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Association of chemotactic chemokine ligand 5 rs2107538 polymorphism with tuberculosis susceptibility: A meta-analysis

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Abstract

A meta-analysis was carried out in this study by summarizing relevant research to evaluate the relationship between rs2107538 polymorphism in the chemotactic chemokine ligand 5 (CCL5) gene and tuberculosis (TB) susceptibility. Published studies were retrieved from PubMed, Embase, and CNKI databases using the keywords 'CCL5', 'TB', and 'polymorphism'. Nine studies involving 2584 patients with TB and 2265 controls were included in the current meta-analysis. The combined results suggested that the *CCL5* rs2107538 polymorphism was correlated with TB susceptibility (recessive model: OR = 1.45, 95% CI = 1.02–2.07). Subgroup analysis according to race indicated that such correlation could be detected in Caucasians (CT versus CC: OR = 1.53, 95% CI = 1.20–1.95; dominant model: OR = 1.58, 95% CI = 1.25–1.99), but not in East Asian, South Asian, and South African populations. In conclusion, the results of our meta-analysis suggest that *CCL5* rs2107538 polymorphism might contribute to the risk of TB, especially in Caucasians. Well-designed studies with more subjects will be required for further validation of these results.

Keywords

rs2107538, CCL5, polymorphism, meta-analysis, TB

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Introduction

Tuberculosis (TB), a type of infectious disease caused by *Mycobacterium tuberculosis* (MTB), is still a leading public health issue worldwide, despite the availability of low-cost and efficient treatment for over 50 years. Nine million TB cases and 1.5 million TB-related deaths (including 360,000 HIV-positive patients) were estimated in 2013.[1] Other factors, such as environmental factors, HIV infection, and diabetes, have also played vital roles in this process.[2] Likewise, genetic factors are also important in determining susceptibility and resistance to MTB, which is considered to be related to susceptibility to TB.[3] The identification of host genetic factors for susceptibility to TB will greatly enhance global control of TB.

As a member of the chemotactic chemokine family, chemotactic chemokine ligand 5 (CCL5) is also referred to as regulated on activation, normal T cell expressed and secreted (RANTES). CCL5 is a crucial chemokine, which mainly participates in immunoregulatory and inflammatory events, which can be ascribed to its abilities for recruiting, activating, and co-stimulating T-cells and monocytes.[4] In fact, CCL5 may play a role in suppressing MTB cellular growth.[5] Typically, the human *CCL5* gene is found on chromosome 17 (17q11.2-q12), which consists of three exons and two introns. The *CCL5* gene is polymorphic, and its rs2107538 polymorphism is suggested to affect CCL5 expression.[6]

Numerous studies have examined the relationship of *CCL5* rs2107538 polymorphism with susceptibility to TB. However, no consistent and conclusive results have

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been obtained. The inconsistent results may be related to the differences in sample sizes and ethnic groups. In addition, individual studies are associated with insufficient power in detecting the overall effect. To solve the problems relating to individual studies based on the above-mentioned shortcomings, this meta-analysis was carried out, aiming to more comprehensively estimate the relationship of *CCL5* rs2107538 polymorphism with human TB susceptibility.

Material and methods

Literature search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Guidelines. Online databases, including PubMed, Embase, Google Scholar, Cochrane Library, the Chinese Biological Medical databases, and Chinese National Knowledge Infrastructure were systemically and comprehensively searched by two reviewers independently to acquire case-control studies regarding the genetic relationship between *CCL5* rs2107538 polymorphism and TB using the medical subject heading as well as the keywords 'CCL5', 'TB', and 'polymorphism', and no language restriction was set.

Inclusion and exclusion criteria

The inclusion criteria in the current meta-analysis included: (1) case-control studies evaluating the relationship between the *CCL5* rs2107538 polymorphism and the susceptibility to TB; (2) research on the basis of irrelevant individuals; (3) published studies with sufficient data for estimating the odds ratio (OR) and the corresponding 95% confidence interval (CI). In addition, reviews, reports, comments, and letters were not included. As for repeated publications, the study with the greatest sample size was enrolled in this meta-analysis.

Data extraction

Related data were extracted from the eligible studies by two reviewers independently, including the name of first author, year of publication, area, race, case number and control number, genotype frequency in both patients and controls, as well as the *P* value for the Hardy–Weinberg equilibrium (HWE) test among the controls.

Statistical analysis

First, the HWE test was performed for each study in the control group through a Chi-square test. Subsequently, the relationship of *CCL5* rs2107538 polymorphism with susceptibility to TB was estimated by calculating the combined OR and corresponding 95% CI using the homozygote comparison (TT vs. CC), the heterozygote comparison (CT vs. CC), a dominant model (TT+CT vs. CC), and a recessive model (TT vs. CC+CT). Meanwhile, potential heterogeneities among the enrolled studies were determined using the I^2 test; typically, an I^2 of >50% suggested heterogeneity among the enrolled studies so the random effects model would be adopted. Otherwise, the fixed-effects model was employed.

Furthermore, a subgroup analysis stratified by race was carried out. To assess result stability, a sensitivity test was conducted by excluding a study one at a time from the combined analysis to determine the impact of each study on the overall ORs. Finally, publication bias was assessed through a funnel plot. The meta-package of the R 3.33 software was used.

Results

Study characteristics

A total of 54 related papers were retrieved according to the retrieval strategy. According to the study inclusion criteria, nine case-control studies were included in the analysis[5,7–14] while the remaining 45 were excluded. The flow chart of study selection is shown in Figure 1. The nine enrolled papers involved 2584 patients and 2265 normal subjects. The publication year ranged from 2005 to 2018. Meanwhile, an HWE test was carried out to examine the genotype distribution among the controls. All nine papers were within the HWE ($P > 0.05$). When articles stratified in race, two East Asian populations (both Chinese), two South Asian populations (both Indian), four Caucasian populations (Iranian, Tunisian, Moldavian, and Spanish), and one South African population (Cape Coloureds) were identified. The baseline characteristics of the enrolled papers are displayed in Table 1.

Meta-analysis results

The main results for the meta-analysis regarding the relationship of *CCL5* rs2107538 polymorphism with TB risk are presented in Table 2. The combined meta-analysis results suggest that the *CCL5* rs2107538 polymorphism was remarkably correlated with susceptibility to TB (recessive model: OR = 1.45, 95% CI = 1.02–2.07). In addition, the subgroup analysis according to race indicated that this polymorphism increased TB risk in Caucasians (CT versus CC: OR = 1.53, 95% CI = 1.20–1.95; dominant model: OR = 1.58, 95% CI = 1.25–1.99, Figure 2a,b), but not

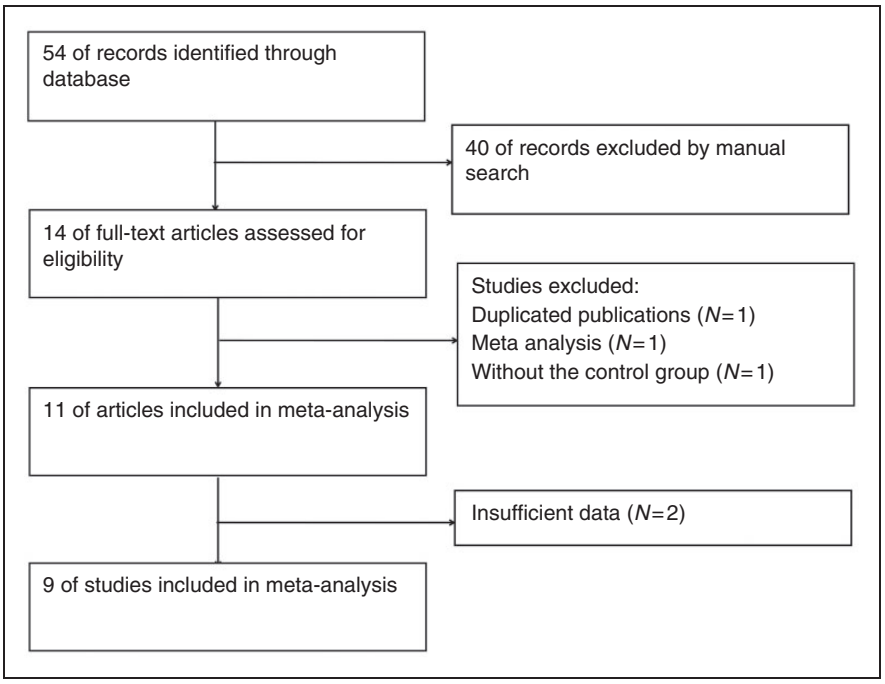

Figure 1. The flow diagram of included/excluded studies.

Table 1. Characteristics of the included studies for meta-analysis.

					Genotype distribution GG/GA/AA		
Study included	Yr	Area	Race	Cases /controls	Case	Control	HWE test
Chu	2007	China	East Asian	462/465	196/173/93 214/199/52		0.58
Sánchez-Castañón	2009	Spain	Caucasian	76/157	43/24/9	116/39/2	0.52
de Wit	2011	South Africa	African	493/309	122/228/143 75/153/81		0.87
Ben-Selma	2011	Tunisia	Caucasian	223/150	149/69/5	119/30/1	0.54
Selvaraj	2011	India	South Asian	212/211	109/82/21	91/97/23	0.71
Mishra	2012	India	South Asian	215/216	125/57/33 131/71/14		0.31
Wang	2016	China	East Asian	494/413	202/224/68 152/209/52		0.13
Kouhpayeh	2016	Iran	Caucasian	160/160	104/54/2	121/36/3	0.87
Varzari	2018	Germany	Caucasian	249/184	144/95/10	113/62/9	0.90

HWE: Hardy–Weinberg equilibrium.

Table 2. Summary of different comparative results.

		TT versus CC		CT versus CC		Dominant model		Recessive model	
Variables	n^a	OR [95%CI]	I^2	OR [95%CI]	I^2	OR [95%CI]	I^2	OR [95%CI]	I^2
Total	9	1.42 (0.96–2.10)	64%	1.06 (0.86–1.31)	60%	1.16 (0.94–1.43)	64%	1.45 (1.02–2.07)	62%
Ethnicity									
East Asian	2	1.39 (0.71–2.72)	82%	0.88 (0.72–1.07)	0%	0.99 (0.72–1.35)	64%	1.49 (0.84–2.67)	79%
South Asian	2	1.37 (0.43–4.33)	83%	0.77 (0.57–1.03)	0%	0.89 (0.58–1.37)	60%	1.53 (0.54–4.35)	81%
Caucasian	4	2.23 (0.57–8.79)	68%	1.53 (1.20–1.95)	0%	1.58 (1.25–1.99)	29%	1.95 (0.51–7.48)	67%
African	1	1.09 (0.73–1.61)	/	0.92 (0.64–1.30)	/	0.97 (0.70–1.36)	/	1.15 (0.84–1.58)	/

OR: odds ratio; CI: confidence interval; n^a: number of comparisons.

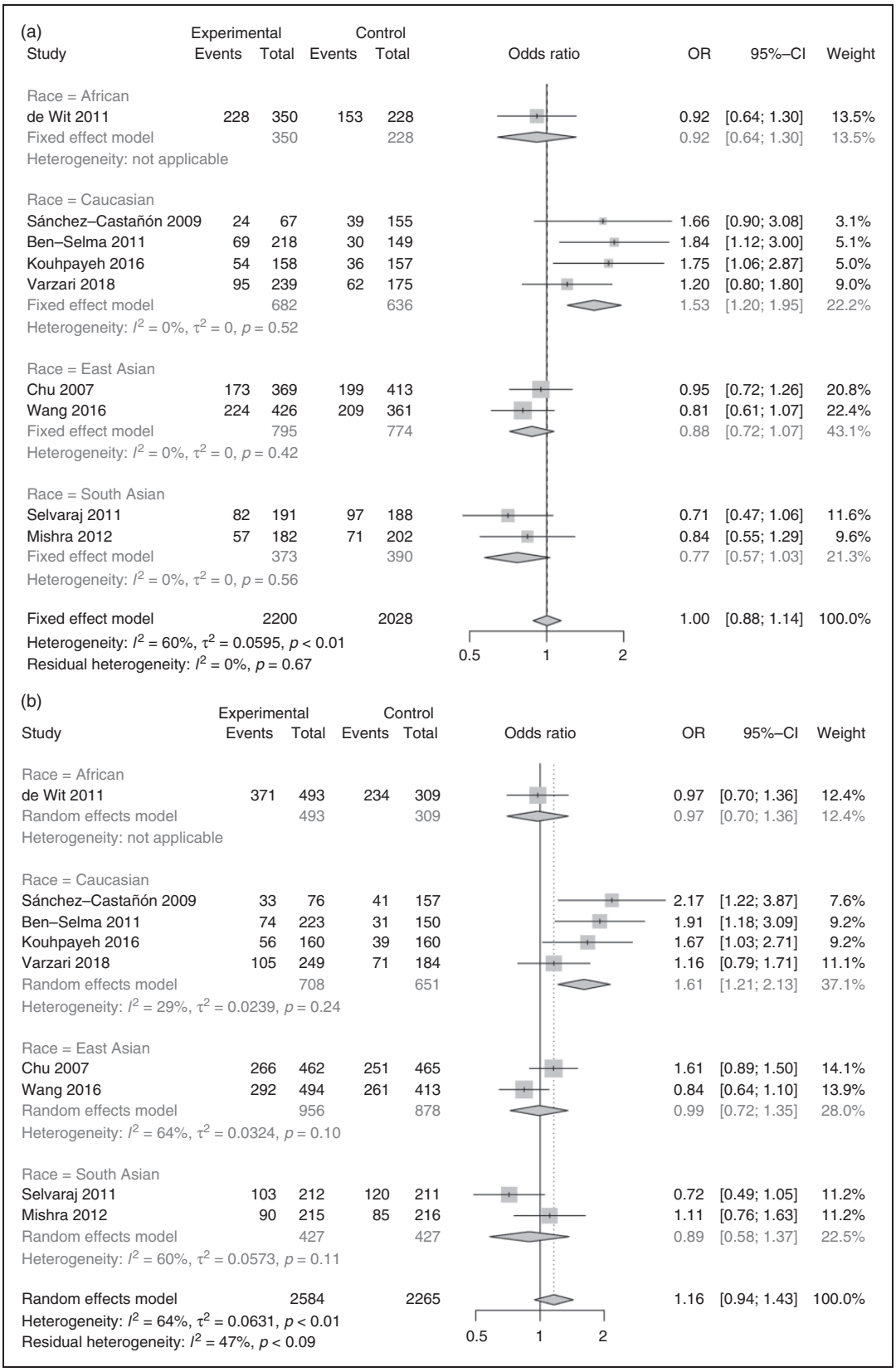

Figure 2. (a) Stratification analyses by ethnicity between CCL5 rs2107538 polymorphism and TB susceptibility under CT versus CC. (b) Stratification analyses by ethnicity between CCL5 rs2107538 polymorphism and TB susceptibility under the dominant model.

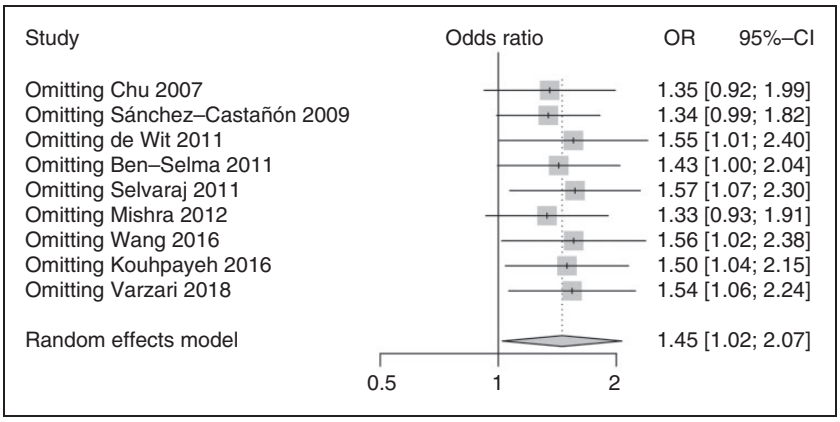

Figure 3. Sensitivity analyses between CCL5 rs2107538 polymorphism and TB susceptibility.

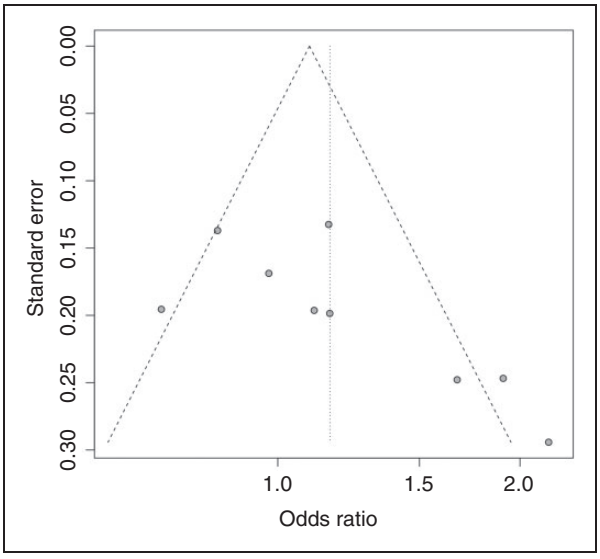

Figure 4. Funnel plot for publication bias test.

in East Asian, South Asian, and South African populations. Furthermore, the sensitivity analysis was carried out by removing one paper at a time. Ultimately, the combined findings were rarely altered after removing each paper, suggesting robust results (Figure 3).

Publication bias

The publication bias was evaluated using a funnel plot. The results suggested no obvious evidence of publication bias in this meta-analysis (Figure 4).

Discussion

Great advances have been made in the effective treatment and control of TB over the last 13 years. Nonetheless, TB is associated with great direct and indirect expenses, which have brought about tremendous burdens along with loss of productivity.[15] Chemokines have been recognized as the crucial regulating factors of the immune system responding to TB infection.[16] Specifically, CCR5, a beta chemokine receptor family member, is reported to be overexpressed in TB patients relative to healthy controls.[17] The *CCR5* gene is located on the short arm of chromosome 3 at the cluster region of the chemokine receptor gene.[11] Numerous studies have discovered that *CCL5* rs2107538 polymorphism is related to susceptibility to TB. However, no consistent or conclusive results have been achieved so far due to small sample sizes and heterogeneity in terms of objects of study. Consequently, the current meta-analysis was carried out on the eligible case-control studies to examine the impact of rs2107538 polymorphism in the *CCL5* gene on susceptibility to TB.

Nine case-control studies meeting the inclusive criteria were enrolled. The results of this meta-analysis suggest that *CCL5* rs2107538 polymorphism is related to susceptibility to TB based on the statistical power of the included studies. However, subgroup analysis stratified by race demonstrated that rs2107538 polymorphism showed a correlation with susceptibility to TB in Caucasians, but not in East Asian, South Asian, and South African populations. The mechanism of how this polymorphism relates to TB risk remains unclear. The underlying function of this polymorphism could be influenced through gene–gene and/or gene–environment interactions. The *CCL5* gene promoter regions (rs2107538 and rs2280788), which are in tight linkage disequilibrium, have been extensively investigated over the past year. Evidence suggests that rs2107538 and rs2280788 polymorphisms may be synergistically related to the risk of TB.[7,9,10] In addition, previous results have also suggested that genetic background may have the greatest impact in cases with early-, rather than late-onset TB.[14] A subgroup analysis based on age may obtain new conclusions.

However, an age-related subgroup analysis was not performed in this study due to the lack of relevant data.

Findings in this meta-analysis must be explained in the context of its related limitations. First, the number of studies and samples were still relatively small. Second, most studies were carried out in Caucasian populations. Further confirmation of the results of this meta-analysis should be obtained from studies of other races. Finally, some important data, including gender, age, family history, and environmental risk factors, could not be obtained. Therefore, no further subgroup and meta-regression analyses were performed.

Conclusion

In summary, the findings of this meta-analysis suggest that *CCL5* rs2107538 polymorphism might contribute to the risk of TB, especially in Caucasians. However, a higher number of well-designed epidemiological studies conducted in carefully matched patients and controls is required to validate our findings. Future studies may concentrate on the impact of gene–gene and gene–environment interactions on the relationship between TB risk and the *CCL5* rs2107538 polymorphism.

Declaration of conflicting interests

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