

Association between *NAT2* polymorphisms and acute leukemia risk

A meta-analysis

Xiaoxiao Zhu, MD^a, Yanbing Liu, PhD^b, Guangwu Chen, PhD^c, Qiang Guo, PhD^a, Zhen Zhang, PhD^a, Lin Zhao, MD^a, Ran Wei, PhD^a, Xunqiang Yin, MD^{a,d}, Yunhong Zhang, MD^{a,d}, Bin Wang, PhD^{e,*}, Xia Li, PhD^{a,*}

Abstract

Background: N-acetyl-transferase 2 (*NAT2*) polymorphisms have been demonstrated to be associated with acute leukemia (AL); however, the results remain controversial. The present meta-analysis was performed to provide more precise results.

Methods: Pubmed, Embase, Cochrane Library, China National Knowledge Infrastructure, and Wanfang databases were used to identify eligible studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between *NAT2* polymorphisms and AL risk.

Results: Increased risk was found under both heterozygous (OR 1.24, 95% CI 1.02–1.51) and recessive model (OR 1.28, 95% CI 1.06–1.55) for rs1801280. The slow acetylator phenotype (OR 1.22, 95% CI 1.07–1.40) also increased AL risk. Subgroup analysis demonstrated that rs1801280 increased AL risk under the recessive model (OR 1.14, 95% CI 0.93–1.41) in Caucasian population and the co-dominant (OR 1.77, 95% CI 1.40–2.23), homozygous (OR 3.06, 95% CI 1.88–4.99), dominant (OR 2.22, 95% CI 1.56–3.17), recessive model (OR 2.06, 95% CI 1.35–3.16) in the Mixed populations. Association between rs1799929 and decreased AL risk was found in the co-dominant (OR 0.82, 95% CI 0.70–0.97), homozygous (OR 0.65, 95% CI 0.46–0.93), heterozygous (OR 0.71, 95% CI 0.51–1.00), and the recessive model (OR 0.68, 95% CI 0.49–0.94) in the Caucasian group. As for rs1799931, the same effects were found in the co-dominant (OR 0.68, 95% CI 0.49–0.94) and the dominant model (OR 0.68, 95% CI 0.48–0.97) in the mixed group.

Conclusion: rs1801280 and the slow acetylator phenotype are risk factors for AL.

Abbreviations: AL = acute leukemia, ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, CI = confidence interval, HWE = Hardy-Weinberg equilibrium, *NAT2* = N-acetyl-transferase 2, NOS = Newcastle-Ottawa Quality Assessment Scale, OR = odds ratios.

Keywords: acute leukemia risk, meta-analysis, N-acetyl-transferase 2, polymorphism

1. Introduction

Acute leukemia (AL) is a hematopoietic system malignant tumor, characterized by deregulated clonal expansion of abnormal white blood cells in the bone marrow and impaired production of normal blood cells.^[1] According to the cell type from which it

arises, AL can be subdivided into 2 clinical forms: acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).^[2] It has been reported that the occurrence of AL is related to genetic disorders, physical and chemical exposure, and chemotherapy^[3,4]; however, the biologic mechanisms and etiology of AL remain unclear.^[5] Studies have demonstrated that major enzymes

Editor: Cheng-Chia Yu.

XZ and YL contributed equally for this work.

This work was supported by the Natural Science Foundation of China (81673981, 81873337, 81601442, 81704116, 81573467), the Primary Research and Development Plan of Shandong Province (2016GSF202016, 2017GSF219118, 2017G006018), the Project of Transformation in High-tech Achievements (2013ZHXX2A0405), the Natural Science Foundation of Shandong Province (ZR2017PH008, ZR2018PH042), the Science and Technology Development Grant of the State Administration of traditional Chinese medicine of Shandong Province (2017–174), the Family Planning Committee of Shandong Province ([2014]14), the Project for Shandong Medical and Health Science and Technology Plan (2016WS0524), the Project of Science and Technology of Shandong Academy of Medical Sciences (2017–15), Taishan Scholars (Tsqn 201812125, ts201712042), and the Innovation Project of Shandong Academy of Medical Sciences.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

^aLaboratory for molecular immunology, Institute of Basic Medicine, Shandong Academy of Medical Sciences, ^bBreast Cancer Center, Shandong Cancer Hospital Affiliated to Shandong University, ^cGaomi Municipal Hospital, Gaomi, ^dSchool of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, ^eDepartment of peripheral vascular disease, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China.

* Correspondence: Bin Wang, Department of peripheral vascular disease, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, 42 Wenhua xi Road, Jinan, Shandong 250011, China (e-mail: 2801505631@qq.com); Xia Li, Laboratory for Molecular Immunology, Institute of Basic Medicine, Shandong Academy of Medical Sciences, 18877 Jingshi Road, Jinan, Shandong 250062, China (e-mail: 786735868@qq.com).

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Medicine (2019) 98:12(e14942)

Received: 26 September 2018 / Received in final form: 30 November 2018 / Accepted: 28 February 2019

<http://dx.doi.org/10.1097/MD.00000000000014942>

associated with metabolism of carcinogens are associated with AL susceptibility.^[6] Different polymorphisms of those enzymes cause the differences among individuals in their ability to metabolize environmental carcinogens via different levels of enzyme activity, and this may contribute to the risk of AL.^[7] Therefore, identification of the role of the polymorphisms of these crucial enzymes may further elucidate the pathogenesis and provide potential novel biomarkers for demonstrating AL risk.

N-acetyltransferase 2 (NAT2) is a phase II enzyme, encoded by NAT2 which is located on chromosome 8. NAT2 is responsible for the metabolism of a number of aromatic and heterocyclic amine carcinogens.^[8–10] NAT2 is highly polymorphic, and its most common variants are rs1799930 (G > A), rs1799929 (C > T), rs1801280 (T > C), and rs1799931 (G > A).^[11] All mentioned sequence variants of NAT2 can lead to a major decrease in NAT2 acetylation activity or protein stability.^[6,12] NAT2 polymorphisms have been associated with drug-induced toxicities and incidence of cancers including colorectal cancer, lung cancer, breast cancer, and AL.^[11,13–16] According to acetylation activity, the phenotype of NAT2 polymorphisms can be classified into slow, intermediate, and rapid acetylator.^[17,18] It was reported that the NAT2 acetylation phenotype was also involved in the pathogenesis of cancers such as bladder cancer and AL.^[19–22] Several studies have explored the association between AL risk and either the NAT2 polymorphisms or the phenotypes of NAT2, but no unanimous conclusion has been reached.^[6,23–25] Therefore, the present meta-analysis included 12 studies comprising 2629 AL cases and 4078 healthy controls was conducted to further assess the association between the four mutations (rs1801280, rs1799929, rs1799930, and rs1799931) of NAT2, and also NAT2 phenotypes and AL risk.

2. Material and methods

2.1. Literature search

The study was performed strictly abiding by the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^[26] We carried out a search in the Pubmed, Embase, Cochrane Library, China National Knowledge Infrastructure, and Wanfang databases for relevant studies published before September 1, 2018. We used the following search terms to identify all potential relevant studies: ('N-acetyltransferase 2' or 'NAT2' or 'acetylator polymorphism') and ('acute leukemia[s]') and ('genetic polymorphism[s]' or 'genetic variant[s]' or 'genetic mutation[s]' or 'single-nucleotide polymorphism'). In addition, the following Mesh terms were used: 'polymorphism, genetic.' The references in the searched studies were examined by manual retrieval to identify the studies that may not be included in these databases.

2.2. Inclusion and exclusion criteria

The first review of the literature search results was conducted to exclude letter, review, not human study, and irrelevant studies. The remaining papers were further reviewed with the following inclusion and exclusion criteria.

Inclusion criteria were as follows: the design of original article was a cohort study or a case-control study; studies that evaluated the association between the NAT2 polymorphisms and/or NAT2 phenotypes with ALL and/or AML; the genotype or phenotype frequencies in cases and controls in each study must be given in the original study or the genetic distribution can help infer the needed results.

Exclusion criteria were as follows: duplication of previous publications; comment, review, meta-analysis, or editorial; study without detailed genotype or phenotype data; study without healthy control population. The selection of these studies was achieved by 2 investigators, according to the inclusion and exclusion criteria by screening the title, abstract, and full-text. Any dispute was solved by discussion.

2.3. Data extraction

The data extraction was conducted by 2 investigators from all the eligible publications. The following information from all identified studies according to a standardized data collection form: the first author name, publication year, study country, leukemia subtype, ethnicity, genotype method, the number of cases and controls for each NAT2 SNP when available, genotype frequencies in cases and controls, and the *P* value of Hardy-Weinberg equilibrium (HWE) in controls. The frequencies of the rapid and slow acetylators were calculated to assess the possible association of NAT2 phenotypes with AL susceptibility. Ethnicities were classified as Caucasian, mixed, and Asian. Divergences were resolved through discussion.

2.4. Quality assessment of included studies

A quality assessment was independently performed for all of the included studies by 2 authors using the Newcastle-Ottawa Quality Assessment Scale (NOS),^[27] and any disagreement was resolved by discussion and consensus. The NOS comprised the following 3 parameters of quality: selection, comparability, and exposure. The range of the score was from 0 to 9 and studies with scores range of 6 to 9 points were considered to be high quality.

2.5. Statistics analysis

We evaluated HWE by goodness-of-fit chi-square test in control groups, and $P < .05$ was considered as a significant departure from HWE. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between NAT2 polymorphisms and AL risk. Meanwhile, we also evaluated the association of NAT2 phenotypes with the risk for AL using the frequencies of the rapid and slow acetylators by ORs and 95% CIs. Pooled ORs were calculated for the homozygous, heterogeneous, dominant, recessive, and co-dominant models based on the genotype frequencies in cases and controls. Heterogeneity belief associated with the selected studies was investigated by the chi-square based *Q* test and *I*² test.^[28] While calculating the pooled ORs, the random-effects model was used when *I*² more than 70%; otherwise, the fixed-effects model was selected.^[29,30] The significance of pooled ORs was determined by *Z* test at the $P < .05$ level of significance. To evaluate the effect of 1 single study on the overall risk of AL, sensitivity analyses were performed by sequential omission of individual studies and the robustness of the pooled estimate was tested. Potential publication bias was explored by funnel plot and Egger linear regression test.^[31,32] Apart from this, subgroup analyses were stratified by ethnicity (Caucasian, mixed, and Asian), and clinical types (AML and ALL). All analyses were performed by STATA software (Version 12.0; State Corporation, College Station, TX). *P* values of 2-sided were considered statistically significant if it was less than .05.

3. Results

3.1. Studies selection results

The detailed process of study selection is summarized in Fig. 1. Based on the search strategy in the “Materials and methods” section, 155 records were retrieved. After screening the titles and abstracts, 139 studies were excluded, and 16 records remained on the association between NAT2 polymorphisms or NAT2 phenotypes and AL risk. After screening the full articles, a total of 12 studies published between 1999 and 2015 were included in the final meta-analyses.^[3,15,21–25,33–37]

3.2. Study characteristics

The characteristics of all included studies on the relationship between NAT2 polymorphisms (rs1799930, rs1799929, rs1801280, and rs1799931) and AL risk are presented in Table 1. A total of 7 studies with 1664 AL cases and 2193

controls were included.^[3,15,21,24,33–35] For rs1799930, 6 studies with 8 datasets involving 1180 cases and 1752 controls were included. For rs1799929, 5 studies with 7 datasets involving 1070 cases and 1608 controls were included. Four studies with 7 datasets involving 1211 cases and 1546 controls were included for rs1801280; 5 studies with 6 datasets involving 777 cases and 1262 controls were included for rs1799931. The NAT2 polymorphisms (rs1799930, rs1799929, rs1801280, and rs1799931) genotypic frequencies in all the subjects of control groups were consistent with HWE except 1 study. Study quality was assessed by NOS, and the scores ranged from 6 to 8, so the studies were considered to be high quality (Table 1). Apart from this, 8 studies with 12 datasets involving 1522 AL patients and 2688 controls of the rapid and slow acetylators phenotypes were included to assess the association between NAT2 phenotypes and AL risk^[15,21–23,25,34,36,37] and study quality was also assessed by NOS, and the scores ranged from 6 to 8, which are summarized in Table 2.

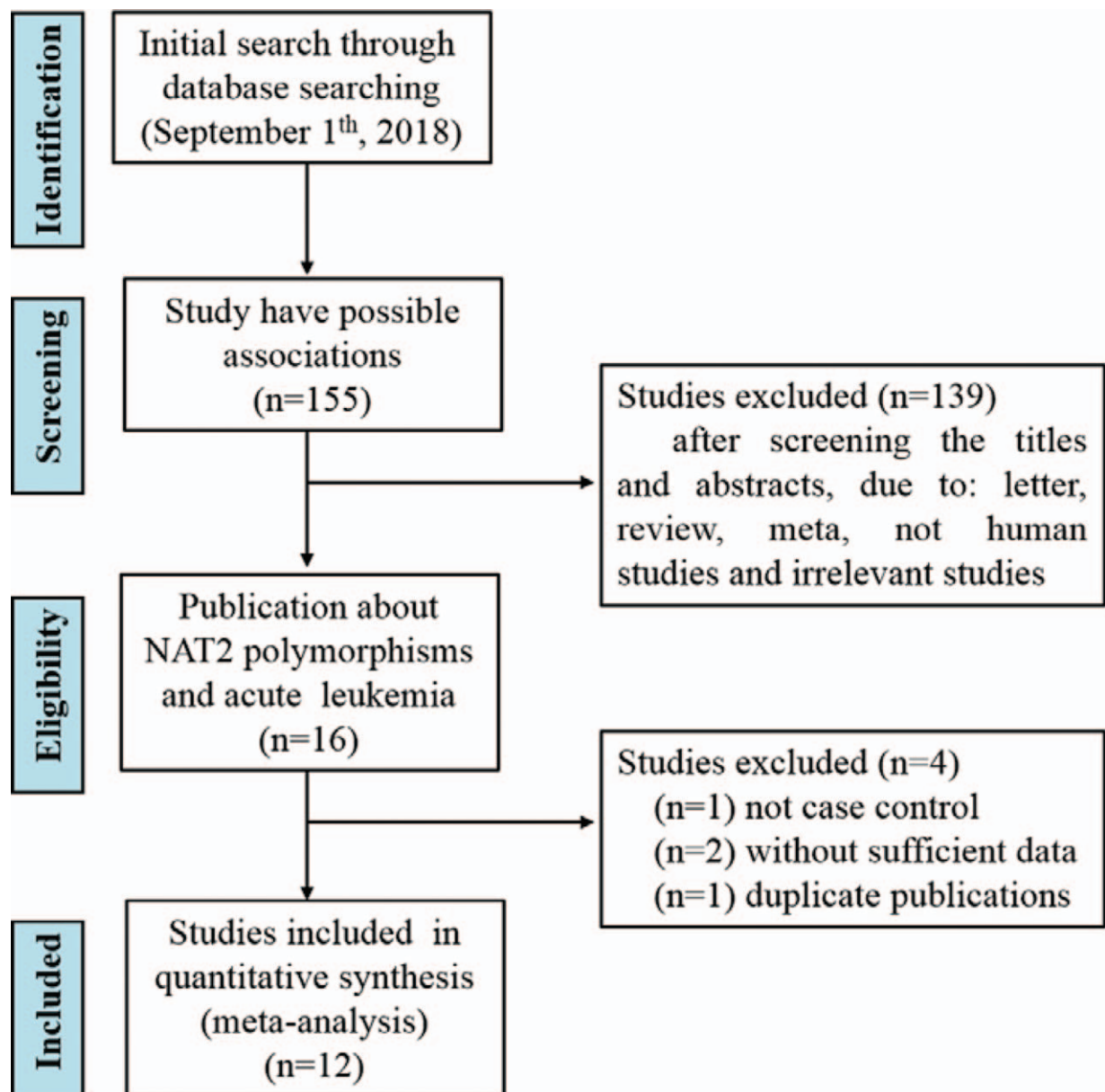


Figure 1. Flow diagram of the study identification and selection process.

Table 1

Summary of major characteristics of the studies on N-acetyl-transferase 2 polymorphisms included in the present meta-analysis.

Gene polymorphism	First author	Year	Country	Ethnicity	Subtype of cases	Sample size		Genotype (WW/MM) [*]		Method	P [†]	Quality score [‡]	
						Case	Control	Case	Control				
rs1799930	Kamel	2015	Egypt	Caucasian	ALL	92	312	41/42/9	152/135/24	PCR-RFLP	.425	7	
	Zanrosso	2012	Brazil	Mixed	ALL	158	303	84/60/10	159/105/25	PCR-RFLP	.206	8	
	Zanrosso	2012	Brazil	Mixed	AML	74	303	31/32/11	159/105/25	PCR-RFLP	.206	8	
	Silveira	2012	Brazil	Mixed	ALL	204	364	111/62/14	198/133/30	PCR-RFLP	.258	6	
	Gra	2007	Russia	Caucasian	ALL	332	490	173/133/26	235/209/46	Multiplex PCR	.961	8	
	Gra	2007	Russia	Caucasian	AML	71	490	39/27/5	235/209/46	Multiplex PCR	.961	8	
	Majumdar	2007	India	Asian	AML	110	144	32/55/23	80/53/11	PCR-RFLP	.593	8	
	Zhu	2005	China	Asian	AL	139	139	65/60/14	108/29/2	PCR-RFLP	.962	8	
Total					1180	1752	576/471/112	932/664/138					
rs1799929	Kamel	2015	Egypt	Caucasian	ALL	92	312	28/51/13	103/104/47	PCR-RFLP	.026	7	
	Zanrosso	2012	Brazil	Mixed	ALL	158	303	65/70/12	119/97/18	PCR-RFLP	.772	8	
	Zanrosso	2012	Brazil	Mixed	AML	74	303	25/29/2	119/97/18	PCR-RFLP	.772	8	
	Silveira	2012	Brazil	Mixed	ALL	204	364	65/92/30	134/167/60	PCR-RFLP	.515	6	
	Gra	2007	Russia	Caucasian	ALL	332	490	145/149/38	178/235/77	Multiplex PCR	.969	8	
	Gra	2007	Russia	Caucasian	AML	71	490	34/30/7	178/235/77	Multiplex PCR	.969	8	
	Zhu	2005	China	Asian	AL	139	139	116/20/3	127/12/0	PCR-RFLP	.540	8	
	Total					1070	1608	478/441/105	661/615/202				
rs1801280	Kamel	2015	Egypt	Caucasian	ALL	92	312	27/47/17	89/124/61	PCR-RFLP	.157	7	
	Zanrosso	2012	Brazil	Mixed	ALL	158	303	40/88/29	113/117/31	PCR-RFLP	.932	8	
	Zanrosso	2012	Brazil	Mixed	AML	74	303	16/29/17	113/117/31	PCR-RFLP	.932	8	
	Bonaventure	2011	France	Caucasian	ALL	433	441	127/180/99	165/265/82	PCR-RFLP	.153	7	
	Bonaventure	2011	France	Caucasian	AML	51	441	16/25/9	165/265/82	PCR-RFLP	.153	7	
	Gra	2007	Russia	Caucasian	ALL	332	490	112/162/58	160/240/90	Multiplex PCR	> .99	8	
	Gra	2007	Russia	Caucasian	AML	71	490	32/31/8	160/240/90	Multiplex PCR	> .99	8	
	Total					1211	1546	370/562/237	527/746/264				
rs1799931	Kamel	2015	Egypt	Caucasian	ALL	92	312	74/17/1	179/15/1	PCR-RFLP	.279	7	
	Zanrosso	2012	Brazil	Mixed	ALL	158	303	122/26/2	178/52/7	PCR-RFLP	.192	8	
	Zanrosso	2012	Brazil	Mixed	AML	74	303	47/8/1	178/52/7	PCR-RFLP	.192	8	
	Silveira	2012	Brazil	Mixed	ALL	204	364	174/13/0	328/32/1	PCR-RFLP	.815	6	
	Majumdar	2007	India	Caucasian	AML	110	144	93/16/1	115/26/3	PCR-RFLP	.302	8	
	Zhu	2005	China	Asian	AL	139	139	64/61/14	70/57/12	PCR-RFLP	.115	8	
	Total					777	1262	574/141/28	870/182/31				

AL = acute leukemia, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, Multiplex PCR = multiplex PCR restriction, PCR-RFLP = polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) techniques.

^{*} Genotype for rs1799930, GG/AG/AA; rs1799931, GG/AG/AA; rs1799929, CC/CT/TT; rs1801280, TT/CT/CC.

[†] P value for Hardy–Weinberg equilibrium in control group.

[‡] Assessed by the Newcastle–Ottawa Assessment Scale for case-control studies.

Table 2

Summary of major characteristics of the studies on the acetylator phenotypes of N-acetyl-transferase 2 included in the present meta-analysis.

First author	Year	Country	Ethnicity	Subtypes of cases	Sample size		Genotype (rapid [*] /slow [†])		Method	Quality score [‡]
					Case	Control	Case	Control		
Silveira	2012	Brazil	Mixed	ALL	186	361	134/52	262/99	PCR-RFLP	6
Zanrosso	2012	Brazil	Mixed	AL	232	303	95/137	190/113	PCR-RFLP	8
Ouerhani	2011	Tunis	Caucasian	ALL	50	309	38/12	213/96	Multiplex PCR	8
Ouerhani	2011	Tunis	Caucasian	AML	47	309	42/5	213/96	Multiplex PCR	8
Muller	2007	Israel	Caucasian	AML	75	109	29/46	40/69	PCR-RFLP	6
Muller	2007	Israel	Caucasian	AML	54	99	19/35	33/63	PCR-RFLP	6
Zhu	2005	China	Asian	AL	139	139	119/20	127/12	PCR-RFLP	8
Rollinson	2001	America	Caucasian	ALL	68	113	26/42	55/58	PCR-RFLP	6
Rollinson	2001	America	Caucasian	AML	461	821	208/253	394/427	PCR-RFLP	6
Krajcinovic	2000	Canada	Caucasian	ALL	176	306	62/114	132/159	PCR-RFLP	7
Lemos	1999	Portugal	Caucasian	ALL	22	128	9/13	46/82	PCR-RFLP	7
Lemos	1999	Portugal	Caucasian	AML	18	128	11/7	46/82	PCR-RFLP	7
Total					1522	2688	684/736	1492/1178		

AL = acute leukemia, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, multiplex PCR = multiplex PCR restriction, PCR-RFLP = polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) techniques.

^{*} Rapid acetylator defined as 4*4, 4*5A, 4*5B, 4*5C, 4*6A, 4*7B, 4*12A, 5B*12A, 6A*12A.

[†] Slow acetylator defined as 5A*5A, 5A*5B, 5A*5C, 5A*6A, 5A*7B, 5B*5B, 5B*5C, 5B*6A, 5B*7B, 5C*5C, 5C*6A, 5C*7B, 6A*6A, 6A*7B, 7B*7B.

[‡] Assessed by the Newcastle–Ottawa Assessment Scale for case-control studies.

Table 3

Pooled odds ratios and 95% confidence intervals of the relationship between four polymorphisms in N-acetyl-transferase 2 gene and acute leukemia risk.

Gene polymorphism	Co-dominant (M vs W)			Homozygous (MM vs WW)			Heterozygous (MM vs WM)			Dominant (WM+MM vs WW)			Recessive (MM vs WM+WW)		
	P for test	OR (95% CI)	P for Q	P for test	OR (95% CI)	P for Q	P for test	OR (95% CI)	P for Q	P for test	OR (95% CI)	P for Q	P for test	OR (95% CI)	P for Q
rs1799930	.000	87.4 (1.29-0.93-1.79)	.133	.000	76.7 (1.50-0.83-2.70)	.179	.445	0.0 (1.10-0.83-1.45)	.500	.000	85.4 (1.35-0.91-2.00)	.136	.008	63.1 (1.18-0.91-1.54)	.214
ALL	.503	0.0 (0.94-0.79-1.11)	.440	.671	0.0 (0.86-0.61-1.20)	.369	.821	0.0 (0.92-0.65-1.29)	.631	.512	0.0 (0.93-0.76-1.15)	.501	.741	0.0 (0.90-0.61-1.32)	.577
AML	.000	91.5 (1.47-0.78-2.77)	.237	.007	2.03 (0.66-6.25)	.217	.416	0.0 (1.43-0.87-2.36)	.156	.000	89.9 (2.12-1.66-2.70)	.244	.010	1.62 (0.70-3.74)	.255
AL	.000	3.44 (2.21-5.35)	<.001	.001	11.63 (2.56-52.82)	.001	—	3.38 (0.72-15.88)	.122	—	3.97 (2.36-6.67)	<.001	—	7.67 (1.71-34.43)	<.001
Caucasian	.000	87.5 (1.17-0.74-1.86)	.500	.001	1.37 (0.56-3.40)	.492	.379	2.8 (0.95-6.3-4.2)	.790	.000	84.9 (1.21-0.70-2.11)	.498	.023	1.16 (0.82-1.64)	.396
Mixed	.045	67.7 (1.03-0.86-1.24)	.728	.102	1.08 (0.70-1.66)	.741	.460	0.0 (1.00-0.64-1.56)	>.99	.084	59.6 (1.09-0.74-1.59)	.668	.203	1.05 (0.69-1.59)	.830
Asian	—	3.44 (2.21-5.35)	<.001	—	11.63 (2.56-52.82)	.001	—	3.38 (0.72-15.88)	.122	—	3.97 (2.36-6.67)	<.001	—	7.67 (1.71-34.43)	.008
rs1799929	.014	62.4 (0.95-0.85-1.07)	.427	.254	22.9 (0.80-6.1-1.05)	.102	.744	0.0 (0.78-0.60-1.01)	.058	.008	65.2 (1.01-0.86-1.19)	.900	.562	0.0 (0.79-0.61-1.01)	.060
ALL	.076	56.3 (0.95-0.84-1.09)	.492	.290	0.84 (0.63-1.12)	.244	.721	0.0 (0.79-0.60-1.05)	.102	.026	67.6 (1.09-0.78-1.53)	.603	.655	0.0 (0.81-0.62-1.06)	.129
AML	.150	51.7 (0.81-0.61-1.09)	.167	.906	0.0 (0.49-0.23-1.03)	.060	.465	0.0 (0.61-0.29-1.29)	.193	.065	70.7 (0.88-0.43-1.79)	.719	.749	0.0 (0.55-0.37-1.13)	.102
AL	—	2.29 (1.13-4.63)	.022	—	7.66 (0.39-149.90)	.180	—	4.27 (0.20-89.72)	.350	—	2.10 (1.00-4.41)	.050	—	7.15 (0.37-13.98)	.195
Caucasian	.108	55.0 (0.82-0.70-0.97)	.017	.367	0.1 (0.65-0.46-0.93)	.017	.747	0.0 (0.71-0.51-1.00)	.050	.020	74.5 (0.88-0.54-1.43)	.596	.919	0.0 (0.68-0.49-0.94)	.021
Mixed	.808	0.0 (1.09-0.91-1.30)	.373	.634	0.0 (1.03-0.67-1.57)	.899	.536	0.0 (0.85-0.57-1.29)	.452	.824	0.0 (1.21-0.94-1.55)	.138	.582	0.0 (0.94-0.63-1.38)	.195
Asian	—	2.29 (1.13-4.63)	.022	—	7.66 (0.39-149.90)	.180	—	4.27 (0.20-89.72)	.350	—	2.10 (1.00-4.41)	.050	—	7.15 (0.37-13.98)	.195
rs1801280	.000	77.5 (1.15-0.91-1.44)	.248	.001	1.33 (0.84-2.08)	.222	.043	53.9 (1.24-1.02-1.51)	.032	.001	72.6 (1.17-0.85-1.60)	.328	.005	1.28 (1.06-1.55)	.009
ALL	.014	71.9 (1.17-0.93-1.47)	.178	.022	1.36 (0.87-2.13)	.183	.037	64.6 (1.23-0.99-1.54)	.062	.012	72.7 (1.23-0.87-1.75)	.241	.032	1.23 (0.84-1.80)	.279
AML	.000	87.3 (1.11-0.58-2.10)	.755	.001	1.25 (0.36-4.41)	.724	.104	55.7 (1.27-0.81-1.99)	.288	.006	80.7 (1.08-0.50-2.31)	.848	.008	1.24 (0.49-3.14)	.650
Caucasian	.064	55.0 (1.02-0.91-1.15)	.722	.056	1.09 (0.86-1.37)	.486	.036	61.1 (1.18-0.94-1.47)	.150	.359	8.3 (0.96-0.81-1.13)	.605	.025	1.14 (0.93-1.41)	.024
Mixed	.488	0.0 (1.77-1.40-2.23)	<.001	.456	3.06 (1.88-4.99)	<.001	.220	33.5 (1.59-0.99-2.44)	.053	.964	0.0 (2.22-1.36-3.17)	<.001	.249	2.06 (1.33-3.16)	.001
Overall	.001	74.7 (0.99-0.63-1.55)	.957	.736	0.0 (0.91-0.48-1.72)	.762	.984	0.0 (1.90-0.47-1.73)	.748	.022	62.1 (0.94-0.73-1.20)	.599	.826	0.0 (0.89-0.48-1.67)	.726
ALL	.005	81.0 (1.06-0.48-2.31)	.892	.561	0.0 (0.64-0.18-2.27)	.498	.959	0.0 (0.66-0.19-2.43)	.533	.006	80.2 (1.09-0.48-2.46)	.839	.631	0.0 (0.65-0.18-2.31)	.505
AML	.713	0.0 (0.66-0.42-1.05)	.081	.864	0.0 (0.48-0.10-2.25)	.350	.744	0.0 (0.72-0.14-3.62)	.690	.661	0.0 (0.66-0.40-1.09)	.102	.837	0.0 (0.51-0.11-2.42)	.400
AL	—	1.63 (1.10-2.40)	.014	—	1.28 (0.55-2.96)	.571	—	1.09 (0.47-2.55)	.842	—	1.19 (0.74-1.90)	.472	—	1.19 (0.53-2.66)	.681
Caucasian	.000	86.5 (1.33-0.38-4.59)	.653	.335	0.0 (0.84-0.14-4.86)	.845	.796	0.0 (0.66-0.11-4.04)	.653	.008	85.7 (1.39-0.38-5.09)	.617	.384	0.0 (0.82-0.14-4.77)	.824
Mixed	.928	0.0 (0.68-0.49-0.94)	.021	.966	0.0 (0.48-0.15-1.56)	.221	.936	0.0 (0.69-0.20-2.36)	.559	.885	0.0 (0.68-0.48-0.97)	.034	.965	0.0 (0.51-0.16-1.60)	.266
Asian	—	1.63 (1.10-2.40)	.014	—	1.28 (0.55-2.96)	.571	—	1.09 (0.47-2.55)	.842	—	1.19 (0.74-1.90)	.472	—	1.19 (0.53-2.66)	.681

AL=acute leukemia, ALL=acute lymphoblastic leukemia, AML=acute myeloid leukemia, CI=confidence interval, M=mutated allele, OR=odds ratio, W=wild-type allele.

3.3. Association between NAT2 SNPs and AL risk

The main results of ORs and 95% CIs estimated in the present analysis on the association between individual NAT2 SNPs and AL susceptibility are shown in Table 3. The fixed-effects model was adopted to calculate the pooled ORs for each individual polymorphism with low heterogeneity; otherwise, the random-effects model

was selected. Overall, significant associations of NAT2 rs1801280 polymorphism with AL risk were shown under the heterozygous model (OR 1.24, 95% CI 1.02–1.51, $P = .032$) and recessive model (OR 1.28, 95% CI 1.06–1.55, $P = .009$) (Fig. 2A and B), indicating that individuals carrying the variant allele at this site may have an increased AL risk compared with those bearing the wild-type allele.

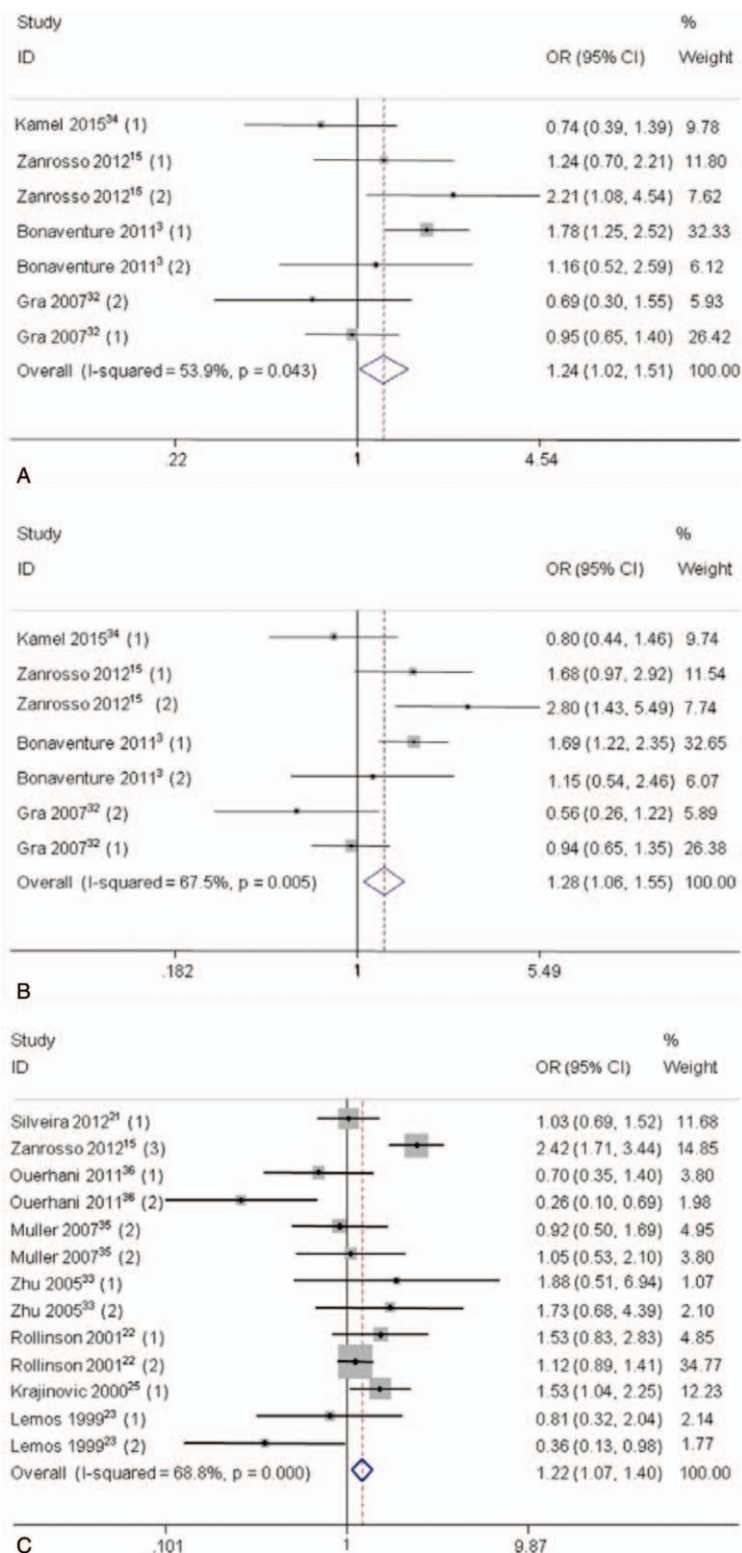


Figure 2. Forest plot for the heterozygous and recessive model of NAT2 rs1801280 and acetylator phenotypes of NAT2. (A) Heterozygous genetic model analysis. (B) Recessive genetic model analysis. (C) Slow versus rapid acetylator phenotypes analysis. NAT2 = N-acetyl-transferase 2.

Table 4**Main results of the pooled data on the association between the acetylator phenotypes of N-acetyl-transferase 2 and acute leukemia risks.**

Overall and subgroups	P for Q test	I ² (%)	OR for slow acetylator (95% CI)	P for OR
Overall	.000	68.8	1.22 (1.07–1.40)	.004
ALL	.289	19.9	1.20 (0.96–1.50)	.118
AML	.017	63.7	1.01 (0.83–1.22)	.923
AL	—	—	2.42 (1.71–3.44)	<.001
Caucasian	.013	58.9	0.93 (0.69–1.26)	.409
Mixed	.001	90.2	1.59 (0.68–3.68)	.637
Asian	.915	0.0	1.78 (0.83–3.80)	.137

AL=acute leukemia, ALL=acute lymphoblastic leukemia, AML=acute myeloid leukemia, CI=confidence interval, OR=odds ratio.

Considering the potential impact of the confounding factors on the overall results, subgroup analyses were stratified by ethnicity (Caucasian, mixed, and Asian) and clinical types (AML and ALL) for 4 individual NAT2 allelic SNPs (Table 3). In subgroup analysis according to ethnicity, as for rs1799929, decreased AL risk was observed in the 4 genetic models among the Caucasian group (co-dominant model: OR 0.82, 95% CI 0.70–0.97, $P=.017$; homozygous model: OR 0.65, 95% CI 0.46–0.93, $P=.017$; heterozygous model: OR 0.71, 95% CI 0.51–1.00, $P=.05$; recessive model: OR 0.68, 95% CI 0.49–0.94, $P=.021$). As for rs1799931, the same effects were found in the co-dominant model (OR 0.68, 95% CI 0.49–0.94, $P=.021$) and the dominant model (OR 0.68, 95% CI 0.48–0.97, $P=.034$) in the mixed group. For rs1801280, an increasing AL risk was found in the 4 models (co-dominant model: OR 1.77, 95% CI 1.40–2.23, $P<.001$; homozygous model: OR 3.06, 95% CI 1.88–4.99, $P<.001$; dominant model: OR 2.22, 95% CI 1.56–3.17, $P<.001$; recessive model: OR 2.06, 95% CI 1.35–3.16, $P=.001$) in the mixed group, and the recessive model (OR 1.14, 95% CI 0.93–1.41, $P=.024$) in the Caucasian group. However, when stratified by clinical types, no significant association was found.

The data above indicated that SNPs rs1799929, rs1799931, and rs1801280 of NAT2 were significantly associated with AL. Among them, rs1799929 and rs1799931 might decrease AL risk, whereas rs1801280 might increase AL risk and those effects were associated with ethnicity.

3.4. Association between acetylator phenotypes and AL risk

The results of the present analysis on the association between acetylator phenotypes and AL susceptibility are shown in Table 4. The meta-analysis results showed a significant association between slow acetylators and AL risk (OR 1.22, 95% CI 1.07–1.40, $P=.004$) (Fig. 2C). Subgroup analyses were also stratified by ethnicity (Caucasian, mixed, and Asian) and clinical types (AML and ALL) for acetylator phenotypes (Table 4). However, the results showed that no significant association between acetylator phenotypes and AL was found for either ethnicity or clinical type analyses. The data indicated that slow acetylators of NAT2 might also increase the AL risk.

3.5. Sensitivity analysis

Sensitivity analysis was conducted to detect the influence of each individual study on the pooled ORs by sequentially removing 1 single study each time. The results demonstrated that when each study was removed, the pooled ORs were stable under any of the

models mentioned above of 4 SNPs and there was also no heterogeneity observed in the meta-analysis of phenotype of NAT2 (Fig. 3A–C).

3.6. Publication bias

Publication bias was assessed using funnel plots and Egger linear regression tests. The funnel plots seemed symmetrical for both the models of NAT2 SNPs and the phenotypes of NAT2, indicating there was no publication bias (Supplementary Fig. 1, <http://links.lww.com/MD/C892>). Additionally, the Egger test also did not find significant publication bias under any models of the four SNPs and phenotype of NAT2 (Table 5).

4. Discussion

The NAT2 gene encodes the drug phase II metabolic enzyme NAT2, which is mainly expressed in liver and gut. The function of NAT2 is to metabolize aromatic and heterocyclic amines comprising drugs, xenobiotics, and carcinogens.^[38] There are some sites of mutation resulting in NAT2 polymorphisms. Among these, SNP rs1801280, SNP rs1799929, SNP rs1799930, and SNP rs1799931 were high-profile and contribute to a change in enzyme activity, leading to the dysfunction in its ability to modify drug toxicity and an increase in the incidence of cancer.^[6,16,39,40] According to enzyme activity, the phenotypes of NAT2 can be divided into slow, intermediate, and rapid acetylators.^[17] It has been demonstrated that NAT2 polymorphisms and acetylator phenotypes were associated with the risk of a variety of tumors such as breast cancer, lung cancer, and AL.^[11,13,15,35,41] There has been a recent focus on the relationship of NAT2 polymorphisms, acetylator phenotypes, and AL risk. However, no consistent opinion has been reached. Some studies had reported that NAT2 polymorphisms and acetylator phenotypes were markedly associated with AL risk.^[15,33,34] While other studies had demonstrated that there was no association between them.^[21,22,36] Therefore, to further assess the relationship between NAT2 polymorphisms, acetylator phenotypes, and susceptibility to AL, we performed the present meta-analysis combining the data from different studies.

We found that rs1801280 of NAT2 increased the risk of AL, which indicates that it may serve as a potential prediction, diagnosis biomarker for AL. Stratified by ethnicity (Caucasian, mixed, Asian), we found that rs1801280 polymorphism contributes to AL risk, particularly in the mixed population in 4 models (co-dominant, homozygous, dominant, and recessive models). As for rs1799929 of NAT2, a significantly decreased AL risk was found in co-dominant, homozygous, heterozygous, and

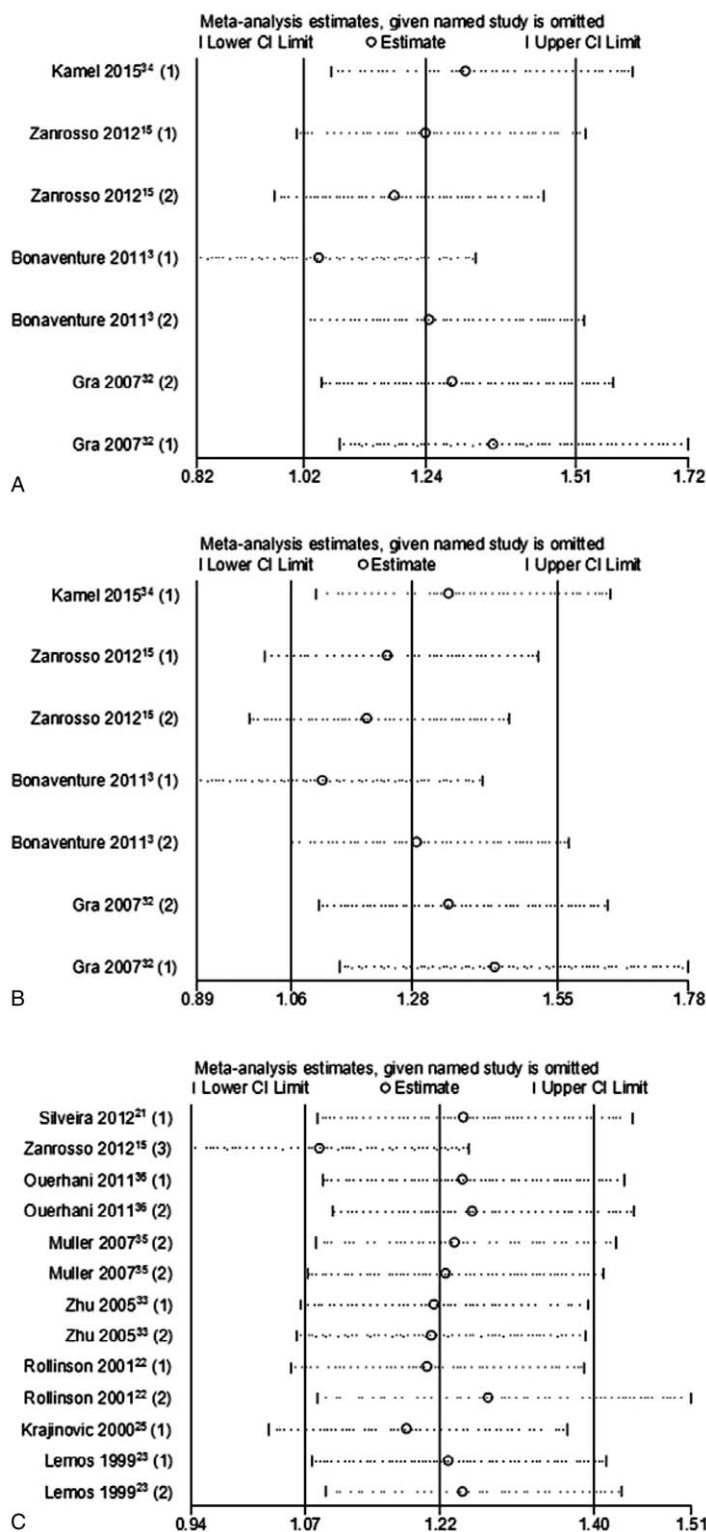


Figure 3. Sensitivity analysis for heterozygous model and recessive model of *NAT2* rs1801280 and acetylator phenotypes of *NAT2*. (A) Heterozygous genetic model analysis. (B) Recessive genetic model analysis. (C) Slow versus rapid acetylator phenotypes analysis. *NAT2*=N-acetyl-transferase 2.

recessive models in the Caucasian population. Additionally, rs1799931 of *NAT2* was also found to be associated with decreased AL risk in both co-dominant and dominant models in the mixed population. Stratified by clinical classification (AML and ALL), no association was found. The results indicated that

different SNPs of *NAT2* might have different association with AL susceptibility in different ethnicities; a possible explanation of this phenomenon is the linkage disequilibrium patterns in alleles between different ethnic populations. Moreover, we also extracted rapid and slow acetylator phenotype frequencies to

Table 5**The result of publication bias tests for the overall data.**

	Models	Egger test	
		t	P
Gene polymorphism			
rs1799930	Co-dominant (M vs W)	-2.25	.065
	Homozygous (MM vs WW)	-1.92	.104
	Heterozygous (MM vs WM)	1.64	.152
	Dominant (WM+MM vs WW)	2.35	.057
	Recessive (MM vs WM+WW)	1.78	.126
rs1799929	Co-dominant (M vs W)	-1.77	.137
	Homozygous (MM vs WW)	-0.89	.413
	Heterozygous (MM vs WM)	0.11	.916
	Dominant (WM+MM vs WW)	1.87	.121
	Recessive (MM vs WM+WW)	0.65	.542
rs1801280	Co-dominant (M vs W)	-0.12	.909
	Homozygous (MM vs WW)	-0.02	.983
	Heterozygous (MM vs WM)	-0.73	.498
	Dominant (WM+MM vs WW)	0.60	.577
	Recessive (MM vs WM+WW)	-0.41	.699
rs1799931	Co-dominant (M vs W)	0.59	.586
	Homozygous (MM vs WW)	1.01	.371
	Heterozygous (MM vs WM)	-1.52	.204
	Dominant (WM+MM vs WW)	0.05	.966
	Recessive (MM vs WM+WW)	-1.01	.368
Phenotype			
	Slow vs rapid	-1.27	.229

M=mutated allele, W=wild-type allele.

evaluate the association between *NAT2* enzyme activity and the risk of AL. These findings indicated that the slow acetylator phenotype of *NAT2* might contribute to the occurrence of AL. Previous studies have demonstrated that rs1801280—1 SNP of *NAT2* associated with the slow acetylator phenotype—conferred an increased risk association with AL.^[3,33] Some articles also suggested that the slow acetylator phenotype was a significant risk determinant of AL.^[15,25] Our results are consistent with those previous studies and further confirmed the relationship between *NAT2* and AL. As stratified by ethnicity and clinical type, no significant association was found in either the rapid or slow acetylators phenotypes. The clinical type of AL is very complicated. AL can be divided into AML and ALL, and AML can be further classified into M0 to M7 subtypes, whereas AL can be classified into L1 to L3 subgroups according to the French-American-British criterion.^[42] However, because of insufficient data in the included studies, we could not perform the accurate subgroups stratification analysis. Additionally, the genotype distribution of the controls in 1 article was deviated from HWE generally, and this may affect the result of the analysis. Regardless, publication bias did not exist according to funnel plot and Egger linear regression test, and the NOS score also indicated that the included studies were credible.

There were several limitations in the present study. First, significant heterogeneity between studies was detected in this meta-analysis that might have an effect on the accuracy of the results, despite the fact that we used the random-effects model to calculate pool ORs. Second, because the data were insufficient, we were unable to conduct relative research on other factors such as gene-gene or gene-environment interactions that, along with *NAT2* polymorphisms, might influence AL susceptibility, and we could not proceed with further subgroup stratification analysis by age, sexual distinction and so on. Third, the polymorphisms of *NAT2* were detected by different methods such as PCR-RFLP

and multiplex PCR, which might influence the accuracy of the result. Moreover, even though all geographical information could be obtained from the included studies, the information of the ethnic origin of AL patients could not be acquired from some included studies.

5. Conclusions

To the best of our knowledge, the present study was the first to systematically analyze the association between *NAT2* polymorphism, *NAT2* acetylator phenotypes, and AL risk. The results revealed that rs1801280 polymorphism and the slow acetylator phenotype are closely correlated with the occurrence of AL. As for the rs1801280 polymorphism, this effect is more pronounced in the mixed population. Meanwhile, our meta-analysis suggested that in the mixed population, rs1799931 polymorphism is related to decreased AL risk, and this phenomenon was also found between rs1799929 polymorphism and AL risk in the Caucasian population. These findings will shed light on the role of gene polymorphism in the risk of AL and provide potential biomarkers for the prediction and prognosis of AL, or even contribute to the exploration novel targets for AL therapy.

Author contributions

Data curation: Yanbing Liu, Guangwu Chen, Qiang Guo.

Formal analysis: Ran Wei, Xunqiang Yin, Yunhong Zhang.

Funding acquisition: Xia Li.

Investigation: Bin Wang, Xia Li.

Methodology: Guangwu Chen, Qiang Guo.

Resources: Xiaoxiao Zhu, Yanbing Liu.

Software: Ran Wei, Xunqiang Yin, Yunhong Zhang.

Supervision: Zhen Zhang, Lin Zhao, Bin Wang.

Validation: Zhen Zhang, Lin Zhao.

Writing – original draft: Xiaoxiao Zhu.

Writing – review & editing: Xia Li.

References

- Meenaghan T, Dowling M, Kelly M. Acute leukaemia: making sense of a complex blood cancer. *Br J Nurs* 2012;21:78–83. 76.
- Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009;114:937–51.
- Bonaventure A, Goujon-Bellec S, Rudant J, et al. Maternal smoking during pregnancy, genetic polymorphisms of metabolic enzymes, and childhood acute leukemia: the ESCALE study (SFCE). *Cancer Causes Control* 2012;23:329–45.
- Wong O, Harris F, Armstrong TW, et al. A hospital-based case-control study of acute myeloid leukemia in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chemicobiol Interact* 2010;184:112–28.
- Schmiegelow K, Vestergaard T, Nielsen SM, et al. Etiology of common childhood acute lymphoblastic leukemia: the adrenal hypothesis. *Leukemia* 2008;22:2137–41.
- Zanrosso CW, Emerenciano M, Goncalves BA, et al. N-acetyltransferase 2 polymorphisms and susceptibility to infant leukemia with maternal exposure to dipyrone during pregnancy. *Cancer Epidemiol Biomarkers Prev* 2010;19:3037–43.
- Gemmati D, Ongaro A, Scapoli GL, et al. Common gene polymorphisms in the metabolic folate and methylation pathway and the risk of acute lymphoblastic leukemia and non-Hodgkin's lymphoma in adults. *Cancer Epidemiol Biomarkers Prev* 2004;13:787–94.
- Meyer UA, Zanger UM. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol* 1997;37:269–96.

- [9] Sim E, Abuhammad A, Ryan A. Arylamine N-acetyltransferases: from drug metabolism and pharmacogenetics to drug discovery. *Br J Pharmacol* 2014;171:2705–25.
- [10] Sim E, Lack N, Wang CJ, et al. Arylamine N-acetyltransferases: structural and functional implications of polymorphisms. *Toxicology* 2008;254:170–83.
- [11] Delort L, Satih S, Kwiatkowski F, et al. Evaluation of breast cancer risk in a multigenic model including low penetrance genes involved in xenobiotic and estrogen metabolisms. *Nutr Cancer* 2010;62:243–51.
- [12] Garcia-Martin E, Esguevillas G, Blanca-Lopez N, et al. Genetic determinants of metamizole metabolism modify the risk of developing anaphylaxis. *Pharmacogenet Genomics* 2015;25:462–4.
- [13] Zgheib NK, Shamseddine AA, Geryess E, et al. Genetic polymorphisms of CYP2E1, GST, and NAT2 enzymes are not associated with risk of breast cancer in a sample of Lebanese women. *Mutat Res* 2013;747:748:40–7.
- [14] Cleary SP, Cotterchio M, Shi E, et al. Cigarette smoking, genetic variants in carcinogen-metabolizing enzymes, and colorectal cancer risk. *Am J Epidemiol* 2010;172:1000–14.
- [15] Zanrosso CW, Emerenciano M, Faro A, et al. Genetic variability in N-acetyltransferase 2 gene determines susceptibility to childhood lymphoid or myeloid leukemia in Brazil. *Leuk Lymphoma* 2012;53:323–7.
- [16] Hein DW. Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. *Mutat Res* 2002;506:507:65–77.
- [17] Garcia-Closas M, Malats N, Silverman D, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 2005;366:649–59.
- [18] Hein DW, Doll MA, Fretland AJ, et al. Molecular genetics and epidemiology of the NAT1 and NAT2 acetylation polymorphisms. *Cancer Epidemiol Biomarkers Prev* 2000;9:29–42.
- [19] Sanderson S, Salanti G, Higgins J. Joint effects of the N-acetyltransferase 1 and 2 (NAT1 and NAT2) genes and smoking on bladder carcinogenesis: a literature-based systematic HuGE review and evidence synthesis. *Am J Epidemiol* 2007;166:741–51.
- [20] Hayes RB, Bi W, Rothman N, et al. N-acetylation phenotype and genotype and risk of bladder cancer in benzidine-exposed workers. *Carcinogenesis* 1993;14:675–8.
- [21] Silveira VS, Canalle R, Scrideli CA, et al. CYP3A5 and NAT2 gene polymorphisms: role in childhood acute lymphoblastic leukemia risk and treatment outcome. *Mol Cell Biochem* 2012;364:217–23.
- [22] Rollinson S, Roddam P, Willett E, et al. NAT2 acetylator genotypes confer no effect on the risk of developing adult acute leukemia: a case-control study. *Cancer Epidemiol Biomarkers Prev* 2001;10:567–8.
- [23] Lemos MC, Cabrera FJ, Silva HA, et al. Genetic polymorphism of CYP2D6, GSTM1 and NAT2 and susceptibility to haematological neoplasias. *Carcinogenesis* 1999;20:1225–9.
- [24] Majumdar S, Mondal BC, Ghosh M, et al. Association of cytochrome P450, glutathione S-transferase and N-acetyl transferase 2 gene polymorphisms with incidence of acute myeloid leukemia. *Eur J Cancer Prev* 2008;17:125–32.
- [25] Krajcinovic M, Richer C, Sinnett H, et al. Genetic polymorphisms of N-acetyltransferases 1 and 2 and gene-gene interaction in the susceptibility to childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev* 2000;9:557–62.
- [26] Swartz MK. The PRISMA statement: a guideline for systematic reviews and meta-analyses. *J Pediatr Health Care* 2011;25:1–2.
- [27] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- [28] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- [29] Khan S, Mandal RK, Jawed A, et al. TNF-alpha -308 G > A (rs1800629) polymorphism is associated with celiac disease: a meta-analysis of 11 case-control studies. *Sci Rep* 2016;6:32677.
- [30] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–48.
- [31] Colditz GA, Burdick E, Mosteller F. Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. *Am J Epidemiol* 1995;142:371–82.
- [32] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [33] Gra OA, Glotov AS, Kozhekbaeva Z, et al. [Genetic polymorphism in GST, NAT2, and MTRR and susceptibility to childhood acute leukemia]. *Mol Biol (Mosk)* 2008;42:214–25.
- [34] Zhu FY, Zhang J, Yin LH, et al. The relationship between polymorphisms of MPO and NAT2 and susceptibility of adult acute leukemia in Chinese Han population. *Chin J Public Health* 2006;22:584–6.
- [35] Kamel AM, Ebid GT, Moussa HS. N-Acetyltransferase 2 (NAT2) polymorphism as a risk modifier of susceptibility to pediatric acute lymphoblastic leukemia. *Tumour Biol* 2015;36:6341–8.
- [36] Muller P, Asher N, Heled M, et al. Polymorphisms in transporter and phase II metabolism genes as potential modifiers of the predisposition to and treatment outcome of de novo acute myeloid leukemia in Israeli ethnic groups. *Leuk Res* 2008;32:919–29.
- [37] Ouerhani S, Nefzi MA, Menif S, et al. Influence of genetic polymorphisms of xenobiotic metabolizing enzymes on the risk of developing leukemia in a Tunisian population. *Bull Cancer* 2011;98:95–106.
- [38] De Stefani E, Boffetta P, Mendilaharsu M, et al. Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: a case-control study in Uruguay. *Nutr Cancer* 1998;30:158–62.
- [39] Grant DM, Hughes NC, Janezic SA, et al. Human acetyltransferase polymorphisms. *Mutat Res* 1997;376:61–70.
- [40] Martinez C, Andreu I, Amo G, et al. Gender and functional CYP2C and NAT2 polymorphisms determine the metabolic profile of metamizole. *Biochem Pharmacol* 2014;92:457–66.
- [41] Nikishina MV, Vavilin VA, Makarova SI, et al. Analysis of associations of NAT2 gene polymorphisms with the risk of lung cancer. *Bull Exp Biol Med* 2007;143:83–6.
- [42] Atkinson J, Hrisinko MA, Weil SC. Erythroleukemia: a review of 15 cases meeting 1985 FAB criteria and survey of the literature. *Blood Rev* 1992;6:204–14.