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Can TERT rs2853669 polymorphysm indicate fibrosis in sarcoidosis?

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Abstract. *Background and aim:* Sarcoidosis is a systemic inflammatory disease of unknown cause, characterized by the presence of non-caseating granulomas, which can affect all organs in the body, especially the lung. The fibrotic stage 4 of sarcoidosis usually does not respond adequately to treatment and may cause respiratory distress in the patient. Some telomerase gene polymorphisms have been significantly associated with lung cancer and idiopathic pulmonary fibrosis. In our study, we aimed to investigate the relationship between telomerase mutation and progression to fibrosis in patients with sarcoidosis. *Methods:* A total of 93 patients, including 18 males and 73 females, who were clinically and histopathologically diagnosed with sarcoidosis were included in the study. The 78 patients included in the study were classified as non-fibrotic and 15 as fibrotic sarcoidosis. In telomerase rs2853669 single nucleotide polymorphism, three genotypes, homozygous TT, homozygous CC and heterozygous TC, were determined as the genotypes of the patients. *Results:* When non-fibrotic and fibrotic sarcoidosis groups were compared, no significant difference was found in terms of genotypes (p=0.76). The FEV1 (forced expiratory volume in the first second) % of the CC genotype was lower than that of the other genotypes (p=0.01). *Conclusions:* In sarcoidosis patients, telomerase rs2853669 polymorphism does not indicate progression to fibrosis, but since FEV1% was found to be lower in individuals with homozygous CC polymorphism, it is thought that it may predict loss of respiratory function. Further studies are needed to evaluate the association of telomerase polymorphisms with fibrosis in sarcoidosis.

Key words: sarcoidosis, telomerase, fibrosis, genetic polymorphism, mutation

Introduction

Telomeres are TTAGG tandem repeat DNA sequences at chromosome ends that maintain genome stability by protecting chromosome ends from shortening during replication. Telomeres shorten with each cell division and when the telomere length reaches a critical length, the cell goes into senescence or apoptosis (1). In studies, decreased telomerase gene expression in idiopathic pulmonary fibrosis suggests that this regulatory gene has an active role in fibrogenesis. Some telomerase gene polymorphisms have been significantly associated with lung cancer and idiopathic pulmonary fibrosis. In our study, we aimed to investigate the relationship between telomerase mutation and progression to fibrosis in patients with sarcoidosis.

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Material and methods

Patient selection

A total of 134 patients with a diagnosis of sarcoidosis admitted to the Chest Diseases outpatient

clinic of Ondokuz Mayıs University Faculty of Medicine Hospital between December 1, 2020 and December 1, 2021 were evaluated. Patients with clinical and radiologic improvement with treatment or spontaneously at 24 months were considered as acute and those without radiologic and clinical improvement in less than 24 months were considered as chronic sarcoidosis. A total of 41 patients were excluded from the study, of which 21 patients were followed for less than 24 months and 20 patients had no histopathological diagnosis. A total of 93 patients, 21 males and 72 females, were included in the study. Three groups were formed as stage 1, non-fibrotic parenchymal involvement (stages 2 and 3) and stage 4.

Demographic information such as age, gender, symptoms, smoking history and physical examination were obtained. Routine laboratory tests (complete blood count, creatinine, aspartate aminotransferase, alanine aminotransferase, calcium) were evaluated. Postero-anterior chest radiography and thoracic computed tomography were analyzed. Histopathologic diagnostic methods, FEV1 (forced expiratory volume in the first second) and FVC (forced vital capacity) ml values, FEV1 and FVC %, FEV1/FVC ratio, DLCO %(diffusing capacity of the lungs for carbon monoxide), extrapulmonary organ involvement, radiologic stages, and medical treatments were evaluated.

The diagnosis of sarcoidosis was obtained by demonstrating non-caseating granulomas histopathologically in the presence of appropriate clinical and radiologic findings as specified in the ATS/ERS/WASOG (American Thoracic Society/Europian Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders) criteria and excluding diseases that may cause similar histopathologic and clinical findings (2).

In addition to pulmonary complaints such as dyspnea, cough, chest pain and/or systemic symptoms such as malaise, fever, pathologic examination findings in the lung, erythema nodosum in the skin, uveitis findings in the eye, elevated serum ACE (Angiotensin Converting Enzyme), serum calcium, and elevated calcium in 24 hour urine were found to support the diagnosis.

Evaluation of chest X-ray and computed tomography images

Radiologic images of patients were considered as below;

Stage 0, normal radiology;
Stage 1, bilateral hilar lymphadenopathy;
Stage 2, bilateral hilar lymphadenopathy and parenchymal infiltrates;
Stage 3, parenchymal infiltrates without bilateral hilar lymphadenopathy;
Stage 4 fibrotic disease.

Treatment and follow-up

Patients with progressive symptomatic disease, persistent pulmonary infiltration on imaging and progressive decline in lung function were started on methyl prednisolone 20-40 mg/day (or equivalent). In case of improvement in symptoms, treatment was planned to be completed for at least 1 year by decreasing the daily dose by 5-10 mg every 1-3 months until the maintenance dose of 5-10 mg/day was reduced. In cases such as lack of response to treatment, toxic side effects or steroid dose reduction was not possible, second and third generation therapies such as methotrexate and infliximab were initiated.

Genetic analysis

DNA was first isolated from the samples taken from the patients who participated in the study in EDTA tubes and stored in the deep freezer. For DNA isolation from 93 patients' blood, Favorgen Blood Genomic DNA Extraction Mini Kit was used. PCR reactions were performed with the DNAs of the samples using GT HS taq and GT rich pcr mix. DNA base sequences of PCR products were determined using ABI 3130 sanger sequencer. Sequence image of a single nucleotid polymorphism region shown in Figure 1.

Results

The mean age of the 93 patients included in the study was 53.2±11.2 years and 72 (77.4%) were female. Sarcoidosis was diagnosed by bronchoscopic biopsy in 37 patients (39.8%), EBUS-guided transbronchial needle aspiration in 13 patients (14%), and mediastinoscopy-guided lymph node sampling in 27 patients (29%).

In 25 patients (26.8%), other organ involvement was present in addition to the lung. These were found as uveitis (12 patients, 12.9%), skin (7 patients, 7.5%) and liver involvement (3 patients, 3.2%) in order of

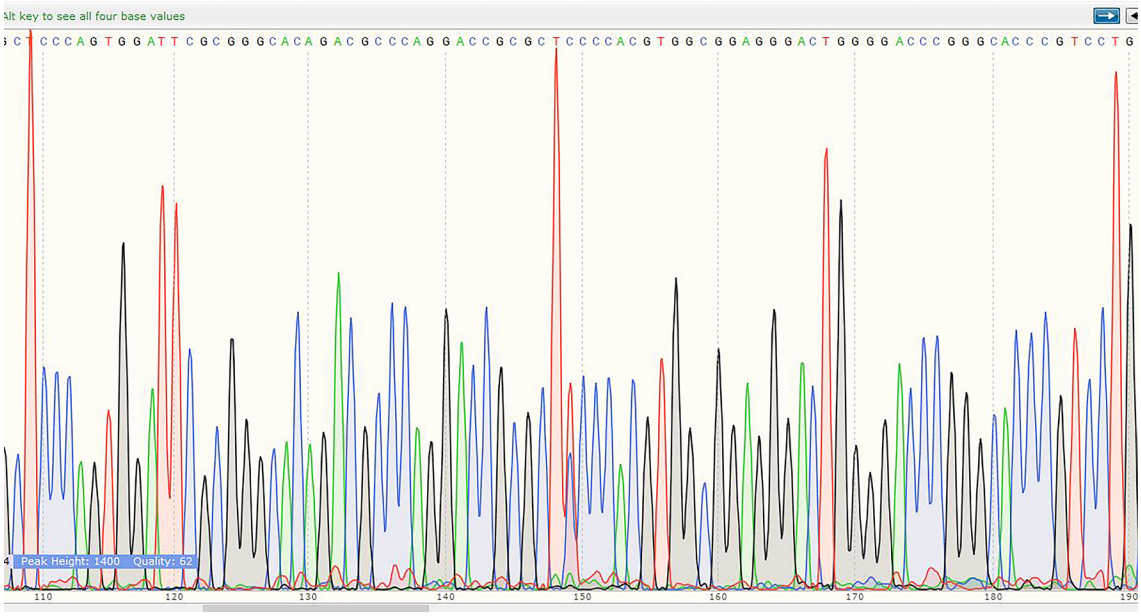

Figure 1. Sequence image of single nucleotid polymorphism region.

frequency. Of the patients, 37 (39.7%) were diagnosed as acute sarcoidosis and 56 (60.2%) as chronic sarcoidosis.

Appropriate results could not be obtained because 8 patients refused spirometry and carbon monoxide diffusion test (DLCO), 7 patients could not cooperate with spirometry and 29 patients could not cooperate with DLCO test. Seventy-eight spirometry of 78 (83.8%) patients and DLCO test of 56 (60.2%) patients were completed under appropriate conditions.

There was no significant difference between the non-fibrotic group consisting of stage 1, 2 and 3 and the stage 4 fibrotic sarcoidosis patients group in terms of gender, smoking status and presence of extrapulmonary involvement (p>0.05). The mean age in the fibrotic sarcoidosis patient group (57.9 ±11.3 years) was higher than in the non-fibrotic group (52.3 ±10.9 years). However, no significant difference was found (p=0.07). FEV1 ml values were significantly lower in the fibrotic sarcoidosis group (p=0.04). No difference (p>0.05) was found between the fibrotic and non-fibrotic groups in terms of FEV1 and FVC %, FVC (ml) and DLCO level (Table 1).

TERT rs283669 single nucleotide polymorphism has three genotypes; homozygous TT, homozygous CC and heterozygous TC. When genotypes were compared with gender, smoking status, acute or chronic sarcoidosis and presence of extrapulmonary involvement, no difference was found (p>0.05). In terms of FEV1 %, a significant difference was found when the three genotypes were compared (p=0.01). Post hoc analysis with Bonferoni showed that the group that made the difference was the patients with CC genotype. When FVC %, DLCO level (Table 2) and treatment status were evaluated, no significant difference was found between genotype groups (Table 3).

In the non-fibrotic sarcoidosis group, there were 27 (34.6%) patients with TT genotype, 39 (50%) with TC genotype and 12 (15.3%) with CC genotype; in the fibrotic group, there were 6 (40%) patients with TT genotype, 6 (40%) with TC genotype and 3 (20%) with CC genotype . No difference (p>0.05) was observed between the TT, TC, CC genotypes of the non-fibrotic and fibrotic sarcoidosis groups, nor between the TT+TC and CC and TT and TC+CC genotypes (Table 4).

No difference was found when sarcoidosis stages were compared with the genotypes specified in Table 5 (p>0.05).

Allele frequency is the relative frequency of an allele (variant of a gene), expressed as a fraction or percentage. The ratio of alleles in a population to the total. No significant difference was found when allele frequency was compared between fibrotic and non-fibrotic groups and sarcoidosis stages (Table 6).

Table 1. Comparison of demographic data, extrapulmonary involvement and pulmonary function tests in fibrotic and non-fibrotic sarcoidosis patients.

		Patients with non-fibrotic sarcoidosis (n= 78)	Patients with fibrotic sarcoidosis (n= 15)	P value
Gender	**Male**	17 (81%)	4 (19%)	0.67
	Female	61 (84.7%)	11 (15.3%)	
Age (years)		52.3 ±10.9	57.9±11.3	0.07
Smoke	**Never smoked**	55 (83.3%)	11 (16.7%)	0.42
	Quit smoking	9 (75%)	3 (25%)	
	Active smoker	14 (93.3%)	1 (6.7%)	
Only pulmonary involvement		56 (82.4%)	12 (17.6%)	0.51
Pulmonary and extrapulmonary involvement		22 (88%)	3 (12%)	
FEV1 (ml) Median (min-max)		2170 (1180-4530)	1750 (1300-3700)	**0.04**
FEV1% Mean±SD*		95.2±18.2	84.6±22.9	0.11
FVC (ml) Median (min-max)		2630 (1380-5580)	2150 (1460-6220)	0.55
FVC % Mean±SD		92.5±15.2	84.8±23.2	0.19
FEV1/FVC Median (min-max)		87 (58-99)	85 (68-97)	0.52
DLCO level Mean±SD		87.9 ±20.5	78.4±25.6	0.27

*SD: Standart Deviation

Table 2. Comparison of genotypes and demographic data, acute-chronic sarcoidosis, extrapulmonary involvement and pulmonary function tests of patients included in the study.

		TT Genotype[a]	TC Genotype[b]	CC Genotype[c]	P value
Age		54.8 ±12.4	52.2 ±10.2	52.8±11	0.59
Smoke	**Never smoked**	23 (34.8%)	32 (48.5%)	11 (16.7%)	0.88
	Quit Smoking	4 (33.3%)	7 (58.3%)	1 (8.3%)	
	Active smoker	6 (40%)	6 (40%)	3 (20%)	
Acute sarcoidosis		12 (32.4%)	20 (54.1%)	5 (13.5%)	0.66
Chronic sarcoidosis		21 (37.5%)	25 (44.6%)	10 (17.9%)	
Only pulmonary involvement		24 (35.3%)	36 (52.9%)	8 (11.8%)	0.13
Pulmonary and extrapulmonary involvement		9 (36%)	9 (36%)	7 (28%)	
FEV1% Mean ± SD*		97.9±17.9	96.0±16.0	79.9±23.8	**0.01**** a-b:1.00 a-**c**:0.01 b-**c**:0.02
FVC % Mean ± SD		93.6±14.7	92.6±15.4	84.6±21.1	0.24
DLCO % Mean ± SD		83.5±23.5	90.4±18.1	78.8±27.2	0.33

*SD: Standard Deviation; **pairwise comparisons will be evaluated

Table 3. Comparison of genotypes and treatment status of patients included in the study.

Treatment	TT Genotype	TC Genotype	CC Genotype	Total	P value
No treatment or topical treatment	4 (33.3%)	8 (66.7%)	0 (0%)	12 (12.9%)	0.44
Received systemic steroid therapy	19 (35.2%)	26 (48.1%)	9 (16.7%)	54 (58%)	
Received second-third generation treatments	10 (37%)	11 (40.7%)	6 (22.2%)	27 (29%)	

*Second-third generation therapies: methotrexate, azathioprine, cyclophosphamide, infliximab, adalimumab etc.

Table 4. Comparison of non-fibrotic and fibrotic sarcoidosis group and genotypes.

	Patients with Non-Fibrotic Sarcoidosis n (%)	Patients with Fibrotic Sarcoidosis n (%)	P value
TT Genotype	27 (81.8%)	6 (18.2%)	0.76
TC Genotype	39 (86.7%)	6 (13.3%)	
CC Genotype	12 (80%)	3 (20%)	
TT+TC	66 (84.6%)	12 (15.4%)	0.65
CC	12 (80%)	3 (20%)	
TT	27 (81.8%)	6 (18.2%)	0.69
TC+CC	51 (85%)	9 (15%)	

Table 5. Comparison of sarcoidosis stages and genotypes.

	Stage 1 n (%)	Stage 2 and 3 n (%)	Stage 4 n (%)	P value
TT Genotype	10 (30.3%)	17 (51.5%)	6 (18.2%)	0.89
TC Genotype	12 (26.7)	27 (60.0)	6 (13.3)	
CC Genotype	5 (33.3)	7 (46.7)	3 (20.0)	
TT,TC	22 (28.2)	44 (56.0)	12 (15.4)	0.78
CC	5 (33.3)	7 (46.7)	3 (20.0)	
TT	10 (30.3%)	17 (51.5%)	6 (18.2%)	0.87
TC+CC	17 (28.3)	34 (56.7)	9 (15.0)	

Table 6. Comparison of allele frequency of patients included in the study and groups.

	T Allele n (%)	C Allele n (%)	P value
Non-fibrotic sarcoidosis	93 (59.6)	63 (40.4)	0.96
Fibrotic sarcoidosis	18 (60.0)	12 (40.0)	
Stage 1	32 (59.3)	22 (40.7)	0.99
Stage 2 and 3	61 (59.8)	41 (40.2)	
Stage 4	18 (60.0)	12 (40.0)	

Discussion

Sarcoidosis is a systemic granulomatous disease of unknown cause that mainly affects the lungs and the lymphatic system throughout the body. Recent views on the etiology indicate interactions between inherited susceptibility and environmental or lifestyle factors (3). Immune and inflammatory processes in sarcoidosis lead to increased local or systemic oxidative stress in patients, resulting in disease-related telomeric alterations.

The ends of eukaryotic cell chromosomes are covered by specialized nucleoprotein structures called telomeres that protect them from destruction. Human telomeres are composed of thousands of TTAGGG hexanucleotide repeats. They protect chromosome ends from destruction, which is essential for chromosome and genome stability. Therefore, maintenance and repair of telomeres are of vital importance for organisms and the stability of cells (4).

The telomerase enzyme complex adds telomere repeats to the end of the chromosome, extending the telomere length with each cell division, thereby partially counteracting telomere shortening. The human telomerase enzyme has two components: a reverse transcriptase protein component (hTERT), which is the catalytic unit, and a functional RNA component (hTR) that forms a template for nucleotide insertion (1, 5, 6). When the telomerase complex loses its function as a result of a damaging stimulus, the healing and cycling of alveolar epithelial cells is thought to be affected. This triggers pulmonary fibrosis. Both ageing and idiopathic pulmonary fibrosis have been associated with shortening of telomeres due to telomerase deficiency (7).

Some single nucleotide polymorphisms in the telomerase gene have been associated with lung cancers and pulmonary fibrosis. In our study, we

investigated the association between fibrotic stage of sarcoidosis and rs2853669 single nucleotide polymorphism, a telomerase mutation, considering that it may predict the risk of progression to fibrosis in sarcoidosis.

In our study, the genotypes of rs2853669 polymorphism in the promoter region of telomerase gene were examined in 78 non-fibrotic and 15 fibrotic sarcoidosis patients. When non-fibrotic and fibrotic sarcoidosis groups were compared, no significant difference was found in terms of genotypes (p=0.76).

The FEV1% of the CC genotype was lower than the others (mean and standard deviations of FEV1% of TT, TC and CC genotypes were 97.9±17.9; 96.0±16.0; 79.9±23.8; p=0.01, respectively). When FVC %, DLCO level and treatment uptake were evaluated, no difference was found between genotype groups (p>0.05). This result may be due to the fact that the majority of our fibrotic patient group consisted of mild patients.

Common single nucleotide polymorphisms (SNPs) are genetic variations that are present in >1% of the general population, often producing unknown effects on protein function or expression (1). Some TERT polymorphisms have been associated with lung cancer, interstitial lung diseases and pulmonary fibrosis.

There are many TERT polymorphisms and their association with various cancers has been studied. For example, TERT rs2736100 and TERT rs2853677 polymorphisms are associated with increased cancer risk (8, 9). TERT rs2853669 polymorphism, which we examined in our study, was found to increase the risk in lung and other cancers (10).

When pulmonary fibrosis and TERT polymorphism studies were examined; TERT rs2736100 polymorphism was found to predispose to the disease in Japanese patients with IPF compared to the control group. The same polymorphism has been reported to predispose to other ILDs other than IPF in European patients (11, 12). Another study showed that compared to the control group, rs2736100 (p=1.7x10-19), rs2853676 (p=3.3x10-8) polymorphisms in TERT and rs1881984 (p=4.5x10-8) polymorphisms close to TERC in the genetic sequence constitute a risk for patients with fibrotic idiopathic interstitial pneumonia in Europeans (13). Although telomerase mutations were found to be associated with fibrosis in the studies mentioned above, no association was found between rs2853669 polymorphism and the progression of sarcoidosis to fibrosis.

In the study by Wei et al. no correlation was found between TERT rs2736100 polymorphism and pulmonary function test parameters (11). However, in our study, FEV1% was found to be lower in patients with the CC genotype of the rs2853669 polymorphism.

As noted in interstitial lung diseases, short telomere length may indicate disease susceptibility to fibrosis. In a few studies investigating telomere length in sarcoidosis, telomere length was found to be shorter than healthy control group (14- 16). Guan et al. reported that telomere length shortens with age in men, whereas it is not related to age in women (15). In another study, no relationship was found between aging and the presence of extrapulmonary organ involvement and telomere length (14). In our study, no association was observed between telomerase rs2853669 polymorphism and extrapulmonary organ involvement and telomere length was not analyzed.

In the study of Kouranos et al. in which they included 1100 patients with pulmonary sarcoidosis, they evaluated the patients as obstructive, restrictive and mixed ventilatory defects according to pulmonary function tests, and their DLCO values were measured. DLCO values were lower in the restrictive group compared to the mixed disease, and stage 4 disease was more frequently associated with a mixed ventilatory defect than with obstructive or restrictive defects (p<0.0001 for both comparisons in all analyses) (17). Therefore, DLCO levels in fibrotic sarcoidosis patients may not be as low as expected when compared to non-fibrotic group.

To date, the relationship between telomere length and telomerase mutations and fibrosis in sarcoidosis has not been investigated in the literature. No studies on any telomerase mutation in sarcoidosis were found. In our study, the relationship between TERT rs2853669 polymorphism, a telomerase mutation, and the development of fibrosis in sarcoidosis was investigated, but no significant relationship was found.

Limitations of the study are different: small number of patients, lack of a control group, non-examination of telomere length and pulmonary function test results, that are not available for a proportion of patients due to non-cooperation or refusal of the test.

Conclusion

The telomerase rs2853669 polymorphism was not associated with the progression of sarcoidosis to fibrosis, but individuals in the CC genotype with this polymorphism had lower FEV1% than other genotypes. Other common single nucleotide polymorphisms should also be examined in sarcoidosis and compared with healthy groups. Telomere length has been examined in studies on telomeres and telomerase in sarcoidosis patients, but no telomerase mutation studies have been found in the literature. Our findings are preliminary, but it is thought that our study will shed light on further studies to investigate telomerase mutations in sarcoidosis patients and to investigate the relationship between polymorphisms and fibrosis.

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Conflict of Interest: Each author declares that she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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