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Original article

Genetic variations within the PSORS1 region affect Kawasaki disease development and coronary artery aneurysm formation

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ARTICLE INFO

Article history:
Received 4 February 2013
Received in revised form
4 February 2013
Accepted 5 February 2013
Available online 16 May 2013

Keywords:
coronary artery aneurysm
Kawasaki disease
PSORS1C1
PSORS1 region
SNPs

ABSTRACT

Background: Kawasaki disease (KD) is a pediatric systemic vasculitis, for which both genetic and environmental factors are suspected. HLA gene clusters within the major histocompatibility complex (MHC) region at chromosome 6p21.3 have been recently linked to KD. However, little was known about the roles of non-MHC genes during KD development. This study examines the association of psoriasis susceptibility 1 (PSORS1) genetic variants at the MHC region with KD development.

Methods: A total of 93 KD patients and 680 healthy children were enrolled. Three unique single nucleotide polymorphisms (SNPs) that cover *PSORS1C1*, *PSORS1C2*, and *CDSN* genes were genotyped by *Taqman* genotyping assay. The frequency of genetic variants was assessed by χ^2 analysis.

Results: Polymorphism rs1064190 located at the promoter region of *PSORS1C1* is found to be associated with KD development ($p = 0.026$) with higher T/T genotype frequency ($p = 0.006$) the T-A-T haplotype is more frequent in KD patients than normal controls ($p = 0.033$). In addition, T allele at rs1064190 shows a protective allele for coronary artery aneurysm (CAA) formation in KD patients ($p = 0.015$). The plasma activity of GOT/GPT, the indicators for KD heart damage, are significantly lower in patients with T/T genotype than in those with non-T/T genotype.

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http://dx.doi.org/10.1016/j.biomed.2013.03.001

Conclusion: Results suggest pivotal roles of polymorphisms within the PSORS1 region in KD pathogenesis. Since this region has been linked to psoriasis, this finding provides molecular evidence to suggest the possible linkage between KD and psoriasis.

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1. Introduction

Kawasaki disease (KD) is an acute, self-limited, and systemic vasculitis, a leading cause of acquired heart disease in children [1,2]. Clinical symptoms include skin rash, inflammation of mucous membranes in the mouth, nose, or throat, plus swollen lymph nodes with persistent high fever. During the acute stage, the activation of vascular endothelial cells and increased serum levels of proinflammatory cytokines are involved in the occurrence of inflamed and injured vessels. The inflammation of blood vessels can affect functions of coronary arteries and lead to worse complications. Cardiac sequelae, such as coronary artery aneurysm (CAA), are among the key aspects of this disease [3,4]. Patients with these cardiovascular complications are at increased risk of developing ischemic heart disease, which may lead to myocardial infarction and sudden death.

Currently, there is no specific test for KD because its etiology remains uncertain, although many clinical observations support the involvement of microorganism infection [5,6]. Molecular mimicry or superantigens from *Staphylococci* are suspected as the causes to trigger the activation of common immune pathways, resulting in inflammation [7]. Nevertheless, the epidemiological study indicates KD affecting all ethnic groups, yet it is more prevalent among the children of Asian and Pacific Island descent. Therefore, both host immune dysregulation and genetic susceptibility were suggested as key factors to determine KD development [8,9]. Genome-wide studies further provided cogent evidence that functional polymorphisms play important roles in KD development [10–12]. Variations in the genes involved in regulating immune functions and inflammation have been found related to KD susceptibility [13–15]. Some genes playing roles in cardiovascular pathogenesis, e.g., formation of CAAs, likewise also proved elemental to KD development [12,16].

However, the variations in the gene clusters within the major histocompatibility complex (MHC) region at chromosome 6p21.3 have been linked to dysregulated inflammation disorders such as immune-mediated vascular disease [17]. To date, human leukocyte antigen (HLA) genes within this region remain the best documented association for KD, e.g., variations in HLA-Bw22 (now designated Bw54), HLA-Bw51, and HLA-G [9,18]. Still, potential roles of other non-HLA candidate genes in the MHC region were not well studied in KD patients. The psoriasis susceptibility 1 (PSORS1) region is known as one major susceptibility loci on chromosome 6 located telomeric to HLA-C locus for psoriasis and psoriatic arthritis by a linkage disequilibrium mapping [19–21]. With the completion of the human genome project, at least 10 genes were defined in this region, while only certain genes can express detectable ribonucleic acid (RNA) and protein levels in skin cells, e.g., *PSORS1C1*, *PSORS1C1*, and *CDSN* [22,23]. Although the biological functions of these genes are largely unknown, sequence analysis revealed a highly polymorphic nature of the gene structure with more than 10 SNPs/kb, a common trait shared by HLA genes [24,25]. Therefore, it is widely believed that these genes may still perform critical roles in regulating T-cell responses to self-antigens and local immunological activation [22]. Interestingly, clinical investigations indicated that certain KD cases may develop psoriatic lesions, suggesting common pathogenic mechanisms shared by both these immune-mediated diseases [26–28]. Potential functions in immune regulation arouse interest in genetic variations in the PSORS1 region determining KD susceptibility, as proposed here. The linkage of genetic variation with CAA formation was also studied.

2. Materials and methods

2.1. Study population

A total of 93 patients who fulfilled diagnostic criteria for KD were identified at China Medical University Hospital from 1998 to 2005 and enrolled in this study. Clinical observation indicated that all the patients in this study underwent regular echocardiography examinations, beginning at the acute stage of KD, at 2 and 6 months after onset, and once a year thereafter. For the control group, DNA samples of 680 healthy children were randomly selected from the Han Chinese Cell and Genome Bank. Controls were matched for sex and age with patients. Since the estimated prevalence of KD in Taiwan is less than 1/1000 children, we assume that there are no KD cases in the control group. This study was approved by the Institutional Review Board at China Medical University, and informed consent was obtained from parents.

2.2. Genomic DNA extraction and genotyping of SNPs in the PSORS1 region

Genomic DNA was extracted from peripheral blood leukocytes via a standard protocol (Genomic DNA kit; Qiagen, Valencia, CA). DNA fragments containing rs1064190, rs1265099, and rs1265114 SNP sites were amplified by polymerase chain reaction (PCR) using *Taqman* SNP genotyping assay system from Applied Biosystems, Inc. (Carlsbad, CA). Probe search and design are available on their website (https://products.appliedbiosystems.com/ab/en/US/adirect/ab?cmd=ABGTKeywordSearch). Probe IDs for rs1064190, rs1265099, and rs1265114 were C-2436655-20, C-

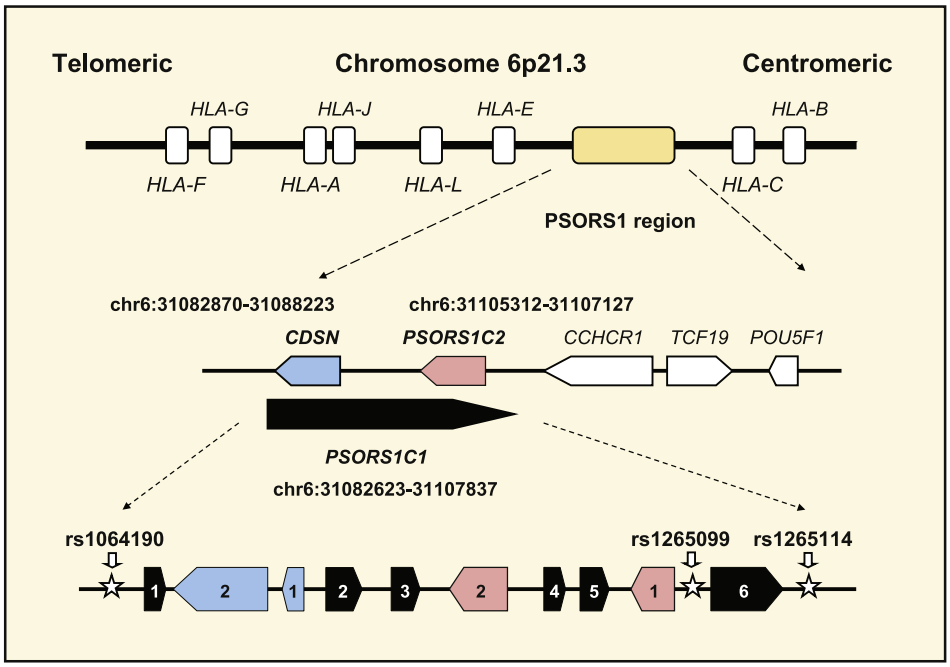

Fig. 1 – Gene map of a subsection of the PSORS1 region located at the MHC gene cluster region on chromosome 6p. *PSORS1C1* gene (black boxes) overlaps with *PSORS1C2* (spotted boxes) and *CDSN* (striped boxes) genes on 6p21.3. Unique SNP sites, rs1064190, rs1265099, and rs2076311, which cover these three genes were studied for association with KD development. Exons for each gene were numbered, albeit not to scale. KD = Kawasaki disease; MHC = major histocompatibility complex; PSORS1 = psoriasis susceptibility 1.

2438331-1, and Sheu-SNP-002, respectively. PCR amplification comprised initial denaturation at 95°C for 5 minutes, followed by 40 cycles at 95°C for 10 seconds, 56°C for 10 seconds, and 72°C for 20 seconds, with one additional cycle at 72°C for 5 minutes.

Genetic variation was detected by reading fluorescence signals of PCR products. Positive signal indicates a perfect match between the probe and tested DNA, thus identifying wild-type alleles.

Table 1 – Polymorphisms within the PSORS1 region in KD and control.

SNP	Genotype/allele	Control	KD	KD vs. Control		
				p	OR	95% CI
rs1064190		(*n* = 659)	(*n* = 93)			
	TT	138 (20.9)	33 (35.5)	***0.006****	1.87	1.07–3.26
	GT	318 (48.3)	34 (36.6)		0.83	0.49–1.43
	GG	203 (30.8)	26 (28.0)		1.00	
	allele T	594 (45.1)	100 (53.8)	***0.026****	1.42	1.04–1.93
	allele G	724 (54.9)	86 (46.2)		1.00	
rs1265099		(*n* = 656)	(*n* = 92)			
	GG	135 (20.6)	21 (22.8)	0.849	1.20	0.65–2.21
	AG	321 (48.9)	45 (48.9)		1.08	0.64–1.80
	AA	200 (30.5)	26 (28.3)		1.00	
	allele A	591 (45.0)	87 (47.3)	0.568	1.09	0.80–1.49
	allele G	721 (55.0)	97 (52.7)		1.00	
rs1265114		(*n* = 664)	(*n* = 93)			
	TT	6 (0.9)	0 (0.0)	0.443	0.00	—
	CT	78 (11.7)	14 (15.1)		1.32	0.71–2.44
	CC	580 (87.3)	79 (84.9)		1.00	
	allele T	90 (6.8)	14 (7.5)	0.705	1.12	0.62–2.01
	allele C	1238 (93.2)	172 (92.5)		1.00	

Numbers in parentheses indicate the percentage of the genotypic or allelic frequency.
CI = confidence interval; KD = Kawasaki disease; OR = odds ratio; PSORS1 = psoriasis susceptibility 1; SNP = single nucleotide polymorphism.
*Numbers in bold italics indicate significant differences.

Table 2 – Polymorphisms within the PSORS1 region in KD patients and associations with CAA formation.

SNP	Genotype/allele	Control	KD-CAA (+)	KD-CAA (–)	KD-CAA (+) vs. Control			KD-CAA (–) vs. Control			KD-CAA (+) vs. KD-CAA (–)		
					p	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI
rs1064190		(*n* = 659)	(*n* = 30)	(*n* = 63)									
	TT	138 (20.9)	11 (36.7)	22 (34.9)	0.623	1.35	0.58–3.14	***0.033****	2.31	1.14–4.67	0.109	0.58	0.2–1.68
	GT	318 (48.3)	7 (23.3)	27 (42.9)		0.37	0.14–0.96		1.23	0.63–2.40		0.30	0.1–0.94
	GG	203 (30.8)	12 (40)	14 (22.2)		1.00			1.00			1.00	
	allele T	594 (45.1)	29 (48.3)	71 (56.3)	0.619	1.14	0.68–1.91	***0.015****	1.57	1.09–2.27	0.305	0.72	0.39–1.34
	allele G	724 (54.9)	31 (51.7)	55 (43.7)		1.00			1.00			1.00	
rs1265099		(*n* = 656)	(*n* = 30)	(*n* = 62)									
	GG	135 (20.6)	8 (26.7)	13 (21)	0.712	1.48	0.54–4.04	0.972	1.07	0.51–2.26	0.830	1.38	0.41–4.65
	AG	321 (48.9)	14 (46.7)	31 (50)		1.09	0.45–2.65		1.07	0.58–1.97		1.02	0.36–2.89
	AA	200 (30.5)	8 (26.7)	18 (29)		1.00			1.00			1.00	
	allele A	591 (45.0)	30 (50)	57 (46)	0.451	1.22	0.73–2.05	0.844	1.04	0.72–1.50	0.608	1.18	0.63–2.18
	allele G	721 (55.0)	30 (50)	67 (54)		1.00			1.00			1.00	
rs2076311		(*n* = 664)	(*n* = 30)	(*n* = 63)									
	TT	6 (0.9)	0 (0)	0 (0)	0.150	0.00	—	0.739	0.00	—		—	—
	CT	78 (11.7)	7 (23.3)	7 (11.1)		2.26	0.94–5.45		0.93	0.41–2.11	0.123	2.43	0.77–7.73
	CC	580 (87.3)	23 (76.7)	56 (88.9)		1.00			1.00			1.00	
	allele T	90 (6.8)	7 (11.7)	7 (5.6)	0.146	1.82	0.8–4.11	0.599	0.81	0.37–1.79	0.140	2.25	0.75–6.72
	allele C	1238 (93.2)	53 (88.3)	119 (94.4)		1.00			1.00			1.00	

Numbers in parentheses indicate percentage of the genotypic or allelic frequency.
CAA = coronary artery aneurysm; CI = confidence interval; KD = Kawasaki disease; OR = odds ratio; PSORS1 = psoriasis susceptibility 1; SNP = single nucleotide polymorphism.
*Numbers in bold italics indicate significant differences.

Table 3 – Haplotype analysis within the PSORS1 region in KD patients and healthy control subjects.

Haplotype	Estimated haplotype frequency				*p*			
	Control ($n = 680$)	KD total ($n = 93$)	KD-CAA (+) ($n = 30$)	KD-CAA (−) ($n = 63$)	KD total vs. Control	KD-CAA (+) vs. Control	KD-CAA (−) vs. Control	KD-CAA (+) vs. KD-CAA (−)
G-A-C	29.1%	23.8%	18.5%	25.8%	0.132	0.077	0.440	0.274
G-A-T	1.0%	0.6%	0.6%	0.7%	0.584	0.798	0.747	0.976
G-G-C	21.6%	19.9%	16.6%	21.9%	0.587	0.350	0.949	0.399
G-G-T	3.3%	2.0%	0.9%	2.4%	0.347	0.305	0.591	0.488
T-A-C	24.9%	27.5%	31.5%	25.4%	0.455	0.247	0.903	0.380
T-A-T	0.1%	1.0%	1.1%	1.3%	***0.033****	0.082	***0.012****	0.923
T-G-C	17.6%	21.4%	26.7%	19.0%	0.212	0.074	0.704	0.231
T-G-T	2.3%	4.0%	4.0%	3.5%	0.183	0.418	0.404	0.882

Numbers in parentheses indicate the percentage of haplotype frequency.
CAA = coronary artery aneurysm; KD = Kawasaki disease; PSORS1 = psoriasis susceptibility 1.
*Numbers in bold italics indicate significant differences.

2.3. *Clinical symptoms and association study*

Clinical information of KD patients in this study was gleaned from clinical notes, e.g., blood tests, muscle function of heart, and fever duration. All the patients in this study were treated with intravenous immunoglobulin (IVIG; 2 g/kg infused over 8-12 hours) and oral aspirin (80-100 mg/kg/day); echocardiographs were obtained by the pediatric cardiologist before or within 14 days of IVIG administration. CAAs were diagnosed according to criteria proposed by the Japanese Kawasaki Disease Research Committee (Research Committee on KD). Coronary arteries were classified as abnormal if the internal lumen diameter was >3 mm in children younger than 5 years or >4 mm in children older than 5 years, the internal diameter of a segment measured ≥1.5 times that of an adjacent segment, or the coronary lumen was clearly irregular.

2.4. *Plasma activity assay of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase*

Blood samples were collected from KD patients and subjected to plasma separation. Determination of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activity in plasma was conducted as per Reitman and Frankel [29] using kits purchased from RANDOX Laboratories (Antrim, UK). After adding the substrate, the developed color was measured using a spectrophotometer at a wavelength of 505 nm; the international activity unit of the sample was calculated by normalizing the data with the standard curve using aspartate as substrate for GOT and alanine as substrate for GPT.

2.5. *Statistic analysis*

Allelic and genotype frequency distributions for three polymorphisms of KD patients and controls were performed by χ^2 analysis with SPSS software (version 10.0, SPSS Inc., Chicago, IL), with $p < 0.05$ considered statistically significant. Allelic and genotype frequencies were expressed as percentages of total alleles and genotypes, The odds ratio (OR) derived from the allelic or genotype frequency with 95% confidence interval (95% CI). Haplotypes were determined by the Bayesian statistical method available in program Phase 2.1; adherence to Hardy-Weinberg equilibrium constant was tested via χ^2 test with one degree of freedom.

3. Results

The gene locus for the PSORS1 region has been mapped to the MHC region on chromosome 6p, a region linked to a range of autoimmune diseases. Within the MHC region, 201 reliable, polymorphic, and evenly spaced SNPs were previously genotyped [24]. Among these defined SNPs, rs1064190, rs1265099, and rs1265114 proved unique to the PSORS1 region covering *PSORS1C1*, *PSORS1C2*, and *CDSN* genes (Fig. 1). Notably, *PSORS1C1* genomic sequence overlaps with genes *CDSN* and *PSORS1C2* such that our study evaluated the association of these three genes with KD development. Genotyping PCR via *Taqman* system analyzed the genetic variants of these three SNPs in study subjects and controls. No significant differences in allele and genotype frequencies for rs1265099 and rs1265114 emerged, yet a significant difference was found in frequency T/T at rs1064190 ($p = 0.006$; OR = 1.87, 95% CI = 1.07-3.26). In addition, KD patients have a higher frequency of T allele at rs1064190 as compared to controls ($p = 0.026$, OR = 1.42, 95% CI = 1.04–1.93) (Table 1).

The formation of CAAs is a prime cause of heart attack and a significant risk of death or disability for KD patients. We aimed to understand the impact of polymorphisms in the PSORS1 region on CAA formation. As shown in Table 2, we analyzed genotype frequency as well as allele frequency at rs1064190, rs1265099, and rs1265114 with respect to the symptoms of CAA formation in KD patients. Data showed no links of rs1265099 or rs1265114 with CAA formation in KD patients, neither in genotype frequency (rs1265099: $p = 0.849$; rs1265114: $p = 0.443$) nor in allele frequency (rs1265099: $p = 0.568$; rs1265114: $p = 0.705$). However, polymorphisms at rs1064190 were found to determine CAA formation in patients. As compared with controls, KD patients not suffering from CAAs showed a greater tendency to carry the T/T genotype ($p = 0.033$; OR = 2.31, 95% CI = 1.14–4.67), as shown in Table 2. T allele at this SNP site was found to be protective against CAA formation in KD patients ($p = 0.015$; OR = 1.57,

Table 4 – Association between rs1064190 alleles and clinical parameters in children with KD CAA (+) and KD CAA (−).

Clinical parameters[a]	KD CAA (+)			KD CAA (−)			p/p_{adj}[b] KD CAA (+) vs. KD CAA (−)		
	TT ($n = 11$)	non-TT ($n = 19$)	Total ($n = 30$)	TT ($n = 22$)	non-TT ($n = 41$)	Total (n = 63)	TT	non-TT	Total
Age, y	1.45 ± 0.95	2.26 ± 2.11	1.88 ± 1.78	1.44 ± 0.97	1.9 ± 1.55	1.80 ± 1.43	0.989/1.0	0.489/1.0	0.825/1.0
WBC, $\times 10^3/mm^3$	16.63 ± 5.8	17.01 ± 6.37	15.94 ± 6.15	13.66 ± 6.11	13.35 ± 4.21	13.97 ± 5.09	0.227/1.0	0.021/0.231	0.159/1.0
Hemoglobin, g/dL	10.82 ± 1.32	11.11 ± 1.29	11.08 ± 1.31	11.29 ± 1.11	11.36 ± 0.94	11.31 ± 0.98	0.404/1.0	0.558/1.0	0.476/1.0
Platelet, $\times 10^3/mm^3$	436.67 ± 193.74	530.36 ± 266.89	475.79 ± 219.75	421.13 ± 149.65	370.67 ± 99.95	393.85 ± 131.80	0.843/1.0	0.018/0.198	0.098/1.0
ESR, mm/h	90 ± 34.95	92.42 ± 30.41	94.21 ± 27.53	81.06 ± 34.32	75.13 ± 33.13	76.33 ± 34.07	0.556/1.0	0.123/1.0	0.045/0.495
CRP, mg/dL	15.75 ± 4.97	13.66 ± 7.84	13.71 ± 7.15	6.55 ± 5.22	7.29 ± 4.88	7.80 ± 5.55	***<0.001/0.009****	***0.001/0.011****	***<0.001/0.009****
GOT, IU/L	48.63 ± 48.26	99.85 ± 123.51	88.00 ± 150.20	53.69 ± 55.63	89.89 ± 127.41	66.36 ± 81.36	0.829/1.0	0.815/1.0	0.155/1.0
GPT, IU/L	47.13 ± 36.36	79.5 ± 93.1	72.83 ± 145.59	38.31 ± 43.95	92.46 ± 117.08	56.74 ± 57.02	0.630/1.0	0.736/1.0	0.050/0.55
Fever duration (before IVIG)	6.67 ± 2.06	7 ± 2.61	7.30 ± 2.15	5.27 ± 0.96	5.94 ± 1.46	5.61 ± 1.37	0.033/0.363	0.084/0.924	***<0.001/0.008****
Fever duration (after IVIG)	1.22 ± 1.09	2.23 ± 3	1.95 ± 2.57	1.33 ± 2.13	1.28 ± 1.59	1.31 ± 1.72	0.886/1.0	0.198/1.0	0.237/1.0
Total fever duration	7.89 ± 1.83	9.23 ± 3.77	8.85 ± 3.45	6.6 ± 1.99	7.19 ± 2.07	6.71 ± 2.27	0.129/1.0	0.024/0.264	***0.003/0.033****

*Numbers in bold italics indicate significant differences.

CAA = coronary artery aneurysm; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GOT = glutamate oxaloacetate transaminase; GPT = glutamic pyruvic transaminase; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; WBC = white blood cell.

a Data for each group are expressed as mean ± SD.

b p_{adj} is adjusted p after Bonferroni correction, i.e., $p_{adj} = p \times 11$.

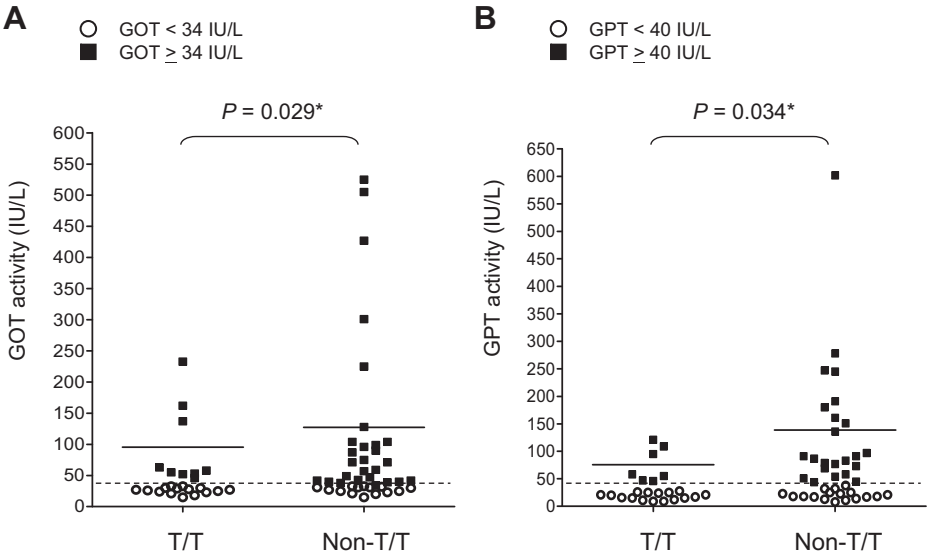

Fig. 2 – Analyses of plasma activity of (A) GOT and (B) GPT in KD patients subgrouped by genotype at SNP site rs1064190. Patients with normal plasma activity of GOT (< 34 IU/L) and GPT (< 40 IU/L) are represented using open circles; those with elevated activity of GOT and GPT, which are indicators for heart damage in KD patients, are represented using filled squares. *$p = 0.029$. **$p = 0.034$. GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; KD = Kawasaki disease.

95% CI = 1.09–2.27). However, none of these can serve as a predictive genetic marker to differentiate patients with or without CAAs.

As genetic variations in the PSORS1 region were found to control KD development and CAA formation, it is interesting to rate the impact of diverse genetic combinations on KD patients. Table 3 plots haplotype frequencies using the three polymorphisms studied. Among eight haplotypes, the most common one in KD patients was T-A-C and that in normal controls was G-A-C. In particular, the T-A-T frequency was found to be higher in KD patients (1.0%) than that in normal controls (0.1%) ($p = 0.033$) and highly frequent in CAA-free KD patients (1.3%) ($p = 0.012$). The G-A-C haplotype appeared to be less in KD patients with CAA (18.5%) than that in normal controls (29.1%), although data did not show statistical significance ($p = 0.077$). In contrast, the frequency of the T-G-C haplotype was found to be higher in KD patients with CAA (26.7%) than that in controls (17.6%), but data were not statistically significant ($p = 0.074$).

Our data indicated rs1064190 SNP plays critical roles in KD development and CAA formation. We, therefore, would like to know whether genetic variations at this SNP site could also associate with clinical parameters critical for KD diagnosis. Table 4 shows KD patients with CAAs averaging higher C-reactive protein (CRP) level and longer fever duration time than those without CAAs, hinting at acute inflammation associated with CAA formation. Yet, the association of increased CRP and fever with CAA did not significantly differ between T/T and non-T/T (G/T or G/G genotype) subsets, maybe owing to relatively small case numbers (Table 4). Hence, we tried another approach to subgroup patients using cutoffs of 34 IU/L for GOT (Fig. 2A) and 40 IU/L for GTP (Fig. 2B), setting standards to define normal ranges of GOT and GPT activity in humans. Our data indicated the association of non-T/T genotype with the abnormal elevated serum activity of GOT ($p = 0.029$) and GPT ($p = 0.034$), which are key indicators for abnormal heart functions in KD patients. Data point to the likelihood that the T/T genotype may possess protective functions to reduce heart damage in KD patients, leading to lower GOP or GTP level.

4. Discussion

To the best of our knowledge, this is the first research to study the association of SNPs in the PSORS1 region and KD development. Among the three SNP sites studied, rs106419 located at the promoter region of the *PSORS1C1* gene (psoriasis susceptibility 1 candidate 1, also known as *SEEK1*) was found to play crucial roles in KD development. Patients with T/T versus G/T or G/G genotypes have a higher probability of developing KD. Interestingly, the T/T genotype is a protective factor associated with a low frequency of CAA formation and heart damage. Considering the haplotype frequencies between the case and control groups, KD patients with the T-A-T haplotype appeared to be significantly "at-risk" compared with other haplotypes. Such data suggest functional roles of genes within the PSORS1 region in KD, also revealing that genetic variations in non-MHC genes at chromosome 6p21.3 could contribute to KD susceptibility. Thus, other non-MHC genes in this susceptible region might also play roles in KD development. With limited sample size in this study, further research must ascertain how these non-MHC genes work with MHC genes in regulating immune functions and KD development.

Besides genetic variations, recent studies indicated that microorganism infection triggered KD [5–7]. Certain subsets

of T-lymphocytes, e.g., V-beta 2+ and V-beta 8+, were constitutively activated in KD patients, suggesting a systemic immunoactivation caused by superantigens [30]. With KD more prevalent among children of Asian and Pacific Island descent, interactions/combinations between genetic and environmental factors may play important roles to control the susceptibility to KD. The genetic variations in the PSORS1 region have been associated with psoriasis and psoriatic arthritis on the basis of a genome-wide association study [19–21]. Our findings provide molecular evidence for the linkage between these kinds of autoimmune diseases. In fact, KD is described in association with the development of several psoriasiform eruptions [26–28]. A number of studies discovered bacterial antigens from *Staphylococcus aureus* and *Streptococcus pyogenes* as common causes for the activation of autoimmune response in both KD and psoriasis patients [28,31,32]. It is, therefore, not surprising that genetic variations in the PSORS1 region can also determine the etiology of KD. Our findings and prior studies support a hypothesis that KD and certain types of psoriasis share common pathogenic mechanisms in disease development [28,33–35]. Currently, it is not clear why genetic variations in the *PSORS1C1* gene contribute to KD development. Previous studies have demonstrated *PSORS1C1* gene as the key gene associated with psoriasis or psoriatic arthritis in the PSORS1 region [23,36], indicating novel functions of PSORS1C1 in inducing autoimmunity. Since the PSORS1C1 protein is extremely variable owing to the highly polymorphic gene structure and splicing variants [23], probing additional SNPs in this gene may clarify susceptibility to KD. Further functional studies may reveal details of mechanisms controlled by PSORS1C1 variants during KD development.

In summary, our study identified an SNP in the PSORS1 region that contributes to KD susceptibility in Taiwanese children of Han Chinese ethnic background. We observed significant association between the *PSORS1C1* gene polymorphism and the occurrence of cardiac artery aneurysm in KD patients. Our data showed that the plasma activity of GOT and GPT was significantly lower in KD patients with the T/T genotype at this SNP site than in those with the G/T or G/G genotype. Results suggest the polymorphism of *PSORS1C1* gene playing roles in KD pathogenesis.

Acknowledgments

We appreciate the kind technical assistance from Ms I-Wen Chiu, Ms Yu-Wen Chiu, and Ms Carmen Chan at China Medical University Hospital. This study was supported by medical science research grant CMU 97-002 from the China Medical University.

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