ОРИГИНАЛНИ СТАТИИ
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INVESTIGATION OF THE RELATIONSHIP BETWEEN PTPN22 POLYMORPHISMS AND LUNG SARCOIDOSIS: A CROSS SECTIONAL STUDY

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Abstract. Objective: *Sarcoidosis is a systemic granulomatous disease with an unknown etiology characterized by noncaseating granuloma formation. It most often affects the lungs. Protein tyrosine phosphatase non-receptor 22 (PTPN22) is a gene that acts as a negative regulator of T-cell activation. Polymorphisms of this gene are associated with multiple human autoimmune diseases. The aim of this study was to assess the relationship between PTPN22 polymorphisms and lung sarcoidosis in a selected population.* ***Methods:*** *The study included 64 patients with lung sarcoidosis and 30 healthy controls. Patients were genotyped to determine two single nucleotide polymorphisms (SNPs) using the polymerase chain reaction (PCR) method. Hardy–Weinberg equilibrium (HWE), an important tool for detecting genotyping errors, was tested. Direct counting was used to estimate genotype frequencies. Logistic regression analysis was performed to compare allele and genotype frequencies between the patient and control groups.* ***Results:*** *The results of the study showed no correlation between lung sarcoidosis and the tested two SNPs of the PTPN22 gene (rs2488457, rs1310182) ($p > 0.05$). The categorization analysis according to the clinical features, laboratory, and radiographic characteristics showed no correlation between the tested polymorphism of PTPN22 and these characteristics ($p > 0.05$).* ***Conclusion:*** *The present study demonstrated that the studied two SNPs of the PTPN22 gene (rs2488457, rs1310182) were not correlated with lung sarcoidosis, suggesting that it might be different from other classic autoimmune disorders. There is a need for more studies to verify these results concerning lung sarcoidosis in other ethnic origins.*

Key words: *Sarcoidosis, PTPN22, Polymorphism*

Introduction

Sarcoidosis is a systemic granulomatous disease with an unknown etiology characterized by noncaseating granuloma formation. It most often affects the lungs [1]. Increased populations of the effector T cells have been demonstrated in lungs in cases of active sarcoidosis. Concerning the Th1 (T helper)/Th2 paradigm, a cornerstone for our understanding of T cell responses, pulmonary sarcoidosis was defined as a Th1-polarized disease based on the aggressive expression of IL12p40 and IFN-gamma in the lung. Nonetheless, other T-cell lineages have also been shown to have a potential role in sarcoidosis inflammation. Several studies have identified the presence of Th17 cells in lung tissue and BAL fluid in sarcoidosis [2, 3]. In addition to their proinflammatory role in autoimmune diseases, IFN-gamma driven immunopathology may be intensified by cells carrying a Th17 phenotype in sarcoidosis. These nonclassical cells of Th17 origin, which are capable of generating Th1, can gain the capacity to produce IFN-gamma partly through the effects of locally expressed IL-2 and TNF-alpha and intrinsic functional plasticity [4]. These cells, called Th17.1 cells, are predominantly present in specimens of pulmonary sarcoidosis patients and are suggested to be the probable major source of IFN-gamma production at active disease sites [5, 6].

Located on chromosomes 1p13.3-p13.1, the PTPN22 gene encodes the lymphoid-specific phosphatase (Lyp) that acts as a negative regulator of

T-cell activation and development [6-8]. Some recent studies have reported that the R620W (rs2476601) polymorphism of the PTPN22 gene enhances susceptibility to develop several autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and insulin-dependent diabetes mellitus (IDDM) [9-13]. The R620W (rs2476601) polymorphism of the PTPN22 gene interrupts the interaction between Lyp and tyrosine-protein kinase CSK, also known as C-terminal Src kinase, and may potentially lead to hyperreactive pathogenic T-cell responses [6]. In addition, it regulates Th17 responses related to IL-1β, which plays a critical role in the pathophysiology of autoimmune/inflammatory diseases [14].

Genetic structures that may be risk factors for the development of sarcoidosis have been described in the literature. However, studies have mostly focused on the relationship between HLA genes and loci associated with TNF [15-21]. On the other hand, it has not been determined whether PTPN22 gene polymorphisms or defects are risk factors for sarcoidosis. This study aimed to assess the relationship between PTPN22 polymorphisms (rs2488457 (-1123C > G) and rs1310182 (-852G > A) and lung sarcoidosis in patients with lung sarcoidosis and normal controls based on the hypothesis that these polymorphisms may be correlated with sarcoidosis and its parameters.

Materials and Methods

This study was designed as a cross-sectional study enrolling 73 patients (21 male, 52 female) with lung sarcoidosis, who presented to the outpatient clinic of internal medicine, chest diseases, or who were admitted to the tertiary care center. All patients were diagnosed based on the presence of the clinical symptoms, radiographic findings of sarcoidosis, and biopsy evidence of noncaseating epithelioid cell granuloma (22). The clinical characteristics of the patients and their laboratory results, including complete blood count, serum biochemistry, and Mantoux test (5TU), were evaluated. Patients with evidence of mycobacterial, fungal, and/or parasitic infections, and those with a history of exposure to organic/inorganic material known to cause granulomatous lung diseases, and PTPN22-associated autoimmune diseases (RA, SLE, T1DM, Graves' disease) were excluded from the study. To determine the association of polymorphisms with clinical parameters, the patients were grouped by their medical treatments, radiological findings, serum angiotensin-converting enzyme (ACE) levels, and disease stage.

Healthy volunteers (7 male, 23 female) were recruited from the general population with the same socioeconomic status and ethnic background as that of the patients. All of the individuals screened were found to have no family history of tuberculosis or any other related disease. In addition, these individuals had a negative tuberculin test, with normal chest radiographs and peripheral blood count levels.

Radiographic Staging of Sarcoidosis

Chest radiographs are commonly used for the staging of sarcoidosis based on its radiographic appearance. This staging system has been widely adopted for the assessment of sarcoidosis. Chest radiographic findings of sarcoidosis were classified by Scadding criteria into five stages [23].

Serum ACE

Serum levels of ACE (Angiotensin-Converting Enzyme) were measured spectrophotometrically. An ACE reagent containing synthetic tripeptide substrate N-(3-(2-furyl) acryloyl) phenylalanylglycylglycine (FAPGG) was used. FAPGG was catalyzed by ACE to form FAB + glycylglycine. In this way, the absorbance decreases at 340 nm, so the reaction rate is calculated and ACE activity is measured [24].

Ethics Statement

The approval for the study was obtained from the local ethics committee (Approval number: 60116787-020/66924). All patients and controls included in the study were informed about the purpose of the study prior to participation. They gave written informed consent. The study was conducted in accordance with the principles of the Helsinki Declaration.

DNA Extraction

A Qiagen DNeasy kit (Catalog no: 69504 Hilden, Germany) was used for the extraction of genomic DNA following the anti-coagulation of peripheral blood leukocytes with ethylene diamine tetraacetic acid (EDTA). After 300 ml of blood was mixed with cell lysis solution, spin-down, nuclei lysis solution (Catalog no: 69504 Hilden, Germany) was used for spin-down and lysis of leukocytes. The protein was eliminated utilizing precipitation solution and centrifugation. DNA samples were then transferred in Ependorf tubes and stored at -20ºC until analysis.

Genotyping

The candidate SNPs of the PTPN22 gene, namely rs2488457 and rs1310182 were selected. Real-time PCR analysis was carried out on the ABI7500 Fast System. The conditions of PCR were as follows: initial denaturation at 95°C for 10 minutes, followed by denaturation at 95°C for 10 seconds, and annealing at 60°C for 60 seconds. Denaturation and annealing were performed for a total of 40 cycles. The master mix information used for PCR is shown in Table 1.

Table 1. Information on Master Mix Used for PCR Reaction

Components	Volume
2X q PCR Probe Master Mix	10 µl
TaqMan™ SNP Genotyping Assay (40X)	0.5 µl
Template DNA	2.5 µl
Water	7 µl
TOTAL	20 µl

PCR: Polymerase chain reaction

Allelic Discrimination Analysis

Based on the real-time PCR result, the „Allelic Discrimination“ analysis option was selected on the device. Accordingly, amplification curves at FAM and VIC wavelengths were obtained from each SNP probe. According to these amplification curves, the device automatically performed allele discrimination of the samples.

Statistics Analysis

The study data were analyzed using IBM SPSS Statistics version 20.0 software (Armonk, NY: IBM Corp.). Quantitative variables were presented as means, medians, and amplitudes, while categorical variables were presented as frequencies and percentages. The non-parametric Mann-Whitney U test was used for two-group comparisons. In the statistical analysis, the level of significance was set at a p-value < 0.05.

The Hardy–Weinberg equilibrium of each SNP was determined and SNPStats software was used to check whether genotype distributions for each studied SNP deviated significantly. The SHEsis online platform was used to calculate the haplotype frequencies. The correlation between different genotypes and different phenotypes was compared using logistic regression analysis with OR after adjusting for age and gender. OR and 95% confidence intervals (CI) were calculated to estimate the correlation between genotypes/alleles and prevalence risk.

Results

Clinical Characteristics of Participants

A total of 73 patients were evaluated for eligibility in this study. Nine patients were excluded from the study after the detailed evaluation. Of these, 3 had RA, 2 had SLE, 2 had DM, 1 had Hashimoto thyroiditis, and one of the patients who did not participate in the evaluation process was excluded from the study.

There was no significant difference between the patients with sarcoidosis and healthy controls in terms of mean age and gender distribution. The mean disease duration of patients with sarcoidosis was 4.6 years. The mean serum ACE level of patients was 56.5. The demographics and clinic characteristics of patients and healthy controls enrolled in this study are presented in Table 2.

The comparison of the Turkish population with rs2488457 and rs1310182 SNPs by the HWE equilibrium revealed an rs2488457 G allele frequency of 67%, C allele frequency of 33%, rs2488457 C allele frequency of 78%, G allele frequency of 32%, rs1310182 A allele frequency of 45%, and G allele frequency of 55%. Based on these results, it was found that the distribution of genotypes and alleles did not deviate from the HWE.

Table 3 shows the genotype and allele frequencies of the tested two SNPs of the PTPN22 gene (rs2488457, rs1310182) in sarcoidosis and healthy controls. The results showed no significant correlation between the rs2488457 and rs1310182 SNPs and lung sarcoidosis. No variant or allele of PTPN22 polymorphism was correlated with stage, serum ACE level, and medical treatment (Table 4).

Table 2. Baseline characteristics of participants (n = 94)

	Sarcoidosis (n = 64)	Healthy controls (n = 30)	p-value
Age, years	45.6 (9.2)	43.4 (6.7)	0.245
Male, gender, n (%)	16 (25)	7 (23.3)	0.861
Duration of sarcoidosis, years, mean (SD)	4.6 (3.8)	-	-
ACE, mean (SD)	56.5 (36.4)	-	-
Scadding staging			
– Stage 1, n (%)	22 (34)		
– Stage 2, n (%)	19 (30)		
– Stage 3, n (%)	23 (36)		
– Stage 4, n (%)	-		
Current therapy for sarcoidosis, n (%)		-	-
Follow-up without medication	47 (73)		
Systemic steroid	14 (22)		
Immunosuppressive therapy	3 (5)		

ACE, Angiotensin-converting Enzyme; SD, Standard deviation

Table 3. Genotype and allele frequencies of gene polymorphisms between lung sarcoidosis patients and healthy controls

SNP	Genotype Allele	Sarcoidosis, n (%)	Controls, n	p-value	OR (95% CI)
rs2488457	CC	41 (64.1)	16 (53)	0 321	1.56 (0.647-3.762)
	CG	16 (25)	11 (37)	0.244	0.576 (0.226-1.464)
	GG	7 (10.9)	3 (10)	0.736	0.798 (0.215-2.968)
	C	98 (76.5)	43 (71.6)	0.111	2.03 (0.845-4.914)
	G	30 (23.4)	30 (50)	0.321	0.641 (0.266-1.546)
rs1310182	AA	14 (21.9)	5 (17)	0.558	1.400 (0.453-4.327)
	AG	32 (50)	16 (53)	0.763	0.875 (0.367-2.086)
	GG	18 (28.1)	9 (30)	0.851	0.913 (0.352-2.366)
	A	60 (46.8)	26 (43.3)	0.836	1.120 (0.383-3.275)
	G	68 (53.1)	21 (35)	0.558	1.055 (0.231-2.208)

*p < 0.05, statistically significant difference; OR, Odds Ratio; 95% CI, 95% confidence interval

Table 4. Comparison of polymorphisms by clinical parameters, medical treatments and serum ACE levels

		RS2488457					RS1310182				
		CC, n (%)	CG, n (%)	GG, n (%)	C, n (%)	G, n (%)	AA, n (%)	AG, n (%)	GG, n (%)	A, n (%)	G, n (%)
Sarcoidosis stage	Stage 1	20 (48.7)	2 (12.5)	2 (28.5)	20 (48.7)	2 (8.6)	4 (18.1)	12 (38.7)	5 (27.9)	4 (28.6)	18 (36)
	Stage 2	8 (19.5)	6 (37.5)	2 (28.5)	8 (19.5)	11 (47.8)	4 (18.1)	9 (27.7)	7 (38.8)	4 (28.6)	15 (30)
	Stage 3	13 (31.7)	8 (50)	3 (43)	13 (31.7)	10 (43.6)	14 (75.8)	10 (30.3)	6 (33.3)	6 (42.9)	17 (34)
	p-value	0.101	0.101	0.912	0.003*	0.003*	0.810	0.400	0.232	0.810	0.810
Medical treatment	Follow-up without treatment	30 (73.1)	11 (68.7)	4 (57.1)	30 (73.2)	17 (73.9)	12 (85.7)	22 (70.9)	13 (27.7)	12 (85.7)	35 (70)
	Systemic steroid	8 (19.5)	5 (31.3)	3 (43.9)	8 (19.5)	6 (26.1)	2 (14.4)	7 (22.5)	4 (28.6)	2 (14.3)	12 (24)
	Immunosuppressive therapy	3 (7.3)	0	0	3 (7.3)	0	0	2 (6.4)	1 (33.3)	0	3 (6)
	p-value	0.372	0.383	0.836	0.372	0.372	0.432	0.293	0.977	0.432	0.432
Serum ACE, U/L	<52	22 (53.6)	8 (50)	3 (43.9)	22 (53.7)	13 (56.5)	6 (42.8)	17 (57.8)	10 (28.6)	6 (42.9)	29 (58)
	>52	19 (46.4)	8 (50)	4 (57.1)	19 (46.3)	10 (43.5)	8 (57.2)	14 (42.2)	8 (27.6)	8 (52.1)	21 (42)
	p-value	0.825	0.664	0.505	0.825	0.825	0.314	0.981	0.930	0.314	0.314

*– p < 0.05 statistically significant; ACE, Angiotensin-converting enzyme

Discussion

This study investigated the two SNPs of the PTPN22 gene in patients with sarcoidosis. The results of the study demonstrated no association of the two SNPs of the PTPN22 gene, rs2488457 (-1123C > G) and rs1310182 (-852G > A) with lung sarcoidosis. The G allele of rs2488457 was found to be correlated with stage in patients with pulmonary sarcoidosis. To our knowledge, this study is the first to investigate the relationship of the two SNPs of the PTPN22 gene, rs1310182 and rs2488457 (-1123C > G), with lung sarcoidosis.

The PTPN22 gene has recently come to the fore as a significant candidate susceptibility factor for several immune diseases [25]. Studies have addressed the role of PTPN22 in clinical uveitis in Turkish, British and the Middle East patients with Behçet's disease and shown a limited (protective) effect of the T1858 allele in Middle East patients with Behçet's disease but not in British patients [26, 27]. Likewise, the study by Martin et al. demonstrated no

relationship between acute anterior uveitis and the R620W (rs2476601) of the PTPN22 gene, 1858C/T genotype [28]. The study by Wagenleiter et al. also showed no effect of the rs2476601polymorphism of the PTPN22 gene in German patients with Crohn‘s disease [29]. Furthermore, the study by Matesanz et al. also demonstrated no relationship between the abovementioned SNP and multiple sclerosis (MS) in Spanish patients [30]. Yet, polymorphisms of the PTPN22 have reportedly been shown to be a susceptibility gene for some autoimmune diseases characterized by specific autoantibodies (31). For example, other candidate polymorphisms of the PTPN22 gene, which are rs2488457, rs3789604, and rs1310182, have been demonstrated to have a relationship with several autoimmune conditions, including Graves‘ disease, T1D, and RA [32-35]. Nevertheless, a rare missense single-nucleotide polymorphism in the PTPN22 catalytic domain, rs33996649, has been shown to function for reducing the risk of RA and SLE [36]. In our study, however, no relationship was found between the tested polymorphisms of rs2488457 (-1123C > G) and rs1310182 (-852G > A) and lung sarcoidosis. The most important reason for different results in autoimmune diseases and our study may be related to sample size and ethnicity. Because it has been genetically confirmed that these polymorphic variants present different allelic frequencies and genotype distribution in ethnic groups [37]. Therefore, there is a need for a study including different ethnic groups with large participation to verify this result.

It is not clear which inflammatory process is involved in the pathophysiology of sarcoidosis. Two previous studies reported that autoimmunity is effective in the physiopathology of sarcoidosis [38, 39]. However, another study found mutations in the CARD15 [caspase activation and recruitment domain (CARD) family, member 15]. or NOD2 (nucleotide-binding oligomerization domain containing 2) genes [40]. Therefore, it has been stated that both autoimmune and autoinflammatory processes may be effective in the physiopathology of sarcoidosis. Polymorphisms of rs2488457 (-1123C > G) and rs1310182 (-852G > A) examined in our study have generally been shown to be effective in autoimmune diseases [28-36]. In our study, however, these polymorphisms were not found to be correlated with sarcoidosis disease. This suggests that autoimmunity is ineffective in the pathophysiology of lung sarcoidosis. Yet, many studies are needed to confirm this.

Changes in serum cytokines caused by dysfunction of different forms of the PTPN gene have been reported in the literature. A study by Spalinger et al. showed increased release of TNF, IFN-γ, and IL-1 β in PTPN22 defect. The same study showed increased release of IL-8 and TNF secondary to the increase in nuclear factor-KB release [41]. Another study showed that the PTPN22 1858 C/T variant changed the cytokine profile in RA patients [42]. TNF, IL-1, IL-6, IL-8, IL-17 have been reported to be effective in the pathophysiology of sarcoidosis [43-45]. Our study demonstrated that the polymorphisms of the PTPN22 gene were ineffective in the development of sarcoidosis and were not correlated with its parameters. However, evaluating only two polymorphisms of this gene and not determining cytokine levels is an important limitation of our study.

Various parameters related to the diagnosis, follow-up, and activity of sarcoidosis have been described in the literature [46-49]. Serum ACE level is one of the most studied laboratory values. Although it is detected in 30-80% of patients, its specificity is low, while its sensitivity is high [46]. In addition, it has been observed that its serum level is not different in patients with active and inactive disease [47]. Therefore, the issue of serum level of ACE for sarcoidosis is controversial. Furthermore, a moderate agreement between the authors has been reported in the literature for the Scadding staging we used in our study [48]. Another study stated that it was insufficient to demonstrate acute exacerbations [49]. In our study, however, no significant relationship was found between these parameters and PTPN22 polymorphisms. The reason for such a result may be related to the aforementioned reasons. Therefore, if radiographic imaging had been used with a highly specific laboratory parameter in our study, it could have had a positive effect on the quality of our study. In addition, it should also be taken into account that the polymorphisms of the PTPN22 gene were not different between those who used immunosuppressive drugs or steroids and those who did not use medical therapy to prevent disease progression in our study. This suggests that both polymorphisms are not associated with disease activity. However, using a more specific marker to demonstrate disease activity would have provided a more robust result.

As with other studies on candidate genes, our study has some limitations. The sample size of the study is relatively small. Participants were only recruited from the Turkish population. Therefore, there is a need for studies with larger sample sizes and other ethnic populations to investigate the correlation between the polymorphisms of the PTPN22 gene and sarcoidosis. Finally, since only two of

the PTPN22 polymorphisms were investigated in this study, the possibility of the association of other SNPs of the PTPN22 gene with sarcoidosis cannot be excluded. More studies are needed to clarify these issues.

Conclusion

Our study demonstrated no relationship between the two SNPs of the PTPN22 gene, namely rs2488457 and rs1310182, with lung sarcoidosis and its clinical characteristics. There is a need for more studies to verify these results concerning lung sarcoidosis in other ethnic origins.

Authors' contributions KS: *Conceptualization, Writing – Original Draft, Writing – Review & Editing. KM: Conceptualization, Writing – Original Draft, Writing – Review & Editing. DA: Conceptualization, Writing – Original Draft, Writing – Review & Editing. KU: Conceptualization, Writing – Original Draft, Writing – Review & Editing. CV: Conceptualization, Writing – Original Draft, Writing – Review & Editing. BS: Conceptualization, Writing – Original Draft, Writing – Review & Editing. SS: Conceptualization, Writing – Original Draft, Writing – Review & Editing.*

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