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HLA and Graves' Disease in Korean

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= **Abstract** =The HLA-A, -B, -C and -DR antigen distribution in 137 and 128 Korean patients with Graves' disease, respectively, was compared with that in 220 controls. The frequency of HLA-B13, HLA-DR5 and HLA-DRw8 was significatly increased in patients with Graves' disease. The relative risk for Graves' disease in the individuals with these HLA antigens was calculated as 3,8, 4.4 and 2.3, respectively. Thus, genes promoting the development of Graves' disease in Korean are positively associated with the B13, DR5 and DRw8 haplotypes. However there was no significant correlation between the presence of these HLA antigens and the clinical features such as age at onset, sex, weight of goiter, exophthalmos, titer of autoantibodies, initial TBII values, and relapse and remission rates. Consequently, factors influencing the clinical features and the course of Graves' disease do not have a strong association with these HLA antigens.

Key Works: ***HLA, Graves' disease***

INTRODUCTION

Graves' disease is a disorder with immunopathic features, which, as in several other autoimmune human diseases, has been shown to be more common in the individuals with certain HLA antigens. The specific allelic association with Graves' disease varies according to the ethnic groups. The susceptibility of Caucacians to Graves' disease has been reported to be associated with particular HLA antigens such as A1, B8 and DR3 (Grumet *et al.* 1974; Bech *et al.* 1977; Irvine *et al.* 1977; Balazs *et al.* 1978; Allanic *et al.* 1980; Farid *et al.* 1980; Dahlberg *et al.* 1981). Graves' disease in Japanese was also reported to be associated with B35, Dw12, and DR5 (Grumet *et al.* 1975; Sasazuki *et al.* 1978; Uno *et al.* 1981). HLA studies in Chinese patients from Singapore and Hong Kong revealed an association with Bw46 (Chan *et al.* 1978; Hawkins *et al.* 1985) and DR5 (Yeo *et al.* 1983).

In the present study, we evaluated whether Korean patients with Graves' disease have the same higher incidence of either certain HLA antigens as Caucacians, Japanese and Chinese or possibly other HLA antigens and we tried to define if these increased antigens have associations with the factors influencing the clinical expression and the course of the disease.

MATERIALS AND METHODS

Patients and Controls

The patients consisted of 32 males and 105 females undergoing the treatment for Graves' disease in the Thyroid Clinic, Seoul National University Hospital, Seoul, Korea. The patients were all unre-

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lated Korean currently living in Korea. In all cases, diagnosis of Graves' disease was based on clinical examinations, thyroid hormone levels, thyroid scintigraphies with $^{99m}TcO_4$-thyroid uptake (20 min), andresults of thyroid autoantibodies and TSH receptor antibodies tests.

Triiodothyronine, thyroxine, TSH and T_3-resin uptake were measured by radioimmunoassay methods routinely used at the Seoul National University Hospital. The reference ranges for normal control were as follows: T_3 100-200 ng/dl, T_4 6.5-13.8 μg/dl, TSH 1-8 uU/ml, T_3 resin uptake 25-33 %. Thyroid antimicrosomal and antithyroglobulin antibodies were measured by hemagglutination methods (Fujirebio, Japan). Antibody titers above 1/100 were taken as positive. TSH receptor antibodies were measured by radioreceptor assay using commercial kits (R.S.R. Ltd, Cardiff, Wales, U.K.) and were expressed through percent inhibition of ^{125}I-bTSH binding to TSH receptor (thyrotropin binding inhibition IgG, TBII). TBII activities above 15% were taken as abnormal or positive.

The majority of the patients were given antithyroid drugs for more than 12 months. At the time of the study, 54 patients had completed the antithyroid treatment course. For the follow up period of 12 months, 24 patients remained in remission and relapses occured in 30 patients. HLA-A, -B, -C and -DR frequencies were obtained from 220 unrelated healthy Korean individuals.

HLA typing

HLA typing for the A, B, C, and DR antigens was performed by the standard microlymphocytotoxicity test (Terasaki *et al.* 1978) using antisera supplied for the Third Asia-Oceania Histocompatibility Workshop Conference (3rd AOHWC, 1986) in 137 patients and 128 patients with Graves' disease, respectively. For the determination of HLA-DR antigens, B lymphocyte enrichment was performed by the nylon wool column technique (Danilovs *et al.* 1980). The following specificities were included in the study:

HLA-A1, 2, 3, 11, 24, 30, 31, w33
HLA-B7, B8, 13, 27, 35, 38, 39, 44, w46, w47, w48, 51, w52, w53, w54, w55, w56, w58, w60, w61, w62, w63, w67
HLA-Cw1, w2, w3, w4, w5, w6, w7, w8
HLA-DR1, 1, 2, 3, 4, 5, w6, 7, w8

Statistical analysis

Comparisons of HLA antigens frequencies in the patients and the controls were performed using a 2 x 2 contigency analysis (X^2 test). Corrected P-values (cP) were obtained after multiplication by the number of HLA specifieities tested (9 for HLA-A; 24 for -B; 8 for -C and 8 for HLA-DR). Relative risk (RR) values were calculated according to Svejgaard *et al.* (1974). Etiologic fraction (EF) and preventive fraction (PF) were calculated with the following formula:

$$EF = (RR-1) \times \text{antigen frequency}/RR$$

$$PF = \frac{(1-RR) \times \text{antigen frequency}}{RR\ (1\text{-antigen frequency}) + \text{antigen frequency}}$$

RESULTS

The frequencies of HLA-A and -C antigens in patients and controls were not different (data not shown). The frequency and the relative risk (RR) values of HLA-B antigens are shown in Table 1. HLA-B13 antigen was found in 21 of the 137 patients, and the frequency of HLA-B13 in patients with Graves' disease was significantly higher than that in the controls (15.3 % vs 4.5 %, $X^3 = 11.8$, $cP = 0.02$). The calculated RR value for Graves' diseas in the B13 positive individuals was 3.8. The frequencies of HLA-B44 and HLA-Bw61 were found to be significantly decreased in the patients (5.1 % vs 20.5 %, $X^2 = 15.8$, $cP = 0.002$, $RR = 0.2$ for B44 and 5.8 %, vs 17.5 %, $X^2 = 9.9$, $cP = 0.04$, $RR = 0.3$ for Bw61). The calculated preventive fractions of HLA-B44 and HLA-Bw61 were 0.16 and 0.12, respectively.

The frequency of HLA-DR antigens in the patients and the controls is shown in Table 2. HLA-DR5 was found in 17.2 % of the patients compared with 4.5 % in the controls,and the difference was statistically significant ($X^2 = 1.5$., $cP = 0.007$). The calculated RR value for Graves' disease in the DR5 positive individuals was 4.4. An increased frequency of HLA-DRw8 was also observed in the patients (29.7 % vs 15.5 %, $X^2 = 10.0$, $cP = 0.02$, $RR = 2.3$). However the calculated etiologic fractions of HLA-DR5 and HLA-DRw8 were 0.13 and 0.17, respectively. Only 4 (0.035) out of 116 patients with Graves' disease had both HLA-B13 and -DR5 antigens. The theoretical frequency of B13/DR5 was 0.026 (0.153 x 0.172), thus the delta value was 0.009. However, the diference was not statistically significant ($p > 0.1$).

There was no evidence of association between the frequency of HLA-B13 or HLA-DR5 and the clinical features such as age at onset, sex, family history, weight of goiter, ophthalmopathy, titer of

Table 1. HLA-B antigen frequencies in Korean patients with Graves' disease and controls.

HLA	Antigen frequencies (%)		RR	EF (PF)	X^2	P	CP
	Patients n=137	Controls n=220					
B7	3.6	9.0	0.4	(0.06)	3.66	0.66	NS
B8	1.5	0.5	3.0	0.01	0.85	0.36	NS
B13	15.3	4.5	3.8	0.11	11.76	0.0006	0.02
B27	2.9	4.0	0.7	(0.01)	0.28	0.60	NS
B35	15.3	16.0	1.0	0.01	0.03	0.87	NS
B38	5.8	2.0	3.0	0.04	3.49	0.06	NS
B39	4.4	1.5	3.0	0.03	2.59	0.11	NS
B44	5.1	20.5	0.2	(0.16)	15.77	0.0001	0.002
Bw46	8.0	4.0	2.1	0.04	2.48	0.12	NS
Bw47	0.7	0.0	4.4	0.01	1.46	0.23	NS
Bw48	2.2	0.5	4.5	0.02	2.00	0.16	NS
B51	19.0	16.5	1.2	0.03	0.35	0.56	NS
Bw52	2.2	5.5	0.4	(0.03)	2.24	0.13	NS
Bw53	0.7	0.5	1.5	0.00	0.07	0.79	NS
Bw54	16.8	11.0	1.6	0.07	2.35	0.13	NS
Bw55	2.2	5.5	0.4	(0.03)	2.24	0.13	NS
Bw56	0.7	0.0	4.4	0.01	1.46	0.23	NS
Bw58	1.5	3.5	0.4	(0.02)	1.30	0.25	NS
Bw59	5.1	2.0	2.6	0.03	2.49	0.11	NS
Bw60	9.5	13.0	0.7	(0.04)	0.98	0.32	NS
Bw61	5.8	17.5	0.3	(0.12)	9.93	0.002	0.04
Bw62	24.8	16.5	1.7	0.10	3.53	0.06	NS
Bw63	0.7	0.0	4.4	0.01	1.46	0.23	NS
Bw67	1.5	1.0	1.5	0.40	0.15	0.70	NS

RR: Relative risk, EF: Etiologic fraction, PF: Preventive fraction (if RR < 1)
CP: Corrected P value (P x No. of tested antigen), NS: Not significant.

Table 2. HLA-DR antigen frequencies in Korean patients with Graves' disease and controls.

HLA	Antigen frequencies (%)		RR	EF (PF)	X^2	P	CP
	Patients n=128	Controls n=220					
DR1	4.7	8.2	0.6	(0.04)	1.54	0.21	NS
DR2	33.6	34.6	1.0	0.01	0.03	0.86	NS
DR3	9.4	2.7	3.7	0.07	7.29	0.007	NS
DR4	36.7	37.7	1.0	0.02	0.04	0.85	NS
DR5	17.2	4.5	4.4	0.13	15.49	0.00008	0.007
DRw6	9.4	20.5	0.4	0.12	7.25	0.007	NS
DR7	2.3	3.6	0.6	0.01	0.44	0.50	NS
DRw8	29.7	15.5	2.3	0.17	9.99	0.002	0.02

RR: Relative risk, EF: Etiologic fraction, PF: Preventive fraction (if RR < 1)
CP: Corrected P value (P x No. of tested antigen), NS: Not significant.

autoantibodies, initial TBII values, and remission and relapse rates. As shown in Table 3, DR5 antigen was present in 5 (16.7 %) of 30 patients who relapsed and 6 (25 %) of 24 patients who remained in remission. The frequency of DR5 antigen was not significantly different between the pa

Table 3. Distribution of HLA-DR5 with respect to remission and relapse in patients with Graves' disease

HLA-DR5	Remission group		Relapse group	
	No.	%	No.	%
Positive	6	25	5	16.7
Negative	18	75	25	83.3
Total	24		30	

tients with relapse and those with remission.

DISCUSSION

The present study of Korean patients with Graves' disease revealed a significant increase in the frequency of HLA-B13, -DR5, and -DRw8. This results was different from those of the studies on other ethnic groups - Caucacians, Japanese and Chinese. We did not find any positive A1 association with Graves' disease in Koreans. It is similar to the other reports on Japanese (Grumet *et al.* 1975; Sasazuki *et al* 1978; Uno *et al.* 1981) and Chinese patients from Singapore (Chan *et al.* 1978). The absence of the positive A1 association in the Korean population may be the result of a rare incidence of HLA-A1 in Mongoloid population including Korean (Farid and Bear 1981). We observed that the frequency of HLA-A1 was very low in the patients (0.7 %) as well as in the controls (3.5 %).

In the present study, the frequency of HLA-B13 was significantly increased in Koreans with Graves' disease in contrast to the positive associations with B8 in the Caucacian patients (Grumet *et al.* 1974; Bech *et al.* 1977; Irvine *et al* 1977; Balaze *et al.* 1978), B35 in the Japanese (Grumet *et al.* 1975; Nakao *et al.* 1978), and Bw46 in the Chinese (Chan *et al.* 1978). The calculated RR for Graves' disease in the B13 positive patients was 3.8 ($cP = 0.02$). On the other hand, the frequencies of HLA-B44 and -Bw61 were significantly decreased in the Korean patients in contrst to the negative associations with Bw52 in the Japanese (Kawa *et al.* 1979) and B15 in the Chinese patients (Chan *et al.* 1978). However the calculated preventive fractions for Graves' disease in the patients with these HLA antigens were very low (0.16 and 0.12, respectively).

We found positive associations with HLA-DR5 and DRw8 in Korean patients with Graves' disease. The RR values for DR5 and DRw8 were 4.4 and 2.3, respectively. However the calculated etiologic fractions for Graves' disease in the patients with these antigens were low (0.13 for DR5, 0.17 for DRw8). This was probably due to the relatively low frequencies of these antigens in the controls (4.5 % for DR5, 15.5 % for DRw8). Huh *et al.* (1986) reported that the frequencies of HLA-All and -DRw8 were increased in the Korean patients with Graves' disease. The reason for the discrepancies between the results is not known, but could be due to a different number of individuals studied and different method of statistical analysis. In Japanese patients with Graves' disease, Sasazuki *et al.* (1978) reported the possitive association with Dw12, one of the split product of DR5, and Uno *et al.* (1981) reported the positive DR5 association. The frequency of DRw8 was increased in Japanese patients (36.7 % vs 16.3 % $X^2 = 5.8$, RR = 3.1), although statistically insingificant (Uno *et al.* 1981). The results from this study and other investigations suggest that the genetic susceptibility to Graves' disease is similar to a certain extent and that association of the disease susceptibility gene for Graves' disease arise as a result of a cross-over from a DR3 haplotype to DR5 haplotype in the Korean and Japanese populations.

We did not find any significant correlation between the HLA types (B13, DR5) and the clinical expressions such as age at onset, sex, family history, weight of goiter, ophthalmopathy, titer of autoantibodies, initial TBII values. Although Irvine *et al* (1977) reported higher B8 and McGregor *et al.* (1980) reported higher DR3 frequencies in the partients with relapse, we have not found any correlation between relapse-remission and HLA. Our results are consonant with the reports of Allannic *et al* (1983), who did not find any significant differences of HLA type (B8 or DR3) between relapse and remission groups. Therefore, factors influencing the clinical features and the course of Graves' disease do not have a strong association with these HLA antigens.

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= 국문초록 =

한국인에서 Graves병과 HLA

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한국인 Graves병 환자에서 HLA-A, -B, -C항원(137명)과 -DR항원(128명)의 분포를 정상 대조군 220명과 비교하였다. Graves병 환자에서 HLA-B13, HLA-DR5 및 HLA-DRw8의 빈도가 유의하게 증가되어 있었으며, 동 항원을 가진 사람에서의 Graves병에 대한 relative risk는 각각 3.8, 4.4 및 2.3이었다. 따라서 한국인에서 Graves병 발생에 관여하는 유전자는 HLA-B13, DR5 및 DRw8 haplotype과 연관이 있었다. 그러나 이러한 HLA항원의 존재와 발병시기, 성별, 갑상선종의 크기, 안구 돌출증, 자가항체의 역가, TSH 수용체 항체의 역가 및 예후 등의 임상상과 사이에 유의한 상관 관계가 없었다. 결국 Graves병의 임상상 및 그 경과에 영향을 주는 요인들은 HLA항원과 밀접한 관계에 있지는 않았다.