

Evolutionary Patterns in the Genus Homo

Ridaul Fatima¹ and Nisar A. Shar^{2*}

*Department of Biomedical Engineering, NED University of Engineering & Technology,
Karachi, Pakistan, 75270*

Contact: ²<+92346-5237181>

E-mail: ¹<ridaulfatima95@gmail.com>, ²<nisarshar@neduet.edu.pk>

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ABSTRACT The demographic history of *Homo sapiens* is complex; it involves a wide range of migrations and genetic adaptations. One of the closely related species to *Homo sapiens* is Neanderthals, which became extinct about 30,000 years ago. The aim of this research is to compare *Homo sapiens* with Neanderthals and chimpanzees to understand the patterns of inheritance and survival instincts of *Homo sapiens*. Results show that out of all selected groups of genes in this study, metabolism, and language genes are found to be the most evolving group of genes. This shows that these most evolving genes are contributing to the advancement of *Homo sapiens*. However, after comparing human intelligence genes with the primates, it is found that exonic regions are contributing more to the evolution of human intelligence hence, making *Homo sapiens* unique in terms of intelligence.

INTRODUCTION

Homo sapiens experience innovation in their inherited characteristics from generation to generation through natural selection (Li et al. 2018) and migration (Figs. 1 and 2). For a better understanding of DNA of modern *Homo sapiens*, a detailed study of the human genome in comparison with archaic species is required. The analysis of the human genome and archaic species indicates that most of the mutations are inherited from their ancestors that may have positive and negative effects (AkashPeshin 2017; Cooper 2000; Pickrell 2006).

By tracing back to the human lineage, it is found that one of the closely related species to *Homo sapiens* is Neanderthals that became extinct about 30,000 years ago (Wood 2019). The study of human evolution reveals that *Homo sapiens* and Neanderthals are the two complex and related species (Worthington 2016). Studies show that the traces of the Neanderthal DNA is still present in modern human beings at around ten to twenty percent (Yong 2014); however, not every population carries the same proportion of genes, and therefore modern non-African population has approximately two to four percent of Neanderthal DNA (Dannemann and Kelso 2017). According to Stringer (2016), differences be-

tween the lineage of Neanderthals and *Homo sapiens* could be the result of natural selection or genetic drift (Stringer 2016). Rodriguez-Perez et al. (2018) studied the scapular glenoid fossa of Neanderthals and revealed that the morphological differences present between *Homo sapiens* and Neanderthals are due to the influence of structural and functional factors on them (Pickrell 2006). The genetic variations might have contributed to the survival of *Homo sapiens* as other species like Neanderthals became extinct. According to Pickrell (2006), intelligence and creative thinking has made *Homo sapiens* unique from other species hence, have huge contribution in their survival. The behavioral and genetic differences between *Homo sapiens* and Neanderthals will be helpful to find out the unique evolutionary patterns of *Homo sapiens*, which helped in the survival of *Homo sapiens* (Galway Witham et al. 2019).

Changes between *Homo sapiens* and Neanderthals are also observed in the overall anatomy and physiology of the body, including brain development, immune system, cardiovascular system, and resistance mechanism to certain diseases, including smoke resistance (Kochiyama et al. 2018). Modern humans can better deal with toxic chemicals in the environment than Neanderthals (Aarts et al. 2020). It became possible because, in modern humans, receptors of aromatic hydrocarbon are more dominant and responsible for the catabolism of noxious sub-

^{*}Address for correspondence:
Dr. Nisar A. Shar

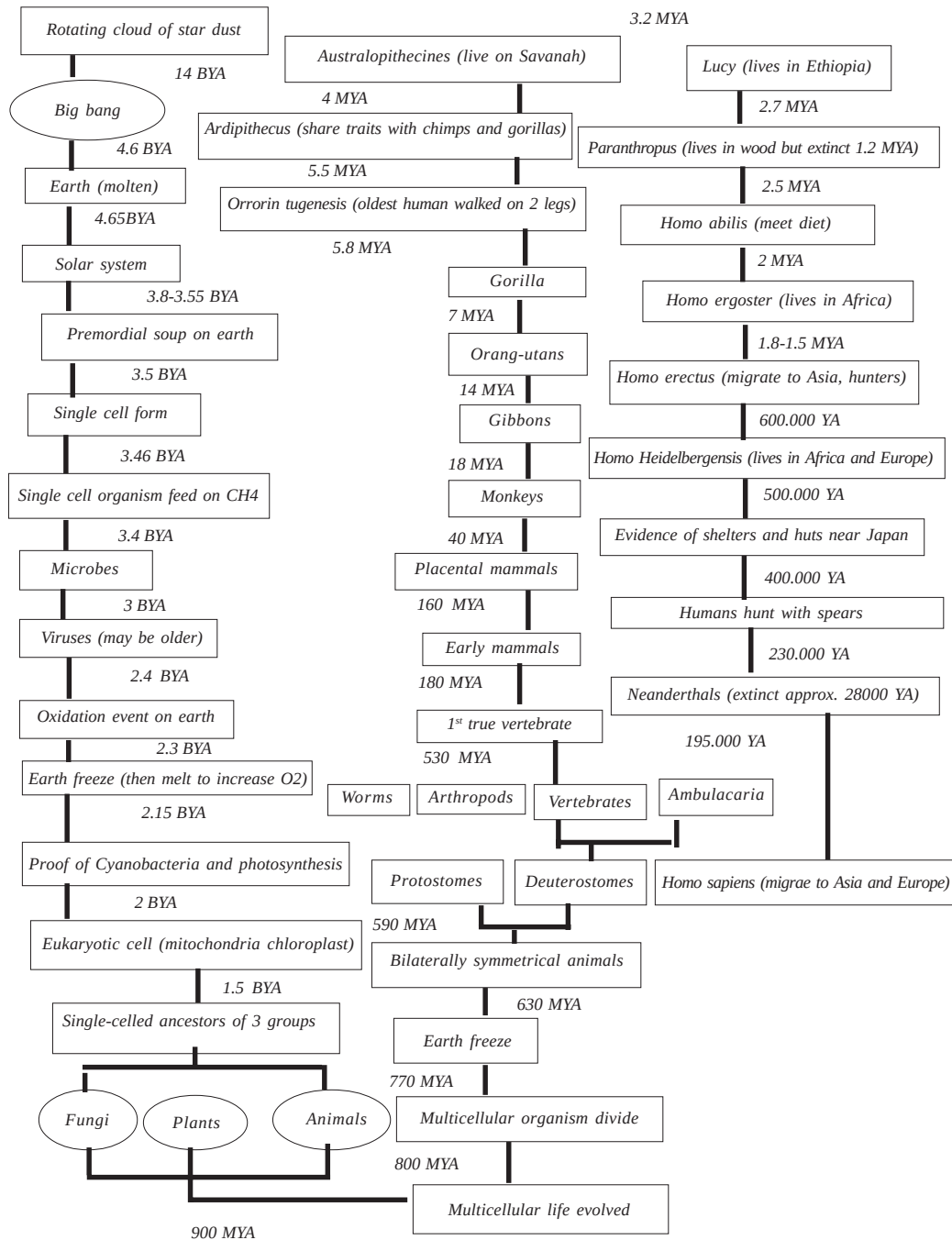


Fig. 1. Timeline from the beginning of life to the migration of *Homo sapiens*

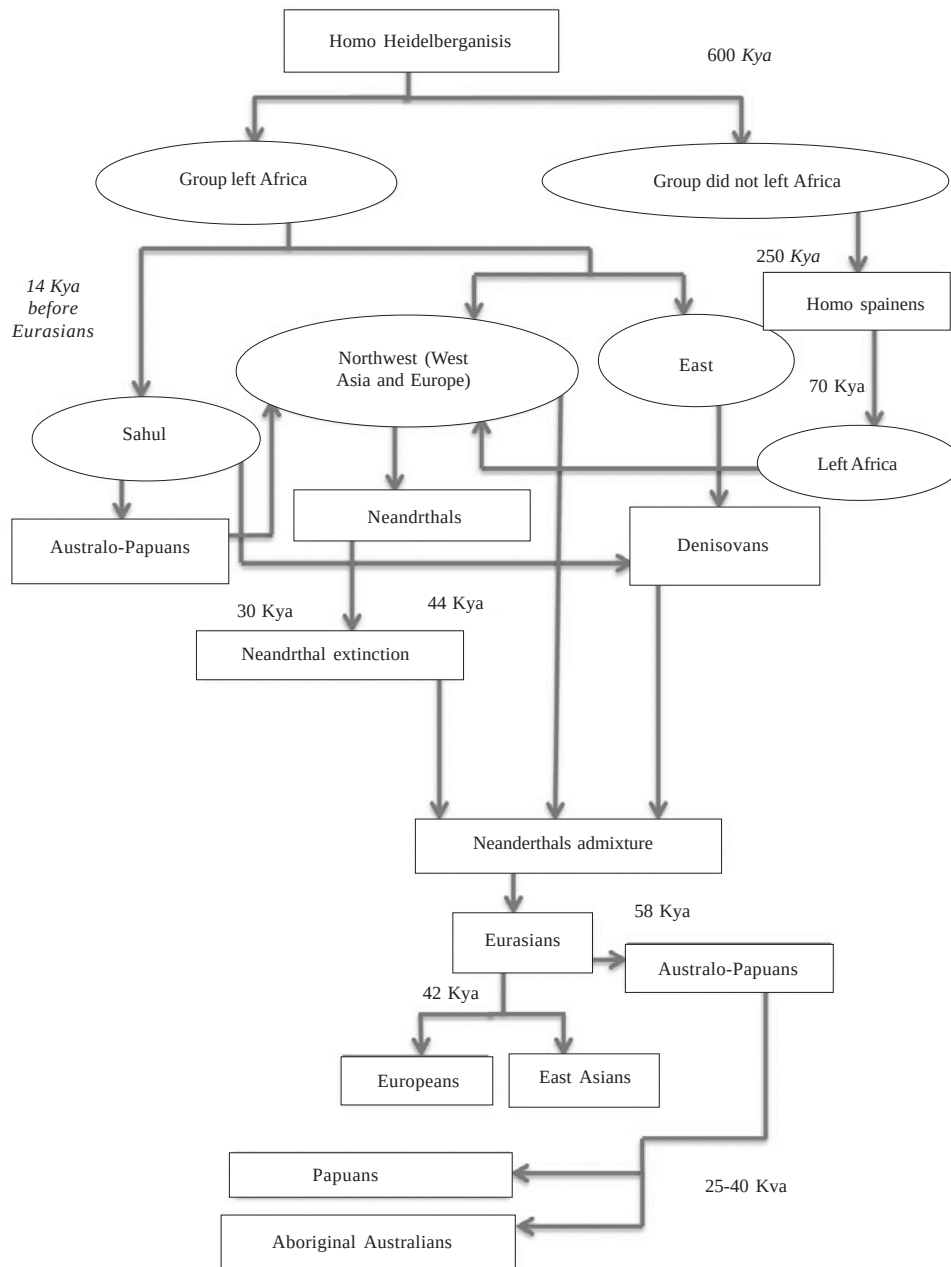


Fig. 2. Historical study of *Homo Heidelbergensis* migration shows that Neanderthals, Denisovans, and modern humans have a common ancestor. Arrows are used to show the evolution from one population to another after thousands of years ago (Kya)

stances and provide resistance against smoke (Aarts et al. 2018). Inheritance from Neanderthals also contributes to a few psychiatric disorders, skin disorders, schizophrenia, autism, and Alzheimer's disease (Melchionna et al. 2018). It is also observed that the number of copies of a particular gene evolves from generation to generation, which results in disease adaptations (Melchionna et al. 2018). Around one percent of all the cases of autism are the result of copy number variation (Nuttall et al. 2016). This percentage was approximately fixed in early generations, which can give the idea that Neanderthals might have fixed copy numbers. Different studies reveal that *Homo sapiens* interbred with Neanderthals after the split from modern humans (Ko 2016) as traces of Neanderthal DNA were found in East Asian and European populations (Mafessoni 2019). Different theories of their extinction are characterised by frequent changes in climate, weather conditions, high metabolic rate, vegetation, and faunal turnover (Timmermann 2020). According to Weisberger (2019), fossils of Neanderthals were found in different areas, including France, Spain, Portugal, and Belgium. These fossils show different signs of butchery, including cut marks and depressions from hammering, and therefore, it can also be predicted that Neanderthals might have involved in cannibalism (Weisberger 2019). Moreover, studies show that Neanderthals required more food for their survival as compared to *Homo sapiens* in those scarce and unstable conditions with little or no food because metabolic rates of Neanderthals were found to be higher than modern humans (Dorey 2019). As a result of these factors, the extinction of Neanderthals might have occurred even though Neanderthals were skillful, active, and intelligent species (Finlayson 2019). This debate can come to an end by increasing the understanding of the ecology of different human species (Finlayson 2004).

According to Zeberg and Pääbo (2020), few nucleotide segments responsible for the risk factors of COVID-19 are inherited from Neanderthals in *Homo sapiens* (Zeberg and Pääbo 2020). The genomic comparison of modern humans and archaic species can help to understand that most of the mutations may be inherited from the ancestors or due to interbreeding with other species. Therefore, the analysis of the evolutionary

pattern of genes is essential in predicting future mutations that can lead to estimate the cause and effect of unique inherited diseases. A better understanding of human lineage requires further analysis and detailed study of human fossils.

Objectives

The aim of this research paper is to evaluate the reasons for the extinction of Neanderthals and to understand the survival of *Homo sapiens* to become the most advanced and intelligent species. It will provide a proper understanding of the evolutionary patterns and will help to analyse the similarities and differences in their behavior, language ability, social organisation, physical characteristics, and mental capabilities. This study may also be helpful in the identification of prior measures to be taken before the inherited mutant genes express themselves.

MATERIAL AND METHODS

Comparative Analysis of Different Genes of Interest between Modern Humans and Neanderthals

Neanderthals and modern humans are closely related species. This indicates that modern humans might have interbred with the Neanderthals. To test this hypothesis, sequence alignment between few randomly selected genes of modern humans and Neanderthals has been performed on Clustal Omega (Sievers and Higgins 2018). Eleven immune genes, five memory genes, four language genes, seven regulatory genes, seven carbohydrate metabolism genes, five protein metabolism genes, and five lipid metabolism genes are randomly selected. Nucleotide sequences in FASTA format of Neanderthal genes are retrieved from the Neanderthal Genome Browser - Ensembl Projects (Neanderthal Ensembl Genomes 2010). This browser represents data by mapping Neanderthal genome sequencing reads to the human genome, whereas Nucleotide sequences in FASTA format of *Homo sapiens* are retrieved from Ensembl genome browser 95 (Zerbino et al. 2018). Language genes have a large nucleotide sequence more than the file size of 4 MB. that crosses the threshold of Clustal omega. To find protein similarity of language

genes, nucleotide sequences in FASTA format are converted into protein from ORF finder (Rombel et al. 2002). Nucleotide similarity for the comparison of immune, memory, regulatory, and metabolism genes is calculated by the following formula:

$$\text{Nucleotide similarity} = 100 * X$$

$$\text{Where, } X = \frac{\text{shortsequence}}{\text{largesequence} + \text{shortsequence}}$$

$$\text{nt} = \text{nucleotide}^2$$

X represents dissimilarity between the sequence of Neanderthals and *Homo sapiens* for a particular gene.

Evolution of Intelligence Genes

To study the human intelligence difference between human beings and primates, human intelligence genes are compared with them.

Conservation of Human Intelligence Genes

To find the conservation of human intelligence genes in *Homo sapiens* and primates, the UCSC genome browser is used (Karolchik et al. 2009).

Retrieval of Orthologous Regions of Human Intelligence Genes

Non-coding orthologous regions are retrieved from VISTA Enhancer (Visel et al. 2007).

Conservation of Non-coding Orthologous Regions of Human Intelligence Genes

To find the conservation of these regions in primates, the UCSC genome browser is used (Karolchik et al. 2009).

Retrieval of Functional Orthologous of Intelligence Genes

Conserved regulatory regions of intelligence genes are subjected to evaluating whether these genes have orthologs or not. To retrieve the orthologs of these genes, the KEGG orthology database (Kanehisa and Goto 2000) is used.

Comparison of Mitochondrial Genome of Neanderthals with Other Population

Complete mitochondrial genome sequences of Neanderthals, Denisovans, South East Asians, Americans, Europeans, South African and chimpanzees are retrieved (Green et al. 2008; Duong et al. 2018; Andrews et al. 1999; Pala et al. 2012; Walt et al. 2012; Fischer et al. 2011) for the comparison of mitochondrial DNA of Neanderthals with other populations including Denisovans, South East Asia, America, Europe and South Africa and chimpanzee for understanding the evolutionary pattern of mitochondrial DNA.

RESULTS

Sequence Alignment of Different Genes of Interest between Modern Humans and Neanderthals

The results of the comparative analysis of selected genes between *Homo sapiens* and Neanderthals are discussed below.

Sequence Alignment of Immune Genes

The comparison of immune genes between Neanderthals-*Homo sapiens* and *Homo sapiens*-chimpanzees (Fig. 3) clearly showed that the SOD1 gene is one hundred percent identical between Neanderthals and *Homo sapiens*. Other results of the gene comparison show that Nucleotide sequences of immune genes of Neanderthals and chimpanzees are identical with *Homo sapiens*, but there are some insertions in the beginning or at the end of the modern human sequences, which make them unique from Neanderthals and chimpanzees. From these results, it can be interpreted that the regions that are absent in Neanderthals and chimpanzees but present in *Homo sapiens* are the result of evolution that contributes to human advancement. The nucleotide sequence of *Homo sapiens* was found to be more close to Neanderthals than chimpanzees. It justifies the hypothesis that *Homo sapiens* are closer to Neanderthals than chimpanzees, and it might be possible that *Homo sapiens* interbred with them.

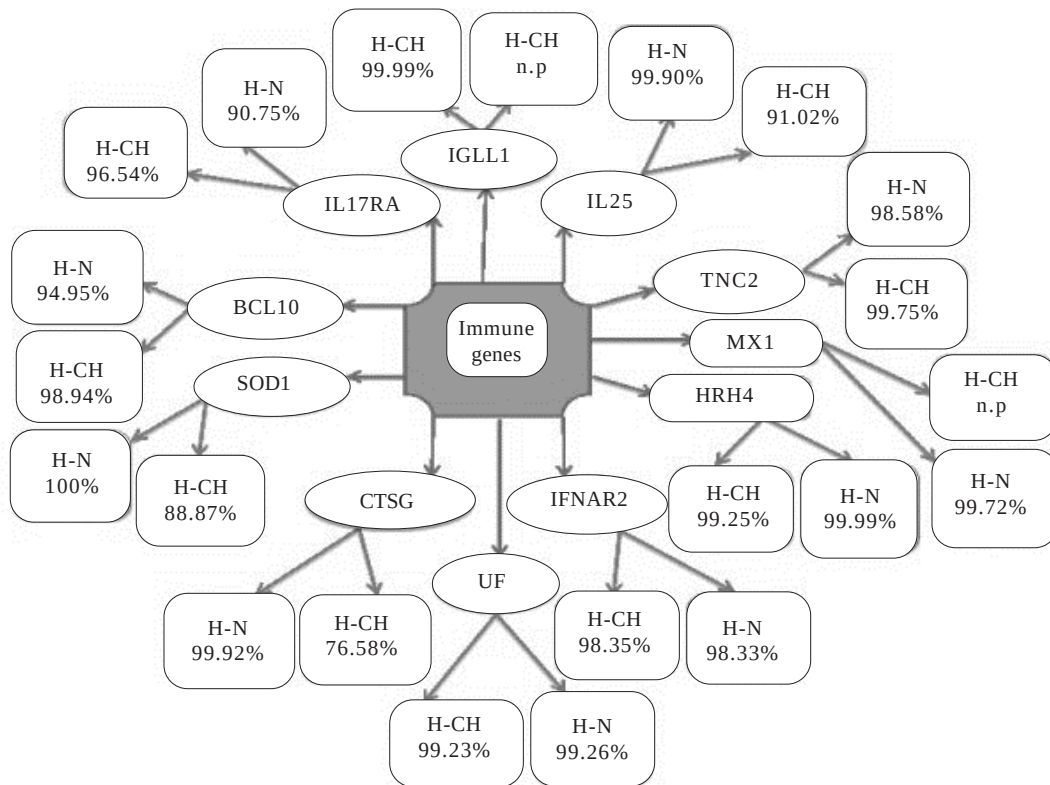


Fig. 3. Nucleotide identity between immune genes of Neanderthals-Homo sapiens (H-N) and Homo sapiens-Chimpanzees (H-CH) is shown in percentages. SOD1 does not show any evolutionary change between Neanderthals and Homo sapiens. CTSG has shown the highest divergence between chimpanzees and Homo sapiens. Whereas IGLL1 and MX1 are not present in chimpanzees (n.p)

Sequence Alignment of Memory Genes

The comparison of memory genes between Neanderthal and *Homo sapiens* (Fig. 4) reveals that BDNF is one hundred identical. This shows that BDNF does not evolve with high frequency. Whereas DLG3 and APOE slightly evolved as few unique insertions are found in *Homo sapiens*, which are absent in Neanderthals. Other genes are more evolved as a large numbers of nucleotides are inserted in *Homo sapiens*, which was previously absent in Neanderthals. The selected memory genes were not present in chimpanzees. This reveals that the pattern of memory is different in chimpanzees but might be similar in Neanderthals and *Homo sapiens*.

Sequence Alignment of Language Genes

The protein comparison of language genes between Neanderthals, chimpanzees and *Homo sapiens* (Fig. 5) has been done. Slight diversity has been observed between the ROBO1 gene of *Homo sapiens* and chimpanzees, and more diversity has been observed between the CNTNAP2 gene of *Homo sapiens* and chimpanzees. On the other hand, FOXP2 and ROBO2 genes are evolved at a higher rate than other genes, as they are negligibly identical. This shows that the language capabilities of the selected species are different. However, Neanderthals might have some vocal communication or used any sort of language as ROBO1 and CNTNAP2 does not show any diversity between Neanderthals and *Homo sapiens*.

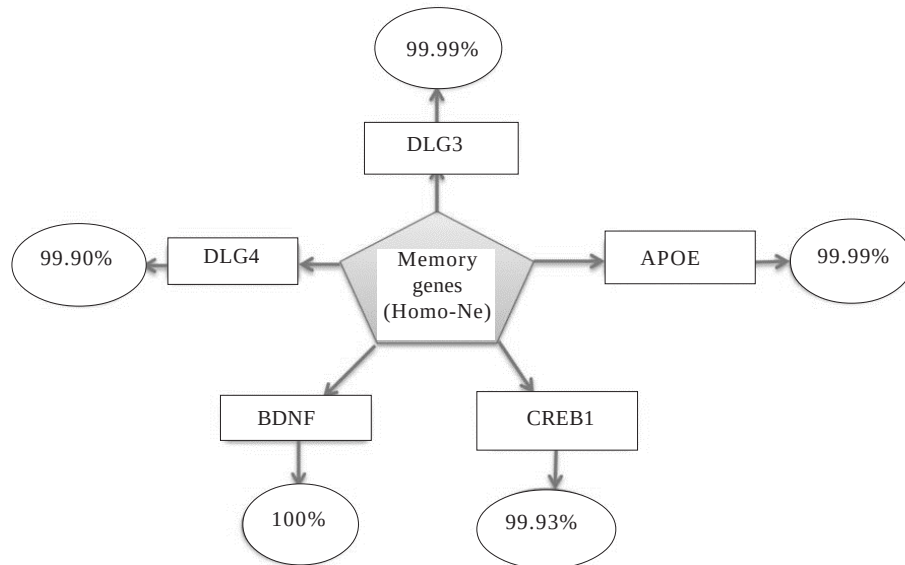


Fig. 4. Nucleotide identity between memory genes of Neanderthals and *Homo sapiens* is shown in percentage. DLGL3 and APOE are almost identical. BDNF is found to be 100% identical. The selected memory genes are absent in chimpanzees

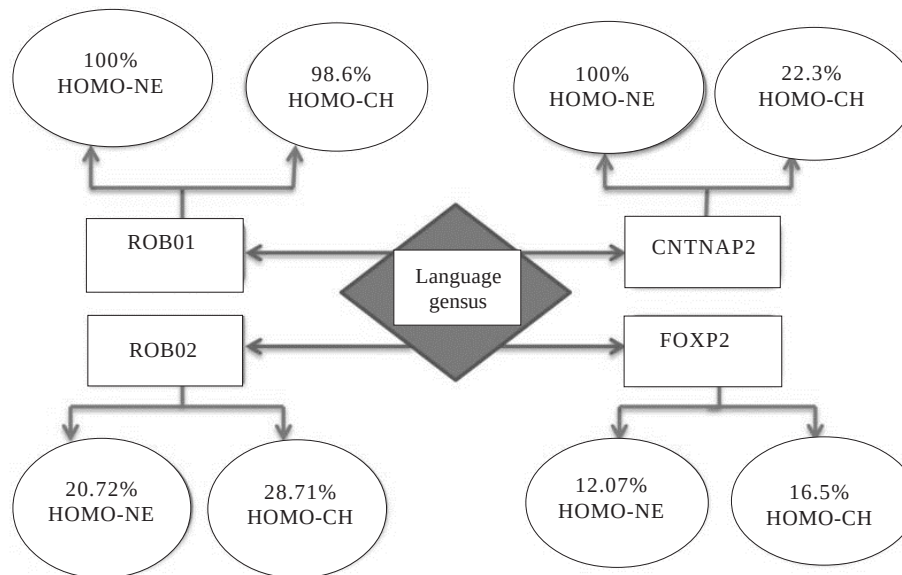


Fig. 5. Protein identity between language genes of Neanderthals and Homo sapiens (HOMO-NE) and Homo sapiens and chimpanzees (HOMO-CH)) is shown in percentages. The most evolving gene found to be FOXP2 and ROB02

Sequence Alignment of Regulatory Genes

The comparison of regulatory genes between Neanderthals-*Homo sapiens* and *Homo sapiens*-chimpanzees (Fig. 6) shows that most of the genes are similar between Neanderthals and *Homo sapiens* with few insertions and deletions in the beginning and the end sequence of *Homo sapiens*. The least similar gene out of them is TP53 in comparison with both the species. This shows that the beginning and end sequences are the most susceptible to evolution.

Sequence Alignment of Metabolism Genes

The comparison of metabolism genes between Neanderthals-*Homo sapiens* and *Homo sapiens*-chimpanzees (Fig. 7) shows that the metabolism genes are the most evolving genes

among all selected genes of this study. GYS2, APH1 and G6PC have shown more than fifty percent divergence in chimpanzees. PDP1 is not present in chimpanzees. LDHB, FADS1, and AKR1C3 have shown more than fifty percent divergence in Neanderthals and *Homo sapiens*. This provides an estimate that Neanderthals have a different metabolism from *Homo sapiens* and might be possible that due to deviation in the metabolic rate from *Homo sapiens*, got extinct in those scarce conditions while *Homo sapiens* survived.

Influence of Intelligence Genes on Human Evolution

Homo sapiens are the most intelligent species and have various mutations. Some genes are found to be beneficial for their survival. In-

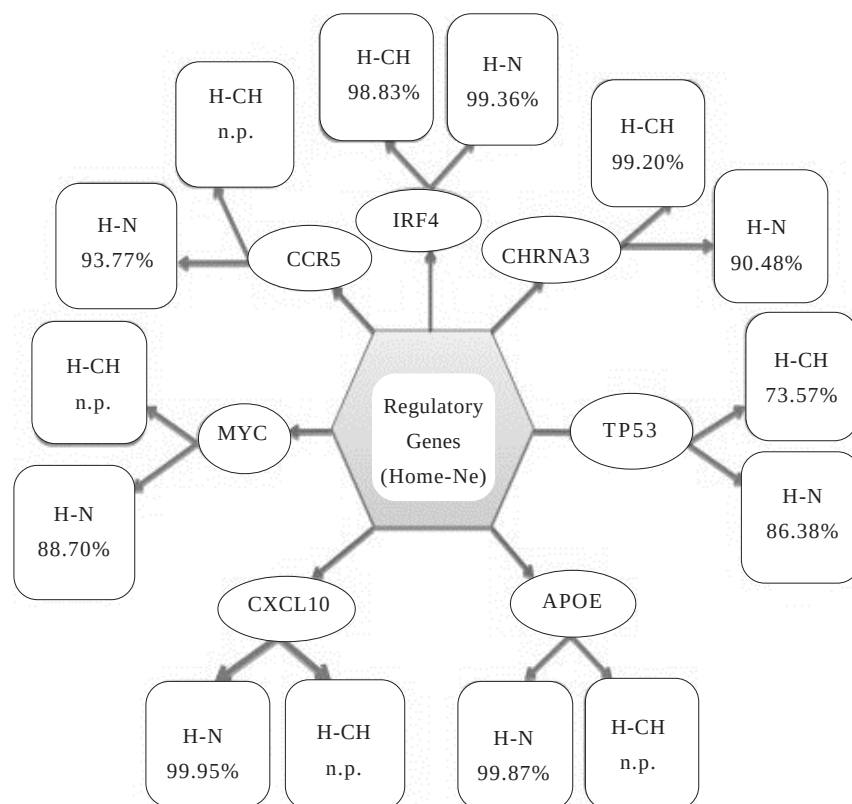


Fig. 6. Nucleotide identity between regulatory genes of Neanderthals-*Homo sapiens* and *Homo sapiens*-chimpanzees is shown in percentages. CXCL10, APOE, CHRNA3, and IRF4 are almost identical in Neanderthals and *Homo sapiens*. MYC, CXCL10, APOE, and CCR5 are not present in Chimpanzees

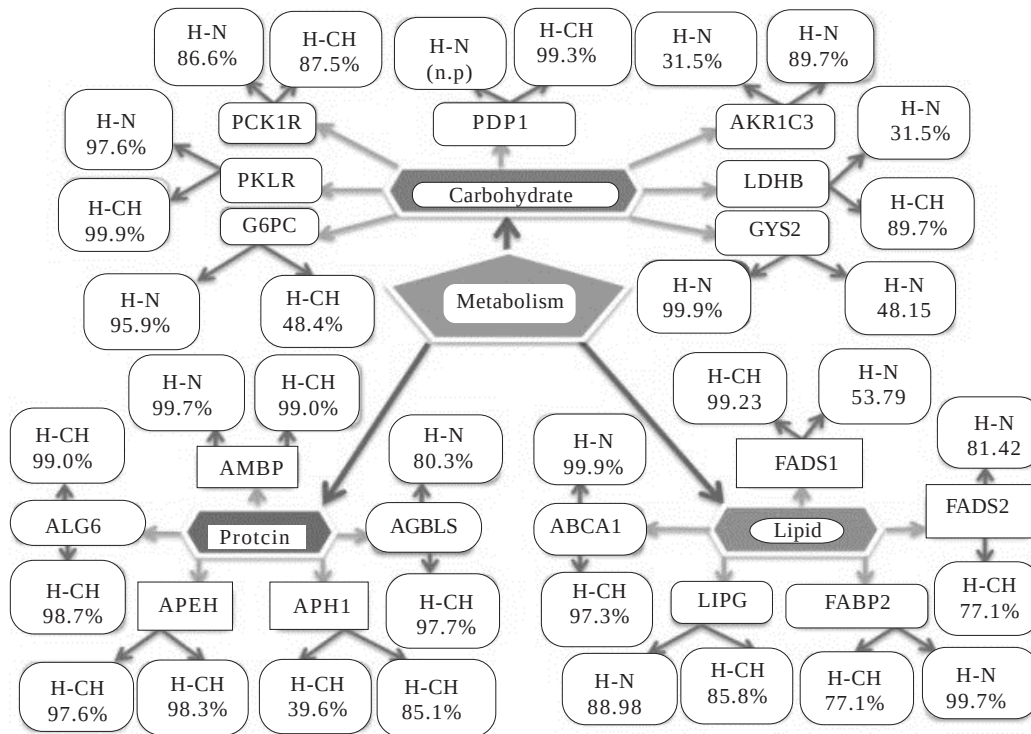


Fig. 7. Nucleotide identity between metabolism genes, including lipid, carbohydrate, and protein of Neanderthals-Homo sapiens and Homo sapiens-chimpanzees is shown in percentages. PDP1 is not present in Chimpanzees. LDHB, FADS1, AKR1C3 has shown more than 50% divergence in Neanderthals and Homo sapiens. GYS2, APH1, and G6PC have shown more than 50% divergence in chimpanzees

telligence can also play a key role in the survival of *Homo sapiens*, and therefore, evolutionary patterns of intelligence genes are studied.

Conservation of Intelligence Genes in Homo sapiens and Primates

Out of 50 intelligence genes, DCC and EXOC4 genes are not conserved, whereas other genes have conserved exonic regions. Results show that 14 genes have highly conserved exonic regions (HCE), 11 genes have slightly conserved exonic regions (SCE) and 23 genes have marginally conserved exonic regions (MCE) (Table 1).

Retrieval of Non-coding Orthologous Regions of Intelligence Genes

Out of 50 genes, non-coding orthologous regions are found in only 5 genes. Other 45 genes

do not have orthologous regions. This shows that the regulatory regions of the 45 genes work differently, and the gene expression is different in *Homo sapiens* and primates.

Conservation of Non-coding Orthologous Regions of Intelligence Genes

Non-coding orthologous regions are found in 5 genes. Results are required to find out whether these regions are conserved in primates and *Homo sapiens*. Results show that only one region of MEF2C is least conserved (L.C.), two regions of ZFHX3 out of 10, and one region of MEF2C out of 4 are slightly conserved (S.C.), while other regions are marginally conserved (MC) and highly conserved (H.C.). This shows that these few genes of *Homo sapiens* and primates have a common ancestor, and their ex-

Table 1: List of intelligence genes with conserved regions and conservation of non-coding regions

S. No.	Genes	Conserved regions	Non-coding orthologous regions	Conservation of non-coding orthologous regions in primates
1	DCAF5	HCE		
2	ZNF 407	HCE		
3	GBFA	MCE		
4	CCDC101	HCE		
5	RNF123	HCE		
6	EFTUD1	MCE		
7	TUFM	HCE		
8	ARFGEF2	MCE		
9	CSE1L	HCE		
10	DRG1	MCE		
11	NDUFA6	HCE		
12	PEF1	MCE		
13	STAU1	MCE		
14	RNF185	SCE		
15	EXOC4	NC		
16	TCF20	MCE		
17	BMPR2	MCE		
18	ZNF638	MCE		
19	SH2B1	HCE		
20	IP6K1	HCE		
21	JMJD1C	MCE		
22	ATXN2L	HCE		
23	CYP2D6	MCE		
24	FOXO3	MCE	1	MC=hs2394
25	PIK3IP1	MCE		
26	NAGA	MCE		
27	EEA1	MCE		
28	ZFHX3	MCE	10	MC=hs16, HS17, HS18, HS20, HS21, HS22, HS108, HS165, SC=CHS519, HS19
29	FAM109D	MCE		
30	COL16A1	SCE		
31	ARHGAP15	SCE	4	HC=HS402, HS403, HS663, HS675
32	GRK6	HCE		
33	APOBR	SCE		
34	SKAP1	SCE	1	HC=HS697
35	ATP2A1	HCE		
36	NEGR1	MCE		
37	PDE1C	SCE		
38	NKIRAS1	MCE		
39	APBA1	SCE		
40	PRR7	MCE		
41	SHANK3	HCE		
42	MEF2C	MCE	4	HC= HS429,HS503 SC= HS789, LC=HS234
43	SEPT4	HCE		
44	HCRTR1	MCE		
45	WNT4	SCE		
46	DDN	SCE		
47	SETP3	HCE		
48	DCC	NC		
49	WBP2NL	SCE		
50	YIPF7	MCE		

*HCE= highly conserved exonic regions, MCE= marginally conserved exonic regions, SCE= slightly conserved exonic regions, HC=highly conserved non-coding regions, MC= marginally conserved non-coding regions, SC= slightly conserved non-coding region

pression might be slightly or completely similar (Table 1) whereas, other intelligence genes are found to be unique in *Homo sapiens*. This con-

tributes to the fact that *Homo sapiens* are the most intelligent species, as their genes do not have orthologous regions.

Comparison of Mitochondrial Genomes

Mitochondrial DNA has some differences from nuclear DNA with respect to structure, nucleotide numbers, and functions. Different studies show that mitochondrial DNA is inherited from the mother, so if the mother has some disorder, it can be inherited into her offsprings. In this study, the mitochondrial DNA of Neanderthals is compared with other populations for analysing their evolutionary patterns. Mitochondrial DNA of Neanderthals is compared with that of Denisovans, Europeans, Americans, South East Asians, South Africans, Aborigines,

and chimpanzees (Fig. 8). After the comparison of the mitochondrial genome, it is found that mitochondrial DNA of Neanderthals is closely related to South Africans than South East Asians as compared to other populations and least similar with chimpanzee than Aborigines. This shows that Neanderthals are more close to different populations of *Homo sapiens* as compared to chimpanzees and might have interbred with the South African population.

A phylogenetic tree is also constructed (Fig. 9) in order to understand evolution in mitochondrial DNA of different populations, including Neanderthals, Denisovans, Europeans, Ameri-

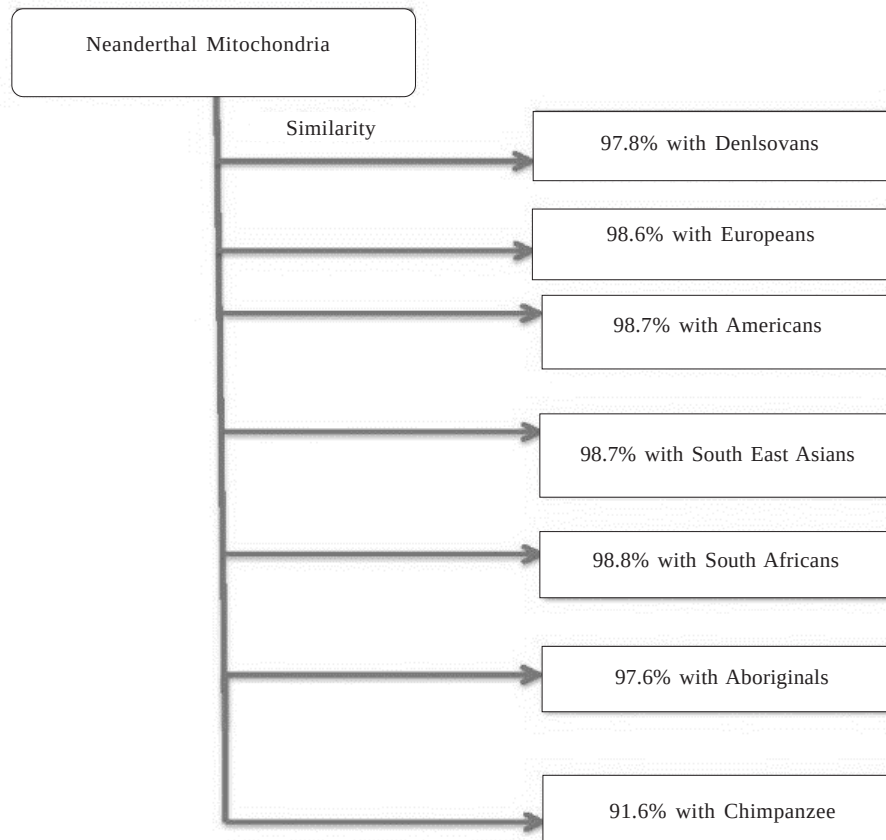


Fig. 8. Percent similarity between Neanderthals and other Modern human populations, including Denisovans, Europeans, Southeast Asians, Aborigines, Chimpanzees, South Africans, and Americans, shows that mitochondria of Neanderthals is least similar to Chimpanzees

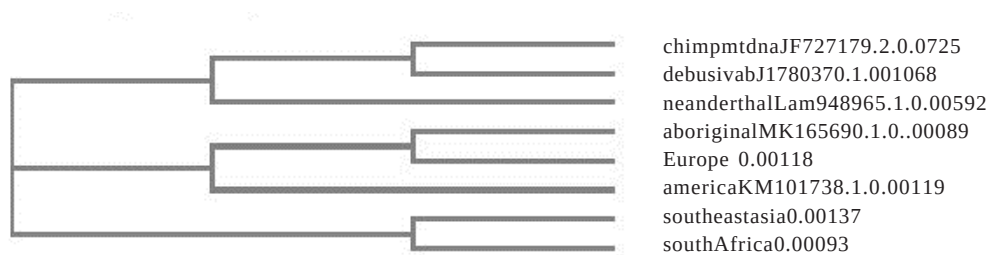


Fig. 9. Phylogenetic tree for the understanding of evolution in mitochondria of different populations shows that all these ancestors have a common origin, which shows that all these species are evolved from a common ancestor.

cans, South East Asians, South Africans, Aborigines, and chimpanzees. Results reveal that all of the selected species have common ancestors.

DISCUSSION

Human beings are one of the most complex species as each individual has unique characteristics from other individuals. Mutations in their genome rapidly occur with the period as for their survival, changes are required (Messer et al. 2016). These changes depend on the environmental conditions and their habitat (Romeo-Mujalli et al. 2019). For the detailed study of *Homo sapiens*, the genome of modern humans is compared with closely related species like chimpanzees and Neanderthals to understand the evolutionary patterns in Neanderthals and modern humans, which might hint at the evolution of modern humans and how they survived and carried innovative evolutionary patterns and traits.

The comparison of the selected genes between Neanderthals and *Homo sapiens* indicates that the genes of *Homo sapiens* evolved from Neanderthals. Surprisingly, genes, including SOD1, which is an immune gene, and BDNF, which is the memory gene, are one hundred percent identical in *Homo sapiens* and Neanderthals, which could not be possible in real conditions. This is due to the Neanderthal sequences used in this study are obtained from Neanderthal Genome Browser - Ensembl Projects (Neanderthal Ensemble Genomes 2010) in which sequences were obtained by mapping Neanderthal genome sequencing reads to the human genome.

However, it has shown that these two genes have high similarity as compared to the other genes and evolved less as compared to other selected genes. As a result, it might be possible that diseases associated with these genes, like Alzheimer's diseases, could be present in both species (Barbash et al. 2017). According to Mozzi et al. (2016), *Homo sapiens* experienced high-frequency alteration in non-coding regions of ROBO2, ROBO1, FOXP2, and CNTNAP2 after the separation from archaic species. In the study, due to the large size of language genes, their protein alignment was performed, which reveals that FOXP2 is highly evolving, whereas ROBO1 and CNTNAP2 did not evolve much. However, FOXP2 of *Homo sapiens* shows more diversity with chimpanzees as compared to Neanderthals. This is because Neanderthals were like humans, and they might have certain languages for communication purposes due to which these genes are more similar to Neanderthals than chimpanzees (Murphy et al. 2018). The difference in the nucleotide sequences of Neanderthals and *Homo sapiens* is helpful in identifying the cognitive differences between both species (Dediu et al. 2018). Additionally, metabolism genes are found to be the most evolving genes, as few genes have shown more than fifty percent nucleotide diversity. This shows that the low rate of metabolism in *Homo sapiens* contributes to the survival and advancement of *Homo sapiens*.

In the advancement and survival of *Homo sapiens*, human intelligence also plays a key role. From the results of this study, it is proved that the intelligence genes are unique in *Homo sapiens*, due to which they are the most advanced species.

Mitochondrion evolution is also studied, as it is an essential organelle inherited from the mother (Kramer et al. 2018), and it can show unique evolutionary patterns. By comparing the Neanderthal genome with other populations of *Homo sapiens* and chimpanzees, it is found that mitochondrial DNA of Neanderthals is closely related with South Africans, then southeast Asians and least similar with chimpanzees than Aborigines. This concludes that Neanderthals are closer to *Homo sapiens* than chimpanzees.

CONCLUSION

Homo sapiens are unique in intelligence, metabolism, memory, language, and immune, which might have contributed to their survival. Moreover, Neanderthals got extinct, and the comparison of Neanderthals with *Homo sapiens* and chimpanzees indicates that they are more close to *Homo sapiens*, but their mitochondrial and language genes show a high diversity among all. Most of the mutations present in modern humans are inherited from their ancestors and due to interbreeding with other species.

RECOMMENDATIONS

Mutations that are inherited from the ancestors provide insights into diseases, which can be useful in disease predictions and in identifying their origin. If the frequency of disease can be known in archaic species, one can predict the disease inherited in modern humans. This study contributes to understanding how *Homo sapiens* have evolved to survive and became the most advanced species. From previous knowledge of evolution in *Homo sapiens*, one can predict future genetic and physiological divergence in new upcoming generations. Nevertheless, it will help to analyse the similarities and differences in the behavior, language ability, social organisation, physical characteristics, and mental capabilities of both species. It may also be helpful in introducing prior measures to be taken before the inherited mutant gene express itself. Further research and advancements in technologies are required for discovering more fossils of Neanderthals that can assist in the better understanding of evolutionary patterns in the human genome.

LIMITATIONS

Selected Neanderthal sequences were the result of the mapping of Neanderthal genome sequencing reads to the human genome, and therefore, the researchers obtained a great identity in all selected groups. Further research is required on Neanderthals for a more detailed and precise comparison.

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