

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Responsible Genetic Factors for Vasculitis in Kawasaki Disease

Yoshihiro Onouchi and Akira Hata
RIKEN & Chiba University
Japan

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.

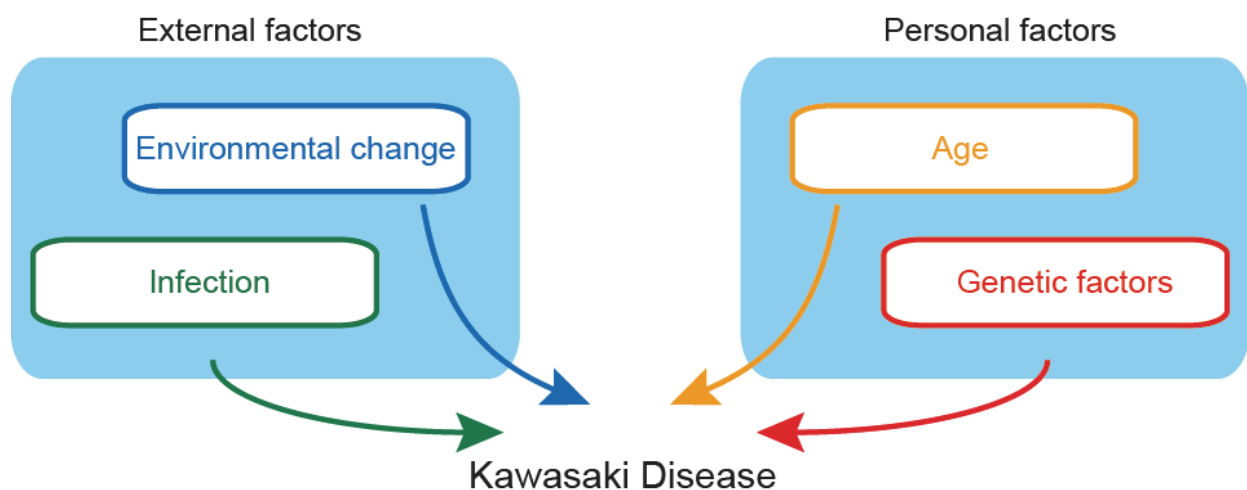


Fig. 1. Multiple factors that are linked to KD.

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			
<i>IL-10</i>	1q31-q32	Hsueh et al., 2009	Jin et al., 2007 Weng et al., 2010a
<i>TGFB2</i>	1q41	Shimizu et al., 2011	
<i>IL-1α</i>	2q14		Weng et al., 2010b S.K. Kim et al., 2011
<i>IL-1β</i>	2q14		S.F. Wu et al., 2005 Weng et al., 2010b S.K. Kim et al., 2011
<i>IL-1Ra</i>	2q14.2	S.F. Wu et al., 2005	Weng et al., 2010b S.K. Kim et al., 2011
<i>CXCR2</i>	2q35		Breunis et al., 2007
<i>CXCR1</i>	2q35		Breunis et al., 2007
<i>TGFB2</i>	3p22	Shimizu et al., 2011	
<i>CX3CR1</i>	3p21.3		Breunis et al., 2007
<i>CCR3</i>	3p21	Breunis et al., 2007	
<i>CCR2</i>	3p21	Breunis et al., 2007	
<i>CCR5</i>	3p21	Burns et al., 2005 Jhang et al., 2009 Breunis et al., 2007	Mamtani et al., 2010 Chaudhuri et al., 2011
<i>IL-8</i>	4q13-q21		Weng et al., 2010b
<i>IL-4</i>	5q31.1	Burns et al., 2005	S.F. Wu et al., 2005 F.Y. Huang et al., 2008a Weng et al., 2010b
<i>LTA</i>	6p21.3	Quasney et al., 2001	
<i>TNF-α</i>	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
<i>IL-6</i>	7p21		Sohn et al., 2001 Weng et al., 2010b
<i>IL-18</i>	11q22.2-q22.3	Hsueh et al., 2008a Chen et al., 2009	
<i>TNFRSF1A</i>	12p13.2	Wang et al., 2011	
<i>MCP1</i>	17q11.2-q12		Jibiki et al., 2001
<i>CCL5</i>	17q11.2-q12		Chaundhuri et al., 2011
<i>CCL3L1</i>	17q11.2	Burns et al., 2005 Mamtani et al., 2010	
<i>TGFB1</i>	19q13.1		Weng et al., 2010b
<i>MIF</i>	22q11.2		Simonini et al., 2009
Vasoactive molecules or molecules related to vascular remodeling			
<i>AGTR1</i>	3q21-q25		Fukazawa et al., 2004
<i>TIMP4</i>	3p25		Ban et al., 2009
<i>VEGFR2</i>	4q12		Kariyazono et al., 2004
<i>VEGFA</i>	6p12	Breunis et al., 2006 Hsueh et al., 2008b	Kariyazono et al., 2004 F.Y. Huang et al., 2008b
<i>eNOS</i>	7q36		Khajooe 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		Khajoei 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
<i>MTHFR</i>	CAL	Tsukahara et al., 2000	
<i>CRP</i>	CAL		Cheung et al., 2008
	Intima-media thickness	Cheung et al., 2008	
	Arterial stiffness	Cheung et al., 2008	
<i>IL-10</i>	CAL	Jin et al., 2007	Hseuh et al., 2009
	Serum albumin	Jin et al., 2007	
<i>FCGR2A</i>	CAL	Taniuchi et al., 2005	Biezeveld et al., 2007
<i>FCGR2B</i>	CAL		Biezeveld et al., 2007
<i>FCGR3A</i>	CAL		Taniuchi et al., 2005 Biezeveld et al., 2007
<i>FCGR3B</i>	CAL		Taniuchi et al., 2005 Biezeveld et al., 2007
<i>TGFB2</i>	CAL/ coronary z score	Shimizu et al., 2011	
	Diameter of aortic root	Shimizu et al., 2011	
	Response to IVIG	Shimizu et al., 2011	
<i>IL-1α</i>	CAL		S.K. Kim et al., 2011
<i>IL-1β</i>	Response to IVIG	Weng et al., 2010	S.K. Kim et al., 2011
<i>IL-1Ra</i>	CAL		S.K. Kim et al., 2011
<i>CTLA4</i>	CAL	Kuo et al., 2010	
<i>PD-1</i>	CAL		Chun et al., 2010
<i>TIMP4</i>	CAL	Ban et al., 2009	
<i>TGFBR2</i>	CAL/ coronary z score	Shimizu et al., 2011	
	Diameter of aortic root	Shimizu et al., 2011	
	Response to IVIG	Shimizu et al., 2011	
<i>CCR5</i>	CAL	Mamtani et al., 2010 Chaudhuri et al., 2011	Jhang et al., 2009
<i>AGTR1</i>	Coronary stenosis	Fukazawa et al., 2004	
<i>VEGFR2</i>	CAL	Kariyazono et al., 2003	
<i>IL-4</i>	CAL		Burns et al., 2005 F.Y.Huang et al., 2008a
<i>CD14</i>	CAL	Nishimura et al., 2003	
<i>VEGFA</i>	CAL	Kariyazono et al., 2003	Hsueh et al., 2008b F.Y.Huang et al., 2008b
<i>MICA</i>	CAL	F.Y. Huang et al., 2000	
<i>LTA</i>	CAL		Quasney et al., 2001
<i>TNF-α</i>	CAL	Quasney et al., 2001	Cheung et al., 2008

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

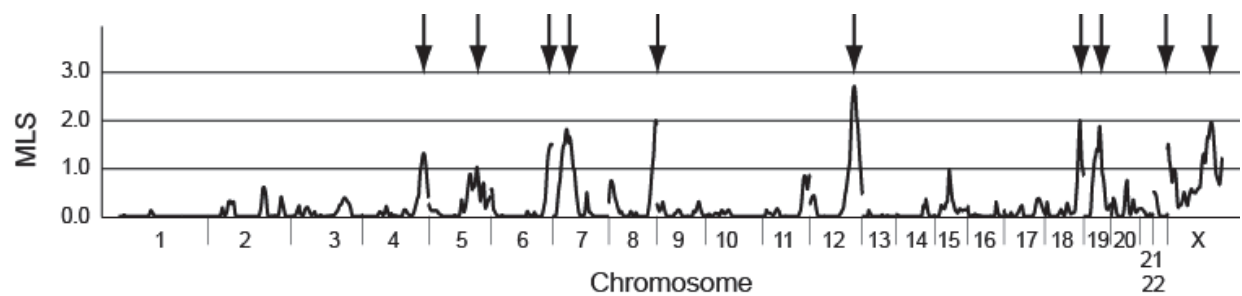


Fig. 2. Results from an affected sib-pair study (Y. Onouchi et al., 2007). Arrows indicate those chromosomal regions with a maximum LOD score (MLS) >1.0.

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. ¹Risk allele is underlined. ²Dominant inheritance model. ³Transmitted: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.

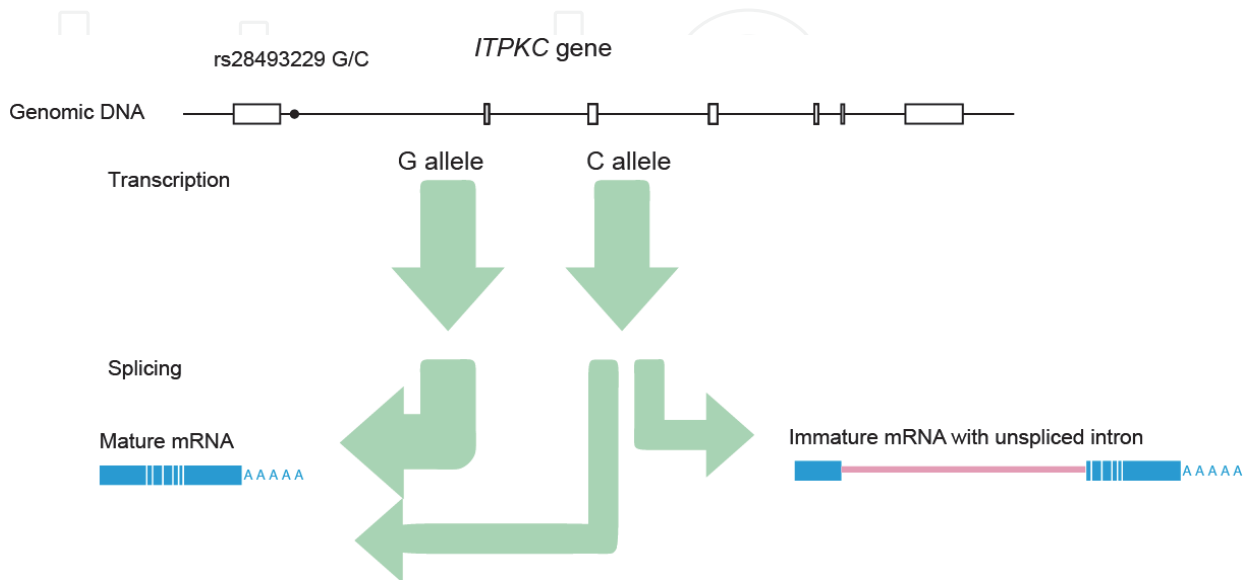


Fig. 3. Functional significance of rs28493229 on ITPKC mRNA.

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	No. of families	T:U ³	OR (95% CI)
	KD n=920	Control n=1,409	P value ²			P value
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. ¹Risk allele is underlined. ²Allelic model. ³Transmitted:untransmitted ratio. TDT: transmission disequilibrium test, OR: odds ratio, CI: confidence interval.

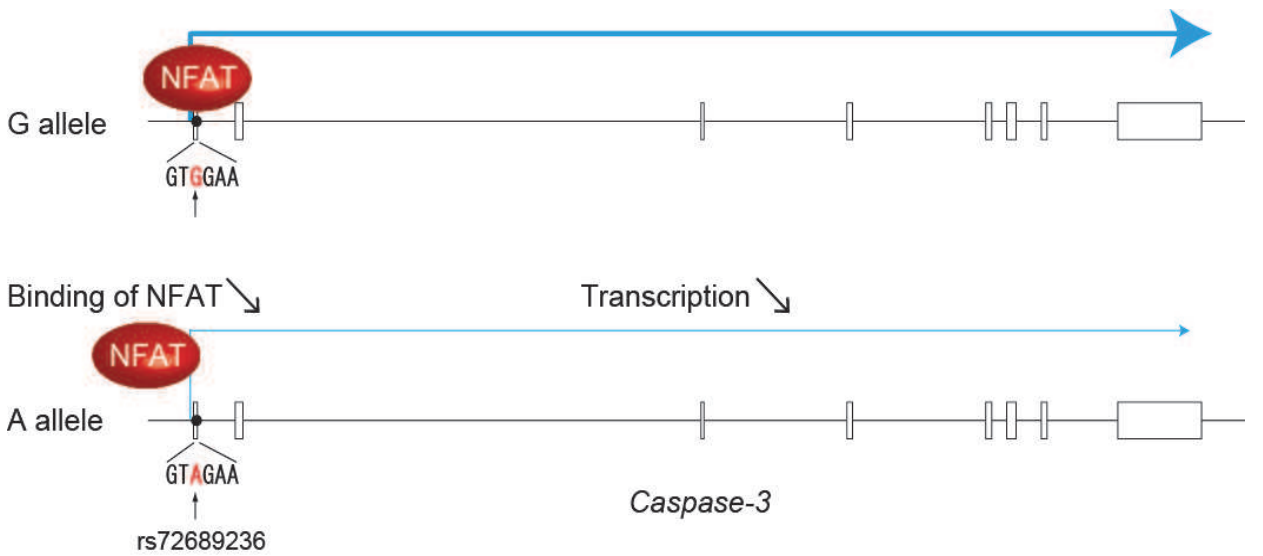


Fig. 4. Functional significance of rs72689236 on caspase-3 mRNA.

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). ¹583 KD patients and their unaffected siblings and biological parents. ²KD patients with coronary artery lesions and healthy controls.

SNP	Chr	Position	P value	Gene	Reference
rs527409	1	58,757,915	1.5 × 10 ⁻⁶	<i>DAB1</i>	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	<i>PELI1</i> *	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	<i>MRPS22,</i> <i>COPB2,</i> <i>RBP2</i>	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	<i>NAALADL2</i>	Burgner et al., 2009
rs3773986	3	190,278,915	6.2 × 10 ⁻⁵	<i>IL1RAP</i> *	J.J. Kim et al., 2011
rs4864471	4	54,426,184	3.4 × 10 ⁻⁵	<i>LNK1,</i> <i>LOC441016</i>	Burgner et al., 2009
rs13128867	4	138,840,995	2.2 × 10 ⁻⁵	<i>SLC7A11</i>	Tsai et al., 2011
rs149481	5	96,114,346	4.6 × 10 ⁻⁵	<i>ERAP1</i>	Tsai et al., 2011
rs9392158	6	7,427,350	8.5 × 10 ⁻⁵	<i>RIOK1</i>	Burgner et al., 2009
rs9364166	6	72,106,622	9.8 × 10 ⁻⁵	<i>OGFRL1,</i> <i>C6orf155</i>	J.J. Kim et al., 2011
rs362794	7	103,201,263	3.0 × 10 ⁻⁵	<i>RELN</i>	Tsai et al., 2011
rs6469101	8	108,252,238	5.4 × 10 ⁻⁵	<i>ANGPT1</i>	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	<i>FARP1</i>	Burgner et al., 2009
rs34246750	14	52,868,757	4.8 × 10 ⁻⁵	<i>PTGER2,</i> <i>TXNDC16</i>	J.J. Kim et al., 2011
rs10129255	14	107,176,213	6.8 × 10 ⁻⁶	<i>IGHV</i>	Tsai et al., 2011
rs1568657	15	83,726,179	6.6 × 10 ⁻⁶	<i>BTBD1</i>	Tsai et al., 2011
rs7199343	16	73,009,024	2.4 × 10 ⁻⁶	<i>ZFHX3</i>	Burgner et al., 2009
rs8059315	16	74,506,447	8.5 × 10 ⁻⁵	<i>GLG1</i>	Burgner et al., 2009
rs2270133	17	61,473,325	4.6 × 10 ⁻⁵	<i>TANC2</i> *	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.

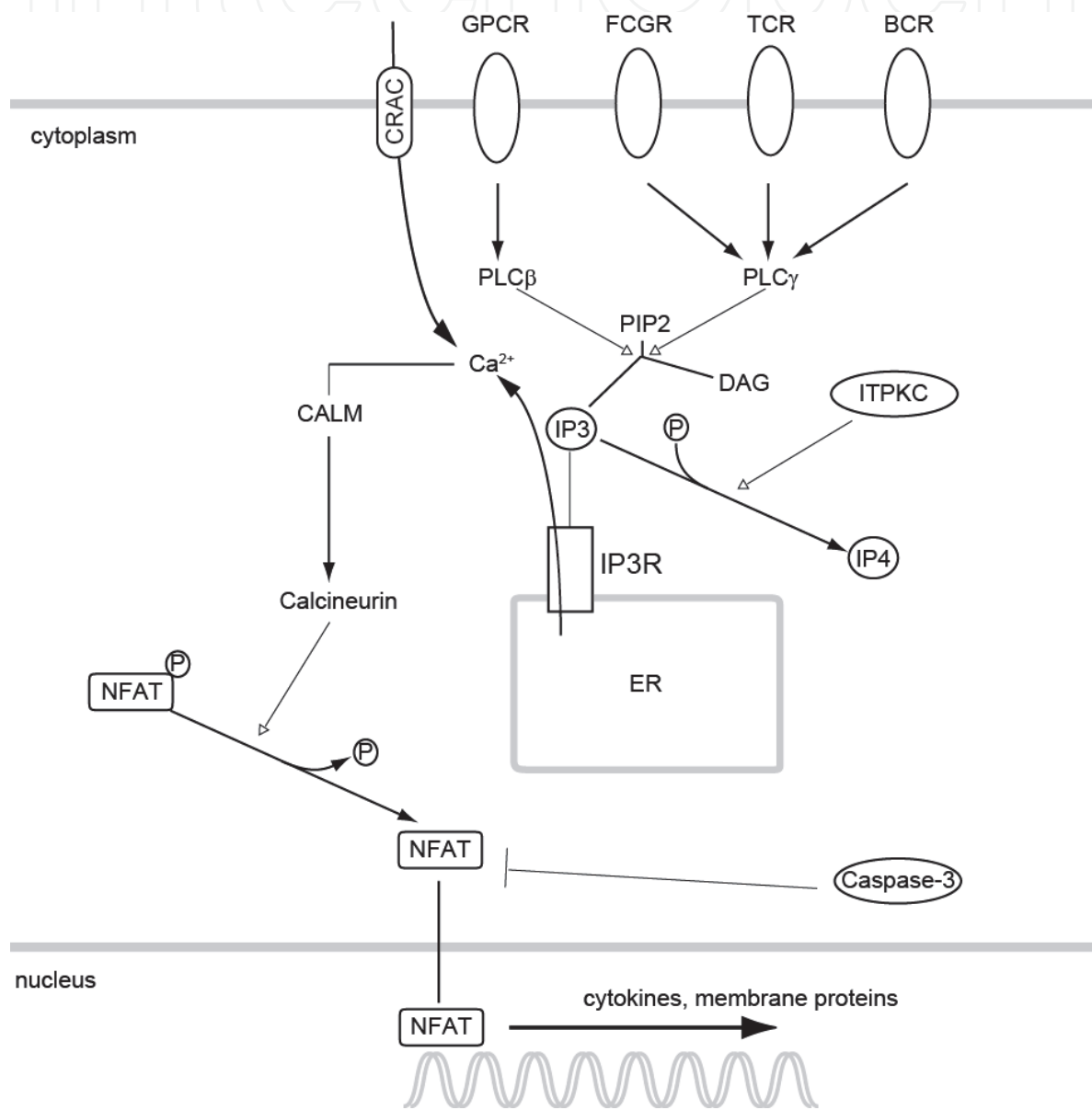


Fig. 5. Possible role of ITPKC and caspase-3 in the immune response.

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.

6. References

- Ahn, SY.; Jang, GC.; Shin, JS.; Shin, KM. & Kim DS. (2003). Tumor necrosis factor- α levels and promoter polymorphism in patients with Kawasaki disease in Korea. *Yonsei Medical Journal*, Vol.44, No.6, pp. 1021-1026, (December 2003). ISSN 0513-5796
- Amano, S.; Hazama, F. & Hamashima Y. (1979). Pathology of Kawasaki disease: II. Distribution and incidence of the vascular lesions. *Japanese Circulation Journal*, Vol.43, No.8, pp. 741-748, (August 1979), ISSN 0047-1828
- Ari-Ong, S.; Thakkestian, A.; McEvoy, M. & Attia, J. (2010). A systematic review and meta-analysis of tumor necrosis factor α -308 polymorphism and Kawasaki disease. *Pediatrics International*, Vol.52, No.4, pp. 527-532, (February 2010), ISSN 1328-8067
- Ban, JY.; Yoon, KL.; Kim, SK.; Kang, S. & Chung, JH. (2009). Promoter polymorphism (rs3755724, -55C/T) of tissue inhibitor of metalloproteinase 4 (TIMP4) as a risk factor for Kawasaki disease with coronary artery lesions in a Korean population. *Pediatric Cardiology*, Vol.30, No.3, pp. 331-335, (April 2009). ISSN 0172-0643
- Ban, JY.; Kim, SK.; Kang, SW.; Yoon, KL. & Chung, JH. (2010). Association between polymorphisms of matrix metalloproteinase 11 (MMP-11) and Kawasaki disease in

- the Korean population. *Life Sciences*, Vol.86, No.19-20, pp. 756-759, (May 2010). ISSN 0024-3205
- Biezeveld, MH.; Kuipers, IM.; Geissler, J.; Lam, J.; Ottenkamp, JJ.; Hack, CE. & Kuijpers, TW. (2003). Association of mannose-binding lectin genotype with cardiovascular abnormalities in Kawasaki disease. *The Lancet*, Vol.361, No.9365, pp. 1268-1270, (April 2003). ISSN 0140-6736
- Biezeveld, MH.; Geissler, J.; Weverling, GJ.; Kuipers, IM.; Lam, J.; Ottenkamp, J. & Kuijpers, TW. (2006). Polymorphisms in the mannose-binding lectin gene as determinants of age-defined risk of coronary artery lesions in Kawasaki disease. *Arthritis & Rheumatism*, Vol.54, No.1, pp. 369-376, (January 2006). ISSN 0004-3591
- Biezeveld, M.; Geissler, J.; Merkus, M.; Kuipers, IM.; Ottenkamp, J. & Kuijpers, T. (2007). The involvement of Fc gamma receptor gene polymorphisms in Kawasaki disease. *Clinical & Experimental Immunology*, Vol.147, No.1, pp. 106-111, (January 2007). ISSN 0009-9104
- Breunis, WB.; Biezeveld, MH.; Geissler, J.; Ottenkamp, J.; Kuipers, IM.; Lam, J.; Hutchinson, A.; Welch, R.; Chanock, SJ. & Kuijpers, TW. (2006). Vascular endothelial growth factor gene haplotypes in Kawasaki disease. *Arthritis & Rheumatism*, Vol.54, No.5, pp. 1588-1594, (May 2006). ISSN 0004-3591
- Breunis, WB.; Biezeveld, MH.; Geissler, J.; Kuipers, IM.; Lam, J.; Ottenkamp, J.; Hutchinson, A.; Welch, R.; Chanock, SJ. & Kuijpers, TW. (2007). Polymorphisms in chemokine receptor genes and susceptibility to Kawasaki disease. *Clinical & Experimental Immunology*, Vol.150, No.1, pp. 83-90, (October 2007). ISSN 0009-9104
- Burgner, D.; Davila, S.; Breunis, WB.; Ng, SB.; Li, Y.; Bonnard, C.; Ling, L.; Wright, VJ.; Thalamuthu, A.; Odam, M.; Shimizu, C.; Burns, JC.; Levin, M.; Kuijpers, TW. & Hibberd, ML; International Kawasaki Disease Genetics Consortium. (2009). A genome-wide association study identifies novel and functionally related susceptibility loci for Kawasaki disease. *PLoS Genetics*, Vol.5, No.1, pp. e1000319, (January 2009). ISSN 1553-7404
- Burns, JC.; Shimizu, C.; Gonzalez, E.; Kulkarni, H.; Patel, S.; Shike, H.; Sundel, RS.; Newburger, JW. & Ahuja SK. (2005). Genetic variations in the receptor-ligand pair CCR5 and CCL3L1 are important determinants of susceptibility to Kawasaki disease. *The Journal of Infectious Diseases*, Vol.192, No.2, pp. 344-349. (July 2005). ISSN 0022-1899
- Burns, JC.; Shimizu, C.; Shike, H.; Newburger, JW.; Sundel, RP.; Baker, AL.; Matsubara, T.; Ishikawa, Y.; Brophy, VA.; Cheng, S.; Grow, MA.; Steiner, LL.; Kono, N. & Cantor RM. (2005). Family-based association analysis implicates IL-4 in susceptibility to Kawasaki disease. *Genes & Immunity*, Vol.6, No.5, pp. 438-444, (August 2005). ISSN 1466-4879
- Chaudhuri, K.; Singh, Ahluwalia, T.; Singh, S.; Binopal, G. & Khullar, M. (2011). Polymorphism in the promoter of the CCL5 gene (CCL5G-403A) in a cohort of North Indian children with Kawasaki disease. A preliminary study. *Clinical & Experimental Rheumatology*, Vol.29, No.1, pp. 126-130, (May 2011). ISSN 0392-856X
- Chen, SY.; Wan, L.; Huang, YC.; Sheu, JJ.; Lan, YC.; Lai, CH.; Lin, CW.; Chang, JS.; Tsai, Y.; Liu, SP.; Lin, YJ. & Tsai, FJ. (2009). Interleukin-18 gene 105A/C genetic

- polymorphism is associated with the susceptibility of Kawasaki disease. *Journal of Clinical Laboratory Analysis*, Vol.23, No.2, pp. 71-76. (n.d. 2009). ISSN 0887-8013
- Cheung, YF.; Ho, MH.; Ip, WK.; Fok, SF.; Yung, TC. & Lau, YL. (2004). Modulating effects of mannose binding lectin genotype on arterial stiffness in children after Kawasaki disease. *Pediatric Research*, Vol.56, No.4, pp. 591-596, (October 2004).ISSN 0031-3998
- Cheung, YF.; Huang, GY.; Chen, SB.; Liu, XQ.; Xi, L.; Liang, XC.; Huang, MR.; Chen, S.; Huang, LS.; Liu, XQ.; Chan, KW. & Lau, YL. (2008). Inflammatory gene polymorphisms and susceptibility to kawasaki disease and its arterial sequelae. *Pediatrics*, Vol. 122, No.3, pp. e608-614, (September 2008). ISSN 0031-4005
- Chi, H.; Huang, FY.; Chen, MR.; Chiu, NC.; Lee, HC.; Lin, SP.; Chen, WF.; Lin, CL.; Chan, HW.; Liu, HF.; Huang, LM. & Lee, YJ. (2010). ITPKC gene SNP rs28493229 and Kawasaki disease in Taiwanese children. *Human Molecular Genetics*, Vol.15, No.6, pp. 1147-1151, (March 2010). ISSN 1434-5161
- Chien, YH.; Chang, KW.; Yang, YH.; Lu, MY.; Lin, YT. & Chiang BL. (2003). Association between levels of TNF-alpha and TNF-alpha promoter -308 A/A polymorphism in children with Kawasaki disease. *Journal of the Formosan Medical Association*, Vol.102, No. 3, pp. 147-150, (March 2003). ISSN 0929-6646
- Chun, JK.; Kang, DW.; Yoo, BW.; Shin, JS. & Kim, DS. (2010). Programmed death-1 (PD-1) gene polymorphisms lodged in the genetic predispositions of Kawasaki Disease. *European Journal of Pediatrics*, Vol.169, No.2, pp. 181-185, (February 2010). ISSN 0340-6199
- Fujita, Y.; Nakamura, Y.; Sakata, K.; Hara, N.; Kobayashi, M.; Nagai, M.; Yanagawa, H. & Kawasaki, T. (1989). Kawasaki disease in families. *Pediatrics*, Vol.84, No.4, pp. 666-669, (October 1989). ISSN 1098-4275
- Fukazawa, R.; Sonobe, T.; Hamamoto, K.; Hamaoka, K.; Sakata, K.; Asano, T.; Imai, T.; Kamisago, M.; Ohkubo, T.; Uchikoba, Y.; Ikegami, E.; Watanabe, M. & Ogawa, S. (2004). Possible synergic effect of angiotensin-I converting enzyme gene insertion/deletion polymorphism and angiotensin-II type-1 receptor 1166A/C gene polymorphism on ischemic heart disease in patients with Kawasaki disease. *Pediatric Research*, Vol.56, No.4, pp. 597-601, (October 2004). ISSN 0031-3998
- Furuno, K.; Takada, H.; Yamamoto, K.; Ikeda, K.; Ohno, T.; Khajooe, V.; Mizuno, Y. & Hara T. (2007). Tissue inhibitor of metalloproteinase 2 and coronary artery lesions in Kawasaki disease. *The Journal of Pediatrics*, Vol.151, No.2, pp. 155-160, (August 2007). ISSN 1085-8695
- Holman, RC.; Christensen, KY.; Belay, ED.; Steiner, CA.; Effler, PV.; Miyamura, J.; Forbes, S.; Schonberger, LB. & Melish, M. (2010). Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Medical Journal*, Vol.69, No.8, pp. 194-197, (August 2010). ISSN 0017-8594
- Hong, YM.; Jin, HS.; Park, IS. & Hong, SJ. Association of the matrix metalloproteinase-3 (-439C/G) promoter polymorphism with Kawasaki disease in Korean children. *Heart and Vessels*, Vol.23, No.5, pp. 341-347, (September 2008). ISSN 0910-8327
- Hsieh, YY.; Lin, YJ.; Chang, CC.; Chen, DY.; Hsu, CM.; Wang, YK.; Hsu, KH. & Tsai FJ. (2010). Human lymphocyte antigen B-associated transcript 2, 3, and 5 polymorphisms and haplotypes are associated with susceptibility of Kawasaki

- disease and coronary artery aneurysm. *Journal of Clinical Laboratory Analysis*, Vol.24, No.4, pp. 262-268, (n.d. 2010). ISSN 0887-8013
- Hsueh, KC.; Lin, YJ.; Chang, JS.; Wan, L.; Tsai, YH.; Tsai, CH.; Chen, CP. & Tsai FJ. (2008). Association of vascular endothelial growth factor C-634 G polymorphism in Taiwanese children with Kawasaki disease. *Pediatric Cardiology*, Vol.29, No.2, pp. 292-296, (March 2008). ISSN 0172-0643
- Hsueh, KC.; Lin, YJ.; Chang, JS.; Wan, L.; Tsai, YH.; Tsai, CH. & Tsai, FJ. (2008). Influence of interleukin 18 promoter polymorphisms in susceptibility to Kawasaki disease in Taiwan. *The Journal of Rheumatology*, Vol.35, No.7, pp. 1408-1413, (July 2008). ISSN 0315-162X
- Hsueh, KC.; Lin, YJ.; Chang, JS.; Wan, L.; Tsai, YH.; Tsai, CH.; Chen, CP. & Tsai, FJ. (2009). Association of interleukin-10 A-592C polymorphism in Taiwanese children with Kawasaki disease. *Journal of Korean Medical Science*, Vol.24, No.3, pp. 438-442, (June 2009). ISSN: 1011-8934
- Hsueh, KC.; Lin, YJ.; Chang, JS.; Wan, L. & Tsai, FJ. (2010). BTNL2 gene polymorphisms may be associated with susceptibility to Kawasaki disease and formation of coronary artery lesions in Taiwanese children. *European Journal of Pediatrics*, Vol.169, No.6, pp. 713-719, (June 2010). ISSN 0340-6199
- Huang, FY.; Lee, YJ.; Chen, MR.; Hsu, CH.; Lin, SP.; Sung, TC.; Chang, SC. & Chang, JG. (2000). Polymorphism of transmembrane region of MICA gene and Kawasaki disease. *Experimental and Clinical Immunogenetics*, Vol.17, No. 3, pp. 130-137, (June 2000). ISSN 0254-9670
- Huang, FY.; Chang, TY.; Chen, MR.; Lee, HC.; Chiu, NC.; Chi, H.; Hsu, CH.; Lin, SP.; Liu, HF.; Chen, WF.; Chu, CC.; Lin, M. & Lee, YJ. (2008). The -590 C/T and 8375 A/G interleukin-4 polymorphisms are not associated with Kawasaki disease in Taiwanese children. *Human Immunology*, Vol.69, No.1, pp. 52-57, (January 2008). ISSN 0198-8859
- Huang, FY.; Chang, TY.; Chen, MR.; Lee, HC.; Chi, H.; Chiu, NC.; Hsu, CH.; Lin, SP.; Kao, HA.; Chen, WF.; Chan, HW.; Liu, HF.; Chu, CC.; Lin, M. & Lee, YJ. (2008). Lack of association of the vascular endothelial growth factor gene polymorphisms with Kawasaki disease in Taiwanese children. *Journal of Clinical Immunology*, Vol.28, No.4, pp. 322-328, (July 2008). ISSN 0271-9142
- Huang, FY.; Chang, TY.; Chen, MR.; Chiu, NC.; Chi, H.; Lee, HC.; Lin, SP.; Chen, CK.; Chan, HW.; Chen, WF.; Liu, HF.; Chu, CC.; Lin, M. & Lee, YJ. (2008). Genetic polymorphisms in the CD40 ligand gene and Kawasaki disease. *Journal of Clinical Immunology*, Vol.28, No.5, pp. 405-410, (September 2008). ISSN 0271-9142
- Huang, WC.; Huang, LM.; Chang, IS.; Chang, LY.; Chiang, BL.; Chen, PJ.; Wu, MH.; Lue, HC.; & Lee, CY.; Kawasaki Disease Research Group. (2009). Epidemiologic features of Kawasaki disease in Taiwan, 2003-2006. *Pediatrics*, Vol.123, No.3, pp. e401-405, (Mar 2009), ISSN 1098-4275
- Huang, YC.; Lin, YJ.; Chang, JS.; Chen, SY.; Wan, L.; Sheu, JJ.; Lai, CH.; Lin, CW.; Liu, SP.; Chen, CP. & Tsai FJ. (2010). Single nucleotide polymorphism rs2229634 in the ITPR3 gene is associated with the risk of developing coronary artery aneurysm in

- children with Kawasaki disease. *International Journal of Immunogenetics*, Vol.37, No.6, pp. 439-443, (December 2010). ISSN 1744-3121
- Ikeda, K.; Ihara, K.; Yamaguchi, K.; Muneuchi, J.; Ohno, T.; Mizuno, Y. & Hara, T. (2008). Genetic analysis of MMP gene polymorphisms in patients with Kawasaki disease. *Pediatric Research*, Vol.63, No.2, pp. 182-185, (February 2008). ISSN 0031-3998
- Jhang, WK.; Kang, MJ.; Jin, HS.; Yu, J.; Kim, BJ.; Kim, BS.; Lee, JK.; Seo, EJ.; Yoo, HW.; Park, IS.; Hong, YM. & Hong, SJ. (2009). The CCR5 (-2135C/T) polymorphism may be associated with the development of Kawasaki disease in Korean children. *Journal of Clinical Immunology*, Vol.29, No.1, pp. 22-28, (January 2009). ISSN 0271-9142
- Jibiki, T.; Terai, M.; Shima, M.; Ogawa, A.; Hamada, H.; Kanazawa, M.; Yamamoto, S.; Oana, S. & Kohno, Y. (2001). Monocyte chemoattractant protein 1 gene regulatory region polymorphism and serum levels of monocyte chemoattractant protein 1 in Japanese patients with Kawasaki disease. *Arthritis & Rheumatism*, Vol.44, No. 9, pp. 2211-2212, (September 2001). ISSN 0004-3591
- Jin, HS.; Kim, HB.; Kim, BS.; Lee, JK.; Seo, EJ.; Yoo, HW.; Park, IS.; Hong, YM. & Hong, SJ. (2007). The IL-10 (-627 A/C) promoter polymorphism may be associated with coronary aneurysms and low serum albumin in Korean children with Kawasaki disease. *Pediatric Research*, Vol.61, No.5, pp. 584-587, (May 2007). ISSN 0031-3998
- Kamizono, S.; Yamada, A.; Higuchi, T.; Kato, H. & Itoh, K. (1999). Analysis of tumor necrosis factor-alpha production and polymorphisms of the tumor necrosis factor-alpha gene in individuals with a history of Kawasaki disease. *Pediatrics International*, Vol.41, No.4, pp. 341-345, (August 1999). ISSN 0179-0358
- Kanai, M.; Tanabe, S.; Okada, M.; Suzuki, H.; Niki, T.; Katsuura, M.; Akiba, T. & Hayasaka, K. (2003). Polymorphisms of heme oxygenase-1 and bilirubin UDP-glucuronosyltransferase genes are not associated with Kawasaki disease susceptibility. *The Tohoku Journal of Experimental Medicine*, Vol.200, No.3, pp. 155-159, (July 2003). ISSN 0040-8727
- Kang, SW.; Ban, JY.; Yoon, KL.; Kim, SK.; Kang, SW.; Chung, JH. & Cho, J. (2011). Notch Homolog 4 Polymorphism and Kawasaki Disease. *Indian Journal of Pediatrics*, in press. ISSN 0019-5456
- Kariyazono, H.; Ohno, T.; Khajooee, V.; Ihara, K.; Kusuhara, K.; Kinukawa, N.; Mizuno, Y. & Hara, T. (2004). Association of vascular endothelial growth factor (VEGF) and VEGF receptor gene polymorphisms with coronary artery lesions of Kawasaki disease. *Pediatric Research*, Vol.56, No.6, pp. 953-959, (December 2004). ISSN 0031-3998
- Kaslow, RA.; Bailowitz, A.; Lin, FY.; Koslowe, P.; Simonis, T. & Israel, E. (1985). Association of epidemic Kawasaki syndrome with the HLA-A2, B44, Cw5 antigen combination. *Arthritis & Rheumatism*, Vol.28, No.8, pp. 938-940, (August 1985). ISSN 0004-3591
- Kato, H.; Koike, S.; Yamamoto, M.; Ito, Y. & Yano, E. (1975). Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *The Journal of Pediatrics*, Vol.86, No.6, pp. 892-898, (June 1975), ISSN 1085-8695
- Kato, S.; Kimura, M.; Tsuji, K.; Kusakawa, S.; Asai, T., Juji, T. & Kawasaki, T. (1978). HLA antigens in Kawasaki disease. *Pediatrics*, Vol.61, No.2, pp. 252-255, (February 1978). ISSN 1098-4275

- Kawasaki, T. (1967), Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi*, Vol.16, No.3, pp. 178-222, (March 1967), ISSN 0021-4884
- Keren, G.; Danon, YL.; Orgad, S.; Kalt, R. & Gazit, E. (1982). HLA Bw51 is increased in mucocutaneous lymph node syndrome in Israeli patients. *Tissue Antigens*, Vol.20, No.2, pp. 144-146, (August 1982). ISSN 0001-2815
- Khajooee, V.; Kariyazono, H.; Ohno, T.; Ihara, K.; Mizuno, Y.; Kusuhara, K. & Hara T. (2003). Inducible and endothelial constitutive nitric oxide synthase gene polymorphisms in Kawasaki disease. *Pediatrics International*, Vol.45, No.2, pp. 130-134, (April 2003). ISSN 0179-0358
- Kim, JJ.; Hong, SJ.; Hong, YM.; Kim, S.; Kang, MJ.; Kim, KJ.; Seo, EJ.; Yoo, HW.; Cheong, HS.; Shin, HD.; Park, IS & Lee, JK. (2008). Genetic variants in the HLA-G region are associated with Kawasaki disease. *Human Immunology*, Vol.69, No.12, pp.867-871, (December 2008). ISSN 0198-8859
- Kim, JJ.; Hong, YM.; Sohn, S.; Jang, GY.; Ha, KS.; Yun, SW.; Han, MK.; Lee, KY.; Song, MS.; Lee, HD.; Kim, DS.; Lee, JE.; Shin, ES.; Jang, JH.; Lee, YS.; Kim, SY.; Lee, JY.; Han, BG.; Wu, JY.; Kim, KJ.; Park, YM.; Seo, EJ.; Park, IS. & Lee, JK.; Korean Kawasaki Disease Genetics Consortium. (2011). A genome-wide association analysis reveals 1p31 and 2p13.3 as susceptibility loci for Kawasaki disease. *Human Genetics*, Vol.129, No.5, pp. 487-495, (May 2011). ISSN 0340-6717
- Kim, SK.; Kang, SW.; Chung, JH.; Lee, JS.; Park, HK.; Yoon, KL. & Kim, SC. (2011). Coding single-nucleotide polymorphisms of interleukin-1 gene cluster are not associated with Kawasaki disease in the Korean population. *Pediatric Cardiology*, Vol.32, No.4, pp. 381-385, (April 2011). ISSN 0172-0643
- Krensky, AM.; Berenberg, W.; Shanley, K. & Yunis, EJ. (1981). HLA antigens in mucocutaneous lymph node syndrome in New England. *Pediatrics*, Vol.67, No.5, pp. 741-743, (May 1981). ISSN 1098-4275
- Krensky, AM.; Grady, S.; Shanley, KM.; Berenberg, W. & Yunis, EJ. (1983). Epidemic and endemic HLA-B and DR associations in mucocutaneous lymph node syndrome. *Human Immunology*, Vol.6, No.2, pp. 75-77, (February 1983). ISSN 0198-8859
- Kuo, HC.; Liang, CD.; Yu, HR.; Wang, CL.; Lin, IC.; Liu, CA.; Chang, JC.; Lee, CP.; Chang, WC. & Yang, KD. (2010). CTLA-4, Position 49 A/G Polymorphism Associated with Coronary Artery Lesions in Kawasaki Disease. *Journal of Clinical Immunology*, in press. ISSN 0271-9142
- Kuo, HC.; Yu, HR.; Juo, SH.; Yang, KD.; Wang, YS.; Liang, CD.; Chen, WC.; Chang, WP.; Huang, CF.; Lee, CP.; Lin, LY.; Liu, YC.; Guo, YC.; Chiu, CC & Chang, WC. (2011). CASP3 gene single-nucleotide polymorphism (rs72689236) and Kawasaki disease in Taiwanese children. *Journal of Human Genetics*, Vol.56, No.2 pp. 161-165, (February 2011). ISSN 1434-5161
- Lin, YJ.; Wan, L.; Wu, JY.; Sheu, JJ.; Lin, CW.; Lan, YC.; Lai, CH.; Hung, CH.; Tsai, Y.; Tsai, CH.; Lin, TH.; Lin, JG.; Hsueh, KC.; Huang, YM.; Chang, JS & Tsai, FJ. (2009). HLA-E gene polymorphism associated with susceptibility to Kawasaki disease and formation of coronary artery aneurysms. *Arthritis & Rheumatism*, Vol.60, No.2, pp. 604-610, (February 2009). ISSN 0004-3591

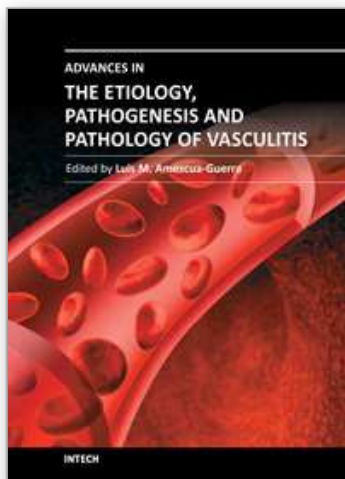
- Lin, MT.; Wang, JK.; Yeh, JL.; Sun, LC.; Chen, PL.; Wu, JF.; Chang, CC.; Lee, WL.; Shen, CT.; Wang, NK.; Wu, CS.; Yeh, SZ.; Chen, CA.; Chiu, SN & Wu, MH. (2011). Clinical Implication of the C Allele of the ITPKC Gene SNP rs28493229 in Kawasaki Disease: Association with Disease Susceptibility and BCG Scar Reactivation. *The Pediatric Infectious Disease Journal*, Vol.30, No.2, pp. 148-152, (February 2011). ISSN 0891-3668
- Macián, F.; García-Cózar, F.; Im, SH.; Horton, HF.; Byrne, MC. & Rao, A. (2002). Transcriptional mechanisms underlying lymphocyte tolerance. *Cell*, Vol.109, No.6, pp. 719-731, (June 2002). ISSN 0092-8674
- Mamtani, M.; Matsubara, T.; Shimizu, C.; Furukawa, S.; Akagi, T.; Onouchi, Y.; Hata, A.; Fujino, A.; He, W.; Ahuja, SK. & Burns, JC. (2010). Association of CCR2-CCR5 haplotypes and CCL3L1 copy number with Kawasaki Disease, coronary artery lesions, and IVIG responses in Japanese children. *PLoS One*, Vol.5, No.7, pp. e11458, (July 2010). ISSN 1932-6203
- Minami, T.; Suzuki, H.; Takeuchi, T.; Uemura, S.; Sugatani, J. & Yoshikawa N. (2005). A polymorphism in plasma platelet-activating factor acetylhydrolase is involved in resistance to immunoglobulin treatment in Kawasaki disease. *Journal of Pediatrics*, Vol.147, No.1, pp. 78-83, (July 2005). ISSN 0022-3476
- Matsuda, I.; Hattori, S.; Nagata, N.; Fruse, A. & Nambu, H. (1977). HLA antigens in mucocutaneous lymph node syndrome. *American Journal of Diseases of Children*, Vol.131, No.12, pp. 1417-1418, (December 1977). ISSN 0002-922X
- Nakamura, Y.; Yashiro, M.; Uehara, R.; Sadakane, A.; Chihara, I.; Aoyama, Y.; Kotani, K. & Yanagawa, H. (2010). Epidemiologic features of Kawasaki disease in Japan: results of the 2007-2008 nationwide survey. *Journal of Epidemiology*, Vol. 20, No. 4, pp. 302-307, (July 2010), ISSN 0917-5040
- Nishimura, S.; Zaitzu, M.; Hara, M.; Yokota, G.; Watanabe, M.; Ueda, Y.; Imayoshi, M.; Ishii, E.; Tasaki, H. & Hamasaki, Y. (2003). A polymorphism in the promoter of the CD14 gene (CD14/-159) is associated with the development of coronary artery lesions in patients with Kawasaki disease. *The Journal of Pediatrics*, Vol.143, No.3, pp. 357-362, (September 2003). ISSN 1085-8695
- Onouchi, Y.; Onoue, S.; Tamari, M.; Wakui, K.; Fukushima, Y.; Yashiro, M.; Nakamura, Y.; Yanagawa, H.; Kishi, F.; Ouchi, K.; Terai, M.; Hamamoto, K.; Kudo, F.; Aotsuka, H.; Sato, Y.; Nariai, A.; Kaburagi, Y.; Miura, M.; Saji, T.; Kawasaki, T.; Nakamura, Y. & Hata, A. (2004). CD40 ligand gene and Kawasaki disease. *European Journal of Human Genetics*, Vol.12, No.12, pp. 1062-1068, (December 2004). ISSN 1018-4813
- Onouchi, Y.; Tamari, M.; Takahashi, A.; Tsunoda, T.; Yashiro, M.; Nakamura, Y.; Yanagawa, H.; Wakui, K.; Fukushima, Y.; Kawasaki, T.; Nakamura, Y. & Hata, A. (2007). A genomewide linkage analysis of Kawasaki disease: evidence for linkage to chromosome 12. *Journal of Human Genetics*, Vol.52, No.2, pp. 179-190, (February 2007), ISSN 1434-5161
- Onouchi, Y.; Gunji, T.; Burns, JC.; Shimizu, C.; Newburger, JW.; Yashiro, M.; Nakamura, Y.; Wakui, K.; Fukushima, Y.; Kishi, F.; Hamamoto, K.; Terai, M.; Sato, Y.; Ouchi, K.; Saji, T.; Nariai, A.; Kaburagi, Y.; Yoshikawa, T.; Suzuki, K.; Tanaka, T.; Nagai, T.; Cho, H.; Fujino, A.; Sekine, A.; Nakamichi, R.; Tsunoda, T.; Kawasaki, T.;

- Nakamura, Y. & Hata, A. (2008). ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. *Nature Genetics*, Vol.40, No.1, pp. 35-42, (January 2008), ISSN 1061-4036
- Onouchi, Y.; Ozaki, K.; Burns, JC.; Shimizu, C.; Hamada, H.; Honda, T.; Terai, M.; Honda, A.; Takeuchi, T.; Shibuta, S.; Suenaga, T.; Suzuki, H.; Higashi, K.; Yasukawa, K.; Suzuki, Y.; Sasago, K.; Kemmotsu, Y.; Takatsuki, S.; Saji, T.; Yoshikawa, T.; Nagai, T.; Hamamoto, K.; Kishi, F.; Ouchi, K.; Sato, Y.; Newburger, JW.; Baker, AL.; Shulman, ST.; Rowley, AH.; Yashiro, M.; Nakamura, Y.; Wakui, K.; Fukushima, Y.; Fujino, A.; Tsunoda, T.; Kawasaki, T.; Hata, A.; Nakamura, Y. & Tanaka, T. (2010). Common variants in CASP3 confer susceptibility to Kawasaki disease. *Human Molecular Genetics*, Vol.19, No.14, pp. 2898-2906, (July 2010), ISSN 0964-6906
- Onouchi, Z & Kawasaki, T. (1999). Overview of pharmacological treatment of Kawasaki disease. *Drugs*, vol.58, No.5, pp. 813-822, (November 1999). ISSN 0012-6667
- Ouchi, K.; Suzuki, Y.; Shirakawa, T. & Kishi, F. (2003). Polymorphism of SLC11A1 (formerly NRAMP1) gene confers susceptibility to Kawasaki disease. *The Journal of Infectious Diseases*, Vol.187, No.2, pp. 326-329, (January 2003). ISSN 0022-1899
- Park, JA.; Shin, KS. & Kim, YW. (2005). Polymorphism of matrix metalloproteinase-3 promoter gene as a risk factor for coronary artery lesions in Kawasaki disease. *Journal of Korean Medical Science*, Vol.20, No.4, pp. 607-611, (August 2005). ISSN 1011-8934
- Park, SW.; Ban, JY.; Yoon, KL.; Kim, HJ.; Chung, JY.; Yi, JW.; Lee, BJ. & Chung, JH. (2010). Involvement of tryptophan hydroxylase 2 (TPH2) gene polymorphisms in susceptibility to coronary artery lesions in Korean children with Kawasaki disease. *European Journal of Pediatrics*, Vol.169, No.4, pp. 457-461, (April 2010). ISSN 0340-6199
- Park, YW.; Han, JW.; Hong, YM.; Ma, JS.; Cha, SH.; Kwon, TC.; Lee, SB.; Kim, CH.; Lee, JS.; & Kim, CH. (2011). Epidemiological features of Kawasaki disease in Korea, 2006-2008. *Pediatrics International*, Vol.53, No.1, pp. 36-39, (February 2011), ISSN 1328-8067
- Quasney, MW.; Bronstein, DE.; Cantor, RM.; Zhang, Q.; Stroupe, C.; Shike, H.; Bastian, JF.; Matsubara, T.; Fujiwara, M.; Akimoto, K.; Newburger, JW. & Burns, JC. (2001). Increased frequency of alleles associated with elevated tumor necrosis factor-alpha levels in children with Kawasaki disease. *Pediatric Research*, Vol.49, No.5, pp. 686-690, (May 2001). ISSN 0031-3998
- Sheu, JJ.; Lin, YJ.; Chang, JS.; Wan, L.; Chen, SY.; Huang, YC.; Chan, C.; Chiu, IW. & Tsai FJ. (2010). Association of COL11A2 polymorphism with susceptibility to Kawasaki disease and development of coronary artery lesions. *International Journal of Immunogenetics*, Vol.37, No.6, pp. 487-492, (December 2010). ISSN 1744-3121
- Shim, YH.; Kim, HS.; Sohn, S. & Hong, YM. (2006). Insertion/deletion polymorphism of angiotensin converting enzyme gene in Kawasaki disease. *Journal of Korean Medical Science*, Vol.21, No.2, pp. 208-211, (April 2006). ISSN 1011-8934
- Shimizu, C.; Jain, S.; Davila, S.; Hibberd, ML.; Lin, KO.; Molkara, D.; Frazer, JR.; Sun, S.; Baker, AL.; Newburger, JW.; Rowley, AH.; Shulman, ST.; Davila, S.; Burgner, D.; Breunis, WB.; Kuijpers, TW.; Wright, VJ.; Levin, M.; Eleftherohorinou, H.; Coin, L;

- Popper, SJ.; Relman, DA.; Fury, W.; Lin, C.; Mellis, S.; Tremoulet, AH. & Burns JC. (2011). Transforming growth factor-beta signaling pathway in patients with Kawasaki disease. *Circulation: Cardiovascular Genetics*, Vol.4, No.1, pp. 16-25, (February 2011). ISSN 1942-325X
- Simonini, G.; Corinaldesi, E.; Massai, C.; Falcini, F.; Fanti, F.; De Martino, M. & Cimaz, R. (2009). Macrophage migration inhibitory factor -173 polymorphism and risk of coronary alterations in children with Kawasaki disease. *Clinical & Experimental Rheumatology*, Vol.27, No. 6, pp. 1026-1030, (2009 November-December). ISSN 0392-856X
- Sohn, MH.; Hur, MW. & Kim DS. (2001). Interleukin 6 gene promoter polymorphism is not associated with Kawasaki disease. *Genes & Immunity*, Vol.2, No.7, pp. 357-362, (October 2001). ISSN 1466-4879
- Takeuchi, K.; Yamamoto, K.; Kataoka, S.; Kakiyama, T.; Tanaka, A.; Sato, S. & Uchiyama, M. (1997). High incidence of angiotensin I converting enzyme genotype II in Kawasaki disease patients with coronary aneurysm. *European Journal of Pediatrics*, Vol.156, No.4, pp. 266-268, (April 1997). ISSN 0340-6199
- Taniuchi, S.; Masuda, M.; Teraguchi, M.; Ikemoto, Y.; Komiyama, Y.; Takahashi, H.; Kino, M. & Kobayashi, Y. (2005). Polymorphism of Fc gamma RIIa may affect the efficacy of gamma-globulin therapy in Kawasaki disease. *Journal of Clinical Immunology*, Vol.25, No.4, pp. 309-313, (July 2005). ISSN 0271-9142
- Tsai, FJ.; Lee, YC.; Chang, JS.; Huang, LM.; Huang, FY.; Chiu, NC.; Chen, MR.; Chi, H.; Lee, YJ.; Chang, LC.; Liu, YM.; Wang, HH.; Chen, CH.; Chen, YT. & Wu, JY. (2011). Identification of novel susceptibility Loci for Kawasaki disease in a Han Chinese population by a genome-wide association study. *PLoS One*. Vol.6, No.2, pp. e16853, (February 2011). ISSN 1817-101X
- Tsukahara, H.; Hiraoka, M.; Saito, M.; Nishida, K.; Kobata, R.; Tsuchida, S.; Toyooka, M.; Kimura, H.; Gejyo, F. & Mayumi, M. (2000). Methylenetetrahydrofolate reductase polymorphism in Kawasaki disease. *Pediatrics International*, Vol.42, No.3, pp. 236-240, (June 2000). ISSN 1328-8067
- Uehara, R.; Yashiro, M.; Nakamura, Y. & Yanagawa, H. (2003). Kawasaki disease in parents and children. *Acta Paediatrica*, Vol.92, No. 6, pp. 694-697, (June 2003). ISSN 0803-5253
- Wang, GB.; Li, CR.; Yang, J.; Wen, PQ. & Jia, SL. (2011). A regulatory polymorphism in promoter region of TNFR1 gene is associated with Kawasaki disease in Chinese individuals. *Human Immunology*, Vol.72, No.5, pp. 451-457, (May 2011). ISSN 0198-8859
- Weng, KP.; Hsieh, KS.; Hwang, YT.; Huang, SH.; Lai, TJ.; Yuh, YS.; Hou, YY.; Lin, CC.; Huang, SC.; Chang, CK.; Lin, MW. & Ger, LP. (2010). IL-10 polymorphisms are associated with coronary artery lesions in acute stage of Kawasaki disease. *Circulation Journal*, Vol.74, No.5, pp. 983-989, (May 2010). ISSN 1346-9843
- Weng, KP.; Ho, TY.; Chiao, YH.; Cheng, JT.; Hsieh, KS.; Huang, SH.; Ou, SF.; Liu, KH.; Hsu, CJ.; Lu, PJ.; Hsiao, M. & Ger LP. (2010). Cytokine genetic polymorphisms and susceptibility to Kawasaki disease in Taiwanese children. *Circulation Journal*, Vol.74, No.12, pp. 2726-2733, (November 2010). ISSN 1346-9843

- Woo, M.; Hakem, R.; Soengas, MS.; Duncan, GS.; Shahinian, A.; Kägi, D.; Hakem, A.; McCurrach, M.; Khoo, W.; Kaufman, SA.; Senaldi, G.; Howard, T.; Lowe, SW & Mak, TW. (1998). Essential contribution of caspase 3/CPP32 to apoptosis and its associated nuclear changes. *Genes & Development* Vol.12, No.6, pp. 806-819, (March 1998). ISSN 0890-9369
- Wu, SF.; Chang, JS.; Peng, CT.; Shi, YR. & Tsai FJ. (2004). Polymorphism of angiotensin-1 converting enzyme gene and Kawasaki disease. *Pediatric Cardiology*, Vol.25, No.5, pp. 529-533, (September-October 2004). ISSN 0172-0643
- Wu, SF.; Chang, JS.; Wan, L.; Tsai, CH. & Tsai, FJ. (2005). Association of IL-1Ra gene polymorphism.; but no association of IL-1beta and IL-4 gene polymorphisms.; with Kawasaki disease. *Journal of Clinical Laboratory Analysis*, Vol.19, No.3, pp. 99-102, (n.d. 2005). ISSN 0887-8013
- Wu, W., Misra, R.S., Russell, J.Q., Flavell, R.A., Rinco'n, M. & Budd, R.C. (2006) Proteolytic regulation of nuclear factor of activated T (NFAT) c2 cells and NFAT activity by caspase-3. *The Journal of Biological Chemistry*, Vol.281, No.16, pp. 10682-10690, (April 2006). ISSN 0021-9258
- Yamaguchi, K.; Ikeda, K.; Ihara, K.; Takada, H.; Kusuvara, K. & Hara, T. (2009). Lack of association between E148Q MEFV variant and Kawasaki disease. *Human Immunology*, Vol.70, No.6, pp. 468-471, (January 2009). ISSN 0198-8859

IntechOpen



Advances in the Etiology, Pathogenesis and Pathology of Vasculitis

Edited by Dr. Luis M Amezcua-Guerra

ISBN 978-953-307-651-5

Hard cover, 438 pages

Publisher InTech

Published online 17, October, 2011

Published in print edition October, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Yoshihiro Onouchi and Akira Hata (2011). Responsible Genetic Factors for Vasculitis in Kawasaki Disease, *Advances in the Etiology, Pathogenesis and Pathology of Vasculitis*, Dr. Luis M Amezcua-Guerra (Ed.), ISBN: 978-953-307-651-5, InTech, Available from: <http://www.intechopen.com/books/advances-in-the-etiology-pathogenesis-and-pathology-of-vasculitis/responsible-genetic-factors-for-vasculitis-in-kawasaki-disease>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen