Association between HLA-DR antigens and rheumatoid arthritis in Arabs

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Abstract
Eighty five Arab patients with classical and definite rheumatoid arthritis were typed to determine the prevalence of HLA A, B, C, and DR antigens. A significant increase in the prevalence of HLA-A10, B8, B21, and DR3 was found in comparison with a control population matched for age and sex. HLA-DR5 was significantly decreased in the patient group. The classical association of HLA-DR4 with rheumatoid arthritis could not be confirmed in the Arab patients resident in Kuwait, supporting reported observations in different ethnic groups of associations with HLA antigens other than HLA-DR4 and indicating a heterogeneous genetic susceptibility to rheumatoid arthritis.

Associations of particular HLA antigens with several rheumatic diseases are well established, though the precise nature of this relation remains unclear.\textsuperscript{1-3} Studies have shown an association between DR antigens and a wide variety of connective tissue disorders.\textsuperscript{4-6} Rheumatoid arthritis is strongly associated with HLA-DR4,\textsuperscript{7-9} and this has been found in studies of white patients,\textsuperscript{8} Orientals,\textsuperscript{10,11} Mexicans,\textsuperscript{12} and black Americans.\textsuperscript{13,14} This association, however, was not observed in immigrant Asian Indians in the United Kingdom,\textsuperscript{15} Yakima Indians in the United States of America,\textsuperscript{16} and Jews in Israel.\textsuperscript{17} In these ethnic groups an association was found with HLA-DR1.

In this study we investigated the prevalence of major histocompatibility complex class I and class II antigens in Arab rheumatoid patients resident in Kuwait.

Patients and methods
Eighty five consecutive Arab rheumatoid patients with classical or definite rheumatoid arthritis\textsuperscript{18} attending a rheumatology clinic were selected for this study. A similar number of controls matched for age and sex were also studied. Data obtained from history and clinical examination were recorded and blood was drawn for haematological, biochemical, and immunological screening, and for HLA, A, B, C, and DR antigen typing. Radiology of the hands, feet, cervical spine, and, if necessary, of other joints, was performed and a full functional and disease severity assessment was undertaken.\textsuperscript{19} The patients were classified as seropositive or seronegative based on the rheumatoid factor, a titre of 1/40 or higher being considered positive. Similarly, the patients were classified as having erosive or non-erosive disease based on the presence or absence of radiological changes in the hands and feet. This was done without prior knowledge of either the HLA typing data or the serology results. HLA typing for antigens of the A, B, C loci was by standard two stage microtoxicity assay\textsuperscript{20} and HLA-DR typing by the two colour fluorescence method.\textsuperscript{21}

The antigen prevalences were calculated by direct counting, and the relative risk and attributable risk were estimated to evaluate the strength of association between the HLA antigens and rheumatoid arthritis.\textsuperscript{22} Statistically significant differences between the relative prevalences of antigens in patients and controls were determined by $\chi^2$ and Fisher's exact tests. The level of significance ($p$ value) was corrected by multiplying by the number of antigens tested at each HLA locus.\textsuperscript{23}

Results
Both the seropositive and seronegative rheumatoid groups were comparable for age, disease duration, erythrocyte sedimentation rate, and functional capacity, but they differed considerably in sex, radiological joint changes, and the presence of extra-articular features (table 1).

Table 2 shows the HLA antigen prevalences that differed significantly from those of the control population. HLA-A10, B8, B21, and DR3 were significantly increased in the patient group and HLA-DR5 was significantly decreased.

Several studies have reported the DR4 antigen to be associated with the presence of

Table 1: Comparison of clinical data from 85 Arab patients with rheumatoid arthritis

\begin{center}
\begin{tabular}{|l|c|c|}
\hline
& Seropositive & Seronegative \\
\hline
Mean age (years) & 40 (5) & 38 (2) \\
Sex (F:M) & 2:6:1 & 3:2:1 \\
Duration of disease (years) & 8 (7) & 8 (0) \\
ESR (mm/1 h, Westergren) & 4 (9) & 4 (9) \\
Functional capacity† & 2/4 & 2/0 \\
Erosions (No (%)) & 30 (56) & 3 (14) \\
ARA* criteria (No (%)) & & \\
Classical & 25 (39) & 4 (19) \\
Definite & 39 (61) & 17 (81) \\
Severe & 8 (12.5) & 3 (14) \\

Extra-articular features (No (%)) & & \\
Rheumatoid nodules & 22 (34) & 8 (38) \\
Pulmonary fibrosis & 8 (12.5) & 2 (9.5) \\
Sacro syndrome & 13 (20) & 2 (9.5) \\
Vasculitis & 4 (6) & 1 (5.3) \\
Féty's syndrome & 2 (3) & 1 (5.3) \\
\hline
\end{tabular}
\end{center}

*ESR=erythrocyte sedimentation rate; ARA=American Rheumatism Association.
†According to Steinbrocker criteria.\textsuperscript{19}
Table 2: Significant HLA differences between patients with rheumatoid arthritis and the control group

<table>
<thead>
<tr>
<th>HLA* locus</th>
<th>Patients (n=85)</th>
<th>Controls (n=101)</th>
<th>Relative risk</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10</td>
<td>24/1</td>
<td>8/9</td>
<td>3.25</td>
<td>0.001</td>
</tr>
<tr>
<td>B8</td>
<td>24/0</td>
<td>8/9</td>
<td>1.55</td>
<td>0.001</td>
</tr>
<tr>
<td>B21</td>
<td>22/9</td>
<td>8/9</td>
<td>3.03</td>
<td>0.001</td>
</tr>
<tr>
<td>DR3+</td>
<td>34/1</td>
<td>2/1</td>
<td>23.56</td>
<td>0.001</td>
</tr>
<tr>
<td>DR5+</td>
<td>35/3</td>
<td>5/3</td>
<td>0.47</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*HLA antigens not significantly different from controls were as follows:
A — A1, A2, A3, A9, A11, A26, A30, A32, A33
B — B7, B17, B13, B14, B15, B17, B18, B22, B27, B35, B38, B50, B40, B42, B44, B53
C — Cw1, Cw2, Cw3, Cw4, Cw6
DR — DR1, DR2, DR4, DR6, DR7, DRw52, DRw53
DQ — DQwl, DQw3

rheumatoid factor, severe disease, and also a poor prognosis. We therefore examined our DR positive rheumatoid subjects to determine the strength of association, based on serology, extra-articular features, American Rheumatism Association (ARA) criteria, severity, duration, and age at onset.

**DR ANTIGEN AND SEROLOGY**

Of the 64 seropositive rheumatoid subjects, 19 (30%) were positive for DR3 antigen as compared with 4/21 (19%) seronegative subjects—a significant difference (p<0.05). Similarly, a significant association with HLA-DRw53 (p<0.005) and DQw3 (p<0.001) antigens was found in seropositive rheumatoid subjects, whereas no significant association was noted with HLA-DR2 and HLA-DR4 antigens only in patients with seronegative RA (p<0.001).

**RADIOLOGICAL JOINT INVOLVEMENT**

Thirty nine (46%) patients had radiographs showing erosions either in the hands (proximal interphalangeal joints, metacarpophalangeal joints, or wrists) or in the feet (metatarsophalangeal and interhaltal joints). Of these, 16 (41%) were positive for DR4 and 6 (15%) positive for the DR3 antigen—significantly different from the control group (p<0.05). Similarly, a significant difference was also seen with the DQw3 antigen found in 14/39 (36%) patients as compared with 59/93 (63%) controls (p<0.004).

**RHEUMATOID NODULES**

Nodules were found in 30/85 (35%) patients, and the data when analysed showed a significant relation with DR3 (p<0.05).

**ARA CRITERIA**

The differences in the antigen prevalences among the rheumatoid subjects were not great. Nevertheless, a significant association of both classical and definite RA with the DR3 antigen was found, giving a 'p' value of <0.05 and <0.01 respectively.

**AGE AT ONSET**

Previous reports of the association between the age at onset of the disease and HLA-DR4/Dw4 have been controversial.23 Our data showed a significant relation with HLA-DR3 when the onset of the disease was at an early age (p<0.008).

**DISEASE SEVERITY**

No significant association could be observed either with DR3 or DR4 antigens and the severity of the disease in our rheumatoid subjects; however, a significant association was noted with the DQw3 antigen (p<0.05).

Sicca syndrome, pulmonary fibrosis, and vasculitis were seen in 13/85 (15%) of our patients. The numbers were too few to determine a significant association with any of the DR antigens.

**Discussion**

The results of our study showed neither a significant nor a strong association with the HLA-DR4 antigen, but a relatively strong association with HLA-DR3 and DQw3 antigens was noted. Failure to show a strong association with the DR4 antigen does not, however, seem to be due to the existence of a different form of disease in this Arab population as the clinical pattern of the disease, based on the same diagnostic criteria, was the same as that found in the west. Results of our study, however, agree with other studies which reported a different DR association in RA.13-15 The comparatively strong association with the HLA-DR3 antigen in this ethnic group is yet another example in which the expected DR4 association could not be confirmed. Thus our findings support the concept of linkage disequilibrium between the marker gene and the disease susceptibility gene; such a gene or genes may well be the same but may have a differing pattern of linkage disequilibrium with various alleles of the DR locus as shown in this study. Furthermore, this study not only showed a significant association with the HLA-DR3 antigen, but also an increased relative risk of developing disease as compared with those with the HLA-DR4 antigen in this Arab rheumatoid population. The low prevalence of HLA-DR5 and DR7 antigens in our patients may indicate a protective role for these antigens against RA; also, these antigens showed a significantly lower relative risk of 0.4 and 0.8 respectively.

The results of this study indicate that there is a fairly strong tendency and susceptibility in HLA-DR3 positive subjects not only to develop rheumatoid arthritis but also its related complications. New techniques of genetic coding, DNA probes, or molecular genetics may provide a new insight and explanation for differing genetic patterns of what is considered to be the same disease in different ethnic groups.

This study was supported by Kuwait University grant MM015. We are grateful to Mr George Varughese for his secretarial help in the preparation of this manuscript.

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