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Editorial

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# New Insight to the Pathogenetic Mechanism of Kawasaki Disease (KD): the Relationship between Clinical Diversity and Genetic Heterogeneity

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▸ See the article "Assessment of the Clinical Heterogeneity of Kawasaki Disease Using Genetic Variants of *BLK* and *FCGR2A*" in volume 49 on page 99.

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Kawasaki disease (KD) or Kawasaki syndrome, an acute systemic vasculitis mainly developed in children younger than 5 years of age, may causes serious, life-threatening, cardiac sequelae including coronary artery aneurysm (CAA). Unfortunately, the disease-specific diagnostic tool of KD is lacking to date, and it has been a major obstacle to detect and treat the patients at the early stage and to prevent coronary artery lesions.

The cause of KD is largely unknown, but one of the most remarkable findings in its epidemiology is the distinct racial and familial tendency. Compared to the Western, the incidence rate in East Asian is 10 times higher.[1] Also, from the data at Hawaii in 1996–2006, the incidence rate of white children was 13.7 per 100,000 children under 5 years old while that of Japanese children was 210.5, which is almost the same as that in mainland Japan. These data, which show very dramatic ethnic dominant pattern in KD, indicate that the different incidences between Western and East Asian are not caused by environmental or geographical factors, but by genetic disparity among ethnicities.[2] On the other hand, the incidence in the family was reported to be 1.4–2.1%, which was more than 10-fold higher than in the general population, and especially with twins, reported 50- to 100-fold higher.[3] These differences in racial and familial incidence strongly suggest that genetic factors play a major role in the development of KD.

Based on this background, to identify the genetic polymorphism associated with susceptibility to KD, numerous candidate genes related to immunologic or inflammatory reaction have been studied over 40 years. However, this kind of approaches failed to identify the definite disease loci because pathogenesis of KD is largely unknown. Therefore, several genome-wide association studies (GWASs) have been conducted worldwide (**Table 1**). Contrary to expectation, those results have not been consistent and the single-nucleotide polymorphisms that were found to be highly significant in one GWAS did not appear to be significant in other racial replication studies.[4-6] The genetic factors associated with CAA, the most important long-term sequela of KD, have been studied in a few studies, but are not conclusive and have not yet been replicated in other study.

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**Table 1.** GWASs for KD

| | | | GWAS | | | Replication |
|---|---|---|---|---|---|---|
| Population | KD | Control | SNP | Gene | Function | |
| European[13] | 119 | 135 | rs1463525 | *NAALADL2* | - | – |
| | | | rs2106261 | *ZFHX3* | - | – |
| | | | rs7193343* | | | |
| Taiwanese[14] | 250 | 446 | rs1873668 | *COPB2* | Regulation of T cell receptor signaling | – |
| | | | rs4243399 | | | |
| | | | rs149481 | *ERAP1* | M1 family of zinc metallopeptidases | – |
| | | | rs17113284 | *IGHV* | Immunoglobulin heavy chain variable region gene | – |
| | | | rs8005468 | | | |
| | | | rs10129255 | | | |
| | | | rs2007467 | | | |
| | | | rs10150241 | | | |
| | | | rs12590667 | | | |
| Korean[15] | 186 | 600 | rs527409 | *DAB1* | - | – |
| | | | rs7604693† | *PELI1* | Negative regulation of T cell R signaling | – |
| European[16] | 405 | 6,252 | rs1801274 | *FCGR2A* | Fc gamma receptor gene | + |
| | | | rs2233152 | *MIA* | Growth inhibition on melanoma cells and neuroectodermal tumors | – |
| | | | rs10403040 | *RAB4B* | Ras-related GTP-binding protein 4b gene (probably involved in vesicular traffic). | – |
| Japanese[17] | 428 | 3,379 | rs2254546 | *FAM167A-BLK* | Involve in B-cell receptor signal transduction | + |
| | | | rs2857151 | *HLA-DQB2-HLA-DOB* | HLA region | – |
| | | | rs4813003 | *CD40* | Increase translation efficiency of CD40 | – |
| Taiwanese[18] | 622 | 1,107 | rs2736340 | *BLK* | Involve in B-cell receptor signal transduction | + |
| | | | rs1883832 | *CD40* | Reduce functionally null isoform of CD40 | – |
| | | | rs1569723 | | | |
| Taiwanese[19],‡ | 157 (11) | - | rs16921209† | *NEBL* | Binds to actin and involves in the assembly of the Z-disk of cardiac muscle | – |
| | | | rs7922552† | | | |
| | | | rs17076896† | *TUBA3C* | Tubulin is a major constituent of microtubules | – |
| Korean[20],‡ | 140 (17) | - | rs17136627† | *KCNN2* | Calcium-activated potassium channel | – |

Numbers in parenthesis indicate KD patients with CAA.
CAA = coronary artery aneurysm; GTP = guanosine-5′-triphosphate; GWAS = genome-wide association study; HLA = human leukocyte antigen; KD = Kawasaki disease; SNP = single nucleiotide polymorphism.
*rs7193343 was associated with protective effect on the risk for KD; †Risk loci associated with coronary artery lesion or aneurysm in patients with KD; ‡GWAS conducted to identify susceptibility genes associated with CAA in KD, the data from KD patients with CAA were compared to the data from KD patients without CAA.

The ethnic differences in the polymorphism of KD-associated gene may have a role in the discrepancy of those results. In fact, a meta-analysis study demonstrated that there is a significant association between the H131R polymorphism of *FCGR2A* gene and KD risk in Asians, but not in Caucasians.[7] On the other hand, the gender difference was reported in the polymorphism of KD-associated gene. In a meta-analysis with 1,461 cases and 5,302 controls, a very strong association of KD with the *FCGR2A* gene was confirmed in males, but not in the females.[8] From these findings, we could infer that the heterogeneous variation of KD-associated genes may contribute to the clinical and epidemiologic characteristics of KD.

Regarding the genetic heterogeneity in each KD patients, Sim et al.[9] revealed a new finding that the genetic variations of related genes were associated with the diversity of clinical features in KD. KD is difficult to be diagnosed, because the number, timing, and duration of the clinical symptoms manifested in each patient are various, as to be referred to as Kawasaki syndrome. The authors provide a clue to this heterogeneity, analyzing the variations of *BLK* and *FCGR2A* gene that were identified in previous GWAS of KD patients and replicated in other population. In their results, the risk allele of *BLK* gene was strongly associated with complete KD in patients younger than 5 years, but not in patients with incomplete KD or older than 5 years old, and the risk allele of *FCGR2A* gene was strongly associated with only male patients younger than 1 year old. These findings suggest that the patients with the risk

allele of *BLK* could develop the KD at a younger age and fully manifest, showing typical KD features. Also, it could be suggested that the risk allele of *FCGR2A* encoding high-affinity Fc gamma receptor that binds to the immunoglobulin G (IgG), could affect the development of KD in infants, who show the rare incidence of KD with the hypothesis that passive transmission of maternal IgG has a preventive effect on KD.

The large sample size is a strong point of Sim' study (1,011 cases and 4,553 controls).[9] However, their results showed some discrepancies with previous reports on the clinical feature of KD. Although treated with immunoglobulin therapy, subjects showed very high incidence of coronary artery lesions (20.8%), and the infant patients showed the similar incidences of incomplete KD (7.6%) and coronary artery complication (15.2%) as the patients older than 1 year. It has been recognized that infants with KD have a high incidence of incomplete KD (45–67%) and coronary artery complication (30.8–64%).[10-12] These discrepancies could be attributed to the selection bias in the sample collection, and their effect on the results is not clearly understood. Nevertheless, Sim's work presents new insight into understanding the pathogenetic mechanism of KD. Although much understanding has been accumulated about the clinical diversity of KD, there has been a little research on the relationship between genetic heterogeneity and clinical features, except polymorphism related to the coronary artery complication. Therefore, their result is very interesting that heterogeneity of associated genes is related to clinical features. I expect that this study will lead to a better understanding for overcoming of KD by triggering further studies on the genetic heterogeneity of KD and its impact. Although it is still the tip of the iceberg that we have revealed about KD, we hope successive new attempts in this kind will reveal the secret nature of KD in near future.

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