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# Immunogenetics of Episcleritis in Leprosy

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**Abstract:** Human leukocyte antigens (HLA) were analyzed among Japanese leprosy patients to identify any possible determinants in the development of episcleritis in leprosy patients. Seventy-nine Japanese leprosy patients (33 patients with history of episcleritis and 46 patients without episcleritis) and 114 healthy control subjects were investigated. Human leukocyte antigen-class I and class II specificities were determined serologically by the standard microcytotoxicity test. The HLA-DRB1, -DRB5, -DQA1, and -DQB1 genotypings were performed by using the polymerase chain reaction (PCR)-single strand conformation polymorphism and PCR-restriction fragment length polymorphism analyses. The frequency of HLA-Cw3 was significantly increased among the patients with episcleritis (66.7%) compared to patients without episcleritis (43.5%; odds ratio = 2.6, $P < 0.05$). The frequency of HLA-DR4 was significantly decreased among the patients with episcleritis (15.2%) compared to patients without episcleritis (39.1%; odds ratio = 0.28, $P < 0.05$) and the controls (46.5%; odds ratio = 0.21, $P < 0.001$). At the genomic level, frequencies of the HLA-DRB1*0405, -DQB1*0401, and -DQB1*0302 alleles were significantly decreased among the patients with episcleritis (0%, 0%, and 6.1%, respectively) compared to patients without episcleritis (15.2%, 13.0%, and 26.1%, respectively; odds ratio = 0.07, 0.09, and 0.18, $P < 0.05$). HLA-DRB1*0405 and -DQB1*0401 were also significantly decreased among the patients with episcleritis compared to the controls (29.8% and 29.8%; odds ratio = 0.04, $P < 0.0001$). Our results suggest that HLA-Cw3 antigen confers the susceptibility to the development of episcleritis among Japanese leprosy patients. Concurrently, the DRB1 (the -DBR1*0405), and/or DQB1 (the -DQB1*0401 and -DQB1*0302) alleles might provide protection against leprous episcleritis.
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**Key Words:** Episcleritis, genomic typing, human leukocyte antigens, leprosy (Hansen's disease).

## Introduction

Leprosy is a chronic granulomatous disease of infectious origin caused by *Mycobacterium leprae*. Ocular complications occur frequently in patients with leprosy.[1–3] A common presentation of ocular leprosy is inflammation of the subconjunctival layer of the sclera (episclera) termed as episcleritis.[1] Despite the same infection, episcleritis does not occur in all leprosy patients. Some cases of episcleritis in leprosy are thought to be related to erythema nodosum leprosum (ENL),[1] a type III hypersensitivity reaction.[4] In most cases of ENL, the eye, including the episclera, is not involved. Episcleritis does occur in skin-smear–negative cases of leprosy.[1] Factors influencing the development or recurrence of episcleritis in leprosy have not yet been clearly demonstrated.

Positive relationships between human leukocyte antigen (HLA)-DRB1*0803 and acute anterior uveitis (AAU) in ankylosing spondylitis (AS) patients and between HLA-DR2 and uveitis in leprosy patients have already been reported.[5–7] These observations suggest that HLA genes are involved to some extent in the development of uveitis in patients with ankylosing spondylitis and leprosy. In this study, we analyzed human leukocyte antigens (HLA) and the HLA alleles among Japanese leprosy patients with and without episcleritis. The main objective of the study is to investigate the role of immunogenetic factor(s) in determining the susceptibility to the development of episcleritis among leprosy patients.

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## Materials and Methods

*Patients*

Seventy-nine leprosy patients comprising 33 with a history of episcleritis (14 men and 19 women) and 46 without episcleritis (21 men and 25 women) were included in this study. All of them were of Japanese ancestry and were unrelated to each other. The patients had been treated in the National Leprosarium, Tama-Zensho-En, in Metropolitan Tokyo. Episcleritis was diagnosed by an ophthalmologist under slit-lamp examination. These features are a nodule localized on the superficial sclera followed by inflammation of the outer surface of the sclera associated with redness and tenderness of the surrounding area in the initial stage.

One-hundred and fourteen control subjects were included in this study. The control subjects were healthy Japanese blood donors at the Saitama Medical Center and were unrelated to each other. All phases of the study were approved by the Ethics Committee of The University of Tokyo. Informed consent was obtained from each subject before participation in the study. The tenets of the Declaration of Helsinki were followed.

## HLA Serologic and Genomic Typing

A standard complement-dependent microcytotoxicity test[8] was used for typing the HLA-A, -B, -C, -DR, and -DQ specificities. DNA analyses for the HLA-DRB1, -DRB5, -DQA1, and -DQB1 alleles were performed by using the polymerase chain reaction (PCR)-single strand conformation polymorphism (SSCP) and PCR-restriction fragment length polymorphism (RFLP) methods.[9–12]

DNA was extracted by using a standard phenol-chloroform extraction method for high molecular weight genomic DNA. After extraction, PCR was performed by using group-specific primers of the second exon as referred to in previous papers.[9–15] Single strand conformation polymorphism and RFLP analyses for HLA genotypings using PCR products were performed according to the methods of standard practice.[9–12,14,15]

## Statistical Analysis

Fisher's exact test or chi-square analysis was employed to determine the statistical significance of the differences between patients and normal controls and between the two groups of patients. $P$ values were corrected by multiplying the $P$ value by the number of antigens tested, that is, 60, or by the number of alleles found in each locus (DRB1 = 23, DRB5 = 3, DQA 1 = 10, and DQB1 = 13).

Relative risk values were calculated as $(a \times d)/(b \times c)$, where a, b, c, and d stand for the number of marker + patients, marker − patients, marker + controls, and marker − controls, respectively. When any value was 0 we applied Haldane's modification, in which 0.5 was added to every number.[16]

## Results

Human leukocyte antigen frequencies are shown in Table 1. The frequency of HLA-Cw3 was significantly higher (66.7%) among the patients with episcleritis, as compared with patients without episcleritis (43.5%; odds ratio = 2.6, $P < 0.05$), but this difference failed to reached significance after $P$ was corrected. The frequency of HLA-DR4 was significantly lower in the patients with episcleritis (15.2%) than in those without episcleritis (39.1%; odds ratio = 0.28, $P < 0.05$) or the controls (46.5%; odds ratio = 0.21, $P < 0.001$), although these differences were not significant after $P$ was corrected.

At the genomic level (Table 2), the frequencies of HLA-DRB1*0405, DQB1*0401, and DQB1*0302 alleles were significantly decreased in the patients with episcleritis (0%, 0%, and 6.1%, respectively) compared to those without episcleritis (15.2%, 13.0%, and 26.1%, respectively; odds ratio = 0.07, 0.09, and 0.18; $P < 0.05$), but these differences failed to reach significance after $P$ was corrected. The HLA-DRB1*0405 and DQB1*0401 alleles were also significantly decreased in the patients with episcleritis compared to the controls (29.8% and 29.8%; odds ratio = 0.04, $P < 0.00005$, $Pc < 0.005$).

## Discussion

Previous studies including ours, have demonstrated that leprosy is strongly associated with HLA-DR2,[17-22] especially the HLA-DRB1*1501 and -DRB5*0101 alleles of the HLA-DR2 group.[23,24]

Episcleritis and uveitis are the common ocular complications of leprosy.[1] In our previous study, we reported a positive association between uveitis in leprosy and HLA-DR2. That study also reported a negative association between HLA-DR4 and uveitis among the patients with leprosy.[6,7] However, there has been no report until now on the relationship between HLA and episcleritis in leprosy patients. There are only a few reports in the literature on the relationship between HLA and episcleritis and/or scleritis in diseases other than leprosy.[25,26]

**Table 1.** Frequencies of Human Leukocyte Antigens (HLA) Among Japanese Leprosy Patients and Controls

| | Patients | | Controls | ES(+) vs. ES(−) | |
|---|---|---|---|---|---|
| | ES(+)[a](33) | ES(−)[b](46) | n = 114 | | |
| HLA | n (%) | n (%) | n (%) | Odds Ratio | *P* Value |
| Class I | | | | | |
| A2 | 16 (48.5) | 20 (43.5) | 45 (39.5) | | |
| A11 | 3 (9.1) | 12 (26.1) | 23 (20.2) | | |
| A24 | 17 (51.5) | 31 (67.4) | 66 (57.9) | | |
| A26 | 6 (18.2) | 6 (13.0) | 28 (24.6) | | |
| A31 | 7 (21.2) | 7 (15.2) | 21 (18.4) | | |
| A33 | 5 (15.2) | 5 (10.9) | 18 (15.8) | | |
| B7 | 4 (12.1) | 6 (13.0) | 11 (9.6) | | |
| B35 | 5 (15.2) | 8 (17.4) | 21 (18.4) | | |
| B44 | 5 (15.2) | 5 (10.9) | 22 (19.3) | | |
| B48 | 3 (9.1) | 5 (10.9) | 4 (3.5) | | |
| B51 | 4 (12.1) | 4 (8.7) | 20 (17.5) | | |
| B52 | 9 (27.3) | 14 (30.4) | 25 (21.9) | | |
| B54 | 0 (0) | 4 (8.7) | 19 (16.7) | | |
| B55 | 3 (9.1) | 3 (6.5) | 3 (2.6) | | |
| B60 | 8 (24.2) | 3 (6.5) | 9 (7.9) | | |
| B61 | 6 (18.2) | 12 (26.1) | 21 (18.4) | | |
| B62 | 6 (18.2) | 7 (15.2) | 23 (20.2) | | |
| B67 | 2 (6.1) | 5 (10.9) | 2 (1.8) | | |
| Bw4 | 18 (54.5) | 25 (54.3) | 64 (56.1) | | |
| Bw6 | 30 (90.9) | 45 (97.8) | 101 (88.6) | | |
| Cw1 | 3 (9.1) | 10 (21.7) | 39 (34.2) | | |
| Cw3 | 22 (66.7) | 20 (43.5) | 55 (48.2) | 2.6 | 0.042 |
| Cw4 | 4 (12.1) | 1 (2.2) | 14 (12.3) | | |
| Cw7 | 8 (24.2) | 18 (39.1) | 23 (20.2) | | |
| Cw9 | 12 (36.4) | 10 (21.7) | 26 (22.8) | | |
| Cw10 | 10 (30.3) | 10 (21.7) | 18 (15.8) | | |
| Class II | | | | | |
| DR 1 | 3 (9.1) | 9 (19.6) | 9 (7.9) | | |
| DR 2 | 22 (66.7) | 27 (58.7) | 38 (33.3) | | |
| DR 4[c] | 5 (15.2) | 18 (39.1) | 53 (46.5) | 0.28 | 0.039 |
| DR 6 | 12 (36.4) | 10 (21.7) | 33 (28.9) | | |
| DR 8 | 4 (12.1) | 4 (8.7) | 28 (24.6) | | |
| DR 9 | 9 (24.2) | 6 (13.0) | 35 (30.7) | | |
| DR11 | 4 (12.1) | 1 (2.2) | 2 (1.8) | | |
| DR12 | 0 | 6 (13.0) | 6 (5.3) | | |
| DR13 | 6 (18.2) | 5 (10.9) | 18 (15.8) | | |
| DR14 | 4 (12.1) | 4 (8.7) | 12 (10.5) | | |
| DR52 | 15 (45.5) | 17 (37.0) | 40 (35.1) | | |
| DR53 | 13 (39.4) | 24 (52.2) | 82 (71.9) | | |
| DQ 1 | 29 (87.9) | 37 (80.4) | 80 (70.2) | | |
| DQ 3 | 20 (60.6) | 23 (50.0) | 62 (54.4) | | |
| DQ 4 | 3 (9.1) | 8 (17.4) | 44 (38.6) | | |
| DQ 7 | 11 (33.3) | 9 (19.6) | 18 (15.8) | | |

[a]ES(+): patients with episcleritis.
[b]ES(−): patients without episcleritis.
[c]ES(+) vs. controls; odds ratio = 0.21, $P = 0.0008$.

In 1977, Joysey and his colleagues[25] reported that the occurrence of HLA-Bw15 was greater among patients with rheumatic heart disease and scleritis than in the control population.[25] Saari and colleagues[26] analyzed HLA-A and -B antigens in 9 patients from three families with ocular rheumatoid diseases, such as inflammation of cornea, episclera, sclera, and uvea.[26] However, they did not statistically analyze the relationship between HLA and involvement of the eye. These two earlier studies were confined to

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**Table 2.** Phenotype Frequencies of HLA-DRB1, DRB5, DQA1, and DQB1 Alleles Among Japanese Leprosy Patients With and Without Episcleritis and Controls

| | Patients | | Controls | ES(+) vs ES.(−) | |
|---|---|---|---|---|---|
| | ES(+)[a](33) | ES(−)[b](46) | n = 114 | | |
| Genotypes | n (%) | n (%) | n (%) | Odds Ratio | *P* Value |
| DRB1 | | | | | |
| *0101 | 3 (9.1) | 9 (19.6) | 9 (7.9) | | |
| *1501 | 13 (39.4) | 16 (34.8) | 16 (14.0) | | |
| *1502 | 9 (27.3) | 17 (40.0) | 24 (21.1) | | |
| *0401 | 1 (3.0) | 2 (4.3) | 1 (0.9) | | |
| *0403 | 1 (3.0) | 5 (10.9) | 9 (7.9) | | |
| *0405[a] | 0 | 7 (15.2) | 34 (29.8) | 0.07 | 0.038 |
| *0406 | 2 (6.1) | 3 (6.5) | 6 (5.3) | | |
| *0407 | 0 | 1 (2.2) | 1 (0.9) | | |
| *0410 | 1 (3.0) | 4 (8.7) | 5 (4.4) | | |
| *0802 | 3 (9.1) | 2 (4.3) | 8 (7.0) | | |
| *0803 | 1 (3.0) | 2 (4.3) | 20 (17.5) | | |
| *0901 | 8 (24.2) | 6 (13.0) | 35 (30.7) | | |
| *1101 | 4 (12.1) | 1 (2.2) | 2 (1.8) | | |
| *1201 | 0 | 5 (10.9) | 4 (3.5) | | |
| *1302 | 6 (18.2) | 5 (10.9) | 16 (14.0) | | |
| *1401 | 1 (3.0) | 3 (6.5) | 10 (8.8) | | |
| *1405 | 2 (6.1) | 1 (2.2) | 3 (2.6) | | |
| *1406 | 4 (12.1) | 0 | 2 (1.8) | | |
| DRB5 | | | | | |
| *0101 | 13 (39.4) | 16 (34.8) | 16 (14.0) | | |
| *0102 | 9 (27.3) | 17 (40.0) | 24 (21.1) | | |
| DQA1 | | | | | |
| *0101 | 7 (21.2) | 13 (28.3) | 22 (19.3) | | |
| *0102 | 17 (51.5) | 21 (45.7) | 31 (27.2) | | |
| *0103 | 10 (30.3) | 19 (41.3) | 39 (34.2) | | |
| *03 | 13 (39.4) | 23 (50.0) | 80 (78.1) | | |
| *0401 | 2 (6.1) | 1 (2.2) | 6 (5.3) | | |
| *0501 | 7 (21.2) | 6 (13.0) | 10 (8.8) | | |
| DQB1 | | | | | |
| *0501 | 3 (9.1) | 9 (19.6) | 11 (9.6) | | |
| *0601 | 10 (30.3) | 20 (43.5) | 38 (33.3) | | |
| *0602 | 12 (36.4) | 15 (32.6) | 15 (13.2) | | |
| *0604 | 5 (15.2) | 5 (10.9) | 15 (13.2) | | |
| *0301 | 11 (33.3) | 9 (19.6) | 18 (15.8) | | |
| *0302 | 2 (6.1) | 12 (26.1) | 18 (15.8) | 0.18 | 0.034 |
| *0303 | 8 (24.2) | 6 (13.0) | 26 (22.8) | | |
| *0401[b] | 0 (0) | 6 (13.0) | 34 (29.8) | 0.09 | 0.038 |
| *0402 | 3 (9.1) | 2 (4.3) | 12 (10.5) | | |

[a]ES(+) vs. controls; odds ratio = 0.04; $P = 0.000046$.
[b]ES(+) vs. controls; odds ratio = 0.04, $P = 0.000046$.

HLA class I antigens only. Moreover, to the best of the author's knowledge, there has been no report on the relationship between HLA class II genotypes and episcleritis.

In the present study, we have analyzed HLA class I and class II antigens and the HLA-DRB1, -DRB5, -DQA1, and -DQB1 genotypes to investigate the immunogenetic background of the development of episcleritis in Japanese patients with leprosy.

By serologic HLA tissue typing, there was no statistical significance between the leprosy patients and controls in the frequency of HLA-Cw3 (data not shown). However, the frequency of HLA-Cw3 was significantly higher among the patients with episcleritis compared to those without episcleritis. This result suggests that HLA-Cw3 is important for the development of episcleritis in Japanese leprosy patients. At the genomic level, HLA-Cw3 antigen is divided into three subtypes, HLA-Cw*0302, *0303, and *0304, in Japanese.[27] Unlike other HLA class I

antigens, serologically undefined HLA-C antigens are still present at a gene frequency of 20 to 50% in humans.[28–29] Human leukocyte antigen-C genotyping could be important for detecting the underlying immunogenetics in the pathogenesis of episcleritis among leprosy patients.

On the other hand, HLA-DR4 is negatively associated with episcleritis in leprosy. This result is consistent with our previous report on uveitis in leprosy,[6,7] and might indicate that HLA-DR4 confers protection to the development of ocular involvement in leprosy.

At the genomic levels, the HLA-DRB1*0405 of the HLA-DR4 alleles is negatively associated with episcleritis. Furthermore, the HLA-DQB1*0302 and -DQB1*0401, which are subtypes of HLA-DQ3 and -DQ4, respectively, were negatively associated with episcleritis in this study. Mainly, six alleles of HLA-DR4 are detected in the Japanese population, namely; HLA-DRB1*0401, *0403, *0405, *0406, *0407, and *0410.[30] HLA-DRB1*0405 is well known to have a linkage disequilibrium with DQB1*0401.[31] Concurrently, HLA-DQB1*0302 is mainly linked with HLA-DRB1*0403, *0406, or *0407.[31] In this study, 6 of the 7 DRB1*0405-positive patients without episcleritis expressed the HLA-DQB1*0401 genotype. These observations indicate that HLA-DRB1*0405 and/or -DQB1*0401 act as suppressive factor(s) for episcleritis in leprosy patients. It is difficult to determine which of these two alleles primarily confers protection against leprous episcleritis.

Likewise, HLA-DQB1*0302 is in linkage disequilibrium with HLA-DRB1*0403, *0406, and *0407, which are subtypes of HLA-DR4.[31] However, these DRB1 alleles were not associated with episcleritis in the present study. Thus, HLA-DQB1*0302 may be considered as an independent protective factor against the development of episcleritis among leprosy patients.

Because of the fact that ocular tissues are difficult to obtain for study, the pathophysiologic aspect of the disease is poorly understood. Previous immunohistochemical study indicated that immune-complex–mediated vasculitis plays an important role in the pathogenesis of scleritis in autoimmune disease such as rheumatoid arthritis.[32] There has been no report of an immunohistochemical study of episcleritis, which is a frequent type of scleritis among leprosy patients. With uveitis, in episcleritis in skin-smear–positive active cases, it can be considered that the inflammation is secondary to the invasion by the leprosy bacillus and/or immune-complex–mediated vasculitis that may be associated with ENL.[1,33] Thus, our results suggest that the HLA genes, especially the HLA-Cw3, -DRB1*0405, -DQB1*0401, and -DQB1*0302, regulate these mechanisms in leprous episcleritis. However, these alleles did not show strong positive or negative association with leprous episcleritis. Therefore, other HLA, a non-HLA gene, and/or environmental factors may play a critical role in the predisposition and resistance to episcleritis in leprosy patients.

The mechanism underlying episcleritis remains unknown in patients who have been in the skin-smear–negative, inactive stage for a long time. In the 1990s, over 95% of Japanese leprosy patients are in this stage, and the risk of the onset of episcleritis still exists among these patients.[34] Further studies including other ethnic groups are expected to elucidate the mechanism of the pathogenesis of episcleritis in patients with skin-smear–negative, inactive stage leprosy.

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