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Review Article

Effect of CCR5 -59029A/G polymorphism on risk of HIV-1 infection: a meta-analysis based on 13 studies

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Abstract: A number of studies have investigated the relationship between CCR5 -59029A/G polymorphism and risk of HIV-1 infection; however, the results have been inconclusive. Electronic databases, including PubMed, Embase, China National Knowledge Infrastructure and Wanfang, were comprehensively searched to identify related studies. Finally, 13 studies with 5915 subjects were considered qualified for meta-analysis. The association of single nucleotide polymorphism with HIV-1 susceptibility was evaluated using odds ratio (OR) with 95% confidence interval (CI). Factoring in healthy controls, results indicate no association between CCR5 -59029A/G polymorphism and HIV-1 infection. Further analysis stratified by ethnicity indicates a significant association among Caucasians under an allelic model (OR = 1.24, 95% CI = 1.02-1.49, P_{het} = 0.532) and a dominant model (OR = 1.51, 95% CI = 1.15-1.98, P_{het} = 0.708). The use of HIV-1-exposed seronegative controls revealed a significant association in a recessive model (OR = 1.38, 95% CI = 1.07-1.78, P_{het} = 0.954). Our findings indicate that the -59029G allele might be a risk factor for HIV-1 infection among Caucasians. Further studies with a large sample size and precise routes of infection should be conducted to verify this association.

Keywords: CCR5, polymorphism, risk, HIV-1, meta-analysis

Introduction

At the end of 2015, nearly 36.7 million people suffer from human immunodeficiency virus-1 (HIV-1) infection. HIV/AIDS remains one of the most severe public health problems worldwide, particularly in low- and middle-income areas (http://www.who.int/hiv/en/). HIV-1-exposed seronegative (HESN) individuals include commercial sex workers, men who have sex with men, intravenous drug abusers, hemophiliacs, and fetuses of infected women [1]. Despite high-risk behaviors and multiple exposures to HIV-1, some individuals remain seronegative, and these cases demonstrate different courses of progression to AIDS and different clinical outcomes [2, 3]. Genetic variation among individuals is widely considered to mediate entry by HIV-1 into host cells, immune response, and other factors that influence the risk of HIV-1 infection, disease progression, and therapy outcomes [4-7].

As an essential coreceptor for macrophage-tropic strains (R5) of HIV-1, the human CC chemokine receptor 5 (CCR5) is the principal coreceptor for HIV-1 entry into $CD4^+$ T lymphocytes [8]. The CCR5 gene, which is located in the 3p21.3 region of the genome, includes CCR5-D32 and promoter region -59029A/G polymorphisms [9]; both polymorphisms are involved in resistance to HIV-1 infection. The presence of CCR5-D32 effectively protects against HIV-1 infection in homozygous subjects and delays the progression of HIV-1 infection to AIDS in heterozygous individuals [10, 11]. A single nucleotide polymorphism (SNP), CCR5 -59029A/G (also named -2459A/G, rs1799987), affects the rate of progression to AIDS in HIV-1-infected individuals. CCR5-59029G exhibits lower promoter activity than 59059A and is thus expected to confer protection, compared with CCR5 -59029A/A. Homozygous 59029G individuals with HIV-infection progress to AIDS 3.8 years more slowly, on the

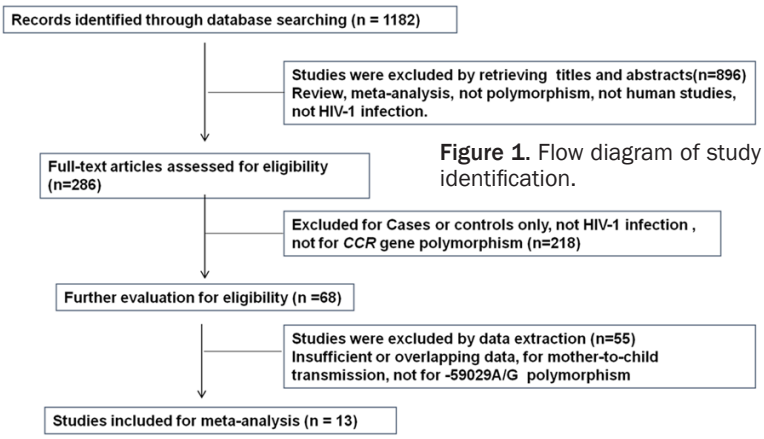

Figure 1. Flow diagram of study identification.

average, than homozygous 59029A individuals [12].

A number of studies have assessed the relationship between CCR5 -59029A/G polymorphism and HIV-1 infection. However, the results have been regarded as controversial and inconclusive probably because of the variety of ethnic populations or the small sample size in each study. Thus, a comprehensive analysis is essential to draw a reliable conclusion.

We performed a meta-analysis to evaluate the relationship between CCR5 gene -59029A/G polymorphism and host susceptibility to HIV-1 infection by using both healthy and HESN controls.

Materials and methods

Publication search strategy

Electronic databases, including PubMed, Embase, Wanfang, and China National Knowledge Infrastructure were screened up to September 2016 using a variable combination of items such as the following: "CCR, CCR5, CC chemokine receptor", "HIV, HIV-1, AIDS, human immunodeficiency viruses", and "polymorphism, polymorphisms, mutation, variant". Article selection was restricted to English and Chinese languages, and titles and related literature abstracts were screened to evaluate the relevance of investigations by two independent reviewers. Full texts of selected initial reports were downloaded for further analysis, and references from selected studies were retrieved to identify relevant studies.

Inclusion and exclusion criteria

The enrolled studies had to meet the following criteria: (1) case-control studies evaluating the relationship of CCR5 -59029A/G polymorphism and HIV-1 infection and (2) studies containing distribution data on CCR5 -59029A/G polymorphism for the case-control population. Primary exclusion criteria included the following: (1) insufficient data for meta-analysis, (2) reviews, and (3) duplication or overlapping of data from previous studies.

Data extraction

According to the listed criteria, two researchers (Gong and Tang) extracted the data independently. Disagreements between researchers were resolved by discussion; in the absence of a resolution, a third investigator was included in the debate. The primary characteristics obtained from final studies are as follows: first author, year of publication, country or area, ethnicity, number of subjects, method of genotyping, and distributions of CCR5 -59029A/G polymorphism across all subjects.

Statistical analysis

We performed the meta-analysis by using healthy controls and HESN controls. To evaluate the association between CCR5 -59029A/G polymorphism and HIV-1 susceptibility, odds ratio (OR), and 95% confidence intervals (CI) were applied. The allelic (G *vs.* A), homozygous (GG *vs.* AA), dominant (GG+AG *vs.* AA), and recessive models (GG *vs.* AG+AA) were used for quantitative analysis. We further performed stratified analysis by ethnicity. Heterogeneity between studies was calculated by χ^2-based *Q*-test. Summary ORs have been computed using a fixed effects model without heterogeneity, where the *P* value for heterogeneity (P_{het}) was more than 0.05. Otherwise, a random effects model was applied to calculate the summary ORs. The Hardy-Weinberg equilibrium (HWE) was applied to estimate the deviation of frequencies of CCR5 polymorphism in the controls. Egger's test and Begg's test with funnel

Table 1. Major details of the studies included for meta-analysis

First author [ref][a]	Year	Country	Ethnicity	HIV-1 cases (GG/GA/AA)	Healthy controls (GG/GA/AA)	HESN[b] controls (GG/GA/AA)
Clegg [13]	2000	Australia	Caucasian	25/59/35	18/43/31	-
Roman [14]	2002	Luxembourg	Caucasian	47/154/73	29/67/54	-
Shrestha [15]	2006	America	African	103/120/43	-	165/271/96
Kaur [16]	2007	India	Asian	64/75/41	42/62/15	-
Torimiro [17]	2007	Cameroon	African	13/13/17	376/477/512	
Rigato [18]	2008	Brazil	Brazilian	32/110/55	11/42/29	-
Rathore [19]	2009	India	Asian	64/73/59	111/123/81[c]	12/27/8
Parczewski [20]	2009	Poland	Caucasian	27/84/57	17/64/69	-
Xu [21]	2011	China	Asian	99/57[d]	76/62[d]	
Lu [22]	2012	China	Asian	24/56/11	30/47/14	-
Nkenfou [23]	2013	Cameroon	African	10/17/5	23/95/29[c]	-
Li [24]	2014	China	Asian	96/141/50	137/180/71	14/27/8
Gupta [25]	2015	India	Asian	18/46/24	39/80/34	-

[a]The [ref] referres to the reference numbers in this study. [b]HESN: HIV-1-exposed but seronegative. [c]The genotype distributions of controls were not consistent with Hardy-Weinberg equilibrium. [d]Genotype of G/A only.

Table 2. Results of CCR5 -59029A/G polymorphism on the risk of HIV-1 infection

	G vs. A			GG vs. AA			GG+GA vs. AA			GG vs. GA+AA		
Variables	N[a]	OR[b] (95% CI[c])	P_{het}[d]	N[a]	OR (95% CI)	P_{het}	OR (95% CI)	P_{het}		OR (95% CI)	P_{het}	
Total	12	1.04 (0.95-1.15)	0.160	11	1.02 (0.83-1.25)	0.209	1.09 (0.93-1.27)	0.007		0.98 (0.83-1.15)	0.133	
Ethnicity												
Asian	6	0.93 (0.82-1.05)	0.864	5	0.81 (0.63-1.05)	0.659	0.85 (0.68-1.06)	0.261		0.89 (0.73-1.08)	0.915	
Caucasian	3	1.24 (1.02-1.49)	0.532	3	1.40 (0.95-2.05)	0.558	1.51 (1.15-1.98)	0.708		1.08 (0.76-1.52)	0.428	
Others	3	1.20 (0.94-1.54)	0.583	3	1.41 (0.86-2.30)	0.452	1.19 (0.81-1.75)	0.917		1.40 (0.91-2.14)	0.556	

[a]N: Number of studies included in the meta-analysis; [b]OR: Odds ratio; [c]CI: Confidence interval; [d]P_{het}: *P* value of the Q-test for the heterogeneity test.

plots were used to evaluate publication bias. Sensitivity analysis was applied to evaluate the effect of individual studies on the stability of results. Stata 9.2 was used for all statistical analyses. Statistical significance was considered when *P* was less than 0.05.

Results

Major study characteristics

As shown in **Figure 1**, 1082 articles were identified after an initial search in accordance with the search strategy. Examination of titles and abstracts from the identified studies reduced the field to 68 studies for further data extraction during which 55 studies were excluded for failing to meet the qualification criteria. Finally, 13 studies were used for meta-analysis [13-25], among which 6 focused on Asians [16, 19, 21, 22, 24, 25], 3 on Caucasians [13, 14, 20], 3 on Africans [15, 17, 23], and 1 on Brazilians [18]. We combined the studies on Africans and Brazilians into a category labeled as Others. The total number of samples was 5915, which consisted of 2097 HIV-1 infected patients, 3190 healthy controls, and 628 HESN controls. Twelve studies focused on healthy controls, and 1 study included the genotype of allelic G and A [21]. Three studies included HESN controls. In two studies, the genotype distributions of healthy controls were inconsistent with HWE [19, 23]. The major characteristics of the included studies are presented in **Table 1**.

Quantitative synthesis using healthy controls

Table 2 and **Figure 2** present the primary results of the meta-analysis. Comparing the results with those of healthy controls, no significant association was found between CCR5 -59029A/G polymorphism and HIV-1 infection. Results from further stratified analysis by ethnicity suggested a significant association am-

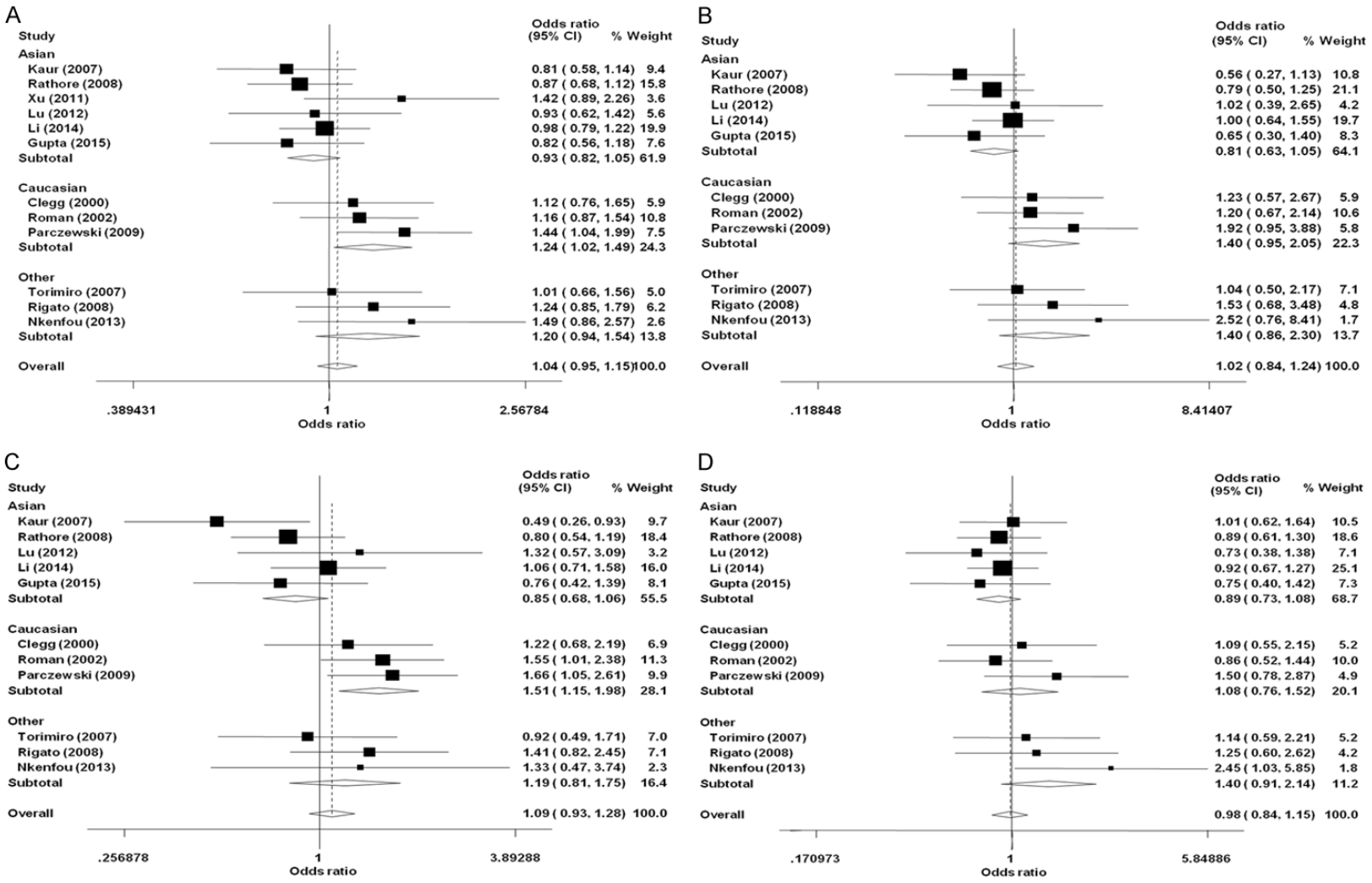

Figure 2. Forest plots of the association between CCR5 -59029A/G polymorphism and HIV-1 infection under the allelic model with the use of healthy controls. A: G *vs*. A; B: GG *vs*. AA; C: GG+GA *vs*. AA; and D: GG *vs*. GA+AA.

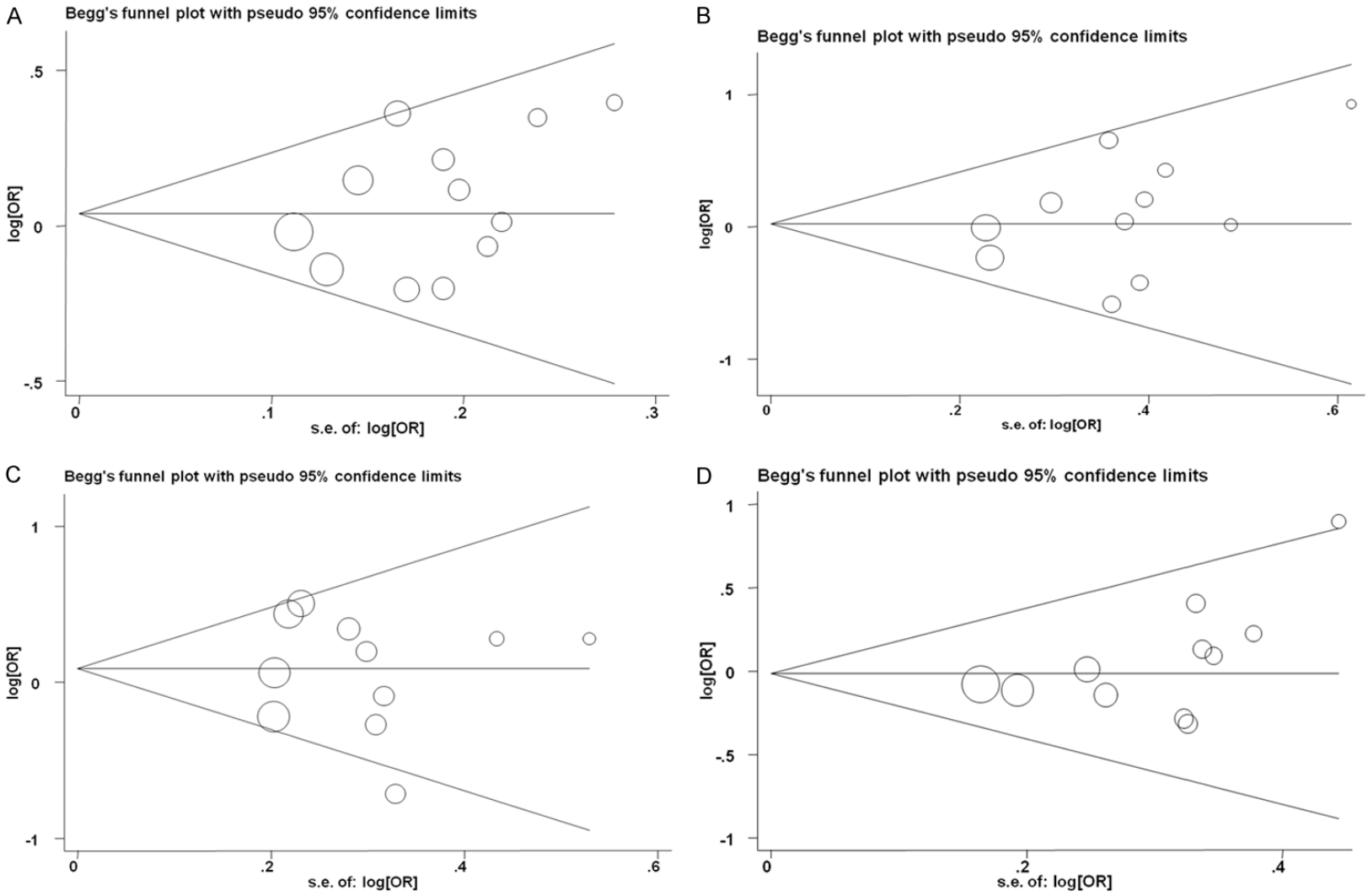

Figure 3. Funnel plots to detect publication bias in all models with the use of healthy controls. A: G *vs.* A; B: GG *vs.* AA; C: GG+GA *vs.* AA; and D: GG *vs.* GA+AA. The horizontal line indicates the pooled log odds ratio (OR) and guidelines to assist in visualizing the funnel are pooled at 95% pseudo confidence limits for this estimate.

ong Caucasians under the allelic model (G *vs.* A: OR = 1.24, 95% CI = 1.02-1.49, P_{het} = 0.532) and the dominant model (GG+GA *vs.* AA: OR = 1.51, 95% CI = 1.15-1.98, P_{het} = 0.708), (**Table 2**).

Quantitative synthesis using HIV-1-exposed but seronegative controls

Applying HESN controls, three studies were enrolled to perform the analysis, which revealed a significant association in the recessive model (GG *vs.* GA+AA: OR = 1.38, 95% CI = 1.07-1.80, P_{het} = 0.954), but not in the other models (G *vs.* A: OR = 1.14, 95% CI = 0.96-1.36, P_{het} = 0.443; GG *vs.* AA: OR = 1.22, 95% CI = 0.85-1.76, P_{het} = 0.462; GG+GA *vs.* AA: OR = 0.95, 95% CI = 0.69-1.30, P_{het} = 0.168).

Sensitivity analysis and publication bias

Sensitivity analysis was applied to estimate the stability of results. The results for all genetic models remained stable (data not shown). Publication bias was assessed using Begg's test and Egger's test. Publication bias was not present in both healthy and HESN controls group under all genetic models (**Figure 3**).

Discussion

An increasing number of studies show that both viral genetic and host genetic background are critical factors for HIV-1 infection and progression of AIDS in human beings [26, 27]. Many studies have evaluated the relationship between chemokine genes, chemokine receptor gene polymorphisms, and risk of HIV-1 infection [28, 29]. Liu et al. performed a meta-analysis and concluded that HIV-1 infection is not significantly associated with heterozygosity in CCR5D32 [30]. The -403A/A genotype chemotactic chemokine ligand 5, the primary ligand for CCR5, could protect against HIV-1 infection among Asian and African populations [31]. Meanwhile, Gong et al. found that the -28G allele could decrease the risk of HIV-1 infection among Asian populations [32]. Studies on the association between CCR5 -59029A/G polymorphism and HIV-1 infection have been conducted; however, the results have been inconclusive. This meta-analysis, which appears to be the first to estimate the association between CCR5 polymorphism and HIV-1 infection, seeks a more reliable and comprehensive conclusion.

Thirteen studies, including 2097 HIV-1 patients, 3190 healthy controls, and 628 HESN controls, were enrolled for this meta-analysis. A significant association among healthy controls was found among Caucasians under the allelic and dominant model by further ethnic stratification.

Many researchers believe that the CCR5 59029G allele limits promoter activity and reduces the number of receptors on the cell surface. The CCR5 59029G allele may delay disease progression and extend the life expectancy of individuals with HIV-1 infection [12, 13, 16]. Results seem counterintuitive that the frequency of CCR5 -59029GG in HIV-seropositive patients was significantly higher than that in HIV-seronegative subjects among Africans [23]. In addition, CCR5 -59029AG genotype carriers exhibit increased vulnerability to HIV-1 infection in a Northern Han Chinese population among Asians [22]. In other studies, no significant relationship was indicated between -59029A/G polymorphism and risk of HIV-1 infection [24, 33, 34]. Many studies have also shown no significant correlation between CCR5-59029 A/G polymorphism and disease progression among HIV-1-positive individuals or those living with AIDS [16, 19, 35].

We speculated that the inconclusive results of studies related to CCR5 -59029A/G polymorphism and HIV-1 infection could be attributed to the following: (1) Different ethnicity with different genetic backgrounds. The distribution of haplotypes of the CCR5 gene promoter is highly variable among various ethnic groups, whereas some CCR5 haplotypes are related to the effect on HIV-1 infection [36]. The CCR5 haplotype ACCAC is related to increase the risk of HIV-1 infection and accelerate the progression of HIV-1 disease among Caucasian populations [37] but not among African-Americans [38]. As shown in this meta-analysis, Asians carry a higher level of -59029G allele than Caucasians. Moreover, only Caucasians show a positive result by this comparison. (2) The linkage disequilibrium of polymorphisms may cause differences in response to HIV-1. Hladik et al. [39], describing a dominant protective effect by the -59029G allele among exposed but uninfected individuals, enhanced by CCR5 D32 mutation. A complete linkage disequilibrium exists with the CCR2-V64I and CCR5 promoter polymor-

phisms in a Northern Han Chinese population, indicating the cooperative action of CCR2-V64I and CCR5 gene polymorphisms on the process of HIV-1 infection [22]. (3) Environmental, as well as social and economic conditions, may play a part. As we know, individuals, including commercial sex workers and intravenous drug users, suffer a considerably higher risk of HIV-1 infection than the general population. HIV/AIDS in South Africa is a prominent health concern, where transmission is mostly heterosexual and not associated with drug use, but is associated with disruption of nuclear families. South Africa reportedly has more people with HIV/AIDS than anywhere else in the world.

The use of HESN controls revealed a significant association in the recessive model (GG *vs*. GA+AA: OR = 1.38, 95% CI = 1.07-1.80, P_{het} = 0.954). Commercial sex workers, people with hemophilia, men who have sex with men, intravenous drug users, and exposure *in utero* are considered the main sources of HESN individuals [1]. In studies concerning HIV-1 susceptibility, taking samples from HESN individuals may provide more useful results than using random healthy individuals as controls. This meta-analysis includes an HESN group with a small sample size consisting of 628 subjects. Our screening collected intravenous drug users and individuals repeatedly having sexual intercourse (twice a week) without protection and with HIV-infected partners for at least one year as the HESN group. Genes affecting the risk for HIV-1 infection of the host and disease progression may exert their effects via different HIV-1 infection routes; thus, future studies involving HESN individuals selected by infection routes can help elucidate this matter.

Although a meta-analysis is expected to provide a comprehensive conclusion, limitations exist. First, potential publication bias exists, given that studies published in English and Chinese are retrieved, whereas those in other languages are not included. Studies with positive associations are more easily published than studies with negative associations [33, 34]. Second, controls for most research in this analysis consisted of healthy individuals even though HESN individuals are more appropriate as controls in studies related to disease susceptibility. Further stratified analyses by high-risk exposure routes (intravenous drug use, sexual contact, etc.) of HESN individuals should be performed to address the association between exposure routes, genetic background, and risk of HIV-1 infection. Third, gene-gene and gene-environment interactions could affect the risk of HIV-1 infection. In fact, many factors such as genes and behaviors have been confirmed to affect HIV-1 infection, but no sufficient data are available to adjust these confounding factors.

In conclusion, our findings indicate that the -59029G allele could be a risk factor for HIV-1 infection among Caucasians. Future studies with a large sample size and precise routes of HIV-1 infection should be conducted to estimate the aforementioned association.

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Disclosure of conflict of interest

None.

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