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Molecular Genetics of Kawasaki Disease

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ABSTRACT: Kawasaki disease (KD) is a leading cause of acquired cardiac disease of children in the developed countries. The pathogen that triggers this perplexing disease is still unknown after 40 y from the first description. Epidemiologic findings have made us believe that there are considerable genetic components in the etiology and some candidate genetic variations, which confer susceptibility to KD or risk for coronary artery lesions have been identified. However, most of them remain to be definitively confirmed by replication studies with large cohorts. In this article, I review the candidate gene association studies to date. I also introduce our recent findings in genome-wide approach, which revealed the importance of Ca^{2+}/nuclear factor of activated T-cells pathway in the pathogenesis of KD.
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Kawasaki disease (KD) is a systemic vasculitis syndrome which preferentially affects infants and children (1,2). Past large epidemics in Japan, peaked incidence at 9–11 mo of age, which coincides with waning of maternal immunity and symptoms partly similar to other infectious disorders suggest that some microorganisms may trigger the disease. However, despite large efforts, the cause of this mysterious disease still remains unknown. Contrary to their initial expectation of a benign illness, coronary artery lesions (CALs) developed in 15–25% of untreated patients has made KD a leading cause of acquired heart disease of children in the developed countries (3). Intravenous gamma globulin (IVIG) therapy dramatically reduced occurrence of CALs, however, about 15% of the patients poorly respond to the treatment and are at higher risk for CALs. Following epidemiologic findings have suggested that genetic predisposition might underlie the etiology of KD. First, KD is much common in East Asian countries. In Japan, incidence of KD is continuously increasing and in recent years, more than 180 per 100,000 children younger than 4 y are affected annually (4).

The incidence is 10–20 times higher than that of Western countries. The same level of incidence in Japanese ancestries living in Hawaii (5) is indicating that the predilection for oriental populations might not be due to geographical reasons. Second, KD has familial accumulation. Relative risk for sibs (λs) is about 10 and recent study revealed that two-generation KD patients exist more than expected (6,7). Thus, KD can be considered as a complex multifactorial disease (Fig. 1). Identification of genetic factors related to individual susceptibility or different incidence among ethnicity might provide a clue to unravel the enigma of KD. Recent advances in molecular genetics have greatly accelerated identification of susceptibility genes for complex diseases. Currently, there are two mainstreams of strategy for identification of disease genes. One is candidate gene approach and the other is genome-wide approach.

Candidate Gene Approach

Most genetic studies of KD have focused on candidate genes. This approach is derived from "functional cloning" used in searching for genes responsible for monogenic disorders. Genes for analyses were selected based on the information of their known function or role in the disease pathophysiology.[1]

HLA

Human leukocyte antigens (HLA) are located on the chromosome 6p21.3 region and their polymorphisms are associated with various diseases directly or indirectly as a consequence of linkage disequilibrium (LD) between polymorphisms of other neighboring genes. There are large differences in distribution of HLA alleles among races or ethnicity. Initial genetic studies of KD were focused on HLA class I antigens. Matsuda *et al.* (8) and Kato *et al.* (9) reported that Japanese specific variant of HLA-Bw22 (now called as Bw54) was predominant in Japanese KD patients. In the studies of white (10,11) and Jewish population (12), association between HLA-Bw51 and KD was found. However, neither trend of association was replicated in the Southern Chinese population (13) and in the Korean population (14). One of the reasons that KD has been regarded as infection-triggered disorder is past epidemic in Japan and in the United States. HLA-B44 was predominant in the epidemic KD cases in Boston (11). This finding was supported by the report by Kaslow *et al*. (15) in which HLA-A2, B44 and Cw5 antigen combination was associated with KD patients involved in an outbreak in Maryland. On the other hand, Harada *et al*. (16) analyzed sharing of HLA-A-B-C-DR haplotypes between 23 affected sib pairs of Japanese KD patients and failed to find evidence of association. Several groups have studied relationship between KD and HLA class II antigens, however, no significant association has been observed until now (17–19).

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Abbreviations: ASP, affected sibpair; **CALs,** coronary artery lesions; **IP3,** inositol 1,4,5-trisphosphate; **ITPKC,** inositol 1,4,5-trisphosphate 3-kinase C; **IVIG,** intravenous gamma globulin; **KD,** Kawasaki disease; **LD,** linkage disequilibrium; **MMP,** matrix metalloproteinase; **NFAT,** nuclear factor of activated T cells; **SNPs,** single nucleotide polymorphisms; **TIMPs,** tissue inhibitors of metalloproteinases

Thus, a single allele or haplotype of HLA that confers KD susceptibility has not been identified yet. Previous studies about association between HLA and KD were summarized in Table 1. Considering that no evidence of linkage was observed near 6p region in the genome-wide affected sib-pair (ASP) study of KD (20), the involvement of HLA in KD pathogenesis might be limited or more complex than expected.

Non-HLA Genes

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine mainly produced by macrophages. The possible involvement of this cytokine in vascular damage and elevated serum level in the acute phase KD patients who developed CALs suggests its key role in the disease pathogenesis (21,22). Recent case series suggesting successful treatment using MAb against TNF-α (infliximab) on IVIG resistant patients (23–25) back up this idea. Association of single nucleotide polymorphisms (SNPs) that may alter TNF-α expression with various inflammatory diseases has been extensively studied. Kamizono *et al*. (26) conducted association study about five SNPs (-1031 T>C, -863 C>A, -857 C>T, -308 G>A and -238 G>A) located at 5′ flanking region of *TNF-α* gene in the Japanese population. In this study, no association was observed between these polymorphisms and KD occurrence or CALs formation. Quasney *et al*. (27) investigated the distribution of + 250 A>G of *lymphotoxin-α* gene in addition to -308 G>A of *TNF-α* and found positive association of *TNF-α* -308 A/G genotype with CALs in white KD patients. Chien *et al*. (28) and Ahn *et al*. (29) reported negative association between polymorphisms in *TNF-α* gene and susceptibility to KD or CALs in the Taiwanese and the Korean populations, respectively. In a recent report by Cheung *et al*. (30), *TNF-α* -308 A allele was associated with KD in the Chinese population. Cheung also showed that this SNP was associated with intima-media thickness of carotid arteries.

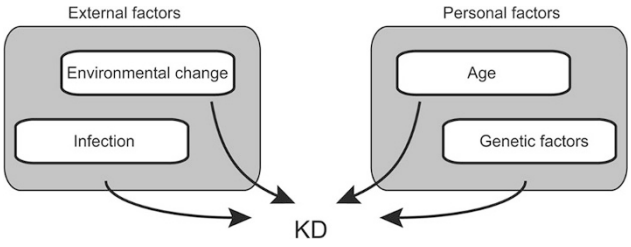

Figure 1. Multiple factors that could be linked to Kawasaki disease.

Burns *et al*. (31) applied family-based association study to KD for the first time. Ninety-five SNPs in 58 candidate genes for cardiovascular diseases and inflammation were selected and their transmission patterns in 269 trios of KD patients and their parents were investigated. They found a SNP in the promoter region of *interleukin* (*IL*)*-4* gene was asymmetrically transmitted. *IL-4* is located in the cytokine gene cluster on 5q31 region where positive linkage signal was observed in a sib-pair linkage study of KD (20). However, replication study performed by two Taiwanese groups failed to validate the finding (32,33). IL-4 is known to promote differentiation of naive T cells into Th2 cells. Elevated serum IL-4 in the acute phase of KD was reported, and many aspects of immune response in KD pathophysiology are associated with Th2 reaction, hence the cytokine could play a role in the pathogenesis of KD. Further investigation is needed to understand the involvement of the SNPs of *IL-4* gene in individual susceptibility to KD. Association studies focused on SNPs or copy number variations of genes for other cytokines, as well as chemokines and their receptors have also been conducted (32,34–40; Table 2).

Table 1. *Association studies between HLA and KD*

Haplotypes	Number of samples (cases/controls)	Ethnicity	References
Reports of positive association			
Bw22J	32/76	Japanese	8
Bw22J2	205/500	Japanese	9
Bw15			
Bw51	23/244	White American	10
Bw51	12/90	Jewish	12
Bw44 (epidemic cases)*	23/246	White American	11
Bw44 (epidemic cases)	16/608	White American	15
DRB3*0301†	21/200	White American	17
B35	74/159	Korean	14
B37			
Cw09			
Reports of negative association			
Loci (number of haplotypes tested)			
HLA-A (10)	62/100	Chinese	13
HLA-B (15)			
HLA-DR (11)			
DRB1 (41)	25/209	White American	17
DQA1 (7)			
DQB1 (13)			
DPB1 (17)			
DRB1 (35)	145/331	Taiwanese	18

*Association was not significant after correction of multiple comparison.
†Association was not confirmed in the authors' subsequent study in the other area of the United States.

Table 2. *Candidate genes previously tested for association with KD*

Symbol*	Gene	Region	Phenotype	References
MTHFR	5,10-methylenetetrahydrofolate reductase	1p36.3	CAL formation	61†
CRP	C-reactive protein	1q21-q23	KD	30
			CAL formation	30‡
			Intima-media thickness§	30
IL-10	Interleukin 10	1q31-q32	KD	37‡
			CAL formation	37
			Serum albumin level	37
FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32)	1q23	KD	62‡, 63‡
			CAL formation	62, 63‡
FCGR2B	Fc fragment of IgG, low affinity IIb, receptor (CD32)	1q23	KD	63‡
			CAL formation	63‡
FCGR3A	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)	1q23	KD	62, 63‡
			CAL formation	62‡, 63‡
FCGR3B	Fc fragment of IgG, low affinity IIIb, receptor (CD16b)	1q23	KD	62‡, 63‡
			CAL formation	62‡, 63‡
IL-1β	Interleukin 1, beta	2q14	KD	32‡
IL-1Ra	Interleukin 1 receptor antagonist	2q14.2	KD	32
CXCR2	Chemokine (C-X-C motif) receptor 2	2q35	KD	40‡
CXCR1	Chemokine (C-X-C motif) receptor 1	2q35	KD	40‡
SLC11A1	Solute carrier family 11	2q35	KD	60
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	2q37	KD	64‡
CX3CR1	Chemokine (C-X3-C motif) receptor 1	3p21.3	KD	40‡
CCR3	Chemokine (C-C) receptor 3	3p21	KD	40
CCR2	Chemokine (C-C) receptor 2	3p21	KD	40
CCR5	Chemokine (C-C) receptor 5	3p21	KD	35, 39, 40
			CAL formation	39‡
AGTR1	Angiotensin II receptor, type 1	3q21-q25	KD	50‡
			Coronary stenosis	50
VEGFR2	Vascular endothelial growth factor receptor 2	4q12	KD	43‡
			CAL formation	43
IL-4	Interleukin 4	5q31.1	KD	31, 32‡, 33‡
			CAL formation	31‡, 33‡
CD14	CD14 antigen	5q31.1	KD	56‡
			CAL formation	56
VEGFA	Vascular endothelial growth factor A	6p12	KD	43‡, 44, 45, 46‡
			CAL formation	43, 45‡, 46‡
MICA	MHC class I polypeptide-related sequence A	6p21.3	CAL formation	65
LTA	Lymphotoxin alpha	6p21.3	KD	27
			CAL formation	27‡
TNF-α	Tumor necrosis factor-α	6p21.3	KD	26‡, 27‡, 29‡, 28‡, 30
			CAL formation	27, 30‡
			Arterial stiffness‖	30
PAFAH	Platelet-activating factor acetylhydrolase	6p21.2-p12	KD	66‡
			CAL formation	66‡
			IVIG unresponsiveness	66
IL-6	Interleukin 6	7p21	KD	36‡
eNOS	Endothelial nitric oxidase synthase	7q36	KD	67‡
			CAL formation	67‡
MBL	Mannose-binding lectin	10q11.2-q21	KD	57, 59‡
			CAL formation	57¶, 58¶, 59‡
			Arterial stiffness‖	59
IL-18	Interleukin 18	11q22.2-q22.3	KD	38
			CAL formation	38‡
MMP3	Matrix metallopeptidase 3	11q22.3	KD	53‡, 54‡, 55‡
			CAL formation	53, 54‡, 55‡

(*Continued*)

Table 2. *(Continued)*

Symbol*	Gene	Region	Phenotype	References
MMP12	Matrix metallopeptidase 12	11q22.3	KD	54‡
			CAL formation	54‡
MMP13	Matrix metallopeptidase 13	11q22.3	KD	54‡
			CAL formation	54
MMP2	Matrix metallopeptidase 2	16q13-q21	KD	54‡
			CAL formation	54‡
iNOS	Nitric oxide synthase 2, inducible	17q11.2-q12	KD	67‡
			CAL formation	67‡
MCP1	Monocyte chemoattractant protein-1	17q11.2-q12	KD	34‡
CCL3L1	Chemokine (C-C motif) ligand 3-like 1	17q11.2	KD	35
ACE	Angiotensin I converting enzyme	17q23	KD	48, 49, 50‡
			CAL formation	47, 48‡, 49‡
			Coronary stenosis	50
TIMP2	Tissue inhibitor of metalloproteinase 2	17q25	KD	52‡
			CAL formation	52
MMP9	Matrix metallopeptidase 9	20q11.2-q13	KD	53‡, 54‡
			CAL formation	53‡, 54‡
HMOX1	Heme oxygenase (decycling) 1	22q12	KD	64‡
CD40L	CD40 ligand	Xq26	KD	68‡, 69‡
			CAL formation	68**, 69‡

*When several gene symbols were available, those used in the references were selected.
†Association only in female patients.
‡Reports of negative association results.
§Intima-media thickness of right common carotid artery was measured.
‖Stiffness of brachioradial artery and carotid artery was measured in reference 59 and 30, respectively.
¶Association in KD patients younger than 1 y.
**Association only in male patients.

Genes related to vasoactive or angiogenic molecules also can be considered as candidates for KD susceptibility or severity. Vascular endothelial growth factor (VEGF) is expressed in various types of cells including leukocytes and vascular smooth muscle cells. Binding of VEGF to its receptor (VEGFR-1 and VEGFR-2) expressed on endothelial cells induces cell proliferation, survival, migration, and angiogenesis. Its ability to induce vascular hyperpermeability and chemotaxis of bone marrow-derived cells suggest significant roles of VEGF in inflammation (41). VEGF is up-regulated in the acute phase of KD and the serum level of this protein is associated with formation of CALs in one study (42). Kariyazono *et al*. (43) reported a SNP in the 5′ untranslated region (UTR) of *VEGF* (rs2010963) was associated with CALs in the Japanese population. In the study of Dutch KD patients, 2 SNPs other than rs2010963 showed association with KD (44). With regard to association of rs2010963 with KD or CALs, two inconsistent results were also reported by Taiwanese groups (45,46).

Association of the insertion/deletion (I/D) polymorphism of a gene for angiotensin I converting enzyme with cardiovascular diseases and hypertension has been extensively examined. This polymorphism is located in intron 16 and is in strong LD with other SNPs in the 5′ and 3′ regions of the gene. Takeuchi *et al*. (47) reported association of I/I genotype with CALs in the Japanese. Taiwanese and Korean groups reported I allele or I/I genotype was associated with KD susceptibility but not with risk for CALs (48,49). Fukazawa *et al*. (50) reported that the D allele in concert with the C allele of the SNP in the 3′ UTR (+1166 A/C) of *angiotensin II type I receptor* gene increased risk for coronary artery stenosis in another Japanese cohort.

Matrix metalloproteinases (MMPs), produced by a variety of cell types, play important roles in various physiologic and pathologic processes by degrading extracellular matrices. The activity of MMPs is controlled by their endogenous inhibitor, the tissue inhibitors of metalloproteinases (TIMPs). Imbalances between MMPs and TIMPs are related to pathologic conditions such as arthritis, tumor metastasis, and aortic aneurysms. MMPs and TIMPs are elevated in the serum or vascular tissue of acute KD patients and association of increased MMP9/TIMP2 and MMP3/TIMP1 ratios with risk for CALs formation was reported (51). Furuno *et al*. (52) identified that promoter polymorphisms of *TIMP2* gene was associated with increased risk of CALs. 6A allele of an insertion/deletion polymorphism (5A/6A) of *MMP-3* gene promoter was more predominant in the Korean KD patients with CAL (53). Although not significant, the 5A allele showed a trend of association with CALs in the Japanese population (54). Another promoter SNP of *MMP-3* was not associated with KD or CALs in the Korean population (55). Ikeda *et al*. (54) conducted association study of five functional polymorphisms of *MMP-2*, *3*, *9*, *12,* and *13* genes and observed significant association between a promoter SNP or a haplotype of *MMP-13* and CALs.

There has been growing interest in involvement of innate immune system in the pathophysiology of inflammatory diseases. Genes for pattern recognition receptors (PRRs) which recognize pathogen-associated molecular patterns and downstream signaling peptides which cause cytokine production

through activating nuclear factor kappa-B (NF-kB) and/or caspase-1 have become an active area of genetic research. As for KD, positive association of the SNPs in the promoter of *CD14*, a PRR for LPS expressed on monocytes/macrophages and neutrophils with CALs was reported (56). Mannose binding lectin (MBL) and C-reactive protein (CRP), known as acute phase proteins produced in liver, also have roles in innate immune reaction. MBL can initiate complement activation directly by binding to mannose and N-acetyl glucosamine residues on the surface of microorganisms. Ligands of CRP are phosphocholine on microorganisms or damaged cell membranes. CRP also initiates complement activation by binding to C1q. Association between functional polymorphisms of *MBL* gene and CALs in KD patients younger than 1 y was described (57,58). Cheung *et al*. (30,59) reported that polymorphisms in *MBL* and *CRP* were associated with arterial stiffness or intima-media thickness. Ouchi *et al*. (60) reported association between a GT repeat polymorphism in 5′ region of solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1 (*SLC11A1*) gene, and KD. SLC11A1 is a divalent cation (Fe^{2+}, Zn^{2+}, and Mn^{2+}) transporter on the endosomes and regulates macrophage activation. Association of polymorphisms in genes for 5,10-methylenetetrahydrofolate reductase (61), Fc gamma receptors (62,63), UDP glucuronosyltransferase (64), heme oxygenase (64), MHC class I polypeptide-related sequence A (65), platelet-activating factor acetylhydrolase (66), NO syntheses (67), and CD40 ligand (68,69) with KD or phenotypes related to KD have also been studied. Previous association studies of candidate genes are summarized in Table 2.

Overview of Previous Candidate Gene Studies

Several candidate genes have been examined in independent cohorts of the same or different ethnicity, however most of the results were conflicting (Table 2). Most of the previous studies have been carried out with a single small cohort of KD patients and findings were reported without validation in additional case-control sets. This step of confirmation is crucial to rule out type I error (false positive). Population stratification in the first association report also can result in irreproducible results. Correction for multiple comparisons, which is essential for genome-wide approach described in the following paragraph, has to be conducted also in candidate gene studies. Recruiting sufficient number of the patients is indispensable not only to reduce false-negative conclusions but also to obtain association, which remains significant after correction. Compared with the other common diseases in the adults, there are difficulties in collecting DNA samples from young patients. Methods to extract genomic DNA from specimens other than blood (mouthwash, saliva, hairs, and nail clippings) and a multicenter collaboration that allows us to increase size of the cohorts and to validate the association in multiple sample sets may be beneficial.

Sometimes association is not replicated in different ethnicity even if the initial observation was definitely validated in the cohorts of the same ethnic group. One of the reasons is different relative importance of particular genetic variants in susceptibility of complex diseases between ethnicity. Difference in LD or haplotype structures among ethnicity may also lead conflicting results. Most of the replication studies tend to focus on only one or several variations significant in previous studies. When the initial positive association was indirect observation due to LD between the markers tested and a particular gene or variation, the association would not be detected in a different ethnic group in which the responsible variation is not linked with the same markers. Therefore, researchers of both discovery and replication studies should be careful in selecting variations to test.

Genome-wide Approach

In contrast to candidate gene approach, which is based on assumption, a strategy for searching disease causing mutations or variations from the whole genome relying only on the positional information is called genome-wide approach. Currently, we and another group are searching for susceptibility genes for KD by this approach predominantly studying Japanese and white KD patients, respectively. In this section, I introduce our recent accomplishments in genome-wide linkage study using microsatellite markers (20) and linkage disequilibrium mapping using SNPs (70).

Linkage Study

In linkage studies, genetic markers linked to diseases are searched by analyzing transmission patterns of the markers within families of multiple patients. Owing to the short history of KD, there is no large kindred with KD available for linkage analysis. Therefore, we applied ASP method, a kind of nonparametric linkage study suitable for investigating genetic factors of complex diseases. ASP method can be conducted only by analyzing DNA samples of siblings affected (and their healthy parents if possible). We have recruited more than 80 families including sibling cases all over Japan and genotyped about 400 polymorphic microsatellite markers. The lod scores were calculated by estimating numbers of shared alleles identical by descent for each marker loci. As a result, in 10 chromosomal loci (4q35, 5q34, 6q27, 7p15, 8q24, 12q24, 18q23, 19q13.2, Xp22, and Xq27) positive linkage signals (maximum lod score > 1.0) were observed (20). Among these candidate loci, 12q24 region showed the most significant evidence of linkage (maximum lod score $= 2.69$).

Linkage Disequilibrium Mapping

Because of limited number of mitosis analyzed in ASP method, the resolution of mapping achieved was relatively low and the responsible genes stand in the crowd of a hundred and several tens of genes around each linkage peak. We tried to narrow down the candidate loci and identify susceptibility genes by LD mapping using SNPs. SNPs distributed in 10–25 Mbp area surrounding the linkage peaks were selected from the database and 94 KD cases and 564 controls were genotyped. To increase the power of screening, patients with a positive family history of KD was chosen by priority. In the systematic SNP screening by case-control association study,

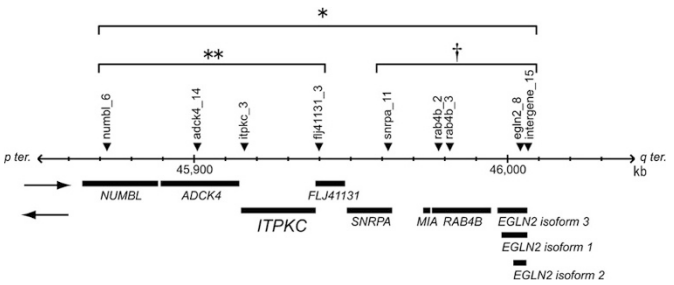

Figure 2. Genes and significant SNPs on the LD block identified in the chromosome 19q13.2 region. Genes oriented *q* terminus to *p* terminus are in *upper row*, with genes in the opposite orientation shown below. *Arrowheads* indicate the position of SNPs significantly associated with KD. *SNPs associated with KD in Japanese. **SNPs associated with KD both in Japanese and Americans. †SNPs associated with KD in Japanese but not in Americans. Adapted from Onouchi *et al.* (70) with permission.

we identified an LD block spanning 150 kb on 19q13.2 region containing three SNPs significantly associated with KD. Subsequent validation study using different case-control sample sets confirmed the association of the SNPs. Resequencing of the block and subsequent case-control study identified additional six SNPs significantly associated with KD. These candidate SNPs were further screened by transmission disequilibrium test conducted on American multiethnic KD patients–parents trios. Because of difference in LD structure among ethnicity, of the nine significant SNPs, only four centromeric SNPs showed the same trend of association (Fig. 2).

Identification of Inositol 1,4,5-trisphosphate 3-kinase C as a Susceptibility Gene for KD

Among the four genes in which the significant four SNPs were located, we focused on the known function of ITPKC as a kinase of inositol 1,4,5-trsiphosphate (IP3). IP3 is a second messenger molecule in various types of cells including T cells, macrophages, and neutrophils involved in the pathogenesis of KD. IP3 transduces signals from cell surface receptors (71) and, in T cells, plays an important role in signal transduction of Ca^{2+}/nuclear factor of activated T-cells (NFAT) pathway (72–74). Although three isoenzymes of ITPK proteins (ITPKA, ITPKB, and ITPKC) have been known, the relative importance of ITPKC in the immune system was unclear. We investigated mRNA expression of *ITPKC* in various normal tissues and revealed that *ITPKC* was greatly induced in PBMCs when activated. Compared with the other isoenzymes, *ITPKC* was most abundantly expressed in PBMCs and leukemic cell lines and most significantly induced in response to cell stimulation (70). Therefore, we speculated that ITPKC might be related to inflammation. Previous *in silico* study (75), which has predicted NF-kB binding sequence in the promoter of *ITPKC,* supported the idea that ITPKC is a potent immune gene.

Negative Regulatory Role of ITPKC in T-cell Receptor Signal Transduction

Overexpression of ITPKC in Jurkat cells resulted in reduced NFAT activation and *IL-2* expression. Conversely, knock down of ITPKC by short hairpin RNA enhances NFAT activity and *IL-2* expression (70). These data indicate that ITPKC acts as a negative regulator of Ca^{2+}/NFAT pathway in T cells by modulating the amount of IP3. Through functional analyses of significant SNPs, we clarified that itpkc_3 G/C (rs28493229), a SNP located in intron 1 of *ITPKC,* reduces mRNA expression of *ITPKC* in PBMCs down to 70% by altering splicing efficiency (70). Increased stability of secondary structure of pre-mRNA and reduced binding affinity of some RNA binding proteins related to splicing by the nucleotide change were though to underlie these observations. Reduced ITPKC activity associated with C allele of itpkc_3 may lead enhanced T-cell activation in the pathophysiology of KD. The proposed role of ITPKC and itpkc_3 in Ca^{2+}/NFAT pathway in T cell was demonstrated in Fig. 3. In mice, itpkB (not itpkC) and IP4 play important roles in development of thymocytes and selection and activation of B cells (76–78). Investigation of the role of human ITPKC and biologic significance of itpkc_3 in other immune cells (*e.g.*, macrophages, B cells, and neutrophils) or nonimmune cells (*e.g.*, endothelial cells and cardiac myocytes) may lead further understanding of the pathogenesis of KD.

Association of itkpc_3 with CAL Formation and IVIG Responsiveness

As 15% of KD patients poorly respond to IVIG and these patients are at higher risk for developing CALs, how to predict patients' risk for CALs and responsiveness to IVIG and start additional or alternative therapy before they are destined to develop CALs is the most pressing issue. The C allele of itpkc_3 was more predominant in patients with CALs and those refractory to IVIG (Table 3, Ref. 70). Considering that these phenotypes somewhat depend on severity of inflammation, our observations may be reasonable. In Japan, experience of treating IVIG resistant KD cases successfully with Cyclosporin A (CsA) is accumulating (unpublished observations). CsA is an immunosuppressant targeting calcineurin that dephosphorylate and lead nuclear translocation of NFAT. Proof of effectiveness of CsA in the treatment of KD would provide additional support for the importance of Ca^{2+}/NFAT pathway activation in the pathogenesis of KD.

There should be genetic variations which directly affects vascular elasticity or anti-inflammatory mechanism of IVIG and increase individual risk for a more severe course when affected with KD. Large-scale association study between KD patients with CAL and those without CAL, as well as between IVIG responders and nonresponders will identify a set of genetic markers efficiently and will contribute in future evidence-based and personalized medicine.

Conclusion

Completion of human genome project and information of frequencies and LD of the SNPs provided by International HapMap project has made genome-wide approach of investigating genes for complex diseases quite feasible. Genome-wide association study (GWAS) with platforms by which 500 thousands to 1 million SNPs can be genotyped at a time has become a mainstream. During the next few years, multiple

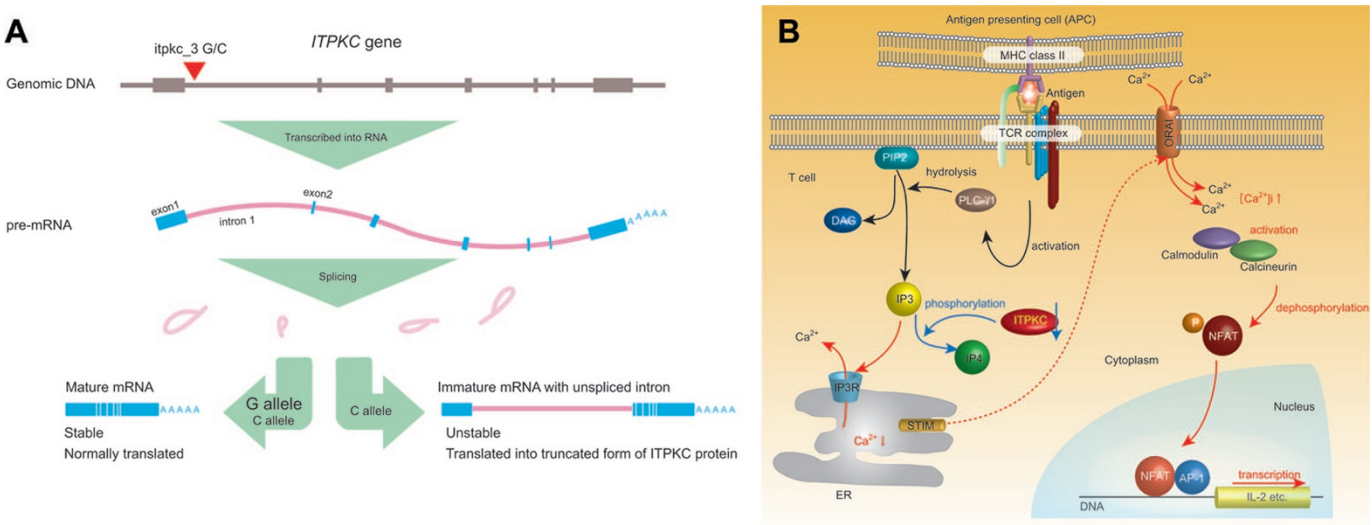

Figure 3. Functional significance of itpkc_3 on *ITPKC* mRNA and Ca^{2+}/NFAT pathway. (*A*) Effect of itpkc_3 C allele on splicing of *ITPKC* pre mRNA. The C allele of itpkc_3 reduces splicing efficiency of *IPTKC* premRNA. mRNAs harboring unspliced intron 1 cannot be translated properly and will be degraded early by nonsense-mediated decay mechanism. (*B*) Proposed role of ITPKC as a negative regulator of Ca^{2+}/NFAT pathway. When the T-cell receptor (TCR) is bound by antigen/MHC complex on antigen presenting cells (APCs), adaptor molecules and kinases are recruited and phospholipse C-γ1 (PLC-γ1) is activated by phosphorylation of its tyrosine residue. IP3 and diacylglycerol (DAG), another second messenger molecule, are generated by hydrolysis of phosphatidyl-inositol 3,4-bisphosphate (PIP2) by activated PLC-γ1. IP3 binds to its receptor expressed on endoplasmic reticulum (ER) membrane and causes the release of Ca^{2+} into the cytoplasm. Then depletion of Ca^{2+} store in ER evokes a process termed as store operated Ca^{2+} entry in which extracellular Ca^{2+} enters through calcium release-activated Ca^{2+} channels on the plasma membrane. Recent advances in research identified the role of stromal interaction molecule (STIM) as a sensor of Ca^{2+} in ER and ORAI as a calcium release-activated Ca^{2+} channel. Cytoplasmic Ca^{2+} binds calmodulin, which in turn activates calcineurin, a calmodulin-dependent phosphatase. Activated calcineurin dephosphorylate NFAT in the cytoplasm and lead nuclear translocation of NFAT. NFAT in the nucleus drives transcription of genes important in T cell activation as a homodimer or heterodimer with other transcription factors. AP1 is one of the transcription partners of NFAT, which is activated by a signal from TCR mediated by DAG (72–74). Reactions and amounts of molecules increased by the effect of itpkc_3 C alleles were represented by *red character*s and *arrows* and those reduced by *blue*, respectively. [Ca^{2+}]i: intracellular free Ca^{2+} concentration.

Table 3. *Association between itpkc_3 and KD*

Samples	itpkc_3 genotype GG	GC	CC	Total	Carrier ratio of C allele	OR*	95% CI	χ^2	*p*
Japanese									
KD	376	234	27	637	41%	1.89	1.53–2.33	35.8	2.2×10^{-9}
KD with CAL†	61	44	2	107	43%	2.05	1.37–3.08	12.4	0.00044
KD without CAL†	172	94	12	278	38%	1.68	1.27–2.21	13.4	0.00025
Control	756	249	29	1034	27%				

Samples	Transmitted C allele	Untransmitted C allele	OR	95% CI	χ^2	*p*
US‡						
KD	64	30	2.13	1.38–3.29	12.3	0.00045
KD with CAL	37	11	3.36	1.72–6.59	14.1	0.00018
KD without CAL	27	18	1.50	0.63–2.72	1.8	0.18
KD IVIG non responder	14	3	4.67	1.34–16.24	7.1	0.0076
KD IVIG responder	39	22	1.77	1.05–2.99	4.7	0.030

*Association study of genotype frequencies in dominant model of inheritance (GG *vs.* GC+CC).
†Samples without clinical information were excluded from analysis.
‡Transmission disequilibrium test of 209 triads of multiethnic KD patients and their parents.
Adapted from Onouchi *et al.* (70) with permission.

susceptibility genes may be identified from such large-scale studies. We can also hope that new insight in the pathophysiology of KD may be derived from the findings in hypothesis-free genetic research. Abovementioned genome resources may also contribute to candidate gene approach. Selecting tag SNPs that represent haplotypes by the information of LD may facilitate an efficient and quality screening of candidate genes. Pathways and molecular networks in which susceptibility genes identified in genome-wide approach are involved will expand the search range of candidate genes. It is suggestive that association of the SNPs in some downstream genes of NFAT (*TNF-α*, *CD40L,* and *IL-4*) with KD and/or outcome has been reported.

Although much remains to be done, it is hoped that both genetic approaches will complement one another in clarifying the genetic background of KD, open the door to elucidation of the etiology, and allow for establishment of new therapeutic and preventive strategies.

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