

The Genomics and Pharmacogenomics of Kawasaki Disease

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Kawasaki Disease (KD) is an acute febrile systemic vasculitis that causes acquired cardiac disease in children in developed countries. It was first described by Kawasaki in 1967 [1] and is now known to occur worldwide. Importantly, KD is markedly more prevalent in Asian countries, including Japan, Korea, and Taiwan. Despite intensive research, several questions about KD remain unanswered, including the ones that follow: (i) What role is played by the genetic effect in disease susceptibility? (ii) What is the therapeutic mechanism of Intravenous Immunoglobulin (IVIG) for KD?

Although several genes have been proposed as causes of KD, their molecular mechanism has not been consistently confirmed [2]. By using linkage analysis, Onouchi et al. [3] identified the inositol 1,4,5-trisphosphate 3-kinase C (*ITPKC*) gene, which is significantly associated with KD susceptibility and with an increased risk of coronary artery lesions. The correlation between rs28493229 of *ITPKC* and susceptibility to KD was further confirmed by a meta-analysis of a Taiwanese population [4]. Subsequently, more straightforward evidence for susceptibility genes was obtained through screening of TGF- β pathways. Shimizu et al. [5] indicated that genetic variation in the TGF- β signaling pathway is associated with susceptibility to KD. In support of this study, an additional study by Kuo et al. [6] performed a replication study in a Taiwanese population to confirm the genetic contributions of SMAD in KD. In 2012, a major advancement in the genomics of KD was made using a Genome-Wide Association Study (GWAS). Lee et al. [7] and Onouchi et al. [8] published GWAS data of Taiwanese and Japanese populations, respectively. Coincidentally, their results suggested 2 novel susceptibility genes for KD: *BLK* (encoding B-lymphoid tyrosine kinase) and *CD40*. Kuo et al. [9] further identified another polymorphism in the *CD40* gene that is associated with the risk of developing KD, which is consistent with these findings. Collectively, evidence has accumulated that suggests that genetic polymorphism plays a major role in susceptibility to KD.

The standard treatment for KD is IVIG (2 g/kg) infusion for 8–12 hours with high-dose aspirin (80–100 mg/[kg·day]) [10]. The pharmacological mechanism of IVIG is still unclear. The potential mechanisms of IVIG action include modulation of cytokine production and suppression of antibody synthesis. Although the introduction of IVIG therapy has greatly decreased the rate of coronary artery lesions, some patients are unresponsive to initial IVIG (2 g/kg) treatment. The incidence of IVIG resistance varies from 9.4% to 23% in different countries [11]. On the basis of the work on *ITPKC/CASP3*, Onouchi et al. [12] reported that a combination of *ITPKC* (rs28493229) and *CASP3* (rs113420705) polymorphisms affects IVIG treatment response and the risk of CAL formation. Recently, Khor et al. [13] suggested that the *FcyR2A* (rs1801274) locus is important in understanding immune activation in KD pathogenesis and the mechanism of response to IVIG. The encoded *FcyR2A* receptor is involved in immune responses and therefore broadly fits with the current consensus regarding the

pathogenesis of KD. The involvement of *FcyR2A* in the susceptibility to KD highlights the importance of IgG receptors in the pathogenesis of this inflammatory disease, and thereby provides a biological basis for the use of intravenous immunoglobulin for treatment of KD.

Genetic polymorphisms play a fundamental role in both the KD susceptibility and IVIG treatment responses. With high-throughput genomic technology, researchers can expect to obtain more genomic and pharmacogenomic information regarding the etiology and treatment of KD.

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