ORIGINAL ARTICLE

Polymorphisms of transforming growth factor- β signaling pathway and Kawasaki disease in the Taiwanese population

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Kawasaki disease (KD) is a systemic vasculitis associated with cardiovascular symptom. A previous study in the European descent has indicated that genetic variants of the transforming growth factor- β (TGF- β) pathway are involved in the KD susceptibility and clinical status. This study was conducted to investigate if polymorphisms in TGF- β signaling pathway are associated with KD susceptibility, and the coronary artery lesion formation. A total of 950 subjects (381 KD patients and 569 controls) were investigated to identify 12 single-nucleotide polymorphisms in the TGF- β signaling pathway (rs2796817, rs10482751, rs2027567, rs12029576, rs11466480, rs4776338, rs12901071, rs7162912, rs1438386, rs6494633, rs12910698 and rs4776339) by using TaqMan Allelic Discrimination assay. Our results indicated that rs1438386 in the *SMAD3* is significantly associated with the susceptibility of KD. Additionally, both haplotypes of *TGF β 2* and *SMAD3* were also associated with the risk of KD. This study showed that genetic polymorphisms in TGF- β signaling pathway are associated with KD susceptibility, but not coronary artery lesions formation, or intravenous immunoglobulin treatment response in the Taiwanese population.

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INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis that was first described by Kawasaki *et al.* in 1974.¹ It has been the leading cause of acquired heart diseases in children but its etiology remains unknown.^{2–4} It occurs worldwide and mainly affects children less than 5 year old, especially in Asia. The highest incidence was found in Japan, Korea and then Taiwan.^{5–7} The most common and serious complication of KD is coronary artery lesions (CAL), including myocardial infarction,⁸ coronary artery dilatation/ectasia and coronary artery aneurysm.⁹

The etiology of KD is still unclear and no consistent etiological agent for KD has been identified yet. Although incidence of KD varies in different ethnic population, several lines of evidence have indicated the significant association between genetic polymorphisms and the

susceptibility of KD. For example, polymorphisms in the genes including *monocyte chemoattractant protein 1*,¹⁰ *IL-10*,¹¹ *CD40L*,¹² *IL-4*,¹³ *CASP3*,^{14,15} *IL-18*,¹⁶ *HLA-E*,¹⁷ *C-C chemokine receptor 5*¹⁸ and inositol 1,4,5-trisphosphate 3-kinase C^{19,20} have been reported to be involved in the development of KD. However, only few genes from these studies could be deduced in the second populations that support the hypothesis that multiple polymorphic alleles influence the susceptibility and clinical phenotypes of KD.²¹

Shimizu *et al.*²² firstly reported that genetics polymorphisms of transforming growth factor- β (TGF- β) pathway including *TGF β 2*, *TGF β 2* and *SMAD3* associated with KD susceptibility, the development of CAL and treatment response from the European and US population but without KD patient from the Asian population. TGF- β

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is a multifunctional molecule, which is important in the regulation of cytokine expression and immune responses.²³ Animal studies from TGF- β -deficient mice indicated an essential physiological role in the health and disease.²⁴ It has been shown that TGF- β -mediated signaling pathways are mainly via transcription factors, mothers against decapentaplegic, *Drosophila*, homolog of (Smads), which includes at least three common proteins: Smad2, Smad3 and Smad4. The binding of TGF- β to its receptor resulted in the phosphorylation of Smad2 or Smad3, which heterodimerizes with Smad4. The formation of the Smad complex further translocates to nucleus to regulate the activation of target genes.²⁵ In the cardiovascular system which is an important target of KD, TGF- β signaling is involved in the pathogenesis of multiple cardiovascular diseases via an aberrant vascular remodeling. Low expression level of endogenous TGF- β activity in blood may contribute to the development of atherosclerotic cardiovascular disease.²⁶

In this study, we examined the association between the genetic polymorphisms of TGF- β pathway and the risk of KD using a case-control study in the Taiwanese populations. The relationship of clinical data (CAL and responses of intravenous immunoglobulin (IVIG) treatment) and genetic polymorphisms of *TGFB2*, *TGFBR2* and *SMAD3* were also evaluated. Our studies indicated that a genetic polymorphism in *SMAD3* influences KD susceptibility in the Taiwanese population.

MATERIALS AND METHODS

Patients studied

All subjects studied were children who fulfilled the diagnostic criteria for KD and were admitted at Chang Gung Memorial Hospital-Kaohsiung Medical Center, between 2000 and 2010. All patients were treated with a single infusion of IVIG (2 g kg⁻¹) administered over a 12-h period. Aspirin (3–5 mg kg⁻¹ per day) was administered until all signs of inflammation were resolved or regression of CAL was detected under two-dimensional echocardiography as our previous studies.^{4,27–29} This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. All the subjects signed the consent form. We excluded patients who did not meet the diagnostic criteria for KD. CAL was defined by the internal diameter of the coronary artery being at least 3 mm (4 mm, if the subject was over the age of 5 years) or the internal diameter of a segment being at least 1.5 times that of an adjacent segment, as observed in the echocardiogram.^{15,30,31} IVIG responsiveness was defined as defervescence 48 h after the completion of IVIG treatment and no fever (temperature, >38 °C) recurrence for at least 7 days after IVIG with marked improvement or normalization of inflammatory signs.^{4,32}

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⁻¹) for digestion of nuclear protein for 4 h at 60 °C. Total DNA was harvested by using the Gentra extraction kit (QIAGEN, Germantown, MA, USA) followed by 70% alcohol precipitation.²⁷

Genotyping

Genotyping was carried out using the TaqMan Allelic Discrimination Assay (Applied Biosystems, Foster city, CA, USA) as our previous report.¹⁵ The PCR was performed by using a 96-well microplate with the ABI9700 Thermal Cycler (Applied Biosystems, Carlsbad, CA, USA). After PCR, fluorescence was detected and analyzed using the System SDS software version 1.2.3 (Applied Biosystems).

Statistical analysis

SAS 9.1 (SAS, Cary, NC, USA) for Windows was used for analysis. The statistical differences between case and control in genotype and allele frequency were assessed by the χ^2 -test. Statistical differences in genotype and allele frequency of the KD patients with/without CAL formation were assessed using the χ^2 -test. Bonferroni correction was used for correcting multiple tests. Linkage disequilibrium 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, MA, USA).

RESULTS

A significant association between the genetic polymorphisms in the TGF- β signaling pathway and susceptibility to KD

In this study, we recruited a total of 950 subjects including 381 KD patients and 569 controls. Table 1 shows the characteristics of the subjects. The average age in the cases was 1.7 years and that in the controls was 5.7 years. In all, 9.7% of KD patients were observed with CAL formation 8 weeks after the disease onset, and 12.9% of patients were initial IVIG treatment resistant. Previous studies have identified that genetic polymorphisms (*TGFB2*: rs2796817, rs10482751, rs2027567 and rs12029576; *TGFBR2*: rs11466480; *SMAD3*: rs4776338, rs12901071, rs7162912, rs1438386, rs6494633, rs12910698 and rs4776339) influenced KD susceptibility or the coronary artery outcome.²² We analyzed the association between the genetic variants and susceptibility or severity of KD. As shown in the Tables 2a and b, the genotype frequencies of the controls and patients were in the Hardy–Weinberg equilibrium. None of polymorphisms in the *TGFB2* and *TGFBR2* were found to be significantly associated with the susceptibility of KD under three genetic models (dominant, recessive or allelic models) (Table 2a). However, one of the seven polymorphisms in *SMAD3* (rs1438386) associated with the susceptibility to KD. *P*-value is 0.001 under the dominant model after Bonferroni correction (Table 2b).

Lack of association between the genetic polymorphisms in the TGF- β signaling pathway and CAL formation in the KD patients

A total of 381 KD patients were genotyped. No polymorphisms in the *TGFB2*, *TGFBR2* or *SMAD3* were significantly associated with CAL formation in the KD patients (Tables 3a and 3b). Additionally, we did not find a statistically significant association between the genetic polymorphisms and IVIG treatment response in the Taiwanese children (data not shown). Haplotype analysis was performed using genotype data in this study. There was no significant association between haplotypes and CAL formation or IVIG treatment in the KD patients (data not shown).

Haplotype analysis of *TGFB2* and *SMAD3* in the susceptibility of KD patients

We further calculated pairwise linkage disequilibrium (Figures 1 and 2) and analyzed haplotypes of *TGFB2* and *SMAD3*, respectively. The haplotype frequency of *TGFB2* gene polymorphisms rs10482751/rs2027567/rs1209576 among the study subjects was shown in Table 4. rs10482751/rs2027567/rs1209576 pairwise allele analysis indicated that T/G/G haplotype had a significant association with the risk of KD in comparison with the C/A/T haplotype (*P*=0.0420). Additionally, *SMAD3* haplotypes T/A/A and C/C/G in block 1 were also

Table 1 Basal characteristics of patients with Kawasaki disease (KD) and of normal controls

Characteristics	Patients with KD	Normal control
Number of subjects	381	569
Gender: male, no (%)	247 (66.8%)	314 (56.2%)
Age (years) ^a	1.7 $\pm$ 1.6	5.7 $\pm$ 4.9
Range (years)	0–11	0–51
Coronary artery lesions (CAL)	37 (9.7%)	
Aneurysm formation	16 (4.2%)	
Intravenous immunoglobulin (IVIG) resistant	49 (12.9%)	

^aMean $\pm$ s.d.

Table 2a Genotype frequencies for *TGFB2/TGFB2* single-nucleotide polymorphisms and Kawasaki disease susceptibility

	Genotype	Case (%) (n=381)	Control subjects (%) (n=569)	Allele	Case (%) (n=381)	Control subjects (%) (n=569)	Genotype P-value	Dominant P-value	Recessive P-value	Allelic P-value
rs2796817	GG	17 (4.6)	20 (3.7)	G	144 (19.3)	208 (19.5)	0.702	0.688	0.551	0.897
	GT	110 (29.5)	168 (31.6)	T	602 (80.7)	856 (80.5)				
	TT	246 (65.9)	344 (64.7)							
rs10482751	TT	111 (29.7)	135 (24.1)	T	394 (52.7)	546 (48.7)	0.165	0.436	0.058	0.097
	CT	172 (46.0)	276 (49.3)	C	354 (47.3)	574 (51.3)				
	CC	91 (24.3)	149 (26.6)							
rs2027567	GG	72 (19.0)	71 (12.7)	G	317 (41.8)	406 (36.3)	0.025	0.136	0.008	0.015
	GA	173 (45.6)	264 (47.1)	A	441 (58.2)	714 (63.7)				
	AA	134 (35.4)	225 (40.2)							
rs12029576	GG	120 (31.9)	134 (23.9)	G	398 (52.9)	543 (48.3)	0.020	0.694	0.006	0.050
	TG	158 (42.0)	275 (48.9)	T	354 (47.1)	581 (51.7)				
	TT	98 (26.1)	153 (27.2)							
rs11466480	GG	0 (0.0)	0 (0.0)	G	0 (0.0)	0 (0.0)				
	GT	0 (0.0)	0 (0.0)	T	758 (100.0)	1122 (100.0)				
	TT	379 (100)	561 (100)							

Table 2b Genotype frequencies for *SMAD3* single-nucleotide polymorphisms and Kawasaki disease susceptibility

	Genotype	Case (%) (n=381)	Control subjects (%) (n=569)	Allele	Case (%) (n=381)	Control subjects (%) (n=569)	Genotype P-value	Dominant P-value	Recessive P-value	Allelic P-value
rs4776338	TT	72 (19.0)	110 (19.7)	T	348 (45.9)	507 (45.3)	0.748	0.547	0.796	0.811
	TC	204 (53.8)	287 (51.3)	C	410 (54.1)	611 (54.7)				
	CC	103 (27.2)	162 (29.0)							
rs7162912	AA	56 (14.7)	100 (18.0)	A	316 (41.6)	462 (41.6)	0.133	0.309	0.186	0.985
	AC	204 (53.7)	262 (47.2)	C	444 (58.4)	648 (58.4)				
	CC	120 (31.6)	193 (34.8)							
rs12901071	GG	19 (5.0)	27 (4.8)	G	152 (20.1)	229 (20.3)	0.949	0.827	0.872	0.902
	GA	114 (30.0)	175 (31.1)	A	604 (79.9)	897 (79.7)				
	AA	245 (65.0)	361 (64.1)							
rs12910698	TT	50 (13.1)	68 (12.2)	T	267 (35.2)	404 (36.1)	0.504	0.384	0.641	0.686
	TG	167 (44.4)	268 (47.9)	G	491 (64.8)	714 (63.9)				
	GG	162 (42.5)	223 (39.9)							
rs4776339	GG	51 (13.3)	75 (13.4)	G	277 (36.4)	428 (38.2)	0.481	0.250	0.998	0.413
	GA	175 (46.2)	278 (49.6)	A	485 (63.6)	692 (61.8)				
	AA	155 (40.5)	207 (37.0)							
rs1438386	TT	109 (29.7)	113 (23.1)	T	398 (54.2)	448 (45.7)	0.002*	0.001*	0.028	0.001*
	CT	180 (49.0)	222 (45.3)	C	336 (45.8)	532 (54.3)				
	CC	78 (21.3)	155 (31.6)							
rs6494633	AA	0 (0.0)	1 (0.2)	A	58 (7.7)	92 (8.2)		0.697		0.660
	AG	58 (15.2)	90 (16.1)	G	700 (92.3)	1028 (91.8)				
	GG	321 (84.8)	469 (83.7)							

strongly associated with KD susceptibility ($P < 0.0001$) (Table 5). The *SMAD3* haplotype rs12910698/rs4776339 (block 2) had no significant association with the risk of KD (Table 5).

DISCUSSION

In 2011, a large genetic study has revealed a significant association between the polymorphisms in TGF- β pathways and KD susceptibility or coronary artery lesion (CAL) formation in the Europe and US population.²² Therefore, a replication study of 12 polymorphisms in 950 subjects was performed in the Taiwanese population. We found a SNP in the *SMAD3* (rs1438386) and haplotypes in *SMAD3* and

TGFB2 that contribute to the susceptibility of KD. To our knowledge, this is the first analysis to find the association between the genetic variants of TGF- β pathways and KD susceptibility in the Asian population. In this study, we recruited only children from the south of Taiwan to avoid heterogeneity. Therefore, the study population was relatively homogenous in terms of age, ethnicity and geographic location.

Several lines of evidence have indicated the role TGF- β pathways in the immunity and inflammation.²³ For example, the activation of *IL-2* gene could be suppressed by TGF- β -mediated Smad signaling pathways, and leads to the antiproliferative effects in T cells.³³

Table 3a Genotype frequencies for *TGFB2/TGFB2* single-nucleotide polymorphisms in patients with coronary artery lesion (CAL) and without CAL

	Genotype	CAL (%) (n=37)	Without (%) (n=336)	Allele	CAL (%) (n=37)	Without (%) (n=336)	Genotype P-value	Dominant P-value	Recessive P-value	Allelic P-value
rs2796817	GG	0 (0.0)	17 (5.1)	G	7 (10.0)	134 (20.3)	0.066	0.066	0.038	
	GT	7 (20.0)	100 (30.3)	T	63 (90.0)	526 (79.7)				
	TT	28 (80.0)	213 (64.6)							
rs10482751	TT	10 (27.8)	100 (30.3)	T	39 (54.2)	351 (53.2)	0.707	0.546	0.754	0.874
	CT	19 (52.8)	151 (45.8)	C	33 (45.8)	309 (46.8)				
	CC	7 (19.4)	79 (23.9)							
rs2027567	GG	6 (16.7)	65 (19.4)	G	29 (40.3)	284 (42.4)	0.924	0.859	0.692	0.730
	GA	17 (47.2)	154 (46.0)	A	43 (59.7)	386 (57.6)				
	AA	13 (36.1)	116 (34.6)							
rs12029576	GG	13 (35.2)	106 (32.0)	G	42 (56.8)	351 (53.0)	0.835	0.701	0.564	0.541
	TG	16 (43.2)	139 (42.0)	T	32 (43.2)	311 (47.0)				
	TT	8 (21.6)	86 (26.0)							
rs11466480	GG	0 (0.0)	0 (0.0)	G	0 (0.0)	0 (0.0)				
	GT	0 (0.0)	0 (0.0)	T	74 (100.0)	668 (100.0)				
	TT	37 (100.0)	334 (100.0)							

Table 3b Genotype frequencies for *SMAD3* single-nucleotide polymorphisms in patients with coronary artery lesion (CAL) and without CAL

	Genotype	CAL (%) (n=37)	Without (%) (n=336)	Allele	CAL (%) (n=37)	Without (%) (n=336)	Genotype P-value	Dominant P-value	Recessive P-value	Allelic P-value
rs4776338	TT	9 (24.3)	61 (18.3)	T	38 (51.4)	304 (45.5)	0.593	0.463	0.371	0.339
	TC	20 (54.1)	182 (54.5)	C	36 (48.6)	364 (54.5)				
	CC	8 (21.6)	91 (27.2)							
rs7162912	AA	7 (18.9)	47 (14.0)	A	31 (41.9)	278 (41.5)	0.543	0.611	0.423	0.947
	AC	17 (46.0)	184 (54.9)	C	43 (58.1)	392 (58.5)				
	CC	13 (35.1)	104 (31.1)							
rs12901071	GG	3 (8.1)	16 (4.8)	G	13 (17.6)	135 (20.3)	0.258	0.292	0.388	0.581
	GA	7 (18.9)	103 (30.9)	A	61 (82.4)	531 (79.7)				
	AA	27 (73.0)	214 (64.3)							
rs12910698	TT	5 (13.5)	43 (12.9)	T	24 (32.4)	235 (35.2)	0.723	0.475	0.913	0.638
	TG	14 (37.8)	149 (44.6)	G	50 (67.6)	433 (64.8)				
	GG	18 (48.7)	142 (42.5)							
rs4776339	GG	5 (13.5)	44 (13.1)	G	25 (33.8)	244 (36.3)	0.779	0.521	0.943	0.668
	GA	15 (40.5)	156 (46.4)	A	49 (66.2)	428 (63.7)				
	AA	17 (46.0)	136 (40.5)							
rs1438386	TT	14 (38.9)	95 (29.3)	T	47 (65.3)	347 (53.5)	0.129	0.052	0.236	0.058
	CT	19 (52.8)	157 (48.5)	C	25 (34.7)	301 (46.5)				
	CC	3 (8.3)	72 (22.2)							
rs6494633	AA	0 (0.0)	0 (0.0)	A	4 (5.4)	53 (7.9)	0.422	0.422		0.442
	AG	4 (10.8)	53 (15.8)	G	70 (94.6)	617 (92.1)				
	GG	33 (89.2)	282 (84.2)							

A transcription factor, nuclear factor of activated T cells, is one of the most important mediated for IL-2 mRNA induction. The activation of nuclear factor of activated T cells has been shown to be regulated by inositol 1,4,5-trisphosphate 3-kinase C, an important gene in the susceptibility of KD.²⁰ Therefore, nuclear factor of activated T cells could be a target of Smad2 and Smad3. In addition, the activation of TGF- β -mediated signaling pathways is much dependent on the co-mediator Smad4 that forms active complexes to be translocated into the nucleus to regulate the target genes. We did not examine

SMAD4 polymorphisms because it is not as polymorphic as other molecules in the TGF- β pathways.

Genome-wide association study for KD was firstly performed by Burgner *et al.*²¹ A total of 40 SNPs and 6 haplotypes were confirmed in an independent cohort of KD families. They also identified a SNP within N-acetylated alpha-linked acidic dipeptidase-like 2 (*NAA-LADL2*; rs17531088) that significantly associated to the susceptibility of KD. In the Asian population, Onouchi *et al.*²⁰ identified the susceptibility loci on chromosome 19q13.2 and further confirmed

Figure 1 *TGF β 2* gene linkage disequilibrium and haplotype block structure in KD. The number on the cell is the LOD score of D' . A full color version of this figure is available at the *Journal of Human Genetics* journal online.

Figure 2 *SMAD3* gene linkage disequilibrium and haplotype block structure in KD. The number on the cell is the LOD score of D' . A full color version of this figure is available at the *Journal of Human Genetics* journal online.

the functional SNP of inositol 1,4,5-trisphosphate 3-kinase C in the disease activity of KD. Recently, another genome-wide association study was conducted in the Korean population. A total of 786 subjects (186 KD patients and 600 controls) were recruited. A very careful

Table 4 Haplotype frequencies of the *TGFB2* gene in controls and patients with Kawasaki disease

<i>Rs10482751/ rs2027567/ rs12029576</i>	Case (%) (n=381)	Control (%) (n=569)	OR (95% CI)	P-value
T/G/G	294 (40.1)	392 (35.5)	1.24 (1.01–1.52)	0.0420^a
C/G/G	9 (1.2)	9 (0.8)	1.65 (0.65–4.19)	0.2902
C/A/G	9 (1.2)	11 (1.0)	1.35 (0.55–3.29)	0.5102
T/A/G	76 (10.4)	129 (11.7)	0.97 (0.71–1.33)	0.8525
T/A/T	14 (1.9)	21 (1.9)	1.10 (0.55–2.19)	0.7900
C/A/T	329 (44.8)	542 (49.1)	Reference	

^aSignificant ($P < 0.05$) values are in bold.

Table 5 Haplotype frequencies of the *SMAD3* gene in patients in controls and patients with Kawasaki disease

	Case (%) (n=381)	Control (%) (n=569)	OR (95% CI)	P-value
Block 1 <i>rs4776338/rs7162912/rs12901071</i>				
T/C/A	321 (42.6)	482 (44.1)	1.13 (0.87–1.46)	0.3720
T/A/A	25 (3.3)	9 (0.8)	4.69 (2.13–10.37)	<0.0001^a
C/C/A	97 (12.9)	155 (14.2)	1.06 (0.76–1.48)	0.7428
C/A/A	159 (21.1)	225 (20.6)	1.19 (0.89–1.61)	0.2424
C/C/G	22 (2.9)	1 (0.1)	37.18 (4.95–279.09)	<0.0001^a
C/A/G	129 (17.1)	218 (20.0)	Reference	
Block 2 <i>rs12910698/rs4776339</i>				
G/A	477 (62.9)	674 (60.8)	1.62 (0.85–3.06)	0.1367
T/G	260 (34.3)	393 (35.5)	1.51 (0.79–2.89)	0.2078
G/G	14 (1.9)	32 (2.9)	Reference	

^aSignificant ($P < 0.01$) values are in bold.

study from Kim *et al.*³⁴ indicated 1p31 region as susceptibility loci for KD. Furthermore, *PEL1* gene locus in the 2p13.3 region was confirmed to associate with the development of CAL in the KD patients. Importantly, genome-wide association study results from the Taiwanese population suggest another three novel susceptibility loci for KD.³⁵ The human *SMAD3* gene is located on chromosome 15, which has not been identified by genome-wide association study as a risk locus in the Asian population. These observations in combination with those of the present study support the presence of ethnic differences or environmental factors for the susceptibility or severity of KD.

Shimizu *et al.*²² firstly identified that 16 SNPs in six genes (*TGFB2*, *TGFB2*, *SMAD1*, *ENG*, *ACVRL1* and *SMAD3*) associated with the susceptibility of KD. The significance of genetic variation in the three genes (*SMAD3*, *TGFB2* and *TGFB2*) could be replicated in the multiethnic transmission disequilibrium test (TDT) analysis from the independent United States/United Kingdom/Australia subjects. In our study, we found one of the seven polymorphisms in *SMAD3* (*rs1438386*) associated with the susceptibility to KD in the Taiwanese population. Regarding the CAL formation and IVIG treatment response, Shimizu *et al.*²² reported that genetic variants in *TGFB2*, *TGFB2* and *SMAD3* consistently influenced the coronary artery outcome in two independent, non-overlapping cohorts. However, the SNPs identified from these two cohorts were not identical. In

this study, there were no polymorphisms in the TGF β 2, TGFBR2 or SMAD3 that were significantly associated with the CAL formation and IVIG treatment response in KD patients in the Taiwanese population. We acknowledge the limitations in our study. We only genotyped the SNPs that have been shown to be associated with the KD susceptibility in multiethnic TDT analysis from the independent United States/United Kingdom/Australia subjects.

Therefore, the rare causal genetic polymorphisms at the TGF- β pathway would not be detected in this study. In addition, the SNP of SMAD3 identified in this study is located in intron. Future studies are needed to address the mechanism by which SMAD3 genotypes contribute to the development of KD.

In conclusion, our results indicated that a SNP (rs1438386) and haplotypes in the TGF- β pathways associated with the susceptibility to KD in the Taiwanese population. However, we did not provide evidence to support the role of polymorphisms in the TGF- β pathways leading to CALs in this study. We attribute this to the different genetic backgrounds in the populations, due to ethnic differences in the distribution of polymorphisms in the TGF- β pathways. Consistent with this, KD susceptibility loci identified from the genome-wide association studies exhibited distinct distributions in different populations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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