# A 300,000 Year History of Human Evolution

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Anatomically modern humans evolved in Africa around 300,000 years ago. Like all species, our history since then has been strongly shaped by evolutionary forces, but until recently this genetic legacy has remained enigmatic. However, in recent years the power of whole genome sequencing, combined with remarkable palaeontological discoveries, has started to reveal some of the major events that have shaped modern humans. In this lecture, we will lift the lid on some of those findings and, in doing so, discover some of the unexpected ways that these ancestral events may still impact on our day-to-day lives in the 21st century.

## It's all in the genes…

Evolution is about successful reproduction. Genes are passed to our offspring, their offspring, and so on down the generations. Consequently, genetic changes that enhance either fertility or the survival of progeny to reproductive age will be strongly selected for, whilst traits which lead to higher infant mortality will be rapidly eradicated from the population by natural selection. Using this knowledge, we can interrogate modern human genomes and look for genes that are either 'missing' or over-represented and thereby infer the selective pressures that our ancestors may have experienced.

Just over a decade ago, pioneering DNA sequencing approaches produced a near-complete genome sequence for our extinct relatives, the Neanderthals, and for a hitherto unknown second group of hominins, the Denisovans. This analysis also produced incontrovertible evidence of interbreeding between *Homo sapiens* and these two extinct lineages. In the years since that discovery, the genomic revolution has led thousands of us to have our own genomes sequenced, shedding light on our individual differences but also providing an invaluable resource for mapping the evolution of our species.

We can use this wealth of genomic data to look for genes that entered the *Homo sapiens* population via interbreeding with Neanderthals and Denisovans (a process known as introgression). These genes will be inherited more or less randomly if they have no direct effect on the survival of their 'host'. But a Neanderthal gene that confers a survival advantage on its new human host will be inherited slightly more often than expected by chance, whilst a deleterious gene will be lost from the population at a rate that reflects how significantly it reduces the ability of the host to successfully reproduce.

## Winning and losing the genetic lottery

Such a pattern is immediately visible in modern human genomes. Although most Eurasians derive about 2% of their genome from Neanderthals, there are regions of the genome that are devoid of any Neanderthal DNA – so called 'genomic deserts' – and others which are disproportionately enriched for Neanderthal sequences.

One Neanderthal desert lies on chromosome 7, in a region which includes the gene *FoxP2*. *FoxP2* plays a critical role in language skills and rapid evolution of this gene is thought to have underpinned the acquisition of advanced communication by early humans. If we assume that Neanderthal linguistic abilities were inferior to early *Homo sapiens*, then, it seems reasonable to assume that inheriting the Neanderthal 'version' of FoxP2 might lead to language impairment – presumably a significant disadvantage in terms of both survival and reproduction, thereby accounting for the absence of Neanderthal sequences in this region of the

genome.

Conversely, there is a region on chromosome 12 of modern humans in which more of us carry Neanderthal sequences than would be expected by chance, suggesting that Neanderthal gene(s) lying in this segment have conferred an advantage on the individuals carrying them. When we look more closely, this region contains three related genes – *OAS1, 2* and *3* – that are known to be important in driving immunity to viruses. And indeed during laboratory tests, these Neanderthal versions of the *OAS* genes trigger a more robust response to infections such as West Nile virus or Hepatitis C than their *Homo sapiens* counterparts. Most surprisingly, during the Covid-19 pandemic it became apparent that people carrying the 'Neanderthal' version of *OAS3* had a significantly lower risk of developing severe Covid symptoms – a remarkable demonstration of how modern human life is still being shaped by historical evolutionary forces.

## Evolution spawns evolution

For the majority of our history, humans have been nomadic hunter-gatherers. But around 10-12,000 years ago, small groups of humans started to return to the same locations repeatedly, creating settlements. Probably as a result of spillage of gathered fruits and seeds, edible crops started to spring up around these sites, starting humanity's journey towards agriculture and, ultimately, urbanisation.

These earliest agricultural developments have been most intensely studied in the 'Fertile Crescent' – an area of the Middle East that today encompasses parts of Egypt, Iraq, Israel, Syria and Turkey. But we now know that agriculture was also being developed in parallel in the Americas and Asia – albeit with a different set of crop plants. Regardless of where it was occurring, however, the transition from roaming hunter-gatherers to sedentary agriculturalists had a profound effect on human evolution. Although one might intuitively think that the development of agriculture would have improved human health, in fact there is ample evidence that it initially had a negative impact on our species, reducing dietary diversity, micronutrient availability and overall nutritional balance. In addition, the domestication of livestock brought us into close association with many animal species, exposing us (and them) to a new range of pathogens. Finally, the development of agriculture went hand in hand with the development of villages, towns and ultimately cities. As we have all experienced first hand in recent years with the Covid-19 pandemic, large groups of humans living in close proximity are the ideal conditions for outbreaks, and so the agricultural revolution opened the door to repeated waves of disease which grew larger and more devastating as the human population expanded.

These profound lifestyle changes exerted a potent selective force on the human population – something that is still visible in our genomes today. One example of this is *OCTN1*. Like many parts of our DNA, this gene varies in sequence between individuals. One particular sequence difference leads to increased production of the corresponding protein, whose role is to help take up a range of small molecules including the amino acid ergothioneine. Ergothioneine is made by only a small number of organisms, not including humans, so we have to absorb this nutrient from our diet. The loss of dietary diversity that resulted from the transition to agriculture is likely to have resulted in ergothioneine insufficiency in early humans. As a result, those individuals with a more efficient uptake pathway, driven by the *OCTN1* gene variant, would have had a survival advantage, ultimately leading to the abundance of this particular variant in modern human populations.

## Plagues and pandemics

Evolution is a slow process and consequently the impact of evolutionary events is usually discernible only on a timescale of many thousands of years. But occasionally, events of such catastrophic magnitude occur that they leave a clear genetic fingerprint over much shorter timescales.

Such an event has been the emergence of bubonic plague. We do not know when this disease first entered the human population, but its preferred transmission route via infected fleas made it ideally adapted to densely populated human settlements and their co-occupying rodents. As cities grew, and trade between them increased, it became ever easier for the plague bacterium, *Yersinia pestis*, to spread swiftly and devastatingly across large geographical areas. In the year 541, the Plague of Justinian swept around the Mediterranean coastline, leaving an estimated 25% of the population dead. A similarly devastating pandemic in 1348-1350 crossed mediaeval Europe in a wave of destruction that became known as The Black Death, killing an estimated 30-60% of the population.

With such massive mortality, evolutionary theory predicts that any genetic variant providing even a small level of resistance would rapidly become abundant in the survivor population. And, just as predicted, examples of such genes abound in the modern human genome. In fact, applying quantitative analysis to the entire human genome to identify genes that have been under strong, recent selective pressure produces a list that is heavily dominated by large families of genes that regulate immunity, such as the *TLR*, *MHC* or *ERAP* gene families. In most cases, the selective survival advantage during the Bubonic plague resulted from increased activity of the corresponding protein; in other words, a more active immune response. But, like many aspects of biology, a more active immune response comes at a cost. In our modern, plague-free existence, these same hyperactive immune gene variants are associate with increased risk of autoimmune disorders such as rheumatoid arthritis – the painful price of past evolutionary success.

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