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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.](www.intechopen.com)

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           |            |                           |                    |
| HLA-B | B75           | Genotyping | Korean (74/159)           | Oh et al., 2008    |
| HLA-C | Cw09          | Genotyping |                           |                    |
| HLA-DRB3 | DRB3*0301     | Genotyping | Caucasian (21/200)       | Barron et al., 1992 |
| HLA-G | rs12722477 A  | Genotyping | Korean (308/90)          | J.J. Kim et al., 2008 |
|       | C/A alleles   |            |                           |                    |
| HLA-E | rs2844724 C   | Genotyping | Taiwanese (680/3312)     | Y.J. Lin et al., 2009 |
|       | T alleles     |            |                           |                    |

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                        |
|-----------------|--------------------|----------------------------------|
| **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               | Wen 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             |
|                 |                    | Wen 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               | S.F. Wu et al., 2005             |
|                 |                    | F.Y. Huang et al., 2008a         |
|                 |                    | Weng et al., 2010b               |
| CCR5            | 3p21               | Burns et al., 2005               |
|                 |                    | Jhang et al., 2009               |
|                 |                    | Brennys et al., 2007             |
|                 |                    | Mamtani et al., 2010             |
|                 |                    | Chaudhuri et al., 2011           |
| IL-8            | 4q13-q21           | Quasney et al., 2001             |
| IL-4            | 5q31.1             | Burns et al., 2005               |
| LTA             | 6p21.3             | Cheung et al., 2008              |
|                 |                    | Kamizono et al., 1999            |
|                 |                    | Quasney et al., 2001             |
|                 |                    | Ahn et al., 2003                 |
|                 |                    | Chien et al., 2003               |
|                 |                    | Wen et al., 2010b                |
| IL-6            | 7p21               | S.F. Wu et al., 2005             |
|                 |                    | F.Y. Huang et al., 2008a         |
|                 |                    | Wen 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             |
### 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                          | Phenotype | Reference                          |
|--------|-----------|------------------------------------|-----------|------------------------------------|
| **MTHFR** | CAL       | Tsukahara et al., 2000           | **CRP**   | CAL                                |
|        |           |                                    |           | Intima-media thickness             |
|        |           |                                    |           | Cheung et al., 2008                |
|        |           |                                    |           | Arterial stiffness                 |
|        |           |                                    |           | Cheung et al., 2008                |
| **IL-10** | CAL       | Jin et al., 2007                  | **IL-10** | Serum albumin                      |
|        |           |                                    |           | Jin et al., 2007                   |
|        |           |                                    |           |                                    |
| **FCGR2A** | CAL       | Taniuchi et al., 2005            | **FCGR2B** | CAL                              |
|        |           |                                    |           |                                    |
| **FCGR3A** | CAL       | Taniuchi et al., 2005            | **FCGR3B** | CAL                             |
|        |           |                                    |           | Taniuchi et al., 2005              |
|        |           |                                    |           | Biezeveld et al., 2007             |
| **TGFB2** | CAL       | Shimizu et al., 2011             | **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       |                                    | **IL-1β** | Response to IVIG                  |
|        |           |                                    |           | Weng et al., 2010                  |
|        |           |                                    |           | S.K. Kim et al., 2011             |
| **IL-1Ra** | CAL       |                                    | **IL-1Ra** | CAL                         |
|        |           |                                    |           |                                    |
| **AGTR1** | Coronary stenosis | Fukazawa et al., 2004 | **VEGFR2** | CAL                                |
|        |           |                                    |           | Kariyazono et al., 2003            |
| **IL-4** | CAL       |                                    | **IL-4**  | CAL                               |
|        |           |                                    |           | Kariyazono et al., 2003            |
| **CD14** | CAL       | Nishimura et al., 2003            | **VEGFA** | CAL                                |
|        |           |                                    |           | Kariyazono et al., 2003            |
| **MICA** | CAL       | F.Y. Huang et al., 2000           | **LT**    | CAL                               |
|        |           |                                    |           | Quasney et al., 2001              |
| **TNF-α** | CAL       | Quasney et al., 2001             | **TNF-α** | CAL                             |
|        |           |                                    |           | Cheung et al., 2008               |
|        |           |                                    |           |                                    |
| Gene | Function | Reference |
|------|----------|-----------|
| BAT2, 3, 5 | Arterial stiffness | Cheung et al., 2008 |
| NOTCH4 | | Hsieh et al., 2010 |
| BTNL2 | | Hsueh et al., 2010 |
| COL11A2 | | Shue et al., 2010 |
| ITPR3 | | Y.C. Huang et al., 2010 |
| CRP | | Y.C. Huang et al., 2010 |
| PAFAH | Response to IVIG | Minami et al., 2005 |
| eNOS | Arterial stiffness | Khajoee et al., 2003 |
| MBL | | Biezeveld et al., 2003 |
| MMP26 | | Ban et al., 2010 |
| IL-18 | | Hsueh et al., 2008a |
| MMP7 | | Ban et al., 2010 |
| MMP3 | | J.A. Park et al., 2005 |
| MMP12 | | Ikeda et al., 2008 |
| MMP13 | | Ikeda et al., 2008 |
| TPH2 | | Ikeda et al., 2008 |
| SMAD3 | | S.W. Park et al., 2010 |
| MEFV | Response to IVIG | Yamaguchi et al., 2009 |
| MMP2 | | Ikeda et al., 2008 |
| iNOS | | Khajoee et al., 2003 |
| CCL3L1 | Response to IVIG | Mamtani et al., 2010 |
| CCL% | | Chaundhuri et al., 2011 |
| ACE | Coronary stenosis | Fukazawa et al., 2004 |
| TIMP2 | | Furuno et al., 2007 |
| MMP9 | | J.A. Park et al., 2005 |
| MIF | | Simonini et al., 2009 |
| MMP11 | | Ban et al., 2010 |
| CD40L | | Y. Onouchi et al., 2004 |

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.](image)

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 | Japanese Case-control study | USA TDT |
|---------|-----------------------------|---------|
|         | Risk allele frequency       | OR (95% CI)² | No. of families | T:U³ | OR (95% CI)² | P value |
| KD n=637 | Control n=1034              | P value² |                |       | P value |
| G/C     | 0.23                        | 0.15     | 1.89 (1.53 – 2.33) | 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.](image)

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 | Japanese case-control study | United States TDT |
|---------|----------------------------|-------------------|
|         | Risk allele frequency                   | P value^2 | No. of families | T:U^3 | OR (95% CI) |
|         | KD n=920 | Control n=1,409 | OR (95% CI) | |
| G/A     | 0.45     | 0.37            | 1.40 (1.24−1.57) | 249  | 1.54 (1.16−2.05) |
|         |          |                 | 4.2 × 10^{-6}   |      | 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 | No. of SNPs | Reference |
|--------------|--------------------|-------------|-----------|
|              | GWAS               | Follow-up   |           |
| Caucasian    | 119/135            | 583/1357    | 223,922   | Burgner et al., 2009 |
| Korean       | 186/600            | 266/600     | 641,760   | J.J. Kim et al., 2011 |
| Korean       | 63/600             | 86/600      | 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). *583 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  | \(1.5 \times 10^{-6}\) | DAB1                  | J.J. Kim et al., 2011 |
| rs952354     | 1   | 63,549,282  | \(3.1 \times 10^{-5}\) | -                     | J.J. Kim et al., 2011 |
| rs7604693    | 2   | 64,349,202  | \(2.0 \times 10^{-6}\) | PELI1*               | J.J. Kim et al., 2011 |
| rs10183521   | 2   | 123,762,542 | \(9.5 \times 10^{-5}\) | -                     | J.J. Kim et al., 2011 |
| rs16849083   | 3   | 139,184,279 | \(2.2 \times 10^{-5}\) | MRPS22, COPB2, RBP2  | Tsai et al., 2011    |
| rs9834548    | 3   | 165,139,947 | \(9.8 \times 10^{-6}\) | -                     | Burgner et al., 2009 |
| rs17531088   | 3   | 174,893,775 | \(1.1 \times 10^{-6}\) | NAALADL2             | Burgner et al., 2009 |
| rs3773986    | 3   | 190,278,915 | \(6.2 \times 10^{-5}\) | IL1RAP*              | J.J. Kim et al., 2011 |
| rs4864471    | 4   | 54,426,184  | \(3.4 \times 10^{-5}\) | -                     | Burgner et al., 2009 |
| rs13128867   | 4   | 138,840,995 | \(2.2 \times 10^{-5}\) | SLC7A11              | Tsai et al., 2011    |
| rs149481     | 5   | 96,114,346  | \(4.6 \times 10^{-5}\) | ERAP1                | Tsai et al., 2011    |
| rs9392158    | 6   | 7,427,350   | \(8.5 \times 10^{-5}\) | RIOK1                | Burgner et al., 2009 |
| rs9364166    | 6   | 72,106,622  | \(9.8 \times 10^{-5}\) | OGFRL1, C6orf155     | J.J. Kim et al., 2011 |
| rs362794     | 7   | 103,201,263 | \(3.0 \times 10^{-5}\) | RELN                 | Tsai et al., 2011    |
| rs6469101    | 8   | 108,252,238 | \(5.4 \times 10^{-5}\) | ANGPT1               | Burgner et al., 2009 |
| rs328879     | 9   | 107,789,252 | \(1.2 \times 10^{-5}\) | -                     | Burgner et al., 2009 |
| rs10984642   | 9   | 122,450,340 | \(2.6 \times 10^{-5}\) | -                     | Burgner et al., 2009 |
| rs10984642   | 9   | 122,450,340 | \(5.8 \times 10^{-5}\) | -                     | Burgner et al., 2009 |
| rs4918458    | 10  | 111,505,407 | \(9.8 \times 10^{-5}\) | -                     | J.J. Kim et al., 2011 |
| rs285032     | 13  | 98,786,532  | \(1.7 \times 10^{-5}\) | FARPI                | Burgner et al., 2009 |
| rs34246750   | 14  | 52,868,757  | \(4.8 \times 10^{-5}\) | PTGER2, TXNDC16      | J.J. Kim et al., 2011 |
| rs10129255   | 14  | 107,176,213 | \(6.8 \times 10^{-6}\) | IGHV                 | Tsai et al., 2011    |
| rs1568657    | 15  | 83,726,179  | \(6.6 \times 10^{-6}\) | BTBD1                | Tsai et al., 2011    |
| rs7199343    | 16  | 73,009,024  | \(2.4 \times 10^{-5}\) | ZFHX3                | Burgner et al., 2009 |
| rs8059315    | 16  | 74,506,447  | \(8.5 \times 10^{-5}\) | GLG1                 | Burgner et al., 2009 |
| rs2270133    | 17  | 61,473,325  | \(4.6 \times 10^{-5}\) | 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.

6. References

Ahn, SY.; Jang, GC.; Shin, JS.; Shin, KM. & Kim DS. (2003). Tumor necrosis factor-alpha 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.; Thakkinstian, A.; McEvoy, M. & Attia, J. (2010). A systematic review and meta-analysis of tumor necrosis factor a-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, J.; 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. (2007). 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. (2006). 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.; Binepal, 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.; Khajoeve, 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 Hawai‘i. *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

Hsueh, 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. *Human Molecular Genetics*, Vol.19, No.11, pp. 2165-2173, (May 2010). ISSN 1362-3018

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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, CH.; 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 0198-8859

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.; 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, HC.; Chiu, NC.; Hsu, CH.; 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 0179-0338

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.; Khajoeve, 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

Khajoe, 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, JI.; 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.; Zaitsu, 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, J.C.; 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.; Kenmotsu, Y.; Takatsuki, S.; Saji, T.; Yoshikawa, T.; Nagai, T.; Hamamoto, K.; Kishi, F.; Ouchi, K.; Sato, Y.; Newburger, J.W.; Baker, A.L.; Shulman, S.T.; Rowley, A.H.; 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, J.A.; Shin, K.S. & Kim, Y.W. (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, S.W.; Ban, J.Y.; Yoon, K.L.; Kim, H.J.; Chung, J.Y.; Yi, J.W.; Lee, B.J. & Chung, J.H. (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, Y.W.; Han, J.W.; Hong, Y.M.; Ma, J.S.; Cha, S.H.; Kwon, T.C.; Lee, S.B.; Kim, C.H.; Lee, J.S.; & Kim, C.H. (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, M.W.; Bronstein, D.E.; Cantor, R.M.; Zhang, Q.; Stroupe, C.; Shike, H.; Bastian, J.F.; Matsubara, T.; Fujiwara, M.; Akimoto, K.; Newburger, J.W. & Burns, J.C. (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, J.J.; Lin, Y.J.; Chang, J.S.; Wan, L.; Chen, S.Y.; Huang, Y.C.; Chan, C.; Chiu, I.W. & Tsai F.J. (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, Y.H.; Kim, H.S.; Sohn, S. & Hong, Y.M. (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, M.L.; Lin, K.O.; Molkara, D.; Frazer, J.R.; Sun, S.; Baker, A.L.; Newburger, J.W.; Rowley, A.H.; Shulman, S.T.; Davila, S.; Burgner, D.; Breunis, W.B.; Kuijpers, T.W.; Wright, V.J.; Levin, M.; Eleftherohorinou, H.; Coin, L.;
Responsible Genetic Factors for Vasculitis in Kawasaki Disease

91

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.; Kakihara, 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). Methylene tetrahydrofolate 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 TNFRI 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.; Kusuhara, 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
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