Distribution of HLA-DQA1*01, *03, *05 and DQB1*02 Subtypes and the Associated Haplotypes in the Korean Population

Chul-Woo Pyo, Seo-Young Chung, Seong-Suk Hur, Hyoung-Jae Kim, Jee-Yeoun Choi, Yang-Kyum Kim, Ha-Jung Yoo, Hee-Baeg Choi and Tai-Gyu Kim

Catholic Hemopoietic Stem Cell Bank, College of Medicine, The Catholic University of Korea, Seoul, Korea

ABSTRACT

Background: As all HLA class II genes, the DQ genes show their polymorphic variation mainly in the second exon, which encodes the first extracellular domain of the molecule. PCR-SSOP (Polymerase chain reaction-Sequence specific oligonucleotide probe) techniques were frequently used for HLA-DQA1 and DQB1 typing but certain alleles, DQA1*0101/0104/0105, *0302/0303, *0501/0505 and DQB1*0201/*0202, which differ from each other in segment other than exon 2, could not be unequivocally assigned. **Methods:** To overcome this problem, we applied additional PCR-SSP (PCR-Sequence specific primer) method to analyze DQA1 exons 1, 3 and 4 and DQB1 exon 3. And we investigated the distributions and haplotypes of HLA-DRB1, DQA1 and DQB1 alleles in 406 unrelated Korean healthy individuals. **Results:** Using this method the indistinguishable alleles of DQA1 and DQB1 in PCR-SSOP were typed definitively. We also found several important associations between DQA1 and DQB1 alleles in the Korean population; DQA1*0101-DQB1*0501, DQA1*0104-DQB1*0502 or -*0503, DQA1 *0105-DQB1*0501, DQA1*0302-DQB1*0303, DQA1*0303-DQB1*0401 or -*0402, DQA1 *0501-DQB1*0201, DQA1*0505-DQB1*0301, and DQA1*0201-DQB1*0202. The haplotypes of DRB1-DQA1-DQB1 associated with DQA1*01, *03, *05, and DQB1*02 subtypes were investigated. Several haplotypes associated with these alleles were observed in the Korean population. **Conclusion:** Our results can be helpful to find potential unrelated donors for bone marrow registries and study the HLA-associated disease and anthropology at high-resolution allelic level. **(Immune Network 2003;3(2):103-109)**

Key Words: DQA1, DQB1, subtype, haplotype

Introduction

HLA-DQ proteins are encoded by the HLA-DQ genes and expressed as heterodimers of α and β chains at the cell surface (1-4). The HLA-DQ region consists of the matched genes (DQA1 and DQB1) and the pseudogenes (DQA2 and DQB2) (5,6). They are in linkage disequilibrium with the HLA-DR genes. Similarly to other HLA class II genes, the DQ genes show their polymorphic variation mainly in the second exon, which encodes the first extracellular domain of the molecule (5,7). However, distinct DQA1 alleles differ in exons other than the second exon. In particular, HLA-DQA1*0101, DQA1*0104, and DQA1*0105 alleles are distinguished in exons 1 and 4; identification of HLA-DQA1*0301, DQA1* 0302, and DQA1*0303 alleles require typing of exons 1 and 3; and HLA-DQA1*0505 differs from DQA1* 0501 alleles in exons 1 and 3 (8). Polymorphism at the HLA-DQB1 locus used to be determined by serology and recognized the specificities DQ1, DQ2, DQ3 and DQ4 (9). Subdivision of DQ1 and DQ3 resulted in the assignment of 5 additional serological DQB1 types, DQ5, DQ6, DQ7, DQ8 and DQ9 (10,11). The use of DNA typing techniques has increased the number of alleles. The allelic sequence diversity is also predominantly present in exon 2 and, except for DQB1*0201 and DQB1*0202, all alleles can be discriminated by PCR-SSOP in this exon. The nucleotide difference between DQB1*0201 and DQB1*0202 is located in exon 3 at codon 135 (12). The allele combination DQB1*0301/0302 and DQB1*0303/ *0304 yield an identical heterozygous sequence and there-

Correspondence to: Tai-Gyu Kim, Catholic Hemopoietic Stem Cell Bank, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Seocho-gu, Seoul 137-701, Korea. (Tel) 822-590-1216, (Fax) 822-594-7355, (E-mail) kimtg@cmc.cuk.ac.kr

fore result in ambiguous typing (13).

The aim of the present study was to discriminate the indistinguishable alleles of HLA-DQA1 and DQB1 by PCR-SSOP method based on exon 2 sequences and to investigate the associations of these alleles with other class II alleles. For this purpose, we applied additional PCR-SSP assays in DQA1 exons 1, 3, and 4 and DQB1 exon 3. By using these assays, we found strong associations between some DQA1 and DQB1 alleles in the Korean population.

Materials and Methods

DNA samples. 406 potential bone marrow donors in the Korean population were studied. DNA was isolated from peripheral blood samples following the procedure described by Kawasaki (14). Mononuclear cells were isolated from 1 to 2 ml of blood by density gradient centrifugation and washed twice by centrifugation in 10 ml PBS. The cells were resuspended in 100μl of K buffer (50 mM KCl, 10 mM Tris-Cl (pH 8.3), 2.5 mM $MgCl_2$, 0.5% Tween 20, 100 ug/ml Proteinase K), which were incubated for 60 minutes at 56°C to digest the cells, then 10 minutes at 95°C to inactivate the protease K.

PCR-SSOP. HLA-DRB1, DQA1 and DQB1 typing was performed by the PCR-SSOP method, which was essentially the same as that described at the 12th International Workshop, with minor modifications (15). For each locus, specific primers were used to amplify products, which were then denatured and

Table I-1. The primer sequences for additional PCR-SSP subtyping of HLA-DQA1 exon 1, 3, and 4 analysis

Name	Primer	Nucleotide sequences	Name	Primer	Nucleotide sequences	Size
A500	Internal	ACCTGTCACCACAGGAGTGTC	CTR2	Internal	CAGACCCACAGTCAGGCCC	560 bp
QA3-1	Ex2aa50-56	CTGTTCCGCAGATTTAGAAGA	160-2CR	Ex3aa160-166	GCAGTCATAAATCTCATCAG	763 bp
QA3-1	Ex2aa50-56	CTGTTCCGCAGATTTAGAAGA	160-2AR	Ex3aa160-167	T GCAGTCATAAATCTCATCAG	764 bp
0104/0105F	Ex1aa-13_-7	GCCCTCGCTCTGACCACCA	DQAIntRev	Intron 1	AGTGGTTGGGGCTCTGGTTT	221 bp
0101 F	Ex1aa-13_-7	CCCTCGCTCTGACCACCG	DQAIntRev	Intron 1	AGTGGTTGGGGCTCTGGTTT	220 bp
DQA1 0104 F	Ex4aa193-197	CACAGAGACTGTGGTCTGCA	QA1 0104/5R	Ex4aa219-224	ACCAACTGAACGCAGGCCTT	97 bp
DQA1 0105 F	Ex4aa193-197	ACAGAGACTGTGGTCTGCG	QA1 0104/5R	Ex4aa219-224	ACCAACTGAACGCAGGCCTT	96 bp
0302 F	Ex1aa-12_-6	TCGCCCTGACCACCGTGAT	DQAIntRev	Intron 1	AGTGGTTGGGGCTCTGGTTT	217 bp
0301/0303 F	Ex1aa-12_-6	CGCCCTGACCACCGTGAC	DQAIntRev	Intron 1	AGTGGTTGGGGCTCTGGTTT	216 bp
3DQA1F	Ex3aa93-99	ACAGTGTTTTCCAAGTCTCCC	0301R	Ex3aa160-166	TTGCTGTCATAAATCTCATCAG	224 bp
3DQA1F	Ex3aa93-99	ACAGTGTTTTCCAAGTCTCCC	0302/3R	Ex3aa160-166	CTTGCAGTCATAAATCTCATCAT	225 bp
0505F	Ex1aa-20_-13	ACAAAGCTCTGATGCTGGGGA	DQAIntRev	Intron 1	AGTGGTTGGGGCTCTGGTTT	241 bp
0501F	Ex1aa-20_-13	ACAAAGCTCTGATGCTGGGGG	DQAIntRev	Intron 1	AGTGGTTGGGGCTCTGGTTT	241 bp
3DQA1F	Ex3aa93-99	ACAGTGTTTTCCAAGTCTCCC	05011/3Ex3 R	Ex3aa172-177	TCAGAAGAGGCTTGTCCAGGC	259 bp
3DQA1F	Ex3aa93-99	ACAGTGTTTTCCAAGTCTCCC	0505 Ex3 R	Ex3aa172-177	TTCAGAAGAGGCTTGTCCAGT	260 bp
3DQA1F	Ex3aa93-99	ACAGTGTTTTCCAAGTCTCCC	0503R	Ex3aa160-167	TGCAGTCATAACTCTCCTCAGA	223 bp
3DQA1F	Ex3aa93-99	ACAGTGTTTTCCAAGTCTCCC	No0503R	Ex3aa160-167	GCAGTCATAACTCTCCTCAGC	222 bp

Table I-2. The primer sequences for additional PCR-SSP subtyping of HLA-DQB1 exon 3 analysis

Name	Primer	Nucleotide sequences	Name	Primer	Nucleotide sequences	Size
A500	Internal	ACCTGTCACCACAGGAGTGTC	CTR2	Internal	CAGACCCACAGTCAGGCCC	560 bp
DQB1						
0301/0304 F	Ex2aa7_13	TTCGTGTACCAGTTTAAGGC	0302/0304 R	Ex2aa57_63	TGTTCCAGTACTCGGCGG	169 bp
0302/03032 F	Ex2aa7_13	TTCGTGTACCAGTTTAAGGG	0301/03032 R	Ex2aa57_63	CGTTCCAGTACTCGGCGGT	169 bp
0301/0304 F	Ex2aa7_13	TTCGTGTACCAGTTTAAGGC	0301/03032 R	Ex2aa57_63	CGTTCCAGTACTCGGCGGT	169 bp
0302/03032 F	Ex2aa7_13	TTCGTGTACCAGTTTAAGGG	0302/0304 R	Ex2aa57_63	TGTTCCAGTACTCGGCGG	169 bp
DQB1*02genF	Ex3aa96_102	AGCCCACAGTGACCATCTC		Ex3aa135-141	CCAGCTGTCTCCTCCTGGT	118 bp
DQB1*02genF	Ex3aa96_102	AGCCCACAGTGACCATCTC	DQB1*0202R	Ex3aa135-141	CAGCTGTCTCCTCCTGC	117 bp
3DQB1F	Ex3aa95_101	GTGGAGCCCACAGTGACCAT	DQB1*03011	Ex3aa169_175	CACGTGGCAGGTGTAGACGT	224 bp
3DQB1F	Ex3aa95_101	GTGGAGCCCACAGTGACCAT	DQB1*0309	Ex3aa169_175	CACGTGGCAGGTGTAGACGG	224 bp

immobilized on a nylon membrane and probed with a series of digoxigenin labeled oligonucleotides specific for the known hyper-variable sequences. Stringent washing was performed in the presence of tetramethyl Ammonium Chloride (TMAC) (Sigma, St. Louis, USA). The hybridized probe was detected according to the manufacturer's instructions with the anti-digoxigenin antibody conjugated with alkaline phosphatase and followed by the addition of chemiluminescent substrate CSPD (Boehringer Mannheim, Mannheim, Germany). Chemiluminescence was detected by exposure to X-ray film.

*PCR-SSP subtyping of HLA-DQA1*01, *03, *05 and DQB1*02.* The subtyping of HLA-DQA1 and DQB1 by PCR-SSP of HLA-DQA1 exons 1, 3, 4 and DQB1 exon 3 analyses was performed using primer mixes as described previously (Table I-1 and I-2)(8). In subtyping of HLA-DQB1 exon 3, the forward and the reverse primers were used in four different primer mixes in order to amplify each allele of the ambiguous heterozygous combination. Each PCR reaction was performed as followings; the PCR reaction volume was 50μl, containing 1μM each primer, 67 mM Tris-Base (pH 8.8), 16.6 mM $(NH_4)_2SO_4$, 2 mM $MgCl_2$, 0.01% Tween 20, 100 ng Genomic DNA, and 0.2 units Taq polymerase (Boehringer Mannheim). PCR was carried out in a GeneAmp PCR system 9,600 thermocycler (Perkin Elmer, Foster City, CA, USA) under the following conditions: 1 min at 96°C, 5 cycles of [25 sec at 96°C, 45 sec at 70°C, and 30 sec at 72°C], 21 cycles of [25 sec at 96°C, 45 sec at 65°C, and 30 sec at 72°C], 4 cycles of [25 sec at 96°C, 60 sec at 55°C, and 120 sec at 72°C] and finally a single cycle of 10 mins at 72°C. Amplification products were visualized on 2% agarose gels containing 0.5μg/ml ethidium bromide.

Statistical analysis. Allele frequencies were estimated by maximum-likelihood using the program provided by Excoffier and Slatkin (16). This program was also used to estimate maximum-likelihood two-and three-locus haplotype frequencies from genotypic data through an expectation-maximization (EM) algorithm (17,18), i.e., an iterative method to compute successive sets of haplotype frequencies. The values of linkage disequilibrium (LD) and relative linkage disequilibrium (RLD) and their level of significance were determined using the formulae of the 11th International Histocompatibility Workshop methodology (19).

Results

*Discrimination of HLA-DQA1*01, 03, 05 and DQB1 *02 subtypes by PCR-SSP and the frequencies of these subtypes and associated haplotypes.* For PCR-SSP subtyping of the indistinguishable alleles of DQA1 and DQB1 in PCR-SSOP, DQA1*0101/0104/0105, *0302/0303, *0501/0505, and DQB1*0201/0202, we used the primers described by Pera et al. in this study (Table I-1 and I-2) (8). The primer mixes for subtyping of DQA1*01 were located between exon 1 and 4; DQA1*03 and DQA1*05 between exon 1 and 3; DQB1*02 in exon 3. Table II-1 and II-2 show the primer combinations producing specific patterns for DQA1 and DQB1 alleles. Using this PCR-SSP, these

Table II-1. Primer combinations producing patterns for DQA1 alleles

Forward	0104/5F	0101F	0104F	0105F	QA3-1	QA3-1	0302F	3DQA1F	3DQA1F	0505F	3 DQA1F	3 DQA1F	3 DQA1F	3 DQA1F
Reverse	QAIntR	QAIntR	0104/5R	0104/5R	160-2CR	160-2AR	QAIntR	0301R	0302/3R	QAIntR	05011/3R	0505R	0503R	No0503R
Allele														
0101		○		○				○						
0102								○						
0103		○						○						
0104	○		○					○						
0105	○			○				○						
0106								○						
0201								○						
0301					○			○						
0302						○	○		○					
0303						○			○					
0401								○						
0501											○			○
0503											○		○	
0505										○		○		○
0601								○						

"○" idicates that the individual primer mix should produce the specific PCR-product band

Table II-2. Primer combinations producing patterns for DQB1 alleles

Forward Reverse	0301/4F 0302/4R	0301/4F 0301/32R	0302/32F 0302/4R	0302/32F 0301/32R	3DQB1F 03011R	3DQB1F 0309R	02genF 0201R	02genF 0202/3R
Allele								
0201			○		○		○	
0202			○		○			○
0203				○				○
03011		○			○			
03012		○						
0302			○		○			
03032				○	○			
03033				○				
0304	○				○			
03051			○		○			
03052			○					
0307			○					
0308			○					
0309		○				○		
0310		○			○			
0401					○			
0402					○			
05031				○				
06011				○			○	

"○" indicates that the individual primer mix should produce the specific PCR-product band

Table III. Frequencies of HLA-DQA1 and DQB1 alleles in unrelated Korean healthy individuals

DQA1	Gene frequency n=406	Gene frequency n=406	DQB1
0101	6.9	0201	3.0
0102	21.0	0202	6.4
0103	10.0	0203	0.1
0104	5.8	0301	14.0
0105	1.7	0302	10.0
0201	6.8	0303	10.0
0301	9.9	0304	0.1
0302	9.9	0401	8.0
0303	11.0	0402	3.6
0401	1.2	0501	8.4
0501	3.0	0502	4.8
0503	2.7	0503	3.1
0505	7.5	0601	9.2
0601	3.7	0602	7.5
		0603	1.2
		0604	6.5
		0605	3.9

indistinguishable DQA1 and DQB1 alleles were typed definitively (Fig. 1). And the allele combinations DQB1*0301/0302 and DQB1*0303/0304 was also resolved by this PCR-SSP.

The frequencies of DQA1 and DQB1 alleles in the Korean population are shown in Table III. In the subtyping for the DQA1*0101/0104/0105 (14.4%) alleles by PCR-SSP, the gene frequency of each allele was shown as DQA1*0101 (6.9%), *0104 (5.8), and *0105 (1.7%), respectively. All the DQA1-DQB1 haplotypes associated with DQA1*0101, *0104, and *0105 are shown in Table III. DQA1*0101 was strongly associated with DQB1*0501, and DQA1*0104 was significantly associated with DQB1*0502 or *0503. DQA1*0105 had also a strong association with DQB1*0501 (Table IV). The DQA1*03 was

Table IV. HLA-DQA1 and DQB1 haplotypes associated with DQA1*01, 03, 05 and DQB1*02 subtypes in unrelated Korean healthy individuals

DQA1	DQB1	HF (%)	LD (%)	RLD	X2
0101	0501	5.9	5.3	0.8	468.6
0104	0502	2.4	2.1	0.5	146.2
0104	0503	3.0	2.8	1.0	385.0
0105	0501	1.7	1.6	1.0	155.9
0201	0202	6.0	5.6	0.9	672.9
0302	0303	9.2	8.2	0.9	656.7
0303	0401	7.4	6.5	0.9	498.2
0303	0402	2.6	2.2	0.7	121.4
0501	0201	2.2	2.1	0.7	447.5
0505	0301	6.5	5.5	0.9	301.6

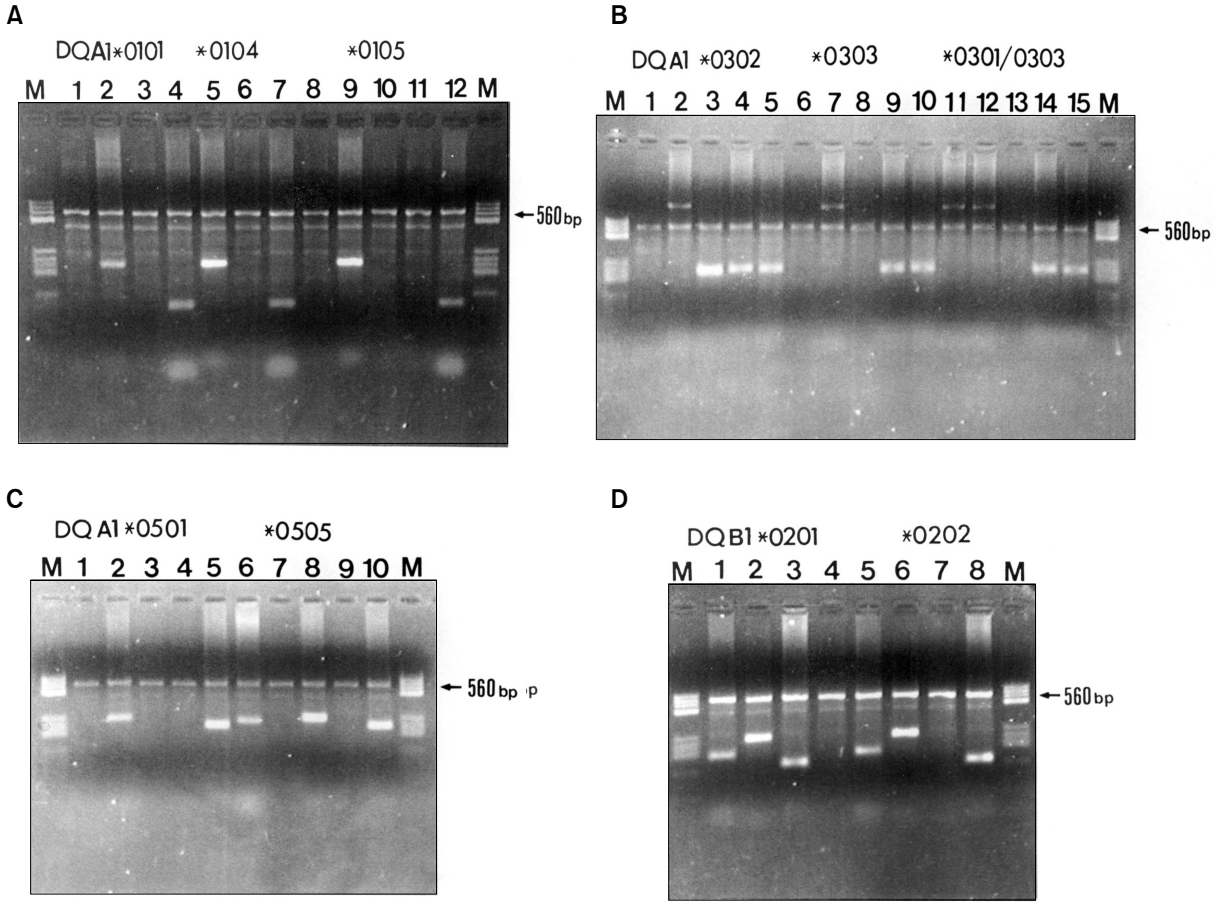

Figure 1. Additional PCR-SSP subtyping. Each PCR reaction included the positive control primer pair of A500 and CTR2, which gave rise to a 560bp-amplified fragment. The number of each lane that the primer mix corresponds to is the primer mix of interest. The length of the allele-specific PCR products was shown in Table I. (A) HLA-DQA1*0101, *0104, and *0105 subtyping by PCR-SSP: lane 1, 5, 9 (corresponding to primer mix 0104/5 F+QA Int.R), lane 2, 6, 10 (0101F+QA Int.R), lane 3, 7, 11 (0104F+0104/5R), and lane 4, 8, 12 (0105F+0104/5R), (B) HLA-DQA1*0301, *0302, and *0303 subtyping: lane 1, 6, 11 (corresponding to primer mix QA3-1+160-2CR), lane 2, 7, 12 (QA3-1+160-2AR), lane 3, 8, 13 (0302F+QA Int.R), lane 4, 9, 14 (3DQA1F+0301R), and lane 5, 10, 15 (3DQA1F+0302/3R), (C) HLA-DQA1*0501 and *0505 subtyping: lane 1, 6 (corresponding to primer mix 0505F+QA Int.R), lane 2, 7 (3DQA1F+0501/3R), lane 3, 8 (3DQA1F+0505R), lane 4, 9 (3DQA1F+0503 R), and lane 5, 10 (3 DQA1F+No0503R), (D) HLA-DQB1*0201 and *0202 subtyping: lane 1, 5 (corresponding to primer mix 0302/32F+0302/4R), lane 2, 6 (3DQB1F+ 03011R), lane 3, 7 (02genF+0201R), and lane 4, 8 (02genF+0202/3R).

subtyped as DQA1*03011 and DQA1*0302/*0303 by PCR-SSOP, and DQA1*0302 and *0303 were typed definitively by additional PCR-SSP. DQA1* 0302 displayed a strong association with DQB1*0303 and DQA1*0303 was significantly associated with DQB1*0401 and *0402. DQA1*0501 and *0505 were also strongly associated with DQB1 alleles, DQB1* 0201 and DQB1*0301, respectively. And we also discriminated DQB1*0201/*0202 and found a significant association with DQA1 alleles, DQA1* 0501-DQB1*0201 and DQA1*0201-DQB1*0202.

*Association of DRB1 with DQA1-DQB1 haplotypes of DQA1*01, *03, *05, and DQB1*02 subtypes.* The haplotypes of DRB1-DQA1-DQB1 associated with DQA1*01, *03, *05, and DQB1*02 subtypes are

Table V. HLA-DRB1, DQA1 and DQB1 haplotypes associated with DQA1*01, *03, *05 and DQB1*02 subtypes in unrelated Korean healthy individuals

DRB1	DQA1	DQB1	HF (%)	LD (%)
0101	0101	0501	5.3	5.3
0301	0501	0201	2.2	2.2
0404	0303	0402	1.5	1.5
0405	0303	0401	7.4	7.3
0901	0302	0303	8.3	8.2
1001	0105	0501	1.7	1.7
1101	0505	0301	3.6	3.5
1201	0505	0301	2.3	2.3
1401	0104	0502	2.4	2.4
1405	0104	0503	2.0	2.0
0701	0201	0202	6.0	6.0

shown in Table V. DQA1*0101-DQB1*0501 was strongly associated with DRB1*0101 and DQA1*0104-DQB1*0502 with DRB1*1401, and DQA1*0104-DQB1*0503 with DRB1*1405 in the Korean population. DQA1*0105-DQB1*0501 was found in association with DRB1*1001. DRB1*0901-DQA1*0302-DQB1*0303 was the most frequent in the Korean population. The haplotypes of DRB1*0404-DQA1*0303-DQB1*0402 and DRB1*0405-DQA1*0303-DQB1*0401 was also found. DQA1*0501-DQB1*0201 were associated with DRB1*0301 and DQA1*0505-DQB1*0301 with DRB1*1101 and *1201.

Discussion

The α1 and β1 domains of HLA-DQ molecules which bind antigenic peptides and present to CD4-positive T cells, have been known to display a high degree of polymorphism (12). Polymorphisms of HLA-DQ alleles have mainly been analyzed for exon 2, which includes a large number of functional residues responsible for antigen peptide-binding and T cell receptor-recognition in the structural model of DRB1*0101 (20).

The polymerase chain reaction-sequence-specific oligonucleotide probe (PCR-SSOP) techniques were frequently used for HLA-DQA1 and DQB1 typing, but certain alleles could not be unequivocally assigned. These indistinguishable alleles differ from each other in segment other than exon 2 and additional amplifications will be needed for their distinction. In this study we applied additional PCR-SSP method, decribed by Pera et al (8), to PCR-SSOP based on exon 2 in DQA1 and DQB1. The indistinguishable alleles of DQA1 and DQB1 in PCR-SSOP, DQA1*0101/0104/0105, *0302/0303, and *0501/0505 and DQB1*0201/*0202, were typed definitively by the PCR-SSP. The allele combinations DQB1*0301/0302 and DQB1*0303/0304 yield an identical heterozygous sequence, resulting in ambiguous typing in PCR-SSOP. This problem was easily resolved by the PCR-SSP.

Previous studies showed that DQA1*0101 and *0105 were linked to DQB1*0501, whereas DQA1*0104 was linked to DQB1*0502 or *0503 (21). We found the same results in the Korean population. DQA1*0302/0303 was split to DQA1*0302 and DQA1*0303 by the difference in the leader sequence (exon 1). DQA1*0302 carried ACG (Thr) at codon 6 and was associated with DRB1*0901-DQB1*0303, whereas DQA1*0303 had ATG (Met) at codon 6 and was linked to DRB1*0405-DQB1*0401 and DRB1*0410-DQB1*0402 (21-24). DRB1*0404-DQA1*0303-DQB1*0402, not found in Japanese normal controls, was found at the frequency of 1.5% in the Korean population, although genetically similar to Japanese. In addition, we confirmed the previous reported haplotypes of DRB1*1101-DQA1*0505-DQB1*0301 and DRB1*0701-DQA1*0201-DQB1*0202 (23,24). We also found the strong association of DRB1*0301-DQA1*0501-DQB1*0201 and DRB1*1201-DQA1*0505-DQB1*0301 in the Korean population. The results in this study were similar to that of the previous Korean population study reported by Song et al (25).

HLA-DQA1 and DQB1 molecules are involved in a number of pathological conditions, which include susceptibility to autoimmune diseases, graft rejection and graft vs. host reaction after bone marrow transplantation (BMT) (26). As a consequence, it is imperative to obtain a complete and accurate typing of HLA-DQA1 and HLA-DQB1 gene polymorphisms. Our study showed that the indistinguishable alleles of HLA-DQA1 and DQB1, not precisely assigned by general typing methods based on exon 2, were unambiguously typed by the use of additional PCR-SSP and the haplotypes associated with these alleles were found in the Korean population. Our results can be helpful in finding potential unrelated donors for bone marrow registries and in studying the HLA-associated diseases and anthropology at high-resolution allelic level.

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