MAX PLANCK SOCIETY

Press Release

G / 2009 (18) February 12th, 2009

Embargoed: February 12th, 2009, 16:00

Neanderthal genome completed

The Max Planck Institute for Evolutionary Anthropology and 454 Life Sciences Corporation have completed a draft sequence of the Neanderthal genome

The Max Planck Institute for Evolutionary Anthropology, in Leipzig, Germany, and the 454 Life Sciences Corporation, in Branford, Connecticut, will announce on 12 February during the 2009 Annual Meeting of the American Association for the Advancement of Science (AAAS) and at a simultaneous European press briefing that they have completed a first draft version of the Neanderthal genome. The project, made possible by financing from the Max Planck Society, is directed by Prof. Svante Pääbo, Director of the Institute's Department of Evolutionary Anthropology. Pääbo and his colleagues have sequenced more than one billion DNA fragments extracted from three Croatian Neanderthal fossils, using novel methods developed for this project. The Neanderthal genome sequence will clarify the evolutionary relationship between humans and Neanderthals as well as help identify those genetic changes that enabled modern humans to leave Africa and rapidly spread around the world, starting around 100,000 years ago.

Figure *The Neanderthal genome research group: Johannes Krause, Adrian Briggs, Richard E. Green, Svante Pääbo (from left to right)*

Image: Max Planck Institute for Evolutionary Anthropology

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ISSN 0170-4656

Neanderthals were the closest relatives of currently living humans. They lived in Europe and parts of Asia until they became extinct about 30,000 years ago. For more than a hundred years, palaeontologists and anthropologists have been striving to uncover their evolutionary relationship to modern humans. Pääbo, a pioneer in the field of ancient DNA research, made the first contribution to the understanding of our genetic relationship to Neanderthals when he sequenced Neanderthal mitochondrial DNA in 1997. Together with the company 454 Life Sciences, Pääbo has now announced a new milestone in Neanderthal research. The two groups have sequenced a total of more than 3 billion bases of Neanderthal DNA, generating a first draft sequence of the entire Neanderthal genome. Altogether, these fragments make up more than 60% of the entire Neanderthal genome. These DNA sequences can now be compared to the previously sequenced human and chimpanzee genomes in order to arrive at some initial insights into how the genome of this extinct form differed from that of modern humans.

In 2006, Pääbo's group published papers together with 454 Life Sciences which showed that it was possible to use the 454 technology to determine large amounts of nuclear DNA sequences from late Pleistocene animals such as mammoths as well as the Neanderthal. Building on these results, Pääbo and Dr. Michael Egholm, Vice President of Research and Technology of 454 Life Sciences, a Roche Company, initiated an ambitious project to sequence the Neanderthal genome. Together, the groups have overcome a number of technical obstacles in order to arrive at this first view of the entire genome of an extinct form of human.

One essential element developed by Pääbo's group was the production of sequencing libraries under "clean-room" conditions to avoid contamination of experiments through human DNA. They also designed DNA sequence tags that carry unique identifiers and are attached to the ancient DNA molecules in the clean room. This makes it possible to avoid contamination from other sources of DNA during the sequencing procedure, which was a problem in the initial proof-of-principle experiments in 2006. They also used minute amounts of radioactively labelled DNA to identify and modify those steps in the sequencing procedure where losses occur. Together with other advances implemented during the project, these innovations drastically reduced the need for precious fossil material so that less than half a gram of bone was used to produce the draft sequence of 3 billion base pairs.

In order to reliably compare the Neanderthal DNA sequences to those of humans and chimpanzees, the Leipzig group has performed detailed studies of where chemical damage tends to occur in the ancient DNA and how it causes errors in the DNA sequences. The researchers found that such errors occur most frequently towards the ends of molecules and that the vast majority of them are due to a particular modification of one of the bases in the DNA that occurs over time in fossil remains. They then applied this knowledge to identify which of the DNA fragments from the fossils come from the Neanderthal genome and which from microorganisms that have colonized the bones during the thousands of years they lay buried in the caves. They have also developed novel and more sensitive computer algorithms to put the Neanderthal DNA fragments in order and compare them to the human genome.

In total, the group has determined over 100 million DNA sequence fragments from fossils by the 454 technology and over a billion DNA sequences with the Solexa technology, another sequencing technology which is particularly efficient in reading many short sequences. The majority of the sequence comes from Neanderthal bones from Vindija Cave in Croatia, which the group studies as a part of a long-term collaboration between the Croatian Academy of Sciences and Arts and the Berlin-Brandenburg Academy. In order to test if the findings from this Neanderthal are typical of those of other Neanderthals, the researchers have also sequenced several million base pairs from Neanderthals from other sites. Professor Javier Fortea and colleagues from Oviedo, Spain, have excavated 43,000-year-old Neanderthal bones under sterile conditions at El Sidron, Spain, that have yielded DNA sequences, while Dr. Lubov Golovanova and Dr. Vladimir Doronichev from St. Petersburg, Russia, have contributed a 60-70,000-year-old bone from Mezmaiskaya Cave in the Caucasus. In addition, Dr. Ralf Schmitz from the LVR-Landesmuseum in Bonn, Germany has allowed a sample to be removed from the 40,000-year-old Neanderthal type specimen, which was found in 1856 in the Neander Valley, the source of the name, Neanderthal. This will allow crucial

findings from the Croatian Neanderthal to be verified in several Neanderthals including the specimen that defines the Neanderthals as a distinct group.

In order to aid in the analysis of the Neanderthal genome, Dr. Pääbo has organized a consortium of researchers from around the world that plans to publish their results later this year. They will look at many genes of special interest in recent human evolution, such as FOXP2, which is involved in speech and language in modern humans, as well as genes such as the Tau locus and the microcephalin-1, implicated in brain aging and development, respectively. Variants of the latter genes found among present-day humans have been suggested to have come from Neanderthals. The preliminary results suggest that Neanderthals have contributed, at most, a very small fraction of the variation found in contemporary human populations.

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On February 12th Dr. Pääbo and other scientists from the Institute, Dr. Egholm from 454 Life Sciences, as well as palaeontologists and anthropologists from Croatia, Spain, and Germany, who contributed to the project, will be available at a press conference, held simultaneously at the AAAS Annual Meeting in Chicago and in Leipzig, to present further details and answer questions. The news briefing will begin at 9:00 a.m. CST/16:00 CET. Reporters will be able to log onto a special Internet site to prepare for the live video-streaming teleconference beginning one hour prior to the event at 15:00 CET at http://www.eva.mpg.de/english/events.htm. Questions can be submitted via email to neandertal@eva.mpg.de both before and during the conference. Dr. Pääbo will also present the scientific findings at a plenary talk at the AAAS meeting in Chicago on February 15th.

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