Extreme mtDNA Homogeneity in Continental Asian Populations

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KEY WORDS mtDNA; Asian population; patrilocality; genetic homogeneity

ABSTRACT Mitochondrial DNA (mtDNA) variation in continental Asia has not been well-studied. Here, we report mtDNA HV1 sequences for 84 Xi'an and 82 Changsha Han Chinese, 89 Honshu Japanese, and 35 Vietnamese. Comparison of these sequences with other Asian mtDNA sequences reveals high variability within populations, but extremely low differentiation among Asian populations. Correlations between genetic distance and geographic distance, based on mtDNA and Y chromosome variation, indicate a higher migration rate in females than in males. This may reflect patrilocality, as suggested previously, but another plausible hypothesis is that the demographic expansion associated with the spread of agriculture in Asia may be responsible for the extreme genetic homogeneity in Asia. Am J Phys Anthropol 118:146–153, 2002.

The Asian continent encompasses the eastern part of Eurasian continent and is the source from which emanated the circum-Pacific peoples, such as Native Americans and the Oceanians. Molecular anthropologists and geneticists have studied mtDNA variation of populations from the Americas (Ward et al., 1991; Shields et al., 1993; Torroni et al., 1993a,b; Kolman et al., 1995) and Oceania (Redd et al., 1995; Redd and Stoneking, 1999; Sykes et al., 1995) to understand their biological history. The prehistoric migrations from the Asian continent to the Japanese archipelago (Horai et al., 1996) and to aboriginal Taiwan (Melton et al., 1998) have also been studied by analyzing mtDNA variation. However, regarding the present peoples of the source area, the Asian continental region, very little is known about mtDNA variation. To date, sequences of the first hypervariable region (HV1) have been obtained only for a few populations (Kolman et al., 1996; Horai et al., 1996; Lee et al., 1997; Comas et al., 1998), with some additional data in the form of restriction fragment length polymorphisms (Ballinger et al., 1992; Ding et al., 2000). Asian HV1 sequences overall account for only 10% of the more than 6,000 human mtDNA sequences currently deposited in databases such as DDBJ/EMBL/GenBank and HvrBase (Handt et al., 1998; Burckhardt et al., 1999). Additional continental Asian sequence data are therefore necessary to characterize Asian populations in comparison with European, African, and circum-Pacific populations.

Moreover, recently Y-chromosome haplotype data based on single nucleotide polymorphism (SNP) have been reported for continental Asian populations (Chu et al., 1998; Perez-Lezaun et al., 1999; Su et al., 1999). Additional mtDNA data would thus enable a comparison of migration rates between males and females in continental Asia, as previous studies have done in other areas (Seielstad et al., 1998; Perez-Lezaun et al., 1999). Here we report mtDNA nucleotide sequences from four Asian populations, including two Han Chinese (Xi'an and Changsha), Honshu Japanese, and Vietnamese, and analyze Asian mtDNA variability in a comparative framework using 2,629 sequences from 54 worldwide populations. To investigate migration patterns in males and females, we also compare mtDNA variation with published Y-chromosome variation and analyze the relationship between genetic distance and geographic distance for these two loci.

MATERIALS AND METHODS

Sampling and DNA extraction

Figure 1 shows the locations of the population samples in this study. The Han Chinese blood samples

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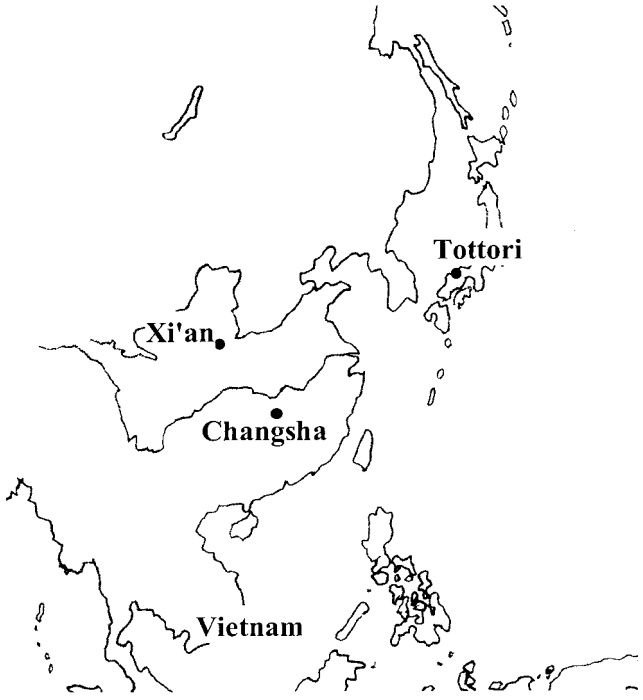

Fig. 1. Map of sampling locations for populations analyzed in this study.

came from two cities, Xi'an and Changsha, located on the Yellow and Yangtse Rivers, respectively. The Japanese blood samples were collected in Tottori Prefecture, Honshu, while the Vietnamese DNA samples were obtained from first-generation South Vietnamese immigrants to California. Genomic DNA was extracted by the QIAamp Blood Kit (QIAGEN).

Amplification and direct sequencing

PCR amplification of the HV1 region was performed using primers L15996 and H16401 (Vigilant et al., 1989). Since the Vietnamese samples did not amplify with these primers, presumably because of DNA degradation, additional primers H16218 and L16209 (Stone and Stoneking, 1998) were used to amplify these samples. PCR was carried out as follows: initial denaturation at 92°C for 90 sec, followed by 40 cycles of denaturation at 92°C for 30 sec, annealing at 57°C for 30 sec, and extension at 72°C for 30 sec, followed by a final extension of 5 min at 72°C. PCR products were sequenced directly with the same primers on an ABI PRISM 377 (Perkin-Elmer) by means of the Dye Terminator Cycle Sequencing kit (Perkin-Elmer). A total of 374 nucleotides (positions 16026–16399; Anderson et al., 1981) of the HV1 region were obtained from the four Asian populations. The nucleotide sequences have been submitted to DDBJ, http://www.ddbj.nig.ac.jp/Welcome-e.htm [accession numbers AB047980-AB048181 (Xi'an, Changsha, and Vietnamese), and AB048424-AB048512 (Tottori)], and will also become available in HvrBase, http://db.eva.mpg.de/hvrbase/ (Handt et al., 1998; Burckhardt et al., 1999).

Data analysis

Published data on HV1 sequences from additional 54 additional human populations from around the world (Table 1) were included. Estimates of genetic diversity and genetic distances were computed using the program ARLEQUIN version 2.000, http://lgb.unige.ch/arlequin, developed by S. Schneider, D. Roessli, and L. Excoffier. A neighbor-joining (NJ) tree (Saitou and Nei, 1987) was constructed using SENDBS, http://www.cib.nig.ac.jp/dda/ntakezak.html#sendbs, developed by N. Takezaki. Bootstrap probabilities were computed with 1,000 replicates, using D_a distances (Nei at al., 1983) and the model by Tamura and Nei (1993) of substitution, with $\alpha = 0.26$ (Meyer et al., 1999). Multidimensional scaling (MDS) analysis was carried out with STATISTICA (StateSoft Software, Ltd.), using F_{st} values calculated under the model by Tamura and Nei (1993).

RESULTS AND DISCUSSION

Overall, Asian populations exhibited high levels of within-population mtDNA variation (Table 1). Among all populations in Eurasia, the Vietnamese had the highest number of mean pairwise differences (MPD) (9.10 ± 4.29), and the Changsha population had the second highest number (7.91 ± 3.72), suggesting that in general, continental Asians exhibit higher levels of mtDNA variation in the south than in the north. The decreasing cline in mtDNA genetic diversity from the south to the north in Asia agrees with studies on classical genetic markers (Saitou et al., 1994), microsatellites (Chu et al., 1998), and Y-chromosomal biallelic markers (Su et al., 1999). The average MPD for Asians was higher in the continental region (7.12) than the non-continental region (6.57), and was 1.5 times higher than that of 12 European populations from the continental region (4.63), and nearly equal to that of 15 sub-Saharan African populations (7.99) (Table 2).

In spite of the high variability within populations, phylogenetic analyses demonstrate that genetic distances between Asian populations are very small. The NJ tree (Fig. 2) for 35 worldwide populations exhibits three major branches; including additional populations from Table 1 does not change the structure of this tree (data not shown). The majority of the populations enclosed by the ellipse come from east/central Asia, with all branches in the ellipse supported with less than 10% bootstrap probabilities, suggesting that the branching pattern in the ellipse has little statistical support. Figure 3 shows a multidimensional scaling (MDS) plot with the same populations as the NJ tree of Figure 2, except for three African populations. Six populations (Basques, British, Finns, Anatolia Turks, Turks, and Ainu), who were in the central ellipse in Figure 2, are now separate from the center. However, the Asian populations remain closely grouped spatially in the MDS plot. Thus the Asian populations are quite closely related to one another.

TABLE 1. Geographical classification of populations and diversity statistics[1]

	Name of population	Size	MPD	Tajima's D	Reference
Eurasia					
Asia					
	Continental				
	East Asia				
	Xi'an Han Chinese	**84**	**7.40 ± 3.49**	**−1.78***	**Present study**
	Changsha Han Chinese	**82**	**7.91 ± 3.72**	**−1.90***	**Present study**
	Cantonese	18	7.44 ± 3.65	−1.53	Betty et al., 1996
	Korean	370	6.52 ± 3.09	−2.19*	Horai et al., 1996; Lee et al., 1997
	Mongolian	103	7.68 ± 3.61	−1.83*	Kolman et al., 1996
	Siberian Altai	17	5.99 ± 3.00	−1.35	Shields et al., 1993
	Russian Siberians	16	5.79 ± 2.92	−1.11	Torroni et al., 1993b
	Central Asia				
	Kazakh	55	7.33 ± 3.48	−1.85*	Comas et al., 1998
	Lowland Kirghiz	48	7.26 ± 3.46	−1.72*	Comas et al., 1998
	Highland Kirghiz	47	6.58 ± 3.16	−1.92*	Comas et al., 1998
	Uighurs	55	6.49 ± 3.12	−1.97*	Comas et al., 1998
	Southeast Asia				
	Vietnamese	**35**	**9.10 ± 4.29**	**−1.89***	**Present study**
	Noncontinental				
	East Asia				
	Honshu Japanese	**89**	**5.94 ± 2.86**	**−2.05***	**Present study**
	Ainu	51	7.03 ± 3.35	−1.28	Horai et al., 1996
	Taiwan Han Chinese	52	7.62 ± 3.61	−1.61*	Horai et al., 1996
	Taiwanese	28	7.31 ± 3.52	−0.95	Melton et al., 1998
	Southeast Asia				
	Philippines	25	5.54 ± 2.76	−1.76*	Sykes et al., 1995
	Borneo Indonesia	26	4.60 ± 2.33	−0.33	Sykes et al., 1995
	East Indonesia	84	7.96 ± 3.74	−1.32	Vigilant et al., 1991; Redd et al., 1995; Redd and Stoneking, 1999
India					
	Indian	127	7.07 ± 3.34	−1.47*	Mountain et al., 1995
Middle East					
	Turks	29	7.33 ± 3.53	−1.97*	Calafell et al., 1996
	Anatolia Turks	45	6.06 ± 2.94	−2.04*	Comas et al., 1996
Europe					
	Continental				
	Basques	106	3.29 ± 1.70	−2.23*	Bertranpetit et al., 1995
	Bulgaria	30	5.25 ± 2.61	−1.93*	Calafell et al., 1996
	Danish	24	6.17 ± 3.01	−0.93	Richards et al., 1996
	Estonia	28	4.96 ± 2.49	−1.73*	Sajantila et al., 1995
	Finns	50	4.23 ± 2.13	−1.82*	Sajantila et al., 1995
	Germany	107	5.58 ± 2.70	−1.87*	Richards et al., 1996
	Italy (Tuscany)	49	5.70 ± 2.78	−2.06*	Francalacci et al., 1996
	North Spain	30	5.08 ± 2.53	−1.85*	Corte-Real et al., 1996
	Portugal	54	4.02 ± 2.04	−1.98*	Corte-Real et al., 1996
	Switzerland	76	3.98 ± 2.01	−1.78*	Pult et al., 1994
	Saami (Norway)	82	3.67 ± 1.88	−0.56	Sajantila et al., 1995
	Saami (Sweden)	25	3.62 ± 1.90	−0.99	Sajantila et al., 1995
	Noncontinental				
	British	100	5.04 ± 2.46	−1.92*	Piercy et al., 1993
	Icelanders	39	5.72 ± 2.80	−1.17	Sajantila et al., 1995
	Sardinian	69	4.74 ± 2.35	−2.03*	Di Rienzo et al., 1991
Africa					
	!Kung	25	3.59 ± 1.89	−1.04	Vigilant et al., 1991
	Biaka Pygmy	17	9.84 ± 4.74	1.22	Vigilant et al., 1991
	Mubti Pygmy	20	8.47 ± 4.09	2.16	Vigilant et al., 1991
	Mandenka	119	8.32 ± 3.88	−1.04	Graven et al., 1995
	Egyptians	69	8.41 ± 3.94	−1.61*	Krings et al., 1999
	Fulbe	61	8.27 ± 3.89	−0.86	Watson et al., 1996
	Hadza	17	4.32 ± 2.25	2.23	Vigilant et al., 1991
	Hausa	20	6.74 ± 3.31	−1.03	Watson et al., 1996
	Herero	27	2.37 ± 1.33	−1.34	Vigilant et al., 1991
	Kanuri	14	8.52 ± 4.19	−1.16	Watson et al., 1996
	Kikuyu	25	9.97 ± 4.72	−1.10	Watson et al., 1996
	Nubians	67	9.86 ± 4.57	−1.42	Krings et al., 1999
	Southern Sudanese	79	10.08 ± 4.65	−1.40	Krings et al., 1999
	Turkana	37	12.57 ± 5.80	−0.93	Watson et al., 1996
	Yoruban	13	8.54 ± 4.22	−0.17	Vigilant et al., 1991
Americas					
	Amerind (Brazil)	29	4.45 ± 2.26	−0.20	Ward et al., 1991
	Ngoebe	46	5.07 ± 2.51	1.68	Kolman et al., 1995
	Argentina	18	5.29 ± 2.68	−0.07	Ginther et al., 1993; Torroni et al., 1993a
Oceania					
	Australians	53	7.62 ± 3.61	−1.80*	Redd and Stoneking, 1999
	PNG	38	9.406 ± 4.42	−0.86	Vigilant et al., 1991; Redd et al., 1995
	Vanuata	41	6.98 ± 3.35	−1.05	Sykes et al., 1995

[1] Mean pairwise differences (MPD) were calculated using the distance method of Tamura and Nei (1993) ($\alpha = 0.26$). Populations in boldface are data from this study.
* $P < 0.05$.

TABLE 2. Genetic diversity within/between continental populations

	No. of populations	Within-populations average MPD	Between-populations average F_{st}
Africa	15	7.99 ± 2.72	0.201
Europe	12	4.63 ± 0.94	0.066
Asia	12	7.12 ± 0.91	0.033
Eurasia	27	5.95 ± 1.51	0.086

The homogeneity of Asian populations is also evidenced by F_{st} analyses. The average pairwise F_{st} value for 12 continental Asian populations (0.033) was 2, 3, and 6 times lower than that for 12 populations from continental European populations (0.066), 27 populations from the Eurasian continent (0.086), and 15 populations from Africa (0.201), respectively (Table 2). Inclusion of additional populations does not alter these conclusions (data not shown). Table 3 shows the average F_{st} values for Asian populations in various combinations. The average F_{st} value of 0.005 was extremely low for the four Han Chinese populations (Xi'an, Changsh, Cantonese, and Taiwan Han), similar to the average F_{st} of 0.006 for the four central Asian populations (Kazakh, Lowland Kirghiz, Highland Kirghiz, and Uighurs). The average F_{st} was slightly increased to 0.019 for other East Asian populations (Korean, Mongolian, Siberia Altai, and Honshu Japanese). F_{st} values for other combinations of Chinese and Asian populations ranged from 0.010–0.016 (Table 3). The average F_{st} for all 15 populations from East and Central Asia was 0.038, which is not significantly different from that of 12 continental Asian populations, confirming that homogeneity extends from East to Central Asia. However, the average F_{st} value for four Southeast Asian populations (0.099) was about three times higher than that for 12 populations from East and Central Asia.

The average F_{st} in Southeast Asian populations was also high in the insular region. The average F_{st} of three insular Southeast Asian groups (0.121) was about 1.5 times higher than that of 27 populations (see Table 1) from the whole Eurasian continent. For 2 of 3 insular Southeast Asian populations (Borneo and Indonesian), Tajima's D value (1989) was not significantly different from 0 (Table 1), indicating no signal of demographic expansions (Aris-Brosou and Excoffier, 1996). Tajima's statistic was also not significantly different from 0 (Table 1) for five East Asian populations (Cantonese, Siberian Altai, Russian Siberians, Ainu, and Taiwanese). Eliminating these five populations results in an average F_{st} value of 0.015 for the remaining 10 East and Central Asian populations, which is about half of the F_{st} value obtained when these five populations are included (Table 3). Thus, overall, low levels of between-population differentiation are observed in Asian populations, especially in the continental region. This conclusion agrees with a recent, smaller-scale study of mtDNA restriction site polymorphisms in Asian populations (Ding et al., 2000).

What might account for this extreme mtDNA homogeneity in Asia? There is more than one possible explanation. For example, all of the Asian populations are food-producing groups, so one possibility is that a low level of mtDNA differentiation between populations might be a general phenomenon among food-producing populations that share aspects of demographic history. In support of this observation, elimination of two food-gathering populations (Saamis from Norway and Sweden) from the European sample also results in an extremely low F_{st} value (0.014). Archaeological evidence suggests that in East Asia, agriculture (mainly based on domestic rice) probably developed first on the Yangtse River by at least 5,000 years ago, and was spread by expanding populations of rice-cultivators (Harris, 1996). The presumed area where agriculture first developed corresponds quite closely to the geographic region inhabited by Changsha Han Chinese and Vietnamese, who have extremely high levels of within-population mtDNA variation. This trend, higher within-population variation in the south than in the north, is consistent with a recent analysis of mtDNA, Y chromosome, autosomal short-tandem repeat loci (Ding et al., 2000), and JC virus variation in East Asian populations (Ding et al., 2000; Guo et al., 2001), that suggests a lack of significant genetic boundaries between northern and southern populations (Ding et al., 2000; Guo et al., 2001). Thus, an Asian demographic expansion associated with the spread of large-scale agriculture may be responsible for the low levels of between-population differentiation. Alternatively, a recent analysis of Y-chromosome variation points to an important role of Central Asia as a source of Eurasian genetic diversity (Wells et al., 2001). Perhaps recent migrations from Central Asia explain the homogeneity of eastern Asian populations. Further analyses of Y-chromosome polymorphisms in eastern Asian populations, and of mtDNA and other loci in Central Asian populations, are required to evaluate this hypothesis.

The geographic distribution of mtDNA was generated exclusively by female migration, and male and female migrations patterns may differ. To compare female migration patterns with male migration patterns in Asia, we examined the correlation between genetic distance (F_{st}) and geographic distance (km), based on the mtDNA sequences and the haplotype frequency data of Y-chromosome biallelic markers (Su et al., 1999) (Fig. 4). The populations in these analyses are not identical, but they do come from the same geographic regions in East and Southeast Asia, including both the continental and the insular regions. For mtDNA, there was a significant correlation between F_{st} and geographic distance ($r = 0.633$, $P < 0.01$). Moreover, the slope of the best-fit line for the Asian population data (2.0×10^{-5}) was not significantly different from that for European

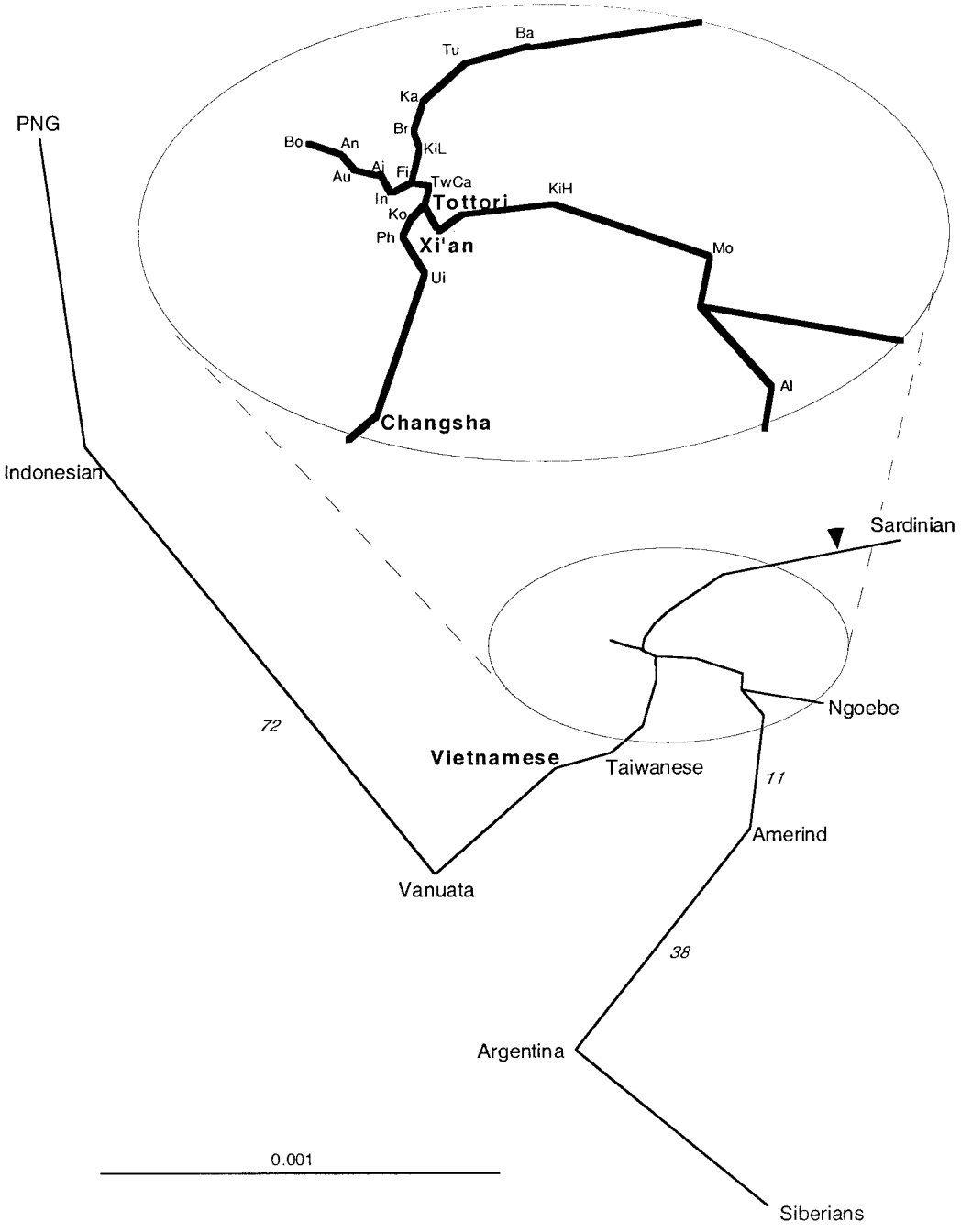

Fig. 2. Population tree, showing mtDNA homogeneity in Asia. Population tree was constructed by the NJ method (Saitou and Nei, 1987), with 1,000 bootstrap replications. Scale bar below tree indicates genetic distance (D_a), and numbers on branches indicate bootstrap values (when greater than 10%). Ai, Ainu; Al, Altai of Siberia; An, Anatolia Turks; Au, Aboriginal Australian; Ba, Basques; Bo, Borneo; Br, British; Ca, Cantonese; Fi, Finns; In, Indian; Ka, Kazakh; KiH, Kirghiz Highlander; KiL, Kirghiz Lowlander; Ko, Korean; Mo, Mongolian; Ph, Philippines; PNG, Papua New Guinean; Tu, Turks; Tw, Taiwan Han Chinese; Ui, Uighurs. Arrow represents root of the tree, using Mandenka, !Kung, and Pygmies as an outgroup. Populations in boldface are data from this study.

populations (1.3×10^{-5}; Seielstad et al., 1998). On the other hand, the F_{st} values based on Y-SNP haplotypes were not significantly correlated with geographic distance ($r = -0.051, P > 0.05$). The average F_{st} value among Asian populations for the Y-chromosome (0.096) was about two times higher than that for mtDNA (0.056).

These results indicate that the rate of migration for females, but not males, is related to geographic distance. Moreover, the higher average F_{st} value for the Y-chromosome, compared to mtDNA, indicates that males have not been moving as much as females. Thus, the lack of a correlation with geographic distance for the Y-chromosome could indi-

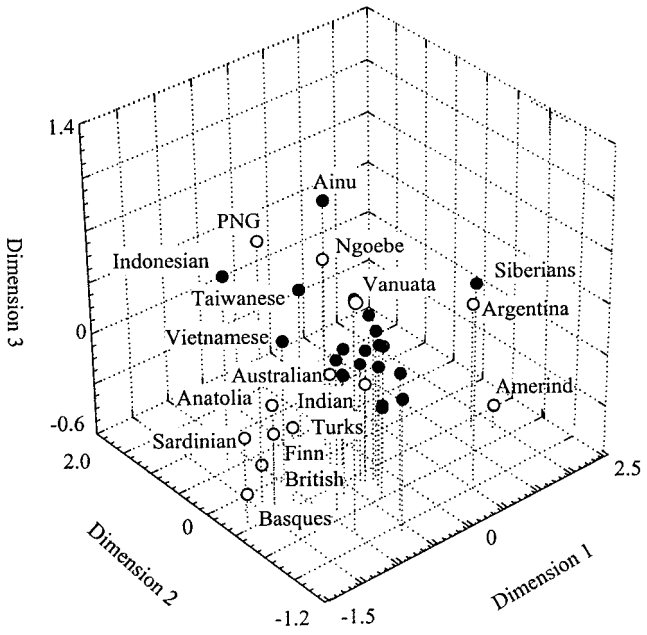

Fig. 3. MDS plot based on F_{st} values for 32 populations (omitting the three African populations from the NJ tree). Names of outlying and intermediate populations are shown, while unlabelled solid circles are Asian populations.

TABLE 3. Average F_{st} values in various combinations[1]

Various population combinations	Average F_{st}
4 Chinese (Xian, Changsha, Cantonese, and Taiwan Han)	0.005
4 Central Asians (Kazakh, Lowland Kirghiz, Highland Kirghiz, and Uighurs)	0.006
4 East Asians (Korean, Mongolian, Altai, and Japanese)	0.019
4 Chinese + 4 Central Asians	0.010
4 Chinese + 4 East Asians	0.016
4 Chinese + 4 Central Asians + 4 East Asians	0.015
15 East and Central Asians (4 Chinese + 4 Central Asians + 4 East Asians + Russian Siberians, Ainu, and Taiwanese)	0.038
10 East and Central Asians (eliminating 5 populations whose Tajima D was not significantly different from 0)	0.015
4 Southeast Asians (Vietnamese, Philipines, Borneo, and Indonesians)	0.099

[1] Pairwise F_{st} values were calculated under the distance method of Tamura and Nei (1993), with $\alpha = 0.26$.

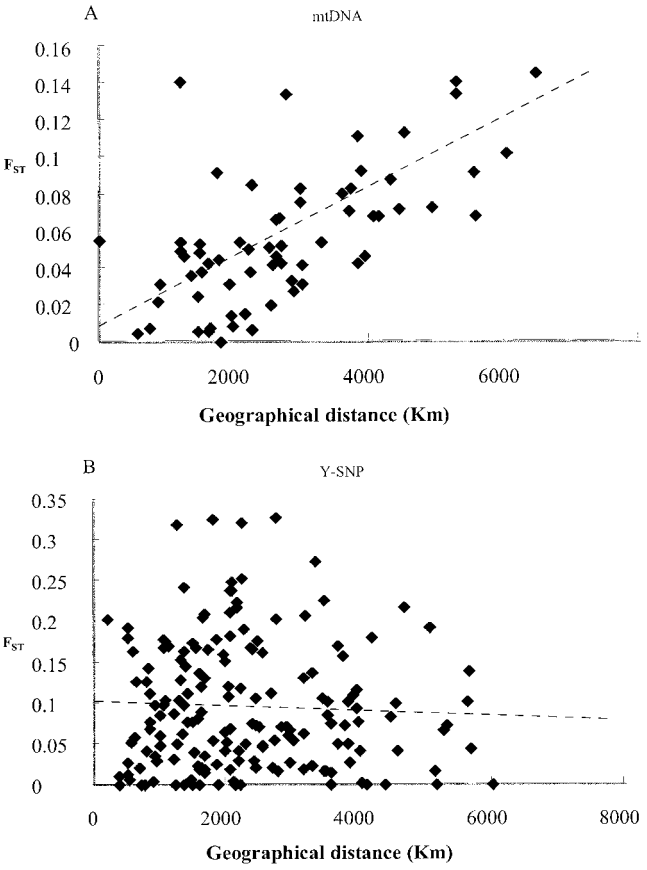

Fig. 4. Correlation between genetic distance (F_{st}), based on (**A**) mtDNA and (B) Y-SNP haplotypes, and geographic distance (km) for East and Southeast Asian populations (12 and 19 populations for mtDNA and Y-chromosome, respectively). Dashed line represents regression line for mtDNA (slope, 2.0×10^{-5}, r = 0.633, $P < 0.01$), and for Y-SNP haplotypes (r = −0.051, $P > 0.05$).

cate that the rate of male migration is so low that genetic drift is overcoming the influence of isolation by distance. This pattern of higher female mobility in Asian populations agrees with previous results from European and central Asian populations (Seielstad et al., 1998; Perez-Lezaun et al., 1999). Seielstad et al. (1998) attributed higher female mobility to the widespread practice of patrilocality, in which the female moves to the residence of the male after marriage. This explanation recently received strong support from a comparison of mtDNA and Y-chromosome variation in patrilocal and matrilocal groups in northern Thailand (Oota et al., 2001), which revealed the usual pattern observed in patrilocal groups, of bigger differences between groups based on assessment of the Y chromosome than based on mtDNA, but exactly the opposite pattern (bigger differences between groups based on mtDNA than on the Y chromosome) for matrilocal groups.

In conclusion, we suggest that the extreme mtDNA homogeneity observed in Asian populations may reflect a recent demographic expansion arising from successful subsistence due to rice agriculture. The reduced homogeneity for the Y-chromosome than for mtDNA in these cultivators could reflect the influence of patrilocality operating within this demographic expansion. In this respect, we note thatrelative to other populations elsewhere, the average F_{st} value for the Y-chromosome among Asian populations was 0.096, which is about half of the F_{st} value for European populations ($F_{st} = 0.215$, as calculated from the data of Semino et al., 2000). Asian populations also appear more homogeneous for the Y-chromosome. However, it would be desirable to have data on mtDNA, the Y chromosome, and autosomal loci from the same populations, to rule out any sampling artifacts. Analyses of food-gathering populations should provide further insights into the

reason(s) for the apparent genetic homogeneity of Asian food-producing populations.

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