Commentary
Volume 9:8, 2021

Journal of
Phylogenetics & Evolutionary Biology

ISSN: 2329-9002 Open Access

Revisiting the Hominin Phylogeny: An Alternative Introgression Scenario to Reconcile the Uniparental and autosomal DNA Topologies

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Abstract

Ancient DNA has given a new vision to the recent history of human evolution. For example, it has allowed establishing the phylogenetic relationships among modern and archaic humans as the Neanderthals and Denisovans. However, introgressive hybridization between these lineages has produced autosomal based relationships that are in disagreement with the topologies obtained from non-recombinant uniparental markers. In this case, it is the congruent phylogeny obtained from the Y-chromosome and mitochondrial DNA sequences which gives the true historical branching order of these human lineages, shedding light on an alternative hominin evolutive scenario in which humans and Neanderthals are sister subspecies, the Sima de los Huesos specimens are the result of hybridization between evolved erectus and the ancestor of Neanderthals, and Denisovans represent one of the worldwide synchronically evolved erectus subspecies.

Keywords: Hominins • Phylogeny • Autosomes • Mitochondrial DNA • Y chromosome

Introduction

Ancient DNA, coupled with whole genome analysis, is revealing the real complexity of the recent human history, far from the straightforward vision drawn by previous genetic analysis. The sequencing of the Neanderthal mitochondrial DNA (mt DNA) genome [1] and the discovery of the Denisovans from molecular sequences alone [2] are two fundamental milestones. Thus, ancient DNA has also allowed the direct comparison of autosomes and the non-recombining mt DNA between archaic and modern humans [2-5]. The surprise was that the hominin phylogenies obtained using mt DNA or autosomal sequences were discordant. Mt DNA phylogenies showed that Neanderthals and modern humans were sister lineages whereas genome-wide data joints Denisovans and Neanderthals as the closest pair leaving modern humans as an out-group. Based on the assumption that mt DNA is transmitted as a single gene and does not necessarily reflect the true relationships between individuals and populations as the whole autosomes do, several hypotheses have been proposed to explain the discrepancies observed. In summary, it has been proposed the existence of hybridization between Denisovans and a genetically very divergent archaic hominin which could have introgressed its mt DNA that later was fixed into the Denisovan population, phylogenetically distancing it from its next relatives the Neanderthals [5] or, alternatively, an ancestor of modern humans could have introgressed their mDNA into Neanderthals which, upon fixation in this group, would bring them closer to modern humans and away from their closest relatives the Denisovans [3,6]. However, recently, hominin phylogenies based on Y-chromosome sequences have been published [7-9] and it was found that the Denisovan Y chromosomes split from a lineage shared by Neanderthal and modern human Y-chromosomes. These phylogenetic relationships mirror those observed previously with mt DNA and, therefore, differ from the one observed from their autosomal genomes. Once again, the authors [8,9] trusted on the autosomal topology as more reliable and explained its discrepancy with those of the uniparental markers suggesting that both mt DNA and Y-chromosomes of Neanderthals were completely replaced via gene flow from an early lineage related to modern humans. However, as the own proponents recognize, this hypothesis faces severe drawbacks and an alternative hypothesis, based on the congruence of the uniparental markers is conceptually possible. Under neutral theory conditions, the average number of generations elapsed between the introgression and fixation of a haploid lineage is 2Ne, being Ne the effective population size [10]. Assuming Ne = 5,000 and a mean generation time of 25 years, a fixation event would last about 10,000 generations or around 250,000 years, but this would occur only as long as the lineage is transmitted each time to the next generation which has a 1/Ne probability. Thus, the chance of a lineage to be lost in the process is very high. In addition, this unlikely event has to occur twice, once for the mitochondrial and once for the Y-chromosome. Certainly, a frequent sex-biased introgression could substitute one of the sex-linked markers of the recipient population [11] but this would occur in detriment of the other sex-linked marker. Furthermore, in hybridization events, it usually happens that the male heterogametic offspring is totally or partially infertile [12]. There are clues that this type of incompatibility occurred in crosses between Neanderthals and Denisovans with humans [13], so that, the probability of fixation for the Y-chromosome is even lower. As if this were not enough, it must be remembered that these haploid lineages are introgressed as whole gametes that also introduce specific autosomal variants from the putative super-archaic hominin into the Denisovan genome, or specific autosomal human variants into the Neanderthal genome. These variants have also to be eliminated in order to keep the inferred autosomal phylogenetic relationships. Finally, invoking selection as the main cause of this double uniparental replacement hardly can explain how two divergent lineages could simultaneously replace the two genome-coadapted uniparental markers of the recipient population.

However, what is the case if we trust mt DNA and Y-chromosome as more reliable tools than autosomes to recover the true history of relatively deep population phylogenies and accept the uniparental phylogenetic alternative?

First, we must admit that the anomalous genomic relationships found are due to non-uniform interspecific gene flow. That is, more gene flow occurred between Denisovan and Neanderthals than between the later and modern humans. This could be true because, as deduced by their respective geographic ranges, Denisovans and Neanderthals were in partial sympatry more time than any of them with modern humans. Although, in a first analysis only a small amount of gene flow from Neanderthals into Denisovans was detected [5], a later finding of a F 1 hybrid descendant of a cross between a Neanderthal female and a Denisovan male, the later with traces of Neanderthal admixture in their ancestors [14], suggests that these interbreeding events

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Received 26 July 2021; **Accepted** 18 August 2021; **Published** 25 August 2021

could be frequent. However, more samples and analyses are necessary to confirm this supposition. The second requirement necessary to justify our hypothesis is to explain why, if the interspecific gene-flow was relatively frequent to leave a significant signal in the autosomes; no uniparental Neanderthal markers have been detected in the Denisovan gene pool or vice versa? As we commented previously, under neutrality conditions the loss, in the next generation, of a haploid marker introduced in a population is an event with a high probability of success ((Ne-1)/Ne). However, under the same conditions, the simultaneous introduction of a whole genome has a different destiny since, from the first meiosis; it will recombine with the receptor genome, giving rise to hybrid chromosomes and will continue recombining in successive generations, giving smaller fragments dispersed into more chromosomes following a slow dilution process. In addition, the Y-chromosome could be lost by male hybrid sterility. Furthermore, if the interbreeding events were male biased, and females raise their hybrid offspring in their native population, their mt DNAs would not pass to the population of the external fertilizing male.

Methodology

To emphasize the important changes that this hypothesis introduces in human evolution, we reconstructed the hominin mt DNA phylogeny using the Neighbor-Joining method [15], taking as representative of modern humans a sub-Saharan African individual belonging to haplogroup L 1c (Accession code: MF 621129), the Mezmaiskaya 1 specimen (Accession code: FM 865411) as representative of Neanderthals, the Denisovan 3 specimen (Accession code: NC 013993) as representative of Denisovans, and the Sima de los Huesos specimen (Accession code: NC 023100) as representative of the Middle Pleistocene hominins found in Atapuerca (Spain). Alignment data are available as supplementary data. The tree has a 100% bootstrap support for all the nodes (Figure 1). To graphically compare the alternative hominin phylogenies, we added in the same figure simplified trees for the Y-chromosome (Figure 1) and autosomes (Figure 1) based on those respectively published in [9,16].

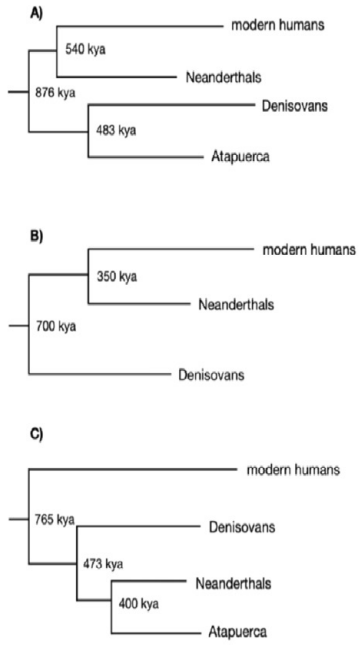

Figure 1. Phylogenetic relationships among archaic and modern humans based on mitochondrial DNA (A), Y chromosome (B) and autosomal (C) sequences. All branch splits are supported by 100% bootstrap iterations. Rough age estimations in years, are represented at the basal nodes.

Results

In the mt DNA tree, branch shortening between Denisova and Atapuerca is as expected by the different age of death of both specimens. Subtracting the specific number of substitutions in their respective terminal branches gives a difference of 89 mutations between them that, transformed in time using a mutation rate of 1.92 × 10-8 per site per year (1.16–2.68 × 10-8, 95% CI) [17], gives a difference of about 360,000 years between the death of these two lineages. Assuming an approximate age of 50,000 years old for Denisova 3 [18], the age of the Atapuerca specimen would be around 410,000 years old which is similar to its age dated by archaeological methods (430,000 years old) [19].

However, applying the same calculations to the modern human-Neanderthal pair resulted in a difference age of 127,000 years, which is greater than twice the age calculated for the Mezmaiskaya remains by archaeological methods [20]. We suggest that this difference could be attributed to the marked acceleration of the human mutation rate in recent times [21]. Coalescence between Neanderthal and modern humans occurred 540,370 years ago (ya) (95% CI: 494,782 to 585,958 ya). And that of the Atapuerca-Denisova 3 pair 482,780 ya (95% CI: 439,705 to 565,855 ya). The most recent common ancestor (TMRCA) between Atapuerca and the Neanderthal-modern human pair is approximately 671,822 years old, and that of the later pair and Denisovan is approximately 815,585 years old. As expected by the respective age of the specimens compared, the split age between Denisovan and modern humans (876,357; 95%CI: 818,314 to 934,400 ya) is older that the split age of Denisovan and Neanderthals (754,814; 95% CI: 700,957 to 808,671 ya). These relationships and the ages when branches split are within the range found by other authors for the same groups of hominins [1, 3,22-24]. The analysis of Y-chromosome sequences for the same hominin groups (excluding Atapuerca) reflects the same tree topology as that obtained with mt DNA [7-9]. However, TMRCA of Denisovan and modern human Y-chromosome was estimated around 700 thousand years ago (kya) which is younger than the one obtained for the same pair using mt DNA. Similarly, The Neanderthal and modern human Y-chromosome divergence around 370 kya [9] is notably more recent than the ones estimated with the maternal marker. For the later pair, the mt DNA divergence is more in agreement with the Y-chromosome split age, around 588 kya, estimated by other authors [7].

Regardless of the minor differences in split ages estimated with mt DNA or Y-chromosome markers, the acceptance of the identical phylogenetic relationships between the different hominin groups, found by the use of uniparental markers, has important implications for the recent hominin history and their most probable geographic origins.

Discussion

The first question raised to us is to search the fossil record for a lineage that, like to Denisovans at molecular level, could represent a valid phylogenetic outgroup for humans and Neanderthals. Denisovans are a mysterious hominin group that until recently lacked of any morphological identification. It's surprising genetic discover at the Denisovan Cave was facilitated by successful ancient DNA extractions from undetermined remains [2]. More recently, Denisovans have been genetically detected in the Tibet from a Late Middle Pleistocene mandible and from coetaneous sediments [25, 26], which provided evidence that some fossil remains, described as archaic hominins in different regions of China, could also belong to Denisovan related groups [27,28]. It deserves mention that many of the morphological characteristics attributable to Denisovan anatomy were foreseen from DNA methylation patterns [29]. Other possible localization of Denisovan populations in Asia were inferred by the presence of Denisovan introgressed DNA in the genome of fossil or present-day modern human genomes, sampled from regions as distant as Mongolia, South Asia, South east Asia and Australasia [30-36]. All this evidence points to Denisovans as a species with an ample geographic continental range going from the Iberian Peninsula at the west to the Southern East Asian corner at the east. Besides modern humans, the only hominin species with a similar geographic range is Homo erectus s. l. so, we believe that Denisovans could represent different subspecies of this clade. The fact that the Denisovan genomes sequenced or extracted from

populations of different regions are very divergent between them, reaching split times near to one million years ago when compared with modern humans, strongly reinforces our suggestion [37]. Certainly, this erectus-origin hypothesis alternative for Denisovans needs further empirical support from both archaeology and genetics.

Following the phylogenetic relationships found with uniparental markers, we faced a second problem that implies the position of the Sima de los Huesos specimens, closest to Denisovans by their mt DNA lineages but with strong Neanderthal ties according to genomic [16] and morphological data [19]. Our best explanation for this dilemma is that the Sima de los Huesos specimens are the result of hybridization between the ancestors of Neanderthals and an evolved erectus European lineage. Subsequent phyletic differentiation of that hybrid population most probably gave origin to the mature Neanderthals.

The third phylogenetic question posed is to explain what was the most probable geographic origin of the ancestor of modern humans and Neanderthals, and how these became differentiated lineages.

In a first appreciation, as the sister clade of the common ancestor of modern humans and Neanderthals are the Denisovans which had a Eurasian range, the most parsimonious hypothesis was to suppose that the common ancestor of modern humans and Neanderthal also had Eurasian roots. However, the archaeological evidence turned us to assign a most probable northern African origin for it. In addition, we have to suppose that some geographic barrier must have existed to interrupt gene flow between the ancestors or Neanderthals and modern humans in order to facilitate its genetic divergence. It is well known from the archaeological record, also contrasted by ancient DNA studies, that Neanderthal groups moved across Europe reaching Central Asia and the Middle East well before of 100 kya [38-42]. In contrast, the direct ancestors of modern humans have not been detected in Europe at that time. Assuming a North African origin for the ancestral population of modern humans and Neanderthals, it seems appropriate to suppose that a group of that population emigrated to the Iberian Peninsula giving rise to the European Neanderthals, while another group remained in the Maghreb evolving as early or recent anatomically modern humans as attested by the fossil remains and Middle Stone Age artifacts excavated at Jebel Irhoud site (Morocco), and dated around 300 kya [43,44]. It is worth mentioning that there are strong archaeological affinities between the older northern African and the more recent Iberian large flake Acheulean technologies, which suggests a northern African demic movement to the Iberian Peninsula around 500-400 kya [45,46]. This is chronologically compatible with the above proposed migration of the pre-Neanderthal African population to Europe. The proposed African origin for the common ancestor of modern human and Neanderthals would also satisfactorily explain the fact that modern human African genomes share about 13-16% more fixed derived alleles with the Neanderthal genome than with the Denisovan genome [5].

The corollary of this hypothesis is that the cradle of the human evolution in Africa began in northwestern Africa and, from there, spread to the rest of the continent. From this, it follows that any hominin African lineage assumed to be direct ancestor of modern humans has to be derived from the Jebel Irhoud population.

Finally, around 150 kya a group of not fully evolved modern humans left Africa for Eurasia where they met, again, its sister relatives, the Neanderthals and Denisovans [47].

Conflict of Interest

The author declares no conflict of interest.

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How to cite this article: Vicente M. Cabrera. "Revisiting the Hominin Phylogeny: An Alternative Introgression Scenario to Reconcile the Uniparental and autosomal DNA Topologies." *J Phylogenetics Evol Biol* 9 (2021): 171.