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ORIGINAL ARTICLE

Genetic polymorphisms of ARID5B rs7089424 and rs10994982 are associated with B-lineage ALL susceptibility in Chinese pediatric population

Ran Tao[a], Yu-Jie Liu[a], Li-Fang Liu[a], Wei Li[a], Yun Zhao[a], Hua-Mei Li[a], Xiao-Lian Yi[b], Zheng-Yan Zhao[a,*]

[a]Laboratory Center, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China; [b]Department of Pediatrics, Affiliated Hospital of Hangzhou Normal University, Hangzhou, China

Abstract

Background: Several ARID5B single nucleotide polymorphisms (SNPs) were confirmed to be significantly associated with the susceptibility of childhood acute lymphoblastic leukemia (ALL) based on Caucasian populations in previous studies. Similar investigations in Asian populations were less. The aim of this study is to explore the relationship between ARID5B SNPs rs7089424, rs10994982, and the risk of ALL in Chinese pediatric population.

Methods: A total of 190 pediatric ALL patients and 270 controls were enrolled in this study. PCR amplification combined with mass spectrometry were used to evaluate the genotypes of ARID5B rs7089424 and rs10994982. χ^2 test was used in allele frequencies and genotype distributions of the SNPs for analyzing statistical differences between patients and controls.

Results: There were significant differences in the risk allele frequencies of ARID5B rs7089424 and rs10994982 between B-lineage ALL (B-ALL) patients and controls (rs7089424, G allele: $p = 0.001$; rs10994982, A allele: $p = 0.000$). The genotype distributions of ARID5B rs7089424 and rs10994982 were also statistically different in B-ALL patients compared with controls (rs7089424, $p = 0.004$; rs10994982, $p = 0.001$). Further analyzing the relevance of ARID5B rs7089424 and rs10994982 genotypes to clinical risk classification of ALL showed GG genotype of rs7089424 and AA genotype of rs10994982 were strikingly correlated with the medium-risk and low-risk groups of B-ALL. Finally, GG and GT genotypes of rs7089424 and AA genotype of rs10994982 seemed to be responsible for the hyperdiploid subtype susceptibility of childhood B-ALL.

Conclusion: ARID5B rs7089424 and rs10994982 might serve as genetic susceptibility markers for B-ALL in Chinese pediatric population. Moreover, the two ARID5B SNPs are associated with the risk of B-hyperdiploid ALL, which had a better therapeutic response than other ALL subtypes.

Keywords: Acute lymphoblastic leukemia; ARID5B; Children; Single nucleotide polymorphism; Susceptibility

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common malignancy of childhood, is a genetically complex entity that remains as a major cause of childhood cancer-related mortality.[1] The etiology of ALL is believed to be multifactorial and likely to involve an interplay of environmental and genetic variables. Recent advances in genome-wide association studies (GWASs) substantially improved our outstanding of genetic susceptibility to the development of childhood ALL.[2] In 2009, two independent studies reported several single nucleotide polymorphisms (SNPs) located on 10q21.2 (ARID5B), 7p12.2 (IKZF1), and 14q11.2 (CEBPE) had the strongest association with the risk of developing ALL in children.[3,4]

Address correspondence: Prof. Zheng-Yan Zhao, Children's Hospital, Zhejiang University School of Medicine, 3333, Binsheng Road, Binjiang District, Hangzhou City, Zhejiang Province, China. E-mail address: zhaozy@zju.edu.cn (Z.-Y. Zhao).

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ARID5B, a member of the AT-rich interaction domain family of transcription factors, plays a vital role in the regulation of embryonic development, cell growth, and differentiation through tissue-specific repression of specific gene expression.[5] Several ARID5B SNPs such as rs10824936, rs10994982, rs7089424, rs7073837, and rs10740055 were confirmed to be significantly associated with the susceptibility of childhood ALL in Caucasian populations.[3,4,6–9] However, studies on the relationships between ARID5B SNPs and childhood ALL in Asian populations were relatively less. ARID5B rs10821938 genotype was reported to be significantly associated with B-cell precursor ALL in Thai population.[10] Wang et al.[11] concluded ARID5B rs10821936 could serve as a potential biomarker for assessing the risk of childhood ALL in Chinese children. Another study conducted in Chinese population found that the distribution of genotype rs7073837 in ARID5B significantly differed between ALL and controls.[12] Bhandari et al.[13] unexpectedly provided the first evidence that ARID5B rs10821936 was associated with decreased B-lineage ALL (B-ALL) susceptibility in Indian children.

A meta-analysis emphasized ARID5B SNPs rs7089424 and rs10994982 were indeed significantly associated with increased risk of childhood ALL, and also provided strong evidence that rs10994982 was highly associated with the risk of developing B-hyperdiploid ALL.[14] In spite of this, these two SNPs in ARID5B were never confirmed having relevance to childhood

ALL in Chinese populations. In the current study, we conducted a case–control study including 190 ALL cases and 270 controls to validate the relationship between ARID5B SNPs rs7089424, rs10994982 and the risk of ALL in Chinese pediatric population.

2. METHODS

2.1. Study subjects

A total of 190 pediatric patients initially diagnosed with ALL at Children's Hospital, Zhejiang University School of Medicine and 270 healthy controls excluding cases with history or family history of malignant tumors and hematological system diseases were enrolled in this study from May 2015 to December 2015. All patients were conformed to French–American–British classification, and definitely diagnosed with ALL by morphology, immunology, cytogenetics, and molecular biology. The clinical risk classification and immunophenotype of the ALL patients were determined based on the guideline for diagnosis and treatment of childhood ALL, which was designed by the Chinese Medical Association in 2006.[12]

This study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine and in accordance with the principles of the Declaration of Helsinki.

2.2. Genomic DNA extraction

EDTA-anticoagulated blood samples (200 μL) were collected from the 190 ALL patients and 270 controls. The genomic DNA was extracted according to the instruction of the Whole Blood Genomic DNA Extraction Kit (Tissuebank Biotechnology Co, Ltd, Shanghai, China). The extracted DNA was then stored at −80°C for further use.

2.3. PCR amplification

The forward primers and reverse primers of ARID5B rs7089424 and rs10994982 were synthesized by Sangon Biotech (Shanghai) company (Table 1). The PCR reaction system was 5 μL including 0.95 μL of deionized water, 0.625 μL of 10× buffer (containing 15 mM $MgCl_2$), 0.325 μL of 25 mM $MgCl_2$, 1 μL of dNTP (2.5 mM each), 1 μL of PCR primers, 0.1 μL of 5 U/μL HotStar Taq (Qiagen), and 1 μL of DNA sample. PCR reaction was carried out at 94°C for 15 minutes, followed by 45 cycles consisting of 20 seconds at 94°C, 30 seconds at 56°C, and 1 minute at 72°C, and a final extension at 72°C for 3 minutes.

2.4. SAP processing

For removing the remnant dNTPs, 1.53 μL of deionized water, 0.17 μL of SAP buffer, and 0.3 U shrimp alkalinephosphatase (Sequenom) were added to the PCR reaction system after PCR amplification. This reaction was incubated at 37°C for 40 minutes, then followed by incubation at 85°C for 5 minutes to inactivate the enzyme.

2.5. iPLEX single base extension reaction

The single base extension reaction system was 2 μL including deionized water, 0.755 μL; 10× iPLEX buffer, 0.2 μL; iPLEX termination mix, 0.2 μL; iPLEX enzyme (Sequenom), 0.041 μL; single base extension primer (sequences showed in Table 1), 0.804 μL. The extension reaction was performed at 94°C for 30 seconds, followed by 40 cycles consisting of 5 seconds at 94°C, 5 cycles of 5 seconds at 52°C and 5 seconds at 80°C, and 3 minutes at 72°C.

2.6. Resin desalination and mass spectrometry

The single base extension reactant was centrifuged at 1000 rpm for 1 minute and resuspended in 25 μL deionized water. The resuspension solution was prepared for genotyping after desalination with cation exchange resin (Sequenom). MassARRAY Nanodispenser (Sequenom) was used to add the samples to be genotyped to a 384 well spectroCHIP (Sequenom). The genotyping reaction was performed on the matrix-assisted laser desorption ionization time-of-flight mass spectrometer, and the results were analyzed by using software MassARRAY Typer version 3.4 (Sequenom).

2.7. Statistical analysis

Goodness-of-fit χ^2 test was used to determine the Hardy–Weinberg equilibrium for each SNP. For analyzing statistical differences between patients and controls, χ^2 test was used in allele frequencies and genotype distributions of the SNPs. In addition, the odds ratios (OR) and 95% CI were obtained by using Logistic regression analysis. $p < 0.05$ was considered statistically significant.

3. RESULTS

In the current study, the pediatric ALL patients were aged from 5 months to 15-years-old with the average age of 5.86 ± 3.59 years at diagnosis. The proportions of age group 0-1 year, 1-3 years, 3-6 years, 6-9 years, 9-12 years, and above 12 years were 2.6%, 22.1%, 36.8%, 17.9%, 13.7%, and 6.9%, respectively. The 3-6 years age group was apparently the peak age bracket of ALL diagnosis in children. In addition, ALL patients were composed of 119 boys and 71 girls with the gender ratio of 1.7:1. No significant differences were found in term of age and gender between patients and controls (Table 2). The detailed information about the clinical risk classification, immunophenotype, subtypes of cytogenetics and molecular biology of ALL patients in this study were shown in Table 2.

The genotyping results of ARID5B rs7089424 and rs10994982 were represented in Figure 1. The two SNPs were tested by Hardy–Weinberg equilibrium in ALL patients and controls, and no significant differences were found in either rs7089424 ($p = 0.29$) or rs10994982 ($p = 0.32$). As showed in Table 3, there were significant differences in the risk allele frequencies of ARID5B rs7089424 and rs10994982 between B-ALL patients and controls (rs7089424, G allele: $p = 0.001$, OR = 1.59, 95% CI = 1.21-2.09; rs10994982, A allele: $p = 0.000$, OR = 1.67, 95% CI = 1.27-2.19). The genotype distributions of ARID5B rs7089424 and rs10994982 were also

Table 1

Primers of PCR amplification and iPLEX single base extension of ARID5B rs7089424 and rs10994982

SNP	Primer	Sequence
rs7089424	Forward	5′-ACGTTGGATGGCTTTTGCCCTCACTATTGC-3′
	Reverse	5′-ACGTTGGATGGTTACTCAGAGTGGTAGCAG-3′
	Single base extension	5′-CTCAAGAAAAAAAACATCACA-3′
rs10994982	Forward	5′-ACGTTGGATGAGCACATCTGAGGTACAGAG-3′
	Reverse	5′-ACGTTGGATGGGACCATCATGGTCTTTTAA-3′
	Single base extension	5′-AATGAGGTACAGAGTCAGTG-3′

SNP = single nucleotide polymorphism.

Table 2

General and clinical characteristics of ALL patients and controls

General and clinical characteristics			Patients	Controls	*p*
Age (mean ± SD, years)			5.86 ± 3.59	4.33 ± 3.62	0.06
Gender [n (%)]	Male		119 (62.6)	177 (65.6)	0.52
	Female		71 (37.4)	93 (34.4)	
Clinical risk classification [n (%)]	High risk		54 (28.4)		
	Medium risk		76 (40.0)		
	Low risk		60 (31.6)		
Immunophenotype [n (%)]	B-lineage	Common	139 (73.2)		
		Pro-B	12 (6.3)		
		Pre-B	17 (8.9)		
		Mature B	7 (3.7)		
	T-lineage	Pre-T	1 (0.5)		
		Mature T	14 (7.4)		
Genetic abnormality [n (%)]	*TEL/AML1* fusion gene		35 (18.4)		
	E2A/PBX1 fusion gene		11 (5.8)		
	BCR/ABL (p190) fusion gene		10 (5.3)		
	SIL/TAL1 fusion gene		6 (3.2)		
	EVI1 gene		4 (2.1)		
	MLL/ENL fusion gene		3 (1.6)		
	MLL/AF9 fusion gene		2 (1.1)		
	BCR/ABL (p210) fusion gene		1 (0.5)		
	HOX11 gene		1 (0.5)		
	MLL/AF10 fusion gene		1 (0.5)		
	TLS/ERG fusion gene		1 (0.5)		
Chromosomal abnormality [n (%)]	Hyperdiploid		45 (23.7)		
	Hypodiploid		17 (8.9)		

statistically different in B-ALL patients compared with controls (rs7089424, p = 0.004; rs10994982, p = 0.001). However, no differences in the risk allele frequencies and genotype distributions of ARID5B rs7089424 and rs10994982 between T-lineage ALL (T-ALL) patients and controls were found (Supplementary Table 1).

After further analyzing the relevance of ARID5B rs7089424 and rs10994982 genotypes to clinical risk classification of ALL, we found that GG genotype of ARID5B rs7089424 was strikingly correlated with the medium-risk and low-risk groups of B-ALL patients (medium risk: OR = 3.10, 95% CI = 1.47-6.44; low risk: OR = 2.98, 95% CI = 1.34-6.66), while GT genotype of this SNP had no relationship to B-ALL clinical risk classification. Similarly, AA genotype of ARID5B rs10994982 was also significantly correlated with the medium-risk and low-risk groups of B-ALL (medium risk: OR = 2.64, 95% CI = 1.24-5.60; low risk: OR = 3.55, 95% CI = 1.50-8.40) but no correlation was found between rs10994982 AG genotype and clinical risk classification of B-ALL (Table 4). For T-ALL patients, no correlation was found between genotypes of ARID5B rs7089424 or rs10994982 and clinical risk groups (Supplementary Table 2).

We finally compared the genotype distributions of ARID5B rs7089424 and rs10994982 among the dominant subtypes of cytogenetics and molecular biology in B-ALL patients, and found GG and GT genotypes of ARID5B rs7089424 and AA genotype of rs10994982 seemed to be responsible for the hyperdiploid subtype susceptibility of childhood B-ALL (rs7089424, GG genotype: OR = 5.74, 95% CI = 1.88-17.54; rs7089424, GT genotype: OR = 4.39, 95% CI = 1.62-11.86; rs10994982, AA genotype: OR = 4.92, 95% CI = 1.58-15.28) (Table 5).

4. DISCUSSION

In this case–control study, we confirmed the association of ARID5B rs7089424 and rs10994982 with B-ALL susceptibility in a Chinese pediatric population. The G-allele carriers of ARID5B rs7089424 and A-allele carriers of ARID5B rs10994982 had a higher B-ALL incidence than the T-allele carriers of rs7089424 and G-allele carriers of rs10994982, respectively. Therefore, the G allele of ARID5B rs7089424 and A allele of ARID5B rs10994982 seemed to be potential predictive markers for developing childhood B-ALL in Chinese population.

As most previous studies,[14] the correlation analysis between the genotypes of ARID5B SNPs and ALL immunophenotypes in this study confirmed ARID5B rs7089424 and rs10994982 were associated with the risk of developing B-ALL. The mechanisms possibly involved the recombination activating gene 1 (*RAG1*), which plays a role in early B-cell differentiation. Two rounds of DNA recombination necessary for precursor B-cell development in bone marrow depended on the activation of RAG-1 and RAG-2 endonucleases.[15] Moreover, the expression of ARID5B had been reported to be associated with RAG1 expression in bone marrow,[16] providing a possible explanation about how ARID5B participated in the pathogenesis of B-ALL.

The conclusions on the association of ARID5B rs7089424 and rs10994982 with B-ALL were not consistent in several studies based on Asian population. The results of the case–control study carried out in Yemeni children agreed with ours, revealing the two SNPs of ARID5B were the risk factors for ALL.[17] A GWAS conducted in Korean population merely found an association between ARID5B rs7089426 which was tightly linked with rs7089424 and pediatric ALL risk.[18] However, no statistically significant association between ARID5B rs7089424 and B-cell precursor ALL was found in a study conducted in Thai population.[10] Similarly, the genotype distribution of ARID5B rs7089424 was reported showing no significant difference between Chinese ALL cases and controls.[12] The reasons for this discrepancy probably included the size of research sample, the selection criteria of study objects, the techniques for detecting polymorphisms, and the statistical methods of genotyping results.

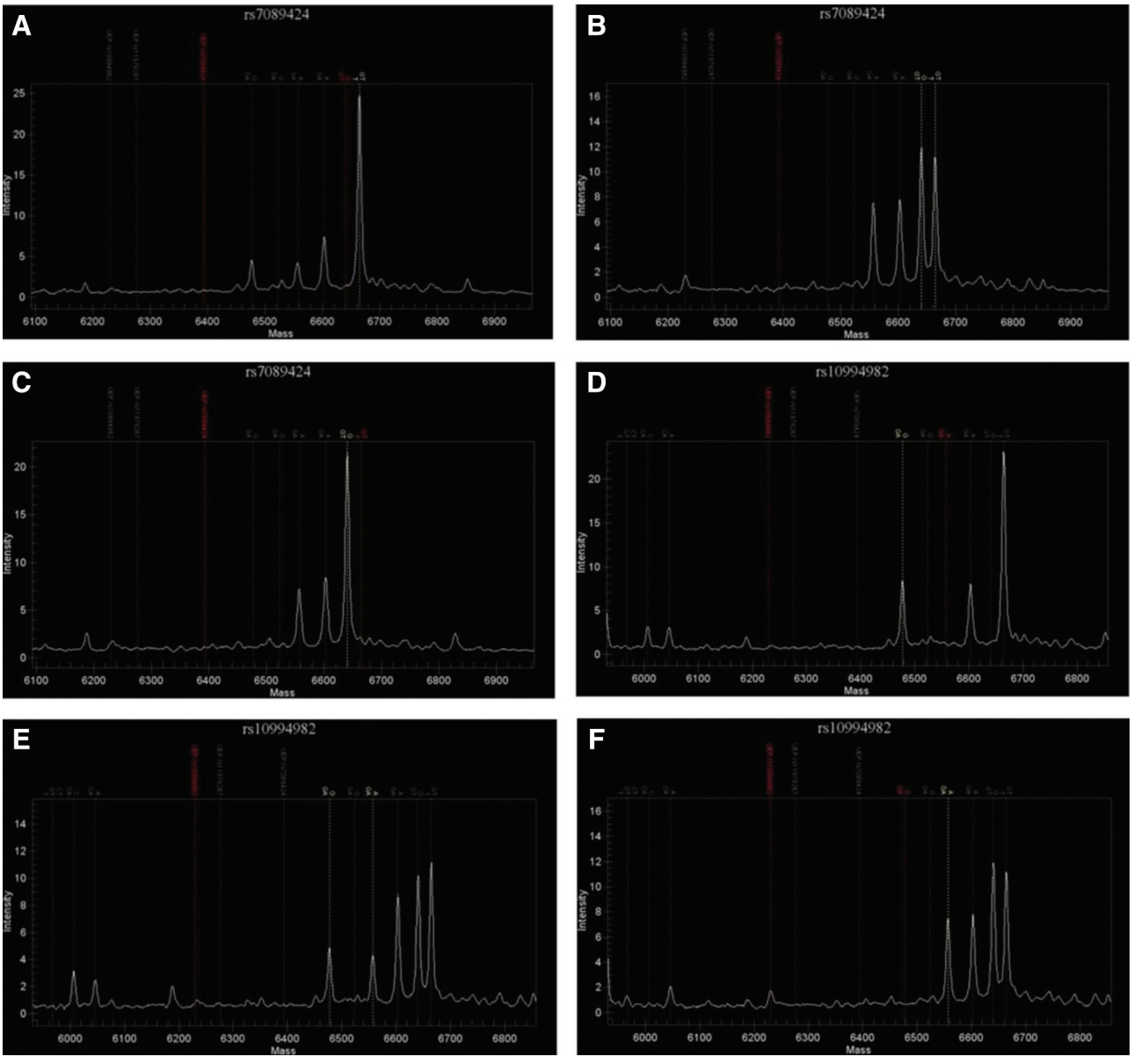

Fig. 1 Genotyping results of ARID5B rs7089424 and rs10994982. A, TT genotype of rs7089424; B, GT genotype of rs7089424; C, GG genotype of rs7089424; D, GG genotype of rs10994982; E, AG genotype of rs10994982; F, AA genotype of rs10994982.

Table 3

Allele frequencies and genotype distributions of ARID5B rs7089424 and rs10994982 in B-ALL patients and controls

	Patients		Controls					
Genotype	**n**	**%**	**n**	**%**	**χ^2**	***p***	**OR**	**95% CI**
rs7089424								
T > G					10.88	0.004		
TT	46	26.3	107	39.6			1.0	
GT	86	49.1	122	45.2			1.64	1.05-2.55
GG	43	24.6	41	15.2			2.44	1.41-4.23
G allele	172	49.1	204	37.8	11.21	0.001	1.59	1.21-2.09
rs10994982								
G > A					13.77	0.001		
GG	30	17.1	71	26.3			1.0	
AG	75	42.9	134	49.6			1.33	0.79-2.21
AA	70	40.0	65	24.1			2.55	1.48-4.39
A allele	215	61.4	264	48.9	13.51	0.000	1.67	1.27-2.19

OR = odds ratio.

Table 4

Relationships between genotypes of ARID5B rs7089424 and rs10994982 and clinical risk classification of B-ALL

	Controls		B-ALL patients						OR (95% CI)		
			High risk		Medium risk		Low risk				
Genotype	n	%	n	%	n	%	n	%	High risk	Medium risk	Low risk
rs7089424											
TT	107	39.6	15	34.9	17	23.6	14	23.3	1.0	1.0	1.0
GT	122	45.2	21	48.8	35	48.6	30	50.0	1.23(0.60-2.50)	1.81(0.96-3.41)	1.88(0.95-3.73)
GG	41	15.2	7	16.3	20	27.8	16	26.7	1.22(0.46-3.20)	3.10(1.47-6.44)	2.98(1.34-6.66)
rs10994982											
GG	71	26.3	10	23.2	12	16.7	8	13.3	1.0	1.0	1.0
AG	134	49.6	18	41.9	31	43.1	26	43.3	0.95(0.42-2.18)	1.37(0.66-2.83)	1.72(0.74-4.00)
AA	65	24.1	15	34.9	29	40.2	26	43.3	1.64(0.67-3.90)	2.64(1.24-5.60)	3.55(1.50-8.40)

B-ALL = B-lineage acute lymphoblastic leukemia; OR = odds ratio.

Table 5

Relationships between genotypes of ARID5B rs7089424 and rs10994982 and the dominant subtypes of B-ALL cytogenetics and molecular biology

	Controls		B-ALL patients						OR (95% CI)		
			Hyperdiploid		TEL/AML1		Others				
Genotype	n	%	N	%	n	%	n	%	Hyperdiploid	TEL/AML1	Others
rs7089424											
TT	107	39.6	5	12.2	16	45.7	16	40.0	1.0	1.0	1.0
GT	122	45.2	25	61.0	15	42.9	16	40.0	4.39(1.62-11.86)	0.82(0.39-1.74)	0.88(0.42-1.84)
GG	41	15.2	11	26.8	4	11.4	8	20.0	5.74 (1.88-17.54)	0.65 (0.21-2.07)	1.31 (0.52-3.28)
rs10994982											
GG	71	26.3	4	9.8	10	28.6	10	25.0	1.0	1.0	1.0
AG	134	49.6	19	46.3	14	40.0	14	35.0	2.52(0.83-7.68)	0.74(0.31-1.76)	0.74(0.31-1.76)
AA	65	24.1	18	43.9	11	31.4	16	40.0	4.92(1.58-15.28)	1.20(0.48-3.01)	1.75(0.74-4.13)

B-ALL = B-lineage acute lymphoblastic leukemia; OR, odds ratio.

On subtype analysis, we found GG genotype of ARID5B rs7089424 and AA genotype of ARID5B rs10994982 were significantly correlated with the medium-risk and low-risk subgroups of B-ALL, suggesting homozygous mutation of the two SNPs might have bigger chances to develop into medium or low risk B-ALL.

By further analysis on the subtypes of B-ALL in this study, GG and GT genotype of ARID5B rs7089424 and AA genotype of ARID5B rs10994982 distinguished B-hyperdiploid ALL from other subtypes. The partial results were in line with those of previous studies, which verified the association between ARID5B rs10994982 and B-hyperdiploid ALL.[14] Furthermore, there was no previous study focusing on the role of ARID5B rs7089424 in the risk of developing B-hyperdiploid ALL. In consideration of B-hyperdiploid ALL having a better response to methotrexate chemotherapy than other ALL subtypes,[19] ARID5B SNPs might be helpful to instruct treatment and estimate prognosis of ALL besides predicting the risk of this disease.

In conclusion, the results of the current study suggest ARID5B rs7089424 and rs10994982 might serve as genetic susceptibility markers for B-ALL in Chinese pediatric population. Moreover, ARID5B rs7089424 and rs10994982 are associated with the risk of B-hyperdiploid ALL, which has a better therapeutic response than other ALL subtypes.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A16

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