RESEARCH ARTICLE

WILEY

Association between the *miRNA-149* rs2292832 T>C polymorphism and Kawasaki disease susceptibility in a southern Chinese population

Jiawen Li[1] | Jinxin Wang[1] | Xiaoping Su[1] | Zhiyong Jiang[2] | Xing Rong[1] | Xueping Gu[2] 🆔 | Chang Jia[1] | Lanlan Zeng[3] | Hao Zheng[3] | Xiaoqiong Gu[4] | Maoping Chu[1] 🆔

[1]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

[2]Department of Blood Transfusion and Clinical Lab, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

[3]Department of Clinical Lab, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

[4]Department of Blood Transfusion, Clinical Biological Resource Bank and Clinical Lab, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

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

Xiaoqiong Gu, Department of Blood Transfusion, Clinical Biological Resource Bank and Clinical Lab, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China.
Email: guxiaoqiong@163.com

Abstract

Background: Kawasaki disease (KD), which is characterized by vasculitis, is prone to occur in patients under 5 years of age, has an ambiguous etiology, and displays coronary artery lesions as the chief complication. Previous studies have linked *miRNA-149* to cancers, and rs2292832 T>C is related to allergic diseases and inflammatory bowel disease, which both show immune system disorders and coronary artery disease. Therefore, we performed a study concentrating on the association between the *miRNA-149* rs2292832 T>C polymorphism and KD susceptibility.

Methods: The subjects enrolled were 532 children with KD and 623 controls. We used TaqMan real-time PCR to obtain the genotypes of the rs2292832 T>C polymorphism.

Results: Ultimately, no significant association was found between the *miRNA-149* rs2292832 T>C polymorphism and KD susceptibility, even in stratification analysis.

Conclusion: Our results indicated that in southern Chinese patients, the *miRNA-149* rs2292832 T>C polymorphism did not affect KD susceptibility, which needs to be further confirmed.

KEYWORDS
Kawasaki disease, *miRNA-149*, polymorphism

- -

1 | INTRODUCTION

Kawasaki disease (KD), an autoimmune syndrome characterized by vasculitis, is prone to emerge in children under 5 years of age and was first detected in 1967.[1] Currently, acquired heart disease is most likely caused by KD in numerous developed countries.[2] Multiple complications of KD affect the cardiovascular and non-cardiovascular systems. As common complications in the cardiovascular system, coronary artery aneurysms are increasingly being studied along with coronary artery dilatation.[3] According to some investigations, the annual incidence of KD has gradually increased in recent years in multiple places, such as Italy, Australia, South Korea, Japan, Inner Mongolia, and Jilin.[4-9] Therefore, the incidence of KD is gradually rising in most regions, which is one of the reasons for studying this disease. The number of boys suffering from KD is approximately twice that of girls, and the mean age of onset in most regions is approximately 28 months.[4,5,9-12] In individuals with KD, the occurrence rate of coronary artery lesions (CALs) was 23.5%, 32.6%, 40.2%, 41%, and 41.4% in Australia, Athens, Inner Mongolia, Jordan, and Jilin, respectively.[4,5,8,13,14]

Thus far, the pathogenesis of KD has not been fully elucidated. Single or multiple pathogens could stimulate an excessive immune response in susceptible individuals, easily inducing a systemic inflammatory response, which may give rise to KD.[15-17] Through the analysis of bacteria and KD in the pharynx and serum, researchers found that streptococcus might be related to the onset of KD.[18] The American Heart Association introduced criteria to distinguish the classic and incomplete forms of KD from other diseases. Classic KD is diagnosed in patients sustaining a fever for at least 4 days who have ≥4 chief clinical signs. Uncommon KD presents as a fever with an unexplained cause, <4 chief clinical signs, and corresponding echocardiographic and laboratory findings.[2]

MicroRNAs (miRNAs) are noncoding RNA molecules of approximately 20 nucleotides that can affect the expression of some genes.[19,20] More than 25 miRNAs have been identified for differentiating patients with KD from patients with fever using next-generation sequencing. Quantitative polymerase chain reaction was selected for further analysis of some of these miRNAs, but researchers did not find a connection between *miRNA-149* and KD.[21] In searching the literature, we found that *miRNA-149* has a definite association with some cancers, such as lung cancer, colorectal cancer, laryngeal squamous cell carcinoma, hepatocellular carcinoma, and neuroblastoma.[22-26] To a certain extent, the alteration of rs2292832 T>C in *miRNA-149* may cause alterations in expression and susceptibility to diseases. For example, Sun et al[27] reported that in a Korean population, some miRNAs and combinations of genotype polymorphisms, such as *miRNA-149* rs2292832 T>C, could contribute to the occurrence of coronary artery disease, a major complication in KD. A study in a Chinese population might obtain similar results. A previous report revealed that the rs2292832 T>C polymorphism might have a potential connection with comorbid diseases, including allergic rhinitis and asthma and allergic rhinitis alone, and these allergic illnesses are caused by disorders in the immune system, such as the abnormal activation of T cells.[28] The rs2292832 T allele could enhance the severity of inflammatory bowel disease, which is similar to KD, as it is caused by abnormal activation of the immune system by a pathogen.[29]

Nevertheless, no study has examined the association of the *miRNA-149* rs2292832 T>C polymorphism with KD susceptibility. Based on data from our medical center, we examined 532 KD children and 623 controls to carry out a case-control study and evaluate the relationship between the *miRNA-149* rs2292832 T>C polymorphism and KD susceptibility in a southern Chinese population.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

The present study conducted at Guangzhou Women and Children's Medical Center satisfied the criterion for human subjects in the Declaration of Helsinki. The Review Committee (2014073009) of the medical center approved this study. Written informed consent was obtained from the legal guardians of all participants.

2.2 | Study subjects

All participants recruited were unrelated Chinese Han individuals from southern China. A total of 623 healthy controls and 532 patients diagnosed with KD were recruited from January 2012 to January 2017 as we described previously.[30-33] Two milliliters of fresh blood was collected from each participant, and 200 μL of each blood sample was employed to extract DNA.

2.3 | DNA extraction and genotyping

A TIANamp Blood DNA Kit (Centrifugal column, Tiangen) was used to extract DNA from the blood samples according to the manufacturer's instructions.[34-36] TaqMan real-time PCR assays were set up in 384-well plates containing positive and negative samples and were carried out in an ABI Q6 system (Applied Biosystems) to genotype the *miRNA-149* rs2292832 T>C polymorphism.[37-39]

2.4 | Statistical analysis

Utilizing two-sided chi-square test and chi-square test, we obtained the distribution of various parameters and the genotype distribution between cases and controls. A goodness-of-fit chi-square test was used to assess the control genotype distributions for Hardy-Weinberg equilibrium. Odds ratios (ORs) and 95% confidence intervals (CIs) of homozygotes (CC in comparison with TT), heterozygotes (TC in comparison with TT), the recessive model (CC in comparison with TT + TC), and the dominant model (CC + TC in comparison with TT) were obtained by univariate logistic regression and used to

illustrate the relationship between the *miRNA-149* rs2292832 T>C polymorphism and KD susceptibility. As data were divided into subgroups on the basis of coronary lesion (CAL), coronary artery aneurysm (CAA), age, gender, and genotypes (TT, TC/CC), associations between KD susceptibility and the polymorphism were considered in depth via stratification. In accordance with the Japanese Kawasaki Disease Research Committee as well as the coronary z score, artery lesions with a luminal diameter ≥4.0 mm in children ≥5 years of age or ≥3.0 mm in children <5 years of age, a section with a diameter ≥1.5 times larger than a proximal segment or clearly irregular profile of the artery, were defined as CALs. Depending on the diameter of the personal coronary artery, CAAs were defined as major damage of the coronary artery.[40] SAS software (version 9.4; SAS Institute) was applied to implement all statistical analyses.

3 | RESULTS

3.1 | Population features

A total of 623 healthy controls and 532 KD children were included in the current study (Table S1). The average age of morbidity of KD patients was 28.39 months, and in contrast, the average age of the controls was 28.48 months. There were 167 (31.39%) female KD patients, a lower number than the 365 (68.61%) male KD patients. The differences in age (*P* = .602) or gender (*P* = .143) were not significant between KD patients and healthy controls. Based on coronary lesions, 168 (31.58%) and 364 (68.42%) subjects were grouped into the CAL and no coronary artery lesion (NCAL) groups, respectively. In addition, 51 (9.59%) patients had CAAs, and 481 (90.41%) had no CAAs.

3.2 | The *miRNA-149* rs2292832 polymorphism and KD susceptibility

We successfully genotyped 507 KD patients and 612 healthy controls, as illustrated in Table 1. We employed the goodness-of-fit chi-square test, and the *P* value obtained was .791, satisfying Hardy-Weinberg equilibrium. The genotype distributions of *miRNA-149* rs2292832 were as follows: 67.26% (TT), 23.67% (TC), and 9.07% (CC) in the KD patients and 70.10% (TT), 22.06% (TC), and 7.84% (CC) in the healthy controls. No significant association was discovered between the *miRNA-149* rs2292832 T>C polymorphism and KD susceptibility (TC compared with TT: OR = 1.12, 95% CI = 0.84-1.48; CC compared with TT: OR = 1.20, 95% CI = 0.78-1.84; CC compared with TT + TC: OR = 1.17, 95% CI = 0.76-1.78, CC + TC compared with TT: OR = 1.14, 95% CI = 0.88-1.47).

3.3 | Stratification analysis

We assessed the connection between the rs2292832 T>C polymorphism and KD susceptibility after stratification by age, gender, CAL,

and CAA. As shown in Table 2, the adjusted *P* values of the differences between the associations of CAL, NCAL, CAA, and no coronary artery aneurysm (NCAA) with the TT genotype and the TC/CC genotypes of rs2292832 were 0.306, 0.507, 0.178, and 0.452, respectively. No notable association was observed in any of the subgroups.

4 | DISCUSSION

There are few studies on miRNAs and KD, and there is no research on the rs2292832 T>C polymorphism and KD susceptibility. In the first genome-wide association study (GWAS) for KD, variants of several genes (such as *Inx1*, *CAMK2D*, *ZFHX3*, *CSMD1*, and *tcp1*) were suggested to be associated with KD susceptibility.[41] In addition, SNPs in rs2254546, rs2857151, rs4813003, rs16921209, rs7922552, rs17076896, rs12068753, rs4786091, and rs2833195 and some SNPs in *BLK*, *CD40*, and *FCGR2A* may be relevant to susceptibility, clinical presentations (such as CAA and CAL), laboratory data (such as CRP), treatment of KD, and gender in KD in GWASs.[42-48]

Therefore, we examined the relationship between the occurrence of KD and the *miRNA-149* rs2292832 T>C polymorphism in this case-control trial. We failed to acquire meaningful positive results that could assist future experiments. KD-related allergic diseases, inflammatory bowel disease, and coronary artery disease may be related to the rs2292832 T>C polymorphism. A study of the relationship between the rs2292832 T>C polymorphism and KD is necessary. The negative results of this article will not only assist others in excluding the possibility of this association in a southern Chinese population but will also provide similar ideas for further studies, such as studying the nexus between the rs2292832 T>C polymorphism and KD susceptibility in other populations around the world.

As mentioned above, 168 (31.58%) children suffering from CAL were reported in southern China. In Inner Mongolia, Jilin, and Jordan, the incidence of CAL in KD was approximately 40%.[4,8,13] In Australia, the incidence of CAL in KD was approximately 23%.[5] The incidences of CAL in Western countries, such as Ireland, Italy, and Athens, Greece, were 2.9%, 15.6%, and 32.6%, respectively, which was close to that in southern China.[14,49,50] The distinct occurrence of CAL in KD patients worldwide may be related to the frequency of rs2292832 genotypes due to differences in race based on diverse hereditary susceptibility, geography, time, definition of coronary artery injury, and other factors.

Studies have shown that genetic variants may increase the susceptibility to asthma and allergic rhinitis, and asthma was suggested to be connected with the *miR-149* rs2292832 T>C polymorphism in a study by Hu et al[28] Similar to KD, these are all inflammatory diseases, and correlations with these diseases are possible. From a laboratory and clinical perspective, according to the relevant literature and Harada score, age, gender, plasma albumin, CRP, WBC, and Hc, all could be risk factors for CAL in KD patients.[51-53] Bai et al[54] reported that increased CRP levels (≥30 mg/L), hepatomegaly, ESR acceleration (≥ 40 mm/h), and IVIG ineffectiveness had a significant effect on CAL. Particularly in patients aged <24 months, age-dependent

TABLE 1 Genotype distributions of rs2292832 T>C polymorphism and Kawasaki disease susceptibility

Genotype	Cases (N = 507)	Controls (N = 612)	P^a	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P^b
TT	341 (67.26)	429 (70.10)		1.00		1.00	
TC	120 (23.67)	135 (22.06)		1.13 (0.85-1.50)	.403	1.12 (0.84-1.48)	.450
CC	46 (9.07)	48 (7.84)		1.22 (0.79-1.87)	.369	1.20 (0.78-1.84)	.409
Additive			.566	1.11 (0.92-1.33)	.289	1.10 (0.92-1.33)	.303
Dominant	166 (32.74)	183 (29.90)	.307	1.14 (0.89-1.47)	.308	1.14 (0.88-1.47)	.320
Recessive	461 (90.93)	564 (92.17)	.460	1.17 (0.77-1.79)	.461	1.17 (0.76-1.78)	.478

Abbreviations: CI: confidence interval; OR, odds ratio.

[a]χ^2 test for genotype distributions between Kawasaki disease suffers and controls.

[b]Adjusted for age and gender.

TABLE 2 Stratification analysis for the connection between rs2292832 T>C polymorphism and Kawasaki disease susceptibility

Variables	TT	TC/CC	Crude OR (95% CI)	P	Adjusted OR[a] (95% CI)	P^a
	Cases/controls					
Age, month						
<12	84/115	44/49	1.23 (0.75-2.02)	.413	1.14 (0.69-1.88)	.614
12-60	232/274	105/113	1.10 (0.80-1.51)	.566	1.11 (0.80-1.52)	.536
>60	25/40	17/21	1.30 (0.58-2.92)	.532	1.44 (0.62-3.36)	.398
Gender						
Females	109/158	50/63	1.15 (0.74-1.79)	.536	1.11 (0.70-1.74)	.666
Males	232/271	116/120	1.13 (0.83-1.54)	.442	1.14 (0.83-1.55)	.417
Coronary artery aneurysm						
CAA	29/429	19/183	1.54 (0.84-2.81)	.164	1.52 (0.83-2.78)	.178
NCAA	312/429	147/183	1.11 (0.85-1.44)	.456	1.11 (0.85-1.44)	.452
Coronary artery lesion						
CAL	106/429	55/183	1.22 (0.84-1.76)	.298	1.21 (0.84-1.76)	.306
NCAL	235/429	111/183	1.11 (0.83-1.47)	.483	1.10 (0.83-1.46)	.507

Abbreviations: CAA, coronary artery aneurysm; CAL, coronary artery lesion; CI: confidence interval; NCAA, patients without CAA; NCAL, patients without CAL; OR, odds ratio.

[a]Adjusted for age and gender, omitting the corresponding stratify factor.

increases in the LDH level, white blood cell count, erythrocyte sedimentation rate, and platelet count in Korean patients diagnosed with KD were caused by polymorphisms in two genes, ITPKC and SLC11A1.[55] The diverse incidences of CAL may be due to different averages in various laboratory indices. According to epidemiology reports from Athens, 42.2% of sufferers with classic KD had CAL, but only 4.5% of sufferers with incomplete KD had CAL.[14] We suspect that the ratio of typical KD to incomplete KD is also one of the factors contributing to the diverse incidence of CAL.

The *miRNA-149* rs2292832 T>C polymorphism might not have an influence on the occurrence of KD in our current research. Nevertheless, our finding of no positive relationship is needed to assess further related aspects or exclude other interferential conditions. For instance, our study subjects were limited to children in southern China, an uncharacteristic Chinese population. The effect of low-penetrance hereditary variation on the result may not have been detected because of the small sample size and relatively high morbidity. In addition, some relevant mutation sites or genes

exert a substantial effect on the final result. The functions of the rs2292832 T>C polymorphism might be concealed by interacting elements.[56] The mechanism of KD caused by multiple factors is still unclear.[57] Therefore, our research is not convincing without other useful data, such as disease history and living environment. Based on these results, we will try to address these issues in the future.

5 | CONCLUSIONS

In conclusion, we found that the *miRNA-149* rs2292832 T>C polymorphism did not affect KD susceptibility in southern Chinese patients, which needs to be further investigated in other populations.

from the Clinical Biological Resource Bank of Guangzhou Women and Children's Medical Center provided are key to the experiment.

ORCID

Xueping Gu https://orcid.org/0000-0002-5893-7440
Maoping Chu https://orcid.org/0000-0003-0975-7176

DATA AVAILABILITY STATEMENT

Data are available upon request.

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi*. 1967;16:178-222.
2. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of kawasaki disease: a scientific statement for health professionals from the american heart association. *Circulation*. 2017;135:e927-e999.
3. Hirose O, Misawa H, Kijima Y, et al. Two-dimensional echocardiography of coronary artery in Kawasaki disease (MCLS): detection, changes in acute phase, and follow-up observation of the aneurysm (author's transl). *J Cardiogr*. 1981;11:89-104.
4. Piao JH, Jin L-H, Lv J, Zhou Y, Jin C-J, Jin Z-Y. Epidemiological investigation of Kawasaki disease in Jilin province of China from 2000 to 2008. *Cardiol Young*. 2010;20:426-432.
5. Saundankar J, Yim D, Itotoh B, et al. The epidemiology and clinical features of Kawasaki disease in Australia. *Pediatrics*. 2014;133:e1009-e1014.
6. Makino N, Nakamura Y, Yashiro M, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. *J Epidemiol*. 2015;25:239-245.
7. Ha S, Seo GH, Kim KY, Kim DS. Epidemiologic study on Kawasaki disease in Korea, 2007–2014: based on health insurance review & assessment service claims. *J Korean Med Sci*. 2016;31:1445-1449.
8. Zhang X, Liang Y, Feng W, Su X, Zhu H. Epidemiologic survey of Kawasaki disease in Inner Mongolia, China, between 2001 and 2013. *Exp Ther Med*. 2016;12:1220-1224.
9. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: surveillance from national hospitalization records. *Eur J Pediatr*. 2017;176:1061-1065.
10. Lee EJ, Park YW, Hong YM, Lee JS, Han JW. Epidemiology of Kawasaki disease in infants 3 months of age and younger. *Korean J Pediatr*. 2012;55:202-205.
11. Kim GB, Park S, Eun LY, et al. Epidemiology and clinical features of Kawasaki disease in South Korea, 2012–2014. *Pediatr Infect Dis J*. 2017;36:482-485.
12. Pinto FF, Laranjo S, Mota Carmo M, Brito MJ, Cruz Ferreira R. Twelve years of Kawasaki disease in Portugal: epidemiology in hospitalized children. *Pediatr Infect Dis J*. 2017;36:364-368.
13. Al-Ammouri I, Al-Wahsh S, Khuri-Bulos N. Kawasaki disease in Jordan: demographics, presentation, and outcome. *Cardiol Young*. 2012;22:390-395.
14. Giannouli G, Tzoumaka-Bakoula C, Kopsidas I, Papadogeorgou P, Chrousos GP, Michos A. Epidemiology and risk factors for coronary artery abnormalities in children with complete and incomplete Kawasaki disease during a 10-year period. *Pediatr Cardiol*. 2013;34:1476-1481.
15. Huang HP, Lai Y-C, Tsai I-J, Chen S-Y, Cheng C-H, Tsau Y-K. Nephromegaly in children with Kawasaki disease: new supporting evidence for diagnosis and its possible mechanism. *Pediatr Res*. 2008;63:207-210.
16. Takahashi K, Oharaseki T, Yokouchi Y. Pathogenesis of Kawasaki disease. *Clin Exp Immunol*. 2011;164(Suppl 1):20-22.
17. Yim D, Curtis N, Cheung M, Burgner D. Update on Kawasaki disease: epidemiology, aetiology and pathogenesis. *J Paediatr Child Health*. 2013;49:704-708.
18. Hamada H, Sekizuka T, Oba K, et al. Comprehensive pathogen detection associated with four recurrent episodes of Kawasaki disease in a patient during a single year using next-generation sequencing. *JMM Case Rep*. 2016;3:e005019.
19. Schwab R, Palatnik JF, Riester M, Schommer C, Schmid M, Weigel D. Specific effects of microRNAs on the plant transcriptome. *Dev Cell*. 2005;8:517-527.
20. Achour C, Bogard B, Hubé F, Mani SA, Santulli G, Taube JH. The Non-coding RNA journal club: highlights on recent papers-5. *Noncoding RNA*. 2017;3.
21. Kuo HC, Hsieh K-S, Ming-Huey Guo M, et al. Next-generation sequencing identifies micro-RNA-based biomarker panel for Kawasaki disease. *J Allergy Clin Immunol*. 2016;138:1227-1230.
22. Wang F, Ma Y-L, Zhang P, et al. SP1 mediates the link between methylation of the tumour suppressor miR-149 and outcome in colorectal cancer. *J Pathol*. 2013;229:12-24.
23. Silva Bde O, Lima KF, Goncalves LR, Silveira MB, Moraes KC. MicroRNA profiling of the effect of the heptapeptide angiotensin-(1–7) in A549 lung tumor cells reveals a role for miRNA149-3p in cellular migration processes. *PLoS ONE*. 2016;11:e0162094.
24. Xu Y, Lin YP, Yang D, Zhang G, Zhou HF. Clinical significance of miR-149 in the survival of patients with laryngeal squamous cell carcinoma. *Biomed Res Int*. 2016;2016:1-6.
25. Ye LX, Fu CW, Jiang F, Cui YX, Meng W. A meta-analysis of microRNA-149, microRNA-499 gene polymorphism and susceptibility to hepatocellular carcinoma. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2016;50:445-450.
26. He J, Zou Y, Liu X, et al. Association of common genetic variants in pre-microRNAs and neuroblastoma susceptibility: a two-center study in Chinese children. *Mol Ther Nucleic Acids*. 2018;11:1-8.
27. Sung JH, Kim S-H, Yang W-I, et al. miRNA polymorphisms (miR146a, miR149, miR196a2 and miR499) are associated with the risk of coronary artery disease. *Mol Med Rep*. 2016;14:2328-2342.
28. Hu D, Zhang Z, Ke X, Kang H, Hong S. A functional variant of miRNA-149 confers risk for allergic rhinitis and comorbid asthma in Chinese children. *Int J Immunogenet*. 2017;44:62-70.
29. Zhu M, Li D, Jin M, Li M. Association between microRNA polymorphisms and the risk of inflammatory bowel disease. *Mol Med Rep*. 2016;13:5297-5308.
30. Che D, Li J, Fu L, et al. The rs1625579 T>G polymorphism in the miRNA-13 gene confers a risk of early- onset Kawasaki disease in a southern Chinese population. *Infect Drug Resist*. 2018;11: 1055-1060.
31. Pi L, Fu L, Xu Y, et al. Lack of association between miR-218 rs11134527 A>G and Kawasaki disease susceptibility. *Biosci Rep*. 2018;38(3): BSR20180367. https://doi.org/10.1042/BSR20 180367
32. Zhang L, Wang J, Che D, et al. The association between the miR-146a rs2910164 C>G polymorphism and Kawasaki disease in a southern Chinese population. *Biosci Rep*. 2018;38(4): BSR20180749. https://doi.org/10.1042/BSR20180749

33. Wang J, Li J, Qiu H, et al. Association between miRNA-196a2 rs11614913 T>C polymorphism and Kawasaki disease susceptibility in southern Chinese children. *J Clin Lab Anal.* 2019;33:e22925.

34. He J, Wang F, Zhu J, et al. Association of potentially functional variants in the XPG gene with neuroblastoma risk in a Chinese population. *J Cell Mol Med.* 2016;20:1481-1490.

35. He J, Yang T, Zhang R, et al. Potentially functional polymorphisms in the LIN28B gene contribute to neuroblastoma susceptibility in Chinese children. *J Cell Mol Med.* 2016;20:1534-1541.

36. He J, Zhang R, Zou Y, et al. Evaluation of GWAS-identified SNPs at 6p22 with neuroblastoma susceptibility in a Chinese population. *Tumour Biol.* 2016;37:1635-1639.

37. He J, Qiu L-X, Wang M-Y, et al. Polymorphisms in the XPG gene and risk of gastric cancer in Chinese populations. *Hum Genet.* 2012;131:1235-1244.

38. Hua RX, Zhu J, Jiang D-H, et al. Association of XPC gene polymorphisms with colorectal cancer risk in a southern Chinese population: a case-control study and meta-analysis. *Genes (Basel).* 2016;7:73.

39. Hua RX, Zhuo ZJ, Shen GP, et al. Polymorphisms in the XPC gene and gastric cancer susceptibility in a Southern Chinese population. *Onco Targets Ther.* 2016;9:5513-5519.

40. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young. American Heart Association. *Circulation.* 2004;110:2747-2771.

41. Burgner D, Davila S, Breunis WB, et al. A genome-wide association study identifies novel and functionally related susceptibility Loci for Kawasaki disease. *PLoS Genet.* 2009;5:e1000319.

42. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. *Nat Genet.* 2011;43:1241-1246.

43. Lee YC, Kuo H-C, Chang J-S, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. *Nat Genet.* 2012;44:522-525.

44. Onouchi Y, Ozaki K, Burns JC, et al. A genome-wide association study identifies three new risk loci for Kawasaki disease. *Nat Genet.* 2012;44:517-521.

45. Lin MT, Hsu CL, Chen PL, et al. A genome-wide association analysis identifies novel susceptibility loci for coronary arterial lesions in patients with Kawasaki disease. *Transl Res.* 2013;161:513-515.

46. Kim JJ, Yun SW, Yu JJ, et al. Common variants in the CRP promoter are associated with a high C-reactive protein level in Kawasaki disease. *Pediatr Cardiol.* 2015;36:438-444.

47. Kuo HC, Li S-C, Guo MM-H, et al. Genome-wide association study identifies novel susceptibility genes associated with coronary artery aneurysm formation in Kawasaki disease. *PLoS ONE.* 2016;11:e0154943.

48. Kwon YC, Kim JJ, Yun SW, et al. Male-specific association of the FCGR2A His167Arg polymorphism with Kawasaki disease. *PLoS ONE.* 2017;12:e0184248.

49. Rigante D, Valentini P, Rizzo D, et al. Responsiveness to intravenous immunoglobulins and occurrence of coronary artery abnormalities in a single-center cohort of Italian patients with Kawasaki syndrome. *Rheumatol Int.* 2010;30:841-846.

50. Bar-Meir M, Haklai Z, Dor M. Kawasaki disease in Israel. *Pediatr Infect Dis J.* 2011;30:589-592.

51. Anderson MS, Todd JK, Glode MP. Delayed diagnosis of Kawasaki syndrome: an analysis of the problem. *Pediatrics.* 2005;115:e428-e433.

52. Kim DS. Kawasaki disease. *Yonsei Med J.* 2006;47:759-772.

53. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation.* 2006;113:2606-2612.

54. Bai L, Feng T, Yang L, et al. Retrospective analysis of risk factors associated with Kawasaki disease in China. *Oncotarget.* 2017;8:54357-54363.

55. Kim KY, Bae YS, Ji W, Shin D, Kim HS, Kim DS. ITPKC and SLC11A1 gene polymorphisms and gene-gene interactions in Korean patients with Kawasaki disease. *Yonsei Med J.* 2018;59:119-127.

56. Stoll C, Baretton G, Lohrs U. The influence of p53 and associated factors on the outcome of patients with oral squamous cell carcinoma. *Virchows Arch.* 1998;433:427-433.

57. Burgner D, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? *Int J Infect Dis.* 2005;9:185-194.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.