Original Article

DOI: 10.5152/eurasianjmed.2019.18424

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 Senturk[1] and Mahmut Cerkez Ergoren*[2]

[1]Department of Biomedical Engineering, Near East University Faculty of Engineering, Near East Boulevard, Nicosia, 99138, Cyprus

ORCID ID: 0000-0001-9593-9325

[2]Department of Medical Biology, Near East University Faculty of Medicine Near East Boulevard, Nicosia, 99138, Cyprus

ORCID ID: 0000-0003-1368-5195

***Correspondonding author:** Mahmut Cerkez Ergoren, Department, Department of Medical Biology, Near East University Faculty of Medicine, Near East Boulevard, Nicosia, 99138, Cyprus.

E-mail: mahmutcerkez.ergoren@neu.edu.tr

You may cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

Abstract

Objectives: Mutations or introgression can cause and rise adaptive allele up which some can be beneficial alleles. Archaic humans lived more than 200,000 years in Europe and Western Asia. They were adapted to these environments and local pathogens of these environments. It is therefore thinkable that modern humans obtained a significant immune advantage from the archaic alleles.

Materials and methods: Firstly, the data collected by meta-analysis from previously identified the genetic disease caused alleles that are intogressed from Archaics. Secondly, the *in-silico* model portal (http://www.archaics2phenotype.xxx.edu.tr) was designed to trace the history of the Neanderthal allele, however also it shows current distribution of the genotypes of those selected alleles within different populations and correlates with the persons' phenotype.

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

Conclusion: This precise medicine model will help the individuals and their belonged populations to receive the best treatment. Finally, it will be the strong answer of the question of why there are differences in disease phenotypes in modern humans.

1 Introduction

Archaic humans lived in more than 200,000 years 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*. Anatomically, there is a difference between Archaic and modern humans. Modern humans have evolved from archaic and *Homo erectus*. While modern humans were migrating 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 human.

Neanderthals have evolved 250,000 years ago and known as *Homo neanderthalensis* [3]. Neanderthals were included geographical spread ranging from England to Siberia. They were squat and powerful hunters. 30,000 years ago, *Homo sapiens* began to spread in the world from Africa [4]. Therefore, Neanderthals and early humans encountered and they mated. Modern genetic data shows, Neanderthals mated with modern humans in Europe when they encountered. As a result, almost 1%- 4% of the modern humans' genome consists from Neanderthal specific genes. Those genes that passed from Neanderthals, provide us to fight against deadly viruses such as Epstein-Barr. However, modern humans have received some origin of disease genes from Neanderthals such as Crohn's disease, type 2 diabetes, lupus, heart diseases, depression [1].

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

As a significant proportion of these archaic-specific DNA are found within *TLR1-TLR6-TLR10* gene cluster that are belong to Toll-Like Receptors (TLRs). TLRs provide natural immunity against many pathogens and these receptors recognize the structure of pathogens. Therefore, they are an important defense against pathogens. TLRs are known to respond to stimuli associated with

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

various pathogens and to provide signal responses necessary for the activation of innate immune effector mechanisms and subsequent development of adaptive immunity [1].

Previous study indicated that modern humans carry three archaic-like haplotypes and three toll-like receptors passing from archaic humans were identified. Two of these haplotypes resemble to Neanderthal genome and the third haplotype resemble to Denisovan genome. Single nucleotide polymorphisms (SNPs) frequency commonly shared in Neanderthal-like haplotypes vary in continents and populations. In Europe, allelic frequencies of Neanderthal-like core haplotypes are higher in Southern European populations [1].

We aimed to collect previously identified archaic-like SNPs that have clinical significance via meta-analysis. Then, we combined scientific knowledge and outcome from previous studies to determine diseases that related genetically to modern humans that received from Neanderthals. Secondly, the software program is developed to merge previously identified archaic-like SNPs and their clinical pathogenity. Thus, this study and developed software give us clues about the origin of the disease for modern humans. Finally, an *in-silico* model is designed for clinicians and researchers to trace the history of the archaic alleles and determine the possible correlation with the persons' phenotype will provide better understanding to interpret the underlying mechanisms of the diseases.

2 Materials and methods

2.1 Determining SNPs within Tool-like Receptor (*TLR*) Genes in Human Genome

Recent data by Dannemann *et al.* was used to determine the archaic-like SNPs that are represented within the human genome. The research group previously identified 79 archaic-like alleles within *TLR6-TLR1-TLR10* gene cluster which indicate repeated introgression from archaic Humans.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

Meta-analysis was performed to find out the possible clinical significance of those genetic markers from 1000genome populations.

Neanderthal introgression maps of Sankararaman *et al.* [5] and Vernot *et al*. [6] were used for identification of archaic-like haplotypes that potentially observed in modern human genomes. The introgression map presented by Sankararaman *et al.* provides the possibility of emerging of SNPs on polymorphic positions of Neanderthals in modern humans [5]. Vernot *et al.* were detected introgressed regions of modern human reference sequence and they had compared these candidate regions with reference from Neanderthal genome [6]. It used introgression possibilities per SNP for all Asian and all European individuals. It was calculated the difference between Neandertal probabilities according to distance between neighboring SNP pairs, including three *TLR* genes and an additional region of 50kb (Chromosome 4:38,723,860-38,908,438) [1]. Potentially archaic-like SNPs in this region have identified different SNPs in 109 Yoruba individuals in the genome dataset of Neanderthal or Denisovan genomes. Consequently, Deamann *et al.* [6] have been 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].

2.2 Creating Software with C Programming Language on Microsoft Visual Studio C++ 2008 Edition

Computer and Microsoft visual studio C++ 2008 edition and the C programming language were used to build this software. Integrated development environment (IDE) of software is Microsoft visual studio C++ 2008 edition. In this study, the software was created with the C programming language.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

Generated software can be divided into two separate sections. The first section allows the user to search on the created database. In the first part, software was created to allow the user to search at the created database in two different ways. User can search with SNP ID and chromosome location in created software. The second section is the part where the database was created.

2.3 Designing the *in-silico* Genome Browser

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

2.4 Designing the http://archaics2phenotype.xxx.edu.tr/

The website was designed as four main sections. These sections were *homepage, about us, user guide* and contact.

In *homepage* section, the user can search by SNP IDs or chromosome locations with search browser in this section as mentioned before. If there is a matching result in the database about the SNP ID or chromosome location, the user will be able to see this matching result on the screen. In the *About Us* section, the user can get general information about the website. The *user guide* section was designed to guide the users on the website. In short, it shows the user how to use the

website and give general knowledge. The *Contact section* was designed to allow the user to communicate with the website administrator. If the user wants to ask anything about the website, or if user wants to learn anything about the website, they can contact from this section.

3 Results

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

Secondly, 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 website. As a result, http://archaics2phenotype.xxx.edu.tr/has been become globally online free.

To conclude, 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 for the origin of the genetic diseases/traits that are association with archaic genomes. Moreover, it provides quick access to data for researchers and clinicians via genome browser.

3.1 Collecting the Data from Previously Identified Archaic-like Single Nucleotide Polymorphisms (SNPs)

At the beginning, meta-analysis was conducted to collect all the identified archaic-like SNPs. Meta-analysis combines the results of multiple independent studies in a given subject. We used three

international genome browsers and scientific articles for meta-analysis. We determined 79 archaic-like SNPs from study of Dannemann *et al.* [1]. Then, 1000genome was used to check for SNPs registration and identification in the 1000genome populations.

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

Allele frequency is frequency of occurrence of a specific allele in a population. The number of individuals in a genotype to the ratio of individuals in the population is called the genotype frequency. 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 or 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. So, numbers of A divided to total numbers of allele (total of A + total of T) or T divided to total numbers of allele in population.

Minor Allele Frequency (MAF) is less common allele frequencies in the populations for each identified SNPs. MAF amount was selected 0,005 or more at the HapMap project. But, that amount was selected less than 0.005 at 1000genome Project [http://www.internationalgenome.org/]. Thus, researchers were aimed to investigate low and rare variants for different populations.

3.2 Merging the Population Genetics Data with Registered Archaic–like Single Nucleotide Polymorphisms (SNPs)

Total number of thirty-one populations' genetic information was used. Those SNPs are registered three mentioned genome browsers. For each SNP, allele and genotype frequencies, MAF, ancestral SNP information, chromosomal location, and importantly, clinical significance was created.

Five populations and twenty-six sub-populations were used in this study. These populations were African, American, Eastern Asia, European and Southern Asia. The African sub-populations 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. Colombian in Medellin, Peruvian in Lima, Mexican ancestry in Los Angeles and Puerto Ricon in Puerto Rico were included to American population. Chinese Dai in Xishuangbanna, Kinth in Ho Chi Minh City, Han Chinese in Bejiing, Japanese in Tokyo and Southern Han Chinese were included to East Asian population. Toscani in Italy, Finnish in Finland, Utah residents with Northern and Western European ancestry, Iberian populations in Spain and Biritish in England and Scotland were included to European population. Lastly, Gujarati Indian in Houston Bengali in Bangladesh, Indian Telugu in the UK, Sri Lankan Tamil in the UK and Punjabi in Lahore were included to South Asian population. All those population genetics data merged with allele and genotype frequencies for each determined archaic–like single nucleotide polymorphisms (Table 1).

Table 1

3.3 Determining Diseases Caused Archaic-like Single Nucleotide Polymorphisms

Dating between Archaic humans and modern humans resulted adaptation in their environment and local pathogens. Admixture of both homins were resulted the introgression of common alleles, therefore modern human gained adaptive immunity from archaic and survived as a result of natural selection. Archaic-like alleles regulate gene expression of *TLR* genes [7]. Additionally,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

these alleles are also associated with the microbial resistance and allergic diseases. Different alleles together with variety of gene expressions lead different disease phenotypes in modern humans. These archaic-like SNPs are responsible for some disease and disease susceptibility in the human genome (Figure 1). Our meta-analysis report listed each archaic-like SNP and its association with pathogenic disease (Table 2).

Figure 1

Table 2

3.4 The archaics2phenotpe Software is generated by C Language on Visual Studio C++ 2008 Edition

During the stage of the designing the database, C language on visual studio C++ 2008 edition was used and all program codes written in C language in Visual Studio. The software of this study was basically divided into two parts.

In the first section, users can enter three different inputs independently or together. Meaning that, the software was designed to allow users search by SNP ID, chromosome location of the interested SNP or both. In the second section, outputs of searched input are display on the screen. In this section, out accumulated data were used to create the *in silico* browser. After the necessary and required algorithms were created, all collected informative data about 79 archaic-like SNPs were combined with the new software. Therefore, the archaics2phenotpe software was generated.

3.5 Creating *in-silico* Genome Browser: archaics2phenotype.xxx.edu.tr

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

After created the software and the database, the final step of this study, the website, is generated. This created database combined to website for online access. The website is an information sharing platform, which is available online to users. The domain name and hosting are required to create the website.

Firstly, the domain, archaics2phenotype.xxx.edu.tr, was created to setup the website for any internet browsers. Secondly, the hosting was created for activating the website. The hosting provides access to all data by users from the website. In addition, all data of 79 archaic-like SNP were stored in the hosting service. The created database by using software was transferred into the hosting service. Then, the both domain name and hosting service were connected to each other and the website eventually was activated. As a final step, the interface of the website was designed. The appearance of the *in-silico* genome browser is important for easy use. After the database transferred to website for online access, http://archaics2phenotype.xxx.edu.tr/is freely opened to the globally public.

4 Discussions

Genetic and archaeological studies showed that Neanderthals and modern humans were interbred 50,000 years ago. The fossil findings revealed the population of Neanderthals began to decline 40,000 years ago, and the generations of Neanderthal were exhausted 39,000 years ago. There were many factors for exhausted and many hypotheses about their generation. First possibility, rivalry for resources or direct warfare between Neanderthals and modern humans. Humans were more advanced technologically and they were best hunters than Neanderthals. So, humans had more advantages for survive. Second possibility, Neanderthals were adapted to cold

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

climate. Their lives became harder as climates have changed and warmed up. Other possibility could be that pathogens and parasites in the environment [8].

A great portion of genetic diversity in humans occurs by ancient polymorphisms. So, Neanderthal and modern haplotypes are not more diverged than modern human sequences. In Europe, allelic frequencies of Neanderthal-like core haplotypes are higher in Southern European populations [1]. For example, Toscani in Italy and Iberian populations in Spain (TSI and IBS with frequencies of 39.3% and 38.3%). And other Europe populations are Finnish in Finland (FIN), British in England and Scotland (GBR) and CEU (frequencies between 14.8% and 26.4%). In Asia, Neanderthal-like allele frequency core haplotypes is higher in East Asian populations. Such as, Japanese in Tokio (JPT frequency is 53.4%) and Han Chinese (CHB frequency is 53.6%). Others Asians populations frequencies 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 the DNA of five different modern humans (French, Chinese, Papua New Guinea, and Africans from San and Yaruba groups) [2]. The results from the initial analyzes showed that Neanderthal DNA was much more similar to the non-African population's DNA than the African ones. The simplest explanation of this similarity was that there was a gene flow between Neanderthals and humans. There were significant differences between the modern human and the Neanderthal in four different genes. These were *SPAG17* is responsible from sperm motility [8], *PCD16* is responsible from wound healing [9], *TTF1* is responsible from gene reading, and *RPTN* genes with high expression in hair follicles, skin, and sweat gland [10]. Apart from these, the *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 was not appeared in humans. This mutation had led to

the formation of a pale skin color and red hair for Neanderthals [11]. Another gene from the results is the *FOXP2* gene. In modern humans, when the *FOXP2* gene does not work. This gene is called speech gene because speech disorders occur. Also, this gene found in Neanderthals and chimpanzees [12]. Like these, there are differences in DNA levels among many genes. However, the results show that 99.7% of the human and Neanderthal genome are exactly the same, besides that, human and chimpanzee genome shows 98.8% similarity.

The first encounter between the *Homo sapiens* and the *Homo neanderthalensis* was won by the Neanderthals. 100,000 years ago, sapiens groups migrated to the north, to the east Mediterranean. Those regions were the territory of the Neanderthals and therefore, the sapiens could not settle. This may be due to unfavorable climate, local parasites or diseases. Whatever the cause, the *Homo sapiens* were pulled from that area and the Middle East remained in control of the Neanderthals. About 70 thousand years ago sapiens tribes came out of Africa for the second time. This time the *Homo sapiens* won and dominated the whole earth, not just the Middle East. They reached Europe and Eastern Asia in a short period of time. They passed through the open sea about 45,000 years ago and reached in Australia, which was not reached by other humans-like species until that time [13]. At the basis of these developments lies the cognitive revolution that emerged 70 to 30 thousand years ago. The cognitive revolution has added new thinking and new communication skills to sapiens. According to the most accepted theory for the cognitive revolution, genetic mutations have altered the internal structure of the brain of *Homo sapiens*. This change has allowed them to think in ways that have never been possible before, and to communicate in new languages [13]. Why this mutation took place within DNA of *Homo sapiens* instead of Neanderthals? The reason for this mutation to occur in human DNA is just a coincidence. According to this theory, the reason for our species domination of the world is caused only by a

mutation that happened in our genes by chance. Since cognitive revolution, the *Homo sapiens* have been had the ability to renew their behavior according to changing needs. This is the basis for the *Homo sapiens* to develop more than other *Homo* species and to dominate the world nowadays.

The biggest difference between Neanderthal and modern humans is their strength and endurance [14]. Neanderthals were stronger and endurance than modern human beings like other prehistoric species of *homo*. The arms and thighs of modern human were thinner than Neanderthal. It was important to act quickly because they were hunter-gatherers [15]. Hands of modern humans hand are thought to have evolved for the delicate grip. Neanderthal males averaged 164 to 168 cm and females 152 to 156 cm tall [15].

Introgressed Neanderthal sequences were identified in modern human autosomes and X chromosomes. Nevertheless, Neanderthal mitochondrial genome sequences were not reported within modern human genome. Y chromosome a sequence of Neanderthal has not been characterized yet. In 2016 Mendez and colleagues said, full mitochondrial DNA sequences available at eight individuals. These individuals from Spain, Germany, Croatia and Russia. But, relation of Y chromosome still does not know between Neanderthal and present-days human. They obtained Y chromosome from male Neanderthal in El Siron, Spain [16].

Gibbons (2016) conducted a study in the male Neanderthal who lived in Spain 49,000 years ago. Chromosome Y of this Neanderthal did not pass to modern humans. Europeans and Asians are missing chunks of Neanderthal DNA on their Y chromosomes. So, to conclude, female modern humans and male Neanderthals are not exactly compatible. Therefore, they think that Neanderthals may have problem about sperm production. So, they may did not produce many healthy male babies. As a result of this, Neanderthal population might be declined rapidly [17].

As a result of the hybridization of early human and Neanderthals between Europe and West Asia, non-African populations carry almost 1-4% Neanderthal DNA in their genome. Nevertheless, this Neanderthal DNA made both positive and negative effects to modern humans. In study of Dannemann and Kelso (2017), they agreed introgressed genomes provide genetic adaptation to new environments. Thus, could be a positive effect introgression of Neandethal genome to humans. Thus, it provides natural immunity to new environments and pathogens. Neanderthal alleles often are not adaptive to modern human genome [18].

Our generated database will facilitate the work of researchers, because they can obtain all data with references via this website and this developed *in-silico* model provides better understanding for 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 has an interested in this history of early human life.

In the future, the computer software will be needed to develop to evaluate the percentage of Neanderthal delivered sequences in modern humans. Therefore, Neanderthals and modern human genomes will be compared by this software and we can easily evaluate genetic diseases that originally came from Neanderthals.

The drawback of this study was lack of comparative genomic data in the literature and genome browsers. In any case, our developed *in silico* model provides better understanding for the origin of the genetic diseases/traits that are association with archaic genomes and also the data should be developed by using more genetic data. Therefore, by understanding the human genome make up better in the future, this precise medicine model will help the individuals and their belonged populations to receive the precise treatment. Finally, it will be the strong answer of the question of why there are differences in disease phenotypes in modern humans.

Abbreviations: FOXP2, Forkhead box protein P2; **MRC1,** Mannose Receptor C-type 1; **PCD16,** Protocadherin-16; **SNP,** Single-nucleotide polymorphism; **SPAG17,** Sperm associated antigen 17; **TLR,** Toll-Like Receptor

Conflict of interest

The authors do not have any conflict of interest.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

References

[1] Dannemann, M., Andres, A. M., Kelso, J., Introgression of Neandertal and Denisovan like haplotypes contributes to adaptive variation in human toll-like receptors. *Am. J. Hum. Genet.* 2016;*98*: 22–33.

[2] Green, R. E., Krause, J., Briggs, A. W., Maricic, T. et al., A draft sequence of the Neandertal genome. *Science* 2010; doi: 10.1126/science.1188021.

[3] Villa, P., Roebroeks, W., Neandertal demise: An archaeological analysis of the modern human superiority complex. *PLos ONE*. 2014; doi: 10.1371/journal.pone. 0096424.

[4] Groucutt, S., Petraglia, M. D., Bailey, G., Scerri, E. M. et al., Rethinkink the dispersal of homo sapiens out of Africa. *Evol. Anthropol*. 2015; doi: 10.1002/evan.21455.

[5] Sankararaman, S., Mallick, S., Dannemann, M., Prüfer, K. et al., The genomic landscape of Neanderthal ancestry in present-day humans. Nature 2014; doi: 10.1038/nature12961.

[6] Vernot, B., Akey, J. M., Resurrecting surviving Neandertal lineages from modern human genomes. *Science* 2014; *343*:1017–1021.

[7] Akira, S., Uematsu, S., Takeuchi, O., Pathogen recognition and innate immunity. *Cell* 2006; *124*: 783–801.

[8] Zhang, Z., Jones, B. H., Tang, W., Moss, S. B. 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*: 914–923.

[9] Matsuyoshi, N., Imamura, S., Multiple cadherins are expressed in human fibroblasts. *Biochem. Biophys. Res. Commun.* 1997; *235*: 355–358.

[10] Richard, P., Manley, J. L., Transcription termination by nuclear RNA polymerases. *Genes Dev.* 2009;*23*:1247–1269.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

[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, S. E., Lai, C. S. et al., Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* 2002;*418*:869–872.

[13] Harari, Y. N., *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, F. L., Poznik, G. D., Castellano, S., Bustamante, C. D., The Divergence of Neandertal and Modern Human Y Chromosomes. *Am. J. Hum. Genet*. 2016; *98*: 728–734.

[17] Gibbons, A., Modern human females and male Neanderthals had trouble making babies. Here's why. *Hum. Evol*. 2016; doi: 10.1126/science.aaf9886.

[18] Dannemann, M., Kelso, J., The contribution of Neanderthals to phenotypic variation in modern humans. *Am. J. Hum. Genet*. 2017; *101*: 578–589.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.

Figure 1 Illustrates the statistical calculation of most seen diseases that might cause by interested archaic-like SNPs. Axical represents most seen disease and coronal illustrates the frequency of the disease. Self-reported allergy is the most seen disease and *Helicobacter pylori* serological status follows up secondly. Interestingly alcohol consumption and amylotrophic lateral sclerosis (ALS) had an association with archaic-like SNPS (5% and 4%, respectively). The others that are seen less than 1% were endometricsis, blood pressure, coronary artery disease, lymphocyte counts, Paget's disease, height, allergic sensitization, breast cancer, suicide attempts in bipolar disorder and panic disorder.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Senturk N, Cerkez Ergoren M. 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 2019; 10.5152/eurasianjmed.2019.18424.