Association of HLA-DR with Sarcoidosis*
Correlation with Clinical Course

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HLA-DR typing was performed in 58 Japanese patients with sarcoidosis. We found a significantly increased frequency of HLA-DRw52 (p<0.0007; pc<0.009) and DR5J (p<0.004; pc<0.05). (Corrected probability value is given as pc.) In 34 of 58 patients the disease resolved spontaneously. There was no significant difference between the frequency of DRw52 and the resolution rate of disease. The frequency of DR5J was increased significantly in the unresolved cases. Our results also suggest that DRw52 is concerned with onset of sarcoidosis and DR5J antigen has an effect on the clinical course of this disease.

The human leukocyte antigen (HLA) frequencies in patients with sarcoidosis have been studied by many investigators. However, a definite conclusion on this important problem has not been reached. Persson et al reported the association of HLA-B7 with sarcoidosis patients who had negative tuberculin skin reactivity. HLA-B8 was frequently demonstrated in the report of Olenchock et al. Brewerton et al reported the association of HLA-B8 with sarcoidosis patients with arthritis and an increase in the haplotype HLA-A1, B8 in patients with uveitis. Whitsett et al did not find any association of HLA-A, B, C, and DR antigens with sarcoidosis in the black population in North Carolina. Recently, we reported the association of HLA-DRw52 with sarcoidosis in Japanese patients. In this article, we investigate the relationship between HLA-DR antigens and clinical course in Japanese patients with sarcoidosis.

Patients and Methods
Fifty-eight Japanese patients with pulmonary sarcoidosis were studied. The diagnosis was based on compatible chest roentgenographic findings supported by histologic examination of transbronchial lung biopsy and/or peripheral lymph node biopsy. Forty-two of these patients were women, and 16 were men; the ages ranged from 13 to 63 years (mean, 35 years). Thirty-nine patients were in roentgenographic stage 1, 15 patients were in stage 2, and only one patient was in stage 3.

The duration of disease from the time of diagnosis until HLA-typing ranged from 9 months to 15 years 3 months, with a mean of 46 months. In the sarcoidosis cases that resolved, the chest roentgenographic evidence of bilateral hilar or paratracheal lymphadenopathy, or both, disappeared as well as diffuse pulmonary motting. The Japanese control group was comprised of 57 normal healthy volunteers.

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Table 1—Distribution of HLA-DR Antigens Tested

<table>
<thead>
<tr>
<th>HLA Antigens</th>
<th>Sarcoidosis Patients (n=58)</th>
<th>Control Group (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR1</td>
<td>2 (3.4)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>DR2</td>
<td>13 (22.4)</td>
<td>17 (29.8)</td>
</tr>
<tr>
<td>DR3</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DR4</td>
<td>22 (37.9)</td>
<td>32 (56.1)</td>
</tr>
<tr>
<td>DR5J</td>
<td>22 (37.9)</td>
<td>5 (14.0)*</td>
</tr>
<tr>
<td>DRw6J</td>
<td>20 (34.5)</td>
<td>16 (28.0)</td>
</tr>
<tr>
<td>DR7</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DRw8</td>
<td>13 (22.4)</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>DRw9</td>
<td>9 (15.5)</td>
<td>18 (31.6)</td>
</tr>
<tr>
<td>DRw52</td>
<td>47 (81.0)</td>
<td>29 (50.9)†</td>
</tr>
<tr>
<td>DRw53</td>
<td>25 (43.3)</td>
<td>41 (71.9)‡</td>
</tr>
<tr>
<td>DQw1</td>
<td>39 (67.2)</td>
<td>36 (63.2)</td>
</tr>
<tr>
<td>DQw2</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DQw3</td>
<td>42 (72.4)</td>
<td>35 (61.4)</td>
</tr>
</tbody>
</table>

*p<0.05.†p<0.004.‡p<0.0007. pc<0.009.
normal healthy control subjects ($\chi^2 = 11.67; p<0.0007; pc<0.009$). The frequency of HLA-DR5J was 37.9 percent in the sarcoidosis patients and only 14.0 percent in the normal healthy controls. This increase was statistically significant ($\chi^2 = 8.52; p<0.004; pc<0.05$).

In 34 of 58 sarcoidosis patients, the disease resolved spontaneously (Table 2). There was no significant difference between the HLA-DRw52-positive patients and HLA-DRw52-negative patients with respect to spontaneous resolution rate in Japanese sarcoidosis patients. Eight of 22 HLA-DR5J-positive patients and 20 of 25 HLA-DR5J-negative patients experienced spontaneous resolution of the disease. Spontaneous resolution rate of the DR5J-positive Japanese sarcoidosis patients was significantly reduced compared with that of the DR5J-negative patients ($p<0.05$).

**DISCUSSION**

Pulmonary sarcoidosis is a systemic granulomatous disease of unknown cause. The occasional occurrence of sarcoidosis within a family and in identical twins suggests a possible genetic influence, but there has been no definite evidence as to whether this disease is related to genetic predisposition. The HLA antigen system is one of the efficient genetic markers and has been used to explore genetic and familial factors in several diseases.

In order to elucidate involvement of immune mechanisms along with inherited factors in the pathogenesis and pathophysiology of sarcoidosis, HLA association with this granulomatous disease has been studied.

The frequency of HLA-Cw7 was increased in English patients, but it was not found in West Indian patients. The association between HLA-B7 and sarcoidosis in Scandinavian patients has been reported; however, it was not confirmed in English or West Indian sarcoidosis patients. It was also known that HLA-B8 is associated with sarcoidosis in Caucasians. In the Japanese, HLA-B8 is a very rare antigen. In fact, there were no HLA-B8-positive patients in our study.

There is a difference among ethnic groups in the HLA frequencies of sarcoidosis patients.

HLA-DR antigens, which are crucially important in human immune reaction, regulate host response mechanisms to disorders through cell-mediated immunity. Thus, the association of sarcoidosis with HLA-DR antigens may be more relevant than that with HLA-A, B, and C antigens because cell-mediated immunity is known to be involved in the pathogenesis of sarcoidosis.

There have been few reports about HLA-DR antigens in sarcoidosis as well as other diseases in that immune mechanisms are thought to be important. Gardner et al. reported the association of HLA-DR3, a very rare antigen in the Japanese population, with a good prognosis in English patients who have sarcoidosis.

Our recent study on the association between HLA-DR antigens and sarcoidosis in Japanese patients showed an increase in HLA-DRw52.

In this paper, we revealed a significantly increased frequency of HLA-DR5J. Moreover, in HLA-DR5J-positive Japanese patients sarcoidosis was unresolved spontaneously. This seems to be the first such report for any ethnic group.

HLA-DR5J is DR5 broadly defined; DR5J is the name given to the specificities of MT2-positive and MB3'-positive. This specificity includes DR5, a part of DRw8 and some other strange specificities.

In this present report, HLA-DRw52 is concerned primarily with onset in the Japanese sarcoidosis patients and HLA-DR5J may have an effect on the clinical course of this disease.

In conclusion, we have demonstrated a significant association between HLA-DRw52, DR5J and Japanese sarcoidosis patients. In addition, possession of the HLA-DR5J antigen may be associated with unresolved sarcoidosis. Our findings suggest that the clinical picture of sarcoidosis is, at least partly, based on inherited host factors.

**REFERENCES**

6. Abe S, Tsuneta Y, Kawakami Y, Kunikane H, Nakamura K,
American Institute of Ultrasound Medicine

The 32nd Annual Convention of the AIUM will be held in New Orleans, October 6-9. The Institute will host the Fifth Meeting of the World Federation of Ultrasound in Medicine and Biology and the Second World Congress of Sonographers in Washington, DC, October 17-21. For information, contact: Convention Department, AIUM, 4405 East-West Highway, Suite 504, Bethesda 20814 (301:656-6117).

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This symposium will be held November 16-20 at the Doelen Concert Hall, Rotterdam, The Netherlands. For information, contact Dr. Omar Prakash, Erasmus University, PO Box 1738, 3000 DR Rotterdam, The Netherlands.