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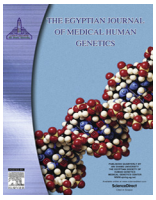

Original article

Distribution of HLA-DRB1/DQB1 alleles and DRB1-DQB1 haplotypes among Tunisian patients with autoimmune hepatitis

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ABSTRACT

Background: Autoimmune hepatitis (AIH) is a chronic inflammatory disease characterized by necrotic inflammation leading to hepatocyte destruction. The association of human leukocyte antigens (HLA) with AIH development and onset is not fully elucidated especially in the Tunisian population.
Objectives: The aim of this study was to determine the association of HLA class II alleles and DRB1-DQB1 haplotypes with AIH in Tunisian population.
Patients and Methods: A total of 30 AIH patients and 60 healthy controls were included in the study. HLA class II typing was performed by Single-specific-primer polymerase chain reaction (PCR-SSP) technique.
Results: Among 13 DRB1 and 5 DQB1 alleles resolved, our results show a positive association of HLA-DRB1*03 (38.3% vs. 21.6%, OR = 2.24, $P = 0.028$) and negative association of HLA-DRB1*11 (3.3% vs. 16.7%, $P = 0.019$). The analysis of DRB1-DQB1 haplotypes in cases and controls revealed 11-shared haplotypes with a frequency exceeding 1%. HLA-DRB1*11-DQB1*03 haplotype showed a decreased frequency in AIH patients (1.6% vs. 15.8%, $P = 0.009$) and may be considered as an haplotype of resistance to AIH.
Conclusions: To our Knowledge, this is the first study performed to detect the HLA-DRB1 and DQB1 alleles associated with predisposition to AIH in Tunisian patients. The search for HLA predisposing genes to AIH may permit an earlier diagnosis allowing a better management and treatment of the disease in order to avoid liver transplantation.
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1. Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by chronic destructive inflammation within the liver parenchyma, an interface hepatitis morphology and a female gender bias [1]. AIH was considered relatively rare, as the incidence of AIH ranges from 0.67 to 2.0 per 100,000 people per year, with a value of 0.83 per 100,000 in Spain [1]. Its prevalence ranges from 4.0 to 42.9 per 100,000 people with a high prevalence in Alaska and Europe [1]. To date, no information was found concerning the incidence of AIH in the North-African populations. The clinical presentations are frequently associated with nonspecific symptoms such as fatigue, jaundice, nausea, abdominal pain, and arthralgia [2]. Moreover, elevated transaminase and immunoglobulin G (IgG) levels, and the presence of antibodies characterize the physiopathology of AIH [3]. Based on the nature of the serum autoantibodies, clinical behavior and age of presentation, two types of AIH are described, type 1 and type 2 AIH [4]. The most prominent antibodies in AIH depend on AIH type. Antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA) are typically associated with type 1 AIH, whereas circulating anti-liver/kidney microsome type1 (LKM1) and/or anti-liver cytosol type 1 (LC-1) antibodies are detected in type 2 AIH [4].

AIH results from the interplay of multiple predisposing causes, genetic and environmental, but the underlying cause remains

Abbreviations: AIH, autoimmune hepatitis; AITDs, autoimmune thyroid diseases; AMA-M2, anti-mitochondrial antibody-M2; EBV, Epstein – Barr virus; ANA, anti-nuclear antibodies; CMV, cytomegalovirus; HLA, human leucocyte antigen; LKM1, anti-liver/kidney microsomal antibodies type 1; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SLA, antibodies against soluble liver antigen; SMA, smooth-muscle antibodies; SSP-PCR, single-specific-primer polymerase chain reaction.

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unknown [5]. It has been suggested that infection with Epstein-Barr virus and Cytomegalovirus causes contribute to the AIH development [6,7]. Several genes confer susceptibility to AIH; most are located within the human leukocyte antigen [HLA] region [8]. About 252 genes are expressed in the extended HLA complex, which span about 7.6 Mb on the short arm of chromosome 6 [9]. These genes are highly polymorphic, especially the HLA class I and II genes, which encode the peptide-presenting HLA molecules. The HLA complex is divided into three regions: class I, class II and class III. The class I region contains the classical *HLA-A*, *HLA-B*, and *HLA-C* genes that encode the heavy chains of class I molecules. The class II region consists of DP, DQ and DR subregions, which contains A and B genes encoding α and β chains, respectively [9]. The class III region contains genes for complement components (C2, C4, factor B), 21-hydroxylase, tumor necrosis factors (TNFs), and some others [9].

The association of HLA class II alleles and haplotypes with susceptibility to AIH was reported in different ethnic groups [10,16]. Indeed, Kekik et al. found a relationship between DRB1*03 or DRB1*03:01 alleles possession and AIH susceptibility in Turkish patients [14]. In Japanese [15,16], Mexican [11] and Korean [17] populations, AIH risk is associated with DRB1*04 allele possession. Hassan et al. studied the HLA class II distribution in 44 Pakistani AIH patients and reported a positive association of DRB1*14 allele with AIH development [18]. In Argentinians [12] and Indians [19], AIH susceptibility was related to DRB1*13 allele presence. Several investigations have also described protective alleles for AIH, including DRB1*08,*11 and DRB1*13, DQB1*03 and DQB1*02 [11,14,20,21]. These differences may be due to ethnicity and genetic backgrounds. The principal susceptibility allele for type 1 AIH in white northern European and American populations is HLA-DRB1*03, and a second, independent risk factor is HLA-DRB1*04 [10,22]. Susceptibility to type 2 AIH was conferred by the possession of DRB1*07, DRB1*13 and DQB1*02 in Brazilian patients [20].

To our knowledge, this is the first report studying the association of HLA class II alleles with AIH in the Tunisian population and in North-Africans. The aim of our study was to investigate the relationship between HLA DRB1/DQB1 alleles and DRB1-DQB1 haplotypes and AIH risk in Tunisian patients.

2. Patients and methods

A total of 30 unrelated patients with definite AIH were recruited from the gastroenterology department of Military hospital of Tunis, Charles Nicolle, La Rabta and Habib Thameur Hospitals, between September 2013 and April 2014. AIH was diagnosed based on International AIH Group criteria using a scoring calculator (10–15) [23]. A score of >15 was taken as definite AIH, and ≥10 as probable AIH. Patients with a score of less than 10 were excluded from the analysis. Clinical and biological features were obtained from the medical records of patients. Sixty unrelated healthy donors were included in our study (47 women and 13 men, mean age 49.6 yrs. ± 7.4) and matched for gender and age with AIH cases. Study participants have signed an informed consent before the study, and ethics committees approved the study protocol. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

2.1. HLA genotyping

Genomic DNA was extracted from lymphocytes separated from whole blood using a Ficoll–Paque solution (density 1.077 ± 0.001 g/ml) (24). DNA extraction was performed using QIAamp® DNA Blood Mini Kit (Qiagen®), following the manufacturer's instructions. HLA-DRB1 and -DQB1 antigens were detected by Single-specific-primer polymerase chain reaction (SSP-PCR) technique, according to Micro SSP Generic HLA class II DNA Typing Trays DRB1/DQB1 (One lambda®). Amplified DNA fragments were analyzed on 2.5% agarose gel stained with ethidium bromide. HLA Fusion Software (2005, One lambda®) was used to detect specific DRB1 and DQB1 alleles.

2.2. Statistical analysis

Statistical analysis was performed using SPSS version 20.0 software (IBM, Armonk, NY). The frequency of DRB1 and DQB1 alleles was obtained using Arlequin Software (25); DRB1-DQB1 haplotype frequencies were determined by the maximum-likelihood method, through expectation-maximization (EM) algorithm. The comparison of alleles and haplotype frequencies between cases and controls was expressed as *P* values, odds ratios (ORs), and 95% confidence intervals (CIs) and was performed by vassarStats (http://vassarstats.net/). *P*-Values were corrected using Yates's correction, and Fisher's exact test was applied for low number of subjects with a specific allele or haplotype. A P-value < 0.05 was considered as statistically significant. Hardy-Weinberg equilibrium (HWE) was tested at each locus in cases and controls.

3. Results

3.1. Clinical and immunological features in AIH patients

Demographic and clinical characteristics of patients are shown in Table 1. AIH is more frequent in women (86.6%). The mean age is 52.9 ± 14.1; the mean age at disease onset is 46.2 ± 15.2 and the disease duration is presented as median (IQR), 4.0 (3.0–7.7). Patients with type 1 AIH are present with a frequency of 93.3% and those with type 2 AIH with 6.6%. The most frequent Clinical presentations are jaundice (80%), asthenia (66.7%), splenomegaly (46.6%) and Pruritus (43.3%). Specific antibodies were found in patients' sera such as ANA (60%) and SMA (53.3%). Three patients had an infection with cytomegalovirus (CMV) and only one patient presented Epstein-Barr virus (EBV) infection. (Table 1)

3.2. Distribution of DRB1 and DQB1 alleles

Of the 12 DRB1 allele groups resolved, DRB1*03 (38.3%) and DQB1*02 (31.6%) were the most frequent alleles in AIH patients, whereas DRB1*03 (21.6%) and DQB1*03 (36.6%) were common in controls. Our results showed a positive association of DRB1*03 allele with AIH risk (38.3% *vs.* 21.6%, OR (95% CI) = 2.24 (1.14–4.42), $P = 0.028 < 0.05$). Conversely, we found a decreased frequency of DRB1*11 in cases compared with controls (3.3% vs. 16.7%, OR (95% CI) = 0.17 (0.03–0.76), $P = 0.019 < 0.05$) (Table 2). A reanalysis was performed using three genotypes (X/X, DRB1*03/X and DRB1*03/DRB1*03), where X represents alleles other than DRB1*03. Subjects with the genotype containing two copies of the DRB1*03 alleles (DRB1*03/DRB1*03) had a high risk of developing AIH (20% *vs.* 5%, OR (95% CI) = 5.69 (1.24–26.11), $P = 0.025 < 0.05$). On the other hand, the distribution of HLA-DQB1 alleles in cases and controls revealed a lack of association with AIH development in Tunisian patients (Table 3).

3.3. Distribution of HLA-DRB1-DQB1 haplotypes

The Table 4 displays the distribution of DRB1-DQB1 haplotypes in cases and controls. Of 10 haplotypes resolved, DRB1*03-DQB1*02 (21.6%) is the most frequent in cases and controls

Table 1
Characteristics of Tunisian autoimmune hepatitis cases and controls.

Parameters	Cases[1]	Controls[1]	*P*-Value
Gender, n (%)			0.341
Women	26 (86.6)	47 (78.3)	
Age[2]	52.9 ± 14.1	49.6 ± 7.4	0.237
Smoking, n (%)			0.188
Yes	2 (6.7)	28 (46.6)	
Alcohol use, n (%)			0.600
Yes	2 (6.7)	28 (46.6)	
Age at onset[2]	46.2 ± 15.2	NA	–
Disease duration[3]	4.0 (3.0–7.7)	NA	–
Clinical presentations, n (%)		NA	–
Asthenia	20 (66.7)		
Arthralgia	4 (13.3)		
Nausea	5 (16.7)		
Anorexia	7 (23.3)		
Weight loss	7 (23.3)		
Abdominal pain	12 (40.0)		
Jaundice	24 (80.0)		
Pruritus	13 (43.3)		
Hepatomegaly	10 (33.3)		
Splenomegaly	14 (46.6)		
Antibodies presence, n (%)			
ANA	18 (60.0)		
SMA	16 (53.3)		
LKM1	2 (6.6)		
SLA	1 (3.3)		
AMA-M2	5 (16.7)		
Infections, n (%)			
EBV infection	1 (3.3)		
CMV infection	3 (5.0)		

ANA: anti-nuclear antibodies, SMA: Smooth-muscle antibodies, LKM1: anti-Liver/Kidney Microsomal Antibodies Type 1, SLA: Anti*bodies* against *soluble liver* anti*gen*, *AMA-M2:* anti-mitochondrial anti*body-M2*, *EBV: Epstein - Barr virus*, *CMV: Cytomegalovirus*, *NA: not applicable*

[1] A total of 30 AIH cases and 60 healthy controls were included.

[2] *t*-Student's test for the variable "Age" with normal distribution (mean ± standard deviation).

[3] Variable without normal distribution (median (interquartile range)).

(20%). A decreased frequency of DRB1*11-DQB1*03 haplotype was detected in cases (1.6%) compared with controls (15.8%) (OR (95% CI) = 0.09 (0.01–0.69), $P = 0.009 < 0.05$).

4. Discussion

AIH is an uncommon chronic hepatitis, which may cause cirrhosis and liver failure if it is not treated [26]. These complications impose a comprehension of AIH physiopathology to find genetic biomarkers for early AIH diagnosis and management. Many studies have shown a strong association between the HLA complex genes and susceptibility to AIH in the different populations.

In our study, we examined the relationship between HLA class II alleles/haplotypes and AIH susceptibility in Tunisians. The distribution of HLA-DRB1 alleles revealed a positive association of HLA-DRB1*03 with AIH risk in Tunisian patients ($P = 0.028$). Similar results were reported in American [10], Argentinian [12], Venezuelan [13], Turkish [14] patients. In Japan, where DRB1*03 is extremely rare in the normal population, susceptibility to AIH were associated with DRB1*04 allele possession [16]. By contrast, DRB1*04 allele is uncommon (9.5%) in Tunisian population [27]. These findings suggest that HLA DRB1*03 and HLA DRB1*04 genes may code for HLA molecules that share determinents of susceptibility to AIH. In Pakistani, AIH risk was associated with the presence of DRB1*14 alleles [18], whereas in Argentinians and Indians, AIH susceptibility was related to DRB1*13 allele possession [12,19].

Several disease-associated HLA molecules would differ by ethnicity and genetic background. In fact, a shared amino acid motif in the antigen-presenting grooves of HLA DR3 and DR4 molecules coded by HLA DRB1*03 and HLA DRB1*04 genes respectively may exist [28]. This critical shared motif is consisted of a six-amino-acid sequence represented by the code LLEQ-R which is present predominantly in white North-Americans and North-Europeans with type I AIH [28]. This sequence found in DRB1*03:01 and DRB1*04:01, is located between positions 67 and 72 of the DRβ polypeptide chain of the class II HLA molecule, and lysine K in position 71 is the critical determinant of susceptibility [29,30].

These HLA alleles enhance autoimmune activation by enhancing immunogenicity and influencing the expressed repertoire of T cells, leading to destruction of self-liver antigens [31].

In addition, our association study shows that HLA-DRB1*11 allele is negatively associated with AIH development in Tunisian patients. DRB1*11 allele is common in Tunisian population (14.4%), which may explain its protective role [27]. Similar results were found in Iranians [21] and Argentinians [32]. Previous studies showed that HLA-DRB1*08,*13 and *15 protects against AIH in Turkish and Iranians [14,21].

On the other hand, the present association study showed a lack of association between DQB1 alleles and AIH development in Tunisian patients. Goldberg shared the same results and failed to find an association of DQB1 alleles with AIH onset [33]. Previous studies reported a positive association with DQB1*04 [13,16,17] and DQB1*06 [11,12] alleles; whereas DQB1*03:01 was described as a protective allele [11,20]. Results on relationship between DQB1 alleles and AIH risk remain controversial due to ethnicity and studies scale.

This association study of HLA genes and predisposition to AIH revealed also a protective role of DRB1*11-DQB1*03 haplotype, which may prevent AIH onset (1.8% *vs.* 15.6%, $P = 0.009$). Previous

Table 2
Distribution of HLA-DRB1 alleles in autoimmune hepatitis patients and healthy controls.

Alleles	AIH Patients N = 30		Controls N = 60		Statistical analysis Patients *vs.* Controls	
	AF		AF		OR (95% CI)	*P*-value
*DRB1*01*	5	8.3	8	6.7		0.762
DRB1*03	**23**	**38.3**	**26**	**21.6**	**2.24 (1.14–4.42)**	**0.028**
*DRB1*04*	5	8.3	15	12.5		0.559
*DRB1*07*	6	10.0	13	10.8		0.920
*DRB1*08*	2	3.3	2	1.6		0.601
*DRB1*09*	1	1.6	1	0.8		0.601
DRB1*11	**2**	**3.3**	**20**	**16.7**	**0.17 (0.03–0.76)**	**0.019**
*DRB1*12*	1	1.6	0	0.0		0.333
*DRB1*13*	7	11.6	13	10.8		0.920
*DRB1*14*	0	0.0	3	02.5		0.551
*DRB1*15*	7	11.6	16	13.3		0.920
*DRB1*16*	1	1.6	3	2.5		1.000

N: number of subjects, AIH: autoimmune hepatitis, AF: allele frequency, OR: odds ratio, CI: Confidence interval.

Table 3
Distribution of HLA-DQB1 alleles in autoimmune hepatitis patients and controls.

Alleles	AIH Patients N = 30		Controls N = 60		Statistical analysis Patients *vs.* Controls	
	AF		AF		OR (95% CI)	*P*-value
*DQB1*02*	19	31.6	34	28.3		0.777
*DQB1*03*	15	25	44	36.6		0.160
*DQB1*04*	5	8.3	7	5.8		0.537
*DQB1*05*	8	13.3	15	12.5		0.920
*DQB1*06*	13	21.6	20	16.6		0.537

N: number of subjects, AIH: autoimmune hepatitis, AF: allele frequency, OR: odds ratio, CI: Confidence interval.

Table 4
Distribution of HLA-DRB1-DQB1 haplotypes in autoimmune hepatitis cases and controls.

Haplotypes	AIH Patients N = 30		Controls N = 60		Statistical analysis Patients vs. Controls	
	n	HF	n	HF	OR (CI 95%)	*P*-value
*DRB1*01-DQB1*05*	5	8.3	6	4.9		0.510
*DRB1*03-DQB1*02*	11	21.6	24	20.0		1.000
*DRB1*04-DQB1*03*	4	6.7	12	10.0		0.646
*DRB1*07-DQB1*02*	5	8.3	10	8.3		0.777
DRB1*11-DQB1*03	**1**	**1.6**	**19**	**15.8**	**0.09 (0.01–0.69)**	**0.009**
*DRB1*13-DQB1*06*	2	3.3	6	4.9		0.720
*DRB1*14-DQB1*05*	0	0.0	3	2.5		0.551
*DRB1*15-DQB1*06*	7	11.6	14	11.6		0.806
*DRB1*16-DQB1*04*	1	1.6	0	0.0		0.333
*DRB1*16-DQB1*05*	0	0.0	3	2.5		0.551

N: number of subjects, HF: haplotype frequency, OR: odds ratio, CI: Confidence interval, AIH: autoimmune hepatitis.

studies found different protective haplotypes, including DRB1*15-DQB1*02:01 in Americans [10] and DRB1*15-DQB1*06:02 in Japanese [5]. Moreover, this haplotype is common in Tunisian general population (11.6%), which may explain its protective effect on AIH in Tunisian patients. Several studies showed a positive association of DRB1*13-DQB1*06 and DRB1*04-DQB1*04 haplotypes with AIH risk in Argentinian, Brazilian and Korean patients [12,17,21]; however, these haplotypes are uncommon in Tunisian population (4.5%, 3.5%, respectively) [27].

AIH can be associated with many autoimmune diseases, which share almost the same genetic predisposing genes. Besides overlap syndromes for primary biliary cirrhosis (PBC) and Primary sclerosing cholangitis (PSC), autoimmune thyroiditis are the most common concurrent disease [30,34]. Other concurrent disorders are type 1 diabetes mellitus, vitiligo, Sjogren's syndrome and ulcerative colitis [34]. HLA-DRB1*03 or HLA-DRB1*04 alleles were found to be related with PBC in European and Asian populations [35]. Patients with AIH-PBC overlap syndrome presented a predominant HLA-B8, DRB1*03, or DRB1*04 alleles similar to AIH [36]. Among autoimmune thyroid diseases (AITDs), autoimmune hypothyroidism has been weakly associated with HLA-DRB1*03 or *04 alleles [37]. In Tunisia, it has been shown that DRB1*03 and DRB1*04 are risk alleles for type 1 diabetes, while DRB1*11 is a protective allele [38,39]. AIH susceptibility may be associated with concurrent disorders present in AIH patients.

The present study has some strengths, but also limitations. Questionnaire-based personal interviews were conducted for assessment for baseline data of studied subjects. Moreover, all subjects included were Arabs. Non-Arab subjects, in particular (native) Berbers and individuals of European origin were excluded, which decrease the impact of ethnicity on genetic associations found in current study. However, technical limitations including high-resolution typing was not performed for DR3 group and others; consequently, the amino-acid alignment and association with the first and the third hyper-variable regions cannot be studied now. Finally, since our study had a modest sample size, alleles with low frequency in patients or controls were difficult to assess. Although this point constitutes a criticism, our results replicate those reported in other studies.

5. Conclusions

To our knowledge, this is the first report studying the relationship between HLA class II alleles and AIH susceptibility in North-Africans; our results bring out similarities and differences in HLA basis from those reported in other countries. We found a positive association of DRB1*03 with AIH onset. By contrast, DRB1*11 allele and DRB1*11-DQB1*03 haplotype were less frequent among patients and hence, could be involved in disease resistance. Large-scale studies and stratified clinical groups can be performed to verify our findings.

Declaration of interest

All authors have no conflict of interest.

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