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Lack of association between IRGM1 (rs13361189), PTGER4 (rs 1373692) and CARD8 (rs 2043211) polymorphism and Behçet's disease: A study from Turkey

Sibel Dogan[a*], Basak Yalcin[b,c], Nilgun Atakan[a], Ahu Yorulmaz[c], Ferda Artuz[c,d]

[a] *Department of Dermatology And Venereology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[b] *Department of Dermatology And Venereology, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey*
[c] *Clinic of Dermatology and Venereology, Ankara Numune Training and Research Hospital, Ankara, Turkey*
[d] *Department of Dermatology and Venereology, Faculty of Medicine, Hitit University, Çorum, Turkey*

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*** Correspondence to:**
Sibel Dogan
Department of Dermatology and Venereology,
Faculty of Medicine,
Hacettepe University,
Ankara, Turkey
e-mail: sibel.dogan@hacettepe.edu.tr

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ABSTRACT

Behçet's disease (BD) is a severe inflammatory vasculitis which is very common among Turkish population. Recently, IRGM1 (rs13361189), PTGER4 (rs1373692) and CARD8 (rs2043211) polymorphisms are shown to be associated with several inflammatory diseases. In this study, we investigated the association of IRGM1 (rs13361189), PTGER4 (rs1373692) and CARD8 (rs2043211) polymorphisms with BD and their probable implications on clinical manifestations of BD in a Turkish patient cohort. 116 patients and 150 healthy controls genomic DNA were studied. Allele-specific primers were used for genotyping. No significant difference was found between patient and controls according to genotypic distribution and allelic frequencies of IRGM1 (rs13361189), PTGER4 (rs1373692) and CARD8 (rs2043211) ($p>0.05$). No statistically significant difference was found in genotypic or allellic distribution of the same polymorphisms according to gender or clinical characteristics between patients and controls ($p>0.05$). Our study is to our knowledge the first report from Turkey regarding BD and IRGM1 (rs13361189), PTGER4 (rs1373692) and CARD8 (rs2043211) polymorphisms. IRGM gene polymorphisms seems to cause predilection for autoimmunity in certain ethnic groups but not in Turkish BD patients. CARD8 gene polymorphisms and other inflammasome related genes may play a role in immune pathomechanisms in BD and separate studies including BD patients with similar clinical characteristics are required for investigating different SNPs as a probable disease susceptibility factor.

1. Introduction

Behçet's disease (BD) is a complex vasculitic syndrome characterized by relapsing oral and genital aphthae, papulo-pustular cutaneous lesions, genital erythema nodosum like lesions, pathergy positivity accompanied with ocular and vascular involvement (Mat et al., 2013). Immune system disregularities which cause the cutaneous and other systemic features of the syndrome are believed to be triggered by microbial and/or enviromental agents (Gül, 2001; Krause and Weinberger, 2008). BD is known as a sporadic disease but it has a typical geographic distribution. Its highest prevalence is along the old Silk Road which extends from the Middle East to China. HLA-B51/HLAB5 that is more prevalent in Turkish, Middle Eastern, and Japanese populations is a predictive factor for BD development (Gül, 2001; Krause and Weinberger, 2008; Mat et al., 2013). Several genes whose functional polymorphisms are suggested to take role in pathogenesis of inflammatory diseases such as

inflammatory bowel diseases, ankylosing spondylitis and systemic lupus erythematosus are described however the role of these genetic polymorphisms in BD patients have not been investigated yet (Chai et al., 2013; Duraes et al., 2013).

The aim of this study was to investigate single nucleotide polymorphisms (SNP) of candidate susceptibility genes for BD. We investigated the association of IRGM1 (rs13361189), PTGER4 (rs 1373692) and CARD8 (rs 2043211) polymorphisms with BD and their probable implications on clinical manifestations of BD in a Turkish patient cohort including immune related GTPase M (IRGM1) gene (rs13361189), prostaglandin E2 receptor subtype EP4 (PTGER4) gene (rs 1373692) and caspase activating and recruitment domain 8 (CARD8) gene (rs 2043211).

2. Materials and methods

Ethic statements

A subject's written consent was obtained according to declaration of Helsinki and the design of the study was approved by the ethics committee of Ankara Numune Training and Research Hospital.

Experimental subjects

Patients

One hundred and sixteen BD patients who met the criteria of International Study Group criteria for BD and who were diagnosed at our hospital's dermatology and venerology clinic were recruited for this study. A hundred fifty age and sex matched healthy individuals without any inflammatory disorders were recruited for healthy control group.

Table 2. PCR component and protocol

8 PCRs are set for each sample, according to the following protocol

Component	Volume Per Reaction (μl)
dH_20	17.8
10x Buffer Complete (Bioron Inc.)	2.5
dNTP mix, 10mM each	0.5
Primer Forward (5 μM)	1
Primer Reverse (5 μM)	1
SuperHotTaq (Bioron Inc.)	0.2
DNA template (20-50 ng/μl)	2
Total	2.5

Thermal cycler protocol for PCRs is as follows

Temperature (^{0}C)	Time (min:sec)	Cycle
95	10:00	1
95	00:45	
60	00:45	35
72	00:45	
72	10:00	1
4	∞	1

Genotyping

200 μl peripheric blood sample was used to isolate genomic DNA. SnaPshot® multiplex system (Applied Biosystems Inc.) was used for polymorphism screening. Three primers were designed for each 3 polymorphisms; 2 for PCR and 1 for SnaPshot® reaction. Primer sequences are shown below (Table 1, 2).

NucleoFast® 96 PCR kit (MACHEREY-NAGEL GmbH) was used for the purification and combination of all 3 reactions. Electropherograms obtained from capillary electrophoresis were interpreted by GeneMapper 4.0 software (Applied Biosystems Inc.).

Table 1. Experimental data (Primer sequences)

Pr#29_rs 13361189	GACTGACTGACTGACTGACTGACTGACTGACTGTGAGCACGGGGTCTACTAATATACATCC
Pr#29_rs 1373692	ACTGACTGACTGACTGACTGACTGACTGACTGTGATGGTTTGACACCAAAAGGAGA
Pr#29_rs 2043211	GACTGACTGACTGACTGACTGACTGACTGACTGACTGACTGTGAGACAGAGGCAGAGCCATTATTG

Demographic and clinical data of the patients

Personal demographic features including sex, date of birth; age of disease onset, disease duration and family history for BD were asked and collected via standardized questionnaires. Clinical findings including mucocutaneous findings (recurring oral and genital aphthous ulceration, papulo-pustular cutaneous lesions, erythema nodosum like lesions, pathergy positivity); ocular lesions (diagnosed by an ophtalmologist consultations), presence of arthralgia/arthritis, gastrointestinal involvement (diagnosed by endoscopy and colonoscopy), cardiovascular involvement (superficial thrombophlebitis, arterial disease, aneurysms, thrombosis, vasculitis) and central nervous system disorders (behavioral disorder, epilepsy, thrombus induced neurologic symptoms, vasculitis) were also investigated.

Statistical analyses

SPSS 13.0 was used for statistical analysis. Fischer exact chi-square test and chi-square test was used for comparisons of allele frequency and polymorphic genotypes. P values which are <0.05 were accepted to show statistical significance.

3. Results

One hundred and sixteen (male: 44; female: 72) patients with BD and 150 controls (male: 47; female: 103) were included. Mean age was 38.6±9.7 years for patients and 40.6±13.1 years for controls. Mean disease onset age was 29.4±8.0 years and mean disease duration was 8.5±4.2 years. The features of clinics of BD patients are shown in Table 3.

Genotype and allele frequencies of polymorphisms in IRGM1 (rs13361189), PTGER4 (rs 1373692) and

Table 3. Clinical characteristics of patients with BD

Clinical characteristics	Number of patients
	n (%)
Oral aphthae	116 (100)
Genital aphthae	105 (90.5)
Erythema nodosum like lesions	77 (66.3)
Papulopustular skin lesions	72 (62.0)
Skin Test Positivity (Pathergy)	49 (42.2)
Ocular involvement	33 (28.4)
Joint involvement	32 (27.5)
Vascular system involvement	23 (19.8)
Gastrointestinal system involvement	11 (9.5)
Nervous system involvement	8 (6.8)
Family history	22 (19)

BD: Behçet's disease

CARD8 (rs2043211) in patient and control groups are shown in Table 4. There was no significant difference detected between patients and controls according to genotypic distribution of all three SNP polymorpisms ($p>0.05$). No statistically significant difference was found between patients and controls according to the allele frequencies regarding studied polymorphisms ($p>0.05$).

Genotypic and allelic distribution of SNPs in BD patients were compared according to the presence of clinical features of BD and family history. No statistically significant difference was found in genotypic or allellic distribution of studied polymorphisms according to gender or other clinical characteristics between patient and control groups ($p>0.05$ for each).

4. Discussion

Autoimmunity and immune dysregulatory mechanisms are considered to be the pathogenesis of BD in genetically predisposed individuals (Gül, 2001; Krause and Weinberger, 2008; Mat et al., 2013). Geographic distribution, increased frequency of the disease in some ethnic populations and the presence of familial cases hint for BD's genetic background and studies towards genetic associations of the disease have been supporting literature in this aspect (Gül, 2001; Krause and Weinberger, 2008; Seyahi et al., 2010; Kaneko et al., 2011; Mat et al., 2013). Genes related to immune response and autoinflammation may predispose and set clinical predominance of disease characteristics for BD which is a complex vasculitic syndrome affecting various organ systems (Gül, 2001; Krause and Weinberger, 2008; Kaneko et al., 2011). The identification of a probable gene for a role of predisposition and prognosis is therefore crucial in BD patients for diagnosis, preventive measures for certain complications and follow-up. Although the exact pathomechanism of aberran immun response initiating inflammation in BD is still unknown, autoimmunity has been suggested as a main pathomechanism (Gül, 2001; Direskeneli, 2006; Krause and Weinberger, 2008; Kaneko et al., 2011; Mat et al., 2013). The recognition of self antigens which show molecular homology with some infectious molecules is suggested to act as a a lead in autoreactive immune response in BD.

Enhanced T-cell response against heat shock protein (HSP)-60 and HSP-65 is obtained after exposure to both bacterial and human homogenates in BD patients (Kaneko et al., 2008). Systemic involvement observed in BD results from the development of vasculitic/vasculopathic lesions which exhibit microscopic evidence of inflammatory tissue infiltration with T cells and neutrophils that are triggered by self recognition mechanisms (Direskeneli, 2006; Krause and Weinberger, 2008; Kaneko et al., 2011). T-helper type 1 (TH1) predominant response and elevations of cytokines such as interleukin (IL)-2 and interferon-γ (IFN-γ) are responsible for the systemic inflammatory

Table 4. Genotype and allele frequencies of polymorphisms in IRGM1 (rs13361189), PTGER4 (rs1373692) and CARD8 (rs2043211) in patient and control groups

Gene	SNP	Genotype allele	Patients (N) (%)	Controls (N) (%)	*p*
IRGM	rs13361189	GG	75 (64,6)	108 (72.0)	>0.05
		GC	38 (32.8)	40 (26.7)	>0.05
		CC	3 (2.6)	2 (1.3)	>0.05
		G	189 (81.5)	256 (85.3)	>0.05
		C	43 (18.5)	44 (14.7)	>0.05
PTGER4	rs1373692	GG	45 (38.8)	54 (36)	>0.05
		GT	51 (44)	66 (44)	>0.05
		TT	20 (17.2)	30 (20)	>0.05
		G	142 (61.2)	175 (58.3)	>0.05
		T	90 (38.8)	125 (41.7)	>0.05
CARD8	rs2043211	TT	59 (50.9)	72 (48)	>0.05
		TA	46 (39.7)	61 (40.7)	>0.05
		AA	11 (9.4)	17 (11.3)	>0.05
		T	165 (71.1)	205 (68.3)	>0.05
		A	67 (28.9)	95 (31.7)	>0.05

nature of the disease (Gül, 2001; Direskeneli, 2006; Krause and Weinberger, 2008; Kaneko et al., 2011; Mat et al., 2013). Nuclear factor kappa B (NFKB), tumor necrosis factor (TNF), interleukin-1 (IL-1), coagulation factor V, intercelluler adhesion molecule- 1 (ICAM-1), endothelial nitric oxide synthetase (eNOS), Mediterranean Fever gene (MEFV) and HSP genes are reported as the cause of inflammatory overreactivity by their protein products for BD in the literature (Gül, 2001; Direskeneli, 2006; Kaneko et al., 2008; Krause and Weinberger, 2008, Seyahi et al., 2010; Kaneko et al., 2011; Mat et al., 2013) Therefore we evaluated the selected inflammation related SNP's for susceptibility for BD and their associations with BD's clinical characteristics in this study.

IRGM1 gene is located on 5q33.1 and encodes a protein which is a member of the p47 immunity-related GTPase family. This protein is shown to affect immune response by its regulatory capacity upon innate immune system (Roberts et al., 2008; Meggyesi et al., 2010; Prescott et al., 2010; Palomino-Morales et al., 2009). IRGM interacts and supports autophagosome biogenesis from mitochondria membrane leading to autophagy. IRGM-mediated autophagy is also suggested to decrease IFN-γ synthesis and permits viral replication. Polymorphisms of IRGM1 gene are associated with Crohn's disease (CD), tuberculosis, gastric cancer and systemic lupus erythematosus (SLE) (Roberts et al., 2008; Megyessi et al., 2010; Prescott et al., 2010; Palomino-Morales et al., 2010). In our study, BD patients were investigated for rs13361189 variant. Although SNPs in autophagy related genes including rs13361189 are associated with CD, there was no statistical difference between the frequency of SNP in our patient and control groups. Interestingly, analysed IRGM variants were not found causal in a study including asian patients with CD and it was concluded that the involvement of IRGM risk haplotype in the pathogenesis requires gene-gene or gene-environment interactions that are absent in Asian population (Prescott et al., 2010). This explanation also supports our results as the study included Turkish BD patients and IRGM can cause predilection in certain ethnic groups. Additionally, autophagy related innate system disturbances may not play a role in BD at all.

PTGER4 is located on 5p13.1 and is a protein coding gene whose product is a member of G-protein coupled receptor family. Product protein of this gene serves as one of the four receptors for PGE2. Besides its effects on cyclooxgenase-2 mRNA, PTGER4 is suspected to play a role in the initiation of skin immune response by activating T-cell signaling and act as binding sites for NFκB (Libioulle et al., 2007; Latiano et al., 2011; Glas et al., 2012). In a recent study, the genetic variation within 5p13.1 locus was proved to influence PTGER4 expression leading to a susceptibility for CD and rs1373692 variant was found significantly higher in patients than controls statistically (Libioulle et al., 2007). Other variants of PTGER4 polymorphisms were also identified to be associated with the severity of ancylosing spondilitis and CD (Latiano et al., 2011; Glas et al., 2012; Chai et al., 2013). Nevertheless we did not find any association of PTGER4 variant rs1373692 in BD patients and conclude that other SNPs within this proinflammatory gene should be further investigated for its effects on BD predisposition.

NALP3 inflammasomes consist of Caspase recruitment domain (CARD) containing protein 8 (CARD8), node-like receptor family, pyrin domain containing 3 (NALP3) and apoptosis-associated speck-like protein containing a CARD (ASC). Inflammasomes are multiprotein complexes which are activated by intracellular microbial components, cell injury and stress (Roberts et al., 2010; Yang et al., 2011). Activated inflammasomes trigger caspase 1 mediated IL-1b and IL-18 release as a part of innate immune response. CARD8 is accepted as a candidate susceptibility gene for inflammatory diseases for its implication in apoptosis via caspase proteins and inflammation through NFKB pathway (Roberts et al., 2010; Yang et al., 2011). The rs2043211 variant is a functional polymorphism of CARD8 gene which is located on chromosome 19q13 and this variant is known to induce damaging changes in the CARD8 protein. Some studies provide evidence that rs2043211 in CARD8 gene may cause predisposition to autoimmune and inflammatory diseases such as Crohn's disease, rheumatoid arthritis, ulcerative cholitis, ankylosing spondylitis and psoriasis (Roberts et al., 2010; Yang et al., 2011; Ben Hamad et al., 2012; Carlström, 2012). Inflammasomes may also play a role in the autoimmune inflammatory mechanisms of BD pathogenesis. Liang et al. (2013) showed production of IL-1β was significantly decreased after NLRP3 inflammasome downregulation in BD patients with ocular involvement and reactive oxygen species (ROS)-NLRP3 inflammasome dependent pathways are involved in active BD. Nevertheless, no associations considering rs2043211 variant in CARD8 gene was found in BD patients in our study. This can be due to the fact that our study group included all BD patients with different clinical feature. We think inflammasome associated pathways may become significant in BD patients with particular characteristics by causing predilection to certain end organ/system involvements (for example BD patients with predominantly ocular manifestations). Therefore, we suggest that inflammasomes are still a possible pathway of pathomechanism in BD and separate assembly of studies including BD patients with similar clinical characteristics are required for defining genes and SNPs as a disease susceptibility factor.

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