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Original Article

Associations of *TNF-A -308* and *-238* Polymorphisms with Inflammatory Bowel Disease: A Case-Control Study and Meta-Analysis of Published Data

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory disease of the intestinal tract. Tumor necrosis factor-alpha (TNF-α) signaling plays a major role in the pathogenesis of IBD and is commonly targeted for therapeutic purposes. Results on the contribution of *TNF-α -308* and *-238* single nucleotide polymorphisms (SNP) to the susceptibility to IBD have been contradictory in different populations.

Methods: Allele frequency and genotype status of *TNF-α -308* and *-238* SNPs were investigated in 75 unrelated patients with IBD [40 Crohn's disease (CD) and 35 ulcerative colitis (UC)] and 140 healthy controls by polymerase chain reaction with sequence-specific primers (PCR-SSP). We also conducted a systematic review and meta-analysis of the published reports.

Results: *TNF-α -238* GG was detected at a higher frequency in CD and UC. *TNF-α -308* GG was more frequently detected in UC compared to control. There was no significant association between *TNF-α -238* or *-308* gene polymorphisms and patients' demography (i.e., gender and age) or disease phenotype (i.e., extraintestinal manifestations, treatment, activity index, age at onset, and duration of the disease). In the meta-analysis, *TNF-α -238* (AA/AG) genotype tended to be less frequent in patients with UC compared to healthy controls. There was no association between *TNF-α -238* gene polymorphisms (AA/AG or GG genotypes) and either form of IBD.

Conclusion: *TNF-α -308* and *-238* SNPs are associated with IBD in Iranian patients. The *TNF-α -308* AA genotype is positively correlated with UC in this meta-analysis.

Keywords: Allele Frequency; Crohn's Disease; Inflammatory Bowel Disease; Meta-Analysis; Polymorphisms; Ulcerative Colitis

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Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic relapsing-remitting inflammatory disease of the intestinal tract. The highest reported prevalence of IBD is in Europe and North America. While it is believed that IBD is less prevalent and has a milder course in Asian and Middle Eastern populations, nowadays, its prevalence is increasing, and more severe cases are observed in different regions (1, 2). The ethnicity and regional differences in the incidence of IBD, as well as its clinical course, may be attributed to environmental, lifestyle, or genetic factors (2). Although the pathogenesis of IBD is not completely understood, it occurs in the context of host-microbiota dysbiosis in a genetically susceptible host. The aberrant immune response results in chronic inflammation, which leads to disruption of the epithelial barrier integrity, thus accentuating the cycle of inappropriate immune response to the microbiota. The pattern of inflammation and the regional involvement differ in CD and UC.

Immune cells are abundantly present in the intestinal tract. Disruption of the normal host-microbiota interaction in IBD results in activation of innate and adaptive immunity, which results in excessive production of proinflammatory cytokines. However, CD and UC have distinct immune responses; while Th1 and Th17 are more active in CD, Th17 and Th2 are the predominant cells in UC (3). Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine that is crucial in multiple cellular events, including nuclear factor kappa-B (NF-κB) activation and inflammatory cytokine induction (4). TNF-α signaling plays a major role in the pathogenesis of IBD and is commonly targeted for therapeutic purposes (5-7). Fecal TNF-α is increased in active pediatric IBD and was shown to be a useful marker of disease activity in children with IBD (8).

Serum TNF-α is also elevated in active CD (9). TNF-α is highly increased in colon biopsies from inflamed and non-inflamed areas in CD (10, 11). The capacity of different immune cells to produce TNF-α is affected in IBD. In peripheral blood mononuclear cells, TNF-α expression is not increased CD (11), while TNF-α expression is increased in lamina propria mononuclear cells in inflamed areas in IBD (12). Furthermore, macrophages from IBD patients demonstrate a reduced level of bacteria-induced TNF-α production (13). The differences observed in mucosal or systemic TNF-α profiles and TNF-α based therapy in IBD significantly show the importance of the proinflammatory cytokine in the pathophysiology of IBD; however, it is not yet clear whether altered TNF-α profile transpires in the disease context or is, at least partially, a genetically driven phenomenon. The promoter region of the *TNF-α* coding gene contains multiple single nucleotide polymorphisms (SNP). SNP at position -308 correlates with the cell-specific transcriptional activity of the gene (14-22). SNPs at positions -308 and -238 in the *TNF-α* promoter region have been previously studied in several diseases (23-31), including IBD (32, 33); however, the results are contradictory in different populations. *TNF-α* promoter polymorphisms are not reported in Iranian IBD patients. Based on the lack of data in Iranian patients with IBD and conflicting findings of *TNF-α* gene polymorphisms in different IBD populations, we designed the current study to investigate (a) *TNF-α -308* and *-238* polymorphisms and their correlation with the susceptibility to IBD in Iran, and (b) the global distribution of these gene polymorphisms in IBD.

Materials and Methods

Case-Control Study

Patients

Seventy-five unrelated patients with IBD (40 CD and 35 UC) were recruited from the gastroenterology department at Imam Khomeini Hospital Complex, Tehran University of Medical Sciences. Diagnosis of CD and UC was made based on endoscopy, radiology, and pathology findings. Clinical features of the disease, including age at onset, anatomic location, extraintestinal manifestations, immunosuppressive therapy, and history of surgery, were recorded. The disease activity index was measured by the colitis activity index (CAI) in UC (34) and the CD activity index (CDAI) in CD (35). Patients' clinical records were obtained before genotyping. Patients with indeterminate colitis and other systemic inflammatory diseases were not included in this study. The control group was comprised of unrelated, age- and sex-matched, healthy blood donors with no history of

IBD or systemic diseases as previously described (36). The study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Tehran University of Medical Sciences. Written informed consent was obtained from patients before enrolment.

Genotyping

Five mL of peripheral venous blood was collected in EDTA-anticoagulated tubes and stored at -20°C for further processing. Genomic DNA was extracted by the salting out method and stored at -20°C. Genotyping was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP assay kit; Heidelberg University, Heidelberg, Germany) as previously described (36). PCR was performed in primer pair-coated 96-well plates with a thermal cycler Techne Flexigene apparatus (Rosche, Cambridge, UK). Amplification condition was as follows: initial denaturation 94°C, 2 min; denaturation 94°C, 10 sec; annealing + extension 65°C, 1 min (10 cycles); denaturation 94°C, 10 sec; annealing 61°C, 50 sec; extension 72°C, 30 sec (20 cycles). Each well also contained primer pairs for housekeeping genes β-globin or C-reactive protein. PCR products were visualized on a 2% agarose gel with an ultraviolet transilluminator.

Statistical Analysis

Data are expressed as either number (percent) or mean ± standard deviation (SD). Allele and genotype frequencies were compared by χ2 test, and odds ratio (OR) (95% confidence interval; CI) was calculated. Genotype-phenotype correlations were assessed by χ2 test for categorical variables and ANOVA for continuous variables. Statistical analyses were performed with SPSS (version 19; SPSS, Chicago, IL, USA). *p*-values of less than 0.05 were considered statistically significant.

Systematic Review and Meta-analysis

Search Strategy, Study Selection, and Data Extraction

A literature search was conducted in PubMed with the combination of the following keywords: inflammatory bowel disease, IBD, ulcerative colitis, UC, Crohn's disease, CD, TNF, Tumor necrosis factor, SNP, single nucleotide polymorphism, polymorphism. The search was updated until June 2020. Inclusion criteria were English language, case-control study, and availability of genotype status results. Studies on pediatric cases and variants of IBD (e.g., fistulizing CD) were excluded. Abstracts and full-texts were systematically reviewed by SM. Genotype frequencies were extracted from included studies by SM. The flow diagram of the literature review and study selection is shown in **Figure 1**.

Meta-Analysis

Meta-analysis was performed as previously described (37). For individual studies, genotype frequencies were converted into individual 2 × 2 tables, and OR (95% CI) was reported. For the whole group, pooled OR of the genotypes using

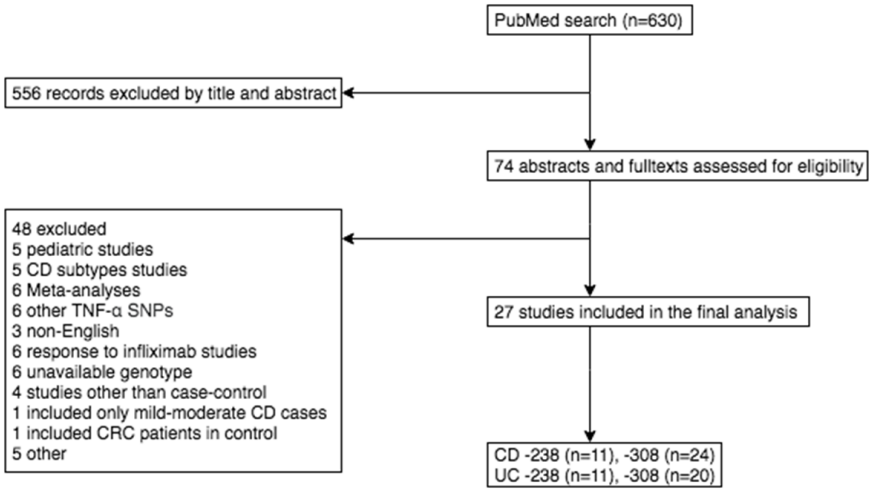

Figure 1. Systematic review flow diagram

random- or fixed-effects models was calculated. $I^2 > 50\%$ indicated inconsistency and heterogeneity and necessitated a random-effect model, while $I^2 \leq 50\%$ was an indication for a fixed-effect model. Review Manager version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, 2011) was used to analyze the data.

Results

TNF-α -238 and *TNF-α -308* Gene Polymorphisms Are Associated with IBD in Iranian Population

Overall, 40 CD (19, 47.5% male), 35 UC (17, 48.6% male), and 140 healthy controls were investigated. The mean age of the individuals was 37.70 ± 2.14 and 32.03 ± 1.36 years in the CD and UC groups, respectively. Patients' characteristics are summarised in **Table 1**. *TNF-α -238* GG was detected at a higher frequency in CD [OR=0.072; $p<0.001$] and UC [OR=0.085; $p<0.001$] compared to the control. Likewise, *TNF-α -308* GG was more frequent in UC compared to control [OR=0.157; $p=0.006$] **Table 2**. There was no significant association between *TNF-α -238* or *-308* gene polymorphisms and patients' demography (i.e., gender and age) or disease phenotype (i.e., extraintestinal manifestations, treatment, activity index, age at onset, and duration of the disease).

Table 1. Patients' characteristics

Features	CD (n=40)	UC (n=35)
Age, mean ± SD	37.70 ± 2.14	32.03 ± 1.36
Gender, male, n (%)	19 (47.5)	17 (48.6)
Anatomic location, n (%)	Jejunoileitis 7 (17.5) Terminal Ileum 6 (15) Ileocolitis 13 (32) Colitis 14 (35)	Ileocolitis 1 (2.9) Left Colitis 21 (60) Pancolitis 6 (17.1) Proctitis 7 (20)
Age at onset, mean ± SD	31.0 ±12.30	24.48 ± 6.05
Duration, mean ± SD	6.7 ± 5.93	7.27 ± 5.49
Disease activity index, mean ± SD	165.23 ± 118.10	7.03 ± 9.89
Extraintestinal Manifestation, n (%)		
Yes	6 (15)	9 (25.7)
No	34 (85)	26 (74.3)
Immunosuppressive, n (%)		
Yes	30 (75)	23 (65.7)
No	10 (25)	12 (34.3)
Surgery, n (%)		
Yes	10 (25)	2 (5.7)
No	30 (75)	33 (94.3)

TNF-α -238 and *-308* Gene Polymorphisms Are not Associated with IBD Based on the Meta-analysis.

The characteristics of the included studies are summarised in **Table 3**. *TNF-α -238* (AA/AG) genotype tended to be less frequent in patients with UC compared to healthy controls **(Figure 2)**. Further analysis of *TNF-α* -238 based on AG genotypes revealed a shift toward less frequent *TNF-α* -238 (AG) genotype in UC versus control (OR= 0.78; $p=0.06$) **(Figure 3)**. There was no association between *TNF-α* -308 gene polymorphisms (AA/AG or GG genotypes) and either form of IBD **(Figure 4)**. In addition, further analysis based on the high-producer AA genotype did not show any significant association between this genotype and risk of UC **(Figure 5)**.

Discussion

TNF-α plays a major role in the pathogenesis of IBD and is being targeted for its treatment (5-7). *TNF-α* promoter is a polymorphic region and contains multiple SNPs. Polymorphisms in the promoter region can affect the transcription regulation of the gene. *TNF-α -308* and *-238* haplotypes affect TNF-α expression by PBMCs in vitro (38). No significant association was found between *TNF -308* genotype and TNF-α production by the colon tissue in inflamed areas in CD (39). Serum level of TNF-α was significantly af-

Table 2. Frequency of *TNF-α -308* and *-238* promoter polymorphisms in patients with IBD compared to the controls.

Disease	Position	Allele/ Genotype	Control n(%)	Case n(%)	*P*-value	OR (95% CI)
IBD	-308	A	39(14.2)	8 (5.4)	**0.006**	0.344 (0.156-0.758)
		G	235(85.8)	140 (94.6)		
		AA	0(0)	0	-	-
		AG	39(28.5)	8 (10.8)	**0.003**	3.283 (1.443-7.471)
		GG	98(71.5)	66 (89.2)	**0.003**	0.305 (0.134-0.693)
	-238	A	59(21.5)	4 (2.7)	**0.000**	0.101 (0.036-0.285)
		G	215(78.5)	144 (97.3)		
		AA	1(0.7)	0	0.461	1.007 (0.993-1.022)
		AG	57(41.6)	4 (5.4)	**0.000**	12.469 (4.306-36.109)
		GG	79(57.7)	70 (94.6)	**0.000**	0.078 (0.027-0.225)
CD	-308	A	39(14.2)	6 (7.5)	0.112	0.489 (0.199-1.200)
		G	235(85.8)	74 (92.5)		
		AA	0(0)	0	-	-
		AG	39(28.5)	6 (15.0)	0.085	2.255 (0.877-5.796)
		GG	98(71.5)	34 (85.0)	0.085	0.443 (0.173-1.140)
	-238	A	59(21.5)	2 (2.5)	**0.000**	0.093 (0.022-0.392)
		G	215(78.5)	78 (97.5)		
		AA	1(0.7)	0	0.588	-
		AG	57(41.6)	2 (5.0)	**0.000**	13.538 (3.138-58.404)
		GG	79(57.7)	38 (95.0)	**0.000**	0.072 (0.017-0.309)
UC	-308	A	39(14.2)	2 (2.9)	**0.010**	0.183 (0.043-0.776)
		G	235(85.8)	66 (97.1)		
		AA	0(0)	0	-	-
		AG	39(28.5)	2 (5.9)	**0.006**	6.367 (1.455-27.859)
		GG	98(71.5)	32 (94.1)	**0.006**	0.157 (0.036-0.687)
	-238	A	59(21.5)	2 (2.9)	**0.000**	0.110 (0.026-0.464)
		G	215(78.5)	66 (97.1)		
		AA	1(0.7)	0	0.617	-
		AG	57(41.6)	2 (5.9)	**0.000**	11.400 (2.625-49.502)
		GG	79(57.7)	32 (94.1)	**0.000**	0.085 (0.020-0.370)

OR, Odds ratio (95% CI; Wald's 95% confidence interval)

fected by the *TNF -308* genotype in fistulized CD (40). *TNF-α -308* and *-238* SNPs have been previously studied in IBD. However, the results are controversial. We investigated the *TNF-α -308* and *-238* SNPs in Iranian patients with IBD. We detected a significant association of *TNF-α -238* GG genotype with both CD and UC compared to healthy controls. Similarly, a positive association was detected between *TNF-α -238* allele frequency and UC in a Mexican Mestizo population (41). However, previous reports on the association of *TNF-α -238* genotype with IBD are unclear. No significant association between *TNF-α -238* genotype and UC or CD was observed in other reports (32), (42-49). We also detected an association between *TNF-α -308* allele frequency and genotype with UC. Likewise, *TNF-α -308* allele frequency was significantly associated with UC in Japanese patients (42). Similarly, a positive association was detected between *TNF-α -308* allele frequency and genotype and UC in Mexican Mestizo (41), Chinese (50), and Hungarian patients (44). *TNF-α -308* genotype was not associated with CD in Iranian patients. In contrast, *TNF-α -308* allele frequency and genotype were significantly associated with CD in Korean (43), Hungarian (44), and Portuguese patients (51). Previous meta-analyses did not detect a significant association between *TNF-α -308* and *-238* status with susceptibility to UC or CD (32, 52, 53). However, in other meta-analyses, the *TNF-α -308* genotype was significantly associated with UC and CD in pooled and ethnicity analyses (33, 54). In a meta-analysis of previously published reports, *TNF-α -238* AA/AG genotype tended to be less frequent in patients with UC compared to healthy controls. There was no association between *TNF-α -308* gene polymorphisms (AA/AG or GG genotypes) and either form of IBD. In addition, further analysis based on the high-producer AA genotype did not show any significant association between this genotype and risk of UC. Genotype-phenotype association

Table 3. Studies included in the meta-analysis.

SNP	Disease	Significant Association	Country	Study	Reference
-238, -308	CD, UC	No	The Netherlands	Bouma 1996	(2)
			Turkey	Celik 2006	(3)
			New Zealand	Ferguson 2008	(4)
			Spain	Lopez Hernandez 2013	(5)
			Japan	Negoro 1999	(6)
			Japan	Sashio 2002	(7)
			Iran	Naderi 2014	(8)
	CD	No	Korea	Yang 2006	(9)
			Canada	Zipperlen 2005	(10)
-238	CD, UC	No	Hungary	Vatay 2003	(11)
			Serbia	Stankovic 2015	(12)
	UC	No	Mexico	Yamamuto-furusho 2004	(13)
-308	CD, UC	No	Canada	Cantor 2005	(14)
			Spain	Castro-santos 2006	(15)
			India	Mittal 2007	(16)
			Iran	Bonyadi 2014	(17)
		Yes	Hungary	Vatay 2003	(11)
			Saudi	Al-Meghaiseeb 2016	(18)
	CD	No	Ireland	Balding 2004	(19)
			Portugal	Ferreira 2005	(20)
			Australia	Fowler 2005	(21)
			New Zealand	Hong 2008	(22)
			Czech Republic	Hradsky 2008	(23)
			Brazil	Santana 2011	(24)
			China	Song 2005	(25)
		Yes	Serbia	Stankovic 2015	(12)
	UC	Yes	Ireland	Balding 2004	(19)
			China	Cao 2006	(26)
			Japan	Sashio 2002	(7)
			China	Song 2005	(25)
			Mexico	Yamamuto-furusho 2004	(13)
			Turkey	Gok 2014	(27)
			Brazil	Tavares 2016	(28)

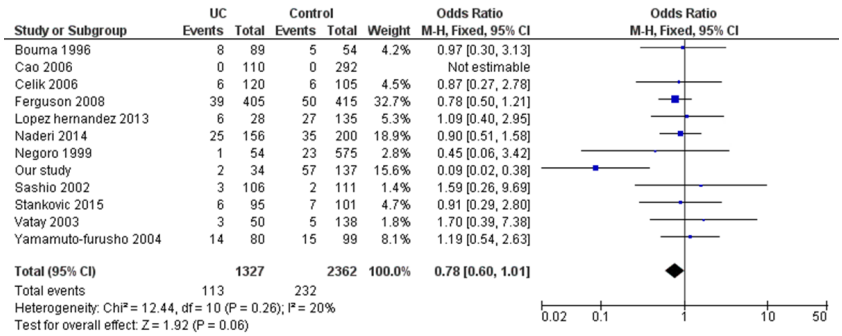

Figure 2. Meta-analysis of *TNF–α 238* (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AA/AG genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

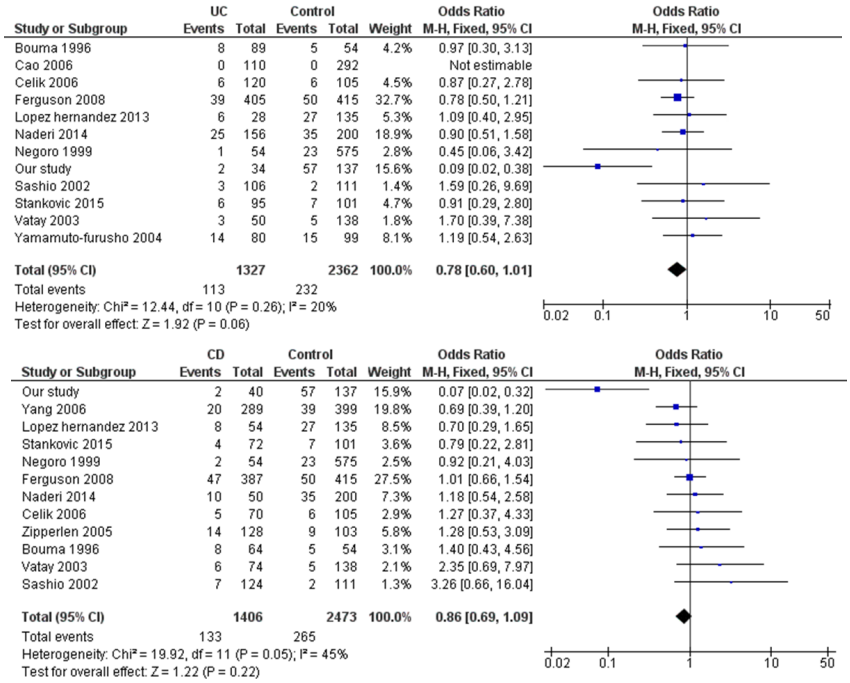

Figure 3. Meta-analysis of *TNF–α 238* (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AG genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

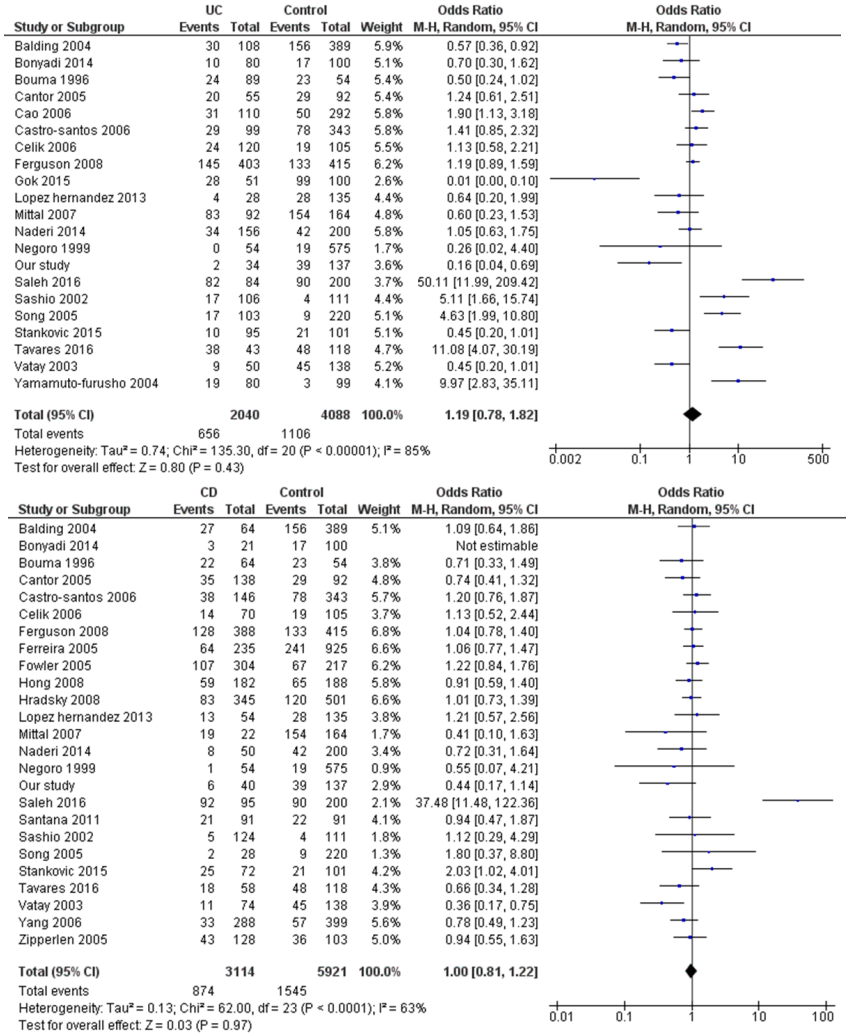

Figure 4. Meta-analysis of *TNF–α -308* (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AA/AG genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

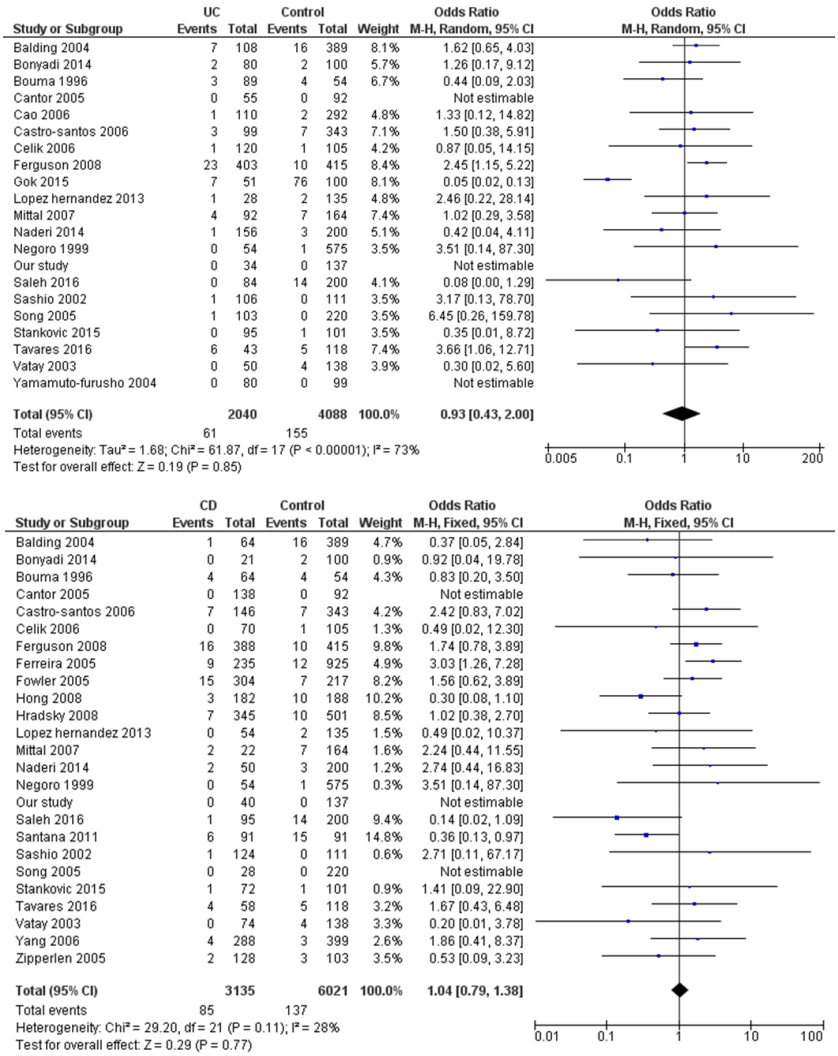

Figure 5. Meta-analysis of *TNF–α -308* (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AA genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

was examined in CD, UC, or IBD for gender, age, extraintestinal manifestations, immunosuppressive therapy, surgery, DAI, age at onset, and duration of the disease. *TNF-α -238* and *-308* SNPs had no significant association with clinical features in our study. Similarly, no association was observed between *TNF-α -308* and *-238* status and the presence of extraintestinal manifestations, surgery, disease activity, age, age at onset, location, gender, family history, presence of granuloma, response to treatment, and steroid dependency in CD or UC (40, 41, 44, 45, 47, 48, 50, 55, 56). The association of *TNF-α -308* and *-238* with clinical features of IBD is summarized in **Table 4**. TNF-α plays a major role in the pathogenesis of IBD and is being targeted for its treatment. We identified a positive correlation between *TNF-α -308* and *-238* promoter polymorphisms with the occurrence of CD and UC in Iranian patients. Although the meta-analysis did not reveal a significant association between *TNF-α -308* and *-238* genotypes and risk of CD or UC, previous reports have identified a correlation between these SNPs status and clinical features such as disease behavior, steroid dependency, and undergoing surgery (32, 39, 51, 57), which could affect the clinical decision making. However, no association with response to Infliximab has been identified (58-60).

Conclusion

The Association of *TNF-α -308* and *-238* genotypes with IBD and its clinical attributes demonstrates a country-specific pattern that underscores the importance of a personalized approach to IBD diagnosis and management.

Table 4. Association of *TNF-α -308* and *-238* SNPs with clinical features in IBD

SNP	Cases	Country	Clinical features	Association	Reference
TNF-α -238	Pediatric CD	Canada	Anatomic location	**Yes**	(29)
	CD and UC	Iran	Gender Age Extraintestinal manifestations, Immunosuppressive therapy Surgery DAI Age at onset Duration of the disease	No	This study
		Hungary	Extraintestinal manifestations	No	(11)
	CD	Korea	Gender	No	(9)
			Perianal lesion	**Yes**	(30)
		USA, Europe, Canada, Israel	Response to Infliximab	No	(31)
		Israel	Granuloma	No	(32)
		Hungary	Disease behavior	No	(11)
		Canada	Age at onset Anatomic location Response to treatment	No	(10)
	UC	Mexico	Anatomic location Extraintestinal manifestations Surgery	No	(13)
		Japan	Anatomic location	**Yes**	(7)
	Pediatric CD and UC	Czech Republic	Serum CRP Disease activity index	**Yes**	(33)
TNF-α -308	Pediatric CD	Canada	Anatomic location	**Yes**	(29)
	CD and UC	Iran	Gender Age Extraintestinal manifestations, Immunosuppressive therapy Surgery DAI Age at onset Duration of the disease	No	This study
		Korea	ANCA positive	**Yes**	(30)
		Hungary	Serum CRP Disease activity	**Yes**	(11)
			Extraintestinal manifestations Surgery Disease activity	No	
		Canada	Gender Age at onset Family history Response to treatment Surgery	No	(14)
		Saudi	Gender	No	(18)
		Serbia	IBD development	Yes	(12)
TNF-α -308	CD	Brazil	Fistulizing	No	(28)
	CD and UC	China	Age Gender Disease duration Anatomic location Disease activity	No	(25)
	CD	USA, Europe, Canada, Israel	Response to Infliximab	No	(31)
		Hungary	Disease behavior	No	(11)
		Korea	Gender	No	(9)
		Israel	Granuloma	No	(32)

Table 4. Continued

	Canada	Age at onset Anatomic location Response to treatment	No	(10)
	Brazil	Disease behavior Surgery	**Yes**	(24)
	Spain	Extraintestinal manifestations	**Yes**	(15)
		Steroid dependency Anatomic location Disease behavior	No	
	Portugal	Extraintestinal manifestations Anatomic location Surgery	**Yes**	(20)
	Belgium	Steroid-dependency Anatomic location Disease behaviour	**Yes**	(34)
		TNF-α production by the colon tissue in inflamed areas	No	
		Response to infliximab	No	(35)
Fistulizing CD	Spain	Gender Anatomic location Duration Disease activity index	No	(36)
		Serum level of TNF-α Extraintestinal manifestations	**Yes**	
UC	Spain	Presence of ANCA	**Yes**	(37)
			No	(38)
		Response to infliximab Serum TNF-α	No	(39)
		Steroid dependency Extraintestinal manifestations Anatomic location	No	(37)
	Japan	Anatomic location	No	(7)
	New Zealand	Anatomic location Surgery	**Yes**	(4)
	Mexico	Anatomic location Extraintestinal manifestations Surgery	No	(13)
	Canada	Anatomic location	**Yes**	(14)

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement

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Ethics

The research was compliant with ethical rules, and no humans participated.

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