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HOT TOPICS

"Archealization" of human brain organoids

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The fossil record has revealed many hominin lineage branches during evolution, but only *Homo sapiens* survived to the present. Neanderthals and Denisovans, two extinct lineages, are our closest evolutionary relatives. While the fossil record can reveal information about their anatomy and lifestyle, it cannot provide information about how their brains develop. Phenotypic data is only possible from comparisons between humans and living primates, underscoring differences in brain development that have evolved since our last common ancestor around 6 million years ago [1]. However, recent evolutionary changes in brain development—such as those differentiating us from our extinct relatives, could not be studied due to the lack of soft tissue.

Ancient DNA sequencing has opened the door for comparative paleogenomics, providing the genetic information of our closest relatives. Most of the comparative genetics between archaic and modern humans has been on introgressed genomic sites [2]. These are regions in our genomes where modern humans have adopted archaic elements via ancestral interbreeding and admixture. While many research focuses have been on these introgressed sites' clinical benefits and consequences, studying the sites where modern and archaic humans diverge can be of important clinical value.

We have recently performed a comprehensive analysis of genetic variation available from diverse modern human populations, revealing that only 61 non-synonymous, derived coding variants are fixed or nearly fixed in modern humans [3] (Fig. 1A). Of these candidates, the Neuro-Oncological Ventral Antigen 1 (NOVA1) is a disease-related RNA binding protein that contains a non-synonymous change not seen in the Neanderthal or Denisovan genomes (Fig. 1B). We have selected *NOVA1* because this gene is activated during neural development and influences the expression and splicing of hundreds of downstream genes, increasing the chances to alter neurodevelopment. To study the functional significance of NOVA1 amino acid change, the modern human *NOVA1* was replaced with the archaic allele in human pluripotent stem cells. The stem cells were then differentiated into brain organoids, self-assembled tridimensional cellular structures that mimic human neurodevelopment [4]. The "archealization" (reversion to the archaic allele) of *NOVA1* in organoids led to early excitatory synaptic maturation [3]. Interestingly, the early maturation of cortical neurons carrying the archaic *NOVA1* mimics the behavior of chimpanzee-derived cortical neurons [5].

The study of human brain evolution using this novel "archealization" strategy might change our ability to understand and treat human-specific neurological disorders. Future directions in this field will include studying the other 60 genes, alone or in combination, plus the epistatic interactions with thousands of human-specific regulatory regions. Neurodevelopmental differences between species are essential components in evolutionary studies, as small changes in the timing of development can often turn into functional implications. Thus, just as understanding the evolutionary history of bipedalism has contextualized the hernias, hemorrhoids, varicose veins, spine disorders, osteoarthritis, uterine prolapse, and difficult childbirth experienced by humans today [6], so too will understanding the evolutionary history of brain

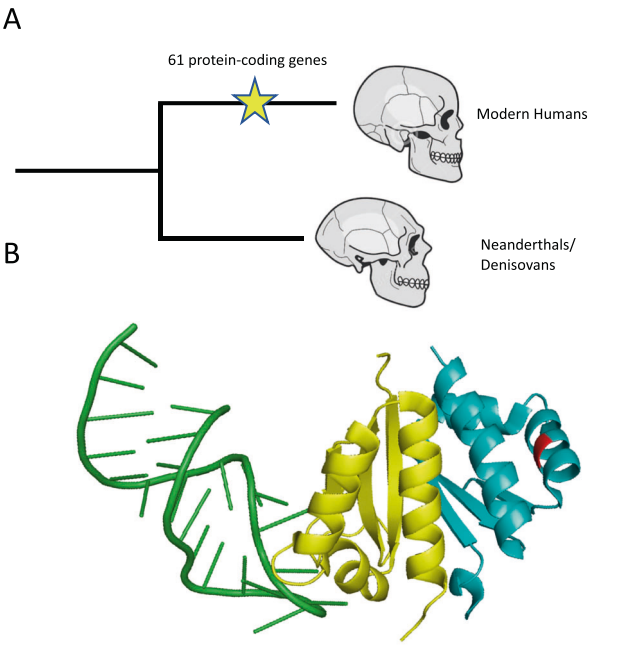

Fig. 1 Genomic differences between modern and extinct humans. **A** Phylogeny of modern humans and Neanderthals/Denisovans, revealing the 61 genetic variants that are specific to modern humans [3]. **B** Tertiary partial structure of NOVA1, highlighting the KH1 (yellow) and KH2 (blue) domains binding to RNA (green). Both NOVA1 domains can simultaneously bind to RNA molecules. The location of the amino acid change between modern and extinct humans is shown in red. The archaic version of NOVA1 mis-regulate the expression and splicing of hundreds downstream genes, affecting human neurodevelopment [3].

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development illuminate conditions, such as autism, schizophrenia, speech and language disorders, learning disabilities among others. Defining the contribution of archaic alleles will provide a leap in our further understanding of the origins of modern neurological conditions.

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COMPETING INTERESTS

ARM is a co-founder and has equity interest in TISMOO, a company dedicated to genetic analysis and brain organoid modeling focusing on therapeutic applications customized for autism spectrum disorder and other neurological disorders with genetic origins. The terms of this arrangement have been reviewed and approved by the University of California San Diego in accordance with its competing interests policies.

ADDITIONAL INFORMATION

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