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EVOLUTIONARY GENETICS

Haunted by the past — modern consequences of Neanderthal DNA

An accumulating wealth of DNA sequencing data from ancient and modern humans has uncovered multiple historic phases of interbreeding that have left a considerable fraction (~1.5–4%) of Neanderthal DNA in modern human genomes. A new study takes advantage of the matched genotypes and medical records of modern humans to uncover the impact of Neanderthal DNA remnants on medically relevant human traits.

Since the identification of Neanderthal-derived DNA in modern human genomes, a major goal has been to understand its functional consequences. To date, Neanderthal DNA has been associated with specific human adaptations or individual traits, such as skin and hair phenotypes, lipid metabolism and depression, on the basis of the types of genes found in Neanderthal-derived genomic regions. Simonti *et al.* sought a comprehensive assessment of the impact of Neanderthal-derived DNA genome-wide on diverse human medical traits. They used a set of ~6,000 Neanderthal-derived haplotypes — which had been previously identified based on comparisons between the Atlai Neanderthal genome and modern human genomes from the 1000 Genomes Project — and extracted a set of 1,495 common Neanderthal single-nucleotide polymorphisms (SNPs). To gain insight into the phenotypic effects of these Neanderthal SNPs, they analysed data from ~28,000 human adults of European ancestry in the Electronic Medical Records and Genomics (eMERGE) Network. The eMERGE Network contains SNP genotype data, accompanied by de-identified clinical phenotypic data from electronic health records (EHRs). Individuals were already subdivided approximately equally between phases 1 and 2 of the eMERGE Network, which allowed the investigators to use separate discovery and validation cohorts for statistical robustness.

Initial analyses used genome-wide complex trait analysis (GCTA) to quantitatively assess the contribution of Neanderthal SNPs genome-wide to the risk of 46 EHR-derived traits that are related to previously proposed Neanderthal-associated phenotypes. These analyses supported links to traits such as mood disorders, depression, obesity and different types of keratosis. The most significant associations were for mood disorders and depression, for which Neanderthal SNPs can explain up to ~1% of the risk. Analysing the genomic locations of the subset of Neanderthal SNPs most associated with the traits revealed plausible biological mechanisms: for depression, SNPs were enriched in circadian clock, cell migration and neurological disease genes, whereas for actinic keratosis, SNPs were enriched in keratinocyte differentiation and immune function genes.

To analyse additional traits beyond those with previous Neanderthal links, the authors carried out a phenome-wide association study (PheWAS), in which the 1,495 Neanderthal SNPs were tested individually for association with 1,152 diverse EHR-derived phenotypes. One finding was a SNP in an intron of the coagulation gene P-selectin (*SELP*) that was associated with a hypercoagulable state, and data from the Genotype–Tissue expression (GTEx) Project indicated that the Neanderthal SNP increases *SELP* expression. Additionally, a SNP in an intron of solute carrier family 35 member F3 (*SLC35F3*), a putative thiamine transporter, was associated with malnutrition. Beyond these individual associations, the PheWAS revealed that Neanderthal SNPs were consistently associated with neurological and psychiatric phenotypes, and expression quantitative trait locus (eQTL) analysis revealed an influence of Neanderthal SNPs on gene expression in the brain.

Overall, this study underscores the modest but significant functional consequences of Neanderthal-derived DNA for modern human health, especially for influencing psychiatric traits. The continued presence of these alleles might be due to their historical benefit or tolerance in the environmental conditions experienced by ancestral humans migrating out of Africa. For example, depression SNPs (especially those affecting circadian clock genes) and skin phenotype SNPs are possibly relevant to sun exposure at different latitudes; blood-coagulation SNPs may have been involved in the defence against historic pathogens; and SNPs associated with lipid or thiamine metabolism might have been beneficial for the diets at the time. Future studies are likely to provide further insight into the molecular underpinnings of these associations.

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ORIGINAL ARTICLE Simonti, C. N. *et al.* The phenotypic legacy of admixture between modern humans and Neandertals. *Science* **351**, 737–741 (2016)

FURTHER READING Racimo, F. *et al.* Evidence for archaic adaptive introgression in humans. *Nat. Rev. Genet.* **16**, 359–371 (2015) | Bush, W. S., Oetjens, M. T. & Crawford, D. C. Unravelling the human genome-phenome relationship using phenome-wide association studies. *Nat. Rev. Genet.* **17**, 129–145 (2016)