Association Between the lncRNA TDRG1 rs8506 C>T Polymorphism and Susceptibility To Kawasaki Disease in Chinese Children

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Research Article

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Abstract

Background

Kawasaki disease (KD) is an acute systemic vasculitis with unknown pathogen, and the formation of coronary artery lesions/aneurysm (CAL/CAA) is the most common sequela. Environmental and genetic factors have been suggested to be involved in the pathogenesis of KD. Human testis development related 1(TDRG1) is a newly identified long non-coding RNA (lncRNA) which stimulates the vascular endothelial growth factor (VEGF) pathway. The aim of this study was to investigate the association between genetic polymorphism of TDRG1 and the risk of KD.

Methods

A total of two cohorts from Guangzhou (988 KD patients and 1054 controls) and Beijing (564 KD patients and 1221 controls) were enrolled in the present study. Rs8506 of TDRG1 was chosen for TaqMan genotyping assay.

Results

Logistic regression suggested that lncRNA TDRG1 rs8506 C > T polymorphism was not associated with the risk of KD in both Guangzhou and Beijing cohort (dominant model and recessive model: P > 0.05). Moreover, we also did not observe a significant association between the lncRNA TDRG1 rs8506 C > T polymorphism and the risk of KD patients with different ages, gender or coronary artery outcomes in both Guangzhou and Beijing cohort.

Conclusions

The present study revealed that the lncRNA TDRG1 rs8506 C > T polymorphism might not be associated with susceptibility to KD in Chinese children. Future research with a larger sample size should be performed to confirm these results.

Introduction

Kawasaki disease (KD) is defined as an acute systemic vasculitis with microvascular hyperpermeability, which predominantly affecting the children from 6 months to 5 years of age[1, 2]. The development of coronary artery lesions/aneurysm (CAL/CAA) has made KD the leading cause of acquired heart disease among children in developed countries[3]. It is generally agreed that KD may be triggered by infectious agents that elicit systemic inflammatory responses especially at cardiovascular tissues. Furthermore, researches demonstrate that endothelial dysfunction and vascular permeability change also contribute to the occurrence of CAL/CAA[3, 4]. Indeed, several genetic aberrations related to these inflammatory or
vasoactive mediators, such as TNF, MMP, IL-6, VEGF, have been identified to be associated with KD susceptibility. These studies help us to make a better understanding of the pathological process of KD[5–9]. Thus, it is useful to investigate KD development by evaluating the associations between the gene polymorphisms and susceptibility of KD.

Human testis development related 1 (TDRG1), also known as LincRNA-NR_024015, is a newly identified long non-coding RNA (lncRNA). Numerous studies have demonstrated that lncRNA TDRG1 could serve as a proto-oncogene in many different types of tumor[10–13]. Moreover, Chen and colleagues revealed that lncRNA TDRG1 might promote endometrial carcinoma cell proliferation and invasion by targeting vascular endothelial growth factor (VEGF)[12]. Studies show that VEGF promotes migration and proliferation of smooth muscle cells and vascular permeability which is considered to be involved in the pathogenesis of KD[14–16]. With respect to the potential role of lncRNA TDRG1 in vascular biology, we predicted it might interact with VEGF and modulate the coronary artery dilation to affect KD progression. Thus, this study aimed to explore whether KD susceptibility is associated with the lncRNA TDRG1 rs8506 polymorphism in a hospital-based case–control study, which included two cohorts from northern and southern Chinese child population.

Methods

Study population

The primary cohort (Guangzhou) included 988 patients with KD and 1054 control, who were recruited from the Guangzhou Women and Children's Medical Center between January 2014 and December 2019. Additionally, an independent external validation cohort (Beijing) with 564 KD patients and 1221 controls were recruited from Beijing Children's Hospital between July 2018 and December 2020. All of KD patients who diagnosed according to the criteria of American Heart Association[17, 18]. And age- and gender-matched controls were recruited in accordance with the inclusion criteria: 1) without family history of KD, 2) without history of cancer, 3) selected from the same hospital during the same period. The study had received the ethics approval of the Ethics Committee of Guangzhou Women and Children's Medical Center (2014073009) and the Institutional Committee of Beijing Children's Hospital (2019-4). Written informed consent was obtained from each participant’s guardian.

DNA extraction and SNP genotyping

Genomic DNA were extracted from peripheral blood samples by the phenol–chloroform method using the Blood DNAIsolation Kit (TianGen Biotech, Beijing, China) according to the manufacturer's instructions. The selected single nucleotide polymorphism (SNP) of LincRNA-NR_024015 (namely, lncRNA TDRG1) was performed in the 384-well plate using Taqman PCR method. A specific fluorescent probe for genotyping rs8506 was purchased from ABI (Thermo Fisher Scientific, USA). Genotyping was performed blindly to the status of the case or control.

Statistical Analysis
Hardy–Weinberg equilibrium (HWE) of the healthy controls for rs8506 was tested using the goodness-of-fit $\chi^2$ test. The differences in age, gender, demographic variables and the genotype frequencies of rs8506 between sepsis cases and healthy controls were compared using the $\chi^2$ test. Multivariate logistic regression analyses were carried out to calculate the odd ratios (ORs) and their 95% confidence intervals (CIs) for risk of sepsis, which were also stratified by the age, gender, and the number of organs with dysfunction.

**Results**

**General population characteristics**

To explore whether SNP in the lncRNA *TDRG1* rs8506 was associated with susceptibility to KD in one Chinese child population, we carried out the case–control study with two cohorts from Guangzhou (South China) and Beijing (North China). The general and clinical characteristics of the two populations were summarized in Table 1. For Guangzhou cohort, there were no significant differences between the case and control in terms of age (Case, 24.0 ± 21.3 months vs. Control, 27.0 ± 25.8 months; $P = 0.109$; Table 1) and gender ($P = 0.211$, Table 1). According to Two-Dimensional Echocardiography, 369 (37.3%) patients developed CAA. For Beijing cohort, no statistically significant differences were found between case and control groups with respect to age ($P = 0.105$) and gender ($P = 0.130$). And 33 (6.0%) patients developed CAA during the observation period.
Table 1
Frequency of selected characteristics in Kawasaki disease and healthy controls

| Variables                  | Guangzhou cohort                                      | Beijing cohort                                       |
|----------------------------|-------------------------------------------------------|------------------------------------------------------|
|                            | Cases (n = 988)                                        | Controls (n = 1054)                                   | Cases (n = 564)                                      | Controls (n = 1221)                                   |  
|                            | P[alpha]                                              |                                                     | P[alpha]                                            |                                                     |  
| No.                        | % No. %                                               |                                                     | No. %                                               |                                                     |  
| Age (range, month)         | 1-151 1-156                                           |                                                     | 1-192 1-204                                         |                                                     |  
| Mean ± SD                  | 24.0 ± 21.3 27.0 ± 25.8                               |                                                     | 33.4 ± 28.5 37.3 ± 35.3                            |                                                     |  
| ≤ 60                       | 933 94.4 977 92.7 0.109                                |                                                     | 498 88.3 1044 85.5 0.105                            |                                                     |  
| > 60                       | 55 5.6 77 7.3                                        |                                                     | 66 11.7 177 14.5                                   |                                                     |  
| Gender                     |                                                       |                                                     |                                                     |                                                     |  
| Male                       | 656 66.4 672 63.8 0.211                                |                                                     | 362 64.2 738 60.4 0.130                             |                                                     |  
| Female                     | 332 33.6 382 36.2                                    |                                                     | 202 35.8 483 39.6                                   |                                                     |  
| Coronary artery outcomes   |                                                       |                                                     |                                                     |                                                     |  
| CAA                        | 369 37.3 - - NA                                      |                                                     | 33 6.0 - - NA                                      |                                                     |  
| NCAA                       | 619 62.7 - -                                          |                                                     | 520 94.0 - -                                       |                                                     |  
| Note:                      | a Two-sided χ² test for differences between Kawasaki disease patients and controls. |                                                     |                                                     |                                                     |  
| Abbreviations:             | CAA, coronary artery aneurysm; NCAA, non-coronary artery aneurysm; NA, not applicable |                                                     |                                                     |                                                     |  

Association analysis

The genotypes of lncRNA TDRG1 rs8506 were successfully examined in the populations from both Guangzhou and Beijing cohort of the present study. For Guangzhou cohort, the genotype of rs8506 among the controls were in accordance with Hardy-Weinberg equilibrium (HWE, P = 0.437). As shown in Table 2, the difference of genotype of rs8506 between the disease case and control was of no statistical significance (P = 0.425). Multivariate logistic regression analysis suggested that there was no significant association between the lncRNA TDRG1 rs8506 C > T polymorphism and susceptibility to KD (CT vs. CC: adjusted OR = 0.9, 95% CI = 0.7–1.1, P = 0.235; TT vs. CC: adjusted OR = 1.2, 95% CI = 0.8–1.8, P = 0.469; dominant model, CT + TT vs. CC: adjusted OR = 0.9, 95% CI = 0.8–1.1, P = 0.377; recessive model, TT vs. CC + CT: adjusted OR = 1.2, 95% CI = 0.8–1.9, P = 0.360).
| Genotype                  | Cases  | Controls | \( P^a \) | OR (95% CI)     | \( P \) | Adjusted OR (95% CI) \( b \) | \( P^b \) |
|--------------------------|-------|----------|--------|----------------|--------|-------------------------------|--------|
| Guangzhou cohort: rs8506 C > T (HWE = 0.437) |
| CC                       | 624(63.2) | 647(61.4) | 0.425  | 1.000          | 1.000  |                                |        |
| CT                       | 316(32.0) | 363(34.4) |        | 0.9(0.7–1.1)   | 0.282  | 0.9(0.7–1.1)                  | 0.235  |
| TT                       | 48(4.8) | 44(4.2) |        | 1.1(0.7–1.7)   | 0.568  | 1.2(0.8–1.8)                  | 0.469  |
| Dominant                 | 364(36.8) | 407(38.6) | 0.409  | 0.9(0.8–1.1)   | 0.409  | 0.9(0.8–1.1)                  | 0.377  |
| Recessive                | 940(95.1) | 1010(95.8) | 0.457  | 1.2(0.8–1.8)   | 0.457  | 1.2(0.8–1.9)                  | 0.360  |
| Beijing cohort: rs8506 C > T (HWE = 0.944) |
| CC                       | 374(66.3) | 821(67.2) | 0.928  | 1.00           | 1.00   |                                |        |
| CT                       | 171(30.3) | 360(29.5) |        | 1.0(0.8–1.3)   | 0.708  | 1.0(0.8–1.3)                  | 0.700  |
| TT                       | 19(3.4) | 40(3.3) |        | 1.0(0.6–1.8)   | 0.883  | 1.1(0.6–1.9)                  | 0.838  |
| Dominant                 | 190(33.7) | 400(32.8) | 0.699  | 1.0(0.8–1.3)   | 0.700  | 1.0(0.8–1.3)                  | 0.680  |
| Recessive                | 545(96.6) | 1181(96.7) | 0.919  | 1.0(0.6–1.8)   | 0.918  | 1.0(0.6–1.8)                  | 0.873  |

Note: \( \chi^2 \) tests were used to determine differences in genotype distributions between the patients with Kawasaki disease and the healthy controls. \( b \) Adjusted for age and gender. The values are shown in bold if \( P < 0.05 \).

**Abbreviations**: CI, confidence interval; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.

In addition, we also performed the same analysis in Beijing cohort. The genotype of rs8506 in the control group from Beijing also met the condition of HWE (\( P = 0.944 \)). The Pearson \( \chi^2 \) test and multivariate logistic regression analysis indicated that no significant association between the lncRNA TDRG1 rs8506 C > T polymorphism and susceptibility to KD was observed in Beijing cohort (\( \chi^2 \) test, \( P = 0.928 \); CT vs. CC: adjusted OR = 1.0, 95% CI = 0.8–1.3, \( P = 0.700 \); TT vs. CC: adjusted OR = 1.1, 95% CI = 0.6–1.9, \( P = 0.838 \); dominant model, CT + TT vs. CC: adjusted OR = 1.0, 95% CI = 0.8–1.3, \( P = 0.680 \); recessive model, TT vs. CC + CT: adjusted OR = 1.0, 95% CI = 0.6–1.8, \( P = 0.873 \)).

**Stratification analysis**
To further estimate the association between IncRNA \textit{TDRG1 rs8506} C > T polymorphism and the risk of KD in different subgroups, we stratified the cases according to age, gender and coronary artery outcomes. As shown in Table 3, there was no significant association between the IncRNA \textit{TDRG1 rs8506} C > T polymorphism and the risk of KD in different ages, gender, and outcomes of coronary artery in both Guangzhou and Beijing cohort.
Table 3
Stratification analysis of susceptibility in Kawasaki disease patients

| Variables                     | CC cases/controls | CT + TT cases/controls | \( P^{a} \) | OR (95% CI) | \( P^{b} \) | OR (Adjusted 95% CI) | \( P^{b} \) |
|-------------------------------|-------------------|------------------------|-------------|-------------|-------------|----------------------|-------------|
| **Guangzhou cohort**          |                   |                        |             |             |             |                      |             |
| Age, months                   | ≤ 60              | 592/594                | 0.232       | 0.9(0.7–1.1) | 0.233       | 0.9(0.7–1.1)         | 0.238       |
|                               | > 60              | 32/53                  | 0.209       | 1.6(0.8–3.3) | 0.209       | 1.7(0.8–3.7)         | 0.167       |
| Gender                        | Male              | 409/421                | 0.910       | 1.0(0.8–1.3) | 0.910       | 1.0(0.8–1.3)         | 0.995       |
|                               | Female            | 215/226                | 0.124       | 0.8(0.6–1.1) | 0.125       | 0.8(0.6–1.1)         | 0.126       |
| Coronary artery outcomes      | CAA               | 234/647                | 0.489       | 0.9(0.7–1.2) | 0.490       | 0.9(0.7–1.2)         | 0.519       |
|                               | NCAA              | 390/647                | 0.510       | 0.9(0.8–1.1) | 0.511       | 0.9(0.7–1.1)         | 0.441       |
| **Beijing cohort**            |                   |                        |             |             |             |                      |             |
| Age, months                   | ≤ 60              | 331/708                | 0.597       | 1.1(0.8–1.3) | 0.597       | 1.1(0.9–1.3)         | 0.569       |
|                               | > 60              | 43/113                 | 0.850       | 0.9(0.5–1.7) | 0.850       | 1.0(0.5–1.7)         | 0.879       |
| Gender                        | Male              | 247/494                | 0.667       | 0.9(0.7–1.2) | 0.668       | 0.9(0.7–1.2)         | 0.681       |
|                               | Female            | 127/327                | 0.225       | 1.2(0.9–1.7) | 0.223       | 1.2(0.9–1.7)         | 0.223       |
| Coronary artery outcomes      | CAA               | 23/821                 | 0.765       | 0.9(0.4–1.9) | 0.767       | 0.9(0.4–1.9)         | 0.763       |
|                               | NCAA              | 342/821                | 0.552       | 1.1(0.9–1.3) | 0.551       | 1.1(0.9–1.3)         | 0.531       |

**Note:** \( \chi^2 \) tests were used to determine differences in genotype distributions between the patients with sepsis and the healthy controls. \( P^{b} \) Adjusted for age and gender.

**Abbreviations:** CAA, coronary artery aneurysm; NCAA, non-coronary artery aneurysm; OR, odds ratio

**Discussion**
In the present case–control study, we enrolled Guangzhou cohort (988 cases and 1054 controls) and Beijing cohort (564 cases and 1221 controls) to evaluate the association between lncRNA TDRG1 rs8506 C>T polymorphism and KD in Chinese children. The results showed that there were no significant association between rs8506 C>T of the lncRNA TDRG1 and the KD susceptibility in both southern and northern Chinese children. To the best of our knowledge, this is the first study to evaluate the association between lncRNA TDRG1 rs8506 polymorphism and the risk of KD in Chinese child population.

LncRNA is a type of transcripts greater than 200 nucleotides in length that lack protein-coding capacity[19, 20]. It has been found to be involved in many pathological processes of human diseases, such as chromatin remodeling, alternative splicing, transcriptional control and post-transcriptional processing[19]. Zhao et al provided evidences that lncRNA SOCS2 antisense RNA 1 is highly expressed in the serum of KD patients and contributes to proliferation of human umbilical vein endothelial cells[21]. Furthermore, a study reported by Ko TM found that lncRNA XLOC_006277 is significantly up-regulated in acute phase of KD and its level is associated with coronary artery aneurysm[22]. LncRNA TDRG1 was firstly identified as a novel human testis-specific gene which served as a regulator in sperm motility and the development of testicular germ cell tumors[23, 24]. A number of researches suggest that LncRNA TDRG1 play critical roles in tumorigenesis and progression in several cancer types including cervical[10], esophageal[25], ovarian[13] and endometrial carcinoma[12]. Chen et al found that lncRNA TDRG1 promotes the progression of endometrial carcinoma via binding to VEGF-A protein and upregulated its expression [12]. Importantly, the expression level of IncRNA TDRG1 in esophageal tumor tissues with rs8506 CT and TT genotype was significantly higher than those with rs8506 CC genotype[25]. Moreover, IncRNA TDRG1 and VEGF were found to be co-expressed in diabetic retinopathy patients [26]. These reported data indicated that IncRNA TDRG1 might be beneficial to stimulate the VEGF pathway[26]. VEGF is a potent mediator that promotes proliferation of smooth muscle cells and increases the vascular permeability[14–16]. It has been found that VEGF is up-regulated in the acute phase of KD and the expression level is associated with the formation of CALs[27–29]. Furthermore, polymorphisms of the VEGF gene also play a role in the pathogenesis of KD[6, 30, 31]. Therefore, we speculated that IncRNA TDRG1 rs8506 polymorphism might be associated with the risk of KD.

However, in our case–control study, the results suggested there were no significant association between rs8506 C>T of the IncRNA TDRG1 and the risk of KD in both southern and northern Chinese children. Additionally, we did not observe the significant association between the rs8506 C>T polymorphism and the risk of KD in patients with different ages, genders or coronary artery outcomes group. Thinking of the population and distribution limitations, further study is needed to confirmed this finding in the future.

Although this is the first study to explore the susceptibility of patients with the IncRNA TDRG1 rs8506 polymorphism to KD, several possible limitations should be noted in present study. First, we only included the rs8506 T allele; other TDRG1 gene polymorphisms with potential function remain to be involved in this study. Second, due to the retrospective study design, we could only collect frequency-matched cases and controls by geographical factor, age and gender, other factors, such as environmental exposures and eating habits, were not collected. Third, although
there are two cohorts recruited from the south and the north of China, the sample size in the current study might have impact on the test power of statistical analysis.

Conclusions

In summary, the current study revealed that lncRNA TDRG1 rs8506 C > T polymorphism might not be associated with susceptibility to KD in Chinese children. However, future studies with other TDRG1 gene polymorphisms and larger sample size should be conducted to confirm the role of the lncRNA TDRG1 rs8506 C > T polymorphism in the risk of KD for children.

Abbreviations

CAA, coronary artery aneurysm; CAL, coronary artery lesion; CI, confidence interval; HWE, Hardy Weinberg equilibrium; KD, Kawasaki disease; lncRNA, long non-coding RNA; NCAA, non-coronary artery aneurysm; OR, odd ratio; SNP, single nucleotide polymorphism; TDRG1, testis development related 1; VEGF, vascular endothelial growth factor

Declarations

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Authors’ contributions

Li JQ and Guo K designed the experiments; Li JQ, Guo K, Yu HY and Xu YF performed the experiments; Xu YF, Yang CZ and Qiu LJ analyzed the data; Zhou HZ, Pi L, Che D, Fu LY and Wei B collected the samples and clinical data; Li JQ wrote the manuscript; Ma SX and Gu XQ revised and finalized the manuscript.

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Availability of data and materials

The analyzed datasets used during the current study are available from the corresponding author on reasonable request.
Ethics approval and consent to participate

The study had received the ethics approval of the Ethics Committee of Guangzhou Women and Children's Medical Center (2014073009) and the Institutional Committee of Beijing Children's Hospital (2019-4). Written informed consent was obtained from each participant’s guardian.

Consent for publication

All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare that there is no conflict of interest.

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