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Responsible Genetic Factors for Vasculitis in Kawasaki Disease

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1. Introduction

Kawasaki disease (KD) is an acute febrile illness of early childhood that is characterized by high fever, bilateral conjunctivitis, redness of the oral mucosa, polymorphous skin rash, indurative edema of the hands and feet, and cervical lymphadenopathy (Kawasaki, 1967). The major pathological lesion of KD is vasculitis of small and medium-sized arteries (Amano et al., 1979). The coronary arteries are the most severely affected and coronary artery lesions (CALs) occur in 15–25% of untreated patients (Kato et al., 1975), making KD a leading cause of childhood acquired heart disease in developed countries. The fact that the peak incidence of KD is at 9–11 months of age, which coincides with the waning of maternal immunity, indicates that infections could contribute to the pathogenesis of KD. However, despite more than 40 years of intensive research, the causative microorganism of KD remains unknown. On the other hand, epidemiological studies have revealed a significant role of genetic components in host susceptibility to KD pathogenesis.

2. Epidemiological features of KD suggesting a genetic predisposition

Since the first description of KD (Kawasaki, 1967) more than four decades ago, biannual epidemiological surveys conducted in Japan and epidemiological studies performed in almost all ethnic groups during this period have highlighted the contribution of genetic factors in the pathogenesis of KD.

2.1 Ethnic differences in the incidence of KD

KD is much more prevalent in East Asia than in any other countries of the world. In Japan, its incidence was 218.6 per 100,000 children younger than 4 years old in 2008 and continues to rise (Nakamura et al., 2010). Its incidence in Korea and Taiwan, the neighboring countries to Japan, are the second (113.1) and third (69.0) highest, respectively (Huang et al., 2009; Park et al., 2011). The incidence of KD in Western countries is 10–20 times lower than in Japan. Recent surveillance of KD in Hawaii revealed that Asian children, especially those of Japanese ancestry, had the highest incidence (210.5), and that the incidence among Caucasian children in Hawaii (13.7) was similar to that of the continental United States (Holman et al., 2010). These facts indicate

that the high incidence of KD in East Asian countries is due to the racial/ethnic genetic background rather than to geographic factors.

2.2 Individual susceptibility to KD

In Japan, a total of 20 nationwide biannual continued surveillances of KD have been carried out since 1970. Epidemiological evidence collected from these surveys suggested individual susceptibility to KD, which was mainly composed of multiple genetic factors. For example, sibling cases of KD have a ≥10 times higher incidence than expected (Fujita et al., 1989). In addition, parents of KD patients, who were affected by KD during their childhood, were observed 2 times more often than expected (Uehara et al., 2003).

3. Genetic studies of KD

KD is considered to be a multifactorial disease that is caused by the interplay of external and personal factors (Fig. 1). Thus, identification of the responsible genetic factors, which presumably determine an individual's susceptibility to KD, should provide clues to the pathogenesis of the disease. Furthermore, it could contribute to the development of novel clinical applications, such as a severity prediction method and new therapeutic measures.

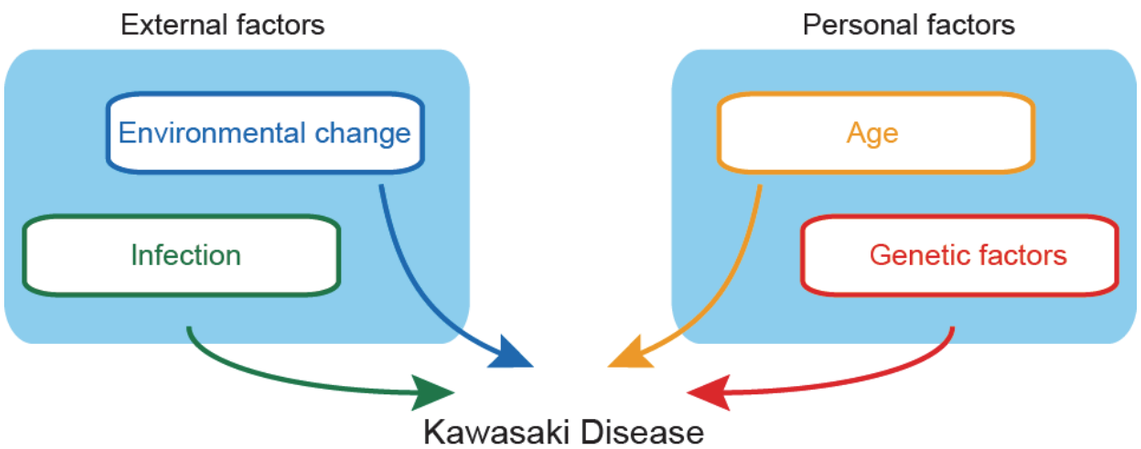

Fig. 1. Multiple factors that are linked to KD.

3.1 Candidate gene studies

KD is an immune-mediated vasculitis syndrome; therefore, genes encoding proteins related to innate and acquired immune function or to vascular remodeling could be involved in its pathogenesis, response to treatment, and prognosis. Variations within such "candidate genes" have been extensively studied.

3.1.1 Human leukocyte antigen (HLA) genes

Genetic studies of KD were initially conducted by focusing on the HLA class I genes, and several serotypes of the HLA-B locus have been associated with KD in different ethnic groups (Table 1).

Recently, significant associations of single nucleotide polymorphisms (SNPs) within the HLA-G and HLA-E genes were reported (J.J. Kim et al., 2008; Y.J. Lin et al., 2009). However, most of the previous studies, including those describing negative association results, were conducted by analyzing a relatively small number of cases and controls, while replication studies with larger cohorts have not been performed yet.

Locus	Haplotype /SNP	Method	Ethnicity (cases/controls)	Reference
HLA-B	Bw22J	Serotyping	Japanese (32/76)	Matsuda et al., 1977
HLA-B	Bw22J2	Serotyping	Japanese (205/500)	Kato et al., 1978
HLA-B	Bw15			
HLA-B	Bw51	Serotyping	Caucasian (23/244)	Krensky et al., 1981
HLA-B	Bw51	Serotyping	Jewish (12/90)	Keren et al., 1982
HLA-B	Bw44	Serotyping	Caucasian (23/246)	Krensky et al., 1983
HLA-B	Bw44	Serotyping	Caucasian (16/608)	Kaslow et al., 1985
HLA-B	B35	Genotyping	Korean (74/159)	Oh et al., 2008
HLA-B	B75			
HLA-C	Cw09			
HLA-DRB3	DRB3*0301	Genotyping	Caucasian (21/200)	Barron et al., 1992
HLA-G	rs12722477 C/A A allele	Genotyping	Korean (92/90)	J.J. Kim et al., 2008
HLA-E	rs2844724 C/T C allele	Genotyping	Taiwanese (680/3312)	Y.J. Lin et al., 2009

Table 1. Association studies between HLA genes and KD.

3.1.2 Non-HLA genes

Advances from the Human Genome and Hapmap projects have dramatically reduced the effort and cost of conducting genetic association studies of complex diseases, leading to a recent increase in the number of candidate gene studies, especially since 2005 (Table 2). Among the genes studied, tumor necrosis factor (TNF), which is a proinflammatory cytokine deeply related to the pathogenesis of KD, has been most frequently analyzed. Although many of these studies have failed to identify a statistically significant association, a systematic meta-analysis revealed a trend of association between the G allele of rs180629, which is located 308 bases upstream of the TNF gene, and KD (Ari-Ong et al., 2010).

Gene	Chromosomal region	Reference	
		Associated	Not associated
Cytokines, chemokines, and their receptors			
IL-10	1q31-q32	Hsueh et al., 2009	Jin et al., 2007 Weng et al., 2010a
TGFB2	1q41	Shimizu et al., 2011	
IL-1α	2q14		Weng et al., 2010b S.K. Kim et al., 2011
IL-1β	2q14		S.F. Wu et al., 2005 Weng et al., 2010b S.K. Kim et al., 2011
IL-1Ra	2q14.2	S.F. Wu et al., 2005	Weng et al., 2010b S.K. Kim et al., 2011
CXCR2	2q35		Breunis et al., 2007
CXCR1	2q35		Breunis et al., 2007
TGFBR2	3p22	Shimizu et al., 2011	
CX3CR1	3p21.3		Breunis et al., 2007
CCR3	3p21	Breunis et al., 2007	
CCR2	3p21	Breunis et al., 2007	
CCR5	3p21	Burns et al., 2005 Jhang et al., 2009 Breunis et al., 2007	Mamtani et al., 2010 Chaudhuri et al., 2011
IL-8	4q13-q21		Weng et al., 2010b
IL-4	5q31.1	Burns et al., 2005	S.F. Wu et al., 2005 F.Y. Huang et al., 2008a Weng et al., 2010b
LTA	6p21.3	Quasney et al., 2001	
TNF-α	6p21.3	Cheung et al., 2008	Kamizono et al., 1999 Quasney et al., 2001 Ahn et al., 2003 Chien et al., 2003 Weng et al., 2010b
IL-6	7p21		Sohn et al., 2001 Weng et al., 2010b
IL-18	11q22.2-q22.3	Hsueh et al., 2008a Chen et al., 2009	
TNFRSF1A	12p13.2	Wang et al., 2011	
MCP1	17q11.2-q12		Jibiki et al., 2001
CCL5	17q11.2-q12		Chaundhuri et al., 2011
CCL3L1	17q11.2	Burns et al., 2005 Mamtani et al., 2010	
TGFB1	19q13.1		Weng et al., 2010b
MIF	22q11.2		Simonini et al., 2009
Vasoactive molecules or molecules related to vascular remodeling			
AGTR1	3q21-q25		Fukazawa et al., 2004
TIMP4	3p25		Ban et al., 2009
VEGFR2	4q12		Kariyazono et al., 2004
VEGFA	6p12	Breunis et al., 2006 Hsueh et al., 2008b	Kariyazono et al., 2004 F.Y. Huang et al., 2008b
eNOS	7q36		Khajoee et al., 2003

MMP26	11p15		Ban et al., 2010
MMP7	11q21-22		Ban et al., 2010
MMP3	11q22.3		J.A. Park et al., 2005 Ikeda et al., 2008 Hong et al., 2008
MMP12	11q22.3		Ikeda et al., 2008 Ban et al., 2010
MMP13	11q22.3		Ikeda et al., 2008
MMP2	16q13-q21		Ikeda et al., 2008
iNOS	17q11.2-q12		Khajoee et al., 2003
ACE	17q23	S.F. Wu et al., 2004 Shim et al., 2006	Fukazawa et al., 2004
TIMP2	17q25		Furuno et al., 2007
MMP9	20q11.2-q13		J.A. Park et al., 2005 Ikeda et al., 2008
MMP11	22q11.2	Ban et al., 2010	
Molecules related to innate immune functions			
CRP	1q21-q23	Cheung et al., 2008	
SLC11A1	2q35	Ouchi et al., 2003	
CD14	5q31.1		Nishimura et al., 2003
MBL	10q11.2-q21	Biezeveld et al., 2003	Cheung et al., 2004
Molecules related to acquired immune functions			
FCGR2A	1q23		Taniuchi et al., 2005 Biezeveld et al., 2007
FCGR2B	1q23		Biezeveld et al., 2007
FCGR3A	1q23	Taniuchi et al., 2005	Biezeveld et al., 2007
FCGR3B	1q23		Taniuchi et al., 2005 Biezeveld et al., 2007
CTLA4	2q33		Kuo et al., 2010
PD-1	2q37.3	Chun et al., 2010	
MICA	6p21.3	F.Y. Huang et al., 2000	
BTNL2	6p21.3	Hsueh et al., 2010	
CD40L	Xq26		Y. Onouchi et al., 2004 F.Y. Huang et al., 2008c
Others			
MTHFR	1p36.3	Tsukahara et al., 2000	
UGT1A1	2q37		Kanai et al., 2003
BAT2, 3, 5	6p21.3	Hsieh et al., 2010	
NOTCH4	6p21.3		Kang et al., 2011
COL11A2	6p21.3	Shue et al., 2010	
ITPR3			Y.C. Huang et al., 2010
PAFAH	6p21.2-p12		Minami et al., 2005
TPH2	12q21.1		S.W. Park et al., 2010
SMAD3	15q22.33	Shimizu et al., 2011	
MEFV	16p13		Yamaguchi et al., 2009
HMOX1	22q12		Kanai et al., 2003

Table 2. Association studies between polymorphisms of candidate genes and KD.

The association of these candidate SNPs and patient response to intravenous immunoglobulin (IVIG) therapy and the development of CALs has also been studied (Table 3).

Gene	Phenotype	Reference	
		Association	No association
MTHFR	CAL	Tsukahara et al., 2000	
CRP	CAL		Cheung et al., 2008
	Intima-media thickness	Cheung et al., 2008	
	Arterial stiffness	Cheung et al., 2008	
IL-10	CAL	Jin et al., 2007	Hseuh et al., 2009
	Serum albumin	Jin et al., 2007	
FCGR2A	CAL	Taniuchi et al., 2005	Biezeveld et al., 2007
FCGR2B	CAL		Biezeveld et al., 2007
FCGR3A	CAL		Taniuchi et al., 2005 Biezeveld et al., 2007
FCGR3B	CAL		Taniuchi et al., 2005 Biezeveld et al., 2007
TGFB2	CAL/ coronary z score	Shimizu et al., 2011	
	Diameter of aortic root	Shimizu et al., 2011	
	Response to IVIG	Shimizu et al., 2011	
IL-1α	CAL		S.K. Kim et al., 2011
IL-1β	Response to IVIG	Weng et al., 2010	S.K. Kim et al., 2011
IL-1Ra	CAL		S.K. Kim et al., 2011
CTLA4	CAL	Kuo et al., 2010	
PD-1	CAL		Chun et al., 2010
TIMP4	CAL	Ban et al., 2009	
TGFBR2	CAL/ coronary z score	Shimizu et al., 2011	
	Diameter of aortic root	Shimizu et al., 2011	
	Response to IVIG	Shimizu et al., 2011	
CCR5	CAL	Mamtani et al., 2010 Chaudhuri et al., 2011	Jhang et al., 2009
AGTR1	Coronary stenosis	Fukazawa et al., 2004	
VEGFR2	CAL	Kariyazono et al., 2003	
IL-4	CAL		Burns et al., 2005 F.Y.Huang et al., 2008a
CD14	CAL	Nishimura et al., 2003	
VEGFA	CAL	Kariyazono et al., 2003	Hsueh et al., 2008b F.Y.Huang et al., 2008b
MICA	CAL	F.Y. Huang et al., 2000	
LTA	CAL		Quasney et al., 2001
TNF-α	CAL	Quasney et al., 2001	Cheung et al., 2008

	Arterial stiffness	Cheung et al., 2008	
BAT2, 3, 5	CAL	Hsieh et al., 2010	
NOTCH4	CAL		Kang et al., 2011
BTNL2	CAL	Hsueh et al., 2010	
COL11A2	CAL	Shue et al., 2010	
ITPR3	CAL	Y.C. Huang et al., 2010	
	CRP	Y.C. Huang et al., 2010	
PAFAH	CAL		Minami et al., 2005
PAFAH	Response to IVIG	Minami et al., 2005	
eNOS	CAL		Khajoee et al., 2003
MBL	CAL	Biezeveld et al., 2003 Biezeveld et al., 2006	Cheung et al., 2004
	Arterial stiffness	Cheung et al., 2004	
MMP26	CAL		Ban et al., 2010
IL-18	CAL		Hsueh et al., 2008a
MMP7	CAL		Ban et al., 2010
MMP3	CAL	J.A. Park et al., 2005	Ikeda et al., 2008 Hong et al., 2008
MMP12	CAL		Ikeda et al., 2008 Ban et al., 2010
MMP13	CAL	Ikeda et al., 2008	
TPH2	CAL	S.W. Park et al., 2010	
SMAD3	CAL/ coronary z score	Shimizu et al., 2010	
	Diameter of aortic root	Shimizu et al., 2010	
	Response to IVIG	Shimizu et al., 2010	
MEFV	CAL		Yamaguchi et al., 2009
MMP2	CAL		Ikeda et al., 2008
iNOS	CAL		Khajoee et al., 2003
CCL3L1	CAL		Mamtani et al., 2010
	Response to IVIG	Mamtani et al., 2010	
CCL%	CAL		Chaundhuri et al., 2011
ACE	CAL	Takeuchi et al., 1997	S.F. Wu et al., 2004 Shim et al., 2006
	Coronary stenosis	Fukazawa et al., 2004	
TIMP2	CAL	Furuno et al., 2007	
MMP9	CAL		J.A. Park et al., 2005 Ikeda et al., 2008
MIF	CAL	Simonini et al., 2009	
MMP11	CAL		Ban et al., 2010
CD40L	CAL	Y. Onouchi et al., 2004	Huang et al., 2008c

Table 3. Association studies between candidate gene polymorphisms and KD-related phenotypes.

3.2 Genome-wide studies

In contrast to candidate gene studies, which are based on an assumption of the underlying cause of the disease, a strategy to identify disease-causing mutations or variations from the whole genome relies solely on positional information and was originally developed to map and identify the genes for Mendelian disorders. This genome-wide strategy has been adapted for complex diseases and has become the most reliable tool to identify disease-related genes following the completion of the Human Genome Project.

3.2.1 Linkage study

The first genome-wide study for KD was conducted by our group (Y. Onouchi et al., 2007). In this study, 399 microsatellite marker alleles that were shared identical by descent between 78 affected KD sib-pairs were analyzed, and 10 chromosomal regions linked with the disease were identified (Fig. 2).

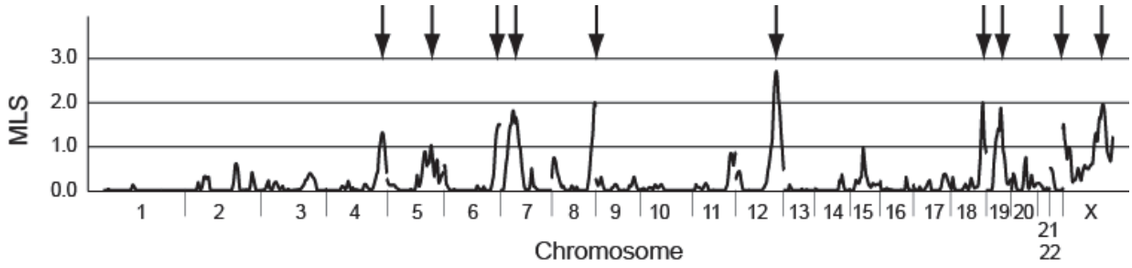

Fig. 2. Results from an affected sib-pair study (Y. Onouchi et al., 2007). Arrows indicate those chromosomal regions with a maximum LOD score (MLS) >1.0.

3.2.1.1 Linkage disequilibrium mapping

We narrowed down the candidate regions identified in the sib-pair study with a case–control association study using "tagging" SNPs. Chunks of genomic regions containing the associated tagging SNPs were extensively analyzed by re-sequencing and a further association study. We identified a SNP that was associated with KD in both the Japanese and US populations (Y. Onouchi et al., 2008) (Table 4). The SNP, rs28493229, is located in intron 1 of the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene, which catalyzes the phosphorylation of inositol 1,4,5-trisphosphate (IP3).

Alleles[1]	Japanese Case-control study			USA TDT		
	Risk allele frequency		OR (95% CI)[2]	No. of families	T:U[3]	OR (95% CI)
	KD n=637	Control n=1034	P value[2]			P value
G/C	0.23	0.15	1.89 (1.53 – 2.33) $2.2x10^{-9}$	209	64:30	2.13 (1.38 – 3.29) 0.00045

Table 4. Association of rs28493229 with KD. [1]Risk allele is underlined. [2]Dominant inheritance model. [3]Transmitted:untransmitted ratio. TDT: transmission disequilibrium test, OR: odds ratio, CI: confidence interval.

The at-risk allele of rs28493229 (C) reduces the splicing efficiency of ITPKC (Fig. 3). Transcripts with an unspliced intron are not properly translated because of premature termination. An increase in the number of such immature transcripts might lead to reduced ITPKC activity. IP3 is a second messenger molecule of the Ca^{2+}/NFAT pathway in a wide variety of cells and, in mammals, 3 iso-enzymes (ITPKA, ITPKB, and ITPKC) have been identified with the same enzyme activity.

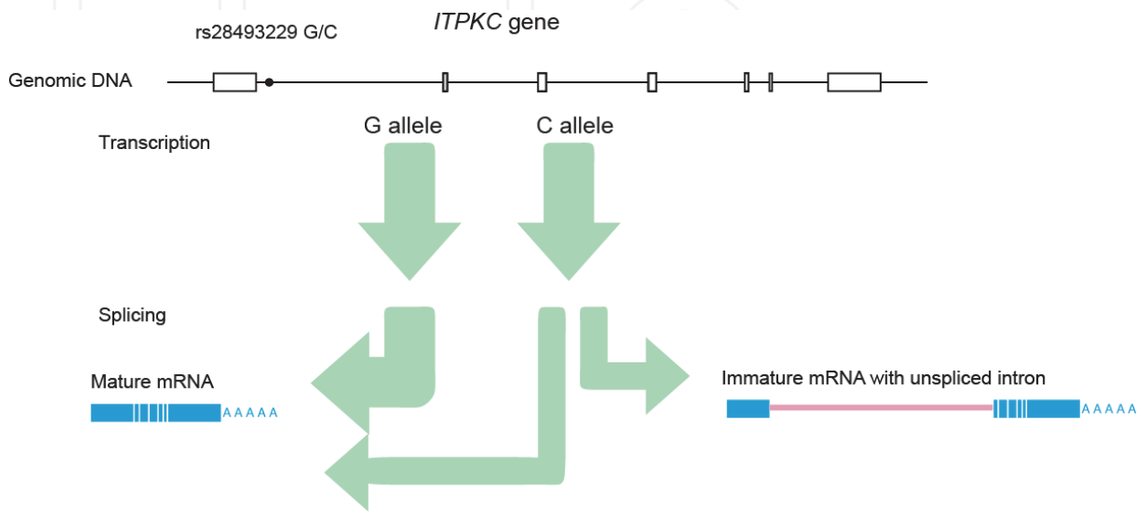

Fig. 3. Functional significance of rs28493229 on ITPKC mRNA.

Knockdown and overexpression experiments of ITPKC in the Jurkat cell line result in increased and decreased NFAT activity, respectively, as well as the expression of interleukin 2 mRNA. These findings highlighted the importance of the Ca^{2+}/NFAT pathway in the pathogenesis of KD. The association with the at-risk SNP allele was higher in KD patients with CAL than in those without CAL in both the Japanese and US populations. The same trend was also observed in KD patients in the US who responded poorly to intravenous immunoglobulin (IVIG) therapy. Two replication studies for the association of this SNP to KD, one negative and one positive, have been reported in the Taiwanese population (Chi et al., 2010; M.T. Lin et al., 2011). In the positive report, the SNP was also associated with the reactivation of previous BCG inoculation sites (M.T. Lin et al., 2011).

3.2.1.2 Positional candidate gene analysis

From the candidate region of chromosome 4, we identified the susceptibility gene via a different approach. The caspase-3 gene, which is located at 185.8 Mb, close to the linkage peak at 184.9 Mb, was focused on and studied as a positional candidate gene (Y. Onouchi et al. 2010). Multiple SNPs around the gene in linkage disequilibrium were associated with KD in the Japanese and US Caucasian populations. The functional SNP (rs72689236 G/A) was located in the 5′-untranslated region of the gene, and the risk allele (A) reduces the enhancer activity around the SNP to which NFATc2 is related (Table 5, Fig. 4).

Caspase-3 is an effector caspase with a central role in apoptosis. T cells from caspase-3-deficient mice have a reduced susceptibility to activation-induced cell death (Woo et al, 1998). It was also reported that caspase-3 cleaves Nfatc2 as a substrate (W. Wu et al, 2006). Transient anergy of peripheral T cells in the convalescent phase of KD, which has been

documented in a couple of reports, is suggestive because the NFAT-driven expression of caspase-3 in T cells is related to T cell anergy (Macián et al., 2002). Currently, only one replication study has examined the association between rs72689236 and KD (Kuo et al, 2011). Although not statistically significant, the same trend of association was observed in the Taiwanese population. Notably, in this report, the SNP was associated with increased risk for IVIG resistance and CAL formation.

Alleles[1]	Japanese case-control study			United States TDT		
	Risk allele frequency		OR (95% CI)[2] P value[2]	No. of families	T:U[3]	OR (95% CI) P value
	KD n=920	Control n=1,409				
G/A	0.45	0.37	1.40 (1.24–1.57) 4.2×10^{-9}	249	120:79	1.54 (1.16–2.05) 0.0037

Table 5. Association of rs72689236 with KD. [1]Risk allele is underlined. [2]Allelic model. [3]Transmitted:untransmitted ratio. TDT: transmission disequilibrium test, OR: odds ratio, CI: confidence interval.

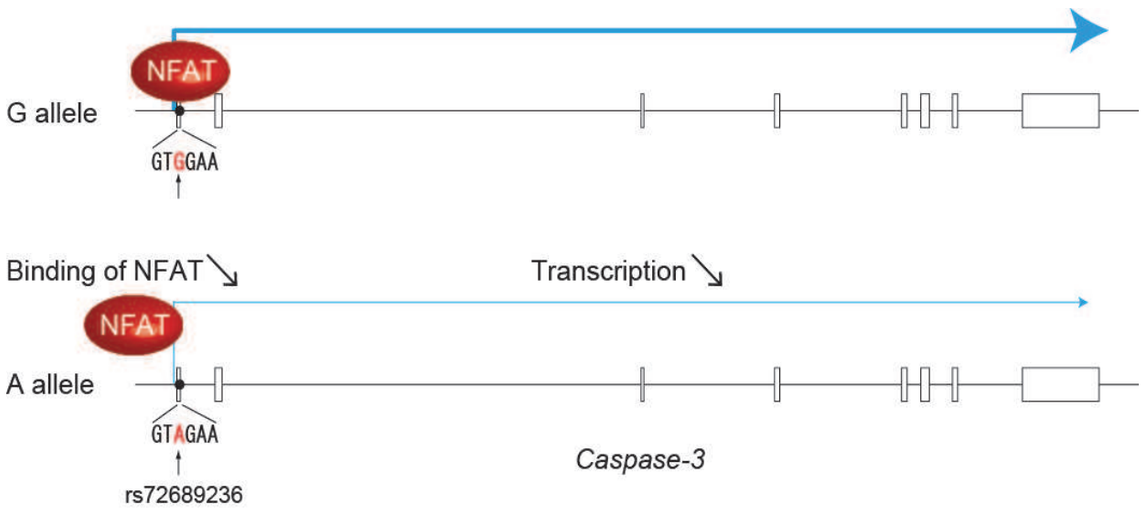

Fig. 4. Functional significance of rs72689236 on caspase-3 mRNA.

3.2.2 Genome-wide association studies (GWAS)

Today, GWAS using platforms by which 5.0×10^5 to 1×10^6 SNPs can be genotyped at a time have become commonplace for the analysis of complex disorders. GWAS for KD have been performed in 3 different ethnic groups: Caucasian, Korean, and Taiwanese (Burgner et al., 2009; J.J. Kim et al., 2011; Tsai et al., 2011). The number of subjects and SNPs analyzed in each study are summarized in Table 6.

Although many candidate SNPs were identified, no locus was repeatedly associated with KD in these studies (Table 7). Considering that none of these associations fulfilled the genome-wide level significance threshold, further validation of the association at each locus within the same populations is essential.

Ethnic group	Number of subjects KD/controls		No. of SNPs	Reference
	GWAS	Follow-up		
Caucasian	119/135	583/1357[1]	223,922	Burgner et al., 2009
Korean	186/600	266/600	641,760	J.J. Kim et al., 2011
Korean	63/600 [2]	86/600[2]	641,760	J.J. Kim et al., 2011
Taiwanese	250/446	208/366	723,638	Tsai et al., 2011

Table 6. Summary of GWAS for KD (I). [1]583 KD patients and their unaffected siblings and biological parents. [2]KD patients with coronary artery lesions and healthy controls.

SNP	Chr	Position	P value	Gene	Reference
rs527409	1	58,757,915	1.5×10^{-6}	*DAB1*	J.J. Kim et al., 2011
rs952354	1	63,549,282	3.1×10^{-5}	-*	J.J. Kim et al., 2011
rs7604693	2	64,349,202	2.0×10^{-6}	*PELI1**	J.J. Kim et al., 2011
rs10183521	2	123,762,542	9.5×10^{-5}	-	Burgner et al., 2009
rs16849083	3	139,184,279	2.2×10^{-5}	*MRPS22, COPB2, RBP2*	Tsai et al., 2011
rs9834548	3	165,139,947	9.8×10^{-6}	-	Burgner et al., 2009
rs17531088	3	174,893,775	1.1×10^{-6}	*NAALADL2*	Burgner et al., 2009
rs3773986	3	190,278,915	6.2×10^{-5}	*IL1RAP**	J.J. Kim et al., 2011
rs4864471	4	54,426,184	3.4×10^{-5}	*LNX1, LOC441016*	Burgner et al., 2009
rs13128867	4	138,840,995	2.2×10^{-5}	*SLC7A11*	Tsai et al., 2011
rs149481	5	96,114,346	4.6×10^{-5}	*ERAP1*	Tsai et al., 2011
rs9392158	6	7,427,350	8.5×10^{-5}	*RIOK1*	Burgner et al., 2009
rs9364166	6	72,106,622	9.8×10^{-5}	*OGFRL1, C6orf155*	J.J. Kim et al., 2011
rs362794	7	103,201,263	3.0×10^{-5}	*RELN*	Tsai et al., 2011
rs6469101	8	108,252,238	5.4×10^{-5}	*ANGPT1*	Burgner et al., 2009
rs328879	9	107,789,252	1.2×10^{-5}	-	Burgner et al., 2009
rs10984642	9	122,450,340	2.6×10^{-5}	-	Burgner et al., 2009
rs10984642	9	122,450,340	5.8×10^{-5}	-	Burgner et al., 2009
rs4918458	10	111,505,407	9.8×10^{-5}	-*	J.J. Kim et al., 2011
rs285032	13	98,786,532	1.7×10^{-5}	*FARP1*	Burgner et al., 2009
rs34246750	14	52,868,757	4.8×10^{-5}	*PTGER2, TXNDC16*	J.J. Kim et al., 2011
rs10129255	14	107,176,213	6.8×10^{-6}	*IGHV*	Tsai et al., 2011
rs1568657	15	83,726,179	6.6×10^{-6}	*BTBD1*	Tsai et al., 2011
rs7199343	16	73,009,024	2.4×10^{-6}	*ZFHX3*	Burgner et al., 2009
rs8059315	16	74,506,447	8.5×10^{-5}	*GLG1*	Burgner et al., 2009
rs2270133	17	61,473,325	4.6×10^{-5}	*TANC2**	J.J. Kim et al., 2011

Table 7. Summary of GWAS for KD (II). * Association was observed between KD patients with CAL and healthy controls. Chr: chromosome.

4. Clinical implementation of genetic findings

The standard treatment for KD is a combination of oral aspirin and high-dose IVIG (Z. Onouchi & Kawasaki, 1999). While the majority of patients respond to this therapy, around 15% are resistant and require additional IVIG or alternative drugs to prevent the development of CAL. As the etiology and pathophysiology of KD are largely unknown, the mechanism of action of these therapies on the disease is not fully understood. The identification of genetic factors that influence patient response to therapy might provide an insight to this problem.

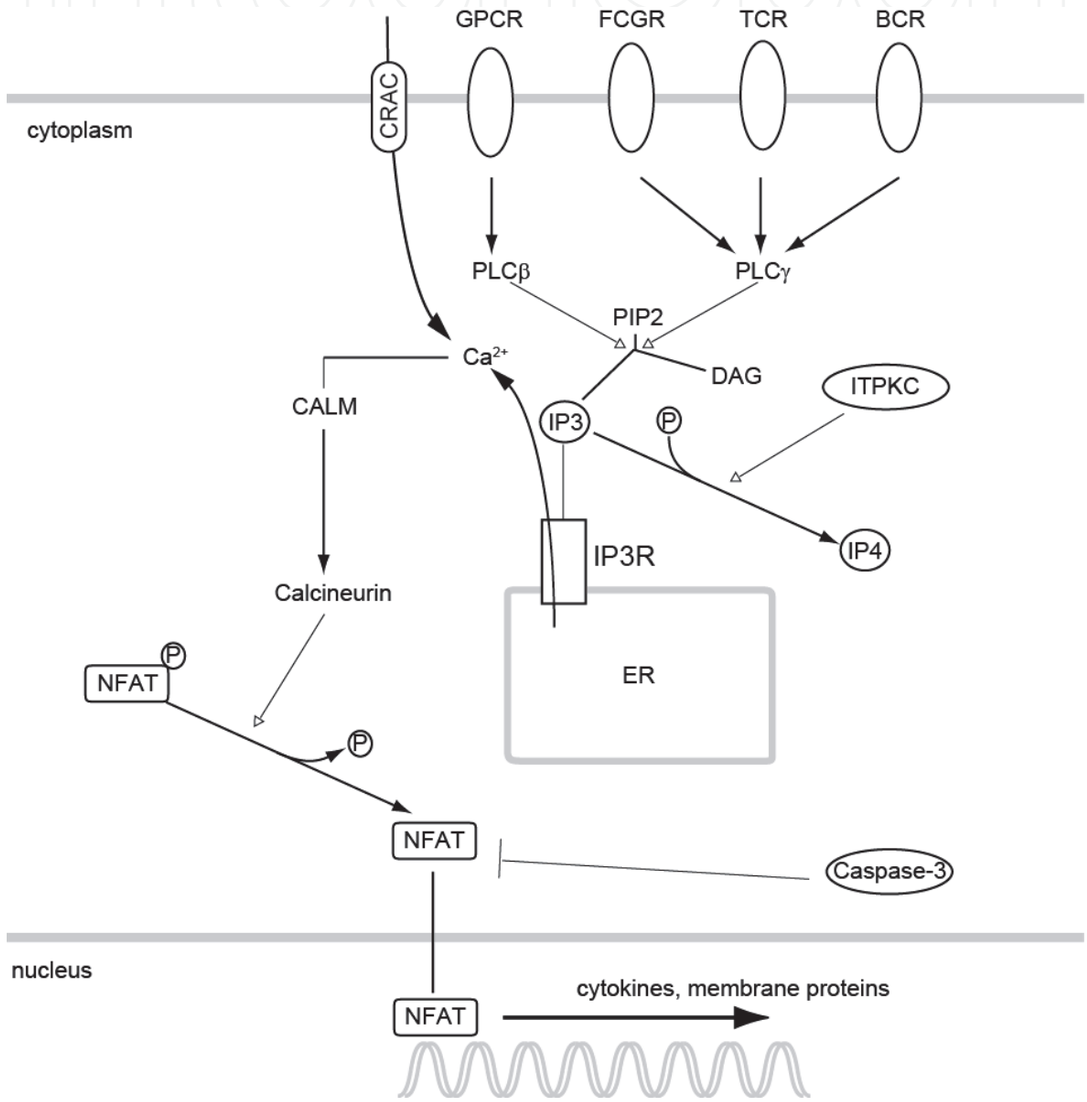

Fig. 5. Possible role of ITPKC and caspase-3 in the immune response.

CRAC: calcium release-activated calcium channel, GPCR: G-protein-coupled receptor, FCGR: Fc gamma receptor, BCR: B cell receptor, TCR: T cell receptor, NFAT: nuclear factor of activated T cells, PLC: phospholipase, PIP2: phosphatidylinositol 4,5-bisphosphate, DAG: diacylglycerol, CALM: calmodulin, IP3R: IP3 receptor, ER: endoplasmic reticulum.

We investigated the association between the functional SNPs in the ITPKC and caspase-3 genes with IVIG unresponsiveness and CAL formation, and found that patients with at least 1 susceptible allele at both SNPs had 2.7–2.9 times higher risk for these unfavorable events (manuscript submitted). Considering that ITPKC and caspase-3 are possibly negative regulators of the Ca^{2+}/NFAT pathway (Fig. 5), hyperactivation of the pathway might underlie a more severe clinical manifestation of the disease.

From this point of view, Cyclosporine A, an immunosuppressant drug which potently suppresses the activity of T cells by targeting calcineurin, a key molecule of the Ca^{2+}/NFAT pathway (Fig. 5), may be a good option for refractory cases of KD. In Japan, a study to investigate the tolerability, safety, and efficacy of Cyclosporine A for KD has been started.

5. Conclusion

Many candidate variations for susceptibility to KD have been reported from candidate gene and genome-wide studies; however, most of the findings from these studies are not robust and have yet to be confirmed by replication studies. Considering the modest odds ratios observed in recent GWAS for complex disorders, discovery studies should be conducted with much larger cohorts. Replication studies in different ethnic groups should be designed with careful attention to their power to detect a significant association and, most importantly, to the difference in the linkage disequilibrium structure. As the majority of KD patients are infants and children and the disease incidence is low, especially in countries outside East Asia, there are limitations in collecting subjects. In an attempt to overcome this difficulty, several consortia have been formed. Those engaged in KD research hope to unravel the mystery of this vasculitis and save these children from damage to their heart. We wish to contribute to this important mission by identifying the underlying genetic components of this disease.

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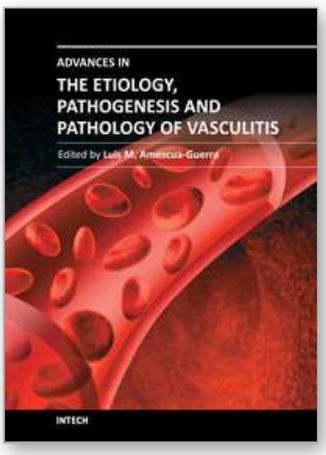

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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