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HOT TOPICS

Echoes of ancient DNA in living modern humans affect risk for neuropsychiatric disease and brain structure and function of networks subserving higher-order cognition

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New, ground-breaking technological advances have enabled sequencing of ancient DNA from fossil remains, revealing unprecedented insights into our evolutionary biology and genetic influences on neuropsychiatric disease. These methods have demonstrated that ancestors of modern humans mixed with Neanderthals, our closest evolutionary cousins, approximately 40,000–75,000 years ago [1, 2], leaving residual echoes in our DNA. This inheritance is not just an idle feature of our genome, but is indeed functional in modern humans, for example, imparting changes in keratin to help skin and hair adapt to non-African climates and associating with risk for autoimmune conditions [2].

These genetic remnants of admixture with Neanderthals also convey Neanderthal-like phenotypes on modern humans. Specifically, living individuals harboring more Neanderthal-derived genetic variation have skull shapes that more resemble Neanderthal cranial remains, and brain regions underlying these skull shape changes exhibit structural variation that relates to the degree of Neanderthal introgression [3]. Further, through recent resting-state functional MRI analyses, these same brain regions show functional connectivity patterns of increased cooperativity between an important evolutionarily-conserved hub, the intraparietal cortex, with neural circuits responsible for visual processing; in contrast, connectivity with social processing networks was decreased [4]. These results suggest that Neanderthal admixture differentially affects brain systems responsible for higher-order cognitive abilities.

Further, some genomic regions inherited from Neanderthals overlap with regions implicated through GWAS studies as harboring risk for schizophrenia [1], potentially consistent with long-held beliefs that the evolutionary origins of schizophrenia developed in modern humans with the emergence of higher-order cognitive abilities.

We tested the hypothesis that schizophrenia is a human-specific condition by investigating the link between ancient DNA and risk for the disease [5], and showed that individuals with schizophrenia are endowed with less Neanderthal-derived genetic variation than unaffected individuals. Moreover, among individuals affected with schizophrenia, those patients with more Neanderthal admixture show less severe psychotic symptoms. Additionally, using 18F-Fluordopa PET imaging, we demonstrated that the degree of Neanderthal-derived variation was significantly related to dopamine synthesis capacity in both the pons and striatum, such that individuals with greater Neanderthal introgression had lower striatal dopamine synthesis capacity, suggesting a neurobiological mechanism underlying the associations with schizophrenia risk [5].

Other work using translational models has highlighted the application of Neanderthal-derived genetic information to in vitro experiments. For example, a genetic variant found in Neanderthals was introduced into human induced pluripotent stem cells using CRISPER-Cas9 methods; the introduction of this archaic variant significantly affected the morphology and neural function of cortical organoids [6]. Taken together, through in vivo and in vitro experiments, genetic variation derived from admixture with Neanderthals has been shown to affect neural morphology and function in modern humans, and also to impact higher-order cognitive abilities and risk for neuropsychiatric disease. Though work in this domain is still in its infancy and gaps in knowledge surrounding neuropsychiatric impacts of ancient DNA remain, continued investigation promises to provide a lens through which we may gain insights into who we are as a species, our remarkable interindividual variability, and what may go awry to produce serious neuropsychiatric diseases.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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