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Original Article

Genetic polymorphisms of *Trim5a* are associated with disease progression in acutely and chronically HIV-infected patients

Xin Sun[1*], Wei Li[1*], Wenzhen Liu[2], Rui Wang[1], Qunhui Li[1], Hao Wu[1]

[1]Minimally Invasive Therapy Center of Liver Cancer, Beijing You'an Hospital, Capital Medical University, 8 Xitoutiao Youwai St, Fengtai District, Beijing 100069, P. R. China; [2]Department of Comprehensive Medicine, Baoding Hospital for Infectious Diseases, Baoding, Hebei Province, China. [*]Equal contributors.

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Abstract: Background: The tripartite interaction motif 5a (*Trim5a*) plays critical roles in restricting various kinds of retroviruses in different species. It has been shown that *Trim5a* could inhibit HIV-1 inhibition *in vitro*. Methods: In this study, 16 SNPs of *Trim5a* gene were screened in 236 acutely HIV-infected patients (169 common type (CT) patients and 67 patients with rapid disease progression). In addition, they were screened in 162 chronically HIV-infected patients (147 common type patients and 15 long-term non-progressors (LTNP)). The potential effects of polymorphisms at *Trim5a* genes on HIV-infection disease progression were analyzed. Results: Among all tested SNP sites, 3 SNPs (rs3824949, rs2291841 and rs11038628) were identified to be associated with rapid disease progression in acutely HIV-infected patients. Carriage of rs3824949 allele G, rs2291841 allele C or rs11038628 allele T associated with rapid disease progression. In chronically HIV-infected patients, Patients carrying rs3802981 allele C or rs3802980 allele A had increased opportunity to be LTNP. We also found that greater age was associated with disease deterioration. Conclusions: Different genetic polymorphisms of *Trim5a* may have an impact on the clinical course of both acute and chronic stages of HIV-infection.

Keywords: HIV-1, *Trim5a*, genetic polymorphisms, disease progression

Introduction

Human immunodeficiency virus-1 (HIV-1), as a pathogen that damages the human immune system and causes acquired immune deficiency syndrome (AIDS), remains a major concern worldwide due to the lack of effective cure and vaccine after 30 years of efforts. Recent research on host genetic variations contributes to better understanding of disease progression rates and spontaneous clearance of the virus and provides useful information for developing novel strategies for clinical diagnosis and therapy. Early host genetic variation studies targeting candidate genes relevant to HIV-1 infection together with recent genome-wide association studies (GWAS) of the whole genome of HIV-1 infected and non-infected people have identified multiple important host polymorphisms associated with HIV-1 infection, pathogenesis and disease progression [1-5]. However, different studies published in this area report contradictory results and only variants in the human leukocyte antigen (HLA) region and the HIV-1 co-receptor CCR5 have produced results that have been consistently replicated in multiple studies [1].

Recently, the tripartite interaction motif 5a (*Trim5a*) has been repeatedly reported to be part of the intrinsic immunity that fights against retroviral infections [1, 2]. In previous genetic studies, it has been reported that genetic variations in *Trim5a* played critical roles in specific viral invasion in different species [3-7]. In term of HIV infection, publications have shown that *Trim5a* gene polymorphism may have potential roles in HIV-1 susceptibility [8-10] and clinical course of the infection [4]. However, the conclusion still cannot be drawn on the roles of *Trim5a* gene polymorphism due to insufficient studies on this topic.

Table 1. Primers

	Forward	Reverse
rs3802981	ACGTTGGATGATCATGCCACTTCTTCTGAC	ACGTTGGATGCGAAAAAGGGCACCTTTTCT
rs3802980	GGAACCGCAGGAAATTCTTGCTCAC	CTCAGGGCAGGAAAGTGAAAGATAA
rs11821656	ACGTTGGATGCATCCCAGAAGACTCATGTG	ACGTTGGATGATGTCCCATCTGCAGAAACC
rs11038628	CCCACAATACCTTTTTATGACGCCATCCACA	CCTAGGAAGAAGAGAGAAAACATCAATTAAG
rs885002	GGCATTATCTGGCACATGCAGTTAAACAAGAA	GACAACAGGGTACAGAAGTATGTGCATGA
rs10769175	ACGTTGGATGAACAGGAGTGGGTTGAGATG	ACGTTGGATGTCCTCACCATGAGTAGACTG
rs10838534	ACGTTGGATGGGTGACACAGCAGTTATCTT	ACGTTGGATGTAGATATGAAGATATATAGC
rs3740996	ACGTTGGATGTTCTGCCAAGCATGCCTCAC	ACGTTGGATGCAGCTACTCTCTCCTTTGTC
rs7122620	ACGTTGGATGGCTCAAAACTTGGGAAAGAG	ACGTTGGATGAACGGATGTTTATGAAGGGC
rs10734538	ACCCCCTCCACACTGTACCCCCGCAGCTTTC	GTTTCATGAAATCAGGTAGGGGGCTTTTGCA
rs11601507	ACGTTGGATGTCCTGAGACCGCTCACAAAG	ACGTTGGATGACGCCATGGAGAGAAACTTC
rs3740995	ACGTTGGATGTTCTGCCAAGCATGCCTCAC	ACGTTGGATGCAGCTACTCTCTCCTTTGTC
rs2291841	ACGTTGGATGAACCCTGGGGAAAGTAATGC	ACGTTGGATGAGGAAGTAGTGACTGAGTGC
rs6578672	TTTATTTTGCTTTTAATTGACAAATAATAAAT	TACATATTTATGTGGTACAGTGTGATGTTTTG
rs10838525	ATCCCAGTCTCTTACTTGGTACTCC	GGGCAACCTCCTCTGTGAGGAACGT
rs3824949	ACGTTGGATGCCTCCTCCTTTACATTAACC	ACGTTGGATGAACAAGAGGAACCTCAGCAG

Based on the accumulated information, there is limited information on the influence of *Trim5a* polymorphisms on AIDS progression and there are no published studies on *Trim5a* polymorphisms in Chinese population. The lack of information on the association of genetic polymorphisms of *Trim5a* with AIDS disease progression rate in Chinese patients and its relationship to other factors such as co-infections and aging led to our current study. In this study, SNPs of *Trim5a* were selected from either HapMap project or published literatures on *Trim5a* polymorphisms relevant to viral diseases. We collected blood samples from newly identified HIV-1 infected patients with different $CD4^+$ T cell counts in Beijing, China, and *Trim5a* gene polymorphisms were investigated. The aim of this study is to investigate the potential associations between *Trim5a* gene polymorphism and disease progression in patients infected with HIV in China. We also looked at the association of these SNPs with concomitant co-infections and age.

Materials and methods

Study participants

The study population was enrolled in the Beijing PRIMO cohort study of primary HIV-1-infected individuals between Jan 2010 and May 2014. The cohort is based on an ongoing, open cohort of HIV-1 seronegative men who have sex with men (MSM) who are provided with risk-education counseling before being tested for HIV antibody and HIV-1-RNA every 2 months. As of May 2014, a total of 236 patients with primary (acute) HIV-infection (21 with an indeterminate Western blot, 188 with a negative test followed by a positive one, and 27 ELISA negative whereas HIV-RNA positive) and 162 chronically HIV-infected patients were recruited in this study. After seroconversion, clinical and laboratory measurements are taken at weeks 1, 2, 4, 8, and 12, then every 3 months. Patients with different $CD4^+$ counts were classified into three groups of >350 cells/μL, 200-350 cells/μL and <200 cells/μL. Blood samples were collected from patients before ART. Rapid progressors (RP) in acutely-infected patients were defined if a patient who failed to take ART had a blood CD4 count lower than 200/ul within 24 months. Long-term non-progressors (LTNP) in chronically HIV-infected patients were defined if a patient infected for more than 120 months without taking any antiviral therapy had a CD4 count never lower than 500/ul during the follow-up. There were totally 67 RP and 15 LTNP. Rest of the patients were defined as common type (CT).

The ethical approvals were obtained from the Human Ethics Committee, Beijing You'an Hospital, Capital Medical University, P.R. China. All involved subjects have signed a written informed consent form and agreed that their

Table 2. Baseline characteristics of acutely HIV-infected patients

Variables	Rapid progressor (RP) (n=67)	Common type (CT) (n=169)	*P* value
Age (years, mean ± SD)	32.16±8.75	30.63±7.71	0.338
Gender			
Male	40	96	
Female	0	0	
Race			0.911
Han	38	89	
Minority	2	7	
Education			0.496
Middle school and below	14	39	
High school	12	33	
College and above	14	24	
History of MSM			0.909
<3 yrs	25	59	
≥3 yrs	15	37	
Number of sex partners			0.825
<4	20	46	
≥4	20	50	
Condom use			0.532
<70%	16	44	
≥70%	24	52	
Co-infected with STD			0.352
Yes	22	61	
No	18	35	
HIV subtype			0.918
CRF01_AE	23	54	
B	13	30	
Others	4	12	
CD4 setpoint			0.002
Log <5	15	77	
log ≥5	10	10	

MSM: men who have sex with men; STD: sexual transmitted diseases.

blood samples and medical records would be used for this study.

SNPs identification and selection

Trim5a SNP candidates were searched using NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), and the international HapMap project (www.hapmap.org). Published related literatures were also searched. The inclusion criteria of SNPs are as follows: (1) SNPs with a minor allele frequency (MAF) >5% in Chinese population, (2) SNPs located at the 5'-flanking region, 3'-flanking region, or exons with amino acid changes, (3) reported SNPs associated with HIV disease progression. There were totally 16 SNPs selected and they were: rs3802981, rs3802980, rs11821656, rs11038628, rs885002, rs10769175, rs10838534, rs3740996, rs3824949, rs7122620, rs10734538, rs11601507, rs3740995, rs2291841, rs6578672, and rs10838525. The primers used in this study were listed in **Table 1**.

DNA genotyping

Genotyping was performed by the iPLEX system (MassARRAY SNP Genotyping; Sequenom, SanDiego, CA, USA). Total DNAs were extracted from peripheral blood using Whole Blood DNA extraction kits (BioTeke, China). DNA samples were blind coded then tested using a 384 format Spectro-CHIPTM microarray (Sequenom). A matrix-assisted laser desorption/ionization time-of-flight mass spectrometer was used for data acquisitions from the Spectro-CHIPTM. Results were analyzed using Sequenom's MassARRAY RTTM software (Sequenom). Samples were amplified, and the ampli-cons were subjected to direct sequencing using the Big Dyes Termination version 1.1 kit (ABI) and the ABI Prism 3730 genetic analyser (Applied Biosystems, Foster City, CA, USA). Sequence results were analyzed using Polyphred software (Applied Biosystems). Results of the iPLEX system and direct sequencing were compared.

Statistical analysis

The statistical analysis was conducted using SPSS software version 17.0 (SPSS, Chicago, IL). Three groups were defined based on $CD4^+$ T cell count values (>350, 200-350 and <200/ul) and used for genetic association analysis. Fisher's exact test was applied to analyze association between disease progression and factors such as genetic polymorphisms, gender and etc. In the univariate and multivariate logistic regression analysis, all the differences

Table 3. Baseline characteristics of chronically HIV-infected patients

Variables	long-term non-progressor (LTNP) (n=15)	Common type (CT) (n=147)	*P* value
Age (years, mean ± SD)	46.68±7.25	39.25±6.50	0.517
Duration of infection	19.05±1.25	17.31±1.71	0.146
Gender			
Male	9	17	0.572
Female	13	18	
Race			
Han	22	35	
Others	0	0	
Route of transmission			<0.001
Blood donation	22	17	
Others	0	18	
Co-infected with HCV			0.071
Yes	21	26	
No	1	9	
Co-infected with HBV			0.518
Yes	0	2	
No	22	33	

Table 4. Distribution of SNP genotypes in each study group

SNPs	Genotypes	Total (n (%))	RP (n (%))	CT (n (%))	*P* value
rs3824949	GG	38 (28.5)	17 (39.5)	21 (22.1)	0.045
	CG	62 (46.4)	16 (42.1)	46 (48.4)	0.139
	CC	33 (24.8)	5 (11.2)	28 (29.4)	0.029
	MAF (C)*	0.481	0.342	0.537	0.018
rs2291841	AA	62 (46.6)	11 (28.9)	51 (53.7)	0.021
	AC	60 (45.1)	23 (60.5)	37 (38.9)	0.089
	CC	11 (8.3)	4 (10.5)	7 (7.4)	0.038
	MAF (C)*	0.308	0.323	0.268	0.035
rs11038628	CC	45 (33.8)	10 (26.3)	35 (36.8)	0.233
	CT	66 (49.6)	17 (44.7)	49 (51.6)	0.082
	TT	22 (16.5)	11 (28.9)	11 (11.6)	0.032
	MAF (T)*	0.414	0.406	0.374	0.047

*: Minor allele frequency; RP: rapid progressor, CT: common type, MAF: minor allele frequency.

between or among the groups with a *P* value of <0.05 were considered statistically significant. Quantitative data were also analyzed by the chi-square test and odds ratio (OR) with 95% confidence intervals (95% CI). Genotype frequencies were obtained by direct counting. Kaplan Meier and Cox proportional hazard analysis were conducted to investigate the correlation between different genotypes of SNP sites in *Trim5a* gene and disease progression. The end point of this analysis is blood CD4 T cell count below 200/ul.

Results

Patient characteristics

The basic information of characteristics on 398 enrolled patients (236 acutely HIV-infected and 162 chronic patients) is summarized in **Table 2**. The frequency-matching was adequate in age, gender, races, education sexual behaviors, and viral genotypes (all P>0.05). The CD4 set-points were significantly different between RP and CT groups (P=0.002), which was consistent to previous publications upon RP patients. Among all involved patients, the successful genotyped rates for all SNPs tested were above 95%. The MAF of all selected SNPs were >5% according to the frequencies recorded in NCBI dbSNP database. The genotype distribution of *Trim5a* SNPs showed no deviation from the Hardy-Weinberg equilibrium.

Co-infection of other pathogens (HBV, HCV, syphilis and other sexual transmitted pathogens) were investigated and found in 272 (68.3%) subjects. The most common co-infection with HIV-infection was syphilis (146/398, 36.7%), followed by HBV (35/398, 8.8%) and HCV (12/398, 3.0%). However, no statistically significant difference in concomitant sexual transmitted diseases was identified between RP and CT groups (P=0.352) (**Table 2**).

In the other arm of this study, chronically HIV-infected patients were included and their basic characteristics are summarized in **Table 3**. Among all compared parameters, only route of

Table 5. Distribution of SNP genotypes in each study group of chronically HIV-infected patients

SNPs	Genotypes	Total (n (%))	LTNP (n (%))	CT (n (%))	*P* value
rs3802981	CC	11 (11.3)	7 (31.8)	4 (11.8)	0.031
	CT	35 (61.4)	14 (63.6)	20 (58.8.0)	0.298
	TT	11 (11.3)	1 (4.5)	10 (29.4)	0.008
	MAF (T)*	0.5	0.364	0.588	0.014
rs3802980	GG	14 (24.6)	3 (13.6)	11 (32.4)	0.031
	AG	32 (56.1)	12 (54.5)	19 (55.9)	0.192
	AA	11 (19.3)	7 (31.8)	4 (11.7)	0.011
	MAF (A)*	0.474	0.591	0.397	0.040

*: Minor allele frequency; LTPN: long-term non-progressor, CT: common type, MAF: minor allele frequency.

transmission was significantly different between the LTNP and CT groups (P<0.001).

Association of Trim5a gene polymorphisms with disease progression rate in acute phase of HIV infection

Among all tested *Trim5a* SNPs, we identified three SNPs associated with rapid disease progression (rs3824949, rs2291841 and rs11038628) (**Table 4**). By comparing to the reference genotype, patients carrying rs3824949 GG had significantly increased risk of rapid disease progression (OR=1.77, 95% CI=1.33-1.99, P=0.018). Patients carrying rs3824949 CC had reduced risk of rapid disease progression (OR=0.68, 95% CI=0.49-0.88, P=0.005). Carriage of G allele was associated with elevated risk of rapid disease progression (OR=2.57, 95% CI=1.59-2.98, P=0.002). For SNP rs2291841, patients carrying rs2291841 AC had significantly increased risk of rapid disease progression (OR=2.31, 95% CI=1.56-2.76, P=0.003). Patients carrying rs2291841 AA had reduced risk of rapid disease progression (OR=0.63, 95% CI=0.41-0.79, P=0.035). Carriage of C allele was associated with elevated risk of rapid disease progression (OR=2.89, 95% CI=2.31-3.25, P=0.004). For SNP r11038628, patients carrying r11038628 TT had significantly increased risk of rapid disease progression (OR=1.98, 95% CI=1.67-2.43, P=0.008). Patients carrying r11038628 CC had reduced risk of rapid disease progression (OR=0.58, 95% CI=0.21-0.77, P=0.032). Carriage of T allele was associated with elevated risk of rapid disease progression (OR=2.01, 95% CI=1.59-2.68, P=0.007).

Association of Trim5a gene polymorphisms with disease progression rate in chronic phase of HIV infection

In the second study arm targeting at chronically HIV-infected patients, we investigated 16 SNP sites and identified two sites associated with disease progression of HIV infection. Patients carrying rs3802981 C allele was associated with elevated chances of being LTNP (OR=3.21, 95% CI=2.59-3.82, P=0.014). For SNP rs3802980, carriage of A allele was associated with increased opportunity for patients to be LTNP (OR=1.71, 95% CI=1.39-1.97, P=0.040) (**Table 5**).

Effects of TRIM5a genotype on the Clinical Course of HIV-1 Infection

Kaplan Meier and Cox Proportional Hazard analysis was done with blood CD4 count <200/ul as the end point to investigate the effects of gene polymorphism in the *Trim5a* gene on disease progression in HIV-1 infection. An accelerated disease progression was observed in the group carrying G allele at rs3824949 (**Figure 1A**). Patients with C allele at rs2291841 had a more rapid disease progression if compared to those with A allele (**Figure 1B**). For SNP site rs11038628, the group carrying T allele showed an accelerated progression when blood CD4 count <200/ul was used as the end point (**Figure 1C**).

Advanced age was associated with rapid disease progression

Other factors including co-infection with sexual transmitted diseases (STD) and age were also analyzed for their associations with AIDS progression. Due to the limited sample size, we were unable to compare many parameters from each patient group. Only age and co-infection with STD were involved in the analysis. Our study found no correlation between co-infection with STD and AIDS progression. However, we did find a correlation between greater age and disease deterioration in acutely HIV-infected patients, with a higher proportion (152/236, 64.4%) of patients with $CD4^+$ T cell count

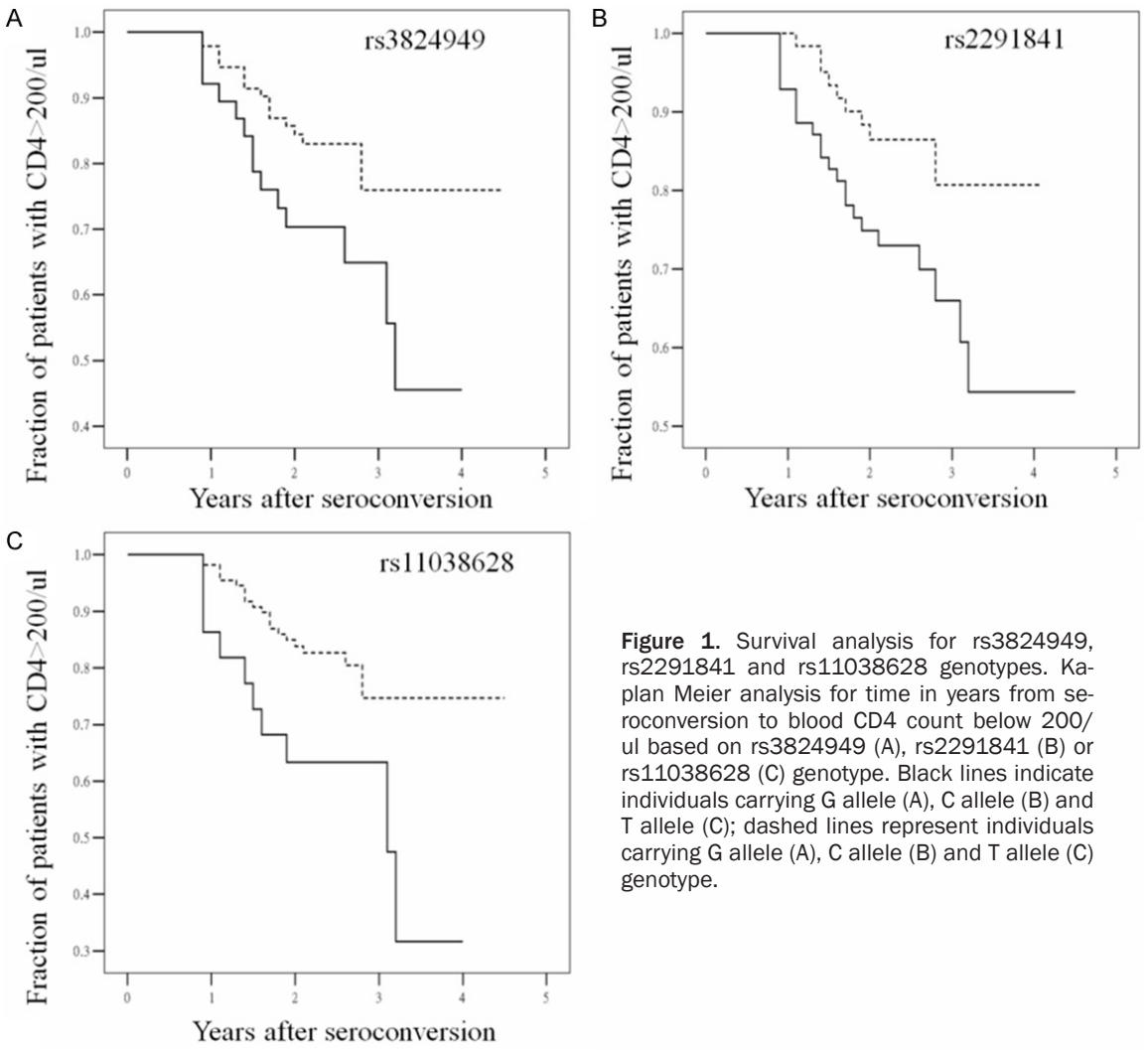

Figure 1. Survival analysis for rs3824949, rs2291841 and rs11038628 genotypes. Kaplan Meier analysis for time in years from seroconversion to blood CD4 count below 200/ul based on rs3824949 (A), rs2291841 (B) or rs11038628 (C) genotype. Black lines indicate individuals carrying G allele (A), C allele (B) and T allele (C); dashed lines represent individuals carrying G allele (A), C allele (B) and T allele (C) genotype.

below 200 cells/μL in patients >30 years old than in those ≤30 years old (P=0.032).

Discussion

HIV-1 infection is currently one of the most significant infectious diseases in the world. TRIM5 has been repeatedly identified as one of the key players in host responses to HIV-infection [9-11]. In our study, we investigated the correlations of SNPs of *Trim5a* gene and disease progression of HIV infections. We discovered 3 SNPs in acutely 2 SNPs in chronically HIV-infected patients (**Tables 2**, **3**). Our results from this study also indicated that HIV-1 infection in the MSM patient cohort in China tended to affect younger people (53.7% in age group <30 years old) more than older people in this cohort.

HIV-infected patient groups are classified based on clinical pattern of AIDS progression [12]. AIDS rapid progressors defined as those with symptomatic HIV-1 infection within 3 years, as indicated by two or more $CD4^+$ T cell measurements below 350 cells/μL without ART, immunodeficiency, and/or had AIDS or related death. Moderate or typical progressors are patients with AIDS developed around 3-10 years period. Long term non progressors are the 2-5% of HIV-1 infected patients who do not show symptoms of AIDS for a long period of time [13-16]. These natural uneven susceptibilities of host to HIV-1 infection indicate the genetic variations are important factor influencing HIV-1 infection and AIDS progression status [17]. In this study, we have recruited newly HIV-1 infected patients at around 3 years period and classified patients into three different groups based on $CD4^+$ T cell counts: (A) $CD4^+$ T cell count above 350 cells/μL which no need ART; (B) $CD4^+$ T cell count below 350 cells/μL

which are required ART; and (C) $CD4^+$ T cell count below 200 cells/μL which need more attention. All the blood samples were collect before ART. Genetic variations were then studied on these groups to identify the association between polymorphisms of *Trim5a* gene and AIDS progression. Co-infections and age were also considered.

Genetic variations of *Trim5a* have been reported to play roles in various processes of HIV infection. SNP loci associated with disease progression have been described in studies, but the conclusions are controversial, especially in Chinese population [3, 4, 9, 10]. Here we reported SNP rs3824949, rs2291841 and rs11038628 are associated with disease progression in acute phase of HIV infection. SNP rs3802981 and rs3802980 were linked to disease progression in chronically HIV-infected patients. These are novel discoveries that may contribute to clinical diagnosis and management of HIV infection. However, the relatively small sample size may limit the validity of our conclusions. Study with a larger population is required to confirm our data.

An earlier study of patients with haemophilia in UK suggested there is a relationship between age and AIDS development and survival. Greater age is known to be associated with faster AIDS progression and shorter survival time [18]. Our study found that greater age was associated with faster AIDS deterioration, which is consistent with this previous report.

In summary, we identified 2 *Trim5a* SNPs associated with disease progression in acutely HIV-infected patients, and another 2 SNPS associated with disease progression in chronically HIV-infected patients. Aging was also found to be a factor associated with AIDS deterioration. Genetic variation of *Trim5a* gene may be used as a marker to early differentiate different types of HIV-infected patients in term of disease progression.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hao Wu, Center for Infectious Diseases, Beijing You'an Hospital, Capital Medical University, 8 Xitoutiao Youwai St, Fengtai District, Beijing 100069, P. R. China. Tel: 86 10 83997162; Fax: 86 10 83997644; E-mail: wuhaodoc@126.com

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