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Mitochondrial DNA and Human Evolution

Mark Stoneking[1]

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For the past seven years or so, much discussion and controversy in the field of human evolution has revolved around the application and interpretation of studies of human mitochondrial DNA variation, particularly the hypothesis that all mtDNA types in contemporary populations can be traced back to a single African ancestor who lived about 200,000 years ago. In this review I describe the evidence that led to this hypothesis, subsequent work, and where things stand now, particularly with respect to recent criticisms concerning the adequacy of phylogenetic analyses of the mtDNA data. I also describe a new method of analyzing mtDNA data that suggests that all human populations underwent a dramatic expansion some 40,000 years ago, possibly in association with revolutionary advances in human behavior, as well as an important implication of population expansions for mtDNA disease studies.

Mitochondrial DNA (mtDNA) comprises only about 0.00006% of the total human genome, but the contribution of mtDNA to our understanding of human evolution far outweighs its minuscule contribution to our genome. The properties of mtDNA that make it so valuable for evolutionary studies include the high copy number, maternal mode of inheritance, and rapid rate of evolution (Wilson *et al.*, 1985; Avise, 1986; Stoneking and Wilson, 1989). MtDNA is also perhaps the best-characterized eukaryotic genome, with the complete sequence and gene organization known for humans (Anderson *et al.*, 1981) and several other organisms. The detailed knowledge of the molecular biology of the molecule, made possible by the complete sequence, has not only facilitated evolutionary studies but also enhanced our understanding of mtDNA diseases, as discussed in other papers in this issue; mtDNA thus offers a paradigm for what we can expect to gain from the effort to determine the complete sequence of the human genome.

In 1987, Rebecca Cann, the late Allan Wilson, and I proposed from our study of human mtDNA variation what has come to be popularly known as the "African Eve" hypothesis (Cann *et al.*, 1987), although we prefer to call it the "recent African origin" hypothesis. In this review I will briefly describe the evidence that led to this hypothesis, as well as subsequent work (and criticism) relating to it; a more thorough review, from which much of this material is condensed, has recently appeared elsewhere (Stoneking, 1993). I will also describe a new way of analyzing mtDNA data that provides insights into the demographic history of human populations.

THE RECENT AFRICAN ORIGIN HYPOTHESIS

There are three aspects to the recent African origin hypothesis: (1) all mtDNA types in contemporary human populations can be traced back to a single common ancestor; (2) this ancestor probably lived in Africa; and (3) this ancestor probably lived about 200,000 years ago. I shall consider each of these three aspects in turn.

A Single Ancestor

What appeared to us to be a straightforward and logical conclusion from simple biological principles has in fact been responsible for more consternation and misinterpretation, particularly (but

[1] Department of Anthropology, Pennsylvania State University, University Park, Pennsylvania.

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not exclusively) by the popular press, than any other aspect of the hypothesis. Simply put, given that there was a single origin of life on this planet, and that all living things are descended from this single point of origin, then it must be true that *all* of the variation in *any* segment of DNA (mitochondrial or nuclear) *must* ultimately trace back to just one ancestor. The only alternative would be to suppose multiple origins of life on this planet, or perhaps an extraterrestrial origin for mtDNA types in some individuals!

Although this is a simple principle, there are additional implications that have also led to misunderstanding. First, because mtDNA is maternally inherited, the mtDNA ancestor must have been female. However, she was not the only female alive; she was a member of a population, but the mtDNA types of her contemporaries eventually became extinct because they or their maternal descendants either left no surviving offspring or left only male offspring. This process of random extinction is illustrated in Fig. 1.

Second, she was not the first human to have appeared on this planet. Like everyone else, she had ancestors, but she represents the point of coalescence of all contemporary mtDNA types. Indeed, she need not even have been human; in principle the coalescence to a single mtDNA ancestor could extend back to any point in our evolutionary history, going all the way back to the origin of life. For example, some alleles of the MHC are shared between humans and African apes (Figueroa *et al.*, 1988; Lawlor *et al.*, 1988; Gyllensten and Erlich, 1989), indicating that the ancestor for these alleles predates the human–African ape divergence, some 5 million years ago.

Finally, the mtDNA ancestor need not have contributed any other genes or DNA segments to contemporary populations. While every gene or DNA segment must have a common ancestor, in principle each ancestor could be a different individual, living in different places at different times. Clearly, then, the idea of a single common ancestor is not of particular interest or concern; what is interesting is determining where and when the mtDNA ancestor lived, and the implications this has for human evolution.

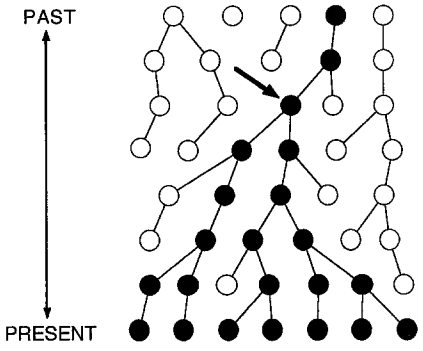

Fig. 1. An illustration of the principle that all mtDNA types in contemporary populations must trace back to a single common ancestor. Solid circles indicate the path of descent from the ancestor (arrow) to the present generation; empty circles represent mtDNA types that went extinct (from Stoneking, 1993).

African Origin

Two lines of evidence have been interpreted as supporting an African origin for the human mtDNA ancestor. The first of these is phylogenetic (tree) analysis of the data. The maternal, haploid inheritance of human mtDNA means that, with no recombination, the only source of new variation is mutation. Therefore, the number of mutations separating two mtDNA types reflects how closely related they are—the larger the number of mutations, the more distantly related the mtDNA types. Trees depicting the phylogenetic relationships of mtDNA types can therefore be readily constructed and interpreted as reflecting the maternal genealogical history of our species.

Cann *et al.* (1987) used the maximum parsimony method, which attempts to derive a tree that requires the fewest number of mutations, to construct a tree for 134 mtDNA types determined by high-resolution mapping of restriction site polymorphisms from 148 individuals. The resulting tree, shown schematically in Fig. 2, had two primary branches, one consisting only of mtDNA types from Africa, the other consisting of all of the mtDNA types from everywhere else in the world, as well as some from Africa. This pattern was interpreted as indicating an African origin of the ancestor, with subsequent migrations out of Africa to the rest of the world.

The same type of tree as shown in Fig. 2 was found in other RFLP analyses of human mtDNA

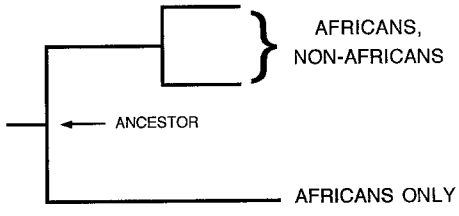

Fig. 2. A simplified version of phylogenetic trees relating contemporary mtDNA types. Invariably, such trees consist of two primary branches, with only Africans represented on both branches (from Stoneking, 1993).

variation (Johnson *et al.*, 1983; Horai *et al.*, 1987; Merriweather *et al.*, 1991), as well as in studies that used the polymerase chain reaction (PCR) to amplify and sequence hypervariable segments of noncoding portions of the mtDNA genome (Vigilant *et al.*, 1989; Horai and Hayasaka, 1990; Kocher and Wilson, 1991; Vigilant *et al.*, 1991). However, the adequacy of the phylogenetic analysis performed by Cann *et al.* (1987) and Vigilant *et al.* (1991) has been called into question (Maddison, 1991; Hedges *et al.*, 1992; Maddison *et al.*, 1992; Templeton, 1992, 1993). These re-analyses have shown that maximum parsimony trees requiring fewer mutations can be constructed from the data, and that at least some of these trees do not conform to the pattern in Fig. 2.

These re-analyses have been widely publicized, leading some to conclude that the geographic origin of the human mtDNA ancestor cannot be determined at all with existing data. A thorough discussion of the problem is outside the scope of this review; the interested reader should consult the above papers, as well as additional comments on these re-analyses (Wilson *et al.*, 1991; Stoneking *et al.*, 1992b; Stoneking, 1993, 1994). However, I believe this to be an overly pessimistic conclusion. Briefly, the crux of the problem lies specifically with present computer-based methods of maximum parsimony analysis of large datasets. For example, for the data of Vigilant *et al.* (1991), consisting of 135 distinct mtDNA types, there are about 8×10^{264} different bifurcating, unrooted trees, and there is thus no way to guarantee that the tree requiring the fewest number of mutations has been found. Furthermore, for these data there does not seem to be one single best parsimony tree; instead, there is an extremely large number of trees of equal length, and there is at present no way to guarantee that computer searches will recover all equally parsimonious trees.

Since this problem specifically concerns maximum parsimony analysis, one way around it is to use alternative methods of tree construction, such as neighbor-joining (NJ) tree analysis (Saitou and Nei, 1987). NJ analysis will produce a single "best" tree, even for very large datasets, and the NJ tree for the data of Vigilant *et al.* (1991) does conform to the pattern in Fig. 2 (Hedges *et al.*, 1992). However, the drawback of NJ tree analysis is that there is no direct way of determining if the NJ tree provides a statistically significantly better fit to the data than alternative trees. An indirect method that addresses this issue, bootstrap resampling of the data, does not indicate strong statistical support for the NJ tree for the Vigilant *et al.* (1991) data (Hedges *et al.*, 1992).

The second line of evidence for an African origin of the human mtDNA ancestor is that all studies of worldwide human mtDNA variation have found that African populations, on average, exhibit more mtDNA sequence divergence than non-African populations (Johnson *et al.*, 1983; Cann *et al.*, 1987; Horai and Hayasaka, 1990; Merriweather *et al.*, 1991; Vigilant *et al.*, 1991). Figure 3 illustrates this for one set of data, namely sequences of one of the hypervariable segments of the noncoding control region of the human mtDNA genome. It is important to note that the measure of mtDNA variation used is not a simple gene frequency-based measure of allelic variation, such as the average heterozygosity values typically calculated for blood group, serum protein, red cell enzyme, or other autosomal loci. Rather, it directly reflects the average number of mutations that have accumulated within populations, so the fact that African populations have the most mtDNA diversity means that they have accumulated the most mtDNA mutations. Since the expectation is that the ancestral population will have the most mutations, it follows that the greater mtDNA mutational diversity in African populations indicates an African origin for contemporary human mtDNA diversity.

Thus, two lines of evidence appear to indicate an African origin for the human mtDNA ancestor: phylogenetic analysis indicating that the most divergent mtDNA types are in African populations, and more mtDNA diversity in African populations. To

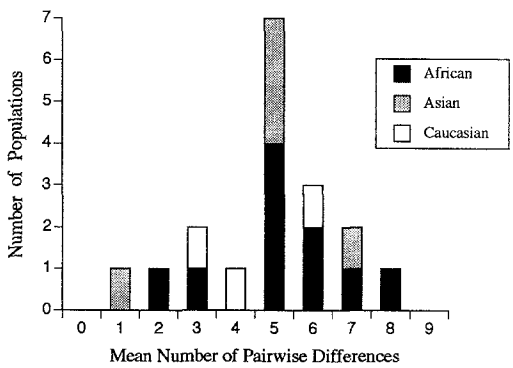

Fig. 3. Histogram of the number of pairwise differences for 18 populations for which sequences of the first hypervariable segment of the noncoding mtDNA control region were obtained. Data include published studies (Horai and Hayasaka, 1990; DiRienzo and Wilson, 1991; Vigilant *et al.*, 1991; Ward *et al.*, 1991) and unpublished data from my laboratory. African populations clearly exhibit the most mtDNA diversity (from Stoneking, 1993).

be sure, the adequacy of phylogenetic analysis for determining geographic origin remains debatable. However, lack of statistical support does not mean that there is no information regarding geographic origin, but rather that the probability of a non-African origin is greater than 5%. Given that different methods of phylogenetic analysis on different datasets invariably lead to trees of the type depicted in Fig. 2, and given that all worldwide studies of human mtDNA variation find the greatest divergence in African populations (a finding that has not been questioned in any of the re-analyses), an African origin of the human mtDNA ancestor still appears to provide the best explanation.

Age of the Ancestor

The age of the human mtDNA ancestor can be inferred from the amount of sequence divergence that has arisen among contemporary human mtDNA types, if one knows the rate of mtDNA evolution. The rate of human mtDNA evolution is typically estimated by calculating the average amount of sequence divergence between human and chimpanzee mtDNA (our closest nonhuman relative), and dividing by the divergence time for humans and chimpanzees. Thus, based on an average rate of mtDNA divergence of 2–4% per million years (Wilson *et al.*, 1985) and an observed sequence divergence since the human ancestor of 0.56%, we previously calculated that the human ancestor lived between 140,000 and 280,000 years ago (Cann *et al.*, 1987). This relatively recent date for the age of the human mtDNA ancestor was supported by the control region sequences of Vigilant *et al.* (1991), who obtained estimates of 11.5–17.3% per million years for the rate of divergence of these rapidly evolving portions of the mtDNA genome, 2.87% for the amount of sequence divergence since the mtDNA ancestor, and hence an age for the mtDNA ancestor of 166,000 to 249,000 years ago.

However, there are several factors which complicate this seemingly straightforward procedure. First, the time of divergence between human and chimpanzee mtDNA must be known with reasonable accuracy. While most studies do support a date of about five million years ago for this divergence (Hasegawa and Kishino, 1991; Horai *et al.*, 1992), others have suggested that the divergence occurred as much as eight to ten million years ago (Gingerich, 1985). Older divergence dates will lead to slower rates and hence older dates for the age of the human mtDNA ancestor.

Second, in estimating the amount of sequence divergence between human and chimpanzee mtDNA, correcting for multiple substitutions at the same nucleotide position becomes a factor. The peculiar dynamics of mtDNA sequence evolution (rapid rate of change, greatly elevated frequency of transitions vs. transversions, and existence of mutational "hotspots") make this correction particularly troublesome; standard methods, which generally assume an equal probability of all types of mutations across all sites, are inadequate (Hasegawa and Horai, 1991; Kocher and Wilson, 1991).

Third, the above estimates of the age of the human mtDNA ancestor do not include standard errors. Thus, even though we estimate a relatively recent age for the human mtDNA ancestor, it could be that much older ages (even approaching a million years ago) would not be ruled out statistically. This is also not a trivial problem, as there are multiple sources of variance that must be considered in estimating a standard error, including variances related to the sampling of individuals, the sampling of mtDNA diversity, and the inherently stochastic nature of mtDNA evolution (Tajima, 1983).

Nevertheless, a number of studies have recently attacked this problem, using a variety of methods and datasets. We have also developed an alternative approach that calibrates the rate of human mtDNA evolution not by comparing human mtDNA with chimpanzee mtDNA, but rather by estimating the amount of mtDNA sequence divergence that has accumulated within relatively isolated regions of the world (in particular, Papua New Guinea) since the time of first colonization, which is known from archaeological investigations (Stoneking *et al.*, 1986, 1992a). The results of all of these studies are summarized in Fig. 4 in the form of approximate 95% confidence intervals for the age of the human mtDNA ancestor. Despite the variety of methods and data used, the upper limits for the age of the human mtDNA ancestor are generally in good agreement, about 500,000 years ago.

Significance for Human Evolution

In summary, the available evidence would appear to indicate that the human mtDNA ancestor probably lived in Africa about 200,000 years ago (and not more

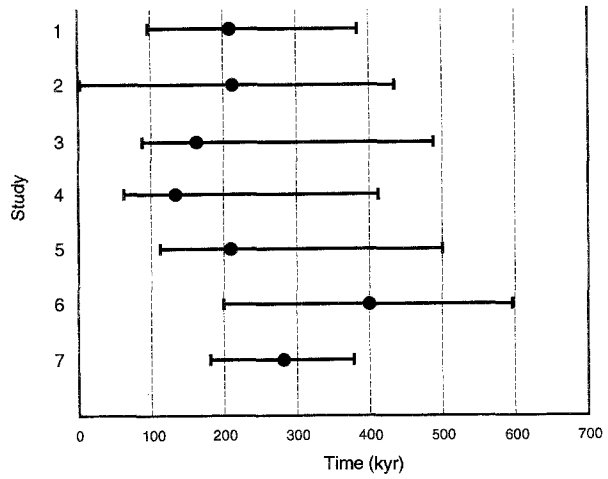

Fig. 4. Estimates of the age and approximate 95% confidence interval for the human mtDNA ancestor from seven studies. Data are from: (1) Templeton, 1993; (2) Hasegawa *et al.*, 1993; (3) Tamura and Nei, 1993; (4) Stoneking *et al.*, 1992a; (5) Nei, 1992; (6) Pesole *et al.*, 1992; and (7) Hasegawa and Horai, 1991. All ages and confidence intervals are based on a human–chimpanzee divergence date of four to six million years ago, with the exception of study (4), which used mtDNA divergence specific to Papua New Guinea and an initial colonization date for New Guinea of 60,000 years ago to calibrate the rate of human mtDNA evolution.

than about 500,000 years ago). What, if anything, does this tell us about the origin of our species? There are currently two theories that dominate the study of recent human evolution. Both theories begin with the presumption that hominids (members of our genus, *Homo*) originated in Africa and first left Africa about one million years ago, dispersing throughout the old world. The multiregional evolution hypothesis holds that this was the only major dispersal in human evolution, and that there was no single origin of modern humans (our species, *Homo sapiens*). According to this hypothesis, old world populations are characterized by regional continuity in the fossil record, indicating genetic continuity over the past million years, and the mutations and biological traits that led to modern humans were spread in concert throughout the old world by gene flow (Wolpoff, 1989, 1992). By contrast, the single origin hypothesis (also known as the "Garden of Eden" hypothesis) holds that there was a single origin of our species in Africa about 100,000 years ago, and that modern humans subsequently dispersed from Africa, mixing little or perhaps even not at all with the non-modern old world populations (Stringer and Andrews, 1988; Stringer, 1992).

Clearly, the mtDNA evidence is most easily reconciled with the latter hypothesis. In this regard, it is important to realize that a 200,000 year old date for the age of the human mtDNA ancestor does not mean that modern humans arose 200,000 years ago. The significance of the age of the human mtDNA ancestor is that it marks a *genetic* divergence, which need not correlate at all with a *population* divergence (Nei, 1987). However, as Fig. 5 illustrates, in general we expect genetic divergence to *precede*

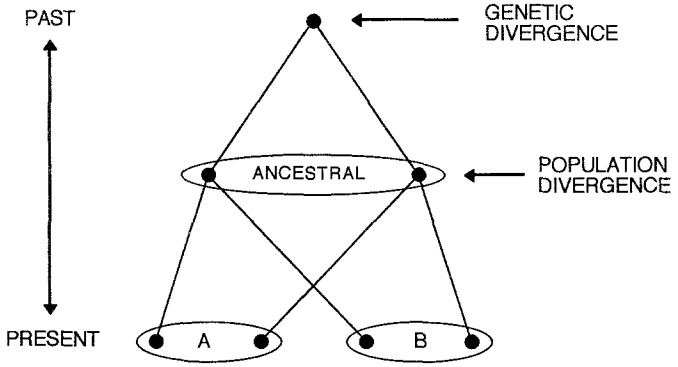

Fig. 5. An illustration of the principle that genetic divergence tends to precede population divergence. An ancestral population is depicted that gave rise to two descendent populations (A and B), each with two mtDNA types. The two mtDNA types in each population did not diverge when the populations split, illustrating that a genetic divergence need not correspond to any population event (cf. Nei, 1987). However, the genetic divergence predates and hence places an upper limit on the population divergence, which is expected to be the case whenever the ancestral population is polymorphic (from Stoneking, 1993).

population divergence. This will be the case whenever the ancestral population is polymorphic, containing more than one mtDNA type, which certainly seems more reasonable than supposing that the ancestral population had only one mtDNA type. Consequently, the coalescence for the polymorphism must predate the population divergence. Therefore, if the human mtDNA ancestor really lived no more than 500,000 years ago, the corresponding inference is that human population differences are also not more than 500,000 years old. Thus, an African mtDNA ancestor dated to approximately 200,000 years ago is easily reconciled with an African origin of our species about 100,000 years ago. By contrast, the mtDNA evidence does not appear to be compatible with multiregional evolution, which holds that human population differences should be upwards of one million years old, and hence genetic divergences should be even older.

However, a recent African origin of our species is far from proven. Much work remains to be done. For statistical resolution of the controversies surrounding the mtDNA story, more sequence information from more individuals is needed. We also need comprehensive genetic data from nuclear loci, in order to verify that the inferences based on patterns of mtDNA variation truly reflect the history of our species, and not just something peculiar about the evolutionary history of human mtDNA. After all, mtDNA is but a single locus (albeit a highly interesting and informative one), and even those of us who are enamored of mtDNA will grudgingly admit that, when it comes to understanding human evolution, it would help to know something about the other 99.99994% of the human genome! Gathering such comprehensive information on patterns of mtDNA and nuclear DNA variation in human populations is the goal of the Human Genome Diversity initiative (Cavalli-Sforza *et al.*, 1991), so if this project comes to fruition we can expect that our knowledge of patterns of genetic variation in contemporary human populations will become as good as it will need to be. In addition, other promising lines of research involving ancient DNA and the genetic basis of normal morphological variation should also shed light on modern human origins, as discussed in more detail elsewhere (Stoneking, 1993). We can thus expect that applications of molecular genetics will continue to play a prominent role in furthering our understanding of the origin of our species.

POPULATION EXPANSIONS

In the meantime, another approach to understanding modern human origins is to develop new ways of analyzing the data we already have. One such method is the analysis of mismatch distributions, which are histograms of the number of mutational differences (based either on sequences or restriction maps) between each pair of mtDNA types in a sample (DiRienzo and Wilson, 1991; Rogers and Harpending, 1992). Representative examples of mismatch distributions from various populations are shown in Fig. 6. As can be seen, these distributions characteristically take the form of "waves," with a peak in the wave near the average number of pairwise differences in each population. Rogers and Harpending (1992) showed that such waves differ dramatically from what would be expected for a population that was at neutral equilibrium (that is, one that had been constant in size with no selection); in an equilibrium population one expects the distribution to peak at zero differences (that is, the most frequent class should be pairs of mtDNA types that are identical) and to decrease smoothly as one moves to the right, increasing the number of differences.

Following earlier suggestions (DiRienzo and

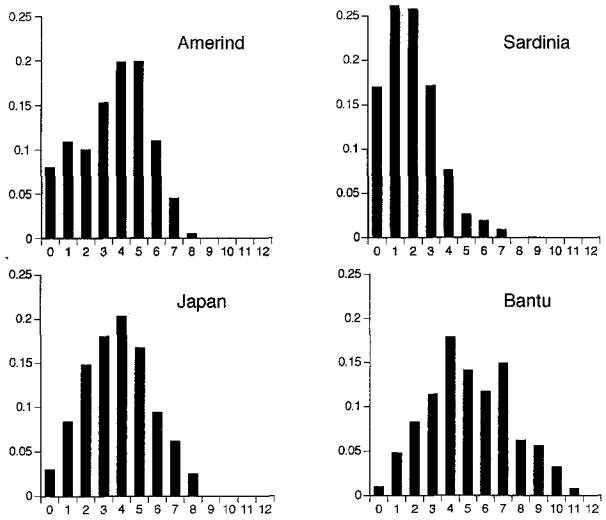

Fig. 6. Mismatch distributions of sequences of the first hypervariable segment of the mtDNA control region from populations from four different continents. Data are from: Amerind—Ward *et al.*, 1991; Japan—Horai and Hayasaka, 1990; Sardinia—DiRienzo and Wilson, 1991; and Bantu—Soodyall, Jenkins, and Stoneking, unpublished data. These mismatch distributions suggest that all of these populations underwent a dramatic prehistoric expansion, about 40,000 years ago (cf. Harpending *et al.*, 1993).

Wilson, 1991; Slatkin and Hudson, 1991), Rogers and Harpending (1992) showed that an episode of prehistoric population expansion could result in the observed waves in the mismatch distributions, and they developed a model that allowed one to estimate when such expansions had occurred. Application of this model to various mtDNA datasets shows that virtually all human populations from around the world experienced a period of dramatic growth approximately 40,000 years ago (Harpending *et al.*, 1993; Sherry *et al.*, 1994).

This date of 40,000 years ago does not correspond to any changes in human anatomy as judged by the fossil (paleontological) record; anatomically modern humans appear substantially earlier, about 100,000 years ago, in Africa and the Near East (Stringer and Andrews, 1988; Bar-Yosef, 1992). However, from the standpoint of human behavior, as judged by the archaeological record, this is a very interesting time in human evolution. Many modern human behaviors make their first appearance in the archaeological record around 40,000 years ago, including the first tools made from bone and antler, the first fishhooks, and the first appearance of art objects and decorative items (Klein, 1989). There is also a dramatic change in the stone tool record itself at this time, from a relatively nonspecialized, Middle Paleolithic tool industry that is temporally and geographically uniform, to the much more advanced and specialized Upper Paleolithic tool industries that vary widely temporally and geographically. This transition is so dramatic that some archaeologists refer to the transition as a revolution in human behavior that might actually be more important for understanding human evolution than the skeletal-based transition to a modern human anatomy that occurred much earlier (Klein, 1992; Mellars, 1992).

The association between the date inferred from mismatch distributions of mtDNA types for human population expansions and the transition in human behavior inferred from the archaeological record is striking, and lends support to the idea that this was indeed an important period in human evolution. Of course, it is not clear what the causal connection might be: did a change in human behavior, perhaps involving advances in material culture and lithic technology, permit a dramatic increase in population growth, or did an increase in population growth result in a sufficient "critical mass" for new advances in technology and culture?

It must be stressed that there is almost as much controversy among archaeologists as to whether there indeed was a great leap between the Middle and Upper Paleolithic, as there is among paleontologists as to whether the human fossil record supports multiregional evolution or a recent African origin. Population expansions may have occurred in the absence of any profound change in human behavior or anatomy. And, of course, the inference of population expansions from mismatch distributions of mtDNA needs to be verified by similar analysis of other loci. Otherwise, these presumed population expansions might reflect an expansion of mtDNA types due to selection, rather than an actual population expansion; attempts to extend this approach to nuclear loci are under way.

RELEVANCE FOR MtDNA DISEASES

The natural curiosity that most humans seem to possess about our evolutionary past is what drives most of the research into mtDNA variation in human populations. Aside from elucidating the patterns of normal human mtDNA variation, little of what comes out of such research is directly relevant to mtDNA disease research. However, there is one insight from the above evolutionary studies that has important implications for research into mtDNA diseases, and that has to do with population expansions. It is well known that expanding populations tend to accumulate an excess of rare mutations over what would be expected for a stable population, and several studies have documented just such an excess of rare variants in human mtDNA (Whittam *et al.*, 1986; Excoffier, 1990; Merriweather *et al.*, 1991).

What does this excess of rare mutations mean for mtDNA disease studies? In the typical mtDNA disease study, mtDNA mutations are screened for in a patient population, and then the frequency of any candidate disease mutations are ascertained in a control, unaffected population. A significant increase in the frequency of a candidate mutation in the patient population, relative to the control population, is taken as evidence for an association of that mutation with the disease. However, the increase in rare mutations due to population expansions during human evolution means that many mtDNA mutations will exist only in one maternal lineage in a population. For example, 50% of the mutations detected by high-resolution restriction maps of the entire mtDNA genome were found only once in a

worldwide sample of 241 individuals (Cann *et al.*, 1987; Stoneking *et al.*, 1990). Studies that rely solely on comparing mtDNA mutations in disease vs. control populations therefore run the risk of false attribution of disease mutations, particularly when the patient population comes from a single maternal lineage. There is a significant probability that *any* maternal lineage will carry at least one unique mtDNA mutation.

In conclusion, analyses of mtDNA variation in contemporary human populations continue to provide provocative and controversial insights into the origin of our species. Despite recent criticisms concerning lack of statistical certainty, a recent African origin appears to be the best explanation for the mtDNA data and, by inference, the origin of modern humans. A new method of analyzing mtDNA data, based on mismatch distributions, indicates that all human populations underwent a dramatic expansion about 40,000 years ago, which might be associated with a major transition in human behavior. Doubtless there is much more to be learned from this small but extraordinarily informative fraction of our genome, and we look forward to other insights into human evolution that might be gleaned from creative new ways of examining patterns of mtDNA variation in human populations.

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