Association of TAP and HLA-DM Genes with Psoriasis in Koreans

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To investigate the possible involvement of antigen-processing genes in the pathogenesis of psoriasis, we analyzed the polymorphisms of the TAP1, TAP2, LMP2, LMP7, DMA, and DMB genes in 98 Korean psoriasis patients and compared them with 184 healthy controls. The frequencies of TAP2*B/B [relative risk (RR) = 3.6, p < 0.0002] and TAP2*B (RR = 1.7, p < 0.05) were significantly increased, but TAP1*B (RR = 0.3, p < 0.002) and TAP2*A (RR = 0.6, p < 0.03) were significantly decreased, in the patients compared to the controls. We performed further analysis on the TAP1 and TAP2 single nucleotide polymorphisms and found significant differences between the patients and controls in TAP1 single nucleotide polymorphism at position 637 and in TAP2 at 665. In HLA-DM, DMA*0102 (RR = 2.5, p < 0.0003) was significantly increased, but DMA*0101/0101 (RR = 0.4, p < 0.0004) and DMB*0103/0103 (RR = 0.3, p < 0.005) were significantly decreased in the patients compared to the controls. The TAP and HLA-DM alleles were also analyzed according to the age of onset of psoriasis in the patients (types I and II). It was found that the HLA-DM alleles showed a greater association in type I than type II patients. An analysis of the linkage disequilibrium and stratification also indicated that the alleles of TAP and HLA-DM might be independently associated with HLA-Cw*0602 in psoriasis patients. The stratification analysis between DMA*0101/0101 and DMB*0103/0103 showed that a certain factor, controlled by a gene located between DMA and DMB, might provide strong protection against psoriasis, independently of Cw*0602, in our Korean population. In conclusion, our data suggest that the TAP and HLA-DM alleles could lead to genetic susceptibility toward psoriasis in Koreans. Key words: psoriasis/HLA-DM/LMP/TAP.


Psoriasis lesions are characterized by epidermal hyperplasia and the presence of acute and chronic inflammatory cells. Activated lymphocytes, other immune accessory cells, and lymphokines have also been detected in psoriasis plaques (Elder et al, 1994; Henseler, 1998). It has been estimated that in most countries 1%–3% of the population are affected by psoriasis (Ikaheimo et al, 1996). Psoriasis is believed to be a multigenic disease, the expression of which is partially dependent on external factors (Traupe, 1995). HLA-Cw6 shows the most pronounced increase without regard to race or ethnicity, supporting the presence of genes within the major histocompatibility complex (MHC) to be the most important genetic factors for determining susceptibility to psoriasis (Tilikainen et al, 1980). Recently, genome-wide scans have provided evidence suggesting a linkage between psoriasis and the HLA and several non-HLA loci. Of these, the HLA-linked locus (PSORS1) has been suggested as the major locus for the susceptibility to psoriasis (Trembath et al, 1997; Veal et al, 2001). PSORS1 contains five known genes, three predicted transcripts, and a number of expressed sequence tags (Oka et al, 1999). These genes have been analyzed, and significant associations have been detected for the nonconservative coding polymorphisms within the corneodesmosin (CDSN) and HCR. Several studies have reported a significant association for a coding single nucleotide polymorphism (SNP) in the CDSN gene (Allen et al, 1999; Jenisch et al, 1999; Tazi Ahnini et al, 1999), but this association was not observed in certain ethnic groups, including the Japanese and Finnish (Ishihara et al, 1996; Enerback et al, 2000). Asumalahliti et al have demonstrated the HCR gene to be ubiquitously expressed but upregulated in psoriatic epidermis, with a significant association between psoriasis and the HCR alleles (Asumalahliti et al, 2000). Other studies have suggested that this association of the HCR with psoriasis was solely due to the linkage disequilibrium (LD) with Cw*0602 and had no pathologic relevance (O’Brien et al, 2001). Therefore, it is still unclear if these genes, or regions, are directly involved in the predisposition to psoriasis, or if they are closely linked to other disease-related genes, forming part of a larger disease-associated haplotype.

In addition to HLA genes, immune responses are dependent on several genes encoding molecules that generate and translocate antigenic peptides. The genes involved in the class I and II antigen processing pathways possess TAP, LMP, and HLA-DM, and may be considered as candidate genes for the susceptibility to psoriasis. The TAP genes are located in the HLA class II region, between the DQBI and DPAl loci, and exhibit genetic polymorphisms. The TAP genes consist of the TAP1 and TAP2 genes, which encode a heterodimeric molecule that forms a heterodimeric complex.

Abbreviations: ARMS, amplification refractory modification system; HP, haplotype frequency; LD, linkage disequilibrium; OR, odds ratio; SNP, single nucleotide polymorphism; SSCP, single-strand conformation polymorphism; TAP, transporter associated with antigen processing.

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MATERIALS AND METHODS

Subjects
The study population comprised of 96 Korean psoriasis patients, 44 females and 52 males, with an age range from 12 to 83 y. The patients were divided into two groups based on their age at the onset of psoriasis; type I (n = 73), below 30 y and II (n = 23), above 30 y (Kim et al., 2000). The average age at onset of psoriasis was 23.4 y. Their results were compared with 84 controls without psoriasis. All the subjects gave their formal agreement for a genomic study and Ethical approval was obtained from The Catholic university of Korea Human Research Ethics Committee.

TAP gene polymorphisms
The TAP alleles were determined by the polymerase chain reaction (PCR) single-strand conformation polymorphism (SSCP) and PCR amplification refractory modification system (ARMs) methods as previously reported (Powsius et al., 1993).

PCR-SSCP analysis of TAP1 at codons 333 and 637, and TAP2 at codons 379 and 665
The PCR were carried out with primers in a volume of 10 μl with 10 μl of PCR buffer (500 mM KCl, 100 mM Tris–HCl pH 8.3 and 15 mM MgCl2); 1 μM each of oligonucleotide primer; 200 μM each of dATP, dGTP, and dCTP; and 100 μM of dTTP; 5 μl [α-32P]dCTP; 100 ng of genomic DNA; and 0.5 μTaq DNA polymerase (Boehringer Mannheim). The PCR were carried out with primers in a volume of 20 μl with 30 μl; 1 μM of each oligonucleotide primer; 200 μM dNTPs; 100 ng of genomic DNA; and 0.5 μTaq DNA polymerase (Boehringer Mannheim). The PCR were carried out in a Perkin Elmer 9600 thermocycler (PE Biosystems) under the following conditions: (i) LMP2, 5 min at 95°C and 35 cycles of 1 s at 95°C (denaturation), 40 s at 67°C (annealing), and 90 s at 72°C (elongation), and finally 10 min at 72°C; and (ii) LMP7, 5 min at 95°C and 35 cycles of 7 s at 95°C (denaturation), 30 s at 62°C (annealing), 30 s at 72°C (elongation), and finally 10 min at 72°C. The amplified PCR products were subjected to digestion with a restriction endonuclease, Hha1 (USB, Cleveland, OH), at 37°C for 1 h. After digestion, the LMP2 fragments were fractionated on an 8% acrylamide gel at 300 V for 2.5 h, and the LMP7 fragments on a 2% agarose gel at 200 V for 30 min, and were visualized by staining with ethidium bromide.

HLA-DMA gene polymorphisms
The one element was genotyped using PCR-ARMS, the other element was genotyped using PCR-ARMS-PCR. The sizes of the PCR products were defined on 1.5% agarose gel, prestained with ethidium bromide.

Allelic assignments for TAP1 and TAP2
The amino acids at the polymorphic positions 333 and 637 in the TAPI gene, and 379, 565, and 665 in the TAP2 gene, were analyzed. Each position is an SNP: TAPI1*13 (A→G, Ile→Val) and TAPI2*65 (A→G, Asp→Gly), and TAP2*79 (G→A, Val→Ile), TAP2*66 (G→A, Ala→Thr), and TAP2*68 (A→G, Thr→Ala). Each allele of the TAPI and TAP2 genes was defined by the combination of polymorphisms at different positions, as follows: TAPI1*A (Ile-333 and Asp→Gly), TAPI1*B (Val-333 and Gly-637), and TAPI1*C (Val-333 and Asp-637); and TAP2*A (Val-379, Ala-565, and Thr-665), TAP2*B (Val-379, Ala-565, and Ala-665), TAP2*C (Ile-379, Ala-565, and Thr-665), TAP2*D (Ile-379, Thr-565, and Thr-665), TAP2*E (Val-379, Thr-565, and Thr-665), and TAP2*G (Ile-379, Ala-565, and Ala-665).

LMP gene polymorphisms
The genotyping of the LMP2 and LMP7 were carried out by PCR restriction fragment length polymorphism as previously described (Kelly et al., 1992b). The polymorphic positions at nucleotides 911, 3912, and 4069 in the LMP7 gene, and at the amino acid position 60 in the LMP7 gene, were analyzed [LMP7*911 (T→G), LMP7*3912 (C→T), and LMP7*4069 (G→A)].

The LMP7 alleles were defined by the combination of polymorphisms at different positions, as follows: LMP7*A (T-3911, C-3912, and C-4069), LMP7*B (G-3911, C-3912, and C-4069), LMP7*C (C-3911, C-3912, and T-4069), and LMP7*D (G-3911, T-3912, and T-4069). LMP2 alleles were assigned as LMP2*R (Arg) and LMP2*T (His). The PCR were carried out with primers in a volume of 20 μl with 30 μl; 1 μM of each oligonucleotide primer; 200 μM dNTPs; 100 ng of genomic DNA; and 0.5 μTaq DNA polymerase (Boehringer Mannheim). The PCR were carried out in a Perkin Elmer 9600 thermocycler (PE Biosystems) under the following conditions: (i) LMP2, 5 min at 95°C and 35 cycles of 1 s at 95°C (denaturation), 40 s at 67°C (annealing), and 90 s at 72°C (elongation), and finally 10 min at 72°C; and (ii) LMP7, 5 min at 95°C and 35 cycles of 7 s at 95°C (denaturation), 30 s at 62°C (annealing), 30 s at 72°C (elongation), and finally 10 min at 72°C. The amplified PCR products were subjected to digestion with a restriction endonuclease, Hha1 (USB, Cleveland, OH), at 37°C for 1 h. After digestion, the LMP2 fragments were fractionated on an 8% acrylamide gel at 300 V for 2.5 h, and the LMP7 fragments on a 2% agarose gel at 200 V for 30 min, and were visualized by staining with ethidium bromide.

Statistics
The odds ratios (OR) were calculated using Woolf’s formula. The odds ratios (OR) were calculated using Woolf’s formula (Woolf, 1955) and by convention, and were expressed as the relative risk (RR). Haldane’s modification of the formula was used when one element

Haldane’s modification of the formula was used when one element
RESULTS

Frequencies of TAP1, TAP2, LMP2, LMP7, DMA, and DMB alleles  We tested the Hardy–Weinberg equilibria of all genes studied in the control group with the exception of the TAP2, as not all heterozygotes can be discriminated using our typing system. The genotype distributions were consistent with the assumption of the Hardy–Weinberg equilibrium, with the possible exception of the LMP7, due to an excess of homozygotes (the observed and expected frequencies were 50.5% and 60.3%, respectively).

The frequencies of the TAPI and TAP2 alleles for the patients and controls are shown in Table I. The frequencies of TAP2*B/B (RR = 3.6, p < 0.0002) and TAP2*B (RR = 1.7, p < 0.05) were significantly increased, but those of TAP1*A/B (RR = 0.4, p < 0.02), TAP1*B (RR = 0.3, p < 0.002), and TAP2*A (RR = 0.6, p < 0.03), were significantly decreased, in the patients compared to the controls. To exclude the uncertain assignment of some alleles due to heterozygosity at more than one residue, we also analyzed individual TAP SNPs. There were significant differences in the frequencies of the TAPI SNP at the 637 position and the TAP2 at the 665 position between the patients and controls (Table I). At the TAP1-637 residue, the genotype frequency of Asp-637/Asp-637 homozygote (RR = 2.6, p < 0.003) and the gene frequency of Asp-637 (RR = 2.5, p < 0.002) were significantly increased in the patients compared to the controls. The phenotype and gene frequencies of Gly-637 position were significantly decreased in the patients compared to the controls. At the TAP2-665 position, the frequencies of Ala-665/Ala-665 (RR = 3.4, p < 0.003), Ala-665 phenotype (RR = 2.0, p < 0.02), and Ala-665 gene (RR = 1.9, p < 0.0004) were significantly increased, but Thr-665/Thr-665 (RR = 0.5, p < 0.02), Thr-665 phenotype (RR = 0.3, p < 0.0002), and Thr-665 gene (RR = 0.5, p < 0.0004) were significantly decreased in the patients compared to the controls. There were no significant differences in the TAPI-333, TAP2-379, and TAP2-565 SNPs between the patients and controls (data not shown).

Table II shows the frequencies of the HLA-DM alleles in the patients and controls. The frequencies of DMA*0101/0102 (RR = 2.0, p < 0.006) and DMA*0102 (RR = 2.5, p < 0.0003) were significantly increased, but DMA*0101/0101 (RR = 0.4, p < 0.0004) and DMB*0103/0103 (RR = 0.3, p < 0.005) were significantly decreased, in the patients compared to the controls. The frequencies of the LMP2 and LMP7 in the patients and controls were studied, but no significant differences were found (data not shown).

Distribution of TAP, LMP, and HLA-DM alleles according to age of onset We previously mentioned that types I and II psoriasis were divided according to the age at onset of psoriasis, i.e., below or above 30 y, respectively, in our Korean population (Kim et al, 2000). We analyzed the frequencies of TAP and HLA-DM alleles for type I and II psoriasis patients (Table III). The frequencies of TAP2*B/B and DMA*0102 were significantly increased in type I patients compared to the controls, but there were no significant differences of these two alleles between types I and II patients, although the frequency of DMA*0102 was relatively increased in type I compared to type II patients.

Table I. TAP genotype and allele frequencies in Korean psoriasis patients and normal controls

<table>
<thead>
<tr>
<th>TAPI</th>
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<th>Controls, n = 184</th>
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<th>p-value</th>
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<tr>
<td>A/A</td>
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<tr>
<td>C/C</td>
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<td>A</td>
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<table>
<thead>
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<tr>
<td>A/B</td>
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<tr>
<td>B/B</td>
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<td>17</td>
<td>3.6</td>
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<tr>
<td>B/E</td>
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<td>12</td>
<td>2.6</td>
<td>0.003</td>
</tr>
<tr>
<td>B/G</td>
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<td>0.6</td>
<td>0.03</td>
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<tr>
<td>C/C</td>
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<td>0.03</td>
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<td>C/D</td>
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<td>0.05</td>
</tr>
<tr>
<td>X/X</td>
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<td>3.4</td>
<td>0.003</td>
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<tr>
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<td>0.03</td>
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<td>0.05</td>
</tr>
<tr>
<td>C</td>
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<td>11</td>
<td>0.6</td>
<td>0.03</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>3</td>
<td>0.6</td>
<td>0.03</td>
</tr>
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<td>E</td>
<td>7</td>
<td>23</td>
<td>0.6</td>
<td>0.03</td>
</tr>
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<td>G</td>
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<td>0.6</td>
<td>0.03</td>
</tr>
<tr>
<td>X</td>
<td>17</td>
<td>29</td>
<td>0.6</td>
<td>0.03</td>
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</table>

| 637 | Asp/Asp | 81        | 124        | 2.6 | 0.003 |
| Gly/Gly | 15       | 56        | 0.4 | 0.007 |
| Asp  | 96      | 380       | 0.5 | 0.003 |
| Gly  | 15      | 60        | 0.4 | 0.003 |
| n = 192 | n = 368  | n = 192   | n = 368   |

| 665 | Asp/Asp | 177       | 304        | 2.5 | 0.002 |
| Gly  | 15      | 64        | 0.4 | 0.002 |

Table II. DM genotype and allele frequencies in Korean psoriasis patients and normal controls

<table>
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<th>DMA</th>
<th>Psoriasis, n = 96</th>
<th>Controls, n = 184</th>
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<th>p-value</th>
<th>DMA</th>
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<th>Controls, n = 184</th>
<th>RR</th>
<th>p-value</th>
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<tbody>
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<td>124</td>
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<td>0101/0101</td>
<td>26</td>
<td>33</td>
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<tr>
<td>001/0102</td>
<td>42</td>
<td>51</td>
<td>2.0</td>
<td>0.006</td>
<td>0102/0102</td>
<td>21</td>
<td>37</td>
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<td></td>
<td></td>
<td>0103/0103</td>
<td>29</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>002/0102</td>
<td>10</td>
<td>8</td>
<td></td>
<td></td>
<td>0202/0102</td>
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<td>15</td>
<td></td>
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<td>0302</td>
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Table III. Distribution of TAP, LMP, and HLA-DM alleles in type I and type II psoriasis patients compared to normal controls

<table>
<thead>
<tr>
<th>Type</th>
<th>Type I, n = 73</th>
<th>RR</th>
<th>p-value</th>
<th>Type II, n = 23</th>
<th>RR</th>
<th>p-value</th>
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<td>0.003</td>
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<td>TAP2*B/B</td>
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<td>6</td>
<td>0.5</td>
<td>0.0001</td>
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<td>0.0002</td>
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<tr>
<td>DMA*0101/0101</td>
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<td>0.0002</td>
<td>14</td>
<td>0.5</td>
<td>0.0001</td>
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There were also significant differences of TAP1*B, DMA*0101/0101, and DMB*0103/0103 between the type I patients and controls. The HLA-DM alleles showed a greater decrease in type I patients than type II, although this was not statistically significant.

LD and HF between the TAPI, TAP2, DMA, and DMB alleles

Table IV shows the two-loci haplotypes of the TAP1, TAP2, DMA, and DMB alleles to have significant positive and negative disequilibria in the patients compared to the controls, but these linked alleles only showed a low LD when compared to the HF. These results show the possibility that the region between the TAP and HLA-DM may have a comparatively high recombination rate in our population, as shown by other populations (van Endert et al., 1992; Carrington et al., 1993a).

Association of the TAPI, TAP2, DMA, and DMB with Cw*0602

We previously reported that HLA-Cw*0602 was strongly associated with psoriasis in Koreans (Kim et al., 2000). In this study, we also found that the frequency of Cw*0602 was significantly increased in psoriasis patients compared to controls (psoriasis patients versus normal controls 75.0% vs 65.0%, RR = 43.0, p < 2 x 10^-5). To determine if the observed associations of the TAPI, TAP2, DMA, and DMB with psoriasis were disease related or the consequence of an LD with Cw*0602, we analyzed the LD and performed stratification analysis between the associated alleles and Cw*0602 in the patients and controls. No significantly positive and negative disequilibria were observed between the alleles and Cw*0602 in either the patients or controls (Table V). The results of the stratification analysis are shown in Table VI (Svejgaard and Ryder, 1994). Cw*0602 and the associated alleles of TAPI, TAP2, DMA, and DMB were significantly associated with psoriasis in the test of individual association [1]. Stratification of Cw*0602 showed that TAP2*B/B was significantly increased in the Cw*0602-negative group, and TAPI*B and DMB*0103/0103 were significantly decreased in the Cw*0602-positive group [2]. Cw*0602 was significantly increased in the patients compared to the controls, irrespective of the positivity or negativity for the associated alleles of TAPI, TAP2, DMA, and DMB [3]. There were significant differences in associations between the associated alleles and Cw*0602 for patients with psoriasis in an investigation of whether the associations between Cw*0602 and the associated alleles differ [4]. TAP2*B/B and DMA*0102 alleles considerably increased the OR value of Cw*0602, but TAPI*B, DMA*0101/0101, and DMB*0103/0103 alleles decreased that of Cw*0602 in the test of a combined association [5]. Taken together with the LD data and the stratified analysis, these results showed that TAPI, TAP2, DMA, and DMB alleles might be independently associated with Cw*0602 in psoriasis patients, although Cw*0602 was more strongly associated with psoriasis than the other alleles.

Combined analysis of DMA*0101/0101 and DMB*0103/0103

We investigated the relation of DMA*0101/0101 and DMB*0103/0103 alleles in psoriasis because the two alleles showed a significant association and LD in the patients (Table VII). DMA*0101/0101 and DMB*0103/0103 were negatively associated with psoriasis in a test of individual association [1].
Table V. Analysis of linkage disequilibrium between the associated alleles and HLA-Cw*0602 in psoriasis patients and normal controls

<table>
<thead>
<tr>
<th>Locus 1</th>
<th>Locus 2</th>
<th>Group</th>
<th>+ +</th>
<th>+−</th>
<th>−+</th>
<th>−−</th>
<th>LD (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP1*B</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>11</td>
<td>4</td>
<td>61</td>
<td>20</td>
<td>0.3</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal controls</td>
<td>6</td>
<td>53</td>
<td>6</td>
<td>119</td>
<td>0.7</td>
<td>ns</td>
</tr>
<tr>
<td>TAP2*A</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>35</td>
<td>13</td>
<td>37</td>
<td>11</td>
<td>1.5</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal controls</td>
<td>6</td>
<td>112</td>
<td>6</td>
<td>60</td>
<td>0.08</td>
<td>ns</td>
</tr>
<tr>
<td>TAP2*B/B</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>19</td>
<td>7</td>
<td>53</td>
<td>17</td>
<td>0.6</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal controls</td>
<td>3</td>
<td>14</td>
<td>9</td>
<td>158</td>
<td>0.6</td>
<td>ns</td>
</tr>
<tr>
<td>TAP2*B</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>50</td>
<td>13</td>
<td>22</td>
<td>11</td>
<td>4.5</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal controls</td>
<td>9</td>
<td>89</td>
<td>3</td>
<td>83</td>
<td>1.1</td>
<td>ns</td>
</tr>
<tr>
<td>DMA*0002</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>41</td>
<td>11</td>
<td>31</td>
<td>13</td>
<td>2.9</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal controls</td>
<td>4</td>
<td>55</td>
<td>8</td>
<td>117</td>
<td>0.1</td>
<td>ns</td>
</tr>
<tr>
<td>DMA*0001,001</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>31</td>
<td>13</td>
<td>41</td>
<td>11</td>
<td>2.9</td>
<td>ns</td>
</tr>
<tr>
<td>DMA*0002</td>
<td>Cw*0602</td>
<td>Normal controls</td>
<td>8</td>
<td>116</td>
<td>4</td>
<td>56</td>
<td>0.04</td>
<td>ns</td>
</tr>
<tr>
<td>DMB*0103,0103</td>
<td>Cw*0602</td>
<td>Psoriasis patients</td>
<td>4</td>
<td>2</td>
<td>68</td>
<td>22</td>
<td>0.05</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal controls</td>
<td>4</td>
<td>29</td>
<td>8</td>
<td>143</td>
<td>0.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns, not significant.

Table VI. Stratification analysis between the associated alleles and HLA-Cw*0602

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor A</td>
<td>Factor B</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>TAP1*B</td>
<td>Cw*0602</td>
<td>0.4</td>
<td>43.0</td>
<td>0.2</td>
<td>24.3</td>
<td>60.5</td>
</tr>
<tr>
<td>TAP2*B/B</td>
<td>Cw*0602</td>
<td>3.6</td>
<td>3.0</td>
<td>4.6</td>
<td>12.7</td>
<td>54.7</td>
</tr>
<tr>
<td>DMA*0002</td>
<td>Cw*0602</td>
<td>2.5</td>
<td>4.3</td>
<td>2.0</td>
<td>51.3</td>
<td>34.9</td>
</tr>
<tr>
<td>DMA*0001,001</td>
<td>Cw*0602</td>
<td>0.4</td>
<td>4.0</td>
<td>0.1</td>
<td>34.6</td>
<td>52.2</td>
</tr>
<tr>
<td>DMA*0003,0103</td>
<td>Cw*0602</td>
<td>0.3</td>
<td>4.3</td>
<td>0.1</td>
<td>14.5</td>
<td>55.3</td>
</tr>
</tbody>
</table>


OR values indicate that the corresponding p-values are significant (p<0.05).

Table VII. Stratification analysis between DMA*001/001 and DMB*0103/0103 and between the haplotype of DMA*001/001—DMB*0103/0103 and HLA-Cw*0602

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor A</td>
<td>Factor B</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>DMA*001/001</td>
<td>DMB*003/0103</td>
<td>0.4</td>
<td>0.3</td>
<td>0.5</td>
<td>0.2</td>
<td>9.5</td>
</tr>
<tr>
<td>DMA–DMB</td>
<td>Cw*0602</td>
<td>0.3</td>
<td>4.3</td>
<td>0.1</td>
<td>14.5</td>
<td>55.3</td>
</tr>
</tbody>
</table>


DMA–DMB, haplotype of DMA*001/001–DMB*003/0103. OR values indicate that the corresponding p-values are significant (p<0.05).

DMA*001/001 only showed a significant decrease in DMB*0103/0103-negative groups but DMB*0103/0103 was insignificantly decreased in both DMA*001/001-positive and DMA*001/001-negative groups in stratification of the two alleles [2, 3]. There were no significant differences between the two associations in a test of difference between the two alleles association [4]. A significant combined association between the two genotypes was shown [5], and there was a significant association between the two genotypes in both the patients and controls [6]. These results proved that DMA*001/001 and DMB*0103/0103 might interact with each other, indicating a certain stronger negative factor. We performed further analysis on the haplotype of DMA*001/001–DMB*003/0103 and Cw*0602, which all showed significant decreases in the psoriasis patients [4]. The haplotype was significantly decreased in the Cw*0602-positive group but not in the Cw*0602-negative group [2]. When Cw*0602 was stratified for the presence or absence of the haplotype, it was significantly increased in both the haplotype-positive and haplotype-negative groups [3]. There was a significant difference between the two factors’ associations.
The TAP genes are polymorphic, and due to their essential involvement in class I antigen presentation might represent additional susceptibility genes to disease. The functional consequences of TAP polymorphisms are unknown. TAP molecules are required not only for peptide transport, however, also for the assembly of class I heavy chain $\alpha_{2}$-microglobulin dimers and the previously designed TAP-associated protein tapasin (Ortmann et al., 1997). This interaction may be a target for consideration in the mechanism where a TAP polymorphism is involved in the pathogenesis of the disease. There have been several reports on the analysis of TAP alleles in patients with psoriasis. Falker et al. (1994) analyzed the TAP2 gene polymorphism in psoriasis, and showed no significant association between the alleles and psoriasis. Saeki et al. (1998) showed a decrease in TAP2$^*$E allele in a Japanese population of psoriasis patients. Mohler et al. (1996) reported an increase in TAP1$^*$A allele in patients with early onset of psoriasis. We found that the frequencies of TAP2$^*$B and TAP2$^*$B/B were significantly increased and TAP1$^*$B and TAP2$^*$A were decreased in psoriasis patients compared with the controls (Table I). We performed further analysis on the TAPI and TAP2 SNPs and found significant differences in the frequencies of the TAPI SNP at the 637 position and the TAP2 at the 665 position between the patients and the controls (Table I). In the TAPI at residue 637, the gene frequency of Asp–637 was significantly increased but Gly–637 was decreased in the patients compared to the controls. In the TAP2 at residue 665, Ala–665 was significantly increased but Thr–665 was decreased in the patients compared to the controls. There was also a significant LD between TAPI$^*$A and TAP2$^*$B (Table IV) and between TAPI Asp–637 and the TAP2 Ala–665 (LD $= 38, p < 0.0001$) in the patients compared to the controls. Quadri and Singal (1998) indicated that TAPI$^*$A and TAP1$^*$C alleles might favor the efficient transport of peptides with a basic C-terminus, whereas TAPI$^*$B allele might translocate peptides regardless of the differences in the C-terminal amino acid residue. This is due to the acidic nature of Asp residue present at the amino acid position 637 of TAPI$^*$A and TAP1$^*$C alleles, in contrast to Gly in TAPI$^*$B allele (Powis et al., 1993). The major contact site(s) in the TAPI might be located in the extreme transmembrane and cytoplasmic domains, close to the ATP binding site (Nijenhuis et al., 1996), which is the region where the human TAP shows polymorphism (Powis et al., 1992). The TAPI allele (TAPI$^*$A or TAPI$^*$C) containing the Asp residue at the 637 position, close to the peptide binding site, might influence the peptide–TAPI interaction and their eventual transport to the ER endoplasmic reticulum (Quadri and Singal, 1998). Asahina et al. reported that the Asp at residue 9 and Ala at residue 73, on HLA-C molecules, were polymorphic (Powis et al., 1991). These residues might contribute to the formation of a peptide-binding pocket in HLA-C molecules, especially Cw$^*$0602 (Kostyu et al., 1997). Although TAP2 alleles have been shown not to affect peptide transport, a commonly coexpressed product of alternative splicing of the human TAP2 transcript, differing in the C-terminal region of the protein, exhibits distinct peptide selectivity (Yan et al., 1999). A single point mutation, generated by site-directed mutagenesis in the human TAP2, has been shown sufficient to affect the peptide transport specificity (Armandola et al., 1996). Neisig et al. (1998) have shown some HLA-C molecules to be more selective in their peptide binding than the HLA-A and HLA-B molecules, resulting in prolonged association with TAP, and a reduced formation of intracellular HLA–C–peptide complexes. Binding of HLA class I and specific inhibitory natural killer (NK) receptors generates dominant inhibitory signals that neutralize any positive signals in NK cells; thus the self class I protects healthy cells from lysis by the NK. If this does not happen, the NK cells trigger cytotoxicity. It has been suggested that psoriasis may be triggered by the direct activation of CD8 and/or NK T cells bearing receptors for MHC class I molecules (Bus and De Rie, 1999). Therefore it could be thought that the interaction of specific TAP molecules and peptides might cause altered activity of specific HLA-C, such as low expression on the cell surface, resulting in the activation of NK cell cytotoxicity to self cells in psoriasis patients, and the associated TAP alleles in this study might play a role in the development of psoriasis.

HLA-DP polymorphisms have been investigated in several autoimmune diseases but the role of HLA-DP polymorphisms in autoimmune diseases is not understood yet. Pinet et al. (1997) observed an increase in both DMB$^*$0104 and DMA$^*$0103 phenotypes in rheumatoid arthritis. The homozygous DMB$^*$0101/0101 was reported to be positively associated with rheumatoid arthritis in Caucasians (Perdriger et al., 1999), but Yan et al. and Takeuchi et al. found no association of the HLA-DM with rheumatoid arthritis in Taiwanese and Japanese populations (Takeuchi et al., 1997; Yan et al., 1997). West and Reed (1999) reported that the frequencies of DMA$^*$0103 and DMB$^*$0102 were increased in patients with juvenile dermatomyositis. Saeki et al. (1999) reported that the frequency of DMA$^*$0102 was increased, and that of DMA$^*$0101 was decreased, in Japanese psoriasis patients, but no significant association between DMB alleles and psoriasis was shown. To determine the association between HLA-DP polymorphisms and psoriasis in the Korean population, we investigated the HLA-DP polymorphisms, and found the frequency of DMA$^*$0102 to be significantly increased and DMA$^*$0101/0101 and DMB$^*$0103/0103 to be decreased in psoriasis patients (Table II). In the analysis of the HLA-DM alleles for the patients divided into types I and II (Table III), the alleles associated with all psoriasis patients showed significant differences between the type I psoriasis patients and the controls. Although no significant differences were found between the type I and type II patients, probably due to the small number of patients in each subgroup, DMA$^*$0102 was more increased and DMA$^*$0101/0101 and DMB$^*$0103/0103 were more decreased in type I compared to type II patients. We also found that these alleles' associations might be independent of the LD with Cw$^*$0602 (Table V). We performed stratification analysis between DMA$^*$0101/0101 and DMB$^*$0103/0103 (Table VII) in order to investigate the relationship of the two alleles with psoriasis. The comparison of DMA$^*$0101/0101 and DMB$^*$0103/0103 might give results indicating an interaction, although several of the critical p-values were not significant, which was possibly due to the small numbers in the $2 \times 2$ tables. We further analyzed the association between the haplotype of DMA$^*$0101/0101–DMB$^*$0103/0103 and Cw$^*$0602, and found that the haplotype association might be independent of Cw$^*$0602. These data therefore suggest that the associated HLA-DM alleles may be an independent genetic marker of psoriasis to Cw$^*$0602, especially type I psoriasis patients, and a factor controlled by a certain gene, located between the DMA and DMB, may provide strong protection against psoriasis in the Korean population, independently of Cw$^*$0602.

In conclusion, we found associations of the TAP and the HLA-DM alleles with psoriasis in our Korean population, suggesting that these alleles could be genetic factors, or markers, of psoriasis. To validate these results, however, additional studies will be required by using an increased sample size and family samples, and investigating the location of the antigen processing genes' region, as well as their functional roles.
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Carrington M, Yeager M, Mann D: Characterization of HLA-DMB polymorphism. Immunogenetics 38:446–449, 1993b