

ABCB1 C3435T polymorphism is associated with leukemia susceptibility: evidence from a meta-analysis

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Introduction and objective: Many studies have been conducted on the association between the adenosine triphosphate-binding cassette, subfamily B, member 1 (*ABCB1*) gene C3435T polymorphism and leukemia risk, however, the previously published findings remain controversial. Thus, a meta-analysis was carried out to accurately evaluate the effect of this polymorphism on leukemia susceptibility.

Methods: A computerized literature search was conducted of PubMed, Elsevier database, the China National Knowledge Infrastructure database, and Wanfang Database, to find published case-control studies exploring the relationship between *ABCB1* C3435T polymorphism and leukemia risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were applied to assess the strength of association.

Results: A total of 17 studies of 2,431 cases and 3,028 controls were included in this meta-analysis. The results of overall comparisons suggest that there is a significant association between *ABCB1* C3435T polymorphism and leukemia risk under two genetic models (TT vs CC: OR=1.39, 95% CI=1.04–1.84, $P=0.02$; CT+TT vs CC: OR=1.20, 95% CI=1.06–1.36, $P=0.004$). In the subgroup analyses by ethnicity, age, and leukemia subtype, a significant association was found in Caucasian (CT vs CC: OR=1.22, 95% CI=1.03–1.45, $P=0.02$; TT vs CC: OR=1.34, 95% CI=1.10–1.64, $P=0.004$; CT+TT vs CC: OR=1.27, 95% CI=1.08–1.49, $P=0.004$), adult leukemia (CT vs CC: OR=1.46, 95% CI=1.17–1.83, $P=0.001$; CT+TT vs CC: OR=1.43, 95% CI=1.01–2.03, $P=0.04$), and lymphocytic leukemia (TT vs CC: OR=1.73, 95% CI=1.19–2.51, $P=0.004$; TT vs CC+CT: OR=1.62, 95% CI=1.10–2.38, $P=0.01$; CT+TT vs CC: OR=1.28, 95% CI=1.10–1.48, $P=0.001$).

Conclusion: The meta-analysis suggests that *ABCB1* C3435T polymorphism is associated with increased risk of leukemia.

Keywords: adenosine triphosphate-binding cassette, subfamily B, member 1 gene, multidrug-resistance gene, meta-analysis

Introduction

Leukemia is a group of malignant diseases of the hematopoietic system, with an estimated 54,270 new cases and 24,450 deaths expected in the USA in 2015.¹ Although the incidence of leukemia increases gradually, with age the most prominent risk factor, the etiology and mechanisms underlying the pathogenesis of leukemia are not yet fully understood.² Epidemiological studies have found that advanced age, radiation, smoking, and exposure to chemical carcinogens are risk factors which contribute to the genesis of leukemia.^{3–5} However, only a small proportion of people exposed to these risk factors develop leukemia, suggesting that host genetic factors might play an important role.⁶ Recent genome-wide association studies have identified the presence

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of inherited genetic susceptibility to this disease.^{7–9} Therefore, multiple factors are considered implicated in the etiology of leukemia, including exogenous or endogenous exposure, genetic susceptibility, and chance.²

The human adenosine triphosphate-binding cassette, subfamily B, member 1 (*ABCB1*) gene, also named multidrug-resistance 1 (*MDR1*) gene, is located at 7q21.1, with 28 exons encoding a 170 kDa membrane transporter called P-glycoprotein (P-gp). The presence of a highly conserved adenosine triphosphate (ATP)-binding site in two homologous halves as well as the linker region makes this protein a member of the adenosine triphosphate-binding cassette (ABC) superfamily.¹⁰ P-gp acts as an efflux pump in an ATP-dependent fashion, transporting exogenous and endogenous substrates from the inside of cells to the outside. P-gp was first identified in human cancer cells as a protein responsible for resistance against many anticancer drugs. Subsequently, this efflux transporter has been found in various normal human tissues, including in the intestinal epithelium, adrenal gland, placenta, kidney, liver, capillary endothelial cells of the brain, and testes. Physiological expression of P-gp in excretory tissues provides a cellular defense mechanism against potentially harmful compounds.^{10–12} *ABCB1* is polymorphic and at least 50 single-nucleotide polymorphisms (SNPs) have been identified within *ABCB1* gene locus.¹³ C3435T at exon 26 is the most widely investigated SNP of *ABCB1* and has been associated with altered P-gp expression and activity in tissue studies including those on placenta, liver, and leukocytes.^{14–16} There is increasing evidence that genetic variants of *ABCB1* affect P-gp activity and expression levels, and the alteration of P-gp transport activity results in decreased extrusion of harmful xenobiotics and cumulative cytotoxicity.^{17,18} The C3435T SNP in *ABCB1* has been associated with the development of various cancers, including breast cancer, hepatocellular carcinoma, and non-Hodgkin lymphoma.^{19–21} Many case–control studies have been conducted to investigate whether the *ABCB1* C3435T polymorphism is associated with leukemia risk but these have yielded controversial results. Therefore, we performed a meta-analysis to accurately evaluate the effect of *ABCB1* C3435T polymorphism on leukemia susceptibility.

Materials and methods

Study identification

A systematic literature search of the PubMed, Elsevier, China National Knowledge Infrastructure, and Wanfang databases was conducted to identify studies that explored the relationship between *ABCB1* C3435T polymorphism and

leukemia risk. The search terms and keywords were as follows: “multidrug resistance gene” or “*MDR1*” or “*ABCB1*”, “polymorphism” or “variant” or “mutant”, and “leukemia” or “leukaemia” or “leukocythemia”. No language restriction was applied and the latest search was undertaken on April 30, 2014. The references cited in the eligible studies were also examined to find additional studies. Two reviewers examined the retrieved literature independently and disagreement was resolved by discussion.

Inclusion criteria

All studies included in this meta-analysis had to meet the following criteria. They had to: (1) be case–control studies assessing the relationship between *ABCB1* C3435T polymorphism and leukemia risk; (2) have confirmed diagnosis in the case group; and (3) have genotype frequencies for both cases and controls available. Reviews, meta-analyses, case reports, and letters were excluded.

Data extraction

Two reviewers independently extracted information from each eligibility study and disagreements were addressed by discussion. The following data were extracted from each study: author(s), year of publication, country, ethnicity, source of controls, genotyping methods, sample size of cases and controls, genotype frequencies of the *ABCB1* C3435T polymorphism for cases and controls, and Hardy–Weinberg equilibrium (HWE) of control group.

Statistical analysis

The HWE of the genotype distribution in the control groups was checked using the χ^2 test and *P*-values <0.05 were designated as deviations from HWE. The strength of association between *ABCB1* C3435T polymorphism and leukemia risk was assessed by odds ratios (ORs) with 95% confidence intervals (CIs) under the heterozygote model (CT vs CC), homozygote model (TT vs CC), dominant model (CT+TT vs CC), and recessive model (TT vs CC+CT). The significance of the combined OR was determined by the *Z* test. The Q-statistic test was used to evaluate the between-study heterogeneity. If *P*<0.05, indicating that there was significant heterogeneity, the random-effects model (DerSimonian–Laird) was applied to combine the data, otherwise, the fixed-effects model (Mantel–Haenszel) was selected. Subgroup analyses were performed by ethnicity, age, and leukemia subtype to find the source of heterogeneity. Funnel plots were produced to evaluate publication bias and sensitivity analysis was performed by omission of studies not in agreement with

HWE to assess the stability of the results. All the tests were two-sided and *P*-values <0.05 were considered as statistically significant. The data analyses were performed using Review Manager software (v 5.2; The Cochrane Collaboration, Oxford, UK).

Results

Characteristics of studies

In accordance with the inclusion criteria, a total of 17 publications with 2,431 leukemia cases and 3,028 controls were included in the meta-analysis presented here.^{22–38} The main characteristics of included studies are summarized in Table 1. All of the 17 studies were case–control studies, 14 of which were population-based controls and the remaining three were hospital-based controls. All the cases had a confirmed diagnosis of leukemia and the controls were mainly matched for age and sex. Among the included studies, six studies were conducted in an Asian population,^{25,28,31,34,36,38} nine studies in a Caucasian population,^{22–24,26,29,30,32,33,35} and two studies in a mixed population.^{27,37} The distribution of genotypes among the control groups in four studies was not in agreement with HWE.^{22,33,35,36}

Meta-analysis results

Table 2 lists the main results of this meta-analysis. When all the eligible studies were pooled into the meta-analysis, a significant association between *ABCB1* C3435T polymorphism and leukemia risk was observed under two genetic models (TT vs CC: OR=1.39, 95% CI=1.04–1.84, *P*=0.02; CT+TT vs CC: OR=1.20, 95% CI=1.06–1.36, *P*=0.004) (Table 2). Subgroup analyses were also performed to explore the effect of ethnicity, age, and leukemia subtype. When stratified by ethnicity, a significantly increased risk was observed in Caucasians (CT vs CC: OR=1.22, 95% CI=1.03–1.45, *P*=0.02; TT vs CC: OR=1.34, 95% CI=1.10–1.64, *P*=0.004; CT+TT vs CC: OR=1.27, 95% CI=1.08–1.49, *P*=0.004) (Table 2). Significant associations were also found in adult leukemia (CT vs CC: OR=1.46, 95% CI=1.17–1.83, *P*=0.001; CT+TT vs CC: OR=1.43, 95% CI=1.01–2.03, *P*=0.04) (Table 2, Figure 1) and lymphocytic leukemia (TT vs CC: OR=1.73, 95% CI=1.19–2.51, *P*=0.004; TT vs CC+CT: OR=1.62, 95% CI=1.10–2.38, *P*=0.01; CT+TT vs CC: OR=1.28, 95% CI=1.10–1.48, *P*=0.001) (Table 2, Figure 2).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by excluding the studies in which the distribution of genotypes in the control groups was not in agreement with HWE. The results show that the

Table 1 Main characteristics of studies included in the meta-analysis

Study	Year	Country	Ethnicity	Illness	Design	Method(s)	Case	Control	CC	CT	TT	CC	CT	TT	HWE
Bektaş-Kayhan et al ³³	2012	Turkey	Caucasian	Child ALL	PB	PCR-RFLP	47	68	11	26	10	11	44	13	0.01
Gréen et al ³⁵	2012	Sweden	Caucasian	Adult AML	PB	Sequencing	100	400	19	47	34	87	175	138	0.03
Hattori et al ²⁵	2007	Japan	Asian	Child ALL	PB	TaqMan® SNP	118	96	39	50	29	40	46	10	0.54
Jamroziak et al ²³	2006	Poland	Caucasian	Adult AML	PB	PCR-RFLP	180	180	44	95	41	62	78	40	0.11
Jamroziak et al ²⁴	2006	Poland	Caucasian	Adult B-CLL	PB	PCR-RFLP	110	201	27	59	24	74	88	39	0.17
Jamroziak et al ²²	2004	Poland	Caucasian	Child ALL	PB	PCR-RFLP	113	175	43	36	34	70	71	34	0.04
Leal-Ugarte et al ²⁷	2008	Mexico	Mixed	Child ALL	PB	PCR-RFLP	107	111	18	65	24	15	59	37	0.26
Liu ²⁸	2008	People's Republic of China	Asian	Child ALL	HB	PCR-RFLP	48	100	10	26	12	45	42	13	0.52
Lü et al ³⁴	2012	People's Republic of China	Asian	Child ALL	HB	SNaPshot® SNP	176	170	67	24	85	71	79	20	0.78
Penna et al ²²	2011	Italy	Caucasian	Adult B-CLL	PB	PCR-RFLP	125	125	26	59	40	45	57	23	0.51
Rao et al ³¹	2010	India	Asian	ALL+AML	PB	PCR-RFLP	290	249	50	126	114	49	128	72	0.56
Rocha et al ³⁰	2009	France	Caucasian	AL+CL	HB	PCR-RFLP	107	107	30	56	21	29	56	22	0.60
Semsei et al ²⁹	2008	Hungary	Caucasian	Child ALL	PB	Single-base extension	378	189	86	177	115	54	84	51	0.13
Singh et al ³⁶	2012	Singapore	Asian	Adult CML	PB	Sequencing	38	275	13	15	10	65	114	96	0.01
Urayama et al ²⁶	2007	USA	Caucasian	Child ALL	PB	Single-base extension	294	369	81	140	73	100	178	91	0.51
Vivona et al ³⁷	2012	Brazil	Mixed	Adult CML	PB	PCR-RFLP	118	120	43	62	13	42	60	18	0.65
Zhai et al ³⁸	2012	People's Republic of China	Asian	Child ALL	PB	SNaPshot SNP	82	93	39	34	9	40	40	13	0.56

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HB, hospital based; HWE, Hardy–Weinberg equilibrium; PB, population based; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNP, single-nucleotide polymorphism.

Table 2 Results of meta-analysis for adenosine triphosphate-binding cassette, subfamily B, member 1 (*ABCB1*) C3435T polymorphism and leukemia risk

Variable	N	CT vs CC			TT vs CC			TT vs CC+CT			CT+TT vs CC		
		OR (95% CI)	P	P _h ^a	OR (95% CI)	P	P _h ^a	OR (95% CI)	P	P _h ^a	OR (95% CI)	P	P _h ^a
Overall	17	1.06 (0.85–1.31)	0.62	<0.01	1.39 (1.04–1.84)	0.02	<0.01	1.31 (0.99–1.72)	0.06	<0.01	1.20 (1.06–1.36)	<0.01	0.06
Ethnicity													
Asian	6	0.88 (0.52–1.48)	0.63	<0.01	1.81 (0.92–3.58)	0.09	<0.01	1.86 (0.92–3.74)	0.08	<0.01	1.18 (0.95–1.48)	0.13	0.05
Caucasian	9	1.22 (1.03–1.45)	0.02	0.16	1.34 (1.10–1.64)	<0.01	0.27	1.17 (0.99–1.39)	0.06	0.45	1.27 (1.08–1.49)	<0.01	0.16
Mixed	2	0.98 (0.62–1.53)	0.92	0.84	0.62 (0.34–1.13)	0.12	0.66	0.62 (0.39–1.00)	0.05	0.70	0.88 (0.57–1.35)	0.56	0.68
Age													
Child	8	0.83 (0.61–1.14)	0.26	0.02	1.38 (0.86–2.23)	0.18	<0.01	1.48 (0.86–2.53)	0.16	<0.01	1.08 (0.91–1.28)	0.38	0.59
Adult	7	1.46 (1.17–1.83)	<0.01	0.14	1.42 (0.89–2.27)	0.14	0.01	1.12 (0.90–1.41)	0.30	0.11	1.43 (1.01–2.03)	0.04	0.02
Subtype													
LL	12	1.05 (0.78–1.41)	0.74	<0.01	1.73 (1.19–2.51)	<0.01	<0.01	1.62 (1.10–2.38)	0.01	<0.01	1.28 (1.10–1.48)	<0.01	0.05
ML	5	1.12 (0.87–1.45)	0.37	0.22	0.95 (0.71–1.28)	0.74	0.30	0.90 (0.70–1.14)	0.37	0.84	1.07 (0.84–1.35)	0.60	0.14

Notes: P_h^a value used to test the heterogeneity. If P_h^a < 0.05, the random-effects model was applied to combine the data, otherwise the fixed-effects model was selected.
Abbreviations: CI, confidence interval; LL, lymphocytic leukemia; ML, myeloid leukemia; N, number of studies; OR, odds ratio.

statistical significance was not changed, suggesting that the results of this meta-analysis are relatively stable and credible. Four funnel plots were produced to assess the publication bias and the shapes of funnel plots reveal no evidence of obvious asymmetry, indicating there is no statistical evidence of publication bias (Figure 3).

Discussion

At least 50 SNPs have been described in all 28 exons of the *ABCB1* gene and the C3435T (rs1045642) polymorphism is a synonymous variant with no effect on amino-acid change at codon 1142 (Ile1142Ile) in the second ATP-binding domain.^{13,17} Studies have shown that 3435T is associated with lower *ABCB1* expression levels and subsequently reduces P-gp activity and alters substrate specificity.^{14,39,40} P-gp is not only expressed in tumor cells, but also in cells of several normal tissues. It was detected in the apical membranes of excretory tissues, such as the intestine, kidney, and liver, suggesting its role in the elimination of xenobiotics.^{41,42} Besides, P-gp is also expressed in peripheral leukocytes and hematopoietic stem cells from which acute myeloid leukemia originates, which indicates that *ABCB1* may play an important role in the etiology of leukemia.^{43,44} Functional polymorphisms in *ABCB1* may cause various human malignancies including leukemia. However, the exact biological mechanism for the association of *ABCB1* polymorphisms with leukemia risk still requires explanation through further studies.

Given the potential influence of this functional polymorphism on cancer susceptibility, many molecular epidemiological studies have been conducted to investigate the association between *ABCB1* C3435T polymorphism and leukemia risk. However, the results from different studies are controversial, which may be owing to different genetic backgrounds in individual studies. To synthetically evaluate the effect of *ABCB1* C3435T polymorphism on susceptibility to leukemia, we performed a meta-analysis of 17 case-control studies that assessed the relationship between *ABCB1* C3435T polymorphism and leukemia risk. In this meta-analysis, in overall comparisons under a homozygote model and dominant model, we found that the *ABCB1* 3435TT genotype significantly increases leukemia risk. When stratified by ethnicity, the results indicate that the individuals with a TT genotype in the C3435T of *ABCB1* had significantly increased risk of leukemia among Caucasian populations, but not in other ethnicities. An explanation for this is that the racial differences in leukemia incidence can partly be attributed to differences in genotype frequencies between different populations at *ABCB1* loci.

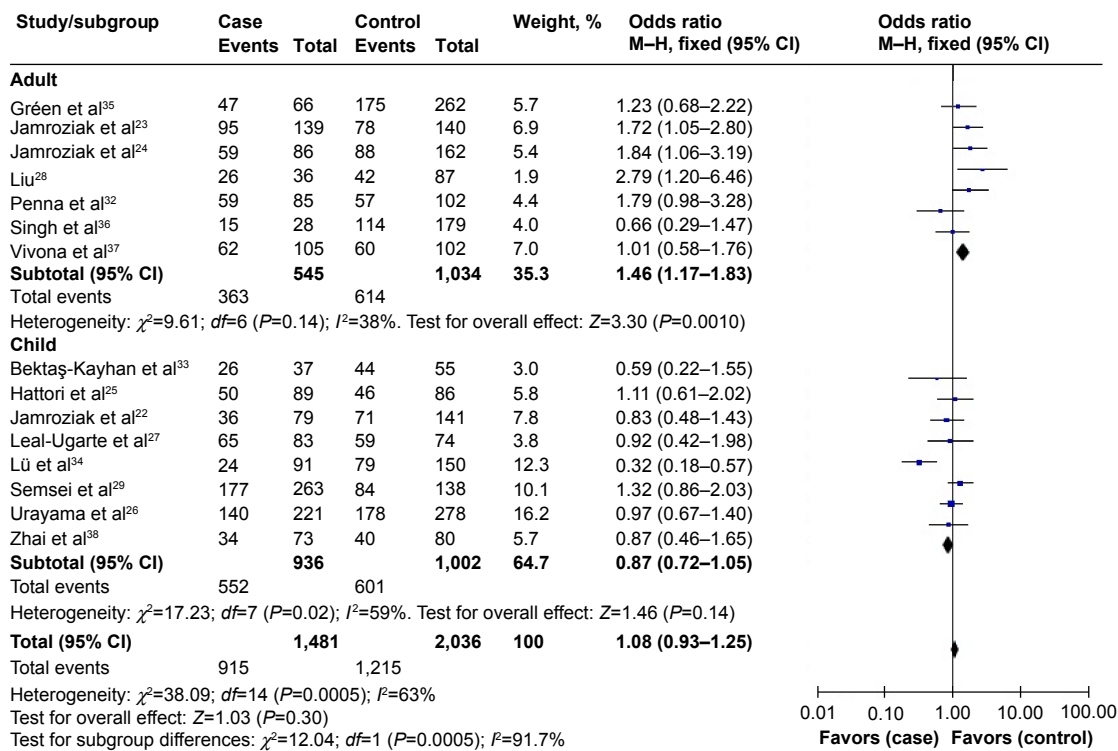


Figure 1 Forest plot of association of adenosine triphosphate-binding cassette, subfamily B, member 1 (ABCB1) C3435T polymorphism with leukemia risk, subgroup analysis by age (CT vs CC).

Abbreviations: CI, confidence interval; df , degrees of freedom; M-H, Mantel-Haenszel method.

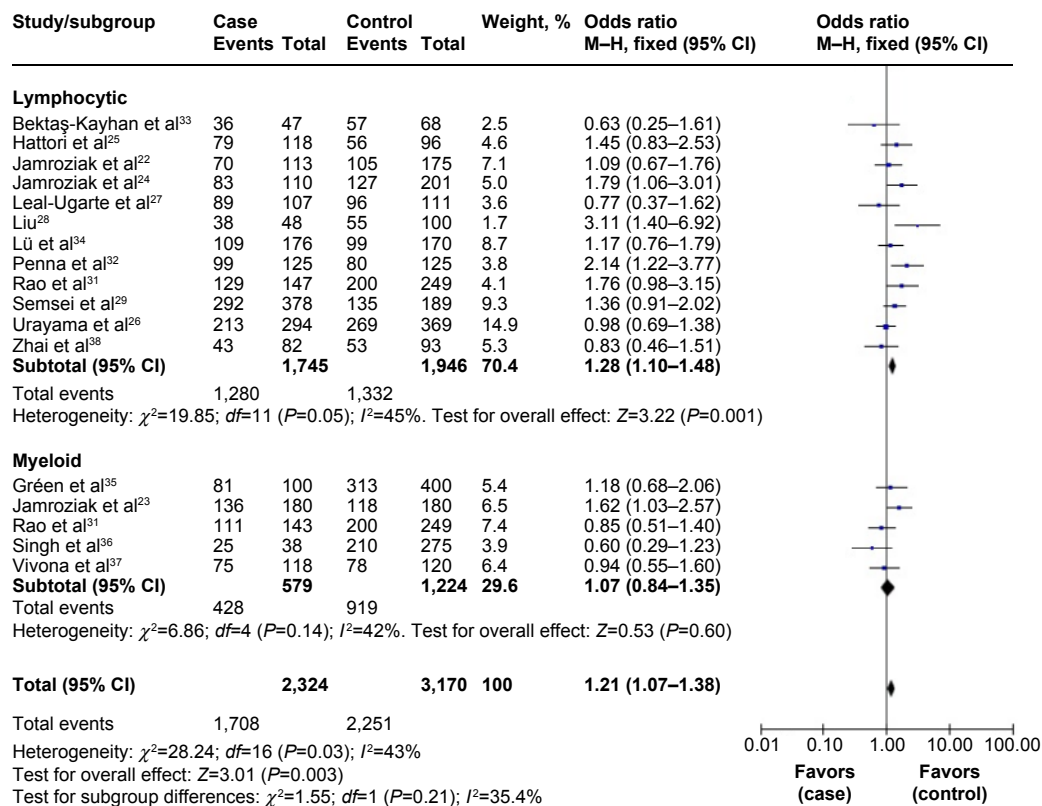


Figure 2 Forest plot of association of adenosine triphosphate-binding cassette, subfamily B, member 1 (ABCB1) C3435T polymorphism with leukemia risk, subgroup analysis by leukemia subtype (CT+TT vs CC).

Abbreviations: CI, confidence interval; df , degrees of freedom; M-H, Mantel-Haenszel method.

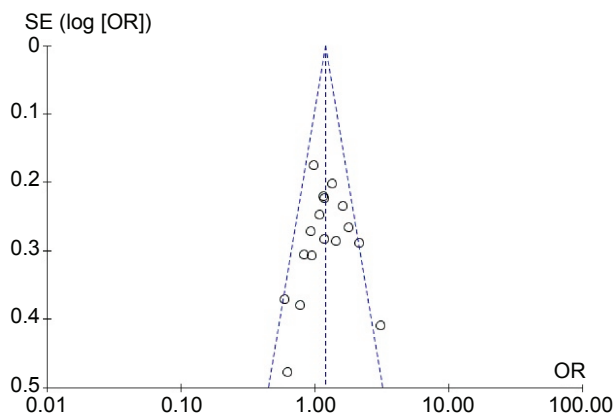


Figure 3 Funnel plot for the publication bias under dominant model (CT+TT vs CC).

Abbreviations: OR, odds ratio; SE, standard error.

In the subgroup analysis by age, we found significant association between *ABCB1* C3435T polymorphism and increased risk in adult leukemia in the heterozygote model and dominant model, but not in children with leukemia under any comparison models. When restricting the analysis to the subtype of leukemia, significant association was found in lymphocytic leukemia in the homozygote model, recessive model, and dominant model, but not in myeloid leukemia in any comparison model, which indicates that clinical type might have a critical effect on the association.

The results of this study show that *ABCB1* C3435T polymorphism might modify susceptibility to leukemia, which is consistent with the meta-analysis reported by Qian et al.⁴⁵ Since our study combined a total of 2,431 cases and 3,028 controls from 17 case-control studies, our results are more convincing.

Limitations

Some limitations of this meta-analysis should be taken into consideration and caution is needed when the results are interpreted. First, non-differential misclassification bias is possible, as the controls were not uniformly defined. Population-based controls and hospital-based controls have different risks of evolving leukemia. Second, our analyses were based on estimates not adjusted for other risk factors such as folate-intake status, lifestyle, and environmental exposures, which might influence the combined results. Third, although subgroup analyses were performed by ethnicity, age, and leukemia subtype to find the sources of heterogeneity, significant heterogeneity still existed in some subgroups. The heterogeneity may have been caused by different lifestyles, exposure to different risk factors, and the different levels of exposure to risk factors. In addition, due

to the limited original data, potential gene-gene and gene-environment interactions which have an important impact on leukemia risk were not evaluated in this study.

Conclusion

This meta-analysis found that *ABCB1* C3435T polymorphism is associated with an increased risk of leukemia and is likely a risk factor facilitating leukemia development. However, well-designed case-control studies with larger sample size focusing on more ethnicities or leukemia subtypes are required to validate our findings in the future.

Disclosure

The authors report no conflicts of interest in this work.

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