The IL-10 (-627 A/C) Promoter Polymorphism May Be Associated With Coronary Aneurysms and Low Serum Albumin in Korean Children With Kawasaki Disease

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ABSTRACT: Kawasaki disease (KD) is an acute febrile vasculitic syndrome of unknown etiology that preferentially affects the coronary artery. Interleukin-10 (IL-10) is a key proinflammatory cytokine, and a polymorphism near the major transcriptional start site of the IL-10 gene was shown to influence IL-10 production *in vitro*. This study investigated the association of the IL-10 promoter polymorphism with KD and its clinical parameters in Korean children. A total of 194 children with congenital heart disease (CHD) and 95 children with KD were included in this study. IL-10 (-627 A/C) polymorphism genotypes were determined using the single-base extension method. There was no difference in the allele frequencies of IL-10 (-627 A/C) polymorphism between CHD children and KD children. KD children with one or two copies of the IL-10 (-627C) allele showed significantly lower albumin levels ($p = 0.020$) and higher frequencies of early coronary artery aneurysm [62.22% versus 37.78%, adjusted odds ratio (aOR) = 3.50, 95% confidence interval (CI): 1.50–8.16] compared with KD children with the common IL-10 (-627A) allele. These findings suggest that the IL-10 (-627 A/C) promoter polymorphism might be a genetic marker for the risk of early coronary artery complication in KD. (*Pediatr Res* 61: 584–587, 2007)

KD is an acute, self-limiting vasculitis of unknown etiology that occurs predominantly in infants and young children. KD is characterized by widespread vascular inflammation of the coronary artery and other medium-sized arteries (1,2). Coronary artery lesions, including coronary artery dilatation or aneurysm, are the most common complications and develop in approximately 20%–25% of untreated children with KD (3). Even after high-dose intravenous immunoglobulin (IVIG) therapy, coronary artery lesions occur in a small percentage of KD patients, occasionally leading to life-threatening complications (e.g. myocardial infarction) and/or acquired heart diseases such as myocardial dysfunction, valvular diseases, and arrhythmias (4,5).

KD is a mysterious disease of unknown etiology that has been attributed to an infection-immunogenetic-based pathogenesis believed to be the combined effects of infectious agents, host immune dysregulation, and genetic susceptibility. Numerous genetic polymorphisms have been associated with KD in different populations, including single nucleotide polymorphisms in the monocyte chemoattractant protein 1 gene regulatory region, and the genes encoding methylenetetrahydrofolate reductase, angiotensin I converting enzyme genotype II82, *SLC11A1* (formerly *NRAMP1*) gene83, and IL-1 α (6–10). In addition, other gene polymorphisms have been associated with an important common complication of KD, coronary artery aneurysm. These include polymorphisms in the genes encoding mannose-binding lectin, vascular endothelial growth factor, and CD14, as well as in the promoter region of the gene encoding metalloproteinase-3 (11–14).

Acute KD is associated with systemic immune activation, including elevated serum levels of IL-1, tumor necrosis factor α , interferon- γ , IL-4, IL-6, IL-8, IL-10, and a variety of other cytokines (15–19) that are believed to play important roles in the onset of KD and the development of coronary artery lesions. Of them, IL-10 is a cytokine synthesis regulatory factor that is produced by Th2 cells and regulates cytokine production from Th1 or Th2 cells. Elevated plasma IL-10 levels have been observed in KD patients, prompting researchers to speculate that IL-10 may be involved in the pathogenesis of KD (20–23). The gene encoding IL-10, located at chromosome 1q32, is under the control of a promoter region harboring several genetic polymorphisms (e.g. -627 A/C) that appear to affect plasma levels of IL-10 (24–26).

Previous studies have showed that IL-10 gene polymorphisms were associated with the development of multiple diseases and other conditions, including alcoholic liver disease, atopic bronchial asthma, rheumatoid arthritis (27–32), renal disease in systemic lupus erythematosus, and response to interferon in chronic hepatitis C. However, no previous study has evaluated the association between KD and the IL-10 (-627 A/C) promoter polymorphism.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, congenital heart disease; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; WBC, white blood cell

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In the present study, we investigated whether the IL-10 (-627 A/C) promoter polymorphism is associated with the development of KD in Korean children and further assessed possible correlations with early coronary artery aneurysms or with clinical risk factors for KD.

MATERIALS AND METHODS

Subjects. We enrolled patients with KD from the Department of Pediatrics at the Asan Medical Center and Ewha Womans University Hospital, Seoul, Korea. The study group included 95 patients (56 males and 39 females, 39.99 ± 33.85 mo old), all of whom met the criteria proposed by the Japanese Kawasaki Disease Research Committee (33) (Table 1). Echocardiographs were obtained by the pediatric cardiologist before or within 2 wk of IVIG administration. Coronary artery aneurysm was diagnosed from the echocardiograms using the criteria proposed by the Japanese Kawasaki Disease Research Committee (33): coronary arteries were classified as abnormal if the internal lumen diameter was >3 mm in children younger than 5 y old or >4 mm in children older than 5 y old, if the internal diameter of a segment measured ≥ 1.5 times that of an adjacent segment, or if the coronary lumen was clearly irregular. Of the 95 enrolled patients, 45 were identified as having coronary artery aneurysms. The control group consisted of 194 children with CHD (88 males and 106 females, 29.01 ± 41.52 mo). Laboratory data were obtained for each child, including white blood cell (WBC) count, platelet count, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, serum total protein, serum albumin, and C-reactive protein (CRP). All blood samples were drawn before IVIG therapy in the KD patient group. The ethics committee of the Asan Medical Center and Ewha Womans University Hospital Institutional Review Board approved the study, and written informed consents were obtained from the parents of all subjects.

Genotyping of the IL-10 (-627 A/C) promoter polymorphism. The SNP in the IL-10 (-627A/C) promoter region was genotyped using the single-base extension method. Polymerase chain reaction (PCR) was performed in reaction mixtures containing 1.25 pmol of each primer (5'-GGT AAA GGA GCC TGG AAC ACA TC-3' and 5'-GCC CTT CCA TTT TAC TTT CCA GAG A-3'), 50 ng of genomic DNA, 250 mM deoxyribonucleoside triphosphate, and 0.15 U *Taq*DNA polymerase (Applied Biosystems, Foster City, CA) in the buffer provided by the manufacturer. Amplification was performed in a GeneAmp PCR System 9700 thermal cycler (Applied Biosystems). To clean up the PCR products for the primer extension reaction, each reaction mixture was incubated with 1 U of shrimp alkaline phosphatase (SAP) (Amersham Life Sciences, Cleveland, OH) and 2 U of ExoI (Amersham Life Sciences) for 1 h at 37°C and then at 72°C for 15 min for enzyme inactivation. The primer extension reactions were performed with a SNaP Shot Dideoxyribonucleoside Triphosphate Primer Extension Kit (Applied Biosystems), according to the

manufacturer's instructions. The primer extension reactions were cleaned up by incubation at 37°C for 1 h in the presence of 1 U of SAP, followed by incubation at 72°C for 15 min. The extension products were then mixed with Genescan 120 Liz size standard solution (Applied Biosystems) and Hi-Di formamide (Applied Biosystems), incubated for 5 min at 95°C, placed on ice for 5 min, and then electrophoresed on an ABI Prism 3100 Genetic Analyzer (Applied Biosystems). The results were analyzed using the ABI Prism GeneScan and Genotyper (Applied Biosystems) software.

Statistical analysis. Clinical phenotypes, including WBC counts, platelet counts, ALT, AST, serum total protein, serum albumin, CRP, and total duration of fever, were each analyzed as a quantitative trait. Differences in clinical phenotypes between groups were analyzed using the Mann-Whitney test according to their distribution patterns. For analysis of associations between genotypes and KD or coronary artery aneurysm, a dominant model was assumed because only a small proportion of individuals were homozygous for the risk allele. A *p* value <0.05 was considered statistically significant. SPSS 12.0 K for Windows (SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Allele frequencies of the IL-10 (-627 A/C) polymorphism in children with KD and CHD. In this study, 194 children with CHD and 95 children with KD were examined for their allele frequencies at the IL-10 (-627 A/C) polymorphism. The genomic frequencies of the IL-10 (-627 A/C) polymorphism in children with CHD were 50.00% (97/194) for AA, 39.18% (76/194) for AC, and 10.82% (21/194) for CC. In children with KD, these frequencies were 53.68% (51/95) for AA, 35.79% (34/95) for AC, and 10.53% (10/95) for CC. The genomic and allelic frequencies at this polymorphism did not significantly differ between children with CHD and KD (aOR = 0.86, 95% CI: 0.76–2.04) (Table 2).

Association between the IL-10 (-627 A/C) polymorphism and clinical parameters in children with KD and CHD. There were no significant differences in the tested clinical parameters among CHD children with genotypes AA, AC, and CC (Table 3). There were also no significant differences in age at illness, WBC count, peak WBC count, neutrophil count, hemoglobin level, platelet count, CRP, peak CRP, ALT, AST, serum total protein, and total fever duration among KD children with genotypes AA, AC, and CC. In contrast, the mean serum albumin level in KD children with the AC and CC genotypes was significantly lower than that of KD children with genotype AA (3.06 ± 0.52 g/dL versus 3.34 ± 0.30 g/dL; *p* = 0.005), and it also was significantly lower than the mean serum albumin level in CHD children with genotypes AA (3.06 ± 0.52 g/dL versus 3.93 ± 0.60 g/dL; *p* < 0.001) and genotype AC+CC (3.06 ± 0.52 g/dL versus 3.86 ± 0.58 g/dL; *p* < 0.001) (Table 3).

Table 1. Clinical characteristics of study subjects

Clinical parameters*	Children with CHD (<i>n</i> = 194)	Children with KD (<i>n</i> = 95)	<i>p</i>
Sex, M/F	88/106	56/39	0.030
Mean age, mo	29.01 ± 41.52	39.99 ± 33.85	<0.001
WBC, $\times 10^3/\text{mm}^3$	10.34 ± 3.82	14.29 ± 6.27	<0.001
WBC peak, $\times 10^3/\text{mm}^3$	NA	15.07 ± 6.50	
Neutrophil, %	38.32 ± 16.46	64.11 ± 18.84	<0.001
Hemoglobin, g/dL	12.95 ± 2.01	11.49 ± 1.21	<0.001
Platelet, $\times 10^3/\text{mm}^3$	323.20 ± 100.47	378.79 ± 147.85	0.001
CRP, mg/dL	NA	10.78 ± 7.34	
CRP peak, mg/dL	NA	11.18 ± 7.42	
ESR, mm/h	NA	58.85 ± 32.17	
AST, IU/L	42.58 ± 24.05	71.41 ± 88.16	0.300
ALT, IU/L	21.86 ± 17.12	84.76 ± 102.57	<0.001
Protein, g/dL	6.30 ± 0.80	6.94 ± 0.73	<0.001
Albumin, g/dL	3.89 ± 0.59	3.41 ± 0.64	<0.001
Total fever duration, d	NA	7.32 ± 3.26	
Early coronary artery aneurysm, no (%)	NA	47 (48.5)	

The significance of clinical parameters according to groups was analyzed using Mann-Whitney test. NA, not available.

*Data for each group are expressed as mean $\pm$ standard deviation (SD).

Table 2. Allele frequencies of the IL-10 (-627 A/C) polymorphism in children with KD and children with CHD

Loci	Children with CHD (<i>n</i> = 194), no. (%)	Children with KD (<i>n</i> = 95)	
		No. (%)	aOR (95% CI)
IL-10 (-627 A/C)			
AA	97 (50.00)	51 (53.68)	1.00
AC	76 (39.18)	34 (35.79)	0.85 (0.50–1.44)
CC	21 (10.82)	10 (10.53)	0.91 (0.40–2.08)
AC+CC	97 (50.00)	44 (46.32)	0.86 (0.76–2.04)
Frequency (A)	0.70	0.72	

Table 3. Association between IL-10 (-627 A/C) alleles and clinical parameters in children with KD and children with CHD

Clinical parameters*	Children with CHD		Children with KD	
	AA (n = 97)	AC+CC (n = 97)	AA (n = 35)	AC+CC (n = 60)
Age, mo	31.73 ± 43.56	26.29 ± 39.42	35.54 ± 36.22	42.15 ± 32.90
WBC, ×10 ³ /mm ³	10.41 ± 4.07	10.27 ± 3.56	13.59 ± 6.02	15.61 ± 6.31
WBC peak, ×10 ³ /mm ³	NA	NA	14.46 ± 6.30	14.46 ± 6.30
Neutrophil, %	39.13 ± 16.94	37.39 ± 15.95	63.80 ± 20.52	66.54 ± 17.99
Hemoglobin, g/dL	13.00 ± 2.13	12.90 ± 1.90	11.72 ± 1.24	11.17 ± 1.26
Platelet, ×10 ³ /mm ³	320.21 ± 97.38	326.25 ± 103.98	353.70 ± 133.24	403.14 ± 145.65
CRP, mg/dL	NA	NA	9.89 ± 5.22	12.98 ± 7.89
CRP peak, mg/dL	NA	NA	11.76 ± 6.18	12.71 ± 7.83
ESR, mm/h	NA	NA	66.20 ± 32.77	67.53 ± 30.19
AST, IU/L	42.53 ± 17.57	42.63 ± 29.33	98.87 ± 94.77	74.20 ± 97.52
ALT, IU/L	21.64 ± 16.86	22.07 ± 17.46	106.00 ± 91.31	103.25 ± 119.84
Protein, g/dL	6.29 ± 0.82	6.30 ± 0.78	6.93 ± 0.45	8.15 ± 8.14
Albumin, g/dL	3.93 ± 0.60†	3.86 ± 0.58‡	3.34 ± 0.30§	3.06 ± 0.52†‡§
Total fever duration, d	NA	NA	7.38 ± 3.64	7.30 ± 3.07

The significance of clinical parameters according to group was analyzed using the Mann-Whitney test.

*Data for each group are expressed as mean ± SD.

†*p* < 0.001; compared between AA genotype in children with CHD and AC+CC genotype in children with KD.

‡*p* < 0.001; compared between AC+CC genotype in children with CHD and AC+CC genotype in children with KD.

§*p* = 0.005; compared between AA and AC+CC genotype in children with KD.

Allele frequencies of the IL-10 (-627 A/C) polymorphism in KD children with and without early coronary artery aneurysms. We next examined whether the IL-10 (-627 A/C) polymorphism was a risk factor for early coronary artery aneurysms in children with KD. Our association analysis revealed that early coronary artery aneurysms were significantly more frequent in KD children harboring one or two copies of the C allele (62.22%) than in children homozygous for the A allele (37.78%; aOR = 3.50, 95% CI: 1.50–8.16). This finding suggests that the (-627C) allele of the IL-10 promoter polymorphism might be associated with the risk of early coronary aneurysmal changes in KD (Table 4).

DISCUSSION

Consistent with the finding that IL-10 is involved in the pathophysiology of KD (20–23), especially in the development of coronary artery aneurysm, our analysis revealed that the risk allele of the IL-10 (-627 A/C) promoter polymorphism was significantly more frequent in Korean KD children with early coronary artery aneurysm than in those without early coronary artery aneurysm. In addition, KD children with the risk allele at the IL-10 (-627 A/C) promoter polymorphism were found to have lower levels of serum albumin than those with the common allele. These findings suggest that the IL-10

(-627 A/C) promoter polymorphism is not associated with the development of KD, but may be a risk factor for early development of coronary artery aneurysm.

Previous studies have identified predictors of coronary artery aneurysms in KD patients, including persistent fever after IVIG therapy, low hemoglobin concentration, low albumin concentration, high WBC count, high band count, high CRP concentration, male sex, and age younger than 1 y (34–38). Thus, the profile of a high-risk patient with KD consists of laboratory evidence of increased inflammation combined with demographic features (male sex, age younger than 6 mo or older than 8 y) and incomplete response to IVIG therapy. Our results showed that KD children harboring one or two copies of the C allele were more frequent than in children homozygous for the A allele and the risk (-627C) allele at the IL-10 promoter polymorphism should potentially be included in this profile.

KD is a systemic vasculitis with inflammation initially involving increased microvascular permeability in microvessels such as capillaries, arterioles, and venules. Increases in vascular permeability have been associated with hypoalbuminemia and noncardiogenic edema (39), and endothelial permeability has been associated with inflammatory mediators, such as IL-10 and vascular endothelial growth factor (40–43). Thus, our findings that KD children harboring the risk (-627C) allele at the IL-10 polymorphism showed significantly lower albumin levels may form a functional connection between IL-10 and early coronary artery aneurysm.

The present study is somewhat limited by the relatively small study population, the possibility of linkage disequilibrium with an unknown risk single nucleotide polymorphism and the lack of function-related experiments. However, our findings provide preliminary data suggesting that the risk allele of the IL-10 (-627 A/C) promoter polymorphism may be associated with KD risk factors, such as lower albumin level, and the pathogenesis of early coronary artery complications in

Table 4. Allele frequencies of the IL-10 (-627 A/C) polymorphism in KD children with and without early coronary artery aneurysm

Loci	KD without coronary artery aneurysm (n = 50), no. (%)	KD with coronary artery aneurysm (n = 45)	
		No. (%)	aOR (95% CI)
IL-10 (-627 A/C)			
AA	34 (68.00)	17 (37.78)	1.00
AC	12 (24.00)	22 (48.89)	3.67 (1.47–9.15)
CC	4 (8.00)	6 (13.33)	3.00 (0.75–12.08)
AC+CC	16 (32.0)	28 (62.22)	3.50 (1.50–8.16)
Frequency (A)	0.80	0.62	

KD patients. These findings suggest that the IL-10 (-627 A/C) promoter polymorphism might prove useful as a genetic marker for the risk of early coronary artery aneurysm in KD and further indicate that the gene encoding IL-10 might prove to be a disease-modifying gene for KD.

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