Journal of Human Genetics (2017) 62, 1023–1029

www.nature.com/jhg

ORIGINAL ARTICLE

A genome-wide association analysis identifies *NMNAT2* and *HCP5* as susceptibility loci for Kawasaki disease

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Kawasaki disease (KD), a systemic vasculitis of infants and children, manifests as fever and mucocutaneous inflammation. Although its etiology is largely unknown, the epidemiological data suggest that genetic factors are important in KD susceptibility. To identify genetic variants influencing KD susceptibility, we performed a genome-wide association study (GWAS) and replication study using a total of 915 children with KD and 4553 controls in the Korean population. Six single-nucleotide polymorphisms (SNPs) in three loci were associated significantly with KD susceptibility ($P < 1.0 \times 10^{-5}$), including the previously reported *BLK* locus (rs6993775, odds ratio (OR) = 1.52, $P = 2.52 \times 10^{-11}$). The other two loci were newly identified: *NMNAT2* on chromosome 1q25.3 (rs2078087, OR = 1.33, $P = 1.15 \times 10^{-6}$) and the human leukocyte antigen (HLA) region on chromosome 6p21.3 (*HLA-C*, *HLA-B*, *MICA* and *HCP5*) (rs9380242, rs9378199, rs9266669 and rs6938467; OR = 1.33–1.51, $P = 8.93 \times 10^{-6}$ to 5.24×10^{-8}). Additionally, SNP rs17280682 in *NLRP14* was associated significantly with KD with a family history (18 cases vs 4553 controls, OR = 6.76, $P = 5.46 \times 10^{-6}$). These results provide new insights into the pathogenesis and pathophysiology of KD.

Journal of Human Genetics (2017) **62,** 1023–1029; doi:10.1038/jhg.2017.87; published online 31 August 2017

INTRODUCTION

Kawasaki disease (KD) is an acute, systemic vasculitis that affects mainly children under the age of 5. The clinical symptoms include the prolonged fever at least for more than 5 days and the following 5 clinical signs: bilateral conjunctival injection; erythema of the oral mucosa, lips, and tongue; polymorphous rash; erythema of the palms and soles; and cervical lymphadenopathy.[1] It is well known that ~15–25% of untreated and 3–5% of treated children develop coronary artery aneurysms,[2–4] making this disease the leading cause of acquired heart disease in infants and young children.

It is thought that KD develops in genetically susceptible children after being exposed by various immunological triggers, including an infectious agent(s).[5,6] More than 11–15 times higher incidence of KD is observed in Japan and Korea than in Caucasian population.[7–9] Compared to children in Japan, in addition, almost same rate of KD incidence was also detected in Japanese–American residents in Hawaii.[10] Furthermore, higher risk of KD occurrence was also observed in sibling cases and cases with parental history of KD.[11–13] Ethnic difference and familial aggregation in KD incidence support that host genetic factors can contribute to disease susceptibility and

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Received 8 June 2017; revised 11 July 2017; accepted 31 July 2017; published online 31 August 2017

outcome. It has been reported that *ITPKC* and *CASP3* were identified as KD susceptibility genes by genome-wide linkage study and association studies.[14,15] In addition, genome-wide association studies (GWASs) reported four KD susceptibility genes: *FCGR2A*, *BLK*, *CD40* and the HLA region, with genome-wide significance.[16–18] These loci have provided a better understanding of the pathophysiology of KD. However, they do not fully explain the genetic risk of KD and some of them do not replicate in the Korean population. Therefore, we performed a GWAS to identify additional genetic risk factors for KD in the Korean population.

MATERIALS AND METHODS

Subjects

Children with KD were recruited from 12 tertiary academic hospitals in Korea that participated in the Korean Kawasaki Disease Genetics Consortium (KKDGC). Pediatricians diagnosed all KD patients according to the diagnostic criteria of the American Heart Association.[19,20] Control subjects were obtained from the adult healthy cohorts of the general population in Korea. These control samples were provided by the Biobank for Health Sciences at the Center for Genome Science in Chungwon, Korea. The GWAS was performed initially on 302 children with KD and 1000 controls. Among the cases, 253 had complete KD with a fever lasting 5 days or longer and more than four principal symptoms of KD, and 14 had a family history of KD. The replication study was performed on 720 KD cases, including 666 complete KD patients and four patients with a family history, and another 3553 controls. The second replication cohort from Japan comprised 428 KD cases and 3379 controls.[17] The Institutional Review Boards of the involved institutions approved the study protocol, and all the parents of the KD patients provided written informed consent.

Genotyping and quality control

Genomic DNA was extracted from whole blood or lymphoblastoid cell lines according to standard protocols. For the GWAS, subjects were genotyped using the Illumina HumanOmni1-Quad BeadChip following the manufacturer's instructions (Illumina, San Diego, CA, USA). All samples had a genotyping call rate of >98%. Six cases were excluded because of inconsistency between their gender on the clinical data sheets and that expected from the genotype data. All samples were unrelated to each other, based on an identity-by-state (IBS) analysis. A total of 296 KD cases and 1000 controls were included in subsequent analyses. To filter the single-nucleotide polymorphism (SNP) markers, we also excluded 488 SNP markers with missing call rates >2%, 43 markers with a Hardy–Weinberg Equilibrium (HWE) *P*-value $<1\times10^{-6}$ in the controls, and 208 625 markers with a minor allele frequency (MAF) <0.01. After filtering, 721,635 SNPs were included in the GWAS analysis. Genotyping for the replication study in the cases was performed on the high-throughput Fluidigm EP1 system (Fluidigm Corp., South San Francisco, CA, USA), using the Fluidigm SNPType assay platform and nanofluidic 96.96 and 48.48 Dynamic Array IFCs (Integrated Fluidic Circuits, Fluidigm). Genotype callings were made using the Fluidigm SNP Genotyping Analysis program (Fluidigm). We were able to genotype all of the selected SNPs for replication. The overall genotype success rate was 99.96%. Genotyping of the 3553 controls was conducted using the Illumina HumanOmni1-Quad BeadChip (Illumina). The Japanese population genotype data was imputed from the genotype data of the Illumina Human Hap550v3 BeadChip (Illumina).[17]

Statistical analysis

All statistical analyses were performed using the PLINK software (version 1.07) (http://pngu.mgh.harvard.edu/~purcell/plink/).[21] A quantile–quantile plot and genomic inflation factor were used to assess the *P*-value distribution and population substructure. χ^2 tests were used to compare allele frequencies between the cases and controls for genetic association study. Conditional analysis was carried out using logistic regression analysis under additive model. LD analysis (D′ and r^2) and meta-analysis were also conducted with PLINK 1.07. Haploview 4.2 was used for drawing a Manhattan plot (https://www.broadinstitute.org/haploview/haploview). In addition, HaploReg v4.1 database (http://archive.broadinstitute.org/mammals/haploreg/haploreg.php) was used to search the quantitative trait loci (QTL) information of the KD-associated SNP rs2078087 in *NMNAT2* locus.

RESULTS

The *NMNAT2* and *HCP5* loci are associated with KD

To identify the genetic loci associated with KD susceptibility, we performed a GWAS using 249 children with KD and 1000 controls (Supplementary Table 1). The genomic control method showed no inflation of *P*-values ($\lambda=1.047$; Supplementary Figure 1). The GWAS results are shown in Supplementary Figure 2. Sixteen SNPs were associated with KD at $P<1\times10^{-5}$. For replication, we selected 98 representative SNPs considering their *P*-values ($P<0.001$ in at least two SNPs in one locus) and their immune-related functions and genotyped them using a Fluidigm SNPType assay platform. Among the 98 SNPs, 14 showed nominal evidence of replication ($P<0.05$) in 666 children with KD and 3553 controls (Supplementary Table 2). In the joint analysis of both the GWAS and the replication samples for these 14 SNPs, six SNPs in three loci were associated significantly with KD susceptibility at $P<1\times10^{-5}$ (Table 1). SNP rs6993775 with genome-wide significance (odds ratio (OR) = 1.52, 95% confidence interval (95% CI) = 1.33–1.72, $P=2.52\times10^{-11}$) was located in the intron of the *BLK* gene, which had been identified previously as a KD susceptibility locus from two recent GWASs.[17,18] The remaining five SNPs were identified for the first time in this study. SNP rs278087 (OR = 1.33, 95% CI = 1.19–1.50, $P=1.15\times10^{-6}$) was located in the intron of the *NMNAT2* gene on chromosome 1q25.3 (Figure 1a), and the other four SNPs (rs6938467, rs9380242, rs9266669 and rs9378179) were mapped to the HLA class I region on chromosome 6p21.3 (Table 1, Figure 1b; $P=8.93\times10^{-6}$ to 5.24×10^{-8}). Although each of the SNPs in the HLA region was located in a different gene (rs9380242 in *HLA-C*, rs9378199 in *HLA-B*, rs9266669 in *MICA* and rs6938467 in *HCP5*), when we analyzed the pair-wise linkage disequilibrium (LD), they all were linked to each other ($D'=0.86$–0.98, $r^2=0.42$–0.91). After subsequent analysis conditioned on the most significant SNP in *HCP5* (rs6938467), the significant associations at the other sites disappeared (Table 1), indicating that all four SNPs that were associated significantly with KD are located on the same LD block. We also performed a replication study in the Japanese population using the imputed genotype data of the Illumina Human Hap550v3 BeadChip in 428 KD cases and 3379 controls. SNP rs278087 in *NMNAT2* showed a statistical trend ($P=0.0608$) and meta-analysis of Korean and Japanese populations showed a more significant association result (OR = 1.27, 95% CI = 1.16–1.40, $P=5.90\times10^{-7}$). However, the other SNPs in the HLA locus were not replicated in the Japanese population (Table 2).

The *NLRP14* locus is associated with KD with family history

Of the 296 children with KD, 14 had a family history of KD. Cases with a family history were more likely to be affected by genetic factors; therefore, we further investigated genetic loci affecting KD with a family history using 14 KD cases with a family history and 1000 controls. Six SNPs were chosen for replication according to the above criteria and tested in the remaining four cases and 3553 controls. In the combined analysis, rs17280682 at the *NLRP14* locus was associated significantly with KD with a family history (OR = 6.76, 95% CI = 2.60–17.6, $P=5.46\times10^{-6}$; Table 3). However, the same SNP showed weak significance for the KD susceptibility in KD cases without a family history (993 cases vs 4553 controls) ($P=0.0392$). These results suggested that the *NLRP14* locus affects the susceptibility of KD predominantly in genetically enriched familial cases.

Table 1 Association results for KD susceptibility

				Allele[c]			RAF		Allelic association			Conditional analysis on rs6938467[d]	
SNP	*Chr.*	*Position*[a]	*Locus*[b]	*1*	*2*	*Stage*	*KD*	*Control*	*OR*	*95% CI*	*P-value*[e]	*OR*	*P-value*
Two newly discovered loci													
rs2078087	1	183358405	*NMNAT2*	A	G	Korea-GWAS[f]	0.307	0.211	1.66	1.33–2.06	**5.00×10^{-6}**		
						Korea-replication[g]	0.241	0.207	1.22	1.06–1.40	**0.005079**		
						Korea-combined[h]	0.259	0.208	1.33	1.19–1.50	**1.15×10^{-6}**		
rs9380242	6	31272392	*HLA-C-HLA-B-MICA-HCP5*	A	G	Korea-GWAS[f]	0.227	0.136	1.87	1.46–2.39	**4.63×10^{-7}**		
						Korea-replication[g]	0.193	0.159	1.27	1.09–1.47	**0.002004**		
						Korea-combined[g]	0.202	0.154	1.40	1.23–1.59	**2.80×10^{-7}**	1.22	0.03006
rs9378199	6	31301658	*HLA-C-HLA-B-MICA-HCP5*	G	A	Korea-GWAS[e]	0.233	0.148	1.75	1.37–2.22	**5.12×10^{-6}**		
						Korea-replication[f]	0.193	0.165	1.21	1.04–1.41	**0.01237**		
						Korea-combined[g]	0.204	0.161	1.33	1.17–1.51	**8.93×10^{-6}**	1.13	0.1863
rs9266669	6	31348077	*HLA-C-HLA-B-MICA-HCP5*	A	G	Korea-GWAS[e]	0.153	0.092	1.79	1.34–2.38	**6.26×10^{-5}**		
						Korea-replication[f]	0.129	0.098	1.37	1.14–1.63	**0.0005714**		
						Korea-combined[h]	0.136	0.096	1.47	1.26–1.71	**5.38×10^{-7}**	1.04	0.8729
rs6938467	6	31407916	*HLA-C-HLA-B-MICA-HCP5*	C	A	Korea-GWAS[f]	0.151	0.092	1.76	1.32–2.35	**0.0001088**		
						Korea-replication[g]	0.135	0.098	1.43	1.20–1.71	**5.24×10^{-5}**		
						Korea-combined[h]	0.139	0.097	1.51	1.30–1.75	**5.24×10^{-8}**		
Three previously reported loci													
rs6993775	8	11369989	*BLK*	C	A	Korea-GWAS[f]	0.801	0.715	1.61	1.27–2.04	**0.0001014**		
						Korea-replication[g]	0.796	0.724	1.49	1.30–1.72	**4.34×10^{-8}**		
						Korea-combined[h]	0.798	0.722	1.52	1.33–1.72	**2.52×10^{-11}**		
rs1801274	1	161479745	*FCGR2A*	C	T	Korea-GWAS[f]	0.823	0.755	1.52	1.18–1.92	**0.001319**		
						Korea-replication[g]	0.796	0.761	1.22	1.06–1.41	**0.005661**		
						Korea-combined[h]	0.803	0.760	1.30	1.14–1.47	**5.65×10^{-5}**		
rs2071471	6	32784645	*HLA-DOB*	T	C	Korea-GWAS[f]	0.149	0.097	1.63	1.23–2.18	**0.0007606**		
						Korea-replication[g]	0.119	0.100	1.22	1.01–1.46	**0.03626**		
						Korea-combined[h]	0.127	0.099	1.32	1.13–1.54	**0.0003763**		

Abbreviations: 95% CI, 95% confidence interval; KD, patients with Kawasaki disease; OR, odds ratio; RAF, risk allele frequency; SNP, single-nucleotide polymorphism.
[a]Chromosome positions are based on NCBI build 37.
[b]In case of the *HLA-C-HLA-B-MICA-HCP5* locus, four SNPs were tested for association analysis and the location of the tested SNP in the gene is marked with an underline.
[c]Allele 1 refers to a minor allele.
[d]Logistic regression analysis was performed conditioned on rs6938467.
[e]Significant *P*-values ($P<0.05$) are shown in bold.
[f]249 KD cases and 1000 controls.
[g]666KD cases and 3553 controls.
[h]915 KD cases and 4553 controls.

DISCUSSION

Using a large number of cases ($n=915$) and controls ($n=4553$) in a Korean population, we identified three known KD loci and two new KD-associated loci, rs2078087 in the *NMNAT2* gene on chromosome 1q25.3, and rs6938467 in HLA class I region on chromosome 6p21.3, including the *HLA-C*, *HLA-B*, *MICA* and *HCP5* genes (Table 1). We also identified the *NLRP14* locus (rs17280682) on the chromosome 11p15.4 as being associated with KD with a family history (Table 3).

NMNAT2 is a member of the nicotinamide mononucleotide adenylyltransferase (NMNAT) enzyme family, which catalyze an essential step in the NAD biosynthetic pathway. A genetic variant (rs2022013) in *NMNAT2* has been associated with susceptibility to systemic lupus erythematosus (SLE) (OR = 0.85, $P=1.08\times10^{-7}$).[22] Recently, Deng *et al.*[23] confirmed the association of *NMNAT2* with SLE, and identified an independent SLE signal at *SMG7*, adjacent to *NMNAT2,* tagged by rs2702178 (OR = 1.23, $P=2.4\times10^{-8}$). *SMG7* encodes a protein that is essential for nonsense-mediated mRNA decay. It has been also reported that a regulatory SNP (rs2275675) in the promoter region of *SMG7* was associated robustly with *SMG7* mRNA expression levels and its risk allele was significantly associated dose-dependently with decreased *SMG7* mRNA levels in peripheral blood mononuclear cells (PBMCs) of patients with SLE and healthy controls, suggesting that differential SMG7 mRNA expression levels contribute to the SLE pathogenesis.[23] SNP rs2022013 in *NMNAT2* showed weak LD with rs2275675 in *SMG7* ($D'=0.61$, $r^2=0.21$); therefore, it is likely that they have independent effects on SLE susceptibility. In our combined analysis of the GWAS and replication samples, rs12144253 in the intron of *SMG7* showed a weak but significant association with KD (OR = 1.25, 95% CI = 1.11–1.41, $P=0.0003726$). Therefore, both *NMNAT2* and *SMG7* are likely to have an effect on the susceptibility of KD. In this study, although we identified *NMNAT2* locus as KD susceptibility, it is not clear why this enzyme in the NAD biosynthetic pathway is associated with KD and SLE. However, BLK locus showing the most significant association with KD was also reported as susceptibility gene for SLE,[24–26] and rheumatoid arthritis.[27] The association of *BLK* and *NMNAT2* genes with both KD and SLE suggests that KD is sharing susceptibility genes with autoimmune diseases such as SLE and rheumatoid arthritis. In addition, the KD-associated SNP rs2078087 in *NMNAT2* locus is associated with QTL for human metabolic trait, serum ratio of (1-oleoylglycerophosphocholine)/(16-anhydroglucose)

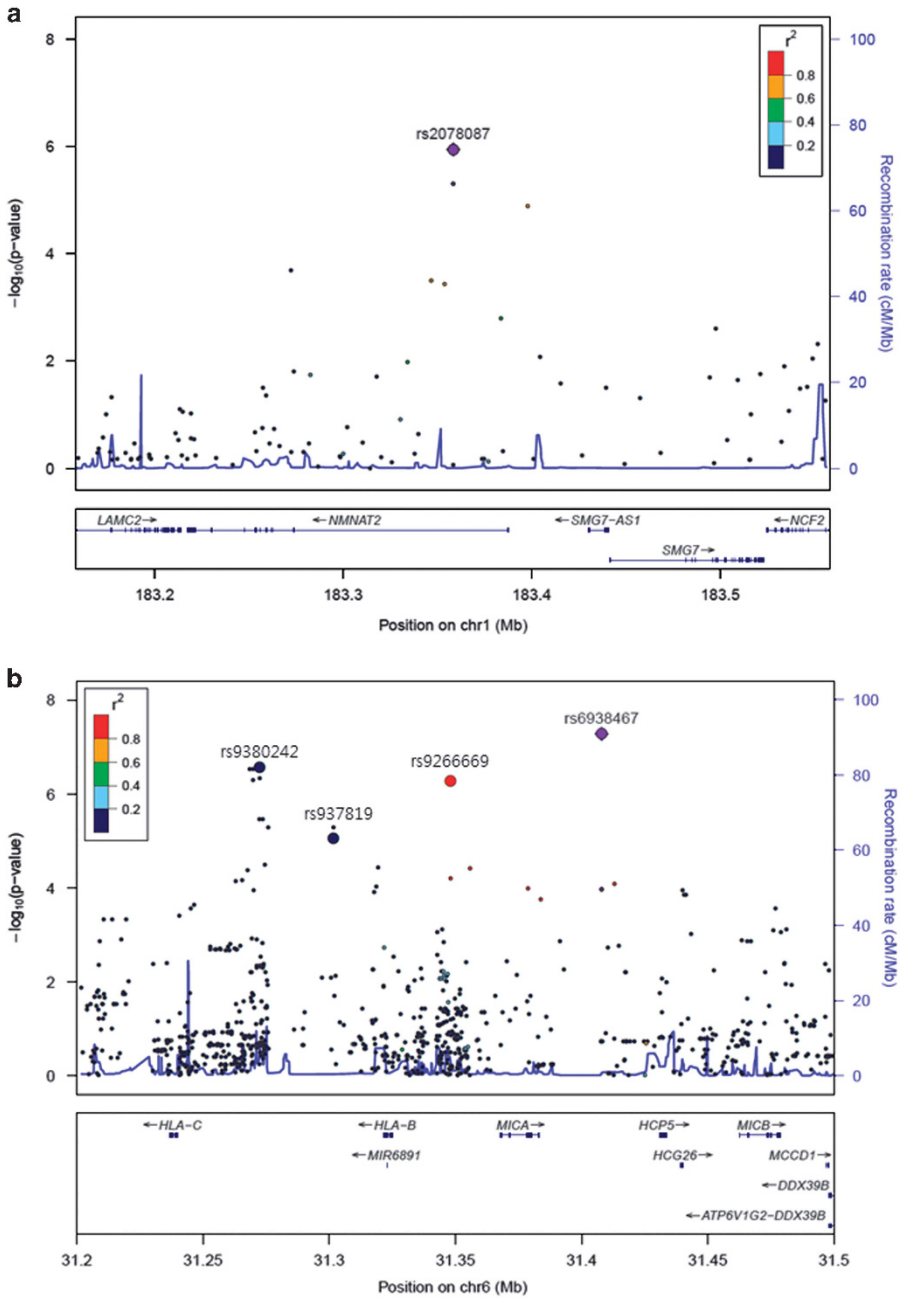

Figure 1 Association plots of *NMNAT2* and HLA genes. Shown are a regional association plot, the recombination rate and the linkage disequilibrium (LD) for the *NMNAT2* region on chromosome 1q25.3 (**a**) and the HLA region on chromosome 6p21.3 (**b**), with gene annotations superimposed. Each single-nucleotide polymorphism (SNP) was plotted with respect to its chromosomal position (*x* axis) and its $-\log_{10}$ *P*-values (left, *y* axis) for the allelic test from the primary genome-wide association study (GWAS) scan (small circle). The significance levels in the combined analysis are also shown (large circle). The estimated recombination rates (right, *y* axis) based on the combined JPT and CHB samples from the 1000 genome project are plotted as a blue line. The color of each SNP symbol represents its LD (using the r^2 algorithm) with the top SNP (large purple diamond) within the association locus. The image above was generated using the LocusZoom program (http://locuszoom.org/).

($P = 1.40 \times 10^{-5}$; accessed by HaploReg), suggesting that the same SNP may also be involved in differential expression of *NMNAT2* gene.

Four SNPs (rs9380242, rs9378199, rs9266669 and rs6938467) in the HLA class I region were associated with KD susceptibility (Table 1). Although they were located in different genes, they all were linked to each other ($D' = 0.86$–0.98, $r^2 = 0.42$–0.91). Furthermore, when we performed logistic regression analysis conditioned on the most significant SNP, rs6938467 in *HCP5* ($P = 5.24 \times 10^{-8}$), the significances at the other SNPs disappeared (Table 1), indicating that the associations at the four SNPs were not independent of each other. *HCP5* encodes an endogenous retroviral element that has been reported to be associated with psoriasis,[28] ulcerative colitis,[29] HIV-1 control,[30] AIDS progression,[31] drug-induced liver injury due to flucloxacillin,[32] Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN)[33,34] and hypothyroidism.[35] Variants in *HCP5* have not been reported to be associated with KD susceptibility,

Table 2 Replication study of *NMNAT2* and HLA loci in the Japanese population

				Allele[c]			RAF		Allelic association		
SNP	*Chr.*	*Position*[a]	*Locus*[b]	*1*	*2*	*Stage*	*KD*	*Control*	*OR*	*95% CI*	P-*value*[d]
rs2078087	1	183358405	*NMNAT2*	A	G	Japan-replication[e]	0.266	0.237	1.17	0.99 – 1.37	0.0608
						Meta-analysis[f]			1.27	1.16 – 1.40	**5.90×10^{-7}**
rs9380242	6	31272392	*HLA-C-HLA-B-MICA-HCP5*	A	G	Japan-replication[e]	0.214	0.192	1.15	0.96 – 1.37	0.1217
						Meta-analysis			1.31	1.18 – 1.45	**2.66×10^{-7}**
rs9378199	6	31301658	*HLA-C-HLA-B-MICA-HCP5*	G	A	Japan-replication[e]	0.219	0.203	1.11	0.93 – 1.33	0.2413
						Meta-analysis			1.26	1.13 – 1.39	**1.49×10^{-5}**
rs9266669	6	31348077	*HLA-C-HLA-B-MICA-HCP5*	A	G	Japan-replication[e]	0.153	0.134	1.17	0.96 – 1.43	0.1241
						Meta-analysis			1.35	1.20 – 1.53	**8.91×10^{-7}**
rs6938467	6	31407916	*HLA-C-HLA-B-MICA-HCP5*	C	A	Japan-replication[e]	0.150	0.132	1.15	0.95 – 1.41	0.1600
						Meta-analysis			1.37	1.22 – 1.55	**2.41×10^{-7}**

Abbreviations: 95% CI, 95% confidence interval; KD, patients with Kawasaki disease; OR, odds ratio; RAF, risk allele frequency; SNP, single-nucleotide polymorphism.
[a]Chromosome positions are based on NCBI build 37.
[b]In case of the *HLA-C-HLA-B-MICA-HCP5* locus, four SNPs were tested for association analysis and the location of the tested SNP in the gene is marked with an underline.
[c]Allele 1 refers to a minor allele.
[d]Significant *P*-values ($P<0.05$) are shown in bold.
[e]428 KD cases and 3379 controls using imputed genotype data.
[f]Meta-analysis was performed using Korea-GWAS, Korea-replication and Japan-replication data.

Table 3 Association results for KD with a family history

				Allele[b]			No.		RAF		Allelic association		
SNP	*Chr.*	*Position*[a]	*Locus*	*1*	*2*	*Stage*	*KD with FH*	*Control*	*KD with FH*	*Control*	*OR*	*95% CI*	P-*value*[c]
rs17280682	11	7091569	*NLRP14*	C	A	GWAS	14	1000	0.143	0.025	6.64	2.22 – 19.9	**9.68×10^{-5}**
						GWAS+remaining samples	18	4553	0.139	0.023	6.76	2.60 – 17.6	**5.46×10^{-6}**

Abbreviations: 95% CI, 95% confidence interval; GWAS, genome-wide association study; KD with FH, cases with family history of Kawasaki disease; No., number; OR, odds ratio; RAF, risk allele frequency; SNP, single-nucleotide polymorphism.
[a]Chromosome positions are based on NCBI build 37.
[b]Allele 1 refers to a minor allele.
[c]Significant *P*-values ($P<0.05$) are shown in bold.

whereas, variants in *HLA-C*, *HLA-B* and *MICA* were shown to be associated with KD susceptibility in candidate gene association studies of KD.[36–40] All these genes are biologically critical for immunity and host defense, suggesting that all four genes are good candidates which can affect the pathogenesis of KD. However, this region contains highly polymorphic and complex genetic structure. Therefore, it is very difficult to reveal and discriminate a true signal from several linked association signals.

Furthermore, we showed that rs17280682 in *NLRP14* was associated significantly with KD with a family history (Table 3). The protein encoded by *NLRP14* gene belongs to the NALP (NACHT, LRR and PYD domains-containing protein 2) protein family and little is known about the function of *NLRP14*. However, it has been suggested that members of the NALP protein family play a role in apoptosis via activation of caspases and in proinflammation signaling processes.[41,42] In addition, the expression of NLRP3 inflammasome-associated genes, including *NLRP1*, *NLRP3* and *NLRP12* was upregulated during acute KD.[43] Although the variants in the *NLRP14* gene were not tested for their association with KD, it has been reported that one member of the NALP protein family, *NLRP1*, was associated with KD.[44] This result supported the view that *NLRP14* acts as a KD susceptibility gene, particularly in genetically enriched familial cases.

Recently, three GWASs reported five KD susceptibility loci exceeding the formal threshold for genome-wide significance: *ITPKC*, *FCGR2A*, *BLK*, *HLA-DQB2 – HLA-DOB* and *CD40*.[16–18] We confirmed that the *BLK* locus was associated significantly with KD susceptibility in our Korean KD samples at a genome-wide significance level (Table 1; $P=2.52\times10^{-11}$), indicating that our genetic association study had sufficient power to detect genetic susceptibility loci in our sample sets. The *FCGR2A* and *HLA-DOB* loci also showed significant associations in our study (Table 1; $P=5.65\times10^{-5}$ in *FCGR2A*, 3.76×10^{-4} in *HLA-DOB*). However, the other two loci (*ITPKC* and *CD40*) were not replicated (data not shown). These observations suggested the presence of ethnic differences in susceptibility to KD. On the other hand, we also tested our findings in the Japanese population using the imputed genotype data of the Illumina Human Hap550v3 BeadChip in 428 KD cases and 3379 controls.[17] rs278087 in *NMNAT2* showed statistical trend (OR = 1.17, $P=0.0608$) and meta-analysis of Korean and Japanese population showed more significant association result (OR = 1.27, $P=5.90\times10^{-7}$). However, rs6938467 in *HCP5* locus did not show significant association with KD (OR = 1.15, $P=0.1600$) (Table 2). Therefore, further studies are necessary to validate our findings in other population using the real genotyping data with larger sample sets rather than the imputed genotype data.

In summary, we identified three known KD loci and two new KD-susceptibility loci in *NMNAT2* and the HLA region in a Korean

population. In addition, we identified the *NLRP14* gene as a novel KD susceptibility locus involved in genetically enriched familial KD cases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank all the patients with Kawasaki disease and their families for participating in this study. This work was supported by a grant from the Ministry of Health & Welfare of the Republic of Korea (HI15C1575) and a grant from the Korea Center for Disease Control and Prevention (2014-ER7402-00).

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