Human evolution: **Origins of modern humans still look recent**

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That modern humans have a relatively ancient origin has been suggested on the basis of fossil and genetic evidence. But DNA sequences from an extinct neanderthal, and phylogenetic analyses of hundreds of human and ape sequences, continue to support a recent origin for modern humans.

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Perhaps the greatest controversy in studies of human evolution concerns the origins of modern humans and our relationship with the first fossils discovered that bear on this question — the neanderthals. Two main hypotheses have been put forth. The 'multiregional model' proposes that modern humans arose independently in different regions of the world, with sufficient gene flow between the regions to maintain the unity of the species, and share a most recent common ancestor who lived over one million years ago. The 'recent replacement model', in contrast, proposes that a single population, most likely of African origin, expanded and replaced archaic populations throughout the world, beginning around 200,000 years ago.

Starting with the original 'African Eve' hypothesis [1], mitochondrial DNA studies have generally supported a 200,000 year old African origin for modern humans mitochondrial variation [2,3]. Numerous studies of Y chromosome and autosomal variation have arrived at the same conclusion [2–4]. Given the relative paucity of the non-European fossil record of specimens dating to this crucial time period, it is not surprising that the most vehement arguments surround the fate of the well-known neanderthals who lived in Europe and western Asia between about 200,000 and 30,000 years ago. Did they evolve into modern Europeans, hybridize with incoming modern invaders, or were they replaced by an invading population?

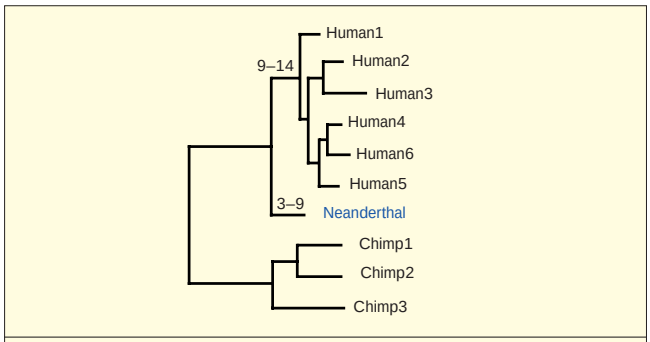
A recently discovered, 24,500 year old skeleton of a four-year-old child found in Portugal has reignited the debate over the possibility that neanderthals and modern humans hybridized. Duarte *et al.* [5] claim that this child displays a mixture of neanderthal and modern traits. Given that neanderthals disappeared from western Europe approximately 29,000–30,000 years ago, this would mean neanderthal morphological traits persisted for over 200 generations of admixture. While this itself is extremely unlikely, reevaluation of the preserved traits has already led many researchers to voice skepticism about hybridization [6].

Although most of the skeletal features of this specimen look most similar to those of a modern human, the body proportions, and other features of the limbs and trunk, are interpreted by Duarte *et al.* [5] as being more similar to those of a neanderthal. Tattersall and Schwartz [6], however, rightly point out how difficult it is to reconstruct and interpret the postcranial skeleton of an immature individual, concluding that "the probability must thus remain that this is simply a chunky Gravettian child, a descendent of the modern invaders who had evicted the Neanderthals from Iberia several millennia earlier". Other claims of neanderthal–modern hybrids in central and eastern Europe have been similarly criticized. Given their many unique adaptations, most paleoanthropologists now view these people as a distinct sort of human and place them in their own species *Homo neanderthalensis*.

The more surprising evidence for separate evolutionary paths has come from analyses of neanderthal DNA. In 1997, Krings *et al.* [7] extracted mitochondrial DNA from the arm of the original neanderthal-type specimen from Feldhofer Cave in Germany's Neander Valley. Under extremely stringent conditions in their laboratory in Munich, which included testing multiple extracts (with one performed in an independent laboratory at Pennsylvania State University), Krings *et al.* [7] were able to amplify and sequence a 378 base-pair region of the mitochondrial control region. The sequence was found to differ significantly from all of their laboratory personnel and all humans sequenced to date, leading to the conclusion that it was indeed from the neanderthal's DNA. Compared to a human reference sequence, the neanderthal sequence differed by 26 nucleotide substitutions and a single base insertion event. Sequence comparisons revealed that the neanderthal sequence fell outside of the variation of modern humans [7]. Phylogenetic analysis suggested that the common ancestor of the neanderthal and modern humans existed around 600,000 years ago, four times the estimate for when the common ancestor of all modern humans existed based on this mitochondrial region.

Two years on, an additional 340 base sequence of the second highly variable region of the mitochondrial control region has been obtained from the same individual [8]. Further analyses of the combined sequences continue to demonstrate that the neanderthal sequence is not closely related to modern Europeans, as would be predicted by

Figure 1



	Human1	Human2	Human3	Human4	Human5	Human6	Neander.	Chimp1	Chimp2
Human1									
Human2	15								
Human3	25	16							
Human4	15	17	25						
Human5	14	18	20	11					
Human6	17	19	23	10	13				
Neander.	20	27	31	23	28	31			
Chimp1	77	79	87	77	80	82	72		
Chimp2	76	80	88	78	80	80	71	23	
Chimp3	77	78	78	82	81	86	72	39	35

Current Biology

Bottom: number of nucleotide substitutions in the region of the mitochondrial control region originally sequenced in the neanderthal [7] and reanalyzed by Wolpoff [9]. Note that, for four modern human pairs (red) the the differences are greater than or equal to those between some modern humans and the neanderthal (blue). Top: maximum parsimony tree inferred from the same sequences. The numbers along the branches leading to the neanderthal and modern humans represent the range of nucleotide substitutions that are inferred to have occurred along each branch.

the multiregional model, but rather that it diverged around 465,000 years ago [8]. This date is slightly younger than the original estimate based upon a shorter sequence, but is still too old to support a neanderthal ancestry for modern Europeans, or any other modern humans for that matter.

Wolpoff, a leading paleoanthropologist who still supports the multiregional model, has reevaluated the neanderthal sequence data [9]. Using a pairwise approach, he compared the neanderthal sequence to a sample of 2051 modern human sequences, noting that 25 of the 27 differences between them varied within modern humans. From further comparison among 994 modern sequences of known geographic origin, Wolpoff [9] concluded "the most surprising finding was that several of the humans were found to differ from each other more than the Neanderthal differs from some humans". Unfortunately, these kinds of pairwise comparisons are not very useful, and indeed, can be misleading. Overall similarity is composed of three components, shared-ancestral traits, shared-derived traits, and homoplasies resulting from convergence or parallelism. Simple pairwise comparisons do not separate out these different kinds of similarity and therefore can yield a mistaken impression of how close the two individuals are with respect to their true evolutionary relatedness [10].

To illustrate this, I have put together a small data set composed of the same mitochondrial region used above for six humans, three chimpanzees and the neanderthal. Pairwise differences, as well as the most parsimonious phylogenetic tree, are shown in Figure 1. For several pairwise comparisons among modern humans, the differences are greater than those between some of them and the neanderthal (Figure 1). Yet the most parsimonious tree unambiguously groups the humans together (Figure 1), with between 12 and 23 nucleotide substitutions occurring between the neanderthal and ancestral human branches (depending upon the model of nucleotide evolution used in the phylogenetic reconstruction).

Proponents of the multiregional model also like to cite several genetic studies which apparently contradict those that support the recent replacement hypothesis. Nearly all the studies using mitochondrial, Y chromosome and autosomal loci reveal greater genetic diversity among modern Africans, place the first branch of the modern human tree within Africa, and infer a date within the last 100,000 or 200,000 years for the derivation of non-African populations [2,3]. Several of these conclusions rest upon the assumption that the effective population size of the human species — or at least of the population that gave rise to modern people — was relatively small, on the order of 10,000 individuals, for tens of thousands of years. Numerous studies support this assumption and elaborate upon it by inferring that this so-called genetic 'bottleneck' existed for a long time, rather than as a relatively short singular event [11].

Two analyses of X chromosome loci, however, have yielded discordant results. An 8 kilobase segment of the X-linked *dystrophin* gene was characterized in 860 chromosomes from 13 populations [12]. Population genetic analyses are consistent with the view that this gene behaves as a neutrally evolving locus in a population with a long-term effective population size of approximately 10,000 [12]. Furthermore, the older alleles (determined by comparing them to those found in the great apes) have similar frequencies in African and non-African populations, while the younger alleles have more limited distributions, implying an African origin [12]. These inferences are in reasonable agreement with those based on the loci discussed above [3].

But the inferences drawn from analyses of another X-linked locus do not fit so easily with the majority view. The *PDHA1* locus was initially sequenced in eight males, including four of sub-Saharan African descent, for a total of 1,769 bases [13]. The sequences from the four non-African individuals do not vary at all, while the African sequences vary at only four sites. A comparison of the four polymorphisms in these sequences to those in the mitochondrial control region led Hey [13] to conclude that mitochondrial sequences have been under selection and

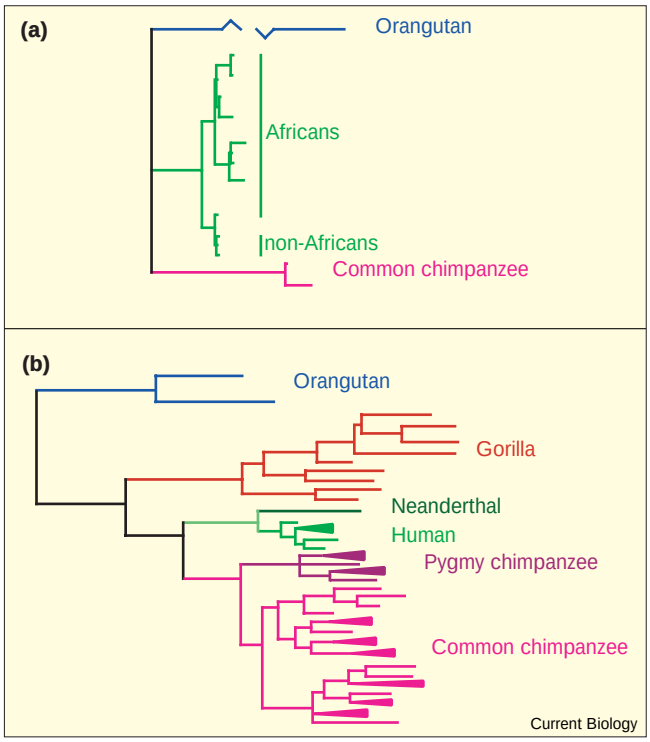
therefore provided misleading estimates of ancestral effective population sizes and thus dates of common ancestry. This result was cited by paleoanthropologists [9] as conflicting with the recent replacement hypothesis. This *PDHA1* data set unfortunately is far too small to allow such inferences to be reached with any confidence.

To rectify this deficiency, a larger *PDHA1* data set was collected, comprising 4,200 nucleotides from 35 human (including eight Africans) and two common chimpanzee males [14]. Twenty-five polymorphic positions were discovered, from which population genetic parameters and a phylogenetic tree were inferred. Eight of the ten lineages in the resulting tree were solely of African origin, with the two European lineages being most closely related to the most divergent African lineage (Figure 2a). By observing the total divergence between the two chimpanzee and the human sequences, and assuming a divergence time of 5 million years, an estimate of the mutation rate was obtained. Applying this rate to the phylogenetic tree gave an estimate of 1.86 million years for the human common ancestral type of this *PDHA1* region [14]. Even though autosomal loci should yield coalescence times four times as old as those of mitochondrial or Y chromosome loci — three times in the case of the X chromosome — because of their larger effective population sizes, this date stands in opposition to most others, which vary between 200,000 years (for mitochondrial and Y chromosome sequences) and 800,000 years (for autosomal sequences).

Several flaws are also apparent in this study [14]. The sampling of only eight Africans and six Europeans means that shared alleles were surely missed [3]. It is also surprising that the two chimpanzee sequences differ at only three positions. The massive data set of human (811) and ape (345) mitochondrial sequences collated and analyzed by Gagneux *et al.* [15] has revealed a tremendous amount of variation within chimpanzee populations, especially as compared to within-human variation (see Figure 2b). Further sampling of both humans and chimpanzees could significantly alter the shape and depth of the tree based on *PDHA1* sequences.

The time estimates are also dependent upon the assumption of equal rates of evolution along the chimpanzee and human lineages. The reanalysis shown in Figure 2a — using a smaller, 1,600 base portion of this *PDHA1* region that was also sequenced in the orangutan — yields a phylogenetic tree that clearly shows unequal rates of evolution. Such rate disparity often indicates the influence of selection, which would then call into question most of the population genetic parameters and conclusions drawn. It would therefore seem to be premature to draw conclusions from the *PDHA1* data until additional human and chimpanzee sequences are collected and new analyses performed.

Figure 2



(a) Maximum likelihood tree inferred from a 1,600 base subset of the *PDHA1* region, with base frequency and probability of change parameters estimated from the data; the tree is drawn with proportional branch lengths (data kindly supplied by Jody Hey). The orangutan branch length is too long to display in full. (b) Neighbor-joining tree – pruned to remove closely related sequences – based on 1,158 mitochondrial control region 1 sequences, with proportional branch lengths (modified from [15]). (Note that (a) and (b) are not drawn to the same scale.)

Thus, the results of Gagneux *et al.* [15] appear to have received considerable support from numerous other genetic systems [2,3]. As illustrated in the tree shown in Figure 2b, human populations are genetically depauperate compared to our great ape cousins. The single neanderthal sequence collected to date falls clearly outside of the modern human lineage, and is best estimated to share common ancestry with our lineage around a half million years ago. Therefore, the most strongly supported hypothesis to date suggests that our ancestry is derived from an African population that may have remained relatively isolated in Africa for tens of thousands of years before migrating out in the last 100,000 years or so, replacing archaic humans, including neanderthals, throughout the old world.

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