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ORIGINAL ARTICLE

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Anthropological implication of the *SDF1*-3′A allele distribution in Southeast Asia and Melanesia

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Abstract The distribution of the *SDF1*-3′A allele among 1848 individuals in Southeast Asia and Melanesia was studied with the polymerase chain reaction-restriction fragment length polymorphism assay. The *SDF1*-3′A allele frequency in the populations of mainland Southeast Asia ranged from 0.0 to 0.355, whereas in the populations of insular Southeast Asia and Melanesia, it ranged from 0.233 to 0.733, with an increasing cline from west to east. Correlation between *SDF1*-3′A frequency and longitude values was highly significant for the populations in the Pacific region ($r = 0.867$, $P < 0.001$). The geographic distribution of the *SDF1*-3′A frequencies in the Pacific region was interpreted by an admixture of Austronesians with the aboriginal people in situ. In addition, this study found high proportions of *SDF1*-3′A/3′A homozygous individuals in several populations, which will enable us to evaluate roles of the *SDF1* genotypes in SDF-1 expression.

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Introduction

It has been documented that chemokine receptors play important roles in human immunodeficiency virus (HIV)-1 infection and acquired immunodeficiency syndrome (AIDS) development or progression, because some chemokine receptors such as CCR5 and CXCR4 serve as essential coreceptors for HIV-1 infection (Feng et al. 1996; Deng et al. 1996; Doranz et al. 1996). Therefore, their genetic variants and HIV-1 and AIDS resistance have been documented intensively.

Stromal cell derived factor-1 (SDF-1) has been known as one of the chemokines and as a physiological ligand for CXCR4, of which genetic variants have not been reported (Bleul et al. 1996a; Oberlin et al. 1996). Besides essential roles in embryonic development, hematopoiesis, and chemoattraction (Nagasawa et al. 1996; Bleul et al. 1996b; Aiuti et al. 1997), SDF-1 has been highlighted because of its intervention in the T cell-line-tropic HIV-1 entry into target cells (Bluel et al. 1996a; Oberlin et al. 1996). After the discovery of a single-nucleotide polymorphism (SNP) in the 3′untranslated region of the *SDF1* gene (*SDF1*-3′A/*SDF1*-3′G), relationships between this SNP and AIDS development or progression have been in dispute (Winkler et al. 1998; van Rij et al. 1998; Mummidi et al. 1998; Hendel et al. 1998; Magierowska et al. 1999). In contrast to the 32-bp deletion in the *CCR5* gene, which is highly specific among peoples with Caucasian traits (Samson et al. 1996; Dean et al. 1996; Martinson et al. 1997), the *SDF1*-3′A allele is distributed throughout the world, with high occurrence in Papua New Guinea (Su et al. 1998). This wide distribution of the 3′A allele suggested its single African origin; however, a comparative ape genome study showing a mutational hot spot on this locus proposed a possible multiple origin of the *SDF1*-3′A allele (Kimura and Ishida 2001).

Because Southeast Asia has served as a bridge from mainland Asia to Oceania, it is worth investigating the distribution of the *SDF1*-3′A allele in this area in detail to map out a global *SDF1*-3′A allele distribution. Another aim of the present study is to identify populations that demonstrate a high *SDF1*-3′A allele frequency and preponderant homozygous carriers for future evaluation of the effect of genotypes on SDF-1 expression.

Subjects and methods

DNA samples. From 26 populations, including ethnic minorities of Southeast Asia and Melanesia, 1848 individuals were screened for the presence of the *SDF1*-3′A allele (Table 1 and Fig. 1). Blood specimens from Mlaburi and Timorese were collected as part of the anthropological studies after obtaining informed consent. Mlaburi have been nomadic hunter-gatherers until recently in northern Thailand and Laos. Timorese are Austronesian speakers in Timor Island. The remaining populations are described elsewhere (Inaoka et al. 1996; Nakazawa et al. 1996; Shimizu et al. 1997, 2000). We used genomic DNAs obtained from peripheral blood lymphocytes or from immortalized cell lines with Epstein-Barr virus. These samples were from unrelated individuals so as to represent populations except for the Mlaburi and the Manni (Semang), whose total populations are remarkably small at present. DNA samples from anonymous Seramese (Austronesian-speaking group in Seram Island, Indonesia) were kindly provided by Dr. M. Hirai.

Genotyping. The DNA samples were subjected to a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. PCR amplification was performed using a primer set, 5′-AGCTGTGCAGGTGG GGAGAC-3′ (sense) and 5′-TGTGGAGGTGCTCGG GATG-3′ (antisense). The PCR products were 301-bp fragments, and subsequent *Msp*I digestion at 37°C overnight cleaved the wild-type allele into two fragments of 198 and 103 bp. These fragments were visualized by 2.5% agarose gel electrophoresis followed by staining with ethidium bromide.

Results and discussion

Genotype distribution and *SDF1*-3′A allele frequency in each group are presented in Table 1. No significant deviation from Hardy-Weinberg equilibrium in the genotype

Table 1. Distribution of *SDF-1* genotypes and frequency of the *SDF1*-3′A allele in Asian and Melanesia populations

Population	*n*	Genotype			χ^2	3′A frequency ± S.E.
		3′G/3′G	3′G/3′A	3′A/3′A		
Mainland Southeast Asia						
Akha	50	24	22	4	0.11	0.300 ± 0.046
Lahu	50	46	4	0	0.09	0.040 ± 0.020
Shan	50	23	24	3	1.02	0.300 ± 0.046
Lisu	50	25	20	5	0.11	0.300 ± 0.046
Red Karen	91	61	27	3	0.00	0.181 ± 0.029
White Karen	101	54	37	10	0.93	0.282 ± 0.032
Hmong	27	18	8	1	0.01	0.185 ± 0.053
Mlaburi	80	80	0	0	—	0.000
Northeastern Thais	59	37	18	4	0.74	0.220 ± 0.038
Central Thais	50	31	16	3	0.23	0.220 ± 0.041
Southern Thais	50	28	18	4	0.21	0.260 ± 0.044
Manni	31	11	18	2	2.23	0.355 ± 0.061
Insular Southeast Asia						
Kahayan	42	24	13	5	2.06	0.274 ± 0.049
Berau	76	41	26	9	2.15	0.289 ± 0.037
Javanese	148	85	57	6	0.88	0.233 ± 0.025
Madurian	60	28	25	7	0.15	0.325 ± 0.043
Bugis	121	38	68	15	3.34	0.405 ± 0.032
Toraja	105	31	53	21	0.04	0.452 ± 0.034
Timorese	105	27	54	24	0.09	0.486 ± 0.034
Seramese	45	3	18	24	0.02	0.733 ± 0.047
Melanesia						
Asmat	15	1	10	4	2.27	0.600 ± 0.089
Dani	32	8	12	12	1.81	0.563 ± 0062
Ekari	92	11	32	49	2.39	0.707 ± 0.034
Biak	25	4	16	5	1.99	0.520 ± 0.071
Gidra	187	22	98	67	2.37	0.620 ± 0.025
Manus	106	16	45	45	0.72	0.637 ± 0.033
Total	1848					

Genotype distribution was tested for conformity with Hardy-Weinberg equilibrium by means of χ^2 test

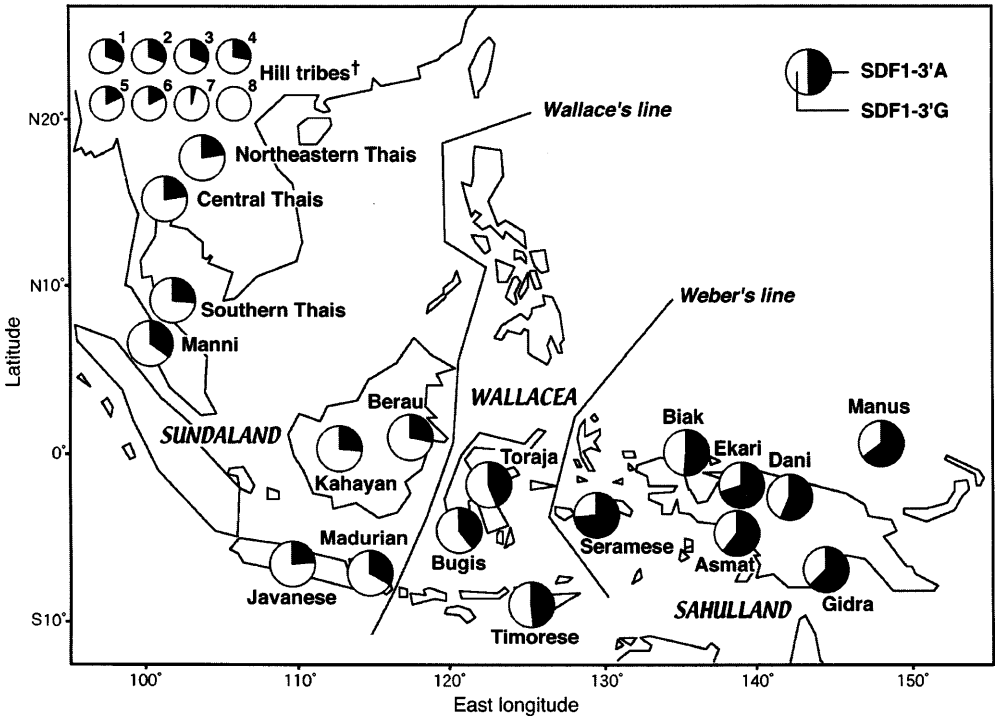

Fig. 1. Geographic distribution of the *SDF1*-3′A allele in Southeast Asia and Melanesia. †*Hill tribes* are 1, Akha; 2, Shan; 3, Lisu; 4, White Karen; 5, Hmong; 6, Red Karen; 7, Lahu; and 8, Mlaburi

distribution was observed in all the populations tested. The *SDF1*-3′A allele frequency in the populations of mainland Southeast Asia ranged from 0.0 to 0.355, whereas in the populations of insular Southeast Asia and Melanesia, it ranged from 0.233 to 0.733, with an increasing cline from west to east (Fig. 1). Correlation between *SDF1*-3′A frequencies and longitude values was highly significant for the populations in the Pacific region ($r = 0.867$, $P < 0.001$).

Low frequencies (0.0–0.355) of the *SDF1*-3′A allele in mainland Southeast Asians in this study were more or less comparable to the data reported elsewhere (Su et al. 1999; Rousset et al. 1999). This is reasonable because the present populations in mainland Southeast Asia are relatively homogeneous and genealogically close to Southern Chinese populations (Tokunaga et al. 1996).

The implication of the *SDF1*-3′A frequency of insular Southeast Asia and Melanesia is rather complicated because people in these areas have different genealogical backgrounds. To interpret differences in the allele frequencies among these populations, we must take into consideration the historical backgrounds of the people in these areas. The first occupation of the Pacific region was achieved by the ancestral Australoids during the glacial era, about 50,000 years ago, when Australia and New Guinea formed a single continent, Sahulland, and Borneo, Sumatra, Java, and the mainland of Southeast Asia connected to form Sundaland (Chappell 1976; Roberts et al. 1990). In the Pacific region, except for New Guinea and Australia, the majority of the descendants of the first settlers were then replaced by Austronesian-speaking people, whose ancestors had started migration from South China about 6000 years ago when the sea level had elevated to the present level to subside Sundaland into Southeast Asian archipelago. These people spread southward through Taiwan and the Philippines to Indonesia, and then westward to mainland Southeast Asia and as far as Madagascar Island or eastward to Oceania (Bellwood 1989).

Four Papuan-speaking groups in our study who have been relatively isolated until recently showed high frequencies of the *SDF1*-3′A allele. Taken together with other reports (Su et al. 1998), the present study shows that Papuans have high *SDF1*-3′A allele frequencies in general. Because none of the populations studied so far showed deviation from Hardy-Weinberg equilibrium, it is presumed that their ancestral population, the first settlers of Oceania, also harbored the *SDF1*-3′A allele with a high frequency. As for the Austronesian-speaking groups, their *SDF1*-3′A allele frequencies showed a west-to-east increasing cline (Fig. 1). This trend becomes obvious when these populations are subcategorized into three groups by their geographic locations corresponding to west of Wallace's line (western Austronesian), east of Weber's line (eastern Austronesian), and between the two lines (middle Austronesian). The *SDF1*-3′A frequencies in the western, middle, and eastern Austronesians were significantly different ($P < 0.05$) (Fig. 2). This geographic distribution of the *SDF1*-3′A frequencies in current Austronesians was interpreted by the past admixture of Austronesians with the aboriginal people in situ; the genetic contribution of ancestral Australoids is large in the eastern Austronesian. Our interpretation of *SDF1*-3′A allele frequency in Austronesians is consistent with the result of Y haplogroups (Capelli et al. 2001).

Arguments about the *SDF1* genotype and AIDS development or progression are still controversial: the homozygous status for the *SDF1*-3′A allele (1) delayed the onset of AIDS (Winkler et al. 1998), (2) accelerated the progression to AIDS but prolonged the survival time after AIDS onset (van Rij et al. 1998), (3) accelerated the progression to

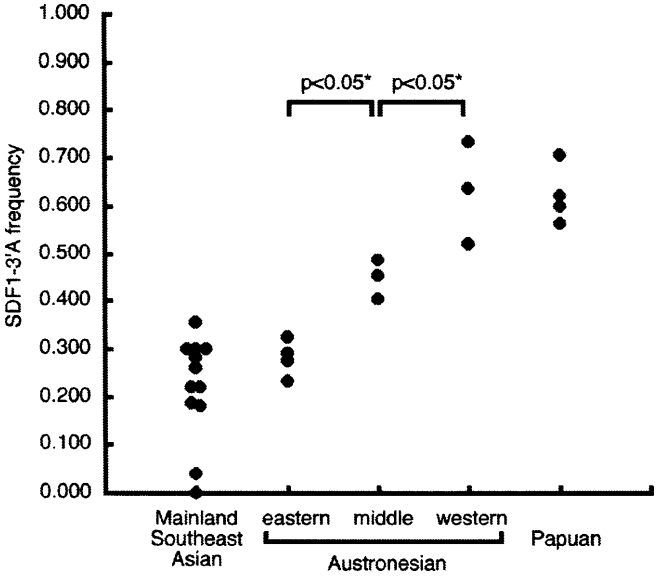

Fig. 2. *SDF1*-3′A allele frequencies among populations studied. Significant differences in the frequency were observed among the Austronesian groups categorized by their location (*Mann-Whitney test)

death but not the clinical end point of AIDS (Mummidi et al. 1998), and (4) was not associated with AIDS progression (Hendel et al. 1998; Magierowska et al. 1999). Recently, it was reported that SDF-1 not only inhibits entry of T-cell-line-tropic HIV-1 into target cells, but also stimulates HIV-1 replication after entry (Marechal et al. 1999). This dual effect of SDF-1 on HIV-1 infection may have contributed to the contradictory relations identified between *SDF1*-3′A and AIDS progression. Because the SNP is located in the 3′ untranslated region, it is thus essential to investigate the status of SDF-1 expression by different genotypes to understand the relationship between *SDF1*-3′A and AIDS progression. In contrast to the rare presence of *SDF1*-3′A/3′A homozygous individuals in Caucasian populations, our study showed a high proportion of these individuals in several populations. This substantial number of homozygotes enables us to evaluate the crucial roles of the *SDF1* genotypes in SDF-1 expression in vivo as well as in vitro. This will lead to insights about the relationship between the *SDF1*-3′A allele and AIDS progression.

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