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Frequency of HLA-A*03 associates with HIV-1 infection in a Chinese cohort

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During the early mid-1990s, a number of rural farmers across central China were employed to the unregulated plasma-selling-activity and many of them were infected by HIV-1. However, AIDS progression in the former blood donors (FBDs) is various. The aim of this study is to assess human leukocyte antigen (HLA) class I allele distribution in FBDs and evaluate its association with HIV-1 infection and disease progression. A total of 353 FBDs were enrolled in the cohort including 294 ART naïve HIV-1 seropositive and 59 HIV-1 seronegative age-matched subjects. The viral load and CD4/CD8 T cell counts were assessed in all subjects. Compared with HIV-seropositive group, the frequency of HLA-A*03 in control was significantly higher. After classifying the HLA-B alleles of the subjects according to the presence of Bw4/Bw6 serological epitopes, detrimental effect of HLA Bw6/ Bw6 homozygosity was also confirmed in the HIV-seropositive subjects. This study provides novel evidence on HLA class I allele distribution and association of HLA-A*03 frequency with HIV-1 infection and viremia in the HIV-1 infected FBDs, which may throw light on intervention strategy for the HIV-1 infection and our understanding how host immunity and genetic background affect HIV infection and AIDS progression.

leukocyte antigen class I, HIV-1 infection, viremia control, Chinese former blood donor cohort

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Human immunodeficiency virus (HIV) infection causes progressive damage to the immune system due to acquired immunodeficiency syndrome (AIDS). The majority (~80%) of individuals with HIV-infection have a mean of 8–10 years' latent infection and subsequently progress to clinical AIDS [1–4]. A proportion of HIV-1 infected individuals, designated as viremic controllers, continuously maintain HIV RNA levels below 2000 copies mL^{-1} for at least one year without antiretroviral treatment. In addition, some HIV-positive individuals, often referred to as "elite controllers" or "aviremic controllers", remain clinically healthy with HIV RNA levels below 50 copies mL^{-1}, and have a higher numbers of $CD4^+$ T helper lymphocytes and cytotoxic T lymphocytes (CTLs) than either viremic controllers or noncontrollers [5–8]. The relative threshold of plasma HIV RNA levels at or below 2000 copies mL^{-1} is important since Gray et al. [9] reported that the risk of HIV transmission was markedly reduced and the progression of disease was mild at these HIV RNA levels. Currently there is no available vaccine to prevent HIV-1 infection; thus, developing a vaccine to suppress viremia in HIV-positive individuals is critical to prevent the spread of HIV infection.

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The mechanism of protection against HIV-1 infection and long-term control of viremia in HIV controllers is not well understood, but may be multifactorial [10–13]. The human leukocyte antigen (HLA) system plays a crucial role in initiating innate and adaptive immune responses, therefore HLA genetic variance may be an important cofactor of HIV infection [14,15], and elucidating the interactions between HLA and HIV may help vaccine research. During HIV infection, HLA class I gene products bind and present pathogen-derived peptides from infected cells to form stable HLA molecule/virus peptide complexes. $CD8^+$ CTLs that recognize their cognate antigen in the context of HLA class I are activated and lyse the infected cells [16–18]. In addition, killer immunoglobulin-like receptors or killer cell inhibitory receptors (KIRs) expressed by nature killer (NK) cells recognize groups of HLA class I alleles. Interactions between KIRs and HLA class I allele products prohibit the activity of NK cells and affect host innate defense to HIV. Thus, there have been continued attempts to correlate HLA gene polymorphisms with HIV-1 infection and disease progression [19].

During the early mid-1990s, a number of rural farmers across central China were involved in the selling of unregulated plasma and many of them were infected by the same clade of HIV-1 B′. However, AIDS progression in the former blood donors (FBDs) was different, and the correlation between host immunity and HIV-1 infection and disease progression is not well understood. In the present study, we examined the association of HLA alleles with HIV-1 infection and disease progression in a HIV-1 positive FBD cohort from Fuyang County, Anhui Province, China. HIV positive FBDs (n=294) and HIV negative blood donors (n=59) were enrolled in the study. The aim of this study was to understand how host immunity and genetic background affects disease progression in a Chinese FBD cohort.

1 Materials and methods

1.1 Study population

A total of 353 subjects enrolled in this study were rural farmers who had a history of unregulated commercial plasma donation in Fuyang County, Anhui Province, China between 1992 and 1995. Among the donors, 294 were antiretrovirus therapy (ART) naïve HIV-1 seropositive FBDs, who were infected with HIV-1 B′ clade by either contaminated blood collection equipment or the re-infusion of pooled buffy coats, and 59 were HIV-1 seronegative age-matched FBDs for controls. The HIV-1 positive group was divided into two subgroups, a viremic controller group and a noncontroller group, according to the criteria developed by the International HIV Controller Consortium. The viremic controllers are asymptomatic FBDs who had been tested seropositive with HIV RNA <2000 copies mL^{-1} and with no antiretroviral treatment, and the plasma HIV RNA level must have been maintained at least one year by three determinations. The rest of HIV-positive FBDs were defined as noncontrollers. All subjects were fully informed of the comprehensive process and the purpose of the research before signing an informed consent in the local language. The informed consent forms and all protocols were reviewed by the Institutional Review Board, Chinese National Center for AIDS/STD Prevention and Control, and Division of AIDS Prevention Science Review Committee, Anhui Provincial Center for Disease Prevention and Control.

1.2 Immunological and virological measurements

$CD4^+$ T cells were measured by single-platform flow cytometry (FACSCanto, BD, San Jose, CA, USA). Plasma HIV-1 RNA levels were measured by the COBAS Amplicor™ HIV-1 Monitor Test, v1.5 (Roche Diagnostics, Shanghai, China) according to the manufacturer's instructions. HIV-1 RNA levels transformed to lg were treated as a continuous variable in separate analysis.

1.3 DNA extraction and HLA class I typing

High-molecular-weight genomic DNA was extracted from EDTA anti-coagulated whole blood using a QIAamp DNA Mini kit (Qiagen, Valencia, CA, USA) following the manufacturer's manual. All DNA samples were stored at –20°C in Tris-EDTA bsuffer (10 mmol L^{-1} Tris-Cl, 0.5 mmol L^{-1} EDTA, pH 9.0). HLA class I genotyping was performed using polymerase chain reaction sequence-specified primers (PCR-SSPs) and commercial PCR-SSP kits (Texas Biogene, Shanghai, China).

1.4 Statistical analysis

Baseline characteristics of differences among HIV-1 negative, positive, viremic controllers and noncontrollers were compared by analysis of variance (ANOVA) for age, lg-transformed-viral loads and $CD4^+$ cell counts and a Chi-square test, when appropriate, for categorical variables. The association between an HLA alleles and infection was described by the odds ratio (*OR*) and 95% confidence interval (*CI*), which was calculated according to Woof's formula or Haldane's modification of the formula [20]. *P*-values were determined by Chi-square analysis or by Fisher's exact test and a *P*-value less than 0.05 was considered statistically significant. All analyses were performed with Statistical Analysis System (version 9.13, SAS Institute, Cary, NC, USA).

2 Results

2.1 Description of the study cohort

The characteristics of 353 individuals in the cohort are shown in Table 1. The median ages of the HIV-1 negative,

HIV-1 positive, controllers and noncontrollers groups were 44.4±8.3, 42.4±7.9, 40.7±6.2 and 42.8±8.2 years, respectively. There was no significant difference in age (P=0.088) or gender (P=0.826) between the HIV-1 negative group and positive group. The $CD4^+$ T cell counts of HIV-1 negative and positive groups were 665±230 and 335±179, respectively (P<0.001), while those of controller and noncontroller groups were 444±115 and 320±183, respectively. The median viral loads were 4.68±0.69 lg copies mm^{-3} in noncontrollers and 2.75±0.23 lg copies mm^{-3} in viremic controllers.

2.2 Distribution of major HLA class I variants in FBDs

Distribution analysis of major HLA class I variants in the FBDs was performed using two-digit allele designation. As shown in Table 2, at the two-digit specificity level, 16 different HLA-A, 27 HLA-B and 13 HLA-Cw variants were observed in the HIV-1 positive group, and nine different HLA-A, 20 HLA-B and 11 HLA-Cw variants in HIV-1 negative group. Twelve HLA class I alleles occurred at a frequency greater than 10% amongst HIV-1 positive subjects as follows: HLA-A*02 (32.99%), HLA-A*11 (15.14%), HLA-A*24 (19.73%), HLA-A*30 (14.97%), HLA-B*13

Table 1 Basic information of the subject cohort[a)]

Attribute	HIV-1 negative group (n=59)	HIV-1 positive group (n=294)	HIV-1 positive group (n=288)*	
			Noncontrollers (n=251)	Viremic controllers (n=37)
Gender (male/female)	30/29	157/137	137/114	16/21
Age (year)	44.4±8.3	42.4±7.9	42.8±8.2	40.7±6.2
$CD4^+$ T cells mm^{-3}	665±230	335±179	444±115	320±183
Viral load (RNA copies mL^{-1})		121460	142144	663
Lg copies mm^{-3}		4.40±0.93	4.68±0.69	2.75±0.23

a) n, the number of FBDs; *, six FBDs were not followed up.

Table 2 Frequencies of human leukocyte antigen alleles in FBDs[a)]

Allele	HIV-1 positive group (2n=588)		HIV-1 negative group (2n=118)		Allele	HIV-1 positive group (2n=588)		HIV-1 negative group (2n=118)	
	N	f(%)	N	f(%)		N	f(%)	N	f(%)
A*01	8	1.36	3	2.54	B*07	27	4.59	4	3.39
A*02	194	32.99	43	36.44	B*08	2	0.34	2	1.69
A*03	23	3.91	11	9.32	B*13	93	15.82	9	7.63
A*11	89	15.14	10	8.47	B*14	2	0.34	n/a	n/a
A*23	1	0.17	n/a	n/a	B*15	80	13.61	21	17.80
A*24	116	19.73	29	24.58	B*18	n/a	n/a	5	4.24
A*26	10	1.70	2	1.69	B*21	1	0.17	n/a	n/a
A*29	7	1.19	n/a	n/a	B*27	14	2.38	n/a	n/a
A*30	88	14.97	14	11.86	B*35	33	5.61	3	2.54
A*31	11	1.87	n/a	n/a	B*37	4	0.68	2	1.69
A*32	8	1.36	n/a	n/a	B*38	14	2.38	n/a	n/a
A*33	22	3.74	5	4.24	B*39	6	1.02	3	2.54
A*36	1	0.17	n/a	n/a	B*40	79	13.44	19	16.10
A*66	1	0.17	n/a	n/a	B*42	1	0.17	n/a	n/a
A*68	7	1.19	1	0.85	B*44	27	4.59	9	7.63
A*69	2	0.34	n/a	n/a	B*45	2	0.34	n/a	n/a
					B*46	31	5.27	5	4.24
Cw*01	73	12.41	14	11.86	B*48	16	2.72	6	5.08
Cw*02	8	1.36	n/a	n/a	B*50	4	0.68	n/a	n/a
Cw*03	103	17.52	31	26.27	B*51	61	10.37	11	9.32
Cw*04	46	7.82	5	4.24	B*52	21	3.57	n/a	n/a
Cw*05	7	1.19	2	1.69	B*54	14	2.38	3	2.54
Cw*06	93	15.82	9	7.63	B*55	15	2.55	3	2.54
Cw*07	37	6.29	11	9.32	B*56	n/a	n/a	1	0.85
Cw*08	82	13.95	20	16.95	B*57	2	0.34	1	0.85
Cw*12	45	7.65	8	6.78	B*58	32	5.44	9	7.63
Cw*14	38	6.46	11	9.32	B*59	2	0.34	n/a	n/a
Cw*15	50	8.50	5	4.24	B*67	4	0.68	1	0.85
Cw*16	5	0.85	2	1.69	B*78	n/a	n/a	1	0.85
Cw*18	1	0.17	n/a	n/a	B*81	1	0.17	n/a	n/a

a) 2n, the number of chromosomes as each gene has two chromosomes; N, the subject number; f, the frequency; n/a, not available.

(15.82%), HLA-B*15 (13.61%), HLA-B*40 (13.44%), HLA-B*51 (10.37%), HLA-Cw*01 (12.41%), HLA-Cw*03 (17.52%), HLA-Cw*06 (15.82%), and HLA-Cw*08 (13.95%). The predominant HLA class I alleles (>10%) in the HIV-1 negative group were HLA-A*02 (36.44%), HLA-A*24 (24.58%), HLA-A*30 (11.86%), HLA-B*15 (17.80%), HLA-B*40 (16.10%), HLA-Cw*01 (11.86%), HLA-Cw*03 (26.27%) and HLA-Cw*08 (16.95%).

2.3 Association of HLA class I alleles with HIV-1 infection and viremic control

Association of HLA allele distribution with the susceptibility/resistance to HIV infection was evaluated by comparing the frequencies of HLA-A, -B, and -Cw in the HIV-1 positive group with those in the negative group. As shown in Table 3, the frequency of HLA-A*03 and Cw*03 in the negative group was more prevalent than in the positive group with *OR*=0.4 (95% *CI*: 0.19–0.84, *P*=0.012) and 0.6 (95% *CI*: 0.38–0.95, *P*=0.028), respectively. However, these data did not achieve statistical significance after correction. To further reveal the correlation of virus replication controlling with HLA class I alleles, we analyzed the distribution of HLA class I allele in 37 viremic controllers and 251 noncontrollers. The results showed that 12.16% of controllers were HLA-A*03 positive compared to 2.39% of noncontrollers (Table 4, *P*<0.0001), suggesting that HLA-A*03 plays an important role in HIV infection and might be a protective allele.

2.4 Association of HLA-Bw6 homozygosity with disease progression

All HLA-B alleles can be categorized by the presence of Bw4 or Bw6 epitopes. According to the "HLA genotype/serotype dictionary" (http://www.anthonynolan.org.uk/HIG/lists/bsplit. html), the HLA-B allele is converted into a serologic equivalent of each genotype and sorted into Bw4 or Bw6 groups. As shown in Table 5, using the "Bw4 and Bw6 associated specificity file", three groups were Bw4/Bw4, Bw4/Bw6, and Bw6/Bw6. Among all HIV-1-infected individuals, the Bw6/Bw6 homozygote was lower in the viremic controller group than that in the noncontroller group. There were 5/37 Bw6/Bw6 homozygotes in the controller group and 80/251 in the noncontroller group (*P*=0.022), in which the Bw4/Bw4 and Bw6/Bw4 frequencies were slightly higher. There were 50 Bw4/Bw4 homozygotes in 251 noncontrollers and 10 Bw4/Bw4 homozygotes in 37 controllers. These data suggest that the Bw6/Bw6 homozygote might be associated with poor virologic control in the Chinese HIV-infected population.

3 Discussion

HIV/AIDS is a leading cause of infectious disease mortality worldwide. Many intensive studies have been designed to identify factors relating to HIV infection and durable HIV control. The correlation between HIV/AIDS and HLA alleles is complicated and often affected by confounding factors. Factors such as populations with different genetic backgrounds, frequency of the allele, methods of HLA typing and standard clinic appraisal can distort allele association with HIV and lead to research bias.

Illegal commercial blood collection began in 1992, and was prevalent among farmers from Fuyang County, Anhui Province, China. HIV infection testing started in 1993, and no HIV infection in the FBDs was reported in this area until

Table 3 Distribution of HLA-A*03, HLA-B*13, HLA-Cw*03, and HLA-Cw*06 in HIV-positive and -negative group

	HIV-positive individual		Control		*P*	*OR*	95% *CI*
	Subject number	Gene frequency (%)	Subject number	Gene frequency (%)			
A*03	23	3.91	11	9.32	0.012	0.40	0.19–0.84
B*13	93	15.82	9	7.63	0.024	2.28	1.11–4.65
Cw*03	103	17.52	31	26.27	0.028	0.60	0.38–0.95
Cw*06	93	15.82	9	7.63	0.024	2.28	1.11–4.65

Table 4 Comparison of HLA-A*03 frequency between viremic controllers and noncontrollers

	Noncontrollers		Viremic controllers		*P*	*OR*	95% *CI*
	Allele	Frequency (%)	Allele	Frequency (%)			
A*03	12	2.39	9	12.16	<0.001	0.18	0.07–0.44

Table 5 HLA-Bw4 and HLA-Bw6 genotype in viremic controllers and noncontrollers[a)]

HLA	*n*	Bw4/Bw4	*f*	*P*	Bw6/Bw4	*f*	*P*	Bw6/Bw6	*f*	*P*	Bw4(f)	Bw6(f)	*P*
Controllers	37	10	0.27		22	0.595		5	0.135		0.568	0.432	
Noncontrollers	251	50	0.199	0.32	121	0.482	0.20	80	0.318	0.022	0.44	0.56	0.147

a) *f*, gene frequency.

1995. It is likely that HIV-1 infection spreads among commercial blood donors at that time due to contaminated blood collection equipment or the re-infusion of pooled buffy coat. Often, individuals may have participated in more than one blood donation group, resulting in virus spreading to the whole FBD population during a short period. The molecular-epidemiologic data showed that the FBD individuals were infected by the same virus, HIV-1 B′ clade, and that the genetic distance among the isolates from this area was limited [19,21]. In the present study, we selected FBDs who were ethnically identical and infected in a narrow-window of time with a homogenous HIV strain to explore the correlation of HIV infection and disease progression with the host HLA allele distribution.

We have identified 12 HLA class I alleles that were present in more than 10% of HIV-infected subjects and 9 HLA class I alleles in the controls. HLA-A*03 and HLA-Cw*03 alleles occurred more frequently in the control group than those in the infected group, whereas B*13 and Cw*06 were relatively enriched in HIV-positive subjects. HLA-B*13, Cw*03 and Cw*06 were more common alleles in the study cohort, while HLA-A*03 was rare or infrequent. Though the *P*-value of the four alleles did not reach significant difference after correction, it suggests a potential trend of allele distribution with susceptibility or resistance to HIV-1 infection.

To investigate the correlation of HLA with virus control, we subgrouped HIV-1 infected individuals according to the criteria of the HIV Controller Consortium. The distribution frequency of HLA-A*03 was significantly higher in the controls ($P<0.001$, $OR=0.18$, 95% $CI=0.07–0.44$), suggesting that HLA-A*03 might be a protective factor for HIV-1 infection and disease progression. We further explored the relationship between the HLA-A loci and virus load (*VL*) and demonstrated that the median VL of HLA-A*03 was markedly lower in the HIV infected group compared with that of other HLA-A alleles (Figure 1). With *VL* increase, the number of HLA-A*03 individuals markedly decreased, whereas carriers of other alleles were normally distributed (Figure 2). Zhai et al. [22] reported that HLA-B35 and HLA-A03 significantly contributed to the total virus-specific CTL responses in Chinese populations. Our data provided further evidence for a potential protective role of HLA-A*03 in HIV infection and virus control in the Chinese population. However, our results do not replicate the report by Gao et al. [23] where HLA-B*57 was a protective factor against HIV infection, and HLA-B*35 was a susceptible factor in a Caucasian population, or a report by Li et al. [24] where HLA-B*44 and HLA-Cw*04 alleles were significantly enriched in HIV-1-seronegative controls in a coh-

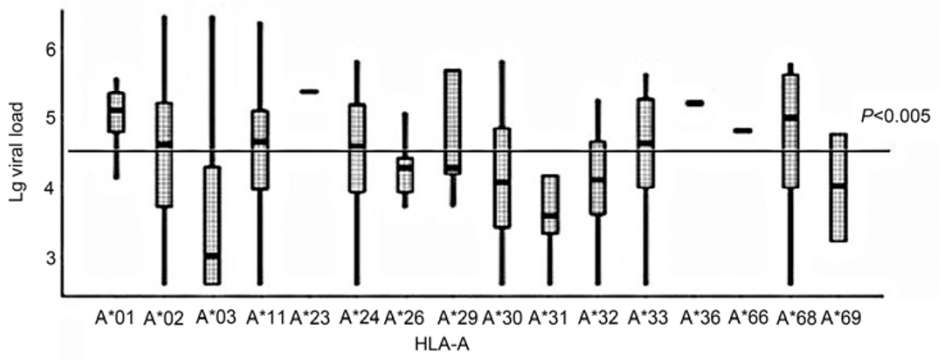

Figure 1 Contributions of HLA-A loci to viral load variation. Viral loads of different HLA-A alleles are shown as box plots, bold lines in boxes indicate median viral load of different alleles. Vertical lines indicate cohort median viral load.

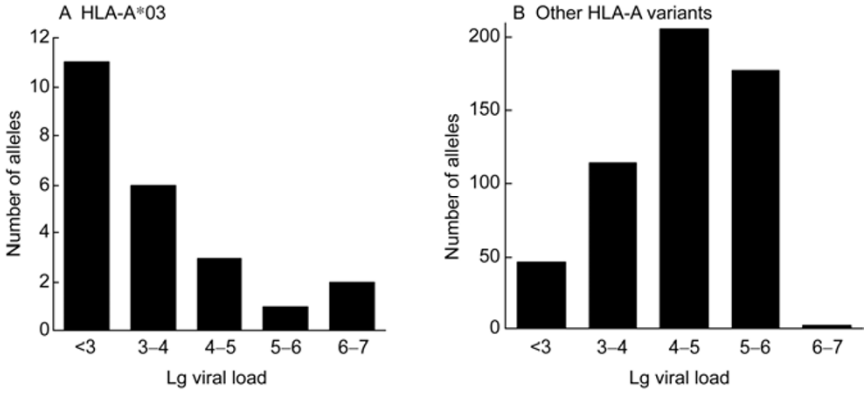

Figure 2 Distributions of HLA-A*03 and other alleles in different viral RNA load. HIV-1 infected individuals were grouped by viral RNA load.

ort of Chinese. This suggests that putative disease alleles play diverse roles in different ethnic populations. Furthermore, the number of HIV-negative FBDs in this study was limited compared with the infected subjects. Taking into account a large number of HLA-A3-restricted HIV-1 epitopes have been reported and the mechanism of T cell receptor cross-recognition of these epitopes has been thoroughly examined [25,26], the potential protective function of HLA-A*03 is worthy of further study.

Pedro et al. [27] reported that KIRs were essential for NK cells to identify "missing-self" and activate innate immunity against viruses. Only the Bw4 molecule is a ligand for NK cell KIRs, so the profound suppression of HIV-1 viremia may be associated with HLA-Bw4 homozygotes. Qing et al. [28] reported that HLA-Bw6 homozygosity had an accelerating effect on Chinese HIV-1-infected patients. In agreement with their report, the HLA-Bw6 homozygote was strongly associated with poor HIV control of the HIV-infected FBDs in the present study.

In summary, this study provides novel evidence on HLA class I allele distribution and association of HLA-A*03 frequency with HIV-1 infection and viremia in the clade of HIV-1 B′ infected FBDs. This may help develop an intervention strategy for the HIV-1 infected Chinese population and our understanding of how host immunity and genetic backgrounds affect HIV infection and AIDS progression.

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