EXTENDED REPORT

HLA class II is associated with distal interphalangeal osteoarthritis

N Riyazi, J Spee, T W J Huizinga, G M T Schreuder, R R P de Vries, F W Dekker, M Kloppenburg

Objective: To investigate whether there is an association between HLA class II and distal interphalangeal osteoarthritis (DIP OA).

Methods: The study group consisted of consecutive patients with and without DIP OA aged between 40 and 70 years. DIP OA was diagnosed by radiology. These patients were referred to an “Early Arthritis Clinic” (EAC) with different types of arthritis at an early stage. Patients with rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathies, and psoriatic arthritis were excluded for the purpose of this study. DNA typing for HLA-DR and x-ray examination of the hands were performed at enrolment in the EAC. To establish whether the study group was representative of the Dutch population, a population based study in Zoetermeer (n=3243) for the prevalence of DIP OA and blood donors in the Leiden area (n=2400) for the HLA-DR antigen frequencies were used as references.

Results: Fifty five patients (33%) of the total study group (n=166) had DIP OA. The prevalence of DIP OA and frequency of the HLA-DR alleles were similar to those of the two reference groups. Within the study group an association between DIP OA and HLA-DR2 and DR4 with respectively odds ratios of 2.4 (95% confidence interval (CI) 1.1 to 5.0) and 0.3 (95% CI 0.1 to 0.7) was found. No association was found between other HLA-DR alleles and DIP OA.

Conclusion: The study group is a representative sample of the Dutch population. The HLA-DR2 allele was more common in patients with DIP OA. Furthermore, an inverse relation was observed between DIP OA and HLA-DR4. The results confirm findings from other investigations implicating HLA-DR2 as a risk factor in the development of DIP OA.

D istal interphalangeal osteoarthritis (DIP OA), a subtype of OA, is a disease with a marked familial disposition. The role of genetics in hand OA was first noted by Stecher, who found a clear hereditary basis for OA of the distal interphalangeal joints (DIP) of the fingers, based on the presence of Heberden’s nodes, with sex and sibship being important determinants. Kellgren et al found a strong genetic component in the subset of patients with affected interphalangeal joints as assessed by radiology. Furthermore, the notion of a genetic influence in nodal OA was confirmed by a subsequent twin study, where heritability was estimated at 39–65%.

Although genetics in hand OA have been the focus of many recent studies, up to this date, the genetic markers involved have not yet been identified. Among genetic markers examined in hand OA are markers on chromosome 6, the HLA class I and HLA class II alleles. An increased frequency of the haplotype HLA-A1B8 has been suggested by several studies. HLA class II antigens are highly polymorphic and are associated with various diseases where inflammation of the joints has a key role in the pathogenesis. Studies examining the distribution of HLA class II antigens have provided conflicting results. One study found a positive association between HLA-DR2 and DIP OA and another study found no association between HLA class II and DIP OA.

The diagnosis of hand OA in the past has been based on the presence of Heberden’s nodes. However, more recent data indicate that radiological changes are more accurate for diagnosing and grading the disease. The prevalence of radiological hand OA in middle aged women in the age range 50–54 has been reported to be 42% in the DIP joints, followed by 16% in the first carpometacarpal joints and 10% in the proximal interphalangeal joints. The prevalence of DIP OA increases with age peaking to a prevalence of about 75% in 70 years olds.

This study aimed at investigating the association of DIP OA with HLA class II in patients aged between 40 and 70. We chose to limit ourselves to this age group for the following two reasons. The presence of OA before 40 years of age is rare and is often exhibited in syndromes with a Mendelian segregation. In people older than 70 hand OA is mainly due to environmental factors.

Our study group is a series of consecutive hospital patients gathered prospectively. This group is representative of the general Dutch population because the prevalence of DIP OA as well as the frequency of HLA-DR alleles is comparable with the general Dutch population. As a reference group for DIP OA and HLA-DR4, the results confirm findings from other investigations implicating HLA-DR2 as a risk factor in the development of DIP OA.

MATERIALS AND METHODS

Reference groups

The prevalence of DIP OA and the distribution HLA-DR alleles in the study group were compared with two reference groups representative of the general Dutch population. As a reference for DIP OA, data were used from the Zoetermeer population, a population survey consisting of 3109 men and 3476 women conducted between 1975 and 1978 in two districts of Zoetermeer, a suburban metropolitan area near Leiden in the Netherlands. Subjects in this study were documented for the presence of OA by radiographs of the hands, forefoot, and lateral cervical spine. As a reference group for the distribution of

Abbreviations: CI, confidence interval; DIP, distal interphalangeal; E, expected; EAC, Early Arthritis Clinic; O, observed; OA, osteoarthritis; OR, odds ratio
The HLA-DR antigens, data were used from blood donors in the Leiden area who had been typed for HLA by serological methods. This is a group of about 2400 people.

Patients

The study group consists of subjects from the outpatient clinic of the department of rheumatology aged between 40 and 70 with and without radiological DIP OA. This group obtained between 1993 and 2000 is part of a continuing project, the Early Arthritis Clinic (EAC). Consecutive patients with arthritis in at least one joint with a short history of complaints are subsequently undergoes full clinical, biochemical, and radiographic assessment. Diagnoses in the EAC are made according to international classification and if necessary revised during up to one year of follow up. For the purpose of this study, patients with a definitive EAC diagnosis after one year of follow up are included. Patients with rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthopathies were excluded because of known associations of these diseases with certain HLA-DR alleles. Patients with psoriatic arthritis were also excluded because DIP involvement is common in psoriatic arthritis and might thus interfere with our readings.

Radiographs and radiographic scoring

Plain dorsovolar hand radiographs were taken during the period of the first visit to the EAC. Only radiographs obtained at a maximum of three months before until three months after the first visit were included.

For the purpose of this study each of the radiographs was independently graded for DIP OA by two of three observers (NR, JS, MK) using the Kellgren/Lawrence scale. Furthermore, the observers scoring the radiographs for the presence of DIP OA were unaware of the underlying EAC diagnosis. This overall score distinguishes five degrees of severity of OA according to the presence of the radiological features: osteophytes, joint space narrowing, subchondral sclerosis, cysts, and deformity. A patient was diagnosed with DIP OA if a Kellgren score of two or more was found in at least one DIP joint. The interrater agreement for the presence or absence of DIP OA was 0.7; Cohen’s κ. In cases of disagreement radiographs were re-evaluated until consensus was reached.

### HLA typing

DNA was isolated from blood lymphocytes. Generic DRB typing was performed with a polymerase chain reaction and biotin labelled sequence specific oligonucleotide method as described previously.

### Statistics

The means were compared using an independent sample Student t test. The observed (O) DIP OA frequencies in the study group, depicted for sex and age, were related to the expected number (E) in the reference group by calculating the O/E (a relative risk). Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to determine the comparability of the distribution of HLA alleles in the study group with the reference group and, furthermore, to assess the association between DIP OA and HLA-DR alleles.

### RESULTS

Six hundred and one consecutive patients aged 40–70 visited the EAC. Of these patients, 166 met the study criteria and were included in this study. The following patients were excluded: 64 patients because typing of HLA-DR had not been performed and 21 patients because no appropriate hand radiographs were taken. Furthermore, 240 patients were excluded with RA, 32 with psoriatic arthritis, nine with a variety of systemic diseases, and 69 because there was no definitive diagnosis made within one year.

Table 1 summarises the clinical characteristics of these patients. The patients in this study were included in the EAC with a broad variety of diagnoses. Fifty five (33%) patients of our study group had DIP OA. Twenty nine (53%) of the patients with DIP OA were women. The average age of patients with DIP OA was significantly higher than that of patients with no DIP OA respectively 57.7 (SD 6.3) years compared with 49.2 (6.9) years (p<0.001). Table 2 compares the study group with the Zoetermeer group depicted for age and sex. The prevalence of DIP OA was comparable with that of the reference group: O/E 1.0 (95% CI 0.7 to 1.3).

Table 3 summarises the distribution of HLA-DR in the study group in comparison with the Leiden blood donors. No significant difference was found in the distribution of the HLA-DR between the two groups as is shown by the odds ratios of around one for each separate DR antigen.

### Table 1 Clinical characteristics of the study population: patients with and patients without distal interphalangeal osteoarthritis (DIP OA)

<table>
<thead>
<tr>
<th></th>
<th>DIP OA</th>
<th>No DIP OA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average age (SD)</strong></td>
<td>57.7 (6.3)</td>
<td>49.2 (6.9)</td>
</tr>
<tr>
<td><strong>Sex (women), No (%)</strong></td>
<td>29 (53)</td>
<td>57 (51)</td>
</tr>
<tr>
<td><strong>EAC diagnoses (No)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Viral reactive arthritis</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Crystal arthritis</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Posttraumatic arthritis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>Para maligne</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 2 Prevalence (%) of distal interphalangeal osteoarthritis (DIP OA) in women and men in the study population (n=166) in comparison with the Zoetermeer population (n=3243) by sex and age categories

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>DIP OA + (Study population)</th>
<th>DIP OA + (Zoetermeer group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>40–44</td>
<td>6.6 (n=15)</td>
<td>0 (n=15)</td>
</tr>
<tr>
<td>45–49</td>
<td>6.3 (n=16)</td>
<td>6.7 (n=15)</td>
</tr>
<tr>
<td>50–54</td>
<td>42.1 (n=19)</td>
<td>34.8 (n=23)</td>
</tr>
<tr>
<td>55–59</td>
<td>47.6 (n=21)</td>
<td>50.0 (n=10)</td>
</tr>
<tr>
<td>60–64</td>
<td>55.5 (n=9)</td>
<td>66.7 (n=9)</td>
</tr>
<tr>
<td>65–69</td>
<td>80.0 (n=5)</td>
<td>66.7 (n=9)</td>
</tr>
</tbody>
</table>
Table 3 The distribution of HLA-DR in the study population (n=166) in comparison with the blood donors (n=2400). This comparison is expressed as odds ratios (ORs) and 95% confidence intervals (95% CI).

<table>
<thead>
<tr>
<th>HLA-DR alleles</th>
<th>Study population positive</th>
<th>Blood donors positive</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR1</td>
<td>37</td>
<td>472</td>
<td>1.2 (0.8 to 1.7)</td>
</tr>
<tr>
<td>DR2</td>
<td>37</td>
<td>688</td>
<td>0.7 (0.5 to 1.1)</td>
</tr>
<tr>
<td>DR3</td>
<td>41</td>
<td>596</td>
<td>1.0 (0.1 to 1.1)</td>
</tr>
<tr>
<td>DR4</td>
<td>51</td>
<td>679</td>
<td>1.1 (0.8 to 1.6)</td>
</tr>
<tr>
<td>DR5</td>
<td>35</td>
<td>453</td>
<td>1.1 (0.8 to 1.7)</td>
</tr>
<tr>
<td>DR6</td>
<td>59</td>
<td>806</td>
<td>1.1 (0.8 to 1.5)</td>
</tr>
<tr>
<td>DR7</td>
<td>31</td>
<td>460</td>
<td>1.0 (0.6 to 1.5)</td>
</tr>
<tr>
<td>DR8</td>
<td>7</td>
<td>128</td>
<td>0.8 (0.3 to 1.8)</td>
</tr>
<tr>
<td>DR9</td>
<td>4</td>
<td>57</td>
<td>1.0 (0.3 to 2.9)</td>
</tr>
<tr>
<td>DR10</td>
<td>6</td>
<td>101</td>
<td>0.9 (0.3 to 2.0)</td>
</tr>
</tbody>
</table>

Table 4 shows the association between DIP OA and HLA-DR in the study group. An association was found between DIP OA and HLA-DR2 and HLA-DR4 with odds ratios of respectively 2.4 (95% CI 1.1 to 5.0) and 0.3 (95% CI 0.1 to 0.7). No association with the other HLA-DR antigens and DIP OA was seen.

**DISCUSSION**

This study aimed at investigating the association of HLA-DR with DIP OA. We found that HLA-DR2 was more frequent in patients with DIP OA than in patients with no radiological evidence of DIP OA with an OR of 2.4 (95% CI 1.1 to 5.0). We also found a lower prevalence of DIP OA in HLA-DR4 positive patients with an OR of 0.3 (95% CI 0.1 to 0.7). This is to our knowledge the first time that an association with HLA-DR4 has been established. Other investigators have suggested a positive association with HLA-DR2.

We had the unique opportunity to study the relationship of these two variables in a relatively large group of well documented patients representative of the general population. This consecutive patient group was collected prospectively and HLA typing and radiological examinations were performed irrespective of the EAC diagnosis. Because the study group consisted of patients included in an EAC we took into consideration the existing correlation between certain rheumatic diseases and HLA alleles when selecting the patients for the present study. Patients with diagnoses with known HLA associations and diseases associated with radiological damage of the DIP joints, such as psoriatic arthritis, were excluded from the study group, although radiological damage would not have been very likely because patients are included in the EAC at an early stage. Furthermore, it was shown that the study group is a representative sample of the general population by finding in this group similar frequencies of DIP OA and HLA antigens.

Only two studies, up until now, have investigated the correlation between HLA class II antigens and hand OA, with conflicting results. These studies were performed in ethnically separate groups, a group of Ashkenazi Jews and a group of Mexican mestizos. The study of the Ashkenazi Jews was performed with a small group of patients with clinical characteristics of hand OA and controls consisting of “healthy subjects”. They found a positive association with HLA-DR2, although this association was not significant. Possibly, the limited sample size might have contributed to the absence of significant results in this study. The second publication studied the relationship between Heberden’s nodes and HLA in a group of Mexican mestizos. The authors of this study found no association between these two variables. This might have been caused by using different diagnostic criteria of hand OA in patients compared with controls. Patients were diagnosed with hand OA on the basis of the combination of clinical and radiographic characteristics whereas the controls were screened for the absence of Heberden’s nodes without radiological assessment. Because there is a discrepancy between signs and symptoms and the radiologicalmanifestations of OA, as is shown in patients with radiological OA who have symptomatic disease in only 20–40% of cases, the absence of radiological assessment of the control group might have led to an underdiagnosis of OA in the reference group used in this study. Recently, further evidence of the role of HLA-DR2 as a risk factor for DIP OA was found in two European populations, one in Germany and the other in Iceland (Jonsson HH, personal communication).

No earlier study has found an association between HLA-DR4 and hand OA. Therefore, further studies in other populations are needed to confirm these results and to rule out the possibility of a false positive association (type 1 error) because of multiple testing.

One may suggest a direct role of HLA-DR antigens in OA. HLA class II molecules are involved in the communication between T cells and antigen presenting cells. Although OA is not generally considered to be an autoimmune disorder with an inflammatory nature, several studies suggest a role for T cells and HLA class II molecules in OA. One study on the synovial membranes of patients with OA indicates T cell mediated immune responses in this disorder. Another recent study demonstrated higher levels of human cartilage glycoprotein 39 (HC gp-39) specific T cells in patients with OA than the study group, although radiological damage would not have been very likely because patients are included in the EAC at a very early stage. Furthermore, it was shown that the study group is a representative sample of the general population by finding in this group similar frequencies of DIP OA and HLA antigens.
Another possibility is that the role of HLA class II alleles implicated in this study is due to linkage disequilibrium with neighbouring genes of HLA-DR class II alleles which may be involved in the pathogenesis of OA. Whether our findings are a matter of haplotype or whether they suggest a direct role for HLA-DR alleles needs to be further investigated.

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doi: 10.1136/ard.62.3.227

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