Neanderthals and Denisovans as biological invaders

John Hawks[a,1]

Humans stand out among our close primate relatives as effective biological invaders. Our recent history has included range expansions into remote and harsh geographic regions, and invasions by some populations into areas long occupied by others. Historians tend to frame these events as a story of technological and economic progress, while admitting that disease sometimes plays a central part—a triad made memorable by *Guns, Germs, and Steel: The Fates of Human Societies* (1). Ancient DNA is revealing a deeper prehistory of human dispersals, however, showing continuity with invasions as understood by biologists, not just historians. Now, in PNAS, Rogers et al. (2) find that not only modern humans but also Neanderthals and Denisovans may share a surprisingly invasive origin.

The story of Neanderthal and Denisovan origins has developed rapidly during the past 7 y. Two high-coverage genomes, and more fragmentary genome data from a handful of other individuals, have yielded powerful insights about the diversity of these ancient groups and their legacy of genetic introgression into recent humans (3). These archaic populations share a deep common history, and individual genomes record a history of high inbreeding and low gene flow across their ancient geographic ranges (4, 5). In their new study, Rogers et al. (2) find that the common ancestral population of the Denisovans and Neanderthals underwent a tight bottleneck, immediately after this population diverged from the African ancestors of modern humans. This bottleneck was rapid, maybe only 300 generations, and the Neanderthal and Denisovan populations separated quickly thereafter.

This archaic human dispersal, which unfolded more than 600 ka, bears a striking parallel to the much later dispersal of modern humans from Africa into Eurasia after 100 ka. In both cases, the small bottleneck is etched into the genomes of all their descendants, and in both cases, this founder population quickly expanded its geographic range and divided into regional populations. Far from the stereotype of plodding, retrograde cavemen, the Neanderthals exhibited explosive dispersal and growth.

A growing synthesis of fossil and genetic data reveals the striking dynamism of these archaic people. Regional-scale dispersals among Neanderthals of the past 100,000 y may explain mitochondrial DNA (mtDNA) clade turnover at sites across Europe (6). Individual genomes show inbreeding and decline in local populations, but the variation across the Neanderthal range was relatively greater than across human populations occupying similar regions today (7). An early Neanderthal population represented at Sima de los Huesos, Spain, had different mtDNA from any later Neanderthals (8), meaning that all later Neanderthals inherited their mtDNA from a second episode of invasion and introgression from Africa (9). A later episode of introgression into Neanderthals from early modern humans is evidenced in Central Asia, but not later European Neanderthals (10). This already-complex picture depicts only the northern tier of the Neanderthal range and likely undersamples their variation; the morphologically diverse Late Pleistocene Neanderthals of Southwest Asia have not yet yielded ancient DNA evidence.

The Denisovans likewise had low local variation and high regional differentiation, evidenced by the genetic distance between the high-coverage genome of Denisova 3 and the Denisovan lineages that introgressed into the ancestors of Melanesian and Australian peoples (5). Ancient DNA evidence of Denisovans comes only from Denisova Cave itself, but population turnover is suggested by the high mtDNA and nuclear genome divergence of earlier and later specimens from this single site (11). The latest Denisovans received introgression both from Neanderthals and from an as-yet-unknown genetically divergent ghost population (4).

What made Neanderthals and Denisovans successful invaders? Twenty years ago, some archaeologists thought that the origin of both Neanderthal and modern human populations could be aligned with the origin and dispersal of technology. In this view, Neanderthals and modern humans emerged around 300 ka, at around the same time that Levallois reduction strategies supplanted the earlier

Acheulean. In this hypothesis, the Neanderthals built upon a Levallois technical heritage by developing Mousterian industries in western Eurasia, and ancestral modern humans developed Middle Stone Age (MSA) industries in Africa. Modern humans within Africa gradually developed yet more advanced technology based upon blades, which ultimately enabled a small group of them to invade Eurasia, supplanting the Neanderthals.

This hypothesis, still found in some textbooks, no longer fits the data. Genetic dates carry much uncertainty, but Neanderthals, Denisovans, and African modern humans diverged more than 200,000 y before the transition from Acheulean to MSA in Africa began. It is now a stretch to connect any technological innovation to Neanderthal and Denisovan origins. Some evidence suggests that Acheulean assemblages, characterized by handaxes and other large cutting tools, first entered Europe only around 600 ka, a possible coincidence with the earliest Neanderthals (12). However, Acheulean industries of India and Southwest Asia have much earlier dates. No known archaeological transition occurred across the plausible Neanderthal-Denisovan range at the time these populations first invaded Eurasia.

Many biological dimensions affect invasive potential in plants, insects, and vertebrates, including pathogen relaxation, life history traits, ecological tolerances, genetic diversity, and release of mutational load (13). Looking more broadly at such traits may help to explain both Neanderthal-Denisovan population dynamics and modern human invasions.

Mutation Load

During the portion of their existence sampled by ancient DNA, Neanderthals were subdivided into small populations with little genetic exchange (2, 3, 7). Inbreeding within these small populations imbued Neanderthal individuals with a higher fraction of deleterious mutations than living people (14). The substantial cost of this mutation load may explain the introgression bias against functional regions in the Neanderthal genome into modern human populations. Although Denisovans are known only from one locality, the high-coverage Denisova genome also indicates a lengthy history of inbreeding (5). Origins may be a different matter, however. A moderate bottleneck can purge deleterious alleles from a population, facilitating biological invasion in some cases (15). Modern humans in Eurasia and Neanderthal-Denisovan ancestors may have benefited from their founding bottlenecks, even as later Neanderthals and Denisovans suffered further deleterious mutations.

Consanguinity and Cooperation

Among social animals, aggressiveness and cooperativeness are strongly affected by the biological relationship of individuals. Founding bottlenecks can foster invasiveness by increasing the coefficient of relatedness, as seen in many biological invasions of social insects, for example, Argentine ants in North America, Europe, and Japan (16). Human cooperation is complex, but cultural and linguistic ties among individuals and groups are mediated by biological kinship. Many archaeologists have suggested that the successful dispersal of modern humans was more strongly influenced by social organization and cooperation than technology. This idea usually has been conceived as a biological ratchet, with progress in social organization and cooperation forming a stable equilibrium that is difficult to reverse. However, in a metapopulation of ancient humans, cooperativeness may have fluctuated across groups with different levels of connectivity and shared ancestry, declining as biological distance and intergroup aggression increased. Initially small, growing groups with high initial consanguinity might easily invade such a metapopulation.

Pathogen Relaxation

Prehistoric evidence about pathogens is sparse, and it was long assumed that epidemic diseases with high mortality costs only appeared within large agricultural populations of the Holocene. However, genetic evidence suggests that the "epidemiological transition" model does not adequately describe the importance of immunity in prehistory (17). Just as mutational load can have strong long-term effects on population growth or decline, so parasite and pathogen load can impact fertility and susceptibility to environmental stresses. Many adaptive genes acquired by introgression from Neanderthals and Denisovans involve immunity. Invasive species sometimes exhibit a "lag" between their first appearance in a new region and their subsequent rapid population growth, during which they may acquire new genes by introgression from resident populations. It is possible that Late Pleistocene modern humans followed a similar pattern, appearing in Southwest Asia more than 100,000 y ago, but taking some time before they dispersed further into Eurasia. Possibly that time was necessary to acquire Neanderthal and Denisovan genes modulating immunity to regional pathogens (17).

Life History Traits

Compared with living great apes, modern humans have short birth intervals, long maturation times, and long life spans. These life history traits reflect tradeoffs that may have influenced the invasion potential of hominin populations. Neanderthals and predispersal modern humans in the Levant both shared relatively high mortality among young adults, possibly limiting cultural transmission via older adults and thereby constraining ecological adaptability (18). Upper Paleolithic Europeans had much lower young adult mortality, possibly contributing to their population growth. As in the case of technology, life history evolution is often imagined as an evolutionary ratchet, but life history traits may have fluctuated under local or regional selection. Neanderthals themselves, sampled relatively late in their existence, had higher adult survivorship than earlier hominin populations, while maintaining faster growth and development than modern humans. Their life history may have been well-suited for rapid growth and dispersal.

From the beginning of our genus, *Homo* has exhibited both high invasive potential and periods of stasis. The initial dispersal of hominins into Eurasia preceded 1.8 Ma, and several distinct pulses of dispersal likely followed (19). The story of Eurasia is likely a minor one within the broad context of human evolution, centered in Africa, yet the fossil record is strikingly incomplete, as evidenced by the recent discovery of *Homo naledi* in the late Middle Pleistocene (20). Remarkably, if Rogers et al. (2) are correct that the common origin of modern humans, Neanderthals, and Denisovans is earlier than 600 ka, no known fossil in Africa or Southwest Asia provides a good candidate for this population. To make progress on these questions, we must find many more fossils in Africa, while making progress in ancient DNA sampling outside the northern tier of Eurasia.

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