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ORIGINAL ARTICLE

Identification of *LEF1* as a Susceptibility Locus for Kawasaki Disease in Patients Younger than 6 Months of Age

Hea-Ji Kim[1], Sin Weon Yun[2], Jeong Jin Yu[3], Kyung Lim Yoon[4], Kyung-Yil Lee[5], Hong-Ryang Kil[6], Gi Beom Kim[7], Myung-Ki Han[8], Min Seob Song[9], Hyoung Doo Lee[10], Kee Soo Ha[11], Sejung Sohn[12], Ryota Ebata[13], Hiromichi Hamada[14], Hiroyuki Suzuki[15], Yoichiro Kamatani[16], Michiaki Kubo[17], Kaoru Ito[18], Yoshihiro Onouchi[18§], Young Mi Hong[12§], Gi Young Jang[11§], Jong-Keuk Lee[1§*], The Korean Kawasaki Disease Genetics Consortium

[1]Asan Institute for Life Sciences, University of Ulsan College of Medicine, Seoul 05505, Korea, [2]Department of Pediatrics, Chung-Ang University Hospital, Seoul 06973, Korea, [3]Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Korea, [4]Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Seoul 05278, Korea, [5]Department of Pediatrics, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon 34943, Korea, [6]Department of Pediatrics, Chungnam National University Hospital, Daejeon 35015, Korea, [7]Department of Pediatrics, Seoul National University Children's Hospital, Seoul 03080, Korea, [8]Department of Pediatrics, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung 25440, Korea, [9]Department of Pediatrics, Inje University Busan Paik Hospital, Busan 47392, Korea, [10]Department of Pediatrics, Pusan National University Hospital, Busan 49241, Korea, [11]Department of Pediatrics, Korea University Ansan Hospital, Ansan 15355, Korea, [12]Department of Pediatrics, Ewha Womans University Hospital, Seoul 07985, Korea, [13]Department of Pediatrics, Chiba-University Graduate School of Medicine, Chiba 260-8670, Japan, [14]Department of Pediatrics, Tokyo Women's Medical University Yachivo Medical Center, Yachivo 276-8524, Japan, [15]Department of Pediatrics, Wakayama Medical University, Wakayama 641-8509, Japan, [16]Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan, [17]Laboratory for Genotyping Development, RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan, [18]Laboratory for Cardiovascular Diseases, RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan

Kawasaki disease (KD) is an acute febrile vasculitis predominately affecting infants and children. The dominant incidence age of KD is from 6 months to 5 years of age, and the incidence is unusual in those younger than 6 months and older than 5 years of age. We tried to identify genetic variants specifically associated with KD in patients younger than 6 months or older than 5 years of age. We performed an age-stratified genome-wide association study using the Illumina HumanOmni1-Quad BeadChip data (296 cases vs. 1,000 controls) and a replication study (1,360 cases vs. 3,553 controls) in the Korean population. Among 26 candidate single nucleotide polymorphisms (SNPs) tested in replication study, only a rare nonsynonymous SNP (rs4365796: c.1106C>T, p.Thr369Met) in the lymphoid enhancer binding factor 1 (*LEF1*) gene was very significantly associated with KD in patients younger than 6 months of age (odds ratio [OR], 3.07; $p_{combined} = 1.10 \times 10^{-5}$), whereas no association of the same SNP was observed in any other age group of KD patients. The same SNP (rs4365796) in the *LEF1* gene showed the same direction of risk effect in Japanese KD patients younger than 6 months of age, although the effect was not statistically significant (OR, 1.42; p = 0.397). This result indicates that the *LEF1* gene may play an important role as a susceptibility gene specifically affecting KD patients younger than 6 months of age.

Keywords: genome-wide association study, Kawasaki disease, lymphoid enhancer binding factor1 (*LEF1*), single nucleotide polymorphism

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***Corresponding author:** Tel: +82-2-3010-4142, Fax: +82-2-488-3312, E-mail: cookie_jklee@hotmail.com
[§]These authors contributed equally to this work.

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Introduction

Kawasaki disease (KD) is an acute, self-limited vasculitis that predominantly occurs in children between the ages of 6 months and 5 years old. Approximately half of all KD patients are between 6 months to 2 years of age, which is the peak incidence age of KD [1, 2]. The etiology of KD is not known, and it has no specific diagnostic test. As such, KD diagnosis is based solely on six clinical symptoms: prolonged fever, bilateral conjunctival injection, erythema of the oral mucosa, lips, and tongue, polymorphous rash, erythema of the palms and soles, and cervical lymphadenopathy [3]. Complete KD is diagnosed when patients have at least five of the above six clinical symptoms, and incomplete KD is diagnosed when patients have less than four of the six clinical symptoms. The standard treatment of KD is a high-dose intravenous immunoglobulin (IVIG), which is derived from pooled plasma of healthy donors, reducing the duration of fever and the incidence of coronary artery abnormalities [4, 5].

KD is considered an abnormal immunological reaction to an infection or unknown immunological triggers in genetically susceptible individuals [6, 7]. B cell–related genes including *BLK*, *CD40*, and *FCGR2A* were also identified as KD susceptibility genes by genome-wide association studies (GWAS) [8-10]. In particular, a reduced level of *BLK* expression in blood B cells may be a crucial reason for dysfunction of B cells and a pathogenesis of KD [10, 11]. Our previous study identified that a risk allele in *FCGR2A* was only susceptible for KD patients younger than 1 year of age, whereas the KD susceptible allele in *BLK* affected all ages of KD patients, except those older than 5 years of age. This result revealed a possibility that there are other genetic variants affecting specific age subgroups of KD patients. In this study, to further identify age-specific susceptibility genes of KD in KD patients younger than 6 months or older than 5 years of age, we performed an age-stratified GWAS and a replication study and identified lymphoid enhancer binding factor 1 (*LEF1*) as a KD susceptibility gene specifically affecting KD patients younger than 6 months of age.

Methods

Study subjects and genotype data

KD patients in this study were collected from 10 hospitals in Korea. The diagnosis of all KD patients was determined by the diagnostic criteria of the American Heart Association [12, 13]. All laboratory test data were performed before the initial IVIG treatment, including white blood cell count, neutrophil count, platelet count, erythrocyte sedimentation rate (ESR), hemoglobin (Hb), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total protein. A total of 1,699 KD patients in Korea were used in this study. Of them, 118 KD patients were younger than 6 months of age and 231 KD patients were older than 5 years of age. A total of 4,553 controls with no history of KD were obtained from the adult health cohort of the general population in Korea, which included 1,000 controls used in the initial GWAS and 3,500 controls used in the replication study. The GWAS was initially performed using our previous Illumina HumanOmni1-Quad BeadChip data (296 KD patients and 1,000 healthy controls) [14]. From the age-stratified GWAS analysis (19 cases; younger than 6 months of age KD patients and 45 cases; older than 5 years of age KD patients), a total of 12 single nucleotide polymorphisms (SNPs) and 14 SNPs were chosen as age-specific KD susceptibility loci for patients younger than 6 months and older than 5 years of age, respectively. Genotyping for the replication study in the 1,403 KD patients, including 99 KD patients younger than 6 months and 186 KD patients older than 5 years of age, were performed using TaqMan assays and analyzed using an Applied Biosystems 7900HT Fast Real-Time PCR system (Thermo Fisher Scientific, Waltham, MA, USA). The genotypes of the control subjects in Korea were provided by the Biobank for Health Sciences at the Center for Genome Sciences in Cheongwon, Korea. The second replication study using a Japanese cohort was comprised of 1,306 KD cases, including 120 KD cases younger than 6 months of age, and 6,893 controls. Genotype data of the Japanese cohort was generated using the Illumina HumanOmniExpressExome BeadChip (Illumina, San Diego, CA, USA). Informed consent was obtained from the parents of all KD patients in this study.

Statistical analysis

Statistical analyses for the genetic associations and meta-analysis of the SNPs were performed using PLINK (ver. 1.07) [15]. To test the association with KD, we performed the chi-square test to compare allele and genotype frequencies between cases and controls. To analyze the significance of differences in the distribution of variables of clinical characteristics in each genotype group, we used SPSS ver. 18 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to test for normality of the continuous variables. The continuous variables with a non-normal distribution were described by median and interquartile range. The Mann-Whitney U test was used in the continuous variables and the chi-square test was used in the categorical variables to contrast the genotype groups depending on the distribution of the data. The functional prediction of nonsynonymous SNP (rs4365796) was performed by PolyPhen and SIFT programs.

Results

Identification of *LEF1* as a KD susceptibility gene specifically associated with KD in patients younger than 6 months of age.

To identify the genetic variants affecting two extreme age subgroups of KD patients (younger than 6 months and older than 5 years of age), we performed an age-stratified GWAS using 19 KD cases younger than 6 months or 45 KD cases older than 5 years of age, respectively, compared to 1,000 controls. A total of 12 SNPs for patients younger than 6 months and 14 SNPs for those older than 5 years of age were chosen for the replication study on the basis of our arbitrary threshold ($p < 1\times10^{-4}$ and genes related to immune functions) for each subgroup. Among 26 candidate SNPs tested in the replication study (Supplementary Tables 1 and 2), only a nonsynonymous SNP (rs4365796: c.1106C>T, p.Thr369Met) in the *LEF1* gene was validated in Korean KD patients younger than 6 months of age (odds ratio [OR], 5.92; p = 0.000268 in GWAS and OR, 2.60; p = 0.00126 in the replication study) (Table 1). The combined analysis of the Korean GWAS and replication for *LEF1* SNP (rs4365796) showed very significant association with KD in patients younger than 6 months of age (118 cases vs. 4,553 controls; OR, 3.07; $p_{combined} = 1.10 \times 10^{-5}$), whereas no association of the same SNP was observed in any other age group of KD patients (Fig. 1, Supplementary Table 3). To further validate our findings in another population, we also performed a replication study in the Japanese cohort comprised of 1,306 KD cases and 6,893 controls. The SNP rs4365796 in the *LEF1* gene showed the same direction of risk effect in Japanese KD patients younger than 6 months of age, although the effect was statistically not significant (OR, 1.42; p = 0.397) (Table 1). In a meta-analysis of Korean and Japanese data, a significant association was observed in KD patients younger than 6 months of age (OR, 2.50; $p = 5.01 \times 10^{-5}$), whereas no association was detected in KD patients older than 6 months of age (OR, 1.10; p = 0.342) (Table 1). This result indicates that the *LEF1* gene is a novel susceptibility gene specifically affecting KD patients younger than 6 months of age.

To determine the effect of the *LEF1* risk allele on clinical features of KD patients, we examined the clinical data classified by the *LEF1* genotypes (rs4365796, risk allele: T)

Table 1. Age-stratified association results for *LEF1* (rs4365796; risk allele: T) in Korean and Japanese populations

Country	Collection	KD (age ≤0.5 y)				KD (age >0.5 y)			
		No. (case/control)	RAF (case/control)	OR (95% CI)	p-value	No. (case/control)	RAF (case/control)	OR (95% CI)	p-value
Korea	GWAS	19/1,000	0.105/0.020	5.92 (2.00–17.48)	**2.68×10^{-4}**	277/1,000	0.032/0.020	1.69 (0.96–2.98)	0.067
	Replication	99/3,553	0.061/0.024	2.60 (1.42–4.75)	**1.26×10^{-3}**	1,261/3,553	0.025/0.024	1.05 (0.78–1.40)	0.744
	Combined	118/4,553	0.068/0.023	3.07 (1.81–5.19)	**1.10×10^{-5}**	1,538/4,553	0.026/0.023	1.15 (0.89–1.50)	0.275
Japan	Replication	120/6,893	0.025/0.018	1.42 (0.63–3.23)	0.397	1,186/6,893	0.018/0.018	1.03 (0.74–1.42)	0.884
Meta	Korea+ Japan	238/11,446		2.50 (1.61–3.90)	**5.01×10^{-5}**	2,724/11,446		1.10 (0.9–1.35)	0.342

A meta-analysis was performed using 2 patient populations (Korea-combined and Japan-replication) with 2,962 cases of KD and 11,446 control subjects.
These statistical values are for the allelic model, and significant p-values ($p < 0.05$) are shown in bold.
KD, Kawasaki disease; RAF, risk allele frequency; OR, odds ratio; 95% CI, 95% confidence interval; GWAS, genome-wide association studies.

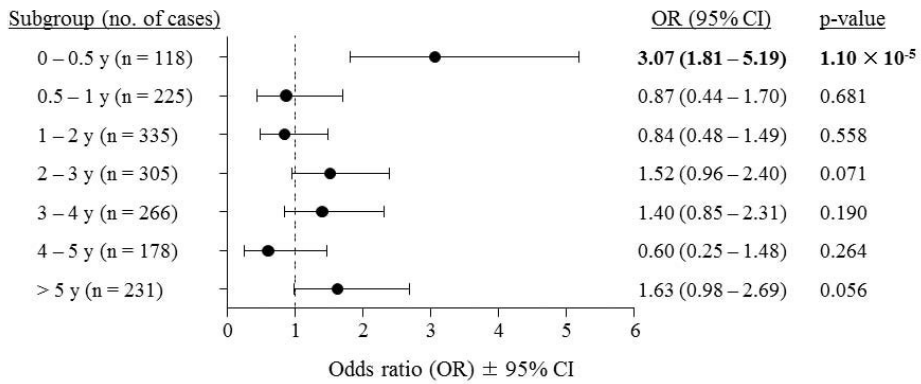

Fig. 1. Odds ratios (ORs) and confidence intervals (CIs) of the *LEF1* (rs4365796) association with Kawasaki disease (KD) according to age of Korean KD patients (total number of KD patients, 1,658). Each horizontal bar is a 95% CI. A total of 4,553 controls were used in the genetic association analysis for each age subgroup of KD patients. Significant p-values ($p < 0.05$) are shown in bold.

in 1,656 Korean KD patients (number of genotype: CC = 1,559, CT/TT = 96/1). When we investigated the effect of genotype of the *LEF1* risk allele in two KD subgroups (younger than 6 months and older than 6 months of age), the risk allele did not show any significant effect on any clinical variables in KD patients with one exception; the risk genotypes (either CT or TT) of the *LEF1* gene (rs4365796) had slightly increased CRP levels (median, 8.48 mg/L; p = 0.032) in KD patients older than 6 months of age compared to the non-risk genotype (CC) of the *LEF1* gene (median, 6.50 mg/L) (Supplementary Table 4).

Discussion

The incidence of KD in patients younger than 6 months and older than 5 years of age was comparatively lower than other age groups. The peak incidence of KD was in the age group between 6 months and 2 years of age. KD has no diagnostic test and the diagnosis depends on clinical symptoms. In particular, KD patients younger than 6 months of age can be difficult to diagnose because they show fewer clinical symptoms, called incomplete KD, which leads to delayed diagnosis or misdiagnosis in infants. Consequently, cardiac complications are more common in KD patients younger than 6 months than in older children [16-18]. Therefore, early and accurate diagnosis of infantile KD is important to reduce the risk of cardiac complications. In this study, we analyzed GWAS data of patients younger than 6 months and older than 5 years of age to identify new risk loci for KD susceptibility in these age groups. We identified a new KD susceptibility locus in the *LEF1* gene (rs4365796: c.1106C>T, p.Thr369Met) on chromosome 4. The associated amino acid-altering SNP (rs4365796) in the *LEF1* gene had an unusually strong effect size, a 3.07-fold increased risk for incidence of KD, in Korean KD patients younger than 6 months of age. This result indicates that the *LEF1* gene plays a crucial role in the pathogenesis of KD in very young children and this amino acid-altering variant can be used as a candidate marker to identify high risk KD patients in infant patients in a clinical setting.

The *LEF1* gene encodes a transcription factor that is expressed in developing B and T cells and at multiple sites of organogenesis during embryonic development [19-21]. *LEF1* is a central mediator of the Wnt signaling pathway through recruiting β-catenin and plays crucial roles during development, including normal hematopoiesis [22, 23]. Abnormal protein expression of *LEF1* has been detected in chronic lymphocytic leukemia (CLL) cells and monoclonal B-cell lymphocytosis, indicating that *LEF1* plays an early role in B-cell development and CLL leukemogenesis [24]. Transplantation of *LEF1*-transduced bone marrow also developed acute myeloid leukemia and B-precursor acute lymphoblastic leukemia in mouse models [25]. Additionally, *LEF1* contributes to the survival and proliferation of pro-B cells during early B cell development [26]. GWAS also identified the *LEF1* gene as a susceptibility locus for systemic lupus erythematosus and CLL [27-29]. These previous results suggest that the dysfunction of the *LEF1* gene is involved in early B lymphocyte development, which is involved in the pathogenesis of KD. In our study, we found that a nonsynonymous SNP (rs4365796: c.1106C>T, p.Thr369Met) was significantly associated with KD in patients younger than 6 months of age. This SNP was predicted as probably damaging and deleterious by PolyPhen and SIFT, respectively, suggesting that this amino acid-altering variant can change the biological functions of *LEF1* protein, probably during the early development of B cells.

Although we found that a nonsynonymous SNP (rs4365796: c.1106C>T, p.Thr369Met) in the *LEF1* gene is significantly associated with KD in Korean patients younger than 6 months of age, the biological role of the *LEF1* variant is still unknown. Therefore, we should investigate how the amino acid-altering *LEF1* variant specifically affects the immune response in infants and subsequently the potential mechanism of *LEF1*-mediated pathogenesis in KD. Additionally, the significantly associated SNP (rs4365796) in the *LEF1* gene in Korean KD patients was not replicated in the Japanese samples, although the same direction of risk effect was detected (Table 1). As shown in Table 1, the risk allele of the *LEF1* gene is a rare variant with lower allele frequency in the Japanese population (risk allele frequency = 0.023 in Korean vs. 0.018 in Japanese control samples). Furthermore, the portions of KD patients younger than 6 months of age was higher in Japan (9.19% in Japan vs. 7.13% in Korea) (Table 1), suggesting that Korean KD patients younger than 6 months of age are a genetically enriched and more homogeneous case population. A previous study also reported that the Japanese population has a higher incidence of KD in patients younger than 6 months of age compared to the Korean population (11.2% in Japanese KD patients vs. 7.7% in Korean KD patients) [30]. Therefore, we assume that no replication of the *LEF1* gene in the Japanese samples may be due to the lower frequency of the risk allele in the *LEF1* gene and/or higher KD incidence in those younger than 6 months of age compared to the Korean population. Conversely, another limitation of our study is the low statistical power due to the small sample size resulting from the selection of a rare variant with an allele frequency less than 2.5% and of age subgroups of KD patients, particularly younger than 6 months of age (less than 10% of total KD cases). Therefore, to support our findings, further replication studies are necessary in more independent sample sets with larger

sample size.

In conclusion, we identified that a nonsynonymous SNP (rs4365796: c.1106C>T, p.Thr369Met) in the *LEF1* gene is significantly associated with KD in children younger than 6 months of age. This amino acid-altering variant in the *LEF1* gene will be useful to identify high risk KD patients younger than 6 months of age because this SNP had a strong effect size (OR, 3.07). This result will provide new insight into the pathogenesis of the KD in infants.

ORCID: Hea-Ji Kim: https://orcid.org/0000-0002-6285-1121; Sin Weon Yun: https://orcid.org/0000-0001-8947-703X; Jeong Jin Yu: https://orcid.org/0000-0003-1601-3685; Kyung Lim Yoon: https://orcid.org/0000-0003-4734-900X; Kyung-Yil Lee: https://orcid.org/0000-0001-6510-1580; Hong-Ryang Kil: https://orcid.org/0000-0003-4925-8240; Gi Beom Kim: https://orcid.org/0000-0002-7880-280X; Myung-Ki Han: https://orcid.org/0000-0003-1817-8088; Min Seob Song: https://orcid.org/0000-0003-3426-6803; Hyoung Doo Lee: https://orcid.org/0000-0002-6125-187X; Kee Soo Ha: https://orcid.org/0000-0001-6753-5411; Sejung Sohn: https://orcid.org/0000-0001-9960-7774; Ryota Ebata: https://orcid.org/0000-0001-8471-1042; Hiromichi Hamada: https://orcid.org/0000-0002-8990-5265; Hiroyuki Suzuki: https://orcid.org/0000-0003-0420-9146; Yoichiro Kamatani: https://orcid.org/0000-0001-8748-5597; Michiaki Kubo: https://orcid.org/0000-0002-0095-2322; Kaoru Ito: https://orcid.org/0000-0003-1843-773X; Yoshihiro Onouchi: https://orcid.org/0000-0002-9272-2689; Young Mi Hong: https://orcid.org/0000-0002-6600-7876; Gi Young Jang: https://orcid.org/0000-0002-4831-1188; Jong-Keuk Lee: 0000-0003-1125-4017

Authors' contribution

Conceptualization: JKL
Data curation: SWY, JJY, KLY, KYL, HRK, GBK, MKH, MSS, HDL, KSH, SS, RE, HH, HS, YK, MK, KI, YO, YMH, GYJ
Formal analysis: HJK
Funding acquisition: JKL
Methodology: HJK
Validation: YO
Supervision: JKL, YMH, GYJ, YO
Writing - original draft: HJK
Writing - review & editing: JKL, YMH, GYJ, YO

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Supplementary materials

Supplementary data including four tables can be found with this article online at https://doi.org/10.5808/GI.2018.16.2.36

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