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The HLA Antigens and Leprosy in Korea

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To investigate the genetic factors in Koreans with leprosy, 157 unrelated leprosy patients have been typed for HLA antigens, and compared with 162 healthy controls. The patient group consisted of 124 with lepromatous leprosy and 33 with tuberculoid leprosy. HLA-A11 was found to be increased in lepromatous leprosy ($p = 0.0005$). HLA-Aw33 was found to be increased in both lepromatous leprosy ($p = 0.0002$) and tuberculoid leprosy ($p = 0.005$). HLA-Cw5 was found to be decreased in lepromatous leprosy ($p = 0.009$). Frequencies of HLA-B antigens did not differ significantly between the leprosy patients and the healthy controls.

Key Words: HLA, Leprosy, Korean.

Leprosy is a chronic infection of man caused by the intracellular microorganism, *Mycobacterium leprae*. The disease is characterized by a wide range of clinicopathological features ranging from high resistant form tuberculoid leprosy to low resistant form lepromatous leprosy (Ridley and Jopling, 1966). The basis of this spectrum is thought to be the patient's immune responses to *M. leprae*.

Although the bacillus, *M. leprae*, was identified over a century ago (Hansen, 1875), the route of infection, factors affecting susceptibility, route of transmission, and effective therapy remain unknown (Fine, 1981). Contact with infectious cases does not always result in disease transmission (Godal and Negassi, 1973), and individuals exposed to the same infectious case often develop different clinical forms of leprosy. There are no known subtypes of *M. leprae* identified that might explain the variation observed in clinical infection (Shepard and McRae, 1971). Study of the *M. leprae* organism is limited because techniques for *in vitro* cultivation of *M. leprae* are not available. Nevertheless susceptibility to infection with *M. leprae* is thought to be primarily determined by host factors including immune response (Massoud *et al.*, 1978; White *et al.*, 1978; Stoner *et al.*, 1978; Smith, 1979; Mehra *et al.*, 1980; Mshana *et al.*, 1982; 1983).

The earlier studies of HLA and leprosy were confined to HLA-A and -B antigens. There were no consistent increases in HLA antigens when different studies and populations were compared (Escobar-Guttierrez *et al.*, 1973; Thorsby *et al.*, 1973; Kreisler *et al.*, 1974; Dasgupta *et al.*, 1975; Smith *et al.*, 1975; Nakajima *et al.*, 1977; Youngchaiyud *et al.*, 1977; Greiner *et al.*, 1978;, Takata *et al.*, 1978; Chen *et al.*, 1979; Chiewsilp *et al.*, 1979; Wolf *et al.*, 1980). More recently, studies of HLA class II antigens have demonstrated an increase in DR2 in tuberculoid leprosy in Indian multicase families (de Vries *et al.*, 1980; van Eden *et al.*, 1980) and in tuberculoid patients in population studies (Rea and Terasaki, 1980; van Eden *et al.*, 1980) and a significant increase of HLA-DR2 in sporadic cases of both tuberculoid and lepromatous leprosy in Japanese (Miyanaga *et al.*, 1981; Serjeantson *et al.*, 1983; Kikuchi *et al.*, 1984).

The present study was undertaken to determine whether HLA determinants are associated with susceptibility to leprosy in Koreans. The frequencies of HLA-A, -B and -C antigens were studied in 157 Koreans with leprosy.

MATERIALS AND METHODS

Clinical Material

All patients were from those attending the World Vision Special Skin Clinic situated in Seoul, Korea. Diagnosis was confirmed by clinical, bacteriological, and immunological examination using previously

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described criteria (Ridley and Jopling, 1966). The 157 leprosy patients studied were comprised of 124 lepromatous leprosy and 33 tuberculoid leprosy patients. Lepromatous leprosy is characterized by nodules or multiple skin lesions containing large numbers of macrophages loaded with *M. leprae* and an absence of cellular immune reactivity toward *M. leprae*. Tuberculoid leprosy is characterized by one or a few well-demonstrated skin lesions with anesthesia containing none or few bacteria with obvious cellular immune reactivity to *M. leprae*.

One hundred and sixty-two healthy, unrelated Koreans were randomly selected as controls. Most of these were staff members and students from the Yonsei University College of Medicine in Seoul.

HLA typing

Peripheral blood lymphocytes (PBL) were separated by centrifugation over Ficoll-Hypaque (Boyum, 1968) and cryopreserved. HLA-A, -B and -C typing was carried out by a standard complement dependent microcytotoxicity assay (NIAID manual, 1980).

Data analysis

Comparison of antigen frequencies between leprosy patients and healthy controls was made using a binary logistic regression model (Cox, 1970; Prentice, 1976).

RESULTS

HLA-A antigen frequencies in 162 healthy Korean controls, 124 lepromatous patients, and 33 tuberculoid patients are summarized in Table 1. HLA-A11 was found to be significantly increased in lepromatous patients (23%) compared to healthy controls (12%) and the relative risk was 3.8. HLA-Aw33 was found to be significantly increased in lepromatous patients (26%) and in tuberculoid patients (30%) compared to healthy controls (14%) and the relative risks were 4.1 and 4.9, respectively. HLA-Cw5 was found to be significantly decreased in the lepromatous patients (1%) compared to both the healthy control (11%) and the tuberculoid patients (9%) (Table 2). No significant differences were observed for any HLA-B antigens when all leprosy patients and types were compared with healthy controls (Table 3).

No significant over all differences in the frequencies of HLA-A,-B, and -C antigens were found between lepromatous leprosy and tuberculoid leprosy at three loci.

Table 1. Comparison of phenotype frequencies (%) of HLA-A specificities in leprosy patients and healthy controls

	lepromatous leprosy	tuberculoid leprosy	healthy control
	N=124	N=33	N=162
A1	2	3	4
A2	47	46	59
A3	2	6	4
A11	23[a]	15	12
A19	0	0	2
A24	44	46	38
A26	13	15	15
A28	1	0	1
A29	1	0	1
A30	10	12	6
A31	12	12	2
A32	1	0	2
Aw33	26[b]	30[c]	14
Aw36	0	0	1

a: RR(relative risk) = 3.8, p value = 0.0005
b: RR = 4.1, p value = 0.0002
c: RR = 4.9, p value = 0.005

Table 2. Comparison of phenotype frequencies (%) of HLA-C specificities in leprosy patients and healthy controls

	lepromatous leprosy	tuberculoid leprosy	healthy control
	N=124	N=33	N=140
Cw1	29	30	28
Cw2	2	0	1
Cw3	54	49	51
Cw4	17	9	12
Cw5	1[a]	6	11
Cw6	8	12	13

a: RR = 0.06, p value = 0.009

DISCUSSION

An analysis of the association of HLA antigens and leprosy in 124 lepromatous leprosy and 33 tuberculoid leprosy patients was performed. Since the report of MHC-linked immune response genes with

Table 3. Comparison of phenotype frequencies (%) of HLA-B specificities in leprosy patients and healthy controls

	lepromatous leprosy	tuberculoid leprosy	healthy control
	N=124	N=33	N=162
B51(5)	15	15	20
Bw52(5)	7	9	6
B7	11	21	9
B8	0	0	1
B44(12)	17	18	20
B45(12)	0	0	1
B13	7	18	9
B14	2	0	1
Bw62(15)	3	27	22
Bw63(15)	0	3	2
B38(16)	3	0	3
B39(16)	2	3	2
Bw57(17)	0	0	2
Bw58(17)	15	15	8
B18	1	0	0
B49(21)	0	0	0
Bw50(21)	0	0	0
Bw54(w22)	6	9	10
Bw55(w22)	3	3	7
Bw56(w22)	0	0	0
B27	7	3	3
B35	14	15	18
B37	3	3	3
Bw60(40)	12	3	10
Bw61(40)	10	6	10
Bw41	0	0	1
Bw42	0	0	0
Bw46	N.T.	N.T.	N.T.
Bw47	0	0	0
Bw48	6	6	4
Bw53	0	0	2
Bw59	1	0	2

N.T. = Not Tested

an associations between the susceptibility to a series of diseases and HLA antigens (Svejaggard *et al.*, 1983), a number of population studies to investigate an association between HLA antigens and leprosy have been performed (Serjeantson, 1983; Serjeantson *et al.*, 1983; de Vries *et al.*, 1984; van Eden and de Vries, 1984). However, no consistent associations were reported in different population. Even the association which were reported was either weak or not confirmed in other populations.

In the present study, it was observed that HLA-A11 occurs more frequently than expected in lepromatous patients and that HLA-Aw33 occurs more frequently than expected in both lepromatous and tuberculoid patients. These findings are consistent with the data reported in the 2nd AOHWC which showed that HLA-Aw33 was increased in Chinese patients with lepromatous leprosy. In contrast to our finding of an increased frequency of HLA-A11 in Korean lepromatous patients, HLA-A11 in Japanese patients was found to be increased in non-lepromatous patients (Serjeantson *et al.*, 1983) and decreased in lepromatous patients (Nakajima *et al.*, 1977).

It was observed that the frequency of the Cw5 antigen among Korean lepromatous patients was found to be lower than the controls.

No significant difference was observed in the frequencies of HLA-B antigens between the controls and the leprosy patients in this study. Several significant differences in the frequency of HLA-B antigens were reported in other pqpulations (Thorsby *et al.*, 1973; Kreisler *et al.*, 1974; Dasgupta *et al.*, 1975; Smith *et al.*, 1975; Nakajima *et al.*, 1977; Youngchaiyud *et al.*, 1977; Greiner *et al.*, 1978; Massoud *et al., 1978; Takata et al.*, 1978; Chan *et al.*, 1979; Bale *et al.*, 1982).

HLA class II antigens have been found to be associated with leprosy in various populations. HLA-DR2 was significantly increased in Indian multicase families (de Vries *et al.*, 1980; van Eden *et al.*, 1980) and in sporadic cases of both tuberculoid and lepromatous leprosy in the Japanese (Miyanaga *et al.*, 1981; Serjeantson *et al.*, 1983; Kikuchi *et al.*, 1984). HLA-DQw1 has been found to be associated with leprosy in various populations (de Vries *et al.*, 1981; Serjeantson *et al.*, 1983; Kikuchi *et al.*, 1984; van Eden *et al.*, 1985). Since more consistent and strong associations were found for the HLA class II antigens than for the HLA class I antigens, further studies are needed to elucidate the role of HLA class II antigens or linked genes in leprosy.

In conclusion, our data suggest that there is an increased relative risk for both lepromatous and tuberculoid leprosy associated with Aw33 and an increased relative risk for lepromatous leprosy associated with A11.

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