

Association between changes in lipid catabolism and increased gene flow from Neanderthals to Europeans

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Neanderthals and modern humans diverged from the same ancestral species approximately 800 to 400 thousand years ago. After the species' separation, Neanderthals left African continent and colonized Europe, Central Asia and might have spread far into the Asian continent. Modern humans spread quickly throughout all continents and co-existed with Neanderthals in Europe and Asia until Neanderthal extinction.

While Neanderthals are extinct, fragments of their genome might still persist in the genomes of contemporary humans living outside of Africa. Our study shows that although Neanderthal-like genomic regions averagely occupy the same percentage in all out-of-Africa human individuals, their distribution varies among human populations. Specifically, contemporary humans of European decent show greater concentration of Neanderthal-like sequences in specific functional categories. Genes involved in lipid catabolism contain large excess Neanderthal-like sequences in Europeans (gene flow estimate: 24.3%), but not in Asians (12.4%), while both values were greater than the genome average (6%). We speculate that genetic changes that evolved on the Neanderthal evolutionary lineage gave ancestors of modern Europeans a certain selective advantage, possibly due to shared environmental conditions.

While lipid catabolism cannot be assayed in Neanderthals, we took advantage of genetic divergence between human populations, chimpanzees and Neanderthals to predict metabolic divergence expected from the observed excess of Neanderthal gene flow. We confirmed predicted changes in lipid catabolism using hydrophobic metabolome measurements in the

human and chimpanzee brains and further linked these metabolic changes to gene expression divergence. Further studies investigating Neanderthal gene flow distribution in contemporary human populations are needed to test this hypothesis and elucidate its functional implications.

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