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The *NF1* Gene in Early Modern Humans

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Background: In this study we consider two points regarding the antiquity and function of the human *NF1* wild type (WT) allele. First, keying off recent publications that have suggested diagnoses of either NF1 or NF2 for the 28,000 year-old early modern human Cro-Magnon 1 specimen, we explore additional evidence that may clarify the diagnosis.[1,2] Second, increasing data suggest that many unique characteristics of modern humans reflect the presence and impact of the modern human WT allele of the ubiquitous eukaryotic Supergene, *NF1.* Originally identified via mutations accounting for the NF1 syndrome, recent studies have also revealed correlations between certain modern human NF1 alleles and social, learning, and musical abilities;[3,4] as well as risks for obesity,[5] diabetes mellitus,[6] alcoholism,[7] and opiate addiction.[8] Neandertal, Denisovan, ancient modern human, and other primate DNA and amino acid (aa) sequences are now available for comparison, offering insights into the antiquity of, and potential functional differences between, human *NF1* WT and ancestral alleles.

Methods: Distinguishing between NF1 and NF2 diagnoses in DNA-poor skeletal remains is complicated by the modest, Schwann-cell-proliferation-related, overlap in presentation between the two syndromes. One phenotype that is associated exclusively with NF1 is macrocephaly, which is defined as a cranial circumference greater than two standard deviations above the mean.[9] Early modern human cranial circumference data are scarce; thus, endocranial volumes of Cro-Magnon 1 and 64 other early modern human specimens were compared. Neurofibromin aa sequences for modern humans and a variety of other primates were also compared, as were the *NF1* coding sequences for today's modern humans, two Neandertals, a Denisovan, and an early modern human.

Results: The endocranial volume for Cro-Magnon 1 is greater than two standard deviations above the mean for early modern humans, supporting the NF1 diagnosis (Fig. 1).[10] Contrary to previous reports,[11,12] we find that the *NF1* human WT allele encodes a neurofibromin protein that exhibits one aa difference from both common and bonobo chimpanzees (*Pan troglodytes* and *Pan paniscus*). In the 2839 aa human neurofibromin Isoform 1, humans have a serine (S) at position 2484, while chimpanzees have a threonine (T) in the same position in their corresponding neurofibromin isoforms (Fig. 2).[13] The 1000 Genomes Project lists only two reported DNA mutations in the associated human codon: one synonymous, and one somatic (in tumor tissue).[14] Neurofibromin sequences for all other primates available in GenBank share T2484 with the chimpanzee, although other areas of the neurofibromin sequence vary among primates, including between all ape species except the two chimps (Fig. 3).[13] The ancient DNA sequences for the two Neandertals, the Denisovan, and the early modern human also share the modern human WT allele (Fig 4).[15] The chimp-human aa difference occurs within a phosphorylation site and the human form is predicted (via NetPhos 3.1) to elicit a slight increase in overall phosphorylation potential within a 19 aa region (9 aa on either side of 2484), and a decreased affinity for certain kinases (i.e., EGFR, PKC, PKG, and SRC).[16] The effects of these differences in phosphorylation potential are as yet unknown and warrant further study.

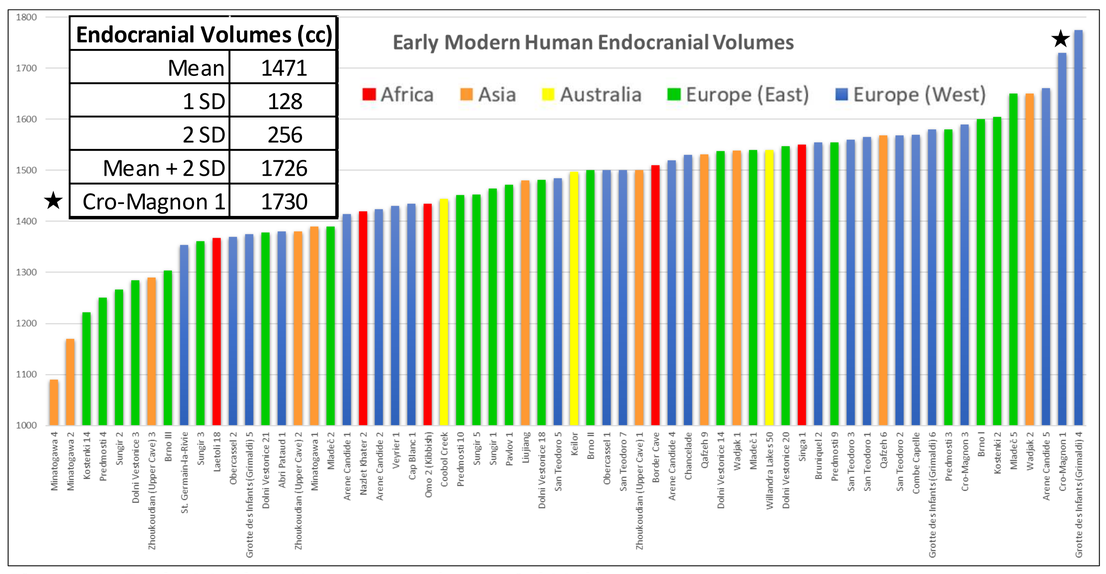

Figure 1. Early Modern Human Endocranial Volumes

Figure 2. GenBank Blast Results Showing Human and Chimpanzee Neurofibromin Variants

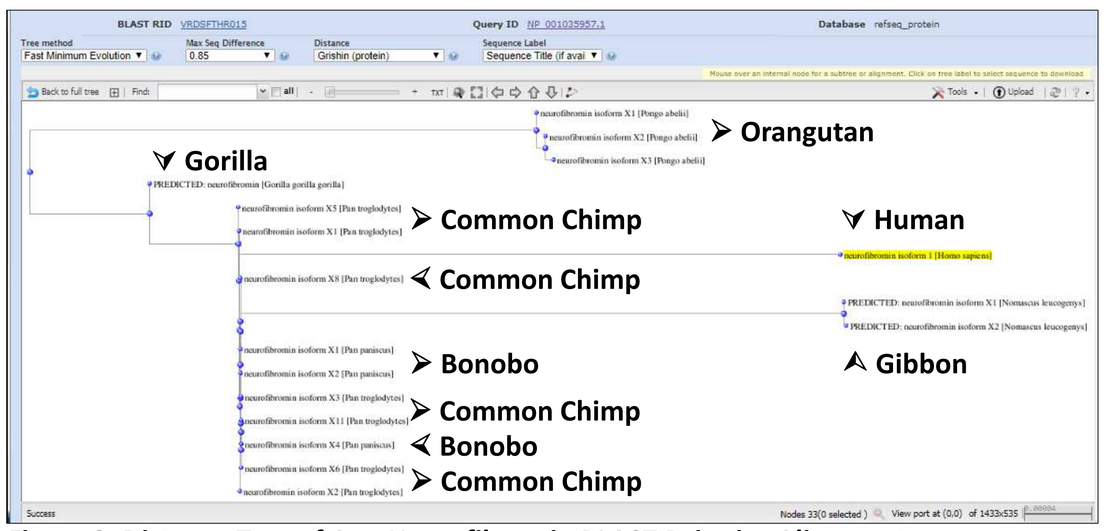

Figure 3. Distance Tree of Ape Neurofibromin BLAST Pairwise Alignments

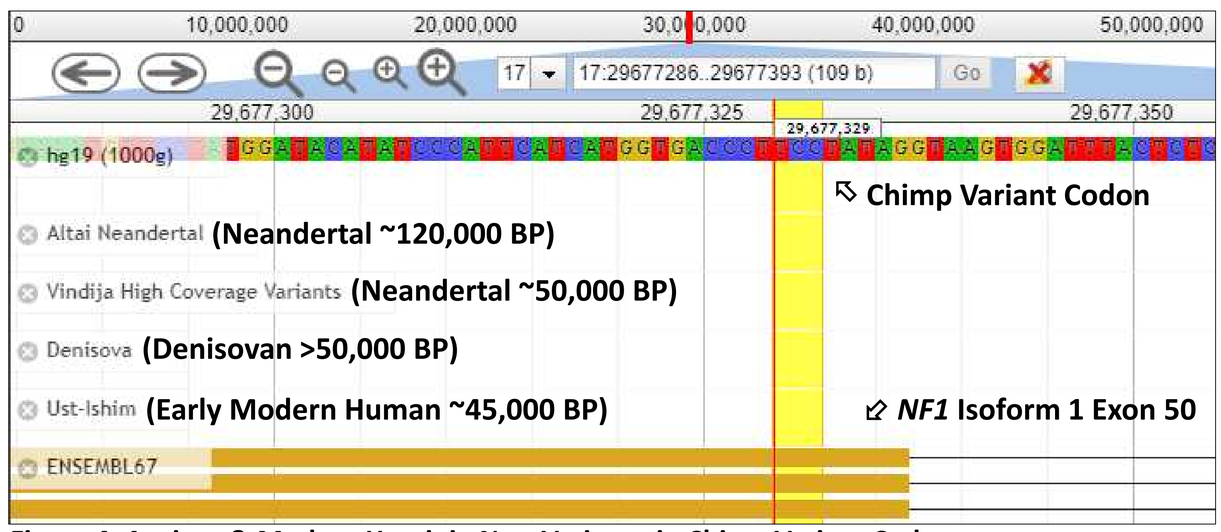

Figure 4. Ancient & Modern Hominin Non-Variance in Chimp Variant Codon

Conclusions: This study has documented new evidence supporting a Cro-Magnon 1 NF1 diagnosis and has explored available evidence regarding the antiquity of the unique human WT *NF1* allele, including one aspect that may impact regulatory function. This supports previous research indicating that NF1 may provide a genetic mechanism for "finessing" multiple elements of the modern human phenotype.[3-8] As we learn more about how WT *NF1* enhances modern humans we will improve both the clinical management of those bearing pathogenic *NF1* alleles and the health and well-being of the general population, as well.

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