ABSTRACT

Objective: Mutations or introgression can cause and rise adaptive alleles of which some can be beneficial. Archaic humans lived more than 200,000 years ago in Europe and Western Asia. They were adapted to the environment and pathogens that prevailed in these locations. It can therefore be thought that modern humans obtained significant immune advantage from the archaics alleles.

Materials and Methods: First, data were collected by meta-analysis from previously identified genetic diseases caused by alleles that were introgressed from archaics. Second, the in silico model portal (http://www.archaics2phenotype.xxx.edu.tr) was designed to trace the history of the Neanderthal allele. The portal also shows the current distribution of the genotypes of the selected alleles within different populations and correlates with the individuals phenotype.

Results: Our developed model provides a better understanding for the origin of genetic diseases or traits that are associated with the Neanderthal genome.

Conclusion: The developed medicine model will help individuals and their populations to receive the best treatment. It also clarifies why there are differences in disease phenotypes in modern humans.

Keywords: Archaic DNA, single nucleotide polymorphism, toll-like receptor

Developing an Online Portal for Determining the Genomic Signature of Archaic DNA that are Associated to Modern Human Genetic Diseases: A Meta-Analysis Study

Niyazi Senturk1 ID, Mahmut Cerkez Ergoren2,3 ID

Cite this article as: Senturk N, Ergoren M.C. Developing an Online Portal for Determining the Genomic Signature of Archaic DNA That Are Associated to Modern Human Genetic Diseases: A Meta-Analysis Study. Eurasian J Med 2020; 52(2): 153-60.

1Department of Biomedical Engineering, Near East University Faculty of Engineering, Nicosia, Cyprus
2Department of Medical Biology, Near East University School of Medicine, Nicosia, Cyprus
3DESAM Institute, Near East University, Nicosia, Cyprus

Received: January 9, 2019
Accepted: August 22, 2019
Available Online Date: June 2, 2020

Correspondence to: Mahmut Cerkez Ergoren
E-mail: mahmutcerkez.ergoren@neu.edu.tr

DOI 10.5152/eurasianjmed.2019.18424

Content of this journal is licensed under a Creative Commons Attribution 4.0 International License.

Introduction

Archaic humans lived more than 200,000 years ago in Europe and Western Asia [1]. They were well adapted to the surrounding environment and pathogens [2]. Archaic humans are the subspecies of Homo sapiens, and include Homo heidelbergensis, Homo rhodesiensis, Homo neanderthalensis, and Homo antecessor. There are anatomical differences between archaic and modern humans. Modern humans have evolved from archaic humans and Homo erectus. When modern humans migrated from Africa, they were faced with some difficulties such as different climate, environmental challenges, and pathogens in the new region [1]. In the regions where they migrated from Africa, they hybridized with Neanderthals and Denisovans. Thus, some alleles passed from Neanderthals to modern humans.

Neanderthals evolved 250,000 years ago and were known as H. neanderthalensis [3]. Neanderthals were geographically spread from England to Siberia. They were powerful hunters. H. sapiens began to spread in the world from Africa around 30,000 years ago [4]. Therefore, Neanderthals and early humans coexisted and mated. Modern genetic data show that Neanderthals mated with modern humans in Europe when they coexisted. As a result, almost 1-4% of the modern humans’ genome consists of genes from Neanderthals. The genes that were inherited from Neanderthals help us fight deadly viruses such as Epstein-Barr. However, gene mutations have also resulted in diseases such as Crohn’s disease, type-2 diabetes, lupus, heart diseases, and depression [1].

This study focused on the genomes that passed from Neanderthals to modern humans.

As a significant proportion of these, archaic-specific DNAs are found within the TLR1-TLR6-TLR10 gene cluster that belong to toll-like receptors (TLRs). TLRs recognize the structure of
pathogens and provide natural immunity against many pathogens. Therefore, they are an important defense against pathogens. TLRs are known to respond to stimuli associated with various pathogens and to provide signal responses necessary for the activation of innate immune effector mechanisms and subsequent development of adaptive immunity [1].

A previous study indicated that modern humans carry three archaic-like haplotypes, and three TLRs that were inherited from archaic humans were identified. Two of these haplotypes resemble those of the Neanderthal genome, and the third haplotype resembles that of the Denisovan genome. The frequency of single nucleotide polymorphisms (SNPs) commonly shared in Neanderthal-like haplotypes varies among continents and populations. In Europe, allelic frequencies of Neanderthal-like core haplotypes are higher in Southern European populations [1].

First, we aimed to collect previously identified archaic-like SNPs that have clinical significance by meta-analysis. Then, we combined scientific knowledge and outcome from previous studies to determine diseases in modern humans, which were received genetically from Neanderthals. Second, a software program was developed to merge previously identified archaic-like SNPs and their clinical pathogenicity. Thus, this study and the developed software give us data regarding the origin of diseases in modern humans. Finally, an in silico model was designed for clinicians and researchers to trace the history of the archaic alleles and determine the possible correlation with the persons’ phenotype, thus providing a better understanding to interpret the underlying mechanisms of the diseases.

**Materials and methods**

Recent data by Dannemann et al. [1] were used to determine the archaic-like SNPs that are represented within the human genome. The research group previously identified 79 archaic-like alleles within the TLR6-TLR1-TLR10 gene cluster, which indicates repeated introgression from archaic humans. Meta-analysis was performed to find out the possible clinical significance of those genetic markers from 1000 genome populations.

Neanderthal introgression maps of Sankararaman et al. [5] and Vernot et al. [6] were used for the identification of archaic-like haplotypes that are potentially observed in modern human genomes. The introgression map presented by Sankararaman et al. [5] provides the possibility of the emergence of SNPs on the polymorphic positions of Neanderthals in modern humans [5]. Vernot et al. [6] detected introgression possibilities per SNP for all Asian and European individuals. They also calculated the difference between Neandertal probabilities from the distance between neighboring SNP pairs, including three TLR genes and an additional region of 50 kb (Chromosome 4:38.723.860-38.908.438) [1]. Potentially archaic-like SNPs in this region were identified in 109 Yoruba individuals in the genome dataset of Neanderthal or Denisovan genomes. Furthermore, Deamann et al. [6] agreed that this introgressed region covers chromosome 4 of 143 kb (Chromosome 4:38.760.338-38.905.731) and contains 61 archaic-like SNPs. This region overlaps with two haplotypes identified by Vernot et al. [6].

Microsoft visual studio C++ 2008 edition served as the integrated development environment and the C programming language was used to build software.

The software was generated in two parts. In the first part, software was created to allow the user to search information via the created database in two different ways. The user could conduct the search using SNP ID and chromosome location. The database was created in the second part.

In the in silico genome browser was designed for the first time to show the data collected so far of all identified archaic-like SNPs and their clinical significance. Therefore, a program was created to generate a database that comprised all the data collected for 79 archaic-like SNPs. The SNP variation of ancestral nucleotides, the diseases caused by the SNPs, and allele frequencies and genotype frequencies according to 1000 genome populations were added to the program, which was created separately for each SNP ID.

The website has four main sections: Homepage, About us, User guide, and Contact.

**Results**

Before we conducted our study, all significant information about archaic SNPs was scattered at different places and various genome browsers. Therefore, we aimed to merge all information as the first step. Our merged meta-analysis data provided a better understanding of the mechanism and background of diseases.

Second, the in silico genome browser was created and transferred to the online platform. This generated genome browser provides online access to researchers and clinicians. After separately creating the domain name and hosting service, they were merged to create the publicly free website http://archaics2phenotype.xxx.edu.tr/.

This website was generated for researchers and clinicians. The created database will facilitate the work of researchers because they can obtain all data with references via our browser. Our developed in silico model provides better understanding of the origin of genetic diseases or traits associated with archaic genomes. Moreover, it provides quick access to data for researchers and clinicians through genome browser.

A meta-analysis, which combines the results of multiple independent studies in a given subject, was performed to collect all the identified archaic-like SNPs. We used three international genome browsers and scientific articles for meta-analysis. We determined 79 archaic-like SNPs from the study of Dannemann et al. [1]. Then, 1000 genomes were used to check for SNP registration and identification in the 1000 genome populations.

The clinical significance of the identified SNPs was determined using the genetic browsers. In this study, three different international databases were used to collect data: Ensemble genome, 1000 genome, and dbSNP. Additionally, population genetic information was collected from 1000 genome data by Ensemble. Thus, for each population, allele frequencies and genotype frequencies were obtained for each determined SNP.

**Main Points**

- Our developed in silico model provides better understanding of the origin of genetic diseases or traits associated with archaic genomes.
- It provides quick access to data for researchers and clinicians through genome browser.
- The developed software was designed to help individuals and their belong populations to receive the best treatment in the future.
Allele frequency is the frequency of occurrence of a specific allele in a population. For example, if A is dominant allele and T is recessive allele, we have three different possibilities for allele combination. These would be AA, AT, and TT. Genotype frequency will be how often we see each allele combination in the population. But, allele frequency is how often we see each allele (A or T) in the population. Thus, allele frequency is the number of A alleles divided by the total number of alleles (A+A+T) or the number of T alleles divided by the total number of alleles in the population.

Minor allele frequency (MAF) is the less common allele frequency in the populations for each identified SNPs. MAF was selected 0.005 or more at the HapMap project. But, it was selected less than 0.005 at 1000 genome Project (http://www.internationalgenome.org/). Thus, researchers aimed to investigate low and rare variants for different populations.

We used the genetic information of 31 populations. The SNPs of these populations are registered in the three genome browsers mentioned earlier. For each SNP, allele and genotype frequencies, MAF, ancestral SNP information, chromosomal location, and importantly clinical significance was added.

Five major populations, namely African, American, Eastern Asia, European, and Southern Asia, and 26 subpopulations were used in this study. The African subpopulations studied were Yoruba in Ibadan, African Caribbean in Barbados, Mende in Sierra Leone, African Ancestry in Southwest US, Gambian in western division, Esan in Nigeria, and Luhya in Webuye. The American subpopulations studied were Colombian in Medellin, Peruvian in Lima, Mexican ancestry in Los Angeles, and Puerto Rican in Puerto Rico. The East Asian subpopulations studied were Chinese Dai in Xishuangbanna in Ho Chi Minh City, Han Chinese in Beijing, Japanese in Tokyo, and Southern Han Chinese. The European subpopulations studied were Toscani in Italy, Romanian in Geneva, and Puerto Rican in Puerto Rico. The American subpopulations studied were Caucasian in Barbados, ASW: Americans of African Ancestry in SW USA; ESP: Estonian in Estonia; GWD: Gambian in Western Division in the Gambia; LWK: Luaha in Webuye, Kenya; MSL: Mende in Sierra Leone; PJL: Punjabi from Lahore, Pakistan; GIH: Gujarati Indian from Houston, Texas.

Table 1 shows a detailed information for the SNP rs5743557. Detailed report was created for each SNP. MAF, chromosomal location, clinical significance, allele frequencies for each population including sub-populations were reported.

| Population | Allele Frequency | Genotype Frequency |
|------------|-----------------|--------------------|
| ALL        | G: 0.821        | A: 0.179           |
| AFRICAN    | G: 0.988        | A: 0.012           |
| ACB        | G: 0.974        | A: 0.026           |
| ASW        | G: 0.926        | A: 0.074           |
| ESN        | G: 1.000        | A: 0.000           |
| GWD        | G: 0.991        | A: 0.009           |
| LWK        | G: 1.000        | A: 0.000           |
| MSL        | G: 1.000        | A: 0.000           |
| YRI        | G: 1.000        | A: 0.000           |
| AMERICAN    | G: 0.852        | A: 0.148           |
| CLM        | G: 0.840        | A: 0.160           |
| MXL        | G: 0.891        | A: 0.109           |
| PEL        | G: 0.941        | A: 0.059           |
| PUR        | G: 0.764        | A: 0.236           |
| EAST ASIAN  | G: 0.607        | A: 0.393           |
| CDX        | G: 0.796        | A: 0.204           |
| CHB        | G: 0.466        | A: 0.534           |
| CHS        | G: 0.600        | A: 0.400           |
| JPT        | G: 0.442        | A: 0.558           |
| KHV        | G: 0.758        | A: 0.242           |
| EUROPEAN   | G: 0.779        | A: 0.221           |
| CEU        | G: 0.813        | A: 0.187           |
| FIN        | G: 0.904        | A: 0.096           |
| GBR        | G: 0.830        | A: 0.170           |
| IBS        | G: 0.692        | A: 0.308           |
| TSI        | G: 0.678        | A: 0.322           |
| SOUTH ASIAN | G: 0.837       | A: 0.163           |
| BEB        | G: 0.779        | A: 0.221           |
| GIH        | G: 0.811        | A: 0.189           |
| ITU        | G: 0.882        | A: 0.118           |
| PJJ        | G: 0.865        | A: 0.135           |
| STU        | G: 0.843        | A: 0.157           |

(SNP: Single Nucleotide Polymorphism; GWAS: Genome-wide association studies; MAF: Minor allele frequency; ACB: African Caribbeans in Barbados; ASW: Americans of African Ancestry in SW USA; ESP: Estonian in Estonia; GWD: Gambian in Western Division in the Gambia; LWK: Luaha in Webuye, Kenya; MSL: Mende in Sierra Leone; PJL: Punjabi from Lahore, Pakistan; GIH: Gujarati Indian from Houston, Texas).
Different input options independently or simultaneously; the software was designed to allow users to search using SNP ID, or chromosome location of the interested SNP, or both. In the second part, the output of the searched input was displayed on the screen. In this part, the data acquired were used to create the in silico browser. After the creation of the necessary algorithms, all collected informative data about the 79 archaic-like SNPs were integrated with the new software. Thus, the archaics2phenotype software was generated.

After creating the software and database, the website was generated and the database was posted on the website for online access. This website is an information sharing platform, which is available online to users.

Domain name and web hosting are required to create a website. First, the domain, archaics2phenotype.xxx.edu.tr, was created to setup the website for internet browsers. Second, the web hosting was created to activate the website. The users of the website could access all available data on the website through the web hosting. In addition, all data of the 79 archaic-like SNPs were stored in the hosting service. The database created using the software was transferred into the hosting service. Then, both the domain name and web hosting service were connected to each other and the website was activated eventually. As a final step, the interface of the website was designed. The appearance of the in silico genome browser is crucial for ease of use. The database was transferred to the website for online access and the data are at present freely available at http://archaics2phenotype.xxx.edu.tr/ to the public worldwide.

Discussion

Genetic and archeological studies showed that Neanderthals and modern humans interbred 50,000 years ago. The fossil findings revealed that the population of Neanderthals began to decline 40,000 years ago and the Neanderthal generations become extinct 39,000 years ago. There were many factors that contributed to their extinction and many hypotheses about their generation. First possibility is the rivalry for resources or direct warfare between Neanderthals and modern humans. Modern humans were more advanced technologically and were better hunters compared to the Neanderthals. Therefore, humans had better chances of survival. Second possibility is that the Neanderthals were adapted to cold climate. Their lives became difficult as the climate became warmer gradually. Another possibility could be the new pathogens and parasites found in the new environment [8].

Considerable genetic diversity occurs in humans by ancient polymorphisms. Thus, Neanderthals and modern haplotypes are not much diverged from modern human sequences. In Europe, the allelic frequencies of Neanderthal-like core haplotypes are higher in Southern European populations [1], for example, Tuscany in Italy and Iberian populations in Spain (TSI and IBS populations) with frequencies of 39.3% and 38.3%, respectively. In Asia, Neanderthal-like allele frequency core haplotypes are higher in East Asian populations, such as Japanese in Tokyo (JPT, frequency 53.4%) and Han Chinese (CHB, frequency 53.6%). The frequencies of other Asian populations are between 21.7% and 41.9% [1].

In Neanderthal genome project, the genome was obtained from the bones found in the Vindija cave. The extracted Neanderthal DNAs were compared to those of five different modern humans (French, Chinese, Papua New

---

Figure 1. Illustration of the statistical calculation of the most common diseases or traits that might have been caused by archaic-like SNPs. The horizontal axis represents the most common diseases or traits and the vertical axis illustrates the frequency of the disease. Self-reported allergy is the most seen disease followed by Helicobacter pylori infection. Interestingly, alcohol consumption and amyotrophic lateral sclerosis had an association with archaic-like SNPs (5% and 4%, respectively). Other traits that were found <1% are endometriosis, blood pressure, coronary artery disease, abnormal lymphocyte counts, Paget’s disease, height, allergic sensitization, breast cancer, and suicide attempts in bipolar and panic disorders.
Table 2. Shows each listed archaic-like SNP and its associated disease. These archaic-like SNPs mainly cause self-reported allergies and *Helicobacter pylori* serologic status.

| SNP ID  | GWAS TRAIT                                                                 |
|---------|-----------------------------------------------------------------------------|
| rs6841698 | Self-reported allergy                                                        |
| rs10024216 | Amyotrophic lateral sclerosis | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs1008492 | Endometriosis | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs10470854 | Self-reported allergy                                                        |
| rs4331786 | Amyotrophic lateral sclerosis | Self-reported allergy | Blood Pressure |
| rs4513579 | Self-reported allergy                                                        |
| rs10776482 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs4129009 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs10776483 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs11466657 | Self-reported allergy                                                        |
| rs11096955 | Self-reported allergy                                                        |
| rs11096956 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs11096957 | Amyotrophic lateral sclerosis | Endometriosis | Self-reported allergy |
| rs4274855 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs1146645 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs1146640 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs7694115 | Self-reported allergy                                                        |
| rs1146617 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs7653908 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs7658893 | v serologic status | Self-reported allergy |
| rs11725309 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs10034903 | Self-reported allergy                                                        |
| rs10004195 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs12233670 | Multiple complex diseases | Coronary Artery Disease | Lymphocyte counts | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs6834581 | Alcohol consumption                                                          |
| rs4833093 | Alcohol consumption                                                          |
| rs6531663 | Alcohol consumption                                                          |
| rs4543123 | Amyotrophic lateral sclerosis | Paget’s disease | *Helicobacter pylori* serologic status | Alcohol consumption | Self-reported allergy |
| rs4624663 | Panic disorder                                                               |
| rs4833095 | Amyotrophic lateral sclerosis | Paget’s disease | *Helicobacter pylori* serologic status | Alcohol consumption | Self-reported allergy |
| rs5743604 | *Helicobacter pylori* serologic status | Alcohol consumption | Self-reported allergy |
| rs5743596 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743595 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743594 | Height                                                                       |
| rs5743592 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743571 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743565 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743563 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743562 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs5743557 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs11722813 | *Helicobacter pylori* serologic status |
| rs1201521 | *Helicobacter pylori* serologic status | Self-reported allergy |
| rs11765434 | *Helicobacter pylori* serologic status | Alcohol consumption | Self-reported allergy | Allergic sensitization |
Guinea, and Africans from San and Yaruba groups) [2]. The results from the initial analyses showed that Neanderthal DNA was more similar to the non-African population’s DNA than to the African one. The simplest explanation of this similarity was that there was a gene flow between Neanderthals and humans. There were significant differences between the modern humans and the Neanderthals in four genes: sperm-associated antigen 17 (SPAG17), which is responsible for sperm motility [8]; protocadherin-16 (PCD16), which is responsible for wound healing [9]; transcription termination factor TTF1, which is responsible for gene reading; and RPTN gene, which is highly expressed in hair follicles, skin, and sweat glands [10]. Apart from these, the mannose receptor C-type 1 (MRC1) gene, also found in Neanderthals and modern humans, played a role in cell communication. However, the Neanderthals carried a special mutation in the MRC1 gene. This mutation did not appear in modern humans. It had led to the formation of a pale skin color and red hair in Neanderthals [11].

| SNP ID     | GWAS TRAIT                                                   |
|------------|--------------------------------------------------------------|
| rs4833103  | Helicobacter pylori serologic status | Self-reported allergy |
| rs6815814  | Helicobacter pylori serologic status | Self-reported allergy |
| rs7696175  | Breast cancer | Multiple complex diseases | Self-reported allergy |
| rs5743810  | Self-reported allergy                                      |
| rs1039559  | Self-reported allergy                                      |
| rs5743794  | Suicide attempts in bipolar disorder | Helicobacter pylori serologic status | Self-reported allergy |
| rs5743788  | Self-reported allergy                                      |
| rs7665774  | Self-reported allergy                                      |
| rs7673348  | Helicobacter pylori serologic status | Self-reported allergy |
| rs7687447  | Helicobacter pylori serologic status | Self-reported allergy |
| rs6531672  | Self-reported allergy                                      |
| rs6531673  | Self-reported allergy                                      |
| rs7681628  | Self-reported allergy                                      |
| rs2174284  | Helicobacter pylori serologic status | Self-reported allergy |
| rs3860069  | Helicobacter pylori serologic status | Self-reported allergy |
| rs17582830 | Helicobacter pylori serologic status | Self-reported allergy |
| rs2130296  | Multiple complex diseases                                  |
| rs721653   | Self-reported allergy                                      |
| rs902136   | Self-reported allergy                                      |
| rs11943027 | Self-reported allergy                                      |
| rs17582893 | Suicide attempts in bipolar disorder | Helicobacter pylori serologic status | Self-reported allergy |
| rs2381345  | Self-reported allergy                                      |
| rs1873195  | Helicobacter pylori serologic status | Self-reported allergy |
| rs17582921 | Helicobacter pylori serologic status | Self-reported allergy |
| rs6851685  | Helicobacter pylori serologic status | Self-reported allergy |
| rs6835514  | Multiple complex diseases | Coronary Artery Disease | Helicobacter pylori serologic status | Self-reported allergy |
| rs1604834  | Multiple complex diseases | Self-reported allergy |
| rs974734   | Self-reported allergy                                      |
| rs7688418  | Self-reported allergy                                      |
| rs7665932  | Self-reported allergy                                      |
| rs6531677  | Self-reported allergy                                      |
| rs12642243 | Self-reported allergy                                      |
| rs12641669 | Self-reported allergy                                      |
| rs1115259  | Self-reported allergy                                      |
| rs6824769  | Multiple complex diseases | Self-reported allergy |
| rs7664107  | Self-reported allergy                                      |
difference was found in the forkhead box protein P2 (FOXP2) gene. In modern humans, the FOXP2 gene does not have any effect. This gene is also called speech gene because speech disorders occur. Also, this gene was found in Neanderthals and chimpanzees [12]. Like these, there are differences in DNA levels among many genes. However, the results showed that 99.7% of the human and Neanderthal genomes are exactly the same while human and chimpanzee genomes showed 98.8% similarity.

The first encounter between H. sapiens and H. neanderthalensis was won by the Neanderthals. Approximately 100,000 years ago, H. sapiens migrated to the north and the east Mediterranean. These regions were the territory of Neanderthals and therefore modern humans could not settle there. This may be due to unfavorable climate, local parasites, and new diseases. Regardless of the cause, H. sapiens were driven out from these areas, and the Middle East remained in control of Neanderthals. About 70,000 years ago, the tribe came out of Africa for the second time. This time H. sapiens won and dominated the whole earth, not just the Middle East. They reached Europe and Eastern Asia within a short period of time. They passed through the open sea about 45,000 years ago and reached Australia, which was not reached by any other human-like species until that time [13]. The basis of these developments is the cognitive revolution that emerged 30,000-70,000 years ago. The cognitive revolution has added new thinking and new communication skills to H. sapiens. According to the most accepted theory of cognitive revolution, genetic mutations have altered the internal structure of the brain of H. sapiens. This change has allowed them to think in ways that have never been possible before and to communicate in new languages [13]. The reason for this mutation to occur in human DNA but not in Neanderthals is just a coincidence. According to this theory, the reason for the domination of H. sapiens in the world was caused only by a mutation that occurred in our genes by chance. Since cognitive revolution, H. sapiens have the ability to renew their behavior according to changing needs. This is the basis for H. sapiens to develop more than other Homo species and to dominate the world nowadays.

The biggest differences between Neanderthal and modern humans are strength and endurance [14]. Neanderthals were stronger and had more endurance than modern humans. The arms and thighs of modern humans are thinner than those of Neanderthals. It was important for Neanderthals to act quickly because they were hunter-gatherers [15]. The hands of modern humans are thought to have evolved for the delicate grip. The average height of Neanderthal men was 164-168 cm and that of women was 152-156 cm [15]. Introgressed Neanderthal sequences were identified in modern human autosomes and X chromosomes. Nevertheless, Neanderthal mitochondrial genome sequences were not reported within modern human genomes. In 2016, Mendez and colleagues stated that full mitochondrial DNA sequences were found in eight individuals. These individuals were from Spain, Germany, Croatia, and Russia. The Y chromosome was obtained from male Neanderthals in El Siron, Spain [16].

Mendez Conduced a study [16] conducted a study of male Neanderthals who lived in Spain 49,000 years ago. The Y chromosome of these Neanderthals did not pass to modern humans. Europeans and Asians are missing chunks of Neanderthal DNA on their Y chromosomes. Thus, to conclude, female modern humans and male Neanderthals are not exactly compatible. Therefore, Mendez think that Neanderthals [16] think that Neanderthals may have problem in sperm production and they may have not produced many healthy male babies. As a result of this, the Neanderthal population might have declined rapidly [16].

As a result of the hybridization of early humans and Neanderthals between Europe and West Asia, non-African populations carry almost 1-4% Neanderthal DNA in their genome. Nevertheless, this Neanderthal DNA had both positive and negative effects on modern humans. Dannemann, et al. [17] agreed that introgressed genomes provide genetic adaptation to new environments. This could be a positive effect introgression of Neanderthal genome to humans. The introgression provides natural immunity to new environments and pathogens. Neanderthal alleles often are not adaptive to modern human genome [17].

Our generated database will facilitate the work of researchers, providing all data with references via this website, and the developed in silico model provides a better understanding of the origin of the genetic diseases that are introgressed from archaic genomes. Furthermore, the genome browser provides quick online access to data for researchers, clinicians, or anyone who is interested in the history of early human life.

This computer software will aid the evaluation of the percentage of Neanderthal-derived sequences in modern humans, thus facilitating the assessment of the genetic diseases that originally came from Neanderthals.

The limitations of this study was the lack of comparative genomic data in the literature and genome browsers; it needs to be developed with the use of more genetic data. However, our in silico model provides better understanding of the origin of genetic diseases or traits that are associated with archaic genomes. Therefore, by better understanding the human genome make up, this precise medicine model will help individuals and their populations to receive precise treatment.

Acknowledgements: We would like to thank Near East University Faculty of Engineering, Department of Biomedical Engineering member Assoc. Prof. Terin Adak for her support and great help.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References
1. Dannemann M, Andres AM, Kelso J. Introggression of Neandertal and Denisovan like haplotypes contributes to adaptive variation in human toll-like receptors. Am J Hum Genet 2016; 98: 22-33. [Crossref]
2. Green RE, Krause J, Briggs AW, et al. A draft sequence of the Neandertal genome. Science 2010; 328: 710-22. [Crossref]
3. Villa P, Roebroeks W. Neandertal demise: An archaeological analysis of the modern human superiority complex. PLoS ONE 2014; 9: e96424. [Crossref]
4. Groucutt S, Pettaglia MD, Bailey G, et al. Rethinking the dispersal of Homo sapiens out of Africa. Evol Anthropol 2015; 24: 149-64. [Crossref]
5. Sankararaman S, Mallick S, Dannemann M, et al. The genomic landscape of Neanderthal ancestry in present-day humans. Nature 2014; 507: 354-7. [Crossref]
6. Vernot B, Akey JM. Resurrecting surviving Neanderthal lineages from modern human genomes. Science 2014; 343: 1017-21. [Crossref]
7. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006; 124: 783-801. [Crossref]
8. Zhang Z, Jones BH, Tang W, et al. Dissecting the axoneme interactome: the mammalian orthologue of Chlamydomonas PF6 interacts with sperm-associated antigen 6, the mammalian orthologue of Chlamydomonas PF16. Mol Cell Proteomics 2005; 4: 914-23. [Crossref]
9. Matsuyoshi N, Imamura S. Multiple cadherins are expressed in human fibroblasts. Biochem Biophys Res Commun 1997; 235: 355-8. [Crossref]
10. Richard P, Manley JL. Transcription termination by nuclear RNA polymerases. Genes Dev 2009; 23: 1247-69. [Crossref]
11. Kundu S, Rahman S, Thakur S. Ancient DNA and Neanderthals mystery. Int J Sci Eng Res 2014; 5: 1189.
12. Enard W, Przeworski M, Fisher SE, et al. Molecular evolution of FOXP2, a gene involved in speech and language. Nature 2002; 418: 869-72. [Crossref]
13. Harari YN. Sapiens: A Brief History of Humankind, Kolektif Kitap, Istanbul; 2015.
14. Papagianni D, Morse M. The Neanderthals Rediscovered. Thames & Hudson, London; 2013.
15. Helmuth H. Body height, body mass and surface area of the Neanderthals. Z. Morphol Anthropol 1998; 82: 1-12.
16. Mendez FL, Poznik GD, Castellano S, et al. The Divergence of Neandertal and Modern Human Y Chromosomes. Am J Hum Genet 2016; 98: 728-34. [Crossref]
17. Dannemann M, Kelso J. The contribution of Neanderthals to phenotypic variation in modern humans. Am J Hum Genet 2017; 101: 578-89. [Crossref]