12. Selection on mitochondrial DNA and the Neanderthal problem

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Abstract

At present, the direct evidence for Neanderthal genetic variation and gene phylogeny is limited to the control region of the mitochondrial DNA (mtDNA). Neanderthal mtDNA sequences are divergent from those of recent humans. This fact, when coupled with the assumptions of selective neutrality and a recently expanding human population, argues for the complete and utter extinction of Neanderthals without living issue. But an alternative hypothesis is that human mtDNA has recently undergone an episode of positive selection, or a "selective sweep." Five converging lines of evidence suggest that mtDNA has undergone recent positive selection: (1) mtDNA variants in living humans are associated with life history and metabolic traits that changed dramatically during recent human evolution; (2) Statistical tests show that the distribution of human mtDNA variation is clearly inconsistent with neutrality; (3) Nuclear genomic variation is not consistent with a single recent population expansion as necessary to explain human mtDNA variation; (4) A neutral mtDNA necessitates a population replacement to explain its pattern of variation, but many autosomal and X chromosomal loci show strong phylogeographic or genealogical evidence for the survival of archaic human gene lineages and therefore reject population replacement; and (5) Anatomical and archaeological evidence shows some degree of anatomical and behavioral continuity between Upper Paleolithic Neanderthals and later Europeans and likewise reject population replacement. The hypothesis of positive selection on mtDNA is in accord with recent estimates of genome-wide rates of selection and is contradicted by no known evidence. Molecular and comparative evidence further suggests that the current pattern of human mtDNA variation represents only the most recent episode of positive selection among many during human evolution. Selection on mtDNA cannot prove that other Neanderthal genomic lineages survived, although such survival may be suggested by other anatomical and genetic evidence. Nevertheless, the substantial probability of such selection renders Neanderthal mtDNA variation phylogenetically uninformative.

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Introduction

As Darwin recognized over a century ago, the most important force leading to the evolution of human populations has been natural selection. Molecular genetic discoveries during the past fifteen years have increasingly demonstrated the importance of adaptive evolution to the variation of human genes and their pattern of similarities and differences compared to other hominoid species. Some of the known genetic targets of selection are tabulated by Vallender and Lahn (2004), including many with roles in neurobiology, the developmental genetics of the skeleton, longevity, and other systems, that have changed substantially during human evolution.

Mitochondrial DNA (mtDNA) has a history of adaptive evolution in recent human populations (reviewed in Wallace, 2005a). This molecule is unique compared to most of the nuclear genome because of its lack of recombination, its clonal transmission, and its maternal pattern of inheritance. All of these factors reduce the expected diversity of the mtDNA within populations, and combine to ensure that any adaptive changes affect the variation of the entire molecule (Spuhler, 1989). On the other hand, the mtDNA has a relatively higher mutation rate than the nuclear genome (Wallace, 2005b). This high mutation rate tends to increase the genetic diversity within populations, but it also may increase the rate of both negative and positive selection. The mtDNA exists in each mitochondrion, meaning that there are thousands of copies in each cell (Wallace, 2005a). This high copy number makes it possible to extract mtDNA more reliably from degraded skeletal remains than nuclear DNA. But it also greatly increases the possibility of deleterious somatic mutations. From these considerations, the selective history of human mtDNA can be expected to be complex.

However, some of these same factors make genealogical reconstruction from mtDNA enormously simpler than for most nuclear genetic loci (Cann et al., 1987). It is possible to trace ancestry along the maternal line back to a single common ancestor for all humans. The high mutation rate means that close and distant relatives may be distinguished easily, even within the past few generations (Howell et al., 1996) – a fact that has enabled the growth of mtDNA genealogy testing services. Because they are clonal, these maternal lineages can be traced over thousands of years, enabling the examination of the relative maternal contribution of different ancient regions to recent populations. And the high copy number has made it possible to extract partial mtDNA sequences from the ancient skeletal remains of Neanderthals (Krings et al., 1997).

Study of these Neanderthal mtDNA sequences has shown them to be distinct from those of living humans in several ways. This distinctiveness is great enough to suggest that Neanderthal mtDNA variants probably do not survive today (Currat and Excoffier, 2004). Under the assumption that mtDNA has not been under selection across the intervening 30,000 or more years, the lack of any Neanderthal mtDNA lineages in living human populations is highly significant: it would indicate that any Neanderthal ancestry for living people must have been next to negligible (Currat and Excoffier, 2004; Weaver and Roseman, 2005). But this conclusion hinges on the assumption that mtDNA has in fact been selectively neutral during this time period.

There are good reasons to think that mtDNA has been significantly selected within the past 30,000 to 50,000 years or more. There are five lines of evidence leading to this conclusion:

1. Presently segregating mtDNA variants are associated with phenotypic variation in longevity, degenerative disease, mortality, metabolic efficiency, brain-related disorders, diet and climate.