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GENETICS OF MODERN HUMAN ORIGINS AND DIVERSITY

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ABSTRACT

A major and continuing debate in anthropology concerns the question of whether modern *Homo sapiens* emerged as a separate species roughly 200,000 years ago in Africa (recent African origin model) or as the consequence of evolution within a polytypic species spread across several regions of the Old World (multiregional model). Genetic data have been used to address this debate, focusing on the analysis of gene trees, genetic diversity within populations, and genetic differences between populations. Although the genetic data do provide support for the recent African origin model, they also are compatible with the multiregional model. The genetic evidence provides little direct inference regarding phylogeny, but it can tell us a great deal about ancient demography. Currently, neither model of modern human origins is unequivocally supported to the exclusion of the other.

INTRODUCTION

During the last decade, the question of modern human origins has been addressed more and more often using genetic data. The motivation behind this research is that genetic variation in the world today is a reflection of the past. Combined with inferences from fossil and archaeological records, genetic data may supply answers to some basic questions about human population history. The primary, and most controversial, focus of such research has been the debate over modern human origins.

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This paper outlines current understanding of the anthropological implications of genetic variation for models of modern human origins. A quick review of recent literature might suggest that the basic question is solved and that there is no further controversy. Numerous genetics papers indicate the genetic data come down firmly in favor of an African replacement model. Most often, however, the data can be interpreted in several ways. Genetics can tell us a great deal about our species' history, but it is not always the information we expect.

MODELS OF MODERN HUMAN ORIGINS

The question of modern human origins is concerned with the evolutionary relationship of anatomically modern humans to hominids that appear earlier in the fossil record. Which populations (both spatially and temporally) contributed to later humanity? Did any become extinct without issue? Did the contributions vary across both time and space? Did the evolutionary transitions take place within a single evolutionary lineage or are they associated with speciation events? The modern human origins debate goes beyond the basic question of reconstructing our family tree. It is also concerned with tempo and mode of evolution, different concepts of species, and the extent to which hominids are (or are not) unique in their evolutionary history.

Before considering how genetic data and analyses contribute to this debate, it is first necessary to summarize the basic models of modern human origins. This is not a simple task. A variety of different models have been proposed, and though many are similar, they have different emphases (Smith & Harrold 1997). This article takes the simple approach of distinguishing between two basic views—recent African origin and multiregional evolution. Other variants, such as Bräuer's (1984) "Afro-European hybridization model" and Smith et al's (1989) "assimilation model" are considered within this general framework.

The Recent African Origin Model

The recent African origin model proposes that anatomically modern humans emerged in Africa roughly 200,000 years ago and then dispersed throughout the Old World, replacing preexisting archaic hominids with little or no admixture (e.g. Cann et al 1987, Stringer & Andrews 1988, Stringer 1990, Stringer & McKie 1996). Implicit in many discussions of the recent African origin model is the idea that anatomically modern *Homo sapiens* are a separate species from archaic *Homo sapiens*. The origin of modern humans is, therefore, often seen as resulting from cladogenesis, the formation of a new lineage.

The Multiregional Evolution Model

The multiregional evolution model is not a specific model of modern human origins but rather a general model focusing on evolutionary process within a

polytypic species (e.g. Wolpoff et al 1984, Wolpoff 1989, Thorne & Wolpoff 1992, Wolpoff & Caspari 1997). Multiregional evolution views all hominid evolution since the origin of *Homo erectus* as taking place within a single evolutionary lineage. Multiregional evolution is a general evolutionary model that attempts to account for species-wide change while allowing for local and regional continuity. It is important to note that despite arguments to the contrary (e.g. Waddle 1994), multiregional evolution does not necessarily argue that the primary genetic input into any region of modern humans came from within the same geographic region. Other models are also possible within the general multiregional framework, including major genetic changes originating within Africa and mixing, through gene flow, with non-African populations. A good example of the range of models accommodated under the general model can be found in Wolpoff et al (1994).

Intermediate Models

The recent African origin and multiregional evolution models are often portrayed as two extremes within a range of possible models dealing with modern human origins. As a result, several "intermediate" models have been proposed. One such is the assimilation model of Smith et al (1989). It views modern humans as resulting from an initial genetic change occurring within Africa, which then spread throughout the rest of the Old World through gene flow and mixture with archaic non-African populations. This model is often labeled intermediate because it appears to combine the initial appearance of modern morphology in Africa with regional continuity outside of Africa. In actuality, this is one of several specific models possible under the general multiregional framework (Wolpoff et al 1994).

Another example is the Afro-European model proposed by Bräuer (1984). In it, modern humans are thought to arise in Africa and from there spread throughout the remainder of the Old World, as suggested by the recent African origin model. However, Bräuer also acknowledges some admixture between the modern humans and preexisting archaic humans outside of Africa. At the most general level, this is similar to the views of Smith et al, even though Bräuer argues that his model is a variant of the recent African origin model (Stringer & Bräuer 1994). The difficulty the newcomer (or professional) faces is clear—at what point do the various specific models labeled as "recent African origin" or "multiregional evolution" overlap with one another? The literature suggests that the same terms are frequently used to mean different things.

A further complication is the frequent dichotomy between models that propose a single region of origin versus those that propose more than one. On this point, multiregional models are often portrayed as implying that all major geographic regions (Europe, Africa, Middle East, East Asia, Australasia) are in-

volved in the transition. Although this is one possible model within the general multiregional framework, it is not the only one. To be multiregional in the most general sense, all that is required is genetic contributions from at least two geographic regions. As a result, many possible specific models can be subsumed under the general multiregional model.

Genetic Perspectives—Phylogenetic Branching or Population Structure?

Population genetics can be brought to bear on the issue of modern human origins by analyzing patterns of genetic variation within and among living populations. These present-day patterns can be interpreted in terms of the likelihood of different past evolutionary patterns giving rise to contemporary variation. This is not as clear cut as it might seem. To start with, there are two different perspectives that can be applied to analyzing patterns of genetic variation.

One perspective is a phylogenetic branching model. Here, genetic differences between populations are thought to have arisen from a series of bifurcating splits. A typical scenario sees modern humans arising as a single population in Africa. At some later time, this parental population splits, giving rise to a non-African daughter population. Later, the non-African population splits further, giving rise to separate regional populations in Europe, Asia, and Australia. Under a phylogenetic branching model, genetic distances between regional populations result from the accumulation of mutations and the action of genetic drift along each branch, such that genetic distance is proportional to time. Also, mutations will accumulate within populations, such that the oldest populations will show the greatest accumulation and, hence, the greatest within-group genetic diversity.

This phylogenetic perspective corresponds to the recent African origin model, which sees a series of population splits over time. As reviewed below, there is ample evidence that sub-Saharan Africans today have the greatest levels of within-group diversity and are generally the most distant regional population in genetic distance analyses. On the surface, the close fit between observed data and the predictions of a phylogenetic branching process would seem to argue for a recent African origin model.

The situation, however, is more complex. The fact that the genetic evidence is compatible with the recent African origin model does not prove it true. The fit of data and theory would be proof only if a phylogenetic branching process was the only way to generate the observed patterns of genetic variation. The fact that data can be fit by a tree does not make it a tree. An alternative is the population structure approach, which focuses on the evolution of populations connected by gene flow. Genetic variation within and among populations is seen as resulting from the balance between gene flow and genetic drift (note

that this discussion assumes that the traits in question are selectively neutral, an assumption also shared by the phylogenetic branching model).

The conflict between these approaches arises because of the indeterminate nature of the results of genetic analyses. As Felsenstein (1982) points out, migration can mimic a phylogenetic branching process and vice versa. This point has also been emphasized by Relethford (1995), Relethford & Harpending (1994, 1995), and Sherry & Batzer (1997). Since phylogenetic branching models and population structure (gene flow-drift) models can give the same results, this means that our analyses are not often likely to tell us which underlying model is correct!

An additional, and often ignored, problem is due to the nature of our units of analysis—living human populations. Many evolutionary questions are directly interpretable from a phylogenetic branching model because we start with living groups that are separate species, such as humans and the living great apes. Because these groups have been separate evolutionary entities (species) for a long time, the issue of gene flow between them is meaningless, and the only appropriate model is based on a phylogenetic branching process. Genetic distances between living hominoids can be taken as an index of the pattern and timing of cladogenesis.

The situation with modern human origins is more problematic. Regardless of the number of species in the past, all living human populations belong to the same species. Any attempt to force data from regional populations (races) into a phylogenetic branching model is invalid because they are not separate evolutionary entities. Regional populations are all interconnected via gene flow and, as far as we can tell, have been so for some time. Even if regional differences began only 100,000 years ago as the result of dispersal from Africa and subsequent branching, the continued action of gene flow makes the reconstruction of phylogenetic trees and the dating of population splits difficult at best (Weiss & Maruyama 1976, Weiss 1988).

GENETIC EVIDENCE FOR MODERN HUMAN ORIGINS

Several lines of genetic evidence bear on the modern human origins debate. Each must be looked at from both the phylogenetic branching model and the alternative population structure approach based on migration-drift models.

Gene Trees and Coalescence

Much of the debate has focused on the genealogical relations between genes rather than populations. Such gene trees describe the process of coalescence (Hudson 1990, Donnelly & Tavaré 1995, Harding 1997, Marjoram & Donnelly 1997). The objective is to determine how and when the genes from any

two individuals join together in a common ancestor (coalescence) at some point in the past. Given knowledge of the mutation rate for a given genetic trait, the date of coalescence can be estimated.

MITOCHONDRIAL DNA Much of the discussion of coalescence theory and gene trees in the modern human origins debate has focused on mitochondrial DNA (mtDNA), a small amount of DNA in the mitochondria of cells that is inherited maternally (Stoneking 1993). The first significant application of mtDNA to the question of modern human origins was in a study by Cann et al (1987). mtDNA for 133 distinct types was collected from 147 people representing ancestry in Africa, Europe, Asia, and Australasia. Their gene tree had two major branches: One consisted entirely of individuals with African ancestry, and the other contained individuals of all different ancestries (including Africa). From this it was concluded that the common mtDNA ancestor of all living humans ("mitochondrial Eve") lived in Africa. By itself, this conclusion was not controversial because proponents of both recent African origin and multiregional evolution models acknowledge an African origin of humanity. The controversy is over timing—the multiregional model claims that the common African ancestor was *Homo erectus*, who lived close to two million years ago, whereas the recent African origin model postulates the origin of modern humans as a separate species whose existence came about within the past 200,000 years.

The controversial point of the paper was the estimate of the age of coalescence. Using a mutation divergence rate of 2–4% per million years, the authors estimated that mtDNA coalescence took place between 140,000 and 290,000 years ago. In their view, this was too recent to be detecting the African origin of *Homo erectus*. In addition, they noted the higher mtDNA diversity within their African sample, which they argued was consistent with a greater age for African populations. Some of the initial criticisms (Spuhler 1988, Excoffier & Langaney 1989, Wolpoff 1989) included discussion of problems in estimating the mutation rate, methods used to derive the genealogical tree, and the use of African Americans to represent African ancestry. A number of these criticisms were addressed in a subsequent study by Vigilant et al (1991), who also found an African root for the genealogical tree and estimated a coalescent date of 166,000–249,000 years ago. Since these papers, numerous studies have dealt with the analysis and interpretation of mtDNA variation. Rather than review these studies extensively, this article focuses on two key findings that have been used to argue for a recent African origin—the African root of the gene tree and the date of coalescence.

An African root The African location of the common mtDNA ancestor has been questioned by several studies that found that the initial application of the

computer algorithm used to find the best-fitting tree was flawed (Maddison 1991, Templeton 1992, Hedges et al 1992). Sometimes the best-fitting trees showed an African origin, but sometimes they did not. However, a newer method that has since been applied to the mtDNA data also argues for an African origin (Penny et al 1995).

A problem that remains is the exact interpretation of such results. Many researchers suggest that the geographic pattern of mtDNA variation is best described by the recent African origin model, but not everyone agrees. Excoffier & Langaney (1989) critiqued the methodology of Cann et al (1987) and suggested that there was no clear support for an African origin. Templeton (1993, 1994, 1996b, 1997) argued that the geographic distribution of mtDNA types is also compatible with recurrent gene flow under a multiregional model. Templeton (1997) further notes that although a non-African root for a gene tree could reject the recent African origin model, the reverse is not true: An African root could be explained by either replacement out of Africa or by low levels of gene flow between geographic regions since the time of coalescence. As Templeton (1997:330) points out, "Under the gene flow hypothesis, the common ancestor could have lived anywhere in the Old World, including Africa."

The date of the mtDNA coalescent Much debate has focused on the initial estimate by Cann et al (1987) of roughly 200,000 years for the date of the common mtDNA ancestor. Many subsequent studies have also argued for a relatively recent date of coalescence, though there are some differences, depending on the specific date used for the human-chimpanzee split, which is used to calibrate estimates of the mutation rate. Vigilant et al (1991) estimated a date of 166,000–249,000 years based on a 4- to 6-million-year date for the human-chimpanzee divergence. Ruvolo et al (1993) used a 6-million-year calibration time and estimated the coalescence to human mtDNA at 298,000 years, with a 95% confidence interval (CI) of 129,000–536,000 years. Horai et al (1995) used a 4.9-million-year divergence to estimate 143,000 years (95% CI = 107,000–179,000 years). Stoneking et al (1992) estimated the date of coalescence with a method that used estimates of the peopling of New Guinea for calibration and obtained a date of 137,000 years (95% CI = 63,000–416,000 years).

Several problems in estimation have been addressed. Templeton (1993) reviewed problems in potential error due to the large variance of such estimates and the choice of calibration date for the human-chimpanzee divergence. Based on the data from Cann et al (1987) and Vigilant et al (1991), Templeton argued that the upper bound for the date of coalescence could be as high as 473,000–844,000 years ago. Wills (1995) pointed out that the failure to adjust for variable mutation rates across mtDNA sites tends to underestimate the date of coalescence. After correction, he suggested a range of 436,000–806,000

years ago, depending on the specific human-chimpanzee calibration date used. Additional problems with mtDNA coalescent dates include the fact that the influence of selection has not been ruled out (Hey 1997, Loewe & Scherer 1997) and new work suggests a wide range of possible mutation rates (Gibbons 1997).

In addition to continued debate over the specific date of coalescence, the whole relevance of coalescent dates has been questioned. Templeton (1994, 1997) questioned the frequent assumption that a mtDNA coalescence prior to 1 million years ago rejects the multiregional model and pointed out that any of the dates estimated so far are compatible with both the recent African origin and the multiregional models. Rogers & Jorde (1995) suggested that such estimates tell us nothing about age per se but rather are an indication that average population size has been small since the time of coalescence (the date of coalescence and population size are both proportional to mtDNA diversity).

THE Y CHROMOSOME Y chromosome polymorphisms provide the male analogue to mtDNA because the Y chromosome is paternally inherited and, excluding a small section, does not recombine (Hammer & Zegura 1996). Although Y chromosome variation is relatively low, several attempts have been made to estimate a coalescence date. Dorit et al (1995) estimated this date to be 270,000 years (95% CI = 0–800,000 years). Using different polymorphisms, Hammer (1995) derived an estimate of 188,000 years (95% CI = 51,000–411,000 years). Both estimates fall within the range of estimates from mtDNA and are consistent with a recent African origin. However, Whitfield et al (1995) came up with a much lower estimate, roughly 40,000 years, using the same polymorphisms. Hammer & Zegura (1996) noted that this difference may reflect differences in sample size (small in both studies) and that revised calculations support Hammer's initial estimate. More recently, Underhill et al (1997) detected 22 Y chromosome polymorphisms in numerous samples of chromosomes. Using two different subsets of their data, they estimated the date of coalescence to be 162,000 (95% CI = 69,000–316,000) years or 186,000 (95% CI = 77,000–372,000) years. The geographic structure of the variation was less clear and suggested the possibility of relatively deep non-African roots.

OTHER GENE TREES Although the mtDNA and Y chromosome data are frequently cited as support for a recent African origin, it has been suggested that the same patterns are expected under a multiregional model (Templeton 1993, 1997). In addition, the application of coalescent theory to nuclear genes has often resulted in different interpretations. Klein et al (1993) and Ayala et al (1994) examined variation in the major histocompatibility complex and concluded that either origin model could be supported and that the major histo-

compatibility complex (as well as mtDNA) tells us primarily about ancient population size (see below). Harding et al (1997) examined the gene tree for the beta-globin gene and estimated coalescence in Africa roughly 800,000 years ago. However, they also found evidence for an ancient Asian influence, dating back more than 200,000 years. They argued that this evidence does not support a recent African origin model where modern humans dispersed from Africa 100,000 years ago and replaced all preexisting non-African populations. Rather, their data suggest that there is significant Asian ancestry well before that time. A recent analysis of *Alu* insertion polymorphisms estimated a date of approximately 1.4 million years ago for the human coalescent (Sherry et al 1997). Considering the likely standard error, this date is not incompatible with the origin of *Homo erectus*.

Genetic Diversity Within Populations

In addition to an estimate of the location and age of coalescence from mtDNA, Cann et al (1987) also noted that mtDNA sequence diversity was greatest within their African sample. A higher level of diversity within Africa was felt to be consistent with the recent African origin model under the assumption that the older a population is, the more mutations have accumulated. Stoneking & Cann (1989:22) note: "If one accepts that mtDNA mutations are largely neutral, then their occurrence and accumulation are mostly a function of time: the more variability a population possesses, the older it is." Since Africa had the greatest level of mtDNA diversity, it was therefore the oldest, in agreement with the prediction from the recent African origin model that modern humans arose in Africa and only later dispersed into other parts of the Old World.

Subsequent analysis has confirmed higher levels of mtDNA diversity (measured in several ways) in sub-Saharan Africa (e.g. Vigilant et al 1991, Bowcock et al 1994, Jorde et al 1995), although the statistical significance has been questioned (Templeton 1993). In any case, excess African diversity has also been observed for microsatellite DNA (Bowcock et al 1994, Deka et al 1995, Jorde et al 1995, 1997; Tishkoff et al 1996; JH Relethford, LB Jorde, unpublished data), craniometric data (Relethford & Harpending 1994), and *Alu* insertion polymorphisms (Stoneking et al 1997).

In general, most of the genetic data to date shows the highest levels of within-group variation in sub-Saharan African populations. There are two exceptions: classic genetic markers and restriction fragment length polymorphisms (RFLPs) (Bowcock et al 1994, Jorde et al 1995). One possible explanation is ascertainment bias (Rogers & Jorde 1996): Because both classic genetic markers and RFLPs were first detected in European populations, the loci that were polymorphic among Europeans were those applied most often elsewhere in the world. As a result, European heterozygosity is biased upwards. Another

contributing factor is mutation rate. Both classic genetic markers and RFLPs have low mutation rates relative to mtDNA, microsatellite DNA, and craniometrics and will therefore not show excess African diversity (Relethford 1997).

Apart from these exceptions, the pattern of within-group diversity appears to be consistent with the recent African origin model. However, a critical assumption is made relating a population's diversity and its age (Relethford 1995). A new daughter population must experience a severe and long-lasting reduction in population size (bottleneck) in order to reduce its level of within-group diversity to zero. Although new founding populations are generally small, the actual reduction must be large and long lasting in order to reduce the initial level of diversity significantly. In addition, as a daughter population increases in size (required by the recent African origin model), the level of within-group diversity will increase. The actual impact of a founding event on within-group diversity in a daughter population depends on the sizes of the parent and daughter population(s) and the extent and duration of the bottleneck. Rogers & Jorde (1995) showed that to produce a strong correlation between age and diversity, such bottlenecks would have to have been much more severe and long lasting than is realistic.

The arguments linking population diversity and age are clearly within the phylogenetic branching framework discussed above. An alternative view, stemming from a population structure perspective, is that the level of within-group diversity is to a large extent a function of population size. Relethford & Harpending (1994) showed that higher levels of craniometric variation in sub-Saharan Africans is most likely the consequence of the long-term population in Africa being more numerous than in any other geographic region. This same finding has also been observed with microsatellite DNA data (JH Relethford, LB Jorde, unpublished data). These results suggest that during recent human evolution, the bulk of our ancestors (estimated between 50% and 70%) lived in sub-Saharan Africa (Relethford & Harpending 1994; JH Relethford, LB Jorde, unpublished data). Using a similar method applied to a worldwide analysis of *Alu* insertion polymorphisms, Stoneking et al (1997) also found evidence for a more numerous African population, although they did not estimate relative population size. It is important to note that a more numerous African population is also expected based on its larger landmass (Thorne et al 1993, Wolpoff & Caspari 1997).

A larger long-term African population size fits the recent African origin model because the non-African daughter populations would initially be small in number and later grow. Because the long-term effective size of a population is closer to the minimum than to the arithmetic average, the demographic history suggested by the recent African origin model would result in a large African size. However, a more numerous African population is also expected by,

and is consistent with, the multiregional evolution model, where Africa serves as the center of the species' distribution and the peripheries are smaller in population (Wolpoff & Caspari 1997).

Genetic Differences Between Populations

The focus of gene trees and coalescent theory is on the relationships of individual genes. Another approach is to examine genetic relationships among populations. Most typically, genetic data are aggregated at a regional level (e.g. sub-Saharan Africa, East Asia, Europe, and so forth). Genetic differences between populations are then computed and used to generate insight into past evolutionary events. Genetic differences may be simply reported or more formally compared using one of a variety of genetic distance measures. The focus of such studies is the reconstruction of population history. On a global level, this reconstruction relates directly to the issue of modern human origins.

GENETIC DISTANCES BETWEEN HUMAN POPULATIONS A variety of genetic data have been examined at the populational level with a consistent result: Sub-Saharan African populations tend to be the most genetically distant, and non-African regional populations tend to be more similar to one another than any are to Africa. This pattern has been found for mtDNA (Vigilant et al 1991, Jorde et al 1995), Y chromosomes (Underhill et al 1997), *Alu* insertion polymorphisms (Batzer et al 1994, Stoneking et al 1997), microsatellite DNA (Bowcock et al 1994, Deka et al 1995, Jorde et al 1995, Tishkoff et al 1996), RFLPs (Bowcock et al 1991, Mountain & Cavalli-Sforza 1994, Jorde et al 1995), classic genetic markers (Nei 1978, Nei & Livshits 1989, Cavalli-Sforza et al 1994, Relethford & Harpending 1995), and craniometrics (Lynch 1989, Relethford & Harpending 1994, 1995).

The greater divergence of Africa is compatible with the recent African origin model, which predicts that the first split is between Africa and a non-African population, with a later split that populates the rest of the Old World. As such, the genetic distances between regional populations (which are often expressed graphically by a cluster analysis tree) are a record of these past splits. Under this view, Europe and Asia are more similar genetically to each other than either is to Africa because they share a more recent common ancestor.

However, the fact that the genetic distances between populations can be represented by a tree structure does not mean that an underlying tree model is correct (Relethford & Harpending 1994, Relethford 1995, Sherry & Batzer 1997). An alternative is that the genetic distances are instead a reflection of varying rates of gene flow. Relethford & Harpending (1994, 1995) have used genetic marker and craniometric data to show that the pattern of genetic distances among living human populations could just as easily be explained by variation in population size and rates of gene flow (see also Relethford 1995).

LEVELS OF GENETIC MICRODIFFERENTIATION Another type of genetic distance analysis focuses on the degree of among-group variation relative to total variation. A number of studies have shown that the relative proportion of among-group variation, F_{ST} (Wright 1951), is low for the human species. The values of F_{ST} as computed among major geographic regions clusters around 0.10–0.15, showing that roughly 10–15% of total genetic variation is between groups and 85–90% is within groups. Estimates in this range have been found in analyses of classic genetic markers (Lewontin 1974, Latter 1980, Nei & Roychoudhury 1982, Ryman et al 1983, Livshits & Nei 1990, Cavalli-Sforza et al 1994), nuclear DNA restriction site polymorphisms (Bowcock et al 1991, Jorde et al 1995, Barbujani et al 1997), microsatellite DNA (Deka et al 1995, Barbujani et al 1997), *Alu* insertion polymorphisms (Batzer et al 1994, Stoneking et al 1997), and craniometrics (Relethford 1994). Lower values of F_{ST} have been found for some microsatellite loci (Jorde et al 1995) and for mtDNA (Whittam et al 1986, Jorde et al 1995, Harpending et al 1996), perhaps reflecting higher mutation rates for these traits.

These F_{ST} values are generally considered low relative to many other animals (Relethford 1995), and they have often been taken as evidence for a recent African origin. Under this model, the relatively low among-group variation of modern humans is a direct reflection of a fairly recent common ancestry where there has not been sufficient time for larger genetic distances to evolve. Again, while such evidence is compatible with a recent African origin, it is also compatible with a migration-based alternative. Perhaps these relatively low F_{ST} values reflect relatively higher rates of migration? Since multiregional evolution requires migration among groups throughout the species, then perhaps all we are seeing is a genetic index of the rate of such migration.

Genetic Demography and Modern Human Origins

In recent years the debate over modern human origins has, to some extent, moved from phylogenetic questions to demographic questions. The specific focus of interest has been on estimating changes in ancient population size from genetic data. Population size figures into virtually every equation relating to genetic variation, and it is therefore of interest to use various population genetic models to estimate species and regional population size during recent human evolution. Such estimates do not focus on phylogenetic history directly but can perhaps indirectly provide us with insight into questions of population relationships (Relethford 1995, Rogers & Jorde 1995).

Central to much of population genetics theory is the concept of effective population size (Wright 1969, Crow & Kimura 1970), or the size of the population needed to explain a given pattern of genetic variation. Effective population size N_e is not the same as census population size (N_c), the total number of

individuals in a population. For one thing, not everyone in a population is of reproductive age. Counting the number of reproductive-age individuals in a population is a first approximation to the genetic size of a population, but it is not the only one. A variety of factors—including sex ratio, differential fertility, age structure, temporal changes, level of differentiation among groups, and others—can affect the genetic size of a population. Effective population size is a concept that adjusts for such factors and provides an estimate of the genetic size of a population under ideal conditions.

THE EFFECTIVE POPULATION SIZE OF THE HUMAN SPECIES The concept of effective population size has been used in several analyses of genetic variation of living humans. Here, levels of genetic variation at equilibrium are used to estimate long-term effective population size of the entire species. The results across traits are surprisingly similar and cluster around an approximate long-term average effective size of roughly 10,000. These estimates have been based on variation in classic genetic polymorphisms (Nei & Graur 1984), mtDNA (Wilson et al 1985, Rogers & Jorde 1995), Y chromosome data (Hammer & Zegura 1996), the beta-globin gene (Harding et al 1997), and nuclear DNA sequences (Takahata 1993, Takahata et al 1995). Using *Alu* insertion polymorphisms, Sherry (1996) and Sherry et al (1997) estimated a slightly higher value of N_e (18,000). A higher value of roughly 100,000 was obtained by Ayala (1995) in his analysis of the DRB1 HLA gene (see Erlich et al 1996 and Ayala 1996 for discussion of this estimate). Differences in long-term effective size are in part related to differences in time frame, most often defined by coalescence dates. The mtDNA and Y chromosome estimates relate back to the time period defined by the past 200,000 years or so, whereas Ayala's (1995) estimate refers back to an initial primate ancestor roughly 60 million years ago. Some estimates refer back to a population ancestral to all hominids, whereas others refer back to recent populations ancestral to modern humans (Ayala 1996).

GENETIC EVIDENCE FOR A PLEISTOCENE POPULATION EXPLOSION Estimates of long-term effective size are useful, but it would be better to have a more specific knowledge of possible changes in population size over time. A long-term average value of $N_e \approx 10{,}000$ over the past 200,000 years could theoretically arise from a variety of different demographic scenarios, including constancy, growth, or decline in overall population size. We are better able to interpret the estimate of N_e if we know even approximately the underlying demographic history.

A major breakthrough in studying the genetic signature of ancient demographic events came with the mismatch analysis of Rogers & Harpending (1992). Their method relies on the comparison of mtDNA sequences between

all pairs of individuals in a sample. For each comparison, the number of nucleotide differences (or restriction site differences) is counted and tallied in a histogram. For worldwide human mtDNA data, the resulting histogram (called a mismatch distribution) resembles a bell-shaped curve and is completely different from the distribution expected under a model of constant population size. Instead, the observed mismatch distribution is the same as that expected under a model of rapid population growth. Further, Rogers & Harpending (1992) developed methods to allow estimation of the time of growth and the size of the initial population prior to growth.

The results to date support a rapid population explosion in the Late Pleistocene from a small initial population size (Rogers 1992, Rogers & Harpending 1992, Harpending et al 1993, Harpending 1994, Sherry et al 1994, Rogers 1995, 1997, Rogers et al 1996; see also Marjoram & Donnelly 1994). Estimates of the timing of population expansion vary across populations (as well as by the specific mutation rate used for calibration) but generally fall within the past 100,000 years or so, clustering at around 50,000 years (Sherry et al 1994). Although tentative, preliminary work suggests that the African population expanded earlier than those of other regions (Sherry et al 1994, Relethford 1998) and that prior to the expansion it was more numerous (Relethford 1998).

Of greater potential significance to the modern human origins debate is the finding of expansion from a very small initial population size, usually estimated at no more than several thousand females. Growth at the time of expansion is estimated to be on the order of 100-fold or more (Rogers 1995, 1997, Rogers & Jorde 1995). The small pre-expansion population size is similar to a somewhat larger (≈10,000) long-term effective size. If the human species had an initial pre-expansion population of several thousand individuals and then later reproduced rapidly, the long-term effective population size would be much closer to the minimum number than the maximum. Thus, our species' relatively low effective population size, compared with our relatively large census size even in the past 10,000 years or so (Weiss 1984), appears to be the result of rapid expansion from a small initial effective size.

IMPLICATIONS FOR MODERN HUMAN ORIGINS The studies noted above suggest that the effective species size of human ancestors was low (10,000) at the start of the Late Pleistocene. This estimate is much lower than the usual (although crude) estimates of total population size obtained from archaeological and ethnographic inference, which typically are about one million during the Middle Pleistocene (Howell 1996). The low estimated species size has most often been interpreted as support for the recent African origin model, which predicts that the Late Pleistocene ancestors of living humans were all from a single region. The multiregional model, on the other hand, predicts that our

Late Pleistocene ancestors were spread out over at least two geographic regions, and perhaps across the entire Old World. A number of papers have suggested that any such widespread distribution is incompatible with a low species population size, and therefore it is more reasonable to interpret the genetic evidence in terms of a localized ancestral population, as predicted by the recent African origin model (Harpending et al 1993, 1996, Rogers & Jorde 1995, Harpending & Relethford 1997).

Templeton (1997) has argued against this interpretation for several reasons. First, the problems in estimating coalescence dates also apply to estimates of species effective size. There is variation due to evolutionary stochasticity and variation due to the specific mutation rate used for inference. As a result, the true long-term effective size of our species could be higher than suggested by the point estimate of $N_e = 10{,}000$.

Templeton (1997) also noted that effective size is usually much lower than census size, often by several orders of magnitude. This point is also clear from a review by Nei & Graur (1984). They examined estimates of long-term effective size versus total census size for a variety of organisms. They found that the effective size is often a small proportion of the census size, often by one or more orders of magnitude. According to their data, the median ratio of effective size to census size among 43 mammalian species (excluding humans) is 0.003. The range is 0.0–0.9, with most ratios less than 0.1. What accounts for such low ratios? One common explanation is a population increase from a small initial size because the long-term effective size will tend to remain low in such cases. This is consistent with Rogers & Harpending's finding of rapid Late Pleistocene population growth from a small initial population size (see above).

A recent African origin could produce a small long-term effective population size. Does low effective species size necessarily support only a recent African origin model? The possibility of a small effective species size being compatible with a multiregional model must also be considered. Is the low long-term effective size compatible with estimated census sizes of several hundred thousands? One possibility is a worldwide reduction in population size prior to the Late Pleistocene. If recent human evolution were multiregional, and if population sizes decreased rapidly across much or all of the Old World, then the net result would be a relatively low long-term effective size over the last 200,000 years or so. If so, then the human species was numerous, shrank in number, and then expanded again later. Given the major climatic shifts that have occurred within the last half a million years or more, this is not that unlikely. However, recent work by Sherry and colleagues (1997) argues against this interpretation; their analysis of *Alu* insertion polymorphisms suggested that the population size of the line ancestral to modern humans has been small over the past 500,000 years or so. Rather than a pattern of population decline and recovery, their work suggests a pattern of continued small size over time.

Another possibility is the frequent extinction and recolonization of local populations over time. Wright (1940) noted that if local populations that were small in size are prone to frequent extinction and recolonization by founders from elsewhere, then the effective population size of a species could be very small even though the census size might be in the millions. Several theoretical treatments suggest that such a demographic history could easily result in a low, long-term effective species size (Slatkin 1977, Maruyama & Kimura 1980, Takahata 1994, 1995, Whitlock & Barton 1997). This model might be appropriate for considering recent hominid evolution. The many climatic shifts throughout most of the Pleistocene suggest the possibility of fairly high rates of local population extinction. Estimates based on simulation of hunting and gathering demographic schedules suggest that the rate of extinction for local bands could have been substantial (Wobst 1974, Gaines & Gaines 1997).

The exact ratio of effective size to census size depends on a number of factors, including local group size, the number of new founders, local extinction rate, and local and long-range migration rates. The critical parameter is the ratio of the local migration rate to the local extinction rate (Maruyama & Kimura 1980). When migration rate is low relative to extinction, the ratio of effective size to census size can be quite low. Thus, the extinction/recolonization process would have its greatest impact when migration rates were low and/or extinction rates were high.

One argument against this model is the fact that low migration rates means greater among-group variation. Several studies have argued that an increase in among-group variation (higher values of F_{ST}) actually inflates the effective population size of a species (Nei & Takahata 1993, Rogers & Jorde 1995). As such, our genetic estimates of effective size might be overestimates, and any reduction because of local population extinction might be offset by such inflation. Recently, however, Whitlock & Barton (1997) found that although this expectation applies to a simple island model of population structure, under more realistic models, increased subdivision acts to decrease effective size. Thus, a general model of relative isolation and frequent extinction of local populations would produce a relatively low effective species size.

It is tempting to suggest that such a scenario actually occurred in the past, but all we can really do is suggest the general conditions under which a small effective species population size is compatible with a multiregional model. Currently, we lack sufficient estimates of the parameters of subdivision and extinction. All we can say is that such a model points to the possibility that low effective species population size is compatible with a multiregional model. Perhaps further simulation and modeling will help narrow the range of likely parameter values such that more definitive statements can be made.

Of course, all such arguments about ancient population size derived from mtDNA are based on the assumption that it is selectively neutral. If this is not the case, as suggested by several studies (e.g. Templeton 1996a, Hey 1997, Loewe & Scherer 1997, Wise et al 1997), then estimates of both coalescent dates and species effective size from mtDNA diversity will not be reliable. A "selective sweep" might be mimicking a low effective species size.

Neandertal DNA

Until recently, all genetic data pertaining to the question of modern human origins came from living humans. This situation changed with the sequencing of a section of mtDNA from a Neandertal fossil (Krings et al 1997). Because extraction of ancient DNA is fraught with problems, this study stands as a milestone of technical achievement. A 378-bp sequence was extracted from the humerus of the Neandertal type specimen and compared with the same sequence from samples of numerous living humans.

Compared with living humans, the Neandertal specimen is different at 27 positions, considerably more than the average of 8 differences among living humans. However, there is some slight overlap: The number of mtDNA differences between living humans and the Neandertal specimen ranges from 22 to 36 substitutions, whereas the number of mtDNA differences among living humans ranges from 1 to 24 substitutions. The authors suggested that these results support the view that Neandertals did not contribute any mtDNA to living humans, although they noted that the possibility that Neandertals contributed other genes could not be ruled out.

Krings et al (1997) further estimated coalescent dates using a 4- to 5-million-year human-chimpanzee divergence date for calibration. They estimated that the common mtDNA ancestor of the Neandertal specimen and living humans lived between 550,000 and 690,000 years ago. These dates are consistent with the view that the ancestor of Neandertals and living humans diverged roughly 600,000 years ago and that Neandertals are a separate species from modern *Homo sapiens*. Again, however, this is not the only possible scenario. As noted above, coalescent dates often tell us more about ancient demography than about phylogeny. It might simply be that the effective species size 600,000 years ago was slightly larger than in more recent times. Given the relationship between long-term effective population size and coalescent date (e.g. Ayala 1995), a coalescent date of 600,000 years would correspond to an effective size of 30,000. Given the large evolutionary and statistical variance of such estimates (Templeton 1993, 1997) and the sample size of $n = 1$ for the Neandertals, there is little point in trying to read too much into such an estimate. Also, if mtDNA is conclusively shown to be affected by natural selection, then the relevance of the Neandertal specimen is less clear.

Krings et al (1997) conducted an additional analysis by comparing the Neandertal mtDNA sequence with different groups of living humans. There was no tendency for Neandertals to more closely resemble modern Europeans than people other from geographic regions. This finding might be taken by some as a rejection of the multiregional model because it is widely assumed that the European Neandertals would be most closely related to living Europeans under the multiregional model. This assumption, however, misrepresents the multiregional model. If living Europeans derive some of their ancestry from the Neandertals, it is not necessary that the majority of their ancestry do so. Under the multiregional model, people from every region have multiple ancestors and multiple descendants (Wolpoff & Caspari 1997). Furthermore, even if additional evidence shows conclusively that Neandertals were a separate species, this does not automatically rule out a multiregional perspective unless the same case could be made for every region other than Africa.

The Neandertal mtDNA sequence data is exciting but not conclusive. Additional specimens are needed to place the 27-bp difference in perspective. Is this specimen different because he belonged to a different species, because he lived many tens of thousands of years ago, because of demographic shifts over time, or because of recent natural selection? Additional sequence data, particularly with definite early European moderns (e.g. Cro-Magnon), would be most informative.

CONCLUSIONS

The use of genetic data for addressing questions of modern human origins is an exciting area and one that serves potentially to unite researchers in the disparate fields of molecular genetics, population genetics, and paleoanthropology. In the past, the genetic evidence for modern human origins has most often been portrayed as support for a recent African origin model of near-complete replacement (e.g. Lewin 1993). All the pieces seemed to fit, ranging from greater African diversity to greater African divergence to the estimates of when "Eve" lived.

Although it is tempting to stick to this interpretation (which might be correct), it is useful to step back and consider possible alternatives. The fact that the genetic evidence suggests compatibility with the recent African origin model does not necessarily rule in its favor unless it can be shown unequivocally that the same evidence is not compatible with a multiregional model. For the bulk of the genetic data discussed here, a multiregional model is also compatible. Each type of evidence can be interpreted from either a phylogenetic branching perspective or a population structure perspective. Patterns of within-group diversity, for example, can be explained by a process of bifurcations or by variation in long-term effective population size.

Of all the genetic evidence analyzed to date, the result that most strongly supports a recent African origin model is the consistent finding across several loci of a small long-term effective species size over at least the last 200,000 years (and perhaps longer). Even here, however, the evidence is not as conclusive as we might think. We need to look much more closely at factors that could affect the relationship between effective population size and census population size and determine if they are likely to have operated in recent human evolution, and further explore the assumption of selective neutrality for mtDNA. We also need more loci, further work on the possible role of selection, and additional fossil specimens. I suspect that the pace of discovery and analysis will soon render this review out of date.

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Literature Cited

Ayala FJ. 1995. The myth of Eve: molecular biology and human origins. *Science* 270: 1930–36

Ayala FJ. 1996. HLA sequence polymorphism and the origin of humans. *Science* 274: 1554

Ayala FJ, Escalante A, O'Huigin C, Klein J. 1994. Molecular genetics of speciation and human origins. *Proc. Natl. Acad. Sci. USA* 91:6787–94

Barbujani G, Magagni A, Minch E, Cavalli-Sforza LL. 1997. An apportionment of human DNA diversity. *Proc. Natl. Acad. Sci. USA* 94:4516–19

Batzer MA, Stoneking M, Alegria-Hartman M, Bazan H, Kass DH, et al. 1994. African origin of human-specific polymorphic *Alu* insertions. *Proc. Natl. Acad. Sci. USA* 91: 12288–92

Bowcock AM, Kidd JR, Mountain JL, Hebert JM, Carstenuto L, et al. 1991. Drift, admixture, and selection in human evolution: a study with DNA polymorphisms. *Proc. Natl. Acad. Sci. USA* 88:839–43

Bowcock AM, Ruiz-Linares A, Tomfohrde J, Minch E, Kidd JR, Cavalli-Sforza LL. 1994. High resolution of human evolutionary trees with polymorphic microsatellites. *Nature* 368: 455–57

Bräuer G. 1984. A craniological approach to the origin of anatomically modern *Homo sapiens* in Africa and implications for the appearance of modern Europeans. See Smith & Spencer 1984, pp. 327–410

Cann RL, Stoneking M, Wilson AC. 1987. Mitochondrial DNA and human evolution. *Nature* 325:31–36

Cavalli-Sforza LL, Menozzi P, Piazza A.

1994. *The History and Geography of Human Genes*. Princeton: Princeton Univ. Press

Clark GA, Willermet CM, eds. 1997. *Conceptual Issues in Modern Human Origins Research*. New York: Adline de Gruyter

Crow JF, Kimura M. 1970. *An Introduction to Population Genetics Theory*. Minneapolis: Burgess

Deka R, Jin L, Shriver MD, Yu LM, DeCroo S, et al. 1995. Population genetics of dinucleotide $(dC\text{-}dA)_n \bullet (dG\text{-}dT)_n$ polymorphisms in world populations. *Am. J. Hum. Genet*. 56:461–74

Donnelly P, Tavaré S. 1995. Coalescents and genealogical structure under neutrality. *Annu. Rev. Genet.* 29:401–21

Donnelly P, Tavaré S, eds. 1997. *Progress in Population Genetics and Human Evolution.* New York: Springer-Verlag

Dorit RL, Akashi H, Gilbert W. 1995. Absence of polymorphism at the ZFY locus on the human Y chromosome. *Science* 268:1183–85

Erlich HA, Bergström TF, Stoneking M, Gyllensten U. 1996. HLA sequence polymorphism and the origin of humans. *Science* 274:1552–54

Excoffier L, Langaney A. 1989. Origin and differentiation of human mitochondrial DNA. *Am. J. Hum. Genet.* 44:73–85

Felsenstein J. 1982. How can we infer geography and history from gene frequencies? *J. Theor. Biol.* 96:9–20

Gaines SW, Gaines WM. 1997. Simulating success or failure: another look at small-population dynamics. *Am. Antiq.* 62: 683–97

Gibbons A. 1997. Calibrating the mitochondrial clock. *Science* 279:28–29

Hammer MF. 1995. A recent common ancestor for human Y chromosomes. *Nature* 378:376–78

Hammer MF, Zegura SL. 1996. The role of the Y chromosome in human evolutionary studies. *Evol. Anthropol.* 5:116–34

Harding RM. 1997. Lines of descent from mitochondrial Eve: an evolutionary look at coalescence. See Donnelly & Tavaré 1997, pp. 15–31

Harding RM, Fullerton SM, Griffiths RC, Bond J, Cox MJ, et al. 1997. Archaic African and Asian lineages in the genetic ancestry of modern humans. *Am. J. Hum. Genet.* 60:772–89

Harpending HC. 1994. Signature of ancient population growth in a low-resolution mitochondrial DNA mismatch distribution. *Hum. Biol.* 66:591–600

Harpending HC, Relethford JH. 1997. Population perspectives on human origins research. See Clark & Willermet 1997, pp. 361–68

Harpending HC, Relethford JH, Sherry ST. 1996. Methods and models for understanding human diversity. In *Molecular Biology and Human Diversity,* ed. AJ Boyce, CGN Mascie-Taylor, pp. 283–99. Cambridge, UK: Cambridge Univ. Press

Harpending HC, Sherry ST, Rogers AR, Stoneking M. 1993. The genetic structure of ancient human populations. *Curr. Anthropol.* 34:483–96

Hedges SB, Kumar S, Tamura K, Stoneking M. 1992. Human origins and analysis of mitochondrial DNA sequences. *Science* 255:737–38

Hey J. 1997. Mitochondrial and nuclear genes present conflicting portraits of human origins. *Mol. Biol. Evol.* 14:166–72

Horai S, Hayasaka K, Kondo R, Tsugane K, Takahata N. 1995. Recent African origin of modern humans revealed by complete sequences of hominoid mitochondrial DNAs. *Proc. Natl. Acad. Sci. USA* 92: 532–36

Howell FC. 1996. Thoughts on the study and interpretation of the human fossil record. In *Contemporary Issues in Human Evolution,* ed. WE Meikle, FC Howell, NG Jablonski, pp. 1–45. San Francisco: Calif. Acad. Sci.

Hudson RR. 1990. Gene genealogies and the coalescent process. *Oxford Surv. Evol. Biol.* 7:1–44

Jorde LB, Bamshad MJ, Watkins WS, Zenger R, Fraley AE, et al. 1995. Origins and affinities of modern humans: a comparison of mitochondrial and nuclear genetic data. *Am. J. Hum. Genet.* 57:523–38

Jorde LB, Rogers AR, Bamshad M, Watkins WS, Krakowiak P, Paabo S. 1997. Microsatellite diversity and the demographic history of modern humans. *Proc. Natl. Acad. Sci. USA* 94:3100–3

Klein J, Takahata N, Ayala FJ. 1993. MHC polymorphism and human origins. *Sci. Am.* 269(12):78–83

Krings M, Stone A, Schmitz RW, Krainitzki H, Stoneking M, et al. 1997. Neandertal DNA sequences and the origin of modern humans. *Cell* 90:19–30

Latter BDH. 1980. Genetic differences within and between populations of the major human groups. *Am. Nat.* 116:220–37

Lewin R. 1993. *The Origin of Modern Humans.* New York: Freeman

Lewontin RC. 1974. The apportionment of human diversity. *Evol. Biol.* 6:381–98

Livshits G, Nei M. 1990. Relationships between intrapopulational and interpopula-

tional genetic diversity in man. *Ann. Hum. Biol.* 6:501–13
Loewe L, Scherer S. 1997. Mitochondrial Eve: the plot thickens. *Trends Ecol. Evol.* 12: 422–23
Lynch M. 1989. Phylogenetic hypotheses under the assumption of neutral quantitative-genetic variation. *Evolution* 43:1–17
Maddison DR. 1991. African origin of human mitochondrial DNA reexamined. *Syst. Zool.* 40:355–63
Marjoram P, Donnelly P. 1994. Pairwise comparisons of mitochondrial DNA sequences in subdivided populations and implications for early human evolution. *Genetics* 136:673–83
Marjoram P, Donnelly P. 1997. Human demography and the time since mitochondrial Eve. See Donnelly & Tavaré 1997, pp. 107–31
Maruyama T, Kimura M. 1980. Genetic variability and effective population size when local extinction and recolonization of subpopulations are frequent. *Proc. Natl. Acad. Sci. USA* 77:6710–14
Mellars PA, Stringer CB, eds. 1989. *The Human Revolution: Behavioral and Biological Perspectives on the Origin of Modern Humans.* Princeton: Princeton Univ. Press
Mountain JL, Cavalli-Sforza LL. 1994. Inference of human evolution through cladistic analysis of nuclear DNA restriction polymorphisms. *Proc. Natl. Acad. Sci. USA* 91:6515–19
Nei M. 1978. The theory of genetic distance and the evolution of human races. *Jpn. J. Hum. Genet.* 23:341–69
Nei M, Graur D. 1984. Extent of protein polymorphism and the neutral mutation theory. *Evol. Biol.* 27:73–118
Nei M, Livshits G. 1989. Genetic relationships of Europeans, Asians and Africans and the origin of modern *Homo sapiens*. *Hum. Hered.* 39:276–81
Nei M, Roychoudhury AK. 1982. Genetic relationship and evolution of human races. *Evol. Biol.* 14:1–59
Nei M, Takahata N. 1993. Effective population size, genetic diversity, and coalescence time in subdivided populations. *J. Mol. Evol.* 37:240–44
Penny D, Steel M, Waddell PJ, Hendy MD. 1995. Improved analyses of human mtDNA sequences support a recent African origin for Homo sapiens. *Mol. Biol. Evol.* 12:863–82
Relethford JH. 1994. Craniometric variation among modern human populations. *Am. J. Phys. Anthropol.* 95:53–62
Relethford JH. 1995. Genetics and modern human origins. *Evol. Anthropol.* 4:53–63
Relethford JH. 1997. Mutation rate and excess African heterozygosity. *Hum. Biol.* 69: 785–92
Relethford JH. 1998. Mitochondrial DNA and ancient population growth. *Am. J. Phys. Anthropol.* 105:1–7
Relethford JH, Harpending HC. 1994. Craniometric variation, genetic theory, and modern human origins. *Am. J. Phys. Anthropol.* 95:249–70
Relethford JH, Harpending HC. 1995. Ancient differences in population size can mimic a recent African origin of modern humans. *Curr. Anthropol.* 36:667–74
Rogers AR. 1992. Error introduced by the infinite-sites model. *Mol. Biol. Evol.* 9: 1181–84
Rogers AR. 1995. Genetic evidence for a Pleistocene population explosion. *Evolution* 49:608–15
Rogers AR. 1997. Population structure and modern human origins. See Donnelly & Tavaré 1997, pp. 55–79
Rogers AR, Fraley AE, Bamshad MJ, Watkins WS, Jorde LB, et al. 1996. Mitochondrial mismatch analysis is insensitive to the mutational process. *Mol. Biol. Evol.* 13: 895–902
Rogers AR, Harpending H. 1992. Population growth makes waves in the distribution of pairwise genetic differences. *Mol. Biol. Evol.* 9:552–69
Rogers AR, Jorde LB. 1995. Genetic evidence on modern human origins. *Hum. Biol.* 67: 1–36
Rogers AR, Jorde LB. 1996. Ascertainment bias in estimates of average heterozygosity. *Am. J. Hum. Genet.* 58:1033–41
Ruvolo M, Zehr S, von Dornum M, Pan D, Chang B, Lin J. 1993. Mitochondrial COII sequences and modern human origins. *Mol. Biol. Evol.* 10:1115–35
Ryman N, Chakraborty R, Nei M. 1983. Differences in the relative distribution of human gene diversity between electrophoretic and red and white cell antigen loci. *Hum. Hered.* 33:93–102
Sherry ST. 1996. *Estimating human effective population sizes with genetic models incorporating demographic fluctuation.* PhD thesis. Penn. State Univ., University Park. 146 pp.
Sherry ST, Batzer MA. 1997. Modeling human evolution—To tree or not to tree? *Genome Res.* 7:947–49
Sherry ST, Harpending HC, Batzer MA, Stoneking M. 1997. *Alu* evolution in human populations: using the coalescent to estimate effective population size. *Genetics* 147:1977–82
Sherry ST, Rogers AR, Harpending H, Sood-

yall H, et al. 1994. Mismatch distributions of mtDNA reveal recent human population expansions. *Hum. Biol.* 66:761–75
Slatkin M. 1977. Gene flow and genetic drift in a species subject to frequent local extinctions. *Theor. Popul. Biol.* 12:253–62
Smith FH, Falsetti AB, Donnelly SM. 1989. Modern human origins. *Yearb. Phys. Anthropol.* 32:35–68
Smith FH, Spencer F, eds. 1984. *The Origins of Modern Humans: A World Survey of the Fossil Evidence.* New York: Liss
Smith SL, Harrold FB. 1997. A paradigm's worth of difference? Understanding the impasse over modern human origins. *Yearb. Phys. Anthropol.* 40:113–38
Spuhler JN. 1988. Evolution of mitochondrial DNA in monkeys, apes, and humans. *Yearb. Phys. Anthropol.* 31:15–48
Stoneking M. 1993. DNA and recent human evolution. *Evol. Anthropol.* 2:60–73
Stoneking M, Cann RL. 1989. African origin of human mitochondrial DNA. See Mellars & Stringer 1989, pp. 17–30
Stoneking M, Fontius JJ, Clifford SL, Soodyall H, Arcot SS, et al. 1997. *Alu* insertion polymorphisms and human evolution: evidence for a larger population size in Africa. *Genome Res.* 7:1061–71
Stoneking M, Sherry ST, Vigilant L. 1992. Geographic origin of human mitochondrial DNA revisited. *Syst. Biol.* 41:384–91
Stringer CB. 1990. The emergence of modern humans. *Sci. Am.* 263(6):98–104
Stringer CB, Andrews P. 1988. Genetic and fossil evidence for the origin of modern humans. *Science* 239:1263–68
Stringer CB, Bräuer G. 1994. Methods, misleading, and bias. *Am. Anthropol.* 96: 416–24
Stringer CB, McKie R. 1996. *African Exodus: The Origins of Modern Humanity.* New York: Holt
Takahata N. 1993. Allelic genealogy and human evolution. *Mol. Biol. Evol.* 10:2–22
Takahata N. 1994. Repeated failures that led to the eventual success in human evolution. *Mol. Bol. Evol.* 11:803–5
Takahata N. 1995. A genetic perspective on the origin and history of humans. *Annu. Rev. Ecol. Syst.* 26:343–72
Takahata N, Satta Y, Klein J. 1995. Divergence time and population size in the lineage leading to modern humans. *Theor. Popul. Biol.* 48:198–221
Templeton AR. 1992. Human origins and analysis of mitochondrial DNA sequences. *Science* 255:737
Templeton AR. 1993. The "Eve" hypothesis: a genetic critique and reanalysis. *Am. Anthropol.* 95:51–72
Templeton AR. 1994. "Eve": hypothesis compatibility versus hypothesis testing. *Am. Anthropol.* 96:141–47
Templeton AR. 1996a. Contingency tests of neutrality using intra/interspecific gene trees: the rejection of neutrality for the evolution of the mitochondrial cytochrome oxidase II gene in the hominoid primates. *Genetics* 144:1263–70
Templeton AR. 1996b. Gene lineages and human evolution. *Science* 272:1363
Templeton AR. 1997. Testing the Out of Africa replacement hypothesis with mitochondrial DNA data. See Clark & Willermet 1997, pp. 329–60
Thorne AG, Wolpoff MH. 1992. The multiregional evolution of humans. *Sci. Am.* 266 (4):76–83
Thorne AG, Wolpoff MH, Eckhardt RB. 1993. Genetic variation in Africa. *Science* 261: 1507–8
Tishkoff SA, Dietzsch E, Speed W, Pakstis AJ, Kidd JR, et al. 1996. Global patterns of linkage disequilibrium at the CD4 locus and modern human origins. *Science* 271: 1380–87
Underhill PA, Jin L, Lin AA, Mehdi SQ, Jenkins T, et al. 1997. Detection of numerous Y chromosome biallelic polymorphisms by denaturing high-performance liquid chromatography. *Genome Res.* 7: 996–1005
Vigilant L, Stoneking M, Harpending H, Hawkes K, Wilson AC. 1991. African populations and the evolution of human mitochondrial DNA. *Science* 253:1503–7
Waddle DM. 1994. Matrix correlation tests support a single origin for modern humans. *Nature* 368:452–54
Weiss KM. 1984. On the number of members of the genus *Homo* who have ever lived, and some evolutionary implications. *Hum. Biol.* 56:637–49
Weiss KM. 1988. In search of times past: gene flow and invasion in the generation of human diversity. In *Biological Aspects of Human Migration,* ed. CGN Mascie-Taylor, GW Lasker, pp. 130–66. Cambridge, UK: Cambridge Univ. Press
Weiss KM, Maruyama T. 1976. Archeology, population genetics and studies of human racial ancestry. *Am. J. Phys. Anthropol.* 44:31–50
Whitfield LS, Sulston JE, Goodfellow PN. 1995. Sequence variation of the human Y chromosome. *Nature* 378:379–80
Whitlock MC, Barton NH. 1997. The effective size of a subdivided population. *Genetics* 146:427–41
Whittam TS, Clark AG, Stoneking M, Cann RL, Wilson AC. 1986. Allelic variation in

human mitochondrial genes based on patterns of restriction site polymorphism. *Proc. Natl. Acad. Sci. USA* 83:9611–15

Wills C. 1995. When did Eve live? An evolutionary detective story. *Evolution* 49: 593–607

Wilson AC, Cann RL, Carr SM, George M, Gyllensten UB, et al. 1985. Mitochondrial DNA and two perspectives on evolutionary genetics. *Biol. J. Linn. Soc.* 26: 375–400

Wise CA, Sraml M, Rubinsztein DC, Easteal S. 1997. Comparative nuclear and mitochondrial genome diversity in humans and chimpanzees. *Mol. Biol. Evol.* 14:707–16

Wobst HM. 1974. Boundary conditions for Paleolithic social systems: a simulation approach. *Am. Antiq.* 39:147–78

Wolpoff MH. 1989. Multiregional evolution: the fossil alternative to Eden. See Mellars & Stringer 1989, pp. 62–108

Wolpoff MH, Caspari R. 1997. *Race and Human Evolution.* New York: Simon & Schuster

Wolpoff MH, Thorne AG, Smith FH, Frayer DW, Pope GG. 1994. Multiregional evolution: a world-wide source for modern human populations. In *Origins of Anatomically Modern Humans,* ed. MH Nitecki, DV Nitecki, pp. 175–99. New York: Plenum

Wolpoff MH, Wu X, Thorne AG. 1984. Modern *Homo sapiens* origins: a general theory of hominid evolution involving the fossil evidence from East Asia. See Smith & Spencer 1984, pp. 411–83

Wright S. 1940. Breeding structure of populations in relation to speciation. *Am. Nat.* 74:232–48

Wright S. 1951. The genetical structure of populations. *Ann. Eugen.* 15:323–54

Wright S. 1969. *Evolution and the Genetics of Populations.* Vol. 2: *The Theory of Gene Frequencies.* Chicago: Univ. Chicago Press