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What Neanderthal Traits Do You Possess?

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The recent sequencing of the Neanderthal (*Homo neanderthalenis)* genome in 2010 has revealed 99.7% homology with *Homo sapiens*. In this interactive mini-workshop, participants examined several physical traits believed to be common in Neanderthals. We discussed the use of genome sequencing services as a personalized learning tool for student engagement in the area of hominin evolution. Participants also worked in groups to make intersecting Venn diagrams with colored acetates that depict genetic overlap among modern humans, Neanderthals, and, an additional hominin group, the Denisovans. The Venn diagrams are based on DNA motifs that are found in the genomes of three hominin species: *Homo sapiens*, and the archaic Neanderthals and Denisovans. Some of the motifs found in common among all three species were found in regulatory genes for tooth development. Over 60 motifs studied were found in modern humans alone, including genes involved with neurological development. Students that conduct this exercise will first make the Venn diagrams, discuss differences among these hominins, and then answer a questionnaire about phenotypes that they might have in common with Neanderthals. One proposed Neanderthal trait is the decreased likelihood of sneezing after eating dark chocolate. We will test that hypothesis by providing participants with a dark chocolate sample.

Keywords: Neanderthal, Human evolution, hominin, Denisovan, modern and archaic

humans **Link to Supplemental Materials: https://doi.org/10.37590/able.v41.sup25**

Introduction

The authors became interested in Neanderthals when they discovered, through their 23 and Me® tests, that they shared over 300 out of 1400 variances in DNA in common with Neanderthal. Callahan and Nolan shared more variances than over 87% of the more than 5 million people who have been tested. See Figure 1 for an example.

Markers tested for Neanderthal ancestry	Markers where you have two Neanderthal variants	Markers where you have one Neanderthal variant	Your Neanderthal total
1436	29 X 2	244	302

Figure 1. Neanderthal variants found in a co-author's DNA.

Upon perusal of the literature, they noted that there were both scientists that discussed phenotypes in both Neanderthal and another of our closely-related subspecies, Denisovan, and researchers that focused more on genetic patterns or motifs they observed in the genomes. The former group made conjectures as to what some of the phenotypes were, usually from gene variants common to the modern and archaic humans.

Akst (2019), in layman's terms, gives us the highlights of what we now know about Neanderthal and Denisovan. Neanderthal remains were first discovered in caves in the Neander valley (Schmitz et al. 2002), and Denisovans fossils were first found in caves in Russia in 2011. *Homo neanderthalensis* has been given a separate species status from *Homo sapiens* (although some deign Neanderthal as a subspecies of *Homo sapiens*). Originally, the *Homo neanderthalensis* ancestors were thought to have migrated out of Africa 50,000 to 70,000 years ago, but not to have mixed with *Homo sapiens*, based on analysis of mitochondrial DNA (Currat and Excoffier 2004).

However, much more additional genetic information in the form of complete genome sequences is now available, (the complete genomes of Neanderthal and Denisovan were sequenced in 2006 and 2010 respectively)

(Green et al., 2010; Reich et al. 2011, and, additionally, Prüfer, 2014). Both Neanderthal and Denisovan are considered "archaic hominins" or archaic humans as opposed to the "anatomically modern human". Gittleman et al. (2016) discovered gene sequences that when introgressed in modern humans, conferred advantages to modern humans as they left Africa.

These genes included those that had immune and pigmentation functions. Vernot and Akey (2015) suggest that migration out of Africa of the ancestors of modern humans may have actually occurred in two pulses; one to Europe and another to East Asia, as modern East Asians also share some Neanderthal genes. Mendez et al. (2016) sequenced the Y chromosome in the remains of an individual Neanderthal and found mutations in part of the DNA not found in the modern human Y chromosome. Some anthropologists, who also used DNA sequences from fossils they located, found that the Neanderthals lived in social groups (Lalueza-Fox et al. 2011; Duveau et al, 2019) and made art (Hoffman et al. 2018). Tool use related to hand morphology is discussed in Churchill (2001).

Reich et al. (2011) found, using single-nucleotide polymorphisms or SNPs isolated from archaic human skeletons and modern day humans, that Denisovans migrated to Southeast Asia from Africa. Some modern day Southeast Asian populations' genotypes contain around 5% of Denisovan sequences. A contribution of a variant of the EPAS1 gene from Denisovan ancestry allows modern day Tibetans to live at high altitudes (Huerta-Sanchez et al. 2014). Students interested in dentistry might want to delve into Zanolli et al. (2017), which was a bioinformatics study in which the authors located polymorphisms in various tooth proteins among Denisovans and modern humans. Weyrich and Cooper (2017) explored diets of Neanderthals by examining dental calculus.

People have wondered for years why the Neanderthals went extinct approximately 40,000 years ago; Degioanni et al. (2019) suggest that a lowered female fertility may have been a non-catastrophic contributor to their extinction. Also, if Neanderthals were assimilated into what has now become modern humans then they really have not gone extinct "in the classical sense of the word" (Smith et al. 2005). Banks et al. (2008), upon studying climate change in Europe, decided that climate change did not contribute to the demise of the Neanderthals, but that perhaps competitive exclusion did. Students will also find it useful to read papers devoted to Denisovan movements and genetics, such as a study by Reich et al. (2011).

The following exercise can be used as a prelude to a human genetics phenotype lab, or as a tool in learning bioinformatics. The exercise is comprised of two parts: the Venn diagram activity and the Neanderthal questionnaire. When we have conducted this exercise, we engage the students in a visual tactile activity in which they make Venn diagrams that depict genetic characters that are unique and those that are shared among the three "human" species (*H. sapiens, H. neanderthalensis and H. denisova*). The bioinformatics behind this activity is then discussed. Then a PowerPoint is shown to the students in which phenotypes shared among humans and Neanderthals are portrayed and discussed. The students then answer a questionnaire in which they ascertain "how Neanderthal they are". The guestimates (percentages) that the students make are added up and averaged for each trait. Students can then see how they vary from "the norm" for the class.

The Venn diagram exercise focuses mostly on "motifs" or "motifomes" which are DNA patterns found by examining the Neanderthal, Denisovan, and human genome (Cserhati et al. 2018). Most of these motifs are found in non-coding regions, and are thought to be regulatory. Cserhati et al. (2018) found major differences in gene sequences found in regions of the genome related to odontogeneis (teeth development) and neurological development.

Whereas the Venn diagram analysis focuses on learning more about bioinformatics, the Neanderthal questionnaire takes its cues from actual phenotypes the students might have shared with Neanderthals, based on associations discovered by Sankararaman et al. (2014), Simonti et al. (2016) and Dannemann and Kelso (2017). (Part of the motivation for developing the questionnaire was from the popular article in *Discover* by Zimmer (2013). The scientists above found associations of certain Neanderthal gene variants with traits that appear to be affiliated with proximity to the sun through latitude, such as skin lesions, depression, and hours for wake preference, and others that the students might be interested in such as a proclivity to smoking, hypercoagulation (which is a heightened response to injury) and other immune system variations.

We were uncertain as to the origin of a Neanderthal variant found that is related to sneezing after eating chocolate presented by 23 and Me ® (Neanderthals are thought not to have that variant), but an anthropologist suggests that this could be because Neanderthals had a large sinus (Mark 2018). However, Mark (2018) also questions this statement on his 23 and Me® report "You have 0 Neanderthal variants associated with a reduced tendancy to sneeze after eating dark chocolate", and wonders if and when Neanderthal would have ever even encountered chocolate! See also Tran et al (2011) for a comprehensive summary of single nucleotide polymorphisms or SNPs associated with "gustatory rhinitis", the symptoms of which include sneezing after eating certain foods.

The fact that we found a reference questioning the validity of some of the genetic testing that is currently the rage is good for the students to read and will aid their critical thinking skills. A discussion might ensue over genetic testing in general and its implications. It is also important for the students to realize, as they are answering their questionnaires, that the Neanderthal variants are found in association with certain phenotypes, but no “cause and effect” has been obtained.

Student Outline

Student Learning Objectives

- Read and evaluate scientific papers
- Interpret Venn diagrams in terms of genetic data
- Cogently compare and contrast modern and archaic humans

Part 1. Venn Diagram Analysis

1. Using a petri dish or a cup, trace three different colored circles on colored acetate paper. Overlap and glue onto a piece of cardboard. Label according to the diagram in Cserhati et al. (2018) or Figure 2 in this paper.

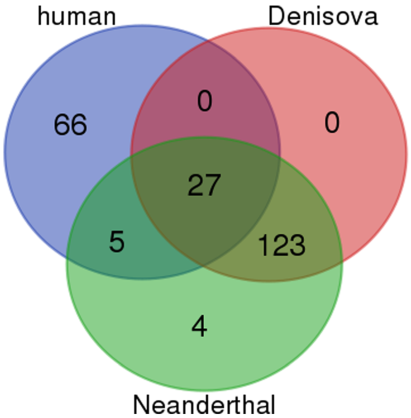

Figure 2. Overlapping DNA sequences found in non-coding regions in modern and archaic humans.

Can you define “Neanderthal” and “Denisova”? How many years ago did they evolve? When did modern humans evolve? Was there overlap in the species?

What do the numbers on the Venn diagram mean? (Refer to to Cserhati et al. (2018) and look up all unfamiliar terms.)

Part 2. Neanderthal Trait Self- Study

2. Students will next perform a self-study checklist (see Appendix) of selected human traits believed to derived from a Neanderthal Variant. Selected traits may vary according to interest and populations of students. You can use a range scale 0---100%, Yes or No, or Likert scale. You might then compare your values to class averages.

3. Students are encouraged to examine and share finding of their own DNA tests and inherited traits relative to *Homo neanderthalis* if they so choose.

Materials

Colored transparent plastic or acetate paper
Light colored card stock or manila folders cut in half
Scissors
Glue sticks
Sharpies
Shapes to cut circles---petri dishes
86-92% cocoa chocolate bars
Computers (optional) if you want them to make a Venn diagram on the computer
If students want to eventually do the 23 and Me® genetic testing, they should do this on their own. It is approximately $100 to do the ancestry testing, and an additional $100 for health and/or disease variants.

Notes for the Instructor

The Venn diagram comes from the paper by Cserhati et al. (2018) that describes common motifs that were observed in the genomes of humans, and the two archaic hominins, Neanderthal and Denisovan. Students will make this Venn diagram by cutting circles out of transparent plastic sheets and overlapping them. They will glue them onto cardboard and label them. They will explain to each other what the numbers in the diagram mean. This activity "slows the students down" and allows them to think more about the interrelationships between the three sub-species.

An Explanation of the Venn Diagram:

The numbers refer to motifs of 6-10 base pairs (bp) in length in intergenic elements found in human accelerated regions (HAR's). There are 49 HAR's which are shared with other vertebrates, but which are significantly different in humans.

Students will read the paper by Cserhati et al. (2018) with their instructor. They will learn that the genomes of all three hominin subspecies (human, Neanderthal and Denisovan) have been sequenced, and will learn a bit more about these genes. Common DNA sequences, or 'motifs' were found in the genomes; some common motifs corresponded to genes found in teeth development; others (found only in humans) were found in genes that control neurological development.

Terminology Covered:

Bioinformatics
Neanderthal
Denisovan
Human—*Homo sapiens*, with respect to a. when we evolved and b. what are characteristics that makes us unique?
Genome
Motif
Motifome
Human accelerated regions (HARs)
Human conserved non-coding sequences
UTRs
miRNAs
hexamer
decamer, etc.
.

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About the Authors

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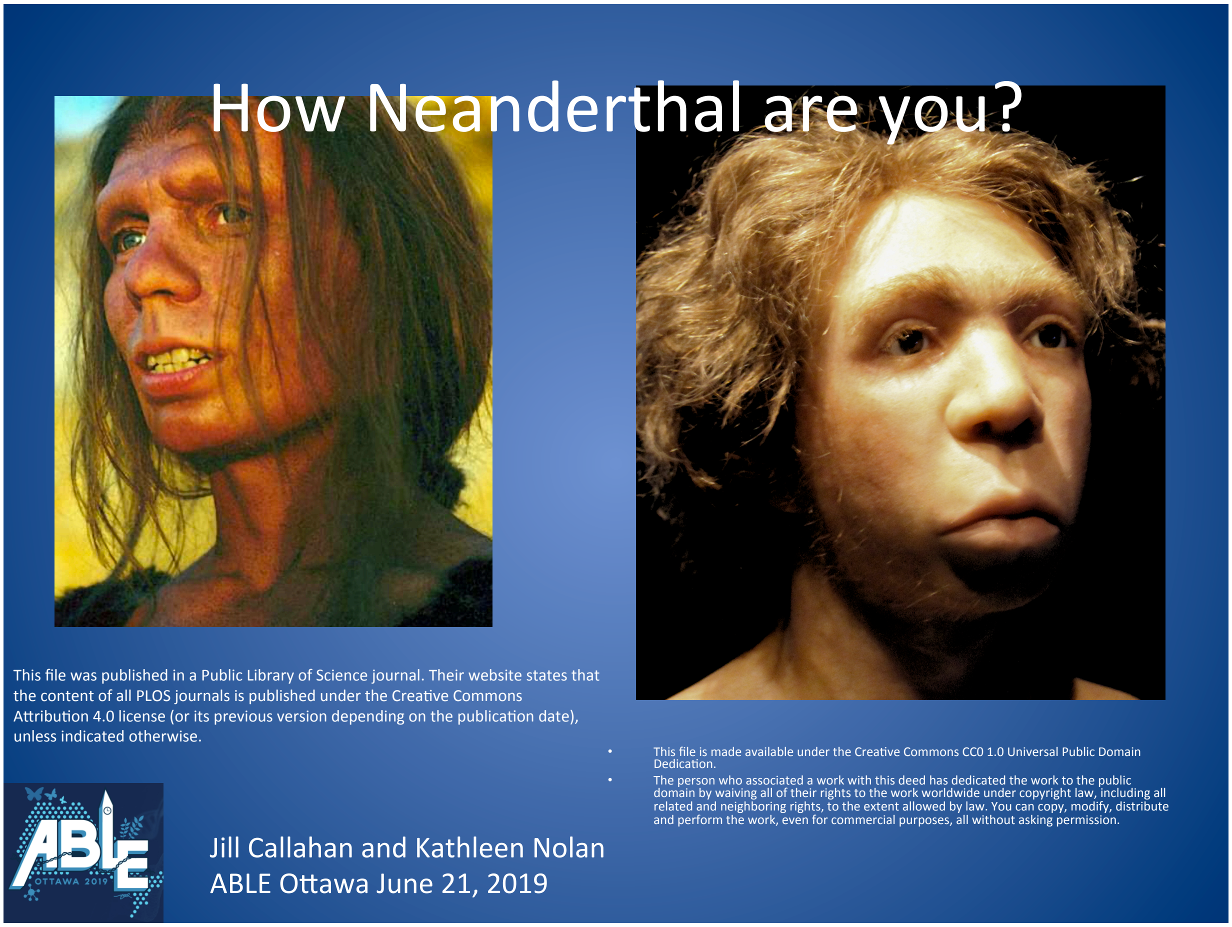
Appendix A: Student Survey

Powerpoint is found in Supplemental Materials



How Neanderthal are you?

Jill Callahan and Kathleen Nolan
ABLE Ottawa June 21, 2019

Student Survey of Neanderthal vs. Human Traits

According to Dannemann and Kelso (2017) there are genes or parts of genes that are shared between modern humans and Neanderthals. If you shared Neanderthal genes, then you would answer on this survey your estimated percentage that you would share in common with Neanderthal. Some of this is, of course, conjecture, because, according to DNA analysis, the Neanderthal themselves were genetically diverse.

	Modern Human Neanderthal
1. Eye color	Light--------------------------------------dark 0%---100%
2. Red hair	0%--100%
3. Tendency to feel isolated, or a lack of motivation	0%--100%
4. Height (were you tall as a child?)	0%--100%
5. Prone to sunburn	0%--100%
6. Night owl	0%--100%
7. Back hair	0%--100%
8. Hair curl	0%--100%
9. Smoking status	0%--100%
10. Not sneezing after eating dark chocolate	0%--100%

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