



ARTICLE

Distribution of three HIV-1 resistance-conferring polymorphisms (SDF1-3'A, CCR2-64I, and CCR5-Δ32) in global populations

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Chemokine receptors (CCR5, CXCR4 and CCR2) have been shown to be important co-receptors for HIV infection. Mutations at CCR5 (CCR5-Δ32), CCR2 (CCR2-64I), and stromal-derived factor SDF1 (SDF1-3'A), a primary ligand for CXCR4, are known to have protective effects against HIV-1 infection and the onset of AIDS symptoms. We studied the three-locus genotype frequency distributions in 70 worldwide populations from a sample of 2341 individuals without any known history of HIV-1 infection and AIDS symptoms. From these data, we estimated the risk of AIDS onset (relative hazard, RH) of each population. This survey shows that the substantial allele frequency differences of each of these mutations translate into an extensive variation in relative hazards for AIDS in worldwide populations. However, no evidence of natural selection against the mutant gene carriers is detected. Finally, the combined three-locus genotype data predict the highest relative hazard (RH) in South-East Asia and Africa where AIDS is known to be more prevalent. *European Journal of Human Genetics* (2000) 8, 975–979.

Keywords: chemokine receptors; HIV-1; resistant polymorphisms; global populations; relative hazard

Introduction

Two chemokine receptors, CXCR4 and CCR5, are major co-receptors required for the entry of T cell line-tropic and macrophage-tropic strains of HIV-1, respectively, into CD4 cells.¹ 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.^{2,3} Other chemokine receptors such as CCR2 may also play a role in HIV infection although their mechanism is less clear.^{1,4} Recent cohort studies have shown that the mutations in the genes encoding these chemokine receptors (CCR5 and CCR2) and ligand (SDF1) are linked to HIV-1 resistance.^{4–12}

The CCR5-Δ32 mutation results in a truncated protein removing the receptor from the cell surface.^{9,13} Individuals homozygous for a 32-bp deletion in CCR5 (CCR5-Δ32) were found to be resistant to HIV infection due to decreased expression levels of the receptor in the patients.^{6,9} Hetero-

zygotes for the CCR5-Δ32 mutation exhibit delayed progression of the disease. The mutant alleles of CCR2 and SDF1 (CCR2-64I and SDF1-3'A) carry point mutations in sequence-conserved regions, and it was suggested that the functional constraints of the regions explained their protective effects of delaying AIDS onset in the cohort studies.^{11,12} 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. The protective effects of CCR5-Δ32 and CCR2-64I were shown to be dominant, whilst that of SDF1-3'A is recessive.^{6,9,11,12}

Methods

Population samples

A total of 2341 individuals without any known history of HIV-1 infection from 70 geographically and ethnically defined populations were sampled for this study. The names and continental origins of each population are listed in Table 1. Informed consent was obtained for the new collected samples.

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Received 22 March 2000; revised 25 July 2000; accepted 8 August 2000

Table 1 The RH values for the 27 possible three-locus genotypes¹²

Genotype	No. of Genotypes	AIDS-1993	AIDS-1987	Death
AABBC-	2	1.00	1.00	1.00
a-b-c-	16	0.65	0.66	0.6
a-BBC-				
AAb-C-				
AABBcc	1	0.63	0.35	0.23
a-b-cc	8	0.55	0.31	0.00
a-BBcc				
Aab-cc				

A, B and C refer to the wild type alleles of CCR5, CCR2 and SDF1, respectively; and a, b and c are mutant alleles at the respective loci.

Genotyping

A PCR RFLP assay was employed for genotyping. Published primer sequences and PCR conditions were adapted to amplify *SDF1*, *CCR2*, and *CCR5* gene fragments covering the polymorphic sites.^{9,11,12} PCR products were subjected to restriction enzyme digestion (*MspI* for *SDF1* and *BsaBI* for *CCR2*) for 4 h. After digestion, the products of digestion for *SDF1* and *CCR2* or the PCR products for *CCR5* were genotyped by agarose gel electrophoresis.

Relative hazard evaluation

In order to evaluate the risk of AIDS onset for the populations screened, relative hazard (RH) was computed for each population based on the three-locus genotype of each individual. As the RH value for the 27 possible three-locus genotypes (adapted from the cohort studies of Winkler *et al*;¹² also shown in Table 1) can be grouped into four distinct values, the RH of a population was estimated by the equation

$$RH = \sum w_i p_i,$$

where w_i and p_i are the genotype-specific RH and frequencies (grouped by distinct RH values in Table 1), and the summation is over all four groups of genotypes. The standard errors (SE) of population-specific RH estimates are computed assuming that the frequency distributions of genotypes are from multinomial samples.¹⁴ Three AIDS definitions were considered in the RH evaluations including AIDS-1993, AIDS-1987, and death, following Dean *et al*.⁹

Results and discussions

To survey the distribution of the three HIV-1 resistance-conferring alleles, we genotyped 2341 individuals with no known history of HIV-1 infection and AIDS symptoms. The samples represent 70 populations from five continents, Africa, Europe, Oceania, America and Asia (Table 2) including Southeast Asia, where the prevalence of AIDS is rapidly increasing.¹⁵ Consistent with previous reports,¹⁶ the deletion mutation, CCR5-Δ32, is primarily found in populations of

European descent. Sporadic occurrences of this mutation in other non-European populations (eg South Carolina Blacks, Brazilian Blacks, Tibetans, and Cambodians) are probably due to Caucasian admixture in these populations. In contrast, the prevalence of SDF1-3'A frequency is quite extensive and it is exceptionally high in Oceania, especially in the New Guinean Highlanders (reaching as high as 72%), reported in our previous study,¹⁷ and relatively low in the populations of African descent (none in 26 individuals from Benin). The frequency of SDF1-3'A in other populations ranged from 3% to 43%. On the other hand, the frequency of the CCR2-64I allele varies little. In several Southeast Asian populations (Ami, Aini, Lahu, Bulang and Yao), this allele is virtually absent.

Analysis of genotype frequency data did not show any significant deviation from the Hardy-Weinberg expectation (HWE) in any population, implying the absence of detectable selection differentials among individuals with and without the mutations in unaffected populations.

These data can be used to determine the potential risk of AIDS onset in different world populations. Based on the three-locus genotype distributions, we estimated the average relative hazard (RH) for each population (Table 2 and Figure 1), by using the genotype-specific RH indices (shown in Table 1) obtained in the cohort studies. In general, RH values vary considerably from population to population. However, geographically and ethnically related populations tend to share comparable allele frequencies at the three loci, resulting in similar RH across these populations. An exception to this is the variation of RH value among three native American populations (Karitiana, Mayan and Surui). Extensive genetic drift in the two isolated populations (Karitiana and Surui) and European admixture in Mayans are probable explanations for this observation. With the exception of American Samoans, the high frequency of the SDF1-3'A allele confers the lowest RH on the Oceanian populations, indicating potentially the highest protection from AIDS onset in these populations. On the other hand, African and Southeast Asian populations exhibit very high RH values, indicative of vulnerability of those populations to HIV infection.

Among 27 populations sampled from Southeast Asia, there are 11 (41%) with $RH \geq 0.9$ for all three criteria (AIDS-1993, AIDS-1997, and death). In 50% of the African populations ($n = 8$) RH is ≥ 0.9 . However, among the other worldwide populations ($n = 35$), only four (11%) meet this criterion. Therefore, this worldwide survey shows that the highest RH values are predominantly found in Africa and Southeast Asia.

Our observation of high RH in Southeast Asia is significant given that the surrounding populations such as the Oceanians and East Asians, including the Chinese, have much lower values of RH. This is probably the synergistic effect of the two reversing clinal trends in frequency distributions of alleles SDF1-3'A and CCR2-64I in the populations in East Asia, Southeast Asia, and Oceania. Previously we have shown

Table 2 Allele frequencies of SDF1-3'A, CCR2-64I and CCR5-Δ32 in 70 world populations. The RH values were calculated based on three AIDS definitions, AIDS-1993 (RH1), AIDS1987 (RH2) and Death (RH3)⁹

Continent	Population	Size	SDF1(SE)	CCR2(SE)	CCR5(SE)	RH1(SE)	RH2(SE)	RH3(SE)
Africa	Benin	26	0	0.11(0.05)	0	0.92(0.03)	0.92(0.030)	0.91(0.04)
	Biaka Pygmy*	35	0.03(0.02)	0.11(0.04)	0	0.92(0.02)	0.92(0.02)	0.91(0.03)
	Sudanese	25	0.50(0.03)	0.19(0.06)	0	0.87(0.04)	0.87(0.04)	0.85(0.04)
	Mbuti Pygmy*	20	0.08(0.04)	0.10(0.05)	0	0.93(0.03)	0.93(0.03)	0.92(0.04)
	Lissongo*	11	0.09(0.06)	0.14(0.07)	0	0.90(0.05)	0.91(0.05)	0.89(0.05)
	South Carolina Blacks	26	0.12(0.05)	0.10(0.04)	0.20(0.02)	0.90(0.03)	0.89(0.04)	0.87(0.04)
	Nigerian	23	0.12(0.06)	0.12(0.06)	0	0.92(0.04)	0.92(0.04)	0.91(0.04)
	Brazilian Blacks	26	0.16(0.05)	0.18(0.05)	0.04(0.03)	0.85(0.03)	0.85(0.03)	0.82(0.04)
America	Karitiana*	36	0.06(0.03)	0.07(0.03)	0	0.93(0.03)	0.92(0.05)	0.90(0.05)
	Mayan*	40	0.15(0.04)	0.33(0.05)	0	0.78(0.03)	0.78(0.03)	0.74(0.03)
	Surui*	20	0.25(0.07)	0.03(0.03)	0	0.96(0.02)	0.95(0.02)	0.95(0.03)
Europe (Caucasian)	Italian*	37	0.15(0.04)	0.13(0.04)	0.03(0.02)	0.88(0.03)	0.86(0.03)	0.84(0.04)
	German	25	0.17(0.06)	0.13(0.05)	0.07(0.04)	0.86(0.04)	0.87(0.03)	0.84(0.04)
	Spanish	26	0.18(0.05)	0.08(0.04)	0.02(0.02)	0.93(0.03)	0.92(0.03)	0.91(0.04)
	Poland	26	0.18(0.06)	0.18(0.06)	0.14(0.05)	0.79(0.04)	0.79(0.04)	0.75(0.05)
	Northern European*	23	0.22(0.06)	0.16(0.05)	0.09(0.04)	0.84(0.04)	0.83(0.04)	0.80(0.05)
	Assam Caste	26	0.24(0.06)	0.22(0.06)	0	0.84(0.04)	0.84(0.04)	0.80(0.05)
	United Arab Emirates	26	0.35(0.07)	0.06(0.03)	0	0.92(0.03)	0.89(0.04)	0.87(0.05)
	Rajasthani	25	0.42(0.08)	0.05(0.04)	0.05(0.04)	0.86(0.04)	0.81(0.06)	0.76(0.08)
Oceania	American Samoan	25	0.22(0.07)	0	0	1.00(0.00)	1.00(0.00)	1.00(0.00)
	Australian Aborigine*	14	0.54(0.09)	0.10(0.06)	0	0.84(0.05)	0.74(0.08)	0.68(0.10)
	New Guinea 1*	69	0.66(0.04)	0.18(0.03)	0	0.76(0.04)	0.63(0.07)	0.53(0.09)
	Nasioi Melanesian*	12	0.67(0.10)	0	0	0.88(0.05)	0.78(0.09)	0.74(0.10)
	New Guinean 2*	21	0.71(0.07)	0.17(0.06)	0	0.76(0.02)	0.64(0.04)	0.55(0.05)
	New Guinean 3*	26	0.72(0.07)	0.07(0.04)	0	0.79(0.04)	0.66(0.07)	0.59(0.08)
Northeast Asia	Ewenki*	17	0.09(0.05)	0.28(0.08)	0	0.84(0.04)	0.84(0.04)	0.81(0.05)
	Baryat*	5	0.10(0.09)	0.57(0.16)	0	0.72(0.06)	0.73(0.06)	0.68(0.07)
	Hui*	19	0.11(0.05)	0.20(0.06)	0	0.87(0.04)	0.87(0.04)	0.85(0.04)
	Tibetan*	25	0.12(0.05)	0.28(0.06)	0.02(0.02)	0.83(0.03)	0.84(0.03)	0.81(0.04)
	Uyghur*	10	0.20(0.09)	0.20(0.09)	0	0.85(0.05)	0.86(0.05)	0.84(0.06)
	Korean*	28	0.27(0.06)	0.26(0.06)	0	0.82(0.03)	0.82(0.04)	0.78(0.05)
	Japanese 2	26	0.33(0.07)	0.24(0.06)	0	0.81(0.04)	0.78(0.05)	0.73(0.06)
	Japanese 1*	15	0.37(0.09)	0.11(0.06)	0	0.81(0.05)	0.74(0.07)	0.69(0.08)
	Manchurian*	33	0.38(0.06)	0.12(0.04)	0	0.89(0.03)	0.86(0.04)	0.82(0.05)
	Southeast Asia	Wa*	35	0.06(0.03)	0.16(0.04)	0	0.89(0.03)	0.89(0.03)
Ami*		10	0.10(0.07)	0	0	1.00(0.00)	1.00(0.00)	1.00(0.00)
Anni*		21	0.12(0.05)	0	0	1.00(0.00)	1.00(0.00)	1.00(0.00)
Atayal 2		20	0.13(0.06)	0.03(0.03)	0	0.95(0.03)	0.93(0.05)	0.92(0.05)
Lahu*		11	0.14(0.07)	0	0	1.00(0.00)	1.00(0.00)	1.00(0.00)
Bulang*		26	0.15(0.05)	0	0	1.00(0.00)	1.00(0.00)	1.00(0.00)
Yi*		19	0.16(0.06)	0.24(0.07)	0	0.83(0.04)	0.82(0.05)	0.79(0.05)
Atayal 1*		32	0.17(0.05)	0.11(0.04)	0	0.93(0.02)	0.94(0.02)	0.93(0.03)
Karachi		26	0.17(0.05)	0.25(0.06)	0	0.83(0.03)	0.83(0.03)	0.80(0.04)
Deang*		6	0.17(0.11)	0.17(0.11)	0	0.88(0.07)	0.89(0.07)	0.87(0.08)
Batak		26	0.20(0.06)	0.25(0.07)	0	0.79(0.04)	0.77(0.05)	0.72(0.06)
Northeast Thailand		26	0.23(0.06)	0.17(0.05)	0	0.90(0.03)	0.90(0.03)	0.88(0.04)
Jingpo*		15	0.23(0.08)	0.07(0.05)	0	0.92(0.04)	0.91(0.05)	0.89(0.06)
Malay		25	0.25(0.07)	0.22(0.07)	0	0.82(0.04)	0.81(0.05)	0.78(0.06)
Ahom		25	0.25(0.07)	0.19(0.07)	0	0.86(0.04)	0.85(0.05)	0.82(0.06)
Tujia*		20	0.28(0.07)	0.25(0.07)	0	0.80(0.04)	0.76(0.05)	0.71(0.07)
Yao-Nandan*		20	0.28(0.07)	0	0	0.98(0.02)	0.97(0.03)	0.96(0.04)
Dong*		20	0.30(0.07)	0.15(0.06)	0	0.89(0.04)	0.86(0.05)	0.82(0.07)
She*		20	0.30(0.07)	0.15(0.06)	0	0.90(0.04)	0.90(0.03)	0.88(0.04)
Yao-Jinxu*		20	0.30(0.07)	0.08(0.04)	0	0.93(0.03)	0.92(0.04)	0.90(0.05)
Cambodian 1*		28	0.32(0.06)	0.15(0.05)	0.02(0.02)	0.87(0.03)	0.86(0.04)	0.82(0.05)
Cambodian 2		26	0.32(0.07)	0.22(0.06)	0	0.83(0.04)	0.81(0.04)	0.78(0.05)
Paiwan*		20	0.33(0.07)	0.03(0.03)	0	0.96(0.02)	0.95(0.03)	0.94(0.04)

Table continues on next page

Table 2 – continued from previous page

Continent	Population	Size	SDF1(SE)	CCR2(SE)	CCR5(SE)	RH1(SE)	RH2(SE)	RH3(SE)
	Dai*	12	0.33(0.10)	0.07(0.05)	0	0.92(0.05)	0.92(0.05)	0.91(0.06)
	Li*	20	0.35(0.08)	0.05(0.03)	0	0.90(0.05)	0.87(0.06)	0.85(0.07)
	Javanese	24	0.37(0.09)	0.10(0.05)	0	0.92(0.04)	0.86(0.07)	0.82(0.10)
	Yami*	20	0.43(0.08)	0.05(0.03)	0	0.90(0.04)	0.84(0.06)	0.81(0.08)
China	Northwest Han*	24	0.19(0.06)	0.23(0.06)	0	0.84(0.04)	0.83(0.04)	0.80(0.05)
	Southwest Han*	48	0.22(0.04)	0.18(0.04)	0	0.83(0.01)	0.82(0.02)	0.79(0.02)
	North Han*	138	0.24(0.03)	0.21(0.02)	0	0.91(0.03)	0.89(0.03)	0.88(0.04)
	East Han*	407	0.25(0.02)	0.20(0.01)	0	0.84(0.03)	0.83(0.03)	0.79(0.04)
	Central Han*	168	0.26(0.02)	0.22(0.02)	0	0.85(0.01)	0.82(0.01)	0.78(0.02)
	Northeast Han*	37	0.26(0.05)	0.24(0.05)	0	0.84(0.02)	0.84(0.02)	0.80(0.02)
	Southeast Han*	40	0.26(0.05)	0.22(0.05)	0	0.85(0.03)	0.82(0.03)	0.78(0.04)
	South Han*	34	0.34(0.06)	0.11(0.04)	0	0.86(0.04)	0.84(0.05)	0.80(0.06)
	Chinese Chengdu	25	0.34(0.07)	0.18(0.05)	0	0.87(0.04)	0.85(0.04)	0.82(0.05)

*Data published in our previous study on SDF1-3'A and CCR2-64I.¹⁸ Standard errors are shown in parentheses. Populations with numbers 1, 2 or 3 were sampled in different geographic locations of the same country.

that the frequency of SDF1-3'A decreases from south to north and the frequency of the CCR2-64I allele increases from south to north.¹⁸ We contend that the resulting intermediate frequencies of the two mutant alleles combined with complete absence of the CCR5-Δ32, yielded the high RH values in Southeast Asian populations, which coincide with the high prevalence and rapid growth of HIV infections in this area.¹⁵

It is important to point out that the estimation of RH indices may not be accurate given the width of the 95% confidence intervals (see Table 1 in Winkler *et al*).¹² It may also vary between studies. Furthermore, the allele frequency estimation may introduce an additional source of error, especially when the sample sizes are small. In this paper, we treated the RH indices for individuals as constants and the standard errors of sampling are presented in Table 2. Such

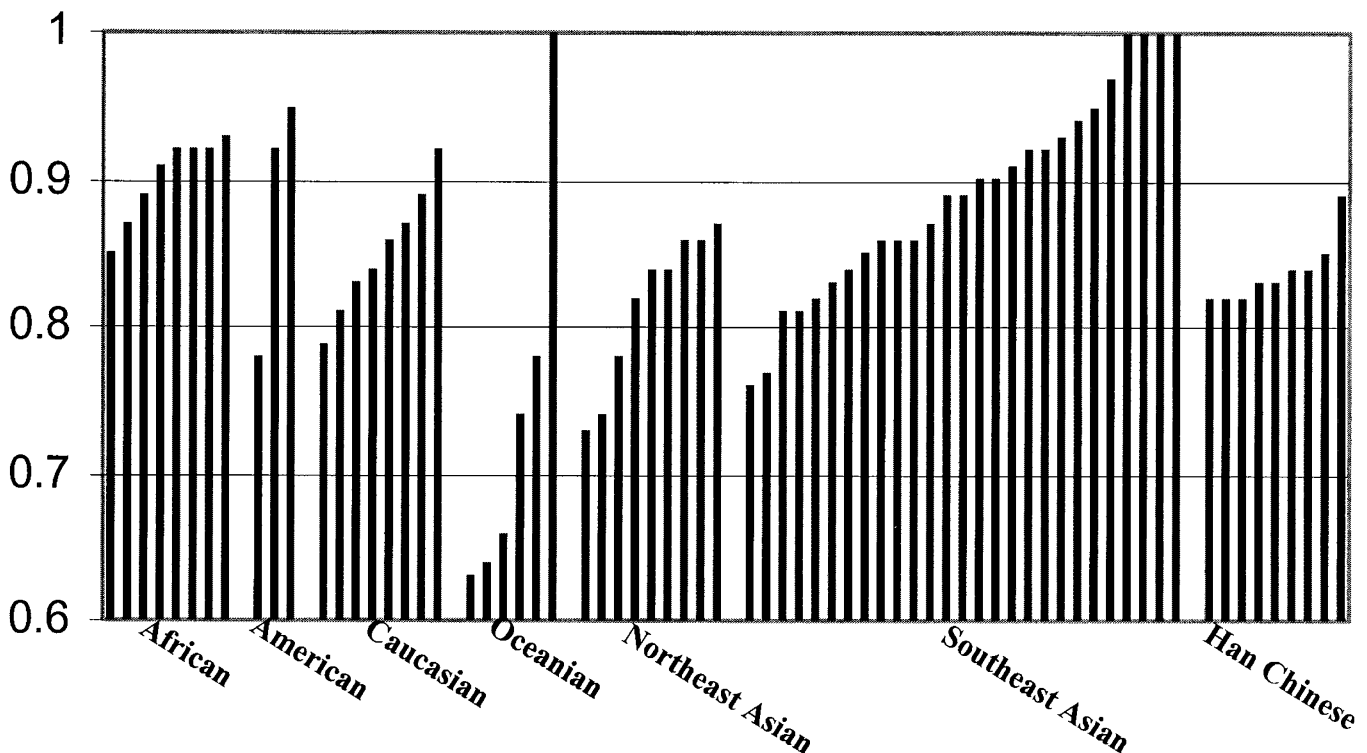


Figure 1 The relative hazard (RH) distribution in 70 world populations. The comparison is based on the AIDS definition of AIDS-1987. The RH values based on the other AIDS definitions, AIDS-1993 and death⁹ show similar distributions among the world populations.

standard errors are surprisingly small even when the sample size of the population is small. In estimating RH indices, the difference in RH indices among racial groups is ignored. The errors introduced by this assumption should be very small, as RH index differences between racial groups are generally small (see Table 1 in Winkler *et al*).¹² However, it was recently shown that the RH indices of the haplotypes containing newly identified polymorphisms in the promoter region of *CCR5*^{19–21} are higher in African Americans than they are in European Americans.¹⁹ Therefore, the RH index in African populations in this study is likely to be underestimated and our conclusion of high RH in Africa still stands.

Acknowledgements

B Su and R Chakraborty are supported by NIH grant GM41399. R Deka is supported by NIH grant GM45861 and NSF grant SBR-9600910. L Jin is supported by the TOKTEN project of the United Nations, the Li Foundation, and NIH grants GM41399 and GM55759.

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