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Immunogenetics of Uveitis in Leprosy

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Purpose: To identify any possible determinants in the development of uveitis in leprosy patients.

Methods: Human leukocyte antigen (HLA) class I and II antigen, and HLA class II genotypings were analyzed among Japanese leprosy patients. Ninety-three unrelated Japanese leprosy patients (46 patients with a history of uveitis and 47 patients without uveitis) and 114 healthy control subjects were investigated.

Results: The occurrence of HLA-DR2 was significantly higher in patients with uveitis (78.3%) than in those without uveitis (57.4%; odds ratio = 2.7, $P < .05$) and in the controls (33.3%; odds ratio = 7.2, $P < .0000005$, $Pc < .00005$). The occurrence of HLA-DR4 was significantly lower in patients with uveitis (15.2%) than in those without it (38.3%; odds ratio = 0.29, $P < .05$) and in the controls (46.5%; odds ratio = 0.21, $P < .0005$, $Pc < .05$). Furthermore, the frequencies of DR2-positive and DR4-negative genotypes were significantly higher in patients with uveitis (69.6%) than in those without it (38.3%; odds ratio = 3.7, $P < .005$) and in the controls (21.9%; odds ratio = 8.1, $P < .00000005$). At the genomic level, the occurrence of HLA-DQB1*0302 was significantly lower in the patients with uveitis (8.7%) than in those without it (25.5%; odds ratio = 0.28, $P < .05$). The distribution of HLA-DRB1 and DQA1 alleles was not significantly different between the patients with and those without uveitis. However, the frequencies of DRB1*1501-positive, as well as DRB1*0405- and DQB1*0302-negative genotypes were significantly higher in the patients with uveitis (47.8%) than in those without it (25.5%; odds ratio = 2.7, $P < .05$) and in the controls (8.8%; odds ratio = 9.5, $P < .00000005$).

Conclusions: Our results suggest that HLA Class II genes confer susceptibility to or protection from leprous uveitis. **Jpn J Ophthalmol 1999;43:97–102**

Key Words: Genomic typing, human leukocyte antigens, leprosy (Hansen's disease), uveitis.

Introduction

Leprosy is one of the six tropical infectious diseases designated by the World Health Organization (WHO), and in developing countries[1] remains the cause of certain health problems such as disabilities involving the hands, feet, and eyes.

Many issues, including the mechanism of the onset of this disease, have remained unsolved. Some individuals infected by *Mycobacterium leprae* develop leprosy, as well as other infectious diseases, such as tuberculosis, toxoplasmosis, and herpes simplex, whereas others do not. Furthermore, the mechanism of ocular complications in leprosy patients is not clear.

Uveitis is the principal ocular manifestation associated with leprosy.[2–5] The factors influencing the occurrence or recurrence of uveitis in leprosy have not yet been clearly demonstrated.[2,3] However, the role of immune mechanisms in the pathogenesis of leprous uveitis have been documented.[6] Our previous study indicated that there is a positive correlation between the uveitis in leprosy and the human leukocyte antigen (HLA)-DR2 defined by serological typing.[7,8]

There have been numerous reports on the association between HLA and other autoimmune or infectious diseases.[9–12] Thus, HLA genes appear to be

Received: March 13, 1998

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Published by Elsevier Science Inc.

0021-5155/99/$–see front matter
PII S0021-5155(98)00068-9

Jpn J Ophthalmol
Vol 43: 97–102, 1999

markers for either susceptibility or resistance to disease. Furthermore, it has been reported that HLA genes are involved in determining the genetic predisposition to uveitis, which is one of the ocular complications in several diseases.[13–15]

In the present study, we have analyzed HLA class II genotyping among Japanese leprosy patients with uveitis and those without uveitis to investigate the role of immunogenetic factors in the pathogenesis of uveitis in leprosy.

Materials and Methods

Patients and Controls

Ninety-three unrelated Japanese leprosy patients were studied. All of them had been hospitalized in the National Leprosarium, Tama-Zensho-En, in Tokyo. The subjects comprised 46 patients with a history of uveitis (27 men and 19 women) and 47 patients without uveitis (22 men and 25 women). The mean age at leprosy disease onset was 16.5 and 16.9 years, respectively. On the contrary, we were unable to obtain the accurate age at uveitis onset. Uveitis was diagnosed by ophthalmologists under slit-lamp examination or by past ophthalmologic records. In the skin smear-positive active stage, all leprosy patients with uveitis had active anterior segment inflammation.

One-hundred fourteen unrelated volunteers were randomly selected as controls from healthy unrelated Japanese blood donors at the Saitama Medical Center. All subjects gave informed consent.

HLA Serologic and Genomic Typing

A standard microcytotoxicity test was used to type HLA-A, -B, -C, -DR, and -DQ antigens as described previously.[16]

Human leukocyte antigen-DRB1, -DQA1, and -DQB1 genotypings were performed by using the polymerase chain reaction (PCR)-single strand conformation polymorphism and PCR-restriction fragment length polymorphism methods.[17–19]

Deoxyribonucleic acid (DNA) was extracted using a standard phenol-chloroform extraction method for high molecular weight genomic DNA. After DNA extraction, PCR was performed by using group-specific primers of the second exon described in previous reports.[17–23]

Statistical Analysis

Fisher's exact test or χ^2 analysis was employed to determine the statistical significance of the differences between patients and normal controls, as well as between the two groups of patients. The P value was considered significant if less than 0.05. The corrected P value (Pc) was obtained by multiplying the P value by the number of antigens used in serology testing (60 types of antigens were used in this study), or by the number of alleles found in each locus (DRB1 = 23, DQA1 = 10, and DQB1 = 13). Odds ratios were estimated according to Woolf's formula with Haldane's modification when necessary.[24]

Results

Distribution of HLA Class I and II Antigens

Table 1 shows selected HLA antigen frequencies in Japanese leprosy patients and the controls. There was no statistically significant difference between the two groups of patients with respect to class I HLA antigens. With respect to class II HLA antigens, the frequency of HLA-DR2 was significantly higher in patients with uveitis (78.3%) than in those without uveitis (57.4%; odds ratio = 2.7, $P < .05$, Pc; not significant) and in the controls (33.3%; odds ratio = 7.2, $P < .0000005$, $Pc < .00005$). Conversely, the frequency of HLA-DR4 was significantly lower in patients with uveitis (15.2%) than in those without uveitis (38.3%; odds ratio = 0.29, $P < .05$, Pc; not significant) and in the controls (46.5%; odds ratio = 0.21, $P < .0005$, $Pc < .05$).

Combination of HLA-DR2 and DR4 Antigen

We analyzed whether the combination of the DR2 and DR4 antigens is associated with the uveitis seen in leprosy patients. The frequency of the DR2-positive and DR4-negative HLA type was significantly higher in patients with uveitis (69.6%) than in those without it (38.3%; odds ratio = 3.7, $P < .005$) and in the controls (21.9%; odds ratio = 8.1, $P < .00000005$) (Table 2).

Distribution of HLA-DRB1, DQA1, and DQB1 Alleles

Table 3 shows the frequencies of selected alleles in leprosy patients and the controls. The DQB1*0302 allele of the DQ3 group was significantly lower in patients with uveitis (8.7%) than in those without uveitis (25.5%; odds ratio = 0.28, $P < .05$), but his difference failed to reach significance after P was corrected. The difference in the distribution of HLA-DRB1 and DQA1 alleles between the two groups of patients was not significant.

Table 1. Phenotype Frequencies of Human Leukocyte Antigens (HLA) Among Leprosy Patients With and Without Uveitis (UV) and Controls

	Patients		Controls	UV (+) vs UV (−)		
	UV(+) (n = 46)	UV (−) (n = 47)	(n = 114)			
HLA	n (%)	n (%)	n (%)	Odds Ratio	P-Value	χ^2
Class I						
A2	19 (41.3)	21 (44.7)	45 (39.5)			
A24	26 (56.5)	31 (66.0)	66 (57.9)			
A26	10 (21.7)	6 (12.8)	28 (24.6)			
B35	8 (17.4)	8 (17.0)	21 (18.4)			
B51	4 (8.7)	5 (10.6)	20 (17.5)			
B52	14 (30.4)	14 (29.8)	25 (21.9)			
B54	0 (0)	4 (8.5)	19 (16.7)			
B61	7 (15.2)	12 (25.5)	21 (18.4)			
B62	9 (19.6)	8 (17.0)	23 (20.2)			
Cw1	9 (19.6)	10 (21.3)	39 (34.2)			
Cw3	26 (56.5)	21 (44.7)	55 (48.2)			
Cw9	16 (34.8)	11 (23.4)	26 (22.8)			
Class II						
DR 2[a]	36 (78.3)	27 (57.4)	38 (33.3)	2.7	<.05	4.6
DR 4[b]	7 (15.2)	18 (38.3)	53 (46.5)	0.29	<.05	6.3
DR 8	4 (8.7)	5 (10.6)	28 (24.6)			
DR 9	9 (19.6)	7 (14.9)	35 (30.7)			
DR 53	16 (34.8)	25 (53.2)	82 (71.9)			
DQ 1	42 (91.3)	38 (80.9)	80 (70.2)			
DQ 3	21 (45.7)	24 (51.1)	62 (54.4)			
DQ 4	3 (6.5)	8 (17.0)	44 (38.6)			

UV(+): patients with uveitis, UV(−): patients without uveitis.
[a]UV(+) vs. controls; odds ratio = 7.2, $P < .0000005$, $\chi^2 = 26.6$.
[b]UV(+) vs. controls; odds ratio = 0.21, $P < .0005$, $\chi^2 = 13.7$.

*Combination of HLA-DRB1*1501, DRB1*0405, and DQB1*0302 Alleles*

We analyzed whether the combination of the DRB1*1501, DRB1*0405, and DQB1*0302 alleles is associated with leprous uveitis. The frequency of DRB1*1501-positive, as well as DRB1*0405- and DQB1*0302-negative genotypes was significantly higher in patients with uveitis (47.8%) than in those without it (25.5%; odds ratio = 2.7, $P = .025$) and in the controls (8.8%; odds ratio = 9.5, $P < .00000005$) (Table 4).

Discussion

Human leukocyte antigen class I and II genes on the short arm of chromosome 6 are characterized by their extraordinary polymorphism.[25–27] Human leu-

Table 2. Combination of Human Leukocyte Antigen DR2/DR4 Among Leprosy Patients With and Without Uveitis

		Patients		Controls	UV(+) vs UV(−)		
		UV(+) (n = 46)	UV(−) (n = 47)	(n = 114)			
DR2	DR4	n (%)	n (%)	n (%)	Odds ratio	P-value	χ^2
(+)	(+)	4 (8.7)	9 (19.1)	13 (11.4)			
(+)	(−)	32 (69.6)[a]	18 (38.3)	25 (21.9)	3.7	.0025	9.1
(−)	(+)	3 (6.5)	9 (19.1)	40 (35.1)			
(−)	(−)	7 (15.2)	11 (23.4)	36 (31.6)			

UV(+): patients with uveitis, UV(−): patients without uveitis, (+): presence of antigen, (−): absence of antigen.
[a]UV(+) vs. controls; odds ratio = 8.1, $P < .00000005$, $\chi^2 = 32.4$.

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Table 3. Phenotype Frequencies of Human Leukocyte Antigen-DRB1, DQA1, and DQB1 Alleles Among Leprosy Patients With and Without Uveitis (UV) and Controls

	Patients		Controls			
	UV(+) (n = 46)	UV(−) (n = 47)	n = 114	UV(+) vs UV(−)		
Genotypes	n (%)	n (%)	n (%)	Odds Ratio	P-value	χ^2
DRB1						
*1501	24 (52.2)	16 (34.0)	16 (14.0)	2.1	.08	3.1
*1502	14 (30.4)	16 (34.0)	24 (21.1)			
*1602	3 (6.5)	1 (2.1)	1 (0.9)			
*0403	1 (2.2)	5 (10.5)	9 (7.9)			
*0405	2 (4.3)	7 (14.9)	34 (29.8)	0.26	.08[a]	
*0406	1 (2.2)	3 (6.4)	6 (5.3)			
*0410	1 (2.2)	1 (2.1)	5 (4.4)			
*0803	3 (6.5)	3 (6.4)	20 (17.5)			
*0901	9 (19.6)	7 (14.9)	35 (30.7)			
DQA1						
*0102	28 (60.9)	21 (44.7)	31 (27.2)			
*0103	17 (37.0)	20 (42.6)	39 (34.2)			
*03	16 (34.8)	24 (51.1)	80 (78.1)			
*0401	1 (2.2)	1 (2.1)	6 (5.3)			
DQB1						
*0601	16 (34.8)	21 (44.7)	38 (33.3)			
*0602	23 (50.0)	15 (31.9)	15 (13.2)	2.1	.08	3.1
*0301	12 (26.1)	9 (19.1)	18 (15.8)			
*0302	4 (8.7)	12 (25.5)	18 (15.8)	0.28	<.05[a]	
*0401	2 (4.3)	6 (12.8)	34 (29.8)			

UV(+): patients with uveitis, UV(−): patients without uveitis.
[a]Fisher exact test.

kocyte antigen class I and II molecules are known to play a key role in immune recognition of foreign antigens and self antigens by CD8- and CD4-positive T cells, respectively.[27] It is suggested that HLA molecules play a critical role in determining the susceptibility or resistance to either infectious or autoimmune disease in humans.

Previous studies, including ours, have demonstrated that leprosy is strongly associated with HLA-DR2,[27–33] especially the HLA-DRB1*1501 and -DRB5*0101 alleles of the HLA-DR2 group.[34,35]

It has been reported that HLA genes are involved in determining the genetic predisposition to uveitis that occurs both in association with systemic disease

Table 4. Combination of Human Leukocyte Antigen DRB1*1501/*0405 and DQB1*0302 Among Leprosy Patients With and Without Uveitis (UV)

		Patients		Controls			
DRB1	DQB1	UV(+) (n = 46)	UV(−) (n = 47)	(n = 114)	UV(+) vs UV(−)		
*1501/*0405	*0302	n (%)	n (%)	n (%)	Odds ratio	P-value	χ^2
(+)/(+)	(+)	0	0	0			
(+)/(+)	(−)	2 (4.3)	1 (2.1)	5 (4.4)			
(+)/(−)	(+)	0	3 (6.3)	1 (0.9)			
(+)/(−)	(−)	22 (47.8)[a]	12 (25.5)	10 (8.8)	2.7	.025	5.0
(−)/(+)	(+)	0	2 (4.3)	3 (2.6)			
(−)/(+)	(−)	0	4 (8.5)	26 (22.8)			
(−)/(−)	(+)	4 (8.6)	7 (14.9)	14 (12.3)			
(−)/(−)	(−)	18 (39.1)	18 (38.3)	55 (48.2)			

UV(+): patients with uveitis, UV(−): patients without uveitis, (+): presence of allele, (−): absence of allele.
[a]UV(+) vs. controls; odds ratio = 9.5, $P < .00000005$, $\chi^2 = 31.0$.

and without it.[13–15] Islam and colleagues[13] reported that there is a positive correlation between HLA-DRB1*0803 and uveitis in ankylosing spondylitis. In 1997, Tang et al[14] reported that the occurrence of HLA-DR15 was higher among patients with mediated uveitis than among the control population. Shindo and coworkers[15] indicated that sympathetic ophthalmia was associated with HLA-DRB1*04, DQA1*03 and DQB1*04. These associations suggest that HLA genes play a role in the pathogenesis of uveitis.

We have reported earlier that uveitis in leprosy patients was associated with HLA-DR2 defined by serological typing.[7,8] Human leukocyte antigen specificities are originally defined by serology, and each is now considered to include many genotypes at the DNA level. Thus, in the present study we have extended those data and analyzed HLA Class I and II antigens and the HLA-DRB1, -DQA1, and -DQB1 genotypes to investigate the immunogenetic background of the development of uveitis in Japanese leprosy patients.

By serologic HLA tissue typing, there were no statistically significant differences between the two groups of patients with respect to Class I HLA antigens. In Class II HLA antigens, HLA-DR2 was positively associated with uveitis. These results confirm our previous findings. Conversely, HLA-DR4 was negatively associated with uveitis in leprosy. This result is consistent with our previous report on episcleritis in leprosy.[36] Thus, HLA-DR4 might provide protection against the development of ocular symptoms in leprosy. From the analysis of combinations of DR2 and DR4 antigens, the HLA-DR2-positive and DR4-negative types indicated a higher risk factor in the patients with uveitis (odds ratio = 3.7, $P < .005$) than DR2 alone (odds ratio = 2.7, $P < .05$). From these observations, it is postulated that HLA-DR2 and DR4 are important for the development of uveitis in Japanese leprosy patients.

At the genomic level, the distribution of the HLA-DRB1, DQB1, and DQA1 alleles was not significantly different between the two groups of patients; however, DQB1*0302, which is a subtype of HLA-DQ3, was negatively associated with uveitis. As for the DR2 subtypes, HLA-DRB1*1501 was observed at a high frequency in the uveitis group, whereas the HLA-DRB1*0405 allele of the DR4 group was observed at a low frequency in the uveitis group. Mainly, HLA-DQB1*0302 is linked with -DRB1*0403, *0406, or *0407, but not with DRB1*1501 and DRB1*0405.[37] We then analyzed whether the combination of the DRB1*1501, DRB1*0405, and DQB1*0302 alleles is associated with leprous uveitis; as a result, the HLA-DRB1*1501-positive, DRB1*0405-, and DQB1*0302-negative genotypes were positively associated with uveitis in the patients. Thus, serologic and genomic HLA analysis indicated that Class II HLA genes confer susceptibility or protection from leprous uveitis.

Uveitis in skin smear-positive active cases can be considered to be inflammation that is secondary to invasion by the leprosy bacillus, or immune complex-mediated vasculitis that may be associated with erythema nodosum leprosum, which is considered to be a Type III hypersensitivity reaction.[1,6] Thus, our results suggest that some HLA-DR and -DQ gene combinations, especially HLA-DR2(DRB1*1501), -DR4, and -DQB1*0302, regulate these mechanisms in leprous uveitis. However, these alleles did not show a strong positive or negative association with leprous uveitis. Thus, other HLA genes, non-HLA genes, or environmental factors may be the major risk factors in the uveitis seen in leprosy patients.

Conversely, the mechanism underlying leprous uveitis in the quiescent stage of the disease remains unknown.[2,3] In the 1990s, over 95% of Japanese leprosy patients are in this stage and the risk of the onset of uveitis, which remains one of the most intractable eye diseases, still exists among these patients.[38] Thus, further studies including other ethnic groups are expected to elucidate the pathogenesis of uveitis in patients with skin smear-negative, inactive stage uveitis.

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