**White Paper 23-05**

**Neanderthal Ancestry Inference**

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(This updated white paper replaces White Paper 23-05, titled “Neanderthal Ancestry Inference” published on October 20, 2015 and last edited December 14, 2015).

## Summary

This white paper serves as a companion to the Neanderthal report offered to 23andMe customers as part of the 23andMe® Personal Genome Service. It offers more details on the methods used in calculating Neanderthal variant counts and in detecting human traits that are associated with Neanderthal variants. We hope that this white paper may also serve the scientific community to understand how genetic variation inherited from Neanderthal ancestors may affect modern-day phenotypes.

# Introduction

A fascinating topic in human evolution is the relationship between present-day humans and our closest evolutionary relatives, the now extinct *Homo neanderthalensis*, or Neanderthals. One of the most debated aspects of this relationship was whether and how much Neanderthals and modern humans interbred during the tens of thousands of years we cohabited in Europe and Western Asia.

Analysis of the first draft of the Neanderthal genome [1] led to the discovery that Neanderthals did indeed interbreed with modern humans. Subsequent research identified specific Neanderthal-derived alleles (variants) that are likely to have been introduced into modern humans, accounting for between 1-2% of the genomes of all non-African populations today [2]. Researchers detected these variants using rigorous statistical modeling, and it is believed that they are seen in present-day populations only because they were introduced by interbreeding with Neanderthals. Therefore, the observation of any of these variants in a living individual is indicative of the presence of DNA that came from Neanderthals.

Scientists at 23andMe further noticed that several of these Neanderthal variants are associated with traits in 23andMe customers. This white paper details not only our method for estimating the number of Neanderthal variants that a 23andMe customer carries, but also our approach to identifying the physical traits associated with those variants that are likely to have entered modern human populations through Neanderthals.

# Methods

## Counts of Neanderthal variants

We obtained, from the authors of [2], a list of 135,171 SNPs (Single Nucleotide Polymorphisms) for which the derived allele (the "Neanderthal variant") is believed to have originated in Neanderthals and later entered the modern human population via interbreeding. Of these, 3,731 SNPs are assayed via our v5 genotyping chip and also pass our genotyping quality criteria, and 1,436 SNPs are assayed via our pre-v5 genotyping chips, with 109 variants overlapping between v5 and previous versions of the chip. For each SNP, an individual carries 0, 1 or 2 Neanderthal variant copies. We report the total number of copies (the Neanderthal variant count) that the individual carries out of a possible 7,462 (v5) or 2,872 (pre-v5).

Although it is theoretically possible for someone to carry all Neanderthal variant copies, most individuals carry only some. A 23andMe customer tested on the v5 genotyping chip carries an average of 236 Neanderthal variant copies,while a customer tested on a pre-v5 genotyping chip carries an average of 269 Neanderthal variant copies (based on all consented customers as of April 18, 2020). The minimum number of Neanderthal variant copies that we've observed on pre-v5 and v5 chips is 0, and maximum Neanderthal variant copies that we've observed are 397 and 434, on pre-v5 and v5, respectively.

A person's Neanderthal variant count is a signal that is likely to be correlated with the amount of Neanderthal DNA in their genome. The proportion of customers who have fewer Neanderthal variant copies is displayed in the report as a percentile and is reported along with the variant count.

## Phenotypes associated with Neanderthal variants

By combining and analyzing data from our large database of customers who have consented to participate in research, 23andMe scientists routinely identify genetic associations for a variety of human traits. These analyses have been used to replicate associations reported in the literature and to publish novel associations in peer reviewed journals [3-13].

We examined our database of GWAS associations across Neanderthal-associated SNPs assayed on the v5 genotyping chip by 23andMe. We focused on 324 phenotypes in European customers, and found 33 SNPs (selected by custom analysis based on lowest p-value within a 100 kb window) associated with 22 unique traits, achieving genome-wide significance with a p-value cutoff of 5e-8 (*see* **Table 1**). Of these 33 SNPs, 9 SNPs overlap with pre-v5 genotyping platforms.

The list was truncated for customer comprehension and product reasons by excluding phenotypes that had associations in both directions with different Neanderthal variants, and limiting to phenotype-associated SNPs for which more than 3% of customers of European descent carry the Neanderthal (derived) allele.

### Inferring the phenotypic impact of carrying Neanderthal variants

By examining the sign of the estimated effect of the variant on the trait, we inferred the impact of carrying the Neanderthal variant on the phenotype in present-day individuals. In our Neanderthal report, we describe which of these Neanderthal variants a customer carries (if any), and the expected effect of each variant on the corresponding trait.

**Table 1. Neanderthal variants significantly associated with traits**

| Phenotype | SNP | Chip version | Neanderthal Allele | Signed effect | p value |
|---|---|---|---|---|---|
| Ability to smell | rs72686076 | v5 only | A | -0.025 | 4.44E-09 |
| Fear of heights | rs62405860 | v5 only | C | -0.022 | 3.15E-08 |
| Body shape | rs114344942 | v5 only | T | -0.235 | 5.55E-79 |
| Body shape | rs62569478 | v5 only | C | -0.096 | 7.91E-11 |
| Chin dimple | rs75906140 | v5 only | A | -0.105 | 5.11E-09 |
| Crying while cutting onions | rs75859481 | v5 only | G | 0.028 | 9.33E-16 |
| Dandruff | rs62243065 | v5 only | T | 0.013 | 3.14E-09 |
| Earlobes | rs17068342 | v5 only | T | 0.079 | 2.22E-13 |
| Fear of public speaking | rs113229445 | v5 only | A | 0.057 | 6.07E-09 |
| Full stomach sneeze reflex | rs2308321 | v5 only | G | -0.132 | 8.95E-10 |
| Feeling hangry | rs7169404 | v5 only | T | -0.068 | 4.89E-08 |
| Hitchhiker's thumb | rs17404153 | v5 only | T | -0.066 | 5.97E-12 |
| Hoarding | rs62405860 | v5 only | C | 0.017 | 2.96E-16 |
| Eating leafy greens | rs3807714 | v5 only | G | -0.024 | 2.08E-18 |
| Mosquito bite itch | rs12440878 | v5 only | A | 0.028 | 7.36E-12 |
| Mosquito bite itch | rs74606019 | v5 only | C | 0.025 | 8.52E-09 |
| Sprint vs. distance | rs17672692 | v5 only | T | -0.027 | 5.39E-10 |
| Sprint vs. distance | rs2562762 | v5 only | G | -0.027 | 4.11E-09 |
| Sprint vs. distance | rs12912713 | v5 only | C | -0.030 | 2.26E-13 |
| Stretch marks | rs114344942 | v5 only | T | -0.065 | 1.12E-10 |
| Sweat during a workout | rs117334853 | v5 only | G | 0.033 | 3.34E-08 |
| Sweet vs. salty (salt preference) | rs78329842 | v5 only | G | -0.039 | 9.29E-09 |
| Sweet vs. salty (sweet preference) | rs3807714 | v5 only | G | 0.030 | 2.65E-15 |
| Sweet vs. salty (salt preference) | rs61740705 | v5 only | G | -0.025 | 2.74E-08 |

| | | | | | |
|---|---|---|---|---|---|
| Fear of heights | rs13097409 | v5 and pre-v5 | G | -0.030 | 4.19E-10 |
| Fear of heights | rs1566479 | v5 and pre-v5 | C | -0.022 | 7.02E-09 |
| Blushing | rs4849721 | v5 and pre-v5 | T | -0.044 | 1.49E-13 |
| Chocolate preference | rs11213819 | v5 and pre-v5 | T | -0.060 | 2.08E-18 |
| Dandruff | rs3818532 | v5 and pre-v5 | G | 0.013 | 3.24E-09 |
| Dark chocolate sneeze reflex | rs11213819 | v5 and pre-v5 | T | -0.222 | 4.91E-20 |
| Sense of direction | rs1364405 | v5 and pre-v5 | A | -0.028 | 1.30E-10 |
| Sprint vs. distance | rs3818532 | v5 and pre-v5 | G | -0.026 | 6.58E-11 |
| Sweat during a workout | rs4849721 | v5 and pre-v5 | T | 0.043 | 1.59E-54 |

## Discussion

The 23andMe Neanderthal report offers 23andMe customers a detailed look at their Neanderthal ancestry by looking at a set of Neanderthal-derived variants. While the Neanderthal report does not provide a customer's overall "percent Neanderthal," it instead provides a detailed map of Neanderthal ancestry and GWAS-based clues regarding how this ancestry might influence traits. Although we are confident that the variants tested for in the Neanderthal report represent signals of Neanderthal ancestry, it is important to note that they represent only a fraction of the total amount of Neanderthal ancestry an individual carries.

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## Revision History

July 24, 2020

- This white paper reflects a change in the methodology for inferring associations between Neanderthal DNA variants and a select group of traits, involving: a dramatically expanded list of trait associations for customers genotyped on the v5 chip, and new parameters by which we selected trait associations to highlight in customers' reports. It replaces the previous 23andMe Neanderthal white paper published on October 20, 2015.

October 20, 2015

- This white paper reflects a fundamental change in the presentation and methodology for inferring Neanderthal ancestry. It replaces the previous 23andMe Neanderthal white paper published on December 5, 2011 (last edited on January 8, 2012), which addressed the calculation of a customer's percentage of Neanderthal DNA. The new method for inferring Neanderthal ancestry

reflected in this white paper counts the number of genetic variants of Neanderthal origin and associations between these variants and a select group of traits.

December 8, 2015

- This minor revision clarifies several aspects of the methodology employed by the new Neanderthal ancestry report.