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Genomic Evidence for an African Expansion of Anatomically Modern Humans by a Southern Route

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Abstract There is general agreement among scientists about a recent (less than 200,000 yrs ago) African origin of anatomically modern humans, whereas there is still uncertainty about whether, and to what extent, they admixed with archaic populations, which thus may have contributed to the modern populations' gene pools. Data on cranial morphology have been interpreted as suggesting that, before the main expansion from Africa through the Near East, anatomically modern humans may also have taken a Southern route from the Horn of Africa through the Arabian peninsula to India, Melanesia and Australia, about 100,000 yrs ago. This view was recently supported by archaeological findings demonstrating human presence in Eastern Arabia >90,000 yrs ago. In this study we analyzed genetic variation at 111,197 nuclear SNPs in nine populations (Kurumba, Chenchu, Kamsali, Madiga, Mala, Irula, Dalit, Chinese, Japanese), chosen because their genealogical relationships are expected to differ under the alternative models of expansion (single vs. multiple dispersals). We calculated correlations between genomic distances, and geographic distances estimated under the alternative assumptions of a single dispersal, or multiple dispersals, and found a significantly stronger association for the multiple dispersal model. If confirmed, this result would cast doubts on the possibility that some non-African populations (i.e., those whose ancestors expanded through the Southern route) may have had any contacts with Neandertals.

Anatomically modern humans emerged in Africa around 200,000 yrs ago (Lahr and Foley 1994) and dispersed from there some 60,000 yrs ago or less (Ramachandran et al. 2005; Liu et al. 2006). In the course of this expansion, they encountered, and largely or completely replaced, all pre-existing humans in Europe and Asia, including Neandertals, *Homo erectus*, and possibly other human forms we do not know yet, or are still being identified (Reich et al. 2010). The first paleontological or archaeological evidence of human presence in both Europe (Mellars 2006b, 2006a) and island Melanesia is dated around 40,000 yrs ago (O'Connell and Allen 2004).

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For decades, the debate on the modes and implications of this expansion focused on two alternative models of human evolution. Under the out-of-Africa, or Replacement, model (Foley 1998; Tattersall 2009) the expanding Africans replaced all the archaic human forms encountered in the process. Conversely, in the initial formulations of the multiregional model (Wolpoff et al. 1988), populations of anatomically archaic humans were regarded as directly ancestral to the modern populations of the same regions (Wolpoff et al. 1988). However, with time, this view became untenable and was modified into a model of admixture between anatomically archaic and modern humans in which the archaic forms gave a limited, but not negligible, contribution to the modern human genome (Wolpoff et al. 2001; Trinkaus, 2007; Relethford 2008). Mitochondrial DNA data showed sharp differences between Neandertals (Green et al. 2008) and both present-time and ancient anatomically modern Europeans, or Cro-Magnoids (Caramelli et al. 2008), which seem incompatible with any degree of admixture between them (Belle et al. 2009; Ghirotto et al. 2011). However, comparisons of the recently published sequence of the nuclear Neandertal genome with modern genomes have shown a greater degree of similarity with non-African than with African modern individuals (Briggs et al. 2009). Although this result is compatible with different hypotheses, the authors' favorite interpretation, also supported by analyses of modern genomes (Wall et al. 2009) is that modern humans, in their expansion from Africa, hybridized with Neandertals in Palestine, whereas those who stayed in Africa did not; the consequences of this process are still evident in the modern humans' genome.

If all non-Africans carry in their genome traces of their ancestors' admixture with Neandertals, they must necessarily be descended from people who had an opportunity to meet the Neandertals. Although this view is reasonable, it is not proved, and in fact it has a scientifically sound alternative. Based on the study of skull morphology, Lahr and Foley (1994) proposed that before the exit through Palestine a group of modern humans also left Africa through a Southern route, directly into the Arabian Peninsula, the Indian subcontinent, and Melanesia. So far, only in a few analyses of mitochondrial DNA was this view taken into any consideration, but the results were consistent with it (Watson et al. 1997; Quintana-Murci et al. 1999; Maca-Meyer et al. 2001; Macaulay et al. 2005). The possibility of an early exit through a Southern route also accounts for an otherwise puzzling observation, namely the very early time of colonization of Melanesia, comparable with that in which Europe was peopled, despite its much greater distance from Palestine. The recent discovery of $>$90,000-yr-old stone tools in Eastern Arabia, near the Strait of Hormuz, seems to give archaeological support to this view (Armitage et al. 2011).

In this study we analyzed genetic diversity at more than 100,000 single-nucleotide polymorphisms (SNPs) in 86 individuals belonging to nine populations selected from two different data set (Reich et al. 2009; Xing et al. 2009). Seven of these populations were chosen along the putative "Southern route," mainly in the Indian subcontinent, whereas two come from China and Japan. To

test which model of African expansion (hereafter referred to as Single Dispersal, SD, and Multiple Dispersals, MD) can better explain the observed patterns of genomic variation, we compared the genomic differences between populations to alternative geographic distance matrices calculated according to the SD and MD models.

Materials and Methods

Criteria for Selecting Populations. We analyzed genetic diversity at more than 100,000 single-nucleotide polymorphisms (SNPs) in 86 individuals belonging to nine populations selected from two different public genomic data set (Reich et al. 2009; Xing et al. 2009). Seven of these populations were chosen along the putative "Southern route," mainly in the Indian subcontinent. The Indian culture and society have been affected by multiple waves of migration and gene flow since historic and prehistoric time, and more than 4500 well-defined endogamous populations in India are currently recognized, culturally stratified in tribes and non-tribes (Thanseem et al. 2006). The tribal groups constitutes about 7.76% of the total Indian population (2001 Census of India) and form tribal communities (Singh 1992) who speak about 750 dialects (Kosambi 1991) belonging to the Austro-Asiatic, Dravidian, and Tibeto-Burman language families. On the contrary, most non-tribal populations of Hindu or Muslim religion predominantly speak Indo-European languages. It is generally believed that the first Indo-European speakers from West Eurasia entered India in a recent wave of migration from the Northwest and spread in the subcontinent, mixing with indigenous Dravidian speaking people. They established the hierarchical Hindu caste system and supposedly placed themselves in castes of higher rank (Cavalli-Sforza et al. 1994). Studying a non-tribal population from Andrha Pradesh, in Southern India, Bamshad et al. (2001) found that indeed the genetic affinity between Europeans and Indians is proportional to the caste rank. Individual belonging to upper castes are more similar to Europeans than to Asians, and the upper castes are significantly more similar to Europeans than are the lower castes. Moreover, a large-scale study of Y-SNPs (from 508 tribal samples and 901 caste samples) showed that lower castes are more similar to the tribal group than to the upper caste populations (Thanseem et al. 2006). For these reasons, we selected from the populations typed by Reich et al. (2009) and Xing et al. (2009) only populations who are considered to be the descendants of the earliest settlers of the continent, excluding Indo-European speakers and the upper castes (Bamshad et al. 2001). After preliminary analyses we also excluded a population from Andaman Island; the enhanced genetic drift acting in these extremely isolated groups might have introduced a bias in our study.

We analyzed a total of 86 individuals belonging to nine populations. From the Reich et al. (2009) data set we selected two tribal and three lower-caste populations, namely Kurumba, Chenchu, Kamsali, Madiga, and Mala; from the Xing et al. (2009) data set we selected a tribal population, Irula, a lower-caste population, Dalit, and the Chinese and Japanese samples (Table 1).

Table 1. Populations Considered in the Analyses

Population	*Pop Label*	*Population Group*	*Language*	*Spatial Coordinates*	*Sample Size*
Kurumba	KUR	Tribal	Betta Kurumba (Dravidian)	10° 54′ N/76° 27′ E	9
Chenchu	CHE	Tribal	Chenchu (Dravidian)	17° 22′ N/78° 28′ E	6
Kamsali	KAM	A. Pradesh lower caste	Telugu (Dravidian)	15° 49′ N/78° 02′ E	4
Madiga	MAD	A. Pradesh lower caste	Telugu (Dravidian)	17° 58′ N/79° 35′ E	4
Mala	MAL	A. Pradesh lower caste	Telugu (Dravidian)	17° 22′N/78° 29′ E	3
Irula	IRU	Tribe	Tamil (Dravidian)	13° 37′ N/79° 45′ E	24
Dalit	DAL	Tamil lower caste	Tamil (Dravidian)	13° 37′ N 79° 45′ E	13
Chinese	CHI	E. Asian	Chinese (Sino-Tibetan)	31° 9′ N/108° 36′ E	10
Japanese	JAP	E. Asian	Japanese (Altaic)	35° 35′ N/138° 5′ E	13

Genetic Data and Distance Matrices. The samples were genotyped by the Affymetrix 6.0 arrays (Reich et al. 2009), and by the Affymetrix Gene chip Human Mapping 500K Array set (Xing et al. 2009). We first selected from each data set the subset of SNPs typed in all the individuals considered, so as to have no missing data, and then we searched for the SNPs shared between data set. We obtained a total of 111,197 SNPs.

To disentangle the effects of the demography from those of selection, we separated sites potentially under selection (i.e., within genes or regulatory regions) from neutral sites. We classified SNPs as genic or intergenic according to their position using Biomart (Figure 1) (Haider et al. 2009), based on ENSEMBL *Homo sapiens* variation (Figure 2). The entire data set of 111,197 SNPs was composed of 50,748 genic SNPs and 60,449 intergenic SNPs. We added to the latter 303 genic SNPs causing synonymous substitutions, obtaining a total of 60,752 polymorphisms for which the effects of selection appeared extremely unlikely, which we shall refer to as the subset.

For both the entire data set and the subset we calculated two genetic distance matrices, namely between individuals and between populations,

Figure 1. Absolute frequencies of genic (grey) and intergenic (black) loci in the database analyzed (111,197 SNPs).

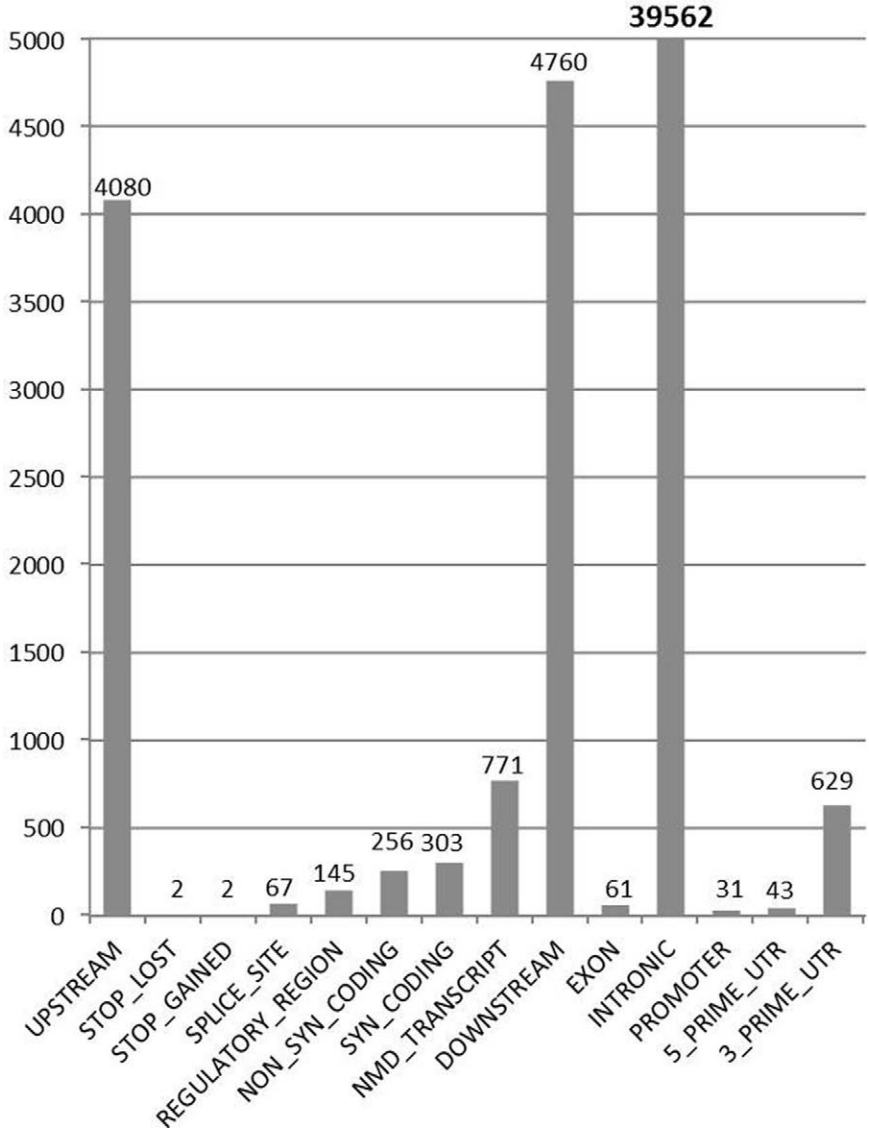

Figure 2. Histogram representing genic loci, subdivided according to Ensembl "consequence to transcript" categories. Thirty-six of the 50,748 loci were not listed there, which brings their total to 50,712.

using our scripts in an R environment (R Development Core Team, 2008). The pairwise genetic distance matrix of individuals (d_ind) was calculated as the number of alleles that differ between individuals, summed across all loci and divided by the maximum number of possible differences, that is twice the

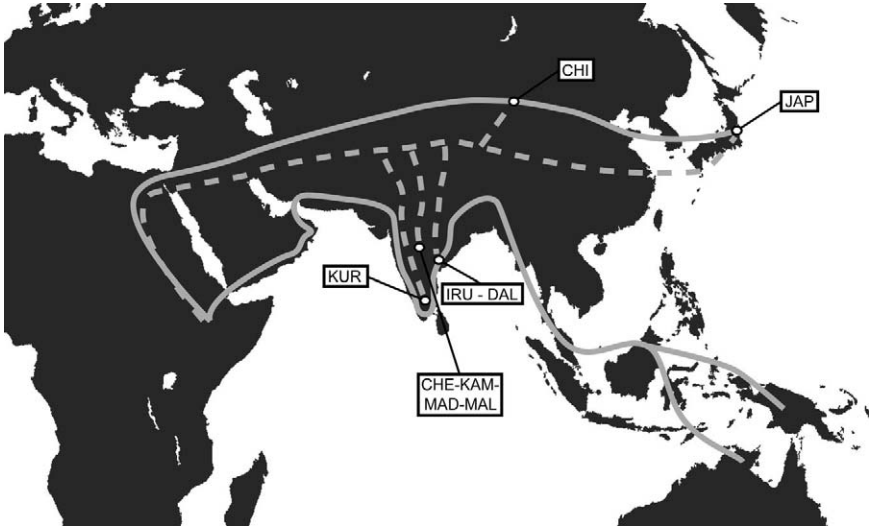

Figure 3. Map of the dispersal routes from Africa toward the Asian continent. The SD (single dispersal) model is indicated by grey lines, the MD (multiple dispersals) model by black lines. Populations labels as in Table 1.

number of SNPs considered. The genetic distance between pairs of populations was calculated according to Cockerham and Weir (1984) (d_Fst). The d Fst genetic distances do not significantly differ between the entire data set and the subset (Kolmogorov-Smirnov D= 0.044 $p = 0.99$).

Matrices of geographic distances between individuals and populations were calculated using PASSaGE version 2 (Rosenberg and Anderson 2011), according to the SD (d_geo1) and the MD (d_geo2) models (Figure 3). We forced the routes through obligated waypoints, to mimic the real waves of migration as suggested in Forster and Matsamura (2005). The starting point for both routes is Addis Abeba, Ethiopia, as in Ramachandran et al. (2005).

Comparison of Genetic and Geographic Data. To visualize genetic relationships suggested by our SNP data we used a Principal Component Analysis performed by the R FactoMineR package (http://cran.r-project.org/web/packages/FactoMineR/index.html) and a Neighbor-Joining reconstruction calculated with MEGA ver. 4.1 (Tamura et al. 2007).

Correlation coefficients were calculated as Mantel tests of matrix correlation (Mantel 1967), using the R Vegan package (http://cran.r-project.org/web/packages/vegan/index.html). To evaluate whether the one_exit or the two_exit model better explains the genetic variation of our samples, we calculated two sets of pairwise correlation, one for each genetic distance matrix (d_ind, d_Fst), compared with both d_geo1 and d_geo2 (Table 2). This kind of comparisons were performed both in the entire data set and in the subset of SNPs. The significance of the correlation coefficients was empirically estimated over 10,000 permutations.

Table 2. Mantel Correlation Calculated between Matrices of Genetic Distance (d_ind, d_Fst) and Geographic Distances according to Each Migration Model (d_geo1, d_geo2)

	Total		*Subset*	
	r	*p*	*r*	*p*
d_ind[a]				
d_geo1(SD)	0.68	0.000	0.66	0.000
d_geo2(MD)	0.73	0.000	0.71	0.000
d_Fst[b]				
d_geo1(SD)	0.39	0.060	0.38	0.064
d_geo2(MD)	0.73	0.006	0.72	0.006

The *r* Pearson coefficient (*r*) and *p* value (*p*) for both the complete dataset (total) and the subset of intergenic and synonymous SNPs (subset) are reported.

a. Correlation between individual genetic distance and geography.

b. Correlation between Cockerham and Weir's Fst and geography.

Results

Principal Component Analysis and Phylogenetic Tree. In the principal components analysis applied to the whole data set of 111,197 SNPs (Figure 4), the first component (Dim 1) accounts for 5.68% of the total variation and separates Chinese and Japanese (on the left) from the other populations. The second principal component (Dim 2), accounting for 2.87% of the variance, reflects differences among Indian populations. When we added to this analysis a population from Andaman Island (Onge), we observed that the Onge form a separate cluster with

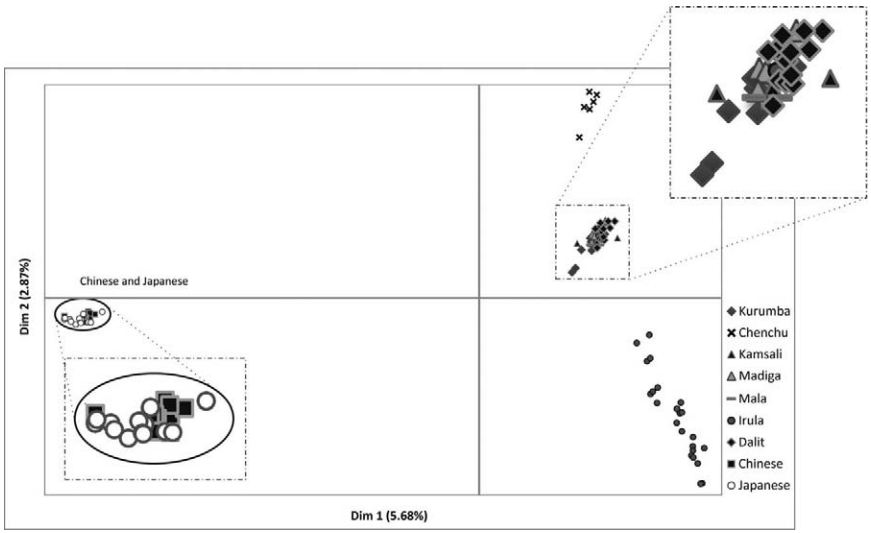

Figure 4. Principal components analysis of the populations under study, based on the whole data set (111,197 SNPs). First two principal components (Dim 1, Dim 2) are shown here, along with the relative percentage of genetic variation described. Different populations are defined by shape labels and different grey intensities.

respect to all other populations, and that their high differentiation causes the genetic relationships among all other populations to become less clear. Because the Onge also show the lowest mean heterozygosity (calculated over all loci), suggesting that their isolation enhanced the effects of genetic drift upon their genome variation (data not shown), we excluded them from further analyses. Note that, in the analysis of large numbers of SNPs, each principal component typically captures a small fraction of the overall variance. For instance, in a study of 500,000 SNPs in Europe, the first two principal components explained, respectively, 0.30% and 0.15% of the total variance (Novembre et al. 2008).

The principal component analysis was confirmed by the pattern observed in the Neighbor-Joining tree (Figure 5) inferred from the d_ind matrix. The Chinese and Japanese individuals cluster together, well separated from the Indian samples, all of which form a different cluster.

Correlation Analyses. Mantel correlation coefficients were estimated for both the entire data set of SNPs and for the subset including intergenic and synonymous polymorphisms. As expected considering the large size of the individual matrices, the correlations between the individual genetic distances and both geographic distance matrices were highly significant (p value around 0) (Table 2). However, the correlation was consistently higher for the MD (whole data set: $r = 0.73$; subset: $r = 0.71$) than for the SD model (whole data set: $r = 0.68$; subset: $r = 0.66$).

These differences are quantitatively small, but a clearer pattern emerged when we moved to examining the relationships between populations rather than between individuals. The methods we chose allows to also account for the variation within populations when the genetic distance is calculated. At this level, considering Fst as a measure of genetic distance among populations, it was possible to clearly distinguish the two models being compared. Indeed, as shown in Table 2, the correlations were significant only for the MD model, with $r = 0.73$ ($p = 0.006$) when calculated averaging over 111,197 SNPs, and $r = 0.72$ ($p = 0.006$) considering the subset of SNPs. Conversely, the correlation coefficients calculated according to the SD model were lower and insignificant for both sets of SNPs (total and subset; Table 2), reaching values of 0.39 ($p = 0.060$) and 0.38 ($p = 0.064$), respectively. As expected from the insignificant Kolmogorov- Smirnov test ($D = 0.044$, $p = 0.99$) it was irrelevant to consider either the whole set of SNPs, or only the intergenic and synonymous subset. These results stand Bonferroni correction for multiple test, which we applied conservatively, considering eight independent tests, even though the two sets of data are not independent because the entire data set contains the subset.

Discussion

There are all reasons to expect that populations from Northeast Asia, in China and Japan, differ from populations of India when analyzed at the genomic level. However, in this study not only did we observe this trivial result, but we

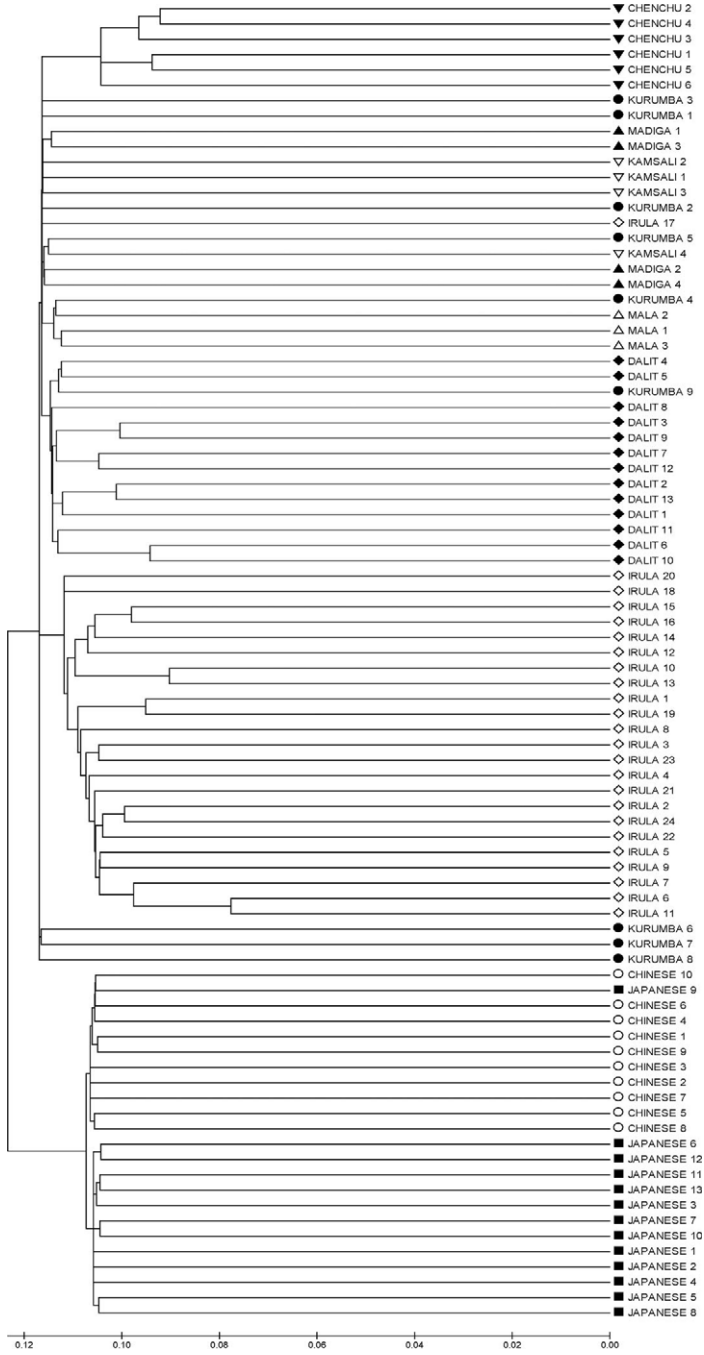

Figure 5. Neighbor-joining linearized tree of studied populations. Each individual is labeled with the corresponding population symbol.

also showed that the observed pattern of genomic differentiation is in significantly better agreement with a model of multiple dispersal from Africa (MD) than with the alternative model assuming that all non-Africans originated from ancestors who expanded through Palestine into Eurasia (SD). This was the case when genomic distances between both individuals and populations were compared with the geographic distances representing the results of multiple and single dispersals. When individual genomes were considered, the correlation was stronger under MD than under SD, but both were significant, which is unsurprising, given the large amount of data considered and the well-known presence of geographical structure in human genomic data (Rosenberg et al. 2002; Jakobsson et al. 2008). However, only for MD did we observe significant correlations at the population level, the correlation coefficients were roughly twice as large as observed under the SD model, and the statistical significance much higher under the MD model. There is no doubt that the present analysis gives greater support to the hypothesis of multiple dispersals, suggesting that several populations of Southern Asia evolved largely independently from those of Northeast Asia because of a different timing and route of dispersal from Africa.

This is the first formal test of the predictions of the SD and MD models at the genomic level. Previous genetic studies on the same subject were limited to phylogeographic analyses of mitochondrial DNA variation but gave results consistent with the present analysis. One of their findings was that the mitochondrial haplogroup M, originating from the African haplogroup L3, reaches high frequencies in India and Ethiopia while, contrary to the expectations of the SD model, it is virtually absent in the Levant (Watson et al. 1997; Quintana-Murci et al. 1999; Maca-Meyer et al. 2001; Macaulay et al. 2005). Indirect support to the MD model also comes from recent archaeological findings of stone tools at Jebel Faya, United Arab Emirates, suggesting that anatomically modern humans were present in the Arabian Peninsula perhaps 125,000 yrs ago, and most likely $>$90,000 yrs ago (Armitage et al. 2011). Although these data do not prove that the Jebel Faya people proceeded further East and left descendants in South and East Asia, they are in nice agreement with one prediction of the MD model and do not seem easy to reconcile with a single exit from Africa through a Northeastern route.

Reconstructing such remote migrations is not straightforward, especially when successive demographic processes, such as back migrations and admixture, are likely to have occurred. Of course, no human population has been totally isolated for tens of thousands of years, and so questions exist about the genomic impact of demographic processes following the first peopling of Asia. However, we do not know of any safe way to identify anything we may consider as an ancestral gene pool, so as to separate it from later contributions; this seems a general problem of all evolutionary studies in which modern samples are used to infer prehistoric processes. At any rate, even if relevant fossil samples were

found, obtaining reliable nuclear sequences from 60,000-yr-old anatomically modern humans would be currently impossible (Green et al. 2009).

We are aware that other options were possible in the choice of the populations to consider, and that other, more sophisticated models may better account for the patterns of variation we observed. On the other hand, we analyzed what seems to date the only suitable public genomic data set. In the future, it may be that the availability of different nuclear markers or populations may alter the emerging picture. Should these results be independently confirmed, their implications would by no means be minor. If part of the modern Asian ancestors left Africa through a Southern route, they had no chance to encounter and admix with Neandertal people; no trace of Neandertal occupation has been found in the Arab peninsula, let alone in Central or Southern Asia. Accordingly, one would have to reconsider the patterns of genetic similarity emerging from the comparison of African and non-African genomes with the only Neandertal genome studied so far.

The possible interpretation of these patterns of genomic similarity between distinct human forms is complex and clearly exceed the limits of the present paper. In particular, a Southern exit from Africa does not rule out the possibility that admixture may have occurred between expanding modern humans from Africa and other, archaic human forms, such as the Denisova people (Hofreiter 2011). However, if a greater degree of similarity with Neandertals is consistently found in the genomes of non-African people (Green et al. 2010), and these people are unlikely to ever have had any contacts with Neandertals (this study), the logical alternative to admixture would be the presence of an ancestral structure, predating the first exit from Africa. This possibility has been envisaged by the authors of the Neandertal genome study (Green et al. 2010); it also seems in good agreement with the results of comparisons of the Neandertal mitochondrial DNA with those of both prehistoric (Cro-Magnoid) and contemporary Europeans of modern morphology (Ghirotto et al. 2011). In other words, it may be that the 1 to 4% of apparent Neandertal contribution to non-African genomes reflects phenomena that did not occur after the first exit of anatomically modern humans from Africa but instead date back to an earlier time. At that time, the African population ancestral to both Neandertals and modern humans may have been genetically structured and internally differentiated, as shown for example by Currat et al. (2004). In this way, some of contemporary humans may still be carrying in their genome traces of a closer genetic relationships with the Neandertals' ancestors, without this necessarily meaning that any admixture took place after anatomically archaic and modern human forms separated.

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