

# The Uteroglobin Gene G38A Polymorphism Is Not Associated with Kawasaki Disease

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This study analyzed the genomic DNA extracted from 170 patients with Kawasaki disease as well as their clinical and laboratory parameters to determine whether uteroglobin gene polymorphism, which may be associated with the morbidity rate and severity of IgA nephropathy, is involved in the pathogenesis of Kawasaki disease, which is another type of vasculitic syndrome in childhood. The uteroglobin genotype at position 38 was determined by *Sau96I* digestion of PCR products. The uteroglobin genotype and allele frequency in Kawasaki disease patients were compared with those of published control data reported by three independent studies on Japanese individuals. The clinical parameters investigated were age at onset, gender, duration of fever, white blood cell count, C-reactive protein, aspartate aminotransferase, alanine aminotransferase and total protein. No significant difference associated with the uteroglobin genotype was observed in the clinical parameters. The genotypic and allele frequencies at position 38 of the uteroglobin gene did not differ significantly in the three studies of Japanese healthy controls and the present study. The logistic regression analysis demonstrated that no clinical parameter was associated with the progression to coronary artery lesions except for the duration of fever (odds ratio = 1.7; 95% confidential interval = 1.42-2.05). In conclusion, the present study failed to prove an association of uteroglobin gene polymorphism with the morbidity rate or the severity of Kawasaki disease, but suggested the existence of a factor contributing to the onset of Kawasaki disease and progression to coronary artery lesions in Kawasaki disease patients.

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## Introduction

Kawasaki disease (KD) is an acute systemic vasculitic syndrome in childhood. Although its etiology remains unknown, its clinical and epidemiological features suggest involvement of both infectious process and genetic predisposition.<sup>1</sup> Innate or mucosal immune reactions contribute significantly to the immunopathogenesis of KD and a number of gene polymorphisms are associated with an increase morbidity rate or severity of KD.<sup>1</sup>

IgA nephropathy (IgAN) is another example of a vasculitic syndrome of unknown etiology. A variety of infections such as streptococcal diseases and mycoplasmal infections are thought to be predis-

posing factors; however, genetic factor(s) may play a critical role in the development and progression of IgAN.<sup>2</sup>

The uteroglobin (UG, SCGB1A1), previously called Clara cell protein (CC16), is a steroid-inducible multifunctional protein that is secreted by mammalian mucosal epithelia in the bronchi, uterus and prostate. It is a potent endogenous immunomodulatory and anti-inflammatory protein.<sup>3</sup> Zheng *et al.* reported that UG-deficient mice developed renal disease with pathological features similar to those of IgAN.<sup>4</sup> Disruption of the UG gene also predisposes to an increased incidence of malignancies and oxygen toxicity in the lungs,<sup>3</sup> thus suggesting the involvement of UG in many immunological events. Several single nucleotide polymorphisms (SNPs) have been identi-

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fied in the UG gene. Among them, c.-26G>A SNP (rs3741240), which localized in the non-coding region of exon 1, is well known, and it has been described as a Guanine-to-Adenine substitution at position 38 (G38A) downstream of the transcription initiation site. That SNP is particularly interesting, because previous studies implicated (1) decreased expression of UG in the 38AA genotype in comparison to the 38GG genotype,<sup>5,6</sup> (2) higher frequency of the 38A allele in patients with asthma<sup>7</sup> or systemic lupus erythematosus,<sup>8</sup> (3) higher frequency of 38AA genotype in IgAN patients in comparison to other genotypes,<sup>6</sup> and (4) an association of the polymorphism at position 38 of the UG gene with severity of IgAN.<sup>5,8-11</sup> These findings led to the hypothesis that this UG gene polymorphism could potentially be another genetic factor predisposing an individual to develop KD.

## Patients and Methods

### Patients

Kawasaki Disease (KD) patients referred to Nagasaki University Hospital, Saga University Hospital or Kyushu University Hospital were enrolled in this study with their parents' written informed consent. The Ethics Committees of Nagasaki University, Saga University and Kyushu University respectively approved the study. The diagnosis of KD was made according to the clinical criteria of the Japan Kawasaki Disease Research Committee.<sup>12</sup> Clinical and epidemiological data of the KD patients, including age, gender, presence or absence of coronary artery lesions (CAL) and treatment, were obtained retrospectively from their medical records. Diagnoses of CAL were made by two-dimensional echocardiography or coronary angiography under the definition in the guideline.<sup>11</sup> Genotyping of UG was performed with written informed consent for a total of 170 KD patients (58 girls and 112 boys) known to either have or not have developed CAL: 51 (30%) patients developed CAL, while 119 (70%) did not.

### Preparation of genomic DNA and the UG gene analyses

Genomic DNA was isolated from whole blood leukocytes with QIAamp blood kit (QIAGEN, Tokyo, Japan). The polymorphism at position 38 of exon 1 of the UG gene was determined as described previously.<sup>7</sup> Briefly, a set of primers for polymerase chain reaction (PCR) were designed: sense, 5'-CAGTATCTTATGTAGAGCCC-3'; and antisense, 5'-CCTGAGAGTTCCTAAGTCCAGG-3'. PCR products were examined by *Sau96I* endonuclease restriction analysis for the G38A polymorphism. *Sau96I*-digested DNA samples were separated by electrophoresis on an 8% polyacrylamide gel containing ethidium bromide.

No healthy controls were available for a genetic analysis in the current study, and therefore the published data on the UG gene polymorphism of Japanese healthy controls reported independently by Hori *et al*,<sup>13</sup> Narita *et al*<sup>10</sup> and Tochigi *et al*<sup>14</sup> were used. Their analytical methods, including DNA preparation by PCR and demonstration of polymorphism by restriction digestion, were the same as those

used in the present study. The equilibrium of genotypes in their reports was compatible with the Hardy-Weinberg principle.

### Statistical analysis

We compared the distribution of the demographic, clinical and laboratory characteristics in KD with the UG genotype in order to evaluate the association of these factors among the UG genotype. In addition, the distribution of the UG genotype and therapeutic factors as well as the above-mentioned factors were compared between the KD patients with and without CAL in order to identify any potential factors contributing to the development of CAL in KD patients. A logistic regression analysis was used to quantify the simultaneous effects of these factors for developing CAL in KD patients: this study selected the most appropriate model by AIC (Akaike information criterion) starting from the full model including all factors.

The distribution of continuous variables was categorized by quartiles with the minimum and maximum; the 1st, 2nd and 3rd quartiles are 25th, 50th and 75th sample percentiles, respectively. If appropriate, the distribution of continuous variables was also exhibited by box-and-whisker plots in order to clarify any group-differences in their distribution.

The Wilcoxon rank-sum test and Kruskal-Wallis test were used to test the equality of the distribution of the continuous variables in the groups depending on whether the number of comparison groups was two and three or more, respectively. Comparisons of the frequency of categories between the groups were carried out using Fisher's exact test for the 2x2 table, and its extension for larger tables if feasible; the chi-square test was used if Fisher's exact test was not feasible and appropriate. Estimation of the logistic parameters was based on the maximum likelihood method and their confidence intervals were derived using the likelihood ratio test. The PROC UNIVARIATE, PROC FREQ, PROC NPARIWAY and PROC LOGISTIC programs of the SAS system<sup>®</sup> were used for the necessary calculations. The results were considered to be significant if the *p*-value was less than 0.05.

## Results

### Characteristics of study subjects by genotype

The UG genotypes of GG, GA and AA were observed in 69, 66 and 35 KD patients, respectively. No significant difference by UG genotype was observed in the distribution of age at onset, gender, duration of fever, white blood cell count (WBC), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total protein (TP; Table 1).

### Genotypic and allelic frequencies at the position 38 of the UG gene in Japanese children with KD

The frequencies of the 38G and 38A alleles in KD patients of the present study were 60% and 40%, respectively. As shown in Table

**Table 1.** Distribution of demographic, clinical and laboratory characteristics in Kawasaki Disease patients by uteroglobin genotype

Characteristics	Uteroglobin genotype			Total (n = 170) <sup>a</sup>	p-value <sup>b</sup>
	GG (n = 69)	GA (n = 66)	AA (n = 35)		
Age at onset (months)	(11.00, 21.96, 46.00) <sup>c</sup> 2.00-151.00 <sup>d</sup>	(8.04, 18.50, 38.04) 1.00-113.00	(11.04, 24.00, 46.00) 4.00-96.00	(11.00, 21.48, 45.00) 1.00-151.00	0.6718
Gender (male/female)	47/22	43/23	22/13	112/58	0.8141
Duration of fever (days)	(6, 7, 10) 4-27	(5, 7, 10) 3-26	(6, 6, 7) 4-20	(6, 7, 10) 3-27	0.2934
WBC (/mm <sup>3</sup> ) <sup>e</sup>	(11 700, 14 400, 18 380) 5860-34 800	(11 480, 14 405, 16 990) 5300-24 060	(11 600, 15 000, 18 300) 7600-25 890	(11 600, 14 615, 18 300) 5300-34 800	0.6816
CRP (mg/dL) <sup>f</sup>	(6.00, 9.60, 17.15) 2.15-26.80	(6.20, 9.37, 14.30) 1.97-25.68	(4.00, 8.05, 12.82) 1.20-24.03	(5.71, 9.37, 14.80) 1.20-26.80	0.2669
AST (U/L) <sup>g</sup>	(30, 39, 63) 15-566	(28, 34, 74.5) 9-597	(25.5, 37, 91) 21-997	(29, 37, 70) 9-997	0.9376
ALT (U/L) <sup>h</sup>	(20, 41, 80) 10-461	(16, 32, 140) 5-406	(16, 26.5, 93.5) 6-613	(16, 37, 103) 5-613	0.9330
TP (g/dL) <sup>i</sup>	(6.0, 6.6, 7.2) 4.8-8.1	(6.1, 6.6, 7.0) 4.9-8.7	(6.3, 6.8, 7.1) 5.6-7.9	(6.1, 6.6, 7.05) 4.8-8.7	0.4948

<sup>a</sup>Number of Kawasaki Disease patients in the respective categories.

<sup>b</sup>Based on the test for the equality of the distributions among GG, GA and AA: Fisher's exact test for gender and Kruskal-Wallis test for others.

<sup>c</sup>Each triplet gives the 25th, 50th and 75th sample percentiles.

<sup>d</sup>Minimum-maximum.

<sup>e</sup>WBC = white blood cell count.

<sup>f</sup>CRP = C-reactive protein.

<sup>g</sup>AST = aspartate aminotransferase: measurements were missed in 2 of GG, 2 of GA and 3 of AA.

<sup>h</sup>ALT = alanine aminotransferase: measurements were missed in 2 of GG, 2 of GA and 3 of AA.

<sup>i</sup>TP = total protein: measurements were missed in 7 of GG, 7 of GA and 4 of AA.

**Table 2.** Association of UG G38A polymorphism with susceptibility to Kawasaki Disease

	Control <sup>a</sup>			Kawasaki Disease <sup>b</sup> (n = 170)	p-value <sup>c</sup>
	Narita <i>et al.</i> <sup>10</sup> (n = 196) <sup>d</sup>	Hori <i>et al.</i> <sup>13</sup> (n = 206)	Tochigi <i>et al.</i> <sup>14</sup> (n = 214)		
Genotype					0.2023
GG	69 (35.2) <sup>e</sup>	61 (29.6)	75 (35.1)	69 (40.6)	
GA	95 (48.5)	109 (52.9)	104 (48.6)	66 (38.8)	
AA	32 (16.3)	36 (17.5)	35 (16.4)	35 (20.6)	
Allele					0.6653
G	233 (59.4)	231 (56.1)	254 (59.4)	204 (60.0)	
A	159 (40.6)	181 (43.9)	174 (40.6)	136 (40.0)	

<sup>a</sup>Data are from published articles indicated by the names of the first authors and the superscript reference number.

<sup>b</sup>Data are from the present study.

<sup>c</sup>Based on the chi-square test for the equality of the genotype and allele frequencies among the 4 studies.

<sup>d</sup>Number of patients.

<sup>e</sup>Number of patients (percentage) in the respective categories.

2, the genotypic and allelic frequencies at the position 38 of the UG gene observed in the four studies (three studies of Japanese healthy controls and the present study) did not differ significantly.

#### Association of the UG genotypes and clinical parameters in KD patients with progression to CAL

Table 3 compares the distribution of the demographic, clinical,

genetic, laboratory, and therapeutic characteristics in KD patients of the present study by progression to CAL. No significant difference between the KD patients with and without CAL was observed in the distribution of the UG gene genotypes and other characteristics except for duration of fever ( $p < 0.0001$ ); the difference in CRP and AST was marginally significant ( $p = 0.0547$  and  $p = 0.0782$ , respectively). Figure 1 compares the distribution of the duration of fever between KD patients with and without CAL.

**Table 3.** Distribution of demographic, clinical, genetic and laboratory, and therapeutic characteristics in Kawasaki Disease patients by progression to coronary artery lesions

Characteristics	Progression to coronary artery lesions (CAL)			p-value <sup>b</sup>
	Yes (n = 51)	No (n = 119)	Total (n = 170) <sup>a</sup>	
Age at onset (months)	(8.00, 21.96, 50.00) <sup>c</sup> 1.00-151.00 <sup>d</sup>	(11.00, 21.00, 45.00) 2.00-120.00	(11.00, 21.48, 45.00) 1.00-151.00	0.5863
Gender (male/female)	38/13	74/45	112/58	0.1578
Duration of fever (days)	(7, 11, 17) 4-27	(5, 6, 7) 3-12	(6, 7, 10) 3-27	<0.0001
UG genotype				0.4673
GG	20 (39.2%)	49 (41.2%)	69 (40.6%)	
GA	23 (45.1%)	43 (36.1%)	66 (38.8%)	
AA	8 (15.7%)	27 (22.7%)	35 (20.6%)	
WBC (/mm <sup>3</sup> ) <sup>e</sup>	(11 910, 15 200, 18 360) 5860-26 100	(11 400, 14 300, 18 300) 5300-34 800	(11 600, 14 615, 18 300) 5300-34 800	0.3849
CRP (mg/dL) <sup>f</sup>	(6.42, 11.30, 17.60) 2.70-25.68	(5.60, 8.60, 13.62) 1.20-26.80	(5.71, 9.37, 14.80) 1.20-26.80	0.0782
AST (U/L) <sup>g</sup>	(32.5, 43, 90) 18-997	(27, 34, 66) 9-597	(29, 37, 70) 9-997	0.0547
ALT (U/L) <sup>h</sup>	(20.5, 40.5, 110) 8-517	(15, 31, 102) 5-613	(16, 37, 103) 5-613	0.2675
TP (g/dL) <sup>i</sup>	(6.1, 6.6, 7.3) 4.8-8.7	(6.1, 6.6, 7.0) 5.0-8.5	(6.1, 6.6, 7.05) 4.8-8.7	0.8828
Given aspirin (Yes/No)	51/0	119/0	170/0	1.0000
Given intravenous immunoglobulin (Yes/No)	49/2	115/4	164/6	1.0000

<sup>a</sup>Number of Kawasaki Disease patients in the respective categories.

<sup>b</sup>Based on the test for the equality of the distributions between patients with and without CAL: Fisher's exact test for gender and treatments, and its extension for UG genotype, and Wilcoxon rank-sum test for others.

<sup>c</sup>Each triplet gives the 25th, 50th and 75th sample percentiles.

<sup>d</sup>Minimum-maximum.

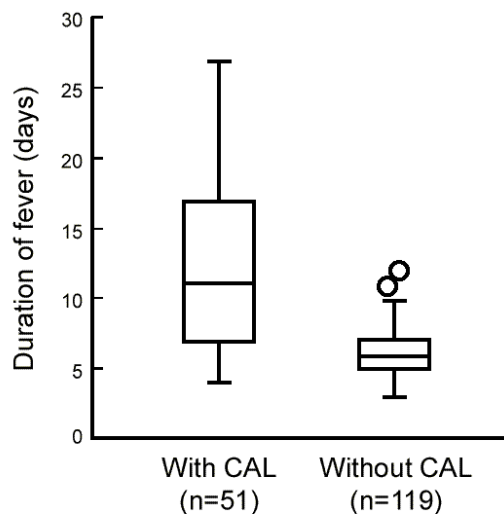
<sup>e</sup>WBC = white blood cell count.

<sup>f</sup>CRP = C-reactive protein.

<sup>g</sup>AST = aspartate aminotransferase: measurements were missed in 3 and 4 patients with and without CAL, respectively.

<sup>h</sup>ALT = alanine aminotransferase: measurements were missed in 3 and 4 patients with and without CAL, respectively.

<sup>i</sup>TP = total protein: measurements were missed in 8 and 10 patients with and without CAL, respectively.



**Figure 1.** The box-and-whisker plots showing the duration of fever in 170 Kawasaki Disease patients with and without coronary artery lesions (CAL). The bottom and top ends of the box and the bar inside the box correspond to the 25, 75 and 50 sample percentiles respectively. Each open circle represents an extreme value, called "outside."

A logistic regression analysis, however, demonstrated only the duration of fever to be associated with the progression to CAL: a one-day increase in the duration of fever was estimated to increase the risk of progression to CAL by ca. 1.7 times (odds ratio = 1.7; 95% confidence interval = 1.42-2.05).

## Discussion

The present study was conducted to determine whether uteroglobin (UG) is involved in the pathogenesis of Kawasaki disease (KD). Accumulating epidemiological and clinical data suggest an association between KD and the infectious process(es) in genetically susceptible individuals.<sup>1</sup> In addition, massive stimulation of the immune system, especially of the innate or mucosal immune systems, has also been demonstrated during the acute phase of KD. For example, the production of proinflammatory cytokines, eicosanoids, nitric oxide and matrix metalloproteinases (MMPs) as well as the expression of cell adhesion molecules has been reported to be increased,<sup>1</sup> and may contribute to the pathogenesis of systemic vasculitis, especially of coronary artery lesions (CAL). Therefore, it is possible that the genetic factors involved in either inflammation or immunomodulation predispose patients to develop KD or demonstrate a progression to CAL. Onouchi<sup>15</sup> summarized the genetic factors that have been reported to be associated with the incidence or severity of KD: they include tumor necrosis factor- $\alpha$ ,<sup>16,17</sup> IL-1R $\alpha$ ,<sup>18</sup> IL-4,<sup>19</sup> IL-10,<sup>20</sup> IL-18,<sup>21</sup> monocyte chemoattractant protein 1,<sup>22</sup> CD14,<sup>23</sup> mannose-binding lectin,<sup>24</sup> CRP,<sup>25</sup> MMP-3,<sup>26</sup> MMP-13,<sup>27</sup> TIMP2,<sup>28</sup> SLC11A1,<sup>29</sup> platelet-activating factor acetylhydrolase,<sup>30</sup> CCR2,<sup>31</sup> CCR3,<sup>31</sup> CCR5,<sup>32</sup> CCL3L1,<sup>32</sup> CD40L,<sup>33</sup> VEGF and its receptor,<sup>34</sup> and ITPKC,<sup>35</sup> and each of them is involved in the development or modulation of inflammation in different ways. Those studies suggest that genetic susceptibility to KD is not simple and it is also associated with many genes.

The UG, a cytokine-like multifunctional protein secreted by the mucosal epithelia, exerts potent anti-inflammatory and immunomodulatory functions.<sup>3</sup> Recombinant human UG or antiinflamins (synthetic nonapeptides corresponding to the region of UG highly homologous to lipocortin-1) inhibit leukocytic adhesion to endothelial cells.<sup>36,37</sup> Therefore, UG may play a critical role in regulating the inflammatory processes on the mucosal surfaces as well as in the vascular system. Interestingly, a polymorphism at position 38 on the UG gene is associated with the onset or severity of various disorders in which the immunopathological processes play a critical role in the pathogenesis.<sup>5-10</sup> It is particularly noteworthy that the UG gene polymorphism is associated with the severity of IgAN, a representative vasculitis syndrome in childhood<sup>5,6,8-11</sup>, although contradictory findings are also reported.<sup>32</sup> A possible association of the same polymorphism was suspected with the onset or severity of KD, which is another type of vasculitis syndrome in childhood.

The present study demonstrated no association of the genotypic and allelic frequencies at the position 38 of the UG gene with clinical parameters which were considered important in KD. The present study had a limitation that UG genotypes of KD were compared

with healthy controls of other studies; however, the bias was minimized by selecting studies that used the same restriction enzyme and homogenous population as that in Japanese individuals. Although this study cannot completely rule out the possibility that UG plays complex roles in the pathogenesis of KD, no association of UG gene G38A polymorphism with the morbidity rate or the severity of KD was demonstrated. It may reflect a probable difference in the vasculitic mechanism between KD and other diseases.

It is noteworthy that a logistic regression analysis of the present study demonstrated an association between the duration of fever and progression to CAL in KD patients, which is similar to those shown by recent studies.<sup>38,39</sup> It is important to recognize that a progression to CAL involves a number of factors, not only the severity of the disease but also any therapeutic intervention. In fact, the current treatment protocol including high-dose intravenous immunoglobulin yielded a marked decrease in the development of CAL. Though difficult to rationalize, the results of the present study led to the suggestion that a proper diagnosis and early intervention would certainly shorten the duration of fever and decrease the progression to CAL in KD patients.

The etiology of KD remains unclear and can be complex. However, it is extremely important to better understand its pathogenesis and identify genetic and environmental factors that predispose patients to development of KD and progression to CAL in order to prevent a serious outcome. Further studies are therefore warranted.

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The authors declare no potential conflict of interest in association with this article.

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