Testing Multiregionality of Modern Human Origins

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In order to examine the possibility of multiple founding populations of anatomically modern *Homo sapiens,* we collected DNA sequence data from 10 X-chromosomal regions, 5 autosomal regions, and 1 Y-chromosomal region, in addition to mitochondrial DNA. Except for five regions which are genealogically uninformative and two other regions for which chimpanzee orthologs are not available, the ancestral sequence and population for each of the remaining regions were successfully inferred. Of these 10 ancestral sequences, 9 occurred in Africa and only 1 occurred in Asia during the Pleistocene. Computer simulation was carried out to quantify the multiregional hypothesis based solely on the premise that there was more than one founding population in the Pleistocene. Allowing the breeding size to vary among the founding populations, the hypothesis may account for the observed African ancestry in 90% of the genomic regions. However, it is required that the founding population in Africa was much larger than that outside Africa. Likelihood estimates of the breeding sizes in the founding populations were more than 9,000 in Africa and less than 1,000 in outside of Africa, although these estimates can be much less biased at the 1% significance level. If the number of African ancestral sequences further increases as more data accumulate in other genomic regions, the conclusion of a single founding population of modern *H. sapiens* is inevitable.

Introduction

The tempo and mode of evolution of Homo are in sharp contrast to those of earlier hominids in Africa (for a review, see Tattersall 2000). Evolution of australopithecines appears to be relatively slow and gradual. For example, the cranial capacity increased only slightly during the 3-Myr history of australopithecines. Something unusual happened in hominids in the Late Pliocene, about 2 MYA. Cranial capacity dramatically increased from 475 cm^3 to 860 cm^3, and body weight was doubled. There were other interrelated modifications. Almost immediately afterward, the first hominid of essentially modern body form emerged (Hawks et al. 2000). It is represented by 1.9-Myr-old *Homo ergaster* (African *Homo erectus*) KNM-ER 3228 and WT 15000 in Eastern Africa, whose cranial capacity was about 1,000 cm^3. It is their direct descendants who first migrated out of Africa 1–2 MYA and populated Europe, ex-Soviet Georgia, Java, China, and perhaps Japan by 500,000 years ago.

It is generally accepted that anatomically modern *Homo sapiens* appeared 130,000–150,000 years ago. However, the origin and evolution of *H. sapiens* have not been fully recovered by the fossil record and have attracted much attention, particularly since the pioneer work on human mitochondrial (mt) DNAs and the proposal of the replacement hypothesis by Cann, Stoneking, and Wilson (1987). A number of population genetics analyses have been carried out, including sequence analyses of mtDNA (Vigilant et al. 1991; Horai et al. 1995; Krings et al. 1997, 1999) and genomic regions of the haploid Y chromosome (Jobling 1994; Hammer 1995; Ruiz Linares et al. 1996; Hammer et al. 1997, 1998; Quintana-Murci et al. 1999), as well as those of the haplo-diploid X chromosome (Nachman et al. 1998; Zietkiewicz et al. 1998; Anagnostopoulos et al. 1999; Harris and Hey 1999) and diploid autosomes (Harding et al. 1997; Clark et al. 1998; Nickerson et al. 1998; Jin et al. 1999). The gene genealogy inferred from these genetic data generally exceeds the tenure of modern *H. sapiens* and goes back to the Pleistocene (Takahata 1993; Hammer 1995). Although all of these DNA sequence data appear to favor the uniregionality (single-origin) of modern *H. sapiens* (Takahata 1995; Jorde, Bamshad, and Rogers 1998; Jorde et al. 2000; Przeworski, Hudson, and Di Rienzo 2000 for reviews), no consensus has yet been reached (Harris and Hey 1999; Hawks et al. 2000; Yu and Li 2000).

The purpose of this paper is to quantify an alternative hypothesis for the origin of modern *H. sapiens,* the multiregional hypothesis proposed by Wolpoff, Wu, and Thorne (1984). This hypothesis is an extension of that of Weidenreich (1946), which allows gene exchanges among multiple founding populations of modern *H. sapiens.* However, it has been difficult to test the multiregional hypothesis because of ambiguity in the assumed population structure (Takahata and Klein 1998). In this paper, we draw several predictions solely from the very premise of multiple founding populations and examine whether these predictions are compatible with the pattern and degree of DNA polymorphism observed in various genomic regions. We collected all nucleotide sequences relevant to this end. To make our argument quantitative, we performed computer simulation based on a population genetics model for the multiregional origin of modern *H. sapiens.*

Materials and Methods

Predictions

The multiregional hypothesis posits that anatomically modern *H. sapiens* emerged in multiple founding populations that had existed worldwide since hominids first migrated out of Africa (fig. 1*a*). We assume that these founding populations were established 1–2 MYA and had given rise to anatomically modern *H. sapiens* by 130,000–150,000 years ago. We designate by T_d the

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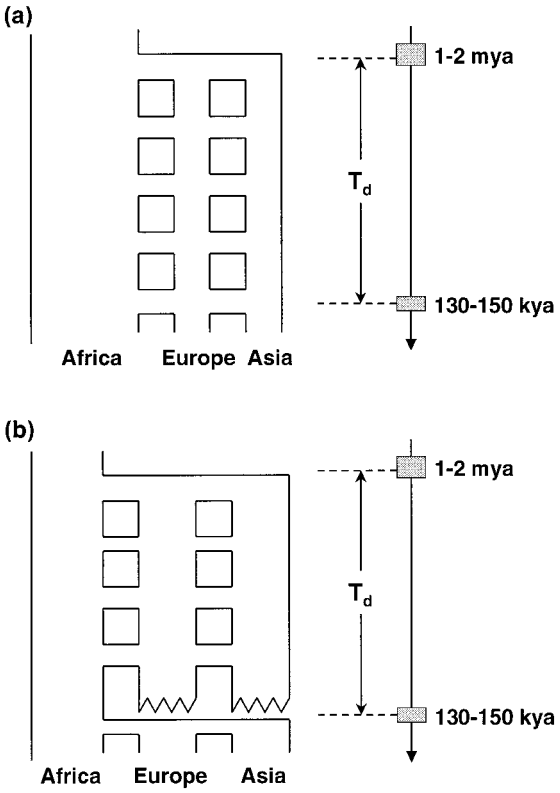


FIG. 1.—Two models for the origin of modern *Homo sapiens*. In the multiregional model (*a*), only three founding populations during the Pleistocene are considered throughout. The founding populations are connected by gene flow. In the uniregional model (*b*), the two founding populations in Europe and Asia are replaced by newcomers from Africa. The coexistence with Neanderthals is ignored. The breeding size difference among populations is emphasized in *a*.

period of the founding populations between 130,000–150,000 years ago and 1–2 MYA. We also assume that these founding populations evolved as a single evolutionary unit and at the same time independently developed regional continuity in some morphological characters. For regional continuity to develop, individual founding populations must be somehow genetically isolated from each other. However, in the complete absence of gene exchange (gene migration or gene flow) among founding populations, the whole population cannot be a single evolutionary unit in the long run. On the other hand, in the presence of frequent gene flow, it would be difficult to maintain regional continuity. This apparent contradiction may be reconciled in the following way. Because these two features are likely represented by different morphological characters, we assume that underlying genes can be different from each other and subject to different forms of natural selection. Of particular interest are two kinds of genes under natural selection. One kind comprises genes that are responsible for the single evolutionary unit and can produce advantageous mutations irrespective of regionality (Takahata 1993; Nei 1995). They are globally advantageous. The other kind comprises genes that are responsible for regional continuity and can produce mutations adaptive to particular founding populations, but are deleterious elsewhere. Were they not deleterious but selectively neutral elsewhere, locally advantageous mutations would be fixed in the original founding population and continue to propagate copy genes to neighboring populations by migration. The end result would be fixation of such mutations in the whole population, and this could not contribute to regional continuity. Locally advantageous mutations might be exemplified by genes involved in skin pigmentation (Cavalli-Sforza, Menozzi, and Piazza 1994). A third kind comprises genes that are selectively neutral everywhere.

The assumption that globally advantageous mutations are so rare that independent parallel occurrences are hardly expected seems reasonable. If this is not the case, we can invoke parallelism among the founding populations as assumed by the candelabra hypothesis (Coon 1962). Globally advantageous mutations can occur in any founding population and spread out by gene flow. Fixation within founding populations is a rapid process. However, the spread over the whole population is regulated by gene flow, so the level should not be extremely low. In this situation, Wright's (1931) fixation index F_{ST} to measure local differentiation becomes so small that there may be little or no variation within and between current populations. If such an advantageous mutation occurred relatively recently, the allelic genealogy would be correspondingly short (fig. 2*a*), and the population of the most recent common ancestor (MRCA) would be the birthplace of the mutation. An important point is that the birthplace can be any of the founding populations. It is conceivable that the birthplace is determined by the relative breeding size, since the number of new mutations per generation in a population is in proportion to its size. Even under these circumstances, there is no reason to think that the MRCA is restricted to only one particular founding population.

Locally advantageous mutations may also be rare, but it is assumed that they can gradually accumulate in founding populations to establish regional continuity. Obviously, these mutations should occur independently in individual founding populations. A noticeable difference between globally and locally advantageous mutations is that since migrants of locally advantageous mutations are deleterious in recipient founding populations, the direct lines of descent of each mutation tend to be restricted in the birthplace. Conversely, the allelic genealogy is traced back to before the occurrence of a locally advantageous mutation. There are two situations for such an ancestral gene lineage. Either the ancestral gene is already locally adapted to some extent, or it is still nonadaptive. In the former situation, the ancestral gene lineage in one founding population must have been prevented from coalescing with gene lineages in other founding populations. In this situation, the MRCA may well go back to the ancestral population that was common to all founding populations. In the latter situation, migrants are selectively neutral, so coalescence is expected to be faster than that in the former situation. Nonetheless, such coalescence must be slower than that of unconditionally neutral genes, so the MRCA tends to

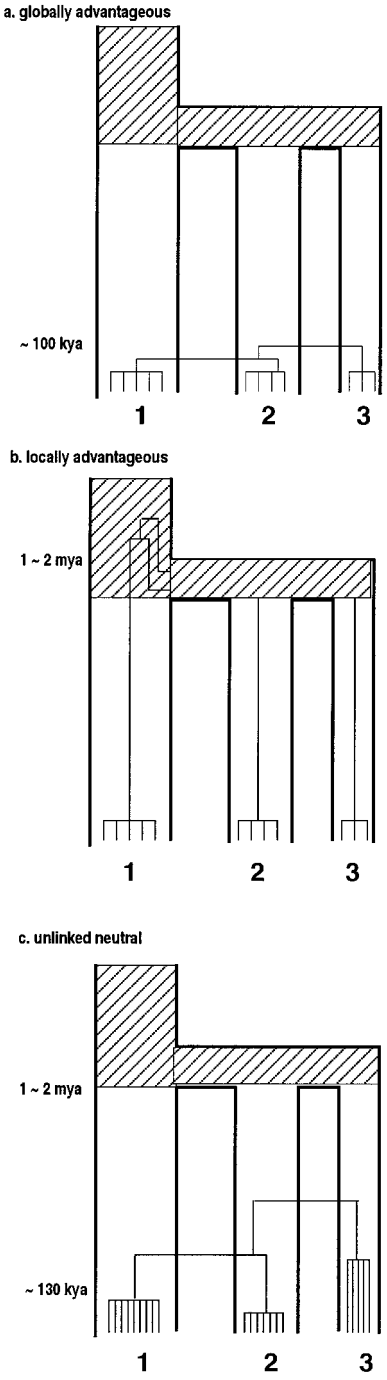


FIG. 2.—Conceptual allelic genealogy for globally and locally advantageous mutations (*a* and *b*) and genealogy of neutral genes (*c*). The numbers 1–3 represent populations. Thin lines represent genealogies of samples from three populations. Gene flow is assumed but is not explicitly depicted. Hatched areas indicate ancestral populations. The timescale is shown along each section.

be found also in the ancestral population (fig. 2*b*). As a result, locally advantageous mutations show deep allelic genealogies and large F_{ST} values.

With gene flow, purely neutral genes may not show extensive local differentiations. The F_{ST} value would be moderately small, and the gene genealogy would be intermediate in its timescale compared with that expected for globally and locally advantageous genes (fig. 2*c*). Again, the birthplace of the MRCA of neutral genes is not unique. We do not know how often or where in the genome these three types of mutations occur. However, under multiregionality, we can make some important predictions largely irrespective of the kind of genes. Most importantly, the MRCA that is found during the T_d period should not be restricted to any particular founding population. Second, the time back to the MRCA (TMRCA) may vary more greatly from locus to locus than that expected under a single randomly mating population. Third, the shorter the TMRCA, the smaller the F_{ST}.

By definition, the uniregional, or replacement, hypothesis posits that only one population during the T_d period founded modern humans (fig. 1*b*). Advantageous genes transformed the founding population of *H. ergaster* or *H. erectus* to modern *H. sapiens* via archaic Homo. Local adaptation in modern *H. sapiens* is assumed to have occurred during its tenure. As a result, the MRCA of locally advantageous genes is comparably recent. The genealogy of selectively neutral genes is even shorter than that of locally advantageous genes under the multiregional hypothesis, but it is deeper than that of globally advantageous genes. Importantly, the MRCA under the uniregional hypothesis must always be traced back to the single founding population, although this trace may be somewhat obscured by random distribution of the ancestral polymorphism into descendant populations, as well as gene flow between them, if present. In general, we do not know a priori which current local populations are more representative of the founding population or how polymorphism in the founding population was sorted out in individual local populations. Nevertheless, should we find such a population specificity in the genealogy at a number of loci, the uniregionality of founding populations appears to be an inevitable conclusion.

Multiregionality may be untenable to population-specific genealogy. If everything is equal regarding the founding populations, there should not be any population specificity. The multiregionality becomes tenable only if one founding population had predominated over the others in terms of the number of breeding individuals. However, emphasizing the overwhelming genetic contribution of only one founding population is equivalent to uniregionality. To be concrete and quantitative, we supposed that during T_d (fig. 1*a*), there were three founding populations, with the relative population sizes being $p_1 : p_2 : p_3$, where $\Sigma^3_{j=1}\, p_j = 1$. If there are n independent genealogies, the probability that we find n_1, n_2, and n_3 MRCAs ($\Sigma^3_{j=1}\, n_j = n$) would be multinomially distributed with parameters p_j. The most likely proportion of the three founding population sizes is given by $\hat{p}_j = n_j/n$ ($j = 1$, 2, and 3). For $n_1 \geq 1$, $n_2 \geq 1$, and $n_3 = 0$, the probability distribution is binomial, and the maximum-likelihood ratio becomes $L = (p_1/\hat{p}_1)^{n_1}\{(1 - p_1)/\hat{p}_2\}^{n_2}$, since $\hat{p}_3 = 0$. The L ratio can be used to set a lower confidence limit for p_1. For instance, if $n_1 = 9$ and $n_2 = 1$, $\hat{p}_1 = 9/10 = 0.9$, and the condition of $L > 0.01$ leads to $0.45 < p_1$. For $n_1 = 19$ and $n_2 = 1$, $\hat{p}_1 =$

19/20 = 0.95, and the 1% lower confidence limit for p_1 is 0.68. The more MRCAs are found in only one founding population, the stronger the required asymmetry in founding population sizes.

In the following, we focus on three quantities; the time (TMRCA) and place (PMRCA) of the MRCA, and F_{ST}. We estimated TMRCA based on the nucleotide differences within humans relative to those between humans and chimpanzees and assuming their 5 Myr old divergence. This simple method provided estimates similar to those reported in some literature which used the coalescence method of Griffiths and Tavaré (1994*a*, 1994*b*). F_{ST} may be estimated according to Wright (1931) or Nei (1973). We have redefined it as $1 - d_w/d$, where d_w is the average maximum nucleotide difference within local populations, and d is the maximum nucleotide difference in the whole sample taken from all local populations. This redefined F_{ST} value is necessarily nonnegative and has properties similar to those of F_{ST} in Slatkin (1991).

To infer PMRCA, we first tried the cladistic method of Slatkin and Maddison (1989). The principle is simple: if we label the sampled sequences in a reconstructed tree by their localities, we may determine the character state in a node by the majority rule. However, it is possible that this method might not work at all if a demography such as that in figure 1*a* is not at equilibrium. In the case of little or no gene flow, three population-specific ancestral lineages remain distinct during T_d and go back to the common ancestral population. In this situation, the method necessarily predicts that the PMRCA can be any founding population. Only with moderate or high levels of gene flow can the MRCA occur during T_d so that the method may identify PMRCA. Another difficulty arises from the fact that the method assumes an accurate phylogeny reconstructed from DNA sequence differences. Actually, this requirement was hardly met in our data, which showed low levels of polymorphism and the presence of recombination or sequence convergence. In a few regions in our data set, the number of phylogenetically informative sites was discouragingly small, and the phylogenetic relationships among sequences became unreliable.

Instead, we used a parsimony method to infer the ancestral state for each nucleotide. If a particular nucleotide of a sample of human sequences was the same as the one in the chimpanzee, the nucleotide was assumed to have remained unchanged after the species divergence and to be the ancestral type. We determined the MRCA sequence as being the closest to the chimpanzee sequence and defined the population that contained this MRCA sequence as the PMRCA. In reality, it is possible that these MRCA sequences are shared by different populations. There are indeed three such genomic regions, as discussed below. In such case, we used the frequency data. Rare haplotypes in a population are likely to be migrants. If there was a large discrepancy in haplotype frequencies between populations, we assumed that the PMRCA was the population that exhibited the higher haplotype frequency.

Computer Simulation

To confirm the predictions in the preceding section, we carried out computer simulation. The simulation model (fig. 1*a*) assumes that there was a single ancestral population in Africa that gave rise to three descendant populations, which founded modern *H. sapiens*. These founding populations are assumed to have evolved into the current African, European, and Asian populations. Each founding population may consist of local mating groups being connected by gene flow or undergoing extinction or recolonization. Further subdivision within a founding population increases the effective size, whereas extinction and recolonization by groups within the same founding population decrease the effective size (Takahata 1993, 1994). However, since these effects of within-population subdivision are less important than those among founding populations (Takahata and Klein 1998), we assume that each of the three founding populations is approximately panmictic. There are N_j breeding individuals in population j (j = 1, 2, and 3), and $\Sigma_{j=1}^{3} N_j = N_T$ in the entire population. Unless specified, we consider genes in an autosomal region, so there are $2N_j$ genes in founding population j.

In simulation, we measured time in units of generations. If one generation spans 20 years, T_d would be 50,000–100,000 generations. Migration occurs from founding population i to population j with a per-generation rate of m_{ij}. In order to keep N_j constant throughout generations, we imposed the condition of $N_i m_{ij} = N_j m_{ji}$; the numbers of immigrants and emigrants between a pair of founding populations were assumed to be the same. We further assumed that $N_1 \geq N_2 = N_3$, where founding populations 1, 2, and 3 are the African, European, and Asian populations, respectively. The African founding population thus assumed to have been no smaller than the European or Asian founding population. Because of these assumptions, there were only three independent parameters among the six m_{ij}s: $m_{21} = m_{31}$, $m_{23} = m_{32}$, and $m_{12} = m_{13}$. In the following simulation, we further assume that $m_{21} = m_{23}$, so that when the ratio of N_1 to N_2 and N_3 is specified, only one migration parameter is free to vary. If we designate $m_{12} = m_{13}$ by m, $m_{21} = m_{31} = m_{23} = m_{32} = N_1 m/N_2$ ($= N_1 m/N_3$). First, we examined the genealogy of k_j neutral genes sampled from the current population of breeding size N_j. Simulation (with 1,000 repeats) was done backward in time to trace the ancestral lines of the sampled genes under genetic drift and migration. Mutations were not superimposed on the genealogical tree. The FORTRAN simulation program (available on request) is a slight extension of that of Takahata (1989) with respect to migration.

Second, based on the infinite-alleles model (Kimura and Crow 1964), we developed forward simulation programs for globally and locally advantageous mutations (also available on request). For globally advantageous mutations, we recorded when and in which population new mutations occurred. A new mutation always had relative fitness $1 + s$ over its parent, $(1 + s)^2$ over its grandparent, and so on. Mutant offspring of the same parent were assumed to be equally advantageous but

Table 1
Simulation Results for Time Back to the Most Recent Common Ancestor (TMRCA) Birthplace of the Most Recent Common Ancestor (PMRCA), F_{ST}

		$r = N_1/(N_2 + N_3)$			
N_1m		0.5	1.5	5	50
Neutral genes					
0.1	TMRCA	7.9 ± 3.3	7.7 ± 3.4	7.5 ± 3.2	7.3 ± 3.3
	PMRCA	0.32 (0.12)	0.63 (0.14)	0.88 (0.15)	0.99 (0.18)
	F_{ST}	0.52 ± 0.21	0.72 ± 0.19	0.85 ± 0.22	0.91 ± 0.08
1.0	TMRCA	6.0 ± 3.4	4.1 ± 2.7	3.2 ± 2.3	2.7 ± 1.8
	PMRCA	0.31 (0.46)	0.66 (0.76)	0.90 (0.86)	0.99 (0.94)
	F_{ST}	0.24 ± 0.19	0.35 ± 0.21	0.52 ± 0.21	0.73 ± 0.14
10	TMRCA	5.6 ± 3.2	3.5 ± 2.6	2.4 ± 1.8	1.9 ± 1.3
	PMRCA	0.35 (0.53)	0.60 (0.85)	0.87 (0.95)	0.99 (0.98)
	F_{ST}	0.16 ± 0.17	0.19 ± 0.17	0.23 ± 0.19	0.51 ± 0.20
Globally advantageous genes					
0.1	TMRCA	2.0 ± 1.0	1.0 ± 0.5	0.6 ± 0.3	
	PMRCA	0.36	0.76	0.92	
	F_{ST}	0.57 ± 0.30	0.55 ± 0.34	0.50 ± 0.45	
1.0	TMRCA	1.1 ± 0.6	0.7 ± 0.4	0.4 ± 0.2	
	PMRCA	0.38	0.65	0.95	
	F_{ST}	0.15 ± 0.19	0.13 ± 0.25	0.13 ± 0.59	
10	TMRCA	1.0 ± 0.5	0.6 ± 0.3	0.4 ± 0.2	
	PMRCA	0.41	0.56	0.82	
	F_{ST}	0.02 ± 0.03	0.04 ± 0.15	0.07 ± 0.38	
Locally advantageous genes					
0.1	TMRCA	14.1 ± 2.0	7.9 ± 0.8	5.7 ± 0.1	
	PMRCA	0	0	0	
	F_{ST}	0.51 ± 0.13	0.53 ± 0.16	0.57 ± 0.11	
1.0	TMRCA	13.9 ± 2.8	7.8 ± 1.1	5.8 ± 0.1	
	PMRCA	0	0	0	
	F_{ST}	0.53 ± 0.13	0.54 ± 0.14	0.59 ± 0.11	
10	TMRCA	13.9 ± 2.8	8.0 ± 0.1	5.7 ± 0.6	
	PMRCA	0	0	0.5	
	F_{ST}	0.49 ± 1.13	0.55 ± 0.14	0.51 ± 0.15	

NOTE.–For neutral genes, five genes were sampled from each of three populations of breeding size N_j (j = 1, 2, and 3). For globally advantageous and locally advantageous genes, N_1 = 200 for r = 0.5, N_1 = 360 for r = 1.5, and N_1 = 500 for r = 5. N_1m is the number of migrants per generation. The migration rate m stands for $m_{12} = m_{13}$. For TMRCA, time is measured in units of $2N_1$ generations, where N_1 is assumed to be no smaller than $N_2 = N_3$. A sample of genes was taken from the whole population for neutral genes and globally advantageous genes, while the sample was from only the African population for locally advantageous genes. PMRCA is shown as the proportion of African PMRCA. The 0 values for locally advantageous genes mean that the ancestry goes back to before the establishment of the three founding populations. The African population size is given by N_1. The probability of TMRCA $< 10N_1$ in figure 1 is given in parentheses. F_{ST} is computed as defined in the text.

mutually neutral. Since fitness exceeded 1, we divided individual fitness by the maximum fitness found within each population at a generation and used the results as relative probabilities for $2N_j$ genes to be chosen for the next generation. This scheme of selection and genetic drift was applied to all three founding populations. A similar but slightly different fitness scheme can be used for locally advantageous mutations. As long as they remain in the birthplace, they are advantageous in exactly the same way as for globally advantageous mutations. However, once locally advantageous mutations move out by migration, they are assumed to become disadvantageous. For an individual gene lineage within each population, we counted the number of mutations which occurred in that population (a), as well as the number of mutations which occurred in the other populations (b). The relative fitness of this gene lineage was determined to be $(1 + s)^a(1 - s)^b$. The relative probability was then computed for simulating selection and genetic drift for the next generation. The selected mutation rate was designated u per gene per generation. To save computer time, we assumed relatively small N_j and correspondingly large s, m_{ij}, and u. Because of this scaling, T_d was also shortened, but $T_d = 10\,N_T$ was kept throughout to imitate a plausible situation. Each simulation starting with three monomorphic populations was repeated 100 times. As under neutrality, we measured TMRCA, PMRCA, and F_{ST}, where $T_d = 10N_T$ generations.

Results

Neutral Mutations

When the number of breeding individuals (N_j) was the same among the three founding populations ($r = N_1/(N_2 + N_3) = 0.5$ in table 1) and the migration rate was high ($N_1m = 10$), TMRCA was about $4N_T = 4\,\Sigma^3_{j=1}\,N_j$, PMRCA was evenly distributed among the three founding populations, and the redefined F_{ST} value was generally greater than that expected from the well-known formula $1/(1 + 4N_1m)$ (Wright 1931). However, TMRCA was sensitive to N_1m, and PMRCA was sensitive to r. When $N_1m = 0.1$, TMRCA became longer than the history of the founding populations (with the probability of TMRCA $> T_d$ being 0.88; table 1), so that the MRCA tended to be found in the ancestral pop-

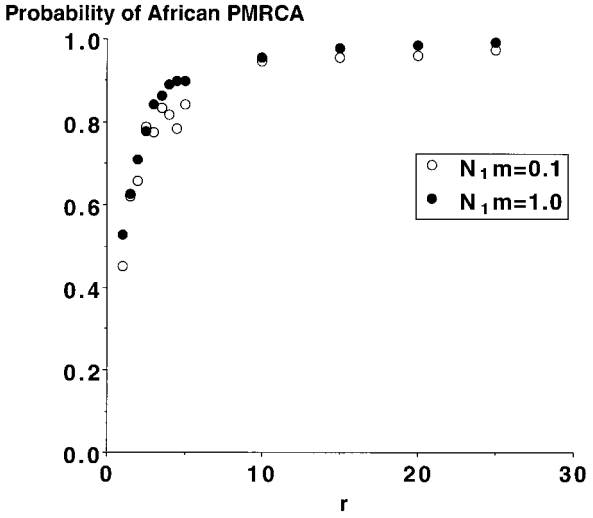


FIG. 3.—Probability of occurrence of African PMRCAs under different founding population sizes (1,000 repeats). It is assumed that N_1 (African) $\geq N_2 + N_3$ (non-African) and $N_2 = N_3$. The abscissa represents $r = N_1/(N_2 + N_3)$. The sample size was five for each population. The cases in which PMRCAs were found in the ancestor population are excluded. Under this condition, the probability does not change for different values of N_1m, where m is the per-generation immigration rate per gene from Africa.

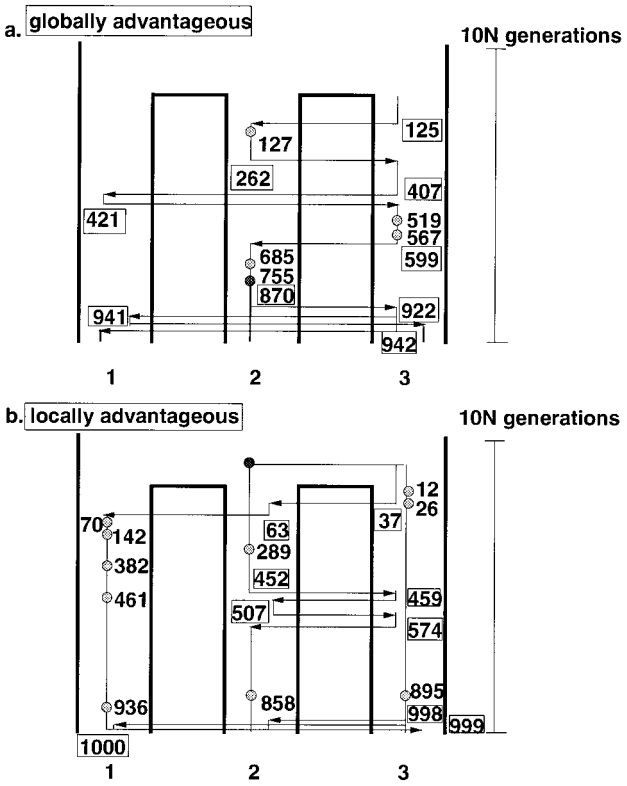


FIG. 4.—Allelic genealogy under globally (*a*) or locally (*b*) advantageous mutations. It is assumed that $N_j = N = 100$ and that $Nu = 0.02$, $Nm = 1.0$, and $s = 0.05$, where u is the mutation rate per gene, m is the migration rate between any pair of founding populations, and s is the selection coefficient. Simulation always started from a monomorphic state, and the allelic genealogy was recorded during the $10N$ generations. A lightly hatched circle indicates a new mutation, and a circle shows the time at which the mutation occurred. A rectangle shows the time at which an allele migrated, and the arrow indicates the direction. The darkly hatched circle shows the MRCA.

ulation. From this viewpoint, the migration rate under the multiregional hypothesis cannot be as small as $N_1m = 0.1$ (Nei 1995; Takahata 1993). Only when N_1m was as large as 1 did the MRCA tend to occur in the T_d time period (with the probability of TMRCA $\leq T_d$ being between 0.46 and 0.94). The effect of uneven population sizes on PMRCA became visible when the African founding population (N_1) was twice or three times as large as the European and Asian founding populations ($N_2 + N_3$). To expect that the MRCA was found exclusively in Africa, the number of breeding individuals in Africa had to be much larger than that in Europe and Asia (fig. 3). Interestingly, however, the sampling effect on PMRCA was small. A small sampling effect on TMRCA is well known in a panmictic population (Griffiths and Tavaré 1994*a*, 1994*b*), but little study on PMRCA has been done in relation to population structure. The present finding suggests that even small samples are useful as long as both TMRCA and PMRCA are taken into account.

Advantageous Mutations

Under the condition $N_1m > 0.1$, globally advantageous mutations can sweep out the whole population, with the rate being mainly determined by the mutation rate (u) and the selection coefficient (s). During T_d, there should be approximately $4N_Tus T_d$ mutations that can be fixed in the whole population of breeding size N_T (Haldane 1927; Kimura 1962). We simulated various cases of $4N_Tus T_d > 1$ and $0.1 \leq N_1m \leq 10.0$. The result (fig. 4*a* and table 1) confirmed our predictions about TMRCA, PMRCA, and F_{ST}. TMRCA was short compared with T_d and with that of neutral genes (table 1). F_{ST} was smaller than the corresponding value under neutrality, and PMRCA occurred in proportion to the relative breeding size. Throughout this simulation, we assumed that $N_T = 600$, $u = 0.0001$, and $s = 0.05$.

Locally advantageous mutations of $N_js > 1$ tend to be restricted in the birthplace even under frequent migration. We simulated cases of $4N_jusT_d \gg 1$ and $0.1 \leq N_1m \leq 10.0$. TMRCA tended to be longer than T_d, and F_{ST} was large (fig. 4*b* and table 1). Thus, the MRCA almost always went back to the ancestral population. Because of the long separation time among the ancestral gene lineages in different founding populations, a number of mutations can accumulate along each ancestral allelic lineage. This also holds true in tightly linked neutral regions. Throughout this simulation, we assumed $N_T = 600$, $u = 0.001$, and $s = 0.05$.

Data Analyses

We examined the currently available DNA sequence data for 10 X-linked and 5 autosomal regions (table 2): *Zfx* (Jaruzelska et al. 1999), *dys44* (Zietkiewicz et al. 1997, 1998; Nachman et al. 1998), *Pdha1* (Nachman et al. 1998; Harris and Hey 1999), Xq13.3 (Kaessmann et al. 1999), *Gk*, *Il2rg*, *Plp*, *Hprt*, and *Ids* (Nachman et al. 1998), Xq22 (Anagnostopoulos et al.

Table 2
Polymorphism in Worldwide DNA Sequence Data, F_{ST} Time Back to the Most Recent Common Ancestor (TMRCA) and Birthplace of the Most Recent Common Ancestor (PMRCA)

Region	Size (bp)	Sample	S[a]	Haplotype	MRCA[b]	F_{ST} (%)	PMRCA	TMRCA (Myr)
Il2rg[c]	1,147	10	0	1	0 (0.39)	—	—	0
Plp[c]	772	10	2 (2)	3	0.100 (0.39)	50	Af (As)	1.28
Hprt[c]	2,676	10	4 (1)	4	0.050 (0.48)	33	(Af, As, Eu)	0.53
Gk[c]	1,899	10	1 (1)	2	0.026 (0.33)	50	As	0.41
Ids[c]	1,909	10	0	1	0 (0.26)	—	—	0
Pdha1[c]	1,657	10	5 (4)	3	0.100 (0.48)	50	As (Af, Eu)	1.05
Pdha1	4,067	35	24 (20)	13	0.175 (0.55)	31	Af	1.59
dys44[c]	1,537	10	8 (5)	7	0.120 (0.45)	33	Af	1.35
dys44	7,622	860	33	64	—	18[d]	—	—
Zfx	1,215	335	10 (4)	10	0.145 (0.78)	—	Af	0.93
Xq13.3	10,163	69	32 (9)	20	0.050 (0.45)	19	Af	0.56
Xq22[e]	87,000	24	102	24	— (0.35[d])	17	—	—
Ace	23,840	22	74	18	—	7.3	—	1.11
Mx1	565	708	9	10	—	14[d]	—	—
Lpl	9,692	142	44 (38)	76	0.135 (0.75)	8.5	(Af, Eu)	0.91
β-globin	2,998	329	21 (7)	15	0.175 (0.65)	14	Af (As, Eu)	1.36
Mc1r	954	242	6 (2)	7	0.130 (0.92)	33	Af (As)	0.71
mtDNA[f]	610	189	201	135	1.1–2.1 (69[d])	46[d]	Af	0.20
YAP[g]	2,638	16	5	5	0.037[d] (1.9[d])	—	Af	0.19

NOTE.—F_{ST} is computed among Africans, Europeans, and Asians (including all others) by the method discussed in the text. TMRCA is estimated from the MRCA sequence differences within humans relative to those between humans and chimpanzees. "Af," "Eu," and "As" indicate Africa, Europe, and Asia, respectively; Af (As) or (Af, Eu) indicates that the ancestral haplotypes are shared by Africans and Asians or by Africans and Europeans, but for the former, the PMRCA is determined as African based on the haplotype frequency. A dash indicates that no inference is permitted because of inadequate samples or lack of polymorphism.

[a] The number of polymorphic sites excluding insertions and deletions (the number of phylogenetically informative sites).

[b] The height of the MRCA in terms of % sequence differences. One half of the mean % sequence differences between humans and chimpanzees is given in parentheses.

[c] After Nachman et al. (1998).

[d] These values are taken from the original papers.

[e] Solid-phase fluorescent chemical-mismatch cleavage by Anagnostopoulos et al. (1999). The sequence data are not available.

[f] Control region 1 (HVRI) from Vigilant et al. (1991).

[g] YAP and polyA-tail polymorphism in addition to three SNPs (Hammer 1995).

1999), *Ace* (Rieder et al. 1999), a small intergenic region near *Mx1* (Jin et al. 1999), *Lpl* (Clark et al. 1998; Nickerson et al. 1998), β-globin (Harding et al. 1997), and *Mc1r* (Rana et al. 1999). We also included a Y-linked region (Hammer 1995) and an mtDNA control region (Vigilant et al. 1991). Table 2 lists all of these regions, estimates of TMRCA and PMRCA wherever possible, the pattern and degree of nucleotide differences, and F_{ST}.

First, assuming the rate constancy of silent substitutions, we computed the average height of the MRCA within a human sample in terms of nucleotide differences, as well as one half of nucleotide differences over all pairs between human and chimpanzee sequences. The ratio of the former to the latter was the height of the TMRCA relative to the sequence divergence since the human lineage branched off. We multiplied the ratio by the species divergence time of 5 Myr to date the MRCA. The estimates ranged from 0.41 MYA to 1.59 MYA for the 10 X-linked regions (table 2). The estimate was 1.36 MYA for the β-globin region. The estimates for the mtDNA and Y-linked regions were taken from Vigilant et al. (1991) and Hammer (1995), respectively. Thus, the MRCA for all these regions appears to have existed during the T_d period. The estimate of F_{ST} varied from region to region. This variation was in good agreement with the haplo-diploid nature of the regions: lowest for autosomal regions, moderate for X-linked regions, and highest for haploid regions (Takahata 1993). Overall, either gene flow among the founding populations or relatively recent population subdivision must have played significant roles in shaping genetic architecture in the current human population.

Second, based on the parsimony method, which allows polychotomy, we inferred the ancestral sequences and the PMRCAs. There were seven regions to which this method was not applied. Both *Il2rg* and *Ids* were monomorphic, *Ace* and *Mx1* lacked chimpanzee orthologs, and the Xq22 sequences were not available. For these five regions, we could not infer the PMRCAs. There were two other regions for which we failed to determine the PMRCAs. In the *Hprt* region, all three ethnic groups possessed the ancestral-type sequences in similar frequencies, and in the *Lpl* region, recombination occurred too frequently (Templeton et al. 2000). Figure 5 shows 10 parsimony trees for 9 other regions in which the ancestral sequences (boxed) could be inferred. The PMRCAs at all but *Gk* loci were determined as Africa. In *Gk*, there was only one informative site, and the ancestral nucleotide at this site was shared by two Asians and the chimpanzee. We therefore assigned Asia as its PMRCA. For Xq13.3, sequence A (four from Africans and four from Asians) and sequence S (from Biaka Pygmy) were the closest to the chimpanzee sequence, but

they differed from each other. Since sequence S branched off earlier than sequence A (fig. 5), we assigned Africa as the PMRCA. The MRCA-type sequences for the *Plp,* β-globin, and *Mc1r* regions occurred in more than one population. As mentioned, we used the haplotype frequency data. In each case, the highest frequency (80%, 49%, and 42%) was observed for Africans, so these three PMRCAs were assigned as Africa.

The two data sets for the *Pdha1* region by Nachman et al. (1998) and Harris and Hey (1999) result in conflicting inferences about the PMRCA. Since the latter encompasses the former, and a larger data set is preferable, we used Harris and Hey (1999) and regarded the *Pdha1* region as evidence for the African PMRCA. Here, we would like to mention one issue concerning this region. The sequence analysis showed that there are two distinct lineages, one giving rise to an African-specific haplotype and the other giving rise to the ancestral lineage leading to African as well as non-African variants—some 200,000 years ago. This observation was taken as evidence for multiregionality or as a challenge of uniregionality (Pennisi 1999). As suggested by this, as well as other data (Yu and Li 2000), there might indeed be a strong population subdivision in Africa. However, this is not the issue here. The real issue is whether any non-African population that existed before modern *H. sapiens* emerged made a significant contribution of genes to the current human population. Unless this is demonstrated, multiregionality is not supported, and the *Pdha1* data alone cannot give such evidence.

In any event, there were six X-linked regions (*Plp, Gk, Pdha1, Dys44, Zfx,* and Xq13.3), two autosomal regions (β-globin, *Mc1r*), and one Y-linked region, as well as mtDNA, in which PMRCAs could be inferred. For these 10 regions, there were 9 African PMRCAs and 1 Asian PMRCA (table 2). If we ignored the *Gk* region because it contained only one informative site, then all 9 regions favored the African PMRCA, and the 1% confidence limit of p_1 was 0.6. This was significantly greater than 0.45 when the *Gk* region was included. To be conservative, however, we considered all 10 regions.

Discussion

The observation of 90% African PMRCAs (table 2) is not easily explained by multiregionality unless the hypothesis assumes that the African founding population (N_1) was much larger than the European and Asian founding populations ($N_2 + N_3$). With a strong asymmetry in breeding sizes (e.g., $r = N_1/(N_2 + N_3) = 50$), the F_{ST} value for neutral genes is expected to be large even when the extent of gene flow is sufficiently high (table 1). F_{ST} values as large as >50% are rarely observed (table 2). More importantly, with this strong asymmetry in relative breeding sizes, the genetic contribution of non-African founding populations becomes considerably small. Whereas this conclusion does not deny the existence of multiple founding populations over the world, it does deny that they all made significant genetic contributions to the evolution of modern *H. sapiens.* This holds true particularly for both globally and locally advantageous genes. In small populations, advantageous mutations become rare, and the effect of natural selection is counterbalanced by that of genetic drift unless selection is strong enough. Thus, neither the single evolutionary unity nor the regional continuity of modern *H. sapiens* during the T_d period is guaranteed if the breeding sizes of some of the founding populations are substantially small.

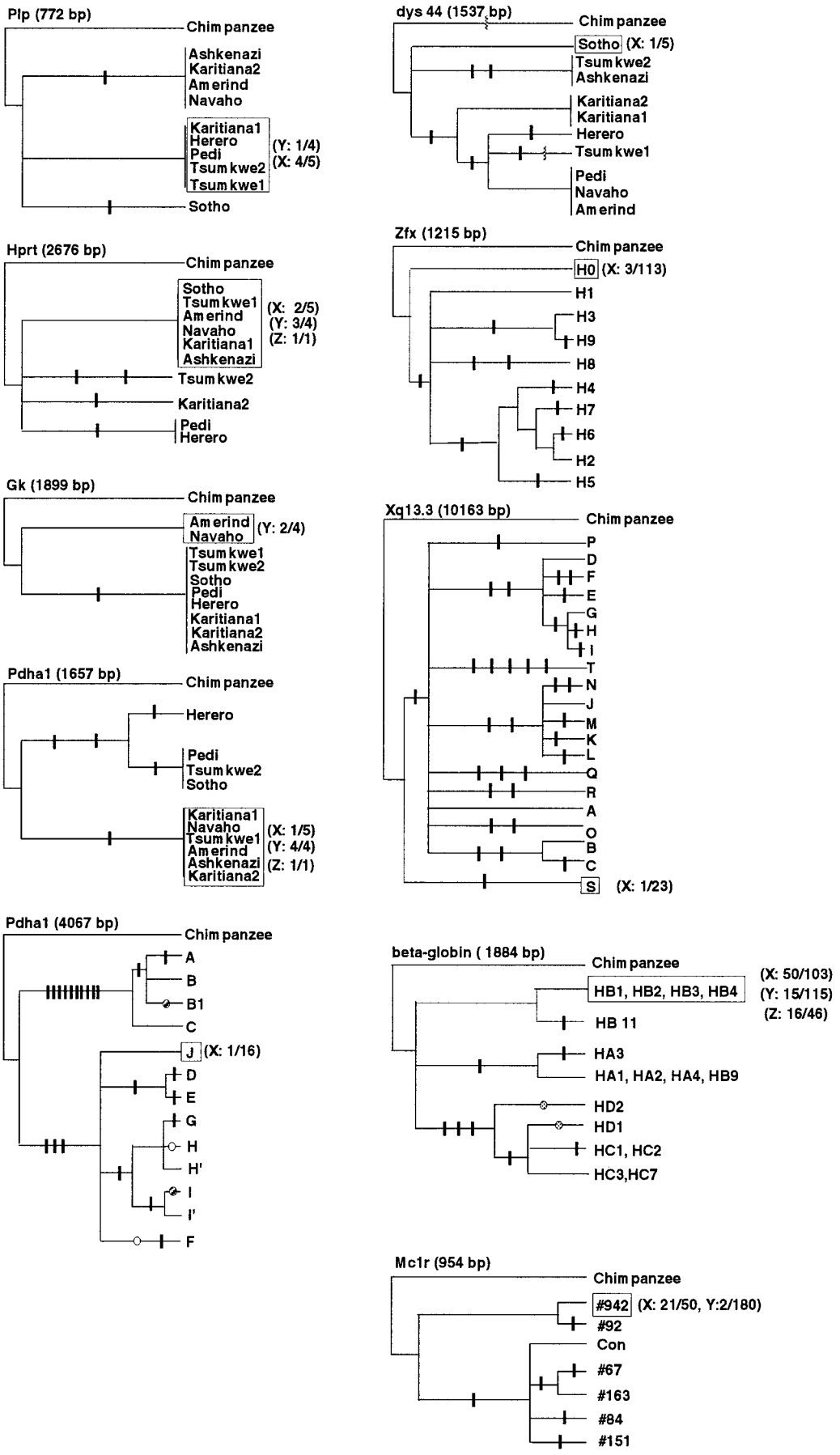
Assuming neutrality, we carried out fairly extensive simulation to set a lower bound of the African population size. Excluding the cases in which PMRCA went back to the ancestral population (fig. 1), simulation yielded the probability of African PMRCAs for various ratios of *r.* We then compared this probability with the observed value of 9/10 = 0.9. The probability of 90% African PMRCA is as low as 0.01 even for $r = 1.5$ and becomes nearly 0.4 for $r = 10$–50 (fig. 6). These values are slightly different from those discussed based on the binomial distribution. We note two points regarding the simulation. First, when $r > 0.5$ or $N_1 > N_2$ and N_3, migration becomes asymmetrical, and the ancestral lineages in smaller founding populations tend to come from a larger founding population. Second, simulation is based on fig. 1*a,* so there are quite a few cases in which the MRCA occurs in the ancestral population, whereas the previous argument, based on the binomial distribution, assumes no such case.

It is instructive to examine the required value of *r* together with the estimate of the effective size (N_e) in the whole human population. Wright (1943, p. 133) provides a formula which relates the effective population size (N_e) to the total number (N_T) of breeding individuals via F_{ST}:

$$N_e = \frac{N_T}{1 - F_{ST}}.$$

Thus, N_e is always greater than N_T in a structured population without extinction and recolonization (Nei and Takahata 1993; Takahata 1993, 1995). Since the estimated N_e in humans is on the order of 10,000, and F_{ST} is about 10% (Takahata 1993), the total number of breeding individuals is also on this order. For simplicity, we assume that $F_{ST} = 0.1$, as observed for three major ethnic groups (Nei and Roychoudhury 1974), and $N_e = 11{,}000$. We then have $N_T = 10{,}000$ from the above formula. Therefore, when $r = 1.5$, we obtain $N_1 = 6{,}000$ and $N_2 + N_3 = 4{,}000$. On the other hand, for a more likely value of $r = 10$, N_1 is 9,000 and $N_2 + N_3$ is only 1,000. Whatever the cause of this small population size in Europe and Asia is, the extent of DNA polymorphism in these geographic areas becomes extremely low, such that it seems difficult to establish regional continuity.

According to the uniregional hypothesis, the transition from *H. erectus* to anatomically modern *H. sapiens* had completed in a single founding population by the end of the T_d period (fig. 1*b*). This transition may have stemmed from globally advantageous mutations. Concerning local differentiation, the hypothesis assumes that a rapid process occurred after modern *H. sapiens*


Plp (772 bp)
Chimpanzee
Ashkenazi
Karitiana2
Amerind
Navaho
Karitiana1
Herero
Pedi
Tsumkwe2
Tsumkwe1
(Y: 1/4)
(X: 4/5)
Sotho
Hprt (2676 bp)
Chimpanzee
Sotho
Tsumkwe1
Amerind
Navaho
Karitiana1
Ashkenazi
(X: 2/5)
(Y: 3/4)
(Z: 1/1)
Tsumkwe2
Karitiana2
Pedi
Herero
Gk (1899 bp)
Chimpanzee
Amerind
Navaho
(Y: 2/4)
Tsumkwe1
Tsumkwe2
Sotho
Pedi
Herero
Karitiana1
Karitiana2
Ashkenazi
Pdha1 (1657 bp)
Chimpanzee
Herero
Pedi
Tsumkwe2
Sotho
Karitiana1
Navaho
Tsumkwe1
Amerind
Ashkenazi
Karitiana2
(X: 1/5)
(Y: 4/4)
(Z: 1/1)
Pdha1 (4067 bp)
Chimpanzee
A
B
B1
C
J
(X: 1/16)
D
E
G
H
H'
I
I'
F
dys 44 (1537 bp)
Chimpanzee
Sotho
(X: 1/5)
Tsumkwe2
Ashkenazi
Karitiana2
Karitiana1
Herero
Tsumkwe1
Pedi
Navaho
Amerind
Zfx (1215 bp)
Chimpanzee
H0
(X: 3/113)
H1
H3
H9
H8
H4
H7
H6
H2
H5
Xq13.3 (10163 bp)
Chimpanzee
P
D
F
E
G
H
I
T
N
J
M
K
L
Q
R
A
O
B
C
S
(X: 1/23)
beta-globin (1884 bp)
Chimpanzee
HB1, HB2, HB3, HB4
(X: 50/103)
(Y: 15/115)
(Z: 16/46)
HB 11
HA3
HA1, HA2, HA4, HB9
HD2
HD1
HC1, HC2
HC3,HC7
Mc1r (954 bp)
Chimpanzee
#942
(X: 21/50, Y:2/180)
#92
Con
#67
#163
#84
#151

evolved. Local differentiation might result from locally advantageous mutations, and this process might be facilitated by limited amounts of gene flow and population expansion. The MRCA of those mutations must have occurred in the single founding population from which modern *H. sapiens* emerged. This also applies to neutral genes in the case of a short tenure of modern *H. sapiens* relative to the coalescence time. The population-specific pattern of allelic lineages is thus in better agreement with uniregionality than with multiregionality.

Uniregionality does not imply that there was only one population at a given time during T_d, but it assumes that one population predominated and the rest played minor roles in the evolution of anatomically modern *H. sapiens*. Regarding this assumption, it would be of particular interest to compare current human DNA sequences with those extracted from extinct Homo species. Hypervariable regions I and II of the Neanderthal mtDNA were sequenced and compared with the homologous sequences of 689 humans as well as 7 chimpanzees and 2 bonobos (Krings et al. 1997, 1999). Although some contemporary human sequences are more divergent from each other than from the Neanderthal, the phylogenetic analysis shows that the Neanderthal sequence diverged before the MRCA in the modern human mtDNA pool, followed by divergences of two distinct African lineages. It appears that the Neanderthal and modern human mtDNA lineages separated 465,000 years ago and the MRCA of the present-day human mtDNA occurred 163,000 years ago. The recent analysis of the second Neanderthal specimen from Caucasus also shows an isolated clade of the two Neanderthal mtDNAs (Ovchinnikov et al. 2000). The long coexistence of the Neanderthal and modern humans has raised questions about the absence of admixture or the possibility that these two species were really reproductively isolated. It turns out that the conditions for detecting admixture are stringent (Nordborg 2001). It is necessary that the population divergence is ancient and the time of admixture is recent. The power of detection of admixture also depends on the extent of admixture. If extensive admixture between Neanderthals and modern human ancestors occurred 30,000 years ago, close to the extinction time of the Neanderthals, and if they diverged 450,000 years ago, close to the estimate of the Neanderthal mtDNA divergence, it may be possible to detect admixture in a sample of current human mtDNAs. However, our inability to detect ancient admixture results largely from single-locus information, and many independent regions are needed to improve the power. This is only possible with autosomal regions, but unfortunately, they may not work at all for the Neanderthals. TMRCA at autosomal regions is on average four times as old as that of mtDNA (table 2). Because of weaker genetic drift for autosomal regions than for mtDNA, the time of admixture can be as ancient as 100,000 years ago. Yet, the population divergence time must be as long as >1 MYA in order to obtain the same power of detection of ancient admixture. Whereas this is feasible for *H. erectus*, it is not feasible for Neanderthals.

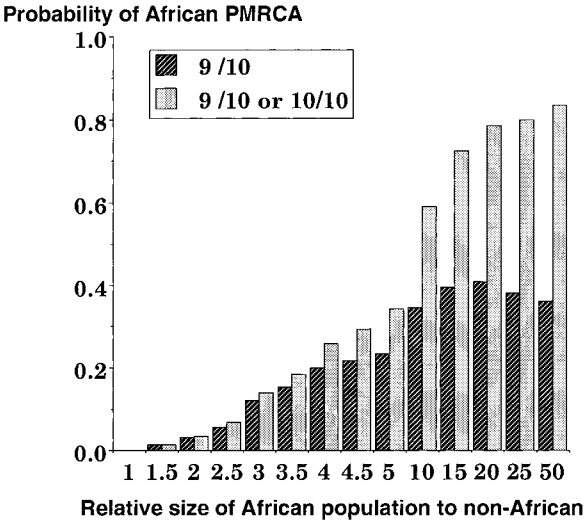


FIG. 6.—Probability of African PMRCAs under different African and non-African founding population sizes when TMRCA is shorter than $10N_1$ (10,000 repeats). The probability is based on the number of cases in which 9 African PMRCAs are found in a sample of 10 unlinked regions. Each sample consists of five sequences from each of the three populations. As in figure 3, $N_1m = 1$ and the abscissa represents $r = N_1/(N_2 + N_3)$. For large r values, the probability of all 10 African PMRCAs also increases, but because $N_1m = 1$, there are cases of more than one non-African PMRCA.

Finally, we would like to discuss one evolutionary feature of 10 X-chromosomal regions. The mean amount of sequence differences between humans and chimpanzees over the regions was 0.87%. This is nearly one half of either 1.58% of the three autosomal regions examined here or 1.75% over 37 autosomal regions of about 6,500 silent sites (N.T. at Dual Congress 1998, South Africa). Concerning the X-chromosomal regions, we examined the extent of polymorphism in the ancestral population between humans and chimpanzees. It turns out that of the average 0.87% sequence differences, 0.17% were attributed to the ancestral polymorphism, and the remaining 0.68% were attributed to the sequence differences during the past 5 Myr. On the other hand, the 37 autosomal regions divided the 1.75% sequence differences into 0.45% and 1.32%, respectively. Thus, both quantities in the X-chromosomal regions were one half of those in the 37 autosomal regions. One possible cause is a reduction in mutation rates in X chromosomes. The ratio of the X-chromosomal to autosomal sequence differences, however, is even smaller than that expected under the male-driven mutation hypothesis (Miyata et al. 1987). Although the small extent of ancestral poly-

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FIG. 5.—Gene genealogies of individual loci. A bar on each branch indicates a mutation that was inferred from comparison with chimpanzee orthologs (see text). There are two parallel mutations in the *Pdha1* tree and one in the β-globin tree. These parallel changes are denoted by three different types of circles. The ancestral type sequences are boxed. Haplotype frequencies are given in parentheses (X, Y, and Z represent African, Asian, and European populations, respectively). The substitutions in the lineage leading to the chimpanzee are suppressed.

morphism at the X-chromosomal regions may be accounted for by a smaller effective size than for the autosomal regions, the reduced substitution rate remains to be elucidated. Despite this, most regions have supported the concept of the uniregionality of modern *H. sapiens.*

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