Review Article

Jun Ni, Dan Wang, Sheng Wang*

The CCR5-Delta32 genetic polymorphism and HIV-1 infection susceptibility: a meta-analysis

https://doi.org/10.1515/med-2018-0062
received July 12, 2018; accepted September 8, 2018

Abstract: The CC chemokine receptor 5 (CCR5) is a chemokine receptor which is widely expressed in several immune cells involved in the inflammatory responses. Previous published studies revealed the relation of the CCR5 gene (CCR5-delta32) with the risk of HIV-1 infection, but the results are debatable and inconclusive. Here by meta-analysis, we have systematically evaluated the relation between the CCR5-delta32 polymorphism and the risk of HIV-1 infection. A comprehensive search in PubMed, EMBASE, CNKI, Cochrane Library, and WanFang database was performed up to April 15, 2018. The pooled odds ratio (ORs) along with its 95% credible interval (95%CI) was used to evaluate the relation between the CCR5-delta32 polymorphism and HIV-1 infection risk. The study included 24 case-control studies involving 4,786 HIV-1 infection patients and 6,283 controls. Compared with the wild-type homozygous genotypes, the results showed that the CCR5-delta32 heterozygotes (OR=1.16, 95%CI=1.02-1.32) had an increased susceptibility to HIV-1 and the delta32 homozygous (OR=0.25, 95%CI=0.09-0.68) had significantly reduced the susceptibility to HIV-1 for healthy controls. Moreover, we have found the delta32 allele carriers (OR=0.71, 95%CI=0.54-0.94) had significantly cut down the HIV-1 infection susceptibility when using exposed uninfected (EU) as controls. We also conducted the stratified analysis by ethnicity, and there significant association was detected in Caucasian in delta32 allele carrier genotype. To summarize, our meta-analysis suggests that the CCR5-delta32 homozygous genotype (delta32/delta32) confer possible protection against HIV-1, especially the exposed uninfected groups.

Keywords: CCR5-Delta32; Polymorphism; HIV-1; Susceptibility; Meta-analysis

1 Introduction

Human Immunodeficiency Virus-1 (HIV-1)/Acquired Immunodeficiency Syndrome (AIDS), the world major infectious killer remains one of the most important public health challenges in the world. It was estimated that about 36.7 (34.0-39.8) million people were living with HIV in 2016, and 1.8 million people have died from HIV/AIDS every year. Therefore, HIV prevalence can be considered as the greatest issue in contemporary society, including economic and health crisis [1]. However, many basic questions about the HIV-1 infection pathogenesis have not been answered. Several studies demonstrated that they have a significant difference in susceptibility and progression of HIV-1 infection [2-4]. Host genetic diversity has an important role in either disease susceptibility or resistance [4, 5]. However, the positive role of different genes in HIV/AIDS progression has still remained controversial [6, 7].

Its chemokines and their natural receptors act a key part in HIV-1 binding and entry [8]. Chemokine receptors act on CD4 as a relevant receptor for HIV-1 to regulate the first step in the entry of HIV-1 virus. CCR5, a chemokine receptor of gene product, is expressed on macrophages, monocytes, T and dendritic cells. This is a specific receptor for the CC ligand 3 (CCL3), CCL4, and CCL5 chemokine and a key part in the transferring of immune cells to inflammatory sites [9]. The CCR5Δ32 variant is characterized by a 32 base-pair (bp) deletion of the CCR5’s gene coding region; the deletion of CCR5-delta32 was initially discovered and gained the greatest interest in the relation to infection with the HIV-1. This lack of homozygosity is associated with preventing the risk of HIV-1 infection [10]. Liu et al performed a meta-analysis and demonstrated that there...
was no statistical correlation between the CCR5-delta32 polymorphism and the risk of HIV-1 infection. For adults, the CCR5-delta32 polymorphism was investigated for their association with the risk of HIV-1 infection, but the results from the previous published researches remains conflicting and inconclusive [11-34]. Thus, we conducted the present meta-analysis by pooling all available publications to evaluate the possible role of CCR5-delta32 polymorphism and HIV-1 infection susceptibility.

2 Methods

2.1 Literature search

From inception to April 2018, we conducted electronic searches using the terms “CCR5-delta32”, “polymorphism*” or “variant*” or “mutation”, “HIV” through PubMed, EMBASE, China National Knowledge Internet (CNKI), WanFang, and the Cochrane Library for relevant studies. No language restriction was applied.

2.2 Selection criteria

Articles must satisfy the following criteria: (a) evaluated the relation between CCR5-delta32 and the risk of HIV-1 infection; (b) case-control studies on human beings, no language restriction was applied; (c) sufficient data to evaluate the odds ratios (ORs) and 95% credible interval (CI), and P values; and (e) genotype distribution in controls must be in Hardy-Weinberg equilibrium (HWE) (P < 0.001). Review articles, conference abstracts, case reports and insufficient data to evaluate ORs and 95%CI were excluded.

2.3 Data extraction

Data extraction was done by two authors through a standardized form independently, such as first author, year of publication, country, ethnicity, source of the controls, genotype distribution of cases and controls, and P values for HWE in controls. Discrepancies were settled by discussion, with disagreements resolved by consensus.

2.4 Statistical analyses

The pooled odds ratio (ORs) along with 95% credible interval (95%CI) was utilized to access the strength of relation between the CCR5-delta32 and HIV-1 infection risk. We also conducted stratified analyses by ethnicity and sources of controls. The F and Cochran’s Q-test statistics were used to quantify the statistical heterogeneity, and the random-effect model was conducted if heterogeneity was significant (P < 0.05) [35]; otherwise, the fixed-effect model was conducted[36]; P < 0.05 was considered as a significant difference in the value between the two groups. Sensitivity analysis was performed by sequentially excluding studies to assess the stability of the pooled results. Begg’s funnel plot and the Egger’s tests was performed to evaluate the potential publication bias of the researches (P < 0.05 was considered significant) [37,38]. The present meta-analysis was carried out by STATA 12.0 (Stata Corp LP, College Station, TX, USA).

3 Results

3.1 Characteristics of included studies

In this meta-analysis, the selection of eligible researches included is shown in Figure 1, 517 potentially relevant researches were initially obtained from the PubMed, EMBASE, China National Knowledge Internet (CNKI), WanFang, and the Cochrane Library. After the exclusion of irrelevant studies, a total of 24 published researches were identified to be eligible for the current study. The flow diagram describing selected studies inclusion or exclusion is in Figure 1. The baseline features of the selected researches are recorded in Table 1.

3.2 Meta-analysis results

A total of 24 case-control studies were included in the present work to estimate the relation between the CCR5-delta32 polymorphism and the HIV-1 infection risk. To sum up, pooled risk evaluations shows a statistically significant relation between the CCR5-delta32 polymorphism and increased HIV-1 infection risk in the CCR5-delta32 heterozygotes genotype (OR=1.16, 95%CI=1.02-1.32, P=0.024) for healthy controls (Figure 2 and Table 3). Meanwhile, we found the risk of HIV-1 infection was significantly reduced in the delta32 homozygous genotype (OR=0.25, 95%CI=0.09-0.68, P=0.006) for healthy
controls (Table 3). When we conducted stratified analysis by sources of control, we also detected a significantly risk decline of HIV-1 infection in the delta32 allele carriers (OR=0.71, 95%CI=0.54-0.94, P=0.015) among exposed uninfected populations (Figure 3 and Table 3). We also performed the stratified analysis by ethnicity, there was significant association in Caucasian with delta32 allele carrier genotype.

3.3 Sensitivity analysis and publication bias

Sensitivity analysis was conducted by sequentially excluding individual studies to assess the impact of each study on the summarized findings. This revealed that the findings were statistically robust and credible (data not shown) (Figure 4). Begg’s and Egger’s test (Table 3) was utilized to examine the potential bias of the publication [37,38]. The shape of the funnel plot was symmetrical as
Discussion

AIDS remains one of the biggest public health challenges of the world, as we all know, it is a complex infectious
disease, including HIV-1 infection, host immune response, and gene-environment interactions. Several studies have already found that both viral genetics and host genetic factors are important determinants of HIV-1 infection [4,5,10]. Chemokines and chemokine receptors are critical for immune response in HIV-1 infection. Although many researches demonstrated the association between chemokine and chemokine receptor gene polymorphisms, and host’s susceptibility to HIV-1 infection, the conclusions are still controversial [11-33].

Meta-analysis, a useful statistical tool through integrating and comparing the results of many related researches and taking into consideration of variations in characteristics that can affect overall estimate of the outcome of interest, which is used to evaluate the literature in both quantitative and qualitative ways. So it is especially worthy when previous researches could not provide significant differences among treatments because of sample sizes limitations, or when there is no consensus [39]. Despina et al. performed a meta-analysis and demonstrated that perinatal infection is not determined by heterozygosity for CCR5-delta32 in the children [40]. In addition, Liu et al. performed a meta-analysis suggested that no statistical relation was detected between the CCR5-delta32 polymorphism and HIV-1 infection risk in any genetic model [41].

Table 2: The distribution of CCR5-delta32 genotype of included studies.

| Author     | Ethnicity | HIV-1 infected | Healthy Controls | Exposed uninfected |
|------------|-----------|----------------|------------------|-------------------|
|            |           | AA | AB | BB | AA | AB | BB | AA | AB | BB | AA | AB | BB |
| Tan        | Asians    | 226| 24 | 1  | 222| 15 | 1  |     |     |     |     |     |     |
| Desgranges | Mixed     | 60 | 3  | 0  | 59 | 3  | 0  |     |     |     |     |     |     |
| Rathore    | Asians    | 190| 0  | 0  | 314| 6  | 0  | 50  | 0  | 0   |     |     |     |
| Xu         | Asians    | 74 | 4  | 0  | 68 | 2  | 0  |     |     |     |     |     |     |
| Shrestha   | Caucasian | 258| 8  | 0  | 516| 16 | 0  |     |     |     |     |     |     |
| Liu        | Caucasian | 261| 55 | 0  | 354| 68 | 3  | 69  | 22 | 3   |     |     |     |
| Veloso     | Caucasian | 144| 40 | 0  | 174| 26 | 0  | 31  | 5  | 0   |     |     |     |
| Munerato   | Caucasian | 162| 21 | 0  | 100| 15 | 0  |     |     |     |     |     |     |
| Adojaan    | Caucasian | 230| 70 | 0  | 371| 117| 0  |     |     |     |     |     |     |
| Alvarez    | Caucasian | 138| 12 | 0  | 205| 42 | 3  |     |     |     |     |     |     |
| Zimmerman | Caucasian | 601| 144| 0  | 846| 121| 4  | 94  | 26 | 5   |     |     |     |
| Mandl      | Caucasian | 182| 43 | 0  | 367| 78 | 6  |     |     |     |     |     |     |
| Wang       | Asians    | 104| 0  | 0  | 104| 0  | 0  | 51  | 0  | 0   |     |     |     |
| Tiensiwakul| Asians    | 116| 0  | 0  | 432| 0  | 0  | 190 | 0  | 0   |     |     |     |
| Rigato     | Caucasian | 185| 15 | 0  | 73 | 9  | 0  |     |     |     |     |     |     |
| Roman      | Mixed     | 226| 62 | 0  | 127| 27 | 1  |     |     |     |     |     |     |
| Wang       | Asians    | 329| 1  | 0  | 473| 1  | 0  |     |     |     |     |     |     |
| Deng       | Asians    | 88 | 0  | 0  | 117| 2  | 0  |     |     |     |     |     |     |
| Balotta    | Caucasian | 136| 15 | 1  | 108| 13 | 1  |     |     |     |     |     |     |
| Ellwanger  | Caucasian | 265| 35 | 0  | 240| 32 | 2  |     |     |     |     |     |     |
| Heydarifard| Asians    | 139| 1  | 0  | 291| 9  | 0  |     |     |     |     |     |     |
| Zapata     | Mixed     | 51 | 6  | 0  | 107| 5  | 0  | 63  | 7  | 0   |     |     |     |
| Li         | Asian     | 23 | 1  | 0  | 45 | 1  | 0  |     |     |     |     |     |     |
| Rugeles    | Mixed     | 33 | 3  | 0  | 47 | 2  | 1  |     |     |     |     |     |     |

AA, CCR5 homozygotes; AB, CCR5-delta32 heterozygotes; BB, delta32 homozygotes.

Figure 5: Funnel plot of publication biases on the association between CCR5-delta32 polymorphism and HIV-1 infection susceptibility.
There are several limitations in the current study. Firstly, suitable English or Chinese-language studies were only enrolled in current meta-analysis, which means related researches published in other languages may have been overlooked, which may also lead to selection bias. Secondly, the number as well as the sample size of some included studies was limited and the results should be interpreted with caution. Finally, the influences of other relevant components such as age, gender, lifestyle as well as their interactions with CCR5-delta32 polymorphism on HIV-1 infection susceptibility were not analyzed due to the lack of original data.

5 Conclusion

In conclusion, our findings indicated that the CCR5-delta32 homozygous genotype (delta32/delta32) confer possible protection against HIV-1 infection, especially in exposed uninfected population. However, this conclusion should be confirmed by multi-center and large-scale studies based on multiple ethnic groups.
Interest conflict: The authors claim no conflict of interest.

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