



### **The first million have been sequenced**

#### **Max Planck researchers in Leipzig decode one million base pairs of the Neandertal genome**

**The Neandertal people are humanity's closest extinct relatives. Their genome could supply the key to the genetic changes that have taken place during the development of modern humans. Using specially developed technology, scientists at the Max Planck Institute for Evolutionary Anthropology in Leipzig and from the 454 Life Sciences Corporation in the US have now found the first million base pairs of the Neandertal genome. This technology allows them to copy the few short pieces of DNA which have survived for 38,000 years in fossilized bones. The researchers assume that they will be able to present a draft version of the whole genome in two years (Nature, 16 November 2006).**

The Neandertal people were spread throughout the whole of Eurasia for at least 300,000 years, developing their own culture until around 45,000 years ago when their relative, modern humans, moved in and displaced them - despite their sturdier build. The first Neandertal bones came to light in 1856, raising questions that still remain unanswered today. What are the differences between the two hominids, apart from the physical characteristics? And how did they come together? For a long time, the only way to answer these questions was to search the dirt of millennia in dark caves for the fossilized remains of our ancestors.

Scientists at the Max Planck Institute for Evolutionary Anthropology in Leipzig and from the 454 Life Sciences Corporation in the US are pursuing a new strategy. As if attempting a huge jigsaw puzzle, they want to construct the complete Neandertal genome from the small pieces of DNA that have survived in fossilized bones. These paleogeneticists have now decoded the first million base pairs, which represent approximately 0.04 percent of the whole Neandertal genome. They hope that this will allow them to look at the "script" that tells the story of the emergence of the Neandertal people and therefore also that of modern humans

Most of the million Neandertal base pairs are identical with the homologous regions of the genomes in humans and in chimpanzees. Humans and the Neandertals share more than ten thousand base pairs; humans differ from the Neandertals and chimpanzees in a little over 400 base pairs. Neandertals differ from humans and chimpanzees in around 3,500 positions. This relatively large number is the result of imperfections caused by the age of the DNA. A direct comparison of the three hominids revealed that only approximately seven percent of the genetic changes between humans and chimpanzees occurred after the human line had separated from that of the Neandertal.

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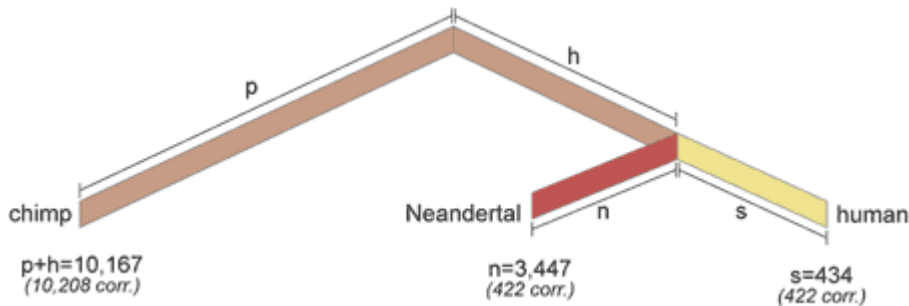
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This makes the question as to what effect these few genetic differences had all the more exciting. How did a few genetic mutations result in the separate development of our ancestors? Modern humans' lineage and that of the Neandertals separated approximately 500,000 years ago - the current data produced by the scientists in Leipzig confirms earlier estimates based on the analysis of mitochondrial DNA (mtDNA). Because there are several occurrences in each cell, this cell organelle supplies more DNA than the nucleus, so it is easier to analyse than nuclear DNA.

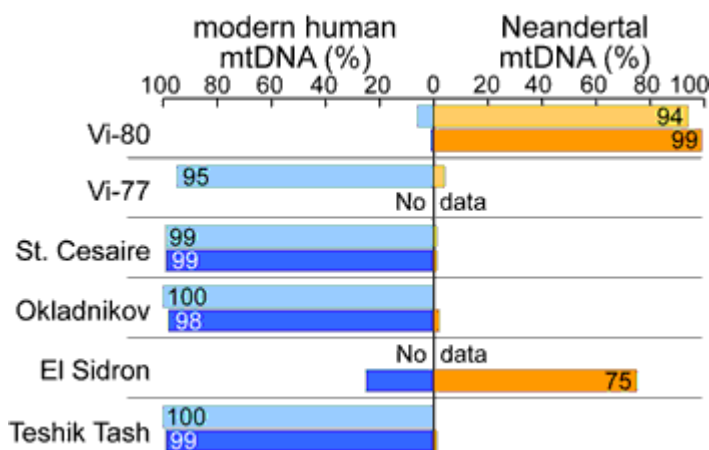


**Fig. 1:** This shows how chimpanzees, Neandertals and humans developed separately. At the top is an unknown ancestor, from whom the chimp developed in the chimp line (p) and the shared ancestor of modern humans and the Neandertals developed in the hominid line (h). The Neandertal line (n) and the modern human line (s) then branched. The figures at the bottom show the number of different base pairs. The numbers in brackets are arrived at when the damage to the Neandertal DNA is corrected for.

*Image: Max Planck Institute for Evolutionary Anthropology*

It is much more complicated to sequence Neandertal DNA than human DNA - in the same way as old manuscripts decompose with the ravages of time, DNA also becomes fragile. Moreover, there is always a great deal of extraneous DNA present, from bacteria and fungi that colonised the body after death and from the people working with the fossils. Precisely because there are so many similarities between human and Neandertal DNA and because the aim is to find the subtle differences between them, it is disastrous if human DNA is found on the bones.

Therefore, the researchers first examined 100-200 mg of different bones and teeth in each case. Analysis of the extracted hominid mtDNA revealed that the samples differed drastically in the amount of contamination from modern human DNA. In some cases only one percent of the pieces of mtDNA originated in prehistoric times, with 99 percent from modern humans. However, the researchers had some luck with a sample from the Vindija cave in Croatia. The reverse was true - 99 percent originated from a Neandertal.



**Fig. 2:** *The graph shows the percentage of the DNA from the fossils examined that originated from Neandertals (yellow) or modern humans (blue). In each case, two different pieces of DNA were examined (light and dark bars). At the top is the most suitable fossil (Vi-80) from the Vindija cave in Croatia.*

*Image: Max-Planck-Institut für evolutionäre Anthropologie*

Thanks to the new technology developed by 454 Life Sciences, the paleogeneticists working with Svante Pääbo were able to reproduce the nucleic DNA from this bone material for the first time and then sequence it. It was possible to identify both an X and a Y chromosome, proving that the bone was from a male individual.

The researchers also wondered how often the Neandertal carries the allele from his ancestors or shared a new variant with modern humans. "In approximately 30 percent of all cases, the Neandertal did indeed have the new gene variant," explained Svante Pääbo. This high value is incompatible with previous thinking, which is that the human and Neandertal populations simply split apart. "It is possible that there was an exchange of genetic material between modern humans and the Neandertals," said Pääbo. As the differences in the X chromosome of the Neandertal are much greater than in the autosomes, the researchers are speculating that this gene flow happened mainly in male representatives of modern humans to the Neandertal. However, more extensive sequencing of the Neandertal genome is required to test this possibility.

The researchers want to use the method they have established with this study to decode all of the Neandertal nuclear genome. They need to extract DNA from around 20 grams of Neandertal bone material to do this. "The genome sequence might then not only offer new information about our extinct relatives," said Pääbo, "but also provide information about the regions in our own genome which have undergone particularly marked changes since the split from the Neandertals 500,000 years ago. It is highly likely that these regions were affected by positive selection and could have played an important part in the emergence of modern humans.

[CB/AJ]

#### **Related Links:**

[1] [MPS Press Release "Neandertal Genome to be Deciphered" 20 July 2006](#)

#### **Original work:**

Richard E. Green, Johannes Krause, Susan E. Ptak, Adrian W. Briggs, Michael T. Ronan, Jan F. Simons, Lei Du, Michael Egholm, Jonathan M. Rothberg, Maja Paunovic & Svante Pääbo

#### **Analysis of one million base pairs of Neandertal DNA**

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