

EVOLUTIONARY GENOMICS

Our Neanderthal cousins

The complete mitochondrial genome sequence of a 38,000 year-old Neanderthal confirms that our closest hominid relatives did not contribute significantly to the mitochondrial DNA (mtDNA) lineage of extant humans, and that the two groups diverged about 660,000 years ago.

Pääbo and colleagues extracted mtDNA from a Neanderthal bone that was discovered in Croatia in 1980. One of the technical challenges they needed to meet was ensuring sufficient sequence coverage so that bases were not miscalled because of contamination with modern human DNA or degradation of the ancient DNA (a process that can lead to C to T transitions) — a feat that was achieved using high-throughput 454 sequencing technology. The authors also kept contamination levels very low using specialized clean-room facilities. The next hurdle

was genome assembly, for which the authors designed a specific procedure for ancient DNA that allows gaps to be ‘filled in’ where coverage is low. This involved aligning sequences with the extant human mitochondrial genome, which established an overall picture of how stretches of Neanderthal mtDNA fit together. This information was then used to design primers for PCR and Sanger sequencing to fill in the missing pieces.

The authors found 206 single nucleotide differences between the Neanderthal sequence and a reference human sequence, only a few of which were located in the 13 coding mitochondrial genes. This level of difference is substantially greater than that within modern human sequences, strongly indicating that the two lineages have not mixed. Using standard molecular

phylogenetic techniques, the authors also showed that the divergence time between Neanderthals and modern humans is 520,000–800,000 years. The ratio of non-synonymous to synonymous substitutions in the Neanderthal lineage was unusually high for primates, implying limited purifying selection and low effective population size in Neanderthals.

The technical advances in this study will be crucial for sequencing the Neanderthal nuclear genome. It will be interesting to see if that genome gives similar results for divergence times, and whether more definite signs of lineage-specific selection can be observed.

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ORIGINAL RESEARCH PAPER Green, R. E. *et al.*
A complete Neanderthal mitochondrial genome sequence determined by high-throughput sequencing. *Cell* 8 Aug 2008 (doi:10.1016/j.cell.2008.06.021)

