern humans to other Pleistocene humans, often called 'archaic' humans. The African fossil sample is heterogeneous [8] and does not record a smooth behavioral or anatomic transition to modernity. The later archaic peoples of Eurasia, including the Neanderthals, were behaviorally similar to contemporary modern humans and adopted their increasingly advanced technologies [9,10]. Not only technology, but also anatomy, followed parallel trends in different archaic populations, including the size of the teeth, brain and face [11]. However, after ~28 000 years ago, no traces of archaic humans have been found. Many anthropologists have argued that this disappearance is explained by the extinction of archaic people and their replacement by modern humans, so that the genes of living people come only from Late Pleistocene

African ancestors [2]. Others maintain that European and Asian populations also contributed to the gene pool of people living today [12].

Emerging evidence from the human genome suggests that some of the genes of archaic people do persist in living populations. This genetic survival does not reflect an equal representation of ancient populations but might involve a minority of genes from Eurasian populations [13]. Some such genes have alleles that have recently undergone positive selection in human populations. Here we hypothesize that introgression of alleles from multiple cultural or ecological backgrounds might have influenced the behavioral evolution of modern humans.

Population genetics of introgression

Molecular techniques have increased the recognition of introgression among mammalian sister species and subspecies [14], including grey wolves and coyotes [15], bison, cattle, zebu, yak and banteng [16,17], European and mountain hares [18], baboons [19], mice [20] and many others (reviewed by Ref. [14]). In large-bodied mammals, including primates, postzygotic isolation follows speciation by a gap of a million years or more [21,22]. Where closely related species are in geographic contact, they may form hybrid zones, areas where a large proportion of individuals have ancestry from two parental species. Even if first-generation (F1) hybrids have reduced fitness, adaptive alleles may still move across such hybrid zones, introgressing into the range of each parental species.

A neutral allele introduced at a low frequency by introgression will most likely disappear within a few generations, and its chance of reaching fixation in the distant future is only $1/2N_e$ for a single copy, where N_e is the effective population size. Early modern humans were geographically heterogeneous and growing rapidly, which might have allowed introgressing alleles to persist somewhat longer at low frequencies [23]. However, even so, a slight trickle of neutral alleles into modern human populations might not be noticeable with the samples currently available. The best-sampled locus, mitochondrial DNA (mtDNA), shows no trace of Neandertal-like mtDNA in recent human populations [24].

Advantageous alleles have a different fate. Like neutral alleles, an advantageous allele has a high chance of being lost initially. However, instead of $1/2N$, its chance of fixation from a single copy is $2s$, where s is the heterozygote fitness advantage. This means that an allele with a 5% advantage has a 10% chance of fixation. In fact, selected

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alleles in an exponentially growing population have a slightly higher probability of fixation, augmented by twice the intrinsic rate of growth [25]. Because each copy of an introduced allele has this fixation probability, only a small number of matings between archaic and modern populations would ensure the eventual fixation of a large proportion of the adaptive archaic alleles. For example, for any and all advantageous archaic variants with $s = 0.01$, a 95% probability of fixation requires only 74 archaic-modern matings, each introducing a single copy of the allele into the modern human population [14]. Widespread introgression of selected alleles would occur with a minimal level of interbreeding, which would leave a negligible effect on even large samples of neutral loci [26].

The process of introgression, in which a selected allele was introduced from an archaic human group into the recent human population, would generate recognizable geographic or genealogic patterns. Some alleles might have adaptive value only locally (e.g. alleles adaptive to cold in Europe), and others may have spread widely from their point of introduction. If a globally adaptive variant was introduced from Neanderthals, for example, it would likely be near fixation in Europe today but would not yet have risen as high in Africa or East Asia. Also, early population contacts would have influenced current genetic variation more than later contacts. A mating contact between populations 100 000 years ago (corresponding to early modern humans in West Asia) would have an immense head start over other copies that resulted from later intermixture [14]. As a result, we would not expect to see the strongest evidence for introgression at the last strongholds of archaic humans, such as Western Europe. Instead, the strongest introgression should have occurred at relatively early archaic-modern

population contacts, possibly in West and South Asia or even within Africa.

Recombination would have been more rare between different genetic variants in different archaic populations, so some introgressive alleles will be very distinctive haplotypes with little evidence of recombination over their histories. The genealogy of such a locus would include one or more deep branches with strong linkage disequilibrium (LD), juxtaposed with many shorter branches with much lower LD among them [27,28]. An introgressive allele under positive selection in the modern human population would have rapidly increased in frequency after its introduction. Positive selection leaves a signature of a long LD block and very low within-haplogroup coalescence times. The contrasting patterns of recent selection on one introgressive allele and neutrality for other alleles constitute a 'lopsided' topology, in which one haplogroup seems to be much more recent than others, and all are connected by very long basal branches (Figure 1). These predicted consequences of introgression may be incorporated into statistical tests, in comparison with neutral or panmictic models of ancient population structure [28]. Evidence for introgression is especially strong when the dates estimated for the locus make archaeological sense with spatiotemporally possible archaic-modern population contacts. These tests make it possible to identify a subset of introgressive variants in recent humans, including some of those with adaptive effects.

Genetic evidence for archaic introgression

Several recent reports have suggested that living humans retain alleles originally from archaic human populations.

Genes that preserve the most diversity in global human populations do not show evidence for recent movement out

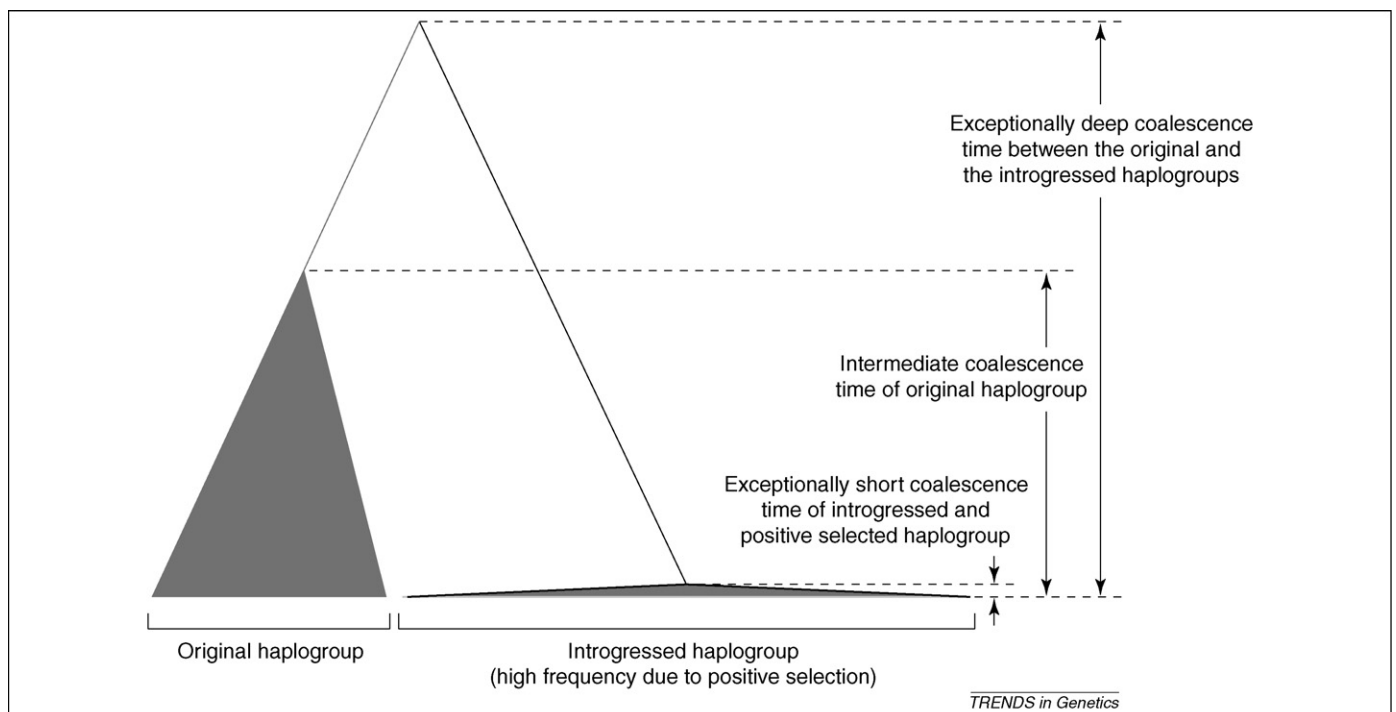


Figure 1. The lopsided genealogy expected of a locus that introgressed into humans from an archaic population through rare interbreeding, followed by a rapid increase in the frequency of the introgressed allele under positive selection.

of Africa, and haplotype diversity has a strong negative relationship with evidence for expansion. Both observations argue for a substantial archaic contribution to the current human genome [29]. A genome-wide analysis found that the pattern of linkage disequilibrium among human single nucleotide polymorphisms is inconsistent with an unstructured ancestral population and estimated that both Europeans and West Africans derive 5% of their present genetic variation from archaic humans [13].

Several other studies have examined individual loci in more detail, finding evidence for introgressive alleles in one or more populations. A striking pattern is the high allelic diversity attributable to ancient population structure in Africa. Genes indicating ancient population interactions include noncoding sequence at chromosome Xp21.1 [30], the region adjacent to the Xp and Yp telomeres [31], and the dystrophin gene [32]. Each of these cases involves the persistence of at least two haplotypes over a million years or more within Africa without substantial recombination. Anatomic evidence suggests that the origin of modern humans within Africa was itself complex, with different mixtures of archaic and modern features in many late Middle Pleistocene specimens [33]. Intermixture among several archaic populations may have been part of this complex evolutionary pattern, which might ultimately have incorporated introgression of alleles from European and Asian populations.

Strong evidence for adaptive introgression comes from the gene encoding microcephalin (*MCPHI*). This gene is one of many regulating the brain development in humans through its effects on the proliferation of neural progenitor cells [34,35]. Haplotype D of *MCPHI* has a remarkably young coalescence age (~37 000 years) despite a high worldwide frequency (~70%), arguing that it has swept to high frequency under positive selection [36]. Extreme demographic scenarios, such as a rapid dispersal of a small founding population throughout the world, might have an equivalent appearance to selection [37], but such scenarios must be validated against archaeological evidence for ancient demography and the distribution of variation for the genome as a whole. In the case of *MCPHI*, the observed pattern is rare in a genome-wide context [38]. In addition to being highly homogeneous, haplotype D sequences show a high degree of sequence divergence from non-D haplotypes. Across the 29-kb region, the average pairwise divergence between D and non-D chromosomes is 3.3 times the divergence seen within non-D chromosomes and 29.5 times the divergence seen within D chromosomes. The D chromosomes have a coalescence time (i.e. a time of divergence from a single ancestral sequence) ~37 000 years ago, whereas the coalescence time of non-D chromosomes is 990 000 years ago and 1 700 000 years for all the chromosomes combined.

The overall genealogy of *MCPHI* haplotypes is atypical for a partial selective sweep wherein the adaptive allele is introduced by a mutation on a random chromosome of a panmictic population. Haplotype D chromosomes bear a large number of derived variants, indicative of a very long branch that is independent from the non-D chromosomes. Haplotype D is most common in Eurasia, New Guinea and New World populations; it is much less

common within Africa. Balancing selection is an unlikely explanation for the high allelic divergence because of the lack of inversion or other factors suppressing recombination across the region and evidence for some recent recombinants [28]. Simulations show that the observed genealogical relationships are extremely unlikely under a panmictic population model and that ancient population structure is therefore a likely explanation. Likewise, long-term balancing selection is an unlikely explanation for the pattern, considering the evidence for ongoing recombination at the locus [28]. Together, these facts suggest that haplotype D may have introgressed into modern humans ~37 000 years ago, possibly by rare interbreeding with a genetically divergent population carrying the haplotype. Haplotype D was subsequently driven to very high frequency by strong positive selection. If this model is correct, the telltale genealogy found at *MCPHI* should be highly unusual relative to other loci in the human genome.

Comparisons based on resequencing have thus far identified a few genes with similar genealogical patterns. The microtubule-associated protein tau (*MAPT*) locus, associated with Parkinson's and other neuropathologies in living people, has two divergent haplotypes in living humans, H1 and H2, which diverged ~3 million years ago [39,40]. The H2 haplotype is common in Europeans, very rare in Africans, and seems to have been recently selected, as reflected by a very young coalescence date for this haplotype. These observations are consistent with introgression of this haplotype from archaic Europeans [39]. However, H1 and H2 are inverted relative to each other, and recombination between the two is absent, so that the extended LD was not necessarily maintained by ancient population structure. Even though the geographic distribution of the two haplotypes is suggestive, it is possible that balancing selection rather than archaic populations maintained them [28].

RRM2P4 is a nonfunctional pseudogene on the X chromosome, but nonetheless exhibits a pattern that might indicate introgression from archaic Asian populations [41]. Two divergent haplotypes share a common ancestor ~2.4 million years ago. One of the haplotypes is very common in East and Central Asia but is nearly absent in African samples. The pseudogene is found in a high-recombination region, which limits the possibility of linkage to an adaptive gene that may be under balancing or positive selection. Thus, the locus is consistent with introgression, but the presumed archaic variant is currently at a surprisingly high frequency for a neutral variant from a small number of interbreeding events. Further work may resolve the reasons for this pattern.

What did archaics have to offer?

Adaptive alleles from archaic humans present a paradox. We recognize archaic humans by their morphology, and that morphology has mostly disappeared. Therefore, if moderns still retain adaptive alleles from archaic humans, those alleles almost certainly were not correlated with traits that we recognize as archaic. Instead, they must be related to phenotypes that we cannot recognize easily in archaic human fossils.

Box 1. Emerging research from the Neanderthal Genome project

1. The Neanderthal Genome Project is finding gene variants directly from ancient Neanderthal skeletal remains, providing the potential to find direct evidence of archaic alleles that survive in modern humans. We may also find positively selected genes that introgressed into Neanderthals from contemporary modern humans. One such gene may be *FoxP2* – recently fixed in the modern human population, the derived human version of this language-related gene has now been discovered in two Neanderthal skeletons from Spain [45]. It remains to be shown whether the unique human variant was selected in the ancestors of humans and Neanderthals or whether it may have introgressed from one to the other.
2. Pigmentation polymorphisms occur in many groups of mammals, including recent humans. Now, Neanderthals are also known to have had unique pigmentation alleles, with a functional variant of the melanocortin-1 receptor (*MC1R*) gene not known from any living humans [46]. Pigmentation phenotypes such as light skin in recent Europeans seem to have been regionally adaptive; however, the current evidence provides no evidence that such variants introgressed from Neanderthals.

Compared with novel mutations, archaic genetic variants would have had several qualities that, in some cases, may have enhanced their selective value. Because they had long existed within human populations, these alleles had a much lower chance of being strongly deleterious. Some alleles may have had a long evolutionary history involving multiple mutational changes; such changes would be extremely unlikely as single mutational events but might nevertheless be strongly adaptive. Alleles with local advantages might never have been selected within the expanding modern population until it reached new climatic regimens. The spread of modern humans may have attained a burst of evolutionary change by drawing on the fruits of the existing adaptations of archaic humans.

Just as intermixture may have provided an adaptive flush to modern humans, it may have spelled the end of archaic populations. Cosmopolitan populations like modern humans are generally a threat to endemics, but this threat intensifies during range expansions and population growth [42]. In endemic species, alleles that promote outbreeding can be selected merely because the cosmopolitan species is expanding, aiding the collapse of former reproductive boundaries. Certainly, the distinctive morphological adaptations of archaic humans lost some of their selective advantage with the increasing technical sophistication of the early Upper Paleolithic (35 000–15 000 years ago). This must especially have been true for populations such as the Neanderthals, whose skeletal and muscular specializations required a high energy budget [43]. In an adaptive context, Neanderthals and other archaic humans were like endangered endemics, suffering from relatively high mortality [44] and high energetic costs. Possibly, the only remaining adaptive strategy for them was mixture with the more cosmopolitan modern humans. Ongoing research in Neanderthals should shed light on this and other issues (Box 1)

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