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Research Article

Lack of Association between *CLEC5A* Gene Single-Nucleotide Polymorphisms and Kawasaki Disease in Taiwanese Children

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Background. Kawasaki disease is characterized by systemic vasculitis of unknown etiology. Previous genetic studies have identified certain candidate genes associated with susceptibility to KD and coronary artery lesions. Host innate immune response factors are involved in modulating the disease outcome. The aim of this study was to investigate CLEC5A (C-type lectin domain family 5) genetic polymorphisms with regards to the susceptibility and outcome of KD. Methods. A total of 1045 subjects (381 KD patients and 664 controls) were enrolled to identify 4 tagging single-nucleotide polymorphisms (tSNPs) of CLEC5A (rs1285968, rs11770855, rs1285935, rs1285933) by using the TaqMan Allelic Discrimination Assay. The Hardy-Weinberg equilibrium was assessed in cases and controls, and genetic effects were evaluated by the chi-square test. Results. No significant associations were noted between the genotypes and allele frequency of the 4 CLEC5A tSNPs between controls and patients. In the patients, polymorphisms of CLEC5A showed no significant association with coronary artery lesion formation and intravenous immunoglobulin treatment response. Conclusions. This study showed for the first time that polymorphisms of CLEC5A are not associated with susceptibility to KD, coronary artery lesion formation, and intravenous immunoglobulin treatment response in a Taiwanese population.

1. Introduction

Kawasaki disease (KD) is characterized by acute, febrile, and systemic vasculitis and was first described by Kawasaki et al. in 1974 [1]. In developed countries, KD is the leading cause of acquired heart diseases in children [2, 3]. KD occurs worldwide and particularly in Japan, Korea, and Taiwan and mainly affects children less than 5 years of age [4–6]. The most serious complication of KD is the occurrence

of coronary artery lesions (CALs) [7, 8]. The prevalence of KD in children younger than 5 years is the highest in Japan, followed by Korea and Taiwan, and lowest in Europe. Previous studies have either failed to identify causative pathogens for KD or reported discrepant results [9–11]. Therefore, it is possible that a genetic background plays an important role in the pathogenesis of KD.

CLEC5A (C-type lectin domain family 5, member A; also known as myeloid DAP12-associating lectin (MDL-1))

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contains a C-type lectin-like fold similar to the naturalkiller T-cell C-type lectin domains and is associated with a 12-kDa DNAX-activating protein (DAP12) on myeloid cells [12–14]. Signaling via this complex constitutes a significant activation pathway in myeloid cells and plays an important role in immune defense. Recently, it has been demonstrated that CLEC5A acts as a signaling receptor for proinflammatory cytokine release, and that blockade of CLEC5A-mediated signaling attenuates the production of proinflammatory cytokines by macrophages infected with dengue virus [14]. In contrast, it has been demonstrated that MDL-1 stimulation induces a significant amount of RANTES and macrophage-derived chemokine (MDC) production in cooperation with signaling through TLR in mouse myeloid cells [15]. Furthermore, there is ample evidence that activation of peripheral blood monocytes/macrophages [16–18], proinflammatory cytokines [16], and the RANTES gene play a central role during acute KD [19, 20]. A persistent or increased expression of chemokine genes in the convalescent phase in patients is associated with coronary artery lesions [17, 19]. In addition, infiltration by the cells is notable in affected tissues in autopsy cases and in skin biopsy specimens from KD patients [21].

However, no *CLEC5A* genetic association with KD has previously been reported. To gain further understanding of the genetic role of *CLEC5A* in the pathogenesis of KD, the aim of our study was to determine if any *CLEC5A* SNPs are associated with susceptibility to KD, CAL formation, or IVIG treatment response in Taiwanese children.

2. Patients and Methods

2.1. Patients Studied. All study cases were children enrolled from Chang Gung Memorial Hospital, Kaohsiung Medical Center, between 2001 and 2009, who fulfilled the diagnostic criteria for KD. All patients were treated with IVIG (2 g/kg) and aspirin as per our previous studies [7, 8, 18]. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Blood samples were collected after informed consent was obtained from parents or guardians. CAL formation was defined as the internal diameter of the coronary artery measuring at least 3 mm (4 mm if the subject was over the age of 5 years) or the internal diameter of a segment at least 1.5 times that of an adjacent segment, as observed in echocardiography [8, 22]. IVIG responsiveness was defined as defervescence within 48 h after the completion of IVIG treatment and no recurrence of fever (temperature > 38°C) for at least 7 days after IVIG with marked improvement or normalization of inflammatory signs [7, 8].

2.2. DNA Extraction. Blood cells were subjected to DNA extraction by treating them first with 0.5% SDS lysis buffer and then protease K (1 mg/mL) for digestion of nuclear protein for 4 h at 60°C. Total DNA was harvested by using a Gentra extraction kit followed by 70% alcohol precipitation as described in our previous report [23].

Table 1: Basal characteristics of the patients with Kawasaki disease and normal controls.

Characteristic	Patients with KD	Normal controls		
	N = 381	N = 664		
Male gender, no. (%)	247 (64.8%)	314 (55.2%)		
Mean (SD) age (years)	1.7 ± 1.6	5.7 ± 4.9		
Age range (years)	0-11	0-51		
CAL formation, no. (%)	37 (9.7%)			
IVIG resistance, no. (%)	49 (12.9%)			

CAL: coronary artery lesion; IVIG: intravenous immunoglobulin; SD: standard deviation.

2.3. SNPs Selection for CLEC5A. We selected tagging SNPs (tSNPs) of CLEC5A from the release 2.0 Phase II data of the HapMap Project (http://www.hapmap.org). tSNPs were chosen according to the following criteria: $r^2 \ge 0.8$, the minor allele frequency (MAF) $\ge 10\%$ in the Han Chinese population, and tSNPs located in exon or 1 kb UTR.

2.4. Genotyping. Genotyping was carried out using the Taq-Man Allelic Discrimination Assay (Applied Biosystems, Foster city, Calif, USA) as per our previous report [24]. The polymerase chain reaction (PCR) was performed using a 96-well microplate with an ABI9700 Thermal Cycler. After PCR, fluorescence was detected and analyzed using System SDS software version 1.2.3.

2.5. Statistical Analysis. JMP 8.0 for Windows was used for analysis. Statistical differences between cases and controls in genotype and allele frequency were assessed using the χ^2 test or Fisher's exact test. The Hardy-Weinberg equilibrium was assessed using the χ^2 test with 1 degree of freedom. Statistical differences in genotype and allele frequency of KD patients with or without CAL formation and patients with IVIG resistance/responsiveness were assessed using the χ^2 test. The Bonferroni test was used to correct for multiple tests. Linkage disequilibrium (LD) was assessed for any pair of SNPs, and haplotype blocks were defined using the default setting of the Haploview software 4.1 (Broad Institute, Cambridge, Mass, USA).

3. Results

3.1. Lack of Association between CLEC5A tSNPs and the Susceptibility of KD. A total of 381 KD patients and 664 controls were included in this study (Table 1). The distribution of CLEC5A genotypes was in accordance with the Hardy-Weinberg equilibrium for both cases and controls (Table 2). However, none of the tSNPs was significantly associated with the genotype or allele frequency of the controls or KD patients under 3 genetic models (dominant, recessive, or allelic models) (Table 2).

	Genotype	Case (%) (n = 381)	Control (%) (n = 664)	Allele	Case (%) (n = 381)	Control (%) (n = 664)	Genotype <i>P</i> value	Dominant <i>P</i> value	Recessive P value	Allelic <i>P</i> value
	GG	70 (18.5)	141 (21.5)	G	325 (42.9)	596 (45.4)				
rs1285968	AG	185 (48.8)	314 (47.9)	A	433 (57.1)	716 (54.6)	0.484	0.488	0.245	0.261
	AA	124 (32.7)	201 (30.6)							
rs11770855	GG	88 (23.5)	147 (22.5)	G	366 (48.9)	623 (47.8)				
	AG	190 (50.8)	329 (50.5)	A	382 (51.1)	681 (52.2)	0.877	0.643	0.718	0.615
	AA	96 (25.7)	176 (27.0)							
rs1285935	AA	29 (7.6)	51 (7.8)	A	208 (27.4)	341 (26.1)				
	GA	150 (39.5)	239 (36.5)	G	552 (72.6)	967 (73.9)	0.640	0.390	0.923	0.519
	GG	201 (52.9)	364 (55.7)							
rs1285933	TT	9 (2.4)	30 (4.6)	T	136 (18.0)	263 (20.2)				
	CT	118 (31.2)	203 (31.1)	С	620 (82.0)	1041 (79.8)	0.194	0.488	0.072	0.228
	CC	251 (66.4)	419 (64.3)							

TABLE 2: Genotype and allele frequencies of the CLEC5A gene in controls and patients with Kawasaki disease.

Table 3: Genotype and allele frequencies of the *CLEC5A* gene in patients with Kawasaki disease with or without coronary artery lesion formation (CAL).

	Genotype	CAL (%) $(n = 37)$	Without $(\%)$ $(n = 336)$	Allele	CAL (%) $(n = 37)$	Without $(\%)$ $(n = 336)$	Genotype <i>P</i> value	Dominant <i>P</i> value	Recessive <i>P</i> value	Allelic <i>P</i> value
rs1285968	GG	6 (17.1)	62 (18.5)	G	31 (44.3)	286 (42.6)				
	AG	19 (54.3)	162 (48.2)	A	39 (55.7)	386 (57.4)	0.784	0.568	0.849	0.781
	AA	10 (28.6)	112 (33.3)							
rs11770855	GG	8 (22.2)	78 (23.6)	G	35 (48.6)	323 (48.9)	0.968	0.921	0.849	0.958
	AG	19 (52.8)	167 (50.6)	A	37 (51.4)	337 (51.1)				
	AA	9 (25.0)	85 (25.8)							
rs1285935	AA	3 (8.1)	26 (7.8)	A	21 (28.4)	184 (27.5)				
	GA	15 (40.5)	132 (39.4)	G	53 (71.6)	486 (72.5)	0.985	0.864	0.941	0.867
	GG	19 (51.4)	177 (52.8)							
rs1285933	TT	1 (2.7)	7 (2.1)	T	12 (16.2)	119 (17.9)				
	CT	10 (27.0)	105 (31.5)	С	62 (83.8)	547 (82.1)	0.840	0.633	0.812	0.724
	CC	26 (70.3)	221 (66.4)							

3.2. Lack of Association between CLEC5A tSNPs and CAL Formation, IVIG Treatment or Aneurysm Formation in KD Patients. In this study, 37 patients (9.9%) had CAL formation and 49 patients (13.1%) had resistance to the initial IVIG treatment (Table 1). However, no tSNPs were significantly associated with genotype or allele frequency in the KD patients with or without CAL formation (Table 3). Additionally, the CLEC5A polymorphisms tested in this study failed to show any significant associations with genotype or allele frequency in the KD patients who showed a response to IVIG treatment (Table 4).

3.3. Haplotype Analysis of CLEC5A Genetic Polymorphisms in the Susceptibility, CAL Formation, and IVIG Treatment of KD Patients. We also calculated pairwise linkage disequilibrium (LD) of the SNPs (see Supplemental Figure 1 in supplementary material available online at doi:10.1155/2012/398628) and analyzed the relationship between the haplotypes of

CLEC5A and susceptibility to KD (Supplemental Table 1), CAL formation (Supplemental Table 2) and IVIG treatment response (Supplemental Table 3) in the KD patients. However, none was significantly associated with the phenotype.

4. Discussion

The C-type lectin-like super domain (CTLD) family has diverse functions, and in particular, is important in innate immunity including nature killer (NK) function or pathogen recognition [25]. CLEC5A belongs to the Group V "NK cell receptors" family, and MDL-1 expression is upregulated in activated myeloid cells [26] and acts as a signaling receptor for proinflammatory cytokine and chemokine release [14]. Even though a number of reports have demonstrated that KD involves activation of a wide array of immunological elements such as T cells and macrophages [16–18, 27], with the subsequent release of several cytokines [28], only a few

	Genotype	Resistant (%) (n = 49)	Responsive (%) (<i>n</i> = 326)	Allele	Resistant (%) (n = 49)	Responsive $(\%)$ $(n = 326)$	Genotype <i>P</i> value	Dominant <i>P</i> value	Recessive P value	Allelic <i>P</i> value
rs1285968	GG	7 (14.6)	63 (19.4)	G	37 (38.5)	286 (44.0)				
	AG	23 (47.9)	160 (49.2)	A	59 (61.5)	364 (56.0)	0.602	0.397	0.427	0.314
	AA	18 (37.5)	102 (31.4)							
rs11770855	GG	12 (24.5)	74 (23.1)	G	52 (53.1)	308 (48.1)				
	AG	28 (57.1)	160 (50.0)	A	46 (46.9)	332 (51.9)	0.437	0.205	0.833	0.363
	AA	9 (18.4)	86 (26.9)							
rs1285935	AA	2 (4.1)	27 (8.3)	A	25 (25.5)	181 (27.8)				
	GA	21 (42.9)	127 (39.1)	G	73 (74.5)	469 (72.2)	0.567	0.954	0.303	0.629
	GG	26 (53.0)	171 (52.6)							
rs1285933	TT	2 (4.1)	7 (2.2)	T	15 (15.3)	121 (18.7)				
	CT	11 (22.4)	107 (33.0)	С	83 (84.7)	527 (81.3)	0.267	0.233	0.414	0.421
	CC	36 (73.5)	210 (64.8)							

Table 4: Genotype and allele frequencies of the *CLEC5A* gene in patients with Kawasaki disease responding or not responding to intravenous immunoglobulin (IVIG) treatment.

reports have addressed the role of lectin in the pathogenesis of KD.

Several genetic associations with susceptibility to KD and CAL formation have been reported, but the results are inconsistent [29-32]. Previous genetic association studies have indicated that the intronic SNP (rs28493229) of ITPKC, 1,4,5-trisphosphate 3-kinase C, reduces gene expression by altering splicing efficiency, and the C allele contributes to immune hyperreactivity in KD patients [29]. Recently, it has been demonstrated that rs28493229 is associated with susceptibility to KD and CAL formation [24, 29]. ITPKC is able to regulate the immune system via calcium-dependent NFAT pathways [29]. Similarly, previous studies have indicated that C-type lectin receptors (CLRs) are critical in the activation of the Syk-mediated NFAT signaling pathway [33]. In addition, CLEC5A has been shown to play a key role in host defense and to be involved in dengue virusmediated disease [14]. This finding suggests CLEC5A may be a potential target protein that involves calcium-dependent immune regulation and contributes to the development of coronary artery lesions. However, we did not find evidence to support a genetic role of CLEC5A in the pathogenesis of KD. Since we picked tagging SNPs from the HapMap database, only the tagging SNPs with a minor allele frequency of more than 10% were selected. Although our tSNP could capture majority of the underlying genetic variances with MAF > 10% across the CLEC5A gene, the rare causal genetic polymorphisms in CLEC5A may not have been detected in this study. Therefore, we cannot rule out or exclude rare causal genetic polymorphisms in CLEC5A. In addition, there are, at least, seventeen groups of CLRs in vertebrates. Indeed, it has been reported that mannose-binding lectin gene polymorphisms are associated with susceptibility to KD [34] and CAL formation [35]. Thus, large-scale DNA sequencing to CLR family is needed to better understand KD.

In conclusion, this study showed for the first time that tSNPs of *CLEC5A* are not associated with susceptibility to

KD, CAL formation, and IVIG treatment response in a Taiwanese population.

Abbreviations

KD: Kawasaki disease

IVIG: Intravenous immunoglobulin CAL: Coronary artery lesions

CLEC5A: C-type lectin domain family 5.

Author's Contribution

Y.-L. Yang and W.-P. Chang contributed equally to this paper.

Competing Interests

The authors declare that no competing interests exist.

Acknowledgments

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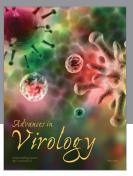
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