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Research Article

Association Analysis between ADCY9 Gene Polymorphism and Asthma in Children of the Zhuang Ethnic Group in Guangxi

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Abstract

Objective: To investigate the association between single nucleotide polymorphisms (SNPs) at rs1967309 and rs2230739 loci of the adenylate cyclase 9 (ADCY9) gene and bronchial asthma (referred to as asthma) in Zhuang children in Guangxi.

Methods: A clinical case-control study was conducted, involving 239 Zhuang children under 16 years old, including 118 in the asthma group and 121 in the healthy control group. The allele and genotype frequencies of the ADCY9 gene at rs1967309 and rs2230739 loci were compared between the two groups. Logistic regression analysis was used to assess the relationship between ADCY9 gene polymorphisms and the risk of childhood asthma. The SHEsis online tool was employed for linkage disequilibrium and haplotype analysis, and the generalized multifactor dimensionality reduction (GMDR) method was used to analyze gene-gene interactions.

Results: Polymorphisms were observed at both loci of the ADCY9 gene in the asthma and control groups. The genotype and allele frequencies at the rs2230739 locus showed no statistically significant difference between the two groups ($P > 0.05$). However, the allele and genotype frequencies at the rs1967309 locus were significantly different between the two groups ($P > 0.05$). The AA genotype and allele A at the rs1967309 locus may increase the risk of asthma, while the AG and GG+AG genotype combinations may reduce the risk. No strong linkage disequilibrium was observed between the two loci ($D' = 0.028$, $r^2 = 0.001$). The haplotype distributions of AC, AT, GC, and GT showed no significant differences between the two groups ($P > 0.05$). GMDR analysis indicated no interaction between the two loci ($P > 0.05$).

Conclusion: The rs1967309 locus of the ADCY9 gene may be a susceptibility locus for bronchial asthma in Zhuang children in Guangxi.

Keywords: Asthma; ADCY9 gene; Gene polymorphism; Guangxi Zhuang

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1 INTRODUCTION

Bronchial asthma (referred to as asthma) is a common chronic inflammatory disease in children, characterized by significant heterogeneity, chronic airway inflammation, and airway hyperresponsiveness. It is marked by recurrent episodes, bronchospasm, and reversible airflow changes[1]. Childhood asthma is a global challenge, directly affecting

the health and quality of life of children and even limiting their future career choices. The development of asthma is influenced by both genetic and environmental factors[2,3]. Previous studies have shown that genetic diversity is a significant factor in asthma susceptibility. Several genes, including IL4 and ADRB2, have been associated with asthma susceptibility, spanning almost all human chromosomes, with different genes contributing to varying degrees of susceptibility[4,5]. Therefore, identifying susceptibility genes and exploring the molecular mechanisms of asthma are crucial for the prevention and treatment of childhood asthma.

The adenylate cyclase 9 (ADCY9) gene, located on chromosome 16p13.3, is a membrane-bound enzyme widely expressed in the lungs and other tissues[6]. Teixeira et al.[7] investigated the association between ADCY9 gene polymorphisms and asthma and allergies in Brazilian children. Kim et al.[8] demonstrated that the rs1967309 locus of the ADCY9 gene is a susceptibility locus for asthma in Korean children. While studies on the association between ADCY9 gene polymorphisms and asthma in Han children in northeastern China have been reported, there is no research on Zhuang children in Guangxi. This study aims to explore the relationship between ADCY9 gene SNPs and the risk of asthma in Zhuang children in Guangxi, providing a basis for individualized treatment strategies for asthma patients in this region.

2 MATERIALS AND METHODS

2.1 Study Subjects

This case-control study included 118 asthma patients (asthma group) and 121 healthy controls (control group) recruited from the outpatient or inpatient departments of the Affiliated Hospital of Youjiang Medical University for Nationalities between September 2023 and December 2023. The diagnosis of asthma was based on the "Guidelines for the Diagnosis and Prevention of Childhood Bronchial Asthma (2016 Edition)"[9]. All participants were Zhuang children from Guangxi, with no familial relationships within three generations, no interethnic marriages, and no history of autoimmune diseases or other medical conditions. Informed consent was obtained from the guardians of all participants, and the study was approved by the hospital's ethics committee.

2.2 ADCY9 Genotyping

Peripheral blood (2 mL) was collected from participants using EDTA-K2 anticoagulant tubes. DNA was extracted using a DNA extraction kit (Sangon Biotech). Real-time fluorescent quantitative polymerase chain reaction (PCR) was used to detect the genotypes of the rs2230739 and rs1967309 polymorphic loci. The upstream primer for ADCY9 rs2230739 was 5'-ACGTTGGATGTGAAGGTGGGACTAGCAAAC-3', and the downstream primer was 5'-ACGT TGGATGTCCCAGTCATTCTGCTCCAC-3', yielding a 199 bp product. The upstream primer for ADCY9 rs1967309 was 5'-CGTTCATGCACCCAGCAGACTA-3', and the downstream primer was 5'-TGAGGTCAAGCATTGGAGTGAAAG-3', yielding a 138 bp product. The total PCR reaction volume was 25 μL, including 2 μL of DNA template (10 ng/μL), 1 μL of upstream primer pool (10 μM), 1 μL of downstream primer pool (10 μM), 15 μL of 2× PCR Ready Mix, and 6 μL of distilled water. The reaction conditions were as follows: 98°C pre-denaturation for 3 minutes, followed by 30 seconds at 98°C, 30 seconds at 50°C, and 30 seconds at 72°C for 8 cycles, then 30 seconds at 98°C, 30 seconds at 66°C, and 30 seconds at 72°C for 25 cycles, with a final extension at 72°C for 5 minutes. The PCR products were purified using AMPure XP beads, and a second round of PCR was performed to obtain sequencing libraries with molecular tags. The final PCR products were sequenced using the HiSeq XTen sequencer (Illumina, San Diego, CA). Genotype results were calculated using samtools software (version 0.1.18), and mutation sites were annotated using Annovar software (2018-04-16).

2.3 Statistical Analysis

SPSS 26.0 software was used for statistical analysis. Normally distributed measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were performed using the independent samples t-test. Non-normally distributed data were expressed as median and interquartile range, and comparisons between groups were performed using the Mann-Whitney U test. Categorical data were expressed as counts and percentages (%), and comparisons between groups were performed using Fisher's exact test. Logistic regression analysis was used to assess the relationship between ADCY9 gene polymorphisms and the risk of childhood asthma. The SHEsis software was used for linkage disequilibrium and haplotype analysis, with $D > 0.8$ indicating strong linkage disequilibrium. The generalized multifactor dimensionality reduction (GMDR) method was used to analyze gene-gene interactions. Hardy-Weinberg equilibrium was tested for both the control and asthma groups. A P-value < 0.05 was considered statistically significant.

3 RESULTS

3.1 Comparison of Baseline Characteristics Between Groups

The asthma group consisted of 118 children (84 males and 34 females), and the control group consisted of 121

children (73 males and 48 females). There were no significant differences in age or gender between the two groups (Z = -0.358, P = 0.720; χ^2 = 3.124, P = 0.077). See Table 2-1 for details.

Table 2-1. Baseline Characteristics of Study Subjects

Group	n	Gender		Age	
		Male	Female	Median	Interquartile Range
Asthma Group	118	84	34	4.32	4.03
Healthy Group	121	73	48	4.00	4.00
χ^2		3.124			
Z				-0.358	
P		0.077		0.720	

3.2 Hardy-Weinberg Equilibrium Test

Hardy-Weinberg equilibrium tests were conducted for the ADCY9 gene rs2230739 and rs1967309 loci in both the asthma and control groups. The results showed P > 0.05, indicating that the study population was in genetic equilibrium and representative (see Table 2-2).

Table 2-2. Hardy-Weinberg Equilibrium Test of Genotype Frequencies of ADCY9 rs2230739 and rs1967309 in the Two Groups

Locus	Genotype	Control Group				Asthma Group			
		Observed value	Expected value	χ^2	P	Observed value	Expected value	χ^2	P
ADCY9 rs1967309	AA	17	19.84	1.150	0.563	32	29	1.219	0.544
	AG	64	58.31			53	59		
	GG	40	42.84			33	30		
ADCY9 rs2230739	TT	53	52.23	0.096	0.953	44	43.93	0.0007	0.999
	TC	53	54.53			56	56.14		
	CC	15	14.23			18	17.93		

3.3 Genotype, Allele Frequency Distribution, and Polymorphism Results of ADCY9 rs1967309 Locus

The genotype and allele frequency distribution of rs1967309 in the asthma and control groups: In the asthma group, the AA genotype accounted for 27.1%, the AG genotype for 44.9%, and the GG genotype for 28%. In the control group, the AA genotype accounted for 14%, the AG genotype for 52.9%, and the GG genotype for 33.1%. In the asthma group, the A allele frequency was 49.6%, and the G allele frequency was 50.4%; in the control group, the A allele frequency was 40.5%, and the G allele frequency was 59.5%. Chi-square tests comparing the genotype and allele frequencies at rs1967309 between the two groups showed statistically significant differences in genotype distribution (χ^2 = 6.261, P = 0.044) and allele frequency distribution (χ^2 = 3.981, P = 0.046). The results are shown in Table 2-3.

Table 2-3. Genotype and Allele Frequency Distribution and Comparison of ADCY9 rs1967309 Locus Between the Asthma and Control Groups

Group	n	Genotype[n (%)]			Allele[n (%)]	
		AA	AG	GG	A	G
Asthma Group	118	32(27.1)	53(44.9)	33(28.0)	117(49.6)	119(50.4)
Control Group	121	17(14.0)	64(52.9)	40(33.1)	98(40.5)	144(59.5)
χ^2			6.261		3.981	
P			0.044		0.046	

3.4 Genotype, Allele Frequency Distribution, and Polymorphism Results of ADCY9 rs2230739 Locus

The genotype and allele frequency distribution of rs2230739 in the asthma and control groups: In the asthma group, the CC genotype accounted for 15.3%, the TC genotype for 47.5%, and the TT genotype for 37.3%. In the control group, the CC genotype accounted for 12.4%, the TC genotype for 43.8%, and the TT genotype for 43.8%. In the

asthma group, the C allele frequency was 39%, and the A allele frequency was 61%; in the control group, the C allele frequency was 34.3%, and the T allele frequency was 65.7%. Chi-square tests comparing the genotype and allele frequencies at rs2230739 between the two groups showed no statistically significant differences in genotype distribution (χ^2 = 1.153, P = 0.562) and allele frequency distribution (χ^2 = 1.130, P = 0.288). The results are shown in Table 2-4.

Table 2-4. Genotype and Allele Frequency Distribution and Comparison of ADCY9 rs2230739 Locus Between the Asthma and Control Groups

Group	n	Genotype[n (%)]			Allele[n (%)]	
		TT	TC	CC	T	C
Asthma Group	118	44(37.3)	56(47.5)	18(15.3)	144(61.0)	92(39.0)
Control Group	121	53(43.8)	53(43.8)	15(12.4)	159(65.7)	83(34.3)
c^2			1.153			1.130
P			0.562			0.288

3.5 Correlation Analysis of ADCY9 rs1967309 Locus with Asthma Under Different Genetic Models

Logistic regression analysis was conducted to examine the correlation between the ADCY9 rs1967309 locus and asthma under five different genetic models (Codominant, Dominant, Recessive, Overdominant, and Log-additive). After adjusting for age and gender, the codominant model showed that the effect of the AA genotype on asthma risk was 2.273 times that of the GG genotype (OR = 2.273, P = 0.021), while the AG genotype was associated with a decreased risk of asthma (OR = 2.282, P = 0.031). The dominant model showed no statistically significant difference in the distribution of GG and (AG+AA) genotypes between the asthma and control groups (OR = 1.049, P = 0.868). The recessive model indicated that the (GG+AG) combined genotype reduced the risk of asthma (OR = 2.276, P = 0.014). The overdominant model showed no statistically significant difference in the distribution of (GG+AA) combined genotypes and the AG genotype between the asthma and control groups (OR = 0.726, P = 0.218). The additive model indicated that the effect of the AA genotype on asthma risk was 2.282 times that of the GG genotype (OR = 2.282, P = 0.031). The ADCY9 gene rs1967309 locus was found to be associated with asthma in Guangxi Zhuang children, as shown in Table 2-5.

Table 2-5. Association of ADCY9 rs1967309 Locus with Asthma Under Different Genetic Models[n (%)]

Genetic Model	Genotype	Control Group	Asthma Group	OR (95% CI)	P-value
Co-dominan	GG	40(33.1)	33(28.0)		
	AG	64(52.9)	53(44.9)	2.282(1.081-4.817)	0.031
	AA	17(14.0)	32(27.1)	2.273(1.138-4.540)	0.020
Dominant	GG	40(33.1)	33(28.0)		
	AG+AA	81(66.9)	85(72)	1.049(0.593-1.856)	0.868
Recessive	GG+AG	104(86.0)	86(72.9)		
	AA	17(14.0)	32(27.1)	2.276(1.184-4.378)	0.014
Overdominant	GG+AA	57(47.1)	65(44.1)		
	AG	64(52.9)	53(44.9)	0.726(0.437-1.208)	0.218
Additive	GG	40(33.1)	33(28.0)		
	AA	17(14.0)	32(27.1)	2.282(1.081-4.817)	0.031

3.6 Correlation Analysis of ADCY9 rs2230739 Locus with Asthma Under Different Genetic Models

Logistic regression analysis was used to examine the correlation between the ADCY9 rs2230739 locus and asthma. After adjusting for age and gender, the results showed that the ADCY9 rs2230739 locus was not significantly associated with asthma under the codominant, dominant, recessive, overdominant, and additive models, as shown in Table 2-6.

Table 2-6. Association of ADCY9 rs2230739 Locus with Asthma Under Different Genetic Models[n (%)]

Genetic Model	Genotype	Control Group	Asthma Group	OR(95%CI)	P
Co-dominan	TT	44(37.3)	53(43.8)		
	TC	56(47.5)	53(43.8)	0.692(0.313-1.529)	0.363
	CC	18(15.3)	15(12.4)	0.723(0.328-1.595)	0.422
Dominant	TT	44(37.3)	53(43.8)		
	TC+CC	74(62.7)	68(56.2)	1.311(0.781-2.200)	0.306
Recessive	TT+TC	100(84.7)	106(87.6)		
	CC	18(15.3)	15(12.4)	1.272(0.608-2.660)	0.523
Overdominant	TT+CC	62(52.5)	68(56.2)		
	TC	56(47.5)	53(43.8)	1.159(0.696-1.929)	0.571
Additive	TT	44(37.3)	53(43.8)		
	CC	18(15.3)	15(12.4)	0.692	0.363

3.7 Linkage Disequilibrium and Haplotypes of Two ADCY9 Gene Loci

Linkage disequilibrium and haplotype analysis of the ADCY9 gene rs2230739 and rs1967309 loci were performed using the SHEsis online tool. The results showed that the D' value for the ADCY9 gene rs1967309 and rs2230739 loci was 0.028, and the r^2 value was 0.001, indicating that there was no linkage disequilibrium between the two loci, as shown in Figure 2-1. A comparison of the distribution of the four haplotypes (AC, AT, GC, and GT) between the groups revealed no statistically significant differences (P > 0.05), as shown in Table 2-7.

Table 2-7: Linkage Disequilibrium and Haplotype Distribution of ADCY9 Gene rs2230739 and rs1967309 Loci

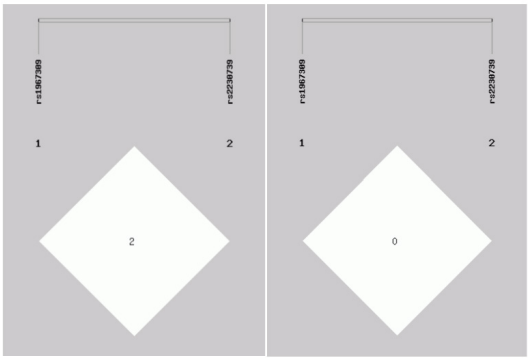

Figure 2-1. Linkage Disequilibrium Plot.
Notes: A is D'value; B is r2 value

Tab.2-7 Comparison of haplotype frequencies at rs2230739 and rs1967309 of ADCY9 gene

Haplotype	Asthma Group n (%)	Control Group n (%)	χ^2	P Value	Odds Ratio (95% CI)
AC*	47 (19.9%)	35 (14.5%)	2.611	0.106	1.483 (0.198-2.395)
AT*	70 (29.6%)	67 (27.7%)	0.199	0.655	1.095 (0.736-1.628)
GC*	45 (19.1%)	48 (19.8%)	0.061	0.804	0.944 (0.600-1.486)
GT*	74 (31.4%)	92 (38.0%)	2.247	0.134	0.749 (0.513-1.093

3.8 Interaction Analysis Between the Two ADCY9 Gene Loci

The interaction between the ADCY9 gene rs1967309 and rs2230739 loci was analyzed using GMDR software. The results showed that the cross-consistency between the two loci was 100%, and rs1967309 was identified as the best model. However, the interaction between the two loci was not statistically significant (P > 0.05), as shown in Table 2-8.

Table 2-8. GMDR Analysis Results of ADCY9 Gene Interaction between Two Loci

Model	Training Sample Accuracy	Test Sample Accuracy	Cross-validation Consistency	P
rs1967309	0.567	0.536	10/10	0.377
rs1967309/rs2230739	0.581	0.505	10/10	0.828

4 DISCUSSION

According to incomplete statistics, there are approximately 150 million asthma patients worldwide, with asthma prevalence rates ranging from 1.0% to 13.6% in different countries, and a significant proportion of these cases are among adolescents[10]. Recurrent asthma attacks have a substantial impact on the lives and education of children with asthma, making early risk assessment crucial for high-risk children. Effective early evaluation and preventive measures can significantly reduce the incidence of asthma in high-risk children[11]. Currently, clinicians primarily use the API to predict the risk of recurrent wheezing in preschool children developing asthma, but even with strict standards, the API still has a certain false positive rate[12]. Recent studies suggest that single nucleotide polymorphisms (SNPs) are key factors in the development of childhood asthma. By detecting variations in the nucleotides of children, the risk of developing asthma can be predicted, which has become a new direction for childhood asthma prevention[13,14].

Studies have shown that the ADCY9 gene may be related to asthma, malaria, and sickle cell disease[13]. The ADCY9 gene is regulated by G protein-coupled receptors, protein kinases, and the calcium family, catalyzing the conversion of adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (cAMP). Reduced expression of ADCY9 leads to decreased cAMP production, which in turn causes immune dysregulation[15]. Additionally, the β2-adrenergic receptor can be activated under the mediation of ADCY9, and this channel plays an important role in regulating smooth muscle and lung function[16]. Li Huijuan et al.[17] found gene polymorphism at the ADCY9 gene rs2230739 locus in children with asthma. Zhang Zhiying et al.[18] also showed that gene polymorphism at the ADCY9 gene rs2230739 locus is associated with wheezing and asthma development in children and can be used to predict asthma risk in children. Subsequently, Jia Jingjing et al.[19] discovered that the interaction of ADCY9 gene rs1967309 with allergens increases asthma risk in Han Chinese children in Northeast China (OR = 1.585, $P < 0.05$), while loci rs2230739, rs2601814, rs2601825, rs2601796, and rs2283497 were not found to be susceptibility loci for asthma in Han Chinese children in Northeast China.

In this study, we selected children with bronchial asthma from the Guangxi Zhuang ethnic group as the research subjects and studied the expression of the ADCY9 gene at rs2230739 and rs1967309 loci. The study found that the AA genotype and A allele of the ADCY9 gene rs1967309 locus were associated with the occurrence of asthma ($P < 0.05$). Further analysis revealed that in the co-dominant model, the asthma risk for children with the AA genotype was 2.273 times higher than for those with the GG genotype (OR = 2.273, P = 0.020), and the AG genotype may be a protective factor for asthma (OR = 2.282, P = 0.031). In contrast, the GG+AG combination genotype may reduce the risk of asthma (OR = 2.276, P = 0.014). Thus, it is speculated that the rs1967309 AA genotype and A allele may be a risk factor for asthma progression in Guangxi Zhuang children, while the AG and GG+AG combination genotypes may reduce asthma risk. However, there were no significant differences in the distribution of rs2230739 in the healthy control and asthma groups, suggesting that rs2230739 may not be associated with asthma susceptibility in Guangxi Zhuang children. Haplotype analysis revealed that the four haplotypes AC*, AT*, GC*, and GT* were present in both the asthma and control groups, with the GT* haplotype being the most common. Comparisons of haplotype distributions between the two groups showed no significant differences ($P > 0.05$), and no linkage disequilibrium was found between the two loci.

5 CONCLUSION

In conclusion, the ADCY9 gene rs1967309 locus is a susceptibility locus for asthma in Guangxi Zhuang children. The risk of asthma in children with the AA genotype at the rs1967309 locus may be higher than in those with the AG or GG genotypes. Therefore, children with this genotype should pay more attention to the risk of asthma attacks. However, rs2230739 may not be associated with asthma susceptibility in Guangxi Zhuang children. Due to regional and ethnic differences and sample size limitations, different susceptibility genes for the same disease may exist, so the relationship between ADCY9 gene polymorphism and childhood asthma cannot be fully explained, and further in-depth research is still needed.

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Not applicable.

Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

The author contributed to the manuscript and approved the final version.

Data Availability

Data sharing is not applicable to this review as no datasets were generated or analyzed during the current study.

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