MILESTONE 12

Waking the dead: sequencing archaic hominin genomes

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The advent of PCR in the 1980s made ancient DNA (aDNA) sequencing a reality, but early attempts to sequence human aDNA were frustrated by sample contamination and degradation. In 2010, the first draft sequence of a Neanderthal genome heralded a revolution in palaeogenomics, advancing our understanding of the relationships between extinct and extant hominin lineages and how modern humans spread throughout the world.

Ancient DNA research has been limited only by the technology, and never by a lack of interesting questions to be asked. The first aDNA studies using soft tissues from museum specimens were hampered by depurination and fragmentation in the sequenced DNA. By the late 1980s, it was possible to extract DNA from ancient bone, but the limited throughput of the Sanger sequencing technology, and the absence of human reference genomes for comparisons or filtering, made the detection of genuine nuclear aDNA sequences challenging. While the field moved forwards with studies of plants and non-human animals, hominins were somewhat neglected, until next-generation sequencing revolutionized the genomics field as a whole.

Credit: The Natural History Museum / Alamy Stock Photo

A major step forwards took place in February 2010, when Rasmussen and colleagues published the first ancient human genome sequence for an extinct Palaeo-Eskimo, quickly followed by the first Neanderthal genome sequences in April. In their 2010 study, Green et al. generated libraries from three Neanderthal bones from Croatia, dating to >38,000 years before present, fine-tuned these to screen out contamination from microorganisms and modern humans, and sequenced them with a combination of 454 and Illumina technologies, combining the three individuals into a 1.3× coverage genome. Comparisons with the human and chimpanzee genomes allowed the identification of Neanderthal sequences, leading to extensive new inferences about hominin molecular evolution, adaptation and — perhaps most controversially — gene flow between hominin groups. The Neanderthal genome shared more genetic variants with present-day Europeans and Asians than with Africans, suggesting some gene flow after the divergence of these lineages of modern humans. Genomic segments with high similarity to Neanderthal DNA were detected in present-day non-African genomes, providing direct evidence for this introgression (and allowing estimation of the time when it occurred).

To tackle the problem of limited endogenous aDNA quantities, Meyer et al. developed a single-stranded DNA library preparation method for a Denisovan sample in 2012. Their approach substantially increased the number of ancient molecules that could be incorporated into the DNA sequencing libraries, thereby yielding enough DNA sequence to obtain the first high-quality ancient genome, with 30× coverage of a single individual. This study provided further evidence for hominin admixture. Serendipitously, a more recent sequencing study revealed the genome of the offspring of a Neanderthal and a Denisovan.

DNA capture technologies have revolutionized our understanding of human disease and their introduction into the palaeogenomics field enabled the study of polymorphisms present in tens or hundreds of ancient genomes. In the first large-scale study by Haak et al. in 2015, capture was used for the analysis of 394,577 polymorphisms in 69 European individuals dating from 8,000–3,000 years ago, allowing the authors to make conclusions about population movements and turnover during the Neolithic period and the spread of Indo-European languages into Europe.

The field of ancient DNA has illuminated aspects of history that fascinate people from all walks of life. With rapid technological advances and many questions already tackled, the limiting factor may now become the availability of suitable samples, in itself a potentially controversial topic for many reasons.

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Nature Communications

ORIGINAL ARTICLES Green, R. E. et al. A draft sequence of the Neandertal genome. *Science* **328**, 710–722 (2010) | Meyer, M. et al. A high-coverage genome sequence from an archaic Denisovan individual. *Science* **338**, 222–226 (2012) | Rasmussen, M. et al. Ancient human genome sequence of an extinct Palaeo-Eskimo. *Nature* **463**, 757–762 (2010)

FURTHER READING Slon, V. et al. The genome of the offspring of a Neanderthal mother and a Denisovan father. *Nature* **561**, 113–116 (2018) | Haak, W. et al. Massive migration from the steppe was a source for Indo-European languages in Europe. *Nature* **522**, 207–211 (2015) | Sankararaman, S. et al. The date of interbreeding between Neandertals and modern humans. *PLoS Genet.* **8**, e1002947 (2012)