Review

Genetic polymorphisms in Kawasaki disease

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Kawasaki disease (KD) is an acute febrile systemic vasculitis, and the cause of KD is not well understood. It is likely due to multiple interactions between genes and environmental factors. The development of genetic association and genome-wide association studies (GWAS) has opened an avenue to better understanding the molecular mechanisms underlying KD. A novel ITPKC signaling pathway was recently found to be responsible for the susceptibility to KD. Furthermore, the GWAS demonstrated the functionally related susceptibility loci for KD in the Caucasian population. In the last decade, the identification of several genomic regions linked to the pathogenesis of KD has made a major breakthrough in understanding the genetics of KD. This review will focus on genetic polymorphisms associated with KD and describe some of the possible clinical implications and molecular mechanisms that can be used to explain how genetic variants regulate the pathogenesis in KD.

Keywords: Kawasaki disease; coronary artery lesions; intravenous immunoglobulin; genetics; SNP

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Introduction

Kawasaki disease (KD) is an acute, febrile systemic vasculitis that was first described by Kawasaki et al [1]. In developed countries, it is the leading cause of acquired heart diseases in children, though its etiology remains unknown [2–5]. KD occurs worldwide, most commonly in Asian countries, and mainly affects children less than 5 years of age. Japan, Korea, and Taiwan region have the highest incidence of KD ranging from 69 to 213 cases per 100 000 children under 5 years of age [6–8]. The incidence of KD has been increasing globally in recent years. The most serious complications of KD are coronary artery lesions (CAL), including myocardial infarction, coronary artery fistula formation [9], coronary artery dilatation/ectasia and coronary artery aneurysm [10].

The clinical characteristics of KD patients include prolonged fever longer than five days, diffuse mucosal inflammation, bilateral non-purulent conjunctivitis, dysmorphous skin rashes, indurative angioedema over the hands and feet, and cervical lymphadenopathy. In addition to the diagnostic criteria, there is a broad range of non-specific clinical features, including irritability, uveitis, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gallbladder hydrops, urethritis, arthralgia, arthritis, hypoalbuminemia [11], liver function impairment and heart failure [4, 11]. Although the clinical features of KD are recognizable, the immuno-pathogenetic mechanism of this disease is still unclear, particularly the causative agent for CAL formation. Transforming growth factor-beta (TGF-β) is a candidate gene for KD pathogenesis because TGF-β-mediated T-cell activation and cardiovascular remodeling are regarded as important features of KD. Indeed, genetic polymorphisms of the TGF-β pathway, including TGBF2, TGBFR2, and SMAD3, are associated with susceptibility to KD and development of CAL in the European and US populations [12]. In the Asian population, we reported that monocytosis, eosinophilia, and eosinophil-related Th2 immune response (especially, plasma level of IL-5) are associated with CAL formation and/or initial intravenous immunoglobulin (IVIG) treatment response [13–16]. Immune-related genes, such as CTLA-4, CASP3 and ITPKC, have also been suggested to influence the susceptibility to and the clinical status of KD [14, 15, 17–21].

The efficacy of IVIG administered during the acute phase of KD to reduce the prevalence of coronary artery abnormalities has been well established [22]. However, the mechanism of action of IVIG is still elusive. IVIG appears to have a generalized anti-inflammatory effect. Possible mechanisms of IVIG include the modulation of cytokine production, neutralization of bacterial super-antigens, suppression of antibody synthesis and inflammatory markers (CD40L, nitric oxide and iNOS expression) [23, 24], and provision of anti-idiotypic
The role of genetic polymorphisms in immune-related genes in the susceptibility to Kawasaki disease

The higher incidence of KD in Asia, in conjunction with a higher incidence of the disease in Asian descendants compared with other ethnic populations in the United States and Europe, suggests that a genetic predisposition might play an important role in the susceptibility to this disease[3, 4, 7, 10, 25–27]. There is also evidence that the incidence of KD is higher among siblings than in the general population[28]. Additionally, KD has a higher incidence rate among males than in females[3, 19]. Further evidence supports the hypothesis that genetic factors contribute to the susceptibility to KD[17]. For example, a number of genes have been reported to have significant associations with the susceptibility to KD in different populations. For instance, single nucleotide polymorphisms (SNPs) in the monocyte chemoattractant protein 1 (MCP-1)[30], IL-10[30–33], CD40L[33], IL-4[34], CASP3[20, 35], IL-1β[36], HLA-E[37], C-C chemokine receptor 5 (CCR5)[38], and inositol 1, 4, 5-trisphosphate 3-kinase C (ITPKC)[21, 39] have been reported to be associated with the development of KD. In early 2011, Shimizu et al[12] first reported that genetic polymorphisms of TGFB2, TGFB2R, and SMAD3 are associated with susceptibility to Kawasaki disease and the development of coronary artery lesions. Taken together, these findings suggest that multiple polymorphic alleles influence KD susceptibility and that different ethnic populations, which have distinct allelic expression patterns, and different sexes may have different susceptibilities to KD[3]. Interestingly, there are some genes associated with susceptibility to KD, but not CAL formation. We hypothesize that the genes responsible for susceptibility and CAL formation may be distinct[20, 39, 40].

Association between the genetic polymorphisms and CAL formation in KD

All KD patients were treated with IVIG, 2 g/kg in a single infusion for 12 h, together with aspirin[22]. This therapy was within 10 d of illness and, if possible, within 7 d of illness. From a serial analysis of coronary artery lesions (n=341) in Chang Gung Memorial Hospital-Kaohsiung[20], 35% of KD patients had dilatation during the acute phase, 17.2% had dilatation one month after disease onset, 10.2% still had dilatation at two months of follow-up, and 4% had persistent CAL for more than one year[49].

The most commonly used definition of CAL (also known as coronary artery abnormality, CAA or CALs) is based on the Japanese Ministry of Health criteria: maximum absolute internal diameter ≥5 mm in children younger than 5 years of age or >4 mm in children 5 years and older, or a segment 1.5 times larger than an adjacent segment, or the presence of luminal irregularity[41–43]. If the body surface area is known, then coronary arteries are normalized to this surface area and expressed as standard deviation units from the mean (Z scores)[44]. Several studies have analyzed CAL using other methods, including the aorta route dimension[12] and transient CAL (although the definition of “transient” varies among studies, from 30 d to 6–8 weeks after disease). Interestingly, some results have indicated that the genetic association was observed only with susceptibility, not with CAL formation. However, other studies have revealed inconsistent results (Table 1)[45–57]. These results indicate that the genes responsible for susceptibility and CAL formation may be different between populations[17, 32, 37, 38, 58–60].

| Gene                                           | Abbreviation | Locus     | Phenotypes               | Reference        |
|------------------------------------------------|--------------|-----------|--------------------------|------------------|
| C-reactive protein                             | CRP          | 1q21-q23  | Susceptibility           | Cheung[55]       |
| Tissue inhibitor of metalloproteinase 4        | TIMP4        | 3p25      | CAL                      | Ban[60]          |
| C-C chemokine receptor 5                      | CCR5         | 3p21      | Susceptibility           | Jhang[38]        |
| Angiotensin-II type-1 receptor                 | AGTR1        | 3q21-q25  | CAL                      | Kariyazono[46]   |
| Vascular endothelial growth factor receptor 2  | VEGFR2       | 4q12      | Susceptibility           | Burns[26]        |
| Interleukin-4                                  | IL-4         | 5q31.1    | CAL                      | Kariyazono[46]   |
| CD14 antigen                                   | CD14         | 5q31.1    | Susceptibility           | Nishimura[47]    |
| Vascular endothelial growth factor A           | VEGFA        | 6p12      | Susceptibility           | Hsueh[48]        |
| Lymphotixin-alpha                              | LTA          | 6p21.3    | Susceptibility           | Kariyazono[46]   |
| Tumor necrosis factor-alpha                    | TNF-α        | 6p21.3    | CAL                      | Quasney[49]      |
| Interleukin-18                                 | IL-18        | 11q22.3-q22.3 | Susceptibility       | Hsueh[51]        |
| Matrix metalloproteinase-3                    | MMP3         | 11q22.3   | CAL                      | Park[52]         |
| Matrix metalloproteinase-13                    | MMP13        | 11q22.3   | Susceptibility           | Ikeda[33]        |
| Angiotensin-1 converting enzyme                | ACE          | 17q23     | Susceptibility           | Wu[44]           |
| Tissue inhibitor of metalloproteinase 2        | TIMP2        | 17q25     | CAL                      | Fukazawa[45]     |
| Macrophage migration inhibitory factor         | MIF          | 22q11.2   | CAL                      | Furuno[56]       |
| CD40 ligand                                    | CD40L        | Xq26      | CAL                      | Onouchi[38]      |
the susceptibility to KD or the formation of CAL in different populations. Although there is evidence to support a role for each candidate gene in the susceptibility to KD and/or development of CAL, there is also evidence that cannot be easily fitted into any (Table 2). Most studies addressing this question are plagued with inconsistencies. First, the sample size varies dramatically across studies. Hence, a small sample size may not have sufficient power to detect minor genetic effects. Second, it is becoming clear that there are different genetic backgrounds within populations that due to variations in allele frequencies or heterogeneity of the phenotype, may also influence the results. Third, the incidence of KD in Asia is much higher than in other places. Thus, the role of environmental factors or infectious agents in the development of KD should also be considered.

**Genetic polymorphisms of the ITPKC signaling pathway in patients with Kawasaki disease**

A major advancement in the genetic study of KD was provided by the discovery of ITPKC. ITPKC is an important molecule in the regulation of T cell activation, and it may function as a calcium channel modulator. In 2008, Onouchi and colleagues first identified the functional polymorphism of ITPKC (rs28493229) that is significantly associated with the susceptibility to KD and coronary artery lesions in both Japanese and US children. Using cell-based functional studies, Onouchi et al. further indicated that the risk allele (C allele) of ITPKC reduces the splicing efficiency of the ITPKC mRNA that, in turn, may contribute to the hyperactivation of Ca\(^{2+}\)-dependent NFAT signaling pathways in T cells. The identification of ITPKC has had an enormous effect on the field of genetic association studies of KD. These novel insights into genetic mechanisms clearly provide a new understanding of the pathogenesis of KD. In contrast, the results obtained from the replication studies in the Taiwanese populations are strikingly controversial.

**Controversial genetic effects on the susceptibility to KD or CAL formation between populations.**

| Gene                                      | Abbreviation | Locus | Phenotypes     | Reference          |
|-------------------------------------------|--------------|-------|----------------|--------------------|
| Fc gamma receptor, low affinity IIa receptor | FCGR2A       | 1q23  | Susceptibility | Taniuchi et al. [75]|
| Fc gamma receptor, low affinity IIa receptor | FCGR3A       | 1q23  | Susceptibility | Biezevel et al. [76]|
| Interleukin-10                             | IL-10        | 1q31-q32 | Susceptibility | Hsu et al. [77] |
| Tumor necrosis factor-alpha               | TNF-alpha    | 6p21.3 | CAL            | Jin et al. [78] |
| CD40 ligand                               | CD40L        | Xq26  | CAL            | Cheung et al. [79]|

**ITPKC is involved in the Ca\(^{2+}\)-dependent NFAT signaling pathways in T cells.** In the non-excitable cells, such as T cells and mast cells, one of the main pathways to increase the intracellular Ca\(^{2+}\) concentration is through store-operated calcium channels (SOC). The activation of store-operated calcium channels can be controlled by the expression level of IP\(_3\), IP\(_3\) binds to its receptor (IP\(_3\)-R) on the endoplasmic reticulum (also called the calcium store) causing the release of calcium from stores. An empty store results in the activation of both store-operated calcium channels and Ca\(^{2+}\)-dependent signaling pathways, including inflammatory reactions and apoptosis. Onouchi et al. reported that a G to A substitution in the 5'-untranslated region of CASP3 (rs72689236) is associated with susceptibility to Kawasaki disease in Japanese and in Americans of European descent. The CASP3 is replicated in the KD patients in the Taiwanese population. Kuo et al. provided further evidence that the A allele of rs72689236 is very likely to be a risk allele in the development of aneurysms in patients with KD.

Another important molecule in the ITPKC signaling pathway is ORAI1 (also known as CRACM1). ORAI1 was identified by Feske et al. in 2006. Modified linkage analysis completed on data generated by single-nucleotide polymorphism arrays and an RNA interference screen led to an important finding. A single missense mutation in ORAI1 was found in patients with severe combined immune deficiency (SCID) syndrome. Furthermore, this mutation in ORAI1 has been shown to cause dysfunctions in Ca\(^{2+}\) release-activated Ca\(^{2+}\) (CRAC) channels and impairs the immune system. In 2011, a genetic polymorphism of ORAI1 was reported to be associated with the risk and recurrence of calcium nephrolithiasis. In the study of Kawasaki disease, no significant association between genotype and allele frequency of the five
GWAS results from a Taiwanese population suggest another locus in the 2p13.3 region was confirmed to be involved in the development of Cornelia de Lange syndrome. In 2010, another GWAS was conducted by Kim et al in a Korean population. A total of 786 subjects (186 KD patients and 600 controls) were recruited. A locus in the 1p31 region was identified as a susceptibility locus for KD. Further, the results of the GWAS from independent groups support the hypothesis that susceptibility loci for KD and CAL formation can be distinct between different ethnic populations.

Figure 1. Model depicting the cellular pathways of ITPKC in T cells.

Genome-wide association study (GWAS) in Kawasaki disease

In 2009, Burgner et al firstly performed a genome-wide association study (GWAS) on 119 Caucasian KD cases and 135 matched controls. Forty SNPs and six haplotypes were confirmed in an independent cohort of KD families. This insightful work led to the identification of a SNP within the N-acetylated alpha-linked acidic dipeptidase-like 2 gene (NAALADL2; rs17531088), which was significantly associated with the susceptibility to KD. Although the function of NAALADL2 remains unclear, mutations in the gene may be involved in the development of Cornelia de Lange syndrome. In 2010, another GWAS was conducted by Kim et al in a Korean population. A total of 786 subjects (186 KD patients and 600 controls) were recruited. A locus in the 1p31 region was identified as a susceptibility locus for KD. Furthermore, the PELI1 gene locus in the 2p13.3 region was confirmed to associate with the development of CAL in KD patients. GWAS results from a Taiwanese population suggest another three novel susceptibility loci for KD. However, the susceptibility loci reported by Kim et al in the Korean population cannot be replicated in a Taiwanese or Caucasian population.

Hence, the results of the GWAS from independent groups support the hypothesis that susceptibility loci for KD and CAL formation can be distinct between different ethnic populations.

Conclusion

Several major advances have been made in understanding the genetic effects of the susceptibility and clinical status of KD over the past decade. Very recently, genome-wide association has led two groups to identify novel susceptibility loci as being important for KD in the Asian population. Although the exact genes in the loci are still unclear at present, these loci could provide a new direction for future studies. Now that the sequencing of the human genome is complete and advanced genotyping tools are readily available to help identify candidate genes, we can expect to see more insightful researches begin to elucidate the genes responsible for KD susceptibility.

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