

ORIGINAL ARTICLE

TNF Polymorphisms in Patients with Behçet Disease: A Meta-analysis

Zahi Touma,^a Chantal Farra,^b Ayad Hamdan,^c Wael Shamseddeen,^d Imad Uthman,^e
Hala Hourani,^f and Thurayya Arayssi^g

^aDepartment of Internal Medicine, Division of Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada

^bDepartments of Pathology and Laboratory Medicine, American University of Beirut, Beirut, Lebanon

^cDepartment of Internal Medicine, Division of Hematology-Oncology, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts

^dChicago Medical School at Rosalind Franklin University, Division of Internal Medicine, Green Bay Road, North Chicago, Illinois

^eDepartment of Internal Medicine, American University of Beirut, Beirut, Lebanon

^fChronic Care Center, Genetic Lab, Hazmieh, Lebanon

^gWeill Cornell Medical College-Qatar, Education City, Doha Qatar

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Background and Aims. Polymorphisms in the tumor necrosis factor (TNF) gene at the locations –308, –238, –863, –857 and –1031 have been studied in various ethnic groups for possible association with Behçet's disease. The aim of this meta-analysis is to examine the association between polymorphism in the TNF gene at the locations –308, –238, –863, –857 and –1031 and Behçet's disease.

Methods. A literature review was performed using MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials for original studies published in English up to October 31, 2009 and that examined the association of the TNF- α promoter polymorphisms with Behçet's disease. All pooled odds ratios (OR) were derived from random-effects model with its 95% confidence intervals (CI). We assessed statistical heterogeneity among studies using Cochrane Q test and by calculating I². The Cochrane collaboration's software program, RevMan 5 was used to prepare and complete this review.

Results. The literature search resulted in 13 studies. Ten studies met the included criteria and thus were selected. Overall, –1031C (OR = 1.35, 95% CI = 1.09–1.68), –238A (OR = 1.51, 95% CI = 1.12–2.04) and –857T (OR = 0.76, 95% CI = 0.58–0.98) had a significant association with Behçet's disease. The pooled estimates for the other polymorphisms were not statistically significantly associated with Behçet's disease; –308A and –863A.

Conclusions. Behçet's disease was associated with the –1031C, –238A and the –857T promoter polymorphisms in various ethnic groups. © 2010 IMSS. Published by Elsevier Inc.

Key Words: Behçet's disease, Tumor necrosis factor alpha, Polymorphisms, Meta-analysis, Middle East.

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder of unclear etiology characterized by recurrent oral and genital ulcers, skin lesions and uveitis. Other manifestations include arthritis, a positive pathergy test, thrombophlebitis, central nervous system disease and gastrointestinal ulcerations (1). HLA-B51 is strongly associated with the disease in various ethnic groups but its presence alone is

not sufficient to explain all of the disease manifestations (1,2). Current evidence suggests a role for tumor necrosis factor- α (TNF) in the pathogenesis of the disease. TNF- α and soluble TNF receptors are elevated in the sera of patients with BD (3). T lymphocytes expressing the $\gamma\delta$ receptors in BD are activated *in vivo* and produce increased amounts of TNF- α and interferon γ compared with healthy controls (4). Additionally, treatment with anti-TNF- α monoclonal antibodies has resulted in improvement of various manifestations of BD (5,6).

Polymorphisms in the TNF gene at the locations –308, –238, –863, –857 and –1031 have been studied in various

Address reprint requests to: Thurayya Arayssi M.D., Weill Cornell Medical College, Qatar, Education City, Doha Qatar; Phone: +974-492-8340; FAX: +974-492-8377; E-mail: tha2002@qatar-med.cornell.edu

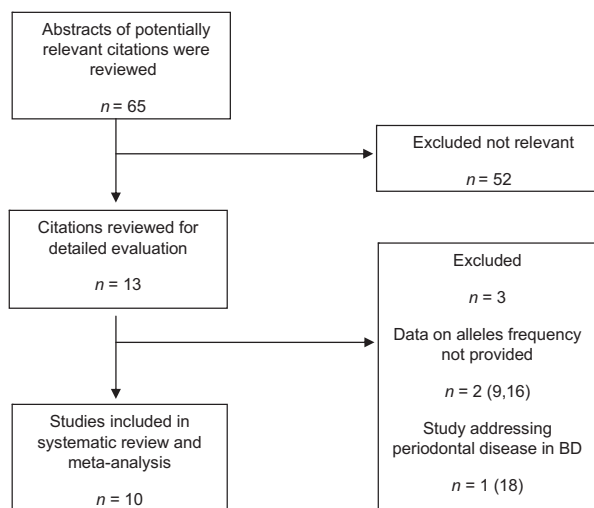


Figure 1. Selection of studies for meta-analysis of TNF polymorphisms in Behçet's disease (BD).

ethnic groups for possible association with BD. However, the allelic and genotypic associations of these studies have been contradictory. Thus, this meta-analysis aims at examining the association between polymorphism in the TNF gene at positions -308 , -238 , -863 , -857 and -1031 and susceptibility to BD.

Materials and Methods

Identification of Eligible Studies and Data Extraction

We searched MEDLINE (1950 to October 31, 2009), EMBASE (1980 to October 30, 2009), and Cochrane Central Register of Controlled Trials (1993 to October 31, 2009) for all relevant studies that examined the association of the TNF- α promoter polymorphisms with BD. We performed the search without language restriction and selected articles for inclusion on the basis of English abstracts and content. After the initial search we maintained an auto-alert and incorporated all articles until the submission date of this paper, October 31, 2009. The search terms used for MEDLINE were

modified according to database requirements. We used the following Medical Subject Heading (MeSH) or Embase terms and/or text words: Behçet's syndrome, Behçet's disease, tumor necrosis factor, genetic polymorphism, genetic predisposition, allele. No restrictions were placed on language, race, ethnicity or geographic area. We reviewed the bibliographies of the identified articles to locate further eligible studies. We identified 65 studies of which 10 were included in this meta-analysis (Figure 1). Corresponding authors were contacted for obtaining information essential for this meta-analysis, which was lacking in the published articles.

Eligible Studies and Data Abstraction (Criteria for selecting articles included in this meta-analysis.)

Two authors (T.A. and Z.T.) scanned the titles and abstracts of the articles initially. Selected articles were retrieved in full; three authors (T.A., A.H. and Z.T.) assessed the articles for eligibility. Extraction from each study was conducted independently by two authors and consensus was achieved for all data. We resolved discrepancies by consensus.

A study was included in this meta-analysis if 1) it was published by October 31, 2009, 2) it had original data and 3) the data reported were adequate to perform statistical analysis (odds ratio). No translator was necessary because no abstracts were found in any languages other than English. Studies were excluded if 1) they contained overlapping data, 2) the frequency of alleles could not be ascertained, 2) family members were studied, and 3) they were review articles and publications in duplicate. A funnel plot was not performed to assess publication bias because it is useless when the number of studies is limited, as all studies are of relatively small size.

Statistical Analysis

Allele frequencies of the TNF polymorphisms at locations -308 , -238 , -863 , -857 and -1031 from each respective study were determined in patients and controls. We estimated the odds ratios (OR) and its 95% confidence interval (CI) for the following alleles: $-308A$, $-238A$, $-863A$, $-857T$ and

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

Study	Number of patients (male/female)	Number of control (male/female)	Patients' mean age (years)	Patients' origin
Arayssi (2008)	48 (39/9)	90	32.5 \pm 11.38	Lebanon
Chang (2007)	115 (50/65)	114	39.3 \pm 9.1	Korea
Alayli (2007)	80 (40/40)	105 (58/47)	35.35 \pm 10.65	Turkey
Kamoun (2007)	89 (60/29)	157	41.4 \pm 11	Tunisia
Park (2006)	254 (130/124)	344	Youngest 3 Oldest 58	Korea
Akman (2006)	99 (52/47)	103 (52/53)	34.10 \pm 10.53	Turkey
Ates (2006)	107 (65/42)	102 (61/41)	35.0 \pm 9.5	Turkey
Lee (2003)	94 (48/46)	94	41 \pm 11	Korea
DuymazTozkir (2003)	99	96	Not available	Turkey
Storz (2008)	121	71	Not available	Turkey and Germany

Table 2. Allele frequencies of TNF- α 308A, 1031C, 238A, 857T and 863A in patients with BD

Author (year)	-308A		-1031C		-238A		-857T		-863A	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Arayssi (2008) ¹	7/88 (7.95)	16/180 (8.88)	16/92 (17.3)	29/180 (16.1)	3/88 (3.41)	7/180 (3.89)	10/88 (11.36)	23/180 (12.78)	12/90 (13.3)	33/180 (18.3)
Chang (2007) ²	13/230 (5.7)	19/228 (8.3)	51/230 (25)	53/228 (26.3)	12/230 (5.2)	7/228 (3.1)	29/230 (12.6)	41/228 (18)	41/230 (17.8)	51/228 (22.4)
Alayli (2007) ³	-	-	-	-	68/160 (42.5)	57/210 (27.1)	-	-	-	-
Kamoun (2007) ⁴	24/178 (13.6)	41/314 (13.05)	58/178 (32.5)	71/314 (22.6)	-	-	-	-	-	-
Park (2006) ²	27/508 (5.3)	64/688 (9.3)	124/508 (24.4)	132/688 (19.2)	21/508 (4.1)	20/688 (2.9)	67/508 (13.2)	112/688 (16.2)	102/508 (20.1)	98/688 (14.2)
Akman (2006) ³	-	-	47/198 (23.7)	30/206 (14.6)	-	-	-	-	-	-
Ates(2006) ³	21/214 (9.8)	20/204 (9.8)	-	-	4/214 (1.9)	6/204 (2.9)	-	-	-	-
Lee (2003) ²	12/188 (6.2)	8/188 (4.3)	-	-	-	-	-	-	-	-
Duymaz-Tozkir (2003) ³	22/198 (11)	32/192 (16.7)	-	-	-	-	-	-	-	-
Storz (2008) ^{3/5}	-	-	-	-	15/242(15.5)	9/142(12.7)	-	-	-	-

¹Lebanon.
²Korea.
³Turkey.
⁴Tunisia.
⁵Germany.

-1031C in BD patients and controls. We assessed the within- and between-study variation or heterogeneity by testing Cochran’s Q statistic and by calculating I² values. A significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies. I² measured the degree of inconsistency in the studies with values of $\leq 25\%$ showing low, 26–50% moderate and $> 50\%$ the greatest degree of heterogeneity (7). We used the random-effect model for meta-analyses because it accounts for random variability both within and among studies.

Results

The literature search identified 65 articles with 13 relevant publications (Tables 1 and 2) (2,3,8–18). Only three studies were excluded. In two studies data on allele frequency were not available and the third study addressed a very specific problem about periodontal disease in BD (9,16,18). The studies included in the meta-analysis consisted of four Turkish, three South Korean, one Tunisian, one Lebanese and one mixed Turkish and German population samples (2,3,8,10–15,17).

The 10 studies included in this meta-analysis were published in full text. Seven studies reported on -308A, five studies on -1031C, six studies on -238A, three studies on -857T and three studies on -863A. Only 3/10 studies examined the association between the polymorphism of the TNF- α gene at all positions (8,10,13). Alayli and colleagues examined the association at position -238 (11). Kamoun et al. examined the association at positions -308 and -1031 (12). Akman et al. examined the association at position -1031 (2). Ates et al. examined the association at positions -308 and -238 (14). Two studies examined the association at position -308 (3,15). One study examined the association at position -238 (17). The total number of patients with BD was 1106 and the total number of controls was 1276.

Overall -1031C (OR = 1.35, 95% CI = 1.09–1.68), -238A (OR = 1.51, 95% CI = 1.12–2.04) and -857T (OR = 0.76, 95% CI = 0.58–0.98) had a statistically significant association with BD. -1031C and -238A increased the risk of BD by 1.35 and 1.51, respectively, whereas -857T was associated with a 0.76 decreased risk of BD. There was low ($\leq 25\%$) statistical heterogeneity for -1031C, I² = 25%. There was no statistical heterogeneity for -238A and -857T, I² = 0%. There was no significant association with -308A (OR = 0.78, 95% CI = 0.61–1.01) and -863A (OR = 0.97, 95% CI = 0.56–1.69). The results of the meta-analysis are summarized in Figure 2 for the TNF- α polymorphisms -308, -1031, -857 and -238, which are the most extensively studied (Figures 2 a–c).

Discussion

Several studies have attempted for many years to determine whether polymorphisms of the TNF- α promoter region

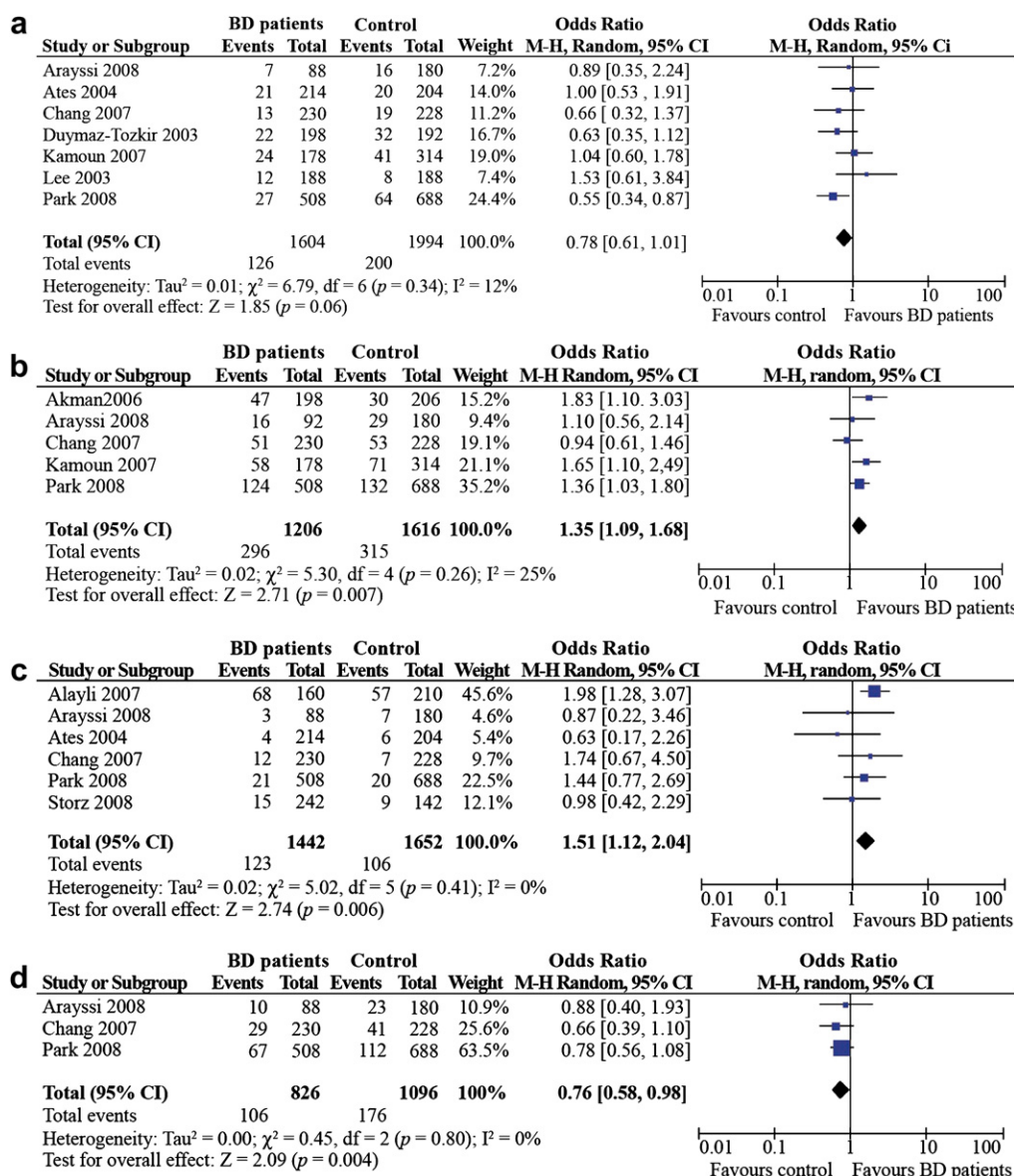


Figure 2. (a) ORs and 95% CI of individual studies and pooled data for the association of TNF- α at the location -308A and BD. (b) ORs and 95% CI of individual studies and pooled data for the association of TNF- α at the location -1031C. (c) ORs and 95% CI of individual studies and pooled data for the association of TNF- α at the location -238A and BD. (d) ORs and 95% CI of individual studies and pooled data for the association of TNF- α at the location -857T and BD. Color version of this figure available online at www.arcmedres.com.

influence the expression of TNF- α in BD, its susceptibility, or its severity and clinical features. The results of these allelic associations, however, are somewhat contradictory because the implicated polymorphic sites and allele frequencies appear to vary substantially among ethnic groups and occasionally within the same ethnic group (10,13).

This meta-analysis of TNF- α promoter polymorphism studies in a BD population of various ethnic backgrounds noted a significant association between -1031C, -857T and the -238A allele and BD and a lack of association between -863A allele with BD. The data also suggest no role for the -308 A/G polymorphism that is described to be positively associated with systemic lupus erythematosus

and erosive rheumatoid arthritis (3,9). A larger sample size is likely needed to study this association further in BD.

In our meta-analysis we excluded the publication by Ahmad et al. simply because data on allele frequency were not readily available. This study, however, confirmed a positive association with the -1031C polymorphism in UK Caucasoid patients and, if included, would further strengthen the association with this polymorphism (16).

Both the -1031C and the -238A alleles are associated with various autoimmune diseases including Crohn's disease, thyroid-associated ophthalmopathy and psoriatic arthritis (19-21). Both polymorphisms have been associated with higher TNF- α production, whether directly or indirectly

as in the case of the association of the –238 with the –376 polymorphism and may serve as useful genetic markers for high TNF production in certain populations (22).

The –857T allele was found to be associated with a decreased risk of BD from the pooled data analyzed in three studies in this meta-analysis (8,10,13). The –857T allele has recently been described to be associated with psoriatic arthritis and is reported to be a risk factor for anterior uveitis indicating biological relevance for this polymorphism (23,24). At a therapeutic level, rheumatoid arthritis patients carrying the –857T allele have a better response to TNF blocking with etanercept as compared to patients homozygous to the –857C allele (25).

In summary, this meta-analysis substantiates the association of BD with the –1031C, –857T and the –238A TNF- α promoter polymorphisms in various ethnic groups along the Silk Road. Further larger studies exploring the association of BD with –308A polymorphic site will be helpful.

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