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RESEARCH ARTICLE

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Association between *miRNA-196a2* rs11614913 T>C polymorphism and Kawasaki disease susceptibility in southern Chinese children

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Abstract

Background: miRNAs play important roles in a variety of diseases. Thus, the association between *miRNA-196a2* rs11614913 T>C polymorphism and Kawasaki disease susceptibility is still unknown.

Methods: We included 532 children with Kawasaki disease and 623 healthy children from South China, and their DNA was extracted for genotyping by TaqMan methodology. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of association.

Results: No significant associations were observed between the *miRNA-196a2* rs11614913 T>C polymorphisms and Kawasaki disease risk (TC vs TT: adjusted OR = 1.04, 95% CI = 0.79-1.37; CC vs TT: adjusted OR = 0.87, 95% CI = 0.63-1.21; dominant model: adjusted OR = 0.99, 95% CI = 0.76-1.27; and recessive model: adjusted OR = 0.85, 95% CI = 0.64-1.13). There was also no significant correlation found in stratified analyses.

Conclusion: This study suggests that *miRNA-196a2* rs11614913 T>C may not be associated with Kawasaki disease susceptibility in a southern Chinese population. Larger, multicenter studies are needed to confirm our conclusions.

KEYWORDS

Kawasaki disease, *miRNA-196a2*, polymorphism, susceptibility

Jinxin Wang and Jiawen Li equally contributed to this work.

1 | INTRODUCTION

Kawasaki disease, a primary cause of acquired heart disease,[1] is a self-limiting disease that mainly affects younger children (younger than 5 years old) and is accompanied by a systemic vascular inflammatory response. With the use of intravenous immunoglobulin (IVIG) standardized treatment, the incidence of coronary lesions has dropped from 15%-25% to 3%-5%.[2] The epidemiology of Kawasaki disease has unique population distribution characteristics. The incidence in Asian populations is much higher than that in other populations; Japan, with an incidence of 304 per 100 000, and South Korea, with an incidence of 194.7 per 100 000, are ranked as the highest in the world. The per 100 000 incidence in the United States,[3] Australia,[4] and England[5] is 25, 9.34, and 8.39, respectively, which are very different from that in East Asia. There is no national statistical survey in China; only local incidence is reported, such as in Beijing, with 49.4 per 100 000 people.[6] At the same time, in the Asian population in non-Asian countries, the incidence rate is also higher than that in other ethnic groups in the same region. The incidence among Asian people on the island of Hawaii is 83.2-210.5/100 000, and the incidence among Caucasian people in Hawaii is only 13.7/100 000.[7]

These data strongly indicate that Kawasaki disease is a genetically susceptible disease. Based on this understanding, numerous studies have explored the association between Kawasaki disease and genetic polymorphism. In Asian populations only, numerous polymorphic genes have been reported, including *VEGF*, *COL11A2* in a Taiwanese population,[8,9] and *FAM167A-BLK*, *HLA-DQB2-HLA-DOB*, and *CD40* in a Japanese population.[10] In addition, *IL-10*, *ITPKC*, *RETN*, and *TNFR1* were reported in a Chinese population.[11-14] However, studies on the association of miRNA polymorphisms with Kawasaki disease are rare.

miRNAs are a class of endogenous small RNAs of approximately 20-24 nucleotides in length that have a variety of important regulatory roles in cells. As a post-transcriptional regulator, it inhibits mRNA translation of target genes in the 3′ untranslated region (3′ UTR) by base pairing.[15] In our previous research, several miRNAs associated with Kawasaki disease were discovered.[16-18] This inspired our confidence, and by exploring further, we noticed *miRNA-196a2* rs11614913 T>C, which is reported to be closely related to cardiovascular diseases.[19,20] Therefore, we carried out this study to explore the association between the *miRNA-196a2* rs11614913 T>C and Kawasaki disease susceptibility.

2 | MATERIALS AND METHODS

2.1 | Study subjects

A total of 532 unrelated Chinese children who went to the Guangzhou Women and Children's Medical Center were diagnosed with Kawasaki disease from January 2012 to January 2017. The control group was composed of 623 healthy Chinese children who went to the hospital for physical examination in the same period.[16-18] Peripheral venous blood was taken from each child to extract DNA. In addition, personal information such as gender, age, and coronary diameter of cases and controls was collected. This study obtained the consent of the Guangzhou Women and Children Medical Center Ethics Committee and the guardian of each child (ethics number: 2014073009).

2.2 | DNA extracting and genotyping

We used a Qiagen kit (Qiagen Inc) to extract genomic DNA from blood and stored in a −80°C freezer and genotyped this SNP using the TaqMan real-time PCR method with an ABI-Q6 instrument (Applied Biosystems), as described previously.[21-23] For accuracy and reliability, each plate was provided with an eight-well blank control, including equal amounts of distilled water but no DNA.

2.3 | Statistical analysis

The chi-square test was used to assess significant differences between the case group and the control group, the risk factors, and the distribution of this SNP in the control and case groups, including additive, dominant, and recessive models. Logistic regression analysis was used to calculate the original odds ratio (OR) value and 95% confidence interval (CI). Stratified analysis was used to analyze subgroups of data, such as gender, age, and coronary artery outcomes. Data were analyzed using SAS 9.1 software, and *P* values <0.05 were considered indicative of statistical significance.

3 | RESULT

3.1 | Research population characteristics

The basic information of the case group and the control group is shown in Table S1. The study included 532 KD children and 623 healthy children matched by age ($P = 0.602$) and gender ($P = 0.143$). The incidence of coronary artery aneurysm and coronary artery lesions was 9.59% and 31.58%, respectively.

3.2 | Genotype distributions of rs11614913 T>C polymorphism and Kawasaki disease susceptibility

Table 1 shows the distribution of genotypes in the case and control groups. We can see that the genotype distribution in the two groups is equivalent, so there is no significant difference (TT, TC, and CC in the two groups are 28.82% vs 28.57%, 51.04% vs 48.64%, and 20.15% vs 22.79%, respectively). There were no significant differences in any genetics models, whether in crude OR or after adjusting for age and gender (TC vs TT: adjusted OR = 1.04, 95% CI = 0.79-1.37; CC vs TT: adjusted OR = 0.87, 95% CI = 0.63-1.21; dominant model: adjusted OR = 0.99, 95% CI = 0.76-1.27; and recessive model: adjusted OR = 0.85, 95% CI = 0.64-1.13).

TABLE 1 Genotype distributions of *miRNA-196a2* rs11614913 T>C polymorphism and Kawasaki disease susceptibility

Genotype	Cases (N = 531)	Controls (N = 623)	P^a	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)[b]	P^b
TT	153 (28.81)	178 (28.57)		1.00		1.00	
TC	271 (51.04)	303 (48.64)		1.06 (0.81-1.39)	0.653	1.04 (0.79-1.37)	0.774
CC	107 (20.15)	142 (22.79)		0.90 (0.64-1.25)	0.516	0.87 (0.63-1.21)	0.413
Additive			0.531	0.94 (0.80-1.11)	0.489	0.94 (0.80-1.11)	0.466
Dominant	378 (71.19)	445 (71.43)	0.928	0.99 (0.77-1.28)	0.928	0.99 (0.76-1.27)	0.916
Recessive	424 (79.85)	481 (77.21)	0.277	0.86 (0.64-1.13)	0.277	0.85 (0.64-1.13)	0.257

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Chi-square test for genotype distributions between Kawasaki disease patients and controls.
[b]Adjusted for age and gender.

TABLE 2 Stratification analysis for the association between *miRNA-196a2* rs11614913 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, mo						
<12	114/127	23/38	0.67 (0.38-1.20)	0.180	0.67 (0.37-1.20)	0.178
12-60	278/306	73/91	0.88 (0.62-1.25)	0.484	0.88 (0.62-1.24)	0.458
>60	32/48	11/13	1.27 (0.51-3.18)	0.611	1.52 (0.59-3.93)	0.391
Gender						
Females	136/176	31/45	0.89 (0.54-1.48)	0.659	0.87 (0.52-1.46)	0.593
Males	288/305	76/97	0.83 (0.59-1.17)	0.283	0.83 (0.59-1.17)	0.290
Coronary artery aneurysm						
CAA	41/481	10/142	0.83 (0.40-1.69)	0.601	0.82 (0.40-1.68)	0.589
NCAA	383/481	97/142	0.86 (0.64-1.15)	0.302	0.85 (0.64-1.14)	0.281
Coronary injury lesion						
CAL	136/481	31/142	0.77 (0.50-1.19)	0.242	0.76 (0.49-1.17)	0.215
NCAL	288/481	76/142	0.89 (0.65-1.22)	0.485	0.89 (0.65-1.22)	0.469

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.

3.3 | Stratification analysis

The results for the stratified analysis are shown in Table 2. No significant difference was found in the stratified analyses of age, gender, and coronary artery outcome.

4 | DISCUSSIONS

In this study, we found that the *miRNA-196a2* rs11614913 T>C may not be associated with Kawasaki disease susceptibility in a southern Chinese population. Over the past 50 years, researchers have tried to find the cause of Kawasaki disease, but it has not been revealed so far. The genetic susceptibility of Kawasaki disease has driven us to study the relationship between miRNA polymorphisms and Kawasaki disease. Our previous study reported that *miRNA-146a* rs2910164 C>G may not be associated with Kawasaki disease susceptibility in children from South China.[18] We found that *miRNA-137* rs1625579 T>G is associated with the onset of Kawasaki disease in the same population in children younger than 1 year old.[16] To our knowledge, this report is the first on the association of *miRNA-196a2* rs11614913 T>C with Kawasaki disease susceptibility among children in South China.

Due to the high conservation and tissue specificity of miRNAs, many studies report them as diagnostic markers of diseases such as cancer,[24,25] nervous system disease,[26] immune disease,[27] and cardiovascular disease.[28] miRNA-196a was identified more than a decade ago.[29] SNPs can alter miRNA function by activating miRNA transcription and processing miRNA precursors to alter miRNA expression.[30] A summary of studies on *miRNA-196a2* polymorphisms in recent years reveals that most of them focus on cancer. Hu et al[31] and Tian et al[32] found that *miRNA-196a2* rs11614913 T>C polymorphism

is associated with susceptibility to lung cancer. The risk of lung cancer was increased by 25% in individuals with the CC genotype of *miRNA-196a2* rs11614913 compared with those having the CT or TT genotypes. Fawzy et al[33] reported that miRNA-196a2 is involved in the progression of gastric cancer. Zhu et al[34] reported that this miRNA is associated with colorectal cancer in a Chinese population.

In another field, Park et al[35] found that the onset of moyamoya disease in South Koreans was associated with *miR-196a2* rs11614913 and that the CT/CC genotypes can increase the risk of moyamoya disease. Furthermore, a recent article reported the association between moyamoya disease and Kawasaki disease gene polymorphism. The authors selected polymorphic loci associated with Kawasaki disease and found that they are also related to moyamoya disease.[36]

Most importantly, we noticed that miRNA-196a2 is associated with cardiovascular disease. Wang et al[37] reported that people with *miRNA-196a2* carrying TC, CC, or TC+CC are more susceptible to coronary artery disease in a Chinese population. Zhi et al[20] reported that in a case-control study involving 956 patients with coronary heart disease and 620 controls from other populations in southeastern China, the *miR-196a2* rsl11614913 C allele could increase the occurrence of acute myocardial infarction and other serious risks of cardiovascular events. Furthermore, Araujo et al[38] confirmed that miR-196a2 targets the *Annexin A1* gene, affecting vascular endothelial cell proliferation and prostaglandin production, and plays a protective role in the anti-inflammatory process.[39,40]

Annexin A1 is expressed by inflammation-related cells such as white blood cells, mast cells, and vascular endothelial cells.[41] In neutrophils, Annexin A1 is mainly distributed in the cytoplasm.[42] The expression of Annexin A1 in circulating neutrophils was higher in inflammatory cells than that in neutrophils, indicating that Annexin A1 was lost during neutrophil adhesion and migration.[43] In vitro, neutrophils interact with endothelial cells to stimulate Annexin A1 externalization through intercellular adhesion molecules and platelet adhesion molecules.[43] Externalized Annexin A1 binds to formyl peptide receptors to exert anti-inflammatory effects,[44] and it regulates the polarization of macrophages to anti-inflammatory phenotypes.[45] These functions are closely related to atherosclerosis. Because of this evidence, we were also curious about whether Annexin A1 is related to Kawasaki disease.

However, in our experiments, the results showed no significant correlation. This negative result may indicate that the pathogenesis of Kawasaki disease and the mechanism of coronary artery injury are different from that underlying traditional adult coronary artery disease or that there are substantial differences between different groups of people. As Zhou et al[46] and Zhi et al[20] reported, in a different Chinese population, the results of *miRNA-196a2* rs11614913 T>C polymorphism in coronary artery disease are different. Liu et al[47] and Jeon et al[48] reported that *miRNA-196a2* rs11614913 T>C polymorphism is a risk factor in ischemic stroke in a Chinese population but not in a Korean population.

In our study, it was revealed that *miRNA-196a2* rs11614913 T>C may not be associated with Kawasaki disease susceptibility in a southern Chinese population and that there was no significant association in the stratified analysis. The advantage of this study is that it is the first report involving *miRNA-196a2* rs11614913 T>C and Kawasaki disease susceptibility. Due to the relatively large number of subjects, the effectiveness of the experimental results is guaranteed. There are also some limitations. First, due to a lack of data, our study examined the incidence of coronary lesions only in children with Kawasaki disease during hospitalization and failed to have long-term follow-up. In the future, we will continue to study and consider these patients. Second, this is a single-center, single-ethnicity study, and as explained in the Discussion, the heterogeneity of the population may produce different results.

Overall, we failed to find any significant association between *miRNA-196a2* rs11614913 T>C polymorphism and Kawasaki disease susceptibility in a southern Chinese population. Larger multicenter, multiethnic research is needed to validate our results.

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SUPPORTING INFORMATION

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