Association of HLA Alleles with Primary Sjögren Syndrome in the South Tunisian Population

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Significance of the Study

- HLA-DR and DQ alleles represent the most common associations reported in primary Sjögren syndrome (pSS).
- In this study, besides HLA-DRB1*03, we found HLA-B15 association with pSS in a cohort of 44 South Tunisian patients.
- Microsatellite analysis supported the hypothesis of the existence of a susceptibility gene to pSS located in the HLA class I and III region.

Keywords

Primary Sjögren syndrome · Human leukocyte antigen · Polymorphism · Microsatellite · Haplotype

Abstract

Objective: In order to investigate human leukocyte antigen (HLA) genes predisposing to primary Sjögren syndrome (pSS), we conducted an association study using HLA loci (A, B, and DRB1) and 9 polymorphic microsatellite markers spanning the HLA region in pSS patients as compared to healthy individuals. **Subjects and Methods:** Forty-four patients fitting the European criteria of pSS and 123 healthy controls were analyzed for their HLA class I and class II alleles. HLA class I typing was performed using a standard microlym-

phocytotoxicity method followed by PCR-SSP. HLA-DRB1 genotyping was performed using PCR-SSP. We studied the polymorphism of 9 microsatellite markers for both groups. Microsatellite genotyping was performed using the PCR fluorescent technique. **Results:** We observed a positive association between HLA-B15 and pSS in the Tunisian population ($p = 0.004$, OR 7.57). The comparison of the frequencies of DRB1 alleles in pSS patients and controls confirmed the association of the DRB1*03 allele with pSS ($p = 0.02$, OR 2.36). On the other hand, the association study of microsatellite markers showed that the a9 allele of D6S265 marker and the a20 of C1.2.C were found to be positively associated with pSS as compared to controls ($p = 0.0003$, OR 10.29, and $p = 0.001$, OR 4.79, respectively). Using the "Haplo.stats" software analysis, we found that the most associated region was located

in the HLA class I region and limited by HLA-A and D6S265 loci ($p = 0.00056$). **Conclusion:** The results of this study support the hypothesis of the existence of a susceptibility gene for pSS located in the HLA class I and III regions.

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Introduction

Sjögren syndrome (SS) is a common, slowly progressive autoimmune disease (AID) characterized by chronic infiltration in the exocrine glands, particularly affecting the salivary and lacrimal glands, which causes conjunctival and oral dryness [1]. SS is called primitive when it manifests in the absence of any other AID such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, and myositis [2]. In addition to the glandular manifestations, extra-glandular manifestations affecting the skin, joints, muscles, nervous system, lungs, kidneys, liver, and hematological involvement may occur [1]. Primary SS (pSS) is one of the most common connective tissue diseases with an estimated prevalence of 0.2–3.39% in the general population. This pathology preferentially affects women (sex ratio = 9.15) between the fourth and fifth decades of life.

SS is a multifactorial disease related to genetic, hormonal, and environmental factors. However, while much progress has been made in recent decades, the pathophysiology of pSS remains unclear. Susceptibility to developing SS has been strongly associated with human leukocyte antigen (HLA) class II genes, particularly some HLA-DR and DQ alleles. Thus, the search for other genes in and/or outside the HLA system is essential. Several approaches have been used, such as the Genetic Linkage analysis, positional candidate gene analysis using microsatellite markers, and more recently the genome-wide association studies conducted on a large series of patients and controls with SNPs (single nucleotide polymorphism) markers [3, 4].

Only one previous microsatellite association study has been performed in the Tunisian population [5], while no association study between pSS and HLA polymorphism (A, B, and DR) has been conducted. Here, we report a case-control study of HLA-A, B, DR alleles and nine microsatellite markers distributed in the HLA region on a sample of 44 patients with pSS and 123 healthy controls from the South Tunisian population in order to identify other susceptibility loci on the short arm of chromosome 6.

Table 1. Distribution of HLA markers in South Tunisian patients with pSS and controls

	Marker	<i>p</i>
HLA-I	D6S276	NS
	HLA-A	NS
	D6S265	0.0002
	C3-2-11	NS
HLA-III	HLA-B	0.0002
	MICA	NS
	C1_2_C	0.04
	TNFA	NS
	TNFC	0.03
HLA-II	D6S273	NS
	HLA-DR	NS
	D6S291	NS

p values are from Pearson's test. HLA, human leukocyte antigen; pSS, primary Sjögren syndrome; NS, not significant.

Subjects and Methods

Subjects

Our case-control association study was focused on a representative sample of the South Tunisian population. The study included 44 patients with pSS and met the criteria established in 2002 by the American European Consensus Group (AECG) [2], clinically followed at the Internal Medicine Department of the Hedi Chaker University Hospital in Sfax between 2012 and 2015. Our control group was made up of 123 healthy unrelated subjects (72 women and 51 men, mean age 32 ± 9.28 years) from the south of Tunisia [6]. All patients and controls gave written informed consent for their participation in the study. This study was approved by our local ethics committee.

Methods

Data Collection

For each patient, we collected the following data: age, gender, clinical and para-clinical data, as well as biological and immunological data (anti-SSA and anti-SSB antibodies; Ab).

HLA Typing

We performed HLA class I typing (A and B) using a standard microlymphocytotoxicity method followed by PCR-SSP (One Lambda®). HLA class II (DRB) genes were typed using a polymerase chain reaction-sequence specific primer (PCR-SSP) kit (One Lambda®).

Microsatellite Markers

For our study we chose nine microsatellite markers that covered the entire HLA region: D6S276, D6S265, C3-2-11 (D6S2701), MICA, C1_2_C (D6S2800), TNFA, TNFC, D6S273, and D6S291 from telomeric to centromeric chromosome 6. The alleles of the markers have been designated by the repetition number of the simple pattern. Genotyping of the microsatellites of the two groups was performed by a fluorescent PCR technique, with specific amplification primer pairs (Perkin-Elmer, Applied Biosystems®) [7].

Table 2. Distribution of HLA and microsatellites alleles according to biological signs in pSS

			Anti-SSA Ab (+ vs. -), %	Anti-SSB Ab (+ vs. -), %	<i>p</i>	OR (95% CI)
HLA-I	a6 (D6S276)	–		4.5 vs. 31.8	0.046	0.10 (0.01–0.91)
	a16 (D6S276)	40.7 vs. 5.9	–		0.015	11 (1.26–95.49)
	a11 (D6S265)	18.5 vs. 47.1	–		0.043	0.25 (0.06–0.99)
	B15	25.9 vs. 0	–		0.032	–
	B15	–		31.8 vs. 0	0.009	–
HLA-III	a6 (TNFa)	40.7 vs. 5.9	–		0.015	11 (1.26–95.49)
HLA-II	DRB1*03	–		63.6 vs. 22.7	0.006	5.95 (1.58–22.33)
	DRB1*04	40.7 vs. 5.9	–		0.015	11 (1.26–95.49)

p values are from Pearson's test. HLA, human leukocyte antigen; pSS, primary Sjögren syndrome.

Statistical Analysis

The statistical analysis was performed using the software SPSS20, SHeSis, and Haplo.stats (R language 3.3.2). χ^2 and nominal *p* value (Pearson's test) calculation were used to evaluate the association of HLA polymorphisms with pSS. Fisher's exact test for small sample sizes (lower than 5 units per cell) was applied to the 2 × 2 tables as appropriate. The risk of association was reported as an odds ratio (OR) with a confidence interval (CI) of 95%. The significance threshold was set at *p* < 0.05. A binary logistic regression test was used to assess the independence of different alleles associated with pSS.

Results

Descriptive Study

The 44 patients consisted of 39 women (88.6%) and 5 men corresponding to a sex ratio of 0.12 (7.8 women for 1 man). The mean age of onset was 46.8 years (+/– 12.2 years). Forty patients (90.9%) had anti-nuclear Ab, 27 patients had anti-SSA Ab (61.4%), and 22 had anti-SSB Ab (50%).

HLA/pSS Association Study

The overall distribution of HLA-A antigens was not significantly different between patients and controls (*p* = 0.06). For HLA-B antigens, the difference in antigen distribution between the two groups was significant (*p* = 0.0002; Table 1). A positive association of HLA-B15 antigen was found in our patients compared to controls (15.91% in pSS vs. 2.44% in controls; *p* = 0.004, OR 7.57, 95% CI 1.8–30.7). All subjects with HLA-B15 had anti-SSA and anti-SSB Ab. This association was significant with *p* values of 0.032 and 0.009, respectively (Table 2). HLA-B8 was more frequent in patients compared to controls (25% in pSS vs. 13.01% in controls), but the difference was not significant (*p* = 0.06).

For HLA class II, a positive association of the HLA-DRB1*03 allele was observed in our patients as compared

to controls (43.18% in pSS vs. 24.39% in controls, *p* = 0.02, OR 2.36, 95% CI 1.14–4.86). The HLA-DRB1*01 allele was negatively associated with pSS compared to controls (2.27% in pSS vs. 18.7% in controls, *p* = 0.01, OR 0.1, 95% CI 0.01–0.77). The frequency of the DRB1*04 allele in patients (27.27%) was close to that found in controls (30.08%). However, HLA-DRB1*03, DRB1*04 heterozygosity was significantly more frequent in patients than in controls (13.64% in pSS vs. 2.44% in controls, *p* = 0.004, OR 6.3, 95% CI 1.5–26.47). As for immunological signs, the DRB1*04 allele was associated with anti-SSA Ab (*p* = 0.015, OR 11, 95% CI 1.26–95.5) while the HLA-DRB1*03 allele was positively associated with the presence of anti-SSB Ab (± anti-SSA Ab; *p* = 0.006, OR 5.95, 95% CI 1.58–22.32; Table 2).

Microsatellites/pSS Association Study

The overall microsatellite association analysis with pSS showed a significant difference for the markers: D6S265, C1_2_C, and TNFc (Table 1). For microsatellite markers in the HLA class I region, only the D6S265 marker showed a positive association with pSS. The a9 allele was significantly more frequent in patients compared to controls (20.45% in pSS vs. 2.44% in controls, *p* = 0.0003, OR 10.29, 95% CI 2.64–40.06). The binary logistic regression analysis showed that this association was independent of HLA-B15 (HLA-B15: *p* = 0.009, OR 6.9; the a9 allele of D6S265: *p* = 0.001, OR 9.6).

Comparing the group of patients with that of the controls, no association was found for the marker D6S276. However, the a16 allele of the D6S276 marker was associated with the presence of anti-SSA Ab (40.7% in pSS vs. 5.9% in controls, *p* = 0.015, OR 11, 95% CI 1.26–95.49). In contrast, the a6 allele was negatively associated with the presence of anti-SSB Ab (4.5% in pSS vs. 31.8% in controls, *p* = 0.046, OR 0.10, 95% CI 0.01–0.91; Table 2).

Fig. 1. Haplotype distribution for patients compared to controls by Haplo.stats software.

For microsatellite markers in the HLA class III region, the a20 allele of the C1_2_C marker was positively associated with pSS (25% in pSS vs. 6.5% in controls, $p = 0.001$, OR 4.79, 95% CI 1.7–12.8). The binary logistic regression analysis showed that the combination of the marker C1_2_C allele a20 with the pSS was independent of all other markers. The TNFc marker a2 allele and the D6S273 marker a13 allele were negatively associated with pSS (36.36% in pSS vs. 53.66% in controls, $p = 0.05$, and 15.91% in pSS vs. 30.89% in controls; $p = 0.05$, OR 0.42, respectively). No allele of the MICA or TNFa markers were associated with the disease. The a6 allele of the TNFa marker was associated with anti-SSA Ab ($p = 0.015$, OR 11, 95% CI 1.26–95.4; Table 2). No allele of the D6S291 marker was associated with the pSS in the HLA class II region.

Haplotype-Association Analysis

The study of haplotypes was carried out using Haplo.stats software. The most strongly associated region was localized in the HLA class I region and bounded by the A and B loci. A significant difference in haplotype distribution between patients or controls was found with three haplotype combinations: A-D6S265 ($p = 0.00056$); D6S265-C3_2_1 ($p = 0.017$), and B-MICA ($p = 0.036$; Fig. 1).

Discussion

SS is a common AID, known to be the second in terms of frequency after RA. However, few studies have focused on the Tunisian population, from which only one previous microsatellite association study has been reported [5, 8]. Here, we report a case-control association study of the HLA-A, B, DR alleles and nine microsatellite markers distributed within the HLA region, on a sample of 44 patients with pSS and 123 healthy controls in South Tunisia. We have described for the first time an association between HLA-B15 and pSS in our population. As with most AID, an association of several HLA alleles with pSS have been described in different ethnic groups [9]. In the literature, the most HLA alleles involved in pSS susceptibility belong to the HLA class II region. Nevertheless, the HLA class I region has also been reported to be associated with pSS (Table 3). The first description of an association between HLA-B8 and SS in the Caucasian population was reported 40 years ago [10–12], but subsequent studies demonstrated that this association was due to linkage disequilibrium with HLA-DR3 [10]. In our study, HLA-B8 was more frequent in patients than in controls, but the difference was not significant. This could be explained by the relatively small number of patients ($n = 44$). Among HLA class I antigens, only HLA-

Table 3. Summary of results from studies on the association of HLA class I and II with pSS

Population (Reference)	Year	Patients, <i>n</i>	Controls, <i>n</i>	Associations found	Pearson's <i>p</i>	OR
Caucasian (USA) [10]	1978	19	96	HLA-B8 HLA-DR3	<0.0001 <0.00001	
Caucasian [20]	2003	149	222	HLA-DRB1*03 HLA-DQB1*02	10 ⁻⁷ 0.0006	3.8 2.2
Colombian [21]	2005	74	76	HLA-DRB1*03:01 HLA-DQB1*02:01 Haplotype DRB1*03:01, DQB1*02:01	0.006 0.02 0.002	1.9 4.3 3.6
Meta-analysis: Colombian [9]	2012	1,166	6,470	HLA-DRB1*03:01 HLA-DQA1*05:01 HLA-DQB1*02:01	<0.001 <0.001 0.01	3,413 2,276 1,845
Meta-analysis: Chinese [22]	2015	492	1,860	HLA-DRB1*08:03	0.0002	3
Our series	2016	44	123	HLA-B15 HLA-DRB1*03 HLA-DRB1*01 Heterozygotes DRB1*03- DRB1*04	0.004 0.02 0.01 0.0047	 6.31 0.1 5.95

HLA, human leukocyte antigen; pSS, primary Sjögren syndrome.

B15 was found to be positively associated with pSS in our series. This antigen has been associated particularly with the presence of anti-SSA and anti-SSB Ab. No previous review has reported the association of HLA-B15 antigen with pSS. However, the combination of HLA-B15 with other AID has been described by several research teams. This antigen has been associated with the peripheral form of ankylosing spondylitis in Colombians [13], with undifferentiated spondyloarthritis among Tunisians [14], and with the severe form of Behçet disease among Moroccans [15]. Other non-autoimmune pathologies (such as periodontitis) have been associated with HLA-B15 [16]. The biological mechanism explaining the association of HLA class I molecules with pSS is not clear, but several hypotheses can be discussed and have been put forward.

An etiopathogenic role has been described for herpes viruses in the development of pSS [17]. A study by Rickinson and Moss [18] demonstrated the existence of a restricted representation of some antigenic EBV peptides “EBNA3” by HLA class I molecules, especially for HLA-B15 (B62), B8, and A24. Molecular mimicry and pathogen co-capture may be involved in the pathogenesis of pSS [19].

Our study also implicates HLA class II alleles, especially the DRB1*03 allele, in susceptibility to pSS. This association has been widely reported in the literature [9, 20, 21] (Table 3). A meta-analysis of 1,166 pSS and 6,470 controls explained the association of the HLA-DRB1*03:01 allele with pSS by high affinity of HLA-DR3 for 24 antigenic peptides derived from SSA, SSB, α -fodrin, and the muscarinic receptor (AChR-M3; the most likely antigenic targets during pSS) [9]. Similarly, the association of the DRB1*08:03 allele in Chinese pSS patients was explained by the particularity of the antigen in cleft of this allele (tyrosine at position 47 and isoleucine or leucine at position 67 of the β -chain) [22].

Regarding the immunological profile of our patients, the anti-SSB and anti-SSA Ab were respectively associated with the DRB1*03 and DRB1*04 alleles. In Caucasians, anti-SSA Ab were associated with HLA-DRB1*03:01 [20, 21]. A French study showed that simultaneous production of anti-SSA and anti-SSB Ab was associated with HLA-DRB1*03, while production of isolated anti-SSA was associated with DRB1*15 [20].

The HLA-DRB1*01 allele was negatively associated with the pSS in our series, a result which is consistent with a Hungarian study [23]. The protective role of the

DRB1*01 allele was confirmed by a meta-analysis in which serological groups DR1 and DR7 were negatively associated with pSS [9]. To better explore the HLA region and its involvement in susceptibility to pSS, we completed our HLA/pSS association study by analyzing microsatellite markers spanning the HLA region and a haplotype association study was conducted using the Haplo.stats software.

Indeed, a strongly significant positive association was found with the D6S265 marker ($p = 0.00056$). This association was independent of other HLA markers. This argues in favor of the presence of a localized susceptibility gene in the HLA class I region. In our South Tunisian population, this marker contributes to the susceptibility to other AID, such as pemphigus [24] and RA. In Caucasians, this marker has been associated with RA [25], SLE [26], and juvenile idiopathic arthritis [27]. Linkage disequilibrium with candidate genes could explain this association. Indeed, several genes located in the vicinity of this marker could be involved in the etiopathogenesis of AID: MICD, HCG9, HLA-J, ZNRD1, PPP1R11, TRIM31, and RNF39 (<http://www.ncbi.nlm.nih.gov/>). The ZNRD1 gene that codes for a protein involved in the regulation of cell proliferation could be a candidate gene for pSS. Hong et al. [28] have shown that the hyperexpression of this gene could be responsible for an increase in the expression of the bcl2 protein generating a lack of apoptosis. High expression of the bcl2 antigen has been reported in self-reactive lymphocytes accumulated in the salivary glands during pSS.

In our study, the only marker of the HLA class III region positively associated with pSS is C1_2_C (a20 allele). This association was independent of the other associated markers. Linkage disequilibrium with a candidate gene could explain this association. This region hosts four functional candidate genes (IkBL, ATP6G, BAT1, and MICB) which can be in linkage disequilibrium with the C1_2_C marker. Of these 4 genes, IkBL could be a susceptibility gene. This gene encodes a protein belonging to the NF- κ B family of transcription factors and can, therefore, be involved in the regulation of the expression of pro-inflammatory cytokines such as TNF α and IL-1. Castiblanco and Anaya [29] reported an association of a polymorphism of the IkBL gene with pSS and SLE. The polymorphism of the SNP IkBL (+ 738C) is three times more likely to develop pSS ($p = 0.009$) and twice more likely to develop SLE ($p = 0.01$) compared with controls.

Several studies have suggested a direct role of TNF α in the pathogenesis of SS. TNF α favors the expression of SSA and SSB antigen on the cell surface, independently of

apoptosis. The association of TNF α polymorphism with pSS or with one of these clinical manifestations has been reported by Guggenbuhl et al. [30]. They suggested a role for the TNF α 10 allele in susceptibility to pSS. It seems to be related to joint manifestations and the presence of anti-SSA Ab [30].

In our study, no association was found with TNF α 10. The TNF α 2 allele was more frequent in patients compared to controls, but this was statistically insignificant. This is consistent with the results of another Tunisian study [5]. However, the TNF α 6 allele has been associated in our patients with the positivity of anti-SSA Ab. The TNF α 6 allele could be associated with hyperexpression of TNF α . Indeed, in humans, a pathogenic relationship has been found between some TNF microsatellite alleles (TNF α) and the amount of TNF produced.

Conclusion

This study confirms the association of the HLA-DRB1*03 allele with pSS in the South Tunisian population. For the HLA class I region, we have described for the first time a strong association between HLA-B15 antigen and pSS in our population. The analysis of microsatellite markers showed a strongly significant positive association with the D6S265 marker located in the HLA class I region. These results indicate the involvement of the HLA class I region in susceptibility to pSS in our South Tunisian population. This effect seems independent of the role played by the HLA-DRB1 locus. Family studies and SNP analysis within HLA class I and class III candidate genes should help clarify the role of these genes in the physiopathology of the disease.

Statement of Ethics

All patients and controls gave written informed consent for their participation in the study. This study was approved by our local ethics committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

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