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Relationship between *IL-17A* gene polymorphism and susceptibility to Kawasaki disease

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ABSTRACT

Objective: Kawasaki disease (KD) is the most common autoimmune vasculitis syndrome in children, which supposed be a complex polygenic disorder. Interleukin-17 (IL-17) is a member of the pro-inflammatory cytokine family, which has a strong pro-inflammatory effect and can participate in various acute and chronic inflammatory responses. This study aims to investigate the relationship between the single-nucleotide polymorphism (SNP) locus rs3819025 in the *IL-17A* gene and the susceptibility to KD.

Methods: A total of 120 patients with KD who met the diagnostic criteria (the KD group) and 120 healthy children (the control group) were enrolled retrospectively in this study. Polymerase chain reaction (PCR) and DNA direct sequencing were used to detect the SNPs of children in the 2 groups.

Results: The frequencies of GG, GA, and AA genotypes of rs3819025 locus in the *IL-17A* gene in the KD group were 82.5%, 17.5%, and 0, respectively, and the frequencies of GG, GA, and AA genotypes in the control group were 72.5%, 22.5%, and 5.0%, respectively. There were significant differences in both genotype (χ^2=7.524, P=0.023). The allele frequencies G and A of rs3819025 locus in the KD group were 91.25% and 8.75%, respectively, while those in the control group were 83.75% and 16.25%, respectively. There was significant difference between the 2 groups (χ^2=6.171, P=0.013). The distribution frequencies of GG or GA genotype and G or A allele were 88.46% or 11.54% and 94.23% or 5.77% in the KD group with coronary artery lesion, respectively. The distribution frequencies of GG or GA genotype and G or A allele were 78.72% or 21.28% and 89.36% or 10.64% in the KD group without coronary artery lesion, respectively. There were no significant differences in genotype and allele frequencies of rs3819025 between the KD with coronary artery lesion group and the KD group without coronary artery lesion (both P> 0.05). Besides, children with the allele A had a 2.023 times higher risk of KD than those

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without the allele A (χ^2=6.171, *P*=0.013; *OR*=2.023, 95% *CI* 1.151 to 3.557).

Conclusions: The locus rs3819025 in the *IL-17A* gene is associated with the pathogenesis of KD. The allele A of the locus rs3819025 in the *IL-17A* gene may be a risk factor for KD.

KEY WORDS Kawasaki disease; *IL-17A* gene; single-nucleotide polymorphism

IL-17A 基因 rs3819025 位点多态性与川崎病的相关性

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[摘 要] 目的：川崎病是儿童中最常见的自身免疫性血管炎综合征，是一种多基因复杂性疾病。IL-17是近年来发现的前炎症细胞因子家族成员，有很强的促炎作用，能参与各种急、慢性炎症反应。本研究旨在探讨*IL-17A*基因rs3819025位点单核苷酸多态性与川崎病易感性的关系。**方法：**回顾性纳入符合诊断标准的120例川崎病患者(川崎病组)和120例健康儿童(对照组)，应用聚合酶链式反应(polymerase chain reaction，PCR)和DNA直接测序法检测2组人群基因多态位点单核苷酸基因多态性。**结果：***IL-17A*基因rs3819025位点在川崎病组中GG、GA、AA基因型频率分别为82.5%、17.5%、0，对照组中GG、GA、AA基因型频率分别为72.5%、22.5%、5.0%，2组比较差异有统计学意义(χ^2=7.524，*P*=0.023)；川崎病组与对照组的G、A等位基因频率分别为91.25%、8.75%和83.75%、16.25%，2组比较差异有统计学意义(χ^2=6.171，*P*=0.013)。川崎病组中合并冠状动脉损伤患者的GG、GA基因型分布频率分别为88.46%、11.54%，G、A等位基因频率分别为94.23%、5.77%，川崎病组中无冠状动脉损伤患者的GG、GA基因型分布频率分别为78.72%、21.28%，G、A等位基因频率分别为89.36%、10.64%。川崎病组合并冠状动脉损害与无冠脉损伤的患者比较，rs3819025的GG、GA基因型和G、A等位基因频率差异均无统计学意义(均*P*>0.05)。有A等位基因比无A等位基因的儿童患川崎病的风险高2.023倍(χ^2=6.171，*P*=0.013；*OR*=2.023，95% *CI* 1.151~3.557)。**结论：***IL-17A*基因rs3819025位点基因多态性与川崎病的发病存在关联性，A等位基因可能是川崎病发病的风险因素。

[关键词] 川崎病；*IL-17A*基因；基因多态性

Kawasaki disease (KD) is an autoimmune vasculitis syndrome that mainly occurs in children under 5 years old and is characterized by high fever, rash, lymphadenopathy, and acute vascular inflammation[1]. The disease is self-limiting, but some children may have coronary artery involvement and even more serious consequences, such as acute myocardial infarction and coronary artery aneurysm rupture[2]. At present, the pathogenesis and etiology of KD are not completely understood. It is known that the incidence of KD varies significantly in different ethnic groups, regions, and seasons. In the course of KD, super-antigens induced by infection can trigger inflammatory responses and immune disorders, indicating that both genetic susceptibility and infection-induced autoimmune dysfunction play a significant role[3]. Previous studies[4-5] have found that genes related to the pathogenesis of KD include: innate immunity-related gene polymorphisms, pro-inflammatory cytokine gene polymorphisms, vascular disease-related gene polymorphisms, polymorphisms of gene associated with major histocompatibility complex class I molecular chain, et al. The abnormality of interleukin (IL) related genes associated with the pathogenesis of KD can affect the expression of cytokines, resulting in strikingly increased expression of a variety of pro-inflammatory and anti-inflammatory cytokines in acute KD[6]. These pro-inflammatory cytokines can induce endothelial cell apoptosis, which may be the cause of KD vascular endothelial injury and participate in the development of the disease. Interleukin 17 (IL-17) is a member of the pro-inflammatory cytokine family[7], mainly produced by Th17 cells of the $CD4^+$ helper T cell subsets. IL-17 is known to promote the expression of varieties of

cytokines (such as IL-6, TNF-α, and IL-8), chemokines, and metalloproteinase, which can enhance the amplification of inflammation, directly damage vascular endothelial cells, and lead to inflammatory damage to the vascular wall. Human IL-17 is a homo-dimeric protein containing 155 amino acids[8]. The encoding gene *IL-17A* is located at 6q12 of the human chromosome and the corresponding mRNA is 1.2 kb. The N-terminus of human IL-17 is a signal peptide composed of 19 to 23 residues. The −197 single-nucleotide polymorphism (SNP) (rs2275913) in the promoter region of *IL-17A* gene is found to be associated with childhood asthma and Henoch-Schonlein purpura[9-10]. The −692 SNP (rs8193036) is found to be a susceptible factor of immune diseases such as ulcerative colitis and rheumatoid arthritis[11-12]. However, up to date, no report has revealed the relationship between the +74 SNP (rs3819025) in the intron 1 region of the *IL-17A* gene and the susceptibility to KD. This study aims to investigate the relationship between the SNP locus rs3819025 in the *IL-17A* gene and the susceptibility to KD.

1 Subjects and methods

1.1 Subjects

A total of 120 patients with KD (the KD group) and 120 healthy children (the control group) were enrolled from 2015 to 2020 in the Third Xiangya Hospital of Central South University in Hunan Province. All the children of the control group had no history of KD, either history of cardiovascular disease, rheumatic diseases, or infectious diseases. All patients in the KD group met at least 5 of the following 6 diagnostic criteria of KD[13]: fever persisting≥5 d; bilateral conjunctival congestion; changes of lips and oral cavity; polymorphous exanthema; changes in peripheral extremities; acute non-purulent cervical lymphadenopathy. Consider incomplete KD in any child with unexplained fever for at least 7 d or fever for at least 5 d combined with 2 or 3 of the principal clinical features. The inclusion criteria for patients with KD were as follows: 1) patients met the diagnostic criteria of KD as mentioned previously, and exclude other diseases. 2) patients were Han Chinese children. 3) blood samples were collected on the first day of admission, and not received immunosuppressive drugs or intravenous immunoglobulin (IVIG) before. The exclusion criteria for this study were as follows: 1) patients were suspected cases of KD but not confirmed. 2) subjects were with previous history of rheumatic or immune disease, cardiovascular disease. According to the results of two-dimensional echocardiography, the diagnostic indicators of KD complicated with coronary artery lesion (CAL) were as follows[14]: a lumen diameter of the left or right coronary artery >3 mm (children under 5 years old) or >4 mm (children over 5 years old); the inner diameter of a segment of the coronary artery is at least 1.5 times that of the adjacent coronary artery or the markedly irregular coronary cavity. According to the presence or absence of coronary artery injury, patients were divided into a KD with coronary artery injury (KD-CAL) group and a KD without coronary artery injury (KD-WO) group. There were 26 (21.7%) cases in the KD-CAL group, and 94 (78.3%) cases in the KD-WO group. This experiment was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (NO. 2016-S155) and with the informed consent of all the children's legal guardians.

1.2 DNA extraction

Venous blood samples of in the KD group and the control group were collected in the disposable blood collection tubes containing anticoagulant (EDTA-K_2). After incubation for 30 min at room temperature, blood samples were naturally coagulated. The collection tubes were centrifuged at 2 500 r/min for 15 min and the sediments were reserved. These samples were immediately transferred to a cryopreservation tube and stored in a −80 ℃ refrigerator. DNA was extracted intensively within half a year by using nucleic acid purification kit (Beijing Jin Biotechnology Co., Ltd) according to the manufacturer's instructions. After the extraction, an ultramicro spectrophotometer was used to detect the concentration and purity of the DNA samples, which were then stored in a −20 ℃ refrigerator.

1.3 Genotyping

The *IL-17A* gene was amplified by polymerase chain reaction (PCR) in a Thermal Cycler 9700 (Applied Biosystem, Foster City, CA, USA) using primers designed by the authors and synthesized by Hunan

Qingke Biotechnology Co., Ltd. (forward: 5'-ACATG-AATTTCTGCCCTCC-3'; reverse: 5'-AAATGCTGCA-CAATGACTTA-3'; length: 426 bp). The PCR reactions were conducted in a total volume of 25 μL, containing 12.5 μL of 2×Taq PCR Green Mix (Tsingke Biotech Co., Beijing), 2 μL of DNA, 0.5 μL of forward primer (10 μmol/L), 0.5 μL of reverse primer (10 μmol/L), and 9.5 μL of deionized water. The thermal cycling conditions were as follows: pre-denaturation at 94 ℃ for 5 min, followed by 35 cycles of denaturation at 94 ℃ for 30 s, annealing at 58 ℃ for 30 s, and extension at 72 ℃ for 30 s, and then an extension at 72 ℃ for 10 min. The PCR products were immediately subjected to agarose gel electrophoresis or stored in a 4 ℃ refrigerator for preservation. Genetic sequencing was carried out by a sequencing company (Boshang Biotechnology Co., Ltd, China) and the results were analyzed by Chromas software. The genotypes of the locus polymorphism were detected by direct sequencing, and the sequencing results were analyzed by the SnapGene software. The Hardy-Weinberg genetic equilibrium law was used to test the genetic balance of each genotype frequency[15].

1.4 Statistical analysis

All data were analyzed by SPSS 20.0 software. The continuous data with normal distribution were described as mean±standard deviation and the categorical data were expressed as number (percentage). The χ^2 test was used to assess the differences in genotype and allele frequencies between the 2 groups. $P<0.05$ was considered statistically significant.

2 Results

2.1 General information of the subjects

The cases of the KD group includes 77 males and 43 females with age from 3 months to 8 years old [(3.4±1.7) years old]. The control group were all Chinese Han children, including 72 males and 48 females with age from 1 to 8 years old [(3.7±1.9) years old]. There were no statistically significant differences of gender and age distribution between the KD group and the control group (all $P>0.05$).

2.2 Gene polymorphism results

There were 3 genotypes (GG, GA, and AA) at locus rs3819025 in the *IL-17A* gene (Figure 1).

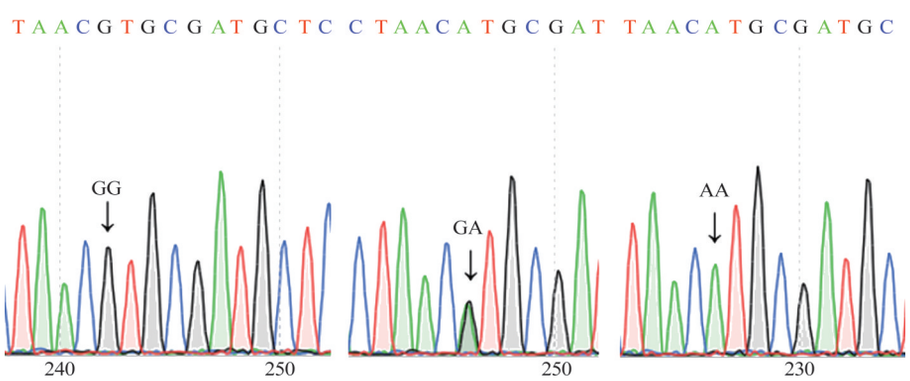

Figure 1 Sequencing map of PCR products at rs3819025 in the *IL-17A* gene

Single peak of GG shown by the arrow indicates that the product is GG homozygote. Double peaks of GA shown by the arrow indicate that the product is a GA heterozygote. Single peak of AA shown by the arrow indicates that the product is AA homozygous.

2.3 Hardy-Weinberg genetic balance test results

The results of Hardy-Weinberg equilibrium law showed that the SNP genotypes were in line with the Hardy-Weinberg equilibrium between the KD group and the control group (both $P>0.05$).

2.4 Association of *IL-17A* gene rs3819025 polymorphism with susceptibility to KD

At locus rs3819025 in the *IL-17A* gene, only GG and GA genotypes were observed in the KD group, while GG, GA, and AA genotypes were observed in the control group. The frequencies of GG, GA, and AA

genotypes of rs 3819025 locus in the *IL-17A* gene in the KD group were 82.5%, 17.5%, and 0, respectively, and the frequencies of GG, GA, and AA genotypes in the control group were 72.5%, 22.5%, and 5.0%, respectively. The allele frequencies G and A of rs3819025 locus in the KD group were 91.25% and 8.75%, respectively, while those in the control group were 83.75% and 16.25%, respectively. There were significant differences in genotype (χ^2=7.524, P=0.023) and allele frequencies (χ^2=6.171, P=0.013) of rs3819025 between the 2 groups (Table 1). As shown in Table 2, children with the allele A had a 2.023 times higher risk of KD than those without the allele A (χ^2=6.171, P=0.013; *OR*=2.023, 95% *CI* 1.151 to 3.557).

2.5 Association between *IL-17A* gene rs3819025 polymorphism and coronary artery injury formation in KD

There were no significant differences of genotype and allele frequencies of rs3819025 between the KD-WO group and the KD-CAL group (both P>0.05, Table 3).

Table 1 Relationship between *IL-17A* gene locus rs3819025 genotype/allele frequencies and susceptibility to KD

Groups	*n*	Genotypes/[No.(%)]			Alleles/[No.(%)]	
		GG	GA	AA	G	A
Control group	120	87(72.50)	27(22.50)	6(5.00)	201(83.75)	39(16.25)
KD group	120	99(82.50)	21(17.50)	0(0)	219(91.25)	21(8.75)
χ^2			7.524		6.171	
P			0.023		0.013	

KD: Kawasaki disease.

Table 2 Relationship between *IL-17A* gene locus rs3819025 genotype/allele frequencies and the risk of KD

Genotypes/alleles	Control group/No.	KD group/No.	χ^2	P	*OR*	95% *CI*
GG	87	99	0.823	0.364	0.843	0.583 to 1.219
GA+AA	33	21	3.363	0.067	1.712	0.959 to 3.057
G	201	219	6.171	0.013	0.494	0.281 to 0.869
A	39	21	6.171	0.013	2.023	1.151 to 3.557

KD: Kawasaki disease; OR: Odds radio; CI: Confidence interval.

Table 3 Relationship between *IL-17A* gene rs3819025 polymorphism and coronary artery injury formation in KD

Groups	*n*	Genotypes/[No.(%)]			Alleles/[No.(%)]	
		GG	GA	AA	G	A
KD-WO group	94	74(78.72)	20(21.28)	0(0)	168(89.36)	20(10.64)
KD-CAL group	26	23(88.46)	3(11.54)	0(0)	49(94.23)	3(5.77)
χ^2			1.247		1.114	
P			0.264		0.426	

KD-WO: Kawasaki disease without coronary artery injury; KD-CAL: Kawasaki disease with coronary artery injury.

3 Discussion

KD is the most common autoimmune vasculitis syndrome in children. The main clinical manifestations of KD are inflammatory symptoms of skin, mucosa, and lymph nodes, such as persistent fever, flushing of lips, hyperemia of bulbar conjunctival, scleroma, and desquamation of hands and feet. Hyperactivation of the

immune system and immune-damaging vasculitis are the 2 main characteristics of KD[16]. The immune pathogenesis of KD has not been sufficiently elucidated so far. Previous study[17] has shown that acute inflammation and immune regulation disorders triggered by infectious factors are the key to the development of coronary artery disease in KD, but the regulatory factors leading to immune abnormalities still remain unclear. It has been reported that a variety of bacteria, viruses, mycoplasma, and their metabolites can become superantigens or common antigens, resulting in systemic immune cell regulation disorders, such as imbalance of T lymphocyte subsets, which is characterized by increase of $CD4^+$ T cells, decrease of $CD8^+$ T cells, and increased ratio of $CD4^+/CD8^+$ T cells[18]. Especially in the acute and subacute stages of KD, $CD4^+$ T cells are abnormally activated and produce a variety of inflammatory cytokines, including IL-6, IL-17A, IL-10, tumor necrosis factor (TNF)-α, and monocyte chemotactic protein-1 (MCP-1), which could damage vascular endothelial cells[19]. Consequentially, B cells could be stimulated to secrete autoantibodies, resulting in further aggravated vascular immune and inflammatory damages. However, aforementioned inflammatory markers are largely nonspecific, as these markers are also elevated in many other inflammatory and infectious conditions. Although these biomarkers can reflect the persistent inflammatory state of KD, they still play a limited role in making a definitive diagnosis.

IL-17 family includes 6 members (IL-17 A to F)[20]. IL-17A, also known as IL-17, is a powerful pro-inflammatory cytokine and a fine-tuning factor of inflammatory response. It can induce monocytes / macrophages, endothelial cells, epithelial cells, and fibroblasts to produce a variety of pro-inflammatory cytokines and chemokines, regulate the expression of adhesion molecules, and recruit neutrophils to enhance the pro-inflammatory effect. Recently, IL-17 has been found to play an important role in various infectious, inflammatory, autoimmune, and cancer diseases, such as rheumatoid arthritis (RA), inflammatory bowel disease, ankylosis spondylitis, psoriasis, atherosclerosis, cervical cancer, and Graves disease[21-27]. Previous study[28] has found that plasma concentrations of IL-17A were significantly higher in the acute phase of KD and KD patient with coronary artery lesion. IL-17 is a highly inflammatory cytokine with robust effects on matrix cells in many tissues, which can mimic other autoimmune diseases such as rheumatic arthritis and KD. IL-17 can activate neutrophils and monocytes / macrophages and secrete a large amount of active substances, such as reactive oxygen species, matrix metalloproteinases and elastases, which can cause damage to the vascular endothelium, induce the occurrence of vasculitis, and participate in the pathogenesis and progression of KD[29]。

SNP can affect critical biological activities, such as gene expression, and ultimately affect the susceptibility, efficacy, and prognosis of complex diseases in different populations. It has important implications in terms of individual differences in diseases and helps explain the susceptibility of different populations to diseases.

Human *IL-17* gene is composed of 3 exons and 2 introns. The length of the gene sequence is 4 264 bp[30], containing 857 SNPs distributed among the variants of near gene (296), untranslated region (163), exon (102) and intron (296) (www.ncbi.nlm.nih. gov/projects/SNP/snp). Some polymorphisms of *IL-17A*, such as rs2275913, rs3819024, rs3748067, and rs8193037, have been found to be associated with the risk of coronary heart disease (CAD)[31]. The SNP rs3819025 (G+45A) is in the intron of *IL-17A*, which may decrease IL-17 serum levels in some occasion[32]. Previous study[27] has found that the allele A frequency of rs3819025 in patients with Graves disease is lower than that in the control group. rs3819025 with G/A+A/A genotypes in patients with Henoch-Schonlein purpura and renal involvement is associated with increased risk of Henoch-Schonlein purpura nephropathy[10], and the AA genotype of rs3819025 (A/G) in patients with brucellosis was significantly lower than that in the control group [33]. Besides, the risk of female RA is significantly correlated with the allele A of rs3819025[12]. The allele G of rs3819025 in patients with graft versus host disease grade 0 to 1 is significantly higher than that in patients with graft versus host disease grade 3 to 4[34]. The presence of *IL-17* (rs3819025) gene G allelic variant was detected more frequently among those who had increased serum IL-17 levels in breast cancer patients[35]. However, there are few studies characterizing the role of *IL-17A* in KD. Also, the relationship between *IL-17A* SNP rs3819025 and the pathogenesis of KD and KD

with coronary artery disease has not been reported up to date.

In this study, no AA genotype was found in the KD group at locus rs3819025 in the *IL-17A* gene, while there were significant differences in the genotype between the KD group and the control group. Similar to patients with Graves disease and brucellosis infection, the frequency of allele A in KD patients was lower than that in the control group. However, in Henoch-Schonlein purpura nephropathy patients and RA patients, the frequency of allele A was higher than that in the control group. The study[38] has shown that the SNP at locus rs3819025 can reduce serum IL-17 concentration in breast cancer patients and healthy controls. In this study, we found that children with the allele A had a 2.023 times higher risk of KD than those without the allele A, which suggested that the allele A of the *IL-17A* gene rs3819025 could be a risk factor for KD. In addition, this study indicated that there was no significant difference in genotype between the KD-WO group and the KD-CAL group, which is consistent with previous study[36] showing that rs3819025 was not significantly associated with CAD susceptibility. However, a study[37] has also shown that there is a high linkage disequilibrium (LD) in the SNPs of rs2275913, rs3819025, and rs3748067 in viral myocarditis. Therefore, whether there is a similar LD in the rs3819025 SNP of KD patients need further research.

There is no gold standard for the diagnosis of KD by laboratory indicators. Many new biomarkers are reported related to KD. For example, a study[38] has found that miR-455-5p is remarkably down-regulated in both acute and recovery phase of the plasma from KD children. In Chinese Han children, the SNP rs2069952, rs9574 and rs1415774 of endothelial protein C receptor are associated with a higher probability for the occurrence of KD[39]. This study suggests that there is a significant difference in the distribution frequency of G/A genotype of rs3819025, a SNP of KD-related cytokine *IL-17A* encoding gene. In the future, it is hoped to expand the sample size, conduct in-depth research on the mechanism, find the diagnostic biomarkers of KD from the aspects of cytokines and genetics, and optimize the KD high-risk scoring system, so as to achieve the purpose of early intervention at the cytokine level of patients with KD and alleviating inflammatory responses.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon request.

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