Arch Rheumatol 2023;38(1):1-8
doi: 10.46497/ArchRheumatol.2022.9239

ORIGINAL ARTICLE

Investigation of the relationship between interferon-gamma receptor 1-56C/T gene polymorphism and genetic susceptibility to lung sarcoidosis: A cross-sectional study

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ABSTRACT

Objectives: This study aims to investigate the relationship between the interferon-gamma receptor 1 (IFNGR1) polymorphism and susceptibility to lung sarcoidosis.

Patients and methods: The study included a total of 55 patients (13 males, 42 females; mean age: 46.5±9.1 years; range, 22 to 66 years) with lung sarcoidosis and 28 healthy controls (6 males, 22 females; mean age: 43.9±5.9 years; range 22 to 60 years) selected from the Turkish population. The polymerase chain reaction was used for genotyping of participants to determine single-nucleotide polymorphisms. Hardy-Weinberg equilibrium, which is considered an important tool for detecting genotyping errors, was tested. Allele and genotype frequencies of patients and controls were compared using logistic regression analysis.

Results: The analyses showed no correlation between the tested IFNGR1 single-nucleotide polymorphism (rs2234711) and lung sarcoidosis (p>0.05). The categorization analysis according to the clinical features, laboratory, and radiographic characteristics showed no correlation between the tested polymorphism of IFNGR1 (rs2234711) and these characteristics (p>0.05).

Conclusion: The results of the study showed that the tested gene polymorphism (rs2234711) of IFNGR1 was not associated with lung sarcoidosis. More comprehensive studies are needed to verify our results.

Keywords: Interferon-gamma receptor 1, sarcoidosis, polymorphism.

Sarcoidosis is a multisystem inflammatory disease. Studies have suggested that inflammation in sarcoidosis is partly induced by activated T-helper (Th) type 1 effector T cells.[1-4] The hypothesis regarding the key role of Th1 cells in sarcoidosis mainly relies on experimental observations of increased levels of (cluster of differentiation) CD41 effector T cells, one of the major immune cells that produce interferon (IFN)-gamma. Increased levels of these cells have been shown in bronchoalveolar lavage fluid of patients with sarcoidosis.[3,5-7] After the recent discovery of Th17 cells, which is a new class of Th cells, numerous researchers have used a range of gating strategies for flow cytometry to identify cells that produce interleukin (IL)-17A in

Received: September 22, 2021 ***Accepted:*** January 26, 2022 ***Published online:*** May 06, 2022

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Citation:
Kaymaz S, Kavas M, Demiray A, Karasu U, Çobankara V, Boğa S. Investigation of the relationship between interferon-gamma receptor 1-56C/T gene polymorphism and genetic susceptibility to lung sarcoidosis: A cross-sectional study. Arch Rheumatol 2023;38(1):1-8.

bronchoalveolar lavage fluid samples of patients with sarcoidosis.[8-13] Some of these studies have also identified Th cells that secrete IL-17 as well as IFN-gamma, with either low or undetermined amounts as a percentage of total CD41 cells.[9,11,12] In numerous studies, Th17 cells have been shown to be plastic and polarizable to differentiate into a Th1-like phenotype to be able to produce significant IFN-gamma.[13-17] Dominantly expressed Th1 cytokines, such as IFN-gamma and IL-12, further increase this differentiation *in vitro*.[16]

Interferon-gamma exerts microbicidal properties by activating macrophages and dendritic cells through interactions with its receptor complex.[17] Moreover, it acts as an extracellular homodimer through activation of its heterotetrameric complex consisting of two subunits: IFN-gamma receptor 1 (IFNGR1 or IFN-γR α subunit), a ligand-binding subunit, and IFN-gamma receptor 2 (IFNGR2 or IFN-γR β subunit), an accessory subunit.[18] The gene coding for IFNGR1 is located on the long arm of chromosome 6 at 6q23.3, with seven exons.[19,20] There are various polymorphisms described in the highly polymorphic minimal promoter region of IFNGR1, including rs2234711, rs1327474, rs41401746, and rs7749390. In their study, Jüliger *et al.*[21] reported that the expression of IFNGR1 was negatively affected by the single-nucleotide polymorphism (SNP) (T→C) at position -56 in the promoter region, demonstrating the potential of the deoxyribonucleic acid (DNA) sequence located at this polymorphic region as a binding site for transcription factor activator protein 4 on both strands, as well as the presence of transcription factor activator protein 4 interactions or interference of other transcription factors such as nuclear factor kappa B. There are previous studies in the literature on the relationship between the IFNGR1-56C/T gene polymorphism and some diseases.[22-25] However, the results of these studies are contradictory.

This study aimed to investigate the relationship between the rs2234711 SNP of IFNGR1 and susceptibility to lung sarcoidosis and to determine the relationship of this polymorphism with clinical, laboratory, and radiographic characteristics. We hypothesized that this polymorphism is associated with lung sarcoidosis due to the role of IFN-gamma in the pathogenesis of the disease.

PATIENTS AND METHODS

The study included 55 patients (13 males, 42 females; mean age: 46.5±9.1 years; range, 22 to 66 years) with lung sarcoidosis who were treated in the outpatient clinic of the Department of Chest Diseases between May 2020 and May 2021 and 28 healthy controls (6 males, 22 females; mean age: 43.9±5.9 years; range 22 to 60 years). The diagnosis of sarcoidosis was made based on consistent clinical presentation along with biopsy-proven noncaseating epithelioid cell granulomas in accordance with the international guidelines.[26] University staff and patient companions who voluntarily participated in the study formed the healthy control group. Demographic characteristics of sarcoidosis patients and healthy controls were recorded. The groups were arranged so that the mean age and sex distribution were similar. The patients with lung sarcoidosis were categorized by their medical treatments, serum angiotensin-converting enzyme (ACE) levels, and disease stage to determine the correlation of the polymorphism with clinical, laboratory, and radiographic characteristics. Radiographic staging of sarcoidosis patients was performed according to the Scadding classification described by Scadding *et al.*[27]

DNA extraction

A commercially available kit (Qiagen DNeasy kit, Catalog no: 69504; Qiagen, Hilden, Germany) was used for the extraction of genomic DNA after the anticoagulation of peripheral blood leukocytes with ethylene diamine tetraacetic acid. After 300 mL of blood was mixed with the cell lysis solution, leukocytes were spun down and lysed with the nuclei lysis solution (Catalog no: 69504; Qiagen, Hilden, Germany). Precipitation solution and centrifugation were utilized to eliminate the protein. Deoxyribonucleic acid samples were then transferred in Eppendorf tubes and stored at -20°C until analysis.

Determination of genotype

The SNP site of the IFN-gamma gene to be tested, namely rs2234711, was selected. Real-time polymerase chain reaction (PCR) analysis was carried out on the Applied Biosystems™ 7500 Real-Time PCR Systems (Applied Biosystems™,

Table 1. Information on master mix used for PCR reaction

Components	Volume (µL)
2X q PCR probe master mix	10
TaqMan™ SNP genotyping assay (40µL)	0.5
Template DNA	2.5
Water	7
Total	20

PCR: Polymerase chain reaction; SNP: Single-nucleotide polymorphism; DNA: Deoxyribonucleic acid.

Massachusetts, United States). The conditions of the PCR analysis were as follows: initial denaturation at 95°C for 10 min, followed by denaturation at 95°C for 10 sec, and annealing at 60°C for 60 sec. Denaturation and annealing were performed for a total of 40 cycles. The information on the master mix used for PCR is shown in Table 1.

Allelic discrimination analysis

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

Statistical analysis

The data were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Quantitative variables were presented as means ± standard deviation, minimum-maximum, medians, and amplitudes, while categorical variables were presented as frequencies and percentages. The nonparametric Mann-Whitney U test was used for two-group comparisons. A chi-square test was performed to evaluate the quality of the genotyping data after the Hardy-Weinberg equilibrium - was verified using the online software platform SHEsis. The correlation between different genotypes and different phenotypes was compared using logistic regression analysis with odds ratio after adjusting for age and sex. Odds ratio and 95% confidence intervals were calculated to estimate the correlation between genotypes/alleles and prevalence risk. The level of significance was set at $p<0.05$.

RESULTS

The mean disease duration of patients with sarcoidosis was 4.7±3.8 years. The mean serum ACE level of patients with sarcoidosis was 56.6±36.3. Of the patients, 29.1% were on medical treatment (Table 2). The success rate

Table 2. Baseline characteristics of participants

	Sarcoidosis (n=55)			Healthy controls (n=28)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			46.5±9.1			43.9±5.9	0.179
Sex							
Male	16	23.6		7	21.4		0.861
Duration of sarcoidosis (year)			4.7±3.8			-	-
Angiotensin-converting enzyme			56.6±36.3			-	-
Scadding stage							-
1	20	36.3		-	-		
2	15	27.4		-	-		
3	20	36.3		-	-		
4	-	-					
Current therapy for sarcoidosis							-
Follow-up without medication	39	70.9		-	-		
Systemic steroid therapy	13	23.6		-	-		
Immunosuppressive therapy	3	5.5		-	-		

SD: Standard deviation.

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

SNP	Genotype allele	Sarcoidosis n	Sarcoidosis %	Controls n	Controls %	*p*	OR	95% CI
Rs2234711	CC	32	58.1	15	53.5	0472	0.600	0.148-2.438
	CT	18	32.7	4	14.2	0.222	0.561	0.221-1.426
	TT	5	19.2	11	39.2	0.103	2.150	0.850-5.442
	C	72	65.4	34	60.4	0.074	0.431	0.170-1.094
	T	28	25.4	26	92.8	0.103	2.150	0.850-5.442

SNP: Single-nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval; * p<0.05: statistically significant difference.

Table 4. Comparison of polymorphism by disease stage, medical treatments, and serum ACE levels

	RS2234711									
	CC		CT		TT		C		T	
	n	%	n	%	n	%	n	%	n	%
Scadding stage										
Stage 1	2	40	5	27.8	13	40.6	6	27.3	13	40.6
Stage 2	2	40	6	33.3	7	21.9	8	36.4	7	21.9
Stage 3	1	20	7	38.9	12	37.5	8	36.4	12	37.5
p-value	0.687		0.622		0.542		0.378		0.542	
Medical treatment										
Follow-up without medication	3	60	13	72.2	23	71.9	15	68.2	23	71.9
Systemic steroid therapy	2	40	4	22.2	7	21.9	6	27.3	7	21.9
Immunosuppressive therapy	0	0	1	5.6	2	6.3	1	4.5	2	6.3
p-value	0.602		0.985		0.836		0.861		0.836	
Serum ACE (U/L)										
<52	4	80	7	38.9	18	56.3	10	45.5	18	56.3
>52	1	20	11	61.1	14	43.7	12	54.5	14	43.7
p-value	0.200		0.152		0.537		0.825		0.152	

ACE: Angiotensin-converting enzyme; * p<0.05: statistically significant difference.

of the tested SNP genotyping was found to be 100% in both patient and healthy control groups. The genotype frequencies of the tested SNP did not deviate significantly from those expected under the Hardy-Weinberg equilibrium. The results of the univariate analysis revealed that the genotype frequencies of IFNGR1-56T/C were not statistically different between the patient and healthy control groups (p>0.05; Table 3). Multivariate logistic regression analysis was carried out to determine the correlation between different genotypes of the IFNGR1 polymorphism and susceptibility to lung sarcoidosis after adjusting for sex and age. The results of the multivariate analysis showed no correlation between the tested polymorphism of IFN-gamma and lung sarcoidosis.

Patients were grouped to examine the correlation of the IFNGR1 polymorphism allele or variants with serum ACE level, pulmonary staging, and treatments. However, no correlation was found between these characteristics and the tested polymorphism allele or variants (Table 4).

DISCUSSION

The findings of accumulated INF-gamma, IL-2, and IL-17-producing Th cells in the lung tissue of sarcoidosis patients have led sarcoidosis to be defined as a Th1 and, more recently, a Th17-mediated disease.[3,12,28,29] The SNP rs2234711 is located in the 5′-UTR region of the IFNGR1 gene, which indicates its potential to be a causal variant involved in the regulation of the promoter activity. This SNP has been revealed by the HaploReg (version 4.1) to be located in a gene regulatory hotspot controlling the majority of gene expression variation. Moreover, this SNP has been demonstrated to be significantly associated with IFNGR1 expression in the database of the Genotype-Tissue Expression (GTEx) project.[30] Accordingly, the risk allele of this SNP decreases promoter activity and cis-regulates IFNGR1 expression.[30] In the IFN signal transduction pathway, IFN-gamma binds to the transmembrane molecular IFNGR1.[31] Furthermore, INF-gamma is involved in the activation of antigen-presenting cells, including dendritic cells, macrophages, and B cells, and the promotion of the local immune response, eventually leading to granuloma formation. Our study showed that the rs2234711 allele of IFNGR1 did not pose a risk for lung sarcoidosis. There was also no correlation between this polymorphism and the relevant parameters when patients were grouped by clinical and laboratory parameters.

In the literature, IFN has been shown to be associated with autoimmune, infectious, and inflammatory diseases.[32,33] Studies have illustrated that chronic hepatitis C virus patients receiving type 1 IFN have an increased risk of being diagnosed with sarcoidosis.[34,35] Resolution of sarcoid lesions following the reduction or discontinuation of this treatment in some cases also demonstrates the efficacy of type 1 IFN treatment for sarcoidosis.[36,37] Moreover, polymorphisms of the IFN gene is associated with susceptibility to sarcoidosis from a genetic viewpoint.[38] Another recent study detected higher serum type I IFN activity in patients with sarcoidosis compared to matched controls in a European-American population.[39] However, the number of studies reviewing the relationship of the IFN-gamma pathway or receptor with sarcoidosis is limited. Ragusa et al.[40] reported that monocyte-induced IFN-gamma increased in sarcoidosis patients compared to healthy controls, suggesting its association with disease activity. In addition, Tøndell et al.[11] produced a higher proportion of IFN-gamma+ Th17, a subcomponent of Th17, than the other components in bronchoalveolar lavage fluid. Another study reported that Th17 decreased IFN-gamma expression, which demonstrated its critical role in the pathogenesis.[9] Although some genotypes (CC, CT) of the IFNGR1 polymorphism examined in our study were numerically high, no statistical correlation was found with the disease or disease-specific characteristics. The important reason for this may be related to the small sample size of our study and the selection of all patients from the Turkish population, as ethnic differences in allele frequency of SNPs associated with autoimmune diseases and genotype distribution of polymorphisms have been genetically confirmed.[41] Therefore, there is a need for large-scale studies including different ethnic groups to verify this result.

Polymorphisms in the promoter region of IFNGR1 appear to be associated with chronic diseases.[42] In the literature, there is no study on the relationship between IFNGR1 polymorphisms and sarcoidosis. However, since IFNGR1 is immunologically effective in host defense, the body may become susceptible to infective agents in the presence of these polymorphisms. In this respect, Bulat-Kardum et al.[23] demonstrated the association of IFNGR1–56 T/C SNP with tuberculosis. A similar study conducted in China also showed an increased risk of tuberculosis in the presence of this polymorphism.[23] Two published studies reported that antigens of infective agents, such as *Mycobacterium tuberculosis*, were effective in the etiology of sarcoidosis.[9,43] The aforementioned studies suggest that tuberculosis, IFNGR1 polymorphism, and sarcoidosis may be associated. Our study, however, found no association between lung sarcoidosis and IFNGR1–56 T/C SNP. The most likely and most important reason for this result is the effect of ethnicity or different genetic makeup on the variation of IFNGR1 gene polymorphisms. For instance, Africans have a deletion/insertion SNP at position -470, but Europeans and Asians do not.[44] Moreover, another point to be taken into account is the contradictory results of studies on IFNGR1 gene polymorphism. Cheong et al.[45]

found no association between the rs2234711 polymorphism and persistent HBV infection, whereas Zhou et al.[30] found an association.

Various laboratory characteristics 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 to 80% of patients, it has a low specificity but high sensitivity.[46] In addition, it has been observed that its serum level is not different in patients with active and inactive diseases.[47] Therefore, the effect of the serum ACE level on sarcoidosis is controversial. Furthermore, there is moderate agreement among the authors in the literature regarding the Scadding staging used in our study.[48] Another study reported that it was insufficient to establish acute exacerbations.[49] In our study, however, no significant relationship was found between these parameters and IFNGR1 gene polymorphism. Therefore, using a laboratory value with a high specificity would have increased the quality of our study. Moreover, it is important to consider that the IFNGR1 gene polymorphism is not different between those who use immunosuppressive or steroids and those who do not use medical treatment, suggesting no relationship between this polymorphism and disease activity. However, further studies are needed to verify this relationship.

As in other studies on candidate genes, our study has several limitations. The sample size of the study was relatively small. Moreover, the present study was conducted only in a single university hospital clinical setting, and participants were only recruited from the Turkish population. Therefore, there is a need for studies with larger sample sizes including other ethnic populations to investigate the correlation between the polymorphisms of the IFNGR1 and lung sarcoidosis. Finally, the fact that the present study only examined one of the IFNGR1 gene polymorphisms does not exclude the possibility of an association between other SNPs of the IFNGR1 and lung sarcoidosis.

In conclusion, our study demonstrated no relationship between the IFNGR1-56C/T gene polymorphism and lung sarcoidosis. Nevertheless, it is recommended that further studies are conducted on the polymorphisms of other important cytokines and their receptors in sarcoidosis patients due to the complexity of lung sarcoidosis.

Ethics Committee Approval: The study protocol was approved by the local ethics committee (approval number: 60116787-020/66924). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Designed the study: K.S., D.A.; Reviewed the articles and provided the data; K.S., D.A., K.U.; Analyzed the data: K.S., D.A., C.V.; Wrote the initial manuscript: K.S.; Reviewed drafts of thepaper: D.A., B.S., KM., K.U.; Prepared the figures: K.S.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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