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# **Neanderthal and Woolly Mammoth Molecular Resemblance: Genetic Similarities Might Underlie Cold Adaptation Suite**

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## **Abstract**

With the ongoing growth of gene-based research in recent decades, the possibility of examining changes that have taken place in structures over the course of evolution has become increasingly accessible. One intriguing subject at the forefront of evolutionary research is that of how environmental pressures affect species evolution through epigenetic adaptation. In this paper we present the available molecular components of adaptation to cold environments in two extinct mammals – the woolly mammoth and the Neanderthal. These two species co-existed in similar

geographic and environmental European settings during the Middle and Upper Pleistocene and both were direct descendants of African ancestors, although both fully evolved and adapted in Europe during the Middle Pleistocene. In order to assess the degree of resemblance between mammoth and Neanderthal genetic components we reviewed three case studies of relevant gene variants and alleles associated with cold-climate adaptation found in both genomes. Our observations present the likelihood of a molecular resemblance between the suites of cold adaptation traits in the two species, and we discuss their possible meaning for future research.

The woolly mammoth (*Mammuthus primigenius*) evolved in the arctic peninsula of Eurasia around 600 thousand years ago (Lister, 2014; Tridico et al., 2014). It originated from an African ancestor known as *Mammuthus rumanus* which most likely migrated into East Eurasia about 3.5 million years ago (Lister, 2014). Compared to its ancestors, the woolly mammoth physiology presents various adaptive traits suitable to a cold climate. A study published in 2015 found a number of gene-based adaptations to the cold in the woolly mammoth genome (Lynch et al., 2015). The researchers conducted a genetic mapping and a series of experiments that allowed them to isolate specific genes and infer their functional implications. The results demonstrate that a vast number of unique woolly mammoth genes present adaptations to surviving in cold environments, compared to their African and European ancestors, as well as to modern-day elephant populations.

Neanderthals (*Homo neanderthalensis*) were highly skilled early humans who evolved in Europe around 400 thousand years ago, and later spread across parts of Asia and the Levant (Hublin, 2009; Arsuaga et al., 2014; Churchill, 2014; Higham et al., 2014). Neanderthals originated from a local European ancestor, who most likely belonged to a population that migrated from Africa into Euro-Asia around 1.2 million years ago (Churchill, 2014; Bermudez de Castro et al., 2015). The study of human paleogenetics, which revolves around identifying the molecular ingredients that compose our natural history, has intensified greatly in recent years, introducing significant discoveries on Paleolithic human genetic characteristics and their possible roles in adaptation.

In recent decades the Neanderthal genome has been reconstructed, resulting in publications discussing various molecular and evolutionary aspects. These studies suggest that European Neanderthals underwent numerous adaptations compared to their African ancestors,

allowing their survival in colder environments in accordance with their life history and the European habitat of the Middle Pleistocene (Lalueza-Fox et al., 2007; Robson et al., 2008; Hublin et al., 2009; Sannizi et al., 2014). Moreover, genetic research on modern human populations living in extreme cold environments has also produced interesting findings such as various epigenetic cold adaptations, genetic drift between modern and archaic human population, an understanding of the effect of nutrition on evolution, and much more (e.g. Cardona et al., 2014; Guil-Guerrero et al., 2014; Sazzini, et al., 2014; Fumagalli et al., 2015; Houldcroft et al., 2016; Racimo et al., 2017).

This brings us to our research question: Is it possible to identify any *molecular resemblance* between the suites of cold adaptation traits found in woolly mammoths and in Neanderthals? Both species evolved and appeared in Euro-Asia after originating from an African ancestor, which had probably appeared and evolved under completely different climatic and environmental conditions. Furthermore, Neanderthals and woolly mammoths co-existed chronologically and geographically— and also disappeared from Western Europe across a generally similar time frame (Hublin, 2009; Higham et al., 2014; Lynch et al., 2015). We believe that if such a molecular resemblance between these two neighboring species can be established, it will open the way to further comparative molecular studies of adaptations and co-evolution between mammoths and Neanderthals in the future. The results of such studies could provide a new perspective regarding the evolution and adaptation of both species, writing a new chapter in the history of the humans and mammoths that shared the European Middle and Upper Pleistocene landscapes for hundreds of thousands of years.

In order to assess the existence of any molecular resemblance between the two species, we first provide some basic background concerning the evolution and general characteristics of

the woolly mammoth and the Neanderthal. We then present several criteria necessary for cold adaptation and conduct a cross-species comparison using three case studies on specific genes and briefly discuss the results. Together, these establish an initial basis of knowledge of the subject under study. Finally, we evaluate whether there are enough grounds to promote the use of the molecular resemblance model as a tool in future evolutionary research.

### **The Woolly Mammoth**

The woolly mammoth is an extinct species of the genus *Mammuthus* and classified under the Proboscidea mammal order and the Elephantidae family – which first appeared in Africa during the Miocene, approximately 23 mya (Roca et al., 2015). *Mammuthus* branched into a new genus within the Elephantidae evolutionary tree upon the appearance of the African mammoth (*Mammoth sunplanifrons*) around 5 mya (Roca et al., 2015). The earliest mammoth finds outside of Africa belong to a species known as *Mammuthus ramunus*, estimated to have migrated into Eurasia around 3.5 mya (Lister et al., 2015; Lynch et al., 2015; Chang et al., 2017).

*M. ramunus* spread across Eurasia but remained relatively southern, preferring warm, woodland environments. Around 2.5 mya, at the beginning of the Quaternary, temperatures declined and led to changes in the habitats of many animals. During that period, the ‘ancestral mammoth’ (*Mammuthus meridionalis*) appeared (Lister et al., 2015). Remains from around 2 mya found in Western Europe, Russia, and China suggest early adaptations in body shape, teeth size, and hair growth, attributed to environmental and climatic changes. These adaptations continued during the Ice Ages and led to the appearance of the ‘steppe mammoth’ (*Mammuthus trogontherii*). This mammoth species spread into colder habitats and entered Eurasia, central

Europe, and even parts of North America around 1.5 mya (Lister et al., 2015; Enk et al., 2016; Chang et al., 2017).

The spread of the steppe mammoth across the arctic peninsula during the glacial episodes was probably a main contributor to the appearance of the woolly mammoth, which first appeared around 800-600 thousand years ago in Asia, and later spread into Europe and North America (Chang et al., 2017). Its dispersion expanded during the glacial episodes across a habitat known as the 'Mammoth Steppe' that encompassed the arctic environments of northern Asia, parts of Europe, and later North America, where temperatures could reach  $-50$  to  $-30^{\circ}\text{C}$  (Tridico et al., 2014; Lister et al., 2015; Roca, 2015; Chang et al., 2017; Kahlke, 2014). The woolly mammoth most likely co-existed alongside the steppe mammoth until around 100 thousand years ago – when the steppe mammoth disappeared but the woolly mammoth prevailed (Enk et al., 2016; Kahlke, 2014).

Woolly mammoth populations began to gradually disappear from Western Europe during the late Pleistocene, around 40 kyr, due to climate changes, limited resources, and possibly hunting by humans (e.g., Agam and Barkai, 2018) – which caused it to completely disappear from Europe by 14 kyr (Palkopoulou et al., 2013). In Siberia, mammoth populations persisted until approximately 9.5 kyr (Nikolskiy et al., 2011; Pitulko & Nikolskiy, 2012). To date, the most recent mammoth remains were discovered on St. Paul island in Alaska, dating to around 5.6 kyr (Graham et al., 2016) and on the Wergel island in Siberia, suggesting that mammoths had dwelled there until approximately 4 kyr (Vartanyan et al., 2008; Lynch et al., 2015; Roca, 2015).

Woolly mammoths were smaller than their ancestors. The estimated average height of a fully grown woolly mammoth male is ca. 3.1 meters, with an estimated average weight of ca. 6 tons. Females were slightly smaller, with an estimated average height of 2.7 meters and an

average weight of ca. 4 tons. The woolly mammoth body was covered with a long and thick double-layered fur; it had a short tail, very small backward-sloping ears, a sloping back and a slightly more domed head compared to other Elephantidae. It has been suggested that the unique fur coat and small ears of mammoths evolved for adaptive reasons such as insulation from cold weather and reduced cold reception (Lynch et al., 2015; Schwartz-Narbonne et al., 2015; Enk et al., 2016; Kahlke, 2014).

The body of the woolly mammoth stored fat in several deposits displaying a unique physiology, such as a thick layer of subcutaneous fat for enhanced insulation from the cold, a hump behind the neck that served as an energy reservoir, and enriched sebaceous glands for insulation (Lynch et al., 2015). Analyzed fat deposits extracted from frozen mammoth remains indicate that the woolly mammoth subcutaneous fat and hump were exceptionally rich in essential fatty acids (such as Omega-3 and Omega-6) due to their large consumption of herbaceous plants and their monogastric stomach (Guil-Guerrero et al., 2014, 2018). This contributes to the contention that woolly mammoths had also an excellent nutritional value for Paleolithic human hunters, providing access to essential fatty acids in arctic environments (Guil-Guerrero et al., 2014, 2018).

In recent decades, researchers have studied the woolly mammoth genome extracted from several specimens around the world. In 2015 the complete genome of the woolly mammoth was published, significantly contributing to our understanding of this ancient species (Miller et al., 2008; Lynch et al., 2015; Palkopoulou et al., 2015; Roca, 2015). Following this genetic research, we now know that the Asian elephant (*Elephas maximus*) is the closest relative to the woolly mammoth, while the African elephant (*Loxodonta africana*) belongs to a different sub-family, which remained in Africa after the separation event (Roca et al., 2015).

Lynch et al. (2015) presented the molecular basis for cold climate adaptation found in the woolly mammoth genome, which allowed it to survive and thrive under arctic conditions. The first part of their study was conducted using comparative genetic material, extracted from three Asian elephants, one African elephant, and two frozen woolly mammoth specimens dated to 20 thousand and 60 thousand years ago. The second part of the study included a series of experiments using knock-out (KO) mice carrying fixed derived alleles specific to the woolly mammoth branch, with the purpose of diagnosing a practical role and external manifestation of these protein-coding genes in relation to climatic conditions. Their results revealed that mice which carried genes with woolly mammoth specific amino-acid changes displayed a variety of behaviors and biological traits correlated with cold adaptation.

During that study the functionality of many woolly mammoth specific genes was linked to adaptation processes that occurred in cold living environments. These genes are expressed through numerous physiological functions, such as unique fat metabolism and morphology, temperature sensation, cold regulation processes, skin and hair morphology and pigmentation, adapted circadian biology cycles, and more (Lynch et al., 2015).

### **Neanderthals (and Other Non-Modern Human Groups, *e.g.*, Denisovans)**

For many years Neanderthals have stood at the center of paleo-anthropological, evolutionary, and pre-historic debate. Due to its nature and the relative scarcity of evidence, many aspects of the study of human evolution are still inconclusive and controversial. Therefore, we settle here for a short introduction aimed at providing some clarification of the subject at hand. This part of the article sets out to establish that Neanderthals appeared *outside* of Africa – most likely on European land –originating from an African ancestor that had arrived to Europe long before

Neanderthal speciation. Furthermore, in order to survive the colder Eurasian climate, Neanderthals probably underwent molecular and anatomical adaptations compared to their ancestors, due to epigenetic/environmental factors (e.g., Ben-Dor et al. 2016).

*Homo neanderthalensis*, as a human group, disappeared (whether by extinction or assimilation) around 40-30 thousand years ago (Churchill, 2014; Higham et al., 2014). The Neanderthal type specimen discovery occurred in 1856 in the valley of the Neander River in Germany – giving the type its name. It seems that the suite of ‘Neanderthal’ morphological features and traits first appears in the European fossil record around 430 thousand years ago (Arsuaga et al., 2014; Churchill, 2014; Meyer et al., 2016), while the fullest most mature manifestation of traits occurred between 200 to 130 thousand years ago (Sanches-Qunito et al., 2015). During the Pleistocene, Neanderthals spread and populated across vast areas of Europe, Asia, and the Levant (Hublin, 2009; Churchill, 2014). Most researchers currently tend to agree that the question of the Neanderthal’s origins is related to some form of migration event(s) into southern Eurasia by a population of humans of an African origin (Churchill, 2014).

The origin of the evolutionary chain that leads to the appearance of the Neanderthals in Europe lies in Africa, where during the last 2.6 million years several human types have evolved. The oldest specimen found in the fossil record is the ‘*Homo habilis*’; its remains were found in the Afar triangle, Ethiopia, and are dated to ca. 2.6 to 1.7 mya (Johnson, 2004; Robson et al., 2008). Later, ca. 1.7 mya, appears ‘*Homo ergaster*’, a species considered by many researchers to be the oldest member of the ‘*Homo erectus*’ clade (Anton, 2003; Robson et al., 2008; Bermudez de Castro et al., 2015; Ruff et al., 2015).

The *erectus* clade also includes a few groups that ventured outside of Africa and spread across the Old World. To date, the earliest human remains in Europe have been found in

Dmanisi, Georgia, from ca. 1.8 mya (Gabunia et al., 2000; Lordkipanidze et al., 2007), and at the Sima del Elefante site (Atapuerca, Spain), dated to ca. 1.2-1.1 mya (Carbonell et al., 2008). At both locations, although some *H. erectus* affinities were noted (Hublin, 2014), the characterization of these human types is currently far from being resolved, while the recent thought on the Dmanisi sample is that it is incompatible with the *H. erectus* clade (Rightmire et al., 2017).

There is no simple answer to the question regarding the most direct ancestor of Neanderthals (Anton 2003; Churchill, 2014). Some researchers contend it to be a species known as '*Homo heidelbergensis*', which spread across Africa ca. 800 thousand years ago and from there most likely ventured into Eurasia and may even have returned to Africa during the Pleistocene (Arsuaga et al., 2014; Manzi, 2016). Others, in contrast, contend it to be '*Homo antecessor*', a species that appeared in Europe around 1 mya and presents a combination of primitive and derived features associated with the Neanderthal lineages as well as the early African/Eurasian human Pleistocene populations (Churchill, 2014; Bermudez de Castro et al., 2015).

The debate arises from the lack of sufficient material evidence and due to the fact that both species demonstrate chronological and geological appearances, as well as physiological traits that seem to fit a direct ancestor (Churchill, 2014; Bermudez de Castro et al., 2015). *H. antecessor* is primal and rare, presenting clearer Erectus traits – while the *H. heidelbergensis* is relatively more geographically widespread and presents more Neanderthal-like features, such as a wide retromolar space, no chin, and protruding/robust eyebrow ridges (Robson et al., 2008; Mounier et al., 2009; Stringer, 2012; Bermudez de Castro et al., 2015; Manzi, 2016; ). Some

researchers even contend that the fossils of both types (*antecessor* and *heidelbergensis*) might actually represent *the same* human species (Churchill, 2014).

Therefore, whether the earlier *H. antecessor* is the direct ancestor of the Neanderthal or whether a more gradual process (e.g., one which may include another evolutionary stage, such as *H. heidelbergensis*) occurred, European Neanderthals belong to a local evolutionary lineage that has its origins in the earlier populations of the region – which originated from an early African clade venturing into Eurasia during the Pleistocene (Arsuaga et al., 2014; Churchill, 2014; Bermudez de Castro et al., 2015; Meyer et al., 2016).

This debate refers to the current state of research state and provides a partial answer to the question regarding the African chain of ancestry through which the Neanderthals appeared in Europe. Neanderthals present a large array of derived physiological traits. Their skeletal anatomy was robust compared to modern humans: the average height of a Neanderthal male is estimated to be 166 cm and of a female ca. 156 cm. The average body mass of an adult male Neanderthal is about 77 kg, while the female average is 65 kg. Neanderthals had a large brain size, estimated to reach an average of 1,400-1,600 cc upon adulthood. Other physiological derived Neanderthal traits include a large nasal opening, wide anterior teeth and taurodont molars with a wide retromolar space, an oval foramen magnum, and more (Churchill, 2014).

The Neanderthal archaeological record is generally associated with the adoption and use of the Levallois core reduction strategy - as part of the Middle Paleolithic Mousterian cultural complex. The Levallois method reflects manual dexterity, and planning depth, as well as advanced technological and cognitive skills, a hallmark of Neanderthal behavior (Eren and Lycett, 2012; Lycett et al. 2016). Another interesting aspect of Neanderthal behavior is the organized burials found at different cave sites (e.g., Rendu et al., 2014). Neanderthals used fire,

most probably as needed, for dietary, aesthetic, and social reasons (Henry et al., 2010; Heyes et al., 2016), while symbolic representations are almost completely absent from the Neanderthal archaeological record (but see Rodríguez-Vidal et al., 2014 and Hoffmann et al., 2018). They made use of red ochre (Roebroeks et al. 2012) and constructed dwellings, in some cases within caves (Jaubert et al. 2016) and in other cases composed of mammoth bones (Demay et al., 2012).

Minimum temperatures in Neanderthal regional distribution areas in Europe and Eurasia can vary between 0 and  $-30^{\circ}\text{C}$  (Churchill, 2014). It has been suggested that some Neanderthal morphological and physiological traits in fact reflect adaptations to cold climates. These include, for example, the development of a more lateral/centered body shape, large muscle mass, increased metabolic rate and activity to supply warmth, and the tendency to store fat which provides insulation (Hublin, 2009; Churchill, 2014). Consequently, the Neanderthals' daily energetic expenditure was high; estimated at an average caloric intake of 3,500 to 7,000 calories per day for an adult male (Snodgrass et al., 2009; Ben-Dor et al., 2016). Supporting a large brain and body mass in a cold climate is not simple. Evidence acquired from the study of stone tools and isotopic analyses of human remains, coupled with the study of extensive faunal records from various sites, reveals that Neanderthals were omnivorous hunters capable of exploiting a variety of different animals, as well as plant and grain sources found in the Eurasian later-Pleistocene landscape (Churchill, 2014; Fiorenza et al., 2015; Ben-Dor et al., 2016; Weyrich et al., 2017; Hardy, 2018; Power et al., 2018).

A recent study suggests that Neanderthals were dependent on fat and meat for providing their daily caloric intake (Ben-Dor et al. 2016) and that they might have been anatomically adapted to the consumption of large quantities of protein, as a potentially enlarged liver might have been located within their enlarged thorax. It was also suggested that early humans,

Neanderthals included, were dependent on calories extracted from mega-herbivores, especially elephants and mammoths (Ben-Dor et al., 2011, 2016; Barkai and Gopher, 2013; Agam and Barkai 2018). Moreover, the repeated presence of mammoth remains at many Neanderthal sites, and in particular the transportation of mammoth remains to Neanderthal cave sites, strongly supports the dietary significance of mammoth fat and meat in their diet (e.g., Blasco and Fernandez-Peris, 2012; Scott et al., 2014; Smith, 2015; Agam and Barkai, 2016; ), supplemented by the use of other animal taxa and to some extent by vegetal resources as well (Estalrich et al., 2017; Weytich et al., 2017).

This notion is also reinforced by the reconstruction of Neanderthal subsistence strategies based on direct isotopic evidence (e.g, Bocherens et al., 2016; Naito et al., 2016). Direct evidence of mammoth hunting is still rare (Pitulko et al., 2016), but indirect evidences for this have been found in several Neanderthal sites (e.g. Weber, 2000; Scott et al., 2014; Mietje et al., 2014; Smith, 2015), and an abundance of archaeological, anthropological and ethno-historic evidence of such activity was recently compiled (Agam and Barkai, 2018). It is thus highly conceivable that Neanderthals were prolific and skillful hunters, capable of procuring different types of prey at will, mammoths included (e.g. Geist, 1981; Churchill et al., 2009; de los Terreros et al., 2014; Guil-Guerrero et al., 2018).

The genetic study of the Neanderthals started in 1997, led by Svante Pääbo alongside an international team of researchers working at the Max Planck Institute for Evolutionary Anthropology in Germany (e.g., Krings et al., 1997; Green et al., 2006, 2010; Pääbo, 2014, 2016; Prüfer et al., 2014). The ‘Neanderthal Genome project’ has offered a significant and powerful source of scientific discoveries in recent decades. All the information on the project is freely accessible online, on the Max Planck Institute website. In an attempt to cover the genetic

components underlying the cold adaptation traits of Neanderthals, their genetic data used for this paper were taken from a variety of published works (e.g., Harding et al., 2000; Chintala et al., 2005; Lalueza-Fox et al., 2007; Villanueva et al., 2008; Khan et al., 2014; Sazzini et al., 2014; Sanchez-Quinto et al., 2015;).

### **Climate Adaptation Processes**

The study published in April 2015 by Lynch and his colleagues on the woolly mammoth genome reveals a diverse range of criteria for adaptation to the arctic cold. We chose to use here the same criteria noted in Lynch's study. The following presents the adaptation criteria as well as the woolly mammoth derived alleles that have been found to reveal cold adaptations and were described by Lynch et al. (2015):

1. **Genes associated with circadian biology** – organisms living in high arctic environments experience long periods of darkness during the winter and near constant light in the summer. The woolly mammoth genome revealed several amino-acid changes in genes associated with circadian systems, such as HRH1, HRH3 and PER2. These genes modulate and coordinate different activities in relation to circadian clocks and cycles in correlation with the specific climate, such as shift in food consumption, regulation of the digestive rhythm, activation of adaptive thermogenesis,<sup>1</sup> and the regulation of energy homeostasis.
2. **Genes associated with insulin signaling, lipid metabolism, and adipose biology** – In total, 54 woolly mammoth-specific changes in genes related to adipose tissue activities that aid in insulation and retention of body heat, were noted. These genes modulate the creation and determine the location of brown and white adipose tissues. Among the genes

identified was the LEPR gene, which relates to the creation and storage of fat cells; DLK1, which serves in retaining subcutaneous fat and is also responsible for the location of adipose tissues around the body; and the GHR gene, which acts as a receptor and modulator for different growth hormone activities, which are in high demand for many high-mass cold-adapted species.

3. **Genes associated with skin, hair, and sebaceous gland development and physiology –**

The woolly mammoth coat consist of two layers – a long outer layer, and a thick and dense inner layer. Additionally, their skin contained large sebaceous glands, which acted as another layer of insulation. Thirty-eight mammoth-specific changes in genes associated with unique coat/hair morphology, such as inner and outer hair root sheath, hair follicle, diluted coat color, and skin and hair pigmentation (SLC7A11 and MC1R to name but a few) were identified. An adaptation of skin and hair pigmentation has been attributed in the past to increased UV radiation–induced vitamin D synthesis in the body, aimed at preventing rickets (Harding et al., 2000).

4. **Genes associated with temperature sensation –** A group of 13 genes associated with abnormal thermal nociception was also identified. Among these were several genes encoding temperature-sensitive transient receptor potential (thermoTRP) channels, which have a well-established role in temperature sensation: for example, TRPA1 and TRPM4 in sensing noxious cold and innocuous warmth and the gene TRPA1 in the regulation of vascular response to cold. In addition, the researchers identified a change in the gene TRPV3, which plays a key role in woolly mammoth temperature sensation and, therefore, contributed to the evolution of cold tolerance and long hair in mammoths.

## **Interspecies Comparison**

It seems that Neanderthals and woolly mammoths shared many environmental and evolutionary features. Both species originated from an African ancestor, appeared and evolved within the same time frame, were impacted by the Pleistocene glacial cycles and co-existed in Eurasia. As noted above, it is evident that Neanderthals and woolly mammoths shared ecological habitats, as the latter were used as food by the former, and their bones were used by them as building and fuel materials (e.g., Chabai and Veselsky, 2007; Demay et al., 2012; Ben-Dor et al. 2016).

In this study we sought to identify possible similarities between Neanderthals and woolly mammoths within the genetic cold adaptation processes. To test this fundamental idea, we chose to focus on three specific case studies, chosen from the long list of genes published by Lynch et al. (2015).

***The First Case Study: Leptin Receptors (LEPR Gene).*** Sazzini et al. (2014) discuss cold adaptations among different human populations, hypothesizing that cold adaptation processes, and more specifically changes in the metabolic system and modulation of non-shivering thermogenesis,<sup>2</sup> are associated with a unique activity of brown adipose tissue. These researchers conducted a number of experiments and found an allele of the gene LEPR which presents strong adaptive behavior to cold and is found among the Neanderthal and Denisovan genome sequences.

The LEPR gene encodes for the leptin receptor. Among other things, this protein is associated with the activity of adipose tissues and the regulation of body heat (Villanueva et al., 2008). This gene was also identified during the mapping of the woolly mammoth genome; it is noted under the category of ‘Genes associated with insulin signaling, lipid metabolism and

adipose biology'. The LEPR gene is described as responsible for the creation and regulation of brown adipose tissue cells (Lynch et al., 2015). As noted, fat deposits take part in several cold adaptation processes, such as contributing to insulation, and may also serve as a stored energy source for times of need (Churchill, 2014; Garstang, 2015; Lynch et al., 2015).

***The Second Case Study: Keratin.*** A recent publication has reviewed the vast paleo-genetic research performed on Neanderthals in the past couple of decades. In their study, Sankararaman et al. (2014) suggested that inferred Neanderthal haplotypes<sup>3</sup> found in present-day Euro-Asian populations contributed to the adaptation of modern humans to non-African living environments. Among the genomic regions with the highest inferred presence of Neanderthal haplotypes are genes encoded for keratin production – a protein expressed in skin, hair, and nails (Khan et al., 2014). In other words, alleles originating from Neanderthals and which affect the hair and skin morphology, could have been beneficial for modern humans adapting to the non-African environment to which Neanderthals were already adapted (Sankararaman et al., 2014).

The study on the woolly mammoth by Lynch and colleagues also refers to keratin as one of the 'thermoTRP' genes investigated as expressed in keratinocytes, skin, and hair. This gene group is associated with several adaptation processes, such as regulation of cold sensation, communicating sensory information to neurons located in the hair and skin, expansion and reduction of blood vessels in adjustment to temperature, as well as regulation of hair growth and hair thickness (Lynch et al., 2015).

Another example of species-specific changes in keratin functionality in the woolly mammoth was provided in a study published in 1970, which presents how the structure of keratin proteins in the woolly mammoth hair demonstrates unique changes that were probably

responsible for thickness and overall quality (Gillespie, 1970). Khan et al. (2014) further demonstrated the keratin functionality among various land mammals, including modern African bush elephants (*Loxodonta Africana*), and concluded that different genes linked to the keratin mechanism are responsible for changes in hair types in mammals, and that they are the result of an ‘ecological and environmental adaptation’.

***The Third Case Study: MC1R & SLC7A11.*** In a study published in 2007, the gene MC1R was presented and termed ‘the ginger gene’, after being extracted from two Neanderthal specimens – discovered in two sites: Monti Lessini, Italy and El-Sidron, Spain (Lalueza-Fox et al., 2007; see a more critical assessment of the evidence in the summary below). The same study also contends that this gene is usually associated with organisms living in cold or high elevation environments where solar radiation is relatively weak.

Variants of the MC1R gene were identified in the genome sequencing of the woolly mammoth (Rompler et al., 2006). Chintala et al. (2005) attribute the MC1R gene a key role in the regulation and synthesis of body pigmentation. They suggest that *induced* activity of MC1R leads to darker hair and skin tones, whereas *reduced* activity can lead to lighter hair and skin colors. Lighter skin and hair are more susceptible to absorption of solar radiation, which is crucial for the synthesis of vitamin D in the body.

A shortage of vitamin D can delay the absorption of calcium into the bones and may lead to rickets, a common condition of decreased bone opacity due to poor bone mineralization, potentially leading to fractures and deformity (Harding et al., 2000). A number of studies have thus suggested that reduced skin and hair pigmentation constitutes an adaptive process, advantageous to organisms living in cold climate environments where solar radiation is naturally

weaker (Harding et al., 2000; Chintala et al., 2005; Laluez-Fox et al., 2007). Other studies suggest that at the end of the Pleistocene, woolly mammoths experienced environmental stress which is manifested in mineral deficiency in their bodies (Leshchinskiy, 2015). The typical effects of this condition are osteoporosis and fractures.

Another gene variation associated with diluted coat color was found in the solute carrier family 7 member 11 (SLC7A11) gene, involved in the regulation of pheomelanin (red pigment) synthesis in hair and melanocyte in many mammals – including humans (e.g., Chintala et al., 2005). SLC7A11 variants were also found in the woolly mammoth genome, described by Lynch and his colleagues as an epigenetic variation associated with cold climate (Lynch et al., 2015). This offers another example that may attest to a resemblance in epigenetic adaptation in both woolly mammoths and humans. In many ways, it is similar to the MC1R gene, and also manifests itself in a pigment regulation, which is speculated to be an adaptive trait to UV radiation in various situations (e.g. Brash, 2003; Rees, 2004; Brenner et al., 2008).

## **Discussion**

This article presents a short comparison between two species, that demonstrate specific adaptive processes to life in cold environments, each of which with an African ancestor. Attempting to link and compare between these two species is not a simple task, but it is a very interesting one. We believe this work can offer a unique perspective on the subject, in creating a type of molecular model of adaptation to specific living environments. The results also throw light on human-elephant relationships during the Pleistocene, following their mutual ecology and shared living environments, in addition to other possible interactions between the two species.

In recent years important studies concentrating on modern human populations living in the arctic have revealed a variety of epigenetic adaptations correlated with climate conditions. For example, two studies reported that specific genes found in modern-day Greenlandic Inuit populations were indeed cold adapted, associated with the unique activity of adipose tissue and body-fat distribution (Fumagalli et al., 2015; Racimo et al., 2017). It was also suggested that Inuit nutrition (which is particularly rich in protein and fatty acids) alongside the cold climate conditions, affected gene regulation and led to hormonal signaling that resulted in changes in body shape, size, and more. Some studies even reported that haplotypes of cold adapted genes found in arctic modern human populations were derived from archaic human lineages (Neanderthal and Denisovan), thereby attesting to early positive selection for genes associated with physiological cold-adaptation, as well as epidemiologic factors (Cardona et al., 2014; Fumagalli et al., 2015; Houldcroft et al., 2016; Racimo et al., 2017).

These molecular changes found in contemporary modern human populations demonstrate how important the understanding of epigenetic process can be, as they shape adaptation and evolution. Moreover, the appearance of specific cold-adapted archaic haplotypes in modern human populations supports the contention that Neanderthal genes were cold-adapted, bringing us back to the question of early human interactions and gene-exchange during the Pleistocene, in light of these suggested advantages in human adaptation.

Another relevant example, published in 2017, engages with genetic adaptations to high altitude in Tibetan human populations (Hu et al., 2017). The study demonstrates that the haplotypes associated with high altitude probably originated from an archaic Denisovan population – a sign of a positive selection towards a modern human adaptive genetic evolution to a unique genetic adaptation for specific living environments (Hu et al., 2017).

Similar to human adaptation, some studies present evidence of molecular ‘convergent evolution’ in various animals. One interesting example can be found in the case of the Yakutian horse (Librado et al., 2015). Yakutia (Sakha Republic, Russian Federation) is a region in eastern Siberia known for its extreme cold climate. In 2015, a group of researchers sequenced and analyzed the genomes of 11 Yakutian horses (both present-day and ancient specimens). The results showed that the present-day population of horses is descended from a stock of ca. 14<sup>th</sup> century domesticated horses. This important discovery supports the contention that genetic cold-climate adaptations of the Yakutian horse were selected within a very short evolutionary time scale (Librado et al., 2015). Yakutian horses today exhibit a great number of unique adaptations to the cold climate, such as a thick and heavy coat of hair, short and compact body morphology, seasonal metabolic phases aimed at the accumulation of fat, and more. The effects of climate pressures on the domesticated horse have translated into molecular changes and present themselves in the modern day Yakutian horse populations – after only a few hundreds of years.

Furthermore, in that same study Librado and colleagues compared adapted genes from the Yakutian horse to those of other ‘well-known’ cold-adapted mammals, such as the woolly mammoth and modern-day Siberian human populations. They detected a shared appearance of the BARX2 gene (involved in skin and hair regulation) in Yakutian horses and the woolly mammoth, and a shared appearance of the PRKG1 gene (involved in constriction of blood vessels to minimize heat loss) between Yakutian horse and Siberian human populations (Librado et al., 2015). We see these remarkable finds as a supporting evidence for the contention regarding the nature of convergent evolution through *molecular resemblance* – in which the similarities in genetic adaptation between adapted species are present, offering a significant topic for future research.

Elephants and humans are both large-brained mammals with long life spans and complex social behavior. Already in 2009, a phylogenomic analysis of elephant and human genetic ancestries had revealed patterns of convergent adaptive evolution (Goodman et al., 2009). Parallelism was found in genes associated with aerobic energy metabolism, related to both species possessing a large-brain. The authors suggested that “If the large brain arose convergently in different mammalian lineages, it is feasible to explore whether putative brain-important genes that evolved at accelerated rates during mankind’s ancestry also evolved at accelerated rates in non-primate lineages where brain mass increased”.

The results of this study indicate that in both mammals (humans and elephants) the DNA coding sequence evolution has slowed down – due to the lengthening of generations' life spans, and present “evidence of convergent patterns of adaptive evolution in nuclear genes that code for mitochondrial functioning proteins” (Goodman et al., 2009). These results support our initial assumption regarding convergent patterns of evolution in elephant and human ancestries, and further attest to the high probability of such patterns in the genetic climate adaptation of both the woolly mammoth and the Neanderthal.

## **Conclusions**

In this study we investigated three case studies in order to examine the possible existence of molecular resemblance in the adaptation processes of Neanderthals and woolly mammoths. The first case study outlines the mutual appearance of the LEPR gene, related to thermogenesis and the regulation of adipose tissue and fat storage throughout the body. Although this seems to attest to the existence of a molecular resemblance, at this point it is hard to determine its comprehensive significance.

The second case study engages with genes related to keratin protein activity in both species. As the study by Lynch and colleagues (2015) does not present in detail the specific genes related to keratin activity in the woolly mammoth, we had to rely on data taken from relatively outdated research which lacks direct genetic information (Gillespie, 1970), as well as another study presenting genetic data extracted from an African bush elephant (Khan et al., 2014). We employed these data to evaluate the contention of the existence of a molecular resemblance based on keratin activity. However, one should bear in mind that these data do not directly apply to the woolly mammoth.

The third case study focuses on skin and hair pigmentation variants in the genes MC1R and SLC7A11, as presented by Lalueza-Fox et al. (2007). Talamo et al. (2016) re-examined the Monti Lessini specimen (one of the two specimens used by Lalueza-Fox et al., 2007), employing more accurate genetic and radiocarbon dating methods. Although their results indicated that the specimen from Monti Lessini might not be a Neanderthal, but a more recent modern human dated to the Bronze Age, the credibility of the El Sidron specimen as a Neanderthal is not impaired. It is worth noting that the 2016 tests were not conducted on the exact same bone fragment as that used by Lalueza-Fox in 2007 which leaves the Monti Lessini specimen somewhat questionable and makes it harder for us to decide in favor of it being an unequivocal case for the sake of our comparison.

The second specimen used for the MC1R gene in the 2007 paper was extracted from the site of El Sidron. Sadly, this specimen was in a relatively bad state of preservation, and almost no useful genetic material could be extracted from it. This also makes the attempt at a gene comparison between Neanderthals and woolly mammoths rather problematic. We bring these two problematic aspects to the attention of the reader, and hope that more relevant and reliable

data will become available in the near future. Gene variants associated with skin and hair pigmentation, however, were found in both species' genomes. These variants were probably not detached from the overall epigenetic and positive selection processes they had undergone – allowing these species to survive in cold climates.

If we were to speculate about future research, we would say it is highly possible that those gene variants or specific alleles will be found to match in both species, and perhaps even with those of other animals that inhabit the same environments – much like the example of the Yakutian horse which demonstrates a variety of cold-climate adaptations similar to those of the woolly mammoth and Siberian human populations (Lynch et al., 2016; Librado et al., 2015). That being said, it would also seem that the variety of adaptation strategies of mammals living in extreme cold conditions such as the Arctic is somewhat limited – which might not come as a surprise due to the harsh nature of these regions, which dictates a specific set of traits, and does not support a great deal of variance.

To summarize: we found that one out of the three above-mentioned case studies displays evidence of genetic similarity between the two discussed species, while the second and third case studies must remain inconclusive at this point. Overall, it seems that the initial question regarding the possible existence of a *molecular resemblance* between the cold-adaptation processes of the two species – Neanderthals and woolly mammoths – may be receiving initial confirmation from the case studies we have examined here. It can be reasonably assumed that the appearance of such similarities in gene pathways, alleles, and even haplotypes, is not accidental, and we believe they attest to a degree of parallelism in the process of adaptation process to cold climates.

Humans and elephants/mammoths shared habitats for hundreds of thousands of years; and it is also highly probable that early humans were actually dependent on the calories derived from these mega-herbivores for their successful survival during the Pleistocene. The findings from the genetic methods further attest to this unique relationship between the species, and strengthen our understanding of their shared life-histories. Moreover, it was recently suggested that the physical, social, and cognitive similarities between recent human groups and contemporary elephants were the driving force behind the way hunter-gatherers perceived elephants as similar and equal to humans (Agam and Barkai, 2018; Lev and Barkai, 2016). Following the ideas presented in this study, it might be suggested that the adaptive genetic resemblance between Neanderthals and woolly mammoths did not go unnoticed by Pleistocene populations, and contributed strongly to the intimate relationships and interactions between the two species. These suggestions will be addressed in future studies. At this point, we believe that the precise nature of the molecular resemblance is still elusive, and it is clear to us that the subject demands further in-depth research– involving further expansion of gene examination, lab tests, and even a comparison of genes and adaptation processes of other species. We believe *molecular resemblance* offers a useful tool in providing a unique approach to evolutionary research across various fields of study.

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## **Endnotes**

<sup>1</sup>Thermogenesis – is a thermo-regulatory process that generates the production of heat in the body. Thermogenesis works by activating unique cells of brown adipose tissue (BAT) and sympathetic nerves that release Norepinephrine (Cannon et al., 2004).

<sup>2</sup>Non-shivering thermogenesis – is a cold-induced increase in heat production, usually not associated with the muscle activity of shivering (Cannon et al., 2004).

<sup>3</sup>Haplotypes – are a group or groups of alleles found together on the same DNA molecule (Feero et al, 2010).