

The HLA allele marker for differentiating ASA hypersensitivity phenotypes

H.-Y. Lee, J.-W. Lee, K.-W. Lee, M.-H. Park, H.-S. Park*

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ASA (aspirin) hypersensitivity occurs in approximately 2–23% of asthmatic patients and 21–30% of chronic urticaria patients (1). The clinical manifestations of ASA hypersensitivity can affect two major target organs, the skin called as

HLA-DPB1*0301 and DRB1*1302-DQB1*0609 HLA alleles are useful for differentiating the AIA and AIU, respectively.

ASA intolerant urticaria (AIU), and the respiratory tract called as ASA intolerant asthma (AIA), though these rarely occur in combination (1). Previous studies have reported that HLA DPB1*0301 may be a HLA allele marker for AIA compared to ASA tolerant asthma group (2) and HLA DRB1*1302-DQB1*0609 may be a marker for AIU compared to controls (3). In this study, in order to evaluate whether HLA alleles can be used as genetic markers for differentiating the two major ASA hypersensitivity phenotypes, we analyzed three HLA alleles, namely, HLA-DPB1*0301, DRB1*1302 and DQB1*0609 by high-resolution genotyping in a larger cohort based on the homogenous Korean population.

The study included 184 AIA patients (female: 62.5%; mean aged 42.7 ± 13.5) and 364 AIU patients (female: 53.8%; mean aged 36.2 ± 12.1). Their ASA hypersensitivities were confirmed by lysine ASA bronchoprovocation test

for AIA and oral ASA challenge test for AIU, as previously described (3), patients with AIA and AIU were excluded. AIU patients were divided into two subgroups, namely, ASA intolerant acute urticaria (AIAU) and ASA intolerant chronic urticaria (AICU). The healthy controls were consisted of 207 unrelated parents from 107 Korean families.

HLA-DRB1*1302, DQB1*0609 and DPB1*0301 types were obtained using amplified gene products with the use of locus-specific primers by direct DNA sequencing. HLA associations were analyzed by Fisher's exact test, odds ratio estimation and confidence intervals with the conditional maximum likelihood estimation, and it was examined by R 2.7.1. Relations between clinical characteristics and HLA alleles were examined by *T*-test and Fisher's exact test (SPSS 12.0.1; Chicago, IL, USA).

The frequencies of HLA-DPB1*0301 (23.4%) in AIA patients was significantly higher than in healthy control (5.3%, $P < 0.00001$, OR = 5.4, 95% CI: 2.6–12.1) and in AIU patients (6.9%, $P < 0.00001$, OR = 4.1, 95% CI: 2.4–7.3, Table 1). The frequency of HLA-DRB1*1302-DQB1*0609 (11.0%) in AIU patients was significantly higher than in healthy control (4.3%, $P = 0.00763$, OR = 2.7, 95% CI: 1.3–6.5, Table 1), but no significant differences between AIAU and AICU groups.

AIA patients carrying HLA-DPB1*0301 had a significantly higher prevalence of rhinosinusitis (77.8% vs 53.7%, $P = 0.012$), and showed more severe fall of FEV1 after lysine ASA inhalation (26.0 ± 12.8 vs 21.4 ± 8.9 , $P = 0.036$) indicating a more severe bronchial responses to ASA/NSAID

Table 1. Distribution of HLA alleles including HLA- DPB1*0301 and DRB1*1302-DQB1*0609

HLA alleles	AIA (<i>n</i> = 184)	AIU (<i>n</i> = 364)	NC (<i>n</i> = 207)
DPB1*0301†‡	43 (23.4%)	25 (6.9%)	11 (5.3%)
DRB1*1302-DQB1*0609*	15 (8.2%)	40 (11.0%)	9 (4.3%)

† $P < 0.05$ vs healthy control; ‡ $P < 0.05$ vs AIU.

Table 2. Clinical characteristics according to the presence of HLA-DPB1*0301 in 184 AIA patients

In AIA	HLA-DPB1*0301		<i>P</i> -value
	+/+ or +/- (<i>n</i> = 43)	-/- (<i>n</i> = 141)	
Sex (female)	35 (81.4%)	80 (56.7%)	0.004
Age (years)	42.4 ± 13.0	42.8 ± 13.6	0.879
Atopy (positive)	20 (50.0%)	64 (48.1%)	0.859
Rhinosinusitis (positive)	28 (77.8%)	65 (53.7%)	0.012
Asthma duration (years)	5.9 ± 5.6	6.8 ± 6.3	0.443
FEV1% predicted	84.5 ± 25.0	81.3 ± 21.2	0.428
%Fall of FEV1	26.0 ± 12.8	21.4 ± 8.9	0.036
PC20 methacholine (mg/ml)	4.6 ± 6.9	3.9 ± 7.5	0.669
Serum total IgE (IU/ml)	357.0 ± 535.8	314.0 ± 369.1	0.601

P-value was applied by *T*-test and Fisher's exact test.

exposure and the typical clinical characteristics of AIA phenotype, as has been suggested by previous studies (4, Table 2). AIU patients carrying HLA-DRB1*1302-DQB1*0609 were significantly higher atopy rate and mean serum total IgE level with younger age than AIA patients carrying other HLA alleles ($P < 0.05$, respectively, data not shown), indicating that the subjects with this HLA allele may develop AIU 10 years earlier which will be increased further in the presence of an atopic status, because atopy is a predisposing factor of AICU patients (5).

Although the pathogenic mechanisms of AIA and AIU are not been fully understood, some evidences suggests that they involve immunologic mechanisms, individually (1, 6). Therefore, further investigations are needed to elucidate the mechanisms involved, and to determine how these two HLA alleles could independently induce these two phenotypes. It is known that oral or bronchoprovocation tests should be done in order to confirm ASA hypersensitivity, but both tests are time consuming and sometimes risky as some subjects present very severe reactions.

Therefore, it is essential to develop immunologic or molecular diagnostic markers to identify the common phenotypes of ASA hypersensitivity. Based on the above findings, we suggest that two HLA allele markers, namely, HLA-DPB1*0301 for AIA and DRB1*1302-DQB1*0609 for AIU, can be used for differentiating two major phenotypes of ASA hypersensitivity.

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*Department of Allergy and Rheumatology
Ajou University School of Medicine, Ajou University, Suwon, Korea
San 5, Wonchun-dong, Yeongtong-gu, Suwon Korea 443-721
Tel.: 82-31-219-5196
Fax: 82-31-219-5154
E-mail: hspark@ajou.ac.kr

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