Infectious disease defenses among ancient hominid contributions to adaptation of modern humans

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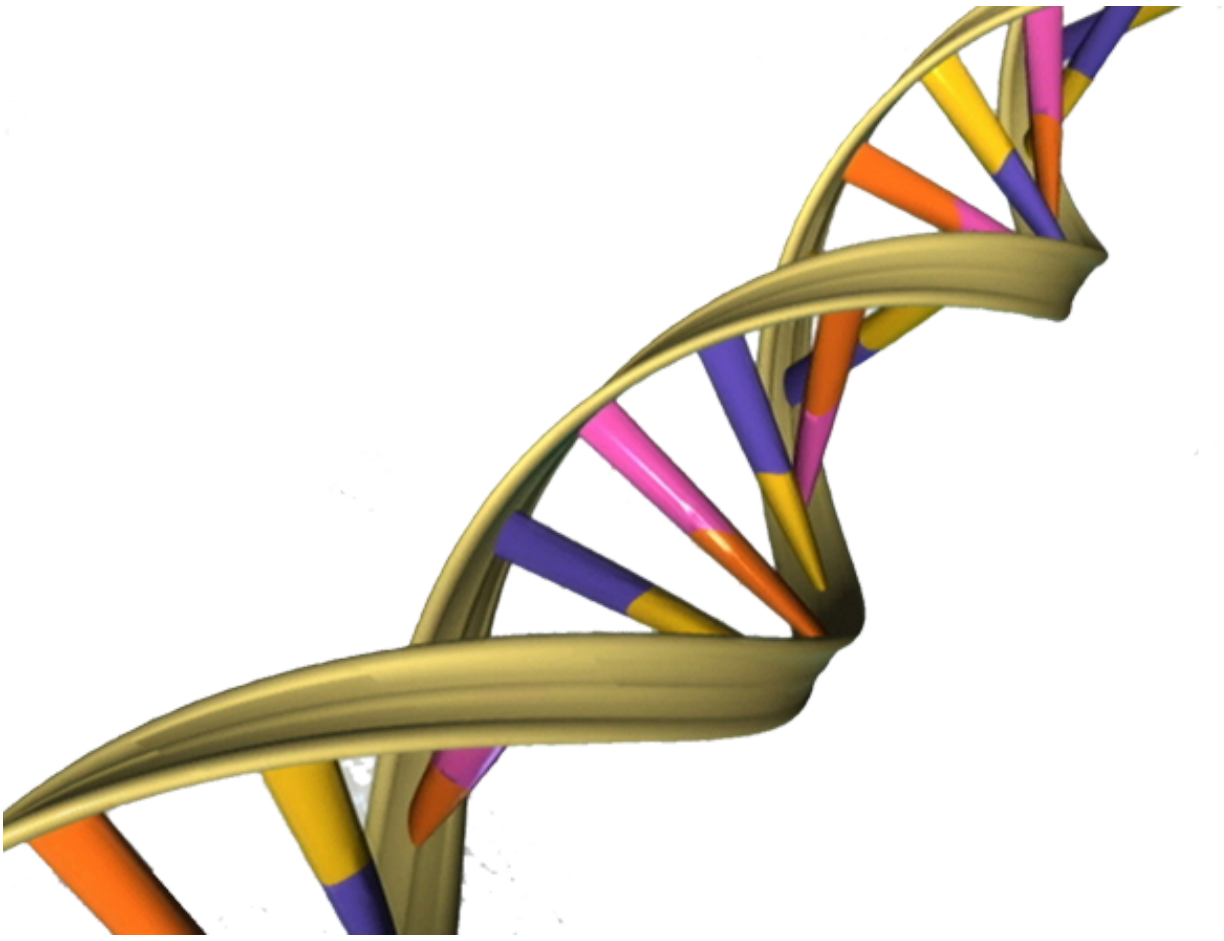

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

During the past decade, our human evolutionary tree has turned into something more resembling an unwieldy bush. Scientists have discovered swapped segments of DNA that we shared from mating between two other hominids, Neanderthals and Denisovans, which were first sequenced in 2010 and 2014, respectively.

How much of our hominid cousins remains in each of us today, and whether or not the presence of ancient hominid DNA has conferred any adaptation advantages or disadvantages has been a prime area of exploration.

Scientists have shown that single hominid genes can convey advantages, including a famous case of high-altitude adaption, which was the result of DNA swapping, otherwise known as genomic introgression, of a Denisovan for the gene EPAS1. That discovery may help explain why Tibetans are uniquely adapted to high-altitude living.

But since most diseases are likely are result of multiple genes and often exhibit complex traits, unpacking ancient hominid contributions to our genomes has been a difficult task.

Now, in a new study published in the advanced online edition of *Molecular Biology and Evolution*, scientists Alexandre Gouy and Laurent Excoffier have developed new computational tools to better analyze human genome datasets, and found more evidence of a legacy of ancient hominid adaptation, particularly to help fight off infectious diseases like malaria.

"Our results confirm that archaic introgression is widespread in immunity-related genes and that pathogens represent a strong selective pressure which could be one of the major causes of adaptive evolution in humans," said the authors. "Overall, our results suggest that archaic introgression has affected human metabolism and response to different

types of pathogens (bacteria, virus and protists), which have been critically determinant during human adaptive history," said Excoffier.

In this study, the duo analyzed the latest archaic introgression maps that have been recently made available for 35 Melanesian individuals as well as samples from the 1000 Genomes project.

"Our results show not only that introgression is found at many genes involved in the same functions, but also that some of these interacting genes carrying archaic DNA have been co-selected," said Gouy.

Rather than analyze individual genes, they set about focusing on methods to detect patterns of introgression based on biological pathway analysis and data sets of connected genes and subnetworks.

They were able to identify highly introgressed subnetworks among three primary biological pathway databases (KEGG, NCI and Reactome), and among each of the three populations they looked at, including East Asians, Europeans and Papua New Guineans.

One of the more striking areas of evidence of possible resistance to malaria among the Papua New Guineans.

"One of the most striking areas of evidence of adaptive introgression is a possible resistance to malaria among Papua New Guineans," said Excoffier.

Also, beyond infectious disease, they also found evidence of introgression in genes related to porphyrins that are involved in energy metabolism (respiratory chain) and iron and oxygen binding in red blood cells (hemoglobin) and muscles (myoglobin), as well as in olfactory receptors showing signals of Neandertal introgression among modern European populations.

One of the more strongly controversial areas is the development of modern human behavior and cognition. Though the authors caution the work is still very preliminary, they did find evidence of introgression among gene networks involved in such functions.

"These results suggest that archaic introgression might have also affected behavioral/neuronal traits, even though it is difficult to link these phenotypes to a precise selective pressure."

Their results build on other studies that have identified Neanderthal variants at two SLC loci (SLC6A11, SLC6A13) that have previously been associated with behavioral traits (depression, mood disorders, smoking behavior) and some gene variants that have been shown to be preferentially expressed in the brain.

"In Papuans, we also found genes showing a significant excess of introgression that have been respectively associated to autism susceptibility and attention deficit/hyperactivity disorder, e.g. SLC9A9," said Gouy. They also reported on other genes from the same family that have a brain-biased expression and show an excess of introgressed segments in East Asians and Europeans, including SLC6A1 (a GABA transporter), SLC6A5 (a neurotransmitter transporter) and SLC28A1, as well as in Papua New Guineans, with SLC4A10 (controlling intracellular pH of neurons and brain extracellular fluid).

Further explorations of these areas of influence will be needed to tease out their contributions to human health and disease.

Even though the overall amount of Neandertal and Denisovan introgression is quite low in modern humans (typically 1-3%), their evidence continues to build the scientific case that the hominid DNA that remains has helped shaped modern human adaptation. It also suggests that these hominid windows into the past have a strong impact

and continue to exert their influence on the present fitness of modern humans.

More information: Alexandre Gouy et al, Polygenic patterns of adaptive introgression in modern humans are mainly shaped by response to pathogens, *Molecular Biology and Evolution* (2019). DOI: 10.1093/molbev/msz306

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