Pediatr Cardiol (2008) 29:402–408
DOI 10.1007/s00246-007-9146-3

ORIGINAL ARTICLE

Polymorphisms of Human Leukocyte Antigen Genes in Korean Children with Kawasaki Disease

Jin Hee Oh · Ji Whan Han · Soon Ju Lee · Kyung Yil Lee · Byung Kyu Suh · Dae Kyun Koh · Joon Sung Lee · Chang Kyu Oh · Tai Gyu Kim · Hee Baeg Choi

Received: 28 February 2007 / Accepted: 25 October 2007 / Published online: 7 December 2007

Abstract
Background Kawasaki disease is a leading cause of acquired heart disease in children. The prevalence rate varies in different ethnic groups. Recently, with the clinical application of molecular genetic technology, human leukocyte antigen (HLA) polymorphisms associated with several diseases have been identified by DNA analysis. This study aimed to assess the association of HLA alleles with susceptibility and complications of Kawasaki disease in Korean children.
Methods In this study, DNA was extracted from 74 children with a diagnosis of Kawasaki disease. The polymorphisms of the HLA-A, -B, -C, and -DRB1 alleles of patients with Kawasaki disease were determined by polymerase chain reaction (PCR)–amplification refractory mutation system (ARMS) and PCR–sequence-specific primer (SSP) analysis. The polymorphisms identified were compared with those of 159 normal healthy control subjects.
Results There was a significant increase in the frequencies of the HLA-B35, -B75, and -Cw09 alleles in patients with Kawasaki disease compared with the healthy control group. There was no increase in the frequency of HLA-DRB1 alleles among the Kawasaki disease patients compared with a healthy control group. When the patients with Kawasaki disease were divided into two subgroups, with or without coronary complications, the Kawasaki disease patients with coronary complications showed a significantly increased frequency of the HLA-DRB1*11 allele compared with the healthy control group and increased frequency of HLA-DRB1*09 in a comparison of the subgroups.
Conclusions This study suggests that polymorphisms in some alleles of B and C in HLA class I genes are associated with Kawasaki disease in Korean children.

Keywords Gene · HLA · Kawasaki disease · Polymorphism

J. H. Oh · J. W. Han · S. J. Lee · K. Y. Lee · B. K. Suh (✉) · D. K. Koh · J. S. Lee · C. K. Oh
Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
e-mail: suhbk@catholic.ac.kr

T. G. Kim
Department of Microbiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

H. B. Choi
Catholic Hemopoietic Stem Cell Bank, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Kawasaki disease is a systemic vasculitis that currently is a leading cause of acquired heart disease in children. The etiology of Kawasaki disease continues to be unknown, although it was described 4 decades ago in 1967 by Kawasaki [15]. Diagnosis continues to depend primarily on clinical manifestations.

It appears that the pathogenesis of Kawasaki disease is related to infection of a susceptible host coupled with epidemiologic and ethnic factors. In a study examining the epidemiologic characteristics of Kawasaki disease in San Diego, CA, USA, Asians/Pacific Islanders were 2.7 times more likely and Hispanics one-third as likely to be hospitalized for Kawasaki disease compared with the children of other ethnic groups combined [4]. The sibling risk ratio is also known to be higher, than the risk of being affected with Kawasaki disease without sibling history, and cases of Kawasaki disease in parents and children have been reported [10, 21].

For these reasons, many reports have suggested involvement of the human leukocyte antigen (HLA) system. The

results of such studies vary depending on the ethnic group studied. Several reports show the association of HLA genotypes with Kawasaki disease including HLA-Bw22 (now referred to as HLA-B54) in Japanese [14, 20], HLA-B51 in white populations [13, 16, 18, 19], and the major histocompatibility complex class I chain-related gene A (MICA) genes and others in southern Chinese population [6, 12].

The major histocompatibility complex (MHC) class II genes in Kawasaki disease show variable correlations [2, 8, 27]. To date, there have been no reports supporting a consistent relationship between Kawasaki disease and HLA genes in Korean patients. Therefore, the current study aimed to assess the association of HLA-A,-B,-C, and -DRB1 alleles with Kawasaki disease in Korean children.

Materials and Methods

Subjects

From March 2004 to December 2004, 74 patients with Kawasaki disease (44 boys and 30 girls) attending the pediatric outpatient clinic or admitted to St. Vincent's Hospital in Korea were recruited for this study. The mean age of the patients at diagnosis was 2.7 ± 1.9 years. For comparison, genetically unrelated healthy Korean adults (n = 159) who had no history of Kawasaki disease were studied as a healthy control group. Blood samples were obtained after informed consent in compliance with the institutional review board of St. Vincent's hospital, College of Medicine, The Catholic University of Korea.

The diagnosis of Kawasaki disease was established by clinical manifestations meeting the defined criteria according to the report of the Research Committee on Kawasaki Disease of the Japanese Ministry of Health and Welfare in addition to exclusion of any other possible illnesses [25]. Coronary complications included the following lesions detected by echocardiography: an internal diameter exceeding 3 mm in patients younger than 5 years and exceeding 4 mm in patients age 5 years or older, dilation of a segmental luminal diameter to at least 1.5 times that of an adjacent segment, or a definitely irregular internal lumen of the coronary arteries. The clinical characteristics of the patients are shown in Table 1.

Genomic DNA was extracted by standard methods using the AccuPrep DNA extraction kit (Bioneer, Daejeon, Korea) from peripheral blood collected (4 ml) with ethylenediaminetetraacetic acid (EDTA) and kept at −20°C.

HLA-A, -B, and -C Genotyping

The genotyping of HLA-A, -B, and -C was performed by the amplification refractory mutation system (ARMS)–polymerase chain reaction (PCR) method. Each reaction contained a primer mix consisting of the allele- or group-specific primer pairs as well as internal control primers matching nonallelic sequences. Specific amplifications of the HLA-A, -B, and -C genes were performed using forward and reverse primers (44 for HLA-A, 47 for HLA-B, and 33 for HLA-C) designed according to the published nucleotide sequences [5, 17, 26].

The PCR procedure was carried out in a reaction (13 μl), containing 100 to 200 ng genomic DNA, 0.8 X buffer (40 mmol/l KCl, 1.2 mmol/l $MgCl_2$, 8 mmol/l Tris-HCl pH 8.8, 0.08% Triton X-100), 5% dimethylsulphoxide (DMSO), 200 μmol/l of each dNTP, 0.25 U Taq DNA polymerase (Boehringer, Mannheim, Germany), 1 μmol/l of each sequence-specific primer, and 0.2 μmol/l of internal control primers.

The amplifications were performed in a My Cycler thermocycler (Bio-Rad, Hercules, USA). For amplification, 30 cycles were performed using the following steps: heating to 96°C for 1 min to denature the DNA; denaturation at 96°C for 25 s and at 70°C for 45 s; annealing and extension at 72°C for 30 s (for the first 5 cycles), 96°C for 25 s, 65°C 45 s, 72°C for 30 s (for the next 21 cycles); 96°C for 25 s, 55°C for 60 s, 72°C for 120 s (for the last 4 cycles); and a final 1 min extension at 72°C. The presence or absence of PCR products was determined after separation of the samples on a 1.5% agarose gel containing 0.5 μg/ml of ethidium bromide.

HLA-DRB1 Genotyping

The PCR sequence-specific primer (SSP) method was used for HLA-DRB1 genotyping. Each reaction contained a primer mix consisting of the allele- or group-specific primer pairs as well as the internal control primers that matched the nonallelic sequences. Specific amplification of

Table 1 Profiles of subjects with Kawasaki disease

	n (%)
Male/female	44/30 (60/40)
Typical KD/atypical KD	65/9 (88/12)
Family history of KD	3 (4.1)
Recurrence history of KD	4 (5.4)
Coronary complications	21 (28)
Other complications of KD	
Gallbladder hydrops	14 (19)
Pyuria	25 (34)
Hepatopathy	38 (51)
Arthritis	10 (14)

KD, Kawasaki disease

Table 2 The allele frequencies of human leukocyte antigen-A (HLA-A) in the patients with Kawasaki disease and the control subjects

HLA alleles	Healthy controls (n =159) n (%)	KD patients (n = 74) n (%)	Coronary complications	
			Present (n = 21) n (%)	Absent (n = 53 n (%)
HLA-A				
01	5 (3.1)	5 (6.8)	2 (9.5)	3 (5.7)
02	85 (53.5)	43 (58.1)	12 (57.1)	31 (58.5)
03	5 (3.1)	3 (4.1)	0 (0.0)	3 (5.7)
11	31 (19.5)	21 (28.4)	6 (28.6)	15 (28.3)
24	57 (35.8)	33 (44.6)	12 (57.1)	21 (39.6)
26	25 (15.7)	6 (8.1)	4 (19.0)	2 (3.8)[a]
30	20 (12.6)	4 (5.4)	1 (4.8)	3 (5.7)
31	14 (8.8)	6 (8.1)	0 (0.0)	6 (11.3)
32	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
33	38 (23.9)	15 (20.3)	2 (9.5)	13 (24.5)
68	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

KD, Kawasaki disease; RR, relative risk

[a] $p < 0.04$; RR = 0.2 (95% confidence interval [CI], 0.05–0.90) vs healthy control subjects

the HLA-DRB1 gene was performed using 47 forward and reverse primers for HLA-DRB1 designed on the basis of the published nucleotide sequences [23].

The PCR procedure was carried out in a reaction (10 µl) containing 100 ng genomic DNA, 1 X buffer (60 mmol/l Tris-HCl pH 9.0, 15 mmol/l ammonium sulphate, 2.5 mmol/l $MgCl_2$), 200 µmol/l of each dNTP, 0.25 U Taq DNA polymerase (Boehringer Mannheim, Germany), 1 µmol/l of each sequence-specific primer, and 0.2 µmol/l of the internal control primers.

The amplifications performed in a My Cycler thermocycler (Bio-Rad, Hercules, USA). For amplification, 27 cycles were performed using the following steps: heating to 96°C for 3 min to denature the DNA; denaturation at 96°C for 20 s; annealing and extension at 66°C for 60 s (for the first 10 cycles), 62°C for 80 s (for the next 10 cycles), and 61°C for 120 s (for the last 7 cycles); and a final 10 min extension at 72°C. The presence or absence of PCR products was determined after separation of samples on a 1.5% agarose gel containing 0.5 µg/ml of ethidium bromide.

Statistical Analysis

Statistical differences between Kawasaki disease patients and healthy control subjects and between subgroups of Kawasaki disease patients were tested with chi-square and Fisher's exact test. The quantification of the relationship of the frequencies studied, in cases with Kawasaki disease, was performed by calculating the relative risks using the method of Woolf. Haldane's modification was applied for cases in which the variables included zero. A p value less than 0.05 was considered to be significant.

In this study, the data were not adjusted for multiple comparisons because the sample size was not large enough for multiple-comparison analysis correction.

Results

The Genotype Distribution and Allele Frequencies of HLA-A for the Patients With Kawasaki Disease and the Healthy Control Group

In the analysis of the polymorphisms of HLA-A alleles, no statistical difference was found in the frequency of alleles between the patients with Kawasaki disease and the control group. However, the frequency of HLA-A26 alleles was significantly decreased in the Kawasaki disease patients without coronary complications (CC) compared with the healthy control group ($p < 0.04$; relative risk (RR) = 0.2). In a comparison between subgroups, with and without CC, no significant difference was identified (Table 2).

The Genotype Distribution and Allele Frequencies of HLA-B for the Patients With Kawasaki Disease and the Healthy Control Group

In analysis of the polymorphisms of HLA-B alleles, there was a significant increase in the frequency of HLA-B35 and -B75 alleles in the patients with Kawasaki disease compared with the control group ($p < 0.006$; RR = 3.1 vs $p < 0.02$; RR = 8.2). When the patients with Kawasaki disease were divided into two subgroups, with or without CC, the Kawasaki disease patients without CC showed a significantly increased frequency of HLA-B35 and -B75 alleles compared with the healthy control group ($p < 0.02$; RR = 3.1 vs $p < 0.003$; RR = 11) (Table 3). Although the frequency of the HLA-B35 alleles were similar in the groups with and without CC (19% vs 18.9%), the HLA-B75 allele was found only in the Kawasaki disease patients without CC (0.0% vs. 13.2%). Therefore, the HLA-B35 allele was implicated in susceptibility to Kawasaki disease

Table 3 The allele frequencies of human leukocyte antigen-B (HLA-B) in the patients with Kawasaki disease and the control subjects

HLA alleles	Healthy controls (n = 159) n (%)	KD patients (n = 74) n (%)	Coronary complications	
			Present (n = 21) n (%)	Absent (n = 53) n (%)
HLA-B				
07	19 (11.9)	9 (12.2)	3 (14.3)	6 (11.3)
08	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
13	20 (12.6)	5 (6.8)	2 (9.5)	3 (5.7)
14	6 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
27	11 (6.9)	3 (4.1)	1 (4.8)	2 (3.8)
35	11 (6.9)	14 (18.9)[a]	4 (19.0)	10 (18.9)[b]
37	5 (3.1)	4 (5.4)	2 (9.5)	2 (3.8)
38	7 (4.4)	3 (4.1)	0 (0.0)	3 (5.7)
39	2 (1.3)	3 (4.1)	2 (9.5)	1 (1.9)
44	29 (18.2)	10 (13.5)	3 (14.3)	7 (13.2)
46	18 (11.3)	7 (9.5)	2 (9.5)	5 (9.4)
47	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.9)
48	13 (8.2)	2 (2.7)	0 (0.0)	2 (3.8)
51	29 (18.2)	13 (17.6)	5 (23.8)	8 (15.1)
52	9 (5.7)	3 (4.1)	2 (9.5)	1 (1.9)
54	23 (14.5)	10 (13.5)	3 (14.3)	7 (13.2)
55	3 (1.9)	4 (5.4)	1 (4.8)	3 (5.7)
56	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
57	2 (1.3)	1 (1.4)	0 (0.0)	1 (1.9)
58	15 (9.4)	5 (6.8)	0 (0.0)	5 (9.4)
59	4 (2.5)	3 (4.1)	0 (0.0)	3 (5.7)
60	11 (6.9)	7 (9.5)	2 (9.5)	5 (9.4)
61	23 (14.5)	13 (17.6)	6 (28.6)	7 (13.2)
62	29 (18.2)	14 (18.9)	1 (4.8)	13 (24.5)
67	4 (2.5)	2 (2.7)	1 (4.8)	1 (1.9)
71	7 (4.4)	1 (1.4)	0 (0.0)	1 (1.9)
75	2 (1.3)	7 (9.5)[c]	0 (0.0)	7 (13.2)[d]

KD, Kawasaki disease; RR, relative risk

[a] $p < 0.006$; RR = 3.1 (95% confidence interval [CI], 1.29–7.62) vs healthy control subjects

[b] $p < 0.02$; RR = 3.1 (95% CI, 1.16–8.43) vs healthy control subjects

[c] $p < 0.02$; RR = 8.2 (95% CI, 1.74–38.68) vs healthy control subjects

[d] $p < 0.003$; RR = 11 (95% CI, 2.79–51.13) vs healthy control subjects

and the HLA-B75 allele in susceptibility to Kawasaki disease without CC. In a comparison between the subgroups, with and without CC, there was no overall significant difference identified between the two groups.

The Genotype Distribution and Allele Frequency of HLA-C for the Patients With Kawasaki Disease and the Healthy Control Group

In the analysis of the polymorphisms of HLA-C alleles, there was a significant increase in the frequency of the HLA-Cw09 allele in the patients with Kawasaki disease compared with the healthy control group ($p < 0.04$; RR = 2.0). When the Kawasaki disease patients were divided into two subgroups, with or without CC, the Kawasaki disease patients without CC showed a significantly increased frequency of the HLA-Cw09 allele compared with the healthy control group ($p < 0.05$; RR = 2.1). However, no significant difference was found between the subgroups with and without CC (Table 4).

The Genotype Distribution and the Allele Frequencies of HLA-DRB1 for the Patients With Kawasaki Disease and the Healthy Control Group

Among the HLA-DRB1 alleles, there was no increase in the frequency of alleles in the Kawasaki disease patients compared with the healthy control group. However, after subgrouping of the Kawasaki disease patients, with or without CC, the frequency of HLA-DRB1*11 was significantly increased in the Kawasaki disease patients with CC compared with the healthy control group ($p < 0.04$; RR = 4.7). In a comparison between the subgroups, with and without CC, the frequency of the HLA-DRB1*09 allele was increased in the Kawasaki disease patients with CC compared with the Kawasaki disease patients without CC (33.3%

Table 4 The allele frequencies of human leukocyte antigen-C (HLA-C) in the patients with Kawasaki disease and the control subjects

HLA alleles	Healthy controls (n = 159) n (%)	KD patients (n = 74) n (%)	Coronary complications	
			Present (n = 21) n (%)	Absent (n = 53) n (%)
HLA-Cw				
01	59 (37.1)	22 (29.7)	6 (28.6)	16 (30.2)
02	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.9)
04	21 (13.2)	11 (14.9)	2 (9.5)	9 (17.0)
05	6 (3.8)	1 (1.4)	0 (0.0)	1 (1.9)
06	25 (15.7)	10 (13.5)	5 (23.8)	5 (9.4)
07	44 (27.7)	20 (27.0)	6 (28.6)	14 (26.4)
08	29 (18.2)	10 (13.5)	3 (14.3)	7 (13.2)
09	23 (14.5)	19 (25.7)[a]	5 (23.8)	14 (26.4)[b]
10	39 (24.5)	24 (32.4)	5 (23.8)	19 (35.8)
12	11 (6.9)	4 (5.4)	2 (9.5)	2 (3.8)
14	34 (21.4)	18 (24.3)	7 (33.3)	11 (20.8)
15	8 (5.0)	1 (1.4)	1 (4.8)	0 (0.0)

KD, Kawasaki disease; RR, relative risk

[a] $p < 0.04$; RR = 2.0 (95% confidence interval [CI], 0.97–4.29) vs healthy control subjects

[b] $p < 0.05$; RR = 2.1 (95% CI, 0.92–4.87) vs healthy control subjects

Table 5 The allele frequencies of human leukocyte antigen-DRB1 (HLA-DRB1) in the patients with Kawasaki disease and the control subjects

HLA alleles	Healthy controls (n = 159) n (%)	KD patients (n = 74) n (%)	Coronary complications	
			Present (n = 21) n (%)	Absent (n = 53) n (%)
HLA-DRB1				
01	29 (18.2)	8 (10.8)	1 (4.8)	7 (13.2)
03	7 (4.4)	1 (1.4)	0 (0.0)	1 (1.9)
04	48 (30.2)	30 (40.5)	6 (28.6)	24 (45.3)[a]
07	26 (16.4)	8 (10.8)	1 (4.8)	7 (13.2)
08	32 (20.1)	14 (18.9)	3 (14.3)	11 (20.8)
09	28 (17.6)	12 (16.2)	7 (33.3)[b]	5 (9.4)
10	4 (2.5)	4 (5.4)	2 (9.5)	2 (3.8)
11	10 (6.3)	8 (10.8)	5 (23.8)[c]	3 (5.7)
12	18 (11.3)	11 (14.9)	2 (9.5)	9 (17.0)
13	32 (20.1)	10 (13.5)	3 (14.3)	7 (13.2)
14	21 (13.2)	10 (13.5)	3 (14.3)	7 (13.2)
15	35 (22.0)	20 (27.0)	5 (23.8)	15(28.3)
16	4 (2.5)	2 (2.7)	1 (4.8)	1 (1.9)

KD, Kawasaki disease; RR, relative risk

[a] $p < 0.05$; RR = 1.9 (95% confidence interval [CI], 0.96–3.82) vs healthy control subjects

[b] $p < 0.04$ between KD patients with and without coronary complication

[c] $p < 0.04$; RR = 4.7 (95% CI, 1.26–17.17) vs healthy control subjects

vs 9.4%; $p < 0.04$). However, there was no significant difference in the frequency of these alleles when each was compared with the healthy control group. The frequency of the HLA-DRB1*04 allele was slightly increased in the Kawasaki disease patients without CC compared with the healthy control group ($p < 0.05$; RR = 1.9) (Table 5).

Discussion

The prevalence of CC among the patients with Kawasaki disease in this study was higher than previously reported (28.4% vs 5%) [22]. This is likely because the patients included had a previous diagnosis of Kawasaki disease and were attending our clinic for this reason. Patients with more severe Kawasaki disease, including those with CC, present for medical care more frequently than patients without CC, and this may explain the higher proportion of CC in our study. Three patients (4%) had a positive family history, and four patients (5.4%) had a history of Kawasaki disease recurrence. Prior studies reported the familial occurrence and recurrence rates for Kawasaki disease to be 1% and 3%, respectively [11, 24, 28].

Our data were confined to Korean children and focused on patients who had Kawasaki disease with CC. Therefore, further research on the effect of the family history and recurrence of Kawasaki disease in association with HLA polymorphisms is needed.

Studies have associated HLA alleles with many different human diseases, such as HLA-B27 with ankylosing

spondylitis and Reiter syndrome, HLA-B35 with subacute thyroiditis, and HLA-DR8 with juvenile rheumatoid arthritis. Most of the early studies on the genetics of Kawasaki disease were conducted using serologic testing that measured HLA antigens. The association of the HLA-Bw22 allele with Kawasaki disease in Japanese studies was evaluated with the microcytotoxicity test used for tissue typing of 205 patients with Kawasaki disease and 500 control samples in the late 1970s [14]. On basis of these studies, a gene was thought to control susceptibility to Kawasaki disease and was linked to the Japanese-specific HLA antigen.

Since the clinical application of genetic technology became available in the 1980s, polymorphisms at many HLA loci have been identified. In addition, there were changes in nomenclature, and the alleles were reclassified. For example, the previously labeled HLA-Bw22 allele was changed to the HLA B54 allele [1, 3].

Our study on the polymorphisms of HLA genes was conducted using the PCR-ARMS method for the HLA class I genes and the PCR-SSP method for the HLA class II genes. There was a significant increase in the frequencies of HLA-B35, -B75, and -Cw09 alleles in the patients with Kawasaki disease compared with the healthy control group. As previously mentioned, this study showed that the HLA-B35 allele was related to susceptibility to Kawasaki disease and the HLA-B75 allele to Kawasaki disease without CC in Korean children. These results suggest that polymorphisms (in some of the B and C loci) in HLA class I genes are associated with Kawasaki disease in Korean children; consistent with prior reports on other ethnic groups [12, 14, 16, 19].

Review of the medical literature on Kawasaki disease and HLA shows that there is a trend toward an association between the HLA-B loci and Kawasaki disease. However, to date, there is no confirmed relationship to a particular locus. It is likely that the HLA-B locus is not the only locus associated with Kawasaki disease. This can be the case because of its functional variation or the potential effects from other related genes around the HLA-B locus. The HLA-B locus and other associated genes might be useful genetic markers for Kawasaki disease.

The HLA-B35 gene is known to play a major role in a variety of infections. For example, in cases with HIV infection, the patients with an increased frequency of HLA-B35 show rapid progression of HIV [9]. Infection has been implicated in the etiology of Kawasaki disease. The finding in our study that the frequency of the HLA-B35 allele was increased in Korean children with Kawasaki disease suggests a role for infection in Kawasaki disease.

The HLA-DRB1 alleles showed no increased frequency in the Kawasaki disease patients compared with the healthy control group. However, when the patients were compared by subgroups, with and without CC, the frequency of HLA-DRB1*11 was significantly increased in the Kawasaki disease patients with CC ($p < 0.04$; RR = 4.7), and HLA-DRB1*04 was increased in the Kawasaki disease patients without CC ($p < 0.05$; RR =1.9) compared with the healthy control group. Comparison of the subgroups with and without CC showed that the frequency of the HLA-DRB1*09 allele was increased in Kawasaki disease patients with CC compared with the Kawasaki disease patients who had no CC (33.3% vs 9.4%; $p < 0.04$), and that there was no significant difference in comparison with the healthy control group. For the HLA-DRB1*11 allele, the finding of a higher allele frequency compared with the healthy control group was amplified by the subgrouping of Kawasaki disease patients with and without CC. Future studies with a larger sample size are needed to confirm these findings.

Several reports describe the presence of HLA-DRB1 and the progression of infections [7]. However, most of the reports on the association of HLA-DRB1 with Kawasaki disease concluded that despite a regional association, their data failed to support a consistent role for HLA class II alleles in Kawasaki disease. If there was any role, it was predicted to be minor [2, 8].

Interpopulation discrepancies of the frequencies of HLA alleles make generalization of results difficult. Matched population profiles are needed for disease association studies because ethnic differences can provide altered disease associations.

In this study, we compared HLA alleles of Kawasaki disease patients with known polymorphic loci of HLA genes in healthy Korean adults. The results we report on the polymorphisms of HLA genes in Kawasaki disease patients may be limited to the Korean population. However, this information may be helpful in future studies on HLA genetic polymorphisms in Kawasaki disease. Further studies with a larger sample size are needed for confirmation of our findings.

References

1. Bannai M, Tokunaga K, Tanaka H, et al. (1997) Five HLA-B22 group alleles in Japanese. Tissue Antigens 49:376–382
2. Barron KS, Silverman ED, Gonzales JC, et al. (1992) Major histocompatibility complex class II alleles in Kawasaki syndrome: Lack of consistent correlation with disease or cardiac involvement. J Rheumatol 19:1790–1793
3. Bodmer JG, Marsh SGE, Albert ED, et al. (1997) Nomenclature for factors of the HLA system, 1996. Tissue Antigens 49: 297–321

4. Bronstein DE, Dille AN, Austin JP, et al. (2000) Relationship of climate, ethnicity and socioeconomic status to Kawasaki disease in San Diego County, 1994 through 1998. Pediatr Infect Dis J 19:1087–1091
5. Bunce M, Welsh KI (1994) Rapid DNA typing for HLA-C using sequence-specific primers (PCR-SSP): Identification of serological and nonserologically defined HLA-C alleles including several new alleles. Tissue Antigen 43:4–17
6. Chang CC, Hawkins BR, Kao HK, et al. (1992) Human leukocyte antigens in southern Chinese with Kawasaki disease. Eur J Pediatr 151:866
7. Cramp ME, Carucci P, Underhill J, et al. (1998) Association between HLA class II genotype and spontaneous clearance of hepatitis C viraemia. J Hepatol 29:207–213
8. Fildes N, Burns JC, Newburger JW, et al. (1992) The HLA class II region and susceptibility to Kawasaki disease. Tissue Antigens 39:99–101
9. Flores-Villanueva PO, Hendel H, Caillat-Zucman S, et al. (2003) Associations of MHC ancestral haplotypes with resistance/susceptibility to AIDS disease development. J Immunol 170: 1925–1929
10. Fujitawa Y, Nakamura Y, Sakata K, et al. (1989) Kawasaki disease in families. Pediatrics 84:666–669
11. Hirata S, Nakamura Y, Yanagawa H (2001) Incidence rate of recurrent Kawasaki disease and related risk factors: From the results of nationwide surveys of Kawasaki disease in Japan. Acta Paediatr 90:40–44
12. Huang Y, Lee YJ, Chen MR, et al. (2000) Polymorphism of transmembrane region of MICA gene and Kawasaki disease. Exp Clin Immunogenet 17:130–137
13. Kaslow RA, Bailowitz A, Lin FY, et al. (1985) Association of epidemic Kawasaki syndrome with the HLA-A2, B44, Cw5 antigen combination. Arthritis Rheum 28:938–940
14. Kato S, Kimura M, Tsuji K, et al. (1978) HLA antigens in Kawasaki disease. Pediatrics 61:252–255
15. Kawasaki T (1967) Acute febrile mucocutaneous lymph node syndrome with lymphoid involvement with specific desquamation of fingers and toes in children. Jpn J Allergy 16:178–222
16. Keren G, Danon YL, Orgad S, et al. (1982) HLA Bw51 is increased in mucocutaneous lymph node syndrome in Israeli patients. Tissue Antigens 20:144–146
17. Krausa P, Moses J, Bodmer W, et al. (1993) HLA-A locus alleles identified by sequence specific PCR. Lancet 341:121–122
18. Krensky AM, Berenberg W, Shanley K, Yunis EJ (1981) HLA antigens in mucocutaneous lymph node syndrome in New England. Pediatrics 67:741–743
19. Krensky AM, Grady S, Shanley KM, et al. (1983) Epidemic and endemic HLA-B and DR associations in mucocutaneous lymph node syndrome. Hum Immunol 6:75–77
20. Matsuda I, Hattori S, Nagata N, et al. (1977) HLA antigens in mucocutaneous lymph node syndrome. Am J Dis Child 131:1417–1418
21. Mori M, Miyamae T, Kurosawa R, et al. (2001) Two-generation Kawasaki disease: Mother and daughter. J Pediatr 139:754–756
22. Newburger JW, Takahashi M, Gerber MA, et al. (2004) Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 114:1708–1733
23. Olerup O, Zetterquist H (1992) HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: An alternative to serological DR typing in clinical practice including donor–recipient matching in cadaveric transplantation. Tissue Antigen 39:225–235
24. Park YW, Han JW, Park IS, et al. (2005) Epidemiologic picture of Kawasaki disease in Korea, 2000–2002. Pediatr Int 47: 382–387
25. Research Committe on Kawasaki disease (1984) Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Ministry of Health and Welfare, Tokyo
26. Sadler AM, Petronzelli F, Krausa P, et al. (1994) Low-resolution DNA typing for HLA-B using sequence-specific primers in allele- or group-specific ARMS/PCR. Tissue Antigen 44:148–154
27. Terai M, Kohno Y, Namba M, et al. (1990) Class II major histocompatibility antigen expression on coronary arterial endothelium in a patient with Kawasaki disease. Hum Pathol 21:231–234
28. Yanagawa H, Nakamura Y, Yashiro M, et al. (1998) Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. Pediatrics 102:E65