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HLA–DR antigens in tuberculoid and lepromatous leprosy

THOMAS H REA* & PAUL I TERASAKI†
**Section of Dermatology, Department of Internal Medicine, University of Southern California School of Medicine; Department of Dermatology, University of Southern California–Los Angeles County Medical Center; and †Department of Surgery, University of California School of Medicine, Los Angeles, California*

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Summary The frequencies of distribution of six histocompatibility antigens of the HLA–DR locus were determined in 38 Mexican patients with lepromatous leprosy and in 19 Mexican patients with tuberculoid leprosy. These were compared with antigen frequencies of 174 Mexicans who did not have leprosy. No evidence of an association between HLA–DR antigens and leprosy could be found. In tuberculoid subjects HLA–DRW2 was more common than in controls, 32% and 15% respectively. Although this difference was not statistically significant, it was in accord with another report of a significant increase in HLA–DRW2 among patients with tuberculoid leprosy. Furthermore, frequencies for 16 HLA–A, 23 HLA–B and five HLA–C antigens did not differ significantly in the two groups of patients as compared with controls.

Introduction

An association has been sought repeatedly between leprosy and antigens of the HLA–A and HLA–B loci of the major histocompatibility complex (Chan *et al.*, 1979;[1] Dasgupta *et al.*, 1975;[2] de Vries *et al.*, 1976;[3] Escobar-Gutierrez *et al.*, 1973;[4] Greiner *et al.*, 1978;[5] Kriesler *et al.*, 1974;[6] Massoud *et al.*, 1978;[7] Rea *et al.*, 1976;[8] Reis *et al.*, 1974;[9] Smith *et al.*, 1975;[10] Takata *et al.*, 1978;[11] Thorsby *et al.*, 1973;[12] and Youngchaiyud *et al.*, 1977[13]). The at least 13 studies reported to date collectively attest to the attractiveness of evidence suggesting that susceptibility to, and mode of expression of, leprosy is under genetic control (Chakravartti and Vogel, 1973;[14] Newell, 1966;[15] and Spickett 1962a,[16]

Correspondence to Dr Thomas H. Rea, Department of Dermatology, LAC/USC Medical Center, 2025 Zonal Avenue, Los Angeles, California 90033.

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1962b[17]). In four of these 13 studies statistically significant associations with an HLA–A (Kriesler *et al.*, 1974[6]) or HLA–B (Chan *et al.*, 1979;[1] Takata *et al.*, 1978;[11] and Thorsby *et al.*, 1973[12]) antigen were found, after correction by multiplying the p-value by the number of specificities tested. Greiner *et al.* (1978)[5] reasoned that this multiplying method of correction was not adequate because frequencies of various antigens are not independent; instead, relative risk was calculated as a measure of the significance of an association. However, whatever method was used to establish statistical significance, even among studies reporting significance, there has been no consistent association of a particular HLA–A and HLA–B antigen with any particular type of leprosy or with leprosy in general. Differing pressures for linkage disequilibrium in differing populations was an attractive explanation for the discordant, but yet significant findings (de Vries *et al.*, 1976).[3]

Study of HLA–A and HLA–B haplotype inheritance has provided further evidence that susceptibility to, and type of, leprosy may be influenced by genes within the major histocompatibility complex (de Vries *et al.*, 1976;[3] Fine *et al.*, 1979[18]).

Because the HLA–D and HLA–DR loci are nearer to the hypothetical immune response (Ir) gene than are HLA–A, –B, or –C loci, and because antigens of HLA–D or HLA–DR loci may show a closer association to a particular disease than can be detected by typing for HLA–A, –B, or –C antigens (Rachelefsky *et al.*, 1976;[19] and Reinertsen *et al.*, 1978[20]), it is logical that an association of HLA–D and HLA–DR antigens with leprosy has been sought. Stoner *et al.* (1978)[21] tested *in vitro* lymphoproliferative responses to *Mycobacterium leprae* in HLA–D identical and non-identical siblings of patients with lepromatous leprosy; finding that the HLA–D identical siblings responded as well as the HLA–D non-identical, they concluded that the *M. leprae* unresponsiveness of lepromatous patients was not the result of an HLA–D or –D-linked gene. In a preliminary report, de Vries *et al.* (1979)[22] found no evidence of an association between lepromatous leprosy and HLA–DR antigens; however, a statistically significant increase in HLA–DRW2 frequency in tuberculoid patients was present. We herein report our study of HAL–DR antigen frequencies in Mexican patients with leprosy.

Patients and methods

Patients were classified according to the histological and clinical criteria of Ridley and co-workers (Ridley, 1974; Ridley and Jopling, 1962; and Waters, 1969[25]). Because of the high incidence of erythema *nodosum leprosum* and Lucio's reaction, a histological distinction between polar and subpolar lepromatous leprosy could not be made (Ridley, 1974;[23] Ridley and Waters, 1969[25]). However, by clinical criteria all patients classed as lepromatous

were polar lepromatous (Ridley and Waters, 1969).[25] Thus 36 of 38 patients had or had had either erythema *nodosum leprosum* of Lucio's reaction, but never a reversal reaction. Also no patient had had a well-defined plaque clinically characteristic of subpolar lepromatous leprosy (Ridley and Waters, 1969).[25] Three of the 38 lepromatous patients showed a slight unilateral contraction of the fourth and fifth fingers but without associated asymmetrical sensory loss or muscle atrophy; other than this there was no suggestion of nerve trunk palsies. Finally, 18 of the 38 lepromatous subjects were known to have had diffuse, non-nodular lepromatous leprosy prior to beginning chemotherapy.

All of the tuberculoid patients were classified as BT (borderline with tuberculoid features). Most were typical of the BT classification. One patient showed some TT (polar tuberculoid) features by histological criteria and others TT by clinical criteria; but none were TT by both clinical and histological criteria.

All patients were Mexican-born or of bilateral Mexican-American ancestry. Controls were Mexican and Mexican-American blood bank and tissue transplant donors.

The microlymphocytotoxic method was employed (Mittal *et al.*, 1968).[26] B-lymphocytes were separated from T-lymphocytes by adherence to nylon wool. Six HLA–DRW antigens were sought, 1–5 and 7 (HLA–DRW6 was sought but is not reported because it probably does not exist). In addition to HLA–DR, 16 HLA–A, 23 HLA–B and five HLA–C antigens were sought.

Statistical analysis employed the ψ^2 test with the Yates' correction.

Results

The results are summarized in Table 1 for HLA–DR and in Table 2 for HLA–A, –B and –C antigens.

HLA–DRW2 was more common in tuberculoid patients (32%) than in controls (15%), but the difference was not statistically significant even uncorrected, $\psi^2 = 2.33$, $p > 0.1$. In the 38 lepromatous patients there was not even a suggestion of a genuine difference in antigen frequency distribution as

Table 1. Frequencies (%) of distributions of HLA–DR antigens in patients and controls

Antigen	Controls (174)	Tuberculoid Leprosy (19)	Lepromatous Leprosy (38)
HLA DRW 1	20	11	21
2	15	32	13
3	20	26	13
4	38	26	42
5	15	16	13
7	14	16	16

Table 2. Frequencies (%) of distribution of HLA–A, –B and –C antigens in patients and controls

Antigen	Controls (332)	Tuberculoid Leprosy (19)	Lepromatous Leprosy (44)
HLA–A1	12	11	7
A2	50	32	64
A3	9	21	14
A11	14	16	2
A25	2	0	0
A26	8	21	7
A28	19	26	23
A29	9	0	11
AW23	5	5	2
AW24	28	32	32
AW30	7	5	11
AW31	10	11	14
AW32	7	5	2
AW33	5	5	2
AW34	0	0	0
AW36	0	0	0
HLA–B7	8	11	9
B8	6	5	11
B13	1	0	5
B14	11	16	14
B15	9	0	7
B17	5	0	5
B18	6	16	2
HLA–B27	6	0	0
B37	2	5	2
B40	21	16	18
BW22	0	0	0
BW35	33	37	36
BW38	11	21	14
BW39	10	5	2
BW42	2	11	0
BW44	16	11	11
BW45	2	0	7
BW49	4	0	2
BW50	4	0	5
BW51	12	5	11
BW52	8	0	2
BW53	0	0	0
BW54	1	0	2
HLA–CW1	8	5	0
CW2	8	11	0
CW3	25	26	16
CW4	31	47	30
CW5	0	0	0

compared with controls; the greatest difference was with HLA–DRW3 and had a p-value of greater than 0.3. Likewise, antigen frequencies for the HLA–A, –B and –C loci did not differ significantly in the two groups of patients and in the controls.

Discussion

No evidence of an association between an HLA–DR antigen and leprosy could be found. However, the finding of a higher incidence of HLA–DRW2 in tuberculoid patients than in controls was in accord with the results of de Vries *et al.* (1979).[22] Although not statistically significant with these small numbers, our data is consistent with an association between HLA–DRW2 and tuberculoid leprosy. Furthermore, the similarity of antigen frequencies in the lepromatous patients and in the controls indicates that stratification between the leprosy patients and the controls was unlikely. Differences between our findings and those of de Vries *et al.* (1979)[22] could be explained by differences in patient classification or pressures for linkage disequilibrium. Also genetic differences might be anticipated, as part of an explanation for the high prevalence rate of tuberculoid leprosy among populations studied by de Vries *et al.* (1976,[3] 1979[22]), 10 per 1000 or more, but the low prevalence rate of tuberculoid leprosy among Mexicans (Villarreal, 1979)[27] 0.03 per 1000 – a difference of over two orders of magnitude.

Two studies of HLA–DR antigen frequencies (de Vries *et al.*, 1979,[22] and the present study) and the study by Stoner *et al.* (1978)[21] have provided no evidence of an association between lepromatous leprosy and antigens of the HLA–DR and HLA–D loci. These negative findings do not undo the evidence that susceptibility to lepromatous leprosy is under genetic control, but suggest that the critical gene(s) will not be found in the major histocompatibility complex. That is to say, the controlling gene(s) for lepromatous leprosy will prove to be neither an HLA antigen nor linked to an HLA antigen. Perhaps leprosy in man may be analogous to *Listeria monocytogenes* infection in mice (Skamene *et al.*, 1979),[28] where resistance and susceptibility are under genetic control outside of the H-2 complex, but footpad reactions to *L. monocytogenes* antigens appear to be linked to the H-2 complex.

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