**INTRODUCTION**

Allergic rhinitis (AR) is an immunologic nasal response, primarily mediated by immunoglobulin E (IgE). It is considered as a heterogeneous state, determined by genetic and environmental interactions. Previous studies have shown the relationships between allergies and polymorphisms in many candidate genes such as IgE, transporters associated with antigen processing (TAP), T cell receptors, and cytokines and their receptors (1-5).

The inhalent antigens are presented to CD4+ T cell by MHC class II in AR (6). However, it was suggested that exogenous antigens can be channeled into the endogenous pathway (MHC class I) by TAP molecules (7). Therefore, it would be very interesting to determine the other possible antigenic presentation pathway, mediated by TAP in AR.

**TAP1 and TAP2 Gene Polymorphisms in Korean Patients with Allergic Rhinitis**

Antigen peptides are actively transported across the endoplasmic reticulum by the transporters associated with antigen presentation (TAP). TAP genes polymorphism could influence the selection process that determines which antigen peptides play a role in the pathogenesis of allergic rhinitis. The aim of this study was to investigate the association of TAP genes polymorphism with allergic rhinitis. TAP1 and TAP2 genotyping were performed on 110 allergic rhinitis patients and 107 healthy controls. TAP1 polymorphic residues at codons 333 and 637, and TAP2 polymorphic residues at codons 379, 565, 651, and 665 were analyzed by the amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). Analysis of TAP1 gene polymorphism demonstrated decreased frequencies of Ile/Val genotype at codon 333, Asp/Gly genotype at codon 637, and haplotype A and B in allergic rhinitis patients when compared to controls (p<0.05). However, there was no significant difference in the genotype, phenotype, or allele frequencies at four TAP2 codons between controls and allergic rhinitis patients. In conclusion, TAP1 gene polymorphism may be an important factor contributing to the genetic susceptibility in the development of allergic rhinitis in the Korean population.

**MATERIALS AND METHODS**

**Subjects**

One hundred and ten consecutive and unrelated patients...
with AR were included in this study. They consisted of 40 females and 70 males, ranging in age from 5 to 72 yr old (mean, 24.1 yr). All patients had nasal symptoms such as watery rhinorrhea, sneezing, itching and/or nasal obstruction, and positive skin prick tests (Allergopharma®, Hamburg, Germany) for one or more inhalant allergens including house dust mites. There was no co-morbid condition such as allergic asthma or atopic dermatitis. The control group consisted of 107 healthy subjects with no personal or family history of allergic diseases, cancers or genetic diseases. There were 40 females and 67 males ranging from 7-65 yr old (mean, 26.2 yr). All control subjects were negative for all nasal symptoms and skin prick tests. Prior to the experiment, informed consents were obtained from all patients and controls.

DNA extraction

Heparinized peripheral venous blood (about 10 mL) was drawn from each individual and stored at -70 °C before being used in the experiment. Genomic DNA was extracted from leukocytes in the collected blood with the Wizard™ Genomic DNA purification kit (Promega, Madison, WI, U.S.A.).

ARMS-PCR

Polymorphic residues at codons 333 and 637 in TAP1, and codons 379, 565, 651 and 665 in TAP2 were analyzed. The dimorphic sites were: TAP1<sup>333</sup> (A→G, Ile→Val, exon 4), TAP1<sup>637</sup> (A→G, Asp→Cys) and TAP2<sup>637</sup> (A→G, Thr→Ala) (13). TAP1 and TAP2 polymorphism analyses were performed by the amplification refractory mutation system-polymerase chain reaction (ARMS-PCR), described by Newton et al. (14). Four primers were used for each dimorphic site (Table 1). Two of these were complementary to one of the dimorphic sites, while the other two allele-nonspecific primers were used as an internal control. The TAP1<sup>333</sup>, TAP1<sup>637</sup>, TAP2<sup>565</sup> and TAP2<sup>650</sup> primers were designed as described by Powis et al. (15). The TAP2<sup>531</sup> primers were designed as described by Jackson et al. (16).

Genomic DNA samples (1 µL) were amplified in a 20 µL reaction mixture containing 1 µL each of all four oligonucleotide primers, 2 µL dNTPs mix (Cat. No. BIO-39029, London, U.K.), 1 µL DNA template, and 13 µL of distilled water. A thermal cycler (GeneAmp PCR system 2400, Perkin Elmer, MA, U.S.A.) was used with the following specifications: 94 °C for 6 min; 35 cycles of 94 °C for 1 min, 62 °C for 1 min and 72 °C for 1 min; there was a final 72 °C incubation for 7 min. The reaction products were separated on a 2% agarose gel stained with ethidium bromide.

Determination of genotypes and haplotypes

Genotyping of the TAP1<sup>333</sup> was done as follows: Ile/Val if 241, 351 and 533 bp bands were visible, Ile/Ile if 241 and 533 bp bands were visible, and Val/Val if 351 and 533 bp bands were visible (Fig. 1). Genotyping of the TAP1<sup>637</sup> was

| Codon | Oligonucleotide primers used for ARMS-PCR TAP1 and TAP2 typing |
|-------|--------------------------------------------------------------|
| TAP1<sup>333</sup> | CCCTGGACCTGAGATTTCGAGACCTCCTGAG | 5′ flanking | Control: 533 |
| TAP1<sup>637</sup> | CATCTCCAGAATCTCTCCTATCACTGTA | 5′ flanking | Control: 429 |
| TAP2<sup>565</sup> | TTGGGAGGCTGACAGCCGTCGAGTATGG | 5′ flanking | Control: 427 |
| TAP2<sup>533</sup> | CTTCACAGATGAACTCAGTCAGCAGA | 5′ flanking | Control: 400 |
| TAP2<sup>565</sup> | GAGACCTGGAACGCCCGCTTGGTACCTGGCG | 5′ flanking | Control: 408 |

ARMS-PCR, amplification refractory mutation system-polymerase chain reaction.
done as follows: Asp/Gly if 180, 307 and 429 bp bands were visible, Asp/Asp if 307 and 429 bp bands were visible, and Gly/Gly if 180 and 429 bp bands were visible. The TAP2 genotypes were also classified using the same methods.

Four possible TAP1 haplotypes (A-D) were determined by a combination of the dimorphic sites at codons 333 and 637. Eight possible TAP2 haplotypes (A-H) were determined by combination of four dimorphic sites at codons 379, 565, 651 and 665. We used TAP1 and TAP2 haplotype nomenclature as proposed by Powis et al. (15) and Jackson et al. (16) (Table 2).

**Statistical analysis**

All statistical analyses were performed with SPSS 10.0 (Chicago, Ill., U.S.A.). A chi-square test was used to compare the distribution of TAP1 and TAP2 genotypes between control and AR groups. Odds ratios (OR) with a 95% confidence interval (CI) were calculated using the Mantel-Haenzel chi-square test. Differences were significant if \( p < 0.05 \).

**RESULTS**

**TAP1 polymorphisms and allergic rhinitis**

Three TAP1 genotypes (Ile/Ile, Ile/Val and Val/Val) were found at codon 333 (Table 3). The Ile/Val genotype was significantly decreased in the AR group when compared to Ile/Ile (OR=0.32, 95% CI=0.17-0.60, \( p = 0.001 \)). The Val phenotype was significantly decreased in the AR group when compared to the Ile phenotype (OR=0.52, 95% CI=0.30-0.92, \( p = 0.016 \)). The Val allele was also significantly decreased in AR patients when compared to the Ile allele (OR=0.48, 95% CI=0.28-0.81, \( p = 0.003 \)).

Three TAP1 genotypes (Asp/Asp, Asp/Gly and Gly/Gly) were seen at codon 637 (Table 3). The Asp/Gly genotype was significantly decreased in the AR group when compared to Asp/Asp (OR=0.43, 95% CI=0.24-0.80, \( p = 0.011 \)). In AR patients, the Gly allele was significantly decreased when compared to the Asp (OR=0.62, 95% CI=0.38-1.01, \( p = 0.04 \)). However, there was no difference between the two TAP1 637 phenotypes, Asp and Gly.

Four possible TAP1 haplotypes (A-D) were found in this study (Table 4). The C and D haplotypes were significantly less than A in the AR group (phenotype, \( p = 0.006 \); allele, \( p = 0.0002 \)). By combining the four haplotypes, the following seven genotypes were found: AA, AB, AC, AD, BC, BD, and DD. The AB (OR=0.31), AC (OR=0.08), and AD (OR=0.13) genotypes were significantly decreased in the AR group when compared with the AA genotype.

**TAP2 polymorphisms and allergic rhinitis**

There was no significant difference in the genotype, phenotype, and allele frequencies of TAP2 at codons 379, 565, 651 and 665 between the AR and control groups (Table 5). The previously reported seven TAP2 haplotypes (A, B, C, D, E, F, and G) were observed; however haplotype H (Ile\(^{379}\)-Thr\(^{565}\)-Arg\(^{651}\)-Ala\(^{665}\), reported by Tacheuchi et al. (17) was not found in this study. A new haplotype (Val\(^{379}\)-Thr\(^{565}\)-Arg\(^{651}\)-Ala\(^{665}\)) was observed in one person (controls), and we named it as haplotype I (Table 2). By combining the eight TAP2 haplotypes, 18 genotypes could be possible from AA to FG. However, their distributions were not different between the AR and control group (Table 6).

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**Table 2. Nomenclature of TAP1 and TAP2 haplotypes**

| TAP1 | 333 | 637 |
|------|-----|-----|
|      | ATC | GTC | GAC | GGC |
| A    | Ile | Asp |     |     |
| B    | Val |     | Gly |     |
| C    | Val |     | Asp |     |
| D    | Ile |     | Gly |     |

| TAP2 | 379 | 565 | 651 | 665 |
|------|-----|-----|-----|-----|
|      | GTA | ATA | GTA | ATA | GTA | ATA | GTA | ATA |
| A    | Val | Ala | Arg | Thr |     |     |     |     |
| B    | Val | Ala | Arg | Thr |     |     |     |     |
| C    | Ile | Ala | Arg | Thr |     |     |     |     |
| D    | Ile | Thr | Arg | Thr |     |     |     |     |
| E    | Val | Thr | Arg | Thr | Cys | Thr |     |     |
| F    | Val | Ala |     |     |     |     |     |     |
| G    | Ile | Ala | Arg | Ala |     |     |     |     |
| H    | Ile | Thr | Arg | Ala |     |     |     |     |
| I    | Val | Thr | Arg | Ala |     |     |     |     |
**DISCUSSION**

It is well known that the major histocompatibility complex (MHC) class I and II have fundamentally different antigen processing pathways. The exogenous antigens such as bacteria are degraded into antigenic peptides within the lysosomes. Upon fusion with endosomes, these peptides may bind MHC II molecules (18). Finally, peptide-loaded MHC class II molecules are delivered to the cell surface, and presented to CD4+ helper T cells. However, the endogenous antigens such as virus and tumor antigens are degraded within the proteasomes and actively transported across the endoplasmic reticulum membrane by TAP (8, 9). These peptides are then assembled with the MHC class I heavy chain and β2-microglobulin. This complex is expressed on the cell surface, where it is recognized by CD8+ T cells. Suto et al. (7) suggested, however, that exogenous antigens can be channeled into the endogenous pathway where antigen presentation is mediated by MHC class I molecules. Therefore, TAP might participate in both endogenous and exogenous antigen processing.

Because AR is a disease caused by inhalant exogenous antigens such as pollens and house dust mites, the preferential pathway of antigen processing is known to be MHC class II. However, it would be possible that inhalant antigenic peptides can be routed into the MHC class I (endogenous) path-

| TAP1 Genotype | Controls (n=107) (%) | Allergic rhinitis (n=110) (%) | Odds ratio | CI* | p value |
|--------------|----------------------|-------------------------------|------------|----|---------|
| TAP1<sup>333</sup> Ile/Ile | 54 50.5 | 82 74.5 | 0.32 | 0.17-0.60 | 0.001 |
| Ile/Val | 53 49.5 | 26 23.7 | 0.43 | 0.24-0.80 | 0.011 |
| Val/Val | 2 1.9 | 4 3.7 | 1.45 | 0.22-1.15 | 0.003 |
| TAP1<sup>637</sup> Asp/Asp | 55 51.4 | 76 69 | 0.52 | 0.30-0.92 | 0.094 |
| Asp/Gly | 50 46.7 | 30 27.3 | 0.65 | 0.38-1.11 | 0.006 |
| Gly/Gly | 2 1.9 | 4 3.7 | 1.63 | 0.16-4.98 | 0.0002 |

| TAP1 Phenotype | Controls (n=107) (%) | Allergic rhinitis (n=110) (%) | Odds ratio | CI* | p value |
|----------------|----------------------|-------------------------------|------------|----|---------|
| TAP1<sup>333</sup> Ile | 161 75.2 | 190 86.4 | 0.31 | 0.14-0.66 | 0.04 |
| Val | 53 49.5 | 28 25.5 | 0.52 | 0.30-0.92 | 0.006 |
| TAP1<sup>637</sup> Asp | 105 98.1 | 106 96.4 | 0.48 | 0.28-0.81 | 0.001 |
| Gly | 52 48.6 | 34 30.9 | 0.65 | 0.38-1.11 | 0.004 |

| TAP1 Allele | Controls (2n=214) (%) | Allergic rhinitis (2n=220) (%) | Odds ratio | CI* | p value |
|-------------|----------------------|-------------------------------|------------|----|---------|
| TAP1<sup>333</sup> Ile | 161 75.2 | 190 86.4 | 0.31 | 0.14-0.66 | 0.04 |
| Val | 53 49.5 | 28 25.5 | 0.52 | 0.30-0.92 | 0.006 |
| TAP1<sup>637</sup> Asp | 105 98.1 | 106 96.4 | 0.48 | 0.28-0.81 | 0.001 |
| Gly | 52 48.6 | 34 30.9 | 0.65 | 0.38-1.11 | 0.004 |

*, 95% confidence interval.
way, involving TAP molecules in AR (2). The genes encoding the two TAP subunits (TAP1 and TAP2) are located within the MHC class II region between the DPB1 and DQB1 loci (8, 9). Two TAP1 dimorphic sites (Ile/Val-333 and Asp/Gly-637) and five TAP2 dimorphic sites (Val/Ile-379, Ala/Thr-565, Arg/Cys-651, Thr/Ala-665 and Stop/Gln-687) have been widely investigated. It is possible that these genetic variations may modify the TAP molecular structures, influencing antigen peptide selection.

TAP gene polymorphisms have been investigated in several MHC-associated diseases (multiple sclerosis, Grave’s disease, and insulin-dependent diabetes mellitus), mostly in Caucasian patients (19–21). Until now, there have been few studies on AR in an Asian population. Ismail et al. (2) provided evidence of a strong association between TAP1 polymorphism and atopy in a Tunisian population. Tacheuchi et al. (12) reported no association between TAP1 gene polymorphism and AR in a Japanese population. Therefore, we believe that it is one of the controversial issues in the pathogenetic mechanism of the AR. In this study, we demonstrated a strong association between AR and TAP1 polymorphism, but not TAP2. In the AR group, Ile/Val at TAP1^333, Asp/Gly at TAPI^637, and TAP1 haplotypes C and D were significantly decreased when compared to controls. These results are different from those of previous studies. To find any causes of such discrepancy, we compared the results of controls in different ethnics. In our study, a decreased TAP1 haplotype A frequency and increased haplotype C and D frequencies were observed when compared to the Tunisian (2) and Japanese (12) controls. TAP1 haplotype D also deserves to be mentioned. In control groups, TAP1 haplotype D was found in 5% of Tunisians (2), 7.3% of Japanese (12). However, in our study, TAP1 haplotype D was found in 11.7% of controls. There might be the various spectrums of genetic pools among different ethnic groups, and therefore, it may be not meaningful to simply compare the results of genetic polymorphisms that have been done in different ethnic groups. Other possible reasons for such discrepancies might be due to multiple factors such as different phenotypic characteristics, heterogeneity within groups of patients and controls, and different genotyping methods.

In this study, we also analyzed the relationships between TAP1 gene polymorphisms and the results of allergy tests such as total serum IgE, and the strength and the multiplic-

Table 5. TAP2 polymorphisms in allergic rhinitis patients and controls

| TAP2 | Controls (n=110) (%) | Allergic rhinitis (n=107) (%) | Odds ratio | CI* | p value |
|------|----------------------|--------------------------------|------------|-----|---------|
| Genotype | | | | | |
| TAP2^379 | Val/Val 84 (76.5) | 81 (76.3) | 1.37 | 0.69-2.70 | 0.373 |
| | Val/Ile 22 (20.6) | 29 (28.4) | | | |
| | Ile/Ile 1 (0.9) | 0 (0) | | | |
| TAP2^636 | Ala/Ala 89 (83.2) | 95 (88.3) | 0.8 | 0.35-1.74 | 0.513 |
| | Ala/Thr 18 (16.8) | 15 (13.6) | | | |
| | Thr/Thr 0 (0) | 0 (0) | | | |
| TAP2^651 | Arg/Arg 83 (77.6) | 81 (73.6) | 1.25 | 0.63-2.46 | 0.789 |
| | Arg/Cys 23 (21.5) | 28 (25.5) | | | |
| | Cys/Cys 1 (0.9) | 1 (0.9) | 1.02 | 0.00-3.82 | 0.548 |
| TAP2^665 | Thr/Thr 39 (36.4) | 41 (37.3) | | | |
| | Thr/Ala 51 (47.7) | 57 (51.8) | 1.06 | 0.57-1.98 | 0.67 |
| | Ala/Ala 17 (15.9) | 12 (10.9) | | | |

| Phenotype | (n=107) (%) | (n=110) (%) | | | |
| TAP2^379 | Val 106 (99.1) | 110 (100) | | | 0.53 |
| | Ile 23 (21.5) | 29 (26.4) | 1.22 | 0.63-2.33 | 0.69 |
| TAP2^636 | Ala 107 (100) | 110 (100) | 1.23 | 0.56-2.74 | 0.60 |
| | Thr 18 (16.8) | 15 (13.6) | | | |
| TAP2^651 | Arg 106 (99.1) | 109 (99.1) | 1.18 | 0.62-2.24 | 0.75 |
| | Cys 24 (22.4) | 29 (26.4) | | | |
| TAP2^665 | Thr 90 (84.1) | 98 (89.1) | | | |
| | Ala 68 (63.6) | 69 (62.7) | 0.93 | 0.59-1.48 | 0.93 |

| Allele | (2n=214) (%) | (2n=220) (%) | | | |
| TAP2^379 | Val 190 (88.8) | 191 (86.8) | | | 0.53 |
| | Ile 24 (11.2) | 29 (13.2) | 1.2 | 0.65-2.22 | 0.53 |
| TAP2^636 | Ala 196 (91.6) | 205 (93.2) | | | |
| | Thr 18 (8.4) | 15 (6.8) | 0.8 | 0.37-1.17 | 0.54 |
| TAP2^651 | Arg 189 (88.3) | 190 (86.4) | | | |
| | Cys 25 (11.7) | 30 (13.6) | 1.19 | 0.65-2.19 | 0.53 |
| TAP2^665 | Thr 129 (60.3) | 139 (63.2) | | | |
| | Ala 85 (39.7) | 81 (36.8) | 1.13 | 0.75-1.70 | 0.53 |

* 95% confidence interval.
ity of positive allergens in skin prick tests; however, there was no association between them (data not shown).

In conclusion, this study showed a meaningful association between AR and a TAP1 polymorphism, but not TAP2. Therefore, it is suggested that a TAP1 gene polymorphism may be an important factor in AR pathogenesis in a Korean population.

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Table 6. TAP2 haplotypes in allergic rhinitis patients and controls

| Genotype | Controls (N=107) (%) | Allergic rhinitis (N=110) (%) | Odds ratio | CI* | p value |
|----------|----------------------|-------------------------------|------------|-----|---------|
| AA       | 13/12.1              | 11/10.0                       | 1.44       | 0.49-4.27 | 0.49-4.27 |
| AB       | 23/21.5              | 28/25.5                       | 1.00       | 1.00-1.00 | 1.00-1.00 |
| AC       | 6/5.7                | 5/4.5                         | 0.98       | 0.19-5.16 | 0.19-5.16 |
| AD       | 2/1.9                | 5/4.5                         | 2.95       | 0.38-27.84 | 0.38-27.84 |
| AE       | 5/4.7                | 3/2.7                         | 0.71       | 0.10-4.68 | 0.10-4.68 |
| AF       | 5/4.7                | 10/9.1                        | 2.36       | 0.51-11.29 | 0.51-11.29 |
| BB       | 16/15.0              | 12/10.9                       | 0.89       | 0.26-3.06 | 0.26-3.06 |
| BC       | 8/7.5                | 11/10.0                       | 3.06       | 0.41-6.56 | 0.41-6.56 |
| BD       | 0/0                  | 2/1.9                         | 1.9        | 1.9        | 1.9       |
| BE       | 8/7.5                | 4/3.7                         | 0.59       | 0.11-3.08 | 0.11-3.08 |
| BF       | 11/10.3              | 11/10.0                       | 1.18       | 0.32-4.43 | 0.32-4.43 |
| BI       | 1/0.9                | 0/0                           | 0          | 0.00-23.81 | 0.00-23.81 |
| CC       | 1/0.9                | 0/0                           | 0          | 0.00-23.81 | 0.00-23.81 |
| CF       | 4/3.7                | 5/4.5                         | 1.48       | 0.25-8.98 | 0.25-8.98 |
| DF       | 1/0.9                | 0/0                           | 0          | 0.00-23.81 | 0.00-23.81 |
| EF       | 1/0.9                | 1/0.9                         | 1.18       | 0.00-50.21 | 0.00-50.21 |
| FF       | 1/0.9                | 1/0.9                         | 1.18       | 0.00-50.21 | 0.00-50.21 |
| FG       | 1/0.9                | 1/0.9                         | 1.18       | 0.00-50.21 | 0.00-50.21 |

* 95% confidence interval.
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