**Early prediction of sarcoidosis prognosis with HLA typing: A 5 year follow-up study**

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**Abstract.** Background: A wide range of HLA-DR alleles have been associated with sarcoidosis either in terms of disease phenotype or extra pulmonary involvement, however the effect on non-resolution in different ethnic groups is not fully understood. The aim of this study was to investigate whether disease characteristics and HLA-DRB1 alleles may early reflect non resolution in sarcoidosis. Methods: 91 patients who were diagnosed in Cukurova University Faculty of Medicine Department of Chest Diseases between 1993-2012 and were followed up until June 2017 were included in the study. All patients underwent HLA analysis by the Sequence Specific Oligonucleotide Prob (SSOP) method. Fifteen of them were excluded from the study group due to lost of follow-up (n=6) and not yet passed 5 years since diagnosis (n=9). Complete resolution at 5th year was defined according to the predefined standard criteria (ACCESS). Results: The resolution rate was 51.3%. The HLA-DRB1*14 allele was significantly higher in patients without resolution (11.8 vs 1.3%)(p=0.006). According to multivariate logistic regression analysis the independent risk factors of non resolution were female gender (OR: 12.6; 95%CI: 2.1-74.9, p=0.005), HLA DRB1*14 allele (OR:51.9; 95%CI: 3.6-735.8, p=0.000), baseline TLCO<75%(predicted) (OR:3.8; 95%CI: 1.1-13.7, p=0.028), extra-pulmonary involvement (OR:3.7; 95%CI: 1.0-13.1, p=0.038) and advanced stage at baseline (OR: 8.3; 95%CI: 1.9-35.4, p=0.001). Conclusions: HLA-DRB1*14 alleles, lower baseline TLCO, advanced stage, female gender or the presence of extra-pulmonary involvement could predict long term non-resolution in sarcoidosis. Early prediction of long term prognosis may affect treatment decisions and avoid further deterioration in these patient groups. (Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 184-191)

**Key words:** sarcoidosis, HLA alleles, resolution, follow-up, predictors

**Introduction**

Sarcoidosis is a multisystemic granulomatous inflammatory disorder of unknown origin. The clinical course and prognosis is quite variable and unpredictable even among affected sibling pairs (1-3). Although previous knowledge indicates that many cases undergo spontaneous regression, nearly one third of them experience a deteriorated course which results in incurable fibrosis. The causal mechanism of spontaneous resolution vice versa progression is still scarce. Corticosteroids which has been the mainstay of treatment used to prevent fibrosis for years, is reported to be linked with higher rate of relapse when tapered or discontinued (4). Thus it remains a critical
challenging to identify the patient with poor prognosis and avoid deterioration early in the course of the disease (4, 5).

The exact mechanism of disease still remains an enigma, however, the variable prevalence in several ethnic groups and the familial clustering, strongly suggest a plausible genetic predisposition (5-9). The hypothesis is that some antigen(s) enter the host and are phagocytosed by antigen presenting cells (APCs), mostly macrophages or dendritic cells. These APCs process the antigen and subsequently present it to a set of T-cell receptors on naïve T-lymphocytes, via human leukocyte antigen (HLA) class II molecules. The immune reaction result in the evolution of the T lymphocytes to a Th1 phenotype which is followed by cellular accumulation, proliferation, and differentiation leading to formation of the sarcoid granulomas (2,10). Therefore, the key event in the pathogenesis of sarcoidosis seems to be the orchestration between the antigen, HLA Class II molecules and T-cell receptors in the genetically susceptible host (10).

Because of the key role in the ability to recognize antigen and initiate an immune response, most of the tremendous evolution about sarcoidosis pathogenesis focused on HLA-Class II molecules since 1970s (9,10). Numerous reports from several different ethnic populations usually indicated HLA-DRB1*01 and *04 to protect from disease whereas HLA-DRB1*03, HLA-DRB1*11, HLA-DRB1*12, HLA-DRB1*14 and HLA-DRB1*15 are associated with an increased risk (5,7,11-13). In the previously published largest HLA-survey, the “A Case Control Etiologic Study of Sarcoidosis” (ACCESS), which includes 474 HLA-typed patients, DRB1*11 and DRB1*15 were documented as risk factors for sarcoidosis (5). In two previous reports from Turkey indicated increased frequency of HLA A2, A24, A26, A62, A69, 12, B22, B38, B49, DR4, DR14 and decreased frequency of A24, A26, B62, B7, DR7 with limited number of patients (14, 15). A recent report of our own group established a strong positive link between the haplotype HLA DRB1*15 and a potential protective effect of HLA DRB1*11 from extra-pulmonary involvement of disease in a Turkish Caucasian population (16).

Subsequent studies using more specific methods for HLA analysis documented that HLA Class II alleles may influence the disease course as well (8,17-20). In a Scandinavian cohort, HLA-DRB1*01 and *03 protected against, while *07, *14 and *15 were related with progressive pulmonary disease (17). Another study including British and Dutch patients identified HLA-DQB1*02 as an indicator of good prognosis (18). As well, other two reports including European and African American populations, documented the strong link between HLA-DRB1*03 allele with disease resolution (19, 20) however, none of these previous studies comment on long term prognosis.

The aim of this prospective study is to further explore the possible relationship between long term prognosis and HLA-DR genetic analysis in Turkish patients with sarcoidosis.

Methods

Ninety-one consecutive adult patients who were diagnosed in Cukurova University Faculty of Medicine Department of Pulmonary Disease from January 1993 to March 2012 and followed up until July 2017 were included in the study. Fifteen of them were excluded from the study group due to lost of follow-up (n=6) or insufficient follow up period (less then 5 years; n=9). The remaining 76 patients were classified as having resolution (complete resolution or minimal activity which is less than 25% of the initial maximal activity) or not according to ACCESS criteria (21). All participants were Caucasians of Turkish origin and were recruited from the Southern area - Eastern Mediterranean region of our country. None were related. The diagnosis of sarcoidosis was established with the presence of clinical symptoms, radiological investigations and biopsy compatible with sarcoidosis, in 94.7% according to the recent guidelines (1). In the remaining 5.3%, the patients were regarded as having Lofgren’s syndrome according to the previously defined criteria. None of the patients were receiving corticosteroid therapy at the time of diagnosis.

After certain diagnosis, all patients underwent a standard evaluation. The following items were recorded: (i) A detailed medical history (including demographical information, environmental exposure, questioning for the each system for extra-pulmonary involvement, current comorbidities, family history of sarcoidosis, and date of sarcoidosis symptoms onset); concurrently physical examination, (ii) posteroanterior-
or chest X-ray and computed tomography (CT); and hand radiography, (iii) lung function tests including carbon monoxide diffusion capacity (TLCO), (iv) electrocardiogram and echocardiogram, (v) abdomen ultrasonography, (vi) ophthalmologic investigation and (vii) tuberculin skin test, (viii) urinary calcium excretion in 24-hours. Magnetic resonance imaging of the brain, gallium scan of heart, CT scan of abdomen was also performed for patients whom further evaluation is required. Organ involvement was defined in each patient, within a previously defined assessment tool (ACCESS). Extra-pulmonary involvement was defined positive if it met the criteria for “definitive” or “probable” involvement.

Venous blood samples were obtained from the patient group at the time of diagnosis for HLA-DR allele analysis. The laboratory examinations except HLA typing were completed at the same day. Chest X-ray at the time of diagnosis was evaluated by an experienced chest physician specialized in diffuse lung disease, blinded to genotype, in terms of five “Scadding Stages” (Stage 0 to IV) in accordance with the ATS/ERS/WASOG Statement (1). Most of the patients were followed-up with the same investigator with clinical, laboratory and radiographical investigations.

According to the WASOG Task Group, which defined clinical phenotypes in association with clinical outcomes in sarcoidosis patients proposed by the ACCESS study, the clinical phenotypes were defined at least 5 years after detection or onset. Five years was identified as the start of a chronic phase, based on rates of remnant shadows on chest radiographs. At the fifth year of follow-up, disease activities were divided into three parts: resolved, minimal, and persistent. Minimal activities are defined as less than 25% of the initial activities (21).

Pulmonary Function Tests

Pulmonary function tests (PFTs) were performed in the stable point by using a calibrated Sensor Medics V Max 20 Spirometer according to the ERS guidelines (22). None of the patients were receiving oral or inhaled short-acting beta 2 agonists 8 h before testing. Baseline forced expiratory volume (FEV₁) and forced vital capacity (FVC) was measured 3 times and the best of 3 measurements was recorded for the analysis. Total lung capacity was measured using the helium dilution technique (Jaeger MS-PFT Analyser Unit). The transfer factor of the lung for carbon monoxide (TLCO) was measured using the single breath method. The results were presented as the percentages of predicted.

The institutional ethics committee approved the study (2011/10) and written informed consents were obtained from all of the participants.

Typing HLA-DRB1 alleles

An isolation kit was used to extract DNA from venous blood sample of each subject (QIAamp DNA blood mini kit, cat no: 51104, QIAGEN Vertriebs GmbH, Vienna, Austria). Typing of HLA-DRB1 alleles from DNA samples were performed by Sequence Specific Oligonucleotide Probes (SSOP) method. Tepnel Lifecodes HLA-DRB (Ref:628759-50, lot no: 10102Y, Connecticut, USA) typing kits were used for polymerase chain reaction and hybridization procedures. This product consists of a combination of locus-specific oligonucleotide probes coupled to color-coded microspheres (Luminex Corp) and two PCR reactions. To type each sample, PCR was performed and the product was hybridized with the SSO-probe mixture using the manufacturer’s protocol. After hybridization, the sample plate was located in a Luminex instrument for analysis.

Statistical Analysis

HLA analysis tool that exist in web page of Los Alamos National Laboratory (http://www.hiv.lanl.gov/content/immunology/hla/) were used for statistical analyses. For each HLA, the tool computes the 2-sided exact Fisher’s p-value, which represents the probability that the observed difference is due to chance. In order to accurate the false discovery rate caused by the calculation of multiple p-values, Storey’s q-value was also provided (23). A logistic regression analyses was performed to determine the independent risk factors. A value of p < 0.05 was considered statistically significant.

Results

Fifty eight female, eighteen male a total of seventy six patients with a mean age of 44.2 ± 8.9 yrs at
HLA-DRB1*14 predicts non resolution in sarcoidosis

the time of diagnosis were included for the study. Patient demographics are summarized at Table 1. Mean duration of follow-up was 100.1 ± 46.4 months (median 85). The majority of patients were never smokers (65.8%), of whom 25% were ex-smokers and 9.2% were current smokers. Any pulmonary symptom was present in 85.5% with cough with being the most common symptom in 44.7% which is followed by dyspnea (36.8%), chest pain (13.2%), sputum production (9.2%) and constitutional symptoms in 27.6%. There were 24 patients in Stage I (31.6%), 43 patients in Stage II (56.6%) and 9 patients in Stage III (11.8%) at the time of diagnosis. None of them was Stage IV.

During follow-up period, twenty-nine of the subjects (38.2%) were given any treatment while 47 of them (61.8%) were never required any treatment. Thirteen of the patients experienced relapse (17.3%) in the study group and all of them were in the treatment group. None of the patients experienced relapse that treatment was not indicated. Treatment requirement and relapse was also more common in patients with non resolution (59.5 and 29.7%, respectively). Extra-pulmonary involvement was documented in 31 patients (40.8%). The most common extra-pulmonary involvement was skin (n=12) followed by Lofgren syndrome (n=8) and eye involvement (n=7) (Table 1).

After 5 years follow-up period, the rate of non-resolution was 51.3% while mortality was 0% in the entire study group. When the patients compared according to the resolution status, age, smoking history and the frequency and the duration of symptoms before diagnosis were comparable however; female gender was more frequent and baseline respiratory function test results; including FEV₁(litres), FVC(litres), TLCO (%) and TLCO/VA (%) values, except FEV₁/FVC ratio, were significantly lower in

### Table 1. Demographical characteristics of the study group

| Characteristics                      | Number (%) |
|--------------------------------------|------------|
| Number of patients                  | 76         |
| Females                             | 58 (76.3)  |
| Males                               | 18 (23.7)  |
| Smoking history (n) (%)              |            |
| Never smokers                       | 50 (65.8)  |
| Ex-smokers                          | 19 (25)    |
| Current smokers                     | 7 (9.2)    |
| Mean age at disease onset (years±SD) (min-max) | 44.2±8.9 (19-61) |
| Females (mean)                      | 45.9±8.8   |
| Males (mean)                        | 38.7±6.9   |
| Duration of follow up (mean) (months) | 100.1±46.4 |
| Biopsy confirmation (n) (%)          | 72 (94.7)  |
| Lofgren’s Syndrome (n) (%)           | 8 (10.5)   |
| Extra-pulmonary involvement (n) (%) | 31 (40.8)  |
| Skin                                 | 12 (15.8)  |
| Eye                                  | 7 (9.2)    |
| Hypercalcemia                        | 5 (6.6)    |
| Peripheral lymph node                | 5 (6.6)    |
| Liver                                | 1 (1.3)    |
| Spleen                               | 1 (1.3)    |
| Joint                                | 2 (2.6)    |
| Neurological                         | 1 (1.3)    |
| Upper respiratory tract              | 1 (1.3)    |

### Table 2. Comparison of the patients according to resolution status at 5 yrs

| Resolution (-) (n=37) | Resolution (+) (n=39) | OR (Univariate) | p   |
|-----------------------|-----------------------|----------------|------|
| Age at diagnosis (years) | 44.6 ± 9.4 | 43.8 ± 8.5 | 0.708 |
| Female Sex (n) (%) | 32 (86.5) | 26 (66.7) | 3.2 (1.0-10.1) | 0.042 |
| Smoker (n) (%) | 10 (27) | 16 (41) | 1.8 (0.7-4.9) | 0.233 |
| Constitutional symptoms (n) (%) | 12 (32.4) | 9 (23.1) | 0.445 |
| FEV₁/FVC | 77 ± 8.8 | 80.3 ± 7.0 | 0.082 |
| FEV₁ (L) | 2.2 ± 0.7 | 2.6 ± 0.8 | 0.017 |
| FVC (L) | 2.7 ± 0.8 | 3.2 ± 1.0 | 0.024 |
| TLCO (%) | 71.6 ± 18.4 | 83.3 ± 14.6 | 0.003 |
| TLCO/VA (%) | 88 ± 19.5 | 96.1± 14 | 0.045 |
| Duration of symptoms (months) | 8.7 ± 11 | 4.4 ± 10 | 0.095 |
| Chest X-ray Stage I (n) (%) | 7 (18.9) | 17 (43.6) | 3.3 (1.1-9.3) | 0.021 |
| Extra-pulmonary involvement (n) (%) | 21 (56.8) | 10 (25.6) | 3.8 (1.4-10) | 0.006 |
patients without resolution (p<0.05). In addition, in the non-resolving group, the rate of advanced stage (II and III) at the time of diagnosis and extra-pulmonary involvement were more prominent according to univariate analysis (Table 2).

Twelve different HLA-DR alleles including HLA-DRB1*14, HLA-DRB7*03, HLA-DRB1*13, HLA-DRB1*01, HLA-DRB1*11, HLA-DRB1*03, HLA-DRB1*16, HLA-DRB1*15, HLA-DRB1*10, HLA-DRB1*08, HLA-DRB1*12 and HLA-DRB1*04 were documented in patients with sarcoidosis (Table 3). The frequency of HLA DRB1*14 allele was more frequent in patients without resolution (% 13.5 vs% 1.2) (p corr=0.002) (Table 4). According to multivariate logistic regression analysis, the independent risk factors of non-resolution were female gender (OR: 12.6; 95% CI: 2.1- 74.9, p=0.005), HLA DRB1*14 allele (OR: 51.9; 95% CI: 3.6- 735.8, p<0.000), baseline TLCO<75% (OR: 3.8; 1.1-13.7, p=0.028), extra-pulmonary involvement (OR: 3.7; 95% CI: 1.0-13.1, p=0.038) and advanced stage (II or III) at baseline (OR: 8.3; 95% CI: 1.9-35.4, p=0.001).

Discussion

The present study showed a positive link between HLA DRB1*14 allele with non-resolution in patients with sarcoidosis. In addition, female sex, advanced stage at the time of diagnosis, limited baseline TLCO and extra-pulmonary involvement were found as independent predictors of non-resolution.

Actually, HLA DRB1*14 is a frequently reported allele from several populations in sarcoidosis (5, 13, 24-26). A large multicentre European study which involved patients from the United Kingdom, Poland and the Czech Republic addressed HLA-DRB1*14 allele with *15 as a risk factor for disease (25). Later, in the largest cohort, the ACCESS study investigators also documented *14 allele as an independent risk factor of sarcoidosis in white patients.

### Table 3. Comparison of HLA Class II alleles among patients according to resolution status

| HLA          | Resolution (-) (n=37) (%) Allele=74 | Resolution (+) (n=39) (%) Allele= 78 | p-Value | P corrected |
|--------------|--------------------------------------|--------------------------------------|---------|-------------|
| DRB1*14      | 10 (13.5)                            | 1 (1.2)                              | 0.003   | 0.002       |
| DRB1*07      | 6 (8.1)                              | 2 (2.5)                              | 0.159   |             |
| DRB1*13      | 5 (6.7)                              | 11 (14.1)                            | 0.188   |             |
| DRB1*01      | 0 (0)                                | 3 (3.8)                              | 0.246   |             |
| DRB1*11      | 20 (27)                              | 20 (25.6)                            | 0.856   |             |
| DRB1*03      | 4 (5.4)                              | 6 (7.6)                              | 0.746   |             |
| DRB1*16      | 5 (6.7)                              | 7 (8.9)                              | 0.766   |             |
| DRB1*15      | 14 (18.9)                            | 16 (20.5)                            | 0.85    |             |
| DRB1*10      | 1 (1.3)                              | 1 (1.2)                              | 1       |             |
| DRB1*08      | 0 (0)                                | 1 (1.3)                              | 1       |             |
| DRB1*12      | 0 (0)                                | 1 (1.3)                              | 1       |             |
| DRB1*04      | 9 (12.1)                             | 9 (11.5)                             | 1       |             |

### Table 4. Multivariate analysis for the risk factors of non resolution

| Variable                  | OR (Multivariate) | 95 % Confidence Interval | p    |
|---------------------------|-------------------|--------------------------|------|
| Female gender             | 12.6              | 2.1 - 74.9               | 0.005|
| HLA DRB1*14 allele        | 51.9              | 3.6 - 735.8              | 0.000|
| Baseline TLCO<75%         | 3.8               | 1.1 - 13.7              | 0.028|
| Extrapulmonary involvement| 3.7               | 1.0 - 13.1              | 0.038|
| Stage II or III at baseline| 8.3              | 1.9 - 35.4              | 0.001|
(5). Another two different studies which were performed among several ethnic populations also confirmed the potential role of *14 in sarcoidosis, especially in lung predominant sarcoidosis (13, 26).

Natural history and prognosis of sarcoidosis is highly variable among different ethnic groups. Previous knowledge on prognosis which indicated a deteriorated course in nearly one third of the patients, have usually been limited with quite short follow-up periods. (4). In this study, we found that the rate of non-resolution is nearly half at 5 yrs among Turkish patients with sarcoidosis. Although it can be concluded as being a reference university hospital in the area which more complicated cases were referred, this is in accordance with some previous studies. In a previous long term follow-up report, 31% of the patients were improved whereas 69% were stable or deteriorated from the baseline (27). In another study, Grunewald et al showed that more than half of the patients developed a non-resolving disease (17). This is a clinical remark since may indicate a more significant health care effect of disease than previously thought after being confirmed in other racial populations.

Several clinical trials proposed that HLA DRB1* alleles may also influence the disease phenotype, as well (8,13, 28-30). Robust associations documented the strong link between HLA-DRB1*03 allele with acute onset, Lofgren Syndrome and spontaneous disease recovery (28). A relationship between HLA-DRB1*04 allele and Heerfordt syndrome has been identified (29). Sato et al associated a link between HLA DQB1*0602 allele and splenomegaly in a Japanese cohort (30). In a recent report, we established a potential protective effect of HLA DRB1*11 from extra-pulmonary involvement of disease in a Turkish Caucasian population (16). The potential role of HLA Class II alleles to influence disease prognosis in Lofgren's Syndrome is a mystery but it has been revealed that these patients display a less pronounced T helper 1 response and those related reduced level of IFN-γ and TNF-α (8).

Previous authors also investigated the relationship between disease course and HLA Class II alleles. The first genetic link between HLA alleles and disease resolution was published nearly 35 years ago (31,32). Later, Berlin and colleagues reported the 2 year follow-up results of 91 Scandinavian patients which 65% of them experienced chronic disease. They showed that HLA DRB1*14 and *15 alleles were related with a chronic course and concluded that HLA Class II typing has a profound influence on disease course in Scandinavian sarcoidosis patients (11). Later, another report addressed that HLA DRB1*14 allele and its linked DQ alleles showed strong positive association with chronic disease course, advanced stage (II and III) on chest radiography and joint involvement (p corr <0.01)(33). More recently, Grunewald and colleagues HLA typed a large Swedish patient population, sub-grouped them according to having Lofgren's Syndrome and followed up for two years. They showed that HLA DRB1*14 (OR: 2.14, p=0.005) and *15 (OR: 1.55, p=0.011) was related with a non-resolving disease (17). Consistent with the previous reports (11,17,33), we have also documented an increased frequency of DRB1*14 alleles in patients with a chronic course however no other allele was documented in this study. The low frequency of most alleles in this limited study group may have posed some difficulties in establishing a further significance between the two groups. Another possible explanation of this result may be the previously well-defined ethnical and geographical difference.

Another significant result of this study was the link between extrapulmonary involvement and non-resolution. Extrapulmonary involvement other than Lofgren's syndrome has been previously associated with unfavourable clinical course. In an early study which involved 122 Scandinavian patients and clinically monitored for up to 10 years, extra thoracic involvement was significantly higher in patients with non-resolution (55% vs 29%, p<0.01) (34). Later, these results were confirmed with two different Scandinavian cohorts (20, 29). Current treatment practice on extra-pulmonary involvement suggest glucocorticoids to patients who has severe single organ (eg, cardiac, neurologic) or multi organ disease (1). Further evaluation of other extra-pulmonary involvement on long term prognosis in larger cohorts may open a new vision to treatment recommendations in sarcoidosis. Other independent risk factors of non-resolution were female gender, advanced stage and lower baseline TLCO in this study. A female preponderance of cases is a well-known feature of sarcoidosis across several racial and ethnic groups. However, herein we showed that female gender is also a risk factor for non-resolution. As well, the relationship between advanced chest radiographic stage
and worse prognosis is a previously well documented feature of disease (35, 36). Lower baseline TLCO is probably a result of higher radiographic stage. In the Berlin study, chest x-ray stage I and normal lung function tests were reported to be related with complete recovery (11).

Despite recent progress in immunopathogenesis of disease, the underlying mechanism of HLA Class II molecules in the clinical course is still an enigma and several hypothesis have been developed. In the first one, Foley et al concluded the possible effect within the biochemical properties of the alleles. They showed that the two well-known protective alleles (HLA DRB1*01 and *04) share a hydrophobic residue at position 11. In contrast, the remaining non-protective alleles (HLA DRB1*08, *09, *12, *14, *15 and *17) share a hydrophilic residue at this position. Position 11 is shown to be located within the pocket of antigen presenting channel of the HLA DR molecule and may regulate immune response (25). This idea was supported with another Dutch study. In this report, Voorter and colleagues investigated the amino acids within the antigen binding parts of DRB1 and DQB1 molecules and showed that four DRB1 residues including Pro 11, Arg13, Ser 37 and Ala71 were related with a chronic disease course (37). From another point of view, it has been shown that different HLA DRB1* alleles present different Th1 responses. In fact, molecular studies documented that while patients with a higher proportion of Vα2.3+ lung T cells display a less pronounced Th1 response with a shorter disease course and better prognosis, the others who express unfavourable Class II molecules including DRB1*14, present a different peptide profile and promote an aberrant Th1 immunity. This response leads to increased IFN-γ, TNF-α and decreased TGF-β levels and results in not only ineffective clearance of the pathogenic antigen(s), but also a continual release of profibrotic cytokines and those related chronic disease course (8, 38-40). The putative mechanism of HLA-DRB1*14 allele on prognosis should further be investigated.

Several limitations of the present study must be taken into account. First, we have classified patients according to ACCESS resolution criteria like many of the previous reports; however the potential limitations of this system may be valid for this study. ACCESS trial is one of the largest cohort studies with follow up however it can be concluded to having a negative effect on this study results with the definitions of resolution. Although it may be quite easy to decide complete resolution according to this criteria, minimal activity which is defined less than 25% of the initial maximal activity may be interpret-able. Second, although being a major characteristic feature of our geographical region; we did not evaluated environmental factors such as high humidity or sunlight, which were beyond the scope of this study. Environmental-genetic interactions have been accused as a potential etiologic factor in sarcoidosis. In fact, in a study using the ACCESS study data, exposures to high humidity and water damage were found to augment the protective effect of the DQB1*02 allele (41). Thus, this should be investigated further. Third, the results of the present study display only a relatively small sample size of one population; however having a quite long time follow-up period of this study group strengthen our results.

In conclusion, this study showed that HLA Class II alleles have a profound influence on long term disease course in Turkish sarcoidosis patients. Female patients with any extrapulmonary involvement, baseline TLCO≤75%, advanced stage or HLA DRB1*14 allele positive should be carefully monitored and early treatment options should always be kept in mind in order to prevent irreversible damage. Further clinical trials in diverse populations and distinct patient phenotypes with particular clinical manifestations are needed to predict disease behaviour and improve prognosis.

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