

# Kawasaki Disease

Ho-Chang Kuo  
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 Springer

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Ho-Chang Kuo

Kawasaki Disease Center, Department of Pediatrics and College of Medicine  
Kaohsiung Chang Gung Memorial Hospital and Chang Gung University  
Kaohsiung, Taiwan

ISBN 978-981-19-2943-4

ISBN 978-981-19-2944-1 (eBook)

<https://doi.org/10.1007/978-981-19-2944-1>

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# Genetic Study of Kawasaki Disease

Imanier Noor Faridah, Dyah Aryani Perwitasari,  
and Wei-Chiao Chang

## Abstract

Kawasaki disease (KD) is a leading cause of acquired heart disease in children; however, the etiology of this disease is still unclear. Several genome-wide association studies (GWASs) indicated that genetic variations contribute to KD susceptibility and intravenous immunoglobulin (IVIG) responses. Application genetic risk score is another example of pharmacogenomics research for predicting IVIG unresponsiveness. High-throughput DNA sequencing technology has

been developed on an unprecedented scale, and more and more genomic information will be available to understand the etiology and treatment of KD.

## Keywords

Genetics · IVIG response · Kawasaki disease · Susceptibility

I. N. Faridah  
Department of Clinical Pharmacy, School of  
Pharmacy, Taipei Medical University, Taipei, Taiwan

Faculty of Pharmacy, University of Ahmad Dahlan,  
Yogyakarta, Indonesia

D. A. Perwitasari  
Faculty of Pharmacy, University of Ahmad Dahlan,  
Yogyakarta, Indonesia

W.-C. Chang (✉)  
Department of Clinical Pharmacy, School of  
Pharmacy, Taipei Medical University, Taipei, Taiwan

Master Program in Clinical Pharmacogenomics and  
Pharmacoproteomics, School of Pharmacy, Taipei  
Medical University, Taipei, Taiwan

Integrative Research Center for Critical Care, Wan  
Fang Hospital, Taipei Medical University,  
Taipei, Taiwan

Department of Medical Research, Shuang Ho  
Hospital, Taipei Medical University,  
New Taipei City, Taiwan  
e-mail: [wcc@tmu.edu.tw](mailto:wcc@tmu.edu.tw)

## Introduction

Kawasaki disease (KD) is an acute disease that frequently affects children under five years of age, and the number of patients increases annually. Family history has been considered one of the important risk factors for KD [1]. KD incidence in northeastern Asian countries, including Japan, Korea, and Taiwan, is higher than in North America, Australia, and Europe. The etiology of this disease is still unclear. Genetic susceptibility has been proposed to interact with several environmental and immunological variables [2]. Infections such as bacterial [3] or viral infections, including enterovirus, adenovirus, human rhinovirus, and coronavirus [4], were reported to cause immune dysfunction and KD. For the treatment of KD, initial therapy with high-dose intravenous immunoglobulin (IVIG) and acetylsalicylic acid (ASA) is recommended as early as possible to reduce the risk of coronary artery abnormalities (CAAs). However, up to 20% of patients are

IVIG-unresponsive patients who show persistent fever 36~48 h after an initial IVIG infusion [5]. The mechanism of IVIG resistance is still unknown. Genetic polymorphisms play an important role in determining an inter-individual difference in the susceptibility of diseases and therapeutic outcomes. This chapter highlights the genetic factors that are becoming accepted as critical to KD susceptibility.

## Genetics and KD

Recently, many studies reported functional roles of genetic polymorphisms in KD susceptibility and the responses to IVIG treatment using either family-based, candidate gene approaches, or genome-wide association studies (GWASs). KD susceptibility genes such as *ITPKC* [6–10], *FCGR2A* [8, 11–13], *BLK* [10, 11, 13–16], and *CD40* [10, 11, 13, 14, 17] have been widely reported in different populations. Moreover, genes such as *SAMD9L* [18], *IL16* [19], and *P2RY12* [20] were involved in pharmacological responses to IVIG treatment. This chapter proposes an overview of genes that have been identified to be related to KD susceptibility and IVIG responses, as summarized in Table 1.

### B Lymphoid Tyrosine Kinase (BLK)

The *BLK* gene encodes an Src-family protein tyrosine kinase, which has important role in regulating of proinflammatory cytokine [34]. Previous genetic studies proved that rs2254546 (the G allele or GG genotype) [11, 13, 14, 21], rs2736340 [15], and rs6993775 [16] on the *BLK* gene were associated with the risk of KD. Furthermore, the single-nucleotide polymorphism (SNP), rs2254546, was validated for KD susceptibility in Taiwanese population. However, there was no evidence of any association with coronary arterial lesions (CALs) [14]. The rs2254546 SNP is located in an intergenic region between the family with sequence similarity 167 member A (*FAM167A*) and *BLK* on chromosome 8. However, the biological function of *FAM167A*, which is predominantly expressed in the human lungs, is still unclear [35]. Several SNPs on the

*BLK* gene are known to be related to immune diseases, such as systemic lupus erythematosus (SLE) [36] and rheumatoid arthritis [37].

### Caspase-3 (CASP3)

*CASP3*, located at 4q35.1, as one of effector caspases contributes to the cell apoptosis process. Activation of effector caspases (caspase-3, caspase-6, and caspase-7) cleaves certain targets leading to cell death [38]. Besides the apoptosis process, other cellular processes in which *CASP3* is involved include regulating B cell homeostasis [39]. Furthermore, the role of *CASP3* in KD follows the nuclear factor of activated T cells (NFAT) c2 pathway in response to signals from T cell receptor [40]. *CASP3* is known to cleave NFATc2 and influence transcriptional activity [41]. Not only *CASP3*, but also *ITPKC* acts as a regulator of the NFAT pathway in response to calcium signals. Decreasing activities of *CASP3* and *ITPKC* are related to hyperactivation of the immune system [9]. *CASP3* polymorphisms are genetic susceptibilities for cancer development, such as squamous cell carcinoma of the head and neck (SCCHN) [42] and endometrial cancer [43]. rs113420705 (G/A) of *CASP3* is related to KD susceptibility, CAL formation, and response to IVIG in Japanese and Han Chinese populations [9, 11]. However, a replication study in a Taiwanese population showed different results for IVIG response either with rs113420705 or a two-locus model (rs113420705 and rs28493229) [44]. In addition, rs72689236 was associated with aneurysm formation in Taiwanese KD children [45] and increased KD risk based on a meta-analysis study [22]. However, there was no significant association between rs72689236 and the IVIG response or CAL formation [45].

### Cluster of Differentiation 40 (CD40) and CD40 Ligand (CD40L)

CD40, a costimulatory receptor, is a type-I transmembrane protein expressed by antigen-presenting cells, such as B cells. At the same time the CD40L is a type II transmembrane protein expressed by activated T cells. Interactions



between CD40 and the CD40L are essential for activation of the immune system, such as turning on signaling pathways including nuclear factor (NF)- $\kappa$ B-signaling pathways through tumor necrosis factor (TNF) receptor (TNFR)-

associated factor (TRAF) proteins [46]. Moreover, ligation of CD40 and the CD40L enhances endothelial cell activation and mediates vascular remodeling and neovessel formation in KD. Expression of the CD40L is known

**Table 1** Gene polymorphisms associated with Kawasaki disease (KD) susceptibility and the response to intravenous immunoglobulin (IVIG)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
<i>Genes related to susceptibility to Kawasaki disease</i>						
<i>BLK</i>	8p23-22	rs2254546	Case-control study and meta-analysis	China	OR = 1.443, CI = 1.154 ~ 1.805	Yan et al. (2013) [11]
			GWAS and replication study	Japan	$p = 8.2 \times 10^{-21}$	Onouchi et al. (2012) [13]
			Case-control study and meta-analysis	China	OR = 1.55, CI = 1.42 ~ 1.70	Wang et al. (2014) [21]
			Case-control study	Taiwan	$p = 1.0 \times 10^{-5}$	Chen et al. (2020) [14]
		rs2736340	Replication and meta-analysis	Taiwan, Japan, Korea	Meta- $p = 4.74 \times 10^{-31}$	Chang et al. (2013) [15]
			Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta- $p = 6.6 \times 10^{-33}$	Johnson et al. (2020) [10]
rs6993775	Case-control study	Korea	$p = 4.63 \times 10^{-11}$	Sim et al. (2019) [16]		
<i>CASP3</i>	4q34-35	rs113420705	Cohort study	Japan	$p = 0.022$	Onouchi et al. (2013) [9]
			Case-control study and meta-analysis	China	OR = 1.33, CI = 1.22 ~ 1.43	Yan et al. (2013) [11]
		rs2720378	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta- $p = 1.6 \times 10^{-8}$	Johnson et al. (2020) [10]
		rs72689236	Meta-analysis study	China, Japan	$p \leq 0.001$	Ferdosian et al. (2019) [22]

(continued)

**Table 1** (continued)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
<i>CD40</i>	20q12-13.2	rs1535045	Case-control study	Taiwan	$p = 0.0405$	Kuo et al. (2012) [17]
		rs4813003	GWAS and replication study	Japan	$p = 4.8 \times 10^{-8}$	Onouchi et al. (2012) [13]
			Case-control study and meta-analysis	China	OR = 1.37, CI = 1.27 ~ 1.47	Yan et al. (2013) [11]
			Case-control study	Taiwan	$p = 8.1 \times 10^{-4}$	Chen et al. (2020) [14]
		rs1883832	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta- $p = 1.5 \times 10^{-13}$	Johnson et al. (2020) [10]
<i>FCGR2A</i>	1q23	rs1801274	Case-control study and meta-analysis	China	OR = 1.331, CI = 1.094 ~ 1.619	Yan et al. (2013) [11]
			GWAS and replication study	Europe, the US, Taiwan, Korea, Hong Kong, and China	Meta- $p = 7.35 \times 10^{-11}$	Khor et al. (2011) [8]
			Family-based genetic study	Europe, Asia	$p = 0.001$	Shrestha et al. (2012) [12]
			GWAS and replication study	Japan	$p = 1.6 \times 10^{-6}$	Onouchi et al. (2012) [13]
			Meta-analysis study	China, Japan, Taiwan, Hong Kong, Korea, the Netherlands, Greece	$p \leq 0.001$	Ferdosian et al. (2019) [22]
<i>HCP5</i>	6	rs6938467	GWAS and replication study	Korea	$p = 5.24 \times 10^{-8}$	Kim et al. (2017) [23]

**Table 1** (continued)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
<i>HLA-DQB2- HLA-DOB</i>	6p21.3	rs2857151	Case-control study and meta-analysis	China	OR = 1.41, CI = 1.27 ~ 1.57	Yan et al. (2013) [11]
			GWAS and replication study	Japan	$p = 4.6 \times 10^{-11}$	Onouchi et al. (2012) [13]
<i>HLA-E</i>		rs2844724	Case-control study	Taiwan	$p < 10^{-7}$	Lin et al. (2009) [24]
<i>IGHV3-66</i>	14q33.32	rs4774175	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta- $p = 3.4 \times 10^{-6}$	Johnson et al. (2020) [10]
		rs6423677	Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta- $p = 6.8 \times 10^{-10}$	Johnson et al. (2020) [10]
<i>IL4</i>	5q31.1	NS	Family-based genetic study		$p_{\text{combined}} = 0.002$	Burns et al. (2005) [25]
	-590	rs2243250	Case-control study	Iran	$p = 0.00$	Assari et al. (2018) [26]
	-33	rs2070874	Case-control study	Iran	$p = 0.00$	Assari et al. (2018) [26]
<i>ITPKC</i>	19q13.2	rs28493229	Case-control study	Japan	$p = 0.000081$	Onouchi et al. (2008) [6]
			Case-control study and meta-analysis	Taiwan	OR = 1.36, CI 1.12 ~ 1.66	Kuo et al. (2011) [7]
			GWAS and replication study	Europe, the US, Taiwan, Korea, Hong Kong, and China	Meta- $p = 1.68 \times 10^{-12}$	Khor et al. (2011) [8]
			Cohort study	Japan	$p = 7.1 \times 10^{-6}$	Onouchi et al. (2013) [9]
			Meta-analysis of GWASs	Japan, Korea, Taiwan	Meta- $p = 1.1 \times 10^{-14}$	Johnson et al. (2020) [10]

(continued)

**Table 1** (continued)

Gene	Chromosome location	Representative variants	Study design	Populations	Results	Reference
<i>MRP4</i>	13q32.1	rs7320375 rs7329490	Family linkage and case-control study	Europe	$p = 8.8 \times 10^{-5}$ $p = 5.8 \times 10^{-4}$	Khor et al. (2011) [27]
		rs7986087	Case-control study	China	$p = 0.0197$	Che et al. (2018) [28]
			Family linkage and case-control study	Europe	$p = 3.0 \times 10^{-4}$	Khor et al. (2011) [27]
<i>NMNAT2</i>	1q25.3	rs2078087	GWAS and replication study	Korea	$p = 1.15 \times 10^{-6}$	Kim et al. (2017) [23]
<i>SMAD3</i>	15	rs4776338	Case-control study	Europe	$p = 0.00002$	Shimizu et al. (2011) [29]
		rs1438386	Case-control study	Taiwan	$p = 0.001$	Kuo et al. (2011) [30]
<i>Genes related to the response of IVIG treatment</i>						
<i>CASP3</i>	4q34-35	rs113420705	Cohort study	Japan	$p = 0.031$	Onouchi et al. (2013) [9]
<i>HMGB1</i>		rs1412125	Case-control study	Korea	$p = 0.027$	Ahn et al. (2019) [31]
<i>ILAR</i>	16p12.1	rs563535954	Case-control study	Japan	$p = 0.0337$	Amano et al. (2019) [32]
<i>IL16</i>	p.Asn1147Lys	rs11556218	GWAS and replication study	Korea	$p = 0.0078$	Kim et al. (2020) [19]
<i>ITPKC</i>	19q13.2	rs28493229	Cohort study	Japan	$p = 0.0099$	Onouchi et al. (2013) [9]
<i>MRP4</i>		rs1751034	Case-control study	China	$p = 0.023$	Wang et al. (2021) [33]
<i>P2RY12</i>	3q25.1	rs6809699	Case-control study	China	$p = 0.011$	Wang et al. (2020) [20]
<i>SAMD9L</i>	7	rs28662	Meta-analysis of GWASs	Korea, Japan	Meta- $p = 5.3 \times 10^{-6}$	Kim et al. (2020) [18]

GWAS genome-wide association study, OR odds ratio, CI confidence interval

to be higher in platelets of KD patients compared to febrile patients [47] and controls [48], and it then decreases 3 days after IVIG administration [47]. Results imply a potential role of CD40/CD40L in the immunopathogenesis of KD. Notably, a GWAS in a Japanese population reported that the CD40 region at 20q13, rs4813003 was associated with KD [13]. This finding was confirmed using meta-analysis data [11] and replication study in different population [14]. Furthermore, a significant correlation was also found between rs1535045 of CD40 and KD susceptibility within a dominant model in a Taiwanese population [17].

### Fc Fragment of IgG Receptor IIa (FCGR2A)

The *FCGR2A* gene encodes a family member of immunoglobulin Fc receptors (FcγRIIA/CD32A). Polymorphisms of *FCGR2A* were associated with KD susceptibility [8, 12, 49] and other autoimmune diseases such as ulcerative colitis [50]. Results from a GWAS and meta-analysis study in various ethnic groups showed that *FCGR2A* on chromosome 1 (rs1801274, coding for His131) was associated with KD susceptibility [8, 22]. Consistent with GWAS results, studies in Asian and Caucasian populations demonstrated that an *FcγRIIA-131H* variant was associated with KD regardless in combination or subgroup populations [12]. The methylation status of the promoter regions of *FCGR2A* was also related to susceptibility to KD in CpG sites of G, H, and J as corresponding loci to NF-κB and Myc-Max [49]. Furthermore, specific findings related to gender (Korean and Japanese populations) showed that rs1801274 (p.His167Arg) in *FCGR2A* was correlated with KD susceptibility in males but not in females [51].

In addition, patients receiving IVIG, but not acute KD patients or controls, showed significant alterations in DNA methylation [52], while DNA methylation is important in regulating gene expressions. Furthermore, the methylation status of the promoter of *FCGR2A* is associated with IVIG treatment outcomes in the CpG sites of B,

E, F, H, and J. The level of methylation was significantly higher in the group nonresponsive to IVIG [49]. Higher *FCGR2A* messenger (m)RNA expression was observed in IVIG-resistant KD patients than in IVIG-sensitive patients [53].

### HLA Complex 5 (HCP5)

*HCP5* is a gene mapped within the HLA class I region, between the *MICA* and *MICB* genes, and thought to play an essential role in immunity to retroviral infections [54]. Previous studies reported associations of *HCP5* in psoriatic disease [55] and Sjögren's syndrome [56]. A GWAS study in a Korean population showed that *HCP5* was associated with the pathogenesis of KD. *HCP5* (rs6938467) is linked to other genes (rs9380242, rs9378199, and rs9266669) within the HLA class I region. Due to the complex genetic structure of the HLA class I region, further research is necessary to confirm the true signals within this region [23].

### Human Leukocyte Antigen (HLA)

*HLA*, which is located on chromosome 6, is one of the critical factors that is highly related to immunity and autoimmune diseases. The *HLA* is divided into three regions, which are class I (containing the classical *HLA-A*, *HLA-B*, *HLA-C*, *HLA-E*, *HLA-F*, and *HLA-G* genes), class II (containing the A and B genes, including *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRA*, *HLA-DRB1*, *HLA-DRB2*, *HLA-DRB3*, *HLA-DRB4*, and *HLA-DRB5*), and class III (containing non-*HLA* genes). HLA class I molecules can present peptides to CD8<sup>+</sup> T cells regardless of whether HLA class II binds to CD4<sup>+</sup> T cells. This binding is responsible for defense against pathogens [57]. Polymorphisms at HLA loci have widely been identified. Previous studies in Japanese and Han Chinese populations demonstrated that rs2857151 (in a genomic region between *HLA-DQB2* and *HLA-DOB*) has a significant association with KD [11, 13]. In contrast, different

results from a validation study in a Taiwanese population showed that rs2857151 exhibited no difference between KD patients and controls [14]. Other significant HLA loci were identified, including *HLA-B* (*HLA-B35* [58], *-B75* [58], and *-B54* [59]), *HLA-C* (*HLA-Cw09* [58]), and *HLA-E* (rs2844724 [24]). However, studies indicated no significant association between *HLA-DRB1* and KD in Korean [58] or Taiwanese [60] populations.

### Immunoglobulin Heavy Chain (IGH) Variable (IGHV)

The *IGH* locus on chromosome 14 is a complex gene family that is important in providing primary components to the adaptive immune system. One group of *IGH* genes, *IGHV*, encodes components of immunoglobulin that are essential for recognizing and binding to particular antigens. *IGHV* has mostly been identified to be associated with chronic lymphocytic leukemia (CLL) [61], rheumatic heart disease [62], and other immune-related diseases [63]. A previous GWAS in Taiwan identified six SNPs (rs17113284, rs8005468, rs10129255, rs2007467, rs10150241, and rs12590667) in the *IGHV* region that are known as KD markers [64]. Furthermore, rs4774175 and rs6423677 in the *IGHV3–66* region were also related to KD pathogenesis [10].

### Interleukin (IL)-4 and the IL-4 Receptor (IL-4R)

IL-4, which is mainly secreted by activated T cells, is a cytokine that plays a role in type 2 immune responses. Higher levels of IL-4 in plasma were found in acute KD patients than those in the convalescent phase or a control group [65]; however, levels showed no significant differences compared to KD shock syndrome [66]. The role of *IL-4* in the pathogenesis of KD was proven in several genetic association studies. A family-based study, which found 95 polymor-

phisms in 58 genes, showed that the C(–589)T variant in *IL-4* was correlated with susceptibility to KD, but not coronary artery aneurysms [25]. Strengthening previous findings, other positions of *IL-4* were also detected for KD. Frequencies of the major C allele and CC genotype at positions –590 (rs2243250) and –33 (rs2070874) of the *IL-4* gene were higher in Iranian KD patients than that in a control group [26].

In addition to the pathogenesis of KD, variants related to IVIG responses were also identified in the *IL4R* locus. For example, a study in a Japanese population indicated a significant association between the minor allele of rs563535954 and patients who were unresponsive to IVIG. In that study, IVIG-unresponsive patients presented with a fever (with an axial temperature of >37.5 °C) for more than 24 h after the first and second IVIG treatments [32].

### Inositol-Triphosphate 3-Kinase C (ITPKC)

*ITPKC*, located on chromosome 19q13.2, is known as a negative regulator of T cells through Ca<sup>2+</sup>-dependent NFAT signaling pathways [6]. The NFAT has important roles in the immune system, as it is associated with vascular stability, angiogenesis, and inflammation in endothelial cells [67–69]. Moreover, vascular endothelial cells (VECs) are involved in the pathogenesis of coronary artery injury in KD. One study showed that damage to endothelial cells increased levels of NFATc1, NFATc3, and inflammatory molecules [69]. *ITPKC* is able to regulate activation of the NLRP3 inflammasome through Ca<sup>2+</sup> mobilization. The NLRP3 inflammasome is a sensor of the innate immune system responsive to harmful stimuli, such as pathogens, dead cells, and environmental irritants [70, 71]. Triggers required to activate the NLRP3 inflammasome include HMGB1/RAGE/cathepsin B signaling, K<sup>+</sup> efflux, and Ca<sup>2+</sup> signaling [72, 73]. Activation of the NLRP3 inflammasome is associated with elevation of circulating protein levels of IL-1β and IL-18 in children with KD [73].

A variant of *ITPKC* with rs28493229 (C allele) was proven to have a significant association with KD susceptibility and CAL formation in Japanese and Taiwanese KD patients [6, 7, 9]. Although there was no association between rs28493229 and the response to IVIG treatment in a Taiwanese population [7, 44], the C allele of rs28493229 was found to be significantly higher in unresponsive IVIG patients compared to responsive patients in a Japanese population [9]. Furthermore, variants of rs7251246 exhibited significant correlations with CAL formation after multiple testing corrections [74].

### Multidrug Resistance Protein 4 (MRP4)

MRP4, also known as ATP-binding cassette, sub-family C member 4 (ABCC4), is a member of the MRP family involved in multidrug resistance. As a molecular transporter, MRP4 can transport endogenous and exogenous components such as cGMP, bile acid, and urate, and is also involved in the distribution and excretion of some drugs such as antivirals (adefovir and tenofovir), antibiotics (cefazolin and cefotaxime), and others [75, 76]. Due to its role in pumping out endogenous and xenobiotic agents, overexpression of MRP4 could contribute to multidrug resistance. Doxorubicin in osteosarcomas [77], antiviral ganciclovir [78], and docetaxel in prostate cancer [79] are examples of drugs that it affects.

Associations of the *MRP4* gene with KD susceptibility were investigated in a European population based on family linkage studies. The genetic susceptibilities of three SNPs (rs7320375, rs7329490, and rs7986087) for KD were reported [27]. Furthermore, rs7986087 (T variant) was successfully replicated in a Chinese population [28]. In addition to KD susceptibility, the *MRP4* gene was reported to be involved in IVIG resistance in a Chinese population. Carriers of the C allele at rs1751034 of the *MRP4* gene were associated with a risk of IVIG resistance [33].

### Nicotinamide Mononucleotide Adenylyl Transferase 2 (NMNAT2)

NMNAT is an enzyme that catalyzes an important step in the nicotinamide adenine dinucleotide (NAD<sup>+</sup>) biosynthetic pathway. The NAD<sup>+</sup> pathway plays a critical role in immune modulation by affecting macrophage-driven inflammation [80]. Some studies related to the role of NAD<sup>+</sup> or NMNAT primarily focused on cancer or aging disorders, and not on KD [81, 82]. NMNAT2 is one of the isoforms of NMNAT enzymes that showed higher expression in colorectal cancer tissues [83]. However, a GWAS study in a Korean population identified rs2078087 in the *NMNAT2* locus to be associated with the pathogenesis of KD [23]. Further studies in other populations are needed to validate this gene.

### SMAD3

*SMAD3*, a gene encodes SMAD family protein, plays a key role in the transforming growth factor (TGF)- $\beta$  signaling pathway. As a multifunctional cytokine, activation of TGF- $\beta$  can mediate growth control of cells of the immune system, regulate T-cell function, and induce cytostatic and apoptotic programs [84]. Functional roles of the TGF- $\beta$  pathway in KD pathogenesis are related to immune responses and inflammatory processes [85]. Five genetic variations on the *SMAD3* gene for KD were found in people of European descent, including rs4776338 (A/G), rs7162912, rs12901071, rs1438386, and rs6494633 [29]. Moreover, a replication study in a Taiwanese population further confirmed the role of rs1438386 in KD [30].

### High-Mobility Group Box 1 (HMGB1)

HMGB1 is a nonhistone DNA-binding protein that contributes to inflammatory processes. HMGB1 levels were higher in acute KD adolescent patients [86] and patients with autoimmune diseases [87]. However, its expression significantly decreased in the convalescent phase [88].

HMGB1 requires binding to the receptor for advanced glycation end products (RAGE) before activating various signaling pathways, such as NF- $\kappa$ B. Expressions of HMGB1, RAGE, and NF- $\kappa$ B were higher in acute KD patients and CAL patients. Findings indicated that HMGB1 might be associated with inflammatory processes during coronary artery injury in KD [89]. Indeed, the rs1412125 polymorphism of *HMGB1* in a Korean population was reported in CALs (in a recessive model) and IVIG resistance (in both recessive and allelic models). Still, it showed no association with KD susceptibility [31].

### Interleukin (IL)-16

IL-16 is responsible for T cell activation and immune-mediated inflammatory disorders, such as SLE [90]. The relationship between *IL-16* and KD susceptibility is unclear; however, this gene was identified to be associated with response to IVIG treatment. A study in a Korean population indicated that a new coding variant, rs11556218 (p.Asn1147Lys), in the *IL-16* gene was associated with IVIG resistance. Further analysis indicated a strong effect from combining two risk variants (*SAMD9L* and *IL16*) for IVIG resistance [19].

### Purinergic Receptor P2Y12 (P2RY12)

P2RY12 is one of eight subtypes of P2Y G-protein coupled receptors that have broad functions, including systemic immune responses [91]. P2Y12 is also known to be involved in platelet activation [92]. P2Y12 inhibitors, such as clopidogrel and prasugrel, were previously used as treatments for coronary artery disease [93]. No evidence clearly indicates an association between *P2RY12* variants and KD susceptibility. One study in China showed no significant association between variants of *P2RY12* and KD susceptibility; however, that study presented the relationship between a polymorphism of *P2RY12* (TT genotype of rs7637803) with CAA risk in KD

patients [94]. Furthermore, one of five variants of the *P2RY12* gene (rs6809699 A > C) was also verified to be involved in IVIG resistance in ethnic Han Chinese individuals [20].

### Sterile Alpha Motif Domain-Containing Protein 9-Like (SAMD9L)

*SAMD9L*, located on chromosome 7, is a gene that encodes a cytoplasmic protein. A mutation of *SAMD9L* was shown to contribute to cytopenia that may predispose persons to myelodysplastic syndrome (MDS) [95] and ataxia–pancytopenia (AP) syndrome [96]. Although evidence related to *SAMD9L* variants and susceptibility of KD has not yet been reported, there is evidence supporting the role of *SAMD9L* in response to IVIG treatment. A GWAS and replication study performed in a Korean population demonstrated that *SAMD9L* (rs28662) was involved in IVIG treatment responses. Those results were replicated in a Japanese cohort, and a stronger association was revealed in meta-analysis data [18].

### Prediction of Intravenous Immunoglobulin Resistance Using a Genetic Risk Score (GSC)

A GSC was developed to estimate the contributions of genetic factors in specific individuals. The first study, which used a combination-weighted GSC (wGSC) algorithm of GWAS data for KD, was published by Chang's lab [97]. The lab integrated the additive effect of 11 SNPs to establish a predictive model for IVIG responsiveness in KD patients. The predictive model provided good performance with a specificity of 88.9% and sensitivity of 79.2% [97]. In light of the fact that genomic profiles are very important and have been linked to therapeutic outcomes of KD, data from the wGSC algorithm indicated the significance as a reasonable early detection method to reduce clinical risks in IVIG-resistant KD patients [97].



## Conclusions

Nowadays, many genetic variations associated with KD pathogenesis or IVIG responses have been reported. Genomic approaches are able to provide excellent opportunities for personalized medicine and healthcare. Furthermore, they can help determine how to improve the specificity and sensitivity for predicting risks of KD and IVIG responses. Therefore, we wish to raise awareness about the value of genomic research and pharmacogenomics studies of KD.

**Acknowledgments** This work was supported by the grants from the Ministry of Science and Technology, Taiwan (MOST-108-2314-B-038-027, MOST-109-2314-B-038-131, and MOST-109-2628-B-038-012) and Taipei Medical University, Taiwan (12310-106079, Yusuke Nakamura Chair Professorship). The authors would like to thank Poppy Diah Palupi for her assistance in editing the script.

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