Human Lymphocyte Antigen B-Associated Transcript 2, 3, and 5 Polymorphisms and Haplotypes are Associated With Susceptibility of Kawasaki Disease and Coronary Artery Aneurysm

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Capsule: HLA-B associated transcript (BAT) 2, 3, and 5 polymorphisms and haplotypes are associated with Kawasaki disease (KD) and coronary artery aneurysm (CAA) formations. **Objective:** KD, an acute vasculitis with unknown etiology, involves a complex interaction of immuno-inflammatory process, cytokines activation, and genetic factors. We aimed to investigate if genetic variants of human lymphocyte antigen (HLA)-BAT2, 3, and 5 (BAT2, 3, and 5) could be used as markers of susceptibility in KD and CAA. **Methods:** Individuals were divided into three groups: (1) normal controls; (2) KD with CAA; and (3) KD without CAA. Polymorphisms for BAT2 (–8671, 16483), BAT3 (8854, 2–24), and BAT5 (22655, 9569) were genotyped by PCR system with TaqMan allelic discrimination assay. Genotype/allelic frequencies and haplotypes (BAT2^{–8671}-BAT2¹⁶⁴⁸³-BAT3⁸⁸⁵⁴-BAT3^{2–24}-BAT5²²⁶⁵⁵-BAT5⁹⁵⁶⁹) in

each group were compared. **Results:** Genotype distribution and allele frequency of BAT2 –8671, BAT3 8854, and BAT5 22655, 9569 polymorphisms in each group were significantly different. BAT2 –8671*G, BAT3 8854*C, BAT5 22655*C, and 9569*A-related genotypes and alleles are correlated with the developments of KD and CAA. BAT haplotypes of ATTGTG and ATCATG are associated with higher susceptibilities of KD with CAA susceptibility. **Conclusion:** BAT2 –8671, BAT3 8854, and BAT5 22655, 9569 polymorphisms as well as BAT haplotypes (ATTGTG and ATCATG) might be associated with higher KD susceptibility and CAA formation. HLA-B region polymorphisms might contribute to the pathogenesis of KD and CAA. *J. Clin. Lab. Anal.* 24:262–268, 2010. © 2010 Wiley-Liss, Inc.

Key words: coronary artery aneurysm; human lymphocyte antigen; HLA; Kawasaki disease; polymorphism

INTRODUCTION

Kawasaki disease (KD), a complex vasculitis, is associated with immunologic and genetic changes. It is characterized by persistent fever, non-purulent conjunctivitis, oropharyngeal inflammation, induration and erythema of hands and feet, rash, and cervical lymphadenopathy.

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Despite its intensive researches, the etiology of KD remains unclear. Current theories suggest that KD is an immunologically mediated vasculitis (1). The features of KD are immune activation and cytokine-mediated generalized vasculitis. The injured vascular tissues show subendothelial edema, vascular damage, gap formation, and fenestration of endothelial cells, which contribute to the pathogenesis of this disorder (2).

Vascular endothelial cells express major histocompatibility complex (MHC) molecules on their surface for presenting antigenic peptides to T cells, which initiate acquired immune responses (3). Human lymphocyte antigen (HLA) from the MHC has been reported to be associated with immune-mediated vascular diseases (4). Recently, with the clinical application of molecular genetic technology, some HLA polymorphisms have been identified to be associated with KD. It is also believed that HLA has regulatory functions upon the innate and adaptive immune responses. The vascular endothelium is a functional barrier between the vessel wall and the blood stream. The endothelial cell damage or vascular injury leads to the expression and release of HLA-E molecules (5).

A large number of genes within HLA class I region have been identified. These genes include HLA-B associated transcript (BAT) genes. HLA class I genes have been demonstrated to be associated with KD development (6). However, few investigators demonstrated the association between HLA-BAT2, 3, and 5 (BAT2, 3, and 5) and KD susceptibility. In this study, we aimed to search for BAT genes that influence the susceptibility to KD and the occurrence of coronary artery aneurysms (CAAs) in Taiwanese children. Six genetic variations and related haplotypes within BAT region were evaluated. To the best of our knowledge, this is the first survey in the related aspect.

MATERIALS AND METHODS

Taiwanese children with and without the histories of KD were recruited. All individuals were divided into: (1) normal controls; (2) KD with CAA; and (3) KD without CAA. The children with KD were evaluated at China Medical University Hospital and met the criteria of KD. Every patient underwent regular echocardiography examinations. The CAA was identified of 3 mm dilated coronary artery in younger children (≤ 5 years) or 4 mm dilation in older children (> 5 years) (7). The control group consisted of healthy children randomly selected from the Han Chinese Cell and Genome Bank (8). Control subjects were matched for sex and age with the study patients. The estimated prevalence of KD is less than 1/1,000 children; therefore, it should be assumed that there were no KD cases in the control group. This

series was approved by the ethical committee and institutional review board of China Medical University Hospital. Informed consents were signed by the children or their parents who donated their blood.

All individuals accepted the peripheral blood samplings for genotype analyses. Genomic DNA was extracted from peripheral blood leukocytes according to standard protocols (Roche Genomic DNA kit, Roche Diagnostics, Indianapolis, USA). The single nucleotide polymorphisms (SNPs) discovery and genotyping for BAT2, 3, and 5 were obtained from dbSNP (<http://ncbi.nih.gov/SNP/>) and Applied Biosystems (<http://www.appliedbiosystems.com>) (Table 1, Fig. 1). The BAT2, 3, and 5 polymorphisms was detected by polymerase chain reaction (PCR) system with TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) (Table 1) (9). Briefly, the PCR was carried out in a total volume of 12.5 μ l using the following amplification protocol: denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 sec, annealing at 60°C for 15 sec, and extension at 72°C for 15 sec. Furthermore, genotyping of each sample was automatically attributed by measuring the allele-specific fluorescence on the ABI Prism 7700 Sequence Detection System, using the SDS 1.9.1 software for allelic discrimination (Applied Biosystems). Genotype frequencies of each SNP were determined by direct counting. The resulting spectra were processed with SpectroTyper (Sequenom, San Diego, CA, USA) software.

The genotype frequency and allelic frequency distributions of these polymorphisms in each group were estimated and analyzed. BAT haplotypes (BAT2⁻⁸⁶⁷¹-BAT2¹⁶⁴⁸³-BAT3⁸⁸⁵⁴-BAT3²⁻²⁴-BAT5²²⁶⁵⁵-BAT5⁹⁵⁶⁹) in each group were compared. Haplotypes were estimated in compound heterozygotes using the PHASE program. The SAS system with χ^2 test was utilized for statistical analyses. Allelic frequencies were expressed as a percentage of the total number of alleles. Odds ratios were calculated from genotype and allelic frequencies with 95% confidence interval. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Genotype distributions and allele frequencies of BAT2, 3, and 5 polymorphisms in each group were significantly different (Table 2). Genotype distribution and allele frequency of BAT2 -8671 polymorphism in each group were significantly different. Proportions of BAT2 -8671*G homozygote/heterozygote/A homozygote in (1) controls; (2) KD with CAA; and (3) KD without CAA were: (1) 16.2/46.2/37.6%; (2) 0/35.7/64.3%; and (3) 1.7/69.5/28.8%, respectively (Table 2). BAT2 -8671*G-related genotypes and alleles are

TABLE 1. Gene Positions, PCR Primers, and Probe Sequences for BAT2, 3, and 5

Gene name	SNP ID	Nucleotide change	Reporter 1 dye	Allele	Reporter 1 quencher	Reporter 2 dye	Allele	Reporter 2 quencher	Context sequence	PCR annealing temperature (°C)
BAT2 -8671	rs2844476	A/G	VIC	A	NFQ	FAM	G	NFQ	CGCTGGGCGACAGAGCAAGACTCCIA/ GJACTCAAAAAAAAAAAAAAGCAGCA	60
BAT2 16483	rs750332	C/T	VIC	C	NFQ	FAM	T	NFQ	GTTGGAGAACGCTGGCCAAAGTCCQI/ TJATGATCCAGCAAGCACACAAGGCC	60
BAT3 8854	rs1052486	T/C	VIC	T	NFQ	FAM	C	NFQ	CATTACACCTCTTCGGTGTGGTCT/ CJGGGAGGTCGGGACCGGGACGTCCG	60
BAT3 2-24	rs3117583	A/G	VIC	A	NFQ	FAM	G	NFQ	TCTCTAAAGAAAGACGAAGGAAGGA/ GJGGCCGCTGTTGCCAGACACAGAGT	60
BAT5 22655	rs805290	T/C	VIC	T	NFQ	FAM	C	NFQ	TCTGAAACACGTCACCAATAGGGTIT/ CJGTAGACTACGTCACCTAAGTTATTG	60
BAT5 9569	rs805281	G/A	VIC	G	NFQ	FAM	A	NFQ	AAAGATTTTGTGATTGAGACTGGGTIG/ AJGGGGTCTCTCTCACCGACTTCCACG	60

The genotyping method was designed by TaqMan[®] Genotyping Assays (Applied Biosystems).

associated with susceptibility of KD and related CAA formation. In contrast, BAT2 16483 T/C genotypes were not associated with susceptibilities of KD and CAA.

Genotype distribution and allele frequency of BAT3 8854 polymorphism in each group were significantly different. Proportions of BAT3 8854*C homozygote/heterozygote/T homozygote were: (1) 39.5/44.9/15.6%; (2) 64.3/28.6/7.1%; and (3) 27.9/60.7/11.5%, respectively (Table 2). BAT3 8854*C-related genotypes and alleles are associated with higher susceptibility of KD and CAA. In contrast, BAT3 2-24 G/A genotypes were not associated with susceptibilities of KD and CAA. Genotype distribution and allele frequency of BAT5 22655 and 9569 polymorphisms in each group were significantly different. Proportions of BAT3 22655*C homozygote/heterozygote/T homozygote were: (1) 42/41.7/16.3%; (2) 60/33.3/6.7%; and (3) 28.6/60.3/11.1%, respectively (Table 2). Proportions of BAT3 9569*A homozygote/heterozygote/G homozygote were: (1) 40.8/43.6/15.6%; (2) 56.7/36.7/6.7%; and (3) 28.6/60.3/11.1%, respectively.

We also observed the associations of BAT haplotypes and KD development. BAT haplotype ATTGTG and ATCATG are associated with higher susceptibilities of KD and CAA (Table 3). Other BAT haplotypes (GTTGTG, GTTATG, GTCACA, GCTATG, GCTATA, GCTACA, and ATTATG) seemed non-associated with KD or CAA susceptibilities.

DISCUSSION

KD, an acute, self-limited, and systemic vasculitis, is one of the leading causes of acquired heart disease in children (10). Although KD is a mysterious disease of unknown etiology and pathogenesis, it is believed to be caused by infectious agents, host immune dysregulation, and genetic susceptibility (11). The development of KD involves complex interactions between immuno-inflammatory process, cytokines activation, and genetic factors. Indeed, KD is a multisystemic disorder with a possible underlying pathology of immune-mediated vasculitis (10).

Recent studies suggest a potential role of bacterial toxins in the immunopathogenesis of KD (12). During the acute stage of KD, activation of vascular endothelial cells and increased serum levels of proinflammatory cytokines might be involved in the occurrence of inflamed and injured vessels (13). The vascular inflammation may cause the development of CAA and cardiac complications. Patients with these cardiovascular complications are at increased risk of ischemic heart disease, which may lead to myocardial infarction and sudden death (14). Although the administration of immunoglobulin significantly reduces the development of CAAs,

Fig. 1. Map of the BAT2, 3, and 5 located within 4 Mb of the MHC region (from 29,900,000 to 33,900,000 bp on chromosome 6). Positions of HLA-B, C, MICA, B, BAT2, 3, and 5, MSH5, LSM2, and HSPA1B lying within this region are indicated.

around 2–15% of KD patients still suffer from this related complication of CAA (15).

Recent studies have shown that the expression of soluble HLA might have important implications upon the pathogenesis of immune-mediated vascular diseases (5). The HLA-B35, B75, and Cw09 are associated with KD susceptibilities (16). HLA-B*5801 allele might present as a genetic marker for severe cutaneous adverse reactions caused by allopurinol (8). The HLA-DR gene variations were not associated with the susceptibility of KD and CAAs in Taiwanese population (8). HLA-G plays a crucial role for the susceptibility to KD and CAA (17). MHC class II was not associated with the pathogenesis of KD (18). In our earlier survey, we also observed the association between HLA-E gene polymorphism and KD (12).

The gene coding for BAT lies adjacent to TNF gene in the central MHC region. BAT1, a member of the BAT family, could regulate the production of inflammatory cytokines and the development of neurological disorders (19). BAT1 plays a potential role for the regulation of inflammatory reactions in Alzheimer's disease pathology (19). BAT1 is also associated with chronic Chagas cardiomyopathy (20). BAT2 polymorphism has been found to be associated with severe malaria (21) and also with asthma (22), rheumatoid arthritis (23), etc.

BAT3, a nuclear protein, encodes a large proline-rich protein with unknown function. BAT3 was originally identified as one of the genes located within MHC. BAT3 is capable of modulating the transforming growth factor (TGF) signaling. BAT3 also acts as a positive regulator of TGF of collagen expression (24). The

intracellular protein of BAT3 is involved in DNA damage-induced apoptosis (25). BAT3 could bind directly to Nkp30 and engage Nkp30 on NK cells. BAT3 also triggered Nkp30-mediated cytotoxicity, which was essential for tumor rejection (26). BAT3 is an essential regulator of p53-mediated responses to genotoxic stress (27). BAT3 controls DNA damage-induced acetylation of p53 (27).

Genetic studies of the multifactorial diseases, such as KD, are difficult to approach owing to the uncertainty of polygenic traits. The SNPs are the most abundant types of DNA sequence variation in human genome (28). The SNP markers provide a new way for the identification of complex gene-associated diseases. In this study, the genotype distributions, allelic frequencies, and haplotypes for BAT2, 3, and 5 polymorphisms in KD and non-KD patients were statistically different. BAT2 –8671*A, BAT3 8854*C, and BAT5 22655*C and 9569*A related genotypes and alleles are correlated with the developments of KD and CAA. We also observed the BAT haplotypes, ATTGTG and ATCATG, were associated with higher susceptibilities of KD or CAA. Our findings suggested that BAT2, 3, and 5 polymorphisms are useful genetic markers in the prediction of the susceptibility of KD. It also suggests that HLA-B gene and BAT2, 3, and 5 polymorphisms might be involved in KD susceptibility and CAA development. These SNPs might influence the production of soluble HLA-B by vascular endothelial cells, which further compromise the illness progressions of KD.

In conclusion, our survey suggests that BAT2, 3, and 5 molecules might be involved in the pathogenesis of

TABLE 2. Genotype and Allele Distributions of BAT2, 3, and 5 Polymorphisms in Healthy Controls and Kawasaki Disease (KD) Patients With or Without Coronary Artery Aneurysm (CAA)

Gene name (SNP database ID)	Genotype/ allele	Ctrl vs. KD total				KD CAA (+) vs. Ctrl				KD CAA (-) vs. Ctrl				KD CAA (+) vs. CAA (-)			
		Ctrl (n = 665)	KD total (n = 87)	KD CAA(+) (n = 28)	KD CAA(-) (n = 59)	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI
BAT2 -8671 rs2844476	GG	108 (0.162)	1 (0.011)	0 (0)	1 (0.017)	0.001	0.07	0.01-0.49	0.006	0.00	ND	0.001	0.14	0.02-1.04	0.006	0.00	ND
	AG	307 (0.462)	51 (0.586)	10 (0.357)	41 (0.695)		1.19	0.75-1.88		0.45	0.21-1		1.96	1.09-3.54		0.23	0.09-0.6
	AA	250 (0.376)	35 (0.402)	18 (0.643)	17 (0.288)		1.00			1.00			1.00			1.00	
	Allele G	523 (0.393)	53 (0.305)	10 (0.179)	43 (0.364)	0.024	0.68	0.48-0.95	0.001	0.34	0.17-0.67	0.539	0.88	0.6-1.31	0.013	0.38	0.17-0.83
	Allele A	807 (0.607)	121 (0.695)	46 (0.821)	75 (0.636)		1.00			1.00			1.00			1.00	
BAT2 16483 rs750332	TT	501 (0.739)	69 (0.742)	26 (0.867)	43 (0.683)	0.528	2.89	0.38-21.84	0.253	0.00	ND	0.379	1.80	0.24-13.73	0.155	0.00	ND
	CT	156 (0.23)	23 (0.247)	4 (0.133)	19 (0.302)		3.10	0.4-24.13		0.49	0.17-1.44		2.56	0.33-20.11		0.35	0.11-1.14
	CC	21 (0.031)	1 (0.011)	0 (0)	1 (0.016)		1.00			1.00			1.00			1.00	
	Allele T	1,158 (0.854)	161 (0.866)	56 (0.933)	105 (0.833)	0.673	1.10	0.7-1.72	0.085	2.39	0.86-6.68	0.532	0.85	0.52-1.4	0.062	2.80	0.92-8.56
	Allele C	198 (0.146)	25 (0.134)	4 (0.067)	21 (0.167)		1.00			1.00			1.00			1.00	
BAT 3 8854 rs1052486	CC	263 (0.395)	35 (0.393)	18 (0.643)	17 (0.279)	0.343	1.54	0.71-3.31	0.031	3.56	0.81-15.61	0.061	0.96	0.39-2.38	0.005	3.71	0.67-20.4
	TC	299 (0.449)	45 (0.506)	8 (0.286)	37 (0.607)		1.74	0.82-3.68		1.39	0.29-6.66		1.84	0.8-4.25		0.76	0.13-4.34
	TT	104 (0.156)	9 (0.101)	2 (0.071)	7 (0.115)		1.00			1.00			1.00			1.00	
	Allele C	825 (0.619)	115 (0.646)	44 (0.786)	71 (0.582)	0.490	1.12	0.81-1.55	0.012	2.25	1.18-4.31	0.416	0.86	0.59-1.25	0.008	2.63	1.27-5.48
	Allele T	507 (0.381)	63 (0.354)	12 (0.214)	51 (0.418)		1.00			1.00			1.00			1.00	
BAT 3 2-24 rs3117583	GG	7 (0.011)	0 (0)	0 (0)	0 (0)	0.292	0.00	ND	0.768	0.00	ND	0.141	0.00	ND	0.186	0.00	ND
	AG	108 (0.163)	20 (0.215)	4 (0.133)	16 (0.254)		1.39	0.81-2.38		0.78	0.27-2.28		1.73	0.94-3.16		0.45	0.14-1.49
	AA	548 (0.827)	73 (0.785)	26 (0.867)	47 (0.746)		1.00			1.00			1.00			1.00	
	Allele G	122 (0.092)	20 (0.108)	4 (0.067)	16 (0.127)	0.497	1.19	0.72-1.96	0.504	0.70	0.25-1.98	0.201	1.44	0.82-2.5	0.214	0.49	0.16-1.54
	Allele A	1,204 (0.908)	166 (0.892)	56 (0.933)	110 (0.873)		1.00			1.00			1.00			1.00	
BAT5 22655 rs805290	CC	269 (0.42)	36 (0.387)	18 (0.6)	18 (0.286)	0.114	1.55	0.72-3.32	0.116	3.48	0.79-15.26	0.018	0.99	0.4-2.45	0.014	3.50	0.64-19.2
	TC	267 (0.417)	48 (0.516)	10 (0.333)	38 (0.603)		2.08	0.98-4.39		1.95	0.42-9.04		2.11	0.92-4.89		0.92	0.17-5.14
	TT	104 (0.163)	9 (0.097)	2 (0.067)	7 (0.111)		1.00			1.00			1.00			1.00	
	Allele C	805 (0.629)	120 (0.645)	46 (0.767)	74 (0.587)	0.668	1.07	0.78-1.48	0.030	1.94	1.05-3.56	0.357	0.84	0.58-1.22	0.017	2.31	1.15-4.63
	Allele T	475 (0.371)	66 (0.355)	14 (0.233)	52 (0.413)		1.00			1.00			1.00			1.00	
BAT5 9569 rs805281	AA	269 (0.408)	35 (0.376)	17 (0.567)	18 (0.286)	0.160	1.49	0.69-3.21	0.168	3.25	0.74-14.34	0.038	0.98	0.4-2.43	0.033	3.31	0.6-18.2
	GA	287 (0.436)	49 (0.527)	11 (0.367)	38 (0.603)		1.95	0.93-4.12		1.97	0.43-9.06		1.95	0.84-4.5		1.01	0.18-5.59
	GG	103 (0.156)	9 (0.097)	2 (0.067)	7 (0.111)		1.00			1.00			1.00			1.00	
	Allele A	825 (0.626)	119 (0.64)	45 (0.75)	74 (0.587)	0.715	1.06	0.77-1.46	0.051	1.79	0.99-3.25	0.393	0.85	0.59-1.23	0.031	2.11	1.06-4.18
	Allele G	493 (0.374)	67 (0.36)	15 (0.25)	52 (0.413)		1.00			1.00			1.00			1.00	

CI, confidence interval; Ctrl, control subject; OR, odds ratio.

Numbers in parentheses indicate percentage of the genotype or allele frequency.

TABLE 3. Haplotype Analysis of the BAT2, 3, and 5 Gene in KD Patients With or Without Coronary Artery Aneurysm (CAA) and Controls Subjects

Haplotype	Estimated haplotype frequency				<i>P</i>		
	Ctrl (<i>n</i> = 601)	KD total (<i>n</i> = 83)	KD CAL(+) (<i>n</i> = 26)	KD CAL(−) (<i>n</i> = 57)	KD total vs.	KD CAA(+) vs.	KD CAA(−) vs.
					Ctrl	Ctrl	Ctrl
GTTGTG	0.09	0.09	0.04	0.11	0.180	0.169	0.718
GTTATG	0.14	0.10	0.10	0.10	0.112	0.356	0.183
GTCACA	0.01	0.00	0.00	0.00	0.135	0.402	0.215
GCTATG	0.13	0.11	0.08	0.12	0.456	0.270	0.851
GCTATA	0.00	0.00	0.00	0.00	0.710	0.835	0.758
GCTACA	0.01	0.01	0.00	0.01	0.975	0.581	0.699
ATTATG	0.00	0.00	0.00	0.00	0.710	0.835	0.758
ATCACA	0.61	0.68	0.77	0.64	0.096	0.024	0.580
ATTGTG	0.00	0.02	0.02	0.02	0.000003	0.000002	0.000004
ATCATG	0.00	0.01	0.00	0.01	0.007	—	0.001
							0.151
							0.995
							—
							0.378
							—
							0.498
							—
							0.099
							0.940
							0.498

KD and CAA. The genotype and allele frequencies of BAT2, 3, and 5 polymorphisms might be useful markers for the prediction of KD or CAA susceptibility. The presences of BAT2 -8671*A, BAT3 8854*C, and BAT5 22655*C and 9569*A as well as BAT haplotypes ATTGTG and ATCATG might be associated with KD or CAA susceptibility. Our findings also provide the database for further survey of BAT gene polymorphisms in other disorders. However, the real roles of the BAT polymorphisms upon the KD remain to be clarified. Furthermore, other HLA gene polymorphisms upon KD development merit further surveys.

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