Meta-Analysis

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Association between *IL1B* −511C/T polymorphism and Behçet's disease: a meta-analysis

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Abstract

Background: Many studies have investigated the relationship between the interleukin-1β gene (*IL1B*) −511C/T polymorphism and the risk of Behçet's disease (BD); however, the conclusions remain controversial.

Methods: In this study, we systemically retrieved relevant studies from the Chinese Biomedicine Database, China National Knowledge Infrastructure, Embase, Cochrane Library, and PubMed databases. We then calculated the odds ratios (ORs) and 95% confidence intervals (CIs) using the meta-package Stata version 12.0.

Results: The *IL1B* −511C/T polymorphism was not related to BD susceptibility using any of the tested models (C vs T: OR = 1.20, 95% CI = 0.97–1.49; CC vs TT: OR = 1.27, 95% CI = 0.95–1.70; CT vs TT: OR = 1.03, 95% CI = 0.781.36; dominant model: OR = 1.12, 95% CI = 0.87–1.46; recessive model: OR = 1.27, 95% CI = 0.89–1.82). Similarly, subgroup analysis including studies consistent with the Hardy–Weinberg equilibrium revealed no association between the *IL1B* polymorphism and BD susceptibility.

Conclusion: This meta-analysis indicates that the *IL1B* −511C/T polymorphism is unlikely to affect the risk of BD; however, further large-scale, carefully designed studies are needed to verify these results.

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Introduction

Behçet's disease (BD) is an inflammatory disorder involving multiple systems and organs, characterized by genital and oral ulcers, uveitis, and skin lesions, and manifested by central nervous system disease, arthritis, thrombophlebitis, gastrointestinal tract ulcers, and a positive pathergy test.[1] Despite its unclear etiology, the immune response is considered to play a vital role in the pathogenesis of BD.[2] Interleukin-1β (IL-1β) is a proinflammatory cytokine with a key role in autoinflammatory diseases.[3] In line with various overlapping clinical manifestations between BD autoinflammatory diseases,[4] high levels of IL-1β are secreted by circulating monocytes in BD patients.[5] Moreover, IL-1β antibody treatment[6] or IL-1 blockade[7] can relieve symptoms in patients with BD who fail to respond to traditional treatments. Single nucleotide polymorphisms in the IL promoter region have been shown to affect their transcription and secretion,[8] suggesting that IL gene polymorphisms may affect the pathological progression of BD.

Interleukin IL-1, including IL-1β and IL-1α, and IL-1 receptor antagonist (IL-1Ra) are encoded by the *IL1B*, *IL1A*, and *IL1RN* genes, respectively, located on the long arm of chromosome 2(2q14-21), together with two IL-1 receptors.[9] A C/T base substitution at position −511 in the promoter region of the *IL1B* gene has been shown to change IL-1β secretion *in vitro*.[8] Moreover, populations harboring the homozygous TT *IL1B* −511C/T genotype were shown to be at higher risk of developing BD;[9] however, this result remains controversial. Nevertheless, small sample sizes and diversity among study subjects suggest that individual studies may be inadequate for assessing the mild impacts of polymorphisms on BD. To this end, we conducted a meta-analysis of all eligible studies to determine the association between the *IL1B* −511C/T polymorphism and BD.

Methods

Search strategy

We systematically searched the China National Knowledge Infrastructure, PubMed, Chinese Biomedicine, Embase, and Cochrane Library databases to select relevant studies concerning the relationship between the *IL1B* −511C/T polymorphism and BD risk from January 2000 to September 2020. The search was restricted to studies published in English or Chinese. The following key words were used: "Interleukin" or "IL" and "Behçet's disease" or "Behcet syndrome" or "BD" and "polymorphism" or "variant" or "allele" or "genotype". We also manually searched for additional studies in the reference lists of the selected articles. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist. We did not register the study with the Prospective Register of Systematic

Reviews (PROSPERO), but will do so for future studies. This meta-analysis did not require ethical approval or written informed consent.

Inclusion and exclusion criteria

Eligible studies were enrolled if the met the following criteria: (1) case-control studies concerning the correlation between *IL1B* −511C/T polymorphism and BD risk; (2) adequate data accessible to calculate odds ratios (ORs) and 95% confidence intervals (95%CIs); (3) frequencies of genotypes or alleles in case and control groups could be calculated from original data; and (4) the diagnostic criteria for BD were clearly defined. Studies that met the following criteria were excluded: (1) no control group set; (2) family-based studies; (3) duplicate data with another study with a smaller sample size; and (4) editorials, comments, abstracts, or reviews without adequate raw data.

Data extraction

Information on first author name, ethnicity, publication year, numbers of cases and controls, frequencies of genotypes in case and control groups, and evidence of Hardy−Weinberg equilibrium (HWE) were retrieved from eligible studies by two investigators (XL Yang and XX Man). Any disagreement was resolved by discussion with a third investigator.

Statistical analysis

This meta-analysis was carried out using Stata version 12.0 (Stata Corporation, TX, USA). ORs and 95% CIs were employed to evaluate the relationship between the *IL1B* −511C/T polymorphism and BD risk using recessive (CC vs TT+CT), heterozygote comparison (CT vs TT), dominant (CT+CC vs TT), and homozygote comparison (CC vs TT) models. Heterogeneity was assessed by I^2 tests. I^2 ranges from 0% to 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively. In the absence of heterogeneity among studies (I^2 <50%), the pooled OR was calculated by a fixed effects model (Mantel−Haenszel); otherwise, a random effects model (DerSimonian and Laird) was used. One-way sensitivity analysis was also conducted to assess if the results were stable. Each study was omitted sequentially to determine its effect on the pooled OR. Finally, funnel plots with Begg's and Egger's tests were created to assess potential publication bias, with $P<0.05$ indicating significant publication bias.

Results

Study characteristics

The database searches yielded 220 publications, including 191 articles from PubMed and 29 articles from the China National Knowledge Infrastructure databases, of which 12 were considered to be potentially eligible by both reviewers. Five articles were excluded during the second phase of the inclusion process, and seven articles were finally enrolled in the meta-analysis.[9–15] The flow chart of study selection is summarized in Figure 1. The controls in most studies were derived from healthy populations. The seven case-control studies selected included 726 patients and 782 healthy controls. All publications were written in English and were published between 2000 and 2020. Genotyping was carried out by polymerase chain reaction/restriction fragment length polymorphism analysis. The genotype frequencies of the controls were in agreement with HWE, except for the studies by Coskun et al., Alayli et al., and Amirzargar et al.[10,11,13] The detailed

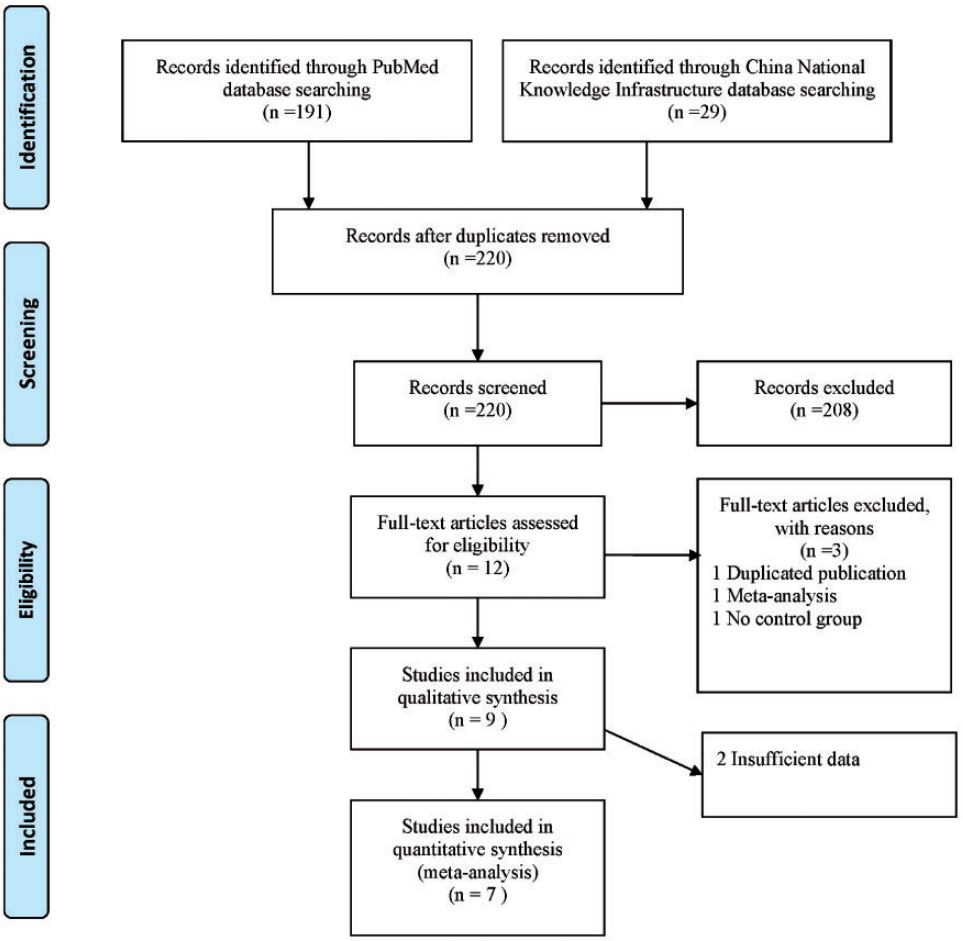

Figure 1. Study selection and inclusion process.

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

					Allele (cases)		Allele (controls)		Genotype (cases)			Genotype (controls)			P for
Author	Year	Race	Cases	Controls	C	T	C	T	CC	CT	TT	CC	CT	TT	HWE
Karasneh et al.[9]	2003	Caucasian	132	104	156	108	108	100	48	60	24	29	50	25	0.71
Coskun et al.[10]	2005	Caucasian	72	163	88	56	185	141	31	26	15	66	53	44	0.00
Alayli et al.[11]	2007	Caucasian	80	105	118	42	118	92	45	28	7	28	62	15	0.04
Akman et al.[12]	2008	Caucasian	57	56	73	41	72	40	22	29	6	25	22	9	0.28
Amirzargar et al.[13]	2010	Caucasian	147	140	161	133	154	124	38	85	24	36	82	21	0.02
Ozçimen et al.[14]	2011	Caucasian	96	74	322	112	372	116	119	78	20	143	3	86	0.67
Barış et al.[15]	2016	Caucasian	142	140	146	138	124	156	38	71	33	27	78	33	0.12

HWE, Hardy–Weinberg equilibrium.

features of the seven studies are presented in Table 1.

Meta-analysis

We collected eligible studies using both electronic and manual searching approaches to ensure inclusion of almost all eligible studies, to allow the quantitative evaluation of the relationship between the *IL1B* −511C/T polymorphism and BD risk. The results are summarized in Table 2. The *IL1B* −511C/T polymorphism was not related to BD susceptibility using any of the tested models. There was also no significant relationship after stratifying studies according to compliance with HWE (Figure 2). There was some heterogeneity among the studies. However, sensitivity analysis to determine the impacts of each individual study on the pooled OR, via sequential deletion, showed that no single study affected the pooled OR, indicating the stability of the outcomes.

Publication bias analysis

Begg's and Egger's tests revealed no publication bias in this meta-analysis (Figure 3).

Discussion

IL-1 initiates the recruitment of immune cells and the inflammatory response.[16] IL-1 levels are significantly elevated and correlate with disease activity in patients with vasculitis.[17] IL-1 production is influenced by gene polymorphisms such as the *IL1B* −511C/T polymorphism,[18] and previous studies showed that this polymorphism might be related to vasculitis, including Kawasaki disease, IgA vasculitis, and giant cell arteritis.[19–21] However, a lack of studies means that this relationship cannot be analyzed further.

BD is a multifactorial disorder and its pathogenesis thus remains unclear. However, both environmental and genetic

Table 2. Summary odds ratios and 95% confidence intervals for association between *IL1B* −511C/T polymorphism and risk of Behçet's disease.

		Allele model		Homozygote comparison		Heterozygote comparison		Dominant model		Recessive model	
Variable	N[a]	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Total	7	1.20 (0.97–1.49)	0.04	1.27 (0.95–1.70)	0.17	1.03 (0.78–1.36)	0.70	1.12 (0.87–1.46)	0.53	1.27 (0.89–1.82)	0.01
HWE											
Yes	4	1.12 (0.94–1.34)	0.23	1.16 (0.79–1.70)	0.22	1.00 (0.70–1.43)	0.41	1.06 (0.76–1.48)	0.34	1.07 (0.83–1.37)	0.19
No	3	1.34 (0.85–2.12)	0.02	1.52 (0.77–3.01)	0.12	1.08 (0.77–3.01)	0.65	1.23 (0.81–1.85)	0.47	1.56 (0.73–3.33)	0.01

[a]Number of comparisons.
CI, confidence interval; OR, odds ratio.

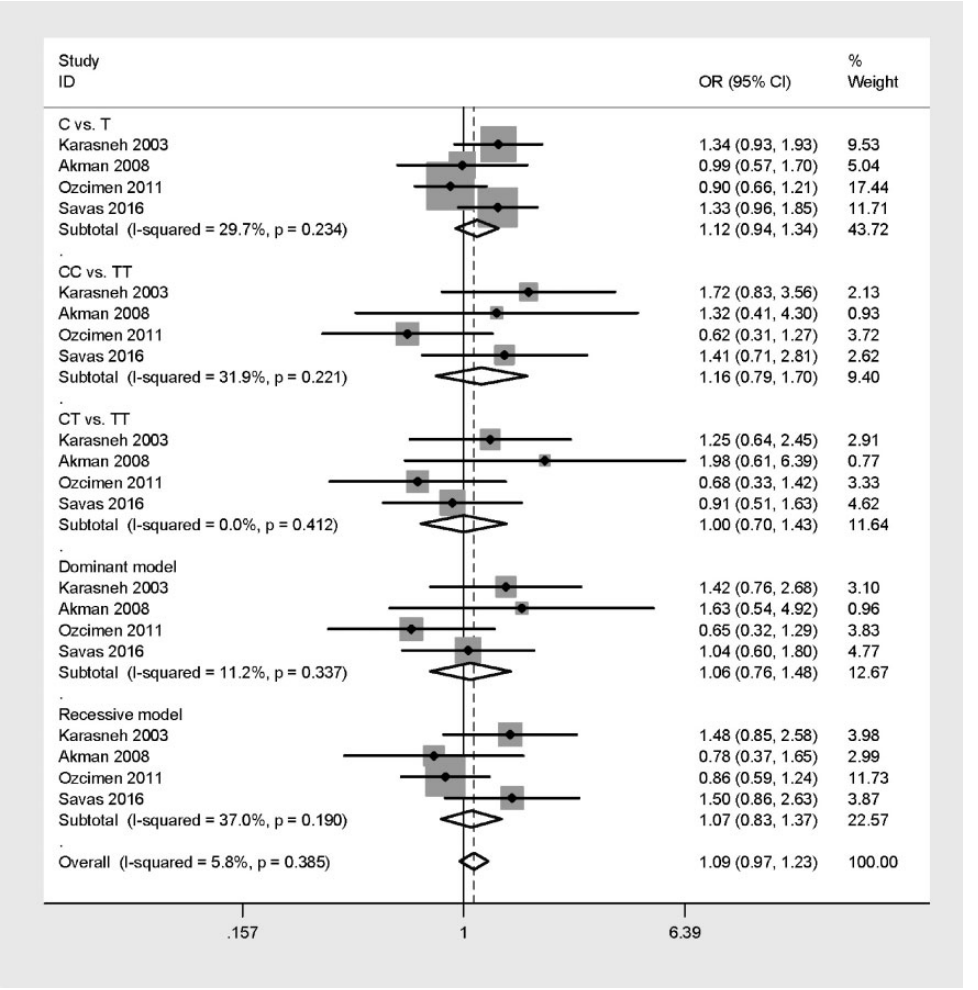

Figure 2. Meta-analysis of relationship between *IL1B* −511C/T polymorphism and risk of Behçet's disease in studies consistent with the Hardy–Weinberg equilibrium.
OR, odds ratio; CI, confidence interval.

factors, including IL-1 gene polymorphisms, have been shown to be involved in the development of BD.[22] Several studies have reported on the possible relationship between the *IL1B* −511C/T polymorphism and BD risk. However, most studies have been case-control studies with relatively small sample sizes, and conclusions about the pathogenesis of BD thus remain controversial. A previous meta-analysis examining the association between IL-1 polymorphism and vasculitis did not specifically study BD.[23] We therefore conducted this meta-analysis to summarize the effects of the *IL1B* −511C/T polymorphism on the risk of BD. The results indicated that this polymorphism may not be a significant susceptibility factor in terms of BD risk. The result was similarly insignificant in subgroup analysis stratified by studies consistent with HWE, indicating that non-HWE studies might affect the final result.

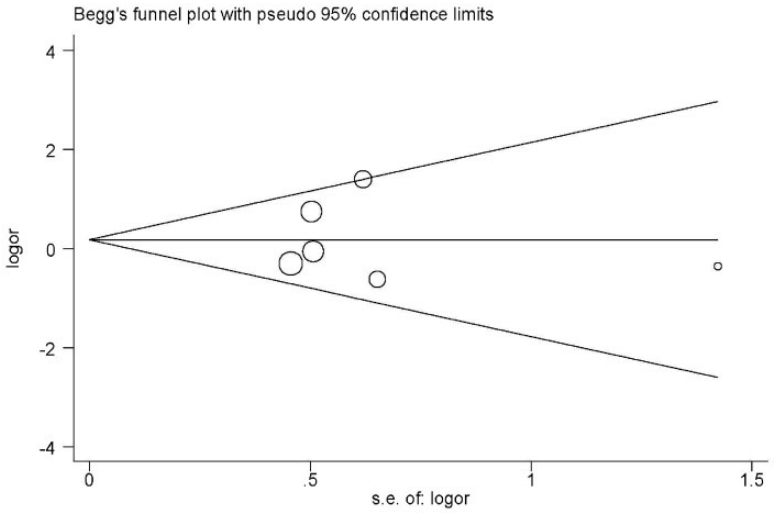

Figure 3. Funnel plot of studies examining the association between *IL1B* −511C/T polymorphism and Behçet's disease.
OR, odds ratio, s.e., standard error.

Although there was heterogeneity among the studies, the specific reason for this was unclear; however, the exclusion of non-HWE studies in the stratified analysis removed this heterogeneity, suggesting that non-HWE studies were a source of heterogeneity. BD is a complex disease with contributions from multiple genes and different genetic backgrounds and environmental factors, and the results of epidemiologic and functional studies thus rarely concur. In addition, genetic association studies designed to detect relationships between genetic variants and complex outcomes must be viewed with caution, given that many factors can potentially influence the results. Similarly, the current results should be interpreted carefully because of the limited number of studies included, which also restricted the analysis of further sub-groups.

This study had several limitations. First, we only searched for publications in English or Chinese, and unpublished studies or studies in other languages were therefore not included. Second, the ORs were not corrected, but should ideally be corrected according to ethnicity, age, and other possible factors. Third, intra-gene and gene–environment interactions might also affect the accuracy of our findings, but further evaluation of these possible interactions were restricted by a lack of original data.

In conclusion, this meta-analysis suggested that there is no association between the *IL1B* –511C/T polymorphism and BD risk. However, further high-quality studies are needed to validate these results.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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