ORIGIAL ARTICLE

HLA-DRB1 alleles in Egyptian rheumatoid arthritis patients: Relations to anti-cyclic citrullinated peptide antibodies, disease activity and severity

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KEYWORDS
DRB1 alleles; Rheumatoid arthritis; Anti-CCP antibodies; RF; Severity; Activity

Abstract  Background: Human leukocyte antigen HLA-DRB1 alleles encoding a common amino acid sequence called shared epitope in the third hypervariable region of DRB1 molecule have been identified as risk alleles for rheumatoid arthritis (RA).

Aim of the work: The aim was to study HLA-DRB1 01, 04 and 10 alleles in Egyptian RA patients and determine their relation with anticyclic citrullinated peptide (anti-CCP) antibody level, disease activity, clinical and radiological severity.

Patients and methods: The study involved 40 RA patients and 20 control. Simplified disease activity index (SDAI) was calculated, clinical severity was assessed using the mechanical joint score (MJS) and radiological severity evaluated using the simple erosion narrowing score (SENS). HLA-DRB1 genotyping and anti-CCP antibodies were detected.

Results: The mean patients' age was 41.6 ± 12.7 years and disease duration 8.9 ± 7.7 years. The frequency of HLA DRB1 01, 04 and 10 in patients was 42.5%, 60% and 25% respectively. Of them 04 was significantly higher than in controls (p = 0.013) and was associated with anti-CCP positive cases (p = 0.0008) while the absence of HLA-DRB1 alleles was significantly associated with negative anti-CCP negative RA (p = 0.0008). There were significant associations between HLA-DRB1 01 and 04 with SDAI (p = 0.0002 and p = 0.005, respectively); between HLA-DRB1 04 and 10 with SENS (p = 0.002 and p = 0.001 respectively) and between HLA-DRB1 01, 04 and 10 with MJS (p = 0.02, p = 0.03 and p = 0.02, respectively).

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease and the genetic factor may be concerned in disease initiation and in the severity of its course [1]. The human leukocyte antigen (HLA) region, also well known as the major histocompatibility complex (MHC), has an impact on the genetic risk and may account for RA susceptibility [2,3] in 50–60% of cases [4]. In particular, HLA-DRB1 alleles encoding a common amino acid sequence called the shared epitope (SE) in the third hyper-variable region have been identified as risk alleles for RA [2]. These alleles are also associated with a more severe disease type [5,6].

Rheumatoid arthritis is characterized by the presence of various autoantibodies [7]. Best well known are the rheumatoid factors (RFs), which are antibodies against the Fc part of the immunoglobulin (IgG) molecules. They are not specific for RA; however, the detection of RF (IgM) is used in RA diagnosis [8]. Yet, anti-cyclic citrullinated peptide (anti-CCP) antibodies are highly specific markers for diagnosis of RA [9], preceding the appearance of the disease [10] and are reported to be good predictors for the development of RA [9]. They are also associated with a more severe disease course [9,11]. These data suggest that these antibodies have a causative role in the pathogenesis of RA [12,13].

The shared epitope hypothesis proposes that the SE plays a role in the presentation of ‘arthritogenic’ antigens to T lymphocytes [3]. Anti-CCP antibodies are directed to antigens containing the non-standard amino acid citrulline [14,15], for example, citrullinated fibrin which is found in the rheumatoid joint [16,17]. Although citrullination or SE deimination of arginine residues of proteins may result in the formation of epitopes that are targets of antibodies, help from T lymphocytes is likely required for long-term B cell responses and antibody isotype switching. Accordingly, in transgenic mice for one of the SE alleles ‘HLA-DRB1*0401’ it was demonstrated that citrullination of arginine residues of peptides at the peptide side-chain position interacting with the SE, significantly increases peptide–MHC affinity. This leads to an increased binding of these citrullinated peptides to MHC class II molecules leading to the activation of CD4-positive T cells [18]. Since not all RA patients have anti-CCP antibodies [14], this suggests that the presence of anti-CCP antibodies is not obligatory for the development of arthritis or that the pathogenic mechanisms underlying anti-CCP-positive and anti-CCP-negative RA are different. It was reported that the phenotype of RA patients with anti-CCP antibodies is similar to that without with respect to clinical presentation but differs in the disease course [19].

Since these data are showing an existing relation between anti-CCP antibodies and SE alleles and anti-CCP is highly specific for RA, a thorough analysis of HLA class II alleles involved in generating autoantibodies to citrullinated antigens is important to gain a better understanding of this particular immune response [12]. In this study, we aimed to study HLA-DRB1 01, 04 and 10 alleles in Egyptian RA patients and determine their relation with anti-CCP antibody level, disease activity, clinical and radiological severity.

2. Patients and methods

This study included 40 RA patients selected from the Rheumatology, Rehabilitation and Physical Medicine Department, Benha University Hospitals, Benha City, Qalyubia governate, Egypt. They were diagnosed according to the 2010 EULAR/ACR criteria [20]. 20 age and sex matched healthy volunteers were included as the control group. Patients were enrolled in the study after taking written informed consents from them. The study was approved by the ethics committee of the Faculty of Medicine, Benha University.

All the patients were subjected to full history taking and thorough clinical examination with stress on the locomotor system. Clinical disease severity was assessed using the mechanical joint score (MJS) [21]. A postero–anterior plain radiographic view of both hands was obtained for the assessment of radiological severity using the simple erosion narrowing score (SENS) [22] derived from the Sharp/van Der Heijde method as a simplified and easier scoring method. Disease activity was assessed using the simplified disease activity index (SDAI) [23].

Laboratory investigations were performed on the patients and control including the erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) (CRP LATEX TEST KIT; BIOTEC Laboratories Ltd) (positive results ≥ 6 μg/ml) and serum rheumatoid factor (RF) by nephelometry (Turbox RF-PAIA KIT; Orion Diagnostica) done on Turbox plus analyzer (positive results ≥ 25 IU/ml). Serum anticyclic citrullinated peptide antibodies (anti-CCP3) were assessed by semi-quantitative enzyme-linked immunosorbent assay (ELISA) (QUANTA LiteTM CCP3 IgG ELISA kit supplied by INOVA Diagnostics, Inc.-USA). Assessment was according to the manufacturer’s instructions. Results ≥ 20 U/ml were considered positive. Blood collected on EDTA containing tubes were stored at –80 °C for later HLA-DRB1 genotyping.

2.1. HLA-DRB1 genotyping

Genomic DNA was extracted from 200 μl of whole blood using QIA amp DNA blood mini kits, catalog number 51104, supplied by Qiagen-Germany according to the manufacturer’s instructions. Two-hundred μl of DNA was eluted. The extracted DNA was then stored at - 20 °C until further processing. HLA-DRB1 alleles (DRB1 01, DRB1 04, DRB1 10) were identified by conventional polymerase chain reaction (PCR) using specific primers, common reverse primer CTC...
GCC GCT GCA CTG TGA AG forward primer for DRB1 01
CTT GTG GCA GCT TAA GTT TGA AT, forward primer
for DRB1 04 GTT TCT TGG AGC AGG TTA AAC and,
forward primer for DRB1 10 CAC AGC ACG TTT CTT
GGA GG [24]. Amplification was done using Taq PCR Master
Mix Kit supplied by Qiagen. The PCR mix for each allele con-
tained 25 l of Taq PCR master. Mix 2/C2, 2.5 l (0.5 l M) of
forward primer, 2.5 l (0.5 l M) of reverse primer, 10 l of
the template DNA and 10 l of nuclease free water to reach
a final volume of 50 l. G storm thermal cycler-UK was used
for amplification according to the following program: initial
denaturation at 94 °C for 3 min., 35 cycles of denaturation at
94 °C for 30 s., annealing at 53 °C for 30 s. and extension at
72 °C for 1 min., followed by final extension at 72 °C for
10 min. then hold at 4 °C. 10 l of each amplified DNA &
1000 bp ladder (molecular weight marker) were separated on
2% agarose gel containing 0.3 g/ml of ethidium bromide,
photographed and analyzed (agarose gel electrophoresis)

Statistical analysis: The collected data were computed and
statistically analyzed using SPSS version 17 software for win-
dows (SPSS Inc., Chicago). Suitable statistical techniques
were calculated as range, mean, standard deviation, median and fre-
quency (percentage). Chi square and Z tests were used to test
the significance for frequency and the corrected Chi square test
for frequencies <5. Student’s t test and ANOVA were used for
comparison of 2 groups and >2 groups respectively. Odds
ratio (OR) with 95% confidence interval (95% CI) values were
also calculated. Pearson correlation coefficient was estimated
to correlate the DRB1 genotypes and anti-CCP antibody level.

3. Results

Forty Egyptian RA patients with a mean age of 41.6 ±
12.7 years (range: 20–66 years) and 20 control with a mean
age of 43.3 ± 13.9 years (range: 20–64 years) were included in
the study. The demographic features and laboratory parame-
ters of the RA patients and control as well as the clinical char-
acteristics of the patients are presented in Table 1.

The frequency of HLA-DRB1 01, 04 and 10 in RA patients
and control are shown in Table 2. Only the frequency of 04
allele was significantly higher in RA patients compared to
the controls.

The relation of the studied HLA-DRB1 01, 04 and 10 alleles
differently in the demographic and clinical parameters in RA
patients is presented in Table 3. The disease duration was sig-
ificantly (p = 0.0014) longer in HLA-DRB1 10 positive cases.
The SDAI was significantly higher in RA patients with positive
01 and 04 alleles (p = 0002 and p = 0.005, respectively). Clinical
disease severity (MJS) was significantly higher in patients
with positive 01, 04 and 10 alleles (p = 0.022, p = 0.03 and

Table 2 Frequency of HLA-DRB1 01, 04 and 10 in RA patients and control.

<table>
<thead>
<tr>
<th>HLA-DRB1 frequency n (%)</th>
<th>RA patients (n = 40)</th>
<th>Control (n = 20)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>17 (42.5)</td>
<td>6 (30)</td>
<td>0.35</td>
</tr>
<tr>
<td>04</td>
<td>24 (60)</td>
<td>5 (25)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>10</td>
<td>10 (25)</td>
<td>2 (10)</td>
<td>0.18</td>
</tr>
<tr>
<td>No alleles</td>
<td>10 (25)</td>
<td>10 (50)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

HLA: Human leukocyte antigen, RA: rheumatoid arthritis. Bold value is significant at \( p < 0.05 \).

\( p = 0.02 \), respectively. However, radiological disease severity (SENS) was significantly higher in those with a positive 04 or 10 allele (\( p = 0.002 \) and \( p = 0.001 \), respectively).

Frequency of HLA-DRB1 genotypes among anti CCP and RF positive and negative RA patients is presented in Table 4. A positive 04 allele was the only HLA-DRB1 significantly associated with anti-CCP positivity (\( p = 0.0008 \)). The presence of \( \geq 1 \) alleles was significantly associated with a positive anti-CCP (\( p = 0.0008 \)). The anti-CCP antibodies were positive in 13 of the 29 RF sero-positive RA patients (44.8%) and in 7 of the 11 RF negative RA patients (63.6%). There was a significant correlation of the serum anti-CCP antibodies level of the 11 RF negative RA patients (63.6%). There was a significant correlation of the serum anti-CCP antibodies level of the 11 RF negative RA patients (63.6%).

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\( p = 0.003 \), a positive 04 and 10 (\( p = 0.035 \), \( p = 0.005 \)) alleles. Anti-CCP antibodies were also significantly correlated with the disease activity (\( p = 0.032 \)), clinical (\( p = 0.034 \)) and radiological severity scores (\( p = 0.033 \)) (Table 5).

4. Discussion

The HLA-DRB1 alleles encoding the SE were found to be associated with the severity and susceptibility of RA and include 0101, 0102, 0104, 0401, 0404, 0405, 0408, 0413, 0416 and 1001 alleles [25]. These alleles are subtypes of HLA-DRB1 (01, 04 and 10). The aim of this study was to evaluate the 01, 04 and 10 alleles in the Egyptian RA patients. Our results reported a frequency of 30%, 25% and 10% for HLA DRB1 01, 04 and 10 respectively in the normal subjects of Benha City in Qualyobia governorate. Their frequency in the normal subjects of Assuit governorate was 5%, 10% and 15% respectively [26]. In Asian populations, the frequency was 5.7%, 4.9% and 7.4% and in the European populations it was 25.3%, 26.5% and 1.1%, respectively. However, in both the Asian and European populations the reported frequency was limited to some SE alleles of HLA DRB1 04 [27]. Moreover, in a Kuwaiti normal population, the frequency was 5.7%, 22.8% and 14.3% respectively [28].

On the other hand, the frequency of HLA DRB1 01, 04 and 10 in RA patients in the present study was 42.5%, 60% and 25% respectively. Of them, HLA DRB1 04 was significantly higher in RA patients than in controls. In accordance, it was reported that there are differences in the strength of the association between different SE alleles and RA. The HLA-DRB1 04 alleles represent a considerably stronger susceptibility factor than the other SE alleles [29]. Also, Alsaeid et al. [28] reported that only HLA-DRB1 04 was significantly higher in the RA patients. Fathi and associates [26] reported a frequency of 45%, 35% and 0% for HLA-DRB1 01, one or two 04 and 10 in RA patients respectively. Both HLA DRB1 01 and 04 were significantly higher and 10 was significantly lower in RA patients than in the normal control of that study. However HLA-DRB1 10 was more prevalent in Spanish RA patients [30]. On the other hand, in Chinese RA patients, HLA-DRB1 01 was not associated with RA but 04 frequency was significantly higher than in the healthy Chinese individuals [31].

Our study reported a significant association of a positive HLA-DRB1 01 and 04 with disease activity and clinical disease severity however, positive HLA-DRB1 04 and 10 alleles were

Table 3 Relation of the studied HLA-DRB1 01, 04 and 10 status with the different demographic and clinical parameters in the rheumatoid arthritis patients.

<table>
<thead>
<tr>
<th>Parameter mean ± SD (range) or n (%)</th>
<th>HLA-DRB1 in RA patients (n = 40)</th>
<th>01</th>
<th>04</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n = 17)</td>
<td>Negative (n = 23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>41.8 ± 14.7</td>
<td>41.4 ± 11.2</td>
<td>43.5 ± 12.4</td>
<td>38.7 ± 12.9</td>
</tr>
<tr>
<td>Age at onset</td>
<td>31.6 ± 6.6</td>
<td>33.4 ± 7.4</td>
<td>33.2 ± 5.5</td>
<td>31.8 ± 8.9</td>
</tr>
<tr>
<td>Disease duration</td>
<td>10.2 ± 9.4</td>
<td>7.9 ± 6.2</td>
<td>10.3 ± 8.4</td>
<td>6.9 ± 6.3</td>
</tr>
<tr>
<td>Sex F:M</td>
<td>17.0</td>
<td>19.4</td>
<td>24.0</td>
<td>12.4*</td>
</tr>
<tr>
<td>Disease activity</td>
<td>SDAI</td>
<td>31.7 ± 13.4</td>
<td>16.5 ± 9.8*</td>
<td>27.7 ± 13.9</td>
</tr>
<tr>
<td>mild</td>
<td>4 (23.5)</td>
<td>19 (82.6)**</td>
<td>10 (41.7)</td>
<td>13 (81.3)*</td>
</tr>
<tr>
<td>moderate</td>
<td>6 (35.3)</td>
<td>4 (17.4)</td>
<td>7 (29.2)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>severe</td>
<td>7 (41.2)</td>
<td>0 (0)</td>
<td>7 (29.2)</td>
<td>0 (0)*</td>
</tr>
<tr>
<td>Disease severity</td>
<td>MJS</td>
<td>17.2 ± 13.4</td>
<td>8.5 ± 9.7*</td>
<td>15.5 ± 12.5</td>
</tr>
<tr>
<td>SENS</td>
<td>31.1 ± 28.1</td>
<td>43.1 ± 13.8</td>
<td>38.9 ± 26.6</td>
<td>13.6 ± 22.9*</td>
</tr>
</tbody>
</table>


* Significant.

** Highly significant difference from the corresponding values at \( p < 0.05 \).
significant association with radiological severity. Fathi and associates [26] reported the significant association of HLA DRB1 04 alleles with more activity of the disease but not 01. They also reported significant association of HLA-DRB1 01 and 04 with the radiologically severe disease. Also, Lin and associates [31] revealed a significant association of HLA-DRB1 04 with clinically and radiologically severe disease in Chinese populations. However, Kinikli and associates [32] reported no association of HLA-DRB1 01 or 04 with the clinical or radiological severity of the disease in the Turkish population.

In a previous study, anti-CCP Abs were detected in 53% of RA patients [25]. Our study also detected them in 50% of RA Egyptian patients. Moreover, our work like previous studies have documented the absence of anti-CCP antibody production among healthy individuals [9,10,31]. Our study reported that carrier of HLA-DRB1 01, 04 and 10 was associated with production of anti-CCP antibodies being significant only with 04. Previous studies found that carrier of one or two HLA-DRB1 SE alleles was significantly associated with production of anti-CCP antibodies in a Dutch RA population [14,25]. Our study revealed that in the Egyptian patients, the presence of one or more of the alleles studied, was significantly associated with anti-CCP positive RA. Berglin et al. [33], Hughes et al. [34] and Kaltenhauser et al. [25] found that the HLA-DRB1 01 and 04 SE alleles conferred the highest risk for development of anti-CCP antibodies in RA patients.

There was a significant correlation between high serum level of anti-CCP antibodies and HLA-DRB1 (04 and 10) alleles, SDAI score, radiological and clinical severity score. This agrees with Gourrand et al. [7] and Berglin et al. [33] who suggested that measurement of serum anti-CCP levels might be of clinical significance for detection of disease severity and activity. They mentioned that RA patients with positive SE and positive anti-CCP had a significantly higher rate of destruction in the joints than did all other patients. Which means that a higher rate of joint damage was only found when both SE alleles and anti-CCP antibodies were present. A previous study reported that the SE alleles correlated with the presence of anti-CCP Abs, but not with the presence of RF [35]. Also Kinikli and associates [32] reported no association with sero-positivity of RA. This coincides with our results. On other hand Ucar et al., found that HLA-DRB1*01 and 04 were determined to be higher in RA patients with + RF [36].

HLA-DRB1 04 was associated with RA in 60% of the patients in our study; therefore, the possibility that other genes may add to the pathogenesis of RA cannot be denied. In addition to genetic factors, some environmental factors have been concerned as predictors of RA. The 2–3-fold higher prevalence of the disease in women, primarily before menopause, has been interpreted as indicating a role for hormonal or reproductive factors [32]. Smoking is a well-established risk factor for the development of RA and it was found that smoking contributes to the development of RA in SE positive and anti-CCP positive patients [15], indicating that the predisposition to RA may be due to an interaction between genetic and environmental factors.

In conclusion, HLA-DRB1 04 was associated with RA Egyptian patients particularly those positive to anti-CCP antibodies. It was strongly associated in the production of elevated titers of anti-CCP antibodies which contribute to the disease development, severity and activity of RA disease. The presence of anti-CCP antibodies and/or HLA-DRB1 04 or 10 is associated with a poor radiological outcome whereas 01 and 04 are associated with higher grade of disease activity and clinical severity. Therefore the identification of susceptible allele in RA patients may assist a physician to take early decision

### Table 4

<table>
<thead>
<tr>
<th>HLA-DRB1 genotype frequency n (%)</th>
<th>Rheumatoid arthritis patients (n = 40)</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-CCP: Positive (n = 20)</td>
<td>Negative (n = 20)</td>
</tr>
<tr>
<td>Allele 01</td>
<td>11 (55)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>04</td>
<td>18 (90)</td>
<td>6 (30)**</td>
</tr>
<tr>
<td>10</td>
<td>7 (35)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>None</td>
<td>0 (0)</td>
<td>10 (50)**</td>
</tr>
</tbody>
</table>


** Highly significant difference from the corresponding values at \( p < 0.05 \).

### Table 5

Correlation of anti-CCP level with the presence of different HLA DRB1 genotypes alleles, with disease activity, clinical and radiological severity score in RA patients.

<table>
<thead>
<tr>
<th>DRB1 genotype</th>
<th>Anti-CCP: Positive (n = 20)</th>
<th>Negative (n = 20)</th>
<th>OR (95CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>0.21 (0.19)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>04</td>
<td>0.43 (0.035)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.53 (0.005)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>≥ 1 allele</td>
<td>0.56 (0.003)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

DRB1 genotype |

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Anti-CCP: Positive (n = 11)</th>
<th>Negative (n = 11)</th>
<th>OR (95CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDAI</td>
<td>0.45 (0.032)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Disease activity |

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Anti-CCP: Positive (n = 29)</th>
<th>Negative (n = 11)</th>
<th>OR (95CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical: MJS</td>
<td>0.42 (0.034)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Radiological: SENS</td>
<td>0.41 (0.033)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Anti-CCP: anti-cyclic citrullinated peptide, SDAI: simplified disease activity index, MJS: mechanical joint score, SENS: simple erosion narrowing score. Bold values are significant at \( p < 0.05 \).
regarding starting of intensive therapy to prevent joint damage. Further longitudinal studies are recommended with large numbers of patients and controls to assess the predictive role of each allele in RA susceptibility, to study the polymorphic character of HLA genes and to emphasize the relationships of environmental with genetic factors.

Conflict of interest

None.

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HLA-DRB1 alleles in rheumatoid arthritis patients


