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ORIGINAL ARTICLE

Meta-analysis of associations between interleukin-10 polymorphisms and susceptibility to Behcet's disease

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Abstract

The aim of this study was to determine whether interleukin-10 (IL-10) polymorphisms are associated with susceptibility to Behcet's disease (BD). A meta-analysis was conducted, examining the associations between the IL-10 − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms and BD in various ethnic groups. Fourteen studies involving 5992 patients and 8966 controls were considered in the meta-analysis. Meta-analysis of the IL-10 − 1082 G/A polymorphism showed no association between BD and the − 1082 G allele (odds ratio (OR) = 0.951, 95% confidence interval (CI) = 0.790–1.146, $p = 0.601$). Meta-analysis of the IL-10 − 819 C/T polymorphism revealed a significant association between BD and the − 819 C allele (OR = 0.751, 95% CI = 0.684–0.825, $p < 0.001$) in all study subjects. Stratification by ethnicity indicated a significant association between the − 819 C allele and BD in Turkish (OR = 0.779, 95% CI = 0.709–0.856, $p < 0.001$) and Asian (OR = 0.676, 95% CI = 0.631–0.725, $p < 0.001$), but not in Middle Eastern populations. Meta-analysis of the − 592 C allele showed an association with BD in all study subjects (OR = 0.792, 95% CI = 0.662–0.948, $p = 0.011$) Stratification by ethnicity indicated a significant association between the − 592 C allele and BD in Asian populations (OR = 0.656, 95% CI = 0.512–0.841, $p = 0.001$). This meta-analysis showed that the IL-10 − 819 C/T and − 592 C/A polymorphisms are associated with BD susceptibility, especially in Asian population.

Keywords Behcet's disease · Interleukin-10 · Polymorphism · Meta-analysis

Introduction

Behcet's disease (BD) is a chronic inflammatory disease characterized by recurrent oral and genital ulcers, skin lesions, and uveitis [1]. BD also affects all types and sizes of blood vessels as well as the joints, central nervous system, lungs, and gastrointestinal system [2]. Although the etiology of BD is not fully understood, it has been suggested that BD occurs owing to interactions between a susceptible genetic background and certain environmental factors.

Interleukin-10 (IL-10) is a multifunctional cytokine that has anti-inflammatory properties conferred by its ability to downregulate antigen presentation and macrophage activation [3]. IL-10, as a survival and differentiation factor, plays an important role in B cell activation and autoantibody production, also acting as an inhibitory factor during the production of T helper 1 (Th1) cytokines [4]. The IL-10 gene maps to 1q31–32 and exhibits polymorphisms in its promoter region that appear to be correlated with variations in transcription. Three of the several IL-10 polymorphisms have been studied in some detail; the − 1082 G to A (rs1800896), − 819 C to T (rs1800871), and − 592 C to A (rs1800872) polymorphisms are located at putative regulatory regions in the IL-10 promoter [5]. The − 1082 G/A polymorphism lies within a putative Ets transcription factor-binding site, while − 892 C/T lies within a putative positive regulatory region, and − 592 C/A is located within a putative STAT-3-binding site and negative regulatory region [6, 7]. Thus, polymorphisms at these sites may alter the binding sites of transcription factors, which may affect IL-10 production [5, 8, 9].

IL-10 is considered a candidate gene for BD based on its chromosomal location and functional relevance [10]. Thus, a number of studies have examined the association between IL-10 polymorphisms and BD, but the reported

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

Studies	Population	Numbers		Studied polymorphism	Findings
		Case	Control		
[11]	Middle Eastern	46	61	− 592	$p < 0.001$
[13]	Asian	1206	2475	− 819	$p < 0.001$
[12]	Turkish	142	140	− 1082	NS
[14]	Asian	718	1753	− 1082, − 819, − 592	All ($p < 0.001$)
[15]	Middle Eastern	552	417	− 819	NS
[16]	Middle Eastern	61	211	− 1082, − 819, − 592	All ($p < 0.051$)
[17]	Middle Eastern	87	97	− 1082, − 819	− 1082 ($p < 0.05$), − 819 (NS)
[18]	Asian	407	679	− 819	$p = 0.024$
[19]	European	304	313	− 592	NS
[20]	Middle Eastern	147	140	− 1082, − 819, − 592	NS
[21]	European	102	102	− 1082, − 819, − 592	NS
[22]	Asian	611	737	− 819, − 592	All ($p < 0.001$)
[22]	Turkish	1215	1279	− 819, − 592	All ($p < 0.001$)
[22]	Asian	119	140	− 819, − 592	All ($p < 0.05$)
[23]	Turkish	97	127	− 1082, − 819, − 592	NS
[24]	European	63	182	− 1082, − 819	− 1082 (NS), − 819 ($p < 0.001$)
[24]	Middle Eastern	115	113	− 1082, − 819	NS

NS, not significant

results are contradictory, possibly because of the low statistical power of individual studies [11–24]. Therefore, in order to overcome the limitations of individual studies and resolve these inconsistencies, we conducted a meta-analysis [25–27]. The aim of the present study was to determine whether the IL-10 − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms are associated with BD susceptibility in various ethnic groups.

Methods

Identification of eligible studies and data extraction

A literature search was performed for studies that examined associations between IL-10 polymorphisms and BD. The PubMed and Embase literature databases were used to identify available studies in which IL-10 polymorphisms were analyzed in patients with BD (up to June 2018). Combinations of keywords, such as "interleukin-10," "IL-10," "polymorphism," and "Behcet's disease," were entered as Medical Subject Headings (MeSH) keywords and as text words. References in the identified studies were also investigated to identify additional studies not indexed by PubMed and Embase. Studies were included in this meta-analysis if (1) they were case-control studies that determined the distributions of the IL-10 − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms in patients with BD and in normal controls; (2) they contained original data; and (3) they provided enough data to calculate odds ratios (ORs). No restrictions were placed on race, language, ethnicity, or geographic area. We excluded the following: (1) studies containing overlapping data; (2) studies in which the number of null and wild genotypes or alleles could not be ascertained; and (3) studies involving family members, because their analysis was based on linkage considerations. The following information was extracted from each study: author(s), year of publication, ethnicity of the study population, demographics, number of cases and controls, and the allele frequencies of the IL-10 − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms. Data were extracted from the original studies by two independent reviewers. Discrepancies between the reviewers were resolved by reaching a consensus, and the meta-analysis was conducted in accordance with PRISMA guidelines [28].

Evaluation of statistical associations

Meta-analyses were performed using allelic contrast of the IL-10 − 1082 G/A, − 892 C/T, and − 592 C/A polymorphisms, respectively. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were estimated for each study. Cochran's Q-statistic was also used to assess intra- and interstudy variations and heterogeneities. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I^2, which ranges from 0 to

Table 2 Meta-analysis of associations between the IL-10 − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms and BD

Polymorphism	Population	No. of studies	Sample size		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*p* value	Model	*p* value	I^2
− 1082 G/A G vs. A	Overall	9	1113	1459	0.951	0.790–1.146	0.601	R	0.062	46.1
	Middle Eastern	4	410	561	0.944	0.779–1.143	0.552	F	0.404	0
	Turkish	3	340	366	1.249	0.974–1.600	0.079	F	0.780	0
	Asian	1	300	350	0.562	0.355–0.890	0.014	na	na	na
	European	1	63	182	0.718	0.475–1.096	0.116	na	na	na
− 819 C/T C vs. T	Overall	12	5351	8154	0.751	0.684–0.825	< 0.001	R	0.011	55.0
	Middle Eastern	3	295	448	0.987	0.782–1.246	0.912	F	0.496	0
	Turkish	4	1995	1922	0.779	0.709–0.856	< 0.001	F	0.307	16.8
	Asian	5	3061	5784	0.676	0.631–0.725	< 0.001	F	0.159	39.3
	European	na	na	na	na	na	na	na	na	na
− 592 C/A C vs. A	Overall	10	3017	3454	0.792	0.662–0.948	0.011	R	< 0.001	75.8
	Middle Eastern	3	254	412	0.814	0.636–1.042	0.103	F	0.268	24.1
	Turkish	3	1443	1505	0.989	0.890–1.099	0.838	F	0.192	0
	Asian	3	1030	1227	0.656	0.512–0.841	0.001	R	0.064	63.6
	European	1	290	310	0.804	0.624–1.037	0.093	na	na	na

OR, odds ration; *CI*, confidence interval; *R*, random effects model; *F*, fixed effects model; *na*, not available

100% and represents the proportion of interstudy variability attributable to heterogeneity rather than chance [29]. I^2 values of 25%, 50%, and 75% are nominally considered low, moderate, and high estimates, respectively. The fixed effects model assumes that a genetic factor has a similar effect on BD susceptibility across all studies investigated and that observed variations among studies are caused by chance alone [30]. On the other hand, the random effects model assumes that different studies show substantial diversity and assesses both intrastudy sampling errors and interstudy variances [31]. When study groups are homogeneous, the two models are similar. However, if this is not the case, the random effects model usually provides wider CIs than the fixed effects model. The random effects model is best used in the presence of significant interstudy heterogeneity [31]. Statistical manipulations were performed using the Comprehensive Meta-Analysis software (Biosta, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To overcome the heterogeneity observed in the meta-analysis, subgroup analysis by ethnicity was performed. Funnel plots are often used to detect publication bias. However, because of the limitations of funnel plotting, which requires a range of studies of varying sizes and involves subjective judgments, we evaluated publication bias using Egger's linear regression test [32], which measures funnel plot asymmetry using a natural logarithmic scale of ORs.

Results

Studies included in the meta-analysis

One hundred five studies were identified by electronic and manual searches, and 17 were selected for a full-text review based on the title and abstract details. Three studies were excluded because they did not contain allele data or involved other diseases. Thus, 14 studies met the inclusion criteria [11–24]. One of these studies contained data on three different groups [22], and another on two different groups [24]. Therefore, we analyzed these groups independently. Accordingly, a total of 17 separate comparisons were considered in this meta-analysis, which included 5992 patients and 8966 controls and consisted of European, Asian, Turkish, and Middle Eastern populations (Table 1). Consequently, an ethnicity-specific meta-analysis was conducted for each of these populations. Nine studies examined the IL-10 − 1082 G/A polymorphism, 12 examined the − 892 C/T polymorphism, and 10 examined the − 592 C/A polymorphism. Selected characteristics of these studies, with respect to associations between IL-10 polymorphisms and BD, are summarized in Table 1.

Meta-analysis of the IL-10 – 1082 G/A, – 892 C/T, and – 592 C/A polymorphisms and BD susceptibility

Meta-analysis of the IL-10 − 1082 G/A polymorphism showed no association between BD and the IL-10 −

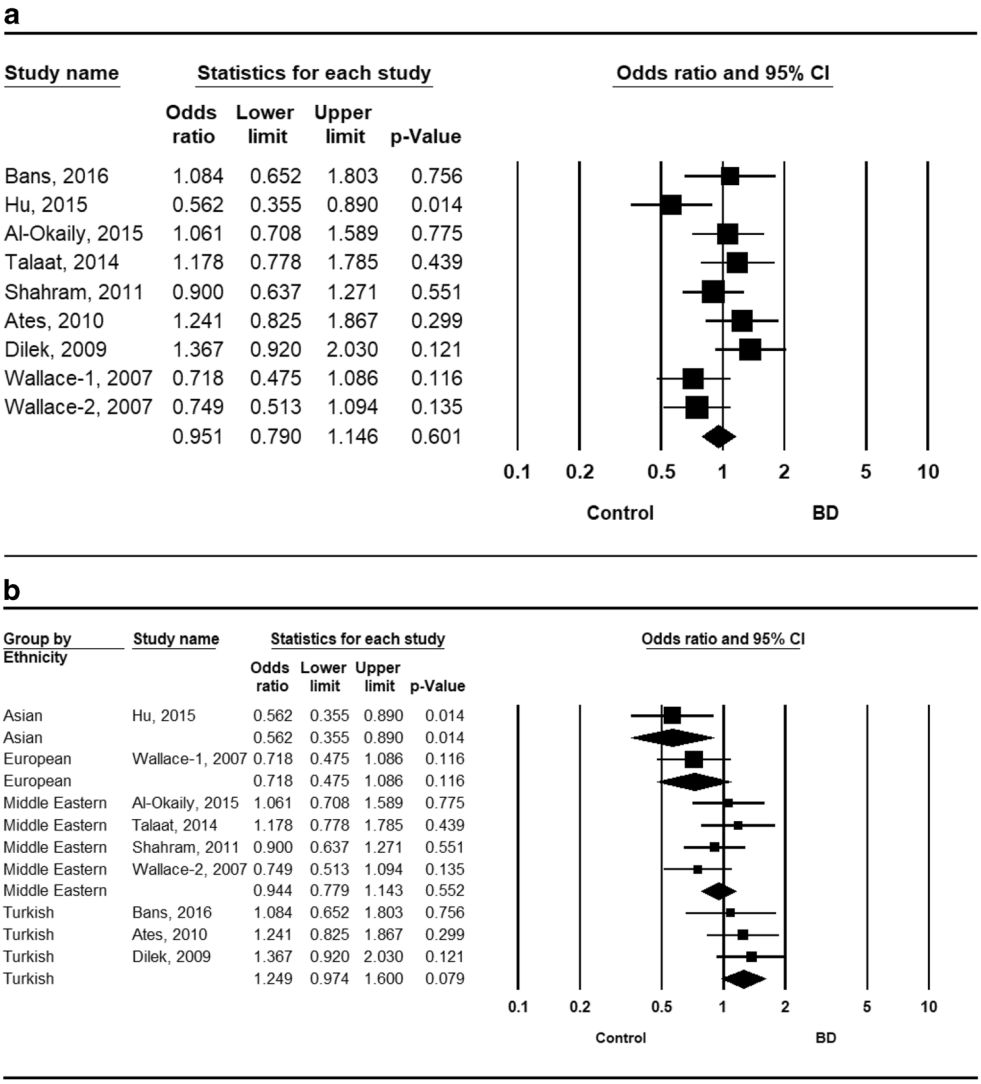

Fig. 1 Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the interleukin (IL)-10 − 1082 G allele and Behcet's disease (BD) in all subjects (**a**) and each ethnic group (**b**)

1082 G allele (OR = 0.951, 95% CI = 0.790–1.146, p = 0.601) (Table 2, Fig. 1). A subgroup meta-analysis by ethnicity showed no association between BD and the IL-10 −1082 G allele in Middle Eastern and Turkish populations (Table 2, Fig. 1). However, a single study showed an association between BD and the IL-10 − 1082 G allele in Asian populations (Table 2, Fig. 1). Meta-analysis of the IL-10 − 819 C/T polymorphism in all study subjects revealed an association between BD and the IL-10 − 819 C allele (OR = 0.751, 95% CI = 0.684–0.825, $p < 0.001$) (Table 2, Fig. 2). Stratification by ethnicity indicated a significant association between the IL-10 − 819 C allele and BD in Turkish and Asian populations (OR = 0.779, 95% CI = 0.709–0.856, $p < 0.001$; OR = 0.676, 95% CI = 0.631–0.725, $p < 0.001$), but not in Middle Eastern populations (Table 2, Fig. 2). Meta-analysis of the IL-10 − 592 C allele showed an association with BD in all study subjects (OR = 0.792, 95% CI = 0.662–0.948, $p = 0.011$) (Table 2, Fig. 3). Stratification by ethnicity indicated a significant association between the IL-10 − 592 C allele and BD in Asian populations (OR = 0.656, 95% CI = 0.512–0.841, $p = 0.001$), but not in Middle Eastern, Turkish, and European populations (Table 2, Fig. 3).

The mean plasma concentration of IL-10 was significantly lower in BD patients compared with controls [17] and the mean plasma concentration of IL-10 − 592 C/A was decreased significantly in BD patients with AA and AC genotype [11]. However, no particular genotype of the IL-10 − 1082 G/A and − 819 C/T polymorphisms could be responsible for the significant reduction of IL-10 level between BD and controls [17]. Patients with genital ulcer had significantly lower frequency of − 1082 GG and G allele, while patients with ocular manifestations had significantly higher frequency of – 1082 G allele [17]. One study showed that significantly higher frequency of GCC/ATA genotype were observed in the patient group [23], while another one indicated no significant correlation was found between IL10 GCC/ATA genotype [21].

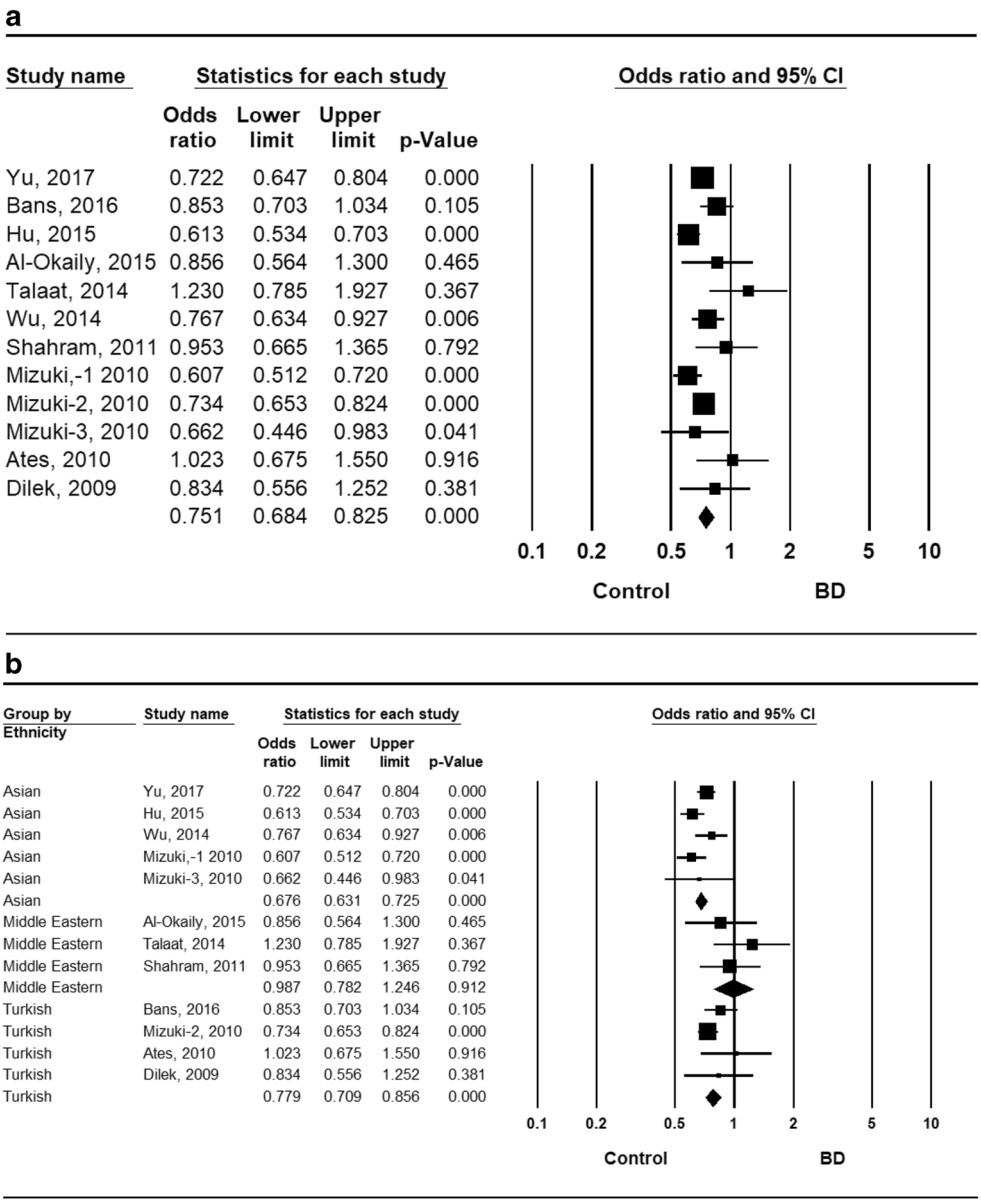

Fig. 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the interleukin (IL)-10 − 819 C allele and Behcet's disease (BD) in all subjects (**a**) and each ethnic group (**b**)

Heterogeneity and publication bias

Some heterogeneity was found in meta-analyses of the IL-10 −1082 G/A, − 819 C/T, and − 592 C/A polymorphisms (Table 2). These heterogeneities might be due to clinical or genetic heterogeneity. However, the heterogeneity was resolved or decreased in subgroup analyses by ethnicity (Table 2). There was no heterogeneity in the meta-analyses of the IL-10 − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms in each ethnic group, except for in the meta-analysis of − 592 C/A polymorphism in Asian populations (Table 2). It was difficult to correlate the funnel plot, which is usually used to detect publication bias, because of the small number of studies included in this analysis. However, Egger's regression test showed no evidence of publication bias ($p > 0.1$).

Discussion

Although the multifactorial nature of BD is well recognized, genetic factors are considered strong determinants of BD [10]. IL-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of pro-inflammatory cytokines and is a potent upregulator of B cell production and differentiation [4]. Levels of IL-10 production are important in immune regulation. IL-10 production is genetically determined and controlled at the transcriptional level, probably via regulatory sequences in the promoter region of its gene. The 5′ flanking region of the IL-10 gene, which regulates transcription, is polymorphic. In particular, three single nucleotide polymorphisms (SNPs), the − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms, have been

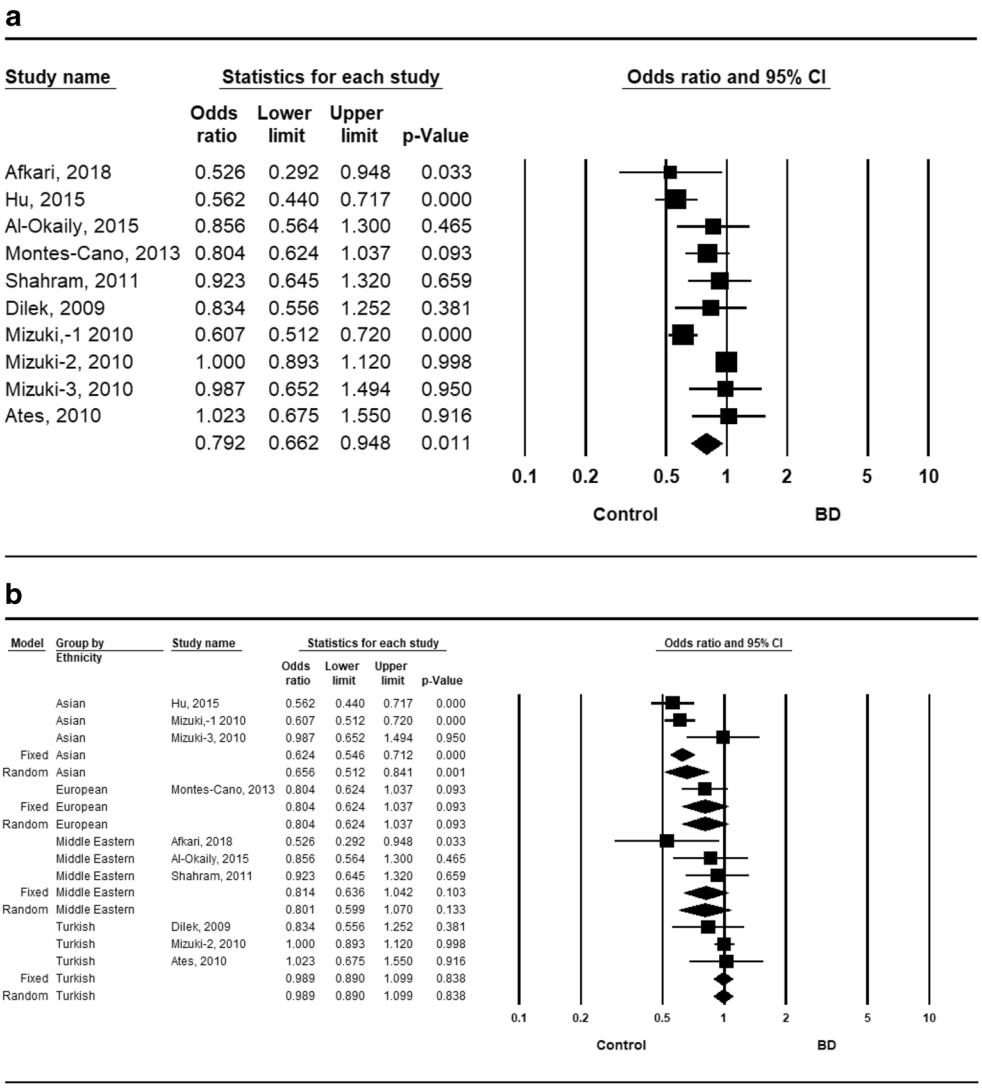

Fig. 3 Odds ratios (ORs) and 95% confidence intervals (CIs) of individual studies and pooled data for the association between the interleukin (IL)-10 − 592 C allele and Behcet's disease (BD) in all subjects (**a**) and each ethnic group (**b**)

correlated with expression and serum levels of IL-10 [5, 8, 9].

In this meta-analysis, we addressed the association between IL-10 polymorphisms and BD susceptibility. Data from published studies were combined to evaluate genetic associations between the most commonly studied polymorphisms of the IL-10 gene, namely, the − 1082 G/A, − 819 C/T, and − 592 C/A polymorphisms. We found significant associations between the IL-10 − 819 C/T and − 592 C/A polymorphisms and BD. There was a significant association between the IL-10 − 819 C allele and BD in Turkish and Asian populations and between the IL-10 − 592 C allele and BD in Asian populations, whereas meta-analysis of the IL-10 − 1082 G/A polymorphism revealed no association with BD. The associations between IL-10 polymorphisms and the risk of BD occurrence observed in this meta-analysis suggested that IL-10 could play a role in BD susceptibility.

The meta-analysis results of the IL-10 − 1082 G/A polymorphism were not consistent with the results of the functional studies of IL-10 polymorphisms. The SNP at position − 1082 lies within a putative Ets-like transcription factor-binding site, and it has been previously shown that the − 1082 G/A polymorphism is associated with serum IL-10 levels. Specifically, an A at position − 1082 is associated with reduced IL-10 levels, whereas a G is associated with higher levels [33], although Eskdale et al. [34] found that the A allele was associated with higher serum IL-10 levels than the G allele. It is not uncommon for epidemiological results to not coincide with the results of functional studies, because BD is a complex disease whose development is influenced by multiple genes, different genetic backgrounds, and environmental factors. We cannot rule out that our meta-analysis results for the IL-10 − 1082 G/A polymorphism may be due to a type II error (false-negative).

BD is associated with predominant Th1-related inflammatory responses, with a significant increase in Th1 cytokine levels [29]. Our results showed that patients with BD had significantly lower frequencies of the IL-10 − 819 C and −

592 C alleles associated with high production of the anti-inflammatory cytokine IL-10. Our meta-analysis result suggested that a genetically determined lack of IL-10 contributes to the development of BD.

The present study has some limitations that should be considered. First, the heterogeneity and confounding factors may have distorted the meta-analysis. Second, IL-10 polymorphisms may be associated with varying degrees of BD severity or with specific clinical findings, as well as susceptibility. However, the small amount of data available did not allow us to perform a meta-analysis of those associations. Third, our ethnicity-specific meta-analysis included data from Turkish, Asian, and Middle Eastern populations, and thus our results are solely applicable to these ethnic groups. Only one European study was included in this analysis. Fourth, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. Linkage disequilibrium was found for the − 1082 G/A, − 592 C/A, and − 892 C/T polymorphisms [35]. Increased IL-10 secretion has been described for the common GCC haplotype, and reduced IL-10 secretion for the least common ATA haplotypes [9]. No meta-analysis of haplotypes was possible because of the insufficiency of haplotype data.

In conclusion, this meta-analysis of the associations between IL-10 polymorphisms and BD showed that the IL-10 − 819 C/T and − 592 C/A polymorphisms are associated with BD susceptibility, especially in Asian population. Accordingly, our findings support the notion that the IL-10 polymorphisms play a role in the pathogenesis of BD. Larger-scale studies in populations comprising different ethnicities are necessary to explore the roles of these IL-10 gene polymorphisms in diverse ethnicities in the pathogenesis of BD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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