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ARTICLES

Has the Combination of Genetic and Fossil Evidence Solved the Riddle of Modern Human Origins?

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Debate over the origin of modern humans continues without a clear end in sight. Currently, the genetic and fossil evidence is still used to support two different interpretations of the origin of modern humans. Some researchers claim that the genetic evidence is compatible with either an Out-of-Africa or a Multiregional model, while other scientists argue that the evidence supports only a Multiregional model of evolution. I argue that the fossil record and archeological evidence constrain interpretation of the genetic evidence and imply that very little, if any, admixture with Eurasian archaic hominins such as the Neanderthals occurred during the spread of modern humans out of Africa.

The rapid accumulation of new genetic data has not settled the issue of the origin of modern humans. However, the wealth of new data and theory has narrowed the range of models that researchers consider plausible. Any survey of the recent literature will reveal conflicting conclusions about the significance of the genetic evidence. These conclusions vary from statements that Multiregional Evolution must have been the means by which our species evolved[1,2] to claims that the debate has been effectively settled in favor of a single recent African origin.[3–5] Other recent reviews remain agnostic, pointing out the fact that either conclusion is possible, especially given differing assumptions about population size or selection.[6,7] How can there be such divergent conclusions? Given the available evidence, is one conclusion more likely than the other?

The goal of this paper is not to provide an exhaustive review and analysis of the genetic evidence. Several excellent recent reviews summarize and evaluate the various sources of data more comprehensively than space permits here.[3,6–9] Instead, this review critically examines several recent papers, paying special attention to one by Templeton[1] and a second by Eswaran,[10] and demonstrates how the combination of genetic evidence and genetic inferences derived from the fossil record can constrain which models are plausible. Templeton's and Eswaran's papers argue that the genetic data supports a Multiregional model of human evolution and provide important critiques of a strict Out-of-Africa model for the origin of modern humans.

The two major competing models for the origin of modern humans are generally described as the Out-of-Africa and Multiregional models. Confusingly, these models have meant, and continue to mean, different things to different researchers.[11,12] Some proponents of variants of the Out-of-Africa model accept that there may have been a small amount of gene flow from archaic Eurasian hominins into the modern gene pool,[11,13,14] while others argue that there was no gene flow.[15,16] Likewise, the Multiregional model encompasses a set of related hypotheses, all of which accept that the late Middle Pleistocene ancestors of modern humans lived in more than one continent. Among the many variants, Templeton's "Out of Africa Again and Again,"[1] Relethford's "Mostly Out of Africa,"[6] and Smith's "Assimilation model"[17] all accept that populations or alleles that spread from Africa played a dominant role in the origin of modern humans. Classic Multiregionalism[18] was less specific in this regard, emphasizing instead that different "modern" traits had arisen in different places and different times, and that selection and drift had acted to maintain distinct, regional patterns of variation in China, Indonesia, and Europe.

The Out-of-Africa and Multiregional models converged following Relethford and Harpending's[19,20] demonstration in 1994–1995 that the worldwide patterns of variation in cranial morphology and allele frequencies could be produced either by population splits, as often implied in interpretations of the Out-of-Africa model,[21] or by a Multiregional model in which Africa had an effective population size three times that of Europe, East Asia, or Java and Australia throughout the Pleistocene (Fig. 1).

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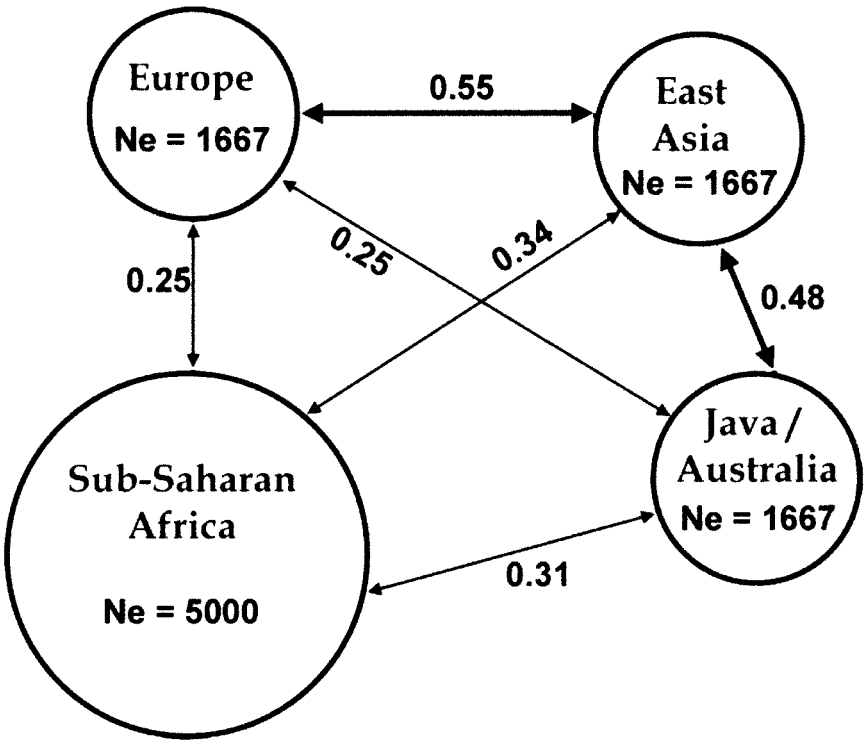

Figure 1. An example of a migration matrix between regions with unequal effective population sizes (N_e) (after Relethford and Harpending[20]). The numbers above the arrows indicate the number of migrants per generation.

Today, the distinction between the models is perhaps more artificial than real. Attention would better be focused on the issue of how much, if any, admixture with archaic humans occurred in each region of Eurasia (Fig. 2). Relethford[6] has proposed that despite the current convergence in opinion, two key questions remain: whether or not a speciation event accounts for the mode of origin of modern humans and how much Eurasian admixture occurred. The first question is tightly intertwined with species concepts and processes of speciation. Speciation can perhaps best be viewed as a process in which different species concepts or criteria apply.[22] It is highly uncertain whether a small amount of interbreeding would indicate that Neanderthals and early modern humans were part of the same species or merely closely related groups. Because the purpose of this review is not to discuss what constitutes speciation and what does not, I will primarily focus on Relethford's second question, the amount of admixture.

THE IMPORTANCE OF DEMOGRAPHIC HISTORY

Human demographic history over the last 200,000 years plays a dominant role in how one interprets the genetic evidence relating to the origin of modern humans.[6,7,23–28] Numerous genetic systems, including mtDNA, Y chromosomes, and most autosomal genes, indicate that *Homo sapiens* has an effective population size (N_e, the number of breeding individuals) of only approximately 10,000 individuals.[23,24] Any model of modern human origins must incorporate this constraint (see Box 1).

Ambrose[29] proposed that the eruption of Mount Toba in Indonesia ~70,000 BP caused a volcanic winter that may have lasted several years and possibly precipitated the onset of the glaciation of oxygen isotope stage 4. The resulting climatic changes may well have caused a bottleneck in all hominin populations, including Neanderthals, early modern humans, and Indonesian *H. erectus*. The Toba eruption very well may have caused a substantial reduction in human population size, but it is unlikely to correspond to the bottleneck that squeezed our effective population size to ~10,000 individuals. Chimpanzee mtDNAs and Y-chromosomes do not show evidence of a bottleneck at the same time,[30–32] despite the fact that they should also have experienced a bottleneck as a result of the eruption. Data from intermatch distributions of

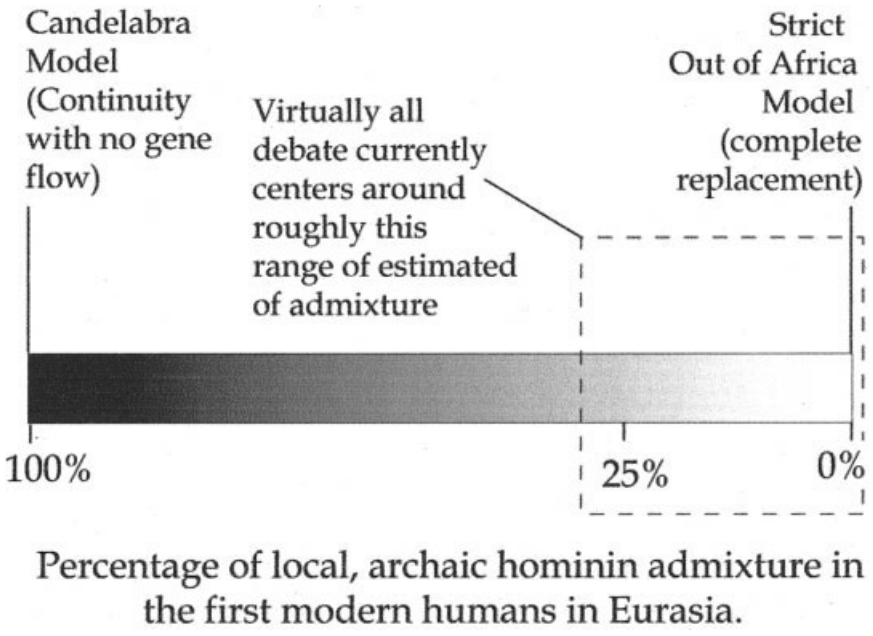

Figure 2. Hypotheses for modern human origins on a continuum from no admixture with migrants from Africa to complete replacement by African migrants.

mtDNA sequences suggest that the ancestors of some major modern populations were already separated by 70,000 BP.[23] Widely separated populations that experience a simultaneous bottleneck will each lose diversity through drift, but they will not all lose the *same* alleles. When conditions improve and contact is reestablished, the effective population size in such a case will tend to reflect the species' precatastrophe effective population size rather than the total number of individuals who existed in all groups combined during the bottleneck.[27,33]

Another recent development regarding demographic history comes from Eller's[34] proposal that our species' low effective population size could have been produced by a process in which numerous extinctions of small populations were followed by recolonizations with founder effects. Such a process could have allowed the census size (the actual number of living individuals) to remain much higher, at ~300,000 or more individuals throughout the Pleistocene. However, Eller's model makes several simplifying assumptions, including that no isolation by distance existed between populations and that gene flow and recolonization could occur between any groups, regardless of their geographical separation. A more realistic model would feature recolonization only from groups in neighboring areas, but such realism entails much more computational complexity and is difficult to model.

The simplifications in Eller's model homogenize the worldwide population and greatly accelerate the rate of drift. It remains to be seen what effect the combination of extinctions of small groups and isolation by distance or geographic subdivisions would have on simulated ancestral populations and their estimated effective population size and F_{st} values (see Box 1). However, the results would probably be in line with Takahata and colleagues'[33] expectation that several subdivided populations would have retained a high amount of the overall diversity of an ancestral population. Much of that diversity would have become geographically localized, so one would expect that F_{st} values between major geographical blocks of populations would be considerably higher than those observed today.

ARE MIGRATION MATRICES THE ANSWER?

Many recent reviews[6,7,19,20,35] leave the reader with the notion that it is possible, and perhaps even equally likely, that the current worldwide pattern of human genetic variation could have been produced by either an Out-of-Africa or Multiregional mode of evolution. Although Relethford and Harpending[19,20] found migration matrices between geographic regions that would be capable of replicating recent distance matrices based on genetic or craniometric data (Fig. 1), one important question about their migration matrices has largely escaped evaluation: How likely are the patterns of migration that are modeled? Inspection of Figure 1 shows that the rates of gene flow in their model do not correspond to geographic distances, as might be expected in a model of isolation by distance. For example, the rate of migration between sub-Saharan Africa and Europe, which are fairly close geographically, is equal to the rate of migration between Europe and Australia, which are maximally separated. Even more troublesome, the migration matrix bears little relationship to what the archeological record shows about the strength of cultural associations, and hence of exchanges of ideas and mates, or the physical expansions of populations, across the Old World.

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The last million years of the archeological record reveal repeated spreads of technological innovations, including Acheulean and prepared-core technology from Africa to western Eurasia (and perhaps vice versa), but very little association between these regions and China or Indonesia.[36] Likewise, there seems to have been relatively little contact between China and Indonesia, although the Paleolithic archeological record across southern Asia and has its own limitations, including many large chronological gaps.

Perhaps the most striking departure from the pattern of contacts required by the migration matrix comes from Australia, which remained culturally isolated from outside influences until ~3,500 BP, when new migrants may have introduced the dingo, some new tools, and perhaps new genes, including mtDNA haplotypes[37] (also H. Harpending, personal communication). The archeological evidence for external sources of the changes in Australian material culture is debatable; many archeologists now view the cultural innovations as local inventions rather than evidence of foreign influences.[39] Regardless of what actually happened in the mid-Holocene, after that time Australia appears to have experienced cultural and genetic isolation until the arrival of European colonists. This pattern of isolation in Australia contradicts the requirements of the migration matrix, as do the patterns of cultural associations that existed across the Old World before 100,000 BP. Likewise, the histograms of all possible pairwise differences between mtDNA haplotypes in widely separated human populations (intermatch distributions) and simulation studies of the effect of varying numbers of immigrants on these dis-

Box 1. Definitions of Some Genetic Terms

Additive effect—in polygenic traits, an additive effect is the influence that the different alleles at a single locus have on the expression of a trait (that is, the phenotype). Conceptually, additive effects are viewed as completely separate from the influence of the effects of alleles at other loci. In reality, however, alleles from different loci may interact with each other in complex ways that are difficult to model.

Allele—one of two or more alternative forms of the sequence of a stretch of DNA. Generally, alleles refer to alternate forms of genes that code for proteins, but the term can also refer more generally to different versions of a homologous DNA sequence.

Autosome—any of the chromosomes except the sex chromosomes (the X and Y chromosomes). In each individual, homologous austosomal chromosomes exchange DNA during meiosis through a process called crossing-over.

Coalescence—the process of tracing DNA sequence variations (that is, alleles) back to a common ancestor. In this process, the observed differences between sequences are considered to have arisen by the gradual accumulation of mutations.

Coalescent age—looking back in time, the coalescent age is the estimated time at which all the sequence variants (alleles) of a given stretch of DNA converge on (that is, just before they diverged from) a single common ancestor. Coalescent ages are estimated from the number of mutational differences that separate the two most divergent sequences and the estimated (or measured) rate at which mutations accumulate.

Effective population size (N_e)—the effective number of breeding individuals in a population from a population geneticist's standpoint. The actual number of individuals (the "census size") in the population can be much higher if most individuals have many ancestors in common. If a population that has a much larger census size than N_e remains stable in size for many generations, N_e will gradually increase as mutations accumulate.

F_{st}—a statistical measure of the portion of genetic variability in a species that corresponds to differences between groups (the major "races" of humans).

Haplotype block—a large stretch of base pairs of chromosomal DNA (5,000 to 200,000) that is almost always inherited as a block.[3,47] Crossing-over seems only rarely to reshuffle a haplotype block.

Haplotype group—a group of closely related, but not completely identical, DNA sequences that presumably arose from a recent common ancestor.

Linkage—a pattern in which alleles at two different loci tend to be inherited together. In autosomes, linkage generally occurs because two loci are physically close together on a chromosome.

Linkage disequilibrium—deviations in allele frequency from the expectation of no association that allow researchers to assess how closely linked two or more loci are. For example, if specific alleles at two different loci occur together 90% of the time, those two loci are closely linked.

Locus (plural: loci)—the physical location on a chromosome where a specific DNA sequence (a gene or a specific noncoding sequence) is located.

N_e—see **Effective population size.**

Polygenic trait—a trait that is influenced in its expression by differences in the alleles that individuals have at several or many different genetic loci.

Quantitative trait linkage analysis—any of a related series of statistical techniques that search for correlation between variants at many loci in the genome and the expression of physical traits, behaviors, or other aspects of phenotypes.[63]

Restriction site—a specific set of DNA base pairs within a sequence that will trigger a special enzyme (a restriction enzyme) to cut the DNA strand at that point. There are many different restriction enzymes, each of which acts when it encounters a specific sequence. Some individuals may have a slight variation (a mutation) in their DNA sequence at a restriction site. Without the "right" sequence, the restriction enzyme that usually works on that site will not cut their DNA. Such individuals will have a different restriction site haplotype than do individuals who have the "right" sequence.

Single nucleotide polymorphism—a difference of one base pair of DNA between two genetic sequences. At least 1.4 million single nucleotide polymorphisms have already been detected in the human chromosomes sequenced as part of the Human Genome Project.[69]

X-linked—a term that refers to a locus on the X-chromosome. In males, traits influenced by different alleles at those loci are inherited through the maternal line. In females, the situation is more complicated because each woman inherits an X chromosome from each parent.

tributions suggest that the number of migrants between populations must have been small (one or fewer migrants per ten generations) before ~50,000 BP to be compatible with the magnitudes of differences that accumulated.[23] These observations should make anthropologists wonder if the migration matrices make sense, given the archeological and other genetic data.

The migration matrices can also be defended. One defense is that the overall amount of migration they require is very small and that they can essentially work even with an identical rate of migration between all regions.[20] Second, it can be argued that over large distances, like those depicted in the matrix, genetic distances between populations will increase with geographic distance until genetic dissimilarity reaches a plateau. The major non-African populations may

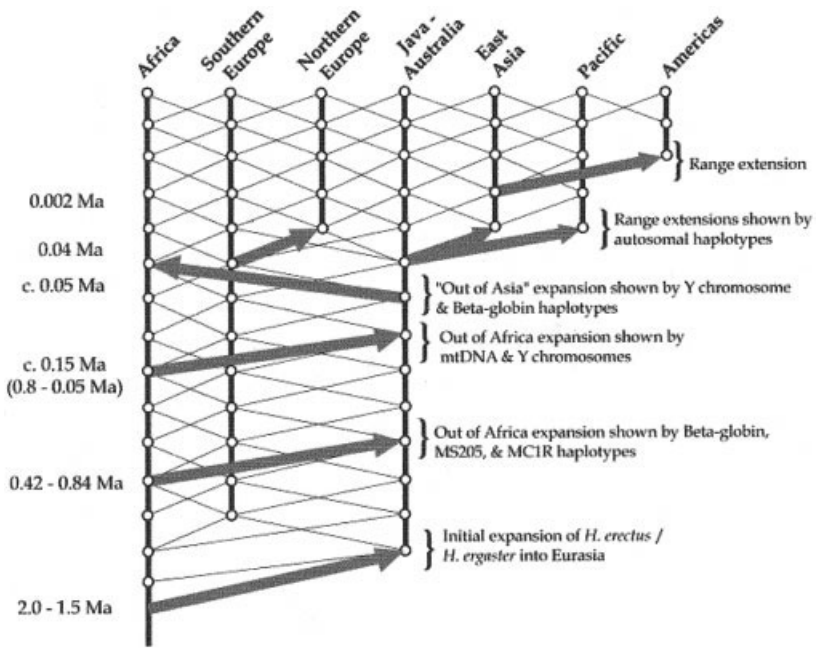

Figure 3. Templeton's model for repeated gene flow from Africa. The large arrows indicate major events reflected in the genetic loci he analyzed; the small arrows indicate a background of reticulating low-level gene flow between regions. After Templeton,[1] with modifications.

occupy that plateau, and thus the expectation that geographic distances should correlate with genetic distances would be invalid. The validity of the first defense can be questioned on the basis of all of the problems I have mentioned. The second defense is not wholly convincing either because observed genetic distances between populations depend on a host of factors, among them the respective populations' histories, including population sizes, migration rates, selective pressures, drift, and mutation rates. Given the amount of disagreement still possible, additional simulation studies like Eller's,[34] which are able to incorporate the effects of ancient gene flow, admixture, migration, and extinctions, would be a fruitful avenue of research.

Templeton's Study

Templeton[1] has presented one of the clearest challenges to the Out-of-Africa model, arguing that the distribution of coalescent ages of the alleles of ten human genetic systems, as well as a nested cladistic analysis of those alleles and their geographic positions, imply that the modern human gene pool is not the result of one Late Pleistocene migration from Africa, but of multiple expansions, many of which took place in the Middle or Lower Pleistocene. According to Templeton, these earlier expansions left a variety of ancient, divergent alleles in Asian and European populations that could not have been derived in the last 100,000 to 200,000 years from alleles present in a single African population that was ancestral to all living humans. Templeton[1] examined the geographical distributions and coalescent ages of seven autosomal sequences, mtDNA, the SRY and Yap sequences on Y chromosomes, and a noncoding region on X chromosomes. The age and patterns of variation in these genetic systems formed the basis of Templeton's conclusion that hominins spread out of Africa in multiple expansions that have been superimposed upon a reticulated pattern of gene flow between regions over the last 1.5 Ma (Fig. 3).

Templeton's analysis has some flaws that may result in an inaccurate picture of our species' history. The analysis failed to consider the implications of Fay and Wu's[40] simulation study, which showed that the observed patterns of regional variation in nuclear DNA allele frequencies (as gauged by a statistic called Tajima's D) could easily have been produced by the same bottleneck that produced much younger (~200,000 to 50,000 BP) coalescent ages for human mtDNA and Y chromosomes. Moreover, Templeton did not fully consider the demographic implications of a recent study by Takahata, Lee, and Satta,[33] although he did consult their paper as one source for estimating the coalescent ages of the various genetic systems that he used in his analysis. Takahata, Lee, and Satta[33] analyzed the diversity present in a worldwide sample of mtDNA, ten regions from the X chromosome, one region from the Y chromosome, and five autosomal regions. They found that the proportion of African ancestors to the pooled sample of Eurasian ancestors would have had to have been about 9:1 in order to produce the genetic homogeneity of humans today. Given that the effective population size of modern humans is about 10,000 breeding individuals,[6,7] this study implies that fewer than 1,000 of those individuals might have lived outside of Africa across the entire expanse of Eurasia. If the effective population size was close to the census size (Box 1), a population density that low would not have allowed a non-African population to survive and would effectively prove the Out-of-Africa model.[7] If the census size was much larger than the effective population size, as it is today, then Takahata, Lee, and Satta's results would imply that the population of Eurasia was much more inbred and homogeneous than it is today, a conclusion the fossil record does not support.

Evidence also exists for a dramatic expansion in population size in the late Pleistocene, but the signature for expansion is found only in some genetic systems and is notably absent from many autosomal sequences.[7,35] Initial evidence of this Pleistocene "population explosion" came from mtDNA rather than autosomal genes.[23,25] Recently Alonso and Armour[41] reported that a highly variable segment of chromosome 16p did show evidence of a population expansion. Marth and cowork-

ers,[42] in a study of ~500,000 single nucleotide polymorphisms from DNA sequenced for the Human Genome Project, found that the nuclear DNA of Europeans shows evidence of a severe population bottleneck in the Late Pleistocene, followed by a population expansion in the Holocene. Genetic drift appears to have played a major role in altering allele frequencies during and after the bottleneck.[42] This finding supports the idea that the frequencies of many alleles in Europe and, perhaps, all other regions outside of Africa, may have been substantially altered by drift after the origin and initial spread of modern humans but before those populations expanded in numbers.[23]

Problems also arise from the assumption that the geography and migrations in Templeton's analysis[1] reflect reality. Genetic analyses show that the population of Africa is strongly subdivided.[43,44] It is possible that gene flow between ancient subdivided populations in Africa, followed by migration out of Africa by members of one of those populations, could have produced the pattern that Templeton[1] assumed to be a worldwide phenomenon with great temporal depth[45] (H. Harpending, personal communication). A recent simulation study by Knowles and Maddison[46] showed that Templeton's method of nested cladistic analysis can fail to make correct phylo-geographic reconstructions when the geographic origins of new mutations are actually known.

A major population bottleneck in the Late Pleistocene also presents difficulties for the Out-of-Africa, or Replacement, model. Harpending and Rogers[7] have shown that a long bottleneck between 100,000 and 40,000 BP, or especially several such bottlenecks acting concurrently on geographically separated populations of ancestral modern humans that had already become geographically dispersed, would be expected to produce more geographical differences in allele frequencies than are observed in modern humans. The disparity between this expectation and the observed patterns appears to be especially marked in Eurasian populations. If population replacement of archaic Eurasians actually occurred and the African-derived moderns expanded greatly in numbers tens of thousands of years after their exodus from Africa,[23] then proponents of the Out-of-Africa model must resort to some special pleading to explain why the frequencies of most of the autosomal haplotype blocks (Box 1) are so similar in non-African populations.[47] One intriguing suggestion is that these blocks have been subjected to long-term balancing selection,[7] but that possibility has not yet been rigorously tested.

The arguments of other geneticists who think that ancient diversity outside of Africa strongly supports Multiregional evolution resemble Templeton's[1] arguments and are subject to the same criticisms. For example, Yu and colleagues[48] analyzed the sequence variation in a 10,000 base pair region of chromosome 1 in 20 Africans, 20 Asians, and 21 Europeans. The results showed a coalescent age for the sequences to be more than one million years. Moreover, the Asians and Europeans had many unique sequence variants that did not exist among the Africans or people from other regions. Yu and coworkers,[48] found unique sequences in 50% of the African, 27.5% of the Asian, and 19% of the European sequences. They interpreted these findings as evidence of ancient near-isolation of the major population groups and a substantial contribution from local archaic hominin populations to the modern gene pool in each region. If accurate, this interpretation would strongly support the Multiregional model and indicate that the proportion of local archaic ancestry in each population of early modern humans was highly substantial. However, there are difficulties with this interpretation that warrant caution.

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Other analyses of worldwide genetic patterns that have been based on larger samples, such as Tishkoff and colleagues'[49] study, have shown that African populations often have many more sequence variants than do other populations, and that Eurasian populations tend to have small subsets of the African genetic sequences but in drastically altered frequencies.[50–56] It is possible that Yu and colleagues'[48] analysis did not consider a sufficient number of sequences from African populations to find the same pattern that Tishkoff and coworkers[49] did. Given the high percentages of unique sequences that Yu and coworkers found, it is likely that a much larger sample of Africans would be needed to be certain that some of the uniquely "Asian" or "European" sequences do not also occur at low frequencies among Africans.

The pattern in Chromosome 1 could also be a byproduct of drift in the three populations. Drift could have eliminated some of the variants from the African gene pool that Yu and coworkers[48] found to be unique to Asians or Europeans but, given the ample evidence of a greater effective population size for Africans than Eurasians, one would expect that rare alleles would have been lost from the African gene pool much less frequently than was the case for Eurasians. If it turns out that many segments of our nuclear DNA show the same geographical pattern that Yu and colleagues described, it would greatly decrease the likelihood that

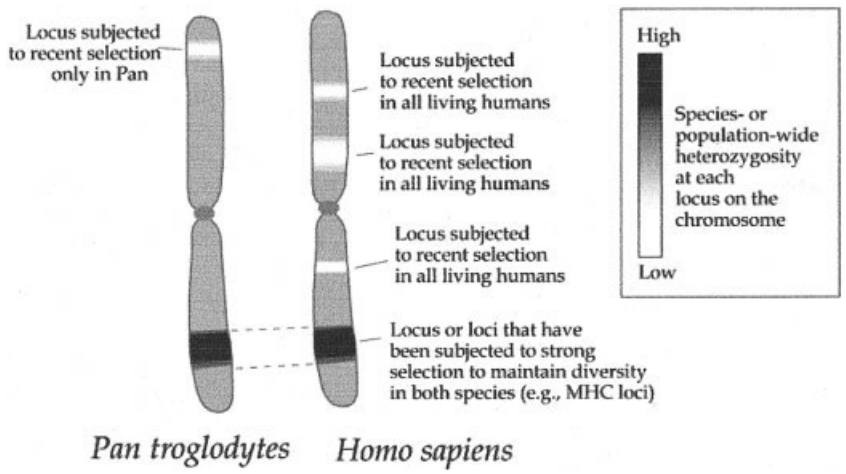

Figure 4. Hypothetical homologous autosomal chromosomes in chimpanzees and humans. Increasing gradients of dark shading indicate higher levels of heterozygosity (genetic diversity) at each locus in the species. Light bands and their lightly shaded colored surrounding zones indicate loci and linked regions that have undergone recent selection or drift that has reduced diversity.

the random effects of drift could be responsible and would increase the chance that their interpretation is correct. Efforts are currently under way to determine if populations from different regions have been subjected to selection on different parts of their genomes. These efforts have already led to the identification of DNA regions that appear to have been subjected to different selection in Europe and Africa.[57] If such patterns turn out to be common and are able to differentiate between Eurasian populations, and if some of the alleles have truly ancient coalescent ages in regions outside of Africa, it would provide better evidence for the Multiregional model than has hitherto been available.

Eswaran's Diffusion-Wave Model

Eswaran[10] has introduced an interesting model of how modern people's genes may have replaced archaic humans' genes and yet allowed admixture during contact between the two groups. The model provides the first rigorous demonstration of how genes and morphological traits of archaic Eurasian hominins could have existed in a fairly high frequency in the earliest modern humans outside of Africa and yet be virtually absent in living populations. Eswaran has proposed that alleles at several genetic loci, illustrated by simulations of four to eight independently assorting genes, may have been responsible for a single trait that conveyed a selective advantage on individuals who possessed all of the favorable alleles. The model predicts that the favorable alleles will gradually increase in frequency, as will all the alleles that lie close to them on the chromosomes, eventually "modernizing" the entire nuclear genome over many generations. Figure 4 presents illustrates the amount of diversity that would be present in different loci in a hypothetical chromosome as a result of this process.

In an initial critique of the Diffusion-Wave model, Anne Stone and I[58] argued that the model faces a major problem in accounting for the way that loci unlinked with those responsible for producing the modern phenotype could also have been "modernized." However, Eswaran[59] (also V. Eswaran, personal communication), A. R. Rogers (personal communication), and H. Harpending (personal communication) have pointed out that the Diffusion-Wave model actually deals elegantly with loci unlinked to those responsible for the "modern" phenotype.

The Diffusion-Wave model proposes that there may have been a variable amount of admixture, including a considerable amount between the first "modern" migrants from Africa and local archaic populations in Eurasia. However, only offspring that inherited the full set of "modern" alleles would have had a ~10% reproductive advantage; archaic and partially archaic individuals having only some of the "modern" alleles would have gained no reproductive advantage. Over the course of several generations, purely "modern" families would consistently have outreproduced "archaic" or "hybrid" families and eventually come to dominate the population. However, after several generations, individuals would be born who had not only the full set of alleles to produce the advantageous, "modern" phenotype, but also a substantial number of archaic-derived alleles not involved in producing the "modern" phenotype. These individuals would then have had the reproductive advantage offered by being "modern" and would also have contributed their archaic-derived genes to the "modern" gene pool. In the simulations, the initial ability of completely "modern" people to out-reproduce "archaic" people effectively swamps the gene pool and leads to the "modernization" of the entire Eurasian gene pool.

A few variables in the Diffusion-Wave model have major implications with respect to how one views the fossil evidence for admixture outside of Africa, as well as what (and how much) evidence of admixture one might expect to find in the human genome. These variables include the amount of admixture per generation (the proportion of phenotypically "modern" people in each generation who had children with phenotypically "archaic" people) and the magnitude of the selective disadvantage of being phenotypically "archaic." If the selective disadvantage of being phenotypically archaic was very high, there would be rapid "modernization" of a population. In addition, one would expect that any archaic alleles that were incorporated into the "modern" Eurasian gene pool early in the process (that is, just outside of Africa) would most likely be those archaic-derived alleles present in the highest frequencies among non-Africans (A. R. Rogers, personal communication). Archaic-derived alleles that entered the gene pool at the endpoints of the Diffusion

Wave (that is, in places like Europe or Australia) would be expected to be present only in very low frequencies. On the other hand, if the selective disadvantage was low for phenotypically "archaic" individuals, then more archaic-derived alleles unlinked with the "modern phenotype" alleles would be incorporated into the modernizing gene pool of Eurasia. If the admixture rates were very high and the selective disadvantage of the "archaic" phenotype was also low, then a great number of archaic alleles would be incorporated into the modern gene pool of Eurasians.

Versions of the Diffusion-Wave model that incorporate a high amount of admixture and low selective pressure against "archaic" phenotypes do not easily fit the available genetic and fossil evidence. Four major difficulties diminish the ability of "high-admixture" versions of the model to explain the origin of modern humans. First, many world-wide surveys of genetic variation at specific loci or multiple polymorphic sites in the genome have found few distinctions among Eurasian populations. Instead, these studies generally have reported an African versus non-African split. Evidence is scarce for the presence of ancient alleles that exist in high frequencies in specific regions and that could have been inherited from local, archaic ancestors. Second, some of the genetic systems that are used as support for evidence of archaic admixture in the modern gene pool are not neutral, and either conserve diversity or may have selected for new alleles. Assuming neutrality for non-neutral loci can skew judgments of what processes produced the diversity at those loci. Third, although some mtDNA haplotypes may have been favored more than others in specific climates,[62] mtDNA and Y-chromosomes probably were not causally related to the origin of modern morphology and argue against any version of the Diffusion-Wave model that features both a large amount of admixture between "near-modern" and archaic humans and only moderate selection against "archaic" phenotypes. Fourth, at least in Europe, data from the fossil record constrain interpretation of the amount of admixture that occurred. The inferences from the fossil record about the level of Neanderthal admixture are incompatible with the notions of low levels of admixture or strong selection against Neanderthal traits.

World-wide patterns of genetic variation

Morphological traits studied through quantitative trait linkage analysis show that most of the genetically based variability in the phenotypes can be explained by about one to ten loci,[63] although it is quite possible that many more loci may have small additive effects or interact in other complex ways. Many of the strategies used in genome-wide screens for quantitative trait linkage analyses do not yet search for interaction effects between loci, largely because of the number of genomes that would have to be typed and studied in the absence of *a priori* hypotheses about what loci should be involved in such interactions. Nevertheless, it is likely that a single morphological difference between archaic and modern humans in rate of facial growth[64] or pelvic shape[65,66] would involve a limited number of loci, perhaps on the order of five to ten or fewer. The human chromosome complement includes twenty-three pairs of chromosomes. If, for example, five to ten new alleles on different chromosomes were required to create a single morphological change, such as a subtle alteration of the rate of facial growth that produces modern morphology, then thirteen to eighteen chromosomes would *not* be subjected to selection for the favorable genes. At least twenty-two loci, each on a separate autosome, would have to underlie a trait in order for linkage disequilibrium to affect the entire human autosomal genome. It seems highly unlikely that any of the comparatively minor morphological changes that accompanied the origin of modern humans would have required changes at so many genetic loci.

Versions of the Diffusion-Wave model that incorporate a high amount of admixture and low selective pressure against "archaic" phenotypes do not easily fit the available genetic and fossil evidence.

If the selective pressure favoring the "anatomically modern" alleles was weak rather than very high, the unaffected chromosomes could persist and show different clinal patterns of genetic variation in populations distributed across the world, as illustrated by the hypothetical levels of diversity present in the chromosomes depicted in Figure 5. Studies of world-wide distributions of nuclear DNA short tandem repeats,[49] single-nucleotide polymorphisms, *Alu* insertion polymorphisms,[9,67] and chromosomal haplotype blocks[47,68] have found very few regionally specific patterns of variation in genetic systems in populations outside of Africa. Given that at least 1.4 million single-nucleotide polymorphisms have been identified thus far in the human genome[69] but not yet characterized in sufficient numbers of individuals or populations to examine worldwide patterns of variation at a fine scale, it is possible that ancient, region-specific patterns of variation exist within the human genome. If such patterns exist, there is ample reason to be optimistic that they will be found soon.

Selection on "neutral" loci

As support for the Diffusion-Wave model, Eswaran[10] discussed a variety of genetic evidence, much of which conforms to the expectation of a rolling bottleneck that could have accompanied a diffusion wave of anatomically modern humans migrating from Africa. Some genetic loci show more variability outside of Africa than is expected under the model. These were explained as possible evidence of the inheritance of extra genetic variation from local Eurasian archaic popula-

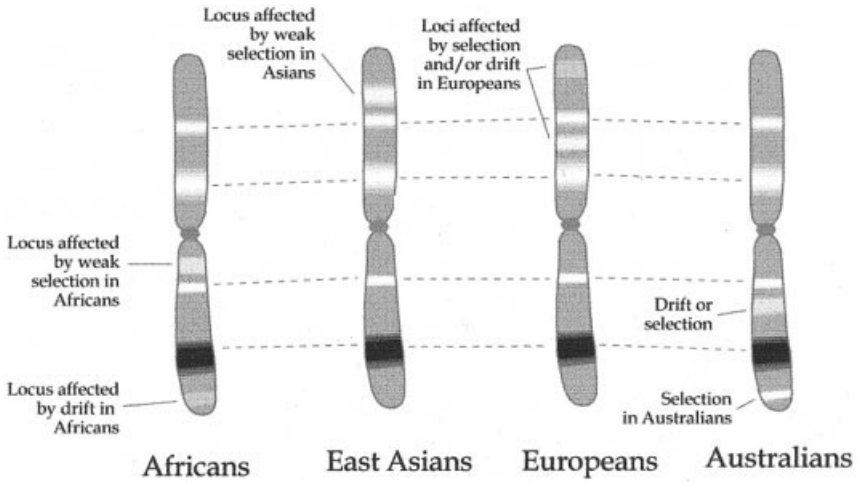

Figure 5. Hypothetical homologous chromosomes in regional populations of humans showing between-region differences in the amount of heterozygosity that could be expected at various loci under a Multiregional model of evolution. In addition, admixture with local archaic humans in each region would be expected to introduce ancient alleles into each regional population. The "archaic" alleles would be expected to be much more rare in other regions.

tions.[1,10] These loci include the major histocompatibility complex loci, MC1R, and beta-globin. In the region selection has acted to maintain alleles that otherwise might have been lost to drift.[70] The MC1R and beta-globin loci also show signs of selection[71,72] that likely maintained ancient alleles longer than would be expected under a model of neutrality. In the case of MC1R alleles, selection appears to have favored the increase in frequency of alleles that had a beneficial effect in certain environments.[73,74]

If these loci have been affected by selection, especially by selection that differed between geographical regions, then applying the expectations of neutrality to their distribution and frequencies could produce misleading conclusions about population history. Additional sequences of functional and nonfunctional autosomal loci and comparison of the patterns of variation present in them from a geographical perspective should help move the field toward a final resolution of this problem.

Data from mtDNA and sex chromosomes

MtDNA and Y chromosomes show similar patterns of low diversity in humans, especially in comparison to their patterns in African apes.[30–32,75] Most chimpanzee subspecies have more genetic variation in their mtDNA and Y chromosome gene pools than does the entire human species,[30,32] despite the fact that each chimpanzee subspecies occupies an area that is much smaller than our species' range. Outside of Africa, human genetic diversity in mtDNA and Y-chromosomes is even further reduced, especially if one looks at ancient haplotype groups. Neither mtDNA nor Y chromosomes carry genes that are clearly associated with the production of morphology during growth and development, although Y chromosomes are essential for the establishment of a male pattern of growth and the development of male genitalia *in utero,* and thus have an initial and perhaps substantial effect on growth and development.[76,77] Human X-chromosomes follow the mitochondrial pattern of variation,[78] despite the fact that the two genetic systems are unlinked. Population replacement remains the simplest way to explain the patterns of variation present in human mtDNA, X chromosomes, and Y chromosomes.

MtDNA and Y chromosomes have effective population sizes that are only one-quarter the size of those calculated from autosomal genes. Thus, frequencies of their haplotypes can drift much faster. Multiregionalists have used this point to advance the reasonable possibility that the modern human mtDNA pattern arose by chance or as a result of drift in small populations during the Upper Paleolithic.[2,79] Nordborg[80] calculated that, given an effective population size of 3,400 females in the Paleolithic of Europe, there would be a 10% chance that up to a 25% admixture with Neanderthals could have left no trace in the mtDNA of living Europeans. Nordborg's analysis assumes that there was no selection against Neanderthal mtDNA. If such selection did exist, it would further reduce the chance that Neanderthal mtDNA survived to the present.

To extend Nordborg's[80] simulation to mtDNA and Y chromosomes in Europe, East Asia, and Indonesia-Australia, one would need to calculate the probability that archaic-derived mtDNAs and Y-chromosomes were lost in all of the regions. If one assumes that the population size was equal in each region, that there was no gene flow between regions, and that there was no selection against the archaic mtDNAs or Y-chromosomes, then there should be approximately a 10% chance for *each* genetic system in *each* region that all archaic alleles would have been lost if the initial proportions of archaic admixture (25%) were equivalent. The overall chance that no archaic mtDNA or Y-chromosomes would have survived in three separate regions would fall to approximately ($1/10^6$), or one in one million. If the population size was higher in one or more regions, the probability of losing all archaic haplotypes would decline even more. Gene flow between regions would also decrease the probability of losing all archaic haplotypes. Similar conclusions come from the analysis performed by Manderscheid and Rogers,[81] who used simulation studies to investigate the effect of drift on the mtDNA gene pool over the last 40,000 years. Their results also suggest that only a very small proportion of archaic admixture (roughly 10% and probably much less) could have occurred in order to escape detection today (see Box 2).

Genetic inferences from the fossil record

The fossil record is often upheld as providing the best evidence of Multiregional Evolution and the clearest indications of interbreeding between archaic Eurasian hominins and early modern humans.[2,79,82–87] However, other paleoanthropologists find the evidence of Neanderthal admixture in the earliest modern Eurasians to be ambiguous at best.[16,88–92] Europe is the area of the world that has the densest and most complete fossil record of humans around the time of the transition to modern morphology. Frayer[82,83,85] studied the frequency of Neanderthal-like traits in Early Upper Paleolithic and later Europeans, including the presence of a suprainiac fossa on the occipital bone, a horizontal-oval mandibular foramen, and a dorsal sulcus on the axillary border of the scapula. Frayer[82,83] found fairly high frequencies of "Neanderthal" traits in Early Upper Paleolithic (Aurignacian and Gravettian) Europeans (Box 3). The frequencies of "Neanderthal" traits diminished in the Late Upper Paleolithic and declined further in the Mesolithic. Recent Europeans have frequencies of only 1% to 2% for each Neanderthal trait. Wolpoff[79] inferred that this pattern could have been produced by approximately 25% Neanderthal admixture in the Early Upper Paleolithic population, followed by selection or drift that slowly reduced the frequencies of Neanderthal genes. The gradual diminution of Neanderthal traits and, presumably, alleles, seems to fit the Diffusion-Wave model quite well. It also fits other models featuring continuing admixture from non-Neanderthal populations.

If the decline in "Neanderthal" traits over the last 30,000 years was due to selection, the selective pressure would have been fairly low. Low selective pressure would have allowed many people carrying Neanderthal alleles to survive and ensured that any parts of Neanderthal chromosomes not under selection would become widely and randomly dispersed in the population. These circumstances should *improve* the chance of detecting archaic admixture today.

Frayer's[82,83] data on frequencies of Neanderthal traits produces somewhat contradictory pictures of the frequency of Neanderthal alleles in later Europeans. As detailed in Box 3, if one assumes that a single dominant allele is responsible for each "Neanderthal" trait, then the frequencies of Neanderthal admixture in the Early Upper Paleolithic population can be estimated to be between 31.0% and 21.5% based on Frayer's data. Alternatively, if single recessive alleles are responsible for the "Neanderthal" traits, then the frequency of Neanderthal admixture in the Early Upper Paleolithic population can be estimated to have been between 63.4% and 50.8%. If one assumes that each "Neanderthal" trait requires eight recessive genes to be expressed, as in Eswaran's model for "modern" traits, the proportion of Neanderthal admixture in Early Upper Paleolithic and recent Europeans would be much higher, up to 79.7% in recent people.

Most chimpanzee subspecies have more genetic variation in their mtDNA and Y chromosome gene pools than does the entire human species, despite the fact that each chimpanzee subspecies occupies an area that is much smaller than our species' range. Outside of Africa, human genetic diversity in mtDNA and Y-chromosomes is even further reduced, especially if one looks at ancient haplotype groups.

We do not actually know the genetic basis of any of the "Neanderthal" traits, so all of these estimates are only heuristic tools. Estimates of Neanderthal admixture derived from a recessive eight-locus model are probably unrealistically high, while those derived from the single-locus dominant model are probably too low. They only serve as approximate upper and lower boundaries for the amount of Neanderthal admixture that can be inferred from the fossil record. Nevertheless, from a Multiregional perspective, at least some, and possibly a substantial amount, of Neanderthal DNA was inherited by living Europeans. Thus far, however, genetic analyses have failed to produce evidence of the expected genetic distinctiveness of Europeans that one might expect to arise from a detectable amount of Neanderthal heritage.

Another possibility is that interbreeding indeed occurred, but selection and drift subsequently erased all traces of it.[6,87] However, as Box 3 demonstrates, the fossil record may suggest that the proportion of Neanderthal alleles still present in Europeans remains high. The hypothesis that virtually all traces of Neanderthal alleles have been selected out of the European gene pool is also contradicted by numerous claims that a prominent nose links living Europeans with Neanderthals. Furthermore, if one accepts that it is easier to inherit "cold-adapted" body proportions from Neanderthals than it is to evolve them again, as implied by the Lagar Velho child,[87] then one might logically conclude that there has been a resurgence of Neanderthal alleles for body proportions in modern Europeans, given the fact that the physiques of modern Europeans more closely resemble those of Neanderthals than did the physiques of their Early Upper Paleolithic predecessors.[93–95] Genetic data currently provide no substantiation for this hypothesis.

In the future, evidence of Neanderthal admixture may still be found. Pääbo[3] notes that admixture with Neanderthals may have left no clear trace in the nuclear genome because the coalescence ages of extant haplo-

Box 2. Admixture and Ancient mtDNA

The extraction and analysis of the first Neanderthal mtDNA sequence[106] created hope that studies of ancient mtDNA, the easiest kind of ancient DNA to study, might be able to settle the question of whether or not any admixture had occurred with Neanderthals. However, inferences about evolution based on single loci (like the mtDNA molecule) can be unreliable. Even a 25% Neanderthal admixture would have about a 10% chance today of leaving no trace in the mtDNA gene pool.[80] Recent analyses of two mtDNA sequences from Italian Upper Paleolithic fossils[107] and five additional early moderns from France and the Czech Republic[108] have been heralded as proof that there was no Neanderthal admixture. None of mtDNAs from the early modern fossils resembles the known Neanderthal sequences. However, diagenesis of ancient DNAs may cause them to appear more distinctive than they originally were.[109] In addition, simulation studies demonstrate that single loci such as mtDNA have a difficult time excluding the possibility of admixture in the extant population.[80,110] How much will additional ancient sequences improve the power to detect admixture?

The number of modern-like mtDNA sequences that would have to be recovered from European fossils of early modern humans in order to rule out varying proportions of Neanderthal ancestry at $p < 0.05$ and $p < 0.01$ can be calculated as $(k)^n < p$, in which k is the proportion of modern-like mtDNAs in the ancient gene pool, n is the sample size of ancient mtDNAs needed, and p is the desired level of probability. Rearranging the terms, one can calculate the number (n) of ancient samples that produce modern-like mtDNAs that would be needed (Table 1) to rule out given levels of Neanderthal admixture. Of course, the recovery of even one Neanderthal-like mtDNA sequence from an anatomically modern fossil would effectively demonstrate that admixture did occur.

TABLE 1. Sample of Ancient MtDNAs from European Early Modern Humans Needed to Exclude Various Levels of Neanderthal Admixture in the Ancient Gene Pool

Original Neanderthal Admixture	Number[a] Needed to Exclude the Admixture at $p < 0.5$	Number[a] Needed to Exclude the Admixture at $p < 0.1$
75%	3	4
50%	5	7
45%	7	11
25%	11	17
10%	29	44
5%	59	90
1%	299	459

[a]The number of ancient mtDNA sequences that would have to be recovered and be similar to those of modern humans (and not similar to Neanderthal mtDNA),[108] rounded up to the nearest whole number.

The results are not encouraging for those who think that the recovery of modern-like mtDNAs from all seven early modern European fossils effectively rules out Neanderthal admixture. The available data only suffice to rule out a 45% Neanderthal admixture at a $p < 0.05$ level of probability. The results differ from analyses presented by Serre and colleagues,[108] who calculated the probability, assuming a constant population size and selective neutrality for all mtDNA haplotypes, that all Neanderthal mtDNAs might be lost via genetic drift by the present. The results in Table 1 do not attempt to incorporate the additional uncertainty created by genetic drift from the Upper Paleolithic to the present and pertain only to the amount of admixture present in the ancient gene pool. Nevertheless, the results in Table 1 are useful even if Neanderthal mtDNAs suffered a selective disadvantage that would have swept them from the gene pool long ago. Although these results may raise doubts that the issue of admixture will ever be resolved, Nordborg[110] has shown that the consideration of addition loci dramatically increases the ability of a study to detect admixture, even if one is able to study only living populations.

type blocks in modern humans exceed the age of the split between Neanderthals and modern humans as gauged from ancient mtDNA. According to this view, Neanderthals and the ancestors of modern humans probably shared their haplotype blocks. However, as Pääbo[3] notes, the geographic center of modern human genetic variation is clearly Africa. Of the 28% of haplotype blocks that are specific to one continent, 90% are found solely among Africans. Given that the effective population size of Neanderthals, as judged from mtDNA,[96] appears to be comparable to that of all extant modern humans, it can be expected that the level of variation in autosomal blocks in Neanderthals would have been comparable to that among living Africans. A small portion of Neanderthal genes in the modern European gene pool could be expected to produce a distinctive pattern: There should be high frequencies of the haplotype blocks inherited from Eurasian modern humans and a low frequency of Europe-specific haplotype blocks inherited from Neanderthals. Again, this is not the pattern that is observed.[47]

On the genetic basis of morphological traits

One possible explanation for the differences some researchers have observed between the morphological and genetic evidence for Neanderthal admixture is that morphologists may have made inaccurate assumptions about the genetic basis of the traits they study. With reference to the pa-

Box 3. From Fossils to Genes

The presence of distinctive traits in fossil humans are generally used to reconstruct phylogeny. If sample sizes are large enough, they can also be used to make inferences about genetic differences between populations. Tables 1 and 2 below present some of Frayer's[82] data on the frequency of "Neanderthal" traits in Early Upper Paleolithic and recent Europeans. Among non-European hominins, the "Neanderthal" traits are very rare or absent.[82,83,85]

Although not all paleoanthropologists agree with Frayer's[82,83,85] assessments of the presence of "Neanderthal" traits in later Europeans, Frayer's data can be used as a point of departure for making heuristic estimates of the degree of Neanderthal admixture implied by the frequency of "Neanderthal" traits in later Europeans. Table 3 presents a series of such estimates of admixture. Each "Neanderthal" trait is modeled as being based on the possession of a single dominant allele at one genetic locus; on the possession of two copies of a recessive allele at one genetic locus; and on the possession of two recessive alleles at each of eight loci (as in simulations of "modern" traits by Eswaran[10]). All of these models assume that the earliest modern humans migrating from Africa had a frequency of zero for each "Neanderthal" trait.

To solve for the amount of admixture, the first two cases can be modeled by a Hardy-Weinberg equilibrium in which the dominant and recessive allele occur with a frequencies of p and q, respectively, and the frequency of genotypes in the population are given by $(p + q)^2 = 1$. After solving for p and q for each trait in each group, the frequency of admixture can be calculated by dividing each group's value for q by the Neanderthals' value for q.

In the third case, the simplifying assumption was made that the frequency of the recessive allele will be the same at all eight loci. The frequency of the Neanderthal alleles in the population can then be calculated as $z^{1/16}$, in which z is the frequency of the Neanderthal quantitative trait in the each population. As before, the proportion of admixture will equal each population's value for z divided by the Neanderthals' value for z.

TABLE 1. FREQUENCIES OF THREE NEANDERTHAL TRAITS IN LATER EUROPEANS[a]

Trait	Neanderthals	Early Upper Paleolithic	Recent
Horizontal-oval foramen	52.6%	18.4%	1.4%
Suprainiac fossa	95.7%	38.5%	2.0%
Dorsal sulcus	64.7%	16.7%	0.4%

[a]From Frayer.[82]

TABLE 2. PERCENTAGE OF NEANDERTHAL ADMIXTURE IMPLIED BY FRAYER'S[82] DATA

	Dominant Trait		Recessive Trait		Eight-locus Recessive Trait	
	Early Upper Paleolithic	Recent	Early Upper Paleolithic	Recent	Early Upper Paleolithic	Recent
Horizontal-oval foramen	31.0%	2.3%	59.1%	16.3%	93.6%	79.7%
Suprainiac fossa	27.2%	1.3%	63.4%	14.5%	94.5%	78.5%
Dorsal sulcus	21.5%	0.5%	50.8%	7.9%	91.9%	72.8%

leoanthropologists involved in the debate, Clark[97] has argued that proponents of the Multiregional and Out-of-Africa models adhere to different research paradigms and essentially end up "talking past" each other. The difference in viewpoints is probably better described as subparadigmatic.[98] Both sides rely on a single, overarching, and generally untested assumption: that the morphological traits they analyze provide a reliable indication of ancestry. This crucial assumption may, in fact, be inaccurate for many of the traits used to trace the origin of modern humans.[99] However, the assumption *is* testable. Nevertheless, with some important exceptions,[99–104] testing hypotheses of homology has not been a major feature of the research on modern human origins. What are the genetic bases of the suprainiac fossa, midfacial prognathism, taurodontism, shovel-shaped incisors, facial flatness, an Inca bone, a long, flat frontal bone, or any of the other features that have been used to support the Multiregional model or, for that matter, the Out-of-Africa model? Our current inability to answer these questions must be changed if we are ever to have a better understanding of how to interpret the morphology of hominin fossils in general or the origin of modern humans in particular.[8] Quantitative trait linkage analysis offers a powerful tool for performing just these kinds of studies—determining the genetic correlates of physical traits[63]—although genetic linkage studies must confront practical and conceptual challenges of their own.[105]

CONCLUSIONS

An important result of the many advances that have been made from the

study of human genetics is that "high-continuity" versions of Multiregional Evolution (about 30% to 10% admixture) do not fit the available data. In order to make such models fit the existing genetic evidence, Multiregionalists would have to invoke a series of requirements. First, the effective population size of ~10,000 individuals for our species would have to have arisen from a bottleneck or series of bottlenecks long before the origin of modern humans, so that the census size was much higher throughout the time in question.[6,34] Second, there must have been specific amounts of gene flow between regions throughout the Pleistocene, even though the archeological evidence of such contacts, especially those linking Africa with Java or Australia, is sparse or even nonexistent. Third, African populations must have made up the bulk of our species' effective population size throughout the Pleistocene. This third requirement may already be contradicted by ancient DNA; Neanderthal mtDNA sequences, although still undesirably few in number, show that the diversity, and thus the effective population size of those hominins, was approximately equal to that of all living modern humans.[96] Fourth, in order to accommodate admixture between Neanderthals and early modern humans in Europe, selection or drift must, by now, have effectively removed virtually all traces of that admixture. However, drift would also be expected to increase the frequency of at least some Neanderthal alleles. The persistence of "Neanderthal" traits for 23,000 years in Europe argues that any selective pressures to remove them were very small. The expectation that selection or drift removed traces of Neanderthal genes is also contradicted by the fact that Neolithic colonists from the Near East, the only major source of new genes to have an impact on Europe after the Mesolithic, could also be expected to have some Neanderthal admixture.

For now, it still appears that the best interpretation of the fossil and genetic evidence is that archaic Eurasian hominins contributed few alleles (<10%), if any, to the modern gene pool. If Neanderthals and other archaic Eurasian hominins were the same species as modern humans, we are faced with a great challenge in explaining why their genetic contribution was so small. Future discoveries in genetic patterns or the genetic basis of "modern" traits should help to narrow down even further the possibilities with respect to exactly what happened with the origin of modern humans. There is reason for optimism that these discoveries will be made soon.

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