The *CD4 C868T* Polymorphism and Its Correlation with HIV-1 Infection in a Chinese Population

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Abstract

Previous studies performed in Kenya have suggested that the *C868T* single nucleotide polymorphism (SNP) in *CD4* increases the risk of HIV-1 acquisition; however, no relevant study has been conducted in China. To evaluate the influence of this SNP on risk of HIV-1 infection in a Chinese population, the *CD4* genotype was determined by DNA sequencing in 101 HIV-1 patients and 102 healthy controls. No significant differences in the genotype and allele distributions of this polymorphism were observed among the patient and control groups. Additionally, binary logistic regression analyses adjusted by age and gender revealed that the *C868T* polymorphism was not associated with risk of HIV-1 infection. Furthermore, when analyses of genotype and allele frequencies were stratified by gender, similar nonsignificant results were found. Our study demonstrates a null association between the *CD4 C868T* polymorphism and an individual's susceptibility of HIV-1 acquisition in a Chinese population. Further studies are warranted to confirm these results.

Introduction

HUMAN IMMUNODEFICIENCY VIRUS (HIV), which by the end of 2013 affected an estimated 35.3 million people worldwide,¹ remains a major challenge within infectious diseases and poses a great burden on public health.² Despite the marked decline in newly infected cases following the introduction of antiretroviral therapy,³ there were still approximately 3.4 million new cases of and 1.5 million deaths due to acquired immune deficiency syndrome (AIDS)-related illnesses in 2013.⁴ HIV infection is associated with a wide range of clinical outcomes, from the “exposed uninfected,” namely, individuals who do not acquire the infection even after an exposure to the virus, to the rapid, regular, or slow disease progression that usually develops to AIDS within 10 years following infection.^{5–7} This variation of clinical progression and outcome has been associated with host factors, including host genetics.

Numerous studies have been conducted to evaluate the association between host genetic polymorphisms and HIV infection and disease progression. One of the best studied genetic polymorphisms is the *CCR5* structural gene encoding the coreceptor for HIV-1 cell entry.^{8–12} In 1996, a 32-base pair deletion allele (*CCR5Delta32*) of *CCR5* was identified and believed to contribute to HIV-1 infection resistance and retardation of AIDS progression.⁸ Various studies have also elucidated an association between the *CCR2-64I* polymor-

phism and a decreased risk of death among perinatally infected children,¹³ as well as protection against early HIV-1 transmission in pregnant women¹⁴ and slower disease progression in adults.¹⁵ Other commonly described polymorphisms include *human leukocyte antigen (HLA)-B27*,^{16,17} *HLA-B57*,¹⁸ stromal cell-derived factor (*SDF*) 1–3'A,^{19–21} and *CD4*.

CD4, a membrane glycoprotein expressed on a subset of T lymphocytes, is considered to be relatively nonpolymorphic, with only five nonsynonymous single nucleotide polymorphisms (SNPs) having been observed.^{22,23} However, *C868T* (*rs28919570*), one of the nonsynonymous SNPs caused by a C-to-T substitution at nucleotide position 868 of *CD4*, has been shown to result in a tertiary structure modification in *CD4*, thus potentially altering an individual's vulnerability to HIV-1 acquisition and disease progression.²⁴ The effects of the *CD4 C868T* SNP have been previously investigated in two Kenyan studies. Oyugi *et al.*²⁵ first revealed a strong correlation between the *CD4 C868T* SNP and an increased susceptibility to HIV-1 infection in Kenyan female commercial sex workers. This was followed by the study of Choi *et al.*,²⁶ demonstrating that infants with the 868T allele were at higher risk of acquiring HIV-1 than those with the wild-type allele.

These reports highlighted the association of *CD4 C868T* SNP with HIV-1 transmission and acquisition. However, the latest continuation study by Choi *et al.*²⁷ failed to observe an influence of this SNP on HIV-1 disease progression. In addition, the prevalence of HIV varies greatly within African

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regions, with the highest prevalence being observed in sub-Saharan Africa and the lowest in the Middle East and northern Africa.¹ Furthermore, the distribution of the *C868T* polymorphism varies between and within ethnicities, ranging from 20% among African Americans to 1% among whites.²⁸ Hence, it is important to assess whether this polymorphism is associated with HIV-1 infection countries and populations other than in Africa. To date, no relevant research has been conducted in China. Therefore, the present study evaluates the relationship between the *CD4 C868T* polymorphism and HIV-1 infection in a Chinese population.

Materials and Methods

Study subjects

This was a retrospective study conducted using materials collected from 101 HIV-1-positive patients who were initially screened to be HIV-1 seropositive at the Department of Clinical Laboratory, First Affiliated Hospital of Guangxi Medical University, Guangxi, China, and then further confirmed by the Guangxi Center for Disease Prevention and Control. A control group of 102 healthy individuals, all randomly selected from the Health Examination Center of the same hospital, were age and gender matched to the patients. Patients who were not confirmed as serum HIV-1 positive for the first time or who had undergone antiretroviral treatment were excluded from the study. Healthy subjects not confirmed as HIV free were also excluded. All the study subjects were recruited between January and December 2013 following written informed consent. The study received ethical approval from the ethics committee of the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.

Blood sample collection and determination of HIV-1-related coinfections

Venous blood (5 ml) was collected from each participant and 3-ml aliquots were placed in serum tubes with an accelerating agent for serum separation. Along with the confirmation of HIV-1 seropositivity, serum markers of HIV-1-related coinfections, including hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), and *Treponema pallidum* (TP) infection, were also investigated in both cases and controls. The remaining 2 ml of venous blood was stored in vacutainer tubes containing EDTA at -80°C for DNA extraction.

FIG. 1. PCR product (556bp) for cases and controls. M, marker; lanes 1–7, control samples; lanes 8–14, case samples.

DNA extraction and *CD4* gene sequence analysis

DNA extraction was performed using different methods for the case and control subjects given that the increased possibility of contamination when using the standard phenol-chloroform method makes it unsuitable for the isolation of HIV-infected DNA, despite it being the most sensitive DNA extraction method. Thus, a commercial DNA extraction kit (Ezup Pillar Blood Genomic DNA Extraction Kit, Shanghai, China) was used, according to the manufacturer's instructions, for the case group. Genomic DNA of the control group was extracted from 2 ml of peripheral white blood cells using the standard phenol-chloroform method.

Polymerase chain reaction (PCR) was used to amplify the target DNA containing nucleotide position 868, with the forward primer 5'-TCCCACTCGCCTTTACAGTT-3' and reverse primer 5'-GGGTCACAGAGGGTTGGTTA-3'. Following amplification, the PCR product (556 bp) was visualized on a 2% agarose gel (Fig. 1) and the positive bands were purified using the QIA Quick Gel Extraction kit (Qiagen, Germany). Cycle sequencing was then performed on all these PCR products, using the ABI Prism Big Dye Terminator kit (version 3.0). The samples were sequenced on an ABI Prism 3730 automated sequencer and analyzed via Chromas software (version 1.21). All these sequencing procedures were conducted by Sangon Biotech Company (Shanghai, China). Homozygote sequences were identified by the appearance of

FIG. 2. Sequencing map of the genotype for the *CD4 C868T* polymorphism. Arrow in parts a–c indicates CC, TT, and C/T genotypes, respectively.

single C or T peaks at nucleotide position 868, while heterozygote sequences were identified by the appearance of C and T peaks overlapping at the same position (Fig. 2); the sense and antisense sequences were concordant.

Statistical analysis

Genotypic frequencies were obtained by direct counting, followed by allele frequency calculations. A test for Hardy-Weinberg equilibrium, which indicated a normal distribution of the population, was initially carried out with a goodness-of-fit χ^2 test. Student's *t*-test and χ^2 test were used to examine the differences in general demographics and clinical data between cases and controls. The χ^2 test and Fisher's exact test were used to compare genotype and allele frequencies of C868T between the patient group and the control subjects, when appropriate. The correlation between the C868T polymorphism and risks of HIV-1 infection were indicated by odds ratio (OR) and 95% confidence intervals (CI) calculated by binary logistic regression, adjusted for age and gender. Considering that gender may be a possible confounder, a stratification of the study population into men and women was also conducted to further assess the association within each stratum. The statistical analyses were specified a priori and data were analyzed using the Statistical Package for Social Sciences (SPSS, version 16.0). All statistical significance was assumed as $p < 0.05$ at two-sided values.

Results

Subject characteristics

Table 1 summarizes the relevant demographics and clinical profiles of the 101 HIV-1 patients and 102 healthy subjects included in this study. The mean ages ($\pm$ standard deviation) of the control and patient groups were 46.06 ± 12.55 and 45.94 ± 14.59 years, respectively, and there were no significant differences for both age and gender, suggesting that the case data were comparable to those of the controls ($p = 0.950$ and $p = 0.430$). However, when considering an individual's susceptibility to other infectious diseases, HIV-1 patients were found to have a significantly higher rate of HBV, HCV, and TP coinfection (all $p < 0.05$).

Association between C868T polymorphism and risk of HIV-1 infection

The genotype and allele frequencies of the C868T CD4 gene polymorphisms for HIV-1 patients and healthy controls

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND CLINICAL PROFILES OF THE STUDY POPULATION

Characteristics	Cases (n = 101)	Controls (n = 102)	p-value
Age (year, mean $\pm$ SD)	45.94 $\pm$ 14.59	46.06 $\pm$ 12.55	0.950
Gender, N (%)			
Male	79 (78.22)	76 (74.51)	0.430
Female	22 (21.78)	26 (25.49)	
HBV coinfection	19 (18.81)	4 (0.04)	0.001
HCV coinfection	11 (10.89)	1 (0.01)	0.003
TP coinfection	5 (0.05)	0 (0)	0.023

HBV, hepatitis B virus; HCV, hepatitis C virus; TP, *Treponema pallidum*.

TABLE 2. GENOTYPE AND ALLELE FREQUENCIES OF C868T CD4 GENE POLYMORPHISM BETWEEN HIV-1 INFECTORS AND HEALTHY CONTROLS

Genotypes	Overall				Men				Women			
	Controls, n = 102 (%)	Cases, n = 101 (%)	OR (95% CI) ^a	p ^a	Controls, n = 76 (%)	Cases, n = 79 (%)	OR (95% CI) ^a	p ^a	Controls, n = 26 (%)	Cases, n = 22 (%)	OR (95% CI) ^a	p ^a
CC	96 (94.11)	91 (90.10)	1.00 ^{ref}		72 (94.74)	71 (89.87)	1.00 ^{ref}		24 (92.31)	20 (90.91)	1.00 ^{ref}	
CT	6 (5.88)	9 (8.91)	1.56 (0.68–3.58)	0.296	4 (5.26)	7 (8.86)	1.44 (0.39–5.33)	0.585	2 (7.69)	2 (9.09)	2 (0.30–13.25)	0.472
TT	0 (0)	1 (0.99)	—	0.999	0 (0)	1 (1.27)	—	1.000	0 (0)	0 (0)	—	—
Dominant model	6 (5.88)	10 (9.90)	1.77 (0.62–5.08)	0.291	4 (5.26)	8 (10.12)	1.94 (0.55–6.79)	0.300	2 (7.69)	2 (9.09)	2 (0.30–13.25)	0.472
Recessive model	0 (0)	1 (0.99)	—	1.000	76 (100)	78 (98.73)	—	1.000	26 (100)	22 (100)	—	—
C allele	198 (97.1)	191 (94.55)	1.00 ^{ref}		148 (97.37)	149 (94.30)	1.00 ^{ref}		50 (96.15)	42 (95.45)	1.00 ^{ref}	
T allele	6 (2.9)	11 (5.45)	1.34 (0.72–2.48)	0.167	4 (2.63)	9 (5.70)	1.713 (0.48–6.11)	0.407	2 (3.85)	2 (4.55)	2 (0.30–13.25)	0.472
P _{HWE}	0.759	0.175										

^aAdjusted by age and gender; dominant model: TT + CT versus CC; recessive model: TT versus CC + CT.

TABLE 3. GENOTYPE AND ALLELE FREQUENCIES OF CD4 C868T POLYMORPHISM IN THE HEALTHY CONTROL SUBJECTS IN THE PRESENT STUDY AND FROM THE HAPMAP PROJECT

Genotypes	Present study, n = 102 (%)	ASW, n = 98 (%)	HCB, n = 86 (%)	JPT, n = 170 (%)	GIH, n = 176 (%)	YRI, n = 226 (%)
CC	96 (94.1)	64 (65.3)	78 (90.7)	148 (87.1)	174 (98.9)	134 (59.3)
CT	6 (5.88)	28 (28.6)	8 (9.3)	22 (12.9)	2 (1.1)	76 (33.6)
TT	0 (0)	6 (6.1)	0 (0)	0 (0)	0 (0)	16 (7.1)
p		<0.001	0.414	0.067	0.055	<0.001
C	198 (97.1)	156 (79.6)	164 (95.3)	318 (93.5)	350 (99.4)	334 (76.1)
T	6 (2.9)	40 (20.4)	8 (4.7)	22 (6.5)	2 (0.6)	108 (23.9)
p		<0.001	0.383	0.071	0.056	<0.001

ASW, African ancestry in Southwest United States; HCB, Han Chinese in Beijing; JPT, Japanese in Tokyo; GIH, Gujarati Indians in Houston, Texas; YRI, Yoruba in Ibadan.

are shown in Table 2. The frequencies of the CC, CT, and TT genotypes of this variant were 90.10%, 8.91%, and 0.99% in cases and 94.11%, 5.89%, and 0.00% in controls, respectively, and all conformed to the Hardy–Weinberg equilibrium ($p=0.175$ and $p=0.759$). No significant differences in the genotype distributions of this polymorphism among HIV-1 patients and controls were observed. Binary logistic regression analyses, adjusted by age and gender, did not indicate an association of the C868T polymorphism with risk of HIV-1 infection. In addition, the dominant genetic model TT+CT versus CC and the recessive model TT versus CC+CT were also not found to be associated with the risk of HIV-1 infection. Furthermore, when analyses of genotype and allele frequencies were stratified by gender, similar nonsignificant results were obtained.

Considering that the CD4 genetic background may be different between various populations, the genotype and allele frequencies of the C868T polymorphism in our control group were further compared with those in different ethnicities from the Haplotype Map (HapMap) project (www.ncbi.nlm.nih.gov/snp/), including African ancestry in Southwest United States (ASW), Han Chinese in Beijing (HCB), Japanese in Tokyo (JPT), Gujarati Indians in Houston, Texas (GIH), and Yoruba in Ibadan (YRI). The data shown in Table 3 suggest that the distribution of the C868T polymorphism in the present study is significantly different from those of some ethnicities included in the HapMap Project. Lower detection rates of the TT genotype (0%) and T allele (2.9%) and higher detection rates of the CC genotype (94.1%) and C allele (97.1%) were observed in the present study, similar to the frequencies observed in healthy HCB, JPT, and GIH. Conversely, the observed frequencies of genotype TT and allele T and the rate of CC genotype and C allele in the ASW and YRI populations were, respectively, significantly higher and significantly lower (both $p<0.001$).

Discussion

To our knowledge, this is the first study to evaluate the association between the CD4 C868T polymorphism and risk of HIV-1 infection in a Chinese population. However, rather than observing an increase in HIV-1 acquisition, as hypothesized, a null association was observed between the C868T SNP genotype and allele and an individual's susceptibility to HIV-1 infection, in both the overall population and the subgroup analysis. These findings are inconsistent with those of

previous studies in which an increased risk of HIV-1 acquisition was observed in infants²⁴ and female commercial sex workers,²⁵ suggesting that the CD4 C868T polymorphism may not be an important factor contributing to the risk of HIV-1 infection, at least in the Chinese population.

The fact that the same SNP plays contradicting roles in the same disease is not surprising given the various genetic backgrounds among diverse ethnic populations. Evidence from the comparison of genotype and allele frequencies between the healthy control subjects in the present study and those from the HapMap project can partly account for this effect. According to the results presented herein, the C868T TT genotype and T allele frequencies in the control group were 0% and 2.9%, respectively. Nevertheless, in the ASW and YRI populations, the TT genotype accounts for 6.1% and 7.1% and the T allele for 20.4% and 23.9%, respectively, of the total study subjects, which were significantly higher than those in the present study as well as those in the HCB, JPT, and GIH populations from the HapMap project. It should also be noted that the genotype distributions of the ASW and YRI populations were similar to those in the Kenyan female commercial sex workers (TT: 10.3% and T: 17.2%) included in the study by Oyugi *et al.*²⁵; these similarities may be due to their common African ancestry. The frequency of the C868T mutation has also been observed to be distinct between African Americans (20%) and whites (<1%).²⁸ Thus, the low mutation rate of the CD4 C868T SNP detected in the present study may be the major factor account for the observed lack of association.

Another possible explanation for the current results is that other genetic polymorphisms may have a stronger effect on HIV-1 acquisition and may mask the mild influence of C868T; such polymorphisms include HLA-B27^{16,17} and HLA-B57,¹⁸ which have been found to contribute to delayed HIV-1 disease progression. It is also possible that CD4 C868T is in linkage disequilibrium with other SNPs, which are the actual predisposing alleles, similar to the role of the CCR2-V64I allele in delaying disease progression and its association with a CCR5 promoter mutation.²⁹ Since other related SNPs were not genotyped, the possible effect could not be assessed.

Other factors, such as the limited sample size, may have also had an impact on the null results given that the strength of an association between a certain polymorphism and a disease is partially dependent on the sample size achieved; thus, the small sample size is inadequate to draw a precise conclusion. In

addition, variations in the use of antiretrovirals may also alter the effect of host genetics on HIV-1 transmission, as observed in a recent study of an HIV-1 mother-to-child transmission population administered preventive antiretrovirals.³⁰

These results further suggest that demographic or behavioral variations might play a role in the observed differences in HIV acquisition vulnerability, although no demographic or behavioral variations related to the *CD4 C868T* SNP have been found to date.³¹

In summary, this study demonstrates a null association between the *CD4 C868T* genetic polymorphism and an individual's susceptibility to HIV-1 acquisition in a Chinese population. Nevertheless, these results are in conflict with those previously observed in two Kenyan studies, the motives for which remain unknown. Thus, further studies are warranted, especially in large cohorts considering various ethnic backgrounds, genetic linkage disequilibrium, and demographic characteristics.

Sequence Data

The nucleotide sequence of *CD4 C868T* polymorphism has been submitted to GenBank with the accession number rs28919570.

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Author Disclosure Statement

No competing financial interests exist.

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