The Implications of Homo Neanderthalensis Genome on Homo Sapiens

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***Abstract*—Neanderthals, the closest evolutionary relatives of present-day humans, had been studied mostly based on their physiological traits. In addition, with the emergence of DNA sequencing technologies, the complete Neanderthal genome has been obtained and published. With that comes studies comparing Neanderthal genomes with that of modern humans. These researches revealed Neanderthal's influences on humans in various ways. This dissertation explores the extent of Neanderthal contributions to modern humans and their physiological influence, demonstrating that Neanderthal-derived genes can have both favorable and adverse effects on humans, depending on the mode of inheritance. Overall, this study provides valuable insights into the potential significance of studying archaic hominins in the context of human evolution and medicine.**

***Keywords*—paleongenetics, neanderthal, human evolution, DNA sequencing**

I. Introduction

After the completion of the Human Genome Project (HGP) in 2003, scientists embarked on investigating the mechanisms behind the chains of nucleotides, giving rise to a new area of research known as genomics. Additionally, the complete Neanderthal genome was sequenced and published in 2013 by a group of scientists led by Svante Pääbo. The DNA sequence was predominantly derived from a well-preserved female Neanderthal from Siberia. By comparing her genome with that of Homo sapiens, specifically those outside Africa, it is discovered that approximately 2% of Neanderthal DNA had been inherited and dispersed throughout the modern human genome, with varying abundance in different regions [1].

Svante Pääbo was awarded the Nobel Prize in Physiology or Medicine for their groundbreaking discoveries concerning the genomes of extinct hominins and human evolution. Although extensive work on DNA sequencing, there is limited literature summarizing the effects, whether advantageous or disadvantageous, of Neanderthal-derived genes on modern humans. Furthermore, the significance of paleogenetic studies is often overlooked. As Neanderthals have had close contact with humans, the varied genetic contribution from Neanderthal can be evidence of the out-of-Africa migration route of early humans.

This paper aims to consolidate the milestones in this specialized area of focus. It will begin with an introductory section on Neanderthals and the history of DNA sequencing technology, followed by a description of how the complete Neanderthal genome was sequenced. Techniques used to overcome contamination will also be included. Considering that Neanderthals have made genome-wide contributions to modern humans, the paper will further discuss the implications of Neanderthal DNA on aspects such as immunity, fertility, and pain sensitivity of Homo sapiens. A conclusion about the significance of the related research will be given at the end.

II. Background on Neanderthal and Sequencing Technology

A. An Introduction to Neanderthal

The species Homo neanderthalensis. was first discovered in 1864 in Germany and is said to be human's closest extinct relative. It is recognized for its elongated oval-shaped skull with ribs that resemble more like carnivorous animals, than those of man [2]. This piece of finding was named Neanderthal 1 as it was the first to be identified in the species, though people later realized that prior fossil discoveries – the one in 1829 at Engis, Belgium, and that in 1848 at Gibraltar also orient from Neanderthal.

Before DNA sequencing technology was introduced to the study of archaic humans, studies of this kind have always been in the regards of archeology and anthropology. By comparing the skeletal features of the remains, researchers have come up with several conclusions including their average brain size. The braincases of Neanderthal men and women averaged 1546 cm^3 in comparison to that of 1402 cm^3 of Anatomically Modern Humans (AMH) with similar ecological habits and adaptations to Neanderthal [3]. However, the larger brain size does not necessarily indicate intelligence. Some argue that much of their brain has been devoted to vision and body control [4]. Neanderthal's adaptations to cold climates are also worth noticing considering their living environment. Most of the Neanderthal population gathered and settled in the harsh Eurasia landscape. Adaptations to the climate include brown adipose tissue that acts as storage of body fat and an enlarged nose to warm air [5].

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Researchers employing the aforementioned methods may find themselves akin to individuals stumbling through a pitch-black cave, arriving at incorrect conclusions occasionally. It is important to note that shared skeletal traits can, in some cases, be a result of adaptation to similar environmental pressures, rather than an indication of shared ancestry. For instance, the enlargement of Neanderthal paranasal sinuses observed by researchers may be explained from a biomechanic perspective [6].

B. The Sequence of Sequencers

The introduction of genetics to the study of Neanderthal became the turning point for the field. Before demonstrating the technologies used in Neanderthal genome sequencing, a brief review of DNA sequencers will be given in this section.

The order of nucleic acids in the polynucleotide chain indicates hereditary ancestry. The chains are like written history coded in organisms, making it critical for scientists to understand evolutionary history and the mechanism of life. Deciphering DNA sequences is significant for this reason.

In the mid-1970s, Fred Sanger made significant improvements to Wu and Kaiser's method, developing the first generation of DNA sequencing technology and making use of electrophoresis. This method involves the use of DNA polymerase to synthesize a DNA strand following the primer. This is based on the random incorporation of chain-terminating dideoxynucleotides during in vitro DNA replication. Radioactively labeled nucleotides are incorporated for identification in DNA synthesis. By running the synthesized DNA fragments on a polyacrylamide gel and observing the gel under UV light, scientists were able to infer the sequence of nucleotides. This is a low-throughput relatively time-consuming technology, though its accuracy is high at 99.99%. The Human Genome Project mostly adopted this method.

Following the invention of DNA sequencing technology by Sanger, another groundbreaking technology known as Polymerase Chain Reaction (PCR) was developed. PCR allows the amplification and replication of specific segments of DNA, leading to the generation of millions of desired copies for detailed analysis. This exponential amplification greatly facilitated the detection and analysis of DNA sequences. PCR amplifies a specific region of a DNA strand which is usually 0.1 and 10 kilobase pairs (kbp) in length. Components involved in PCR setup include the template DNA, a polymerase, two complementary primers, deoxynucleoside triphosphate (dNTPs), and a buffer solution. The primer will pair with the template DNA strand in the process of annealing. dNTPs then bind to the remaining DNA sequence subsequently.

The second generation of DNA sequencing called large-scale sequencing was marked by the introduction of the 454 Genome Sequencer FLX. A large number of samples and very long DNA pieces such as the whole chromosome can be sequenced using this generation of technology, thereby enhancing sequencing efficiency to a large extent. This technology revolutionized the method of DNA library preparation, simplifying it to a large extent. The common approach is to cut large DNA fragments with restriction enzymes into smaller fragments. Fragmented DNA is usually cloned by a DNA vector and sequenced subsequently. The assembly of short DNA fragments into long chains is done electronically. This method of DNA sequencing was adopted for Neanderthal genome sequencing and will be discussed later.

In addition to that, there emerged a promising third-generation sequencing technology known as Single Molecule Sequencing (SMS). This method involves sequencing individual DNA molecules directly, without the need for prior amplification or cloning. SMS technology continues to be refined and optimized, with nanopore sequencing being a prominent example. Nanopore sequencing holds great potential for the future of DNA sequencing with its ability to sequence DNA in real-time by threading DNA strands through a tiny pore and measuring changes in electrical current.

The field of DNA sequencing has witnessed remarkable advancements from the first-generation Sanger sequencing to the second-generation 454 technology, and onward the third-generation SMS methods. The quest for new sequencing technologies remains the driving force in the field of life sciences.

C. Who We Are and How We Got Here

1) Getting DNA involved in paleontology

Russel Higuchi and his colleague sequenced 229 nucleotide pairs of mitochondrial DNA from an extinct member of the horse family, the quagga. Their article came with the first phylogenetic tree drawn for extinct species [7]. This marked the foundation of paleogenetics, the study of the past through the examination of preserved genetic material from the remains of ancient organisms.

Inspired by Rostislav Holthoer, a renowned Egyptologist, Svante Pääbo introduced DNA sequencing technology to the study of archaic organisms. That brought paleontology study to a molecular level. After working on the DNA sequences of extinct mammals and Egyptian mummies, Pääbo switched his interest to archaic humans in the 1990s. He used the prior two generations of DNA sequencing technologies, previously mentioned, after narrowing his focus to Neanderthal mitochondrial DNA and then the entire genome.

2) Sequencing and contamination

The study of Neanderthal genetics began with mitochondrial DNA (mtDNA) due to its abundance, which would make the sequencing process easier. However, it is important to note that mtDNA only provides information about the maternal lineage. It is also relatively short, approximately 16,500 nucleotides in length, compared to the entire chromosome, which consists of around 50 million nucleotides. Therefore, research teams continued their work by working toward nuclear DNA after mtDNA was sequenced. Nuclear DNA contains significantly more genetic information but is less abundant.

Neanderthal DNA, like other archaic DNA, was heavily contaminated and had degraded into segments of approximately 200 base pairs (bp) on average. Consequently, specific experimental techniques were developed to overcome these challenges.

Contamination of ancient DNA can be primarily categorized by postmortem degradation of DNA and contamination from the environment, including microorganisms and bacteria's DNA, as well as human contamination during and after excavation. Postmortem degradation of DNA sequences can introduce inaccuracies to the result. For example, the deamination of Cytosine (C) leads to it being substituted by Thymine (T), and this process tends to occur more frequently toward the 5' end of the DNA sequence. To address this issue, a statistical framework was employed to isolate endogenous ancient DNA sequences from contaminating sequences using postmortem degradation patterns [8]. Additionally, primary contamination, which can be as high as 95% to 99%, is caused by microbes in the burial site. To selectively remove certain DNA sequences, a specially designed restriction enzyme was used, as it targets DNA sequences that differ significantly from human DNA. As a result, the proportion of Neanderthal DNA sequenced increased by 4- to 6-fold. Moreover, contamination after excavation was minimized by regularly bleaching the sterilized room and subjecting it to ultraviolet light, which effectively kills bacteria in the environment. These practices together contribute to the low contamination rate of less than 1% for the published Neanderthal genome. One method used to assess the level of contamination in the sequence involves searching for genetic information of the opposite sex in the sample. For instance, if a sample is identified as female, it can be screened for nonrecombining parts of the Y chromosome, as no Y chromosome genetic information is expected to be present in a female sample.

3) Evidence of gene flow

A question that intrigues scientists is whether Neanderthals have interbred with modern humans. The presence of shared morphological traits observed in Neanderthal fossil remains [9, 10] has long suggested the possibility of interbreeding between Neanderthals and modern humans. However, some genetic studies have presented conflicting results. For example, the sequencing of the Neanderthal mitochondrial DNA revealed that Neanderthal mtDNAs fall outside the variation observed in modern human mtDNAs. Since mtDNA represents the maternal lineage and does not undergo recombination, it is concluded that Neanderthals did not significantly contribute to the modern human mtDNA gene pool [11]. Additionally, a study on Single Nucleotide Polymorphisms (SNPs) also evidenced this argument. It shows that Europeans and Africans share a similar number of SNPs with Neanderthals [12]. If interbreeding has occurred, it would be expected that Europeans, who share a geographic overlap with Neanderthals, would have a greater number of shared SNPs compared to Africans, who do not have Neanderthal ancestry. The final word on this matter came in a paper published in 2010, which confirmed interbreeding between Neanderthals and modern humans [13]. The draft genome sequence of a Neanderthal revealed that Neanderthals share more genetic variants with present-day humans in Eurasia than with sub-Saharan populations. SNP tests were conducted to examine gene flow between Neanderthals and modern humans. If gene flow had ceased before the differentiation of present-day human populations, an equal number of SNPs would be expected, regardless of human demographic factors. However, the study found a greater genetic affinity between Neanderthals Europeans, and Asians than with Africans. Since Neanderthals did not inhabit Africa and no fossil remains have been found there, this study provides strong evidence for Neanderthal-human interbreeding and suggests that the majority of the gene flow occurred from Neanderthals to modern humans. The contribution of the Neanderthal genome varies among populations. Further research, such as the publication of the complete genome of a Neanderthal in 2013, has said that individuals outside Africa inherit approximately 1.5% to 2.1% of their genes from Neanderthals [14]. The exact number is calculated with the use of the molecular clock.

Just to mention, according to Svante Pääbo's book "The Neanderthal Man", this finding was discovered as early as 2009. In an email, Pääbo's colleague reported that high-accuracy data with minimal uncertainty (0.22%) showed evidence of interbreeding. The similarity between the European population and Neanderthals exceeded that of Africans by 2%, which, though minimal, is clear.

After obtaining the full sequence of the Neanderthal genome, the average DNA divergence between Neanderthals and humans was calculated. The divergence for autosomes was 12.7%, while for the X chromosome, it ranged from 11.9% to 12.4% [13]. To determine the divergence between humans and Neanderthals, the chimpanzee genome was used as a reference, which has an average DNA divergence of 6.5 million years with humans. The autosomal DNA sequence divergence was estimated to have occurred approximately 830,000 years ago, while the divergence of the species was predicted to have happened between 553,000 and 589,000 years ago [14].

4) When and where

Initially, there were two hypotheses about how modern humans obtained Neanderthal-derived genetic information. The first hypothesis suggests that it could have resulted from direct interbreeding between modern humans and Neanderthals outside of Africa. The second hypothesis proposes that it could have been inherited from Neanderthal ancestors within Africa. It is suggested that the latter is more likely [15].

Neanderthals first appeared in Europe, with the earliest fossil record dating back to 400,000 years ago. Their territory later expanded to Western Asia, and their extinction is estimated to have occurred around 41,030–39,260 years ago [13, 16]. Around the same time, Anatomically Modern Humans (AMH) migrated out of Africa and ventured into Neanderthal territory, resulting

in a temporal overlap of the two species' living areas. The estimated period of coexistence and interbreeding was 2,600–5,400 years [16]. It was at least 80,000 years ago that the two species came into contact in Europe and Asia [13].

5) To what extent

Determining the extent of Neanderthal ancestry in modern humans involves analyzing DNA sequences and comparing them to the Neanderthal genome. Scientists have used various methods to estimate the percentage of Neanderthal DNA in different populations. One approach is to compare the genomes of modern humans with the Neanderthal genome and identify regions of similarity that are unique to Neanderthals. By quantifying the amount of Neanderthal DNA in these regions, researchers can estimate the proportion of Neanderthal ancestry in different populations.

The percentage of Neanderthal DNA in modern humans has been found to vary across populations. Generally, individuals of non-African descent have a higher proportion of Neanderthal ancestry compared to individuals of African descent. This suggests that interbreeding between Neanderthals and modern humans was more common outside of Africa. It is important to note that the estimated percentages of Neanderthal ancestry are averages and can vary among individuals within a population. Additionally, the methods used to estimate Neanderthal ancestry have limitations and uncertainties. Nevertheless, these analyses have provided valuable insights into the extent of interbreeding between Neanderthals and modern humans.

III. Positive and Negative Effects

A. Positive Effects

1) Heightened pain sensitivity

The SCN9A gene encodes the Nav1.7 voltage-gated sodium channel, which is critical in nociception signaling [17]. This channel facilitates the passage of sodium ions across neuronal membranes during changes in electrical membrane potential.

Amino acid substitutions M932L, V991L, and D1908G in the SCN9A gene are believed to have originated from Neanderthals [18]. These variants entered the modern human population through intermingling with Neanderthals or Denisovans, based on the size of the DNA segment (26 kb around M932L and V991L, and 110 kb around D1908 G) and their recombination rate, rather than being inherited from a common ancestral group.

A study adopting statistical analysis examined the occurrence of these three missense mutations in modern-day humans. Two cohorts were involved: the CANDELA cohort, consisting of individuals from Brazil, Chile, Colombia, Mexico, and Peru, and the Colombian Quantitative Sensory Testing (QST) cohort, which partly overlapped with the CANDELA cohort with 7,594 participants. A 4 Mb region centered around SCN9A was scanned in the genomes of both cohorts to determine Neanderthal ancestry. A total of 12,220 tracts, with an average length of ~123 kb, were identified, indicating 1.83% and 2.51% Neanderthal ancestry in the QST and CANDELA cohorts, respectively. The most significant tract of introgression, occurring on a Native American genomic background, accounted for 5.62% and overlapped with the M932L, V991L, and D1908G coding positions. This finding is consistent with the notion that Neanderthal alleles contributing to Native Americans have also influenced the Latin American population in this study.

A phenotypic study conducted by Pierre Faux *et al.* employed five types of tests: (i) single locus tests, (ii) a joint test of these variants, (iii) haplotype-based tests, (iv) summing the number of Neanderthal alleles across loci, and (v) regional introgression analyses. The study found that Neanderthal ancestry in SCN9A is associated with a lower mechanical pain threshold after sensitization with mustard oil. Mustard oil, used in the research, leads to rapid activation and sensitization to noxious stimuli.

This conclusion aligns with the findings of Zeberg and his colleagues in 2020. The full Neanderthal variant, carrying all three substitutions, or the combination of V991L with D1908G, exhibits reduced inactivation, indicating increased sensitivity of the peripheral nervous system to painful stimuli in Neanderthals. Carriers of the three variants of Nav1.7 experience one or more forms of pain more frequently than non-carriers. They also experience more pain than individuals carrying one or two variants. The research group introduced synthesized genes encoding the modern human and Neanderthal versions of Nav1.7 into Xenopus laevis oocytes and observed an increased availability of sodium channels for activation, as well as a prolonged open state once activated, resulting in a lower threshold for the generation of an action potential. The V991L and D1908G combination also causes a shift in inactivation. Similar results were observed in tests conducted with human embryonic kidney cells. Additionally, the depolarizing shift in the inactivation curve has an excitatory effect on activation when investigating the human peripheral nerve [18].

Heightened pain sensitivity may result in increased awareness of potential dangers and illnesses, giving the population an evolutionary advantage. However, the direct impact of increased pain sensitivity on our ancestors has yet to be fully revealed.

2) Increase fertility

Progesterone is a steroid sex hormone produced by the ovaries, placenta, and adrenal glands that plays a crucial role in menstruation and the early stages of pregnancy. This hormone prepares the uterus for zygote implantation, stimulates the mammary glands during pregnancy, and helps prevent pre-term birth and hemorrhage. Progesterone binds to the Progesterone Receptor (PGR), a steroid receptor that triggers conformational changes. The receptor-steroid complex then dimerizes and interacts with promoters that contain PROG-responsive elements within hormone-regulated target genes [19]. The PGR gene is located on chromosome 11 and consists of 8 exons and 7 introns. Among the present-day population,

there is a polymorphic variant of the progesterone receptor known as V660L, which involves a missense substitution in exon 4 and an Alu insertion between exon 7 and 8. This variant occurs at a frequency of 20% in various populations, including Europeans, Native Americans, and Asians [18]. This PGR variant has also been found in a homologous form in two Neanderthal genomes, where it is located on a DNA segment of at least 56 kb [18].

To investigate the relationship between the V660L polymorphism and its phenotype, a statistical analysis was conducted using data from 452,264 individuals of British descent in the UK Biobank. The findings suggest a negative correlation between the Neanderthal allele and "hemorrhage in early pregnancy". Individuals carrying this allele also reported fewer miscarriages and more sisters, although no significant difference was observed in the number of brothers. In conclusion, it is suggested that the Neanderthal variant of the PGR gene contributes to increased fertility [18].

This study was done through statistical analysis. Further research should be carried out to investigate the physiological influence of the Neanderthal-derived gene.

3) Protection to the SAR-CoV-2 pandemic

COVID-19 has been a topic of great concern in recent years. In 2020, Hugo Zeberg and Svante Pääbo stated that a specific inherited section located on chromosome 3 increases the risk of severe syndrome and prolongs hospitalization for COVID-19. This finding will be discussed in a later section. The negative selective pressure on modern humans caused by this inheritance has sparked their interest. The same research duo also investigated and demonstrated that humans also benefit from an inherited section on chromosome 12 from Neanderthals, protecting against the SAR-CoV-2 pandemic [20].

Among the loci that are known to have significant effects on the risk of severe illness upon COVID-19 infection, a haplotype on chromosome 12 is derived from Neanderthals. The index single-nucleotide polymorphism on this locus matches all three high-quality Neanderthal genomes and is absent among 108 African genomes. This haplotype spans 75 kb, which is longer than the expected maximum length (16.3 kb) derived from a population ancestral to Neanderthals and modern humans [20]. Previous studies have also observed gene flow in this region, supporting the fact that this haplotype is derived from Neanderthals [21].

The Neanderthal haplotype contains parts or all of the three genes OAS1, OAS2, and OAS3, which encode for oligoadenylate synthetases. These enzymes are induced by interferons and activated by double-stranded RNA. They produce short-chain polyadenylates, which, in turn, activate ribonuclease L, an enzyme that degrades intracellular double-stranded RNA and activates other antiviral mechanisms in cells infected by viruses [20]. The rs10774671 SNP is said to affect a splice acceptor site in OAS1.

In conclusion, the Neanderthal OAS variant provides advantages when encountering RNA viruses by increasing enzymatic activity. It has been tested and found to protect against West Nile virus, Hepatitis C virus, and SAR-CoV [22, 23]. The modern human OAS haplotype with lower enzymic activity may conserve human energy. Furthermore, the frequency of the protective Neanderthal haplotype may have increased between 20,000 and 10,000 years ago and again during the past 1,000 years, suggesting positive selection [20].

4) Neanderthal-Derived toll-like receptors

Toll-Like Receptors (TLRs) are a class of proteins responsible for innate immunity. They are expressed on sentinel cells and act as the first line of defense. A study has shown that genes on chromosome 4 code for a cluster of three TLRs (TR1, TLR6, TL10) that carry repeated archaic human introgression, two from Neanderthal and one from Denisovan [24]. These three receptors are expressed on the cell surface membrane and are known to detect bacterial, fungal, and parasite components such as flagellin and glycolipids, eliciting inflammatory and antimicrobial responses in adaptive/innate immunity.

Among the seven core modern human haplotypes of the gene, three are found almost exclusively in non-African populations and share more similarities with archaic genome sequences. The introgression of the 143 kb gene length is evidenced by a low probability of Incomplete Lineage Sorting (ILS). The likelihood of a low recombination rate is also ruled out. The low diversity of the introgressed haplotypes also supports introgression.

Positive selection of the archaic haplotypes is also observed. The estimated proportion of Neanderthal-derived ancestry in non-Africans ranges from 1.5% to 2.1%. Surprisingly, the frequency of haplotype III reaches 11%–51%, whereas haplotype IV is only 2%–10%, exceeding the estimated percentage. This may be due to the evolutionary advantage conferred by archaic-like haplotypes. Individuals carrying these haplotypes show increased microbial resistance and risk of allergic disease. A positive correlation is observed between archaic-like alleles and reduced Helicobacter pylori seroprevalence, as well as increased susceptibility to allergic disease [24].

B. Negative Effects

1) Reduced fertility

Debate exists regarding the classification of Neanderthals as an independent species, the Homo neanderthalensis, distinct from the species they interbred with, Homo sapiens. Although the offspring resulting from the interbreeding of these two species are fertile, the introduction of Neanderthal-derived genetic information into modern humans seems to be associated with a decrease in male fertility, as evidenced by a deficient presence of Neanderthal ancestry on the X chromosome [25].

The largest region with a reduced Neanderthal ancestry is located on the X chromosome, representing approximately one-fifth of the autosomes [25]. This observation is in contrast to the extremely young genetic divergence time between the X chromosome of

chimpanzees and modern humans. The estimated genome divergence between humans and chimpanzees based on autosomal data was approximately 7 million years ago. In comparison, the age difference between the X chromosome and the autosomes is approximately 1.2 million years [26]. This discrepancy suggests that several strong selective sweeps, potentially specific to certain populations, may explain the low Neanderthal ancestry and the high chimpanzee ancestry observed on the X chromosome [27].

These findings align with Haldane's rule, which states that when offspring resulting from the mating of two different animal races exhibit the absence, rarity, or sterility of one sex, that sex is the heterozygous sex. In the case of humans, males are affected. Additionally, previous studies have indicated that 2–3% of the non-African genome may originate from Neanderthals. The low level of Neanderthal ancestry suggests a low rate of interbreeding (< 2%), possibly due to a strong avoidance of interspecific matings and/or reduced fitness of hybrids. However, further research is needed to determine whether these barriers occur pre- or postzygotically [28]. This notion is supported by the reduced Neanderthal ancestry observed in modern non-African populations, which has decreased from 6–9% in the Oase1 individual, one of the oldest European early modern humans remains (approximately 42,000 to 37,000 years old), to approximately 2% of modern non-Africans [25]. The decreasing Neanderthal contribution to humans over time supports the reduced fertility.

In conclusion, Neanderthal DNA inherited by modern humans, particularly on the X chromosome, does not appear to be favored by natural selection and might result from decreased fertility of the hybrid. The reproduction fertility between modern humans and Neanderthal is post-zygotic.

2) Increased severity of COVID-19

COVID-19 has become a topic of great significance in recent years. The influence of genetic and molecular factors on human adaptation and evolution has been recognized for several decades. In addition to the positive impact of the Neanderthal genome on modern humans, as mentioned earlier, recent studies have suggested a positive correlation between the genome and the severity of infection and hospitalization [29, 30]. These findings indicate that specific genetic factors, particularly a gene located on chromosome 3, may play a role in the transmissibility of SARS-CoV-2, the novel coronavirus responsible for COVID-19.

The region on chromosome 3, which includes sex-related genes, has shown a significant association with severe COVID-19. Analysis of multiple Neanderthal samples (Vindija 33.19 Neanderthal, Altai, and Chagyrskaya 8 Neanderthals) confirms the presence of a specific gene variant derived from Neanderthals, rather than from common ancestors. This conclusion is supported by examining the length of the haplotypes and the local recombination rate (0.53 CM per Mb). The probability that the core 49.4-kb haplotype and the 333.8-kb-long Neanderthal-like haplotype in humans result from a common ancestor with Neanderthals is 0.0009 and $1.6\times10-26$, respectively. The former haplotype occurs in South Asia at an allele frequency of 30% and in Europe at 8%. In terms of carrier frequencies, 50% of people in South Asia carry at least one copy of the risk haplotype, whereas 16% of Europeans are carriers. The absence of Neanderthal-derived haplotypes in the African population aligns with the known location of Neanderthal-Homo sapiens interbreeding.

A comparison of the population affected by and deaths caused by SARS-CoV-2 in Iran and Mongolia reveals an interesting phenomenon. Despite Iran having a population 26 times larger than Mongolia, it reported 1170 times more confirmed cases. The presence of the Neanderthal haplotype in the Iranian population may explain this discrepancy. However, it remains unknown which specific feature confers the risk of developing severe COVID-19. It is important to note that the carrier frequency of the haplotype is up to ~65% in South Asia and~16% in Europe, while it is almost absent in East Asia. A hypothesis would be that even though the haplotype is detrimental for its carriers during the current pandemic, it may have been beneficial in earlier times in South Asia.

C. Insights into Adaptation and Survival

The implications of Neanderthals on modern humans typically revolve around immunity and reproduction. These studies have provided insights into the evolutionary advantages conferred by the Neanderthal population. As this archaic group inhabited Europe and Asia before our ancestors, they may have been better adapted to the environment and acquired advantageous traits. Interbreeding with Neanderthals may have therefore increased the likelihood of survival for modern humans. Some arguments in the previous sections may appear conflicting, regarding the effects on fertility and COVID-19 in particular. However, these research studies have focused on various chromosome locations, thus only reflecting the phenotype of the specific loci. In conclusion, introgressed genes may confer advantages on one side while being detrimental from another perspective.

IV. Conclusion

To conclude, about 2% of Neanderthal-derived DNA can be found in non-African populations. Though some of those have limited influence on human physiology, some play a critical role in immunity, fertility, and pain sensitivity. Controversial findings regarding COVID-19 severeness and fertility are concluded by different researchers. This may have to do with the difference in chromosome region studied. Therefore, genes from the Neanderthal may have both advantageous and detrimental effects on humans, depending on the loci.

There are also some limitations to this dissertation. It would be more persuasive if more evidence were available. As DNA sequencing is a fairly new technology, it has been only several decades for introducing it to archaic DNA sequencing. Thus, limited research has been

completed, especially regarding Neanderthal genetic implications on humans. Moreover, some of these researches are based on statistical analysis, rather than from a biological perspective. Further research should be carried out studying the physiological influence of Neanderthal on modern humans.

The significance of studying the contribution of archaic humans to modern humans should not be trivialized and there are promising implications in this area. For example, according to the Eastern scenario, a group of migrating individuals interbred with Neanderthals in East Asia before further spreading to regions including China and even Australia. It is believed that significant population movements have not occurred since then, shaping the current demographic landscape. Moreover, the Denisovan, the first and so far, the only hominin species discovered through genome analysis, has been found to confer high-altitude adaptation in Tibetans by increasing their hemoglobin affinity.

The importance of paleontology is often neglected [31]. Quoting a saying from the book "Who We Are and How We Got Here": "Could the exact position of each individual before the explosion be reconstructed by piecing together the scattered remains and studying the shrapnel in the walls? Could languages long extinct be recalled by unsealing a cave still reverberating with the echoes of words spoken there thousands of years ago?" These questions raised by the young Ph.D. student reflect the core objectives of paleogenetics. The student, David Reich, himself later participated in Pääbo's project. The emergence of paleogenetics offers a more accurate approach to studying the past. Previously, the most commonly employed method in archaeological studies involved anatomical analysis of fossil remains, which is to some extent less precise. In contrast, DNA serves as direct evidence of extinct species and evolutionary events. By incorporating genetic studies into paleontology, the conclusions drawn receive strong support. Some argue the practicality of such research. From a personal perspective, scientific research should not solely focus on medical advancements or other seemingly more practical developments. Research driven by pure curiosity, such as tracing the origins of human beings, holds significant value in itself. As mentioned above, the reconstruction of the complete Neanderthal genome not only confirmed interbreeding with modern humans but also provided insights into human evolution. It revised our understanding of humans' out-of-Africa migration route

Conflict of Interest

The author declares no conflict of interest.

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