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. J Invest Dermatol 120:616–622, 2003***

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 multigene 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 (Tiilikainen *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). Asumalahti *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 (Asumalahti *et al*, 2000). Other studies have suggested that this association of the HCR with psoriasis was solely due to the linkage disequilibria (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 DQB1 and DPA1 loci, and exhibit genetic polymorphisms. The TAP genes consist of the TAP1 and TAP2 genes, which encode a heterodimer molecule that forms a heterodimeric complex

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

for delivering antigenic peptides to the endoplasmic reticulum prior to the assembly of class I molecules (Deverson *et al*, 1990; Spies *et al*, 1990; Trowsdale *et al*, 1990). Two polymorphic sites have been found in the TAP1 gene, and four in the TAP2. With the TAP1 and TAP2 there are four and eight possible allele combinations of polymorphisms, respectively, at these sites (Powis *et al*, 1993). The LMP2 and LMP7 genes are located within the class II region, and encode two subunits of the proteasome complex involved in the degradation of cytosolic proteins and the generation of antigenic peptides (Brown *et al*, 1991; Ortiz-Navarrete *et al*, 1991). Although the LMP proteolytic enzymes may not be essential for the processing of peptides bound by MHC class I molecules (Arnold *et al*, 1992), they may amplify specific endopeptidase activities of the proteasome, generating peptides suitable for MHC class I molecules. The HLA-DM genes catalyze peptide loading into the HLA class II molecules (Kelly *et al*, 1991a), are located in the HLA class II region, between the DQB1 and DPB1 loci, and exhibit genetic polymorphisms (Carrington *et al*, 1993b; Carrington and Harding, 1994). The HLA-DM gene polymorphisms may influence peptide loading on the HLA class II molecules. Thus, the TAP, LMP, and HLA-DM may play a restrictive role in antigen processing and presentation, and so are attractive candidates as additive susceptibility factors toward psoriasis. In this study, we examined the polymorphisms of the TAP1, TAP2, LMP2, LMP7, HLA-DMA, and HLA-DMB genes, and their association with psoriasis, in a population of Korean patients.

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 184 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's 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 (Powis *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 × buffer (500 mM KCl, 100 mM Tris–HCl pH 8.3 and 15 mM MgCl$_2$); 1 pM of each oligonucleotide primer; dNTP (200 µM each of dATP, dGTP, and dTTP, and 100 µM of dCTP); 5 µCi [α-^{32}P]dCTP; 100 ng of genomic DNA; and 0.5 U Taq DNA polymerase (5 U per µl; Boehringer Mannheim, Mannheim, Germany). The PCR were carried out in a Perkin Elmer 9600 thermocycler (PE Biosystems, Foster City, CA) under the following conditions: 5 min at 95°C; 35 cycles of 30 s at 95°C (denaturation), 30 s at 62°C (annealing), and 40 s at 72°C (elongation); and finally 10 min at 72°C. The PCR products were mixed with a solution of 10 mM NaOH, 95% formamide, 0.05% bromophenol, and 0.05% xylene cyanol and denatured at 95°C for 2–3 min. The products were separated on a 6% nondenaturing acrylamide gel for 4 h at 4°C and 50 W. For the autoradiography, the gels were fixed, dried, and exposed for 2–18 h using an X-ray film at −70°C and an intensifying screen.

PCR-ARMS analysis for TAP2 gene polymorphism at codon 565 DNA samples (100 µg per ml) were amplified in reaction mixtures containing Taq DNA polymerase (Boehringer Mannheim), 10 × buffer, primers, 200 µM dNTPs, and distilled water. The PCR was carried out in a Perkin Elmer 9600 thermocycler (PE Biosystems) under the following conditions: 5 min at 95°C; 35 cycles of 1 min at 95°C (denaturation), 1 min at 62°C (annealing), and 1 min at 72°C (elongation); and finally 10 min at 72°C. The amplified PCR products were separated on a 1.5% agarose gel and stained with ethidium bromide.

Allelic assignments for TAP1 and TAP2 The amino acids at the polymorphic positions 333 and 637 in the TAP1 gene, and 379, 565, and 665 in the TAP2 gene, were analyzed. Each position is an SNP: TAP1^{333} (A → G, Ile → Val) and TAP1^{637} (A → G, Asp → Gly); and TAP2^{379} (G → A, Val → Ile), TAP2^{565} (G → A, Ala → Thr), and TAP2^{665} (A → G, Thr → Ala). Each allele of the TAP1 and TAP2 genes was defined by the combination of polymorphisms at different positions, as follows: TAP1*A (Ile-333 and Asp-637), TAP1*B (Val-333 and Gly-637), and TAP1*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*, 1991b). The polymorphic positions at nucleotides 3911, 3912, and 4069 in the LMP7 gene, and at the amino acid position 60 in the LMP2 gene, were analyzed [LMP7^{3911} (T → G), LMP7^{3912} (C → T), and LMP7^{4069} (C → T); and LMP2^{60} (G → A, Arg → His)]. The LMP7 alleles were defined by the combination of polymorphisms at different positions, as follows: LMP7*A (T-3911, C-3912, and C-4069), LMP7B* (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*H (His). The PCR were carried out with primers in a volume of 20 µl with 10 × buffer; 1 pM of each oligonucleotide primer; 200 µM dNTPs; 100 ng of genomic DNA; and 0.5 U Taq 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 15 s at 95°C (denaturation), 40 s at 67°C (annealing), 30 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, *Hha* I (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-DM gene polymorphisms The genotyping of the HLA-DMA and HLA-DMB was carried out by PCR-SSCP, as previously described (Carrington *et al*, 1993b, Carrington and Harding, 1994). Based on sequences from the third exon, four alleles of the DMA (DMA*0101, *0102, *0103, and *0104) and five of the DMB (DMB*0101, *0102, *0103, *0104, and *0105) were analyzed. These nucleotide positions involved codons 140, 155, and 184 in the DMA and codons 144 and 179 in the DMB, which all result in nonsynonymous amino acid changes: DMA^{140} (G → A, Val → Ile), DMA^{155} (G → C, Gly → Ala), DMA$^{184-1}$ (C → T, Val → Ile), and DMA$^{184-2}$ (G → A, Arg → His); DMB^{144} (C → A, Ala → Glu; C → T, Ala → Val) and DMB^{179} (T → C, Ile → Thr). Each DMA and DMB allele was assigned by the combination of polymorphisms at different positions as follows: DMA*0101 (Val-140, Gly-155, and Arg-184), DMA*0102 (Ile-140, Gly-155, and Arg-184), DMA*0103 (Val-140, Ala-155, and His-184), and DMA*0104 (Ile-140, Gly-155, and Cys-184); DMB*0101 (Ala-144 and Ile-179), DMB*0102 (Glu-144 and Ile-179), DMB*0103 (Ala-144 and Thr-179), DMB*0104 (Val-144 and Thr-179), and DMB*0105 (Val-144 and Ile-179). The PCR were carried out with primers in 10 µl with 10 × buffer; 1 pM of each oligonucleotide primer; dNTP (200 µM each of dATP, dGTP, and dTTP, and 100 µM dCTP); 5 µCi [α-^{32}P]dCTP; 100 ng of genomic DNA; and 0.5 U Taq DNA polymerase (Boehringer Mannheim). The PCR were carried out in a Perkin Elmer 9600 thermocycler (PE Biosystems) under the following conditions: 5 min at 95°C; 30 cycles of 30 s at 95°C (denaturation), 60 s at 65°C (annealing), and 90 s at 72°C (elongation); and finally 10 min at 72°C. The PCR products were mixed with a solution containing 10 mM NaOH, 95% formamide, 0.05% bromophenol, and 0.05% xylene cyanol, and denatured at 95°C for 2–3 min. The products were separated on a 6% nondenaturing acrylamide gel for 4 h, at 4°C and 50 W. For the autoradiography, the gels were fixed, dried, and exposed for 2–18 h using an X-ray film at −70°C and an intensifying screen.

HLA-C genotyping The HLA-C typing was performed using PCR-ARMS by the previously described method (Bunce and Welsh, 1994). Each tube contained a primer mix consisting of the allele- or group-specific primer pairs, with a positive control primer matched to the nonallelic sequences. The HLA-C typing included 23 sets of primer mixtures. The PCR were performed in 7 µl, modified from the Twelfth International Histocompatibility Workshop reference manual for class I ARMS-PCR. The sizes of the PCR products were defined on 1.5% agarose gel, prestained with ethidium bromide.

Statistics The odds ratios (OR) were calculated using Woolf's formula (Haldane, 1955) and by convention, and were expressed as the relative risk (RR). Haldane's modification of the formula was used when one element of the equation was zero. Any statistically significant difference was tested by χ^2 analysis with 1 degree of freedom or by a two-tailed Fisher's exact test when the criteria for the χ^2 analysis were not fulfilled. A p-value of less than 0.05 was considered statistically significant. Delta values for the LD and haplotype frequency (HF) were calculated by the formula of Mattiuz *et al* (1970). An exact test (Guo and Thompson, 1992) was employed to evaluate deviations from the expected Hardy–Weinberg genotypic proportions, using the Arlequin computer program package (Schneider *et al*, 1996).

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 TAP1 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 unclear 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 TAP1 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 TAP1-333, 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

TAP1	Psoriasis, *n* = 96	Controls, *n* = 184	RR	p-value	TAP2	Psoriasis, *n* = 96	Controls, *n* = 184	RR	p-value
A/A	66	112			A/A	9	35		
A/B	14	49	0.4	0.02	A/B	32	66		
A/C	13	12			A/C	4	8		
B/B	0	4			A/E	3	9		
B/C	1	6			B/B	26	17	3.6	0.0002
C/C	2	1			*B/E*	4	12		
A	93	173			B/G	1	3		
B	15	59	0.3	0.002	C/C	0	1		
C	16	19			C/D	0	2		
					D/E	0	1		
					E/E	0	1		
					X/X	17	29		
	×				A	48	118	0.6	0.03
					B	63	98	1.7	0.05
					C	4	11		
					D	0	3		
					E	7	23		
					G	1	31.6		
					X	17	29		
637					665				
Asp/Asp	81	124	2.6	0.003	Ala/Ala	28	20	3.4	0.003
Asp/Gly	15	56	0.4	0.007	Ala/Thr	49	103		
Gly/Gly	0	4			Thr/Thr	19	61	0.5	0.02
Asp	96	180			Ala	77	123	2.0	0.02
Gly	15	60	0.4	0.003	Thr	68	164	0.3	0.0002
	n = 192	*n* = 368				*n* = 192	*n* = 368		
Asp	177	304	2.5	0.002	Ala	105	143	1.9	0.0004
Gly	15	64	0.4	0.002	Thr	87	225	0.5	0.0004

X, A/G, B/C, B/D, E/G, A/D, or C/E

(TAP2*A/TAP2*G and TAP2*B/TAP2*C, TAP2*B/TAP2*D and TAP2*E/TAP2*G, TAP2*A/TAP2*D and TAP2*C/TAP2*E heterozygotes cannot be distinguished by the typing system that we designed.)

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

DMA	Psoriasis, *n* = 96	Controls, *n* = 184	RR	p-value	DMB	Psoriasis, *n* = 96	Controls, *n* = 184	RR	p-value
0101/0101	44	124	0.4	0.0004	0101/0101	26	33		
0101/0102	42	51	2.0	0.006	0101/0102	21	37		
0101/0103	0	1			0101/0103	29	55		
0102/0102	10	8			0102/0102	0	7		
					0102/0103	14	19		
					0103/0103	6	33	0.3	0.005
0101	86	176			0101	76	125		
0102	52	59	2.5	0.0003	0102	35	63		
0103	0	1			0103	49	107		

Table III. Distribution of TAP, LMP, and HLA-DM alleles in type I and type II psoriasis patients compared to normal controls

Type	Type I, *n* = 73	RR	p-value	Type II, *n* = 23	RR	p-value	Controls, *n* = 184
TAP1*B	12	0.5	0.02	3			59
TAP2*B/B	20	3.7	0.0002	6			17
TAP2*B	49			14			98
DMA*0101/0101	30	0.3	0.0002	14			124
DMA*0102	43	3.0	0.0002	9			59
DMB*0103/0103	4	0.3	0.02	2			33

Table IV. Analysis of two locus haplotypes among TAP1, TAP2, DMA, and DMB alleles showing significant association with psoriasis in patient group

Haplotype	+ +	+ −	− +	− −	LD (%)	HF (%)	p-value
TAP1*A–TAP2*B	63	12	0	3	11.0	38.0	0.02
DMA*0102–TAP2*B	42	3	21	12	10.7	26.9	0.003
DMA*0101–DMB*0102	35	51	0	10	6.5	15.6	0.02
DMA*0101–DMB*0103	49	37	0	10	9.7	23.1	0.0009
DMA*0102–DMB*0101	50	2	26	18	12.4	27.1	0.00001

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 TAP1, TAP2, DMA, and DMB alleles **Table IV** shows the two-loci haplotypes of the TAP1, TAP2, DMA, and DMB to have significant ($p<0.05$) positive LD and frequencies of more than 5% in the psoriasis patients. We found a number of significant (both positive and negative) LD among these alleles, which were present to different extents in the patients compared with 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 TAP1, 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* 6.5%, RR = 43.0, $p<2\times10^{-32}$). To determine if the observed associations of the TAP1, 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 TAP1, 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 TAP1*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 TAP1, 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 TAP1*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 TAP1, 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

Locus 1	Locus 2	Group	+ +	+ −	− +	− −	LD (%)	p-value
TAP1*B	Cw*0602	Psoriasis patients	11	4	61	20	–0.3	ns
		Normal controls	6	53	6	119	0.7	ns
TAP2*A	Cw*0602	Psoriasis patients	35	13	37	11	–1.5	ns
		Normal controls	6	112	6	60	–0.8	ns
TAP2*B/B	Cw*0602	Psoriasis patients	19	7	53	17	–0.6	ns
		Normal controls	3	14	9	158	0.6	ns
TAP2*B	Cw*0602	Psoriasis patients	50	13	22	11	4.5	ns
		Normal controls	9	89	3	83	1.1	ns
DMA*0102	Cw*0602	Psoriasis patients	41	11	31	13	2.9	ns
		Normal controls	4	55	8	117	0.1	ns
DMA*0101/0101	Cw*0602	Psoriasis patients	31	13	41	11	–2.9	ns
		Normal controls	8	116	4	56	0.04	ns
DMB*0103/0103	Cw*0602	Psoriasis patients	4	2	68	22	−0.5	ns
		Normal controls	4	29	8	143	0.6	ns

ns, not significant.

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

Comparison		[1] Individual association		[2] Independent A-association		[3] Independent B-association		[4] Difference between A and B association	[5] Combined association	[6] Association between A and B	
Factor A	Factor B	A	B	+ + *vs* − +	+ − *vs* − −	+ + *vs* + −	− + *vs* − −	+ − *vs* − +	+ + *vs* − −	Patients	Controls
TAP1*B	Cw*0602	0.4	43.0	0.2		24.3	60.5	0.007	10.9		
TAP2*B/B	Cw*0602	3.6	43.0		4.6	12.7	54.7	0.09	58.9		
DMA*0102	Cw*0602	2.5	43.0			51.3	34.9	0.05	92.3		
DMA*0101/0101	Cw*0602	0.4	43.0			34.6	52.2	0.01	19.7		
DMA*0103/0103	Cw*0602	0.3	43.0	0.1		14.5	55.3	0.008	6.5		

[1] Test of individual factor association (A, A associated?; B, B associated?). [2] Independent factor A association (+ + *vs* − +, A associated in B positives?; + − *vs* − −, A associated in B negatives?). [3] Independent factor B association (+ + *vs* + −, B associated in A positives?; − + *vs* − −, B associated in A negatives?). [4] Difference between A and B associations (− + *vs* − +). [5] Combined A–B association (+ + *vs* − −). [6] Association between A and B (patients, linkage between A and B in patients; controls, linkage between A and B in patients).

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

Table VII. Stratification analysis between DMA*0101/0101 and DMB*0103/0103 and between the haplotype of DMA*0101/0101−DMB*0103/0103 and HLA-Cw*0602

Comparison		[1] Independent association		[2] Independent A association		[3] Independent B association		[4] Difference between A and B association	[5] Combined association	[6] Association between A and B	
Factor A	Factor B	A	B	+ + *vs* − +	+ − *vs* − −	+ + *vs* + −	− + *vs* − −	+ − *vs* − +	+ + *vs* − −	Patients	Controls
DMA*0101/0101	DMB*0103/0103	0.4	0.3		0.5				0.2	9.5	22.5
DMA–DMB	Cw*0602	0.3	43	0.1		14.5	55.3	0.008	6.5		

[1] Test of individual factor association (A, A associated?; B, B associated?). [2] Independent factor A association (+ + *vs* − +, A associated in B positives?; + − *vs* − −, A associated in B negatives?); [3] Independent factor B association (+ + *vs* + −, B associated in A positives?; − + *vs* − −, B associated in A negatives?). [4] Difference between A and B associations (− + *vs* − +). [5] Combined A–B association (+ + *vs* − −). [6] Association between A and B (patients, linkage between A and B in patients; controls, linkage between A and B in patients).

DMA–DMB, haplotype of DMA*0101/0101–DMB*0103/0103. OR values indicate that the corresponding p-values are significant ($p < 0.05$).

DMA*0101/0101 only showed a significant decrease in DMB*0103/0103-negative groups but DMB*0103/0103 was insignificantly decreased in both DMA*0101/0101-positive and DMA*0101/0101-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*0101/0101 and DMB*0103/0103 might interact with each other, indicating a certain stronger negative factor. We performed further analysis on the haplotype of DMA*0101/0101–DMB*0103/0103 and Cw*0602, which all showed significant decreases in the psoriasis patients [1]. 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

[4]. The haplotype considerably decreased the OR value of Cw*0602 with the combined association [5]. There was no significant association between the haplotype and Cw*0602 in either the psoriasis patients or controls [6]. These results therefore indicate that some factor, controlled by a gene located between DMA and DMB, might be associated with a strong protection against psoriasis, independently of Cw*0602 association.

DISCUSSION

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, but also for the assembly of class I heavy chain α_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. Fakler *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. Hohler *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 TAP1 and TAP2 SNPs and found significant differences in the frequencies of the TAP1 SNP at the 637 position and the TAP2 at the 665 position between the patients and the controls (**Table I**). In the TAP1 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 TAP1*A and TAP2*B (**Table IV**) and between TAP1 Asp-637 and the TAP2 Ala-665 ($LD = 3.8$, $p < 0.0001$) in the patients compared to the controls. Quadri and Singal (1998) indicated that TAP1*A and TAP1*C alleles might favor the efficient transport of peptides with a basic C-terminus, whereas TAP1*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 TAP1*A and TAP1*C alleles, in contrast to Gly in TAP1*B allele (Powis *et al*, 1993). The major contact site(s) in the TAP1 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 TAP1 shows polymorphism (Powis *et al*, 1992). The TAP1 allele (TAP1*A or TAP1*C) containing the Asp residue at the 637 position, close to the peptide binding site, might influence the peptide–TAP1 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 strongly associated in Japanese psoriasis patients (Asahina *et al*, 1991; 1996). 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 (Bos 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-DM polymorphisms have been investigated in several autoimmune diseases but the role of HLA-DM 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 Yen *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; Yen *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-DM polymorphisms and psoriasis in the Korean population, we investigated the HLA-DM 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 2×2 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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REFERENCES

Allen MH, Veal C, Faassen A, Powis SH, Vaughan RW, Trembath RC, Barker JN: A non-HLA gene within the MHC in psoriasis. *Lancet* 353:1589–1590, 1999

Armandola EA, Momburg F, Nijenhuis M, Bulbuc N, Fruh K, Hammerling GJ: A point mutation in the human transporter associated with antigen processing (TAP2) alters the peptide transport specificity. *Eur J Immunol* 26:1748–1755, 1996

Arnold D, Driscoll J, Androlewicz M, Hughes E, Cresswell P, Spies T: Proteasome subunits encoded in the MHC are not generally required for the processing of peptides bound by MHC class I molecules. *Nature* 12, 360:171–174, 1992

Asahina A, Akazaki S, Nakagawa H, Kuwata S, Tokunaga K, Ishibashi Y, Juji T: Specific nucleotide sequence of HLA-C is strongly associated with psoriasis vulgaris. *J Invest Dermatol* 97:254–258, 1991

Asahina A, Kuwata S, Tokunaga K, Juji T, Nakagawa H: Study of aspartate at residue 9 of HLA-C molecules in Japanese patients with psoriasis vulgaris. *J Dermatol Sci* 13:125–133, 1996

Asumalahti K, Laitinen T, Itkonen-Vatjus R, *et al*: A candidate gene for psoriasis near HLA-C, HCR (Pg8), is highly polymorphic with a disease-associated susceptibility allele. *Hum Mol Genet* 9:1533–1542, 2000

Bos JD, De Rie MA: The pathogenesis of psoriasis: immunological facts and speculations. *Immunol Today* 20:40–46, 1999

Brown MG, Driscoll J, Monaco JJ: Structural and serological similarity of MHC-linked LMP and proteasome (multicatalytic proteinase) complexes. *Nature* 26, 353:355–357, 1991

Bunce M, Welsh KI: Rapid DNA typing for HLA-C using sequence-specific primers (PCR-SSP). Identification of serological and non-serologically defined HLA-C alleles including several new alleles. *Tissue Antigens* 43:7–17, 1994

Carrington M, Harding A: Sequence analysis of two novel HLA-DMA alleles. *Immunogenetics* 40:165, 1994

Carrington M, Colonna M, Spies T, Stephens JC, Mann DL: Haplotypic variation of the transporter associated with antigen processing (TAP) genes and their extension of HLA class II region haplotypes. *Immunogenetics* 37:266–273, 1993a

Carrington M, Yeager M, Mann D: Characterization of HLA-DMB polymorphism. *Immunogenetics* 38:446–449, 1993b

Deverson EV, Gow IR, Coadwell WJ, Monaco JJ, Butcher GW, Howard JC: MHC class II region encoding proteins related to the multidrug resistance family of transmembrane transporters. *Nature* 20–27, 348:738–741, 1990

Elder JT, Nair RP, Guo SW, Henseler T, Christophers E, Voorhees JJ: The genetics of psoriasis. *Arch Dermatol* 130:216–224, 1994

van Endert PM, Lopez MT, Patel SD, Monaco JJ, McDevitt HO: Genomic polymorphism, recombination, and linkage disequilibrium in human major histocompatibility complex-encoded antigen-processing genes. *Proc Natl Acad Sci USA* 1, 89:11594–11597, 1992

Enerback C, Nilsson S, Enlund F, *et al*: Stronger association with HLA-Cw6 than with corneodesmosin (S-gene) polymorphisms in Swedish psoriasis patients. *Arch Dermatol Res* 292:525–530, 2000

Fakler JW, Schmitt-Egenolf M, Vejbaesya S, Boehncke WH, Sterry W, Eiermann TH: Analysis of TAP2 and HLA-DP gene polymorphism in psoriasis. *Hum Immunol* 40:299–302, 1994

Guo SW, Thompson EA: Performing the exact test of Hardy–Weinberg proportion for multiple alleles. *Biometrics* 48:361–372, 1992

Haldane JBS: The estimation and significance of the logarithm of a ratio of frequencies. *Ann Hum Genet* 20:309–311, 1955

Henseler T: Genetics of psoriasis. *Arch Dermatol Res* 290:463–476, 1998

Hohler T, Weinmann A, Schneider PM, *et al*: TAP-polymorphisms in juvenile onset psoriasis and psoriatic arthritis. *Hum Immunol* 51:49–54, 1996

Ikaheimo I, Silvennoinen-Kassinen S, Karvonen J, Jarvinen T, Tiilikainen A: Immunogenetic profile of psoriasis vulgaris: association with haplotypes A2, B13, Cw6, DR7, DQA1*0201 and A1, B17, Cw6, DR7, DQA1*0201. *Arch Dermatol Res* 288:63–67, 1996

Ishihara M, Yamagata N, Ohno S, *et al*: Genetic polymorphisms in the keratin-like S gene within the human major histocompatibility complex and association analysis on the susceptibility to psoriasis vulgaris. *Tissue Antigens* 48:182–186, 1996

Jenisch S, Koch S, Henseler T, *et al*: Corneodesmosin gene polymorphism demonstrates strong linkage disequilibrium with HLA and association with psoriasis vulgaris. *Tissue Antigens* 54:439–449, 1999

Kelly A, Monaco JJ, Cho SG, Trowsdale J: A new human HLA class II-related locus, DM. *Nature* 10, 353:571–573, 1991a

Kelly A, Powis SH, Glynne R, Radley E, Beck S, Trowsdale J: Second proteasome-related gene in the human MHC class II region. *Nature* 17, 353: 667–668, 1991b

Kim TG, Lee HJ, Youn JI, Kim TY, Han H: The association of psoriasis with human leukocyte antigens in Korean population and the influence of age of onset and sex. *J Invest Dermatol* 114:309–313, 2000

Kostyu DD, Hannick LI, Traweek JL, Ghanayem M, Heilpern D, Dawson DV: HLA class I polymorphism: Structure and function and still questions. *Hum Immunol* 15, 57:1–18, 1997

Mattiuz PL, Ihde D, Piazza A, Ceppellini R, Bodmer WF: New approaches to the population genetic and segregation analysis of the HLA-A system. In: Terasaki PI (ed.) *Histocompatibility Testing 1970.* Copenhagen: Munksgaard, 1970

Neisig A, Melief CJ, Neefjes J: Reduced cell surface expression of HLA-C molecules correlates with restricted peptide binding and stable TAP interaction. *J Immunol* 160:171–179, 1998

Nijenhuis M, Schmitt S, Armandola EA, Obst R, Brunner J, Hammerling GJ: Identification of a contact region for peptide on the TAP1 chain of the transporter associated with antigen processing. *J Immunol* 15, 156:2186–2195, 1996

O'Brien KP, Holm SJ, Nilsson S, *et al*: The HCR gene on 6p21 is unlikely to be a psoriasis susceptibility gene. *J Invest Dermatol* 116:750–754, 2001

Oka A, Tamiya G, Tomizawa M, *et al*: Association analysis using refined microsatellite markers localizes a susceptibility locus for psoriasis vulgaris within a 111 kb segment telomeric to the HLA-C gene. *Hum Mol Genet* 8:2165–2170, 1999

Ortiz-Navarrete V, Seelig A, Gernold M, Frentzel S, Kloetzel PM, Hammerling GJ: Subunit of the '20S' proteasome (multicatalytic proteinase) encoded by the major histocompatibility complex. *Nature* 17, 353:662–664, 1991

Ortmann B, Copeman J, Lehner PJ, *et al*: A critical role for tapasin in the assembly and function of multimeric MHC class I-TAP complexes. *Science* 29, 277:1306–1309, 1997

Perdriger A, Guggenbuhl P, Chales G, *et al*: Positive association of the HLA DMB1*0101–0101 genotype with rheumatoid arthritis. *Rheumatology (Oxford)* 38:448–452, 1999

Pinet V, Combe B, Avinens O, Caillat-Zucman S, Sany J, Clot J, Eliaou JF: Polymorphism of the HLA-DMA and DMB genes in rheumatoid arthritis. *Arthritis Rheum* 40:854–858, 1997

Powis SJ, Deverson EV, Coadwell WJ, *et al*: Effect of polymorphism of an MHC-linked transporter on the peptides assembled in a class I molecule. *Nature* 21, 357:211–215, 1992

Powis SH, Tonks S, Mockridge I, Kelly AP, Bodmer JG, Trowsdale J: Alleles and haplotypes of the MHC-encoded ABC transporters TAP1 and TAP2. *Immunogenetics* 37:373–380, 1993

Quadri SA, Singal DP: Peptide transport in human lymphoblastoid and tumor cells: Effect of transporter associated with antigen presentation (TAP) polymorphism. *Immunol Lett* 61:25–31, 1998

Saeki H, Kuwata S, Nakagawa H, Asahina A, Tamaki K, Shibata Y, Juji T: Analysis of HLA class II and TAP alleles in Japanese patients with psoriasis vulgaris. *Hum Immunol* 59:503–511, 1998

Saeki H, Nakagawa H, Asahina A, Tamaki K, Shibata Y, Kuwata S: Polymorphisms of HLA-DM genes in Japanese patients with psoriasis vulgaris. *Br J Dermatol* 141:113–115, 1999

Schneider S, Kueffer JM, Roessli D, Excoffier L: *Arlequin (ver 1.0): a Software Environment for the Analysis of Population Genetics Data.* Geneva: Genetics and Biometry Lab, 1996

Spies T, Bresnahan M, Bahram S, *et al*: A gene in the human major histocompatibility complex class II region controlling the class I antigen presentation pathway. *Nature* 20–27, 348:744–747, 1990

Svejgaard A, Ryder LP: HLA and disease associations: Detecting the strongest association. *Tissue Antigens* 43:18–27, 1994

Takeuchi F, Nabeta H, Kuwata S, Tanimoto K, Ito K: Association of DMA, DMB with RA in Japanese. *Clin Exp Rheumatol* 15:189–192, 1997

Tazi Ahnini R, Camp NJ, Cork MJ, Mee JB, Keohane SG, Duff GW, di Giovine FS: Novel genetic association between the corneodesmosin (MHC S) gene and susceptibility to psoriasis. *Hum Mol Genet* 8:1135–1140, 1999

Tiilikainen A, Lassus A, Karvonen J, Vartiainen P, Julin M: Psoriasis and HLA-Cw6. *Br J Dermatol* 102:179–184, 1980

Traupe H: The puzzling genetics of psoriasis. *Clin Dermatol* 13:99–103, 1995

Trembath RC, Clough RL, Rosbotham JL, *et al*: Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet* 6:813–820, 1997

Trowsdale J, Hanson I, Mockridge I, Beck S, Townsend A, Kelly A: Sequences encoded in the class II region of the MHC related to the 'ABC' superfamily of transporters. *Nature* 20–27, 348:741–744, 1990

Veal CD, Clough RL, Barber RC, *et al*: Identification of a novel psoriasis susceptibility locus at 1p and evidence of epistasis between PSORS1 and candidate loci. *J Med Genet* 38:7–13, 2001

West JE, Reed AM: Analysis of HLA-DM polymorphism in juvenile dermatomyositis (JDM) patients. *Hum Immunol* 60:255–258, 1999

Yan G, Shi L, Faustman D: Novel splicing of the human MHC-encoded peptide transporter confers unique properties. *J Immunol* 162:852–859, 1999

Yen JH, Chen CJ, Tsai WC, Tsai JJ, Chang JG, Liu HW: HLA-DMA and DMB genotyping in patients with rheumatoid arthritis. *J Rheumatol* 24:442–444, 1997