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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. **(*Pediatr Res* 65: 46R–54R, 2009)**

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.

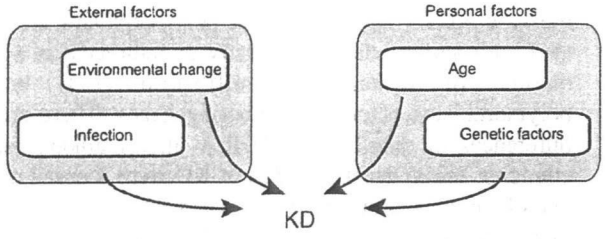

Figure 1. Multiple factors that could be linked to Kawasaki disease.

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,

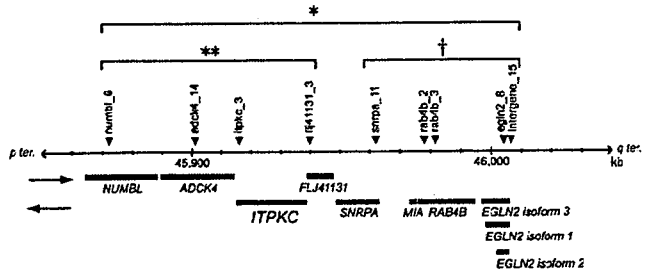

Figure 2. Genes and significant SNPs on the LD block identified in the chromosome 19q13.2 region. Genes oriented *q* terminus to *p* terminus are in *upper row*, with genes in the opposite orientation shown below. *Arrowheads* indicate the position of SNPs significantly associated with KD. *SNPs associated 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

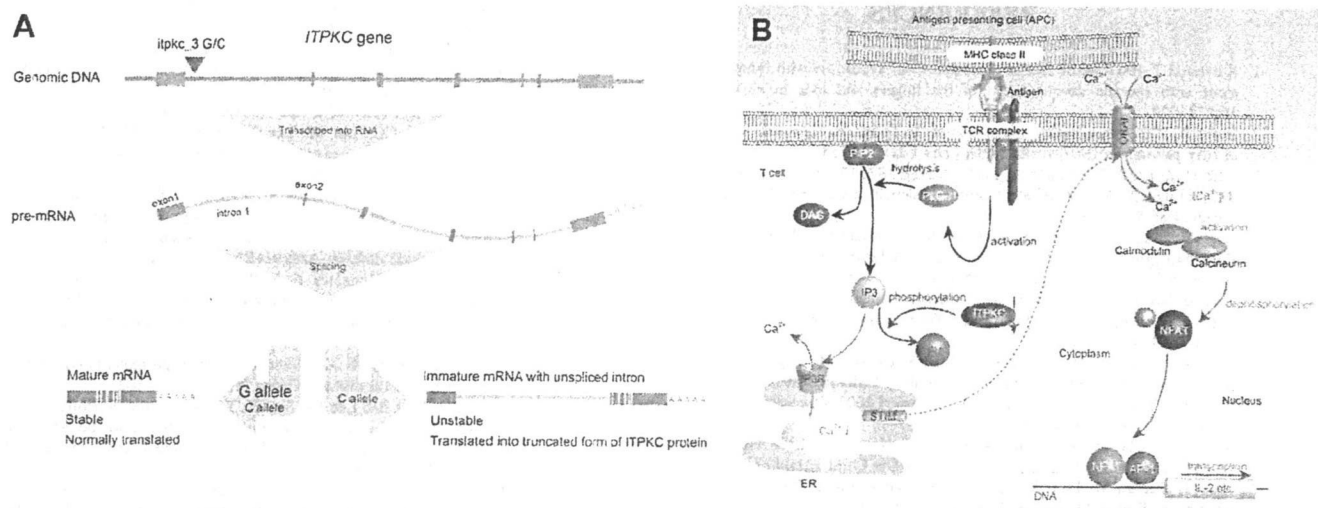

Figure 3. Functional significance of itpkc_3 on *ITPKC* mRNA and Ca^{2+}/NFAT pathway. (*A*) Effect of itpkc_3 C allele on splicing of *ITPKC* pre mRNA. The C allele of itpkc_3 reduces splicing efficiency of *IPTKC* premRNA. mRNAs harboring unspliced intron 1 cannot be translated properly and will be 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 characters* 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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川崎病の感受性遺伝子研究

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川崎病の感受性遺伝子研究

Susceptibility genes for Kawasaki disease

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◎川崎病は乳幼児期に好発する全身の血管炎症候群であり，先進国の小児後天性心疾患の最大の原因となっている．高熱・発疹を主徴とした臨床像から何らかの感染の関与が疑われるが，発見から40年以上が経過した現在においても原因は不明である．疫学データから遺伝的素因の存在が疑われており，罹患感受性や罹患した際の合併症リスクと関連した遺伝子多型が存在すると考えられている．川崎病のゲノム研究は候補遺伝子を中心として比較的小規模なサンプルにより行われてきたが，近年ゲノムワイドな探索も行われるようになり，成果が報告されつつある．

Key word：川崎病，感受性，一塩基多型，ゲノムワイド関連解析

川崎病の原因についてはなお謎が多い．疫学的・臨床的な特徴から何らかの感染因子(環境因子)が関与していることは強く疑われているものの，単一の病原体による発症が説明されるには至っていない．川崎病の罹患感受性に関与する個体側の要因(遺伝的素因)の情報は，病因を考えるうえで非常に有力な手がかりになると考えられる．

川崎病とは

川崎病は，①5日以上続く発熱，②両側眼球結膜の充血，③口唇・口腔所見，④不定形発疹，⑤四肢末端の変化，⑥頸部リンパ節腫脹，を主要症状とする急性熱性疾患であり，1967年に川崎富作医師によりはじめて報告された．自然経過で解熱，症状も消退する“self-limiting”な疾患であり，発見当初は予後良好と考えられたが，無治療で経過した患児15～25%の患者に冠動脈瘤を代表とする心合併症が生じ，瘤内の血栓性閉塞により死亡することもあるということが明らかとなった．合併症の発生を抑えることに主眼をおいたアスピリンの内服とγ-グロブリン大量静注療法(「サイドメモ1」参照)の併用療法が主流であり，冠動脈病変(CAL)の発生は数%にまで抑えられているが，約15%の患者は治療に抵抗性であり，CALのハイリスク群となる．

疫学データにみる川崎病の遺伝的素因

近年のわが国における川崎病の罹患率は5歳未満人口10万対およそ180[1]であり，同じく北東アジアの韓国(105)[2]，台湾(69)[3]とともに他人種と比較して高い．ハワイに居住する日系人の川崎病罹患率は国内と同等であり[4]，川崎病の高罹患率が地理的な理由でなく民族の遺伝的背景に起因している可能性を強く示唆している．また川崎病患児

サイドメモ1　γ-グロブリン大量静注療法

川崎病にγ-グロブリン400 mg/kg/dayを5日間投与する治療法が冠動脈病変(CAL)の発生を有意に低下させることを，1984年に古庄らがはじめて報告した．1986年にNewburgerらによってγ-グロブリンの有効性が追認され，川崎病の標準治療として定着した．現在はNewburgerらの2 g/kg単回投与法が日本でも保険適応となっている．

表 1　川崎病とHLAの相関研究

相関ありの報告				
ローカス	ハプロタイプ	サンプル数(川崎病/対照)	人種	文献
HLA-B	Bw-22J	32/76	日本人	Matsuda(1977)
HLA-B	Bw-22J2	205/500	日本人	Kato(1978)
HLA-B	Bw-15			
HLA-B	Bw-51	23/244	白人(アメリカ)	Krensky(1981)
HLA-B	Bw-51	12/90	ユダヤ人	Keren(1982)
HLA-B	Bw-44(流行期)*	23/246	白人(アメリカ)	Krensky(1983)
HLA-B	Bw-44(流行期)	16/608	白人(アメリカ)	Kaslow(1985)
HLA-DR	DRB3*0301§	21/200	白人(アメリカ)	Barron(1992)
HLA-B	B35			
HLA-B	B75	74/159	韓国人	Oh(2008)
HLA-C	Cw09			
ローカス	SNP	サンプル数(川崎病/対照)	人種	文献
HLA-G	rs12722477	92/90	韓国人	Kim(2008)
HLA-E	rs2844724	93/680	台湾人	Lin(2009)
相関なしの報告				
ローカス	検討したハプロタイプの種類	サンプル数(川崎病/対照)	人種	文献
HLA-A	10			
HLA-B	15	62/100	中国人	Chang(1992)
HLA-DR	11			
HLA-DRB1	41			
HLA-DQA1	7	25/209	白人(アメリカ)	Fildes(1992)
HLA-DQB1	13			
HLA-DPB1	17			
HLA-DRB1	35	145/331	台湾人	Huang(2007)

*：多重検定の補正後有意性消失，§：アメリカ内の別地域における再現性みられず．

の同胞が川崎病に罹患する割合は一般に比べ約10倍高頻度であること[5]，川崎病罹患児の親に川崎病の既往者が期待値よりも多く認められること[6]は，川崎病への罹患しやすさ(感受性)の個人差を規定する遺伝的要因の存在を示唆している．

HLAと川崎病

川崎病の遺伝学的研究は1970年代後半のHLAの関与についての検討にはじまり，国内外の研究者によるHLAに関する患者・対照研究の報告が散見されている(表1)．しかし一部の自己免疫性疾患で示されるような特定の型の強い関与は現在のところ見出されていない．一方，1986年に原田らは，HLA-A-B-C-DR領域のハプロタイプが川崎病に罹患した同胞間において一致する率は期待値と違わず，HLAの関与の可能性は低いと報告した．最近，韓国および台湾のグループからそれぞれHLA-G遺伝子およびHLA-E遺伝子内のSNPと川崎病との有意な相関があいついで報告され，再現性の確認が待たれる．

HLA以外の候補遺伝子と川崎病

川崎病の急性期に血中のTNF-α濃度が高値であること，抗ヒトTNF-αモノクローナル抗体製剤の有効性についての報告が増えてきていることから，TNF-αが川崎病の病態に深く関与していることは疑う余地はない．その発現に影響を与えると考えられるプロモーター領域のSNP(-238 G/A，-308 G/A)は川崎病の発症や冠動脈瘤の形成，γ-グロブリン抵抗性のリスクにかかわる有力な候補とみなされ，これまでにもっとも多く研究が行われている．そのほかにサイトカイン・ケモカイン，血管作動性分子，血管リモデリング関連分子，自然免疫関連分子，FCレセプターなどの候補遺伝子のSNPと川崎病あるいは合併症などとの関連が調べられている(表2)．個々の研究は用いた症例・対照の規模が小さく，検討したSNPも機能的意義や他疾患との相関が過去に報じられてい

表 2　過去に川崎病との関連が調べられた候補遺伝子

遺伝子	遺伝子名	染色体領域	表現型	文献
MTHFR	5,10-methylenetetrahydrofolate reductase	1p36.3	CAL	Tsukahara (2000)[a]
CRP	C-reactive protein	1q21-q23	川崎病	Cheung (2008)
			CAL	Cheung (2008)[d]
			内膜中膜肥厚度（総頸動脈）	Cheung (2008)
IL-10	interleukin-10	1q31-q32	川崎病	Jin (2007)[d]
			CAL	Jin (2007)
			血清アルブミン値	Jin (2007)
FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32)	1q23	川崎病	Taniuchi (2005)[d], Biezeveld (2007)[d]
			CAL	Taniuchi (2005), Biezeveld (2007)[d]
FCGR2B	Fc fragment of IgG, low affinity IIb, receptor (CD32)	1q23	川崎病	Biezeveld (2007)[d]
			CAL	Biezeveld (2007)[d]
FCGR3A	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)	1q23	川崎病	Taniuchi (2005), Biezeveld (2007)[d]
			CAL	Taniuchi (2005)[d], Biezeveld (2007)[d]
FCGR3B	Fc fragment of IgG, low affinity IIIb, receptor (CD16b)	1q23	川崎病	Taniuchi (2005)[d], Biezeveld (2007)[d]
			CAL	Taniuchi (2005)[d], Biezeveld (2007)[d]
IL-1β	interleukin-1, beta	2q14	川崎病	Wu (2005)[d]
IL-1Rα	interleukin-1 receptor antagonist	2q14.2	川崎病	Wu (2005)
CXCR2	chemokine (C-X-C motif) receptor 2	2q35	川崎病	Breunis (2007)[d]
CXCR1	chemokine (C-X-C motif) receptor 1	2q35	川崎病	Breunis (2007)[d]
SLC11A1	solute carrier family 11	2q35	川崎病	Ouchi (2003)
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	2q37	川崎病	Kanai (2003)[d]
CX3CR1	chemokine (C-X3-C motif) receptor 1	3p21.3	川崎病	Breunis (2007)[d]
CCR3	chemokine (C-C) receptor 3	3p21	川崎病	Breunis (2007)
CCR2	chemokine (C-C) receptor 2	3p21	川崎病	Breunis (2007)
CCR5	chemokine (C-C) receptor 5	3p21	川崎病	Burns (2005), Jhang (2008), Breunis (2007)
			CAL	Jhang (2008)[d]
AGTR1	angiotensin II receptor, type 1	3q21-q25	川崎病	Fukazawa (2004)[d]
			冠動脈狭窄	Fukazawa (2004)
VEGFR2	vascular endothelial growth factor receptor 2	4q12	川崎病	Kariyazono (2004)[d]
			CAL	Kariyazono (2004)
IL-4	interleukin-4	5q31.1	川崎病	Burns (2005), Wu (2005)[d], Huang (2008)[d]
CD14	CD14 antigen	5q31.1	川崎病	Nishimura (2003)[d]
			CAL	Nishimura (2003)
VEGFA	vascular endothelial growth factor A	6p12	川崎病	Breunis (2006), Hsueh (2008), Huang (2008)[d]
			CAL	Kariyazono (2004), Huang (2008)[d]
MICA	MHC class I polypeptide-related sequence A	6p21.3	CAL	Huang (2000)
LTA	lymphotoxin α	6p21.3	川崎病	Quasney (2001)
TNF-α	tumor necrosis factor-α	6p21.3	川崎病	Kamizono (1999)[d], Ahn (2003)[d], Chien (2003)[d], Cheung (2008)
			CAL	Quasney (2001), Cheung (2008)[d]
			動脈壁硬化（頸動脈）	Cheung (2008)
PAFAH	platelet-activating factor acetylhydrolase	6p21.2-p12	川崎病	Minami (2005)[d]
			CAL	Minami (2005)[d]
			IVIG 不応	Minami (2005)
IL-6	interleukin-6	7p21	川崎病	Sohn (2001)[d]
eNOS	endothelial nitric oxidase synthase	7q36	川崎病	Khajoee (2003)[d]
			CAL	Khajoee (2003)[d]

表 2　過去に川崎病との関連が調べられた候補遺伝子(つづき)

遺伝子	遺伝子名	染色体領域	表現型	文献
MBL	mannose-binding lectin	10q11.2-q21	川崎病	Biezeveld(2003), Cheung(2004)[d]
			CAL	Biezeveld(2003)[c], Biezeveld(2006)[c], Cheung(2004)[d]
			動脈壁硬化(腕頭動脈)	Cheung(2004)
IL-18	interleukin-18	11q22.2-q22.3	川崎病	Hsueh(2008), Chen(2009)
			CAL	Hsueh(2008)[d]
MMP3	matrix metallopeptidase 3	11q22.3	川崎病	Park(2005)[d], Ikeda(2008)[d], Hong(2008)[d]
			CAL	Park(2005), Ikeda(2008)[d], Hong(2008)[d]
MMP12	matrix metallopeptidase 12	11q22.3	川崎病	Hong(2008)[d]
			CAL	Hong(2008)[d]
MMP13	matrix metallopeptidase 13	11q22.3	川崎病	Hong(2008)[d]
			CAL	Hong(2008)
MMP2	matrix metallopeptidase 2	16q13-q21	川崎病	Hong(2008)[d]
			CAL	Hong(2008)[d]
iNOS	nitric oxide synthase 2, inducible	17q11.2-q12	川崎病	Khajoee(2003)[d]
			CAL	Khajoee(2003)[d]
MCP1	monocyte chemoattractant protein-1	17q11.2-q12	川崎病	Jibiki(2001)[d]
CCL3L1	chemokine(C-C motif)ligand 3-like 1	17q11.2	川崎病	Burns(2005)
ACE	angiotensin I converting enzyme	17q23	川崎病	Wu(2004), Shim(2006), Fukazawa(2004)[d]
			CAL	Takeuchi(1997), Wu(2004)[d], Shim(2006)[d]
			冠動脈狭窄	Fukazawa(2004)
TIMP2	tissue inhibitor of metalloproteinase 2	17q25	川崎病	Furuno(2007)[d]
			CAL	Furuno(2007)
MMP9	matrix metallopeptidase 9	20q11.2-q13	川崎病	Park(2005)[d], Hong(2008)[d]
			CAL	Park(2005)[d]
HMOX1	heme oxygenase(decycling)1	22q12	川崎病	Kanai(2003)[d]
CD40L	CD40 リガンド	Xq26	川崎病	Onouchi(2004)[d], Huang(2008)[d]
			CAL	Onouchi(2004)[b], Huang(2008)[d]

[a]：川崎病女児における相関，[b]：川崎病男児における相関，[c]：1 歳未満の川崎病患児において相関，[d]：相関なしの報告．

サイドメモ 2

罹患同胞対法(affected sib pair method：ASP)

同胞が共有する同じ型の対立遺伝子が同一の祖先に由来するものである場合，同祖的である(identical by descent)という．2 人の同胞がある対立遺伝子を 2 つ同祖的に共有する確率は 0.25，1 つ共有する確率は 0.5，1 つも共有しない確率は 0.25 である．疾患に関連した対立遺伝子は，その疾患にともに罹患した同胞によって共有される確率が高くなる．同祖的共有対立遺伝子の数は同胞と両親あるいは同胞のみで推定することが可能なので，大きな家系を対象としにくい疾患の解析に向いている．

るものが中心であるなどの理由から，相関あり・なしについて明確な結論が出ている遺伝子はほとんどないというのが現状である．

ゲノムワイドアプローチによる川崎病感受性遺伝子ITPKCの同定

候補遺伝子アプローチとは異なり，仮説を設定せず位置的情報を指標に全ゲノムから感受性遺伝子を探索する方法をゲノムワイドアプローチとよぶ．川崎病の病因・病態については解明が進んでいるとはいえ，謎の部分が多い．そのため候補遺伝子の設定のための情報に限りがあるといわざるをえず，著者らはゲノムワイドアプローチが有効

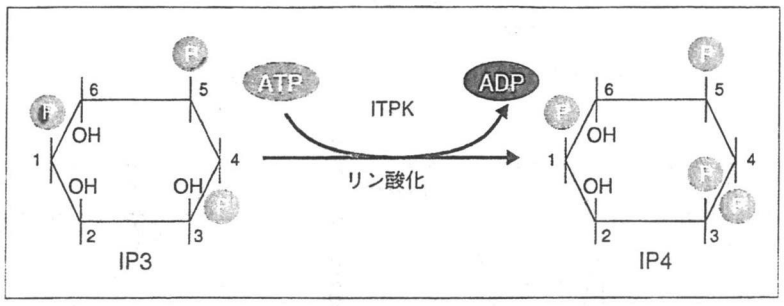

図 1　ITPK蛋白はIP3をIP4へとリン酸化する

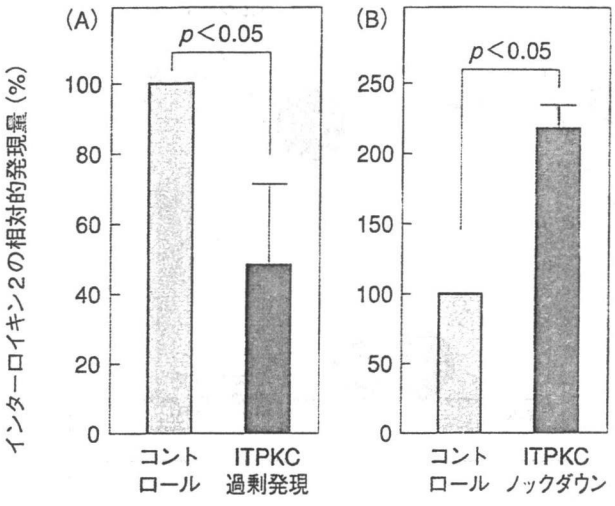

図 2　ITPKCの機能解析
ITPKC を細胞内に過剰発現させるとインターロイキン 2 の転写が抑制(A)され，逆にノックダウンさせると亢進(B)する．

と判断，罹患同胞対解析(「サイドメモ 2」参照)による全ゲノムスキャンを試みた．日本全国から収集した約 80 組の川崎病同胞罹患例およびその家族 DNA について，約 400 カ所のマイクロサテライトマーカーの遺伝子型を決定し，同胞間での同祖的共有アレル数をコンピュータソフト(MAPMAKER/SIBS)で予測，連鎖の傾向を調べた[7]．続いて連鎖の傾向を示した染色体領域について SNP を用いた連鎖不平衡マッピングを体系的に行い，19 番染色体長腕(19q13.2)に存在する inositol 1,4,5-trisphosphate 3-kinase C(ITPKC)が人種を越えた川崎病感受性遺伝子であることを見出した[8]．ITPKC はイノシトール三リン酸(IP3)をイノシトール四リン酸(IP4)へと変換するリン酸化酵素である(図 1)．IP3 は T 細胞受容体からのシグナル伝達(カルシニューリン-NFAT 経路)にかかわるセカンドメッセンジャー分子として重要であるが，ITPKC は IP3 のリン酸化を通じ，T 細胞の活性化を負に制御していることがあらたに明らかとなった(図 2, 3)．ITPKC のイントロン 1 に存在し日米の川崎病患者に共通して相関を示す SNP (rs28493229)が感受性アレル(C)の場合，正常なスプライシングの効率が低下し，有効な転写産物が減少することが ITPKC の活性低下，ひいては T 細胞の過剰な活性化を引き起こしていると考えられる．カルシニューリンを標的とした免疫抑制剤シクロスポリン A が川崎病，とくにγ-グロブリン不応群に対し有効であったとする症例報告の存在は，著者らの考えを支持すると考えている．また，rs28493229 は川崎病患者のなかでも CAL の合併例やγ-グロブリン不応例でより強く相関する傾向があり(表 3)，川崎病の重症化を予測する指標になる可能性を秘めていと考え，確認を急いでいる．

川崎病のゲノムワイド関連解析

オランダ，オーストラリア，イギリス，アメリカを中心として発足した国際川崎病コンソーシアムが実施したゲノムワイド関連解析の結果が 2009 年に発表され，*N*-acetylated alpha-linked acidic dipeptidase-like 2 遺伝子，zinc finger homeobox 3 遺伝子などが新規の川崎病感受性遺伝子の候補として示された[9]．しかし 262,264SNP の一次スクリーニングに用いられた患者・対照の数が 107 名および 134 名と極端に少なく，約 500 組の白人川崎病親子検体による伝達不平衡試験(「サイドメモ 3」参照)にて追加解析した結果を合わせても，上記 2 遺伝子を含めゲノムワイド関連解析の有意水準をクリアしているものはない．相当な偽陰性もあるものと考えられ，今後さらなる検体の

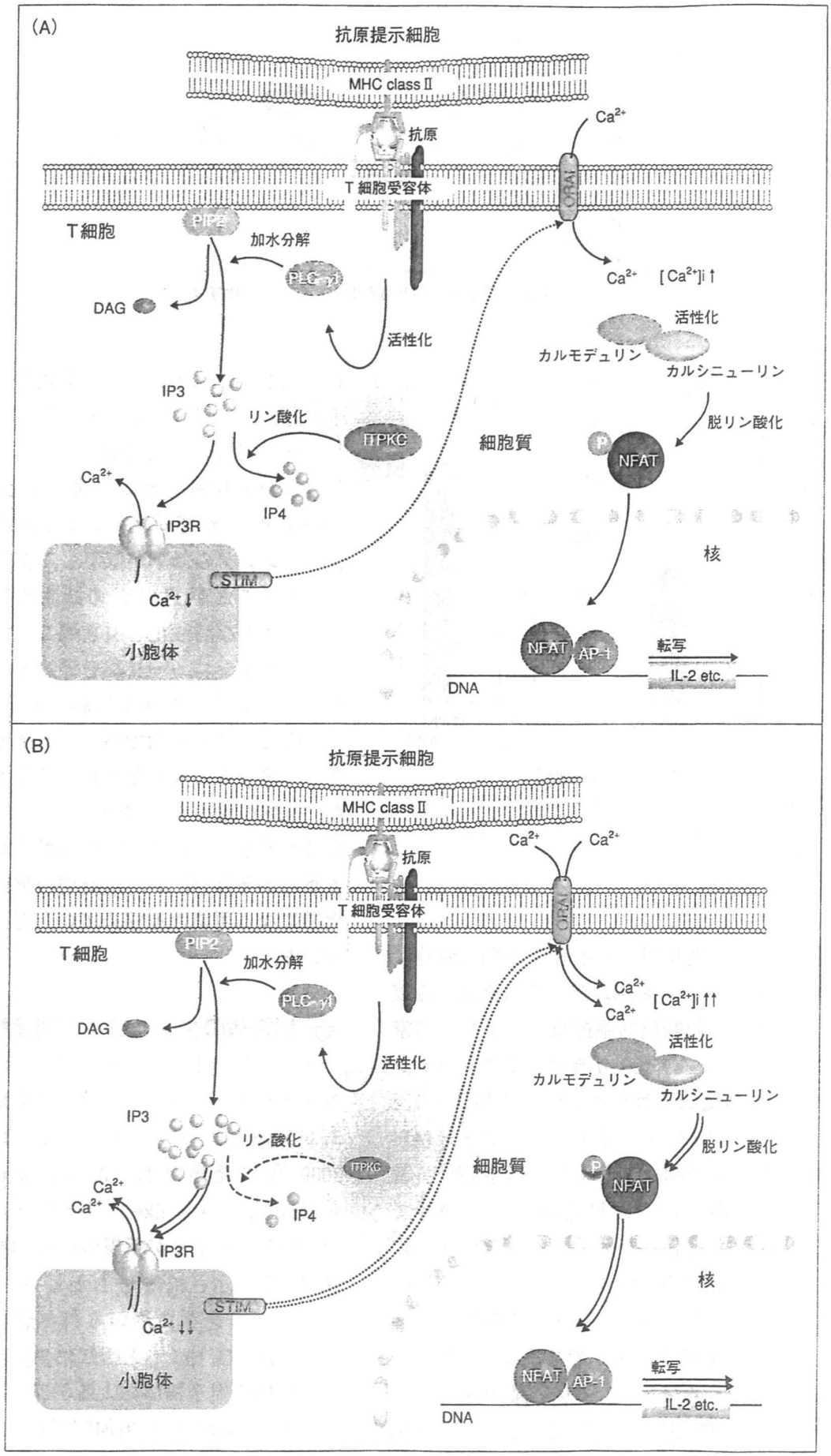

図 3　ITPKCの機能

A：T 細胞受容体からのシグナル伝達経路.

B：SNP の影響で ITPKC の活性が低下すると，IP3 を介したシグナル伝達が亢進すると考えられる.

表 3　ITPKC 遺伝子の相関解析の結果

日本人									
	rs28493229 遺伝子型			合計	C アレルをもつヒトの割合	オッズ比[a]	95%CI	χ^2値	p 値
	GG	GC	CC						
川崎病(全体)	376	234	27	637	41%	1.89	1.53～2.33	35.8	2.2×10^{-9}
CAL(+)[b]	61	44	2	107	43%	2.05	1.37～3.08	12.4	0.00044
CAL(−)[b]	172	94	12	278	38%	1.68	1.27～2.21	13.4	0.00025
対照	756	249	29	1,034	27%				

アメリカ人[c]						
	伝達した C アレル	伝達しなかった C アレル	オッズ比	95%CI	χ^2値	p 値
川崎病(全体)	64	30	2.13	1.38～3.29	12.3	0.00045
CAL(+)	37	11	3.36	1.72～6.59	14.1	0.00018
CAL(−)	27	18	1.50	0.63～2.72	1.8	0.18
γ-グロブリン不応	14	3	4.67	1.34～16.24	7.1	0.0076
γ-グロブリン有効	39	22	1.77	1.05～2.99	4.7	0.030

[a]優性遺伝モデル(GG 対 GC+CC), [b]CAL の有無について情報があるもののみで解析, [c]209 組の親子検体による伝達不平衡試験(「サイドメモ 3」)の結果.

収集を行ったうえでの再検討が待たれる.

川崎病ゲノム研究の今後

遺伝的背景の追究が川崎病の謎を解き明かすヒントをもたらすという期待は，他の疾患よりも大きいといえる．現在著者らは，あらたに日本人における川崎病のゲノムワイド関連解析を実施中であり，複数の新規川崎病感受性遺伝子を同定しつつある．これらの遺伝子がどのように分子ネットワークを形成し川崎病の病因や病態と関連するのか，新しい視点から考えるきっかけをもたらすのではないかと考えている．今後，国内外双方で研究が進めば人種間に共通の，あるいは人種に特異的な遺伝的背景が明らかになってくると思われる．川崎病がなぜアジア人に多いのかという疑問にも答えが出る日が近いかもしれない．

サイドメモ 3　伝達不平衡試験(transmission disequilibrium test：TDT)

親から子に対し 2 つある対立遺伝子のうちのいずれが伝達されるかは，ランダムな選択による．疾患のリスクを高める対立遺伝子はそうでない対立遺伝子に比べ，親からその疾患の患者である子に伝達されている頻度が高くなる．ある対立遺伝子が親から子に対して“伝わった”か“伝わらなかった”かの比をとると 1：1 となる帰無仮説からの偏りを検定する解析法である．通常の患者・対照研究で用いられる相関解析と異なり，集団の階層化の影響を回避できるので，多民族からなる集団での研究に向いている．

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6

ゲノム解析からみた罹患遺伝子、冠動脈関連遺伝子を考察する

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ゲノム解析からみた罹患遺伝子，冠動脈病変関連遺伝子を考察する

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川崎病にはその背景に遺伝的要因が存在することが指摘されており，感受性遺伝子同定の試みが成果を上げつつある．筆者らはゲノムワイドアプローチにより *ITPKC* 遺伝子上の一塩基多型（SNP）が人種を超えて川崎病の罹患感受性や冠動脈病変リスク等と関連することを見出した．SNP のリスクアレルによる ITPKC の発現低下が ITPKC の T 細胞活性化抑制因子としての作用を減弱させることが川崎病の罹患や重症化の背景となっていると考えられる．今後さらに遺伝的要因の研究が進めば川崎病の病因や人種差の謎が解明され，遺伝子型にもとづくオーダーメイド医療にも道が開けると期待される．

KEY WORDS
一塩基多型　感受性遺伝子　ゲノムワイド

はじめに

川崎病はその疫学的な特徴および臨床像から，感染を契機として遺伝的感受性を有する乳幼児に発症する多因子疾患ととらえられている．原因となるであろう病原体には諸説あるが，その特定はいまだなされていない．一方で遺伝的背景として，病原体の感染に関連する遺伝子，炎症反応に関連する遺伝子，血管のリモデリングに関連する遺伝子等の多型が川崎病の発症や，冠動脈病変の発症のしやすさにかかわっていることが予想される．多因子疾患の遺伝要因の解明が急ピッチで進んでいる現在，川崎病の遺伝学的研究についての今日までの知見および今後の展望について述べる．

川崎病はなぜ日本人に多いのか

最近のわが国の川崎病罹患率は 0〜4 歳人口 10 万人あたり約 200 人と世界で最も高く，欧米諸国にくらべると 10〜20 倍の高頻度である[1]．わが国に次いで高い罹患率が同じく東アジアの韓国および台湾で報告されている[2][3]．川崎病は感染を含む外的要因がトリガーとなって引き起こされる疾患であるとすれば，これらの地域に共通の生活習慣や気候，病原体が関連した風土病と考えることもできる．しかしながらハワイ在住の日系人の罹患率がや