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Institute of Genomics, Institute of Molecular and Cell Biology, University of Tartu, Estonia

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REF I: Data analysis (inferring archaic haplotypes).

REF II: Study design, data analysis, interpreting results, and writing the article.

REF III: Study design, data analysis, interpreting results, and writing the article.

ABBREVIATIONS

a-cTF	TF regulated by cis-eQTL of Neandertal ancestry, i.e. aSNP
AMH	anatomically modern human(s)
aSNP	introgressed archaic variant – archaic SNP
CNS	central nervous system
cTF	TF regulated by cis-eQTL of AMH ancestry
eQTL	expression quantitative trait loci
FDR	false discovery rate
F_{ST}	fixation index
GO	gene ontology
GWAS	genome-wide association study
HARs	human accelerated regions
kya	kilo (thousand of) years ago
LD	linkage disequilibrium
logLR	log-likelihood ratio
Mb	megabases
MPRA	massive parallel reporter assay
mya	millions of years ago
NGS	next-generation sequencing
OR	odds ratio
PNG	Papua New Guinea(ns)
SNP	single nucleotide polymorphism
TF	transcription factor
UV	ultraviolet

1. INTRODUCTION

Anatomically modern humans (AMH) as a species formed in the long process of evolution from other great apes that took millions of years. Through this time, a sequence of nowadays extinct hominin species succeeded one another, a process which was revealed by paleontological analysis (Antón et al., 2014; Cartmill and Smith, 2022). Specifically, the archeological record has helped to reconstruct the evolutionary history of AMH across their existence throughout the last 300,000 years (Hublin et al., 2017; Trinkaus, 2005; Vidal et al., 2022; White et al., 2003). Paleontological data has also shown the presence of other human groups that have coexisted at the same time period with AMH, such as Neandertals. However, these two groups were separated for most parts of their existence geographically, with AMH living in Africa, and Neandertals in West and Central Eurasia (Arsuaga et al., 2014; Hublin, 2009; Neves et al., 2024; Schmitz et al., 2002). This changed when AMH started to move out of Africa around ~120 thousand of years ago (kya), with the subsequent major dispersal from the continent around 60 kya that led to the population of the rest of the whole world (Bae et al., 2017; Dennell and Petraglia, 2012; Stewart et al., 2020). Their arrival into distant regions of Eurasia around 40 kya also coincided with the Neandertal extinction (Smith et al., 2005). However, fossil remains and cultural artifacts of Neandertals and AMH could not provide a conclusive answer on whether these human groups interacted and admixed or AMH were involved in the disappearance of Neandertals (Duarte et al., 1999; Trinkaus et al., 2003).

New insights to answer this question came from genomic information of Neandertals, which was made possible by developments in sequencing technologies that enabled researchers to sequence ancient DNA remains (Green et al., 2010). The availability of genomic data from Neandertals provided a new means to quantify the evolutionary relationship between Neandertals and AMH. It demonstrated that there was interbreeding between the two groups (Green et al., 2010). The Neandertal genome also helped to estimate the time of admixture, which has been dated to happen 47–65 kya and likely took place in one major pulse of admixture between Neandertals and ancestors of all non-Africans (Sankararaman et al., 2012). As a result, ~2% of the genomes of present-day populations outside Africa are still of Neandertal ancestry (Mafessoni et al., 2020; Prüfer et al., 2017, 2013). Using the new sequencing technologies on old fossil remains, it was also revealed that AMH coexisted not only with Neandertals, but also with Denisovans, a previously unknown archaic human group (Meyer et al., 2012; Reich et al., 2010). Compared to Neandertals, Denisovans have an extremely sparse fossil record, which limits the ability to robustly reconstruct their physiology and habitat (Peyrégne et al., 2023). However, just like Neandertals, Denisovans admixed with AMH, and a substantial amount of up to 5% of their introgressed DNA can be found in genomes of present-day Oceanians (Meyer et al., 2012; Sankararaman et al., 2016).

Additional genomic data from more archaic individuals over the last decade helped to develop new methods to refine our understanding of the archaic admixture events and quantify Neandertal and Denisovan introgressed DNA in present-day humans (Reilly et al., 2022; Sankararaman, 2020). An important question following these discoveries centered around the functional implication of the introgressed DNA (Gittelman et al., 2016; Racimo et al., 2015; Sankararaman et al., 2016, 2014; Vernot et al., 2016). The biological interpretation of introgressed DNA in their carriers today also provided an inroad for a better understanding of the biology of Neandertals and Denisovans (Peyrégne et al., 2023; Zeberg et al., 2024). The investigation of the phenotypic consequences of Neandertal DNA relied on the analysis of functional datasets, such as association data, including genome-wide association studies and eQTL information, as well as other computational and experimental phenotypic databases (Guigo and de Hoon, 2018; Uffelmann et al., 2021). These approaches are possible because Neandertal DNA is found in all non-African populations (Sankararaman et al., 2014), including Europeans and Asians which are disproportionately often represented in such functional datasets (Sirugo et al., 2019). The results of studies exploring the phenotypic impact of Neandertal introgression have shown different biological systems to be significantly linked to Neandertal DNA, including behavior, immunity, skin and hair, with some of the underlying genetic variants also showing signatures of positive selection (Dannemann and Racimo, 2018). Also, it has been demonstrated that gene expression regulation as a molecular mechanism is significantly influenced by Neandertal DNA, both through positive and negative evolutionary processes (Reilly et al., 2022). At the same time, our knowledge of the functional implications of introgressed Denisovan is substantially smaller (Zeberg et al., 2024). A primary factor is the limited genomic and functional data available for populations carrying Denisovan ancestry (Martin et al., 2019). Nevertheless, in some instances also Denisovan introgressed DNA has been linked to signatures of local adaptation and to influence particular biological pathways, including high altitude adaptation, metabolism, and immune response processes (Peyrégne et al., 2023).

The growing development of computational and experimental technologies continues to facilitate the generation of new functional and genomic datasets, which also further empowers the investigation of the phenotypic implications of Neandertal and Denisovan introgression. This thesis is compiled of three studies that aim to extend the current knowledge about the functional implications of archaic introgression in present-day humans. The first study investigates the role of Neandertal DNA on neuropsychiatric disorders and associated non-disease behavioral traits in present-day humans (REF I). The second study explored the impact of Neandertal introgressed DNA on long-range regulatory effects in people today (REF II). The third study investigated the implications of Neandertal and Denisovan introgressed DNA on processes of local adaptation in two Papua New Guinea populations (REF III).

2. LITERATURE OVERVIEW

2.1. Investigation of human evolution as a key to understanding human-specific traits

2.1.1. Comparative biology as a means to study human uniqueness

Today, humans occupy a distinct place in the animal world due to their unique physical, mental, behavioral, social, and cultural traits. These include features such as bipedalism, muscle and adipose tissue composition, extended developmental period, relatively large brain volume, complex language, tool crafting and food preparation, hyper cooperation, dynamic material and symbolic cultures (Carmody and Wrangham, 2009; Foley and Gamble, 2009; Fuentes, 2015; Marean, 2015; Pollen et al., 2023). Humans acquired these specific features in the long process of evolution from other great apes that took millions of years (Figure 1). Consequently, the deconvolution of the evolution processes on different levels of biological organization provides a path to understanding the emergence of present-day human traits (Benton et al., 2021). One powerful approach used to discern these human-specific features is the comparison of AMH with the rest of the animal kingdom, particularly with their closest living relatives, other great apes (Darwin, 1871). The comparisons can be carried out based on various types of levels, including morphological, behavioral, anatomical, physiological, biomolecular, and other characteristics (Foley and Gamble, 2009; Owen Lovejoy et al., 2003; Pollen et al., 2023; Wood and Richmond, 2000). Particularly, developments in molecular biology advanced our understanding of the bases of human uniqueness. The discoveries of the protein and DNA structures laid the foundation for the central dogma of molecular biology, which in the field of evolutionary biology continued with the development of the theory of neutral sequence evolution (Cobb, 2017; Sanger, 1949; Watson and Crick, 1953). One of the theory outcomes is the molecular clock concept that uses changes in protein and DNA sequence to trace back the origin of ancestor states between species based on expected mutation rates (Margoliash, 1963; Zuckerkandl, 1987; Zuckerkandl and Pauling, 1962). This approach confirmed chimpanzees and bonobos as the closest living human relatives. It also allowed scientists to estimate the time of divergence between AMH and these other two great apes, which different methods place between 4–13 millions of years ago (mya) (Amster and Sella, 2016; Grabowski and Jungers, 2017; Kuderna et al., 2023; Langergraber et al., 2012; Moorjani et al., 2016; Sarich and Wilson, 1967; Steiper and Seiffert, 2012).

2.1.2. Comparative genomics highlights the basis of human-specific features

Besides clarifying the phylogenetic relationships between species, DNA information is also a key resource to study functional genomic elements, such as proteins, their inheritance and potential link to an organism's traits. Hence, a comprehensive comparison between the genomes of the human and the closest great apes provided an avenue for studying the origin of human-specific features as well. However, only at the end of the 20th century, the methodological and technological advances led to the possibility of sequencing entire genomes of species from the animal kingdom (Shendure et al., 2017). A huge effort of sequencing consortiums resulted in assembling the first human and a little later the first chimpanzee genomes in the early 2000s (Chimpanzee Sequencing and Analysis Consortium, 2005; Craig Venter et al., 2001). The comparison between these aligned genomes revealed 1.23% nucleotide differences across regions that could be directly compared, which is equivalent to 35 million single base pair differences between the genomes. At the protein level, 29% of genes were identical, whenever orthologous proteins showed on average approximately two amino acid changes between chimpanzees and humans – one per lineage (Chimpanzee Sequencing and Analysis Consortium, 2005). The discovery that most of the protein sequences evolved in neutral mode between both species suggested that crucial biological differences may have arisen through other processes, such as differences in the abundance of the proteins (King and Wilson, 1975). This hypothesis shifted investigations toward the analysis of differences in gene regulation which became possible on a genome-wide scale using high-throughput methodologies, such as microarrays or RNA-Seq (Keightley et al., 2005; Khaitovich et al., 2005; Pollard et al., 2006a; Suntsova and Buzdin, 2020). One example of the evolutionary importance of gene expression is a study that explored human accelerated regions (HARs). HARs are highly conserved in vertebrates but gained a prominent number of substitutions on the lineage of AMH, and have been shown to be commonly situated in non-coding parts of the human genome, with many of them close to genes involved in transcription and DNA binding processes, as well as developmental gene regulatory elements and RNA genes (Hubisz and Pollard, 2014; Pollard et al., 2006a, 2006b). In general, the advances in sequencing technologies facilitated genomic research, including primate studies and helped to generate a large number of genomes from more than 200 primate species, including all great apes (Kuderna et al., 2023; Kuhlwilm et al., 2016; Prado-Martinez et al., 2013; Shao et al., 2023; Yoo et al., 2024). The data enabled researchers to refine comparative studies between humans and great apes, as well as intraspecies genomic variability and relatedness among primates. However, a significant limitation in the genetic comparison of AMH to their closest relatives, chimpanzees and bonobos, lies in the fact that the last common ancestor of humans and these apes are inferred to live 4–13 mya (Grabowski and Jungers, 2017). Over the course of this extensive time span, numerous mutations have accumulated along both the human and chimpanzee/bonobo lineages (Prüfer

et al., 2012). The majority of these millions of nucleotide substitutions are assumed to represent neutral drift. Since most experimental setups are time-consuming, costly, and low-throughput, the huge number of variants to test hinders the ability to find and experimentally confirm the functional relevance of genetic substitutions that encode human-specific traits (Pollard et al., 2006b).

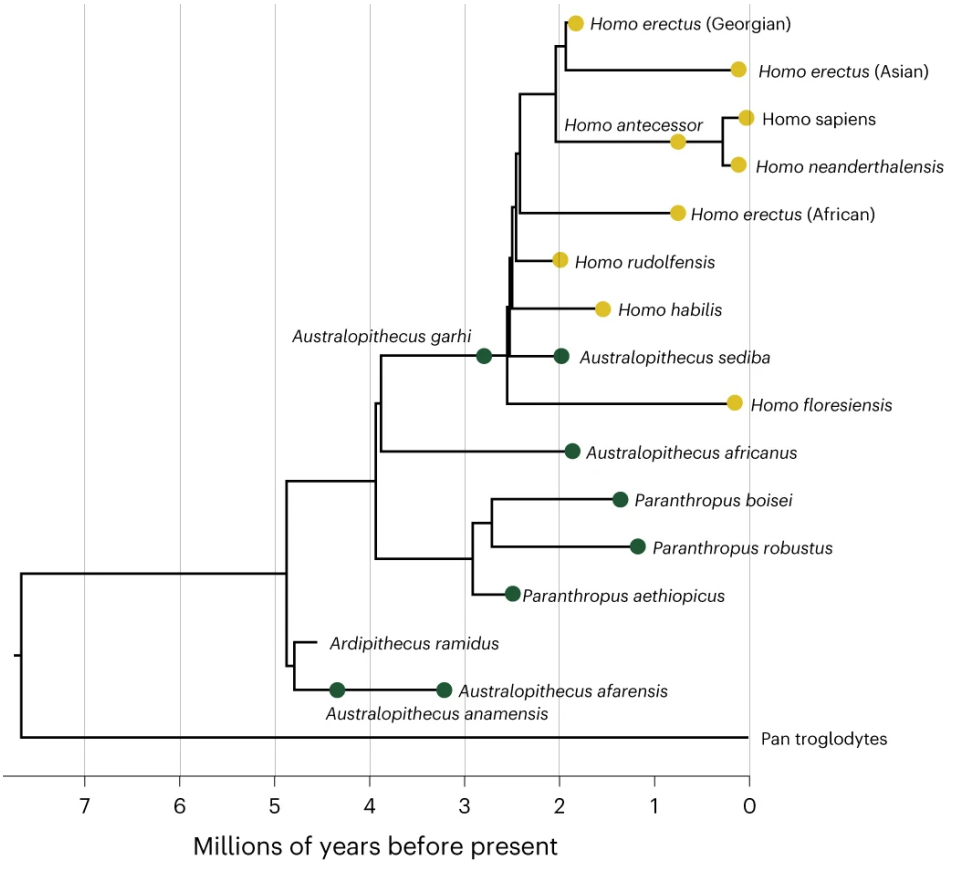

Figure 1: Phylogenetic relationships between 19 hominin species.

The (Parins-Fukuchi et al., 2019) phylogeny of 19 hominins, which is computed based on the best Akaike information criterion score for measures of fossil preservation and morphological evolution. Species are colored by taxonomic grouping (yellow: Homo; green: non-Homo). The figure illustrates the long process of human evolution from other great apes and the relatively short time of existence of AMH. Reprinted from Figure 1b (van Holstein and Foley, 2024), licensed under CC BY 4.0.

2.1.3. Investigating genomes of present-day human populations as an inroad to studying recent evolutionary episodes in human history

The ancestors of AMH emerged in Africa around 300 kya – a period that covers only a relatively short time frame across the 4–13 mya since the divergence from chimpanzees and bonobos (Grabowski and Jungers, 2017; Hublin et al., 2017). Therefore, only a fraction of the large numbers of human-specific nucleotide changes inferred from the comparison with these great apes are likely directly relevant for AMH evolution. In order to address this issue, other approaches were developed to study evolutionary processes in AMH. One such approach involves the investigation of genomic variation in contemporary populations to assess processes such migrations, admixture and selection (Hernandez et al., 2011; Zheng-Bradley and Flicek, 2016). However, this required the sequencing of large numbers of individuals from diverse populations – a major limitation for decades. This limitation was addressed with the transition from slow, low-throughput, and expensive sequencing technologies, such as Sanger sequencing, to next-generation sequencing (NGS) technologies in the mid 2000's (Heather and Chain, 2016; Pareek et al., 2011; Shendure et al., 2017). Ever since, the cost and time of genome sequencing dramatically decreased due to the constant improvements of these technologies. The usage of NGS facilitated the sequencing of hundreds of human genomes from diverse populations across the globe in projects such as the 1000 Genomes Project (1000 Genomes Project Consortium et al., 2015) and the Simons Genome Diversity Project (Mallick et al., 2016). Furthermore, hundreds of thousands of genomes have been sequenced in other cohorts over the last years, many of which are part of biobanks (Bycroft et al., 2018; GenomeAsia100K Consortium, 2019; Gurdasani et al., 2014; Hudjashov et al., 2017; Karczewski et al., 2020; Nagai et al., 2017; Pagani et al., 2016). These cohorts are often restricted to specific populations and show biases in their ancestry representation of present-day human populations (Bentley et al., 2017; Carress et al., 2021). Nevertheless, these datasets continue to help to refine the relatedness between populations, define their genomic structure, and outline admixture and migration events that took place in the recent past (Gravel et al., 2013; Liu et al., 2006; Novembre et al., 2008; Veeramah and Hammer, 2014; Zakharia et al., 2009; Zheng-Bradley and Flicek, 2016). In the context of recent AMH evolution, the exponentially growing number of different genomic datasets also facilitated the study of natural selection on a population level which prompted the development of various types of selection tests. The tests were designed to detect the genomic footprints of selection, such as reduction in genetic diversity around the genetic variant under selection or larger than expected allele frequency difference between different populations (Hejase et al., 2020; Holsinger and Weir, 2009; Lewanski et al., 2024; Speidel et al., 2019; Stern et al., 2019; Vitti et al., 2013). The studies on natural selection, combined with other population genomics inferences allowed scientists to reconstruct the dynamic interactions between human populations and their evolutionary history over the last thousands of years (Fu

and Akey, 2013; Pankratov et al., 2020). One prominent example has been how the introduction of agriculture in Europe as a cultural transition was driven by the migration of Neolithic farmers from the south and Steppe pastoralists from the east. In this context, it has also been shown that this transition is linked with the strong selection in the lactase (*LCT*) gene. This selection has often been attributed to an adaptation to lactose persistence – a trait potentially more advantageous in an agricultural environment (Irving-Pease et al., 2024; Zheng-Bradley and Flicek, 2016).

The growing number of genomes from great apes and diverse present-day human populations have continuously advanced our understanding about human evolution at a species and population level. However, this approach also faces challenges as many inferences that are based on the reconstruction of past events through present-day human genomes become more uncertain the further they date back in time. Consequently, genetic information for intermediate genomic information across the human lineage would add a powerful resource to further improve our knowledge on unique genome features that make AMH distinct.

2.2. Ancient DNA facilitates the investigation of recent time frames in human history

2.2.1. Neandertals and anatomically modern humans from a paleontological perspective

The exploration of primitive cultural artifacts and fossil remains, matched with routine radiocarbon dating (Arnold and Libby, 1949), revealed a sequence of extinct species within the Hominini tribe, illustrating how they evolved over time, succeeding and replacing one another (Antón et al., 2014; Cartmill and Smith, 2022). The archeological analysis identified multiple human groups from over several millions of years (Figure 1) (Begun, 2010). However, older fossil remains are substantially more sparse compared to more recent ones, thus creating a lower resolution towards older time frames (Harvati and Reyes-Centeno, 2022). The quality and quantity of more recent remains from the last hundreds of thousands of years have allowed scientists to describe the evolution of AMH in more detail (Trinkaus, 2005). The paleontological data showed that AMH originated and evolved in Africa, with the oldest fossil remains found in multiple locations across the continent around 300 kya (Hublin et al., 2017; Trinkaus, 2005; Vidal et al., 2022; White et al., 2003). During their evolution in Africa, the major role in the formation of AMH is attributed to the coalescence of East and South African human lineages (Mounier and Mirazón Lahr, 2019). The AMH fossil remains and cultural artifacts across the globe suggest two episodes of their dispersal out of Africa, with the late major migration happening around 60 kya through the Arabian Peninsula, with AMH fossil remains dated in distant regions of Eurasia around 40 kya, and South America around 15 kya. (Bae et al., 2017; Dillehay

et al., 2015; Gicqueau et al., 2023; Goebel et al., 2008; Mylopotamitaki et al., 2024; Smith et al., 2005).

However, the analysis of fossil remains revealed that when AMH arrived in Eurasia, this part of the world had already been inhabited by archaic humans known as Neandertals (Neves et al., 2024; Schmitz et al., 2002). Neandertals populated large parts of Eurasia, with fossil remains excavated across West Eurasia, from Portugal to the Altai Mountains and Northwest Europe to the Middle East (Figure 2). These findings highlight their plausible range with highly diverse environmental conditions that showed significant differences to the habitat AMH evolved in (Devièse et al., 2021; Grün et al., 2005; Villa and Roebroeks, 2014; Yaworsky et al., 2024). While many of the Neandertal remains are dated to before 130 kya, archaic skulls from Spain were assigned to be of Neandertal ancestors and dated as far back as 430 thousand years ago, suggesting that Neandertals could have been present in West Eurasia for hundreds of thousands of years (Arsuaga et al., 2014; Hublin, 2009). The geographically wide distribution of Neandertals across an extensive time period likely required them to adapt to the distinct environmental challenges their diverse habitats presented. For example, based on the fossil record, reconstructed Neandertals appeared to be wider and shorter in stature compared to AMH – features that are associated with adaptation to colder environments (Weaver, 2009). In addition to the colder climate, several other major environmental factors differed between the habitats of Neandertals and AMH. For instance, Neandertals lived in higher latitudes that are characterized by differences in the levels of seasonality and UV light exposure compared to Africa. In addition, local pathogens likely posed an additional challenge (Fisman, 2007; Moriyama et al., 2020). The dating of the Neandertal and AMH fossil remains in Eurasia suggested that both groups co-existed in space and time for thousands of years, until Neandertals went extinct around 40 kya (Marín-Arroyo et al., 2023; Mellars, 2006; Mylopotamitaki et al., 2024; Petraglia et al., 2010; Pinhasi et al., 2011; Shea, 2001; Yaworsky et al., 2024). However, based on the archeological record it was not possible to conclusively assess whether AMH and Neandertals met and interbred, which provoked decades of debates (Bailey et al., 2009; Duarte et al., 1999; Stringer and Crété, 2022; Trinkaus et al., 2003). Another unresolved question is the cause of Neandertal extinction. One hypothesis for their disappearance was their replacement by AMH who outcompeted them in terms of cultural, behavioral, and cognitive capacities (Villa and Roebroeks, 2014). However, the archaeological records of AMH and Neandertals suggest a high similarity of many traits between the human groups, and the observable difference between the groups does not imply any supremacy of AMH (Roebroeks and Soressi, 2016; Trinkaus, 1986). These similar traits include the presence of proto-language, symbolic behavior (cave paintings, personal adornment), capacity for innovation, hunting strategies and diet, usage of fire, tool and cloth making, landscape modification, and organization of living space (Johansson, 2013; Nowell, 2023, 2010; Villa and Roebroeks, 2014). However, despite these observations, the arrival of AMH into Eurasia is still considered a potential factor leading to the subsequent replacement

and possible assimilation of local archaic humans. Nevertheless, the cause of the process still remains unknown based on the available archeological data (Smith et al., 2005).

2.2.2. Genomic information from extinct archaic humans

The development of methods to extract and sequence DNA from fossils has opened a new direction for investigating past evolutionary processes. DNA generally degrades quickly, making the analysis of ancient genomic remains challenging or even impossible. However, under certain conditions when fossils are stored in favorable conditions to preserve them, such as caves, enough genetic material can be retained for extraction. Due to issues like contamination, degradation, and damage of ancient DNA, new laboratory and computational methods had to be developed to successfully extract and analyze DNA from human fossil remains. (Chen and Nedoluzhko, 2023; Higuchi et al., 1984; Hofreiter et al., 2001; Orlando et al., 2021; Pääbo et al., 1989; Rizzi et al., 2012). These advances led to the sequencing of genomes of Neandertals and AMH from fossil remains found across different sites in Eurasia from extended time frames of several thousands to in some instances more than a hundred thousand years ago (Fu et al., 2014; Prüfer et al., 2021; Reilly et al., 2022; Slatkin and Racimo, 2016).

The first low-coverage draft genome of Neandertals was generated from three bones excavated in the Vindija cave and dated approximately 40 kya (Green et al., 2010). The analysis of this genome showed that AMH and Neandertals shared a common ancestor around 825 kya. Furthermore, the comparison of the Neandertal genome with those of present-day humans suggested gene flow from Neandertals into the ancestors of all non-African populations. Subsequent efforts led to sequencing of dozens of low-coverage and three high-coverage Neandertal genomes, two from two distinct caves in Siberia dated around 125 kya and 80 kya respectively, and one 50 thousand years old individual from a site in Croatia (Mafessoni et al., 2020; Prüfer et al., 2017, 2013; Reilly et al., 2022; Skov et al., 2022). The availability of Neandertal high-coverage genomes helped to further refine the relationship between Neandertals and AMH, and facilitated the studies of human uniqueness and characteristics of Neandertal admixture in different populations. The genomic data from Neandertals also showed that they had lower levels of heterozygosity compared to ancient and present-day AMH, implying that these archaic humans lived in small, isolated, and highly inbred populations (Bennett and Fu, 2024; Fu et al., 2014; Prüfer et al., 2017; Skov et al., 2022). Genetically, early Neandertals can be partitioned into Western and Eastern groups that lived in Europe and Siberia, respectively. The genomic analysis showed genetic continuity of European Neandertals through time, while Neandertals from the Siberian group might have been replaced by the expanding Western Neandertal population towards the East around 100 kya (Hajdinjak et al., 2018; Mafessoni et al., 2020; Peyrégne et al., 2019).

The sequencing of DNA extracted from fossil remains in Denisova cave in the Altai Mountains showed that it was inhabited not only by Neandertals and AMH (Essel et al., 2023; Z. Jacobs et al., 2019; Zavala et al., 2021). DNA obtained from a finger bone found in the cave showed an unexpected genomic relationship with Neandertals and AMH. Even though the genome of the sequenced individual was closer related to Neandertals than AMH, it was distinctively different from the Neandertal draft genome (Reich et al., 2010). This observation justified the bone to be assigned to a new archaic group, which was named "Denisovan" after the cave where the fossil was found. Subsequently, a high-coverage genome was generated from the same sample (Meyer et al., 2012). Compared to Neandertals, the genomic analysis of that sample showed evidence for gene flow from Denisovans in present-day Melanesians. The finding of high levels of Denisovan introgression in Oceanian populations suggested that the plausible range of Denisovans possibly expanded further south than the range of Neandertals – a result that went beyond what was known from scarce fossil remains, which were limited to parts of Siberia and Tibet (Table 1) (Figure 2) (Peyrégne et al., 2023). The low number of fossil remains is a significant limitation of reconstructing Denisovan history, such as their diversity, biology and dispersal. Compared to Neandertals, only a handful of fragmented fossil remains dated in the period of 200 – 40 kya was found in Denisova Cave in Siberia and Baishiya Karst Cave on the Tibetan Plateau and confidently assigned to Denisovan through biomolecular analysis (Chen et al., 2019; Demeter et al., 2022; Xia et al., 2024). A comparison of Neandertal and Denisovan populations that included partial genomes from two Denisovan individuals found in Denisova cave showed that Denisovans were genetically more diverse with slightly higher levels of heterozygosity. However, these levels were still substantially below those of ancient and present-day human populations (Meyer et al., 2012; Prüfer et al., 2013). In addition, the analysis also revealed signatures of admixture between the two groups of archaic humans (Sawyer et al., 2015; Slatkin and Racimo, 2016). More recently, the discovery of the direct offspring of a Denisovan father and a Neandertal mother in the Denisova Cave showed even direct evidence of interbreeding between these two archaic human groups (Slon et al., 2018). All nuclear Denisovan DNA data was generated from fossil remains found in neighboring layers in one Siberian cave. The limited diversity coupled with the generally sparse fossil record is therefore likely biasing our understanding of Denisovan evolutionary history and their relations with AMH (Peyrégne et al., 2023; Sawyer et al., 2015).

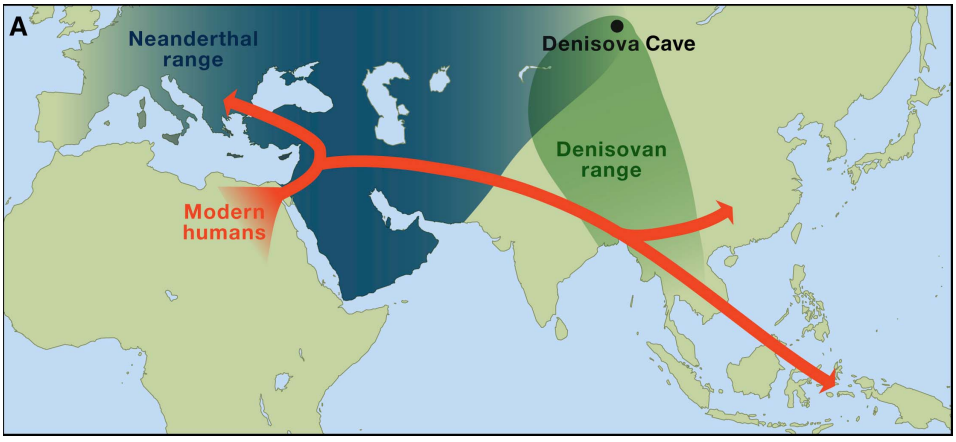

Figure 2: Insights gleaned from studying archaic hominin admixture (A).

Schematic illustration of the out-of-Africa dispersal of AMH (red). Blue and green shading roughly indicates the regions inhabited by Neandertals and Denisovans, respectively. Although fossil evidence of Denisovans has been found only at Denisova Cave, the observed pattern of Denisovan admixture suggests they had a wide range that extended southeast. Reprinted from Figure 1A (Vattathil and Akey, 2015) with permission from Elsevier.

2.2.3. Archaic genomes clarify the evolutionary relationship between human groups

The availability of genomic data from Neandertals and Denisovans facilitated the study of AMH uniqueness and their relation with these closest archaic relatives. The growing number of available archaic genomes helped to improve the divergence time estimates between AMH and archaic humans (Green et al., 2010; Meyer et al., 2012; Prüfer et al., 2013). The genomic analysis of early Neandertals from Sima de Los Huesos, dated 430 kya, aligned with the most recent estimates, according to which the divergence time between AMH and archaic humans is estimated at 520–630 kya, while Neandertals diverged from Denisovans 390–440 kya (Meyer et al., 2016; Prüfer et al., 2017). While comparisons of the nuclear genomes show that Neandertal and Denisovan are closer to each other than to AMH, mitochondrial DNA between Neandertal and AMH shares more similarities than any of them to Denisovan, with the exception of early Neandertals from Sima de Los Huesos. It suggests the possibility of earlier contacts between AMH and Neandertals which might have resulted in the substitution of mtDNA in Neandertals (Meyer et al., 2016; Posth et al., 2017). Consistent with this hypothesis, recent studies provided evidence for two-directional gene flow between AMH and Neandertals and inferred that Neandertals have 2.5 to 3.7% of AMH ancestry (Kuhlwilm et al., 2016; Li et al., 2024). Moreover, gene flow has not only been shown among these human groups but also from an unknown super-archaic human group that contributed up to 6% to the genetic makeup of the Denisovan

and has been dated more than 200 kya (Figure 3) (Hubisz et al., 2020; Prüfer et al., 2017).

The availability of genomic data from archaic humans also presented a powerful dataset to advance the understanding of human uniqueness. The comparison of archaic and present-day human genomes helped to narrow down further human-specific genomic variation that was derived before from human-chimpanzee genomes comparison (Burbano et al., 2012; Castellano et al., 2014; Kuhlwilm and Boeckx, 2019; Pääbo, 2014). The archaic genomes opened up the possibility to identify human-specific variants from a more recent timeframe of human evolution which includes the last 200,000–300,000 years of AMH existence. Already the analysis of the Neandertal draft genome presented potential candidates of selection in the AMH lineage, some of which were associated with genes linked to skin morphology and physiology (Green et al., 2010). Furthermore, HARs contained a significantly larger number of human-derived alleles shared between AMH and the Neandertal compared to human-specific variants in the rest of the genome, suggesting that, on average, human-chimpanzee derived substitutions arose before the divergence between AMH and Neandertals (Green et al., 2010). The subsequent investigation of high-coverage Denisovan and Neandertal genomes showed that they both have nearly 12% positions with ancestral alleles among those that differ between chimpanzees and humans (Peyrégne et al., 2023). The comparison of the first high-coverage Neandertal and Denisovan genomes with present-day human populations resulted in a catalog of AMH-fixed derived substitutions. These include around 32,000 single nucleotide polymorphisms (SNPs) and 4,000 short indels, which encode 96 amino acid substitutions in 87 proteins, and nearly 3,000 changes with a regulatory potential (Prüfer et al., 2013). The functional and evolutionary analyses of AMH-specific genomic variations showed that they are linked to genes related to the development and function of the brain, behavior and cognitive traits, and facial and vocal tract anatomy (Meyer et al., 2012; Peyrégne et al., 2023, 2017; Prüfer et al., 2013). A later study which leveraged additional archaic genomes, a much larger present-day human variation source, and different filtering techniques, identified 647 non-synonymous fixed or high frequency amino acid changes in 571 genes. The genes are linked to cell division and cellular components of neurons, brain development, and cognitive traits, thus aligning with the previous findings (Kuhlwilm and Boeckx, 2019).

2.2.4. Gene flow between archaic and anatomically modern humans

Already the analysis of the first genomic data from Neandertals and Denisovans suggested gene flow from Neandertals into the ancestors of non-Africans (Green et al., 2010), and from Denisovan into Melanesians (Reich et al., 2010). The sequencing of high-coverage genomes helped to refine these initial findings (Mafessoni et al., 2020; Meyer et al., 2012; Prüfer et al., 2017, 2013). As a result, it has been shown that individuals of non-African ancestry carry in their genomes

∽2% of Neandertal introgressed DNA, while Denisovan DNA is found at levels of 2–5% in Oceanian populations, and at low levels of <0.5% in some mainland Asians (Table 1) (Figure 3) (Larena et al., 2021; Meyer et al., 2012; Prüfer et al., 2017, 2013; Qin and Stoneking, 2015; Sankararaman et al., 2016; Vernot et al., 2016). There is evidence for one major admixture event between AMH and Neandertals that is dated to happen 47–65 kya and possibly took place in the Middle East (Sankararaman et al., 2012). Among the sequenced Neandertals, the Vindija Neandertal shows the closest genetic relationship to the introgressing Neandertal population (Mafessoni et al., 2020; Prüfer et al., 2017; Veeramah and Hammer, 2014; Zeberg et al., 2024). Neandertal introgressed DNA segments vary between individuals, and in total still cover at least 40% of the human genome (Dannemann and Racimo, 2018). It has been shown that the amounts of introgressed DNA varies among populations as well. For instance, East Asians have been shown to carry slightly higher levels of Neandertal DNA (Chen et al., 2020; Prüfer et al., 2017; Quilodrán et al., 2023; Reilly et al., 2022; Sankararaman et al., 2014; Wall et al., 2013). Furthermore, while there is some correlation in the distribution of Neandertal DNA between Europeans and Asians, there are also substantial differences between the Neandertal DNA content between populations (Sankararaman et al., 2014; Vernot and Akey, 2014). Compared to AMH admixture with Neandertals, admixture with Denisovans is more complex, and our inferences about it are limited by restricting factors such as a lower number of genomic data from Denisovans than Neandertals. Additionally, the only available high-coverage Denisovan genome is less closely related to introgressing Denisovan populations than sequences Neandertals to the introgressing Neandertal population, further restricting the analysis of admixture and relationship patterns (Peyrégne et al., 2023). Furthermore, the presence of Neandertal admixture in populations with Denisovan ancestry presents another challenge, which can lead to misclassification of the correct archaic source (Sankararaman et al., 2016; Vernot et al., 2016). Moreover, there is accumulating evidence of at least two pulses of AMH admixture with genetically distinct Denisovan populations in Southeast Asia (Table 1) (Browning et al., 2018; Choin et al., 2021; G. S. Jacobs et al., 2019; Zeberg et al., 2024). Finally, the substantially reduced amount of genomic data from populations with Oceanian ancestry adds another limitation to the analysis of Denisovan DNA in present-day people (Carress et al., 2021; Sirugo et al., 2019) (Carress et al., 2021).

In general, both Neandertal and Denisovan DNA in present-day populations is unevenly distributed across the genome. While some regions are enriched, others are depleted for archaic ancestry (Sankararaman et al., 2014; Vernot et al., 2016). These frequency differences might reflect different modes of selection that in the case of high frequency variants could have contributed to adaptive processes or in instances of regions without archaic DNA could be the result of negative selection removing archaic variation. Adaptive processes involving archaic DNA in AMH might mirror past adaptations in archaic humans to their living environments in Eurasia that they populated for hundreds of thousands of years, and from which AMH benefited in their quest to move out of Africa and

populate these regions as well. To test this hypothesis, scientists sought to study the functional consequences of archaic DNA in present-day people using the rapidly evolving computational and experimental framework that was developed in the last decade.

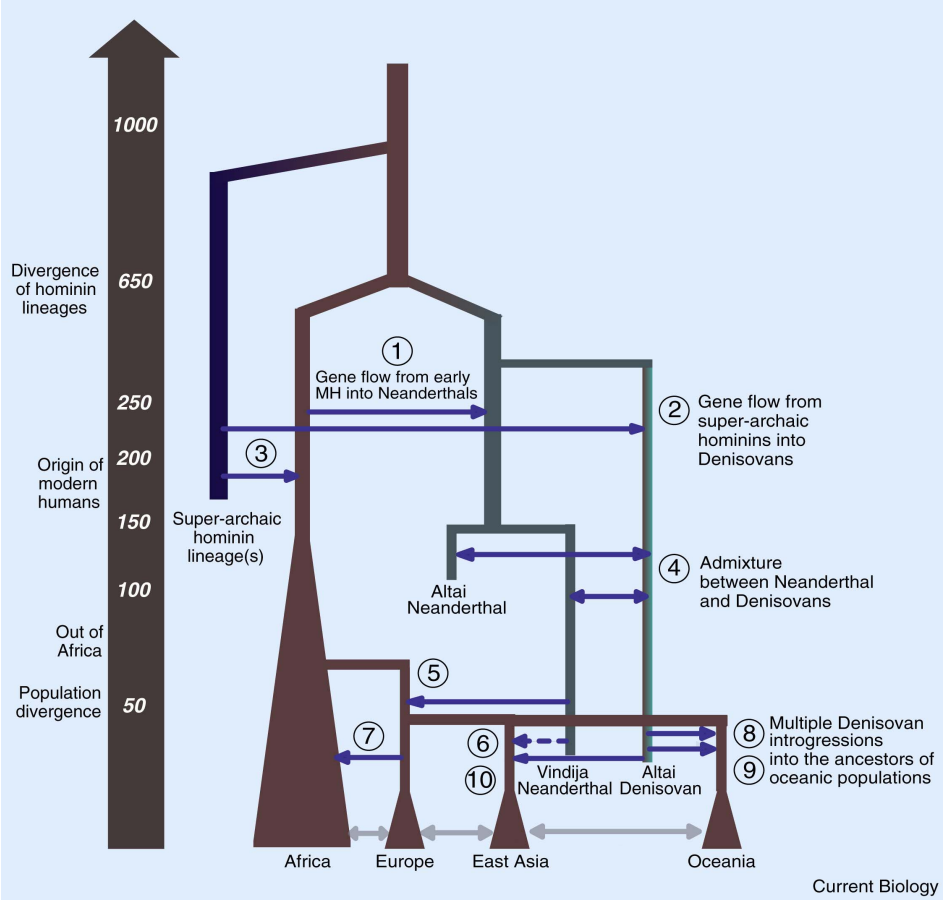

Figure 3: Simplified demographic model illustrating inferred population relationships and admixture events among anatomically modern humans and archaic hominins.

Events depicted include (1) gene flow from early (anatomically) modern humans (MH) into Neandertals, (2) from a super-archaic hominin lineage into Denisovans, and (3) gene flow from a super-archaic hominin lineage into early modern humans in Africa; (4) admixture events between Neandertals and Denisovans in the Altai Mountains, also supported by the sequencing of the first generation offspring of a Neandertal mother and a Denisovan father; (5) gene flow from Neandertals into the ancestors of all non-Africans, (6) putative gene flow from Neandertals into the ancestors of East Asians (dashed arrow), (7) back migration from Eurasia to Africa; and multiple Denisovan introgressions into the ancestors of (8,9) Oceanians and (10) East Asians12. For simplicity the multiple, distinct introgressing Denisovan-like lineages are represented as arising from a single Denisovan source. Reprinted from Figure 2 (Reilly et al., 2022) with permission from Elsevier.

2.3. Evolutionary history of complex traits

The joint analysis of the genomes of ancient and present-day humans, as well as Neandertals and Denisovans helped to identify genomic regions of evolutionary importance. These include regions unique to AMH as well as those subject to archaic introgression. One particular question of special interest has been the role of DNA inherited from these archaic humans and its potential role in facilitating adaptation to environmental pressures in AMH. Similarly, the functional interpretation of regions devoid of archaic DNA in the genomes of present-day populations, possibly as a result of negative selection against introgressed DNA, might shed light on fundamental differences in the biology of anatomically modern and archaic humans. In order to address these questions, genomic information has been linked to different types of phenotypic data (Table 1) (Benton et al., 2021). One such approach, which has been applied to both types of genomic regions with and without archaic DNA, was the investigation of their gene content and functional potential of genetic variants.

Table 1: A comparison of features of Neandertals and Denisovans as well as admixture patterns between both groups and AMH

	Neandertals	**Denisovans**
Habitat	West Eurasia	East Eurasia
Fossil remains	abundant and from different geographic locations and time periods	sparse and geographically restricted but from different time periods
Number of sequenced genomes	Three high-coverage genomes and 10+ low coverage genomes	One high-coverage genome and 2 low-coverage genomes
Present-day populations carrying archaic DNA	Non-Africans	Oceanians and some mainland Asians
Admixture pattern	One pulse into the ancestor of non-Africans	At least two pulses of admixture in Asia
Phenotype groups with significant links in present-day populations	immunity, behavior, skin and hair	immunity, high-altitude and lipid metabolism

The data leveraged to address this topic can be classified into four main categories: i) functionally annotated human genome maps, that include information on coding and non-coding genes and associated functional elements such as regulatory elements (Ashburner et al., 2000; Craig Venter et al., 2001; Harrow et al., 2012; Luo et al., 2019; Melé et al., 2015); ii) association-based results that establish a link between genetic variation and molecular and organism phenotypes, including expression quantitative trait loci (eQTL) and genome-wide association study (GWAS) information (Aguet et al., 2020; Sollis et al., 2023;

Uffelmann et al., 2021); iii) computational prediction derived data such as deleteriousness scores (Adzhubei et al., 2010; Benegas et al., 2024; Kircher et al., 2014) or predicted expression levels (Al taweraqi and King, 2022; Avsec et al., 2021; Colbran et al., 2019); iv) results from experimental assays, including high-throughput methods such as multiple parallel reporter assay that test for the regulatory potential of genetic variants (Gallego Romero and Lea, 2023; Pollen et al., 2023). These data types possess distinct advantages and limitations. Some of those are particularly relevant when studying genetic variation in present-day people that was introduced by archaic introgression and will be discussed throughout this chapter.

2.3.1. Patterns of negative selection against archaic introgressed DNA sequences

The analysis of archaic admixture in present-day humans has demonstrated that negative selection has played an important role in shaping the introgressed landscape in the genomes of AMH – particularly in the first generations after the introgression (Fu et al., 2016; Petr et al., 2019). To investigate the patterns and potential functional targets of negative selection, scientists have focussed on genomic regions depleted of archaic introgressed DNA (Sankararaman et al., 2016, 2014; Vernot et al., 2016; Vernot and Akey, 2014). However, finding the functional targets and their underlying genetic variation poses distinct challenges. One target is genetic variants unique to archaic humans that were likely introgressed but removed after admixture. The absence of such variation limits the pathways for the functional testing of their effects. Computational and statistical approaches are not applicable because of the absence of the tested archaic variants in people today. Furthermore, some of the largest genomic regions depleted of both Neandertal and Denisovan DNA span several million bases (Mb) and contain hundreds of genes and thousands of candidate variants that differ between anatomically modern and archaic humans (Vernot et al., 2016). The large number of such variants therefore requires high-throughput computational and experimental methods, which are only available in limited forms. For instance, one particular experimental approach, massive parallel reporter assay (MPRA), is a high-throughput experimental method to test for the regulatory potential of genetic variation and can be applied to simultaneously test thousands of human-specific variants for regulatory activity in different cell types (McAfee et al., 2022; Tewhey et al., 2018; Uebbing et al., 2021; Weiss et al., 2021). However, MPRA's are still an exception, and many experimental setups are still too limited in their throughput to comprehensively test large sets of genetic variation, such as variants that differ between anatomically modern and archaic humans. Due to these challenges, the majority of approaches to investigating AMH-specific variants and genomic regions depleted of archaic DNA so far have been computational. Using such approaches, it has for example been shown that regions devoid of Neandertal

and Denisovan ancestry are enriched for testis-expressed genes and genes transcribed in meiotic germ cells (Jégou et al., 2017; Sankararaman et al., 2016, 2014). Moreover, chromosome X shows on average four-fold reduction of both Neandertal and Denisovan ancestry compared to autosomes in non-African populations. Because the depleted genomic loci included genes involved in male-specific biology, this observation sparked a hypothesis about potential sex-biased admixture patterns between anatomically modern and archaic humans and possibly reduced hybrid male fertility (Chevy et al., 2023; Sankararaman et al., 2016; Skov et al., 2023). Among the genomic regions devoid of both Denisovan and Neandertal ancestry, a particular focus was placed on the five longest regions on the autosomes – each between 11 and 20 Mb long – which are now often referred to as "archaic deserts" (Sankararaman et al., 2016; Vernot et al., 2016). Given that archaic DNA from both Neandertals and Denisovans was removed from these regions more than once, this observation sparked hypotheses that these regions overlap genetic variation linked to human-specific traits. The analysis of the gene content of these deserts has shown that they are enriched for genes expressed in the developing cortex and adult striatum, as well as genes associated with autism spectrum disorders (Vernot et al., 2016). Furthermore, the largest desert on chromosome 7 also encompasses the *FOXP2* gene which is crucial for the development of speech and language areas of the brain (Sankararaman et al., 2016). The gene has a particular AMH-specific substitution in a binding site for the transcription factor *POU3F2* which has experimentally been shown to be regulatory active (Maricic et al., 2012). Despite the challenge of identifying the exact targets of negative selection, the insights presented by these studies suggest a plausible link of negative selection to genes involved in brain biology and sex-specific admixture processes. These results are also noteworthy in the context of other studies, which have shown that genome-wide signals of negative selection acting on both Neandertal and Denisovan introgressed sequences are particularly pronounced in regulatory regions such as promoters, as well as both conserved noncoding and protein-coding sequences (Petr et al., 2019; Sankararaman et al., 2016; Telis et al., 2020). The discovered functional characteristics of negative selection are most compatible with two main mechanisms: i) there is archaic and anatomically modern human genomes' partial incompatibility related to reproduction and AMH-specific traits (Sankararaman et al., 2014); ii) archaic genomes contain on average higher deleterious burden compared to AMH due to weaker negative selection in the archaic small populations (Steinrücken et al., 2018). Both of the hypotheses assume the favoring of some of the AMH variants in their genetic environment thus creating permanent selection pressure against some archaic DNA segments (Harris and Nielsen, 2016; Juric et al., 2016).

2.3.2. Functional implications of Neandertal introgression

One particular emphasis since the discovery of admixture between anatomically modern and archaic humans was the annotation of the functional and phenotypic effects of archaic DNA in their carriers today. Of specific interest in that context

was the discovery of biological systems significantly affected by Neandertal DNA as those could highlight potential Neandertal genetic adaptations to their habitat, which might have also helped AMH to cope with the new environments they entered (Reilly et al., 2022). However, the establishment of a link between genetic variation and their potential functional and phenotypic effects is often challenging (Uffelmann et al., 2021). One common approach to identify the biological potential of genomic regions is to study their gene content (Gittelman et al., 2016; Racimo et al., 2015). In the case of Neandertal admixture several studies applied this approach to investigate genomic regions carrying high frequency Neandertal introgressed haplotypes in people today. They showed that genomic regions of high Neandertal ancestry were enriched for genes involved in skin and hair morphology, as well as for genes linked to immunity (Table 1) (Deschamps et al., 2016; Enard and Petrov, 2018; Gower et al., 2021; Quach et al., 2016; Quach and Quintana-Murci, 2017; Sankararaman et al., 2016, 2014). In general, the analysis of the functional nature of genes within genomic regions has its strengths and limitations. While it can be readily applied to genomic data and, in combination with functional annotations, such as those from ontologies, be a powerful method to identify the enriched biological pathways, it oftentimes lacks any direct link between archaic genetic variants and putative phenotypic effects.

In order to overcome these limitations, several studies have taken advantage of the growing number of data that is becoming available from association datasets such as genome-wide association and eQTL studies (Aguet et al., 2020; Dannemann and Kelso, 2017; Gittelman et al., 2016; Sollis et al., 2023; Stephens et al., 2015). In contrast to the analysis of the gene content overlapping Neandertal haplotypes, this approach allows for the testing of the potential phenotypic impact of archaic variants in present-day populations. Particularly data from large cohorts with available genotype and phenotype data, such as population biobanks, have been an important resource to facilitate this research (Carress et al., 2021; Lazareva et al., 2022). These datasets often consist of hundreds of thousands of individuals, a sample size large enough to confidently infer genetic associations for low frequency variants, including a large portion of introgressed Neandertal variants. Studies that have employed GWAS data to study the potential phenotypic effect of Neandertal introgressed alleles have shown that Neandertal DNA is significantly more often associated with immunological, behavioral, psychiatric, and neurological traits, as well as with phenotypes linked to skin, bones, and lung characteristics (Dannemann, 2021; Dannemann and Kelso, 2017; McArthur et al., 2021; Quach et al., 2016; Simonti et al., 2016). However, for the vast majority of investigated phenotypes, introgressed Neandertal DNA showed either a similar or lower number of associations compared to non-archaic DNA (McArthur et al., 2021; Wei et al., 2023). Both of these approaches, testing for the genomic gene content and phenotypic association of archaic DNA, provided an inroad to test for the potential functional role of Neandertal admixture and identified biological systems with a significant link to introgressed Neandertal DNA. Three of the most prominent systems are discussed in more detail in the following sections.

2.3.2.1. Morphological traits

High frequency Neandertal haplotypes have repeatedly been situated in genomic regions encompassing genes associated with skin and hair biology. For example, genes involved in keratin filament formation are significantly enriched for Neandertal high frequency haplotypes in both European and East Asian populations (Sankararaman et al., 2014). Additionally, two of the four most differentiated Neandertal haplotypes between these populations encompass skin-related genes (Vernot and Akey, 2014). The haplotype overlapping the skin-color-associated gene *BNC2* (Jacobs et al., 2013) is the most frequent haplotype in Europeans with a frequency of 70% and is absent in East Asians. In general, little is known about the potential phenotypic effects of Neandertal DNA linked to these genes. One exception is the aforementioned high-frequency Neandertal haplotype linked to the *BNC2* gene, which is associated with an increased incidence of childhood sunburn, risk of keratosis, and poor tanning in the UK Biobank cohort (Dannemann and Kelso, 2017; Simonti et al., 2016).

2.3.2.2. Immunity

Another phenotypic group that has frequently been linked to high frequency Neandertal DNA is immunity. For example, genes coding for proteins that interact with viruses are significantly enriched among high frequency Neandertal haplotypes in present-day humans. This enrichment is particularly pronounced in Europeans for proteins that provide defense against RNA viruses (Enard and Petrov, 2018). This result is consistent with experimental data that showed that Neandertal variants are enriched among cis-eQTLs in immune cells exposed to various viral stimuli (Quach et al., 2016). In addition to these enrichment results, a number of individual immune loci have been linked to high frequency Neandertal DNA, many of which also show a direct link to pathogen response processes (Racimo et al., 2015; Zeberg et al., 2024). Among those loci are genes involved in the innate immune response (Deschamps et al., 2016), the immune-associated transcription factor *STAT2* (Mendez et al., 2012), *OAS* enzymes (*OAS1-3*) (Sams et al., 2016), *PNMA1* (Quach et al., 2016), and Toll-like receptors (*TLR6-TLR1-TLR10*) (Dannemann et al., 2016). At the *OAS* locus, the Neandertal haplotype is linked to regulatory variants that modulate the expression of *OAS3* in response to infection and affect alternative splicing for *OAS1* and *OAS2* genes (Sams et al., 2016). Similarly, the expression of the *PNMA1* gene in response to the Influenza A virus is associated with high-frequency Neandertal variants (Quach et al., 2016; Shapira et al., 2009). The Neandertal introgressed alleles at a Toll-like receptors gene cluster are linked to increased expression of these genes in lymphoblastoid cell lines, and associated with reduced *Helicobacter pylori* seroprevalence and higher susceptibility to allergic disease (Dannemann et al., 2016). Compared to other loci, the Toll-like receptors contain three distinct archaic haplotypes with one of likely Denisovan ancestry, which might indicate balancing selection towards the locus variability – a pattern also suggested for some of the observed Neandertal

haplotypes in the Major Histocompatibility Complex (Abi-Rached et al., 2011). The coronavirus SARS-CoV-2 outbreak provoked the investigation of genomic associations to the disease, which identified two Neandertal haplotypes on chromosomes 3 and 12 that have been associated with opposite effects on the severity of COVID-19 progression (Zeberg et al., 2020b; Zeberg and Pääbo, 2021, 2020). Furthermore, Neandertal DNA has also repeatedly been linked to autoimmune disorders such as systemic lupus erythematosus, dermatitis, rheumatoid arthritis, Crohn's and Grave's diseases, highlighting the complex consequences of Neandertal introgression for present-day human health (Dannemann, 2021; McArthur et al., 2021; Sankararaman et al., 2014). In general, Neandertal variants at immune loci were often associated with an immune-activating effect, a result that is possibly connected to the link of Neandertal DNA to several autoimmune conditions, which are disorders that are often caused by an overstimulated immune system as well.

2.3.2.3. Behavior and other brain-related traits

Another group of phenotypes with significant links to introgressed Neandertal DNA, that has specifically been identified through the analysis of GWAS data, are behavioral phenotypes. For example, through the analysis of phenotypic association of Neandertal DNA in the UK Biobank it has been shown that compared to frequency-matched non-archaic variants, introgressed variants show significantly more associations with a number of behavioral traits, including smoking status, mood, and sleeping patterns (Dannemann and Kelso, 2017). In particular, a Neandertal variant near the *EXOC6* gene, which plays a role in intracellular transport and exocytosis, is associated with an increased propensity for narcolepsy and napping during daytime. Another significant association with evening activity is related to a Neandertal allele near the *ASB1* gene, a gene participating in cytokine signaling regulation. The frequency of the allele is correlated with latitude, which could reflect the difference in sunlight exposure compared to Africa (Dannemann and Kelso, 2017). These results were consistent with a similar enrichment of Neandertal variant associations with neurological disorders in a large disease cohort (Simonti et al., 2016). Furthermore, a recent study of the role of archaic introgression on the underlying genetics of chronotype investigated regulatory differences of circadian genes between archaic and anatomically modern humans. It demonstrated that introgressed Neandertal alleles are enriched among eQTLs for circadian genes. Further, the archaic alleles associated with these eQTLs were predominantly associated with increased morningness and several of the loci showed signatures of adaptive introgression (Velazquez-Arcelay et al., 2023). Moreover, there are two Neandertal variants associated with smoking status (Sankararaman et al., 2014) and tobacco use disorder, one of which is situated in an intron of the *SLC6A11* gene (Simonti et al., 2016). The gene's protein is responsible for the reabsorption of the GABA neurotransmitter, while nicotine decreases the *SLC6A11* expression and oppresses GABA-related signaling in the brain (D'Souza and Markou, 2013; Pickering et al., 2008). Another phenotype

with a link to brain function is pain sensation. Introgressed Neandertal variants that modify the protein sequence of *SCN9A*, which encodes a sodium channel of pain receptors, were found to be associated with increased pain sensitivity in UK BioBank (Zeberg et al., 2020a). These variants show high frequency in Latin Americans and experimentally have been linked to a lower mechanical pain threshold in Colombians (Faux et al., 2023). It is noteworthy that in addition to behavior-related phenotypes derived from GWASs, also differentially methylated regions between Neandertal and AMH were shown to be enriched for genes linked to psychiatric and neurological disorders (Gokhman et al., 2014). The importance of regulatory mechanisms related to such diseases and the role of introgression is also suggested by the significant enrichment of Neandertal alleles among brain cis-eQTL compared to the control SNPs of AMH ancestry (Simonti et al., 2016).

2.3.2.4. Gene regulation

Previous studies of selective pressures on introgressed Neandertal DNA in present-day humans have demonstrated that both archaic DNA under positive and negative selection is often associated with gene expression regulation processes (Gittelman et al., 2016; Gokhman et al., 2014; Petr et al., 2019; Quintana-Murci, 2019; Sankararaman et al., 2014). It has also been shown that Neandertal DNA in present-day humans is more often associated with gene expression changes than frequency-matched non-archaic variants (Dannemann et al., 2017). Furthermore, an analysis of allele-specific expression showed that in testes and the brain archaic alleles are significantly downregulated (McCoy et al., 2017). In addition, by leveraging data from more than a hundred epigenomes, a study showed an enrichment of Neandertal introgressed variants among enhancers across almost one-third of the tested tissues, particularly pronounced in primary T cells and adipose-related tissues (Silvert et al., 2019). However, a subsequent study that differentiated enhancers by various classes, showed them to be depleted of Neandertal ancestry compared to expectations from background selection (Telis et al., 2020). The study demonstrated that the signal was mainly driven by young archaic variants that emerged not long before the admixture with AMH. Moreover, pleiotropic enhancers and those active in fetal brain and muscle tissues show the strongest reduction in the amount of Neandertal SNPs (Telis et al., 2020). All these observations indicate a significant impact of Neandertal introgression on the gene expression landscape in present-day people and also suggest a molecular mechanism through which Neandertal DNA affects phenotypic variation in present-day humans.

2.3.2.5. Limitations and approaches for mitigation

Neandertal DNA in present-day humans has certain characteristics, which are associated with limitations for several of the presented methods of functional annotation. Firstly, there are substantial differences between non-African populations in the distribution of introgressed Neandertal DNA. Therefore, phenotypic

implication of Neandertal introgression can be substantially different between populations. The bias of association studies (GWAS/eQTL analysis) towards cohorts of European ancestry (Carress et al., 2021; Martin et al., 2019; Sirugo et al., 2019) limits an unbiased assessment of the phenotypic impact of Neandertal DNA between populations using association-based datasets. Secondly, most of the introgressed Neandertal haplotypes are segregating at low frequencies in present-day populations (Sankararaman et al., 2014; Skov et al., 2020; Vernot and Akey, 2014). In order to assess the impact of such variations, association studies need large sample sizes, which became possible only with the widespread introduction of high-throughput NGS and microarray technologies (Aguet et al., 2020; Bycroft et al., 2018; Sollis et al., 2023; Võsa et al., 2021; Zhou et al., 2022). Thirdly, due to relatively recent admixture, archaic haplotypes span tens of thousands of bases, and carry tens of archaic variants in high and linkage disequilibrium (LD) (Sankararaman et al., 2012; Skov et al., 2018). The LD between these variants introduces an additional challenge of pinpointing the causal variant(s) for a potentially functionally relevant archaic haplotype. At the same time, due to their extended length, introgressed haplotypes often overlap multiple genes, further complicating the establishment of a link to its causal genetic targets. Furthermore, most studies investigating archaic introgression use haplotype-based approaches to infer the landscape of introgression represented through DNA segments (Sankararaman, 2020). However, these methods capture only a subset of introgressed DNA which is substantially lower than the expected 2% evaluated through allele-sharing methods like F4 statistics (Prüfer et al., 2017, 2013). This is partially due to the fact that some of the reconstructed archaic-like haplotype show a similar lengths like from haplotypes that are the result of incomplete lineage sorting, making is difficult to distinguish both.

In order to address these issues, specific methods, including computational effect predictors and experimental assays can offer potential solutions. For example, through identifying genetic variations with regulatory potential or evolutionary conservation, machine learning approaches provide resources to prioritize archaic genetic variants in high LD or in cases when other genomic and phenotypic data is not available (Benegas et al., 2024; Dong et al., 2023; Kircher et al., 2014; Sim et al., 2012). Some methods were developed particularly for the prediction of the effects of nucleotide sequence variants on protein structure (Adzhubei et al., 2010; Jumper et al., 2021; Sim et al., 2012). For instance, through leveraging deleteriousness scores of two computational prediction algorithms, a study showed non-synonymous Neandertal introgressed variants possess lower predicted functional effects on proteins compared to background non-archaic mutations (Dannemann et al., 2017). Such computational approaches can also aid the selection of potential variants tested in experimental assays, which are often low throughput as well as cost and time-consuming and do not allow for the testing of hundreds or even thousands of variants (Gasperskaja and Kučinskas, 2017; Guigo and de Hoon, 2018). However, the methodological developments in recent years have introduced suitable high throughput experimental assays for testing introgressed Neandertal variants, such as the aforementioned MPRAs

(Gallego Romero and Lea, 2023). A study applying an MPRA on Neandertal introgressed high frequency variants, found nearly half of 5,353 tested variants to be active putative cis-regulatory elements in multipotent hematopoietic cells. Among those were 292 variants with an expression-modulating effect (Jagoda et al., 2021). The usage of MPRA promises to create large resources of the experimentally tested linkage between genomic variations and gene expression, which would help to assess the impact of archaic admixture on complex traits (Agarwal et al., 2023; Siraj et al., 2024).

2.3.3. Functional implications of Denisovan introgression

Compared to the functional and phenotypic annotation of Neandertal introgression, our knowledge about the consequences of Denisovan admixture in present-day humans is more limited. While Neandertal and Denisovan introgressed haplotypes share characteristics such as being mostly rare and of similar lengths with variants in high LD, the result of Denisovan introgression has additional crucial features that limit the ability for its functional annotation (Peyrégne et al., 2023). The main limitation is the presence of a substantial amount of Denisovan introgressed DNA segments only in Island Southeast Asians and Oceanians. Compared to other present-day populations, substantially less genomic and phenotypic data is available for those populations (Martin et al., 2019; Sirugo et al., 2019). The analysis of Denisovan DNA is further complicated by the issue of correctly classifying Denisovan introgressed haplotypes in their carriers. For example, because all present-day populations with Denisovan ancestry also carry Neandertal DNA (Sankararaman et al., 2016) and due to the large sequence divergence of the sequenced Denisovan individual and the introgressing Denisovan populations, a considerable number of Denisovan DNA segments is expected to be closer in sequence to Neandertals and therefore be misclassified when solely annotated based on sequence similarity (Vernot et al., 2016). This phenomenon is further enhanced by the fact that Oceanians carry Denisovan DNA that can be traced back to multiple pulses of introgression from genetically distinct Denisovan populations, that show varying sequence relationships to the Denisovan reference sequence (G. S. Jacobs et al., 2019).

However, despite these limitations, previous studies have shed light on the potential phenotypic role of Denisovan DNA in people today. For example, analyses of genotype data from Oceanian populations have shown an enrichment of high frequency Denisovan introgressed haplotypes among genes linked to the smell-detecting, lipid metabolism, and immune response processes (Table 1) (Choin et al., 2021; Gittelman et al., 2016; G. S. Jacobs et al., 2019; Sankararaman et al., 2016). Furthermore, there are two well-described cases of adaptive introgression from Denisovan, both found using populations living in unique environmental conditions. The first example is related to the analysis of genomes from Tibetans. More than 80% of Tibetans carry a haplotype that shows strong signatures of positive selection in that population. This haplotype was shown to be of Denisovan ancestry and encompass the *EPAS1* gene that is involved in

response to hypoxia (Huerta-Sánchez et al., 2014; Zhang et al., 2021). In another study, Greenlandic Inuits have been shown to carry an almost fixed Denisovan introgressed haplotype encompassing the *TBX15* and *WARS2* genes. Both genes, which are involved in adipocyte differentiation and body-fat distribution, have been linked to signatures of local adaptation (Racimo et al., 2017). Recently, this haplotype has also been shown to be associated with lip thickness in Latin Americans (Bonfante et al., 2021). Furthermore, various studies exploring the regulation of gene expression showed a significant link of introgressed Denisovan DNA to immunity. Despite the previously reported depletion among enhancers for Neandertal and Denisovan DNA (Telis et al., 2020), the analysis of epigenomic maps across various cell types on Papaun genomes revealed enrichment of Denisovan alleles in transcribed regions and cis-regulatory elements, with a particularly strong effect on regulatory elements within immune-related cells (Vespasiani et al., 2022). Another study that characterized the impact of Denisovan introgression on methylation levels and gene expression in the Indonesian population, showed that differentially expressed genes between populations are enriched for immune function and Denisovan introgressed DNA (Natri et al., 2020). In addition, an experimental study in mice showed that two missense substitutions in *TNFAIP3* that are associated with a Denisovan haplotype, increase immune response patterns without a typically associated inflammation response (Gittelman et al., 2016; Zammit et al., 2019). In general, the analysis of the potential impact of Denisovan introgression has shown a significant role in metabolism and immunity in present-day humans. Future efforts using the growing number of genomic and phenotypic data from Oceanian populations, in combination with new computational and experimental approaches will be vital to further expand the knowledge of Denisovan admixture in people today.

2.3.4. Variation of phenotypes between human groups inferred from archaic introgression and functional prediction

The analysis of the phenotypic role of Neandertal admixture in present-day people has helped to identify biological systems with a significant link to Neandertal DNA. Among those are traits related to the immune system, skin and hair biology and behavior. Several of the identified phenotypes show a strong correlation with latitude and UV light exposure, including skin and hair color or chronotype. These results potentially highlight instances of Neandertal adaptation to environmental conditions in Eurasia which differ compared to those in Africa, the origin of AMH. The results also indicate a plausible role of Neandertal admixture as a source of genetic variation, some of which might have been beneficial for AMH for their adaptation to new environment challenges after moving out of Africa, including local pathogens, sunlight exposure, and seasonality. The results also suggest that one of the major mechanisms through which Neandertal introgressed DNA affects phenotypes is through gene expression regulation. Despite the limitation of the analysis of Denisovan DNA in people today compared to the analysis

of Neandertal DNA, there are several overlapping patterns between both. Introgressed DNA from both archaic humans has been significantly linked to immune phenotypes. Furthermore, several introgressed haplotypes from both archaic groups have shown patterns of positive selection, indicating the role of adaptive admixture with Neandertals and Denisovans. Finally, gene expression regulation has been established as a major molecular mechanism through which both Neandertal and Denisovan introgressed DNA influence human traits.

The output derived from the analysis of introgressed Neandertal DNA also provides potential insights into the biology of archaic humans beyond the measurable inferences of fossil remains. This is particularly relevant for Denisovans due to their scarce fossil record and therefore limited knowledge about their biology derived from the fossil remains. However, predicting phenotypes across populations and species is still challenging. Nevertheless, those approaches provide an inroad to predict archaic human phenotypes from their genomes where other information is not available. For example, various machine learning techniques were used to reconstruct the potential expression regulation, methylation, and splicing patterns in Denisovans and Neandertals, linking to them the difference in particular traits between human groups such as human face and vocal tract anatomy, skeletal and dental morphology, rib cage structure, immune system and epidermis features (Brand et al., 2023; Colbran et al., 2019; Gokhman et al., 2020, 2019). Such approaches do not only highlight potential differences in Neandertal and Denisovan biology compared to AMH, but they also provide new hypotheses and phenotype groups that can be tested in experimental settings. Finally, those insights then provide the means to further understanding of the evolutionary processes that shaped anatomically modern and archaic humans.

3. AIMS OF THE STUDIES

The migration of anatomically modern humans (AMH) out of Africa around 60,000 years ago marked the beginning of the settlement of the rest of the world (Bae et al., 2017). On their way, AMH met and admixed with Neandertals and Denisovans that lived in different parts of Eurasia for hundreds of thousands of years (Veeramah and Hammer, 2014). As a result of these past admixture events, the genomes of present-day non-Africans are composed of ~2% of Neandertal DNA, and the genomes of Oceanians contain an additional 2–5% of Denisovan DNA (Sankararaman et al., 2016; Vernot et al., 2016). The analysis of introgressed DNA in present-day humans has shown significant links to different functional consequences at the molecular and individual phenotype levels (Peyrégne et al., 2023; Reilly et al., 2022). However, the continuous development of computational and experimental technologies empowers the growth of functional and genomic datasets, which open up new angles to investigate the functional implication of archaic introgressions (Cano-Gamez and Trynka, 2020; Guigo and de Hoon, 2018; Stephens et al., 2015). The aim of this thesis is to expand the knowledge about the functional impact of Neandertal and Denisovan introgression. This thesis presents three studies that take advantage of recent advances in the generation and functional annotation of genomic data to address these aims.

3.1. Aims of the first study (REF I)

The analysis of the phenotypic effects of Neandertal admixture in present-day humans has identified multiple traits with significant links to introgressed DNA, including traits related to immunology, behavior, skin and hair (Reilly et al., 2022). Among the traits associated with behavior were both disease and non-disease phenotypes (Dannemann and Kelso, 2017; Simonti et al., 2016). However, these inferences came from different studies that employed distinct methods and used cohorts with substantial differences in size and phenotyping technique. These differences prevent a robust comparison of the proportional impact of Neandertal DNA on behavioral disease and non-disease phenotypes and possible interactions between both. This study will leverage behavioral disease and non-disease information from more than 350,000 participants of the UK Biobanks to address this gap. Furthermore, we will evaluate findings in additional cohorts of European and Asian ancestry. Finally, this study will investigate the role of selection in shaping Neandertal DNA associated with behavioral trait risk loci. Together, the results will evaluate the relative contribution of Neandertal DNA to disease and non-disease behavioral traits and provide insights on their evolutionary implications.

3.2. Aims of the second study (REF II)

Previous studies that have investigated the functional effects of Neandertal admixture in present-day humans have repeatedly shown a significant impact of introgressed DNA on the gene expression landscape, including an enrichment of Neandertal variants among cis-eQTLs (Dannemann et al., 2017; McCoy et al., 2017). However, regulatory mechanisms such as cis-eQTL are only able to capture short-range regulatory effects, while the role of introgressed Neandertal DNA on long-range regulatory effects, such as trans-eQTLs, remains mostly elusive. Importantly, trans-eQTLs have been shown to explain ~3 times more gene expression variation than cis-eQTL (20% against 6%) (Ouwens et al., 2019). Thus, the analysis of trans-eQTLs can substantially increase our knowledge of the regulatory role of Neandertal DNA in present-day people. However, robustly identifying trans-eQTLs remains difficult due to statistical and computational challenges it requires to annotate them (Shan et al., 2019). A recent study that attempted to address these challenges by analyzing a large expression dataset showed that one of the major mechanisms behind trans-eQTLs is the cis-regulation of a transcription factor (TF), which in turn can regulate hundreds or thousands of genes genome-wide (Võsa et al., 2021). Building on this finding, in this study we will assess the long-range regulatory potential of Neandertal DNA in humans today by investigating cis-eQTL for TFs genes that are linked to Neandertal variants. We will explore the functional signatures of those Neandertal variants through the analysis of TF target genes and phenotypic associations. Furthermore, we will study the evolutionary role of those Neandertal variants, by assessing potential signatures of selection. The results of our study will provide new insights into the regulatory potential of Neandertal DNA in people today, in particular, the long-range effects mediated by introgressed sequences.

3.3. Aims of the third study (REF III)

Denisovans populated parts of eastern Eurasia for over 200,000 years. This extended time gave Denisovans ample time to adapt to the environments they faced in this part of the world. However, the limited fossil record of Denisovans severely limits the inferences on the extent of their habitat and their biology (Peyrégne et al., 2023). The analysis of the phenotypic impact of Denisovan DNA on people today therefore provides an inroad to learning more about the phenotypic makeup (Zeberg et al., 2024). Previous studies have shown links between Denisovan DNA and metabolism, high-altitude adaptation and immunity (Peyrégne et al., 2023). In this study, we will investigate the archaic introgression landscape in two populations from Papua New Guinea (PNG). These two populations inhabit two contrasting environments; the highlands of the regions around Mt. Wilhelm and the lowlands on Daru Island (André et al., 2021). These two environments pose distinct challenges, like for example the high tropical pathogen exposure in the lowlands and hypoxia in the highlands (André et al., 2024).

Interestingly, some of those environmental differences mirror the phenotypes previously associated with introgressed Denisovan haplotypes, possibly suggesting that these environmental features may parallel the challenges that Denisovans once confronted and adapted to (Choin et al., 2021; Huerta-Sánchez et al., 2014). This study will take advantage of genomic data from individuals sampled from both populations and investigate the distribution of introgressed Denisovan and Neandertal DNA within them. By inferring Denisovan haplotypes that show large levels of population differentiation, we will screen for candidates of local adaptation. Finally, we will explore the gene content associated with these haplotypes and use this information to identify population-specific phenotypic targets of Denisovan admixture. The results of this study will help to understand the role of Denisovan admixture in facilitating environmental adaptation in PNG and also highlight potential phenotypic differences between AMH and Denisovan.

4. MATERIAL AND METHODS

4.1. REF I

For the evaluation of the association of Neandertal DNA with behavioral phenotypes, we leveraged summary statistics from genome-wide association studies (GWAS) from the UK Biobank (Bycroft et al., 2018). We included summary statistics from 261 GWAS related to neurological and psychiatric disorders, nervous system drug prescriptions as a proxy for disease, and related, non-disease phenotypes grouped into mental health, sleep, pain, smoking and alcohol consumption categories. The GWAS data was generated based on 361,194 individuals, and ~8.6 million SNPs with minor allele frequency larger than 1%. Among those SNPs we screened for candidates of likely archaic ancestry using the previously inferred list of putative introgressed Neandertal variants, and referred to them as aSNPs (Dannemann, 2021). The aSNPs were defined using the 1,000 Genomes cohort (1000 Genomes Project Consortium et al., 2015) and two high-coverage Neandertal genomes (Prüfer et al., 2017, 2013). We then tested for a disproportionate number of aSNP associations for phenotypes by calculating the number of LD-corrected tag aSNP associations and comparing it to the numbers of associations in 1000 random sets of frequency-matched and LD-corrected non-archaic tag SNPs (Dannemann, 2021). We conducted the analysis using five association P value cutoffs to account for trait-specific features such as heritability or prevalence that could lead to a low number of associations at higher cut-offs. Next, we replicated one major smoking risk factor in four additional cohorts of European ancestry. Furthermore, we explored the signatures of positive selection for genome-wide significant aSNP associations, by identifying frequency outliers among 1000 Genomes populations. Next, for each significantly associated aSNP, we inferred its associated archaic haplotype and annotated all aSNPs on a given haplotype with their putative molecular consequences using ENSEMBL's Variant Effect Predictor (Aguet et al., 2020; McLaren et al., 2016). Finally, to evaluate the findings, we conducted a similar Neandertal enrichment analysis for overlapping phenotypes in two independent cohorts of European (NESDA) (Spinhoven et al., 2021) and Asian (Biobank Japan) (Matoba et al., 2019) ancestry.

4.2. REF II

To investigate the long-range regulatory effects of Neandertal DNA, we analyzed eQTL data from large expression databases, including GTEx (Aguet et al., 2020) and eQTLGen (Võsa et al., 2021) for cis and trans-eQTLs that are associated with Neandertal variants. As a source for Neandertal introgressed DNA, we used a list of introgressed Neandertal variants, referred to as archaic SNPs – "aSNPs", derived from an analysis of the 1,000 Genomes project and 3 high-coverage Neandertal genomes (Byrska-Bishop et al., 2022; Dannemann, 2021; Mafessoni

et al., 2020; Prüfer et al., 2017, 2013). Due to limited trans-eQTL data in the eQTL databases, which would likely bias the analysis of Neandertal trans-eQTLs, we instead opted to investigate the characteristics of one major mechanism for mediating long-range effects, which is TF activity. For example, genetic variants associated with trans-eQTLs have been shown to often also be associated with cis-eQTLs of TFs. We, therefore, identified Neandertal cis-eQTLs of TFs (called "a-cTFs") by combining the list of aSNPs and top cis-eQTLs for transcription factors across diverse tissues in the GTEx expression cohort. We then tested common biological pathways between a-cTFs by testing for their connectivity in protein-protein interaction networks (Szklarczyk et al., 2019). In order to assess the significance of their connectivity we compared it to interaction networks of background sets of non-archaic cTFs, TFs regulated by cis-eQTLs of AMH ancestry. Furthermore, leveraging computational prediction (Mathelier et al., 2014; Matys et al., 2006; Plaisier et al., 2016; Xie et al., 2009) and experimental (ENCODE Project Consortium, 2011; Lachmann et al., 2010; Matys et al., 2006) databases of TFs' target genes, we explored the potential genomic reach of a-cTFs. Here we particularly focused on regions that are devoid of both Neandertal and Denisovan sequences (Sankararaman et al., 2016; Vernot et al., 2016). We tested for a-cTFs that show an enrichment of target genes within these regions devoids of archaic introgression using Fisher's exact test. Moreover, we investigated the putative molecular and phenotypic consequences of a-cTF aSNPs using information from association studies (Astle et al., 2016; Sakaue et al., 2021) and computational prediction databases (Boyle et al., 2012; McLaren et al., 2016; Rinker et al., 2020). Finally, we explored whether a-cTF associated aSNPs show signatures of positive selection by identifying frequency outliers in present-day populations and reconstructing allele frequency trajectories in an Estonian population cohort (Pankratov et al., 2020; Speidel et al., 2019; Stern et al., 2019).

4.3. REF III

In order to study the distributions of archaic ancestry in PNG populations, we reconstructed Neandertal and Denisovan introgressed haplotypes in genomes of 74 PNG individuals from the lowlands of Daru Island and 54 highlanders from the Mt Wilhelm region (André et al., 2021) using two different approaches (Dannemann, 2021; Skov et al., 2018). Next, we assigned archaic haplotypes to their most probable archaic source by evaluating their sequence similarity with the genomes of three Neandertals (Mafessoni et al., 2020; Prüfer et al., 2017, 2013) and the Denisovan (Meyer et al., 2012). Furthermore, we categorized Neandertal-like haplotypes in subgroups based on their presence in any of the three Eurasian super populations from the 1,000 Genomes project (Byrska-Bishop et al., 2022). This resulted in three sets of archaic haplotypes: (i) Denisovan-like set 1 which is composed of all Denisovan-like haplotypes; (ii) Denisovan-like set 2, composed of all haplotypes in (i) and all Neandertal-like haplotypes that are found in PNG, but not Eurasia; (iii) Neandertal-like set with all Neandertal-

like haplotype shared between PNG and 1,000 Genomes Eurasians. This categorization was chosen to address the challenges of assigning archaic haplotypes to their archaic source population solely based on sequence similarity analysis, as this method alone is prone to misclassify a substantial amount of Denisovan haplotypes (Vernot et al., 2016). Finally, in addition to the classification of these three archaic categories, we further partitioned each of them into two groups depending on whether they show a higher frequency in highlander or lowlander populations. Then, for archaic haplotypes within each of the six archaic ancestry and population groups, we assessed the extent of population differentiation (Danecek et al., 2011) between PNG highlanders and lowlanders and compared it to corresponding background sets. To evaluate the selection inferences based on population differentiation methods, we statistically reconstructed allele frequency trajectories for archaic haplotypes that have frequency > 5% (André et al., 2024; Speidel et al., 2019; Stern et al., 2019). Subsequently, we conducted gene ontology (GO) functional enrichment analysis (Ashburner et al., 2000; Grote, 2018) for the top 1% differentiated archaic haplotypes versus all remaining haplotypes within a given archaic ancestry and population group. Finally, we annotated archaic SNPs residing in introgressed haplotypes with phenotypic and regulatory consequences (Bycroft et al., 2018; McLaren et al., 2016; Nagai et al., 2017).

5. RESULTS AND DISCUSSION

This section includes summarized main results and discussions of the three scientific articles that lay the basis for this thesis. The original publications and their supplementary materials can be inspected for more detailed information.

5.1. Investigating the associations of introgressed Neandertal DNA with neuropsychiatric disorders and related behavioral phenotypes (REF I)

5.1.1. The enrichment of Neandertal associations among brain-related phenotypes in UK Biobank

In order to test for the impact of Neandertal admixture (Figure 4a) on behavioral phenotypes in people today, we analyzed GWAS summary statistics from the UK Biobank for different neurobehavioral disorders and their associated non-disease behavioral phenotypes. To identify traits with a significant link to introgressed Neandertal DNA, we performed an enrichment analysis and first quantified the number of significant Neandertal marker variants – called aSNPs – across all tested phenotypes using five distinct GWAS association P value cutoffs. Next, we compared these numbers to those of background sets of frequency-matched random non-archaic SNPs (Figure 4b,c). We found that among the group of tested neurobehavioral disorders, generally there was no enrichment of aSNP associations compared to SNPs of the background sets. The only exception were nervous system diseases for which we found for the least conservative GWAS association significance P value cut-off of 10^{-3} a larger number of aSNPs, a result that is consistent with observations from a prior study (Simonti et al., 2016). To complement the results, we additionally investigated GWAS information for medication prescriptions for central nervous system (CNS) diseases as a proxy for the disease. Similarly, CNS medication did not show significant enrichment for Neandertal associations averaged across all significance cutoffs (Figure 4b,c,d). However, when investigating the subcategories of these medications, we identified a significantly larger number of Neandertal DNA associations for two specific classes of pain medications.

Next, we explored Neandertal associations with disease-related but "non-disease" behavioral phenotypes which can be categorized into groups of mental health, sleep, pain, smoking and alcohol consumption. Following the same procedure as for the disease phenotypes, we identified several groups of phenotypes with a found enrichment of aSNP association. Those included smoking, sleep and alcohol intake categories, with each of the groups showing significant results across varying association P value significance thresholds (Figure 4c).

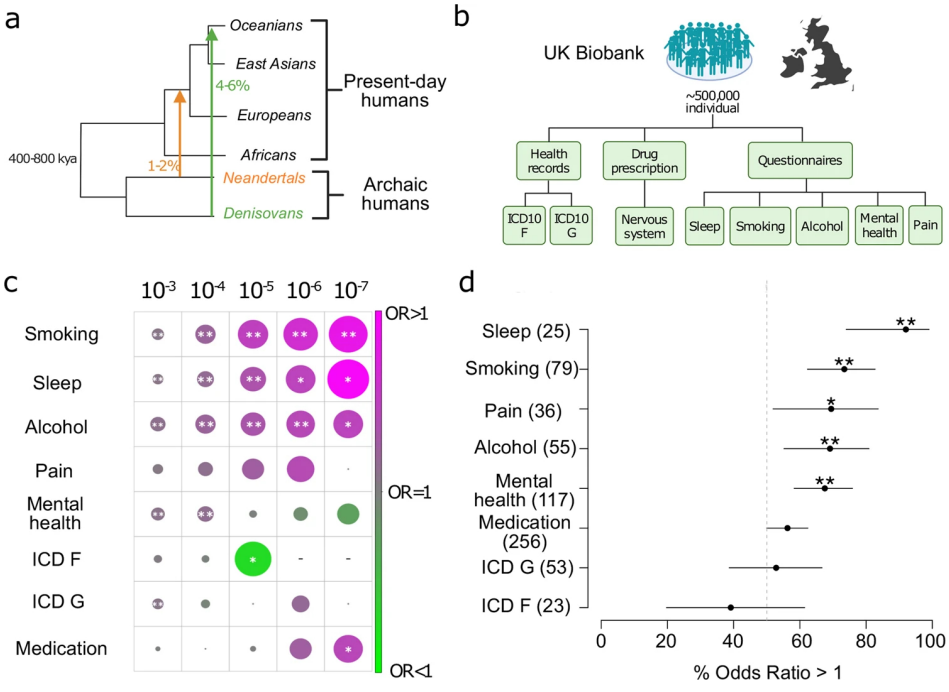

Figure 4: The proportional association of Neandertal DNA with mental and behavioral disease and non-disease phenotypes.

a) Schematic representation of archaic admixture, including the admixture proportions in different present-day human populations. b) Overview of GWAS from the UK Biobank included in this study. c) The combined numbers of aSNP associations with all phenotypes from one of eight tested groups in the UK Biobank compared to the average of the combined numbers of associations for 1,000 sets of frequency-matched non-archaic SNPs, the significance levels are indicated by asterisks (*P < 0.05, **FDR < 0.05). The resulting average odds ratios based on five significance cutoffs (shown on top) are displayed and color-coded and shown in size proportional to the corresponding log of the average odds ratio. d) The average odds ratio between the number of associations of tag aSNPs compared to the number of associations for 1,000 sets of frequency-matched non-archaic tag SNPs for each individual phenotype from eight phenotype groups from the UK Biobank were calculated. The proportion of these odds ratios that are larger than one for a given phenotype group (y-axis, number of tests across all significance cutoffs for each group shown in parenthesis), together with the binomial 95% confidence intervals are displayed. Phenotype groups for which this proportion is significantly different from the random expectation of 50% are highlighted (*P < 0.05, **FDR < 0.05). Reprinted from Figure 1 (Dannemann et al., 2022), licensed under CC BY 4.0.

To further refine this result, we analyzed individual phenotype GWAS within each enriched group and found that 6 out of 33 smoking-related phenotypes showed a robust enrichment signature; including the traits describing the smoking status and the number of consumed cigarettes. Six traits among the 26 in the alcohol group showed over-proportional association numbers, with the phenotype characterizing alcohol consumption during meals reaching a significant enrichment. Moreover, all but one of the six tested phenotypes related to chronotype and sleep showed significant enrichment (Figure 4c,d).

The group of mental health phenotypes showed significant enrichment results for the two most relaxed GWAS association significance P value cut-offs $P < 10^{-3}$ and $P < 10^{-4}$ (Figure 4c,d). We found an over-proportional number of aSNP associations among 14 of 47 phenotypes in this group, and these traits were linked to various mood-related questions. A significant enrichment was linked to the length of a depressive episode. However, while all 31 aforementioned phenotypes showed a larger number of aSNP associations compared to background sets (OR > 1), this group also includes the trait 'Longest period of unenthusiasm/ disinterest' which showed a depletion of Neandertal DNA associations. Finally, the group of pain phenotypes showed no enrichment for Neandertal associations. Out of the 17 individual phenotypes within this group, three traits related to general, back, and knee pain respectively, showed a larger number of aSNP associations compared to background sets, and one related to long-term facial pain showed a depletion.

5.1.2. Distribution, frequency and biological context of Neandertal risk loci

To explore signatures of positive selection on individual risk loci for behavioral phenotypes, we analyzed the frequency distribution for genome-wide significant ($P < 5 \times 10^{-8}$) Neandertal associations. We identified 27 instances of significant Neandertal DNA associations across all tested phenotypes, which were linked to 18 independent Neandertal risk loci. Those cases were required to be linked to an aSNP which was either the top associated SNP or in high linkage disequilibrium with the lead SNP in a given region. Eighteen of the 27 associations were linked to smoking and sleeping patterns, suggesting that these phenotypes are more often linked to risk loci that are of Neandertal ancestry. We found 11 of the 18 Neandertal risk loci fall into the top 5% of aSNPs frequency distribution in at least one of the 19 non-African populations within the 1,000 Genomes cohort. Several of these loci were associated with multiple traits. In general, among the associated phenotypes of these 11 risk loci were ten sleep-related traits, four mental health phenotypes, and two related to smoking habits. Furthermore, we annotated Neandertal risk loci with putative molecular consequences, by annotating aSNPs linked to the loci using variant effect prediction tools. We found two instances where associated aSNPs modify the amino acid sequences of *SCML4* and *CHRNA5*. The two aSNPs showed associations with 'period of unenthusiasm/ disinterest' and 'cigarette consumption per day' phenotypes, respectively. We also found that archaic SNPs associated with sleep, pain, smoking, and mental

health traits show potential regulatory effects in various tissues including arteries, testis, thyroid, muscle spleen, brain, and ovaries. One example that involved aSNPs with signatures of selection and association with expression modification in brain regions and nerve tissue was linked to a chronotype-associated Neandertal risk locus on chromosome 5 (Figure 5).

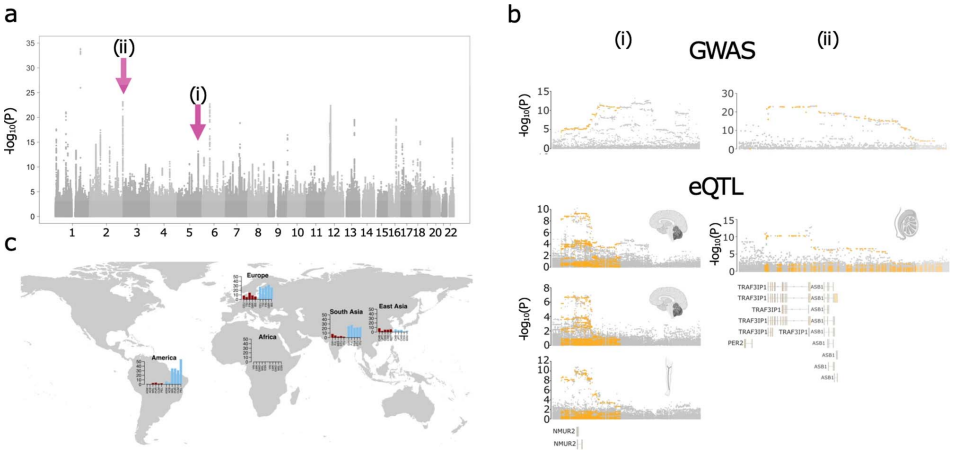

Figure 5: Neandertal DNA contributes to chronotype risk loci.

a) Manhattan plot for a Chronotype GWAS in the UK Biobank. b) Magnified views of the association score with chronotype on chromosomes 5 (left) and 2 (right) are shown on the top part of each panel. aSNPs are highlighted in orange. The lower part of each panel shows gene expression associations in GTEx tissues for the respective regions (eQTL −log [10] transformed association P values for—from top—Cerebellar_Hemisphere, Cerebellum and Tibial Nerve and Testis. Models of overlapping gene are illustrated at the bottom. c) The frequency of the top associated aSNPs from the two illustrated regions (rs76939124, chromosome 2 in red and rs4958550, chromosome 5 in blue) across 1000 Genomes populations. The aSNP on chromosome 5 reaches the top 1% of the aSNP frequency distribution in 14 out of 15 of all these populations. Reprinted from Figure 3 (Dannemann et al., 2022), licensed under CC BY 4.0.

Next, we explored Neandertal risk loci in Biobank Japan, another large Asian cohort with available GWAS summary statistics for 4 smoking traits. We found that for the same smoking trait, both UK Biobank and Biobank Japan have their genome-wide lead risk locus for smoking status linked to an aSNP on chromosomes 9 and 8, respectively. The archaic allele for both lead aSNPs was associated with an increased smoking risk and showed population-specific frequency differences between Europeans and Asians. The presence of independent Neandertal associations for the same trait in different cohorts might suggest the presence of an increased number of variants affecting addictive traits, such as smoking in present-day people, in the genomes of Neandertals. Next, we explored other smoking-related GWAS across varying cohorts, in an attempt to replicate the association results for both top-associated aSNPs from UK Biobank and Biobank Japan. We did not find another cohort that had tested the aSNP found in Biobank

Japan. Nevertheless, we were able to find similar association results for the aSNP found in UK Biobank in other cohorts, including NESDA, FinnGen, deCode and the Estonian Biobank. Although some of the smoking-related phenotypes in these cohorts did not exactly match the definition of smoking status in UK Biobank, we still found consistently low association P values ($P < 0.05$) with aSNPs related to the Neandertal risk loci.

5.1.3. Replication of the Neandertal association enrichment in two independent cohorts

We further sought to test for the robustness of our Neandertal association enrichment results in two independent cohorts. In the Netherlands Study of Depression and Anxiety (NESDA) cohort, we were able to test eight behavioral traits: four mental health and two sleep-related phenotypes, as well as one smoking and alcohol consumption phenotype each. For the enrichment test, we had to adjust our GWAS association P value cutoffs to 10^{-2}, 10^{-3} due to the substantially lower statistical power in NESDA. Among the tested phenotypes, we found two instances that replicated our initial results and showed substantially larger numbers of tag SNP associations: alcohol intake and chronotype. In order to explore how our results translate to non-European populations, we explored available summary statistics for four smoking traits from Biobank Japan. Consistent with our results from the UK Biobank, we also found an enrichment of Neandertal association for a smoking status phenotype in this cohort.

5.2. Exploring the effect of introgressed Neandertal DNA on transcription factor-mediated long-range gene regulation (Ref II)

5.2.1. The range of empirical and predicted Neandertal-linked trans-eQTL effects

In order to explore long-range regulatory effects of Neandertal DNA, we first screened the GTEx and eQTLGen cohorts for empirical trans-eQTL of Neandertal ancestry. We found that none of the 163 trans-eQTLs in GTEx were of Neandertal ancestry, in eQTLGen we found that 18 of 3,853 significant trans-eQTLs were of likely Neandertal origin. The small numbers of Neandertal variants among the limited amount of trans-eQTL results in these cohorts prevented us from robustly testing whether Neandertal variants are showing an enrichment among trans-eQTLs compared to background variants in these expression datasets. Nevertheless, it has previously been shown that a significant proportion of long-range regulatory effects is mediated through TF activity which in turn has the potential to regulate the expression of numerous downstream target genes (Võsa et al., 2021). We therefore decided to focus on one such mechanism and screen for Neandertal variants associated with a cis-eQTL of a TF in the GTEx

cohort. In 40 of the 49 analyzed tissues, we found a total of 60 TFs for which the top cis-eQTL SNP was an aSNP, and named them "a-cTFs". Most of these a-cTFs were found to be significantly regulated in only one (70%) or two (17%) tissues, while the biggest number of a-cTFs were found in skeletal muscle, lung, adipose, skin, and thyroid tissues. Across all tissues, 65% of a-cTFs showed a higher expression in the presence of the archaic allele, a bias that was even more pronounced in brain tissues (85% vs 62% in non-brain tissues). We found a significant correlation of effect sizes for a-cTFs between GTEx and eQTLGen. Additionally, we found one a-cTF associated with the *STAT2* transcription factor for which the predicted target gene showed an empirical Neandertal-associated trans-eQTL in eQTLGen. Both observations demonstrate the replicability of the proposed regulatory mechanism.

5.2.2. Interactions between a-cTFs and their regulatory reach

Next, in order to test for their potential functional relationship, we analyzed the level of interaction between all 60 a-cTFs. We first generated protein-protein interaction networks between all 60 a-cTFs using eight different types of protein linkage resources. Overall, we found that the connectivity for a-cTFs was significantly larger compared to the connectivity levels of background sets of non-archaic cTFs. However, the numbers of interactions for the top a-cTFs were not statistically different from the interactions of the top cTFs in the background sets suggesting that the elevated connectivity levels for a-cTFs were not primarily driven by the a-cTFs with the most interactions (Szklarczyk et al., 2019). Furthermore, we found that all but five a-cTFs were predicted to interact with one or more other a-cTF. The gene with the most interactions was *JUN* with 21 links to other a-cTFs.

In order to understand the potential genomic reach of a-cTFs, we analyzed their predicted target genes. A total of 27 of the 60 GTEx a-cTFs had target gene prediction information available in at least one of seven prediction databases. One particular focus in that context was the analysis of a-cTF target genes in archaic deserts, five large autosomal regions devoid of Neandertal and Denisovan ancestry (Sankararaman et al., 2016; Vernot et al., 2016). Given that the regulatory potential of all a-cTFs combined reaches the majority of all protein-coding genes, almost all genes within these deserts (95%) were predicted to be regulated by at least one of the 27 GTEx a-cTFs. We also found one empirical archaic trans-eQTL in eQTLGen for which the affected gene is located within the desert on chromosome 8 (Figure 6c). However, to assess whether a significant regulatory link exists between Neandertal DNA and desert genes, we tested for a-cTFs with predicted target genes that were over-represented in archaic deserts. We found two a-cTFs with enriched target genes in archaic deserts. The a-cTFs were *JUN* and *PRDM5*, two a-cTFs with cis-eQTLs in brain tissues (Figure 6a,b). Two genes within one desert on chromosome 7 that have been associated with AMH-specific biology are *FOXP2* and *ROBO2*. Both genes are among the targets of a couple of a-cTFs including *JUN*.

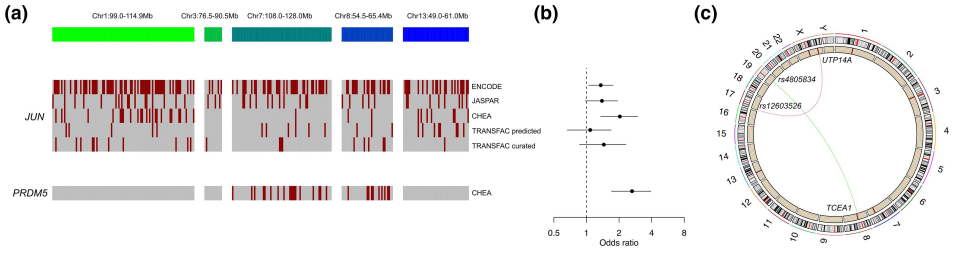

Figure 6: The regulatory impact of Neandertal DNA on archaic deserts.

a) Predicted TF target genes for two a-cTFs (*JUN*, and *PRDM5*) with an over-proportional overlap with genes within autosomal archaic deserts. Each tile represents a desert gene (aligned in chromosomal order) and predicted targets for a given database are highlighted. (b) Odds ratios with 95% confidence intervals representing the proportional overlap between genes in archaic deserts and target genes for a given a-cTF and prediction database, as displayed in panel (a) are shown. c) Circo plot showing the connection between genomic coordinates for two Neandertal trans-eQTL aSNPs and their predicted desert target genes. Archaic deserts are highlighted in the inner band. Reprinted from Figure 2 (Yermakovich et al., 2023), licensed under CC BY-NC-ND 4.0.

5.2.3. The impact of Neandertal-linked trans-eQTLs on phenotype variation

Further, we explored the potential phenotypic effects of a-cTF aSNPs using phenotypic information from GWAS databases. We found that aSNPs of 13 a-cTF loci have significant phenotype associations, including the a-cTF *STAT2* which was also detected as a trans-eQTL in eQTLGen. The aSNPs at the *STAT2* locus are associated with a decreased risk of autoimmune diseases including psoriasis, and several pulmonary functional measurements. Additionally, aSNPs for *STAT2* and seven other a-cTFs showed associations with height measures, making it by far the most frequently associated phenotype among a-cTFs. Evaluating this observation, we found that the height associations among a-cTF aSNPs were on average 1.6 times higher compared with the background sets of non-archaic cTFs SNPs, a result that was borderline significant (P = 0.06). Other non-height phenotype associations included breast cancer, grip strength, body fat measures, varicose veins, and abnormal red blood cell volumes. Among empirical trans-eQTLs from eQTLGen, Neandertal DNA was associated with immune phenotypes, anthropometric, pulmonary, and lipid measures, bone density, colorectal cancer, schizophrenia, and brain connectivity measurements.

5.2.4. Evidence for local adaptation among aSNPs linked to empirical and predicted trans-eQTLs

To identify potential candidates for selection among aSNPs linked to a-cTFs and empirical trans-eQTLs, we applied two approaches. In the first approach, we quantified the frequencies of aSNPs associated with these predicted and empirical trans-eQTL within the entire aSNP distribution in 15 Eurasian populations from the 1,000 Genomes cohort and 16 Papuans from the Simons Genome Diversity Project (1000 Genomes Project Consortium et al., 2015; Mallick et al., 2016) (Figure 7a). In total, we found that aSNPs of nine empirical trans-eQTL candidates and 21 a-cTFs reached the top 5% allele frequency distribution among detected aSNPs in a given population. Most of the aSNPs that reached frequencies within the top 1% aSNP distribution in a given population, showed the highest frequencies in Europeans and were found at elevated frequencies in multiple European and Asian populations (Figure 7b). One example included aSNPs linked to *STAT2*, which showed high frequencies in Papuans – a result that has previously been reported and associated with signatures of positive selection (Mendez et al., 2012). However, we also observed instances where such aSNPs are entirely absent or only found at extremely low frequencies in some 1,000 Genomes populations or show the highest frequencies in non-European populations These results are consistent with a detection bias of association-study-based functional annotation of aSNPs that are more prevalent in Europeans, due to the general over-representation of expression and phenotype data from cohorts of predominantly European ancestry (Dannemann et al., 2020), like GTEx and eQTLGen. The results also illustrate that some of the high-frequency aSNPs show population-specific frequencies, consistent with potential local selection pressures.

Furthermore, to explore signatures of recent selection, we leveraged a statistical approach to reconstruct allele frequency trajectories and infer their deviation from neutrality (Speidel et al., 2019; Stern et al., 2019). Using around 1,800 whole genome sequences from the Estonian Biobank (Pankratov et al., 2020), we investigated the a-cTF and trans-eQTLs aSNPs for significant frequency shifts over the last 500 generations. Most of the frequency changes we observed were characterized by low log-likelihood ratios (logLR) suggesting little evidence for non-neutrality. In order to assess whether any of the reconstructed frequency changes are unexpectedly high, we compared the logLRs to two background distributions of logLRs estimated for non-archaic SNPs linked to trans-eQTL from eQTLGen and cTFs in GTEx. We found that aSNPs associated with four a-cTFs showed logLRs that fell within the top 10% distribution of logLRs for background SNPs (Figure 7c,d,e). Notably, all four a-cTFs aSNP were cis-eQTLs in brain tissues. Furthermore, we also found that the archaic allele frequencies for two trans-eQTL candidates increased by more than two-fold over the last 500 generations (Figure 7c).

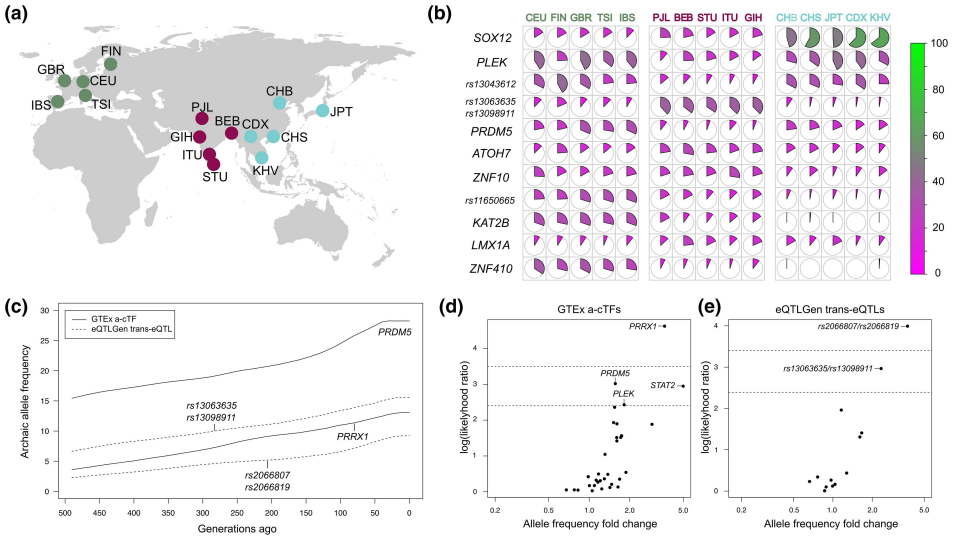

Figure 7: The frequency of trans-eQTL aSNPs in Eurasian populations.

a) Geographic distribution of 15 Eurasian 1,000 Genomes populations, colors match the populations' names in panel (b). b) Pie charts illustrating the frequencies of a-cTF aSNPs (annotated with the corresponding a-cTF) and trans-eQTL (annotated with the rs ID) aSNPs that fall into the top 1% aSNP distribution in at least one of 15 Eurasian 1,000 Genomes populations. c) The estimated posterior probability for the Neandertal allele frequency for two a-cTF and two trans-eQTL aSNP candidates with logLRs above the 90th percentile of the background distributions over the last 500 generations in the Estonian population are shown. For each significant a-cTF (d) and trans-eQTL (e) aSNP locus the average frequency change in the Estonian population over the last 500 generations and the corresponding average log likelihood ratio are displayed. The 90th and 95th percentiles for a given logLR distribution are shown as dotted lines. Reprinted from Figure 3 (Yermakovich et al., 2023), licensed under CC BY-NC-ND 4.0.

5.3. Studying the role of Denisovan admixture in environmental adaptation of Papua New Guineans (Ref III)

5.3.1. Archaic DNA in PNG genomes

First, we reconstructed archaic haplotypes in the genomes of two PNG populations (n=128). We annotated these haplotypes utilizing a previously established method to detect archaic DNA in present-day individuals (Dannemann, 2021), and replicated the inferred archaic introgressed segments using a second method, called HMMIX (Skov et al., 2018). We identified 168,152 aSNPs that were associated with 10,431 unique core haplotypes. Those haplotypes were spanning across 50.0 to 65.5 megabases (Mb) of diploid archaic DNA of the analyzed PNG individuals and covered approximately 21.15% of the human genome. Consistent with previous findings, we found no or only negligible traces of archaic DNA

within all five autosomal genomic regions previously reported to be devoid of archaic DNA, as well as chromosome X (Sankararaman et al., 2016; Vernot et al., 2016) (Figure 8e–g).

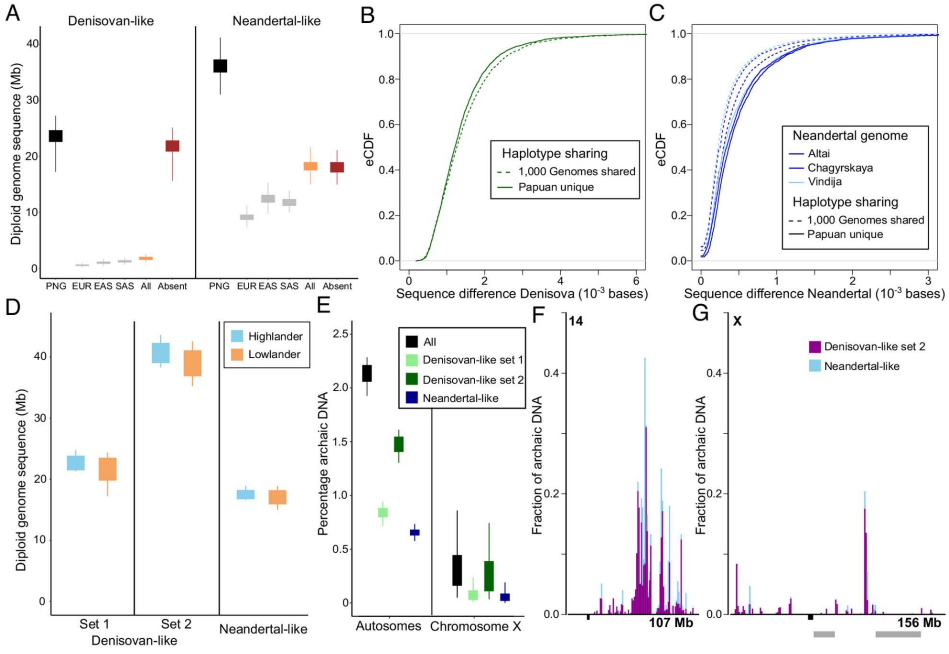

Figure 8: Archaic DNA in PNG genomes.

(a) Amount of diploid genome sequences reconstructed in PNG individuals partitioned into archaic haplotypes exhibiting higher sequence similarity with the Denisovan individual and Neandertals. The total amounts of recovered sequence of archaic DNA (Mb) in PNG for haplotypes found in 1,000 Genomes Super Populations (EUR=Europeans, EAS=East Asians, SAS=South Asians, All of them combined) and unique for PNG populations (Absent). Outer whiskers indicate minimum and maximum values. (b–c) Empirical cumulative density distributions (eCDF) are displayed for the sequence similarity measures of introgressed archaic haplotypes in PNG to archaic genomes. (d) The amount of Denisovan-like (set 1 & 2) and Neandertal-like diploid genome sequence in PNG highlanders and lowlanders after geographic refinement, i.e. when PNG-unique Neandertal-like haplotypes are aggregated with Denisovan-like set 1 haplotypes to form Denisovan-like set 2, and Neandertal-like include only those haplotypes closest to Neandertals that are also found in Eurasians. This version of the archaic categories definition will be used throughout the study. Outer whiskers indicate minimum and maximum values. (e) The percentage of archaic ancestry on the autosomes and X chromosome across PNG individuals is displayed. Outer whiskers indicate the 95% confidence intervals. (f–g) The proportion of archaic introgressed DNA within one-megabase windows is depicted for chromosome 14, which harbors the highest levels of archaic DNA, and chromosome X, which shows the lowest levels of archaic ancestry. Gray areas below the x-axis denote regions that were previously reported to be devoid of archaic ancestry. Reprinted from Figure 1 (Yermakovich et al., 2024), licensed under CC BY-NC-ND 4.0.

Next, in order to assign the introgressed haplotypes to the most probable archaic source, we assessed their sequence similarity to three high-coverage Neandertals genomes (Mafessoni et al., 2020; Prüfer et al., 2017, 2013) and the genome of the Denisovan (Meyer et al., 2012). We observed that, on average, ~61% of the haplotypes per individual displayed a closer sequence resemblance to Neandertals than to the Denisovan individual (Figure 8a). This result stands in stark contrast to the anticipated genome-wide estimates of Neandertal ancestry (~2%) and Denisovan ancestry (~4%) within these populations (G. S. Jacobs et al., 2019; Meyer et al., 2012; Prüfer et al., 2017). Several factors have previously been reported that might contribute to this pattern, including the varying sequence relationships between sequenced archaic individuals and the actual introgressing archaic populations and incomplete lineage sorting among Neandertals and Denisovans. We therefore hypothesized that a substantial proportion of Neandertal-like haplotypes are in fact of Denisovan ancestry. In order to reclassify some of the falsely annotated Denisovan haplotypes, we explored the geographical distribution of all Neandertal-like haplotypes. Here, we hypothesized that the majority of true Neandertal haplotypes in PNG are shared with other Eurasian populations due to Neandertal introgression in the shared ancestors. We therefore partitioned haplotypes with closer sequence similarity to Neandertals in two groups, those shared with Eurasians and those only found in PNG individuals (Figure 8b,c). Subsequently, we opted to build three sets of archaic haplotype groups: "Denisovan-like set 1" includes haplotypes with closer sequence similarity to the Denisovan, "Denisovan-like set 2" is the aggregate of the previous set with PNG-unique haplotypes that are more similar to Neandertal, and the last "Neandertal-like" consists only of the Neandertal-like haplotypes shared with Eurasians (Figure 8d). The combined Denisovan-like set 2 contains around 70% of all archaic haplotypes in PNG, thus aligning more with expected genome-wide estimates of Denisovan-Neandertal ancestry proportion in Oceania individuals.

5.3.2. The evolutionary impact of archaic introgression in PNG lowlanders and highlanders

Next, we evaluated the degree to which DNA inherited from past admixture with archaic humans has contributed to shaping the local adaptation of two geographically distinct PNG populations. The habitats of both populations, namely the lowlands of Daru island and the highlands around Mount Wilhelm, are marked by notable environmental differences such as variations in food availability and pathogen exposure and altitude shifts of more than 2,000 meters. In order to identify potential signatures of local adaptation related to archaic introgression, we explored the level of population differentiation of introgressed haplotypes between both PNG populations. To achieve this, we calculated fixation index (Fst) values for each archaic haplotype between PNG highlanders and lowlanders. We then categorized all archaic haplotypes into six groups, splitting them by (i) archaic ancestry (Denisovan-like sets 1 & 2 or Neandertal-like) and (ii) frequency (higher in highlanders or lowlanders) (Figure 9a).

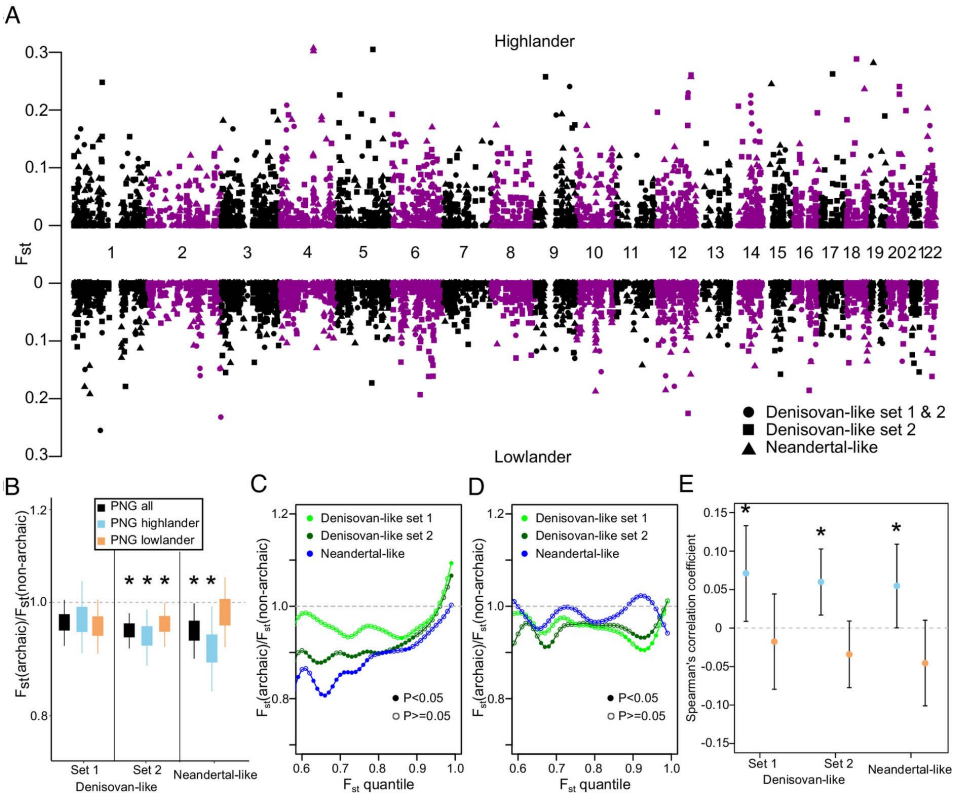

Figure 9: Frequency differences of archaic haplotypes between PNG highlanders and lowlanders.

(a) Manhattan plot visualizes Fst values for introgressed haplotypes frequency differences between PNG populations. Haplotypes that are shared between Denisovan-like set 1 and set 2 are annotated accordingly by distinct shapes. Haplotypes are categorized into two sets: those exhibiting a larger archaic allele frequency in highlanders (upper side) and lowlanders (lower side). These sets with corresponding names will be used throughout all plots in this section and also shown for each archaic ancestry. (b) Distributions of the ratio of the mean Fst value for archaic haplotypes compared to each mean Fst value obtained from 1,000 non-archaic background sets. Outer whiskers indicate the 95% confidence intervals. An asterisk denotes instances where ratios significantly deviate from 1 (P<0.05). (c,d) Distribution of the ratio between Fst quantiles for archaic sets in highlanders (c) and lowlanders (d) relative to the quantile Fst values derived from 1,000 matching non-archaic background sets. Quantiles for which the ratio significantly deviates from one (P<0.05) are shown with filled circles. A gray line is included to represent the neutral expectation of one. (e) Spearman correlation coefficients with 95% confidence intervals were calculated between Fst values and log-likelihood ratios derived from reconstructed allele frequencies. The archaic ancestry sets are categorized as highlanders (blue) and lowlanders (orange). Correlation coefficients that exhibit a significant deviation from a value of 0 (P<0.05) are denoted by an asterisk. Reprinted from Figure 2 (Yermakovich et al., 2024), licensed under CC BY-NC-ND 4.0.

Then, we compared the Fst distributions for these six groups to the Fst distribution of 1,000 randomly generated genomic background sets which were each designed to match the allele frequency distribution of a given archaic set. Overall, our analysis revealed consistently lower mean Fst values for all investigated groups of archaic haplotypes (Figure 9b). However, when we stratified our analysis according to 1% Fst quantile bins, we observed that groups with a higher frequency in highlanders tend to have higher Fst values in higher quantiles compared to non-archaic background sets. Most notably, the Fst distribution for the haplotypes within the top 1% of Fst values for both sets of Denisovan-like haplotypes was significantly higher (set 1: P=0.01, set 2: P=0.04, Figure 9c,d). The observation is consistent with elevated levels of local selective pressures acting on these most differentiated haplotypes. Next, to further investigate selection signatures on archaic DNA, we employed a computational approach to reconstruct the allele frequency trajectories of introgressed haplotypes in both PNG populations within the past 1,000 generations. We found that log-likelihood ratios that denote a deviation from constant allele frequency significantly correlated with Fst values for both sets of Denisovan-like (Spearman correlation, set 1: P=0.05; set 2: P=0.01) and also for Neandertal-like (P=0.03) haplotypes among highlanders, but this correlation was non-significant among lowlanders (P>0.05, Figure 9e). The results suggest that some of the highly differentiated haplotypes in highlanders likely increased their frequency rather recently.

5.3.3. Phenotypic implications of archaic admixture in PNG populations

Previous studies of Papua New Guinea (PNG) populations have indicated physiological differences between highlanders and lowlanders, particularly linked to living in high altitudes such as variation in stature and hemoglobin concentration (André et al., 2021; Cotes et al., 1974; Senn et al., 2010; Woolcock et al., 1972). To investigate whether the phenotypical variation is influenced by archaic introgression, we examined the gene content of highly differentiated archaic haplotypes (top 1%) and the phenotypic associations of aSNPs linked to them. Similarly to the population differentiation analysis, we categorized our haplotypes into six groups regarding i) archaic ancestry and ii) frequency. We didn't observe GO enrichment for both sets of the top 1% Fst of Denisovan-like haplotypes with higher frequencies in highlanders. However, 10 of 16 genes that overlap two of the most differentiated Denisovan-like haplotypes had a direct link to the brain and included pivotal developmental genes like *NEUROD2* and *PAX5*. Conversely, in the most differentiated Denisovan-like haplotypes (set 2) with a higher frequency in lowlanders, we found a GO enrichment for the category 'cellular response to organic substance' (FWER=0.04). In addition, we found three categories showing borderline significance linked to cytokine and protozoan responses (FWER: 0.06–0.07), which might imply a potential connection between the specific response to organic substances and pathogenic elements. Notably, among

the Denisovan-like set 2 haplotypes associated with genes in these categories was a PNG-specific Neandertal-like haplotype encompassing four members of the Guanylate-binding proteins family – proteins crucial in immune response mechanisms (Tretina et al., 2019). This specific haplotype had been previously identified in Melanesians as a candidate for positive selection (André et al., 2024; Vernot et al., 2016) and carries an archaic variant introducing a missense variant to *GBP7*. Among the genes within high-Fst Neandertal-like haplotypes, we only found a significant GO enrichment among the set exhibiting higher frequencies in highlanders. Here, 22 enriched GO categories were related to regulatory and metabolic functions and were largely influenced by genes of the zinc finger family.

To further explore the potential phenotypical implications of archaic DNA within the genomes of PNG, we looked for phenotype associations in UK Biobank (Bycroft et al., 2018) and Biobank Japan (Nagai et al., 2017). We would like to note that using these resources is challenging, as the tested populations carry little or no Denisovan DNA, and it's unclear how well any derived results translate to PNG populations. In total, we found 379 archaic haplotypes, aSNPs of which showed significant phenotype associations in at least one of the two biobank cohorts. Specifically, 48 archaic haplotypes carried aSNPs resulting in amino acid substitutions in various proteins. Missense-carrying haplotypes were associated with traits that included blood biomarkers, measurements related to bone density and body fat, as well as occurrences of diabetes. Additionally, we identified four highly pleiotropic Denisovan-like haplotypes situated within the Major Histocompatibility Complex, a crucial immune-related region in the human genome. Notably, two of these haplotypes ranked among the top 10% differentiated haplotypes between highlanders and lowlanders.

6. CONCLUSIONS

The three studies presented in this dissertation demonstrate that archaic DNA in present-day humans still affects their biology. The results also suggest that some of the introgressed DNA from both Neandertals and Denisovans served as a valuable source of variation that facilitated adapative processes to local environments. At the same time, some of the DNA inherited from archaic humans also increases the disease risk. With several of the significantly affected phenotype groups showing a link to the environment, the results presented in this thesis might also serve as a resource to understand the adaptive forces that have shaped archaic DNA. The results also present new insights of the underlying molecular meachnisms through which archaic DNA influences disease and non-disease phenotypes in people today.

Ref I – In this study, we aimed to investigate the phenotypic link of introgressed Neandertal DNA with disease and non-disease behavioral phenotypes in present-day humans. To achieve this goal, we explored genetic associations for various behavior traits from the UK Biobank and tested them for enrichment of Neandertal DNA. We found enrichment signals with several groups of behavioral non-disease phenotypes, which were particularly pronounced for smoking and sleeping patterns. The absence of similar enrichment results for disease phenotypes, suggests that Neandertal DNA is rather linked to diseases-associated behavioral phenotypes and not to disease itself. Several of the strongest associated Neandertal variants showed signatures of positive selection. Hence, those results may reflect evolutionary adaptive processes. Specifically, sleep patterns, which are linked to circadian rhythm are also linked to differences in UV light exposure, an environmental factor with large differences between Eurasia and Africa, the two regions Neandertals and AMH evolved in, respectively. Our results therefore suggest that the inheritance of Neandertal DNA associated with some of the behavioral phenotypes may have helped AMH adapt to the new environments when they moved out of Africa and into Eurasia and the rest of the world.

Ref II – The main goal of this study was to explore the role of Neandertal DNA on long-range regulatory effects in people today. To address this research question, we analyzed existing eQTL data and investigated the functional role and evolutionary signatures of empirical and predicted trans-eQTLs that were of Neandertal ancestry. We found that transcription factors involved in mediating Neandertal long-range effects form a significant network and participate in regulating gene expression of genes in regions that are devoid of archaic introgressed sequences. Some of the underlying Neandertal variants associated with these processes showed signatures of positive selection and had associations with various traits. Our results, therefore, suggest that not only short but also long-range effects show significant links to Neandertal DNA, and that through these

effects the regulatory reach of Neandertal DNA goes beyond the 40% of genomic sequence that it still covers in present-day non-Africans.

Ref III – This study focused on exploring the role of archaic introgressed DNA on processes of local adaptation in Papua New Guineas. To address this task, we reconstructed Neandertal and Denisovan DNA in the genomes of two cohorts sampled from the highlands and lowlands of Papua New Guinea and explored differences in the frequency distributions of the archaic haplotypes between them. We found that while there is little difference in Neandertal DNA content between populations, high-frequent Denisovan haplotypes among highlanders showed signatures of positive selection. In general, Denisovan haplotypes with population-specific frequency signatures showed phenotypic links to the brain and immunity. Our findings suggest that the presence of Denisovan DNA in PNG genomes has contributed to adaptive processes to environmental challenges and served as a beneficial source of genetic variation. In addition, our study identified phenotype-associated archaic genetic variants which facilitate our understanding of the adaptive role of introgressed Denisovan DNA. Furthermore, these candidates can help to reconstruct the biology of Denisovans and shed light on the adaptive mechanisms within this archaic human group.

SUMMARY IN ESTONIAN

Komplekstunnuste evolutsiooniline ajalugu: arhailise segunemise tagajärjed

Anatoomiliselt kaasaaegsed inimesed (AKI), kujunesid ligi 300 000 aastat tagasi Aafrikas miljonite aastate pikkuse evolutsiooni tulemusena teistest inimahvidest (Hublin et al., 2017; Trinkaus, 2005; Vidal et al., 2022). Umbes 60 000 aastat tagasi tähistas AKI suur ränne Aafrikast välja nende püsiva asustuse algust ülejäänud maailmas (Bae et al., 2017). Rände tulemusena segunesid AKI Euraasiat asustavate Neandertali ja Denissi inimestega (Veeramah and Hammer, 2014). Selle tulemusena on säilinud kaasaegsete mitte-aafriklaste genoomides endiselt ~2% ulatuses neandertallaste DNA-d ja okeaanlaste genoomides lisaks 2–5% denislaste DNA-d (Sankararaman et al., 2016; Vernot et al., 2016). Arhailised geenivariandid tänapäeva inimestel on seotud erinevate molekulaarsete ja individuaalsete fenotüüpidega. Mõningaid neist variantidest on seotud loodusliku valiku signaalidega kaasaegses inimeses, mis tõenäoliselt peegeldavad arhailistelt inimestelt päritud kohastumusi erinevate keskkondadega, milles nad arenesid ja edukad olid (Peyrégne et al., 2023; Reilly et al., 2022). Kuigi arhailiste geenivariantide mõju nüüdisinimeste fenotüübile on viimastel aastatel palju uuritud, on meie teadmised endiselt puudulikud. Sellegipoolest, tänu arvutuslike ja eksperimentaalsete meetodite pidevale arengule, kasvab ka andmehulk, mis võimaldab meil täiendada oma teadmisi arhailiste geenivariantide funktsionaalsest mõjust (Cano-Gamez and Trynka, 2020; Guigo and de Hoon, 2018; Stephens et al., 2015). Selle doktoritöö eesmärk on täiendada teadmisi Neandertali ja Denissi inimeste introgressiooni funktsionaalsest mõjust kaasaaegse inimese fenotüübile. Käesolevas väitekirjas on esitatud kolm teadustööd, milles on kasutatud uusimaid genoomika meetodeid ja andmeanalüüsi, et mõista paremini töös käsitletud probleeme.

Väljasurnud arhailiste inimeste geneetiline pärand nüüdisinimeses mõjutab mitmeid fenotüüpe, sealhulgas immuunsüsteemi funktsiooni, käitumuslikke mustreid ning naha ja juuste omadusi (Reilly et al., 2022). Käitumuslike tunnuste puhul on leitud seoseid nii patoloogiliste seisundite (Simonti et al., 2016) kui ka normaalsete fenotüüpidega (Dannemann and Kelso, 2017). Metodoloogilised erinevused uuringute vahel on takistanud näha neandertallaste geenivariantide tegelikku mõju käitumuslikele fenotüüpidele ja hinnata nende omavahelisi seoseid. Seetõttu püüdsime esimeses uuringus (REF I) lahutada introgresseerunud neandertallaste DNA suhtelised fenotüübilised seosed haiguste ja mittehaiguslike käitumuslike fenotüüpidega tänapäeva inimestel. Selle eesmärgi saavutamiseks uurisime, kuidas neandertallaste geenivariandid on seotud erinevate käitumisviisidega, kasutades Ühendkuningriigi biopanga andmeid (Bycroft et al., 2018). Lisaks hindasime leide täiendavates Euroopa ja Aasia päritolu valimites ja annoteerisime neandertallaste riskilookused valiku signaalide ja molekulaarsete tagajärgedega. Leidsime, et neandertallaste variandid on seotud mitmete käitumuslike

mustritega, olles tugevalt seotud suitsetamise ja unemustritega. Patoloogiliste seoste puudumine viitab sellele, et neandertallaste geenivariandid on pigem seotud käitumuslike mustritega, mis viivad haiguse avaldumiseni, mitte haiguse endaga. Mitmed neandertallaste variandid näitasid positiivse valiku tunnuseid, mis võib peegeldada nende olulisust evolutsioonilises kohastumisprotsess. Täpsemalt, ööpäevarütmiga seotud unemustrid on seotud ka UV-valguse intensiivsuse erinevusega Euraasia ja Aafrika vahel, peegeldades erinevust kahe keskkonna vahel, milles AKI on pidanud kohastuma. Seetõttu viitavad meie tulemused sellele, et mõnede käitumuslike tunnustega seotud neandertallaste geenivariandid võisid olla kasulikud uute keskkondadega kohastumisel, kui AKI rändasid Aafrikast välja.

Varasemad uuringud, mis on keskendunud neandertallastega segunemise funktsionaalsetele mõjudele tänapäeva inimesele, on korduvalt näidanud introgresseerunud DNA mõju geeniekspressioonile. Muuhulgas on täheldatud neandertallaste geenivariantide üleesindatust cis-eQTL-ide hulgas (Dannemann et al., 2017; McCoy et al., 2017). Regulatoorsed mehhanismid, nagu cis-eQTL, on aga võimelised selgitama vaid lokaalseid regulatiivseid mõjusid, samas jääb introgresseerunud neandertallaste DNA roll distaalsetele regulatoorsetele mõjudele, nagu trans-eQTL-idele enamasti analüüsimata. Trans-eQTL-id on olulised, kuna seletavad ~3 korda suuremat geeniekspressiooni variatsiooni kui cis-eQTL-id (20% versus 6%) (Ouwens et al., 2019). Samas nõuab trans-eQTL-ide usaldusväärne tuvastamine suuri geeniekspressiooni andmestikke ja arvutusressursse (Shan et al., 2019), mis piirab selliste andmekogumite genereerimist praeguste arvutustehnoloogiatega. Teises uuringus (REF II) oli põhieesmärgiks uurida neandertallaste DNA rolli tänapäeva inimeste distaalses geeniregulatsioonis. Selle uurimisküsimuse lahendamiseks analüüsisime olemasolevaid eQTL andmeid (Aguet et al., 2020; Võsa et al., 2021) ning uurisime neandertallastelt pärit empiiriliste ja ennustuslike trans-eQTL-ide funktsionaalset rolli ja evolutsioonilisi signaale. Leidsime, et transkriptsioonifaktorid, mis meie ennustuse järgi osalevad neandertallaste distaalse geeniregulatsiooni vahendamises, moodustavad võrgustiku ja reguleerivad geene piirkondades, kus puuduvad arhailised introgresseerunud järjestused. Mõned nende protsessidega seotud neandertallaste variandid on positiivse valiku all ja seotud erinevate tunnustega. Seetõttu näitavad meie tulemused, et mitte ainult lokaalsel, vaid ka distaalsel geeniregulatsioonil on olulisi seoseid neandertallaste DNA-ga ja neandertallaste DNA mõju ulatub väljapoole sellest 40% genoomsest järjestusest, kus seda leidub tänapäeva mitte-aafrika populatsioonides.

Lisaks neandertallastele Lääne-Euraasias, asustasid Ida-Euraasiat üle 200 000 aasta ka teised praeguseks väljasurnud inimesed, Denissi inimesed. Denissi inimeste pikaajaline kohastumine elukeskkonnaga peegeldub ka nende genoomis. Neilt pärit geenivariandid on seotud ainevahetuse, kohastumisega eluks kõrgmäestikes ja immuunsusega (Peyrégne et al., 2023). Võrreldes neandertallastega on denislaste fossiilid haruldased, mis omakorda piirab meie teadmisi nende bioloogia ja elupaiga kohta (Peyrégne et al., 2023). Denissi inimeste geenivariantide mõju uurimine tänapäeva inimestes võimaldab meil seega võimaluse

nende fenotüüpide kohta rohkem teada saada (Zeberg et al., 2024). Kolmandas uuringus (REF III) keskendusime arhailiste geenivariantide rolli uurimisele kohastumise protsessides kahes Paapua Uus-Guinea (PNG) populatsioonis – mägismaa ja madaliku populatsioonides. Erinevused nende keskkondades, nagu kokkupuude patogeenidega ja hüpoksia (André et al., 2024), peegelduvad mõningates kohastumustes, mida varem seostati introgresseerunud Denissi inimese haplotüüpidega. Tulemus võib viidata sellele, et need PNG inimeste elukeskkond võis olla sarnane keskkonnaga, millega Denissi inimesed kunagi silmitsi seisid ja millele kohastusid (Choin et al., 2021; Huerta-Sánchez et al., 2014). Arhailise introgressiooni valiku signaalide uurimiseks rekonstrueerisime Neandertali ja Denissi inimeste DNA kahe PNG kohordi genoomis ja uurisime arhailiste haplotüüpide sagedusjaotuse erinevusi nende vahel. Leidsime, et kuigi populatsioonide vahel on neandertallaste DNA sisalduses vähe erinevusi, kandsid mägismaalased oluliselt rohkem denislaste DNA-d kui madaliku populatsioon. Lisaks näitasid mõned mägismaa elanike seas sageli esinevad Denissi inimeste haplotüübid positiivse valiku tunnuseid. Üldiselt näitasid kahe PNG populatsiooni vahel populatsioonispetsiifiliste sagedusmustritega Denissi inimeste haplotüübid fenotüüpseid seoseid aju ja immuunsusega. Meie leiud viitavad sellele, et Denissi inimese DNA olemasolu PNG genoomides on aidanud kohastumisel keskkonnaga ja olnud kasulik geneetilise variatsiooni allikas. Tuvastasime fenotüübiga seotud arhailised geenivariandid, mis aitavad paremini mõista, kuidas introgresseerunud Denissi inimeste DNA on aidanud kaasa inimeste kohastumisele erinevate keskkondadega. Lisaks võivad need kandidaat variandid aidata rekonstrueerida Denissi inimeste bioloogiat ja mõista selle väljasurnud inimrühma kohastumismehhanisme.

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2019 #NGSchool2019: Machine Learning for Biomedicine. Białobrzegi, Poland. Flash talk: "*Detection of pathogenic variants by targeted NGS: an experience of writing pipelines for raw data processing and variant calling from zero level*"

2019 Systems Biology Workshop 2019. Bioinformatics Institute, St. Petersburg, Russia.

2018 10th Young Scientists School "Systems biology and Bioinformatics". Novosibirsk, Russia. Second place diploma for oral presentation: "*Detection of pathogenic mutations in patients with non-coronary heart diseases by targeted NGS*"

2018 European Human Genetics Conference 2018. Milan, Italy. E-poster: "*Case report of familial dilated cardiomyopathy caused by LMNA mutation*"

2018 Bioinformatics Summer School 2018. Bioinformatics Institute, St. Petersburg, Russia. Talk: "*Identifying mutations in patients with non-coronary heart disease using NGS*"

Publications

2024 Yermakovich D, André M, Brucato N, Kariwiga J, Leavesley M, Pankratov V, Mondal M, Ricaut F-X, Dannemann M. 2024. *Denisovan admixture facilitated environmental adaptation in Papua New Guinean populations*. Proc Natl Acad Sci USA 121:e2405889121.

2024 André M, Brucato N, Hudjasov G, Pankratov V, Yermakovich D, Montinaro F, Kreevan R, Kariwiga J, Muke J, Boland A, Deleuze J-F, Meyer V, Evans N, Cox MP, Leavesley M, Dannemann M, Org T, Metspalu M, Mondal M, Ricaut F-X. 2024. *Positive selection in the genomes of two Papua New Guinean populations at distinct altitude levels*. Nat Commun 15:3352.

2024 Kasyanov E, Pinakhina D, Rakitko A, Vergasova E, Yermakovich D, Rukavishnikov G, Malyshko L, Popov Y, Kovalenko E, Ilinskaya A, Kim A, Plotnikov N, Neznanov N, Ilinsky V, Kibitov A, Mazo G. 2024. *Genetic Associations of Anhedonia: Insights into Overlap of Mental and Somatic Disorders*. Consort Psychiatr 5:5–15.

2023 Yermakovich D, Pankratov V, Võsa U, Yunusbayev B, Estonian Biobank Research Team, Dannemann M. 2023. *Long-range regulatory effects of Neandertal DNA in modern humans*. Genetics 223.

2022 Dannemann M, Milaneschi Y, Yermakovich D, Stiglbauer V, Kariis HM, Krebs K, Friese MA, Otte C, Lehto K, Penninx BWJH, Kelso J, Gold SM. 2022. *Neandertal introgression partitions the genetic landscape of neuropsychiatric disorders and associated behavioral phenotypes*. Transl Psychiatry 12:1–10.

2022 Pinakhina D, Yermakovich D, Vergasova E, Kasyanov E, Rukavishnikov G, Rezapova V, Kolosov N, Sergushichev A, Popov I, Kovalenko E, Ilinskaya A, Kim A, Plotnikov N, Ilinsky V, Neznanov N, Mazo G, Kibitov A, Rakitko A, Artomov M. 2022. *GWAS of depression in 4,520 individuals from the Russian population highlights the role of MAGI2 (S-SCAM) in the gut-brain axis*. Front Genet 13:972196.

2021 COVID-19 Host Genetics Initiative. 2021. *Mapping the human genetic architecture of COVID-19*. Nature 600:472–477.

2020 Sivitskaya L, Vaikhanskaya T, Danilenko N, Siniauskaya M, Liaudanski A, Kurushka T, Yermakovich D, Davydenko O. 2020. *Splicing mutation in LAMP2 gene leading to exon skipping and cardiomyopathy development*. Gene Reports 18:100564.

2018 Yermakovich D, Sivitskaya L, Vaikhanskaya T, Danilenko N, Motuk I. 2018. *Novel desmoplakin mutations in familial Carvajal syndrome*. Acta Myol 37:263–266.

Languages: Belarusian, Russian – native; English – fluent; Polish, Estonian - Elementary

Hobbies: Amateur at Chinese tea parties, film camera photography, hiking and guitar playing

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Haridus

2020–2024	Doktoriõpe, geenitehnoloogia õppekava. Tartu Ülikooli loodus- ja tehnoloogiateaduskonna genoomika instituut
2017–2018	MSc, geneetika eriala. Valgevene Riiklik Ülikool, Minsk
2012–2017	BSc, geneetika eriala, diplom summa cum laude. Geneetika osakond, bioloogiateaduskond, Valgevene Riiklik Ülikool, Minsk

Teenistuskäik

2020–2024	Genoomika instituudi genoomika, evolutsiooni ja meditsiini keskuse evolutsioonigeneetika nooremteadur
2020–2021	Genotek Ltd. statistilise andmeanalüüsi osakonna kvantitatiivse geneetika spetsialist
2019–2020	Valgevene NASi geneetika ja tsütoloogia instituudi bioinformaatika rühma nooremteadur
2017–2020	Valgevene NASi geneetika ja tsütoloogia instituudi tsütoplasmaatilise pärandi laboratooriumi nooremteadur

Õpetamiskogemus

2021–2023	Genoomika, evolutsiooni ja meditsiini keskuse poolt korraldatavate suve-/talvekoolide kaaskorraldaja ja lektor
2022	Online populaarteaduslik loeng Valgevene Välismaa teadlaste ja koolitajate ühingule. Pealkiri: "*Minu kirjad: mida saab DNA-st välja lugeda*"
2019	Kaks loengut NGS Illumina DNA-Seq ja RNA-Seq andmetöötluse kohta. Valgevene NASi geneetika ja tsütoloogia instituut, Minsk

Konverentsi ettekanded ja suvekoolid

2024	Euroopa inimgeneetika konverents 2024. Berliin, Saksamaa. Poster: "*Denisovani segu hõlbustas keskkonnaga kohanemist Paapua Uus-Guinea elanikel*"

2023	Molekulaarbioloogia ja evolutsiooni seltsi aastakoosolek 2023, Ferrara, Itaalia. Poster: *"Neandertali DNA pikamaa regulatiivne mõju tänapäeva inimestele"*
2022	2022. aasta Ameerika Inimgeneetika Seltsi aastakoosolek, Los Angeles, USA. Poster: *"Neandertali DNA pikamaa regulatiivne mõju tänapäeva inimestele"*
2022	Inimmineviku rekonstrueerimine: iidse ja kaasaegse genoomika abil, Heidelberg, Saksamaa. Poster: *"Neandertali DNA pika-ajaline regulatiivne mõju tänapäeva inimestele"*
2019	#NGSchool2019: masinõpe biomeditsiini jaoks. Białobrzegi, Poola. Välkettekanne: *"Patogeensete variantide tuvastamine sihitud NGS-iga: kogemus toorandmete töötlemiseks torujuhtmete kirjutamisest ja variantide väljakutsumisest nulltasemelt"*
2019	Süsteemibioloogia töötuba 2019. Bioinformaatika Instituut, Peterburi, Venemaa.
2018	10. Noorte Teadlaste Kool "Süsteemibioloogia ja bioinformaatika". Novosibirsk, Venemaa. Teise koha diplom suulise ettekande eest: "*Patogeensete mutatsioonide tuvastamine mitte-koronaarsete südamehaigustega patsientidel sihtotstarbelise NGS abil*"
2018	Euroopa inimgeneetika konverents. Milano, Itaalia. E-poster: "*LMNA mutatsioonist põhjustatud perekondliku laienenud kardiomüopaatia juhtumiaruanne*"
2018	Bioinformaatika suvekool 2018. Bioinformaatika Instituut, Peterburi, Venemaa. Suuline ettekanne: "*Mutatsioonide tuvastamine mittekoronaarse südamehaigusega patsientidel NGS-i abil*"

Keeled: valgevene, vene – emakeel; inglise keel – ladus; poola keel, eesti keel – algkool

Hobid: Amatöör Hiina teeõhtud, fotograafia, kitarrimäng ja matkamine

Publikatsioonid: Loetletud inglisekeelse CV rubriigis publikatsioonid ('Publications')

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