

Genetic Analysis of *MMP* Gene Polymorphisms in Patients With Kawasaki Disease

KAZUYUKI IKEDA, KENJI IHARA, KENICHIRO YAMAGUCHI, JUN MUNEUCHI, TAKURO OHNO, YUMI MIZUNO,
AND TOSHIRO HARA

Department of Pediatrics [K.I., K.Y., J.M., T.O., T.H.], Kyushu University, Fukuoka 812-8582, Japan; Fukuoka Children's Hospital and Medical Center for Infectious Disease [Y.M.], Fukuoka 810-0063, Japan

ABSTRACT: Kawasaki disease (KD) is an acute febrile disorder characterized by systemic vasculitis primarily occurring in coronary arteries. Matrix metalloproteinases (MMPs) have been considered to play pathophysiologic roles in the development of coronary artery lesions (CALs); therefore, an evaluation of the genetic contributions of the *MMP* genes to the development of CALs in KD patients would be beneficial for the prediction of CAL formation. We focused on the known functional single nucleotide polymorphisms (SNPs) in the *MMP* genes (*MMP-2-735C>T*, *MMP-3-1612 5A/6A*, *MMP-9-1562C>T*, *MMP-12-82A>G*, and *MMP-13-77A>G*) and performed the association study between these SNPs and CAL formation in KD. The study population consisted of 44 KD patients with CALs and 92 without CALs and 175 healthy controls. As a result, allele and genotype frequencies of *MMP-13-77A>G* showed significant differences between KD patients with CALs and without CALs ($p = 0.00989$ and $p = 0.00551$, respectively). The estimated frequencies of the G-C haplotype in the *MMP-13* gene promoter were significantly lower in KD patients with CALs than in those without CALs. There was no association between other *MMP* genes and CAL formation. In conclusion, the genetic evaluation by association study demonstrated that the *MMP-13* gene, at least in part, contributed to the development of CALs in KD. (*Pediatr Res* 63: 182–185, 2008)

Kawasaki disease (KD) is an acute febrile disorder characterized by systemic vasculitis predominantly occurring in infants and young children. Although the administration of i.v. immunoglobulin (IVIG) in the acute phase of the disease significantly reduces the development of coronary artery lesions (CALs), 2%–15% of KD patients still suffer from this complication (1,2). There is a strong inflammatory predilection for the coronary arteries, and the inflammation in subendothelial layers includes striking edema and infiltration of CD8+ T cells, monocytes, and macrophages with little or no fibrinoid necrosis and few polymorphonuclear cells (3). Inflammatory cells infiltrating from the lumen and from the adventitia to the media appear to mediate transmural damage to the arteries, followed by the development of coronary aneurysms.

The inability to obtain affected coronary arteries has precluded a comprehensive understanding of the mechanism how the pathologic changes in the vessel wall evolve. As a substitute for

pathologic evaluation of the affected tissues, the measurements of cytokines in serum and gene expression levels in peripheral blood cells were studied for the prediction of CAL formation (4). In previous studies, serum vascular endothelial growth factor (VEGF) and hepatocyte growth factor levels in patients with KD were remarkably high in the acute phase and were major risk factors for the occurrence of CALs, probably by an increasing permeability in vessels to cause vascular edema (4–6). A significant elevation of serum matrix metalloproteinase (MMP)-9 levels and a remarkably high expression of the MMP-9 mRNA in the leukocytes were detected during the acute phase of KD (7), suggesting that MMP-9 may play a critical role in the coronary aneurysm formation.

Genetic predisposition to the development of CALs in KD has also been elucidated in various genetic backgrounds, and we previously found that the *VEGF* gene and its receptor *KDR* gene contributed to the development of CALs in KD patients (8–10). We recently found that tissue inhibitor of metalloproteinases 2 (TIMP2) was expressed at higher levels in peripheral blood mononuclear cells in KD with CALs than in those without CALs by cDNA microarray assay. Furthermore, the polymorphisms in the promoter region of the *TIMP2* gene were genetically associated with CAL development in KD (11). Park *et al.* (12) reported that KD patients with CALs had a slightly higher frequency of the *MMP-3-1612 6A* allele and of the combined genotype of the *MMP-3-1612 6A/6A* and the *MMP-9-1562 C/C*, than those without CALs. Other SNPs with functional significances in the *MMP* gene family have not been evaluated.

The aim of this study was to assess the genetic contributions of the *MMP* genes to the development of CALs in the KD patients. We focused on the known functional SNPs in the *MMP* genes (*MMP-2-735C>T*, *MMP-3-1612 5A/6A*, *MMP-9-1562C>T*, *MMP-12-82A>G*, *MMP-13-77A>G*) and performed an association study of the SNPs between KD patients with and without CALs and controls (13–15). To characterize the genetic association between the *MMP-13* gene and CAL formation in KD more fully, we evaluated the haplotype frequency of the *MMP-13* gene in the promoter region between the groups.

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Correspondence: Kazuyuki Ikeda, M.D., Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; e-mail: ikeq@pediatr.med.kyushu-u.ac.jp

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Abbreviations: CALs, coronary artery lesions; IVIG, i.v. immunoglobulin; KD, Kawasaki disease; MMP, matrix metalloproteinase; TIMP2, tissue inhibitor of metalloproteinases 2

METHODS

Patients and controls. The KD patients who were admitted to the Kyushu University Hospital or its affiliated hospitals between 1991 and 2003 were enrolled in this study. All patients met the criteria for the diagnostic guidelines of Kawasaki disease (<http://www.kawasaki-disease.org/diagnostic/index.html>). A CAL was defined as the lumen diameter being at least 3 mm (4 mm in cases of the patients' age older than 5 y) or the internal diameter of one or more segments at least 1.5 times larger than that of the adjacent normal-size segments (16). Informed consent was obtained from patients or their parents. The study population consisted of 44 KD patients with CALs (31 males and 13 females) and 92 without CALs (60 males and 32 females) and 175 normal school children without any history of KD. All patients received IVIG and oral aspirin (30 mg/kg/d). This study was approved by the Ethical Committee of Kyushu University.

Genotyping. Genomic DNA was extracted from whole blood leukocytes with QIAamp Blood Kit (Qiagen, Tokyo, Japan).

Genotyping of the polymorphism *MMP-2-735C>T* (rs2285053) and *MMP-9-1562C>T* (rs3918242) was performed by the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. The sense 5'-GGT GGG TGC TTC CTT TAA CA-3' and antisense 5'-GCG TTA GAG ACG TTG GAA CC-3' primers for the *MMP-2-735C>T*, and sense 5'-AAT GCC TGG CAC ATA GTA GG-3' and antisense 5'-ACT CCT TTC TTC CTA GCC AG-3' primers for the *MMP-9-1562C>T* were used to generate PCR products of 297 bp and 481 bp, respectively. Three genotypes were distinguished as CC (95 and 202 bp), CT (95, 202, and 297 bp), and TT (297 bp) by restriction analysis with *Sau* 96I (New England Biolabs Inc., Beverly, MA) for the *MMP-2-735C>T*, and as CC (481 bp), CT (230, 251, and 481 bp), and TT (230 and 251 bp) by *Sph*I restriction for the *MMP-9-1562C>T* (17).

The polymorphisms *MMP-3-1612 5A/6A* (rs3025058), *MMP-12-82A>G* (rs2276109), *MMP-13-77A>G* (rs2252070), and *MMP-13-3343C>G* (rs675392) were analyzed by the TaqMan SNP Genotyping Assays using ABI PRISM 7700 Sequence Detection System (Applied Biosystems, Tokyo, Japan).

Haplotype estimation. For the supplementary evaluation of the *MMP-13* gene, haplotype blocks were estimated between the two SNP sites using estimating haplotype frequencies (EH) software program (<http://www.linkage.rockefeller.edu/ott/eh.htm>) individually in the patients and control groups. LD coefficients, $D' = D/D_{max}$ (or D/D_{min} if the D' value is negative) were calculated for pairs of alleles between the two sites of polymorphisms in the patients or controls using the method as previously described (18).

Statistical analysis. Genotype and allele distributions were analyzed by χ^2 analysis with 2×2 and 2×3 contingency tables, respectively, using standard statistical software. For the multiple comparisons of the allele, genotype, and estimated haplotype frequencies in the *MMP* genes, Bonferroni's multiple adjustments were made to the level of significance, which was set at $p < 0.0166$ for genotypes, alleles, and estimated haplotypes.

RESULTS

Polymorphisms in the *MMP-2*, *-3*, *-9*, *-12*, and *13* genes.

As shown in Table 1, minor allele frequencies of *MMP-2*, *-3*, *-9*, and *-13* gene polymorphisms were 0.28, 0.14, 0.17, and 0.45, respectively, whereas that of the *MMP-12* gene polymorphism was as low as 0.02. All the genotype frequencies of the analyzed SNPs in the control groups were in Hardy-Weinberg equilibrium. The distribution of *MMP-13-77A>G* genotypes was significantly different between KD patients with CALs and those without CALs ($p = 0.00551$) and the frequency of A allele was significantly higher in KD patients with CALs than in those without CALs and controls ($p = 0.00989$ and $p = 0.0147$, respectively). None of the allele or genotype frequencies of the *MMP-2*, *-3*, *-9*, and *-12* gene polymorphisms showed significant differences between KD patients with CALs, those without CALs, and controls. Then, these frequencies of *MMP* gene polymorphisms were compared between total KD patients and controls, and we did not find significant differences in any SNPs between them ($p > 0.1$).

Haplotype analysis. In the *MMP-13* gene, we analyzed two SNPs (rs2252070 and rs675392) in the promoter region. Three haplotypes with frequencies of more than 0.13 were estimated in the *MMP-13* gene. These haplotypes accounted for about 99% of all haplotypes in both KD patients and controls. The D' value was greater than 0.9 between two SNPs. As shown in Table 2, the frequencies of the estimated haplotype of G-C were significantly lower in KD patients with CALs than in those without CALs ($p = 0.0155$).

DISCUSSION

MMPs are family members of zinc-dependent proteinases, degrade extracellular matrix (ECM) and basement membrane proteins, such as collagen and elastin, and play important roles in the expansion and aggression of cancer cells as well as in the development and progression of atherosclerosis (19). Imbalances between MMPs and their inhibitors TIMPs can result in pathologic matrix degradation of cartilages or bones in rheumatoid arthritis, membranous tissues in aortic aneurysms, or cancer-affected tissues (20–22). In KD, it is possible that inflammatory cells migrate into vascular lesions and produce a large amount of MMPs, and then excreted MMPs play major roles in the development of cardiovascular complications. Actually, *MMP-2* and *MMP-9* were highly expressed in acute KD aneurysms and the plasma *MMP-9* level was significantly increased in KD patients with CALs (23,24); hence, high expression of MMPs might be related to coronary arterial wall destruction and CAL formation in patients with KD. In addition, we recently found that the *TIMP2* overexpression and the *TIMP2* promoter polymorphisms were significantly associated with the development of CALs (11). Although TIMPs inhibit MMP activity, a line of evidence has indicated that *TIMP2* accelerates activation of pro-*MMP-2* (25,26). Gavin *et al.* (24) reported a significant increase in *TIMP2* expression in the adventitia of aneurysmal and nonaneurysmal coronary arteries, predominantly in infiltrating mononuclear cells in KD, which suggests an important role of these genes in the pathogenesis of arteritis in KD. In the present study, we analyzed the reported functional polymorphisms in the promoter regions of the *MMP* genes related to the development of an aneurysm, and we found that *-77A>G* polymorphism in the *MMP-13* gene promoter had a significant association with the development of CALs. This polymorphism was genetically associated with atherosclerosis in a black male population, and the A allele of the *-77A>G* polymorphism in the *MMP-13* gene had transcriptional activity approximately twice as high as that of the G allele (27). *MMP-13* has collagenolytic activity and is abundantly expressed in atherosclerosis and aortic aneurysm lesions (28). Hence, the predisposition to high *MMP-13* expression in arteries might contribute to coronary arterial wall destruction and CAL development in KD as well as progression of atherosclerosis. Furthermore, we found an association between the promoter haplotype of the *MMP-13* gene and the development of CALs. Taken together, the present study suggests that the promoter polymorphisms in the *MMP-13* gene might elevate the levels of *MMP-13* expression

Table 1. Polymorphisms of the MMP-2, -3, -9, -12, and -13 genes in KD patients with and without CALs and control subjects

Gene	Genotype/allele	Ctrl (n = 175)	KD total (n = 136)	KD CAL (+) (n = 44)	KD CAL (-)(n = 92)	Ctrl vs KD total			KD CAL (+) vs Ctrl			KD CAL (+) vs CAL (-)		
						p	OR	95% CI	p	OR	95% CI	p	OR	95% CI
MMP-2	CC	87 (0.50)	71 (0.52)	20 (0.46)	51 (0.55)									
	CT	79 (0.45)	54 (0.40)	19 (0.43)	35 (0.38)	0.437			0.318			0.442		
	TT	9 (0.05)	11 (0.08)	5 (0.11)	6 (0.07)									
MMP-3	Allele C	253 (0.72)	196 (0.72)	59 (0.67)	137 (0.74)	0.950	0.99	0.694-1.40	0.331	0.78	0.471-1.28	0.202	0.70	0.400-1.21
	Allele T	97 (0.28)	76 (0.28)	29 (0.33)	47 (0.26)									
	5A/5A	3 (0.02)	4 (0.03)	1 (0.02)	3 (0.03)	0.336			0.135			0.324		
MMP-9	5A/6A	42 (0.24)	41 (0.30)	17 (0.39)	24 (0.26)									
	6A/6A	130 (0.74)	91 (0.67)	26 (0.59)	65 (0.71)	0.143	1.38	0.895-2.13	0.0665	1.73	0.958-3.13	0.288	1.41	0.744-2.68
	Allele 5A	48 (0.14)	49 (0.18)	19 (0.22)	30 (0.16)									
MMP-12	Allele 6A	302 (0.86)	223 (0.82)	69 (0.78)	154 (0.84)	0.856			0.493		0.451			
	CC	123 (0.70)	95 (0.70)	28 (0.64)	67 (0.73)	0.917	1.02	0.668-1.56	0.585	0.85	0.465-1.54	0.394	0.75	0.385-1.45
	CT	45 (0.26)	37 (0.27)	15 (0.34)	22 (0.24)									
MMP-13	TT	7 (0.04)	4 (0.03)	1 (0.02)	3 (0.03)									
	Allele C	291 (0.83)	227 (0.84)	71 (0.81)	156 (0.85)	0.266	2.09	0.551-7.98	0.994	1.01	0.209-4.82	0.201	0.24	0.0210-2.63
	Allele T	59 (0.17)	45 (0.16)	17 (0.19)	28 (0.15)									
MMP-13	AA	167 (0.95)	133 (0.98)	42 (0.95)	91 (0.99)	0.226			0.0734		0.00551			
	AG	8 (0.05)	3 (0.02)	2 (0.05)	1 (0.01)	0.423	1.14	0.828-1.56	0.0147	1.80	1.11-2.88	0.00989	1.96	1.17-3.29
	GG	0	0	0	0									
MMP-13	Allele A	342 (0.98)	269 (0.99)	86 (0.98)	183 (0.99)									
	Allele G	8 (0.02)	3 (0.01)	2 (0.02)	1 (0.01)									
	AA	41 (0.24)	30 (0.22)	17 (0.39)	13 (0.14)									
MMP-13	AG	74 (0.42)	70 (0.51)	18 (0.41)	52 (0.57)									
	GG	60 (0.34)	36 (0.27)	9 (0.20)	27 (0.29)									
	Allele A	156 (0.45)	130 (0.48)	52 (0.59)	78 (0.42)									
MMP-13	Allele G	194 (0.55)	142 (0.52)	36 (0.41)	106 (0.58)									

CI, confidence interval; Ctrl, control subjects; OR, odds ratio. Numbers in parentheses indicate percentages of the genotype or allele frequency. After Bonferroni's correction of multiple comparison, $p < 0.0166$ was considered to be statistically significant. Numbers in bold italics indicate significant differences.

Table 2. Haplotype analysis of the *MMP-13* gene in KD patients with and without CALs and controls subjects

Haplotype	Estimated haplotype frequency				<i>p</i>		
	Ctrl (<i>n</i> = 175)	KD total (<i>n</i> = 136)	KD CAL (+) (<i>n</i> = 44)	KDCAL (-) (<i>n</i> = 92)	Ctrl vs KD total	KD CAL (+) vs Ctrl	KD CAL (+) vs CAL (-)
G-C	0.548	0.518	0.395	0.576	0.542	0.0388	<i>0.0155</i>
A-G	0.273	0.315	0.360	0.293			
A-C	0.169	0.163	0.230	0.130			

The frequencies were estimated using the EH software program. After Bonferroni's correction of multiple comparison, $p < 0.0166$ was considered to be statistically significant.

Number in bold italics indicates significant differences.

and cause a genetic predisposition to the development of CALs in KD patients.

In a previous report, *MMP-3* and *MMP-9* genes had a minor genetic effects on the development of CALs (12). It is possible that the differences in the genetic backgrounds or the study populations with respect to gender, age at KD onset, or variation of treatment protocol during the acute phase, will cause distinct results. There was a considerable difference in the male-to-female ratio of KD patients with CALs between our study and the previous research by Park *et al.* (12) (2.4 for ours *versus* 4.7 for that of Park *et al.*), whereas there was no difference in the age at KD onset. Details of treatment protocol during the acute phase were not provided in the paper by Park *et al.* (12). Further evaluation with a larger study population would be essential to confirm the genetic predisposition of the *MMP-13* gene to the development of CALs in KD.

There are several limitations that need to be acknowledged and addressed regarding the present study. First, the sample sizes in this study did not have a sufficient power for statistical analysis of the *MMP-2*, *-3*, *-9*, and *-12* genes. The minor allele frequencies of *MMP-2*, *-3*, *-9*, and *-12* genes in the controls were as low as 0.28, 0.14, 0.17, and 0.02, respectively, and allele sizes of KD patients with and without CALs were only 88 and 184, respectively. In this situation, odds ratios of 1.92, 2.04, 2.09, 8.72, or greater were required to reach statistical significance between KD patients with and without CALs. Second, the estimated haplotype frequency in the *MMP-13* gene could have been confirmed by information from their parental genotypes. Consequently, further evaluation with a larger study population and, if possible, with parental genotype information would give us more confirmatory results of this study.

In conclusion, our study has demonstrated that the *MMP-13* gene appears to be a susceptibility gene to the development of CALs in patients with KD. Better understanding of the relationship between *MMP-13* and vascular lesions in KD would contribute to the understanding of the mechanism of CAL formation in KD.

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