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Human Leukocyte Antigen (HLA) in Korean patients with Autoimmune Thyroid Diseases

Kap Bum Huh, M.D., Hyun Chul Lee, M.D., Hyeon Man Kim, M.D., Hye Ree Lee, M.D.
Chein Soo Hong, M.D., Sang Yong Lee, M.D., Heung Jai Choi, M.D.
Kiil Park, M.D.* and Choon Kyu Kim, M.D.*

Department of Internal Medicine, Yonsei University College of Medicine
** Department of Surgery, Yonsei University College of Medicine*

In previous studies, there has been evidence of different allelic associations with a particular disease among various ethnic groups. The present study was done to investigate the associations between HLA and autoimmune thyroid diseases in the Korean.

We found no association between Graves' disease and HLA-B8 or -B35. However, increased frequencies of HLA-A11 and -DRw8, and the decreased frequencies of HLA-A10 and B12 were found in patients with Graves' disease. In the cases of Hashimoto's disease, the frequencies of HLA-A2 and -DRw8 were found to be significantly increased and the frequency of HLA-DRw6y decreased. These data indicate that the association between autoimmune thyroid disease and HLA in the Korean would appear to be different from that in most other racial groups, including Caucasians, Japanese and Chinese.

Key Words: *HLA, Autoimmune thyroid disease*

INTRODUCTION

Since McDevitt and Benacerraf[1] discovered a series of genes that governed immune response, there have been extensive studies. Antigens of the major human histocompatibility locus have been used as markers for hereditary susceptibility in autoimmune disorders, such as systemic lupus erythematosus, chronic active hepatitis and ankylosing spondylitis.[5-8] Although no precise mechanisms for the pathogenesis of Graves' disease and Hashimoto's disease have been established, it is well known that these diseases are closely associated with the autoimmune response.[9] Some racial differences have been revealed in studies on HLA distribution in autoimmune thyroid diseases in Caucasians, Japanese and Chinese.

An attempt was made to further the investigation of racial differences related to the association between both Graves' disease and Hashimoto's disease, and HLAs by studying the association in the Korean.

Address reprint requests: Kap Bum Huh, M.D. Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea

SUBJECTS AND METHODS

1. Subjects and Diagnosis

Ninety-seven patients with Graves' disease, 37 patients with Hashimoto's disease and 100 healthy unrelated Korean subjects were tested for HLA-A, -B and -C antigens to establish normal control values. Also seventy-nine for patients with Graves' disease, 33 patients with Hashimoto's disease and 50 healthy, unrelated Korean subjects were tested for HLA-DR antigens to establish normal control values.

On the basis of classic clinical features, laboratory tests and/or histopathologic findings, the patients were diagnosed as having either Graves' disease or Hashimoto's disease. Serum thyroid hormones (T_3, T_4, FT_4) and thyroid-stimulating hormone were measured by classic radioimmunoassay. Antithyroid antibodies (antibodies to thyroglobulin or thyroid microsome) were detected by the tanned sheep

erythrocyte hemagglutination test using commercial test kits (Fujirebio Inc., Japan). Radioactive iodine uptake studies were done with ^{131}I.

2. Methods

HLA-A, -B, -C and -DR were determined by the microcytotoxicity method described by Terasaki and McClelland[10] and refined by Mittel et al.[11] Antisera were obtained from Dr. Paul Terasaki of the University of California at Los Angeles in the U. S. A.. The HLAs typed were A1, A2, A3, A9, A10, A11, A28, A29, Aw32, B5, B7, B8, B12, B13, B14, B15, B16, B17, B18, B21, B27, B35, B37, B40, Cw1, Cw2, Cw3, Cw4, Cw5, DR1, DR2, DR3, DR4, DR5, DRw6y, DR7, DRw8, DRw9, and DRw10.

Using 2×2 contingency tables, comparisons of the HLA frequencies between patient groups and controls were made. The relative risks were estimated by Woolf's odds ratio.[12] The statistical significance of association was tested by conventional chi-square analysis. Significance was set at the .05 level.

Table 1. Phenotype Frequencies (%) of HLA-A Antigens in Patients with Graves' Disease and Controls

Antigen	Patients (n=97)	Controls (n=100)	P	RR
A1	8.3	4.0	NS*	
A2	52.6	43.0	NS	
A3	2.1	2.0	NS	
A9	42.3	36.0	NS	
A10	10.3	22.0	<.05	0.4
A11	29.9	15.0	<.025	2.4
A28	1.0	1.0	NS	
A29	0.0	0.0	NS	
Aw32	0.0	0.0	NS	

NS*: Not significant

Table 2. Phenotype Frequencies (%) of HLA-B Antigens in Patients with Graves' Disease and Controls

Antigen	Patients (n=97)	Controls (n=100)	P	RR
B5	25.8	25.0	NS*	
B7	5.2	5.0	NS	
B8	1.0	3.0	NS	
B12	4.1	13.0	<.05	0.3
B13	13.4	10.0	NS	
B14	4.1	1.0	NS	
B15	20.6	19.0	NS	
B16	3.1	2.0	NS	
B17	7.2	10.0	NS	
B18	0.0	1.0	NS	
B21	0.0	0.0	NS	
B27	1.0	8.0	NS	
B35	9.0	9.0	NS	
B37	3.0	3.0	NS	
B40	13.4	6.0	NS	

NS*: Not significant

RESULTS

The results of HLA typing in patients with Graves' disease and in the control subjectes are presented in Tables 1, 2, 3 and 4. In these patients, the frequency with which HLA-A11 was found was significantly greater ($p<.025$, relative risk (RR)=2.4), that with which HLA-A10 was found, lower ($p<.05$, RR=.4), that with which HLA-B12 was found, lower ($p<.05$, RR=.3), and that with which HLA-DRw8 was found, greater ($p<.01$, RR=4.0), than those of the controls. The frequencies with which HLA-B8, -B35, -DR3 and -DR5 have been reported

Table 3. Phenotype Frequencies (%) of HLA-C Antigens in Patients with Graves' Disease and Controls

Antigen	Patients (n=97)	Controls (n=100)	P
Cw1	25.8	17.0	NS*
Cw2	2.1	3.0	NS
Cw3	42.3	30.0	NS
Cw4	7.2	15.0	NS
Cw5	1.0	5.0	NS

NS*: Not significant

Table 4. Phenotype Frequencies (%) of HLA-DR Antigens in Patients with Graves' Disease and Controls

Antigen	Patients (n=79)	Controls (n=50)	P	RR
DR1	5.1	12.0	NS*	
DR2	39.2	26.0	NS	
DR3	5.1	2.0	NS	
DR4	22.8	32.0	NS	
DR5	16.5	10.0	NS	
DRw6y	31.6	48.0	NS	
DR7	7.6	6.0	NS	
DRw8	35.4	12.0	<.01	4.0
DRw9	24.1	20.0	NS	
DRw10	0.0	0.0	NS	

NS*: Not significant

to be found in patients with Graves' disease were not different, in our study, compared with those of the controls.

In Tables 5, 6, 7 and 8 are shown the results of HLA typing in patients with Hashimoto's disease and in the control subjects. In these patients, the frequency with which HLA-A2 was found was significantly greater ($p<.05$, RR=2.8), that with which HLA-DRw6y was found, lower ($p<.05$, RR=.3), and that with which HLA-DRw8 was found, greater ($p<.005$, RR=5.4), than those of the controls.

No significant association was found between antithyroid antibodies and HLA-DRw8 in autoimmune thyroid diseases (Table 9, 10).

Table 5. Phenotype Frequencies (%) of HLA-A Antigens in Patients with Hashimoto's Disease and Controls

Antigen	Patients (n=37)	Controls (n=100)	P	RR
A1	0.0	4.0	NS*	
A2	67.6	43.0	<.05	2.8
A3	8.1	2.0	NS	
A9	37.8	36.0	NS	
A10	8.1	22.0	NS	
A11	10.8	15.0	NS	
A28	0.0	1.0	NS	
A29	0.0	0.0	NS	
Aw32	0.0	0.0	NS	

NS*: Not significant

Table 6. Phenotype Frequencies (%) of HLA-B Antigens in Patients with Hashimoto's Disease and Controls

Antigen	Patients (n=37)	Controls (n=100)	P
B5	16.2	25.0	NS*
B7	5.4	5.0	NS
B8	0.0	3.0	NS
B12	2.7	13.0	NS
B13	16.2	10.0	NS
B14	8.1	1.0	NS
B15	18.9	19.0	NS
B16	2.7	2.0	NS
B17	13.5	10.0	NS
B18	0.0	1.0	NS
B21	0.0	0.0	NS
B27	5.4	8.0	NS
B35	10.8	9.0	NS
B37	2.7	3.0	NS
B40	5.4	6.0	NS

NS*: Not significant

DISCUSSION

Since familial tendencies to develop Graves'

Table 7. Phenotype Frequencies (%) of HLA-C Antigens in Patients with Hashimoto's Disease and Controls

Antigen	Patients (n=37)	Controls (n=100)	P
Cw1	16.2	17.0	NS*
Cw2	2.7	3.0	NS
Cw3	40.5	30.0	NS
Cw4	8.1	15.0	NS
Cw5	2.7	5.0	NS

NS*: Not significant

Table 8. Phenotye Frequencies (%) of HLA-DR Antigens in Patients with Hashimoto's Disease and Controls

Antigen	Patients (n=33)	Controls (n=50)	P	RR
DR1	6.1	12.0	NS*	
DR2	30.3	26.0	NS	
DR3	3.0	2.0	NS	
DR4	36.4	32.0	NS	
DR5	3.0	10.0	NS	
DRw6y	24.2	48.0	<.05	0.3
DR7	9.1	6.0	NS	
DRw8	42.4	12.0	<.005	5.4
DRw9	33.3	20.0	NS	
DRw10	0.0	0.0	NS	

NS*: Not significant

Table 9. Association between Antithyroid Antibodies and HLA-DRw8 in Graves' Disease

Antibody	With HLA-DRw8 (n=24)	Without HLA-DRw8 (n=45)	P
Anti-MC Abs(%)	83.3	87.0	NS*
Anti-TG Abs(%)	29.2	30.4	NS

NS*: Not significant

Table 10. Association between Antithyroid Antibodies and HLA-DRw8 in Hashimoto's Disease

Antibody	With HLA-DRw8 (n=22)	Without HLA-DRw8 (n=46)	P
Anti-MC Abs(%)	86.4	89.1	NS*
Anti-TG Abs(%)	31.9	30.4	NS

NS*: Not significant

disease and Hashimoto's disease have been well documented, genetic factors are thought to play an important role in the pathogenesis of these diseases.[13,14] Moreover, the fact that both Graves' disease and Hashimoto's disease commonly occur in the same family strongly suggests that they have a common immunologic basis in their pathogenesis.[13] It is now well known that susceptibility to a certain disease is strongly influenced by genetic information within the major histocompatibility locus in the mouse.

Graves' disease seems to be associated with different HLAs among various ethnic groups. For instance, HLA-B8 was associated with a high risk of Graves' disease in Caucasians ,[14-21] however, in Japanese, HLA-B35 was associated with a high risk of Graves' disease.[5,22,23] As in Japanese, HLA-B8 is not common in Koreans,[24] which suggests the possibility of a racial difference in the HLA system and its association with autoimmune diseases. Chinese patients with Graves' disease were characterized by an association with HLA-Bw46 and by a decreased frequency of HLA-A9.[25] previously no association has been reported between Graves' disease and HLA-A in other racial groups. The increased frequency of HLA-A11 and the decreased frequency of HLA-A10 in Korean patients with Graves' disease probably reflect a racial difference in the genetic role in the pathogenesis of the disease. In this study, there was also a decreased frequency of HLA-B12 in Korean patients with Graves' disease, which was compatible with data reported by Mather et al.[26] and Allanic et al.[27] Farid et al.[28] reported the increased frequency of occurrence of HLA-DR3 in patients with Graves' disease and an increased relative risk of acquiring the disease. Thorsby et al.[18] and Bech et al.[29] have reported that the frequency of occurrence of HLA-Dw3 was increased in Caucasian patients with Graves' disease and that the risk that the disease would be conferred on them by HLA-Dw3 was greater than that it would be conferred on them by HLA-B8, suggesting that the Dw gene is closer to the D than to the B locus. In this way, it is likely that Graves' disease is primarily associated with HLA-DR, and that the increased frequency of occurrence of HLA-A or -B antigens is a phenomenon only secondary to its linkage disequilibrium with HLA-DR. In Korean patients, the frequency of occurrence of HLA-DRw8 was significantly increased and HLA-DR3 only slightly increased without significance, compared with the controls.

Hashimoto's disease is a prototype of organ-specific autoimmune disease.[30] The suggestion that major histocompatibility complex gene products might control the occurrence and the severity of experimental and spontaneous thyroiditis in laboratory animals,[31] has led to the search for possible associations between autoimmune thyroiditis and the HLA system. Sequential analysis of patients with autoimmune thyroiditis from one center[16,32,33] revealed a consistent increased frequency of occurrence of HLA-B8 in patients with Hashimoto's disease, but Van Rood et al.[34] were unable to document this. The discrepancy was resolved when patients with Hashimoto's disease were divided into two groups:[35,36] Goitrous thyroiditis was associated with HLA-DR5 and a slightly decreased frequency of occurrence of HLA-DR3,[37] and on the other hand, atropic thyroiditis was strongly associated with HLA-DR3 and with a slightly decreased frequency of the occurrence of HLA-DR5.[36] There is no report about the association between Hashimoto's disease and HLA-DR in the Japanese. In this study, the antigenic frequencies of occurrence of HLA-A2 and -DRw8 were significantly increased in patients with Hashimoto's disease who were not divided according to its goitrous and atropic forms.

There have been many attempts to investigate the association between antithyroid antibodies and the HLA system. Some investigators[38,39] reported an association of HLA-B8 with antithyroglobulin antibody, but this could not be demonstrated by others.[19,21,33] Several investigators attempted to relate HLA-B8 or -DR3 to the thyroid-stimulating immunoglobulin in Graves' disease without success.[27,40,41] No significant association was observed between antithyroid antibodies and HLA in Korean patients with autoimmune thyroid disease.

In conclusion, our data indicate that HLA-DRw8 is associated with autoimmune thyroid disease in Korean patients, which may serve as an indicator for a particular gene complex influencing immune responsiveness in these patients.

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