Dynamics of Adaptive Introgression from Archaic to Modern Humans

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ABSTRACT

Recent evidence from the genomic variation of living people documents genetic contributions from archaic to later modern humans. This evidence of introgression contrasts with earlier findings from single loci that appeared to exclude archaic human genetic survival. The present evidence indicates that many "archaic" alleles may represent relicts of African archaics, and that some "archaic" variants both inside and outside of Africa have attained relatively high frequencies. Both observations may be surprising under the hypothesis that modern humans originated first in Africa and displaced archaic populations through expansion and drift. Here, we outline how natural selection may have enabled the uptake of introgressive alleles from archaic humans. Even if admixture or gene flow were minimal, the introgression of selected variants would have been highly probable. In contrast to neutral alleles, adaptive alleles may attain high frequencies after minimal genetic introgression. Adaptive introgression can therefore explain why some loci show evidence for some archaic human contribution even as others apparently exclude it. The dynamics of introgression also may explain the distribution of certain deep haplotype branches in Africa. Open questions remain, including the likelihood that archaic alleles retained their adaptive value on the genetic background of modern humans and the scope of functions influenced by adaptive introgression.

> How important is introgressive hybridization? I do not know. One point seems fairly certain: its importance is paradoxical. The more imperceptible introgression becomes, the greater is its biological significance. It may be of the greatest importance when by our present crude methods we can do no more than to demonstrate its existence. . . . Only by the exact comparisons of populations can we demonstrate the phenomenon, yet in such populations the raw material for evolution brought in by introgression must greatly exceed the new genes produced directly by mutation. The wider spread of a few genes (if it exists) might well be imperceptible even from a study of population averages, but it would be of tremendous biological import (Anderson 1949: 102).

> We inevitably reach the conclusion, therefore, that introgressive genotypes not only persist indefinitely, but that also, like polyploids, they can migrate far beyond the areas in which they originated, and *can actually survive after the non-introgressed parental species has become extinct* (Stebbins 1959: 241, emphasis added)

INTRODUCTION

The anatomical and behavioral configuration of today's humans emerged during the Late Pleistocene. Before this time, regional populations of "archaic" humans inhabited the core regions of Africa, Europe, and Asia. By 25,000 years ago, no archaic humans remained, and modern humans occupied Europe, Africa, Asia, and Australia. The evolutionary transformation to modernity began in Africa (Bräuer 1984; Stringer & Andrews 1988; Trinkaus 2005), but the early evolution of modern human anatomy and behavior involved subsequent changes both inside and outside Africa (Smith 1992; Klein 1995; D'Errico 2003). Specialists disagree whether archaic and modern humans should be considered multiple species, subspecies, or evolving varieties of a single metapopulation.

Regardless of their taxonomic rank, similarities in behavioral capacities and recurrent spatiotemporal contacts make it likely that there was at least some interbreeding between archaic and modern populations (Wolpoff et al. 1984; Smith et al. 1989; Trinkaus 2005). The ultimate success of the modern human lineage was presumably a result of behavioral innovations in language, culture, or technology, all of which are implicated in the Late Pleistocene archaeological record with material evidence of symbolic culture (Chase 1999; Klein and Edgar 2002; Mellars 1989, 2005). But some late archaic humans, such as the European Neandertals, left a record of comparable behavioral capabilities to early modern humans (D'Errico 2003; Zilhão 2006). Moreover, modern humans were in West Asia by 100,000 years ago (Stringer and Andrews 1988), in Australia by 50,000 years ago (Turney and Bird 2001), and in Europe by 36,000 years ago (Trinkaus et al. 2003), making it plausible that comparably-skilled archaic and modern humans were in contact for substantial time periods. These populations shared common ancestors during the Early to Middle Pleistocene—for example, the European Neandertals appear to have shared genetic ancestry with modern humans between 300,000 and 700,000 years ago (Krings et al. 1999; Green et al. 2006). This time interval is very short for reproductive isolation to have evolved—for instance, no primates are known to have established postzygotic reproductive isolation during so short a time (Curnoe et al. 2006), and most mammalian sister taxa retain the ability to interbreed far longer (Holliday in press).

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Anatomical evidence from early modern humans also suggests intermixture between archaic and modern populations. At the peripheries of human occupation in Europe and Southeast Asia, early modern humans continued to exhibit some traits that had been common in preceding archaic populations (Wolpoff et al. 2001, 1984; Duarte et al. 1999; Trinkaus 2005). For the most part these traits were initially present at only low frequencies, which declined over time toward the present, at least in Europe (Frayer 1993, 1998). From this decline in frequencies, it seems probable that the alleles underlying archaic human morphological patterns were not adaptive in the modern human population. Likewise, extensive sampling of modern humans for mitochondrial and Y chromosome haplotypes has shown no evidence of ancient lineages such as might have existed within archaic human populations (Serre et al. 2004; Currat and Excoffier 2004; Weaver and Roseman 2005). These data may be consistent with a hypothesis of some gene flow from archaic to modern populations (Smith et al. 1989; Trinkaus 2005), but the amount of such gene flow was evidently slight.

Recent genetic reports have demonstrated that living people retain alleles from multiple archaic populations (Garrigan et al. 2005a, b; Hardy et al. 2005; Plagnol and Wall 2006; Hayakawa et al. 2006; Evans et al. 2006). Plagnol and Wall (2006) found that the pattern of linkage disequilibrium among SNPs in the human genome was inconsistent with an unstructured ancient population, and estimated that five percent of genetic variation in Europe and in West Africa originated in archaic humans such as the Neandertals. Two facts about this possible admixture are surprising from a paleoanthropological perspective. First, evidence for archaic ancestry is nearly as strong in Africa as in Europe, also confirmed by at least one single-locus study (Garrigan et al. 2005b). Second, at least some of the apparent archaic variants have been found at high frequencies in living populations (Garrigan et al. 2005a, b; Hardy et al. 2005). These observations seem inconsistent with the hypothesis that an initially low level of genetic contribution from archaic humans declined over time. In particular, they conflict with evidence that previously suggested near-total genetic replacement of archaic humans (Serre et al. 2004; Currat and Excoffier 2004; Vigilant et al. 1991; Takahata et al. 2001). Preliminary reports suggest that the Neandertal genome also included an excess of human-derived single nucleotide polymorphisms (Green et al. 2006).

Natural selection on introgressive variants from archaic humans can explain these data. Although the morphological pattern of archaic humans has disappeared, their long existence may have led to the persistence or appearance of alleles that did not occur in early modern humans. Some of these alleles may have been globally adaptive even outside the archaic human populations in which they originated. Others may have generated purely local advantages. In both instances, adaptive introgression is the most credible way for alleles from declining populations of archaic humans to survive and reach high frequencies today.

ADAPTIVE INTROGRESSION

Genetic introgression, or "introgressive hybridization," is classically taken as the introduction of alleles from one species into another species through hybridization (Anderson and Hubricht 1938). However, because species and subspecies boundaries are often imprecisely known, or fuzzy in nature, naturalists often adopt a more permissive definition that encompasses gene flow between subspecies, races, or varieties in addition to species (Rieseberg and Wendel 1993). An ecological theory of introgression emerged during the 1930's and 1940's (Anderson and Hubricht 1938; Anderson 1949; Heiser 1949), centered around the observation of introgressive hybridization in sunflowers, iris, and domesticated crops. Introgression has been demonstrated by several different methods for different species, including morphological traits, molecular markers, cytogenetic characters, and karyotypes (Jarvis and Hodgkin 1999).

Traditionally, hybridization and introgression have been considered unimportant in the evolution of animal species (Mallet 2005). The lack of interest in introgression mainly stems from the observation that interspecific hybrids often display reduced fitness or sterility (Mayr 1963), an observation that can be extended to plants as well (Mayr 1992). At first glance, if F_1 hybrids fail to thrive then genetic exchanges appear questionable. But even though reduced hybrid fitness may tend to limit gene flow between populations, it does not prevent relatively high levels of adaptive introgression (Arnold 1997; Arnold et al. 1999). This is because any allele introduced recurrently into a population will succeed or fail based on the strength of selection upon it. This insight and molecular assays of multiple genes have caused a resurgence of interest in hybridization and introgression in mammals. For example, a survey of 13 X-linked loci found evidence for adaptive introgression across a hybrid zone between *Mus domesticus* and *Mus musculus* (Payseur et al. 2004).

Introgressive hybridization often increases between populations when ecological conditions change or are disturbed. In contemporary organisms, such change often results from human disturbance or deliberate introductions (Rhymer and Simberloff 1996). Some of the best known instances involve mallards and endemic ducks (Mank et al. 2004; Rhymer and Simberloff 1996), red and sika deer (Goodman et al. 1999), mule and whitetail deer (Cathey et al. 1998), dogs and coyotes (Adams et al. 2003), coyotes and grey wolves (Lehman et al. 1991), tilapia (Gregg et al. 1998), and brown trout (Marzano et al. 2003; Almodóvar et al. 2001). In extreme cases, hybridization and introgression can result in the merger of formerly separate species or the formation of new species (Rhymer and Simberloff 1996; Dowling and Secor 1997). The effects of historic introgression are also sometimes seen in species with no evidence of current hybridization; this may be a consequence of past ecological changes, changes in species ranges, or expansion from glacial refugia. Examples include coyotes (Lehman et al. 1991), willow (Hardig et al. 2000), water flea (Taylor et al. 2005), lake trout (Wilson and Bernatchez 1998), European newts (Babik et al. 2005), and Japanese land snails

(Shimuzu and Ueshima 2000).

Because hybridizing species share a large proportion of their genetic background, a new allele that is adaptive in one species may retain its selective advantage after introgressing into another (Anderson 1949; Lewontin and Birch 1966; Arnold 2004b). Such adaptive introgression has emerged as an important mechanism for the introduction of adaptive variation (Arnold 2004b; Rieseberg et al. 2004). Many domesticated species originated through hybridization of wild populations; others show evidence of substantial adaptive introgression from wild populations after their origins (Jarvis and Hodgkin 1999; Bruford et al. 2003), a topic discussed further below.

Evidence for the introgression of adaptive alleles in wild populations was once rare, but has increased in recent years because molecular techniques allow easier tests of selection. Long-distance, or "dispersed" introgression involving discrete portions of the genome is a sign that positive selection favors an introgressive allele. Selection may be confirmed by field studies that show that an introgressive allele has observable effects on survival or reproduction. For example, introgression in natural populations of plants has often been noted to spread biotic resistance traits, as in sunflowers (Whitney et al. 2006) and lodgepole and jack pines (Wu et al. 1996). Introgression in Louisiana iris has introduced shade tolerance in local populations (Arnold 2004b), while xeric tolerance apparently spread from Utah cliffrose to bitterbrush (Stutz and Thomas 1964). Examples of adaptive introgression in animals include damselflies (sex-specific color morphs) (Sánchez-Guillén et al. 2005), *Anopheles* mosquitoes (pyrethroid resistance) (Weill et al. 2000), *Lutzomyia* (mating song) (Bauzer et al.2002), cichlid fishes (adaptive radiation under influence of hybridization) (Streelman et al. 2004), mountain and European hares (mtDNA related to climate) (Melo-Ferreira et al. 2005; Thulin et al. 2006), lake trout (mtDNA from arctic charr) (Wilson and Bernatchez 1998), and trypanosomes (drug tolerance) (Machado and Ayala 2001). It is interesting that several examples of adaptive introgression involve mitochondrial genomes, although such cases are probably highly represented because of the widespread use of mtDNA as a population marker. In many other instances, the function of an introgressive allele may not be known, but selection can be inferred from its present molecular variation.

In his monograph on introgressive hybridization, Anderson (1949) concluded with two observations. First, for species in contact with close relatives, introgression might be a greater source of new adaptive variation than new mutations. And second, phenotypically imperceptible introgression may be a more important source of adaptive variation than distinct hybrid zones.

Anderson did not formulate these conclusions in terms of population genetics, but a consideration of the relevant theory confirms their general validity. First, the importance of introgression relative to mutation emerges from the high chance of fixation of introgressive variants. The probability of fixation of an adaptive dominant allele introduced as a single copy is $2s$, where s is the selection coefficient applying to homozygotes (Haldane 1927). This probability applies to any single copy of an adaptive allele, whether it is introduced by mutation or hybridization. But a new adaptive mutation generally occurs initially as a single copy, unless the mutation rate is very high. In contrast, along even a very thin hybrid zone many interbreeding events between two populations will occur. Each of these hybrids may carry adaptive alleles from both populations, and each backcross into a source population provides the opportunity for each of these adaptive alleles to spread to fixation with probability $2s$. At this likelihood, it takes relatively few such hybrids to ensure the ultimate fixation of such an introgressive allele, as calculated below.

Because of the high chance of fixation with recurrent interbreeding, hybridizing species should share a large number of adaptive alleles—probably most of those that retain their selective advantage on the cross-species genetic background. A set of such hybridizing species will effectively pool the adaptive potential of any single one of them, providing a larger source of adaptive variants than mutation alone. Moreover, an adaptive allele from another species may differ by several mutations from the allele it replaces, and some of the intermediate steps may not have been adaptive by themselves in the host species. In effect, introgression may allow species to cross an adaptive valley without the fitness cost of intermediate alleles. In this way, introgression can permit adaptations that might never occur by new mutation in a single population.

Anderson's (1949) second concluding observation was that the fitness importance of morphologically distinct hybrid swarms is likely to be relatively limited. This result may also be derived from population genetic principles. Recognizable parental morphotypes depend on many coadapted genes. Even if some mixture of these genes were advantageous, selection upon such coadapted phenotypes is far less effective than on single alleles (Eswaran 2002). A single introgressive allele may have a more limited phenotypic effect, but selection will be much more effective. For animal species, many morphological characters carry the additional burden of being involved in mate recognition—some may even impede interbreeding at the hybrid zone through reinforcement (Howard 1993). The adaptive value of introgressive alleles may frequently be cryptic, such as resistance to disease or parasites, changes in metabolic or sensory systems, or alterations in developmental schedules. The genetic structure of phenotypes help to explain Anderson's "paradoxical" nature of introgression, in which "the more imperceptible introgression becomes, the greater is its biological significance" (Anderson 1949: p. 102).

INTROGRESSION FROM ARCHAIC HUMANS

Adaptive introgression can explain one of the most important problems in the origin of modern humans. Early modern humans not only retained many of the characters of archaic humans within Africa (Smith 1992), they also retained features of archaic European and Asian populations (Frayer 1993; Frayer et al. 1994; Hawks et al. 2000; Wolpoff et al.

2001; Duarte et al. 1999). Such features provide evidence of intermixture among these populations. But the largest single-locus genetic samples from living people appear to preclude admixture from archaic Europeans or Asians (Manderscheid and Rogers 1996; Currat and Excoffier 2004; Weaver and Roseman 2005; Serre et al. 2004). Neither of these sources of evidence suggests that interbreeding was necessarily very common between archaic and modern humans, and the proportion of archaic traits did decline over time where it can be observed (Frayer 1993). Yet, some genetic loci show evidence of ancient population structure, such as would be expected from an archaic human ancestry (Templeton 2005; Garrigan et al. 2005b, a; Zietkiewicz et al. 2003; Hayakawa et al. 2006; Hardy et al. 2005; Evans et al. 2006), and the presumed "archaic" alleles are sometimes at high frequencies. Introgression of alleles from archaic populations has been proposed as the most probable explanation for these observations. As a note of skepticism, balancing selection on low-recombination regions or genetic inversions remains possible for some of these loci, but has been excluded in at least the case of *MCPH1* (Evans et al. 2006). Here, we investigate the conditions under which introgression is credible, and do not pursue the details of any single gene that might preserve such evidence.

The survival of neutral genetic variants from archaic humans is not a likely explanation for high-frequency alleles. The last archaic human populations existed only around 30,000 years ago, a time during which modern humans expanded from an initially low population size to much higher numbers (Stiner et al. 2000; Harpending et al. 1998). It is true that neutral alleles are unlikely to be lost from an expanding population; even alleles introduced at a very low initial frequency should have had a reasonable chance of surviving into the present-day human population (Manderscheid and Rogers 1996). But the probability of fixation of any neutral alleles introduced during this time frame is essentially zero, and indeed a neutral allele should remain very near the low frequency at which it was introduced. For most genetic samples available today, in particular the HapMap and other large-scale genomic surveys (The International HapMap Consortium 2005), the low frequency of neutral introgressive alleles should make them invisible to ascertainment. Neutral introgression is therefore a poor explanation for many of the observations from modern human genetic variation. However, a denser sampling of human genetic variation in the future may pick up a higher proportion of such neutral introgressive variants, which might be recognizable on the basis of their sequence divergence (Wall 2000).

A positively selected allele behaves according to very different rules from a neutral allele. Whereas the fixation probability for a single copy of a neutral allele is $1/2N$, the corresponding probability for a selected dominant allele is $2s$. Moreover, exponential population expansion, which approximates the modern human demographic history, actually ***increases*** the probability of fixation by double the intrinsic growth rate (Otto and Whitlock 1997).

A relatively small number of interbreeding events will greatly increase the chance of fixation of adaptive introgressive variants. Haldane (1927) arrived at the fixation probability for a selected allele by generalizing from the probability of extinction of all copies of an adaptive allele in each generation following the introduction; we can use a similar process to consider the probability that several copies of an allele resulting from introgression would be lost without being fixed. This probability of total loss of n copies decreases according to

$$\boxed{\Pr[\text{loss of } n \text{ copies}] = [1 - 2(s + r)]^n}$$

If the modern human population expanded at a rate of 1 percent per generation, then an introgressive allele with $s = 0.01$ (i.e., a 1 percent fitness advantage) would have a 95 percent probability of fixation in modern humans, with only 74 archaic-modern matings. For an allele with a 5 percent fitness advantage, the corresponding number of events would be only 24.

After their introduction into the modern human population, adaptive introgressive variants would have rapidly increased in frequency. Today, such variants may therefore occur at high frequencies, especially in their region of origin. Modern humans had dispersed throughout the world by 30,000 years ago. This means that any alleles that introgressed from archaic human populations must have been introduced by approximately 1200 generations ago. Within a panmictic population, the number of generations to fixation of an additive advantageous allele is given by Crow and Kimura (1970):

$$\boxed{\ln p_t/q_t = \ln p_0/q_0 + st / 2}$$

As the allele approaches fixation, the rate of change in frequency is lower, so that the average time to fixation overrepresents the time during which an allele may remain ascertainable in relatively small samples of a population. For the present version of the HapMap (The International HapMap Consortium 2005), the maximal ascertainment frequency of long-range haplotypes is less than 80 percent (Wang et al. 2006; Voight et al. 2006). Different genetic surveys with larger samples may have higher maximal ascertainment frequencies. Here we consider the case in which all variants with frequencies of less than 99 percent will be ascertained. At this level of ascertainment, most variants with $s < 0.015$ would remain segregating in present-day genetic samples. It is notable that this class of variants not only is weakly selected, it also represents those with the *lowest* chance of fixation. Alleles with a stronger chance of fixation (i.e., larger selection coefficients) will in general be more likely to have *already* approached fixation. For instance, a gene with a 4 percent advantage would approach fixation in only around 400 generations, or around 10,000 years.

These are illustrative values, and there are some reasons to be conservative about the rate and time to fixation of such introgressive variants. For example, if the initial frequencies were lower (because the global population was larger), then the time to fixation will be higher. A larger amount of archaic-modern interbreeding would reduce the time to fixation, because it would increase the initial frequency of the introgressive allele. In any case, the alleles most likely to be fixed will come to fixation the fastest, and a substantial number of such archaic alleles may already be near fixation in humans.

HOW IMPORTANT WAS INTROGRESSION?

The emergence of modern humans was a rapid evolutionary event that involved many genetic changes in a population that became increasingly dispersed over time. A flush of adaptive alleles from archaic human populations, which were already geographically dispersed, may have accelerated this evolutionary change. To the extent of their genetic differentiation, archaic human populations would potentially have had different adaptive genetic variants. But no good estimate of the genetic differentiation of archaic human populations is available, and other genetic parameters, such as their effective population sizes, are also uncertain. Without such knowledge, we cannot make an accurate theoretical estimate of the true importance of adaptive introgression in the emergence of modern humans.

However, we can propose some demographic and genetic parameters, and examine the way that variation in such assumptions would affect the expected amount of adaptive introgression. In particular, it is worthwhile to consider whether introgression may have been a larger or smaller source of adaptive variants compared to new mutations in the modern human population. To examine this question, we will assume the following simplified demographic parameters:

1. A population divergence between modern and archaic humans 235,000 years ago. This time is consistent with the divergence of Neandertal mtDNA from recent samples, but a "population divergence" itself may overstate the amount of actual genetic differentiation.
2. Equal effective population sizes in the modern and combined archaic populations. Evidence from living populations indicates a larger long-term effective size in Africa than Eurasia (Relethford 1998), but it is not clear whether this value applies to archaic populations, which would have included some populations within Africa.
3. Reproductive contact between modern and archaic populations 35,000 years ago. This assumption greatly simplifies the true pattern of interaction, which was heterogeneous across time and space.
4. An equal rate of adaptive mutations in modern and archaic lineages, μ per genome per year. It is plausible that environmental changes may have altered the number of new adaptive variants (by rendering some previously deleterious changes adaptive), but we have no data whatsoever on this point.
5. Equal fixation probabilities for mutations in both the modern and archaic populations. Again, environmental changes may have altered the average advantage of mutations under selection.
6. Expansion of the modern human population after contact to ten times its initial size. This is in the range of values estimated for Upper Paleolithic population growth (Biraben 2003), but growth was not instantaneous, which also would affect fixation probabilities for adaptive variants.

The values chosen here are purely for demonstration and we do not propose that they are correct; the effects of various departures from these assumptions are explored below.

The fixation probability of adaptive mutations depends on their selective advantage ($2s$ for dominants, but less for incomplete dominants), but here we are concerned with their relative abundance from introgression versus new mutation, which in both instances need consider only genes that progress toward fixation. Under the assumptions above, both the modern and archaic lineages will have undergone $400{,}000N\mu$ adaptive mutations during the time they are separated, from 235,000 to 35,000 years ago. In contrast, the modern human population after contact will experience $20N\mu$ per year—which over 20,000 years of the Upper Paleolithic would also reach $400{,}000N\mu$. Under these assumptions, adaptive introgression might easily provide as great a source of adaptive variants as new mutation after population contact—even considering a larger population size for the Upper Paleolithic population.

An examination of how each parameter might vary in the prehistoric human case helps to clarify the importance of introgression. For example, if modern and archaic humans diverged earlier than 300,000 years ago, there would have been more time for adaptive mutations to arise in the respective lineages, and more possible introgressive variants as a result. On the other hand, the adaptive mutations in the archaic population would occur upon a genetic background that became progressively more different from modern humans—probably lowering the proportion of these variants that would retain their selective advantage in the modern population. If modern humans arose in a single small population, they would have been low in numbers for a long time, and so might have had a substantially lower number of adaptive mutations than archaic populations. Since archaic humans lived in many different climatic regimes, each would effectively select for some locally adaptive mutations, which would increase the effective rate of adaptive mutation in archaic humans as a whole. And this estimate assumes that all mutations are equal, where in contrast certain introgressive variants may have included multiple sequential mutational changes that would be essentially impossible to occur as novel mutations.

The importance of adaptive introgression depends on what proportion of archaic alleles are adaptive for modern humans. It has often been considered plausible that the origin of modern humans required an exceptional number of adaptive changes, perhaps related to the evolution of language, symbolic culture, or technological capabilities (Klein and Edgar 2002; Mellars 2005). But such a rapid evolutionary process could have involved only a small proportion of the total phenotype, leaving a vast number of characters that might profit from introgression. Moreover, the broadly similar pattern of brain evolution among Middle Pleistocene archaic populations (Hawks and Wolpoff 2001) suggests that archaic humans may have undergone adaptive brain-related mutations as well. Two genes proposed to have undergone adaptive introgression, *MCPH1* and *MAPT*, are both expressed in neural tissue during early development, and may reflect selection on such processes. Recent surveys make clear that the genome of modern humans has undergone an exceptional amount of selection (Wang et al. 2006; Voight et al. 2006; Bustamante et al. 2005). If modern humans were under strong selection related to new cognitive or behavioral characters, then any source of adaptive variants would have been very important to their evolution.

The history of domestication demonstrates the importance of introgression as a source for adaptive variants in strongly selected populations. Wild progenitor species and feral forms of domesticated species have been reservoirs of adaptive variation for both prehistoric and recent breeders (Arnold 2004a). Jarvis and Hodgkin (1999, Table 1) list evidence for introgression within alfalfa (Small 1984), barley (Murphy et al. 1982), beet (Boudry et al. 1993), cabbages and rapes (Eber et al. 1994; Jorgensen and Andersen 1995), carrot (Small 1978), chili (van Raamsdonk and van der Maesen 1996), cocona (Salick 1992), common bean (Beebe et al. 1997), cowpea (Vaillancourt et al. 1993), foxtail millet (Till-Bottraud et al. 1992), hemp (Small 1984), hops (Small 1984), lettuce (Zohary 1991), maize (Doebley 1990; Kato 1996), oats (Baum 1977), pearl millet (Robert et al. 1991), pigeon pea (Smartt 1990), potato (Hawkes 1956; Grun 1990), quinoa (Wilson 1990), radish (Klinger and Ellstrand 1992), raspberry (Luby and McNicol 1995), rice (Langevin et al. 1990), rye (Vences et al. 1987), sorghum (Arriola and Ellstrand 1996), soybean (Singh and Hymowitz 1988), squash (Decker-Walters et al. 1990), sunflower (Rieseberg 1995), tomato (Rick and Holle 1990), watermelon (Zamir et al. 1984), and wheat (Zohary 1971). Additional references may be found in Jarvis and Hodgkin (1999). Several other crops may be added to this list, such as rubber (Seibert 1948), citrus (Federici et al. 1998), apple (Coart et al. 2006), coffee (Anthony et al. 2002), cotton (Wendel et al. 1989), soybeans (Abe et al. 1999), and peas (Vershinin et al. 2003). Deliberate introgressive breeding of many other species has commenced in the last few decades.

Introgression between domesticated animals and single wild ancestor species is nearly ubiquitous, since unlike many plant species, animal domestication has not resulted in polyploidization or major chromosomal rearrangements. But animal domestication may provide a more relevant analogy for modern human origins, considering that in many cases the current diversity of domesticated breeds is the result of introgression from more than one wild progenitor species. In these cases, the present diversity of domesticated breeds derives from ancient variation between two or more long-isolated populations (Bruford et al. 2003). Several domesticated animals that originated in Eurasia have strong east-west phylogeographic clusters, presumably reflecting domestication and continued introgression with wild ancestors from opposite ends of Eurasia. The mitochondrial divergence of such clusters is typically in the hundreds of thousands of years (MacHugh and Bradley 2001), including those for cattle (Loftus et al. 1994; Kikkawa et al. 2003), river and swamp buffalo (Tanaka et al. 1996), pigs (Giuffra et al. 2000) and sheep (Meadows et al. 2005). Other instances of introgression among two or more wild species include yak (Xuebin and Jianlin 2002), banteng (Nijman et al. 2003), cats (Beaumont et al. 2001), water buffalo (Kierstein et al. 2004), and dogs (Adams et al. 2003).

Reticulate evolution of the bovines (including cattle and bison) shows how introgression may drive the adaptation of geographically dispersed species to changing ecologies. Cattle and bison diverged during the Late Pliocene (McDonald 1980). Female F_1 hybrids among cattle and bison species are fertile; most species pairs exhibit male hybrid sterility, including between *Bos* and *Bison*. Despite a history of allopatry and evolution of reproductive barriers, these genera exhibited substantial introgression both before and after domestication. For instance, the Late Pleistocene North American bison *Bison alleni* may have originated by hybridization of long-horned *B. latifrons* and the Eurasian steppe bison, *B. priscus* (Guthrie 1970). The European bison, or wisent (*Bison bonasus*) is morphologically and genetically similar to North American *Bison bison*, except for its mtDNA, a discordance that apparently reflects either recurrent nuclear DNA introgression from bison (probably *B. priscus*) to aurochsen (*Bos primigenius*), or prehistoric mtDNA introgression from aurochsen (Verkaar et al. 2004). The extant species of cattle, including ox (*Bos taurus*), zebu (*Bos indicus*), banteng (*Bos javanicus*), and gaur (*Bos gaurus*), originated as allopatric vicariants across tropical and temperate Eurasia, differentiated in part by ecological adaptations (e.g., arid conditions for zebu; hills for gaur). Their present genetic distances reflect geographic distance (Buntjer et al. 2002). Of these, only ox and zebu are fully interfertile, but the genetic differentiation between them indicates population divergence from ancestral aurochsen sometime before 200,000 years ago (MacHugh et al. 1997). Early domestication in the Near East saw the differentiation of *Bos taurus* breeds and the movement of domesticates into Europe and Africa where they intermixed with local aurochsen (Beja-Pereira et al. 2006; Götherström et al. 2005). In Europe, this introgression from local aurochsen was male-dominated (Götherström et al. 2005), while in Africa it included adaptive introgression of at least one disease-resistance allele at the *CD45* locus (Ballingall et al. 2001). Within the past 4,000 years, introgression from zebu began to absorb indigenous West Asian breeds (Matthews 2002) probably because of their greater tolerance of increasingly arid conditions. The movement of zebu genes continued across Africa, by the preferential breeding of zebu males (MacHugh et al. 1997). In China, indigenous domestic cattle have a blend of ox and zebu ancestry with introgression from yak (*Bos grunniens*) (Yu et al. 1999); yak themselves are actually phylogenetic bison (Buntjer et al. 2002). Both wild and domesticated populations of yak and banteng show introgression from ox and zebu (Ward et al. 1999; Nijman et al. 2003), and kouprey appear to be a feral banteng-zebu hybrid population (Galbreath et al. 2006). Finally, present-day North American bison are a relict population with substantial cattle introgression, probably facilitated by their recent founder effect (Ward et al. 1999), while later deliberate introgression of bison genes into cattle produced Beefalo cattle for beef production.

This is a sample of a very complex population history in which multiple allopatric species with Plio-Pleistocene origins have experienced recurrent introgression. This introgression greatly accelerated both with domestication and with natural ecological changes. Climate change, habitat disturbance, population dispersal, reintroduction of previously isolated populations, and emergence from glacial refugia have all facilitated introgressive hybridization in natural populations. Domestication couples these natural processes with the additional strong selection from human-mediated ecological change. All of these processes to some extent marked the evolution of modern humans. The time period involved in modern human origins, measured either in hundreds of thousands of years or in thousands of generations, is comparable to that of introgressive hybridization in other taxa, including the widespread hybridization and introgression of adaptive alleles in domesticated animals. In terms of time and ecological circumstances, there may be no closer analogy to recent human evolution.

INTROGRESSIVE VARIANTS IN AFRICA

A surprising prediction of introgression is that many genes may have a higher allelic diversity attributable to archaic introgression in Africa, not Eurasia. Many studies have now found divergent haplotypes found within one or more African populations that they attribute to introgression (Plagnol and Wall 2006; Garrigan et al. 2005b; Zietkiewicz et al. 2003; Hayakawa et al. 2006). One possible reason for the persistence of ancient African variants is ancient population structure. If Middle Pleistocene Africa included several more-or-less isolated regional populations, then both genetic and morphological variation in present-day Africans might reflect this ancient variability (Garrigan et al. 2005b).

But another reason for the presence of ancient variation in Africans might be adaptive introgression from archaic non-Africans. An allele increasing under selection would have reached its highest present frequency near its point of introduction. This means that a strongly advantageous Neandertal allele might be near fixation in present-day Europeans, and it may have spread into Africa and Asia where it currently is at lower frequencies. The heterozygosity in Africa and Asia would be markedly higher for such a gene than in Europe. Also, the sequence divergence between this Neandertal allele and other alleles would contribute disproportionately to other measures of diversity such as the mean pairwise difference. In this scenario, the "archaic" allele now found in Africa would actually be the allele that initially predominated in early "modern" populations, before it was mostly replaced by the adaptive allele from "archaic" humans.

We may derive some theoretical expectations for the dispersal of such adaptive alleles, to delimit the chances that they will be detected in samples distant from their initial introgression. Under the Fisher-Kolmogorov diffusion equation (Fisher 1937), the minimum velocity of the wave front of a dominant adaptive allele spreading through a linear population is $\sigma\sqrt{2s}$, where σ is the root mean square distance between parental and offspring birthplaces, and s is the selection coefficient of the adaptive allele. Diffusion waves in two-dimensional populations may be slower, depending on the geometry, with a minimum velocity of $\sigma\sqrt{s}$ in a simple circular model (Skellam 1951). Ancient humans were neither linear nor circular in their geographic arrangement, so the relevant velocity probably was in-between these values.

Applying the diffusion model to ancient humans requires an estimate of how far they dispersed, which appears to have increased in the Upper Paleolithic and Later Stone Age compared to earlier time periods (Gamble 1994; Whallon 1989). Root mean square mating distance varies among recent human hunter-gatherers from less than 10 km to more than 50 km (Wijsman and Cavalli-Sforza 1984; Harpending 1976). The higher end of this range may be more relevant to ancient populations, because they existed at lower densities. Using an estimate of 50 km for σ, a variant with $s = 0.01$ would spread through a linear population at a rate of around 7 km per generation; a more strongly selected variant with $s = 0.05$ would more than double this rate to 16 km per generation. In the 1200 generations since the last Neandertals, such alleles might spread over 8,000 km, and 19,000 km, respectively. Several other factors might tend to diminish this rate of dispersal of introgressive alleles. For example, population pressure probably increased over time and reduced the typical parent-offspring distance, cultural and geographic barriers may have impeded movement, and even globally adaptive alleles might spread more slowly upon a different genetic background. But it is also possible that introgressive alleles entered the modern human population from archaic contacts long before the 30,000 years ago. In any event these distances are more than enough to illustrate the potential of introgressive alleles to spread far from their point of origination, even across the short timespan involved.

This hypothesis of introgression into Africa contrasts with the usual model of genetic dispersal from Africa, which explains lower variation among Eurasian genetic variants as a product of genetic drift associated with the origin of modern humans. Both hypotheses predict that African populations may harbor ancient alleles that are rare or absent in other populations, and each may be true of different genetic loci. Some alleles clearly did follow the out-of-Africa pattern, which may be detected when linkage disequilibrium or SNP variation show the likely direction of dispersal (Templeton 2005). But other alleles may have become common in other regions of the world first, before introgressing into Africa. The usual tests of population movement out of Africa, such as cluster analyses based on population-specific allele frequencies (Zietkiewicz et al. 2003; Tishkoff et al. 1996) cannot resolve whether the relationships of Eurasian and African samples derive from introgression or genetic drift. The scenario may be possible for the *Xp21.1* haplotype observed by Garrigan et al (2005a) if it is linked to noncoding regulatory DNA, and it may encompass an unknown number of loci surveyed by Plagnol and Wall (2006).

Broader sampling may permit relevant tests. Some regions of the world, such as Beringia and the Americas, were settled long after any contacts between modern and archaic humans occurred. These populations would probably carry introgressive alleles that were sufficiently adaptive to disperse after their appearance in modern humans. But the initial settlement of Australia and island Melanesia happened much earlier, and certainly preceded the last Neandertals. These populations would presumably carry alleles that dispersed with modern humans from Africa, but adaptive introgressive alleles from many archaic humans might not have reached them. So a greater understanding of the genomic variation in these populations will contribute to our knowledge of the adaptive circumstances of modern human origins.

DISCUSSION

Modern human populations remain in a transient state with respect to the introduction and fixation of introgressive alleles from archaic humans. We can still find introgressive alleles segregating in human populations, because too little time has elapsed for their evolution to have reached its final disposition. Alleles that genomic surveys can presently ascertain are those at intermediate frequencies. To remain segregating, such alleles must have been relatively weakly selected, over a range of selection coefficients from 0.5 to 2 percent. Some such alleles may have been adaptive in only a local context, and would have remained largely restricted to their region of origin. But others may have spread widely so that present-day gene heterozygosity may not be a good guide to the origin of recently introgressive alleles. More strongly selected alleles may have approached fixation regionally or even globally. In contrast, neutral introgressive alleles should be relatively rare even in their region of origin.

Because introgression under selection and introgression under drift may be associated with linkage blocks of a similar length (because modern-archaic interactions happened during the same limited time interval), it may be difficult to diagnose selected from neutral introgression. Selection and drift may even intergrade, as some alleles with purely local advantages may nevertheless spread beyond their region of origin by gene flow and drift. The study of genetic introgression from archaic to modern humans therefore will require close examination of the functions of putative introgressive alleles and their fine-scale geographic variation in present human populations. Most genomic regions are not well enough known at present to test whether introgression occurred.

The search for archaic genes has so far concentrated on neutral variants, and has employed quite conservative strategies. For example, researchers have focused on genetic regions with very deep coalescence times, as unlikely to occur within a small panmictic population of early modern humans (Wall 2000; Garrigan et al. 2005b; Plagnol and Wall 2006; Hayakawa et al. 2006; Evans et al. 2006). But the mtDNA distance between Neandertal and living human sequences appears to correspond to a genetic divergence time of only 300,000–700,000 years (Krings et al. 1999; Green et al. 2006; Noonan et al. 2006); this date would presumably indicate that gene flow among European archaic humans and the ancestors of modern humans was possible at this date, if not later. So methods that depend on very ancient divergences may find the most extreme introgressive variants, but many introgressive variants will be much less genetically distinctive.

The hypothesis of adaptive introgression suggests several strategies for finding such variants in the living human gene pool:

1. Africa may be a good location for the ascertainment of adaptive introgressive alleles from Eurasian archaic humans. Many alleles with high frequencies in Eurasia may be candidate introgressions even if they also occur in Africa.
2. The direction of spread of alleles shared by Eurasian and northern or eastern African populations should be assessed. Where some models of dispersal suggest that alleles originating in northeastern Africa spread subsequently into Eurasia, the hypothesis of introgression suggests that such alleles may be dispersing into Africa.
3. Introgressive alleles should have extended linkage disequilibrium, and there should have been relatively little mutational differentiation of introgressive haplotypes.
4. Phenotypic consequences of introgression may have become common long after the initial arrival of modern humans into Eurasia.
5. Complex phenotypes like craniofacial morphology that involve many coadapted genes are unlikely to introgress.
6. Since introgression is so much more likely for variants under selection, putative “non-coding” regions that show introgression may be candidate loci for expressed regulatory genes.
7. Possibly most important, the direct sequencing of archaic human DNA would permit comparison with alleles currently segregating in modern humans.

The preliminary data from the Neandertal genome project (Green et al. 2006; Noonan et al. 2006) provides exciting opportunities to examine the degree of adaptive introgression. In particular, the low genetic divergence date estimated for Neandertal and human genome drafts (ca. 520,000 years) makes it clear that potential introgressive alleles need not show vast sequence divergence from other human alleles. Current strategies that screen for highly divergent alleles may be catching only the extreme tail of the distribution of introgressive variants. Even so, a number of such alleles have been found with clear evidence of recent positive selection, including *MCPH1* (Evans et al. 2006) and *MAPT* (Hardy et al. 2005).

From one perspective, introgressive hybridization may help explain why archaic humans disappeared. Cosmopolitan species are generally a threat to endemic species, but this threat is even greater when range expansions open new hybrid zones or cause old ones to grow. Widespread genetic introgression resulting from such contacts sometimes leads to the complete collapse of reproductive barriers and disappearance of the endemic morph (Rhymer and Simberloff 1996). For example, the genetic differentiation between formerly allopatric mallards and American black ducks has almost completely disappeared over the last century due to introgression (Mank et al. 2004), and less than five percent of New Zealand grey ducks lack evidence of introgression after the nineteenth-century introduction of small numbers of mallards (Gillespie 1985). In many cases, it is the sheer abundance of the more cosmopolitan species that endangers the gene pool of the endemic, but in others the evolutionary dynamics eliminate the selective advantages of the characters that originally separated the populations (Taylor et al. 2006). It seems clear that any traits of archaic humans that would have inhibited their mating with modern humans would have been negatively selected *just because the modern human population was expanding*. To the extent that morphological characters influence mating success, the demographic expansion of modern humans may have selected against archaic morphologies that had no strong ecological disadvantage. This scenario is in line with the suggestion that archaic humans were genetically "swamped" by expanding modern populations (Smith et al. 2005).

From an opposite perspective, the study of adaptive introgression in weed species suggests an interesting parallel with human evolution. In a number of instances, non-native plants have become invasive only after a delay of many generations (Ellstrand and Schierenbeck 2000). A lack of native predators is apparently not sufficient to create a weed; in some cases, adaptive alleles in native plants introgress into non-native species, allowing environment-specific adaptations that facilitate survival or dispersal. This introgression requires the delay: for introgressive alleles to be broken into relatively smaller linkage blocks in order to isolate their effects from other, possibly maladaptive, introgressive alleles (Martinsen et al. 2001), and for them to reach an appreciable frequency within the newly invasive population. Breaking of extended linkage disequilibrium is an important strategy for plant breeders also, allowing the introduction of adaptive characters from wild-type plants without the correlated introduction of maladaptive linked characters (Stewart et al. 2003).

We suggest that adaptive introgression of alleles from archaic humans may be one of the central mechanisms leading to the "human revolution." The behavioral characteristics of modern humans, including the employment of symbolic culture and sophisticated technologies, followed the attainment of modern human anatomical features by a considerable delay (Klein and Edgar 2002). The notion that a single small population of incipient modern humans had the perfect genetic combination for ultimate success seems quite improbable. Instead, the long coevolution of modern anatomy and behavior in contact with archaic humans, even as those archaic populations appeared to diminish, provided a rich source of adaptations for the expanding modern population. With current genomic techniques, we are beginning to find these archaic genes. We expect that they will prove central to the story of modern human origins.

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