Association of *BAFF* and *BAFF-R* polymorphisms with sarcoidosis in a Greek patient cohort

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Abstract

Introduction: Sarcoidosis is a disease that results from a combination of environmental and genetic factors. Its genetic basis however, is yet to be clarified. The purpose of this study is to determine whether single nucleotide polymorphisms (SNPs) of the B-cell activating factor (*BAFF*) and its receptor (*BAFF-R*) are associated with sarcoidosis.
Material and methods: Blood samples from one hundred and seventy-three sarcoidosis patients and one hundred and sixty-four controls were collected. All samples were genotyped for *BAFF* rs2893321, rs1041569 and rs9514828, and for *BAFF-R* rs61756766.
Results: Out of the three *BAFF* polymorphisms, none genotype had any significant association with sarcoidosis, although the T allele in rs1041569 and rs9514828 was overrepresented in sarcoidosis patients. A marginally significant association with sarcoidosis was found in the case of the CT genotype and T allele of *BAFF-R* rs61756766. Haplotype analysis of the *BAFF* polymorphisms was also performed, revealing an overrepresentation of the ATT, GTA and GTT haplotypes in the group of patients with cardiac involvement.
Conclusions: Taken together, the results of this study suggest a possible relationship between *BAFF* SNPs, rs1041569 and rs9514828, and *BAFF-R* SNP rs61756766 with sarcoidosis susceptibility and their potential as biomarkers for the disease.

Key words: BAFF, BAFF-R, sarcoidosis, rs2893321, rs1041569, rs9514828, rs61756766.

Introduction

Sarcoidosis is a rare, multisystemic, inflammatory disease, characterized by the formation of non-caseating granulomas [1]. Its prevalence differs depending on the geographic location, ethnicity, gender, and age; female gender and age between 25–45 are more likely to be affected [2]. To date, the etiology of sarcoidosis has been unclear but it is speculated that its occurrence is related to both genetic and environmental factors [3].

Being a multisystemic disease, sarcoidosis can affect almost all organs. However pulmonary sarcoidosis shows the highest morbidity rates

while at the same time lung is the most frequently affected organ [4]. Except of pulmonary involvement, the cardiac manifestation of the disease is not negligible since its clinical symptoms appear in 3–10% of patients, and its prevalence can reach up to 25% according to autopsy studies [5].

The formation of sarcoid granulomas is attributed to an exaggerated immune response, which begins with the aggregation of immunocompetent cells at sarcoid lesions, the consequent triggering and activation of T cells, and ends with cytokine release [6]. Apart from cell-mediated immunity, there are indications that the humoral branch is also involved in disease development, since pulmonary sarcoidosis is associated with polyclonal hypergammaglobulinemia [7], and a large B cell infiltration in granulomatous tissue of multiple organs suggests their implication in disease regardless of the targeted organ [8].

B-lymphocyte-activating factor (*BAFF*) belongs to the tumor necrosis factor (*TNF*) cytokine family [9], and is a type II transmembrane protein expressed by monocytes, macrophages, dendritic cells, bone marrow stroma cells, and T cells as a membrane-bound ligand or as a soluble trimer following cleavage [10]. By binding to the *BAFF* receptor (*BAFF-R*), one of its three receptors, signaling cascades are triggered which constitute/makes *BAFF* a critical factor for the survival and maturation of B cells [11]. *BAFF* levels in the blood have been found to be elevated in patients with several inflammatory diseases, such as Crohn's disease (CD) [12], systemic lupus erythematosus (SLE) [13], and multiple sclerosis [14]. In patients with sarcoidosis, serum and bronchial alveolar lavage fluid *BAFF* levels are increased and positively correlated with the disease's severity [15, 16] and activity [17]. These findings indicate the possible role of *BAFF* in the pathogenesis of sarcoidosis, which could be further explored genetically.

Single nucleotide polymorphisms of *BAFF* and its receptor have been linked to autoimmune diseases, such as SLE [18] and Sjogren's syndrome [19] in multiple studies, hence confirming their impact on disease development. A *BAFF* gene polymorphism of interest is rs2893321, an intronic SNP which has been associated with susceptibility to myasthenia gravis [20], Grave's and autoimmune thyroid diseases [21], and CD [12]. Similarly, two *BAFF* promoter SNPs, rs1041569 and rs9514828, have been characterized as potential risk factors for chronic lymphocytic leukemia (CLL) [22] and SLE [13, 23], and notably, CD development is strongly correlated with rs1041569 [12]. As for *BAFF-R*, the missense variant rs61756766 may contribute to increased susceptibility to non-Hodgkin lymphoma [24], CLL [22], Sjogren's syndrome [25], as well as a higher possibility of developing severe COVID-19 [26]. None of these genetic variants, however, has been investigated for a potential correlation with sarcoidosis susceptibility.

Given the abundance of data linking the aforementioned SNPs with autoimmune and inflammatory disorders, and the lack of their study in the context of sarcoidosis, the aim of this work is to examine the association of *BAFF* SNPs rs2893321, rs1041569, rs9514828, and *BAFF-R* SNP rs61756766 with the risk of developing sarcoidosis in a well-defined cohort of Greek patients. Apart from investigating the pulmonary manifestation of the disease, and taking into consideration the high prevalence of cardiac involvement, patients were also grouped as those with and without cardiac involvement. This type of manifestation can be asymptomatic in many cases, thus making it crucial to distinguish potential biomarkers for its presence. This will be the first time that these polymorphisms are studied for their correlation with the disease in a European population, with the purpose of expanding our knowledge on the genetic basis of sarcoidosis.

Material and methods

Sampling

In the present study, 173 patients with sarcoidosis (42 with cardiac involvement and 131 with pulmonary sarcoidosis) of Greek origin were enrolled. The subjects were recruited from one center, the Outpatient Department of Respiratory Medicine, "Attikon" University Hospital, Athens, Greece. Sarcoidosis diagnosis was set based on clinical and radiological criteria and after excluding other possible causes of granulomatosis in transbronchial biopsies with evidence of noncaseating granulomatosis [27]. Of these cases, 21 were newly diagnosed. All patients underwent a complete clinical, detailed cardiac and pulmonary evaluation, which consisted of standard electrocardiography, transthoracic echocardiography, 24 h Holter monitoring, cardiac magnetic resonance imaging, chest X-ray and pulmonary function testing. The modified criteria of the Japanese Ministry of Health and Welfare were used to evaluate the presence of cardiac involvement in sarcoidosis patients [28]. The age- and gender-matched controls were unrelated healthy individuals recruited from Aeginition Hospital, National and Kapodistrian University of Athens, Athens, Greece. The control population consisted of healthy volunteers recruited to attend a health survey representing the Greek population. The study was conducted in accordance with the Declaration of Helsinki, was approved by the Ethical Committee of the partici-

pating centers, and subjects signed informed consent to their participation in the study.

Genotyping

Genomic DNA was isolated from peripheral blood samples using the NucleoSpin Blood Kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany), according to the manufacturer's instructions. In order to genotype the three SNPs of the *BAFF* gene (rs2893321, rs1041569 and rs9514828), as well as the *BAFF-R* polymorphism (rs61756766), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was performed (Kapa Biosystems, Wilmington, MA, USA). Primer sets (Eurofins Genomics AT GmbH, Vienna, Austria) for PCR amplification of *BAFF* and BAFF-R genes are derived from former studies [21, 29, 30]. All primer sequences used are listed in Table I. The PCR products were digested with restriction enzymes at 37°C overnight and the digestion products were visualized after electrophoresis in 3% agarose gels stained with Gel Red (Biotium, USA). The utilized restriction enzymes and digestion products are listed in Table II.

Statistical analysis

All genotypic and haplotype frequencies were determined and compared using SNPStats [31]. Samples were separated into two categories; sarcoidosis patients and control group, and then further divided into sarcoidosis patients with cardiac involvement and without. For each SNP studied, control group samples were tested for departure from Hardy-Weinberg equilibrium. *P*-values of less than 0.05 were considered to be significant.

Results

The clinicopathological characteristics and demographics of the study population are listed in Table III. Patients were grouped based on the presence of cardiac sarcoidosis, and notably females had a higher frequency of cardiac involvement in comparison to males.

The genotypic frequencies of the studied polymorphisms of the *BAFF* and *BAFF-R* genes are listed in Table IV. All frequencies conformed to Hardy-Weinberg equilibrium ($p > 0.05$). Regarding the rs2893321 polymorphism, there was no significant difference between patients with sarcoidosis and controls. No statistically significant relationship was found for the other two *BAFF* polymorphisms, rs9514828 and rs1041569; in both cases however, the T allele was overrepresented in sarcoidosis samples ($p = 0.03$). As for the *BAFF-R* SNP, rs61756766, the genotype CT and the T allele had a marginally significant association with sarcoidosis ($p = 0.05$). When stratifying the patients regarding cardiac involvement or not, no association was observed.

After conducting haplotype analysis using the 3 SNPs of the *BAFF* gene, 8 haplotypes were formed.

Table I. Primer sequences and annealing temperatures used for *BAFF* and *BAFF-R* SNPs genotyping

SNP	Primer sequence (5'–3')	Tm [°C]
rs2893321	F: TTTTTCGTTGGACTTGGTCA R: CAACCCAAATCCAGAATCCT	55
rs1041569	F:ATTCCCTGTCTTCAGAATTTTCTCT R:CCTATAACTCCCACAATAAGGTGAC	58
rs9514828	F: TTGTACACCGACCTGTTAGGC R: TGGAAGTAAGTCCACTGGGAAT	58
rs61756766	F: CCTCCAGAGGAGTCTTCTAG R: TCCAAGCCCCTGGCTGGG	57

Table II. Base changes, digested products and restriction enzymes used for each BAFF and BAFF-R polymorphism

SNP	Base change	Restriction enzyme	Digested products [bp]
rs2893321	A/G	AseI (New England BioLabs, Beverly, MA, USA)	AA: 121,62 AG: 183,121,62 GG: 183
rs1041569	A/T	DpnII (Nippon Genetics Europe GmbH, Düren, Germany)	AA: 207,167,94 AT: 261,207,167,94 TT: 261,207
rs9514828	C/T	AciI (New England BioLabs, Beverly, MA, USA)	CC: 262,131 TC: 392,262,131 TT: 392
rs61756766	C/T	EaeI (Takara Bio, Shiga, Japan)	CC: 178,70,62 CT: 310,178,70,62 TT: 310

Of those, the ATT, GTA and GTT haplotypes frequencies were significantly higher in patients with cardiac involvement compared to patients without (p = 0.012, p = 0.013 and p = 0.024, respectively) (Table V).

Discussion

In our study we aimed to discover the potential association of *BAFF* and *BAFF-R* SNPs with sarcoidosis. Regarding the polymorphisms of the *BAFF* gene, none the 3 SNPs studied showed a significant difference of their genotypic frequency between patients and the control group. It is worth noting, however, that the T allele in rs1041569 and rs9514828 appeared more frequently in patients, in both cases. Similarly, the T allele in rs61756766, as well as the CT genotype, were overrepresented in sarcoidosis cases, though with a marginal significance. When patients were stratified based on

Table III. Clinicopathological characteristics of sarcoidosis patients and healthy controls

Parameter	Sarcoidosis patients (n = 173)	Healthy controls (n = 164)
Male/female	72/101	68/96
Age at diagnosis [years], mean ± SD	51.5 ±13.99	
Smokers	55	42
Löfgren's syndrome	5	
Chest radiographic stage:		
0	7	
I	55	
II	69	
III	28	
IV	14	

Table IV. rs2893321, rs9514828, rs1041569 (*BAFF*) and rs61756766 (*BAFF-R*) polymorphism distribution in patients with sarcoidosis

SNPs	Sarcoidosis (%) N = 173	Healthy controls (%) N = 164	P-value [OR (95% CI)]
rs2893321 (*BAFF*):			
AA (wt)	74 (42.77)	87 (53.05)	1
AG	75 (43.35)	59 (35.98)	0.10 [1.49 (0.94–2.37)]
GG	24 (13.87)	18 (10.97)	0.23 [1.57 (0.79–3.11)]
Alleles:			
A	223 (64.45)	233 (71.04)	1
G	123 (35.55)	95 (28.96)	0.07 [1.35 (0.98–1.87)]
rs9514828 (*BAFF*):			
CC (wt)	24 (13.87)	32 (19.51)	1
TC	66 (38.15)	71 (43.29)	0.53 [1.24 (0.66–2.32)]
TT	83 (47.98)	61 (37.19)	0.08 [1.81 (0.97–3.38)]
Alleles:			
C	114 (32.95)	135 (41.16)	1
T	232 (67.05)	193 (58.84)	0.03 [1.42; (1.04–1.95)]
rs1041569 (*BAFF*):			
AA (wt)	73 (42.20)	85 (51.83)	1
AT	70 (40.46)	61 (37.19)	0.24 [1.34 (0.84–2.13)]
TT	30 (17.34)	18 (10.97)	0.07 [1.94 (1–3.77)]
Alleles:			
A	216 (62.43)	231 (70.43)	1
T	130 (37.57)	97 (29.57)	0.03 [1.43 (1.04–1.98)]
rs61756766 (*BAFF-R*):			
CC (wt)	118 (68.20)	128 (78.05)	1
CT	48 (27.75)	31 (18.90)	0.05 [1.68 (1–2.81)]
TT	7 (4.05)	5 (3.05)	0.56 [1.52 (0.47–4.92)]
Alleles:			
C	284 (82.08)	287 (87.50)	1
T	62 (17.92)	41 (12.50)	0.05 [1.53 (0.99–2.34)]

Table V. *BAFF* haplotypes and their frequency in patients with or without cardiac involvement

Haplotype	Polymorphism			Cardiac involvement (n = 42)	No cardiac involvement (n = 131)	OR (95% CI)	P-value
	rs2893321	rs9514828	rs1041569				
1	A	T	A	0.22	0.31	1.00	
2	A	C	A	0.17	0.19	0.70 (0.40–1.23)	0.21
3	A	T	T	0.18	0.12	0.43 (0.23–0.83)	0.012
4	G	T	A	0.18	0.12	0.44 (0.23–0.84)	0.013
5	A	C	T	0.07	0.10	1.06 (0.51–2.18)	0.88
6	G	C	A	0.05	0.09	1.25 (0.58–2.68)	0.57
7	G	T	T	0.09	0.04	0.39 (0.17–0.88)	0.024
8	G	C	T	0.04	0.04	0.67 (0.23–1.92)	0.46

the presence of cardiac involvement, there was no correlation between the polymorphisms and sarcoidosis or its cardiac manifestation.

Although this is the first time that these polymorphisms were studied for their role in sarcoidosis susceptibility, they have been associated multiple times with several autoimmune disorders. Our findings suggest that rs2893321 is not associated with sarcoidosis, whereas this SNP has been linked in previous studies with Crohn's disease, where the GG genotype was suggested to have a protective effect [12], myasthenia gravis [20], and Grave's disease [21], although the last two studies mentioned refer to non-European cohorts. As for rs1041569, we report a significant association between T allele carriers and sarcoidosis. This allele has been detected in higher frequency in cases of myositis (p = 0.029; OR = 1.684, 95% CI: 1.050–2.699) [32] with similar p-value and OR with our results (p = 0.03; OR = 1.43, 95% CI: 1.04–1.98).

Herein, we describe a significant difference in the allelic distribution of rs9514828, and more specifically, an elevated frequency of the T allele in sarcoidosis. Nezos *et al.* studied rs9514828, among others, and identified this allele as a characteristic of a high-risk group for B-cell lymphoma development in Sjogren's syndrome [29]. The T allele was also hypothesized to increase susceptibility to SLE in Greek patients [13], yet when it was investigated in a Mexican population, no difference in genotypic or allelic frequency was found [33]. Taken together with our results, these findings suggest a potential role of rs9514828 in immune-related disorders, which differs among ethnic groups.

Regarding the *BAFF-R* SNP, rs61756766, a marginally significant relationship with sarcoidosis is deduced from our analysis. This mutation has been speculated to cause aberrant signaling through *BAFF-R* and to contribute to an enhanced activation of NF-κB pathways [24]. Since high *BAFF* serum levels are a characteristic of active sarcoidosis [17], this variant could be conducive to continuous and defective B cell signaling in this condition. Similar research has strongly linked rs61756766 with Sjogren's syndrome [25], as well as the CT genotype with a higher risk of CLL [22], which is in agreement with our study. A larger cohort however, could possibly elucidate whether an association actually exists.

The influence of genetic variations in the cardiac manifestation of the disease is not yet known, as limited data are available on the subject. Although the deduction that the particular *BAFF* and *BAFF-R* SNPs have an influence on cardiac sarcoidosis cannot be made according to the genotypic distribution presented in this work, haplotype frequency comparison revealed a higher prevalence of 3 *BAFF* haplotypes (ATT, GTA, GTT) in cardiac sarcoidosis patients. Therefore, *BAFF* could still have a role in the genetic predisposition of cardiac sarcoidosis development.

In conclusion, this study provides evidence that *BAFF* and *BAFF-R* could serve as potential biomarkers for sarcoidosis, independent of cardiac involvement. We believe that this is the first work to link polymorphisms of these genes with sarcoidosis, which could contribute to understanding the genetics of the disease and potentially to developing more efficient treatment strategies. Of course, a larger cohort could be used in a future study to validate our results, and their study in patients of different ethnicity would serve as a further proof of their significance.

Conflict of interest

The authors declare no conflict of interest.

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