Denisovans in Asia join the Eurocentric Neanderthal in the awareness of our evolutionary past

A public health view into an unusual scientific domain might enlarge the understanding of genomics and its connection to morbidity and mortality for Asian populations.

One and a half decades ago, an ancient forefather of ‘Homo sapiens’ made it into the awareness of the public. High school knowledge might be almost forgotten, but at least the name Neanderthal was still remembered. The mass media envisioned clones of the extinct human returning to the traffic jams of modern times or thought about romantic relationships between Neanderthal men with homo sapiens women (1). The excitement was caused by scientist sequencing archaic DNA from various remains of the Neanderthal genomes and the detection of fragments of ancient genomes in present-day populations. The Neanderthal DNA within our genome can influence our mood, and skin color, interferes with blood coagulation, and plays a role in the immune system (2). Soon, the Neanderthal was joined by a formerly unknown hominin called Denisovan, detected in Siberia and roaming through Asia and the Pacific (3). Topping the enthusiasm was the finding of a genome from a Neanderthal and Denisovan individual having a child (4). A peculiar new field, Paleogenetic, was recognized by the general public (5). The straightforward high school knowledge about our ancient past, assuming one kind of archaic homo simply gave way to the next one, was challenged.

<u>The Nobel Prize, paleogenetic and admixture</u>

Paleogenetic is not only a fascinating new field in science but should also be considered important to public health. Our evolutionary past influences health and diseases, as this blog pointed out recently (6, 7). A year after the relatively new field was introduced here, Svante Pääbo, whose initiative created this field, got the Nobel prize in 2022 (8). He started his career in Archology and was interested in Egyptology. His attempt to isolate DNA from a Mummy failed because of contamination with modern DNA and, at that time, insufficient technology (9). Nowadays, computer-assisted ‘high-throughput sequencing (HTS) techniques’ with ‘cost-effective’ equipment made it possible to investigate the genetic history of archaic populations and homo sapiens ‘tens of thousands of years’ back, with the help of ancient DNA (aDNA) (10, 11).

Three remarkable publications about the aDNA of a Neanderthal and a Denisovan, as well as from a 4.000-year-old Eskimo, were the beginning of rapid developments of the discipline (3, 12, 13). In the year 2020, relevant publications increased to 1.860 from 43 during the years between 2010 and 2014 (11). Human lineage separated from the Neanderthal about 550.000 years ago and the Denisovan about 400.000 years. Around 370.000 to 220.000 years ago, mitochondrial DNA and the Y chromosome were replaced by the ones from modern humans. How this happened is not known yet. Admixture (a scientific word for having sex) with modern humans occurred with Denisovan for four different time periods and with the Neanderthal for three periods (11, 14).

Transfer of genetic material into the pool of the genome took place between different archaic lineages and both ways. Thus, about 50.000 years ago, a genome of a Denisovan disclosed a

Denisovan father and a Neanderthal mother (4). The youngest mixture of a Neanderthal with modern humans dates to about 40.000 years when the Neanderthals disappeared from Europe around 41.000 yeras (15). Archeological records from France and northern Spain, at least Neanderthal and homo sapiens lived alongside for 1.400 to 2.900 years but might have met even for a much longer time, being five to six thousand years (16).

Denisovans lived in Asia, and archaic genetic material was highest in people of Oceania

While traces of the archaic Neanderthal were found in Europe and north and east Asia, Denisovans populated Asia and Oceania. Gene flows involved Neanderthals, Denisovans, and early modern humans, as could be shown from the genomes of Melanesian individuals (14). A mixture of genes also might have occurred with unknown archaic individuals with Denisovans and left 0.5 to 5% in the genome of present-day humans (17).

Africa excepted, worldwide genetic variation with archaic genetic material is higher derived from Denisovan populations compared with Neanderthals and is highest in the population of Oceana (18). The magnitude of the genome of modern humans from the Neanderthal is estimated to be 1.5 up to 2.1%. The Denisovans contributed 3 to 6% of their genome to the people of Oceania and 0.2% to Asian populations (17). For the inheritance from the Neanderthal, Sven Pääbo favors a different calculation. At birth, our genome depends on 50% of each of our parents and from our grandparents to 25% from each. This decreases to 12%, and we are down to 1.5% of our DNA after six generations. That is equal to the amount we inherited from the Neanderthal. However, recombination follows for each generation because of germ cell formation. This could mean that around 40% of the Neanderthal genome is approximately in the present population (19).

Traces of Denisovans on the Tibetan plateau

Presently, research results about Denisovan genomes don't match in magnitude those from Neanderthal. In the more humid climate of tropical countries, skeletons and bones that could be used for aDNA investigations are rare. Lately, however, further indications of the spread of Denisovans through Asia were found. One of the first indications that Denisovans inhabited East Asia, besides the finding at the Denisovan cave of Siberia, emerged at the Tibetan Plateau in the Baishiya Karst Cave (BKC) at Xiahe, Gansu in China. A lower jawbone with a giant molar and premolar roots differed from the remnant from the Neanderthal. Radioactive uranium decay from the bone's carbonate crust dated the jaw back about 160.000 years. Collagen extracted from the molar revealed an amino acid sequence matching the Denisovans (20).

The fossil was found by a Buddhist monk about 40 years before it was recognized as belonging to a Denisovan. The monk meditated in that cave, still a holy place. The monk gave the unusual find to China's officially designated 'living Buddha', who recognized the finding as a probably important archeological object. It finally ended up on the shelves of the Lanzhou University at Gansu, northwest China until it emerged again as a famous relic (21).

The Baishiya Karst Cave developed to be a treasure for paleontology and especially for research into the Denisovans. While today it is still a Buddhist sanctuary, scientists who explore the cave must avoid disturbing devotees. So, during wintertime and at night, inventors intensively rummaged systematically around the cave's sediments at different locations and depths for Denisovans' mitochondrial DNA and other noteworthy items. The cave is believed to be 50 km long. It seems that working is only allowed within the 60-meter-long entrance chamber. The temperature within the cave during the cold season is about 8 to 9^0 C. Considering that the height of the Tibetan Plateau measures exactly 3.280 meters, the outside temperature might drop to -18^0 C in the wintertime. It seems the place was a perfect shelter for archaic and prehistoric humans.

Denisovan DNA was detected for 100.000 and 60.000 years as well as for 45.000 years back. Over 1300 stone artifacts and almost 580 animal bone fragments were collected. Bones from medium size animals such as gazelles, marmots, and foxes were found. Evidence for extinct animals, i.e., hyenas and rhinoceros, was identified in deeper layers. Most layers contained mammalian mitochondrial DNA. DNA with the 'frequency of apparent terminal substitutions of cytosine (C) to thymine (T) at the 5' end indicates aDNA. Such aDNA was identified as 95 to 100% for Denisovan, 0 to 11% for modern humans, and 0 to 5% for Neanderthal (22, 23).

Whether the Tibetans inherited the adaptation to stay in high altitudes from the Denisovans still is under discussion. A variant of the gene EPAS1 was common for those who lived in the cave. The gene enables red blood cells to catch oxygen easily (24). The gene, however, moved through the population within the past 5.000 years. So, it could not generally be around in archaic hominins. It is hypothesized that the gene is only available for people living at high altitude throughout the year but don't remain in other populations (22).

Two different genera of Denisovans

Probably, there are two different genera of Denisovans. The aDNA of two modern homo individuals derived from the Salkhit Valley in northeastern Mongolia being about 34.000 years old, and another one, a 40.000-year-old hominin from Tianyuan, close to Peking, had genomes clearly from DNA segments derived from Denisovans. Such segments could not be detected in present-day Aboriginals from Australia and Papuans (25).

Denisovans living in the islands of Southeast Asia and Australia and moving around the Pacific were not challenged to adapt to high altitudes. Instead, survival of infectious diseases common in the tropics was of more importance. The genetic variants were 'introgressed' in modern humans from the Denisovans and not from the Neanderthals when modern humans arrived in Southeast Asia about 200.000 years ago. The variants were close to genes of the human immune system responding to viruses, so to flu and the chikungunya virus. (Chikungunya is transmitted by the same mosquito as dengue fever but is a different virus and could cause heavier pain than dengue.) Denisovan DNA in the genome of present-day people from Papua New Guinea affects immune cells and immune-related processes, 'suggesting'… that the… 'variants can impact gene regulation in Vivo' (26).

Ancient genes influence cytokine reactions

The ancient gene variants are associated with the genes OAS2 and OAS3. The OAS complex works differently for Tuberculosis regarding the active and chronic forms and generally inhibits the replication of some RNA and DNA viruses within the cell. The influence of the cytokine reaction is complex. An overreaction of cytokines, known as a 'cytokine storm', which was very much feared at the beginning of the Covid-19 event because it contributed to the mortality, could be modulated. The advantage of those with a high Denisovan genomic inheritance might benefit from fine-tuning the immune response (26-28).

Denisovan face to face

Scientists in Asia working in the field of Paleogenetic may be in favor of findings related to Denisovans. The discipline is leaning more toward Neanderthal, and so is Eurocentric. While museums, such as the one close to where Neanderthal was found in the 19th century, display images of how the ancient hominin might have looked, such a picture is missing for Denisovans. To make good for a missing personification, a Chinese and European team used what is known from the genome of the Altai Denisovan Girl and the findings of the Tibetan cave producing a picture and statue of the head of the Denisovan women (29, 30). She looked like a Neanderthal, with a sloping forehead, protruding lower jaw, and a broad face. Compared with the Neanderthal, she resembles more present-day humans. The lower jaw fits with the fossil of the Tibetan cave.

The Dragon Man

In the future, her image could somehow change in case it is agreed that she is, as a Denisovan, related to the 'Dragon Man'. This is not yet the case, and the 'Dragon Man' is another twist in the Denisovan story. The 'Dragon Man', in the scientific literature referred to as the 'Harbin archaic human cranium', is a scull found in 1933 in northeast China. In Archology, the fossil is important, and the circumstance of how it was found and the environment it was buried in. Its 'unsystematically' recovery and the history before it turned out to be recognized triggered the controversial discussion as to what 'species of homo' it belongs (31).

During the Second Sino-Japanese war, the Japanese invaded an area including the Northeast of China and Russia called Manchuria from September 1931 to February 1932 (?). In what is now China, the Songhua River, a tributary of the Amor River, passes through the city of Harbin. (The place seems to interest tourists now because of the heavy snowfall during winter and the fantastic snow monuments then.) During the construction of the nowadays called Dongjian Bridge, a Chinese man worked for the Japanese as a labor contractor. Discovering the skull, he did hide it from the Japanese boss by burring it in a former well. He probably recognized the value of the fossil because he might have been impressed by the Peking man cranium, which was discovered in 1929 with much public attention. He didn't want to become known that he once cooperated with the Japanese. He returned to farming. Shortly before he died, he finally told his grandchildren about the skull. Qiang Ji, the co-author of three publications related to the fossil, persuaded them to donate it to the Geoscience Museum of Hebel GEO University, China (32). The family wanted to remain anonymous, and unfortunately, the grandfather didn't disclose where he found the skull.

Is Dragon Man a new homo species or a Denisovan?

Various relevant methods of Archology were used to estimate the skull's age from sediments close to the bridge. This included strontium isotopic and non-destructive X-Ray- fluorescence analysis as well as uranium-series disequilibrium dating. It was concluded that the 'Harbin cranium' age was about 138.000 to 146.000 years old (33). The scull is described as having 'a long and low cranial vault, a wide and low face, large and almost square orbits, a massively supraorbital torus, flat and low cheekbones and thick alveolar bone with a large molar'. Comparing the Harbin cranium with Homo erectus, Homo heidelbergensis, Homo sapiens, and additional fossils from East Asia, it appears that the skull 'combines a mosaic of primitive and derived character'. The features are seen as differing from 'all other named Homo species'. It resembles present-day humans and replaces Neanderthal as the most recent ancient homo species before the present-day Homo sapiens. The supposed new Homo species was named 'Homo longi'. (Long means dragon in mandarin.) (34, 35).

A few anthropologists oppose the assumption that the Dragon man belongs to a new homo genus. They argue that the conclusion is premature and needs more evidence, and the mandible from the Tibet plateau fits well with the remains of the Dragon Man. It seems that he is much admired, but those in the discipline of paleoanthropology would like to appreciate him as a Denisovan (31).

Will Denisovans finally also be detected in Thailand?

Following the recent Asian evolutionary ancestor from Russia within the Siberian Altai to the freezing heights of Tibet, and the snowier southwest of the border of China with Russia, then down to tropical Papua New Guinea, one wonders when they will appear on our doorsteps in Thailand. Probably we don't have to wait long. A tooth, being a molar, was unearthed from the Annamite Mountains of northern Lao PDR and assumed to belong to a Middle Stone Age old Denisovan (36). In the Lampang province, traces of humans, unfortunately of the late and not the middle Pleistocene, were discovered (37). The residues are 'only' around 30.000 years old. By waiting long enough, Thai Denisovan relics might be found. It might be expected that a somehow different morbidity and mortality spectrum from the Caucasians of the present-day Asia population will be uncovered due to the Denisovans heritage.

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