Human Demography in the Pleistocene: Do Mitochondrial and Nuclear Genes Tell the Same Story?

Traditionally, research on modern human origins has centered on questions of the time and geographical place of origin, with less attention given to the complex population dynamics of our evolutionary history. Recently, however, a focus has emerged within molecular anthropology that concentrates on the demographic aspects of the origin of modern humans.[1-3] A popular hypothesis proposes that modern human populations passed through a bottleneck (or episodic reduction in size) in the late Middle or early Late Pleistocene, at which time there existed perhaps only several thousand breeding individuals, and that this was followed by a rapid, large expansion.[1,2,4] Supporting evidence comes largely from the pattern of DNA sequence variation observed in mitochondrial genes. However, because the mitochondrial genome is only a very small fraction of the entire genome, its evolutionary history is not necessarily concordant with the history of the bulk of the genome, the nuclear genome.

An important distinction can be made between evolutionary forces that affect just one locus and those forces that act on all the genes of a population. Population-level phenomena such as bottlenecks, expansions, population subdivisions, and speciation events are expected to produce similar patterns of genetic variation across many loci. In contrast, natural selection usually affects a small region of tight linkage, such as a single genetic locus. Therefore, hypotheses about population histories should be tested across many loci.[5-8]

HOW CAN DNA SEQUENCE VARIATION REVEAL DEMOGRAPHIC HISTORY?

Under the simplifying assumption that DNA sequence variation in the genomic region of interest is selectively neutral, the amount and pattern of nucleotide variation is expected to be proportional to the population size,[9] and to track changes in the population over time.[10-12] Another simplifying assumption that is often valid for the nuclear genome (and less so for the mitochondrial genome) is that mutations are rare at any one base position. For example, a common assumption that greatly facilitates the development of mathematical theory is the infinite-sites model whereby mutations are assumed to have occurred only once per polymorphic site.[13]

One way in which nucleotide variation can be described is by the frequency distribution of polymorphic sites within a genomic region. For example, when a nucleotide site is polymorphic, usually just two different bases are found at that site. If we count the occurrences of the least frequent base, this will give us the frequency class for this particular site. Mutations present in a single sequence (for example, at positions 2, 3, and 13 in Fig. 1) represent low-frequency mutations and all appear in frequency class one. Likewise, mutations appearing in half the sequences (positions 5, 10, 12, and 15 in Fig. 1) represent intermediate frequency mutations and appear in the highest frequency class, or half the number of sequences.

The frequency distribution of polymorphic sites in the mtDNA control regions I and II[14] is shown in Figure 2. It indicates an abundance of low frequency polymorphisms and only a small fraction of polymorphisms at intermediate frequency. This left-shifted distribution is typical of human mitochondrial genes.[15,16] This pattern, however, is not expected when sequences have evolved neutrally and when population sizes have remained stable. The expected pattern under selective neutrality and constant population size[10,17] is represented by the hatched bars in Figure 2. The left-shifted distribution of mtDNA polymorphism is consistent with an initially small population that recently has undergone a dramatic increase in size. But, on the other hand, the pattern could have been the result of a history dominated by natural selection on the mitochondria.

If the demographic story told on the basis of the mtDNA variation is accurate and represents the actual history of modern humans, then we expect a similar pattern of variation across most other loci. Because the mitochondrial genome lacks recombination, its constituent genes are all linked in their inheritance. Evidence from this genome's 37 constituent genes and two short noncoding regions cannot be taken as independent evidence. Therefore, patterns of genetic variation must be compared across multiple unlinked genes from the nuclear genome. In units of base pairs, the nuclear genome is about two hundred-thousand times the size of the mitochondrial genome and harbors 50,000 to 100,000 genes. As such, it is a largely untapped resource of information about our genetic and populational history.

In comparing the variation at different genes, the fundamental differences among mitochondrial genes, autosomal genes, and genes on other chromosomes should be kept in mind. First, unlike diploid genes, mitochondrial genes are not maintained on two distinct chromosomes, and though they are numerous in any one cell, the processes of replication and turnover lead to their being passed on in an effectively haploid fashion. Second, whereas autosomal genes are transmitted by both parents, mitochondrial genes are solely transmitted by the

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          1234567891111111
                    0123456
IND 1 ATGTACGTAGCTGCGG
IND 2 ACGTACGTAGCTGCGG
IND 3 ACGTACGTAGCTGCGG
IND 4 ACGTACGTAGCTGCGG
IND 5 ACGTGCGTAACCACAG
IND 6 ACGTGCGTAACCGCAG
IND 7 ACGTGCGTAACCGCAG
IND 8 ACATGCGTAACCGCAG
```

Figure 1. Sample of sequences from a simulated population showing mutated bases that differ in their frequency class.

mother. In contrast, X-linked genes and Y-linked genes show different patterns. X chromosome genes are found as two copies in females but only one copy in males, but can be transmitted by either sex; Y chromosome genes are found as single copies in males and are transmitted solely by them. The differences in number and inheritance of these different genes have significant effects on the amount of variation they harbor. This is solely because of the different number of gene copies existing in the population at any given moment. This point will be returned to later when discussing changes in the effective population size (N_e) of humans over time.

The frequency distributions of polymorphic sites for each nuclear gene can be compared with each other and with mitochondrial genes to test whether they are consistent with a single population history. Hey[15] observed that nuclear genes show an abundance of intermediate-frequency polymorphisms, in contrast to the overabundance of low-frequency polymorphisms found in the mtDNA, and compared several small nuclear gene data sets with the patterns found in the mtDNA. The statistical tests were performed under a model of constant population size as well as a model of rapid population growth, as hypothesized by Rogers and Harpending.[1] In all of the contrasts, the mitochondrial and nuclear genes were inconsistent with the same demographic histories.

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The frequency distribution for the X-linked *PDHA1* region is shown in Figure 3.[18] It shows an abundance of intermediate-frequency mutations and a paucity of low-frequency mutations. This pattern produces a distribution that is right-shifted, which is exactly the opposite of the distribution for mitochondrial genes. Interestingly, as Hey[15] noted, and as data that have emerged since then indicate, the majority of nuclear regions sequenced for human populations show a similar right-shifted distribution, indicating an abundance of intermediate-frequency mutations. These include β-globin (chromosome 11)[19]; lipoprotein lipase (chromosome 8)[20,21]; several X-linked genes, including pyruvate dehydrogenase E1α subunit (*PDHA1*)[15,18]; dystrophin (*Dmd*)[22]; myelin proteolipid protein (*Plp*); and glycerol kinase (*Gk*).[23] When compared with the frequency distribution under a neutral model (the hatched bars in Fig. 2), these nuclear genes show even more mutations than expected at intermediate frequencies.

HOW DO MITOCHONDRIAL AND NUCLEAR GENE TREES DIFFER?

The frequency distribution of polymorphic sites bears a fairly simple relationship to the overall shape of the gene tree. For example, a star-shaped gene tree (Fig. 4) in which the vast majority of coalescent events occur near or at the root is typical of a population that has undergone rapid population growth from an initially small population.[12] The mutations that appear on this tree are not likely to have been inherited by more than a single DNA copy in the sample and will tend to be at low frequency. Such a star-like tree is indicated by the pattern of mutations observed in mtDNA sequences, which show an abundance of low-frequency mutations.

In contrast, a tree with a more balanced branching pattern and in which population size has been constant (Fig.

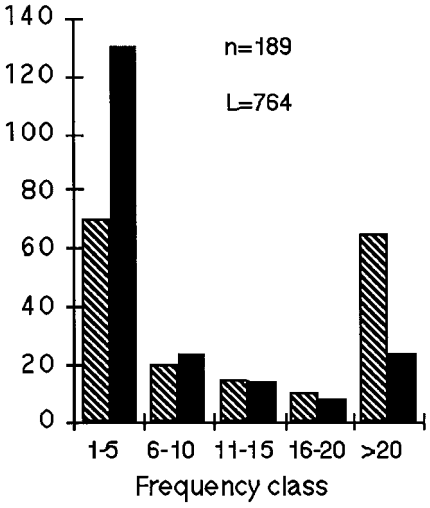

Figure 2. The frequency distribution of polymorphic sites for mtDNA control regions I and II. Black bars are the observed frequencies. Hatched bars are the expected frequencies under constant population size and assuming a neutral evolutionary model.[10,17] The left-shifted distribution of the mtDNA control region sequences is typical of mitochondrial genes.

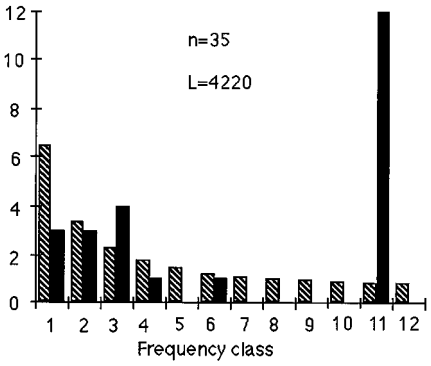

Figure 3. The frequency distribution of polymorphic sites for the PDHA X-linked gene. Black bars are observed frequencies. Hatched bars are the expected frequencies under constant population size and assuming a neutral evolutionary model. The right-shifted distribution of the observed frequencies is typical of all known large DNA sequence data sets for nuclear loci.

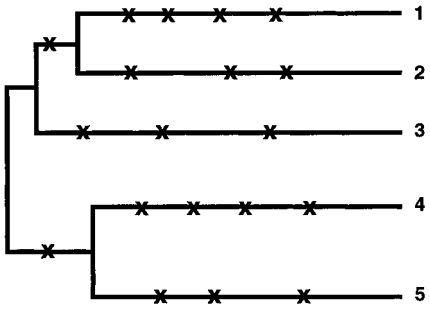

Figure 4. A star-shaped genealogy from a recently growing population with mutations placed along branch lengths. The figure represents a gene tree with DNA sequence copies drawn from five different ''living individuals'' constituting the tips of the branches at the right.

5) has many more mutations occurring on deep (or old) branches. These polymorphisms will tend to be at intermediate frequencies because all of the descendant DNA lineages from an old branch have inherited the mutations that arose on that branch. The polymorphism at nuclear genes, such as *PDHA1*,[18] β-globin,[19] lipoprotein lipase,[20,21] dystrophin,[22] and other genes shows this type of pattern. Such polymorphisms preserve an abundance of mutations that arose early on the tree, a finding that is not expected if the ancestral human population was very small.

But if frequency distributions go hand in hand with gene tree shape, why bother with the frequency distributions? The answer is that the expected frequency distribution does not depend on recombination, whereas the estimation of gene trees becomes quite problematic for data sets from genes that have a history of recombination. Thus, a focus on polymorphism frequencies permits direct and fairly simple comparisons among genes that have experienced different amounts of recombination.

RECONCILING MITOCHONDRIAL AND NUCLEAR GENES

The conflicting patterns of variation between mitochondrial and nuclear genes suggest they cannot both be reconciled with a common demographic history. A simple alternative model is that one gene or class of genes has been shaped by natural selection. In principle, natural selection could have operated on either the mitochondrial or nuclear genome, or both. Parsimoniously, however, the mtDNA genome is the most likely candidate, as it effectively represents one gene (or tight linkage group) in contrast to the multiple unlinked nuclear genes that differ from it. Also, the fact that the mitochondrial genes do form a single linkage group suggests that this genome may be especially susceptible to natural selection, the reason being that natural selection cannot act effectively on multiple polymorphic sites.[15,16,24]

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In recent years, two forms of selection have been emphasized for cases of tight linkage. First, selection for a favorable mtDNA copy that spreads rapidly through the population, known as a selective sweep, could have produced the pattern of human mtDNA variation.[11,24] A sweep causes a reduction of neutral variation at linked sites. The variation we see today among human mtDNA copies has accumulated recently, explaining why it is at low frequency. The result, in effect, is a bottleneck and expansion for just mtDNA, not for the rest of the genome. A second possible mode of natural selection that could cause the shifted pattern of variation in the mtDNA is the accumulation of many slightly deleterious mutations. Again, under tight linkage, natural selection cannot act efficiently on all polymorphisms, making it possible for slightly deleterious mutations to rise in frequency and contribute to a skew in the polymorphism frequency distribution.[25] Evidence in support of this model comes from recent studies of mtDNA showing that human mtDNA samples segregate high levels of so-called nonsynonymous polymorphisms.[16,24] (Nonsynonymous polymorphisms change the amino-acid code, whereas synonymous ones do not). In this model, it is selection against mildly deleterious mutations that results in a reduction of variation at linked sites and in a shifted polymorphism distribution.

There is evidence suggesting that many mutations segregating in the mtDNA genome today are mildly deleterious.[16,26] For instance, diseases such as Leber's hereditary optic neuropathy (LHON) myoclonic epilepsy (MERRE) an encephalomyopathy (MELAS), and even Alzheimer's disease are associated with mtDNA mutations.[27] The fact that these mutations are mildly deleterious, leading to diseases with onset during postreproductive years, may help to explain why they are found at low frequencies in humans.[16,28] Evidence of natural selection's influence on the shape and pattern of human mtDNA variation may limit the usefulness of the mtDNA genetic system for understanding human histories.

So is it resolved that the mtDNA data are a poor reflection of human history? No. Although there are strong differences between the mtDNA and nuclear genes, it remains possible that more complicated demographic models could be found to fit all of the genetic data. So far, the statistical tests have examined both sets of genes under models of constant population size and recent expansion.[15] Recently, Fay and Wu[29] have shown that a model of population reduction, followed quickly

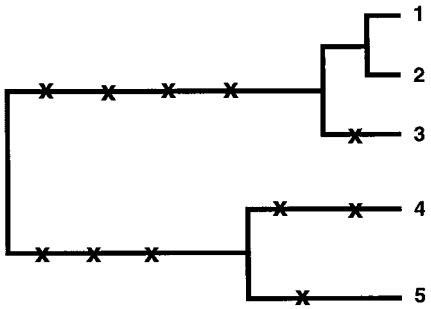

Figure 5. A genealogy from a population with constant size over time. The figure represents a gene tree with DNA sequence copies drawn from five different ''living individuals'' constituting the tips of the branches at the right.

by expansion, could explain some of the difference between the mtDNA and the nuclear genes. If the bottleneck was not long, or if it was very small, then it would be possible for nuclear genes to preserve some old variation, leaving mtDNA to have lost old variation. The difference arises from the different effective sizes, as described earlier, for these two classes of genes. Simulating a bottleneck, Fay and Wu[29] found that the frequency distribution of polymorphisms can differ considerably between the two genomes. Thus, it is possible that the different patterns of variation seen at nuclear and mitochondrial sites were, in fact, shaped by the same history but are out of phase with each other due to their fundamental differences in effective population size. It remains to be seen whether this type of model can be fit to the data.

HUMAN ORIGINS

The size and geographic range of the population ancestral to modern humans are central questions in research on human origins. Implicit in some recent African origin models is the hypothesis that the population that evolved into modern humans was small and localized. This hypothesis is appealing because it conforms to a model in which genetic drift and local adaptation in small populations play significant roles in speciation.[30,31] These explanations associate a small population size with the transformation from archaic *Homo sapiens* to modern *H. sapiens*.[32,33] Small population size has also been suggested for the emigrant population of modern *H. sapiens* that left Africa.[34,35] More recently, others have suggested that population contraction occurred in response to the effects of a late Pleistocene volcanic eruption of Mt. Toba in Sumatra.[36] It is the pattern of variation in the mtDNA that has been the major genetic support for these historical models, as the abundance of low-frequency variation is consistent with a population that expanded greatly from a small size within the past 100,000 years.[14,37]

If the evolutionary history of modern humans is one of rapid expansion from a small ancestral population, we should expect to find evidence of that in the pattern of variation at nuclear genes. However, the nucleotide variation at the few nuclear loci studied to date shows a different pattern than that at mitochondrial genes. The excess of old variation on deep branches of nuclear gene trees is strong evidence that human populations never experienced a very small population size, at least in the time span of the depth of those gene trees. Gene trees derived for a global sample of humans based on nuclear DNA sequences all show an excess of variation that arose before 100,000 years ago. β-globin haplotype variation extends back to 800,000 years,[19] lipoprotein lipase variation to over one million years,[20,21] ZFX variation to 700,000–1.1 million years,[38] intergenic variation Xq 13.3 to about 535,000 years,[38] and *PDHA1* variation to as far back as 1.86 million years.[18]

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Given the pattern emerging from nuclear genes, we are inspired to consider a broad scenario for modern human origins. Patterns of nuclear DNA variation seem to indicate that the ancestral modern human population was not a very small one. Instead, this population may have been relatively large and may have covered a broad geographic range. If so, such a population may well have been subdivided.

Most estimates of effective human population size (N_e) based on a variety of loci are around 10,000.[2] Some estimates are slightly higher, but not considerably so.[18,40] The argument has been made that an N_e of this size contradicts an extreme multiregional model because such a population could not have occupied the entire Old World and remained a cohesive population.[2] However, the relationship between N_e and the census of individuals in a population is a complicated one, and is affected by a variety of factors. The effects of these factors could mean that the census size of the ancestral population was considerably larger than is indicated by low estimates of N_e.[40] Nevertheless, between an extreme multiregional model[42] and African-origin models there are many scenarios that include a broad geography and gene flow. A number of plausible intermediate multiregional models have been elaborated.[43,44] The critical questions are: Exactly how geographically spread were the ancestors of modern humans? Was this population subdivided? And if so, how much gene flow occurred between subpopulations?

Relatively ancient population subdivision is indicated by several unlinked genetic systems. Patterns of polymorphism at the X-linked *PDHA1* locus indicate the presence of multiple populations 200,000 years ago. A global population study of β-globin haplotypes indicates a similar time for the onset of subdivision.[19] Early population splitting between Africans and nonAfricans is also indicated in reports on other genes, including segregating *Alu* insertions (137 Kyr BP),[45] mtDNA mismatch distributions (100 Kyr BP),[4] protein polymorphism (115 Kyr BP),[46] and microsatellite loci (156 Kyr BP).[47] Recent cladistic analyses of mtDNA, Y-chromosome, and β-globin gene regions also point to ancestral population subdivision, and seem to indicate widespread or restricted gene flow among populations.[19,46,47]

The fossil evidence may also point to a relatively large and subdivided ancestral human population within Africa. Transitional fossils with features intermediate between late-archaic and fully modern *H. sapiens* and sharing a roughly similar geologic age (between 200,000 and 100,000 years) come from geographically diverse regions within Africa, including Florisbad (South Africa), Omo Kibish (Ethiopia), Ngaloba (Tanzania), and Djebel Irhoud (Morocco).[50] The modern human fossils in

the Levant at the sites of Skhul and Qafzeh in Israel could represent a roughly contemporaneous subpopulation that was connected by restricted gene flow with African subpopulations.

The presence of near-modern human features in fossils that are geographically dispersed in Africa and roughly of a similar geologic age could easily be explained by limited gene flow aided by natural selection. Natural selection in the context of a subdivided human ancestral population would have increased gene flow for the genes that were favored. For gene flow to be effective, the genes making us modern would, of course, have to be favored over the entire geographic range of our ancestors.

It may be useful to note that the subpopulations of the living baboon (*Papio*) could provide a model for the geographical subdivision and contact among ancestral human populations, particularly if ancestral human subpopulations occupied Africa and, as early modern human fossils in the Levant[51,52] seem to suggest, also extended into Southwest Asia. *Papio* is a broadly distributed African species marked by phenotypic subdivision but united by gene flow at zones of overlap.[51] Together, the major subpopulations of *Papio* form a continuous series of step-clined phenotypic populations having a ring-like geographical distribution in sub-Saharan Africa. Gene flow is presumed or observed to occur at the narrow zones where different forms are contiguous. Genetic continuity at meeting zones creates the potential for the subpopulations of *Papio* to evolve as a coherent unit through time, especially if some favorable genetic alleles have the potential to flow preferentially from subpopulation to subpopulation. A similar situation might have existed for subpopulations of ancestral modern humans. If the ancestral modern human population was subdivided, it will be a challenge for molecular anthropologists to reconstruct the pattern of spread, subdivision, and possible regions of contact between and among these subpopulations.

FUTURE PROSPECTS

The finding that most nuclear genes harbor a wealth of old genetic variation that well predates the origin of modern humans raises hope for further research on the genetic basis of the transformation to modern humans. As human genes are discovered through the efforts of the Human Genome Project, it might well become possible to identify the genes that make us modern. How will we know these "modern" genes when we find them? If these genes carried mutations that were beneficial and that arose in our archaic ancestors, then necessarily they must have experienced a selective sweep within the past 200,000 years. These "modern" genes should show a unique evolutionary history—a history with a very recent coalescence, resembling a bottleneck, with a time that coincides with the earliest modern human fossils. These genes should also show a history of increased gene flow among human populations.

Genetic continuity at meeting zones creates the potential for the subpopulations of *Papio* to evolve as a coherent unit through time, especially if some favorable genetic alleles have the potential to flow preferentially from subpopulation to subpopulation. A similar situation might have existed for subpopulations of ancestral modern humans.

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