2. Genetic evidence for our recent African ancestry

Mark Stoneking

For many years, discussions about the origin of modern humans revolved around two competing theories: the recent African origin hypothesis, which postulates that modern humans originated in Africa about 150 000 years ago and then spread from Africa (Stringer and Andrews, 1988); and the multiregional evolution hypothesis, which postulates that modern humans evolved over the past million years or so from archaic human populations across the Old World via a complex interaction between selection and migration (Wolpoff, 1989). Recently, the debate has shifted focus, as the genetic evidence (reviewed here) as well as the fossil evidence (see the chapter by C Stringer in this volume) for a recent African origin of modern humans is compelling. Nowadays, discussion tends to centre around whether the modern humans migrating from Africa completely replaced archaic human populations elsewhere without interbreeding, or whether in fact some proportion of our genetic ancestry can be traced directly to Neandertals or other archaic human populations. In this chapter, I shall review the genetic evidence for a recent African origin of modern humans, focusing mostly (but not exclusively) on the mitochondrial DNA story, and discuss what the future holds in terms of additional insights from genetics concerning modern human evolution.

The mtDNA story

The first (and still most prominent source) of DNA evidence concerning human origins comes from the mitochondrial DNA (mtDNA) genome.

The human mtDNA genome consists of about 16 500 base-pairs of DNA, or about 0,0006% of the human nuclear DNA genome. However, the importance of mtDNA for evolutionary studies far outweighs its actual contribution to the total human genome, and several properties of mtDNA make it useful for such studies. I have discussed these properties recently in detail elsewhere (Stoneking, 2003), and hence will just briefly touch on them here. First, mtDNA is present in high copy number in human cells. The average somatic cell has just two copies of any given nuclear gene or DNA segment, but hundreds to thousands of copies of mtDNA. This property, along with the extra-nuclear, cytoplasmic location of mtDNA, makes it easier to obtain mtDNA for analysis, and also makes mtDNA the molecule of choice for analyses of ancient DNA and for certain forensic DNA applications.

Second, mtDNA is strictly maternally inherited, with no paternal contribution or recombination. This means that the only source of variation among mtDNA types is mutation, and hence the number of mutations separating two mtDNA types is a direct measure of the length of time since they shared a common ancestor. Strict maternal inheritance of mtDNA was called into question recently by purported claims of evidence for mtDNA recombination (Awadalla et al, 999; Eyre-Walker et al, 1999; Hagelberg et al, 999). Some of these claims have been discredited and/or retracted (Macaulay et al, 1999; Hagelberg et al, 2000), whereas inadequacies of the statistical analyses (Jorde and Bamshad, 2000; Kivisild and Villems, 2000; Kumar et al, 2000; Parsons and Irwin, 2000) have led to the recognition that at present there is no compelling evidence for mtDNA recombination (Eyre-Walker and Awadalla, 2001). A recent demonstration of paternal inheritance of mtDNA (Schwartz and Vissing, 2002) has raised again the possibility of mtDNA recombination (Bronham et al, 2003), but it must be kept in mind that this single example of paternal inheritance involves a heteroplasmic condition that appears to be confined to muscle tissue in the individual. Despite extensive family studies, there is as yet no indication of a paternal contribution or recombination event involving mtDNA that is transmitted across generations (Parsons et al, 1997; Jazin et al, 1998; Sigurdardottir et al, 2000), thus analyses and interpretations of mtDNA variation in humans that rely on the presumption of strict maternal inheritance would, at least for the moment, seem to be on safe ground.

The final property of mtDNA of evolutionary interest is that it evolves rapidly, some 5-10 times faster than the average segment of nuclear DNA. This rapid evolutionary rate means that mtDNA will be most useful for comparisons involving closely-related species or populations of the same species, as a sufficient number of mutations will have occurred even over a short evolutionary time span to permit an assessment of species/population relationships. However, the pattern of mutations in mtDNA is unusual in that transitions are much more frequent than transversions, and moreover some sites are hypervariable, evolving much more rapidly than average (Hasegawa et al, 1993; Wakeley, 1993; Excoffier and Yang, 1999; Meyer et al, 1999). These two aspects of the mutational process result in a high frequency of parallel/multiple substitutions at the same nucleotide position, which in turn greatly complicates phylogenetic reconstruction of the ancestry of human mtDNA types.

MtDNA and human evolution

By making use of these properties of mtDNA, initial studies of human mtDNA variation led to what has become popularly known as the 'African Eve' hypothesis (Cann et al, 1987; Vigilant et al, 1991); subsequent work has (largely) supported and extended this hypothesis. There are three aspects to this hypothesis: first, all mtDNA types in contemporary populations trace back to a single ancestor; second, this ancestor probably lived in Africa; and third, this ancestor probably lived about 150 000-200 000 years ago.

The first aspect, that there was a single common ancestor of all contemporary human mtDNA types, is not a hypothesis but rather a straightforward conclusion: if there was indeed a single origin of life on this planet, then all variation in any segment of DNA must necessarily trace back to a single ancestor at some point in the past. Since mtDNA is maternally inherited, this ancestor must have been female. However, as Figure 1 illustrates, the mtDNA ancestor was not the first or only female alive; she was a member of a population, but the mtDNA types of her contemporaries eventually went extinct, either because they or their descendants left no offspring or left only male offspring. She also had

ancestors, who were then by definition also ancestors of contemporary mtDNA types, but she represents the most recent common ancestor, i.e. the most recent time for which there was a single ancestor alive. Most importantly, she was not even necessarily human (the ancestor could, in theory, have lived at any time in the past), nor was she necessarily the ancestor of all of our genes (all of our genes do have ancestors, but they are likely to be different individuals who lived in different places and at different times).

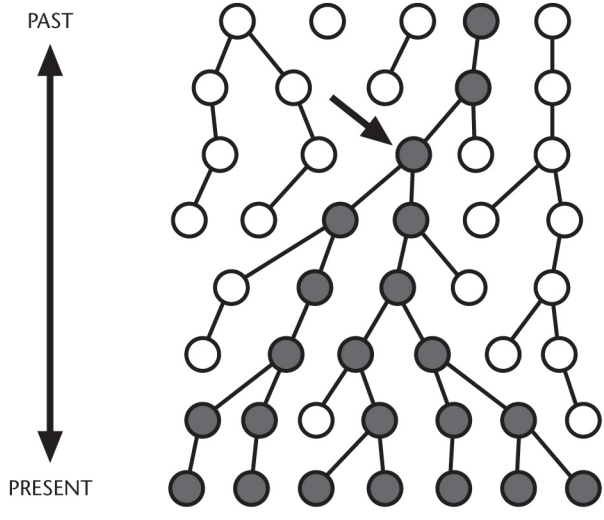

Figure 1. A simplified illustration of the principle that all mtDNA types in a contemporary population must trace back to a single common ancestor at some point in the past. Solid circles indicate the path of descent from the ancestor (arrow) to the present, empty circles represent mtDNA types that went extinct (modified from Stoneking, 1993).

Two types of data have been interpreted as supporting an African origin for the human mtDNA ancestor: phylogenetic analysis; and relative amounts of mtDNA sequence divergence. Phylogenetic trees depicting the evolutionary history of mtDNA types in human populations invariably contain two primary branches, one consisting solely of African mtDNAs, the other consisting of some African and all non-African mtDNAs (Figure 2). While other explanations are possible, the simplest explanation for this pattern is to suppose that the ancestor was indeed African. To be sure, the construction of phylogenetic trees for large da-

tasets, consisting of hundreds of mtDNA types, is far from straightforward; nevertheless, more refined methods of phylogenetic analysis,as well as more informative datasets (consisting of sequences of the entire mtDNA genome) continue to support an African origin of the human mtDNA ancestor (Penny et al, 1995; Ingman et al, 2000).

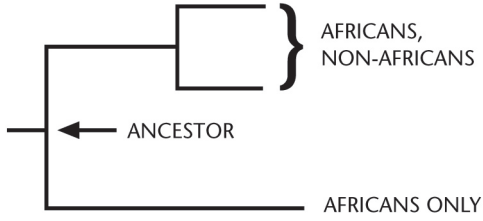

Figure 2. A simplified version of the results of phylogenetic analysis of mtDNA types (and other genes) in human populations. Invariably such trees consist of two primary branches, with only Africans represented on both branches. This sort of pattern is most easily explained by assuming that the ancestor was African (modified from Stoneking, 1993).

In addition to phylogenetic analyses, all studies of worldwide human mtDNA variation have found that, on average, African populations have the greatest mtDNA sequence divergence, followed by Asian and European populations (Johnson et al, 1983; Cann et al, 1987; Merriwether et al, 1991; Vigilant et al, 1991). It is important to note that this measure of mtDNA variation is not a simple gene-frequency based measure of variation, but rather directly reflects the average number of mtDNA mutations that have accumulated within populations. The fact that Africans have the largest mtDNA sequence divergence indicates that they have accumulated the most mtDNA mutations, and the argument for an African origin states that the population with the most diversity is likely to be the ancestral population. Not only do non-African populations have, on average, much less mtDNA diversity, but they also appear to have a subset of the diversity present in Africa. That is, the mtDNA type diversity in Africa appears to encompass all of the diversity found outside of Africa, again in keeping with an African origin.

There are two aspects to estimating the age of the human mtDNA ancestor: (1) determining the amount of sequence divergence that has accumulated since the mtDNA ancestor; and (2) determining the rate of human mtDNA sequence divergence. The amount of sequence

divergence that has accumulated since the mtDNA ancestor is easily determined from the phylogenetic trees. Of more concern, then, is determining the rate of human mtDNA sequence divergence, and two approaches have been used: comparison of chimpanzee and human mtDNA sequence divergence, assuming a 4-6 million year divergence time (e.g. Vigilant et al, 1991); and estimation of the amount of mtDNA sequence divergence accumulating within a relatively isolated human population (such as Papua New Guinea), using archeological evidence to estimate the time of isolation (Stoneking et al, 1992). Both approaches, when applied to a variety of human mtDNA datasets, yield dates for the human mtDNA ancestor of 50 000 – 500 000 years ago, with the majority of dates for the most comprehensive datasets falling between 150 000 and 200 000 years ago (Stoneking and Soodyall, 1996). The best dataset, of complete human mtDNA sequences, yields a date of about 150 000 years ago for the human mtDNA ancestor (Ingman et al, 2000).

Ancient DNA

The above discussion is based on analysing patterns of mtDNA variation in contemporary populations and then attempting to infer what evolutionary scenario would most likely give rise to the observed patterns. There is a potential alternative source of information on mtDNA and human origins, and that is the analysis of mtDNA retrieved from ancient specimens. In particular, the above analyses of contemporary human mtDNA variation make two predictions concerning ancient mtDNA sequences: (1) mtDNA sequences from archaic non-African populations (such as Neandertals) ought to be quite different from contemporary mtDNA sequences; and (2) mtDNA sequences from early modern humans ought to be similar to contemporary mtDNA sequences. With respect to the first prediction, mtDNA sequences have now been published from four Neandertals (Krings et al, 1997; Krings et al, 2000; Ovchinnikov et al, 2000; Schmitz et al, 2002). The Neandertal mtDNA sequences are quite different from modern human mtDNA sequences, falling outside the range of modern human mtDNA variation, and diverged from the lineage leading to modern humans some 600 000

years ago. Thus, the first prediction is fulfilled, namely that Neandertal mtDNA is not closely related to contemporary human mtDNA. The second prediction has proven more problematic to test, since contemporary human mtDNA can be obtained from virtually every fossil tested, even fossils of non-human origin (Hofreiter et al, 2001). Therefore, the recent claim that an authentic mtDNA sequence that is similar to contemporary mtDNA sequences was obtained from a 24 000-year-old fossil of a modern human (Caramelli et al, 2003) must unfortunately be treated with caution, as there still exists the possibility that the sequence obtained was from contaminating contemporary DNA and not from the authentic ancient DNA.

Evidence from other genes

The mtDNA evidence from both contemporary populations and ancient specimens thus points to a recent African origin for all extant human mtDNA types. However, mtDNA is a single genetic locus, and the history of a single locus may be influenced by selection and/or genetic drift. It is therefore necessary to study many loci to obtain accurate insights into human evolution. After mtDNA, the next obvious locus of choice is the Y chromosome, as the paternal and non-recombining mode (over most of the chromosome) of inheritance makes it the natural counterpart to mtDNA. However, unlike mtDNA, the Y chromosome evolves slowly, and hence studies of human Y-DNA variation were frustrated for many years by the lack of suitable polymorphic markers. Fortunately, the situation has changed in the past few years, and there are now a large number of highly informative Y chromosome markers (Underhill et al, 2000; Underhill et al, 2001). Studies of Y chromosome variation also point to an African ancestry, as phylogenetic trees of Y chromosome types are invariably of the same structure as that shown in Figure 2. Dates for the age of the human Y-chromosome common ancestor are also recent, ranging from approximately 40 000 to 200 000 years ago (Hammer, 1995; Hammer et al, 1998; Pritchard et al, 1999; Underhill et al, 2000); thus the Y chromosome appears to match quite closely the mtDNA evidence with respect to human origins.

Data from other nuclear genes has been accumulating rapidly over

the past decade or so, and is also consistent with the recent African origin hypothesis (Bowcock et al, 1994; Tishkoff et al, 1996; Stoneking et al, 1997; Takahata et al, 2001). Indeed, the only serious challenge to the recent African origin hypothesis, based on genetic evidence, comes from the work of Templeton (2002). Templeton developed a method called nested clade analysis (NCA), which provides a statistical framework for making inferences about population structure and history from genetic data. When applied to human genetic data, Templeton concluded that NCA indicated that there was a genetic signature in contemporary human populations of multiple migrations out of Africa over the past million years, and of recurrent gene flow, and not replacement, following the migrations out of Africa. However, NCA has not been subjected to rigorous testing with simulated data. Indeed, in one such test of a simple population history (bifurcation of an ancestral population into two daughter populations which did not exchange migrants after the bifurcation event) using simulated data, NCA did not recover the correct history (Knowles and Maddison, 2002). It is particularly telling that instead of the correct history, NCA gave the interpretation that the simulated data had been generated under a model of recurrent gene flow, which is precisely the inference that NCA gives for the human genetic data (Templeton, 2002). It would seem that any inferences based on NCA should be treated cautiously until the performance of the method is adequately assessed via extensive simulations.

Conclusions and future prospects

Genetic and fossil evidence overwhelmingly support a recent African origin for our species. Indeed, debate in the anthropological community now focuses not on whether there was a recent African origin of modern humans, but rather on this question: Was this recent African origin accompanied by a complete replacement of archaic non-African populations, or was there some genetic contribution of Neandertals or other archaic non-African populations to modern humans? As I have discussed above, currently the genetic evidence from both contemporary populations and ancient specimens gives no indication of any such genetic contribution from archaic non-African populations. What would

conclusive genetic evidence for such a contribution look like? I believe that the strongest indication that there was not complete replacement would be the discovery of a DNA sequence or haplotype which either was not found in Africa or was associated with less diversity in Africa than outside Africa (implying a non-African origin for this sequence/haplotype), and which arose more than about 150 000-200 000 years ago, i.e. prior to the origin of modern humans. The presence of such an ancient, non-African DNA sequence/haplotype would argue strongly for a direct genetic contribution to modern humans from an archaic non-African population, and hence against complete replacement. Indeed, one potential candidate haplotype has recently been described at the dystrophin gene (Zietkiewicz et al, 2003). This haplotype (B006) is virtually absent in Africa and is estimated to have arisen about 165 000 years ago. However, only four native African samples (none from east or south Africa) and one African-American sample were included in the study; as previous work has amply demonstrated, the large genetic diversity in Africa demands that extensive sampling across all geographic regions has to be done before any conclusions can be drawn about the distribution of particular haplotypes in Africa. Moreover, the standard error of the age estimate of 165 000 years was not calculated in the study but is undoubtedly large, probably as large as the age estimate itself since this is based on a single microsatellite locus. Thus, more work needs to be done before the B006 haplotype can be taken as evidence against complete replacement.

What does the future hold for genetic studies in the context of human origins? Some indications have already been given: continuing to characterise genetic variation at other loci, especially to see if there is any evidence that would contradict complete replacement, as well as analysing ancient DNA from other archaic human and from early modern human remains (assuming the current technical difficulties can be overcome). But one of the nice things about answering one question is that other questions always arise, and having determined that a recent African origin was undoubtedly a major (if not THE major) event in the evolution of modern humans, we can ask, what happened next? Tracing the migration(s) of modern humans from (and perhaps back to) Africa, understanding the peopling of the rest of the world in terms of where they came from, when they came, and how many migrations there were

– these sorts of questions have already occupied geneticists for some time and will continue to do so. Moreover, the wealth of information about gene function coming from genomic investigations, as well as new analytical methods, are making it feasible to address other aspects of modern human origins. In particular, the questions about population history and migrations and so forth that have occupied geneticists have been best addressed with neutral genetic markers, i.e. genetic variation that has no influence on an individual's chances of surviving and reproducing. But, as modern humans spread around the world, they were exposed to new environments, sources of nutrition, parasites, diseases, etc., and undoubtedly adaptation via natural selection to these new conditions must have played some role. Which genes and traits have been shaped by such selection, and how important was selection in influencing patterns of genetic variation? In particular, what is the genetic basis of the morphological variation that biological anthropologists have traditionally studied and documented among human populations, and what evolutionary forces were responsible for producing this variation? Studies of genetic variation have made key contributions to our understanding of the origin and evolution of modern humans, and even though the questions are changing, I believe that major new insights (and perhaps even some answers) will continue to come from such studies.

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