Review

No evidence of a Neanderthal contribution to modern human diversity

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Abstract

The relationship between Neanderthals and modern humans is contentious, but recent advances in Neanderthal genomics have shed new light on their evolutionary history. Here we review the available evidence and find no indication of any Neanderthal contribution to modern genetic diversity.

One of the most intriguing questions in human evolution revolves around the Neanderthals, who were the first human-like fossil species to be discovered, more than 150 years ago. What were they like and why did they disappear 30,000 years ago? Do we carry any of their genes? Three hypotheses have been proposed to explain the origin of anatomically modern humans (*Homo sapiens*) and their relation to so-called 'archaic' humans such as the Neanderthals (*Homo neanderthalensis*) (Figure 1). One is the well known 'out of Africa' or 'recent replacement' theory [1,2]; this says that *H. sapiens* evolved in Africa and migrated from there relatively recently, expanding over the world and displacing those archaic humans, such as the Neanderthals, who had evolved independently in Eurasia. An older hypothesis suggests that the evolution of modern humans occurred in both Africa and Eurasia, with gene flow between the various populations; this is known as the 'multiregional' model [3-5]. A Neanderthal genome project based on DNA from fossil specimens is now under way and aims to provide us with much more information about what the Neanderthals might have been like. In particular, it should provide a definitive answer to whether there was any genetic intermixing between them and the modern humans who coexisted with them in Europe for up to 6,000 years [6] and perhaps longer in Western Asia.

Phylogenetic analyses of Neanderthal DNA

Mitochondrial DNA, which is inherited through the maternal line, has been a favored DNA sequence for determining relationships between human populations, and there is a large amount of data on the mitochondrial DNA sequences present in humans of many different ethnic groups from all over the world. In 1997, Krings and colleagues [7] first amplified and sequenced mitochondrial DNA (mtDNA) from a Neanderthal fossil - in fact, the original Neanderthal specimen. By late 2007, 14 other specimens had yielded mitochondrial sequences that could be compared (Figure 2 and Table 1). Several have yielded sequences over 300 bp long from the hypervariable region 1 of the mitochondrial control region (Figure 3). Other sequences are shorter but contain informative nucleotide positions. These mtDNA data indicate that all Neanderthal specimens sequenced up to now form a monophyletic lineage that split from the human lineage several hundred thousand years before populations of modern humans began to diverge from each other (Figure 1a).

Nevertheless, some researchers have argued that the absence of Neanderthal-related haplotypes in modern human populations does not necessarily mean that there was no interbreeding between Neanderthals and modern humans 30,000 or more years ago [8,9]. Sequencing of mtDNA from anatomically modern human fossils 24,000 years old by Caramelli *et al.* [10] strongly suggested that there was no relationship with Neanderthals. But there were questions about the reliability of the DNA techniques and the possibility of contamination by DNA from those who had handled the specimens. To address such problems, Serre *et al.* [11] sequenced a series of Neanderthal specimens and

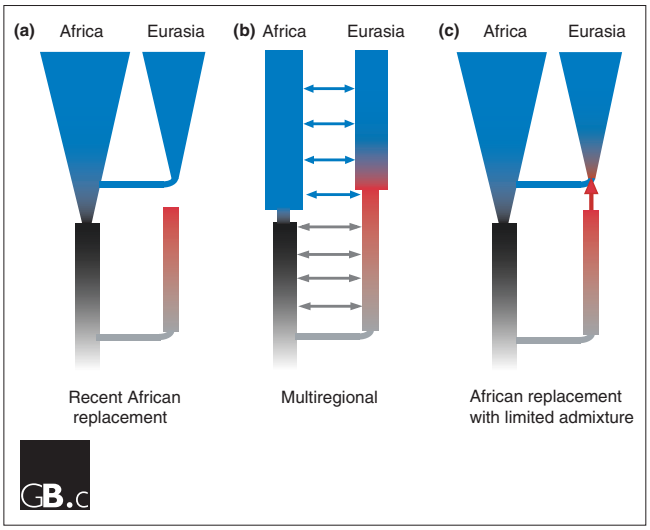

Figure 1
Models of modern human origins. In each case, anatomically modern humans are designated in blue and Neanderthals (and other extinct Eurasian archaic human species) in red. The gray root indicates the common origin of all human species, most probably in Africa. **(a)** The 'African replacement' hypothesis proposes that anatomically modern humans originated in Africa, expanding into Eurasia relatively recently and replacing other human species, such as the Neanderthals, which had evolved independently there [1,2]. **(b)** In contrast, an older hypothesis, the 'multiregional model', envisages that the evolution of modern humans occurred in both Africa and Eurasia, maintaining local genetic continuity but with populations united by gene flow [3-5,6]. **(c)** Some researchers combine these models, seeing a recent African origin for the bulk of the human genome, but limited admixture with existing populations [48].

contemporaneous early modern human fossils using Neanderthal-specific PCR primers, to avoid detecting any contaminating present-day DNA. The Neanderthal fossils yielded Neanderthal mtDNA haplotypes, but no amplifications were obtained from the well-preserved early modern samples. Serre *et al.* interpreted this as a significant lack of evidence of Neanderthal-modern human admixture near the time at which it may have been possible.

More recently, researchers have been successful in isolating and sequencing DNA from the Neanderthal nuclear genome. Ancient DNA entered the genomics age with the publication of around 27,000 bp of Pleistocene cave bear sequence [12] and more than 13 million bp of woolly mammoth DNA [13]. These studies used cell-based and emulsion-bead approaches to create metagenomic libraries of fossil DNA extracts [12-14]. Such libraries contain both endogenous DNA from the fossils and exogenous microbial DNA from modern contaminants and from microbes that colonized the organism after death or lived in the soil matrix. These approaches were applied to Neanderthals. A 38,000-year-old fossil from Vindija in Croatia (Vindija 80, Figure 2 and Table 1) was chosen for analysis because a preliminary PCR and subcloning of the fossil's mtDNA indicated well preserved DNA that was largely free of contamination [15]. Noonan *et al.* [16] obtained 65,250 bp of Neanderthal genomic sequence using a cell-based approach, while Green *et al.* [15] obtained more than 1 Mb of genomic sequence using an emulsion-bead based approach.

Both groups made alignments of their sequences with orthologous chimpanzee and human sequences and characterized the substitutions along each lineage. From these, an average sequence divergence time between Neanderthals and modern humans could be calculated. This parameter does not, however, necessarily measure the time that the two populations actually split. To estimate that, the two groups compared their Neanderthal sequence with information on single nucleotide polymorphisms (SNPs) in present-day humans collected by the HapMap project [17]. If the split between humans and Neanderthals is ancient, Neanderthals should rarely, or almost never, carry the 'derived' variant of a human SNP - that is, a variant that is present in some modern human lineages but not in the ancestral human lineage from which both Neanderthals and modern humans descend. On the other hand, if the split is recent, derived variants will be common in the Neanderthal genome and we should expect alleles to be shared between modern Europeans and Neanderthals.

Although they were working with DNA from the same specimen, the two teams came to very different conclusions. Noonan *et al.* [16] arrived at an average divergence time between Neanderthals and humans of 706,000 years and an estimated time for a population split at 370,000 years ago. They found derived human SNP variants at only three sites in the Neanderthal DNA, two of which are only found in sub-Saharan Africans and not in Europeans. They concluded that the Neanderthal contribution to modern genetic diversity was zero. Green and colleagues [15], on the other hand, calculated the average sequence divergence time between Neanderthals and humans as 516,000 years. To check whether this degree of divergence is comparable to that found within humans, they resequenced a modern human using an identical approach and compared the data to the chimp and human reference genomes. They found the average sequence divergence time between the resequenced human and the reference genome to be 459,000 years. And when Green *et al.* compared their Neanderthal sequence with the corresponding HapMap data, they found that around 30% of the SNPs were of the derived human type. They therefore concluded that a single ancient split between Neanderthals and humans is unlikely, and there must have been some level of recent gene flow.

Such conflicting conclusions from the same DNA sample not surprisingly led to a reanalysis of the data. Contaminating modern DNA should be less fragmented than genuine ancient DNA. To check their data for evidence of contamination, Noonan *et al.* [15] had compared their long sequence reads to their short sequence reads and confirmed an equal

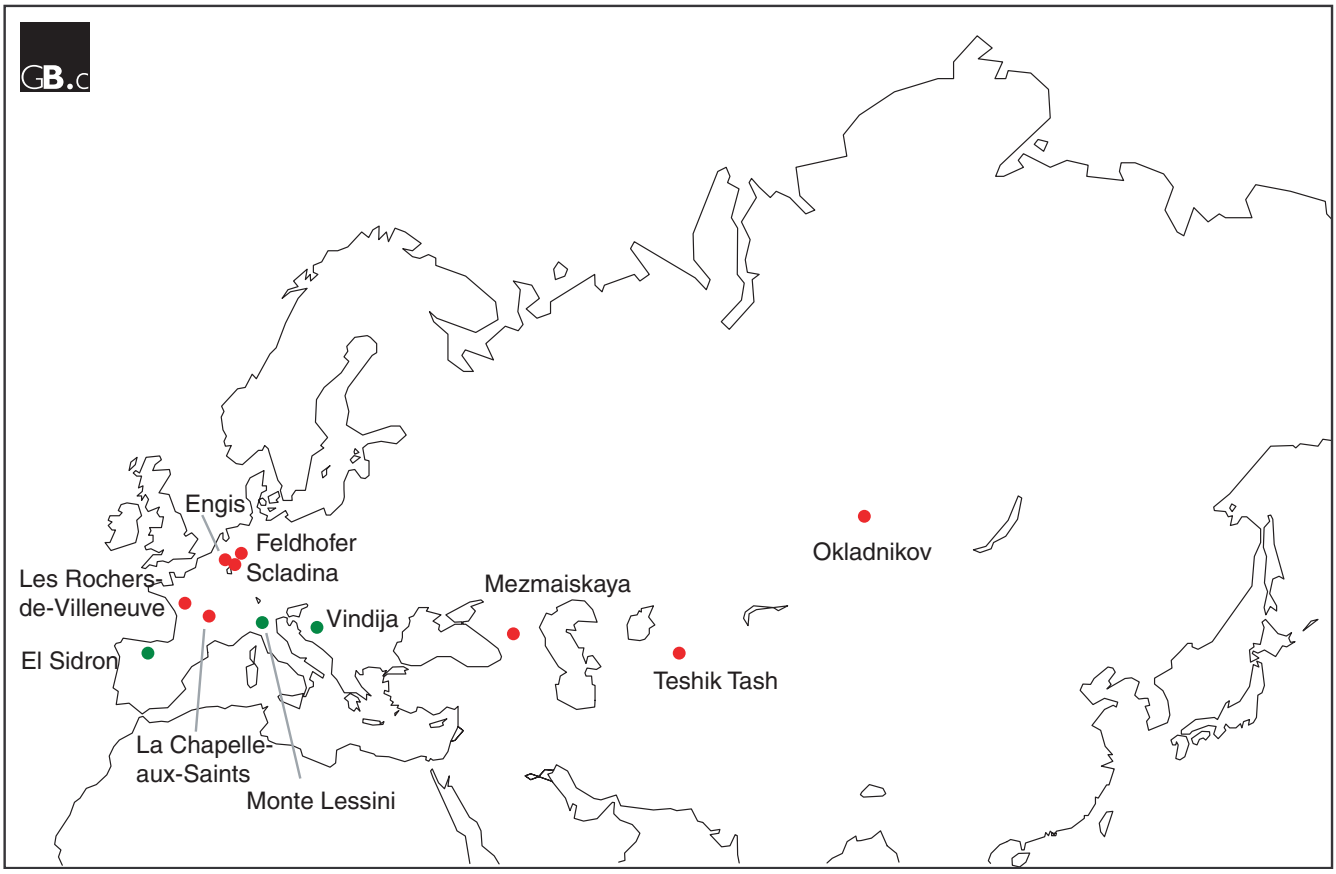

Figure 2
Sites of Neanderthal fossils that have provided ancient DNA. Red, mitochondrial sequences only. Green, mitochondrial and nuclear sequences.

sequence divergence from modern humans across their data, indicating the absence of contamination. Green *et al.* [14] had not taken this step. Wall and Kim [18] reanalyzed Green *et al.*'s dataset and found that their long sequence reads showed significantly lower sequence divergence from modern humans than their short sequence reads, and that their short sequence reads showed an indistinguishable level of sequence divergence from Noonan *et al.*'s data. Wall and Kim concluded that the sequence used by Green *et al.* had been contaminated by human DNA - and, using a maximum likelihood analysis, estimated the contamination to be as high as 78%. We also note that Noonan *et al.* found that 1.3% of their metagenomic library was Neanderthal in origin, whereas Green *et al.* found 6.2% to be Neanderthal. If this difference is due to contamination, then it is in close agreement with Wall and Kim's likelihood estimates. We believe these findings serve as a cautionary tale that even with extremely stringent protocols, contamination of fossils with modern human DNA will remain a problem.

From sequence to function

The analysis of Neanderthal genomic DNA took an exciting step forward recently with the sequencing of two protein-coding genes that are known to have undergone adaptive evolution along the human lineage. The first gene, forkhead box 2 (*FOXP2*), is thought to be involved in language development, whereas the second, melanocortin 1 receptor (*MC1R*), is involved in skin and hair pigmentation.

Krause and colleagues [19] targeted the *FOXP2* sequence in two Neanderthal specimens from El Sidron, Spain (Figure 2), excavated under sterile conditions to avoid contamination, and recovered the derived form of *FOXP2* identical to that found in humans. These researchers largely ruled out human contamination through multiple control PCRs designed to detect it, and by several independent replications of the sequencing result. It has been suggested that the findings of Krause *et al.* mean that Neanderthals had a language ability similar to our own, though we feel that this interpretation is premature. Because no study of ancient DNA has demonstrated gene flow between Neanderthals and modern humans, Krause *et al.* conclude that selection fixed this variant of *FOXP2* before the separation of the Neanderthal and modern human lineages.

Several genes are associated with variation in skin and hair pigmentation in humans [20-22]. *MC1R* affects skin color by

Table 1

Mitochondrial sequences published as of 2007

Fossil specimen	Country	mtDNA region	Length (bp)	Accession number	Reference
Feldhofer 1	Germany	HVR1	379	AF011222	[49]
		HVR2	345	AF142095	[50]
Feldhofer 2	Germany	HVR1	357	AY149291	[51]
Mezmaiskaya	Russia	HVR1	345	AF254446	[52]
Vindija 75	Croatia	HVR1	357	AF282971	[53]
		HVR2	288	AF282972	[53]
Vindija 77	Croatia	HVR1	31	-	[11]
Vindija 80	Croatia	HVR1	31	-	[11]
Engis 2	Belgium	HVR1	31	-	[11]
La Chapelle-aux-Saints	France	HVR1	31	-	[11]
Rochers de Villeneuve	France	HVR1	31	-	[54]
Scladina	Belgium	HVR1	123	DQ464008	[55]
Monte Lessini	Italy	HVR1	378	DQ836132	[56]
El Sidron SD-441	Spain	HVR1	47	-	[57]
El Sidron SD-1252	Spain	HVR1	303	DQ859014	[58]
Teshik Tash	Uzbekistan	HVR1	190	EU078679	[59]
Okladnikov	Russia	HVR1	348	EU078680	[59]

HVR1, hypervariable region 1; HVR2, hypervariable region 2. -, no accession number given.

regulating the expression of the darker eumelanin, and thus altering its ratio to the lighter pheomelanin. Low-activity variants of *MC1R*, for example, produce low ratios of eumelanin to pheomelanin, giving pale skin and blond to ginger hair (reviewed in [23]). Lalueza-Fox and colleagues [24] sequenced a 128 bp fragment of *MC1R* in two Neanderthal DNA samples; an additional one from El Sidron and one from Monti Lessini in Italy (Figure 2). They found an A to G transition, resulting in an arginine to glycine substitution, in both samples. This substitution is not found in humans and is likely to be a legitimate Neanderthal difference because A to G transitions are not typical artifacts of DNA degradation. These results were also replicated in multiple PCR experiments and in different labs.

Lalueza-Fox *et al*. [24] also took the unprecedented step of exploring the phenotypic effects of a Neanderthal sequence by expressing the Neanderthal *MC1R*, a human ancestral high-activity allele, and a derived human low-activity allele in cell culture. They found that the Neanderthal *MC1R* had 40% the activity of the ancestral allele, and was indistinguishable in its effects from the low-activity allele found in some modern Europeans. This study represents the first functional study of Neanderthal DNA and strongly suggests that at least some Neanderthals had pale skin and ginger hair.

The relationship between Neanderthals and modern humans

These new developments in Neanderthal genomics allow us to re-evaluate both the possible Neanderthal contribution to modern gene pools and the modern human contribution to the Neanderthal gene pool. The distribution of genetic variation within present-day humans has been interpreted to support both the recent replacement and the multiregional evolution hypotheses (Figure 1), though a consensus is developing in favor of recent replacement.

Many authors have interpreted the very recent origin of human mitochondrial DNA [25,26], Y chromosomes [27,28] and other loci [29,30] in Africa as evidence for the recent replacement hypothesis. However, Templeton [31,32] argues that there are loci that do not show a recent origin in Africa and that human history is best characterized by several population expansions and continued gene flow between modern and archaic groups. Wall [33] has argued that the data so far are insufficient to answer the question, and that sequence data from between 50 and 100 independently segregating loci in present-day humans will be required. Fagundes *et al*. [34] have now used data from 50 human genomic loci to compare several versions of the multiregional model with the recent replacement model by a likelihood-based approach and found that recent replacement best fits

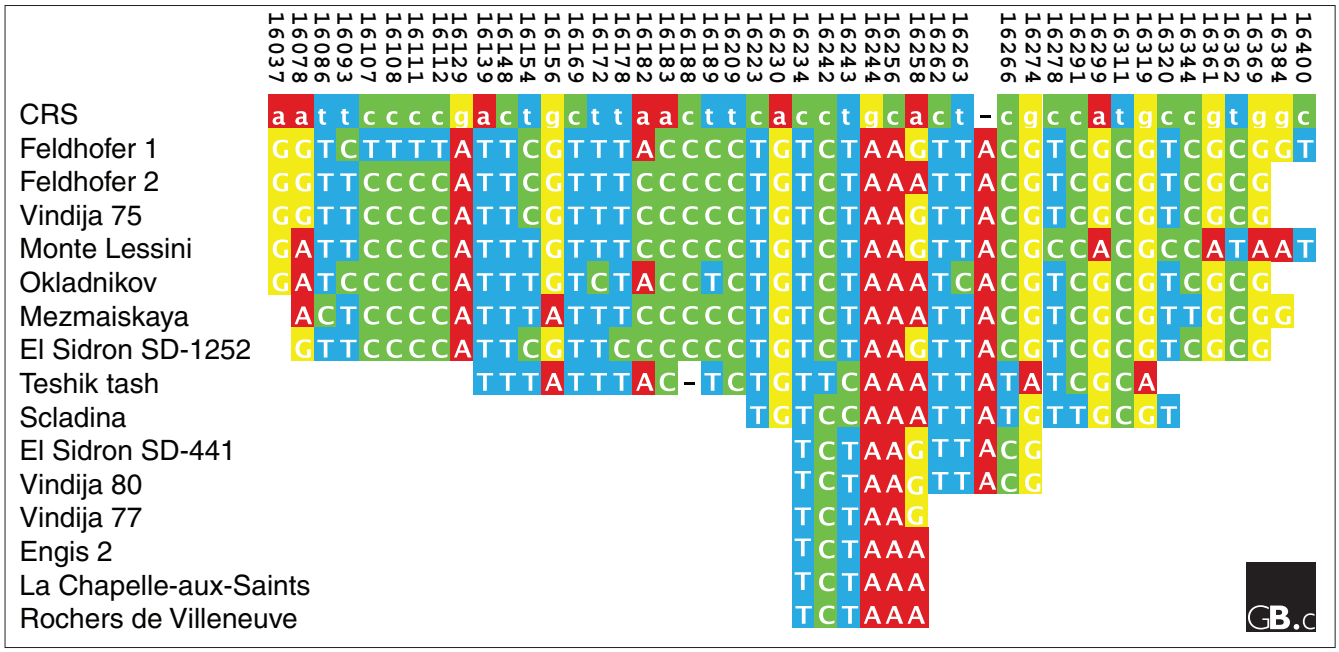

Figure 3
Neanderthal mtDNA sequences. CRS, Cambridge reference sequence [60]. Only nucleotide positions that vary between Neanderthals and humans, or within Neanderthals, are shown. Numbering based on the CRS. See Table 1 for further details of the sequences.

the data, with a posterior probability of 78%. The best estimate from these data is that modern humans arose around 141,000 years ago in Africa, with migration out of Africa around 51,000 years ago, which is in broad agreement with most interpretations of the fossil record [2].

The findings from Neanderthal DNA sequence fit nicely with the analysis of Fagundes *et al*. [34]. First, analysis of mtDNA from multiple Neanderthal samples has revealed a monophyletic origin for the Neanderthal lineage that falls outside the range of diversity of both present-day and fossil modern humans. It has been pointed out that the mitochondrial data alone were insufficient to definitively exclude the possibility of genetic admixture between modern humans and Neanderthals [11,33,35]. To address this question, Currat and Excoffier [36] simulated admixture between Neanderthals and modern humans during the expansion of modern humans into Europe and found that even modest amounts of mixing would result in the complete replacement of the invading modern human mtDNA by endemic Neanderthal mtDNA. Furthermore, they found that even very low levels of admixture would result in a significant minority of Neanderthal mtDNA in extant European populations. They estimate the maximum amount of admixture possible to observe no surviving Neanderthal mtDNA to be less than 0.1%, with no more than 120 admixture events during 12,000 years of overlap.

As long as mitochondria evolve neutrally, the analysis by Currat and Excoffier [36] effectively eliminates the possibility of female-mediated neutral gene flow from Neanderthals to modern humans. This leaves open the formal, although unlikely, possibility of strictly male-mediated gene flow from Neanderthals to modern humans, or the possibility of active selection against Neanderthal mtDNA. Under either of these scenarios there should be evidence for derived Neanderthal nuclear genes in modern populations. But, excluding contamination, the four studies of nuclear DNA reviewed above have all failed to show any contribution, despite the sampling of many independent loci.

It is now clear that the level of interbreeding between the two populations, if any, was so low that we are unlikely to find any neutrally evolving Neanderthal alleles in modern populations. However, it is possible that low levels of interbreeding could have led to the adaptive transfer of some alleles between species (introgression). Beneficial alleles can persist in interspecific hybrids even when the hybrids are less fit than either parent population as long as the hybrids are fertile [37]. As hybrids back-cross to a parent population, most introduced alleles will be lost to drift or to negative selection; some beneficial alleles, however, may be maintained in subsequent generations. Claims have been made for adaptive introgression from Neanderthals into populations of modern humans at the *microcephalin* [38] and the *tau* [39] loci. Some proponents of the multiregional model have gone so far as to suggest that adaptive introgression was a primary source of beneficial alleles during the evolution of modern humans [40]. While we regard this latter idea as unsupported by the available Neanderthal and

human genome sequences, it is worth considering the possibility that a very limited amount of adaptive introgression has occurred.

MC1R is a good *a priori* candidate for adaptive introgression. It is thought that light skin is favored in Europe as a compromise between the need for vitamin D synthesis and the need to prevent folate photolysis, both caused by UV radiation [41]. Several genes affecting skin color are known to have been positively selected in European populations [21,22], though studies of *MC1R* evolution have come to different conclusions [22,42,43]. Jolly has pointed out that the easiest way for early modern humans entering Europe to evolve light skin would be to acquire the necessary genes from Neanderthals rather than to evolve them *de novo* [44]. If the low-activity *MC1R* variant is positively selected in Europe, then *MC1R* presents a good opportunity to test for evidence of adaptive introgression from Neanderthals to modern humans. However, although Neanderthals and modern Europeans share a low-activity MC1R phenotype, the genotype is different (see above), which argues against significant adaptive introgression. The hypothesis could be tested more rigorously using Neanderthal sequence from other loci affecting skin color with a clearer signal of positive selection in Europeans. The failure to find evidence for adaptive introgression would strongly suggest some pre- or post-zygotic barrier to gene flow such as chromosomal incompatibility [45].

Some studies claim evidence of shared morphologies between archaic and modern humans that demonstrates gene flow between the groups ([46,47] but see [48]). The only shared phenotype between Neanderthals and modern humans for which we know the genotype (that is, *MC1R*) has resulted from convergence. It should not be surprising that populations with largely similar genomes living in largely similar environments will sometimes solve evolutionary problems in largely similar ways. In light of the failure to find a Neanderthal contribution to modern gene pools, convergence ought to be considered the null hypothesis with regard to phenotypic similarity between Neanderthals and modern humans.

We interpret the findings discussed above as effectively eliminating the multiregional model of evolution with respect to Neanderthals. It seems unlikely that Neanderthals contributed any substantial fraction of modern variation and it remains to be seen whether any adaptive alleles crossed the human-Neanderthal species boundary. The continuation of the Neanderthal genome project, along with a better understanding of modern genomic diversity, will shed even more light on the origins of modern humans.

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