MHC class I and class II genes in Tunisian patients with reactive and undifferentiated arthritis

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Abstract

Objective

To study HLA class I and class II association in Tunisian patients with reactive (ReA) and undifferentiated arthritis (UA).

Methods

The study included 17 patients with ReA defined according to the European Spondylarthropathy Study Group criteria for spondylarthropathy (SpA), 11 patients classified as having undifferentiated arthritis and 100 unrelated healthy controls. HLA class I antigens were typed serologically and HLA class II alleles were genotyped molecularly by the polymerase chain reaction with sequence-specific primers technique.

Results

*There was a major difference between HLA alleles in ReA and UA patients when compared separately with controls. Increased frequencies of HLA-B27 ($p=7.76\ 10^{-12}$, OR=59.30), HLA-B51 (p=0.015, OR=4.91) and HLA-DRB1*04 (p=0.033, OR=2.90) alleles were found in patients with ReA but not in patients with UA. HLA-B27 was not expressed totally in our cohort of UA patients. A significant increase of HLA-B15 (p=0.002, OR=18.40) and a moderate increase of HLA-B7 (p=0.043, OR=5.15) was found in patients with UA, but not in patients with ReA. In the B27 negative patients, HLA-DRB1*04 association with ReA was found independently of B27.*

Conclusion

*Our data confirmed a significant association of HLA-B27 with ReA in the Tunisian population. Our results also suggested that some of the additional HLA antigens were associated with ReA including HLA-B51 and HLA-DRB1*04 alleles. UA seemed to have a genetic background different from ReA in Tunisian patients.*

Key words

Reactive arthritis, HLA-B27, undifferentiated arthritis, HLA class I and class II.

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Abbreviations:

HLA:	human leukocyte antigen
ReA:	reactive arthritis
UA:	undifferentiated arthritis
PCR-SSP:	polymerase chain reaction-sequence specific primer
MHC:	major histocompatibility complex
SpA:	spondylarthropathies
AS:	ankylosing spondylytis
CREG-B7:	cross-reactive group
RS:	Reiter's syndrome
Ct:	*Chlamydia trachomatis*

Competing interests: none declared.

Introduction

The spondylarthropathies (SpA) are a group of inflammatory rheumatic diseases, typically affecting the axial skeleton, which include ankylosing spondylytis (AS), reactive arthritis (ReA) and the arthritis associated with psoriasis and inflammatory bowel diseases (1). ReA is an inflammatory arthritis occurring approximately 4 weeks after an extraarticular infection. Usually, the initial arthritogenic bacterial infection affects the urogenital tract (for example, *Chlamydia trachomatis*) or the digestive tract (*Yersinia*, *Salmonella* or *Shigella* spp, or *Campylobacter jejeuni*) (2). Epidemiologic studies all over the world have shown that ReA is a rare disease (1, 2). In addition, about 50% of patients with a mono or oligoarthritis remain classified as having an undifferentiated arthritis (UA) even one year after their first presentation. Undifferentiated and reactive arthritis often present in a clinically similar way (the high rate of mono and oligoarthritis and the predominance of synovitis in the lower limbs). This has lead to the hypothesis that UA might be a form of ReA ("forme fruste") with an asymptomatic infection (3-5). The association between HLA-B27 and ReA has been known for several decades and has also been established and demonstrated in different populations (6-8). Since the report of the association of HLA-B27 with SpA, especially ReA and AS, the molecular basis of this association has remained unknown and elusive (1, 9, 10). Findings obtained from ReA patients suggest that HLA-B27 modulates the interplay between ReA-triggering bacteria and immune cells, leading to abnormal host microbe interaction (1, 9, 10). Recent studies detailed the role of bacterial persistence in ReA and how it could be involved in the chronization of this disease (11). In addition, indirect evidence indicates that ReA-triggering bacteria might cause chronic infection in HLA-B27 positive patients (9, 10). In addition to B27, the antigens that cross-react with B27 antigen, including B7, B22, B42 B60 and B61 [called the B7-cross-reactive group (CREG)], are encoded by alleles (B*07, B*54, B*55, B*56, B*42, B*40) that have also been associated with ReA and AS (12). Although HLA-B27 has a central role in the pathogenesis of ReA, it has been suggested that HLA class II molecules might be associated with ReA, as well (6). The strength of the disease association with HLA-B27 varies markedly among the various SpA forms as well as among different ethnic populations (1). To our knowledge, no previous studies of HLA genes have been conducted in Tunisian patients with ReA or UA so far. Accordingly, we aimed to study the HLA class I and class II association with ReA and UA in Tunisia and to investigate the potential of HLA markers in terms of disease susceptibility.

Materials and methods

Patients

Seventeen Tunisian patients with reactive arthritis (ReA) and 11 patients with undifferentiated arthritis (UA) were included in this study after approval from our institutional review board. The demographic characteristic and the clinical features of the patients are shown in Table I. All patients attended one of the three different rheumatologic hospital departments in Tunisia from 1995 to 2006. ReA was defined according to ESSG criteria (13). Inclusion criteria for ReA patients were inflammatory synovitis (asymmetric and predominantly in the lower limbs) together with a positive history of urethritis, cervicitis, or a gastrointestinal symptoms within one month before arthritis. No patient had gonococcal infection. The arthritis was not of a psoriatic type, and none of them had clinical manifestations related to inflammatory bowel diseases (Crohn's disease, or ulcerative colitis).

The UA cohort was defined as having a mono- or oligoarthritis involving 1-4 joints predominantly in the lower limbs that occurred without any signs of a preceding infection (3, 4) and without psoriatic skin lesions. This cohort of patients did not meet the criteria for any well defined rheumatic disease: especially the revised American College of Rheumatology (formerly, the American Rheumatism Association) criteria for RA (14), the New York criteria for ankylosing spondylitis (15), the Centers for Disease Control and Prevention (CDC) criteria for Lyme arthritis (16). ReA and

Table I. Demographic and clinical features of patients.

	All patients (n=28)	ReA (n=17)	UA (n=11)
Sex, no. (%)			
Male	21 (75)	15 (88.20)	6 (54.50)
Female	7 (25)	2 (11.80)	5 (45.50)
Age, years			
Mean ± SD	32.21 ± 10.97	28.41 ± 8.95	38.10 ± 11.57
Range	(20-59)	(20-50)	(22-59)
History			
Duration of arthritis, mean ± SD months	8.91 ±15.56	1.85 ± 1.69	19.81 ± 20.84
Genitourinary symptoms, n. (%)	16 (57.10)	16 (94.10)	0 (0.00)
Gastrointestinal symptoms, n. (%)	1 (3.60)	1 (5.90)	0 (0.00)
Conjunctivitis symptoms, n. (%)	4 (14.30)	4 (23.50)	0 (0.00)
Uveitis symptoms, n. (%)	1 (3.60)	1 (5.90)	0 (0.00)
Skin lesions symptoms, no. (%)	4 (14.30)	3 (17.60)	1 (9.10)
Aphtose symptoms, n. (%)	2 (7.10)	1 (5.90)	1 (9.10)
Inflammatory low back pain > 3months, n. (%)	0 (0.00)	0 (0.00)	0 (0.00)
Inflammatory bowel disease, no. (%)	0 (0.00)	0 (0.00)	0 (0.00)
Clinical presentation, no. (%) of patients			
Monoarthritis	10 (35.70)	4 (23.50)	6 (54.50)
Oligoarthritis of Lower Limbs	13 (46.40)	8 (47.10)	5 (45.50)
Polyarthritis of upper and lower Limbs	5 (17.90)	5 (29.40)	0 (0.00)
swollen joint count, mean (Range)	2.5 (1-6)	3 (1-6)	1.5 (1-3)
Enthesitis, n. (%)	3 (10.70)	3 (17.60)	0 (0.00)
Sacroiliitis, n. (%)	3 (10.70)	2 (11.80)	1 (9.10)
ESR, mean ± SD mm/1 hour	77.50 ± 38.42	86.47 ± 37.31	63.63 ± 37.54
C-reactive protein, mean ± SD mg/liter	62.80 ± 63.33	79.80 ± 61.72	37.30 ± 59.72
Rheumatoid factor>20 units/ml, n. (%)	0 (0.00)	0 (0.00)	0 (0.00)
Antinuclear antibodies positive, n. (%)	0 (0.00)	0 (0.00)	0 (0.00)
Anti-CCP positivity, n. (%)	2 (7.10)	0 (0.00)	2 (18.20)
Radiographic erosions, n. (%)	3 (10.70)	1 (5.90)	2 (18.20)
Positive family history of AS, n. (%)	1 (3.60)	1 (5.90)	0 (0.00)
Positive family history of other forms of SpA, n. (%)	1 (3.60)	1 (5.90)	0 (0.00)
Positive family history of RA, n. (%)	0 (0.00)	0 (0.00)	0 (0.00)

ReA: reactive arthritis; UA: undifferentiated arthritis; SD: standard deviation; ESR: erythrocyte sedimentation rate; AS: ankylosing spondylytis, SpA: spondylarthropathies; RA: rheumatoid arthritis; Anti-CCPl anti-cyclic citrullinated peptide.

UA patients had arthritis with at least one swollen joint, *i.e.* knee synovitis. Each patient's history and examination findings were documented by using a standardized documentation sheet. One hundred unrelated healthy subjects without any symptoms or previous diagnosis of systemic disease from the same geographical area were included in the study as a control group.

HLA typing

For all patients, HLA-class I typing was undertaken by microlymphocytotoxicity test. HLA-class II was made by molecular method using the PCR-sequence specific primer (PCR SSP) (PCR SSP, One Lambda, Pel-Freez, Brown Deer, Wisconsin, USA).

Statistics

The comparison between the different allele frequencies in the patient groups and the control population was performed using chi-square, with Yates' correction as appropriate. After correction, a p-value <0.05 was considered to be significant. The magnitude of associations was assessed using odds ratio (OR).

Results

Our study included 17 patients with ReA (mean age = 28.41±8.95 years), 11 patients with UA (mean age = 38.10±11.57 years) and 100 unrelated healthy controls (mean age = 31.70±9.28 years). The mean age ratio was similar in all patients and the control group (mean ± SD age 32.21±10.97 years versus 31.70±9.28; p=[NS]). The proportion of men in the ReA patients was higher than among the UA patients but the difference was not significant (88.20% *vs*. 54.50%, p=0.076). The levels of the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP) showed no significant differences between ReA and UA groups (mean ± SD 86.47±37.31 *vs*. 63.63±37.54 and 79.80±61.72 *vs*. 37.30±59.72 respectively; p=[NS]). Rheumatoid factor and antinuclear antibodies were negative in all UA and ReA patients. The demographic characteristics and clinical features of the patients are shown in Table I.

The HLA class I antigens frequencies in patients with ReA and/or UA were compared with those in healthy controls (Table II). We found no significant association between ReA and/or UA and HLA-A antigens. There was an increased frequency of HLA-B27 in the whole group of patients (p=3.50 10^{-7}, OR=20.90) and, additionally, a moderate increase of HLA-B15 (p=0.027; OR=8.20) and HLA-B51 (p=0.028; OR=3.60) alleles in the whole group when compared to healthy controls. Other HLA-B alleles were equally distributed between patients and controls including the B7-CREG antigens (Table II). Three out of 100 healthy controls (3%) were B27 positive. In fact, the distribution of the HLA data in our control group consisted of 100 unrelated subjects were in accordance with those published by Ayed *et al*. (17) (data not shown).

In contrast, each patient group showed some specific deviations of HLA antigens markers when compared separately with the controls. For the HLA-B27 allele, the unique association was with ReA (p=7.76 10^{-12}, OR=59.30) since we found that HLA-B27 was not expressed totally in UA subjects. HLA-B51 was increased only in patients with ReA and not in patients with UA (p=0.015, OR=4.91 and p=NS, OR=2, respectively) (Table II). However, B51 was co-expressed with B27 in 4 ReA patients. A significant increase of HLA-B15 (p=0.002, OR=18.40) and a moderate increase of HLA-B7

Table II. Phenotypic frequencies (pf) of HLA Class I antigens in ReA, UA patients and controls.

	ReA + UA (n=28)		ReA (n=17)		UA (n=11)		Controls (n=100)	
HLA	n	pf	n	pf	n	pf	n	pf
A1	8	0.290	2	0.120	6	0.550	28	0.280
A2	9	0.320	6	0.350	3	0.273	34	0.340
A3	5	0.179	3	0.176	2	0.182	14	0.140
A10	1	0.036	1	0.059	0	0	12	0.120
A11	2	0.070	2	0.117	0	0	8	0.080
A19	12	0.429	6	0.350	6	0.545	39	0.390
A28	5	0.179	4	0.235	1	0.091	16	0.160
B35	3	0.107	3	0.176	0	0	17	0.170
B51	8	0.286*	6	0.353$^{\theta}$	2	0.182	10	0.100
B15	4	0.140$^{\blacklozenge}$	1	0.059	3	0.272$^{\clubsuit}$	2	0.020
B22	4	0.140	2	0.117	2	0.182	5	0.050
B27	11	0.393$^{\#}$	11	0.647¶	0	0	3	0.030
B40	0	0.000	0	0	0	0	9	0.090
B42	0	0	0	0	0	0	2	0.020
B44	4	0.140	3	0.176	1	0.091	26	0.260
B7	6	0.214	2	0.117	4	0.363$^{\spadesuit}$	10	0.100
B7-CREG	12	0.420	4	0.230	8	0.727	44	0.440

ReA: reactive arthritis, UA: undifferentiated arthritis, HLA: human leukocyte antigen, $p<0.05$ was significant by chi-square, with Yates' correction where appropriate.
*(p=0.028; OR=3.60) *vs*. controls; $^{\theta}$(p= 0.015; OR= 4.91) *vs*. controls; $^{\blacklozenge}$(p=0.027; OR=8.20) *vs*. controls; $^{\clubsuit}$(p=0.002; OR=18.40) *vs*. controls; $^{\#}$(p= 3.50 10^{-7}; OR=20.90) *vs*. controls; ¶(p=7.76 10^{-12}; OR=59.30) *vs*. controls; $^{\spadesuit}$(p= 0.043; OR =5.15) *vs*. controls.

Table III. Gene frequencies (gf) of HLA Class II antigens in ReA, UA patients and controls.

	ReA + UA (n=23)		ReA (n=13)		UA (n=10)		Controls (n=100)	
DRB1*/DQB1*	n	gf	n	gf	n	gf	n	gf
DRB1*01	3	0.065	1	0.038	2	0.100	22	0.110
DRB1*03	2	0.040	1	0.038	1	0.050	26	0.130
DRB1*04	13	0.280$^{\Theta}$	9	0.346¶	4	0.200	31	0.155
DRB1*07	4	0.087	2	0.076	2	0.100	34	0.170
DRB1*08	0	0.000	0	0.000	0	0.000	8	0.040
DRB1*09	2	0.040	1	0.038	1	0.050	4	0.020
DRB1*10	0	0.000	0	0.000	0	0.000	5	0.025
DRB1*11	7	0.150	4	0.150	3	0.150	26	0.130
DRB1*12	1	0.020	1	0.038	0	0.000	3	0.015
DRB1*13	7	0.150	3	0.115	4	0.200	18	0.090
DRB1*14	3	0.065	1	0.038	2	0.100	6	0.030
DRB1*15	4	0.087	3	0.115	1	0.050	15	0.075
DRB1*16	0	0.000	0	0.000	0	0.000	2	0.010
DQB1*02	6	0.130§	2	0.076‡	4	0.200	67	0.335
DQB1*03	22	0.478$^{\Delta}$	14	0.538$^{\#}$	8	0.400	53	0.265
DQB1*04	2	0.040	2	0.076	0	0.000	9	0.045
DQB1*05	10	0.217	4	0.150	6	0.300	37	0.185
DQB1*06	6	0.130	4	0.150	2	0.100	34	0.170

ReA: reactive arthritis; UA: undifferentiated arthritis; HLA: human leukocyte antigen; $p<0.05$ was significant by chi-square, with Yates' correction where appropriate. NB: HLA-class II typing was performed for 23 patients (13 ReA and 10 UA patients);
$^{\Theta}$(p=0.042; OR=2.15) *vs*. controls; ¶(p=0.033; OR=2.90) *vs*. controls; §(p=0.00) *vs*. controls; ‡(p=0.007) *vs*. controls; $^{\Delta}$(p=0.005) *vs*. controls; $^{\#}$(p=0.004; OR=3.20) *vs*.controls.

(p=0.043, OR=5.15) was found in patients with UA, but not in patients with ReA (Table II). Finally, regarding the HLA-DRB1 alleles distribution, we found an increase of HLA- DRB1*04 allele frequency in patients with ReA and not in patients with UA (p=0.033, OR=2.90) (Table III). For the B27 negative ReA patients, the expression of DRB1*04 allele was also statistically significant compared to controls excluding B27 individuals (p=0.001, OR=7.65). When the frequencies of HLA-DQ alleles were analysed, DQB1*03 was significantly associated with ReA patients compared to controls (p=0.004, OR=3.20) (Table III). The HLA-DRB1-DQB1 alleles frequencies of patients compared to controls are summarised in Table III.

Discussion

We reported here the first study of association of HLA class I and class II with ReA and UA in Tunisia in order to investigate whether MHC genes (class I and II) represent genetic risk factors in both ReA and UA, and especially, whether or not they have a common genetic background since ReA shared approximately the same clinical features with UA. Focus was placed on the molecularly typed class II genes of the patients, since the similarities reported in peptide presentation between HLA-B27 and HLA-DR2 have raised the possibility that the "arthrito-genic peptide could be presented by HLA-B27 and some class II antigens (7). The incidence rate of ReA is not estimated in Tunisia. ReA might be rare in Tunisia since the 17 patients with ReA represented a small proportion of the whole group of SpA who attended the same three hospital services during the same period of time.

HLA-B27 is a polymorphic form of HLA-B molecule that is found in more than 95% patients with AS and 70% with ReA (18). Leirisalo *et al*. (19), in Finland, found a frequency of B27 in 81% of their ReA patients. Vargas-Alarcón *et al*. (20) in Mexican population found that 72% of analysed ReA were positive for B27. In our study, the association of ReA with HLA-B27 was confirmed with a potential high

frequency of B27 positivity (64.70%; p=7.76 10^{-12}). Our data also extended previous studies indicating a lower prevalence of HLA-B27 phenotype in healthy Tunisians (20, 21). The validity of our data is based on the concordance between our healthy subjects HLA data and those of the normal Tunisians presented by Ayed *et al*. (20) (data not shown).

In addition to the strong association between HLA-B27 and ReA in this study, the ReA studied in the Tunisian population was associated with other MHC genes. The prevalence of HLA-B51, an allele previously associated with Reiter syndrome in Japan (8, 22), was increased in the groups of patients and particularly in patients with ReA. The diagnosis of ReA B51 positive patients was checked and none of them had a manifestation of Behçet's disease. Four out of six B51-ReA patients expressed both B27 antigen and B51 concommitantly. This indicated that B51 marker could be an additional susceptibility marker for ReA disease. Interestingly, B51 was previously shown to be characteristic of Mediterranean population (21) and reported to be associated with Behçet's disease (8). Therefore, HLA-B51 might be involved in the development of inflammatory diseases such as reactive arthritis. In this study, the HLA-DRB1*04 allele was significantly associated with ReA. Recently, the association between this allele and ReA has been described in a large group of Finnish ReA patients (6). In contrast, HLA class II antigens were not associated with UA. In the B27 negative ReA patients, independent expression of DRB1*04 was statistically significant, indicating that these two markers were associated independently in the disease susceptibility of ReA. DQB1*0302 allele was shown to be associated with ReA, but this association resulted from linkage disequilibrium with DRB1*04. HLA-B15, an allele known to be associated with AS and ReA (23), was associated only with UA. In previous studies, a significant increase of HLA-B15 was found in Undifferentiated SpA (9) independently of the presence of HLA B27 (16) and in HLA-B27 negative patients with AS associated with inflammatory bowel disease (16). Accordingly, in our study, all the B15 positive UA patients were negative for B27; therefore our data could support the involvement of the B15 allele in the disease susceptibility to UA particularly with the absence of HLA-B27 antigen.

The CREG-B7 antigen group (predominantly B7) can also be found in patients with Reiter's syndrome in North Americans (24), Israelis (25), and African Blacks (26). The association of the B7-CREG was not significant in our study with B27 negative ReA patients (23%) or with UA (72.70%). In the present study, HLA-B7 was the most prevalent allele of the B7-CREG group, predominating in UA patients with a moderate association with this disease.

In conclusion, we found a significant association between ReA and HLA-B27 in Tunisian population. Our results also suggested that some of the additional HLA antigens were associated with ReA including HLA-B51 and HLA-DRB1*04 alleles. Furthermore, our data demonstrated that the class I and II antigen distributions were different in both groups of the Tunisian ReA and UA patients. Thus, in spite of the common clinical pattern in both ReA and UA which is evidenced by the high rate of mono or oligoarthritis predominantly in the lower limbs, a different genetic background seemed to be functioning in each disease.

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