

700,000 year old horse genome sequenced

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Dr. Ludovic Orlando and Professor Eske Willerslev, both of the Centre for GeoGenetics at the University of Copenhagen, have sequenced the genome of the oldest horse ever found on Earth. Bone fragments from a 700,000 year old nag excavated in Yucon, Canada had enough DNA in them to reveal new aspects of the evolutionary history of the horse. Credit: Photo: Uffe Wilken/University of Copenhagen

It is nothing short of a world record in DNA research that scientists at the Centre for GeoGenetics at the Natural History Museum of Denmark (University of Copenhagen) have hit. They have sequenced the so far

oldest genome from a prehistoric creature. They have done so by sequencing and analyzing short pieces of DNA molecules preserved in bone-remnants from a horse that had been kept frozen for the last 700.000 years in the permafrost of Yukon, Canada. By tracking the genomic changes that transformed prehistoric wild horses into domestic breeds, the researchers have revealed the genetic make-up of modern horses with unprecedented details. The spectacular results are now published in the international scientific journal *Nature*.

DNA molecules can survive in fossils well after an organism dies. Not as whole chromosomes, but as short pieces that could be assembled back together, like a puzzle. Sometimes enough molecules survive so that the full [genome sequence](#) of extinct species could be resurrected and over the last years, the full genome sequence of a few [ancient humans](#) and archaic [hominins](#) has been characterized. But so far, none dated back to before 70,000 years.

Now Dr. Ludovic Orlando and Professor Eske Willerslev from the Centre for GeoGenetics have beaten this DNA-record by about 10 times. Thereby the two researchers – in collaboration with Danish and international colleagues – have been able to track major genomic changes over the last 700.000 years of evolution of the horse lineage.

First, by comparing the genome in the 700,000 year old horse with the genome of a 43,000 year old horse, six present day horses and the donkey the researchers could estimate how fast mutations accumulate through time and calibrate a genome-wide [mutation rate](#). This revealed that the last common ancestor of all modern equids was living about 4.0-4.5 million years ago. Therefore, the evolutionary radiation underlying the origin of horses, donkeys and zebras reaches back in time twice as long as previously thought. Additionally, this new clock revealed multiple episodes of severe demographic fluctuation in horse history, in phase with major climatic changes such as the Last Glacial

Maximum, some 20,000 years ago.

The world's only wild horse

The results also put an happy end to a long discussion about the so-called Przewalski's Horse from the Mongolian steppes. This horse population was discovered by the Western world in the second half of the nineteenth century and rapidly became threatened. It almost became extinct in the wild by the 1970s but has survived until now following massive conservation efforts. The evolutionary origin of this horse, that shows striking physical differences compared to domesticated horses, as well as an extra-pair of chromosomes, remained a mystery.

The researchers reveal now that the Przewalski's horse population became isolated from the lineage leading to the present day domesticated horses about 50.000 years ago. As the scientists could detect similar levels of genetic diversity within the Przewalski's Horse genome than in the genomes of several domestic breeds, this suggests that the Przewalski's Horses are likely genetically viable and therefore worthy of conservation efforts.

True Single DNA Molecule Sequencing

The geological context and dating information available was very strong and was built on about ten years of field work. Additionally, cold conditions, such as those from the Arctic permafrost, are known to be favourable for DNA preservation. But even so:

"Sequencing the first genome from the Middle Pleistocene was by no means straightforward," says Dr Ludovic Orlando who, together with his team, spent the most of the last three years on this project.

The researchers first got excited when they detected the signature of those amino-acids that are most abundant in the collagen as this could indicate that proteins had survived in situ. They even got more excited when they succeeded in directly sequencing collagen peptides. When they detected blood proteins, it really started looking promising because those are barely preserved. At that stage, it could well be that ancient DNA could also be preserved.



University of Alberta researcher Duane Froese with the skull of the extinct Late Pleistocene horse *Equus lambei* in the Klondike area, Yukon. Credit: Photo by Grant Zazula

And indeed DNA was present. In tiny amount as the vast majority of

sequences generated actually originated from environmental micro-organisms living in the bone. But with Helicos true Single DNA Molecule Sequencing, the researchers managed to identify molecular preservation niches in the bone and experimental conditions that enabled finishing the full genome sequence.

"This was methodologically challenging but clearly some parameters worked better than others, says Professor Eske Willerslev. But sequencing was just half the way really." Professor Willerslev continues: "Because 700,000 years of evolution and damage, it is not something that does come without any modification to the DNA sequence itself. We had to improve our ability to identify modified and divergent ancient horse sequences by aligning them to the genome of present day horses."

Quite a computational challenge, especially when the level of DNA modification outcompasses that seen in any other Arctic horses from the Late Pleistocene. Dr. Orlando explains: "Levels of base modifications were extremely high, for some regions even so high that every single cytosine was actually damaged. This, and the phylogenetic position of the ancient horse outside the diversity of any horse ever sequenced, provided clear evidence that the data was real."

Professor Willerslev adds: "The results of the studies and the applied techniques open up new doors for the exploration of prehistoric living creatures. Now with genomics and proteomics, we can reach ten times further back in time compared to before. And new knowledge about the horse's evolutionary history has been added – a history which is considered as a classical example in evolutionary biology and a topic which is taught in high schools and universities."

More information: Paper: [DOI: 10.1038/nature12323](https://doi.org/10.1038/nature12323)

Provided by University of Copenhagen

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