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Review

# Kawasaki disease: An evolving paradigm

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ABSTRACT

Kawasaki disease (KD) is a self-limited childhood systemic vasculitis that exhibits a specific predilection for the coronary arteries. KD predominantly affects young children between the ages of 6 months and 4 years. Incidence rates in Asians are up to 20 times higher than Caucasians.
The aetiology of KD is not known. One reasonable open hypothesis is that KD is caused by an infectious agent that produces an autoimmune disease only in genetically predisposed individuals.
The typical presentation of KD is a young child who has exhibited a high swinging fever for five or more days that persists despite antibiotic and/or antipyretic treatment. The lips are dry and cracked. There is a characteristic strawberry tongue, and a diffuse erythema of oropharyngeal mucosal surfaces. Lymphadenopathy is usually unilateral and confined to the anterior cervical triangle. Coronary aneurysms generally appear during the convalescence phase (beginning during the second week).
The absence of any laboratory tests for KD means that the diagnosis is made by the presence of a constellation of clinical features. The aim of echocardiography is to assess the presence of coronary artery dilatation or aneurysm formation.
Effective therapies exist for most patients with acute KD, but the exact mechanisms of action are not clear. Treatment with aspirin and intravenous immunoglobulins (IVIG) are first-line therapies. However, options are plentiful for the children who fail this treatment, but these treatments are not as beneficial. Some centres attempt to salvage resistant patients using intravenous pulsed doses of methylprednisolone. Other centres use infliximab or combinations of these approaches.

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## 1. Introduction

Kawasaki disease (KD) is a self-limited childhood systemic vasculitis of unknown origin characterised by a constellation of clinical signs and symptoms. KD results in coronary artery abnormalities in up to 25% of children if untreated [1].

Dr. Tomisaku Kawasaki first described KD in 1967 in Japan. In his original report, Kawasaki described children with febrile illnesses associated with mucocutaneous involvement that was originally thought to be self-limited and benign [2]. However, KD is now known to be a systemic vasculitis with a specific predilection for the coronary arteries, and it is the most common cause of childhood-acquired heart disease in Western countries. The underlying mechanisms of this enigmatic vasculitis are not fully understood despite ongoing research into its causes and treatment algorithms.

## 2. Epidemiology

KD predominantly affects young children, and 80% of cases occur between the ages of 6 months and 4 years [3,4]. KD, like many childhood infections, exhibits a male predominance (approximately 1.6 times more common).

The incidence of KD varies considerably between ethnic groups. Incidence rates in North East Asians are up to 20 times higher than Caucasians. The highest incidence is reported in Japan (239/100,000 <5 years of age) [5]. The next highest incidence rates are reported in Korea (113.1/100,000 <5 years) [6] and Taiwan (69/100,000 <5 years) [7].

The high incidence in Asian populations is maintained in children who are born and live in low incidence countries, which suggests a genetic predisposition to susceptibility. For example, Japanese Americans in Hawaii have an incidence rate equivalent to Japanese children in Japan whereas European–Caucasian Hawaiians have a rate that is comparable with the overall European–Caucasian US population (13/100,000 <5 years of age) [8].

## 3. Aetiopathogenesis

The aetiology of KD is not known. One reasonable hypothesis is that KD is caused by an infectious agent that produces an autoimmune disease only in genetically predisposed individuals, particularly Asians.

### 3.1. Genetics

The racial predilection of KD to Asian populations suggests a genetic predisposition towards acquiring the disease. Additionally, there is documentation of increased offspring and sibling risk in KD in Japanese populations [9].

Considerable progress has been made in the identification of disease-susceptibility genes since the initiation of genome-wide association studies (GWAS). Table 1 shows candidate KD susceptibility genes that have recently generated interest [10–14]. Two GWAS results were reported independently in 2012 [12,13]. Both studies observed significant associations with KD in the FAM167A-BLK region on chromosome 8p23–p22. B-lymphoid kinase (BLK) is an src family tyrosine kinase that is expressed primarily in B cells, and it is involved in B-cell receptor signal transduction. BLK is also required for the development of interleukin (IL)-17-producing γδ T cells in mice [15]. High levels of IL-17 and increased numbers of activated γδ T cells were reported during the acute phase of KD [16,17]. However, the function of the FAM167A molecule is not clear.

Single-nucleotide polymorphisms (SNPs) around CD40, located on chromosome 20q12–q13.2, were also significantly associated with KD in Japanese and Taiwanese GWAS [12,13]. CD40 is a type I transmembrane protein in the tumour necrosis factor (TNF) receptor superfamily. Its receptor, CD40 ligand (CD40L), is a type II transmembrane protein in the TNF family. Elevated CD40L expression during acute phase KD and significantly higher CD40L expression in KD patients with coronary arterial lesions (CALs) were reported [18]. Therefore, it is likely that CD40L–CD40 signalling plays a facilitating role in KD progression, and it might be an effective target for molecular therapies.

Genome-wide association studies in KD patients of European descent identified a non-synonymous SNP in the FCGR2A gene that influenced susceptibility [19].

Transforming growth factor (TGF)-b2, TGF-bR2 and SMAD3 are members of the TGF-b signalling pathway. SNPs in these genes influence KD susceptibility and coronary artery aneurysm formation [14].

In summary, genetic studies have generated much new information on the background of KD patients. Genetic studies of KD aim to predict disease susceptibility, improve our understanding of the pathogenesis of KD and generate new, improved therapies. The genetic discovery by Onouchi et al. [10] that an SNP within the inositol 1,4,5-triphosphate kinase-C (ITPKC) gene confers a susceptibility to KD and risk for CALs led to the use of calcineurin inhibitors to block this activation pathway in KD patients who are resistant to intravenous immunoglobulin (IVIG) treatment [20,21].

### 3.2. Infections

It is generally accepted that KD may be triggered by an infectious agent that activates the immune system in a genetically susceptible host. First, there is an overlap of the clinical picture of KD and other infectious diseases, such as adenovirus and scarlet fever. Second, seasonal clustering of the disease in the winter and spring is similar to other viral diseases [22]. Third, temporal clusters of epidemics were reported in Japan, the US, Canada, and Finland [23]. Moreover, an outbreak in Japan began in one area and spread throughout the country in a period of 3 months [24]. Lastly, the low incidence in the first 3 months of life suggests at least partial protection from trans-placental antibodies [25]. The relatively low incidence after the age of 4 years suggests a

**Table 1**
Susceptibility genes for Kawasaki disease recently reported.

| Gene | Methods | Reference |
|---|---|---|
| ITPKC | Linkage analysis | [10] |
| CASP3 | Linkage analysis | [11] |
| BLK | GWAS | [12,13] |
| CD40 | GWAS | [12,13] |
| FCGR2A | GWAS | [19] |
| TGFB2, TGFBR2, SMAD3 | Association study | [14] |
| HLA | GWAS | [12] |

BLK, B-lymphoid kinase; CASP3, caspase-3; FCGR2A, low-affinity immunoglobulin gamma Fc region receptor II-a; GWAS, genome-wide association study; HLA, human leukocyte antigen; ITPKC, inositol 1,4,5-triphosphate kinase-C; TGF, transforming growth factor.

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