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ORIGINAL RESEARCH

The *lncRNA CCAT2* Rs6983267 G Variant Contributes to Increased Sepsis Susceptibility in a Southern Chinese Population

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Purpose: Accumulating evidence demonstrates that genetic susceptibility genes can be used as biomarkers to assess sepsis susceptibility, and genetic variation is associated with susceptibility and clinical outcomes in patients with sepsis and inflammatory disease. Although studies have shown that the lncRNA *CCAT2* is involved in inflammatory diseases, it remains unclear whether *CCAT2* gene polymorphisms are associated with susceptibility to inflammatory diseases, such as sepsis, in children.

Methods: We genotyped the rs6983267 *CCAT2* polymorphism in 474 cases (pediatric sepsis) and 678 controls using TaqMan methods, and odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strength of associations.

Results: Our results indicate that the rs6983267 T > G polymorphism is significantly associated with an increased risk of sepsis in children (TG and TT: adjusted OR = 1.311, 95% CI = 1.016–1.743, GG and TT: adjusted OR = 1.444, 95% CI = 1.025–2.034 dominant model: GG/TG vs TT adjusted OR = 1.362, 95% CI = 1.055–1.756). Furthermore, the risk effect was more pronounced in children younger than 60 months who were male and who had sepsis.

Conclusion: We found that the *CCAT2* gene polymorphism rs6983267 T > G may be associated with an increased risk of pediatric sepsis in southern China. A larger multicenter study should be performed to confirm these results.

Keywords: *lncRNA CCAT2*, sepsis, susceptibility, polymorphism

Introduction

Sepsis is a syndrome consisting of pathological, physiological and biochemical abnormalities caused by a dysfunctional response to infection and may cause life-threatening organ dysfunction.[1] Studies have reported that the incidence of sepsis is increasing.[2,3] Despite significant achievements in research and clinical practice, sepsis is the leading cause of death and critical illness worldwide.[4] In addition, the incidence of sepsis in children is gradually increasing and is the main cause of death in neonates.[5] In general, the severity of the inflammatory response is critical to the consequences of sepsis, and numerous studies have shown that genetic polymorphisms may have an impact on host immunity and susceptibility to sepsis as well as prognosis.[6–8] Hence, genetic susceptibility genes might be used as biomarkers to assess susceptibility to sepsis.

Research shows that genetic polymorphisms are associated with susceptibility to multiple diseases, such as glioma, sepsis and diabetes.[9–12] Long noncoding RNAs

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(lncRNAs), RNA molecules longer than 200 nucleotides that have no protein-coding potential,[13] play an important role in a variety of pathological processes, such as cardiovascular diseases and inflammatory responses.[14–16] Accumulating evidence also suggests that lncRNAs are important molecules involved in crosstalk with various pathways pertinent to innate immunity, mitochondrial functions, and apoptosis.[17–19] Indeed, many studies have confirmed that lncRNAs play an important role in the process of innate immunity and apoptosis. It has been reported that noncoding RNA expression is dysregulated in patients with sepsis, and lncRNAs are considered good candidates for biomarkers and therapeutics for sepsis.[17] For example, the lncRNA *colon cancer-associated transcript 2* (*CCAT2*) is associated with a variety of diseases, including colon cancer and gastric cancer.[20,21] Moreover, studies have confirmed that *CCAT2* promotes MYC expression.[20,22,23] Members of the myelodysplastic oncogene (MYC) family, including lung carcinoma-derived MYC (MYCL), cellular MYC (c-Myc) and neuroblastoma-derived MYC (MYCN), have an important oncogenic driver function in human cancers, and MYC family members also play an important regulatory role in the activation of immune cells.[24] A number of studies have found that MYC participates in the pathogenesis of sepsis.[25–27] Together, these findings suggest that *CCAT2* may be involved in the pathology of sepsis. Recent studies have reported that *CCAT2* gene polymorphisms are associated with susceptibility to various diseases, such as recurrent miscarriage, endometrial carcinoma and colorectal cancer,[28–30]and further research has shown that the rs6983267 polymorphism in the *CCAT2* contributes to increases in MYC expression.[22,31,32] Overall, the results of studies indicate that *CCAT2* gene rs6983267 T > G may be associated with septic susceptibility. Nevertheless, the role of the *CCAT2* gene rs6983267 T > G single-nucleotide polymorphism (SNP) in the development and progression of sepsis is still unclear. Therefore, in this study, we assessed the association of the rs6983267 T > G polymorphism in a population of patients with sepsis from South China that consisted of 474 cases and 678 controls.

Materials and Methods

Study Populations

We recruited 474 children with sepsis from the pediatric intensive care unit (PICU) and 678 age- and sex-matched healthy child controls who visited the hospital for medical examinations at the Guangzhou Women and Children Medical Center from January 2016 to December 2018. The diagnosis of sepsis was based on the international definition of sepsis, whereby sepsis is defined as the existence of possible or proven infection and whole-body performance of infection.[33] The diagnostic criteria of organ dysfunction were according to Goldstein et al.[34] The age- and sex-matched healthy child controls were randomly selected from the population undergoing health checkups at the hospital during the same period. No significant difference in age or sex was noted between the sepsis patients and healthy controls. According to the Declaration of Helsinki, this study was approved by the Ethics Committee of Guangzhou Women and Children Medical Center (The ethics number: 2015042202). Informed consent was obtained from the parent or legal guardian of all the patients and healthy controls.

SNP Selection and Genotyping

We collected 2 mL of venous whole blood from each patient; the peripheral blood samples were collected from the patients with sepsis within 24 hours after the diagnosis of sepsis. DNA was extracted from the whole blood (200 μL) of the healthy subjects and patients using a peripheral blood DNA extraction kit (Tiangen, Beijing, China). The yield and purity were measured using a NanoDrop2000 (Thermo Fisher Scientific, USA). The OD260/OD280 of the DNA extracted was between 1.6–1.8, and the purity met the requirements for the experiment. Genotyping was performed with real-time PCR and TaqMan allele discrimination assays. The *CCAT2* (rs6983267) genotyping probe was purchased from ABI (Thermo Fisher Scientific, USA) (CCAT2 rs6983267 [C__29086771_20], Catalog number: 4351379, USA). SNP genotyping was performed using an ABI Q6 instrument (QuantStudioTM 6 Flex Real-Time PCR system, Thermo Fisher Scientific, USA). DNA amplification was performed in a volume of 5 μL containing 2.5 μL of TaqMan master mix (Tiangen, Beijing, China, catalog number: FP211), 1 μL of DNA (2.5 ng), 0.04 μL of primers, and 1.26 μL of H_2O. SNP genotyping and amplification was performed in 384 wells using the TaqMan real-time polymerase chain reaction protocol. PCR was performed under the following conditions: preread stage, 60°C for 30 s; hold stage, 95°C for 10 min; PCR stage, 40 cycles at 95°C for 15 s and 60°C for 60 s; postread stage, 60°C for 30 s.

Statistical Analysis

Differences in sex, age, sepsis subtype, prognosis, number of organs with dysfunction, and genotype distribution between the case and healthy control groups were compared using the $\chi 2$ test. The SNP genotype distribution was assessed using the $\chi 2$ goodness of fit test to determine Hardy-Weinberg equilibrium (HWE) of the control subjects. The association of polymorphism with sepsis risk was examined by the odds ratio (OR), and the 95% confidence interval (95% CI) was determined by unconditional multivariate logistic regression analysis. Furthermore, unconditional logistic regression was used to adjust the OR and 95% CI based on age and sex. The method of calculating FPRP for all important findings was as described in the literature.[35] We determined that the false positive report probability was 0.2; a prior probability of 0.1 was noteworthy. All statistical analyses were performed using SAS statistical analysis software (version 9.3; SAS Institute, Cary, NC, USA). All P values were bilateral, and a significance level of 0.05 was used in this study.

Results

General Characteristics

We recruited 474 patients with sepsis and 678 healthy controls who were 1 to 180 months and 1 to 168 months old, respectively (Table 1). No significant differences in age (35.04 ± 34.26 vs 35.53 ± 29.37 months, P = 0.1811) or sex (P = 0.111) were observed between the case and control groups. In sepsis patients, 74.39% had one or two organ dysfunctions, and 25.61% had three or more organ dysfunctions. The number of patients with sepsis and septic shock was 389 and 85, respectively, and 80 patients with sepsis eventually died. In this study, the main sources of infection in the patients were lung infection (58.65%), respiratory infection (3.8%), urinary tract infection (1.69%), brain infection (7.59%), abdominal infection (5.91%), primary bloodstream infection (7.38%) and others (14.98%).

Associations Between *CCAT2* Gene Rs6983267 Polymorphisms and Sepsis in Children

To explore the relationship between the *CCAT2* rs6983267 T> G polymorphism and susceptibility to childhood sepsis, we performed the $\chi 2$ goodness of fit test to evaluate whether the genotype frequency distribution of the control deviated from HWE (as shown in Table 2), and the results demonstrated that the control group was in HWE (P=0.5241). Single-locus analysis indicated that the rs6983267 T> G polymorphism was significantly associated with an increased risk of sepsis in children (TG and TT: adjusted OR = 1.311, 95% CI = 1.016–1.743, GG and TT: adjusted OR = 1.444, 95% CI = 1.025–2.034, dominant model: GG/TG vs TT adjusted OR = 1.362, 95% CI = 1.055–1.756). Our research results show that compared with the rs6983267 TT genotype, the GG/TG genotypes were significantly associated with an increased risk of sepsis in children.

Stratified Analysis

We further explored the association between the risk genotype of the *CCAT2* rs6983267 T> G polymorphism and susceptibility to childhood sepsis in stratified analysis according to age, sex, sepsis subtype, prognosis, and number of organs with dysfunction (Table 3). Compared with the rs6983267 TT genotype, the risk effect of the TG/GG genotype was more pronounced in children younger than 60 months (adjusted OR = 1.376, 95% CI = 1.044–1.812, P = 0.0233), in males (adjusted OR = 1.463, 95% CI = 1.050–2.037, P = 0.0244) and in sepsis (adjusted OR = 1.311, 95% CI = 1.001–1.717, P = 0.0488). In addition, we observed an increased risk of death for TG/GG genotype carriers (adjusted OR = 2.011, 95% CI = 1.149–3.519, P = 0.0144) and an increased incidence of one or two organs at risk of dysfunction (adjusted OR = 1.445, 95% CI = 1.060–1.969, P = 0.0199).

FPRP values for the *CCAT2* gene are shown in Table 4. Most of the significant findings in this analysis disappeared when the FPRP value was 0.2 and the prior probability was 0.1. Moreover, the effect of the rs6983267 GG/TG genotypes (FPRP = 0.143) on the increased risk of sepsis in children remained credible compared to that of the rs6983267 TT genotype. Regarding stratification analyses, the association between the GG/TG genotypes and the increased risk of sepsis in children younger than 60 months (FPRP = 0.196) and the increased incidence of one or two organs at risk of dysfunction (FPRP = 0.191) were still noteworthy. However, most of the significant findings in the FPRP analysis disappeared, possibly due to the limited sample size, especially for subgroups. Therefore, the important findings from the current research need to be verified in a large-sample prospective study.

Discussion

In our case-control study of 474 children with sepsis and 678 healthy controls, we found that the *CCAT2* rs6983267 TG/GG genotypes were associated with an increased risk

Table 1 Frequency Distribution of Selected Characteristics in Sepsis Cases and Healthy Controls

Variables	Cases (n = 474)	Controls (n = 678)			P^a
	No.	%	No.	%	
Age range, month	1–180	1–168			
Mean ± SD	35.04 ±34.26	35.53±29.37			0.1811
≤60	403	85.02	595	87.76	
>60	71	14.98	83	12.24	
Sex					
Male	301	63.5	399	58.85	0.111
Female	173	36.5	279	41.15	
Sepsis subtypes					
Sepsis	389	82.07	NA		
Septic shock	85	17.93	NA		
Prognosis					
Survivors	394	83.12	NA		
Non-survivors	80	16.88	NA		
Number of organs with dysfunction, n (%)					
1–2	276	74.39	NA		
3 or more	95	25.61	NA		
Source of infection n (%)					
Lung infection	278	58.65	NA		
Brain infection	36	7.59	NA		
Primary bloodstream infection	35	7.38	NA		
Abdominal infection	28	5.91	NA		
Respiratory infection	18	3.8	NA		
Urinary tract infection	8	1.69	NA		
Others	71	14.98	NA		
Infection types n (%)					
Gram-positive	241	50.85	NA		
Gram-negative	117	24.68	NA		
Mixed Gram-negative and -positive	22	4.64	NA		
Fungus	18	3.8	NA		
Polymicrobial	41	8.65	NA		
Negative blood culture	35	7.38	NA		

Notes: [a]Two-sided χ^2 test for distributions between Sepsis patients cases and controls.

of sepsis in children. Furthermore, the risk effect was more pronounced in children younger than 60 months, in those who were male, and in those who had sepsis. To the best of our knowledge, this is the first study to investigate the relationship between *CCAT2* (rs6983267 T> G) gene polymorphism and susceptibility to sepsis in children in southern China.

A growing number of studies have found that the *CCAT2* polymorphism rs6983267 T> G is associated with susceptibility to a variety of diseases. For instance, Sahasrabudhe R et al reported that the rs6983267 G variant is associated with increased thyroid cancer risk,[36] and Zhao X et al suggested that the rs6983267 genotype correlated significantly with endometrial carcinoma susceptibility and lymph node

Table 2 Genotype Frequency Distribution of CCAT2 in Sepsis Cases and Healthy Controls

genotype	Cases (N = 474)	Controls (N =678)	P-value[a]	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value[b]
CCAT2/rs6983267 T>G (HWE =0.5241)							
TT	135(28.48)	240(35.40)	0.0426	1.000		1.000	
TG	243(51.27)	320(47.20)		**1.350(1.032–1.766)**	**0.0287**	**1.311(1.016–1.743)**	**0.0377**
GG	96(20.25)	118(17.40)		**1.446(1.027–2.036)**	**0.0345**	**1.444(1.025–2.034)**	**0.0355**
Dominant	339(71.52)	438(64.60)	**0.0133**	**1.376(1.067–1.774)**	**0.0138**	**1.362(1.055–1.756)**	**0.0175**
Recessive	378(79.75)	560(82.60)	0.2225	1.205(0.893–1.626)	0.2215	1.215(0.900–1.639)	0.2039

Notes: [a]χ^2 tests were used to determine differences in genotype distributions between the children with sepsis and the controls. [b] Adjusted for age and gender. Statistically significant values are shown in bold (P<0.05).
Abbreviations: OR, odds ratio; HWE, Hardy–Weinberg equation.

Table 3 Stratification Analysis of Susceptibility in Sepsis Patients

Variables	TT	TG/GG	P-value	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value[a]
	Patients/controls						
Age, months							
≤60	113/209	290/386	**0.0188**	**1.390(1.056–1.829)**	**0.0190**	**1.376(1.044–1.812)**	**0.0233**
>60	22/31	49/52	0.4066	1.328(0.678–2.599)	0.4079	1.382(0.700–2.729)	0.3516
Sex							
Male	78/135	223/264	**0.0235**	**1.462(1.050–2.035)**	**0.0245**	**1.463(1.050–2.037)**	**0.0244**
Female	57/105	116/174	0.3113	1.228(0.824–1.830)	0.3128	1.241(0.832–1.852)	0.2898
Sepsis subtype							
Sepsis	114/240	275/438	**0.0409**	**1.322(1.010–1.730)**	**0.0422**	**1.311(1.001–1.717)**	**0.0488**
Septic shock	21/240	64/438	0.0448	1.670(0.995–2.802)	0.0521	1.641(0.977–2.756)	0.0612
Prognosis							
Survivors	118/240	276/438	0.0671	1.282(0.981–1.674)	0.0685	1.265(0.968–1.653)	0.0852
Non-survivors	17/240	63/438	**0.0088**	**2.031(1.162–3.549)**	**0.0129**	**2.011(1.149–3.519)**	**0.0144**
Number of organs with dysfunction, n (%)							
1–2	75/240	201/438	**0.0133**	**1.468(1.079–1.999)**	**0.0146**	**1.445(1.060–1.969)**	**0.0199**
3 or more	26/240	69/438	0.1168	1.454(0.902–2.344)	0.1247	1.453(0.900–2.347)	0.1265

Notes: [a]Adjusted for age and gender. Statistically significant values are shown in bold (P<0.05).
Abbreviation: OR, odds ratio.

metastasis.[29] Moreover, the results of a study by Che D et al indicated that the rs6983267 G allele may help reduce the risk of recurrent miscarriage in a population from South China.[28] In our study, the lncRNA *CCAT2* rs6983267 G variant was associated with an increased risk of sepsis in children. In general, gene polymorphisms vary among populations. For example, Monir Sadat Haerian et al reported that the *CCAT2* gene rs6983267 polymorphisms was not relevant to colorectal cancer risk in an Iranian population,[37] though the *CCAT2* rs6983267 TT genotype is slightly more prevalent in colorectal cancer patients than the GG genotype.[38] A study by Keum Ji Jung et al found that *CCAT2* rs6983267 was associated with an increased risk of colorectal cancer in a Korean population.[39] Nevertheless, there is no research to date on *CCAT2* gene polymorphisms and genetic susceptibility to sepsis. Indeed, our study is the first to examine the relationship between *CCAT2* gene polymorphism and genetic susceptibility to sepsis in a population from southern China. It should be noted that our research results need to be verified in other ethnic groups with different genetic backgrounds.

Table 4 False Positive Report Probability Values for Associations Between the Risk of Sepsis and CCAT2 Polymorphism Genotype

Genotype/Allele	OR (95% CI)	p-value[a]	Statistical power[b]	Prior Probability				
				0.25	0.1	0.01	0.001	0.0001
CCAT2/rs6983267 T>G								
TG Vs TT	1.350(1.032–1.766)	0.0287	0.883	**0.089**	0.226	0.763	0.97	0.997
GG Vs TT	1.446(1.027–2.0360)	0.0345	0.735	**0.123**	0.297	0.823	0.979	0.998
GG/TG Vs TT	1.376(1.067–1.774)	0.0138	0.741	**0.053**	**0.143**	0.648	0.949	0.995
GG/TG Vs TT								
≤60	1.390(1.056–1.829)	0.0190	0.703	**0.075**	**0.196**	0.728	0.964	0.996
Male	1.462(1.050–2.035)	0.0245	0.561	**0.116**	0.282	0.812	0.978	0.998
Non-survivors	2.031(1.162–3.549)	0.0129	0.156	**0.198**	0.426	0.891	0.988	0.999
1–2	1.468(1.079–1.999)	0.0146	0.555	**0.073**	**0.191**	0.722	0.963	0.996

Notes: [a]The $\chi 2$ test was used to calculate the genotype frequency distributions. [b]The statistical power was calculated using the number of observations and the OR and P values. Statistically significant values are shown in bold ($P < 0.2$)
Abbreviation: OR, odds ratio.

Olfat G Shaker et al reported that rs6983267 is a potential genetic marker of colorectal cancer and correlates with serum *CCAT2* in Egyptian patients,[30] and it may be involved in disease susceptibility by regulating expression of the lncRNA. Nonetheless, the molecular mechanism remains unclear, and further research is needed. Studies have confirmed that MYC has key functions in mediating inflammation and immune suppression;[40,41] the inflammatory response is crucial to the pathological process of sepsis, which leads to prolonged inflammation, insurmountable infection and, ultimately, death.[42] Liu L et al reported that MYC dependence and HIF1α dependence play an important supporting role in the regulation of the inflammatory response process.[27] Zhang Y et al found that MCP-induced protein 1 regulates macrophage polarization via the JNK/c-MYC pathway to attenuate sepsis-induced acute lung injury,[25] and Lazniak S et al reported that rs6983267 in the lncRNA CCAT2 gene may contribute to increased MYC expression.[22] According to Takatsuno Y et al, by upregulating MYC transcription, the rs6983267 polymorphism is associated with a worse prognosis in colorectal cancer patients.[43] Pomerantz MM et al revealed that the risk region of *CCAT2* gene rs6983267 physically interacts with the MYC proto-oncogene.[44] Because our study was retrospective, we only collected whole blood samples for SNP analysis, and we did not detect MYC expression levels in patients with sepsis. Regardless, all data suggest that *CCAT2* rs6983267 may participate in the pathological process of sepsis by regulating MYC. Of course, this hypothesis requires additional experiments for confirmation.

Studies have also found that genetic polymorphisms are related to the severity and prognosis of sepsis. Mansur A et al reported that rs11536889 in the *Toll-like receptor 4* gene is associated with renal and hepatic organ failure in sepsis patients and may be a useful marker of organ failure in these patients.[45] The study of Chen K et al revealed that a functional Toll-like receptor variant (4/2242 polymorphism) is associated with multiple organ dysfunction scores and higher sepsis morbidity in patients with major trauma.[46] It has been estimated that infection is responsible for the vast majority of death in children under 60 months (nearly 60%).[47] In our study, the *CCAT2* rs6983267 GT/GG genotypes correlated with a significantly increased risk of sepsis in children younger than 60 months, in males, and in those who had sepsis. However, the molecular mechanism requires further study.

Some limitations of this study should be noted. First, the sample size was relatively small, especially with regard to the stratified analysis. For instance, for nonsurvivors, there were only 17 samples, and we calculated a highly significant P-value of 0.0088. This is an extremely small sample size for genetic studies. The statistical power in this study was limited by the sample size, and our results need to be confirmed in a larger, multicenter study. Second, we focused only on the relationship between the *CCAT2* rs6983267 T>G polymorphism and susceptibility to childhood sepsis, and more SNPs need to be included in the future. Third, we included only children in southern China, and as this study was retrospective, some important information (eg, parental exposure) was not collected. Due to differences in the genetic backgrounds and

environmental exposures of different ethnicities, our findings should be cross-validated in different populations.

In conclusion, we found that the *CCAT2* gene rs6983267 T > G polymorphism may be associated with an increased risk of sepsis in children in southern China, especially in males younger than 60 months old and in those with sepsis. However, a larger multicenter study should be performed to confirm the role of *CCAT2* polymorphism in susceptibility to sepsis in children, and further research is needed to elucidate the regulatory mechanism of *CCAT2* in pediatric sepsis.

Data Sharing Statement

Please contact the Correspondence author (Xiaoqiong Gu) for data requests.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest to report.

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