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Ancient humans and the origin of modern humans

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Recent advances in sequencing technologies and molecular methods have facilitated the sequencing of DNA from ancient human remains which has, in turn, provided unprecedented insight into human history. Within the past 4 years the genomes of Neandertals and Denisovans, as well as the genomes of at least two early modern humans, have been sequenced. These sequences showed that there have been several episodes of admixture between modern and archaic groups; including admixture from Neandertals into modern human populations outside of Africa, and admixture from Denisovans into modern human populations in Oceania. Recent results indicate that some of these introgressed regions may have been advantageous for modern humans as they expanded into new regions outside of Africa.

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Introduction

In recent years a growing number of insights into the molecular origins of modern humans have been obtained through the analysis of DNA sequence data. While early analyses focused on using single loci and informative markers to reconstruct human population histories and movements [1–5], high throughput sequencing has made possible the sequencing of whole mitochondrial and nuclear genomes from multiple organisms including humans and non-human primates [6–10].

These same sequencing technologies have revolutionized the field of ancient DNA. Whole mitochondrial and nuclear genome sequences of early modern humans as well as the genomes of now extinct human forms including the Neandertals have been sequenced and analyzed, and have yielded a number of key insights into human history.

We review here advances in the sequencing and analysis of ancient genomes with a focus on archaic human forms and early modern humans older than 12 000 years — a date corresponding with the end of the Paleolithic period. While studies of single genomic loci have yielded information about specific traits in archaic humans, we focus here only on those individuals for which genome-wide sequence data is available, as such data are suitable for studying population history and admixture patterns.

We discuss the challenges associated with generating ancient human genome sequences, describe the genomes that have been sequenced, and highlight the insights into modern human history and demography that have been obtained from the analysis of these genomes.

Sequencing DNA from ancient remains

The DNA extracted from ancient remains has a number of properties that distinguish it from modern DNA, and which lead to very specific challenges. It has been shown that the concentration of endogenous DNA in bone decreases over time with the result that the majority of samples do not contain appreciable amounts of endogenous DNA [11,12]. A major challenge is therefore to identify bones with a sufficient amount of endogenous DNA for sequencing.

Even when a sample with endogenous DNA is identified, the extracted DNA is generally mixed with large quantities of microbial contamination and the endogenous molecules are typically short (<100 nucleotides). Further, it has been shown that deamination of cytosine residues to uracils is common in ancient DNA [13] and that this DNA damage increases with time [14]. Deamination patterns therefore provide an approximate measure of the age of the sample. Though theoretical calculations suggested that highly fragmented DNA could be retrieved from samples up to ~100 000 years old [15] recent studies have yielded DNA from samples exceeding this age [16•,17••,18].

Accurate identification of the truly endogenous DNA sequences from ancient human samples is complicated by contamination with DNA from present-day humans. Since the ancient DNA in a sample is typically present in very small amounts, even low levels of contamination with modern DNA can contribute a large fraction of the final sequences generated and can substantially influence analyses. Contamination was shown to be an issue in the first published sequences from a Neandertal [19]. Subsequently, several approaches to avoid and estimate modern human contamination have been developed [20,21].

These methods rely on sequence differences between archaic and modern humans, an unexpected ratio of reads from the sex chromosomes, or on patterns of ancient DNA damage present in the sequence reads [20,22–24]. Most ancient genome sequencing projects have focused on the analysis of samples with low levels of contamination or on the identification of reads carrying deamination.

Archaic human genomes

Though Neandertals have long been recognized as close relatives of modern humans [25] it was not until 1999 that the first DNA sequences from a Neandertal were produced [26]. Using the sequence of the hypervariable region of the mitochondrial genome of the Neandertal type specimen, Krings *et al.* provided the first molecular evidence that Neandertals fall outside the mitochondrial variation of modern humans, showing that they were not the direct ancestors of modern humans but a sister group [26] (Figure 1a). The advent of next-generation sequencing technologies combined with methodological advances in DNA extraction, sequencing library preparation, and a method to selectively deplete the sequencing libraries of microbial contamination [21] led to the sequencing of the first complete Neandertal mitochondrial genome in 2008 [27], and to a draft nuclear genome sequenced to onefold coverage followed in 2010 [21].

More recently, the discovery of an exceptionally well-preserved bone, with in excess of 75% endogenous DNA, together with further improvements in library preparation [28•] facilitated the sequencing of the nuclear genome to 50-fold coverage from a Neandertal found in Denisova cave in the Altai mountains [29•].

Sparse nuclear data from at least five additional Neandertals have been generated by low coverage shotgun sequencing or targeted genomic capture experiments [21,29•,30].

Similarly, mitochondrial genomes which are present at high copy numbers in cells and therefore more easily accessible, have been sequenced from a number of Neandertals by both capture and shotgun sequencing methods [27,31–33].

The Denisova cave earlier yielded another bone with more than 80% endogenous DNA. Sequencing of the DNA extracted from the bone showed that this individual carried a mitochondrial genome sequence that diverged before the separation of Neandertals and modern humans suggesting that this individual belonged to a distinct human group (Figure 1a). Following the tradition started with the Neandertals, this group was named 'Denisovans' after the place in which they were first identified [34].

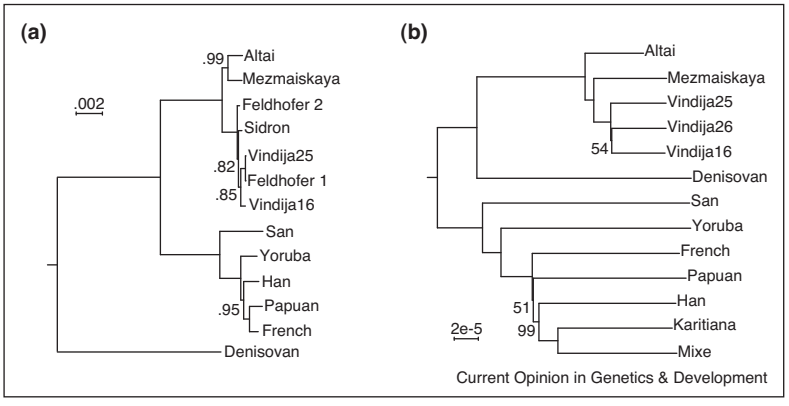
In contrast to the mitochondrial genome, the nuclear genome, sequenced to 30-fold coverage, showed that Denisovans and Neandertals are, in fact, sister groups with respect to modern humans (Figure 1b). The discordant mitochondrial and nuclear genome histories in Denisovans may result from the chance survival of a divergent mtDNA lineage in the Denisovans or may point to introduction of the mtDNA by admixture with another more deeply diverged hominin.

Early modern human genomes

For many years the sequencing of ancient DNA from early modern humans was considered problematic because of the difficulties with distinguishing present-day human contamination from the endogenous DNA.

In 2010 the first mtDNA sequences of a 30 000 year-old modern human from Kostenki were published together

Figure 1



Mitochondrial and nuclear genome relationships between present-day humans, Neandertals and the Denisovan. The Neandertals are from: Sidron (Spain), Vindija (Croatia), Feldhofer (Germany), Mezmaiskaya (Russia), Altai (Russia). **(a)** Bayesian tree of mitochondrial genome sequences. Posterior probabilities are given for branches with support less than one. **(b)** Neighbour-joining tree based on autosomal transversions. Bootstrap values are shown for branches supported by less than 100% of 1000 bootstrap replicates.Figure modified from Prüfer *et al.* [29•].