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Research Article

HLA-DR,-DQ WITH CLINICAL PRESENTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS IN MOROCCAN PATIENTS

Ouahiba Bhallil[1,2,3], Aichal brahimi[4], Samira El fakir [2,6] , Naima Ouzeddoun[1,4] Rabia Bayahia [1,4] and Malika Essakalli[1,5]

[1]Faculty of Medicine and Pharmacy, University Mohamed V, Rabat, Morocco
[2]Department of Basic Sciences, Faculty of Medicine and Pharmacy, University Sidi Mohamed Ben Abdellah, Fez, Morocco
[3]Central Laboratory of Medical Analysis, University Hospital Center, Fez, Morocco
[4]Department of Nephrology, Dialysis and Kidney Transplantation, CHU Ibn Sina, Rabat, Morocco
[5]Department of Immunology and Transfusion, CHU Ibn Sina, Rabat, Morocco
[6]Laboratory of Epidemiology, Clinical Research and Community Health, Faculty of Medicine, Fez, Morocco

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A B S T R A C T

Systemic lupus erythematosus (SLE) is an autoimmune disease with a heterogeneous presentation. The association between clinical presentations in SLE and the Human leukocyte antigen (HLA) genes has never been studied on a Moroccan population. The aim of this work was to evaluate the association between Human leukocyte antigen (HLA) genes and clinical features. HLA class II alleles typing was performed by polymerase chain reaction-sequence-specific primers (PCR-SSP) in 74 patients with SLE. The association between the HLA alleles was identified and compared in patients with and without the various clinical presentations included in the American College of Rheumatology (ACR) criteria.

A significant increase of HLA-DRB1*13 allele (p= 0.028) and decrease of HLA-DRB1*15 allele frequency (38.0% vs. 100.0%) were observed in SLE patients with serositis and arthritis respectively. A significant increase of the HLA-DQB1*04 allele (p = 0.003) were observed in SLE patients with oral ulcers.

The Moroccan population showed protective and predispositional alleles of HLA class II with clinical presentations in SLE patients.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem organ inflammation and diverse clinical features (Lahita, 2014)

The presentation of SLE is unpredictable (Klein-Gitelman *et al*., 2016).The incidence of SLE, in Morocco, was estimated at 6.25 cases per 100,000 persons (Elhattab and Essaadouni, 2013).

The disease is due to the interaction between diverse genetic and environmental factors (Borchers, 2010; Chai, 2010; Castaño-Rodríguez et, 2008). Many candidate genes HLA class II alleles have been shown to be significantly associated with susceptibility for the development of SLE in diverse ethnic backgrounds (Ceccarelli, 2015; Deng, 2013).The association between clinical presentations in SLE and the Human leukocyte antigen (HLA) genes has never been studied on a Moroccan population. The aim of this work was to describe the HLA class II alleles in patients with SLE and to determine of the associations of HLA alleles with SLE clinical manifestations.

Corresponding author:* **Ouahiba Bhallil
Department of Basic Sciences, Faculty of Medicine and Pharmacy, University Sidi Mohamed Ben Abdellah, Fez, Morocco

MATERIALS AND METHODS

Patients

This study included unrelated Moroccan SLE patients recruited from the Departments of Nephrology, Rabat Ibn Sina, University Hospital in the period from January 2013 to March 2014. The diagnosis of SLE was established according to the American College of Rheumatology (ACR) criteria (Hahn *et al*., 2012). Disease activity was recorded at visit, by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Bombardier *et al*., 1992).The written informative consent was obtained from all the patients and the study was approved by the ethical committee of the Rabat Medicine University.

DNA Extraction and HLA typing

DNA was extracted from the buffy coat fraction of blood samples of patients using a commercial kit (Qiagen). HLA typing of class II (DRB1 and DQB1) was tested by ‘‘Polymerase chain reaction sequence specific primers’’ (PCR-SSP) according to micro generic HLA DNA typing trays (One Lambda).

Statistical Analysis

Data entry was done using Excel. Descriptive analysis was performed for demographic and clinical characteristics. The Chi-square test was used to study the association between the allelic phenotype frequencies in SLE patients and clinical manifestations. A p-value of less than 0.05 was considered as statistically significant. The statistical analysis was performed by SPSS, version 13.0, software.

RESULTS

SLE Patients

This study included 74 unrelated Moroccan SLE. Five males and 69 females were recruited with mean age of 35.58 ±10.67 years.

Several clinical manifestations were noted and 71 (95.94 %) were found with arthritis, 20 (16.21%) with serositis, 09 (12.16 %) with oral ulcers. Demographic and clinical characteristics of the patients are recapitulated in Table1.

Table1 Demographic and clinical characteristics of SLE patients.

Variables	SLE (n=74)
Gender	
Female	69
Age (years, mean ± SD)	35.58 ±10.67
Age at disease onset (years, mean ± SD)	27.28 ± 8.94
Disease duration ((months, Mean ± SD)	99.14 ± 72.01
SLEDAI Median (range)	4 (2-45)
Arthritis (%)	71 (95.94)
Hematological disorder (%)	56 (75.67)
Malar rash (%)	55 (74.32)
Photosensitivity (%)	52 (70.27)
Serositis (%)	20 (16.21)
Neurological disorder (%)	10 (13.51)
Oral ulcers (%)	09 (12.16)

SLE: Systemique lupus erythematosus; n: number of individuals;
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

HLA-DRB1 frequencies in SLE patients according to the clinical manifestations

Table 2 shows the HLA-DR allele frequencies observed in Moroccan SLE patients according to the clinical manifestations. The phenotypic frequency of DRB1*15 was lower in SLE patients with arthritis than in those without(38.0% vs. 100.0%, p = 0.001). On the other hand, a significant higherfrequency in SLE patients with serositis than in those without of the DRB1*13 alleles wasobserved (41.7 vs. 14.5 %, p = 0.028). No statistically significant differences between SLE patients with and those without hematological disorder, malar rash, photosensitivity, oral ulcers and neurological disorder respectively were observed for HLA-DRB1* alleles.

HLA-DQB1 frequencies in SLE patients according to the clinical manifestations

The distribution of the HLA-DQB1* allele in SLE patients according to the clinical manifestations is shown in Table 3. The phenotypic frequency of DQB1*04 was significantly higher in patients with oral ulcers than in those without (44.4 % vs. 4.6 %, p = 0.003). No significant differences were found between SLE patients with and those without hematological disorder, malar rash, photosensitivity, serositis, arthritis and neurological disorder respectively were observedfor HLA-DQB1* alleles.

DISCUSSION

This is the first study that shows an association between HLA class II and clinical presentations in SLE patients in the Moroccan population. The distribution of HLA class II alleles in patients suffering from SLE showed that the frequency of HLA-DQB1*04, HLA-DRB1*13 were increased and DRB1*15 was lower, in patients with oral ulcers, serositis and arthrirtis respectively in SLE patients.

Several studies have shown that certain HLA-DR, -DQ alleles are associated with SLE. However, few studies have focused on associations of HLA alleles with clinical presentation in SLE.

In our study we have found a positive association of the DRB1*13 with serositis in lupus patients (41.7 vs. 14.5 %, p = 0.028) suggested a risk effect of this allele for serositis in lupus patients. In other studies, the positive associations of HLA class II alleles with serositis in lupus patients included HLA-DRB1*08:03, HLA-DRB1*07:01, HLA-DRB1*15:01,HLA-DRB1*09:01 and HLA-DRB1*11 (Wadi et al., 2014).

Several studies have found that an association between HLA-DQB1*alleles and SLE (Logar *et al*., 2002).These alleles do not play such important part in lupus nephritis (LN) in the Moroccan population (Bhallil *et al*., 2016). However, our results showed a positive association between HLA-DQB1*04 and oral ulcers in SLE patients suggested a risk effect of this allele fororal ulcers in SLE Moroccan patients. A risk role of the DQB1* 0601 for oral ulcers, has been reported in Malay patients (Azizah *et al*., 2001). Recently, Mokbel (Mokbel *et al*, 2014) found an association between HLA-DQB1*06 allele and SLE but is not related to the clinical presentation.

Worldwide studies have found that certain HLA-DR alleles are positively associated with SLE. However, few studies have reported a negative association of HLA alleles with SLE. In the present study, adecrease in the frequency of HLA-DRB1*15 in SLE patients with arthritis suggested that this allele could play a protective effect against arthritis in Moroccan SLE patients. Furthermore, DRB1*15 predisposes to LN in the Moroccan (Bhallil *et al*.,2016), Italian (Sfar *et al*., 2010), Hispanic (El-Haj *et al*., 2014), Brazilian (Wadi *et al*., 2014), American (Freedman *et al*., 1993), and Japanese (Furukawa *et al*., 2014) populations, as well as in the Saudi population (Wadi *et al*., 2014). A positive association between DQB*0501 and arthritis and a negative association between arthritis and HLA- DQB1* 0201 and 0601 were observed in SLE patients (Azizah *et al*., 2001).

We also explored associations between DQB1*02 alleles and SLE phenotypes including clinical manifestations of disease. In our study, this allele was represented, but not significantly, in the clinical manifestations of SLE.

Table 2 HLA-DRB1 frequencies in SLE patients according to the clinical manifestations.

Manifestations	Arthritis n=71	Malar rash n=55	Photosensitivity n=52	Oral ulcers n=09	Hematologicaldisorder n=56	Neurologicaldisorder n=10	Serositis n=12
DRB1* Alleles	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)
1	7.0/0.0	5.5/10.5	5.8/9.1	0.0/7.7	7.1/5.6	20.0/4.7	16.7/4.8
3	42.3/0.0	43.6/31.6	42.3/36.4	44.4/40.0	37.5/50.0	30.0/42.2	33.3/41.7
4	15.5/ 0.0	14.5/15.8	15,4/13.6	0.0/16.9	17.9/5.6	0,0/17,2	8.3/16.1
7	32.4/33.3	32.7/31.6	32.7/31.8	44.4/30.8	32.1/33.3	50.0/29.7	41.7/30.6
8	11,3/33.3	14.5/5.3	15.4/4.5	33,3/9.2	10.7/16.7	20.0/10,9	8.3/12.9
9	0.0/0.0	0.0/0.0	0.0/0.0	0.0/0.0	0.0/0.0	0.0/0.0	0.0/0.0
10	7.0/0.0	7.3/5.3	7.7/4.5	0.0/7.7	8.9/0.0	0.0/7.8	0.0/8.1
11	12.7/0.0	9.1/21.1	9.6/18.2	11.1/12.3	14.3/5,6	20.0/10.9	0.0/14.5
12	1.4/0.0	1.8/0.0	0.0/4.5	0.0/1.5	0.0/5.6	0.0/1.6	0.0/1.6
13	18.3/33.3	14.5/31.6	15.4/27.3	33.3/16.9	16.1/27.8	10.0/20.3	·1,7/14.5 (*)
14	5.6/0.0	3.6/10.5	5.8/4.5	0.0/6.2	7.1/0.0	0.0/6.2	0,0/6.5
15	38.0/100.0(*)	41.8/36.8	44.2/31.8	22.2/43.1	41.1/38.9	40.0/40.6	41.7/40.3
16	2.8/0.0	1.8/5.3	1.9/4.5	0.0/3.1	3.6/0.0	10.0/1.6	0.0/3.2
Blanks	7.0/0.0	9.1/0.0	5.8/9.1	11,1/6.2	5.4/11.1	0.0/7.8	8.3/6.5

(*): $p < 0.05$: p significant.
Yes/ No: presence/absence the various clinical American College of Rheumatology SLE classification criteria.
n: number of individuals.

Table 3 HLA-DQB1 frequencies in SLE patients divide according to the clinical manifestations.

Manifestations	**Arthritis n=71**	**Malar rash n=55**	**Photosensitivity n=52**	**Oral ulcers n=09**	**Hematologicaldisorder n=56**	**Neurologicaldisorder n=10**	**Serositis n=12**
DQB1*Alleles	Yes/NO (%)	Yes/NO(%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)	Yes/NO (%)
2	64.8/33.3	67.3/52.6	67.3/54.5	66.7/63.1	58.9/77.8	70.0/62.5	66.7/62.9
3	36.6/33.3	32.7/47.4	30.8/50.0	33.3/36.9	37.5/33.6	40.0/35.9	33,3/37.1
4	8.5/33.3	9.1/10.5	11.5/4.5	44.4/4.6 (*)	8.9/11.1	10.0/9.4	16.7/8.1
5	23.9/0.0	20.0/31.6	21.2/27.3	11.1/24.6	26.8/11.1	30.0/21.9	25,0/22.6
6	47.9/100.0	52.7/42.1	51.9/45.5	33.3/52.3	50.0/50.0	40.0/51.6	41.7/51.6
Blanks	18.3/0.0	18.2/15.8	17.3/18.2	11.1/18.5	17.9/16.7	10.0/18.8	16.7/17.7

(*): p < 0.05: p significant.
Yes/ No: presence/absence the various clinical American College of Rheumatology SLE classification criteria.
n: number of individuals.

HLA-DRB1*09 were not found in our patients, a similar result has been shown in healthy Moroccans (Brick *et al*., 2015).

The differences of susceptible genetic factors between populations can be explained by different genetic backgrounds. In conclusion, the current work suggests that the HLA-DRB1*15 allele are a protective genes against arthrirtis in SLE patients and HLADRB 1*13, HLA-DQB 1*04 is the susceptibility genes in SLE patients with serositis, oral ulcers respectively. It would be interesting to confirm the study by increasing the sample size. To our knowledge this is the first study of the frequency of HLA alleles in Moroccan SLE patients according to clinical presentations.

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Declaration of interest

The authors declare that they have no conflicts of interest concerning this article.

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