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Multidrug resistance gene 1 C1236T polymorphism and susceptibility to leukemia: A meta-analysis

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Abstract. Several studies have investigated the association between multidrug resistance gene (*MDR1*) C1236T polymorphism and leukemia risk, however, these published studies have yielded conflicting results. Thus, the present study carried out a meta-analysis to provide a more precise estimate of the effect of this polymorphism on the susceptibility to leukemia. The published case-control studies regarding the association between *MDR1* C1236T polymorphism and leukemia risk were included following a computerized search of PubMed, Elsevier, The Cochrane Library, China National Knowledge Infrastructure and Wanfang Database. Either fixed- or random-effects models were applied to calculate the combined odds ratios (ORs) and 95% confidence intervals (CIs) by RevMan 5.2 software. Seven studies, including 846 cases and 1,523 controls, were included in the present meta-analysis. The results indicated that there was no significant association between the *MDR1* C1236T polymorphism and leukemia risk in overall comparisons in all four genetic models (CT vs. CC: OR, 1.31, 95% CI, 0.89-1.91, P=0.17; TT vs. CC: OR, 2.16, 95% CI, 0.99-4.70, P=0.05; TT vs. CC+CT: OR, 1.72, 95% CI, 0.91-3.25, P=0.09; and CT+TT vs. CC: OR, 1.57, 95% CI, 0.96-2.56, P=0.07). In the subgroup analysis according to specific ethnicity, age and the type of leukemia, a significant association was found in adult leukemia (CT+TT vs. CC: OR, 2.77, 95% CI, 1.05-7.31, P=0.04) and chronic myeloid leukemia (CT vs. CC: OR, 1.71, 95% CI, 1.05-2.80, P=0.03). No significant publication bias was detected by funnel plot. Therefore, the meta-analysis indicated that the *MDR1* C1236T polymorphism may contribute to the susceptibility to adult leukemia and chronic myeloid leukemia. Furthe well-designed studies based on larger sample sizes are required to validate these findings.

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Introduction

Leukemia is a malignant clonal disorder of the hematopoietic system with extreme heterogeneity and bad prognosis. In recent years, the incidence of leukemia increased gradually (1), however, the exact biological mechanisms of leukemia have not been fully clarified (2). Epidemiological and case-control studies have found that significant environmental exposures contribute to the pathogenesis of leukemia (3). In addition, previous candidate gene association approaches and genome-wide association studies have identified the presence of inherited genetic susceptibility to this disease (4-7). Therefore, it is generally considered that the causation is multifactorial and that the interaction between exogenous or endogenous exposures and genetic susceptibility plays an important role in the etiology of leukemia (2).

The human multidrug resistance gene (*MDR1* or *ABCB1*) locates at 7q21.1 and its cDNA spans ~4.5 kb. *MDR1* encodes a 170-kDa membrane transport protein called P-glycoprotein (P-gp), belonging to the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of transporters (8). P-gp functions as an ATP-dependent efflux pump and is responsible for the efflux of a variety of lipophilic compounds, including multiple chemotherapeutic agents, naturally occurring xenobiotics, pesticides and cellular metabolites, providing a cellular defense mechanism against potentially harmful compounds (8-10). Recently, ≥50 single-nucleotide polymorphisms (SNPs) have been identified within the *MDR1* gene locus (11), of which C1236T (silent), G2677T/A (Ala893Ser/Thr) and C3435T (silent) have been associated with altered P-gp expression and activity (12-14). The alteration of the P-gp transport activity and function due to the different genetic polymorphisms resulted in cumulative cytotoxicity of harmful xenobiotics due to decreased extrusion of these xenobiotics. The SNPs in *MDR1* have been associated with the development of various cancers, including acute lymphocytic leukemia and B-cell chronic lymphocytic leukemia (15-17). In addition, the altered activity of P-gp has been shown to affect the absorption and elimination of several drugs, thus, the genetic variants of *MDR1* may also be associated with the pharmacokinetics and treatment response to anticancer agents (18-20). Several case-control studies have investigated the association between *MDR1* C1236T polymorphism and leukemia risk, however, these studies yielded controversial results. To clarify this, a

meta-analysis was performed to provide an improved estimate of the effect of the *MDR1* C1236T polymorphism on the susceptibility to leukemia.

Materials and methods

Publication search. A computer literature search was performed to identify studies regarding the association between the *MDR1* C1236T polymorphism and leukemia risk. PubMed, Elsevier, The Cochrane Library, China National Knowledge Infrastructure and Wanfang Database were searched with the following subject terms and keywords: 'Multidrug resistance gene' or '*MDR1*' or '*ABCB1*', and 'polymorphism' or 'variant' or 'mutant', in combination with 'leukemia' or 'leukaemia' or 'leukocythemia', without any restriction on language. The last search was updated on April 30, 2014. The relevant references cited in the eligible studies were also reviewed to identify additional studies. Two investigators reviewed the retrieved studies independently and any disagreement was resolved by discussion.

Inclusion criteria. The studies included in the present meta-analysis fulfilled the following criteria: i) Raw materials were published studies; ii) case-control study exploring the association between the *MDR1* C1236T polymorphism and leukemia risk; iii) the leukemia group had a pathologically confirmed diagnosis; and iv) genotype frequencies for the case and control groups were available.

Data extraction. Two investigators extracted the information from each study independently with the standard protocol and disagreements were resolved by discussion. For each eligible study, the following information was collected: First author's name, publication year, country, ethnicity, source of control group, genotyping methods, and genotype distribution of the *MDR1* C1236T polymorphism in patients and control populations.

Statistical analysis. The strength of association between the *MDR1* C1236T polymorphism and leukemia risk was assessed by calculating the odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). The significance of the combined OR was determined by the Z-test. The χ^2-based Q-test was applied to assess heterogeneity between the included studies. The heterogeneity was considered present when $P<0.05$, in which case the random-effects model (DerSimonian-Laird) was applied, otherwise, the fixed-effects model (Mantel-Haenszel) was selected to calculate the combined OR. When heterogeneity was observed, subgroup analyses according to specific ethnicity, age and the type of leukemia, were performed to find the source of heterogeneity. Publication bias was evaluated visually through funnel plot and sensitivity analysis was performed by removal of studies not in agreement with the Hardy-Weinberg equilibrium (HWE). HWE in the control group was checked using the χ^2 test. All the P-values were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. The data analyses were performed using the Stata v12.0 software (StataCorp, College Station, TX, USA) and Review Manager v5.2 (The Cochrane Collaboration, Oxford, UK).

Results

Study characteristics. According to the literature retrieval strategies and inclusion criteria, seven case-control studies regarding the association between the *MDR1* C1236T polymorphism and leukemia risk were included in the present meta-analysis, including 846 leukemia cases and 1,523 controls in total (21-27). The countries in which these studies were conducted include China, Singapore, Sweden, Brazil and USA. Among these studies, there were four studies of an Asian population (22,24,25,27), two studies of a Caucasian population (21,23) and one study of a mixed population (26). All the cases had a pathologically confirmed diagnosis of leukemia. The source of controls was based mainly on a healthy population and matched for age and gender. The genotype distribution among the control groups of all the included studies was in agreement with HWE, except one study (27). The detailed characteristics of the included studies are shown in Table I.

Meta-analysis results. The main results of the meta-analysis and the heterogeneity test are shown in Table II. The results indicated that there was no significant association between the *MDR1* C1236T polymorphism and leukemia risk in the overall comparisons in all four genetic models (CT vs. CC: OR, 1.31, 95% CI, 0.89-1.91, P=0.17; TT vs. CC: OR, 2.16, 95% CI, 0.99-4.70, P=0.05; TT vs. CC+CT: OR, 1.72, 95% CI, 0.91-3.25, P=0.09; and CT+TT vs. CC: OR, 1.57, 95% CI, 0.96-2.56, P=0.07) (Table II). Similarly, in the subgroup analysis by specific ethnicity, no significant association was found. In the subgroup analysis according to age and the type of leukemia, however, a significant association was found in adult leukemia (CT+TT vs. CC: OR, 2.77, 95% CI, 1.05-7.31, P=0.04) (Table II and Fig. 1) and chronic myeloid leukemia (CT vs. CC: OR, 1.71, 95% CI, 1.05-2.80, P=0.03) (Table II and Fig. 2).

Publication bias and sensitivity analysis. Funnel plots were used to assess the publication bias and the results showed that all the points in the funnel plots were symmetrically distributed, which indicated that there was no significant bias. Sensitivity analysis was performed by excluding the study by Zhai *et al* (27), in which the distribution of genotypes in the control group was not in agreement with HWE. However, no significant changes on the combined ORs were observed (data not shown), suggesting that the results of the present meta-analysis were relatively stable and credible.

Discussion

Exogenous or endogenous exposures and inherited genetic susceptibility have roles in leukemogenesis. Multiple mutations in the *MDR1* gene have been demonstrated in previous studies and ≥50 SNPs have been identified in all 28 exons of the *MDR1* gene (11,12,18). The most frequent SNP non-synonymous triallelic G2677T/A in exon 21 results in amino acid substitution from the lipophilic residue Ala to the hydrophilic residue Ser or Thr, and this polymorphism was significantly associated with an increased or decreased plasma concentration of P-gp substrates (28). The C3435T polymorphism is a silent mutation in exon 26 of *MDR1* and studies have indicated

Table I. General characteristics of studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Subtype	Control source	Genotyping method	Sample size		Case			Control			HWE	(Refs.)
							Case	Control	CC	CT	TT	CC	CT	TT		
Gréen *et al*	2012	Sweden	Caucasian	Adult AML	PB	Sequencing	100	400	34	44	22	133	187	80	0.33	(23)
Liu	2008	China	Asian	Adult ALL	HB	PCR-RFLP	48	100	2	22	24	44	44	12	0.84	(22)
Lü *et al*	2012	China	Asian	Child ALL	HB	SNaPshot SNP	176	170	23	87	66	20	84	66	0.39	(24)
Singh *et al*	2012	Singapore	Asian	Adult CML	PB	Sequencing	38	275	6	11	21	132	112	31	0.33	(25)
Urayama *et al*	2007	USA	Caucasian	Child ALL	PB	Single base extension	284	365	73	144	67	97	199	69	0.06	(21)
Vivona *et al*	2012	Brazil	Mixed	Adult CML	PB	PCR-RFLP	118	120	39	61	18	51	50	19	0.26	(26)
Zhai *et al*	2012	China	Asian	Child ALL	PB	SNaPshot SNP	82	93	16	37	29	18	32	43	0.01	(27)

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

Table II. Results of meta-analysis for *MDR1* C1236T polymorphism and leukemia risk.

Variables	No.	CT vs. CC			TT vs. CC			TT vs. CC+CT			CT+TT vs. CC		
		OR (95% CI)	P	P_h[a]/I^2	OR (95% CI)	P	P_h[a]/I^2	OR (95% CI)	P	P_h[a]/I^2	OR (95% CI)	P	P_h[a]/I^2
Overall	7	1.31 (0.89-1.91)	0.17	0.03/ 57	2.16 (0.99-4.70)	0.05	<0.01/ 87	1.72 (0.91-3.25)	0.09	<0.01/ 89	1.57 (0.96-2.56)	0.07	<0.01/ 77
Ethnicity													
Asian	4	1.91 (0.81-4.50)	0.14	0.02/ 70	4.16 (0.71-24.30)	0.11	<0.01/ 93	2.49 (0.69-9.00)	0.16	<0.01/ 94	2.62 (0.79-8.65)	0.11	<0.01/ 87
Caucasian	2	0.95 (0.70-1.28)	0.72	0.89/ 0	1.21 (0.84-1.74)	0.30	0.64/ 0	1.26 (0.92-1.71)	0.15	0.63/ 0	1.02 (0.77-1.35)	0.91	0.79/ 0
Mixed	1	1.60 (0.91-2.79)	0.10		1.24 (0.57-2.67)	0.58		0.96 (0.47-1.93)	0.90		1.50 (0.88-2.54)	0.13	
Age													
Child	3	0.99 (0.73-1.34)	0.94	0.77/ 0	1.07 (0.76-1.50)	0.72	0.43/ 0	1.03 (0.79-1.33)	0.83	0.12/ 53	1.00 (0.75-1.34)	0.98	0.91/ 0
Adult	4	1.90 (0.90-4.01)	0.09	0.01/ 73	4.84 (1.03-22.79)	0.05	<0.01/ 92	2.90 (0.89-9.43)	0.08	<0.01/ 91	2.77 (1.05-7.31)	0.04	<0.01/ 86
Subtype													
ALL	4	1.40 (0.71-2.75)	0.33	0.02/ 71	1.92 (0.67-5.53)	0.23	<0.01/ 87	1.46 (0.70-3.07)	0.32	<0.01/ 87	1.52 (0.70-3.32)	0.29	<0.01/ 80
AML	1	0.92 (0.56-1.52)	0.74		1.08 (0.59-1.97)	0.81		1.13 (0.66-1.92)	0.66		0.97 (0.61-1.54)	0.89	
CML	2	1.71 (1.05-2.80)	0.03	0.61/ 0	4.21 (0.37-48.19)	0.25	<0.01/ 93	3.04 (0.31-30.01)	0.34	<0.01/ 95	2.56 (0.79-8.26)	0.12	0.02/ 80

[a]When P_h>0.05, the fixed-effects model was selected to combine the data. Otherwise, the random-effects model was applied. *MDR1*, multidrug resistance gene; OR, odds ratio; CI, confidence interval; P_h, value used to test the heterogeneity; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

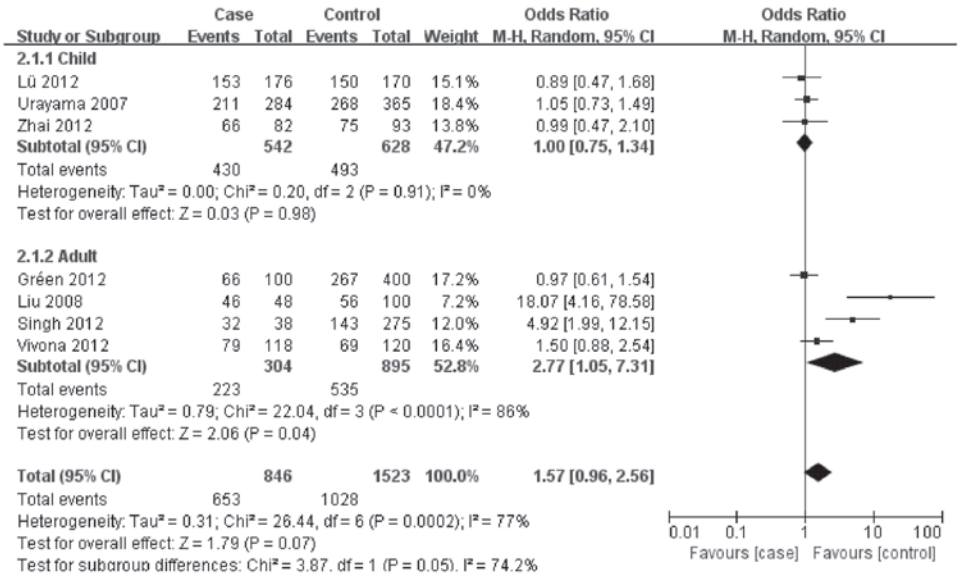

Figure 1. Forest plot for the association between multidrug resistance gene C1236T polymorphism and leukemia risk (CT+TT vs. CC). Subgroup analysis was performed by age. CI, confidence interval.

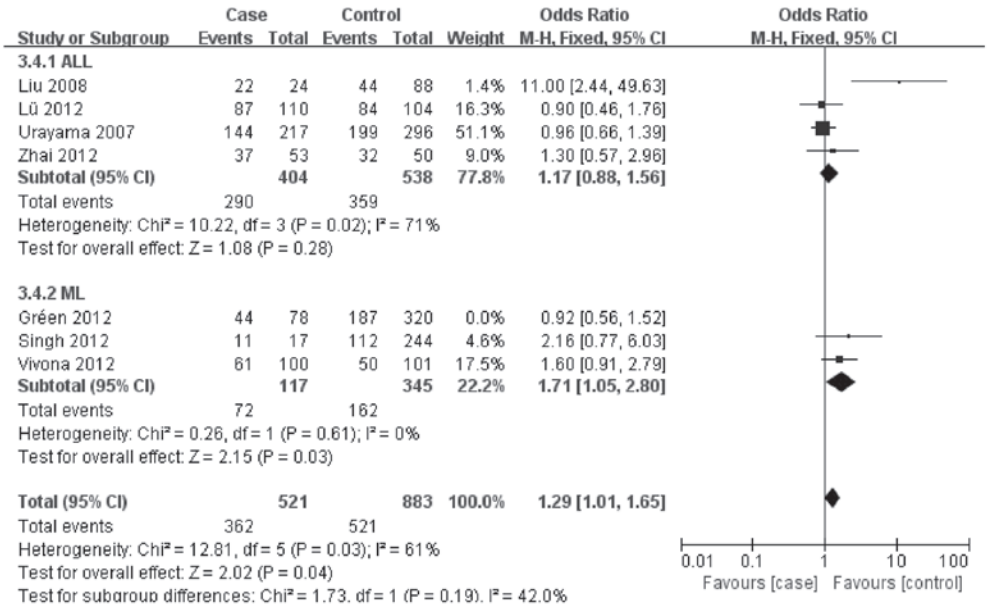

Figure 2. Forest plot for the association between multidrug resistance gene C1236T polymorphism and leukemia risk (CT vs. CC). Subgroup analysis was performed by leukemia subtype. CI, confidence interval; ALL, acute lymphocytic leukemia; ML, myeloid leukemia.

that this polymorphism was associated with altered *MDR1* expression levels and subsequently P-gp activity (12,13,18). The third common polymorphism C1236T of the *MDR1* gene is a synonymous variant in exon 12. These three polymorphisms are closely associated with linkage disequilibrium (29-31). Functional polymorphisms in *MDR1* may play a role in the elimination of xenobiotics, and the mutation of *MDR1* may cause various human malignancies, including leukemia.

Given the potential influence of these SNPs on cancer susceptibility, numerous molecular epidemiological studies were conducted to investigate the association between these SNPs and leukemia risk. However, the results from different studies are inconclusive or controversial, which may be owing to different genetic backgrounds and limitations in individual studies. To clarify this, a meta-analysis was performed from eligible studies focusing on the *MDR1* C3435T and G2677T/A polymorphisms and leukemia risk. The results indicated that the *MDR1* C3435T polymorphism may modify the susceptibility to leukemia (32). Yan *et al* (33) found that there was no association between the *MDR1* G2677T polymorphism and leukemia risk in the overall populations, but a significant association was found in Asian and African populations, and the G2677T polymorphism may be a protective factor in the susceptibility to myeloid leukemia in these populations.

To synthetically evaluate the effect of the *MDR1* C1236T polymorphism on the susceptibility to leukemia, a meta-analysis was performed of seven case-control studies that explored the association between the *MDR1* C1236T polymorphism

and leukemia risk. In the present meta-analysis, no significant impact was found of the *MDR1* C1236T polymorphism on leukemia susceptibility in overall comparisons. A subgroup analysis was also performed by ethnicity, age and the type of leukemia to find the source of heterogeneity. A significant association was found in adult leukemia (CT+TT vs. CC: OR, 2.77, 95% CI, 1.05-7.31, P=0.04) and chronic myeloid leukemia (CT vs. CC: OR, 1.71, 95% CI, 1.05-2.80, P=0.03), indicating that the *MDR1* C1236T polymorphism may alter the development of the adult leukemia and chronic myeloid leukemia risk.

Certain limitations of the present meta-analysis should be considered when interpreting the results. Selection bias may exist as the studies without sufficient data were excluded. The analysis largely used unadjusted estimates, as not all the included studies were adjusted by the same potential confounders, such as lifestyles and exposures, which may influence the combined results. Although subgroup analysis was performed by ethnicity, age and the type of leukemia to find the sources of heterogeneity, significant heterogeneity existed in certain subgroups. Owing to the limited original information, potential gene-gene and gene-environment interactions, which have an important impact on cancer risk, were not evaluated in the study.

In conclusion, the present meta-analysis found that the *MDR1* C1236T polymorphism may be associated with leukemia susceptibility. Since limited studies were included in the study, larger sample sizes and well-designed case-control studies are required in the future to confirm this association.

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