Global human genetics of HIV-1 infection and China

Tuo Fu ZHU [1-3,*], Tie Jian FENG [4], Xin XIAO[5], Hui WANG[6], Bo Ping ZHOU[6]

[1]*Departments of Laboratory Medicine, University of Washington School of Medicine, Seattle, WA 98195-8070, USA*
[2]*Departments of Microbiology, University of Washington School of Medicine, Seattle, WA 98195-8070, USA*
[3]*Programs in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, WA 98195-8070, USA*
[4]*Shenzhen Center for Disease Control and Prevention, Shenzhen, China,*
[5]*Jinan University, Guangzhou, China*
[6]*Shenzhen Municipal Hospital of Infectious Diseases, Shenzhen, China.*

ABSTRACT

Genetic polymorphisms in human genes can influence the risk for HIV-1 infection and disease progression, although the reported effects of these alleles have been inconsistent. This review highlights the recent discoveries on global and Chinese genetic polymorphisms and their association with HIV-1 transmission and disease progression.

Keywords: HIV, genetic polymorphisms, China.

INTRODUCTION

HIV-1 infection results in a variety of clinical outcomes. The majority of HIV-1 infected individuals progress to AIDS within 5 to 10 years, some progress rapidly to AIDS (termed rapid progressors) while others progress to AIDS slowly (slow progressors). A small number of HIV-1 infected individuals, termed long-term non progressors (LTNP), remain clinically healthy for more than a decade after infection [1-4]. There are also some individuals who remain seronegative despite high risk and/or multiple exposures to HIV-1. These exposed seronegatives (ES) include infants born to HIV-1 infected mothers [5-7], commercial sex workers in epidemic areas [8-25], hemophiliacs who received HIV contaminated factor VIII preparations [26, 27], and sexual partners of known HIV-1 infected persons [28-33]. Understanding the mechanisms that account for slower disease progression in LTNP and the protection against HIV-1 infection observed with ES is important for the development of more potent therapeutic regimens and a vaccine. It is likely that both viral and host factors may contribute to these outcomes. Acquired immune responses, including cellular [5, 8-11, 14, 15, 17, 26, 28, 34-37] and humoral [10, 16, 20, 38-44] responses to HIV-1, may play an important role in protecting against and controlling HIV-1 infection. Significant studies in the past few years have also demonstrated that innate immunity including genetic polymorphisms in host genes can affect the risk for HIV-1 infection and disease progression (Tab. 1), although the effect of these alleles has been inconsistent [32, 45-55] (reviewed in [56]). Here, we review global and Chinese studies on human genetic polymorphisms and their association with HIV-1 infection.

VARIATION IN THE CCR5 CODING REGION

HIV-1 requires CD4 as its primary receptor and a chemokine receptor as a co-receptor to enter cells [57-59]. Based on the co-receptor utilization, HIV-1 strains can be classified as "R5 tropic HIV-1" that primarily utilize C-C chemokine receptor 5 (CCR5) and "X4 tropic HIV-1" that use C-X-C chemokine receptor 4 (CXCR4) [60]. R5 tropic viruses dominate in HIV-1 transmission from person to person, while X4 HIV-1 strains are frequently found during the later stages of HIV-1 infection [61]. CCR5-△32, an allele of CCR5 that contains a 32 bp deletion, codes for a nonfunctional co-receptor and cell lines homozygous for CCR5-△32 are resistant to R5-virus but

*Correspondence: Tuo Fu ZHU
Department of Laboratory Medicine, University of Washington School of Medicine, Box 358070, 1959 N.E. Pacific Street, Seattle, WA 98195-8070.
For Federal Express: Department of Laboratory Medicine, University of Washington School of Medicine, 960 Republican Street, Seattle, WA 98109.
Tel: 206-732-6079; Fax: 206-732-6109;
E-mail: tzhu@u.washington.edu

individuals that are CCR5-△32 homozygotes (people who inherited the CCR5-△32 from both parents) are resistant to HIV-1 infection, indicating that genotype CCR5-△32 is highly protective against HIV-1 infection [45-50, 54]. However, this protection is not absolute because rare individuals homozygous for CCR5-△32 are infected with HIV-1 strains that may utilize another co-receptor, such as CXCR4 [64-68]. Furthermore, homozygous CCR5-△32 is found only in 1% of the general population of Caucasians, but not in Africans, Asians or other ethnic groups [45-50, 54], and the majority of highly exposed yet uninfected individuals have two normal CCR5 alleles (called wild-type, or wt). Similarly, we found CCR5-△32 homozygotes in 1.0% (7 out of 705) of HIV-1 seronegative individuals and 3.1% (3 out of 97) of ES.

CCR5-△32 heterozygotes (people who inherited the CCR5-△32 allele from one parent and a functional CCR5 allele from the other parent) are susceptible to HIV-1 infection; most studies have not supported an association of the heterozygous CCR5-△32 genotype with reduced HIV-1 transmission risk for adult and pediatric populations [47-49, 69-73]. However, our recent study suggests that individuals with the combination of heterozygous CCR5-△32 and P1 CCR5 promoter genotype (see below) are relatively resistant to HIV-1 transmission [74]. According to most reports [47-49, 55, 75-81] but not all [82, 83], individuals with heterozygous CCR5-△32 progress from HIV-1 infection to AIDS more slowly than persons with two normal CCR5 alleles.

CCR5-△32 homozygotes make up approximately 1-3% of northern European populations; CCR5-△32 heterozygotes and wt individuals comprise approximately 14% and 83%, respectively, of the remainder [46, 84]. The polymorphism demonstrates a decreasing north-south cline across Eurasia and is largely absent in African, Asian and Oceanic populations [84-86], interestingly this distribution may have become fixed 700 years ago in northwestern Europe [86]. Indeed, studies to date indicate that CCR5-△32 mutant alleles were absent or infrequent in Chinese [87-93]. Homozygous genotypes have not been identified in Chinese populations, while heterozygous CCR5-△32 is extremely rare or absent in most Chinese populations studied [87-93]. There is no evidence that CCR5-△32 influences the HIV-1 transmission or epidemic in China.

Wang *et al* in collaboration with us [87] conducted a large scale investigation on human genetic polymorphisms in three cohorts of Chinese: 1) 3165 indigenous healthy subjects representing eight ethnic groups: Han (n = 1406), Uygur (n = 316), Mongolia (n = 134), Hui (n = 386), Tibetan (n = 330), Zhuang (n = 378), Dai (n = 101), and Jingbo (n =114); 2) 330 HIV-1 infected (86 subjects infected by sexual transmission and 198 subjects infected by HIV-1 contaminated blood or by sharing injection equipment; the remaining 46 subjects said nothing about HIV-1 transmission); and 3) 474 HIV-1 uninfected Han Chinese belonging to one of two HIV-1 high-risk groups: intravenous drug users (n = 215) and individuals with sexually transmitted diseases (n = 259). Heterozygous CCR5-△32 genotypes were found in 3 out of 1254 Han Chinese, with an allele frequency of 0.00119. Findings from this study and others [88, 89] show that CCR5-△32 mutants do occur in Chinese population (all are individuals with heterozygous CCR5-△32), and can be inherited at a very low frequency [87-89].

VARIATION IN CCR5 PROMOTER REGION

Polymorphisms in the CCR5 promoter are associated with altered disease progression but not reduced transmission risk of HIV-1 infection [51, 94]. Of the ten alleles in the CCR5 promoter (CCR5P1 to CCR5P10), only homozygote CCR5P1 is associated with an accelerated progression (by approximately 4 years) to AIDS [51]. This acceleration of disease progression was most marked in the first 5 years of infection. McDermott *et al* reported that a point mutation, 59029A/G, which is linked to the CCR5P1 allele, accelerated progression to AIDS by 3.8 years [94]. However, there is no association between the CCR5P1 or 59029A promoter genotypes to either increased *in vivo* expression of CCR5 mRNA or cell surface proteins [51, 94]. Thus, the mechanisms of action for the CCR5P1 and 59029A promoter remain to be defined.

There is currently little data on the polymorphisms in the CCR5 promoter in Chinese populations. A study on 96 HIV negative Chinese individuals in Taiwan indicates that only CCR5P1 and P4 haplotypes were detected, and the P1/P1, P1/P4 and P4/P4 genotype frequencies were 21.0%, 41.1% and 37.9%, respectively [95]. The sequencing data confirmed the results of previous studies, showing that CCR5P1 exhibited complete linkage disequilibrium with a polymorphic allele 59029A present in the CCR5 promoter. Furthermore, fluorescence-activated cell sorter analysis revealed that, in the absence of the CCR2-64I mutation, individuals carrying CCR5P1 tended to express more surface CCR5 on monocytes and CD4+ cells. However, the association of the CCR5P1 with HIV-1 infection in Chinese populations is currently unknown.

VARIATION IN THE CCR2 CODING REGION

CCR2 is a minor HIV-1 coreceptor. The gene that codes for this chemokine receptor has a variant allele causing a Val-Ile switch at amino acid position 64 (CCR2-64I) in the first transmembrane domain of CCR2. Unlike the

CCR5-△32 allele that inactivated the major HIV-1 coreceptor, CCR2-64I causes a conservative change in a nonexposed portion of a coreceptor of questionable physiologic relevance [68, 96, 97]. CCR2-64I is common and found in 10% of Caucasians, 15% of African-Americans, 25% of Asians and 17% of Hispanics [50]. Epidemiologic studies by Smith *et al* first demonstrated the association of CCR2-64I with delayed HIV-1 disease progression [50], which was confirmed by most subsequent studies [73, 98, 99], but not by others [82, 100, 101]. CCR2-64I is not associated with reduced risk for HIV-1 infection [50]. The mechanism for the association of CCR2-64I with delayed disease progression has not been elucidated despite significant attempts to do so [98, 102, 103].

The frequencies of heterozygous and homozygous CCR2-64I in Chinese were 13-35% and 1-8%, respectively, varying from study to study [87-93]. There is no difference in the frequencies of both heterozygous and homozygous CCR2-64I between HIV-1 infected and HIV seronegative individuals, suggesting no association of CCR2-64I with HIV-1 transmission in Chinese. There is also generally no evidence of association of CCR2-64I with disease progression in HIV-1 infected Chinese individuals [87-93]. The allelic frequency of CCR2-64I was about 20% (95% CI, 15~30%) [87-93], which is significantly higher than that in other ethnic groups including Caucasians. Furthermore the polymorphisms of CCR2-64I in the Han Chinese population were different from those in American Caucasians [87].

CCR2-64I was common in different ethnic groups in Chinese populations [87] (*f* range: 16.23%–28.79%), with the lowest frequency observed in the Jingbo (*f*=16.23%). The Dai, Hui, and Uygur ethnic groups had CCR2-64I allele frequencies similar to that of the Han group (*f* range: 19.15%~21.76%), but the Mongolia and Zhuang groups tended to have a higher frequency (*f* range: 23.41%~24.63%), with the highest frequency observed in the Tibetan population (*f*=28.79%). However, there was no significant differences among CCR2-64I allele and genotype frequencies when the HIV-1 infected group was compared with either the HIV-1 uninfected STD, IDU, or combined at-risk group (dominant model: OR = 0.99-1.08, $p>0.05$; recessive model: OR = 1.22-1.41, $p>0.05$, respectively).

VARIATION IN SDF1

SDF1 (Stromal-Derived Factor 1, also called CXCL12) is the primary ligand for the late-stage HIV-1 receptor CXCR4. Winkler *et al* reported a Gly-Ala transition at position 801 (with position 1 as the A of the initiation codon) of the mRNA for SDF-1b, one of the two isoforms of the CXCR4 chemokine ligand, and demonstrated that homozygosity for this SDF1-3'A allele was associated with delayed disease progression in an analysis of 639 seroincident subjects from four HIV cohorts [104]. Although this observation was confirmed by the French GRIV cohort at the limit of statistical significance (probability=0.05), other studies demonstrated contrastly that the SDF1-3'A homozygous genotype was associated with accelerated disease progression [73, 105]. Ultimately, an international meta-analysis of 19 prospective cohort studies and case-control studies from Europe and Australia demonstrated that SDF1-3'A homozygotes have no decreased risk for AIDS, or death after development of AIDS [55].

The SDF1-3'A allele was also common in different Chinese ethnic groups, with the highest frequencies observed in Chinese Han, Zhuang, and Hui (*f*=27.76%, 25.93%, and 24.87%, respectively) [87]. The SDF1-3'A allele frequency was significantly lower ($p<0.05$) among the Dai, Jingbo, Mongolia, Uygur, and Tibetan populations (20.30%, 17.70%, 19.10%, 20.02%, and 20.41%, respectively). There was a slight decrease in SDF1-3'A homozygotes and heterozygotes in the HIV-1 infected group compared with the healthy HIV-1 negative Han group (*f*=25.61%, 27.76%; $p=0.038$, respectively). After correction for multiple comparisons, this difference was not significant (dominant model: OR=0.84–0.95, $p>0.05$; recessive model: OR=1.28–1.30, $p>0.05$, respectively).

The above results are in general agreement with other studies in Chinese populations [88-93]. For example, we observed a similar frequency of SDF1-3'A in Shenzhen (26.9%, corresponding to 17.6~38.2% of 95% CI) with a mixture of ethnic Chinese groups. We found a weak association of SDF1-3'A with low viral load, and no association with disease progression after HIV-1 infection [106].

VARIATION IN RANTES

RANTES (regulated on activation normal T cell expressed and secreted) is one of the natural ligands for the chemokine receptor CCR5 and potently suppresses *in vitro* replication of the R5 strains of HIV-1 [107], which use CCR5 as a coreceptor. Two single nucleotide polymorphisms (SNP), -403G/A and -28C/G, in the promoter region of RANTES were initially identified by Liu *et al* in Japan [52]. The -403A-28G haplotype was shown to be associated with delayed disease progression in HIV-1 infected Japanese, but exerts no influence on the incidence of HIV-1 infection [52]. In European-Americans, the compound genotype -403G/A -28C/C was reported to be resistant to AIDS progression in one study [53], but not in another [54]. These RANTES polymorphisms have no effect on HIV-1 infection and disease progression in African-Americans [54]. Most recently, An *et al* have found

that 3 SNPs (-403A in the promoter, *In*1.1C in the first intron, and 3'222C in the 3' untranslated region) are associated with increased frequency of HIV-1 infection, and that the *In*1.1C allele or haplotypes display a strong association with rapid progression to AIDS among HIV-1 infected African-Americans and European-Americans [108]. These and other RANTES SNPs may also influence the varied epidemiology of HIV-1 infection throughout the world [54, 108].

There is relatively little information describing variation in the RANTES gene and the association with HIV-1 infection in Chinese populations [109, 110]. Liu *et al* [109] identified 6 genotypes of RANTES promoter -403 and -28 in the Han Chinese group. RANTES genotypes AC/AG, AC/GC, AG/GC, GC/GC were associated with reduced susceptibility to HIV-1 infection. However, there was no significant difference in the allele frequencies between people living with HIV-1 and HIV negative individuals. There were significant differences of RANTES *In*1.1C between HIV-1 infected and healthy individuals in males, suggesting that the *In*1.1C-bearing genotypes could increase susceptibility to HIV-1 infection. No such significance was found in females. A study by Zhao *et al* of 1082 Chinese blood donors from northern and southern China and 249 HIV patients from southern China indicated that Chinese AIDS patients, compared to seronegative adults, had a significantly higher frequency of the -403G allele and haplotype I, -403G/-28C ($p<0.05$), and a lower frequency of the -403A/A genotype ($p<0.01$). Symptomatic patients had a higher frequency of the -28G allele and a lower frequency of the -28C/C genotype ($p<0.01$). These results suggest that -403G may be associated with increased susceptibility to HIV infection, while -28G may be associated with advanced disease progression. The impact of these SNPs on HIV infection appears to be unique in Chinese, while a large scale study would be warranted to verify these findings.

VARIATION IN HLA

The HLA (human leukocyte antigen) region includes 128 expressed genes, of which, about 43 genes are associated with human immunity [111]. HLA class I (A, B and C) and II genes (IDR, DQ and DP) have considerable allele variation between individuals and populations, which provides a broad range for individual recognition of viral agents to which they have been exposed in the past, as well as those to which they have not [112]. Because different HLA alleles specify cell-surface molecules with specific motif recognition sites for infectious agents [113], differential HIV-1 peptide motif recognition can influence both the time interval from infection to AIDS [114] and the kinetics of HIV-1 adaptive escape from immune surveillance in an infected individual [115]. For example, Carrington *et al* demonstrated the association of heterozygosity of HLA alleles B35 and Cw4 with accelerated disease progression [116]. Two HLA alleles, HLA-B27 and HLA-B57 are associated with a delayed progression to AIDS [117, 118]. Activating the killer immunoglobulin-like receptors (KIRs) allele KIR3DS1, in combination with HLA alleles (HLA-Bw4) that encode molecules with isoleucine at position 80 (HLA-B Bw4-80Ile), was associated with delayed progression to AIDS [119].

Xu *et al* [120] determined the distribution of HLA-B alleles in 106 healthy HIV negative and 73 HIV positive Chinese Yi ethnic individuals and its association with HIV infection. The frequency of alleles B*07, B*35, and B*46 were increased in HIV-1 positive subjects, whereas the alleles B*55, B*44 and B*78 were absent in the HIV infected persons studied. The B*46 allele was present in a significantly higher gene frequency among HIV-1 positive individuals (P=0.02, OR=3.32, 95% CI=1.13-9.78) compared with control subjects, suggesting that HLA-B*46 may be associated with its increased susceptibility to HIV-1 infections.

VARIATION IN DC-SIGN AND DC-SIGNR CODING AND PROMOTER REGION

Because dendritic cells (DCs) are among the first cells encountered by HIV-1 during sexual transmission and DCs migrate from mucosal sites to the secondary lymphoid organs upon capturing antigen [121, 122], it has been proposed that HIV-1 uses DCs as carriers to gain entry into lymph nodes and subsequently infect CD4+ T cells [123]. DC-SIGN (Dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin) on DCs, originally described as a C-type (*calcium-dependent*) lectin, is able to capture HIV-1, HIV-2 and SIV [124], and retains the attached virus in an infectious state for days and then transmits the virus to CD4 and co-receptor positive cells [123]. DC-SIGNR (DC-SIGN related) shows similar functions to DC-SIGN for capturing HIV-1 and enhancing HIV-1 infection of T cells [125, 126]. Studies including ours have shown that mRNA encoding DC-SIGN and DC-SIGNR is present in DCs [127-129], though the DC-SIGNR transcripts are largely alternatively spliced isoforms [127].

Both DC-SIGN and DC-SIGNR, clustered on chromosome 19 [125, 128], are organized into three domains: an N-terminal cytoplasmic region, a neck region containing seven repeats of a 23 amino acid sequence, and a C-terminal domain with homology to C-type lectins [128]. We assessed whether polymorphisms in the DC-SIGN and DC-SIGNR repeat region could affect individual HIV-1 susceptibility and subsequent disease progression by

analyzing DC-SIGN and DC-SIGNR repeat polymorphisms in diverse cohorts of ES, HIV-1 seropositive (HIV-1+), long-term non-progressors (LTNP), and HIV-1 seronegative (HIV-1-) individuals. We identified novel variants in DC-SIGN repeat region and observed that heterozygous (7/6 and 7/8) DC-SIGN reduced the risk of HIV-1 infection (3.2% in ES, 0.0% in HIV-1+, $P = 0.011$) [32]. Of the 835 individuals we tested, all 8 individuals with DC-SIGN repeat region variations were from HIV-1- individuals, of whom 3 were in ES. Compared with HIV-1+ individuals, a higher prevalence of DC-SIGN variations in the repeat region was observed among ES individuals, suggesting an association of DC-SIGN variation with resistance to HIV-1 infection in ES [32]. We further assessed polymorphisms in the DC-SIGNR repeat region in diverse cohorts of multiply exposed seronegative or high-risk seronegative, HIV-1 infected and HIV-1 seronegative individuals from Seattle and the Multicenter AIDS Cohort Study (MACS) cohorts [130]. Our results suggest that individuals with a 7/7 genotype in the DC-SIGNR repeat region are associated with an increased risk for HIV-1 infection (P=0.0015). However, these effects were much stronger in the Seattle cohort (P=0.0014) than in the MACS cohort (P=0.1890). Individuals with a 7/5 genotype in the DC-SIGNR repeat region are more frequently in the multiply exposed seronegative or high-risk seronegative cohorts in the Seattle-MACS combined cohort (P=0.029) or in the Seattle cohort only (P =0.027). Most recently, we identified the "resistant" variants of DC-SIGN and DC-SIGNR heterozygous 7/5 in Chinese populations, and are further determining their association with HIV-1 infection in China (Zhu *et al*, personnel communication).

Matin *et al* examined 1,611 European-American individuals at risk for parental (n=713) or mucosal (n=898) infection for genetic polymorphisms in DC-SIGN promoter region [131]. It was found that individuals at risk for parentally acquired infection who had -336C were more susceptible to infection than were persons with -336T (odd ratio=1.87, p= 0.001). However, this association was not observed in those at risk for mucosally acquired infection.

CONCLUSION

Results from us and others indicate that homozygous CCR5-△32, the combination of heterozygous CCR5-△32 and CCR5-59029A, and the DC-SIGN and DC-SIGNR repeat polymorphisms affect HIV-1 transmission (Tab. 1). However, homozygous CCR5-△32 has not been identified and heterozygous CCR5-△32 is extremely rare in Chinese populations, indicating no or little effect of CCR5-△32 on HIV-1 transmission and epidemic in China. Genetic polymorphisms that have been shown to influence HIV-1 transmission are relatively rare and only account for the resistance of a small proportion of ES individuals to infection [32, 45-54], underscoring the need for more

Tab. 1 Human gene alleles that affect HIV-1 infection

Gene Allele	Effects on HIV-1 transmission and disease progression
CCR5-△32	Homozygosity: decrease susceptibility to infection with R5 HIV-1
	Heterozygosity: delay progression to AIDS
	CCR5-△32 plus CCR5-P1: decrease susceptibility to HIV-1 infection
CCR5-P1	Accelerate progression to AIDS
	Combined with CCR5-△32: decrease susceptibility to HIV-1 infection
CCR2-V64I	Heterozygosity: delay progression to AIDS
SDF1-3′A	Homozygosity: may or may not delay progression to AIDS
RANTES-403A-28G	May or may not delay progression to AIDS
RANTES-403A-28C	May or may not resist to HIV-1 infection
RANTES-In1.1C	Accelerate disease progression
HLA-B*27	Delay disease progression
HLA-B*57	Delay disease progression
HLA-B*35-Px	Accelerate disease progression
KIR3DS1	Combined with HLA-Bw4: delay disease progression
DC-SIGN-7/6 or 7/8	Heterozygosity: decrease susceptibility to HIV-1 infection
DC-SIGNR-7/5	Heterozygosity: decrease susceptibility to HIV-1 infection
DC-SIGNR-7/7	Homozygosity: increase susceptibility to HIV-1 infection
DC-SIGN-P-336C	Increase susceptibility to parenteral transmission of HIV-1

research.

There are relatively more genetic polymorphisms in human genes that may alter disease progression of HIV-1 infection (Tab. 1). However, the associations of genetic variants with HIV-1 disease progression in Chinese have not been well established. Only RANTES -403A and -28G, and SDF1-3'A alleles have been shown to have a weak influence on the disease progression in HIV-1 infected Chinese.

The relatively negative results from studies to date on Chinese populations may not necessarily indicate that the genetic polymorphisms have little effect on HIV-1 infection in Chinese populations. Instead, more efforts should be made to establish good study cohorts including longitudinally followed "resistant" ES, LTNP and primary HIV-1 infection. Further investigation of the association of these polymorphisms with HIV-1 infection with well established study cohorts, and the identification of new polymorphisms that may influence infection and disease progression is warranted. In addition, some less common polymorphisms identified such as in CCR5 [132-136] and CXCR4 [137, 138] might be included in large scale studies with well-established cohorts.

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