

Distribution of Two HIV-1–Resistant Polymorphisms (SDF1-3'A and CCR2-64I) in East Asian and World Populations and Its Implication in AIDS Epidemiology

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Summary

Chemokine receptor CCR2 and stromal-derived factor (SDF-1) are involved in HIV infection and AIDS symptom onset. Recent cohort studies showed that point mutations in these two genes, CCR2-64I and SDF1-3'A, can delay AIDS onset ≥ 16 years after seroconversions. The protective effect of CCR2-64I is dominant, whereas that of SDF1-3'A is recessive. SDF1-3'A homozygotes also showed possible protection against HIV-1 infection. In this study, we surveyed the frequency distributions of the two alleles at both loci in world populations, with emphasis on those in east Asia. The CCR2-64I frequencies do not vary significantly in the different continents, having a range of 0.1–0.2 in most populations. A decreasing cline of the CCR2-64I frequency from north to south was observed in east Asia. In contrast, the distribution of SDF1-3'A in world populations varies substantially, and the highest frequency was observed in Oceanian populations. Moreover, an increasing cline of the SDF1-3'A frequency from north to south was observed in east Asia. The relative hazard values were computed to evaluate the risk of AIDS onset on the basis of two-locus genotypes in the east Asian and world populations.

Introduction

The discoveries that chemokines can block HIV replication and that their receptors play an important role in fusion of HIV to target cells raised expectations that chemokines might hold the key to understanding HIV-mediated pathogenesis (Premack et al. 1996; Littman 1998). Two chemokine receptors, CXCR4 and CCR5, are major coreceptors required for entry of, respectively, T cell line-tropic and macrophage-tropic strains of HIV-1 into CD4 cells (for review, see Littman 1998, and references therein). In addition, the expression of the stromal-derived factor (SDF1), the only known ligand of CXCR4, may inhibit transmission of T cell line-tropic HIV strains (Bluel et al. 1996; Feng et al. 1996). Other chemokine receptors, such as CCR2, may also play a role in HIV infection, although their mechanisms are less clear (Littman 1998; Mummidi et al. 1998).

Recently, the mutations in the genes encoding the aforementioned chemokine receptors (CCR5 and CCR2) and ligand (SDF1) in natural populations were linked to HIV-1 resistance in cohort studies (Dean et al. 1996; Fauci et al. 1996; Hill et al. 1996; Liu et al. 1996; Paxton et al. 1996; Samson et al. 1996; Smith et al. 1997; Mummidi et al. 1998; Winkler et al. 1998). Homozygous individuals with a 32-bp deletion in CCR5 (CCR5- $\Delta 32$) were found to be resistant to HIV infection (Dean et al. 1996; Liu et al. 1996). Heterozygotes for the CCR5- $\Delta 32$ mutation exhibit a delayed progression to disease. The CCR5- $\Delta 32$ mutation results in a truncated protein removing the receptor from cells (Liu et al. 1996). The benefit of carrying the deletion mutation was thought to result from decreased expression levels of the receptor in the patients, which led either to resistance to virus infection for the homozygotes or to delayed disease progression for the heterozygotes (Dean et al. 1996).

The mutant alleles of CCR2 and SDF1 (CCR2-64I

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and SDF1-3'A) carry point mutations in sequence-conserved regions, and the functional constraints of the regions were suggested to explain their protective effects of delaying AIDS onset in the cohort studies (Smith et al. 1997; Winkler et al. 1998). The SDF1-3'A mutation is located in the untranslated region of the transcript. The molecular mechanisms of the effect of the mutations in the CCR2 gene and SDF1 gene are not yet understood (Littman 1998; Mummidi et al. 1998), but a recent study has affirmed the protective effects of the mutations in these two genes (Martin et al. 1998). The protective effects of CCR5-Δ32 and CCR2-64I were shown to be dominant, whereas the protective effect of SDF1-3'A is recessive (Dean et al. 1996; Liu et al. 1996; Smith et al. 1997; Winkler et al. 1998).

The deletion mutant, CCR5-Δ32, was found primarily (~10%) in the populations of European descent, but no mutant alleles were reported in indigenous non-European populations (Martinson et al. 1997). However, the distributions of CCR2-64I and SDF1-3'A were found in different ethnic populations in America, and the relative hazard (RH) indices for all genotype combinations at these three loci were estimated in the cohort studies (Smith et al. 1997; Winkler et al. 1998).

In the present study, we investigated the distributions of CCR2-64I and SDF1-3'A in worldwide populations, with emphasis on east Asian populations. The RH index was estimated for each population studied to evaluate natural resistance, and, therefore, these indices are of special importance for the prevention of AIDS in those populations.

Methods

Genotyping

A PCR-RFLP assay was used for genotyping. The published primer sequences and PCR conditions were adapted to amplify SDF1 and CCR2 gene fragments covering the polymorphic sites (Smith et al. 1997; Winkler et al. 1998). PCR products were then subjected to restriction enzyme digestion (*Msp* I for SDF1 and *Bsa*B I for CCR2) for 4 h. After digestion, the products were genotyped by means of agarose gel electrophoresis.

RH Evaluation

To evaluate risk of AIDS onset for the populations screened, the RH value was computed for each population on the basis of the two-locus genotype of each individual. The RH value for each of the nine possible two-locus genotypes was adapted on the basis of the published data of the cohort studies (Winkler et al. 1998). Three AIDS definitions were considered in the RH evaluations: AIDS-1993, AIDS-1987, and Death (Dean et al. 1996). The RH indices for each two-locus

genotype used in this report are: RH of [CCR2-64I/+, SDF1-3'A/SDF1-3'A] or [CCR2-64I/CCR2-64I, SDF1-3'A/SDF1-3'A] are 0.55, 0.31, 0.0 (for AIDS-1993, AIDS-1987, and Death, respectively, and hereafter); RH of [+/+, SDF1-3'A/SDF1-3'A] are 0.63, 0.35, and 0.23; RH of [CCR2-64I/+, +/+], [CCR2-64I/+, SDF1-3'A/+], [CCR2-64I/CCR2-64I, +/+], [CCR2-64I/CCR2-64I, SDF1-3'A/+] are 0.65, 0.66, and 0.60.

Results and Discussion

To survey the distribution of the two HIV-1-resistant alleles, we genotyped 1,768 individuals representing presumably unaffected populations from five continents—Africa, Europe, Oceania, Asia, and America (table 1). Special efforts were made to study the populations in east Asia where AIDS prevalence is rapidly increasing, including the Han Chinese from 28 provinces (of the 30 provinces in the mainland) and 22 Chinese ethnic minority groups. The Han Chinese from the 28 provincial regions were grouped into eight geographical regions (not official administrative regions) on the basis of the frequencies of the alleles studied. The populations from neighboring provinces that showed similar allele frequencies at both loci studied were grouped together. All the samples were collected before AIDS became an epidemic in the corresponding regions.

Table 1 shows the frequencies of SDF1-3'A and CCR2-64I in 48 populations studied. The variation of SDF1-3'A frequency is quite extensive, and it is exceptionally high in Oceania, especially in the New Guinean Highlanders, which we have previously reported (Su et al. 1998). The frequency of SDF1-3'A in the other populations ranges from .029–.366. In contrast, the frequency of the CCR2-64I allele varies moderately, except that it is absent in the Nasioi Melanesians. In three American Indian populations, however, there is a significant frequency difference. The frequency in the Mayans is >10 times as much as that in the Surui, which could be the consequence of genetic drift in the Surui populations and extensive admixture in the Mayans. Analysis of genotype frequency data did not show any significant deviation from Hardy-Weinberg expectation in any population, implying the absence of detectable selection differentials between the individuals with and without the mutations in unaffected populations.

The frequencies of SDF1-3'A and CCR2-64I were plotted against the geographical distributions of the populations in east Asia (see fig. 1 and 2). In general, frequencies of both alleles in the east Asian populations are comparable to previous studies on Asians residing in the United States (Smith et al. 1997; Winkler et al. 1998). Interestingly, frequency distributions of CCR2-64I and SDF1-3'A revealed opposite patterns. The frequencies of CCR2-64I increase from south to north,

Table 1
Frequency Distribution of SDF1-3'A and CCR2-64I and RH Indices in 48 World Populations

Continent	Population	Size	SDF1 (SE)	CCR2 (SE)	RH1 (SE)	RH2 (SE)	RH3 (SE)	
Africa	Biaka pygmy	35	.03 (.02)	.11 (.04)	.92 (.02)	.92 (.02)	.91 (.03)	
	Mbuti pygmy	20	.08 (.04)	.10 (.05)	.93 (.03)	.93 (.03)	.92 (.04)	
	Lissongo	11	.09 (.06)	.14 (.07)	.90 (.05)	.91 (.05)	.89 (.05)	
America	Karitiana	36	.06 (.03)	.07 (.03)	.93 (.03)	.92 (.05)	.90 (.05)	
	Mayan	40	.15 (.04)	.33 (.05)	.78 (.03)	.78 (.03)	.74 (.03)	
	Surui	20	.25 (.07)	.03 (.03)	.96 (.02)	.95 (.02)	.95 (.03)	
Europe	Italian	37	.15 (.04)	.13 (.04)	.88 (.03)	.86 (.03)	.84 (.04)	
	Northern European	23	.22 (.06)	.16 (.05)	.84 (.04)	.83 (.04)	.80 (.05)	
Oceania	Australian Aborigine	14	.54 (.09)	.10 (.06)	.84 (.05)	.74 (.08)	.68 (.10)	
	New Guinean1	69	.66 (.04)	.18 (.03)	.76 (.04)	.63 (.07)	.53 (.09)	
	Nasioi Melanesian	12	.67 (.10)	0	.88 (.05)	.78 (.09)	.74 (.10)	
Asia (North)	New Guinean2	21	.71 (.07)	.17 (.06)	.76 (.02)	.64 (.04)	.55 (.05)	
	Ewenki	17	.09 (.05)	.28 (.08)	.84 (.04)	.84 (.04)	.81 (.05)	
	Buryat	5	.10 (.09)	.57 (.16)	.72 (.06)	.73 (.06)	.68 (.07)	
	Hui	19	.11 (.05)	.20 (.06)	.87 (.04)	.87 (.04)	.85 (.04)	
	Tibetan	25	.12 (.05)	.28 (.06)	.83 (.03)	.84 (.03)	.81 (.04)	
	Uyghur	10	.20 (.09)	.20 (.09)	.85 (.05)	.86 (.05)	.84 (.06)	
	Korean	28	.27 (.06)	.26 (.06)	.82 (.03)	.82 (.04)	.78 (.05)	
	Tamir	7	.29 (.12)	.07 (.07)	.95 (.05)	.95 (.04)	.94 (.05)	
	Japanese	15	.37 (.09)	.11 (.06)	.81 (.05)	.74 (.07)	.69 (.08)	
	Manchurian	33	.38 (.06)	.12 (.04)	.89 (.03)	.86 (.04)	.82 (.05)	
	Asia (South)	Wa	35	.06 (.03)	.16 (.04)	.89 (.03)	.89 (.03)	.87 (.03)
		Ami	10	.10 (.07)	0	1.00 (.00)	1.00 (.00)	1.00 (.00)
		Anni	21	.12 (.05)	0	1.00 (.00)	1.00 (.00)	1.00 (.00)
		Lahu	11	.14 (.07)	0	1.00 (.00)	1.00 (.00)	1.00 (.00)
		Bulang	26	.15 (.05)	0	1.00 (.00)	1.00 (.00)	1.00 (.00)
Yi		19	.16 (.06)	.24 (.07)	.83 (.04)	.82 (.05)	.79 (.05)	
Atayal		32	.17 (.05)	.11 (.04)	.93 (.02)	.94 (.02)	.93 (.03)	
Deang		6	.17 (.11)	.17 (.11)	.88 (.07)	.89 (.07)	.87 (.08)	
Jingpo		15	.23 (.08)	.07 (.05)	.92 (.04)	.91 (.05)	.89 (.06)	
Tujia		20	.28 (.07)	.25 (.07)	.80 (.04)	.76 (.05)	.71 (.07)	
Yao-Nandan		20	.28 (.07)	0	.98 (.02)	.97 (.03)	.96 (.04)	
Dong		20	.30 (.07)	.15 (.06)	.89 (.04)	.86 (.05)	.82 (.07)	
She		20	.30 (.07)	.15 (.06)	.90 (.04)	.90 (.03)	.88 (.04)	
Yao-Jinxiu		20	.30 (.07)	.08 (.04)	.93 (.03)	.92 (.04)	.90 (.05)	
Cambodian		28	.32 (.06)	.15 (.05)	.87 (.03)	.86 (.04)	.82 (.05)	
Paiwan		20	.33 (.07)	.03 (.03)	.96 (.02)	.95 (.03)	.94 (.04)	
Dai		12	.33 (.10)	.07 (.05)	.92 (.05)	.92 (.05)	.91 (.06)	
Li		20	.35 (.08)	.05 (.03)	.90 (.05)	.87 (.06)	.85 (.07)	
Yami		20	.43 (.08)	.05 (.03)	.90 (.04)	.84 (.06)	.81 (.08)	
Han Chinese		Northwest Han	24	.19 (.06)	.23 (.06)	.84 (.04)	.83 (.04)	.80 (.05)
	North Han	138	.24 (.03)	.21 (.02)	.83 (.01)	.82 (.02)	.79 (.02)	
	Northeast Han	37	.26 (.05)	.24 (.05)	.91 (.03)	.89 (.03)	.88 (.04)	
	Southwest Han	48	.22 (.04)	.18 (.04)	.84 (.03)	.83 (.03)	.79 (.04)	
	East Han	407	.25 (.02)	.20 (.01)	.85 (.01)	.82 (.01)	.78 (.02)	
	Central Han	168	.26 (.02)	.22 (.02)	.84 (.02)	.84 (.02)	.80 (.02)	
	Southeast Han	40	.26 (.05)	.22 (.05)	.85 (.03)	.82 (.03)	.78 (.04)	
	South Han	34	.34 (.06)	.11 (.04)	.86 (.04)	.84 (.05)	.80 (.06)	
	Total	1,768						

NOTE.—RH1, RH2, and RH3 were calculated under three different AIDS definitions—AIDS-1993, AIDS-1987, and Death, respectively.

whereas the clinal trend is reversed for the SDF1-3'A allele in east Asian populations. The sample sizes of Han Chinese populations are generally large; therefore, it is unlikely that this observation is simply due to sampling error. This observation can be confirmed by the result of a similar study in Southeast Asian populations, where the frequency of CCR2-64I is relatively low and that of

SDF1-3'A is relatively high compared with Chinese populations (R. Deka, personal communication). The north-south differences for both alleles in the east Asian populations are generally consistent with the observations made with other genetic markers (see Chu et al. 1998 and references therein). It was hypothesized that modern humans entered east Asia from the south, possibly from

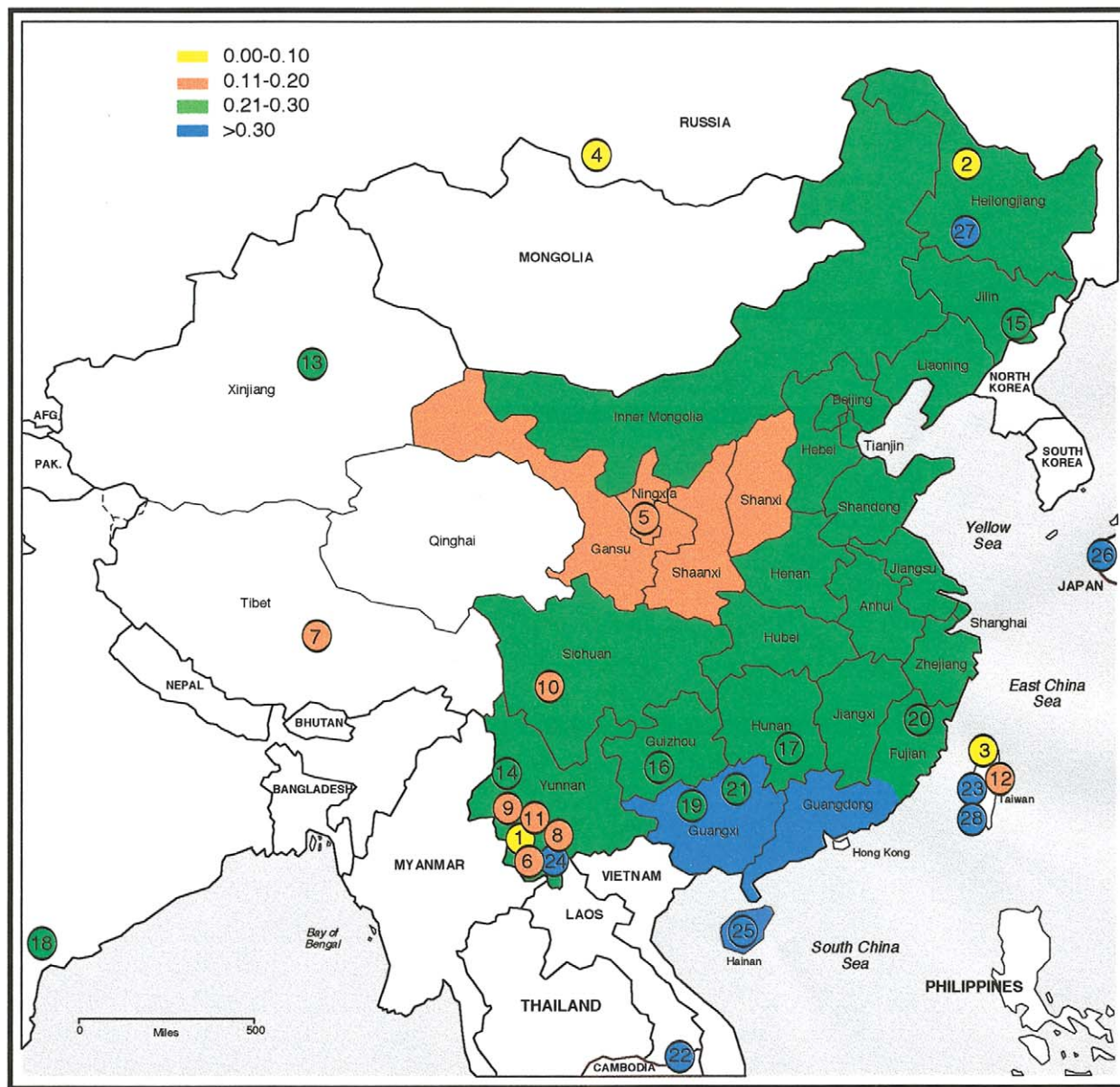


Figure 1 Allele frequency distribution of SDF1-3'A in the east Asian populations. The Chinese Han, from 28 provincial regions, were grouped into eight geographical regions, as shown in table 1: south (Guangdong, Guangxi, and Hainan), southeast (Fujian and Taiwan), southwest (Guizhou, Sichuan, and Yunnan), central (Anhui, Jiangxi, Hubei, and Hunan), east (Jiangsu, Shanghai, and Zhejiang), north (Shandong, Beijing, Tianjin, Hebei, and Henan), northeast (Inner Mongolia, Liaoning, Jilin, and Heilongjiang), and northwest (Shanxi, Shaanxi, Gansu, Ningxia, and Xinjiang). The frequencies of these populations were presented in color patches. The colored circles refer to the Chinese ethnic minority groups and other east Asian populations, defined as follows: 1 = Wa, 2 = Ewenki, 3 = Ami, 4 = Baryat, 5 = Hui, 6 = Anni, 7 = Tibetan, 8 = Lahu, 9 = Bulang, 10 = Yi, 11 = Deang, 12 = Atayal, 13 = Uyghur, 14 = Jingpo, 15 = Korean, 16 = Yao (Nandan), 17 = Tujia, 18 = Tamir, 19 = Dong, 20 = She, 21 = Yao (Jinxiu), 22 = Cambodian, 23 = Paiwan, 24 = Dai, 25 = Li, 26 = Japanese, 27 = Manchurian, and 28 = Yami.

Southeast Asia, ~50,000–70,000 years ago, and later populations expanded from the south to the north of Asia (Chu et al. 1998). It is well recorded that, in the past 7,000 years, migrations in China have been pre-

dominantly from north to south. Therefore, two-way migrations could provide a mechanism to generate and sustain the two opposing north-to-south clines that we are currently observing. However, the minority popu-

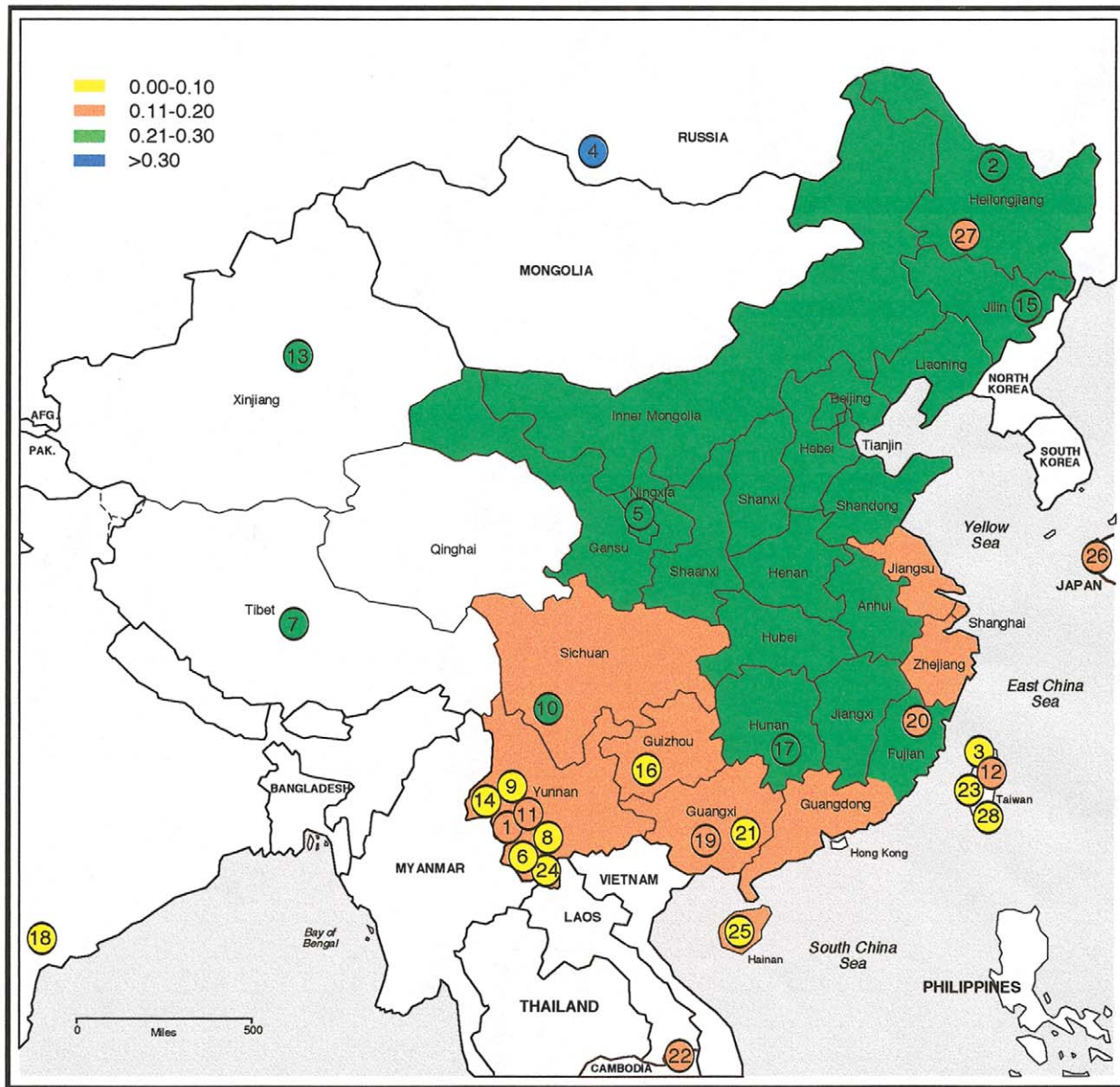


Figure 2 Allele frequency distribution of CCR2-64I in the east Asian populations. The description of the populations follows figure 1.

lations studied are relatively isolated and small in size; therefore, genetic drift can play a significant role in influencing their allele frequencies. The frequencies of the two alleles in those populations may or may not be consistent with those in the nearby Han Chinese populations, depending largely on the level of gene flow between them and their respective ethnohistories.

Unlike CCR5-Δ32, which is only present in the white population, the SDF1-3'A and CCR2-64I are distributed in all populations of the world. Stephens et al. (1998)

estimated, on the basis of the coalescence of haplotypes of two microsatellite loci, that the origin of the CCR5-Δ32-containing ancestral haplotype is very recent, occurring only ~700 years ago. If this estimate is correct, the origins of SDF1-3'A and CCR2-64I could be much more ancient, and probably happened before the out-of-Africa migrations of modern humans, which is reflected by their patterns of ubiquitous distributions in world populations.

Evaluating the risk of AIDS onset in different world

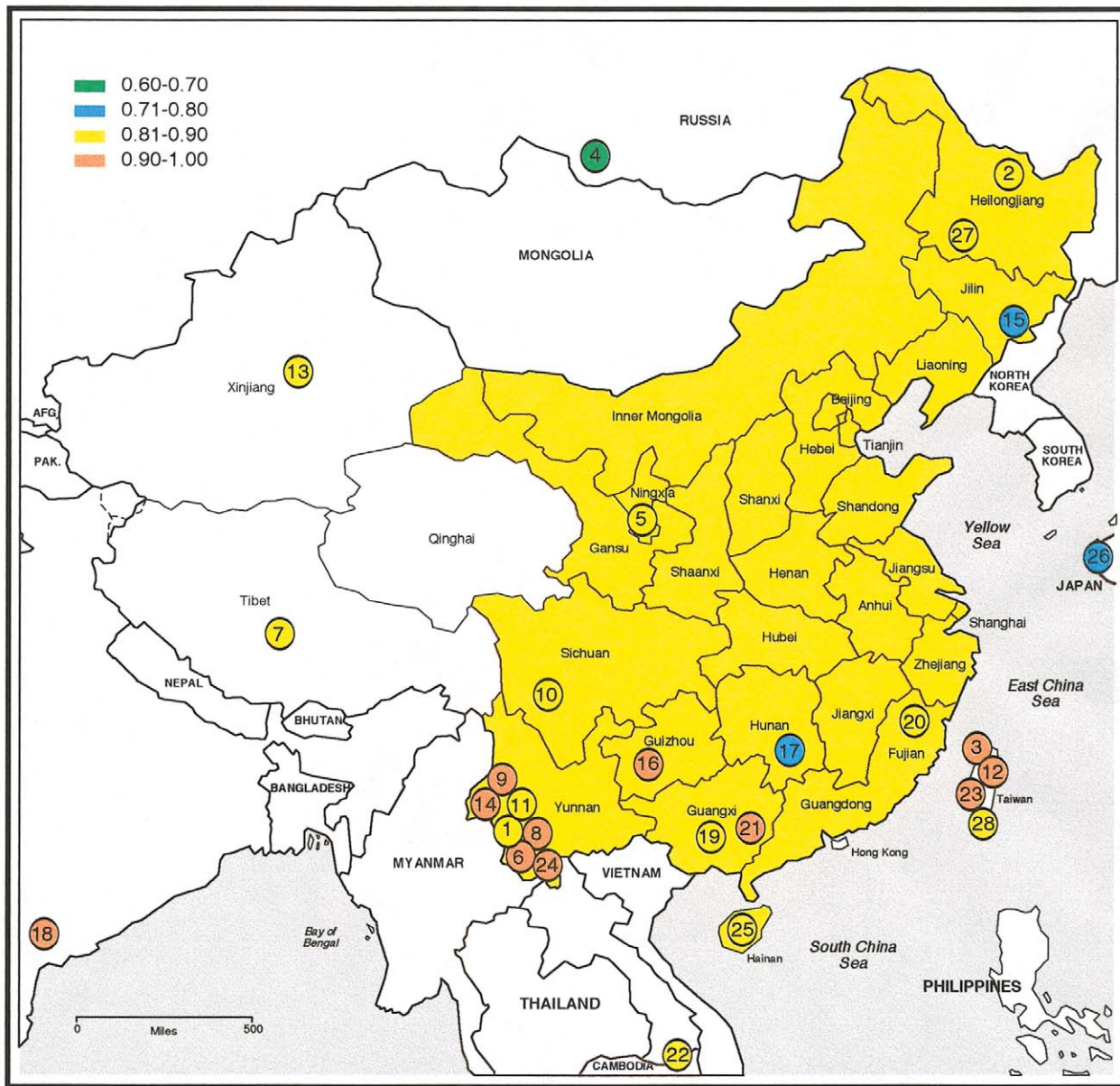


Figure 3 RH2 distribution in the east Asian populations. The description of the populations follows figure 1.

populations provides important information to AIDS epidemiological issues. Using the RH indices in the cohort studies (see Methods, for details), we estimated, on the basis of the two-locus genotype distributions, the RH indices for each population (table 1). In general, RH values vary from population to population. Holding a high frequency of SDF1-3'A homozygotes, Oceanian populations have the lowest RH values, which indicates possibly the highest protection from AIDS onset or even HIV infection in those populations. African populations,

in contrast, exhibit very high RH values. The RH values in the three American Indian populations are quite variable because of the large allele frequency difference. There is little variation of RH indices among Chinese Han populations, as shown in figure 3, largely because of the opposite clines of SDF1-3'A and CCR2-64I. However, high RH indices were observed in most of the southern Chinese ethnic groups, in contrast with the relatively low RH in northern Chinese ethnic groups, in Japanese ethnic groups, and in Korean ethnic groups. Most of

those minority groups are in Yunnan (Wa, Deang, Jingpo, Dai, Anni, Bulang, and Lahu), where the prevalence of AIDS is highest in China.

It is important to note that the estimation of RH indices may not be accurate, given the width of the 95% confidence intervals (see table 1, Winkler et al. 1998). Furthermore, the allele frequency estimation may introduce an additional source of error, especially when the sample sizes are small. In this report, we treated the RH indices for individuals as constants, and the standard errors of sampling are presented in table 1. Such standard errors are surprisingly small, even when the sample size of the population is small.

Several assumptions were made in the above evaluation. First, the protective effect of CCR5 is ignored. Given the rarity of the CCR5-Δ32 allele in nonwhite populations, the RH values of those populations are generally accurate, whereas in white populations they are overestimated. The overestimation is introduced, in particular, for individuals with the following groups of genotypes: [CCR5-Δ32/CCR5-Δ32, +/+, SDF1-3'A/SDF1-3'A], [CCR5-Δ32/+, +/+, SDF1-3'A/SDF1-3'A], [CCR5-Δ32/CCR5-Δ32, +/+, SDF1-3'A/+], [CCR5-Δ32/CCR5-Δ32, +/+, +/+], [CCR5-Δ32/+, +/+, SDF1-3'A/+], and [CCR5-Δ32/+, +/+, +/+]. However, the overestimation of RH indices for whites is <0.1%. Second, the difference of RH indices among racial groups is ignored. The errors introduced by this assumption should be very small, if not negligible, since the RH index differences between racial groups are generally small (see table 1, Winkler et al. 1998).

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