

# The rs1625579 T>G polymorphism in the *miRNA-137* gene confers a risk of early-onset Kawasaki disease in a southern Chinese population

Di Che,<sup>1,\*</sup> Jiawen Li,<sup>2,\*</sup> Lanyan Fu,<sup>1,\*</sup> Lei Pi,<sup>1</sup> Xing Rong,<sup>2</sup> Yanfei Wang,<sup>3</sup> Yufen Xu,<sup>1</sup> Ping Huang,<sup>3</sup> Maoping Chu,<sup>2</sup> Xiaoqiong Gu<sup>1,4</sup>

<sup>1</sup>Department of Clinical Biological Resource Bank, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China; <sup>2</sup>Children's Heart Center, the Second Affiliated Hospital and Yuying Children's Hospital, Institute of Cardiovascular Development and Translational Medicine, Wenzhou Medical University, Wenzhou, China; <sup>3</sup>Department of Cardiology, Guangzhou Women and Children's Hospital, Guangzhou Medical University, Guangzhou, China; <sup>4</sup>Department of Clinical Lab, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

\*These authors contributed equally to this work

Correspondence: Maoping Chu  
Children's Heart Center, The Second Affiliated Hospital and Yuying Children's Hospital, Institute of Cardiovascular Development and Translational Medicine, Wenzhou Medical University, 109 West Xueyuan Road, Wenzhou 325027, Zhejiang, China  
Email [chmping@hotmail.com](mailto:chmping@hotmail.com)

Xiaoqiong Gu  
Department of Clinical Biological Resource Bank, Department of Clinical Lab, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou 510623, Guangdong, China  
Email [guxiaoqiong@163.com](mailto:guxiaoqiong@163.com)

**Background:** Kawasaki disease (KD) mainly manifests as excessive inflammation and vascular endothelial cell injury. This disease generally occurs in children younger than 5 years of age and is more severe in children younger than 12 months. KD affects males and females at a ratio of 1.5:1. Polymorphisms of the rs1625579 locus in the *miR-137* gene are associated with schizophrenia susceptibility, and high glucose-induced upregulation of miR-137 in vascular endothelial cells promotes monocyte chemotaxis and inflammatory cytokine secretion in gestational diabetes mellitus. However, researchers have not reported whether rs1625579 is associated with KD susceptibility or onset. Therefore, we investigated the relationship between the *miRNA-137* rs1625579 T>G polymorphism and KD susceptibility.

**Methods:** TaqMan real-time polymerase chain reaction was applied to determine the genotypes of 532 patients with KD (365 males and 167 females) and 623 control subjects (402 males and 221 females).

**Results:** Comparison of all cases with all controls revealed that the rs1625579 T>G polymorphism was not associated with KD susceptibility. However, a subgroup analysis revealed that subjects with the rs1625579 TG/GG genotypes exhibited a significantly higher onset risk for KD before 12 months of age than carriers of the TT genotype (adjusted age and gender odds ratio=1.99, 95% CI=1.04–3.83;  $P=0.039$ ).

**Conclusion:** Our results indicate that the rs1625579 T>G polymorphism confers a risk of early-onset KD in southern Chinese children.

**Keywords:** Kawasaki disease, miRNA-137, rs1625579, susceptibility, early onset

## Introduction

Kawasaki disease (KD) was first reported by Dr Kawasaki in 1967.<sup>1</sup> The peak incidence of the onset of KD is from 9 to 11 months of age, and excessive inflammation and vascular endothelial cell (VEC) injury are its main pathological features.<sup>2,3</sup> Over a 10-year period, we observed a significant increase in the proportion of coronary artery stenosis in patients who were <12 months of age at KD onset compared with patients who were older than 1 year.<sup>4</sup> Coronary artery embolism is a severe complication of KD caused by systemic vasculitis and is particularly common in infants and children aged <60 months.<sup>5,6</sup> Teenagers and adults also suffer from KD,<sup>7</sup> which affects males and females at a ratio of 1.5:1.<sup>5,6</sup> Moreover, Leonardi et al reported a case of severe KD in a 3-month-old patient.<sup>8</sup>

The etiopathogenesis of KD is unknown, but the immune response, microbial infections, and genetic factors are thought to contribute to its development. A recent

genome-wide association study identified some remarkable candidate genes associated with KD.<sup>9,10</sup> KD is a type of autoimmune disease that causes immune-related multisystem vasculitis. Some polymorphisms in inflammation-related genes, such as *BLK*, *CD40*, *HLA*, *COPB2* and *FCGR2A*, have been confirmed to be associated with KD susceptibility in the Han Chinese population.<sup>11–15</sup> Polymorphisms in the *ITPKC* and *SLC11A1* genes caused age-dependent elevations in the white blood cell count, platelet count, LDH level, and erythrocyte sedimentation rate in Korean patients with KD, particularly those aged <24 months.<sup>16</sup> These studies provide insights into the etiology of KD, and thus, many interesting immune-related genes should be studied to assess their relationships with susceptibility to KD.

Non-coding miRNAs, which are ~20 nucleotides in length, are involved in the regulation of gene expression and affect protein-coding genes that participate in various biological processes, including the immune response.<sup>17</sup> miRNAs are associated with many diseases, including diabetes mellitus, congenital heart disease, coronary artery disease, Parkinson's disease, and inflammatory bowel diseases.<sup>18–22</sup> KD is one of the most common causes of acute febrile systemic vasculitis,<sup>3</sup> and recent studies have reported that overexpression of *miRNA-137* inhibits upregulation of the inflammatory cytokines IL-6, VCAM-1 and ICAM-1, and human umbilical vein endothelial cell angiogenesis in vitro.<sup>23</sup> Next-generation sequencing has identified >20 miRNAs that distinguish patients with fever from patients with KD; 10 of these miRNAs were selected for further analysis by quantitative polymerase chain reaction,<sup>24</sup> but the authors did not mention a relationship between *miRNA-137* and KD. Using frozen serum samples, Jia et al identified a set of four serum exosomal miRNAs that distinguished patients with KD from other patients with fever and healthy individuals,<sup>25</sup> but this set of miRNAs did not include *miRNA-137*. The *miRNA-137* variant rs1625579 was identified as the strongest predictor of the risk of schizophrenia in a genome-wide association study.<sup>26</sup> Askari et al found that a 31-year-old man with schizophrenia also had microscopic polyangiitis, which is a type of small vessel vasculitis.<sup>27</sup> As shown in some case reports, cerebral hemorrhage, blood vessel expansion, and other phenomena occur in the brains of patients with KD, which suggests that these patients suffer from cerebral vascular inflammation.<sup>28,29</sup> Upregulated *miR-137* expression may play a crucial role in high glucose-induced VEC dysfunction by promoting monocyte chemotaxis and adhesion to VECs in gestational diabetes mellitus.<sup>23</sup> Because *miRNA-137* is involved in VEC injury and inflammation and the rs1625579 T>G polymorphism is related to schizophre-

nia, which may be accompanied by vasculitis, KD may have some relationship with *miRNA-137* polymorphisms. However, no study has investigated the association of the *miRNA-137* rs1625579 T>G polymorphism with KD susceptibility. In the present case-control study, we investigated the association between this polymorphism and KD susceptibility in a southern Chinese population comprising 532 children with KD and 623 healthy controls.

## Materials and methods

### Ethics statement

The study was approved by the Medical Ethics Committee of Guangzhou Women and Children's Medical Center (2014073009) and was conducted according to the International Ethical Guidelines for Research Involving Human Subjects stated in the Declaration of Helsinki. Informed written consent was obtained from the guardians of the patients and controls.

### Study population

Most of the participants reside in southern China. A total of 532 patients who had been recently diagnosed with KD, and 623 healthy controls were recruited from January 2012 to January 2017. KD was diagnosed according to the American Heart Association guidelines.<sup>3</sup> Each participant provided 2 mL of fresh blood. Total genomic DNA extracted from 200 µL of each specimen yielded a sufficient amount for the genomic DNA analysis. The remaining specimens were stored in the clinical biological sample bank at our hospital for further study.

### DNA extraction and genotyping

Genomic DNA was extracted from 200 µL of blood collected from each participant using a TIANamp Blood DNA Kit (centrifugal column; Tiangen, Beijing city, China) according to the manufacturer's specifications. Each 384-well plate contained positive and negative samples, which were used for comparisons. TaqMan real-time polymerase chain reaction was performed with an ABI Q6 instrument (Thermo Fisher Scientific) to genotype *miRNA-137* rs1625579 polymorphisms.

### Statistical analysis

The genotype distributions of the control group, which were expected to be in Hardy-Weinberg equilibrium, were confirmed using a goodness-of-fit chi-squared test, and the differences in variables and genotype frequency distributions between the patients and controls were tested using a two-sided chi-squared test. The relationship between the *miRNA-137* rs1625579 T>G polymorphism and KD

susceptibility was described by calculating odds ratios and 95% CIs through a univariate logistic regression analysis. Multivariate analyses were performed after adjusting for gender and age. The relationships between KD susceptibility and genotypes were analyzed in different subgroups based on age, gender, and the presence of coronary artery lesions (CALs) or coronary artery aneurysms (CAAs). According to the Japanese Kawasaki Disease Research Committee and the coronary z score, CALs were defined as lesions with a luminal diameter  $\geq 3.0$  mm in a child <5 years of age or  $\geq 4.0$  mm in a child  $\geq 5$  years of age, a segment with an internal diameter  $\geq 1.5$  times larger than an adjacent segment or a clearly irregular luminal contour. According to the internal diameters of the coronary vessels, patients with CALs were divided into groups with dilatations or a small CAA (<5.0 mm), middle CAA (5.0–8.0 mm) and large CAA (>8.0 mm).<sup>3</sup> The SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used to rapidly perform all statistical analyses.

## Ethical approval and consent to participate

This study was performed with the approval of the Institutional Committee of Guangzhou Women and Children's Medical Center (2014073009). All participants provided written informed consent.

## Results

### Population characteristics

A total of 532 KD cases and 623 healthy controls comprised the population analyzed in our study. The demographics of all participants are shown in Table 1. The average age of KD onset was 28.39 months. The KD group comprised 365 (68.61%) male patients and 167 (31.39%) female patients. No differences in age ( $P=0.602$ ) or gender ( $P=0.143$ ) were observed between the patients with KD and healthy controls. An analysis of the degree of coronary artery damage in the KD cases revealed 51 (9.59%) patients with CAAs and 481 (90.41%) patients without CAAs (NCAAs), as well as 168 (31.58%) patients with CALs and 364 (68.42%) patients without CALs (NCALs).

### Relationship between the *miRNA-137* rs1625579 T>G polymorphism and KD susceptibility

To explore the association between *miRNA-137* rs1625579 T>G polymorphism and KD susceptibility, we detected the genotype frequency distributions of KD cases and controls.

**Table 1** Variable frequencies and distributions among the patients and controls

Variables	Patients (n=532)	Controls (n=623)	P-value <sup>a</sup>
Age, range (months)	1.00–166.0	0.07–166	0.602
Mean $\pm$ SD	28.39 $\pm$ 24.68	28.48 $\pm$ 25.33	
<12	137 (25.75)	165 (26.48)	
12–60	351 (65.98)	397 (63.72)	
>60	44 (8.27)	61 (9.79)	
Gender			0.143
Female	167 (31.39)	221 (35.47)	
Male	365 (68.61)	402 (64.53)	
CAA	51 (9.59)		
NCAA	481 (90.41)		
CAL	168 (31.58)		
NCAL	364 (68.42)		

**Note:** <sup>a</sup>Two-sided chi-squared tests were used to determine differences in distributions between the patients and the controls. Data shown as n (%) unless indicated otherwise.

**Abbreviations:** CAA, coronary artery aneurysm; CAL, coronary artery lesion; NCAA, patients without CAA; NCAL, patients without CAL.

As shown in Table 2, the controls satisfied the conditions for Hardy–Weinberg equilibrium ( $P=0.791$ ). The genotype frequency distributions of the *miRNA-137* rs1625579 polymorphisms were 85.58% (TT), 13.47% (TG), and 0.95% (GG) in the KD group and 87.94% (TT), 11.74% (TG), and 0.32% (GG) in the controls. No significant relationship was observed between the rs1625579 T>G polymorphism and KD susceptibility.

### Stratification analysis

KD is a disease that related to age and gender, and CAL is the most common complication of KD. After stratifying the subjects by age, gender, and the degree of damage of the coronary artery, we explored the relationship between the rs1625579 T>G polymorphism and KD susceptibility. As illustrated in Table 3, when the patients were stratified by age after adjusting for gender, the TG/GG genotypes of the rs1625579 T>G polymorphism contributed to a higher occurrence of KD compared with carriers of the TT genotype in patients aged <12 months (adjusted odds ratio=1.99, 95% CI=1.04–3.83;  $P=0.039$ ). We also studied other subgroups stratified by gender (adjusted for age), the degree of damage of the coronary artery by CALs and NCALs or CAAs and NCAAs (adjusted for gender and age), but did not detect other notable relationships.

## Discussion

The association between KD susceptibility and rs1625579 T>G polymorphism was analyzed in our case–control

**Table 2** Genotype distributions of the rs1625579 T>G polymorphism and KD susceptibility

Genotype	Patients (n=527)	Controls (n=622)	P-value <sup>a</sup>	Crude OR (95% CI)	P-value	Adjusted OR <sup>b</sup> (95% CI)	P-value <sup>b</sup>
rs1625579 (HWE=0.791)							
TT	451 (85.58)	547 (87.94)		1.00		1.00	
TG	71 (13.47)	73 (11.74)		1.19 (0.84–1.69)	0.334	1.20 (0.85–1.71)	0.301
GG	5 (0.95)	2 (0.32)		3.05 (0.59–15.81)	0.183	3.19 (0.61–16.56)	0.168
Additive			0.258	1.26 (0.91–1.73)	0.164	1.28 (0.93–1.77)	0.130
Dominant	76 (14.42)	75 (12.06)	0.237	1.23 (0.87–1.73)	0.238	1.26 (0.89–1.77)	0.196
Recessive	522 (99.05)	620 (99.68)	0.173	2.97 (0.57–15.36)	0.195	3.11 (0.60–16.12)	0.178

**Notes:** <sup>a</sup>Chi-squared tests were used to determine differences in genotype distributions between the children with KD and the controls. <sup>b</sup>Adjusted for age and gender. Data shown as n (%). Additive, homozygous rare vs homozygous frequent allele; dominant, homozygous rare + heterozygous vs homozygous frequent allele; and recessive, homozygous rare vs heterozygous + homozygous frequent allele.

**Abbreviations:** HWE, Hardy–Weinberg equation; KD, Kawasaki disease; OR, odds ratio.

**Table 3** Subgroup analyses of the relationship between the rs1625579 T>G polymorphism and KD susceptibility

Variables	TT	TG/GG	Crude OR (95% CI)	P-value	Adjusted OR <sup>a</sup> (95% CI)	P-value <sup>a</sup>
	Patients/controls, n					
Age, months						
<12	109/145	26/20	1.73 (0.92–3.26)	0.090	<b>1.99 (1.04–3.83)</b>	<b>0.039</b>
12–60	306/346	42/50	0.95 (0.61–1.47)	0.818	0.96 (0.62–1.49)	0.862
>60	36/56	8/5	2.49 (0.76–8.21)	0.134	2.37 (0.69–8.13)	0.169
Gender						
Female	133/189	33/32	1.47 (0.86–2.50)	0.161	1.52 (0.88–2.62)	0.132
Male	318/358	43/43	1.13 (0.72–1.76)	0.604	1.12 (0.71–1.76)	0.619
CAA	42/547	8/75	1.39 (0.63–3.07)	0.417	1.42 (0.64–3.16)	0.388
NCAA	409/547	68/75	1.21 (0.85–1.73)	0.284	1.23 (0.86–1.75)	0.251
CAL	145/547	22/75	1.11 (0.67–1.84)	0.697	1.15 (0.69–1.93)	0.585
NCAL	306/547	54/75	1.29 (0.88–1.88)	0.189	1.31 (0.89–1.91)	0.168

**Notes:** <sup>a</sup>Adjusted for age and gender. Statistically significant values are shown in bold ( $P < 0.05$ ).

**Abbreviations:** CAA, coronary artery aneurysm; CAL, coronary artery lesion; KD, Kawasaki disease; NCAA, patients without CAA; NCAL, patients without CAL; OR, odds ratio.

investigation. No significant association between the rs1625579 T>G polymorphism and KD susceptibility was noted in the patients (Table 2). The subgroup analysis indicated that the *miRNA-137* rs1625579 TG/GG genotypes increased the risk of KD in patients aged <12 months (Table 3). KD affects children aged between 6 months and 5 years. However, in our subgroup analysis, we did not conclude that the occurrence of CALs or CAAs in patients with KD aged <1 year was related to the *miRNA-137* rs1625579 T>G polymorphism. We intend to collect more samples from patients with KD aged <1 year and presenting with coronary complications to confirm this discovery.

This study is the first to examine *miRNA-137* rs1625579 polymorphisms in patients with KD. Recent research showed that overexpression of *miRNA-137* significantly inhibited tumor necrosis factor alpha-induced protein 1 (TNFAIP1) production both in vivo and in vitro,<sup>30</sup> and *miRNA-137* suppressed vascular smooth muscle cell proliferation and migration.<sup>31</sup> Overexpression of miR-137 inhibited upregulation of

the inflammatory cytokines IL-6, VCAM-1 and ICAM-1, and human umbilical vein endothelial cell angiogenesis in vitro.<sup>23</sup> Central nervous system vasculitis has been reported to cause psychosis.<sup>27</sup> Chen et al noted remarkable relationships between autoimmune diseases, such as psoriasis, Graves' disease and pernicious anemia, and schizophrenia.<sup>32</sup> KD is a type of autoimmune disease that causes immune-related multisystem vasculitis. Based on our results, doctors should be more aware of vasculitis in the brains of patients with KD, particularly in patients aged <1 year. The majority of brain growth occurs from birth to 2 years of age, and the brain is easily injured during this period.<sup>33</sup> The hypothalamus is the area most likely to be affected. A meta-analysis by Zhang et al revealed that the rs1625579 single-nucleotide polymorphism in the *miR-137* gene might be involved in schizophrenia susceptibility in a Chinese Han population,<sup>34</sup> but another meta-analysis by Pu and Xiao did not identify a significant association between rs1625579 and schizophrenia in an Asian population.<sup>35</sup> The finding that rs1625579 in *miRNA-137* is



associated with schizophrenia in southern Chinese patients has been verified.<sup>36</sup> Schizophrenia is associated with decreases in the volumes of many brain structures, including the hypothalamus.<sup>37</sup> Thus, rs1625579 polymorphisms are associated with the development of the hypothalamus, particularly in infants, which may explain why children in that age group are prone to vasculitis, especially if they are diagnosed with KD.

To the best of our knowledge, KD is an age- and gender-related disease that generally occurs in children aged <5 years and is more severe in children aged <12 months.<sup>3,38</sup> However, why KD occurs in children younger than 5 years old is unclear. Wang et al reported that *miRNA-137* appeared to influence age at onset in patients with schizophrenia, but might not be related to susceptibility.<sup>39</sup> Similarly, based on the results from the present study, the rs1625579 T>G polymorphism in *miRNA-137* is not associated with KD susceptibility in patients with KD. However, further subgroup analyses revealed a significantly earlier onset of KD in subjects with the rs1625579 TG/GG genotypes in whom disease onset occurred before 12 months of age than in patients with the TT genotype. Thus, our study suggests that the rs1625579 T>G polymorphism confers a risk of early-onset KD in southern Chinese children. This factor may be one reason why onset of KD is early in children aged <12 months. The limitations of this study are related to the insufficient number of patients with coronary aneurysms, and further studies with a larger sample size are needed to confirm the results.

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## Disclosure

The authors report no conflicts of interest in this work.

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