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ORIGINAL ARTICLES

HLA Antigen Profiles in Thai Tuberculosis Patients

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SUMMARY **HLA antigens were studied in 35 Thai patients suffering from active pulmonary tuberculosis. An increase in the frequency of HLA-Bw46 and -DR4 and a decrease in the frequency of HLA-B12 were found when compared with the matched controls. These findings suggest that the pathogenetic role of HLA-B12 is to confer resistance and that HLA-Bw46 and -DR4 are associated with susceptibility. In addition it provided further information on HLA antigen profiles in pulmonary tuberculosis patients in another ethnic group (*viz.* Thais). Conclusions regarding genetic control over therapeutic efficacy must await further study.**

For some time, genetic markers have been recognized as important tools for understanding the pathogenetic mechanisms underlying susceptibility and/or resistance and for indigenous risks that control the course of diseases. In the past, the relationship between polymorphic hereditary factors and diseases had been based on red cell antigens. Then emerged the knowledge of the major histocompatibility complex (MHC) and its immunogenetic roles. Later studies have shifted to research on expressed human leukocyte antigens (HLA).

Recent reports concerning the HLA system and tuberculosis remain limited compared with those on other infections. Previous studies of ethnic populations (not Thais) did not stipulate clear genetic factors controlling the course of *Mycobacterium tuberculosis* infection and consequent disease.[1] One investigation detected an increase of HLA-DR2 and a decrease of DRw6,[2] and another reported a prevalence of HLA-B27.[3] These indications that the HLA system is involved in the pathogenesis of the disease require further studies for substantiation.

The present communication describes results of a preliminary investigation on pulmonary tuber culosis patients aimed at obtaining a base-line for ethnic Thais.

MATERIALS AND METHODS

Investigation on HLA-A, -B and -DR antigens was conducted on 35 Thai patients, ages were between 18-72 years old, suffering from active pulmonary tuberculosis who failed to recuperate from adequate treatment with effective drug regimens. Diagnosis was based on clinical evidence (symptomatic patients with lesions seen in chest radiographs) and bacteriological confirmation (positive sputum direct smear and culture for *M. tuberculosis*) in all cases. Thirty age matched blood donors served as controls.

Peripheral blood lymphocytes were separated by centrifugation over Ficoll-Hypaque. HLA-A, B typing was performed by using a standard complement dependent microlymphocytotoxicity assay.[4] Typing for HLA-DR was carried out by a modified complement dependent microlymphocytotoxicity assay.[5] A set of well defined sera were used, comprising 15 specificities for the A locus, 21 specificities for the B locus including Bw4 and Bw6, and 12 specificities for the DR locus including DRw52 and DRw53. For each specificity a minimum of 2 or

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more sera of well-characterized specificities were used.

For statistical analysis, the Chi-square test (Yates' correction) and Fisher's exact test were used. The Odds ratio (OR) was also calculated.

RESULTS

The results are summarized in Table 1. There was a significant decrease in HLA-B12 ($P = 0.017$) and a significant increase in Bw46 ($P = 0.051$) and DR4 ($P = 0.051$) as compared with the matched controls.

Table 1. Frequency of HLA antigens in 35 Thai patients and 30 age matched healthy controls

HLA type	Patients (n=35) No.	AF	Controls (n=30) No.	AF	*P* value	Odds ratio	Significance
A1	1	0.0286	5	0.1667	0.087	0.15	ns
A2	16	0.4571	12	0.4000	0.832	1.26	ns
A3	1	0.0286	0	0	1.000	1.33	ns
A23	0	0	0	0		–	
A24	10	0.2857	9	0.3000	0.883	0.93	ns
A25	0	0	0	0		–	
A26	5	0.1429	0	0	0.057	11.00	ns
A11	17	0.4857	11	0.3667	0.475	1.63	ns
A28	0	0	2	0.0667	0.209	0.16	ns
A29	0	0	1	0.0333	0.469	0.29	ns
A30	0	0	0	0		–	
A31	0	0	0	0		–	
A32	0	0	0	0		–	
Aw33	12	0.3429	12	0.4000	0.827	0.78	ns
Aw34	0	0	1	0.0333	0.469	0.29	ns
B5	4	0.1143	1	0.0333	0.363	3.74	ns
B7	0	0	3	0.1000	0.093	0.11	ns
B8	0	0	1	0.0333	0.469	0.29	ns
B12	4	0.1143	12	0.4000	0.017	0.19	s*
B13	7	0.2000	3	0.1000	0.320	2.25	ns
B14	0	0	0	0		–	
B15	12	0.3429	12	0.4000	0.827	0.78	ns
B38	0	0	0	0		–	
B39	4	0.1143	1	0.0333	0.363	3.74	ns
B17	5	0.1429	1	0.0333	0.205	4.83	ns
B18	2	0.0571	4	0.1333	0.530	0.39	ns
B21	0	0	0	0		–	
B27	2	0.0571	2	0.0667	1.000	0.85	ns
B35	5	0.1429	0	0	0.057	10.00	ns
B37	0	0	0	0		–	
B40	6	0.1714	7	0.2333	0.756	0.68	ns
Bw22	2	0.0571	3	0.1000	0.857	0.55	ns
Bw54	0	0	0	0		–	
Bw46	10	0.2857	2	0.0667	0.051	5.60	s*
DR1	3	0.0857	0	0	0.243	3.28	ns
DR2	13	0.3714	13	0.4333	0.780	0.77	ns
DR3	4	0.1143	1	0.0333	0.363	3.74	ns
DR4	10	0.2857	2	0.0667	0.051	5.60	s*
DR5	4	0.1143	7	0.2333	0.345	0.42	ns
DRw6	5	0.1429	0	0	0.057	10.00	ns
DR7	8	0.2286	13	0.4333	0.135	0.39	ns
DRw8	0	0	0	0		–	
DRw9	5	0.1429	3	0.1000	0.716	1.50	ns
DRw10	0	0	2	0.0667	0.209	0.16	ns

AF = Antigen Frequency
*Chi–square (Yates' correction), Fisher's exact test

DISCUSSION

Only in recent years, have there been investigations on HLA and tuberculosis. However, the findings are inconclusive and conflicting. Table 2 displays data from relevant reports on various ethnic groups. As is evident, the associated antigen in almost all these studies is variable and does not reach statistical significance when *P* correction is applied [1] for the number of antigens studied. Notwithstanding, one study involving HLA-DR antigens and carried out in a North Indian population showed a marginal increase in HLA-DR2 and a concurrent significant decrease of antigen DRw6 in the pulmonary tuberculosis patient group as compared with controls. It indicated the existence of MHC-related genes controlling the course of *M. tuberculosis* infection, although with a low penetrance. [2] This, together with another more recent report of a significantly increased frequency of the HLA-B27 antigen in Greek patients suffering from pulmonary tuberculosis, suggested a genetic role in the pathogenesis of the disease. [3]

Findings of the present investigation, however, showed a significant decrease in HLA-B12 and marginally significant increases in Bw46 and DR4 when compared with the controls. Hence, in addition to the HLA antigen profiles of Thai tuberculosis patients, the prevalence of HLA-Bw46 and DR4 suggests an immunogenetic association with susceptibility, and the decrease of HLA-B12 with resistance of the host during the course of tuberculous infection.

Since the subjects of our study comprised all active cases in whom medical treatment failed, Is it possible that a comparison of the HLA antigen profiles between patients with therapy-success and patients with therapy-failure would show differences? A definite answer requires matched results between two such treatment-groups.

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Table 2. HLA antigen association in tuberculosis patients of different ethnic groups

Ethnic group	Number tested		HLA association	% Phenotype frequency		
	Patients	Controls		Patients		Controls
European Caucasoid[6]			No			
Japanese[7]	70		No			
Newfoundlander[8]	46	543	B8	56.5		20.2
N. American Black[9]	60	100	B15	20.0		3.0
Russian[10]	18	50	No			
Mexican[11]	100	100	No			
Chinese[12]	101	310	B35	32.7		6.1
North Indian[13]	45	95	B15	35.7		16.9
ref. # 14	124	109	No			
ref. # 15	63	59	B18	29.0		8.0
ref. # 2	63	42	DR2	50.8		38.5
	15	26	DRw6	12.1		23.9
Egyptian[16]	42	156	A2	57.1		35.8
			B5	40.5		21.7
Korean[17]	50	196	A33		$P < 0.05$	
			B8		< 0.05	
			B51		< 0.01	
			B52		< 0.01	
			B54		< 0.05	
			B61		< 0.001	
			B62		< 0.001	
			C1		< 0.05	
			DR1		< 0.001	
			DR3		< 0.001	
			DR5		< 0.01	
			DR9		< 0.001	
Greek[3]	16	27	B27	28.0		7.0
Thai*	35	30	B12	11.4		40.0
			BW46	28.6		6.7
			DR4	29.6		6.7

*Present study

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