

## Original Article

# **ABCB1** polymorphism and susceptibility to acute lymphoblastic leukemia: a meta analysis

Haiyan Zhang<sup>1</sup>, Zhen Zhang<sup>1</sup>, Guang Li<sup>2</sup>

<sup>1</sup>Gynaecology Ward-1, Linyi City People's Hospital, Linyi 276000, Shandong Province, China; <sup>2</sup>Gastrointestinal Surgery, Linyi City People's Hospital, Linyi 276000, Shandong Province, China

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**Abstract:** Background: A large body of studies has investigated the potential role of *ABCB1* polymorphism in ALL susceptibility. However, the results are conflicting. The aim of the present meta-analysis was to define the effect of *ABCB1* polymorphism on ALL risk. Methods: We identified 8 eligible studies involving 1,308 cases and 1,427 controls through searching PubMed and Enbase databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association with both fixed effects and random effect models. Results: We found *ABCB1* polymorphism was associated with an increased risk of ALL under the homozygote genotypes (TT vs. CC: OR, 1.29, 95% CI, 1.08-1.54), the recessive model (TT vs. CT + CC: OR, 1.47, 95% CI, 1.02-2.13) and the allele model (T vs. C: OR, 1.14, 95% CI, 1.04-1.25). Similar results were indicated in Asian populations (TT vs. CC: OR, 1.79, 95% CI, 1.32-2.43; TT vs. CT + CC: OR, 2.55, 95% CI, 1.47-4.43; T vs. C: OR, 1.38, 95% CI, 1.18-1.62), but not in Caucasian populations. Conclusions: These findings indicate that *ABCB1* polymorphism may play a critical role in the development of ALL in Asians.

**Keywords:** *ABCB1*, polymorphism, ALL

## Introduction

Acute lymphoblastic leukemia (ALL) is a malignant neoplasm of hematopoietic stem cells, highly occurring among children with a proportion of 30% of all pediatric malignancies [1, 2]. The initial peak incidence of this hematologic malignancy is at 2 to 5 years of age, followed by a second peak over age 50. Although the etiology is currently unknown, environmental factors interacting with genetic components may jointly contribute to leukemogenesis [3, 4].

*ABCB1* gene is mapped to chromosome 7 and encodes for P-glycoprotein (P-gp), a 170-kDa member belonging to ATP-binding cassette (ABC) superfamily of membrane transporters [5]. P-gp responsible for transporting phospholipids across the cell membrane may act as an anti-apoptotic molecule. Dysregulation of P-gp expression in cancer cells induces accumulation of carcinogens and decreases drug accumulation, thereby regulating cellular resistance to various anti-cancer agents [6]. P-gp mainly expressed in liver, kidney, testis, placenta, gas-

trointestinal tract, and blood-tissue barrier [7]. A large body of evidence also showed that P-gp is involved in the release of interleukin-2, interleukin-4, and IFN- $\gamma$  from lymphocytes [8-10]. In addition, over-expression of *ABCB1* has been indicated in peripheral leukocytes and bone marrow [11-14].

*ABCB1* is a highly polymorphic gene, in which more than 28 single nucleotide polymorphisms (SNPs) have been identified in genetic studies [15-17]. The SNP located in exon 26 at position 3435 led to over 2-fold lower P-gp expression in duodenum and higher plasma concentration of P-gp substrate digoxin TT genotype carriers in comparison with carriers with CC genotype [15]. A case-control study conducted in Poland demonstrated a significant association between the silent *ABCB1* polymorphism (rs1045642) and ALL risk [18]. Later, a subsequent report addressing four *ABCB1* SNPs (T-129C, C1236T, G2677T/A, C3435T) did not show evidence of a statistically significant association with ALL in non-Hispanic White or Hispanic children [19]. Possible reasons for these discrepancies are

## ABCB1 and acute lymphoblastic leukemia

**Table 1.** Characteristics of literatures included in the meta-analysis

First author (year)	Country	Ethnicity	Control source	Genotyping method	Gender (F/M)	Mean age	Cases	Controls	HWE
Jamroziak (2004)	Poland	Caucasian	Population	PCR-RFLP	96/79	21.4	113	175	0.043
Urayama (2007)	USA	Caucasian	Population	TaqMan	NR	NR	294	369	0.506
Hattori (2007)	Japan	Asian	Population	TaqMan	67/90	6.1	118	96	0.543
Semsei (2008)	HunCtry	Caucasian	Population	TaqMan	180/126	6.1 ± 3.9	378	189	0.127
Leal-Ugarte (2008)	Mexico	Caucasian	Population	PCR-RFLP	44/63	7.0	107	111	0.298
Rao (2010)	India	Asian	Population	PCR-RFLP	47/100	16.5	147	249	0.560
Bektas-Kayhan (2012)	Turkey	Caucasian	Population	PCR-RFLP	13/34	8.7 ± 4.9	47	68	0.015
Lv (2012)	China	Asian	Hospital	PCR-RFLP	68/108	5.7 ± 3.3	176	170	0.781

PCR-RFLP: polymerase chain reaction- restriction fragment length polymorphism; NR: not report; HWE: Hardy-Weinberg equilibrium.

differences in small or non-homogeneous populations, and the subjects of diverse ethnicities.

In this study, we undertook a meta-analysis based on all available data, in an attempt to determine the relationship between *ABCB1* polymorphism and susceptibility to ALL.

### Methods

#### Identification and eligibility of relevant studies

We performed an exhaustive search in PubMed and Embase to identify studies concerning the association between *ABCB1* polymorphism and susceptibility to ALL until February 2013. The keywords used in the search strategy were “multidrug resistance 1” or “*ABCB1*” or “rs-1045642”, “polymorphism” or “variant”, and “acute lymphoblastic leukemia” or “ALL”. All references of the retrieved articles were then reviewed to identify additional relevant works. The inclusion criteria for eligible studies required that the study had to investigate the association of *ABCB1* polymorphism and susceptibility to ALL; that each study must be based on a case-control design; and that the original article provided adequate data of genotype frequency. The article was not considered if required information was not supplied or a case-only design was used.

#### Data extraction

Data extraction was conducted independently by two reviewers. The information gathered from each study included first author’s name, year of publication, study country, race/ethnicity, total cases and controls, gender distribution,

mean age, genotyping method, and genotype frequency in cases and controls. A third reviewer was consulted to reach a consensus when disagreements were encountered.

#### Statistical analysis

Using the genetic data extracted from each study and meta orders, we calculated pooled odds ratios (ORs) along with 95% confidence intervals (CIs) with Stata software, to evaluate the strength of association between *ABCB1* polymorphism and ALL risk. Statistical significance of the pooled ORs was examined by Z-test, and  $P < 0.10$  was deemed significant.  $\chi^2$ -based Q-test and the  $I^2$  statistic were performed to measure heterogeneity across the studies. A  $P$  value more than 0.10 and  $I^2 < 50\%$  represented absence of heterogeneity. In such a case, the fixed-effects model based on Mantel-Haenszel method that assumes the same homogeneity of effect size among studies was used to pool the summary ORs [20]. Otherwise, the random-effects model based on DerSimonian and Laird method was performed in order to provide wider 95% CIs for the studies with different findings [21]. We created funnel plots where the standard error of log (OR) of each study is plotted against its log (OR) to assess publication bias. The funnel plot asymmetry was further examined using Egger’s liner regression test and  $P < 0.10$  was considered statistically significant [22]. Deviation of genotype distributions from Hardy-Weinberg equilibrium (HWE) was checked in controls by the chi-square test ( $P < 0.10$  indicated significant HWE violation). Sensitivity analysis by sequentially excluding the independent studies was performed to assess the influence on pooled ORs.

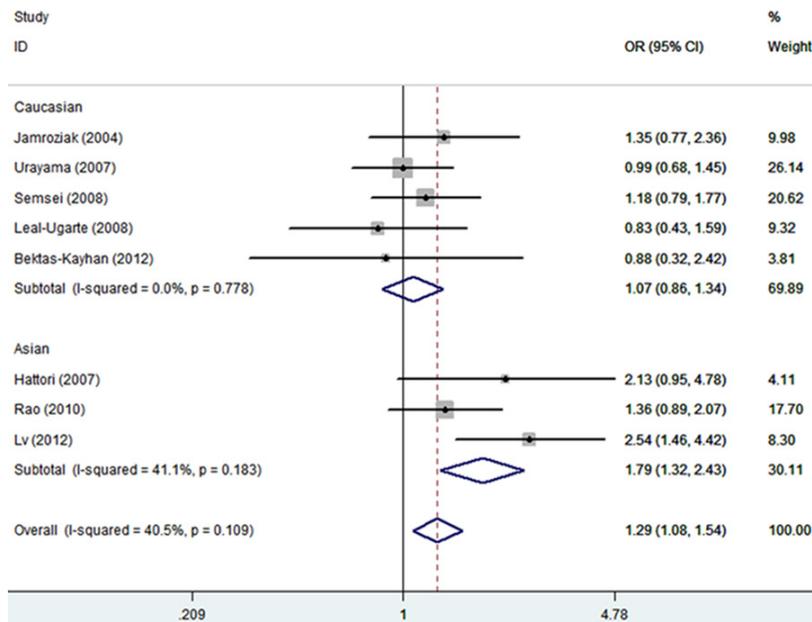
## ABCB1 and acute lymphoblastic leukemia

**Table 2.** Meta-analysis of *ABCB1* polymorphism and AMD risk

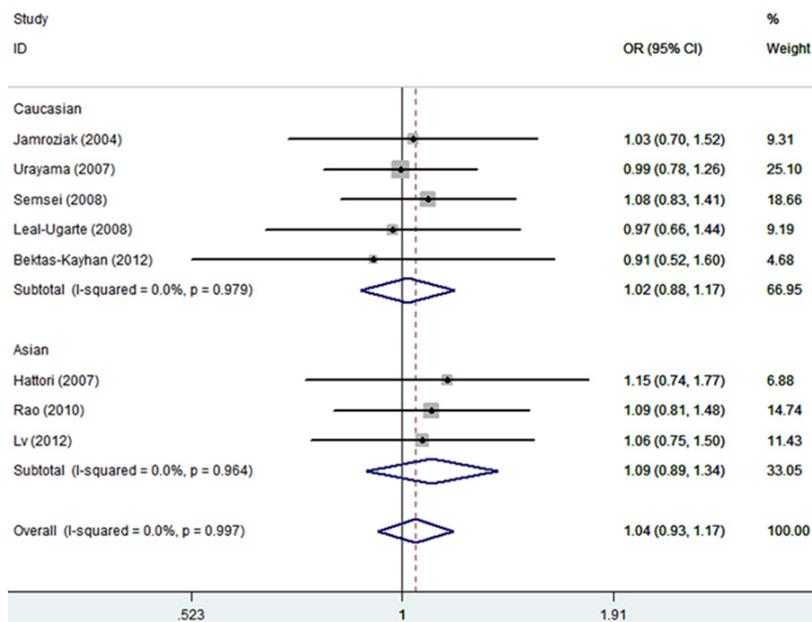
Variables	TT vs. CC (FM)			TT + CT vs. CC (FM)			TT vs. CT + CC (RM)			T vs. C (FM)			CT vs. CC (FM)		
	OR (95% CI)	$P_h$	$I^2$	OR (95% CI)	$P_h$	$I^2$	OR (95% CI)	$P_h$	$I^2$	OR (95% CI)	$P_h$	$I^2$	OR (95% CI)	$P_h$	$I^2$
Ethnicity															
Total	1.29 (1.08, 1.54)	0.109	40.5%	1.04 (0.93, 1.17)	0.997	0	1.47 (1.02, 2.13)	< 0.10	76.7%	1.14 (1.04, 1.25)	0.101	41.6%	0.95 (0.82, 1.10)	0.427	0.2%
Caucasian	1.07 (0.86, 1.34)	0.778	0	1.02 (0.88, 1.17)	0.979	0	1.07 (0.86, 1.32)	0.375	5.5%	1.03 (0.92, 1.15)	0.757	0	1.00 (0.84, 1.19)	0.954	0
Asian	1.79 (1.32, 2.43)	0.183	41.1%	1.09 (0.89, 1.34)	0.964	0	2.55 (1.47, 4.43)	0.044	68.0%	1.38 (1.18, 1.62)	0.503	0	0.84 (0.64, 1.11)	0.067	63.0%
Source of control															
Population	1.17 (0.97, 1.42)	0.546	0	1.04 (0.92, 1.18)	0.991	0	1.26 (0.96, 1.65)	0.052	52.0%	1.09 (0.99, 1.20)	0.441	0	1.01 (0.87, 1.18)	0.994	0
Hospital	2.54 (1.46, 4.42)	-	-	1.06 (0.75, 1.50)	-	-	4.11 (2.41, 6.98)	-	-	1.57 (1.20, 2.07)	-	-	0.50 (0.30, 0.85)	-	-

$P_h$ :  $P$  value of heterogeneity test; CI: confidence interval; OR: odds ratio; FM: fixed-effects model; RM: random-effects model.

## ABCB1 and acute lymphoblastic leukemia



**Figure 1.** Forest plot of estimates of the odds ratios (ORs) for *ABCB1* polymorphism in acute lymphoblastic leukemia (ALL) under TT vs. CC.



**Figure 2.** Forest plot of estimates of the odds ratios (ORs) for *ABCB1* polymorphism in ALL under TT + CT vs. CC.

## Results

### Eligible studies and studies' characteristics

We identified 203 records in the initial search of PubMed and Embase. After eliminating the obviously irrelevant records, 137 articles were

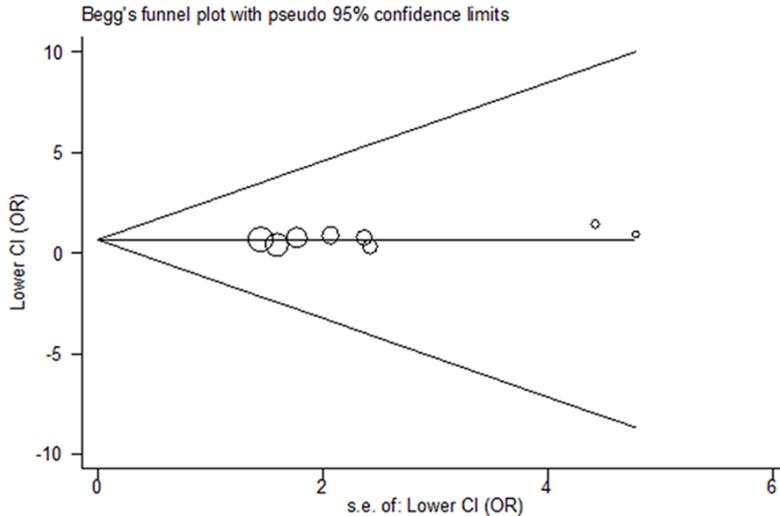
left for further review. Of these, 121 were discarded after reviewing the key words and abstracts. The full texts of the remaining 16 articles were examined in detail. Among them, 8 studies [6, 18, 19, 23-27] satisfied the pre-described inclusion criteria and were finally included in the meta-analysis. The genotype distributions among the controls of all studies were in agreement with HWE except for two studies [18, 26]. The genotyping for *ABCB1* polymorphism was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and Taqman PCR on the genomic DNA from the human blood samples. Moreover, of the 8 studies, five were for the population of Caucasian ancestry, and three were for the subjects of Asian ancestry. The summary characteristics of the eligible studies are described in **Table 1**.

### Meta-analysis

**Table 2** shows the detailed results of the meta-analysis. By combining all available studies in one dataset, the homozygote genotypes of *ABCB1* polymorphism was found to be associated with an elevated risk of ALL (TT vs. CC: OR, 1.29, 95% CI, 1.08-1.54) (**Figure 1**). Meanwhile, the recessive model (TT vs. CT + CC: OR, 1.47, 95% CI, 1.02-2.13) and the allele model (T vs. C: OR, 1.14, 95% CI, 1.04-1.25) also showed a significant trend to increase ALL risk (**Figure 2**).

In the stratified analysis based on ethnicity, an obviously increased risk of ALL risk was indi-

## ABCB1 and acute lymphoblastic leukemia



**Figure 3.** Funnel plot for publication bias test (TT vs. CC).

cated among Asians under the homozygote genotypes, the recessive model, and the allele model (TT vs. CC: OR, 1.79, 95% CI, 1.32-2.43; TT vs. CT + CC: OR, 2.55, 95% CI, 1.47-4.43; T vs. C: OR, 1.38, 95% CI, 1.18-1.62, respectively) (Table 2). However, there was no indication of significant association under any genetic model among Caucasian populations.

When stratifying the general population according to control source, we found that the OR of the homozygote genotypes was 2.54 (TT vs. CC: 95% CI, 1.46-4.42), and that of the recessive model was 4.11 (TT vs. CT + CC: 95% CI, 2.41-6.98) in the studies based on hospital controls. Interestingly, we observed a reverse association under the heterozygote genotypes (CT vs. CC: OR, 0.50, 95% CI, 0.30-0.85).

Significant heterogeneity was observed in the recessive model and the random-effects model was selected to pool the OR. Sensitivity analysis was subsequently performed and identified Lv et al. [27] was the main source of the between-study heterogeneity. Exclusion of this study increased the homogeneity across the studies. No significant publication bias was tested by performing Begg's funnel plot and Egger's test ( $P = 0.223$  for TT vs. CC) (Figure 3).

### Discussion

ALL is the primary subtype of childhood leukemia characterized by the uncontrolled proliferation of hematopoietic cells in the bone marrow.

Approximately 80% of children with newly diagnosed ALL and 50% of them with myeloid neoplasm can be cured, due to contemporary improvements in risk assessment, chemotherapy, hematopoietic stem cell transplantation and supportive care [28]. However, the resistance to chemotherapeutic drugs remains a major problem that results in poor treatment outcome of this disease [29, 30]. The human *ABCB1* is located on chromosome 7q21, encoding a 170 KD integral membrane protein product Pgp, which functions as a protective role against harmful chemicals and active metabolites.

Available data reported that an increased risk of ALL is attributable to polymorphisms in genes that participate in transport and metabolism of xenobiotics [31]. The widely studied *ABCB1* gene contains a number of polymorphisms that may confer susceptibility to ALL [18].

The *ABCB1* polymorphism has been consistently investigated in the epidemiological studies regarding the risk of ALL. Nevertheless, the results are controversial [24, 27]. Therefore, it is necessary to perform this meta-analysis to identify the association between *ABCB1* polymorphism and ALL risk by combining the relevant studies published to date. After pooling available data from all included studies, we found a significantly elevated risk of ALL. When stratified according to ethnic origin, an obvious correlation between *ABCB1* polymorphism and ALL risk was observed in Asian populations, but not in Caucasian populations. Interestingly, the subgroup analysis by source of controls showed *ABCB1* polymorphism was likely to increase or decrease the risk of suffering ALL in the hospital-based studies.

A previous meta-analysis of the association between this polymorphism and cancer risk (five studies for ALL) demonstrated no significant association in ALL under all analyzed genetic models, either in Asians or in Caucasians [32]. While the current study expanded the sample size by adding additional three sub-

separately published articles showed very different results. The explanation may be that the *ABCB1* is a low-penetrant polymorphism that needs a sufficiently large study to detect the susceptibility to cancer. Besides, the use of typical control populations is vitally important, especially for the genetic association studies. The failure to reach a statistical significance in population-based studies implies that the selection of representative controls may reduce bias of the results.

Several strong points need to be addressed. First, this is the first study on the association between *ABCB1* polymorphism and susceptibility to ALL to date, which supplies reference information to future studies. Second, our meta-analysis based on all available data may provide new insights into the role of *ABCB1* polymorphism in ALL risk. Three are also some limitations. Significant between-study heterogeneity indicated across the studies may have potentially influenced the results. Furthermore, we failed to carry out further stratification analysis by other confounders such as gender, because only one study supplied genotype frequency of this polymorphism in man and women [6].

In summary, we conclude that there is statistical evidence to support *ABCB1* polymorphism is associated with an increased risk of ALL in Asians. However, larger studies taking gender into consideration is required to validate the current findings.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Guang Li, Gastrointestinal Surgery, Linyi City People's Hospital, Linyi 276000, Shandong Province, China. Tel: 86-135-83967678; E-mail: 13583967678@163.com

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## ABCB1 and acute lymphoblastic leukemia

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