Systematic Review and Meta-Analysis

Medicine®

OPEN

Association between *CYP2B6* c.516G >T variant and acute leukaemia

A protocol for systematic review and meta-analysis

Xuan Xiong, MD[a,b], Dongke Yu, PhD[a,b], Qiaoyue Gao, BS[c], Yuan Zhang, MD[a,b], Qinan Yin, MD[a,b], Xiaotao Chen, BS[a,b], Hongtao Xiao, PhD[d,*], Rongsheng Tong, PhD[a,b,*]

Abstract

Background: Acute leukemia (AL) is a kind of malignant tumor of hematopoietic system. A number of studies have suggested that Single Nucleotide Polymorphisms are significantly associated with risk of AL. Present study performs meta-analysis to evaluate the association between *CYP2B6* c.516G>T variant and AL risk.

Methods: Databases including PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), and Wanfang were searched for literatures to September 30, 2019, both in English and Chinese. Relative risk and its 95% confidence intervals were used to assess the associations. Statistical analyses of this meta-analysis were conducted by using STATA 13.0. software.

Results: A total of 7 studies, including 1038 cases and 1648 controls, were analyzed. Our results indicated that *CYP2B6* c.516G>T variant was significantly related to an increased the risk of AL under dominant model, recessive model, homozygote model, and allelic model. In addition, subgroup analyses were also performed by disease classification, country, and study design. No significant associations were obtained between *CYP2B6* c.516G>T variant and the risk of AL under the recessive model in the design of hospital-based (relative risk = 0.98; 95% confidence interval: 0.95–1.01; $P = 0.118$).

Conclusion: Our meta-analysis indicated that the *CYP2B6* variant is significantly associated with AL risk, in which *CYP2B6* c.516G>T is related to an increased risk of AL.

Abbreviations: AL = acute leukemia, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, HWE = Hardy-Weinberg equilibrium, RR = relative risk.

Keywords: cytochrome P-450 CYP2B6, leukemia, meta-analysis

1. Introduction

Acute leukemia (AL) is a kind of malignant tumor of hematopoietic system characterized by the enhanced self-renewal and proliferation as well as inhibited differentiation and apoptosis of leukemia cells.[1] The malignant of hematopoietic cells leads to aggregation of leukemia cells and subsequential extensive infiltration into bone marrow, liver, spleen, lymph nodes and other organs, which eventually leads to bleeding, anemia infection and other phenomena.[2–4] According to the involved cell types, AL can be divided into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).[5]

ALL originated from the malignant clonal disease of hematopoietic stem/progenitor cells, and its molecular mechanism has not been fully defined.[6] In the United States, about

Editor: Doaa Attia.

XX, DY, and QG contributed equally to this study.

Ethics: Ethical approval was not necessary as this article is a systematic review.

A data sharing statement: All data generated or analyzed during this study are included in this article.

No additional unpublished data are available.

The author(s) report no conflicts of interest.

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

[a] *Department of Pharmacy, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital,* [b] *Personalized Drug Therapy Key Laboratory of Sichuan Province, School of Medicine, University of Electronic Science and Technology of China,* [c] *Department of Pharmacy, Wenjiang District People 's Hospital of Chengdu,* [d] *Department of Pharmacy, Sichuan Cancer Hospital & Institute, The Affiliated Cancer Hospital, School of medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan Province, China.*

[*] *Correspondence: Rongsheng Tong, Department of Pharmacy, Sichuan Cancer Hospital & Institute, The Affiliated Cancer Hospital, School of medicine, University of Electronic Science and Technology of China, Chengdu 610089, Sichuan Province, China (e-mail: tongrs0701@sina.com); Hongtao Xiao, (e-mail: xht927@163.com).*

How to cite this article: Xiong X, Yu D, Gao Q, Zhang Y, Yin Q, Chen X, Xiao H, Tong R. Association between CYP2B6 c.516G >T variant and acute leukaemia: A protocol for systematic review and meta-analysis. Medicine 2021;100:32(e26740).

Received: 24 August 2020 / Received in final form: 27 April 2021 / Accepted: 28 June 2021

http://dx.doi.org/10.1097/MD.0000000000026740

5000 new cases of ALL are diagnosed each year, more than half of them in children.[7] ALL is the most common malignant tumor in pediatrics, accounting for more than 25% of cancer in children.[8] The peak incidence of all was 2 to 5 years' old, slightly higher in men than in women, and the risk for white people was twice that of African Americans.[9,10] Genetic factors such as trisomy 21 (Down syndrome) have a 15-fold increased relative risk (RR).[11] Other inducing conditions include immune deficiency and chromosome breakage syndrome, and most of them cannot be found in these potential diseases. Epstein Barr virus infection is associated with a small number of mature B cells ALL.[12,13] Increasing evidences suggest that the environmental exposure, such as benzene exposure, formaldehyde exposure, ionizing radiation, and particulate matters increase the risk of ALL.[14–16]

AML is a group of heterogeneous diseases characterized by uncontrolled proliferation of myeloid precursor cells which gradually replace normal hematopoiesis of bone marrow [17]. Genetic changes in tumor clones lead to molecular cascade reactions, which in turn lead to abnormal proliferation and differentiation of malignant cells and inhibit normal hematopoiesis, but its molecular origin is still unclear.[18]

The variant of cytochrome P450 enzyme has an important effect on biotransformation of chemicals, especially pre carcinogens.[19] CYP2B6 enzyme is widely distributed in macrophages, peripheral blood, lymphocytes, brain, liver, kidney, lung, small intestine, endometrium, and alveoli of bronchioles, and participates in the synthesis and metabolism of various endogenous and exogenous substances.[20,21]

CYP2B6 gene is located in 19q12–13.2, with a total length of 27.1 kb, including 11 exons which encode 491 amino acids.[22] A number of variants have been found in *CYP2B6* such as NM_000767.5:c.516G>T (*CYP2B6* c.516G>T) variant which affects the activity of CYP2B6, and reduces the rate of human transformation of carcinogenic substances into inactive metabolites, which leads to the accumulation of carcinogenic substances, and a series of diseases.[23–26]

To date, many studies have been performed to detect the correlation between *CYP2B6* c.516G>T variant and AL. However, the results of published studies are inconsistent and inconclusive, which may be attributed to differences in sample size and ethnic diversity of the population. Therefore, we carried out this meta-analysis to investigate the association between *CYP2B6* variant and AL.

2. Materials and methods

This meta-analysis was performed on the basis of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement.

2.1. Search strategy

PubMed, EMBASE, CNKI, and Wanfang databases were systematically searched for relevant studies until September 30, 2019.

The search was limited to the studies published in English or Chinese with the combination of the keyword:("polymorphism" OR "polymorphisms" OR "variant" OR "mutation" OR "genotype" OR"allele" OR "SNP") AND ("Cytochrome P-450 CYP2B6" OR "Cytochrome P450 CYP2B6"OR"P-450 CYP2B6, Cytochrome"OR"CYPIIB6"OR"1,4-Cineole 2-exo-Monooxygenase"OR"1,4 Cineole 2 exo Monooxygenase" OR" 2-exo-Monooxygenase, 1,4-Cineole" OR "Cytochrome P450 2B6"OR"P450 2B6, Cytochrome" OR "CYP2B6") AND ("leukemia" OR "Leukemias" OR "Leucocythaemia" OR "Leucocythaemias" OR "Leucocythemia" OR "Leucocythemias")

2.2. Inclusion and exclusion criteria

Studies enrolled in this meta-analysis were screened according to the following criteria: *CYP2B6* were investigated, case–control, genotype distribution were available in both cases and controls, publication in English or Chinese. The main exclusion criteria of this meta-analysis were as follow: obviously irrelevant studies, reviews or meta-analysis, duplicate publication in bi languages, not English or Chinese.

2.3. Data extraction and document quality evaluation

Two different individuals reviewed all eligible studies. The following data of articles were recorded: first author, year of publication, country and ethnicity of study, study design, genotyping method, the number of cases and controls, genotype/allele distribution in cases and controls, and P value of Hardy-Weinberg equilibrium (HWE). In addition, the methodological quality of studies was assessed using the Newcastle-Ottawa scale. The Newcastle-Ottawa scale scores vary from 0 to 9 points: studies with scores of 0 to 4 were considered low quality and 5 to 9 were considered high quality.

2.4. Statistical analysis

This meta-analysis was performed using STATA13 software (STATA Corp., College Station, TX). The association between *CYP2B6* variant and AL were estimated using RR and its 95% confidence intervals (CIs). Heterogeneity was expressed using the χ^2-based Cochrane Q test and I^2 index. A random-effects model was used when heterogeneity was observed in studies ($P < .10$, $I^2 > 50\%$); otherwise, ORs were pooled by the fixed-effects model ($P > .10$, $I^2 < 50\%$). HWE in the controls was calculated using the χ^2 test and $P > .05$ was considered as consistent with HWE. Sensitivity analysis was used to estimate the stability of the results by omitting individual study sequentially. An estimate of publication bias was calculated using Begg rank correlation test and Egger linear regression test. A probability level of $P < .05$ was considered statistically significant.[27]

3. Results

3.1. 1. Search results and study characteristics

The selection process in this meta-analysis was shown in Figure 1. A total of 451 articles were identified in the initial search. After exclusion of irrelevant records by screening titles and abstracts, 9 articles were assessed for further evaluation. Finally, a total of 4 articles including 7 studies and1038 cases and 1648 controls were enrolled in this meta-analysis, the main characteristics of enrolled studies were summarized in Table 1.[28–31] In all eligible studies,3 studies were involved ALL and 4 were involved AML. Among the studies, 4 were conducted in Asians, and others were white. All the studies were considered to be high quality. Apart from that, the design of these studies was based on hospital or population. After HWE test, except Yu's study, other studies were in accordance with HWE equilibrium ($P > .05$).

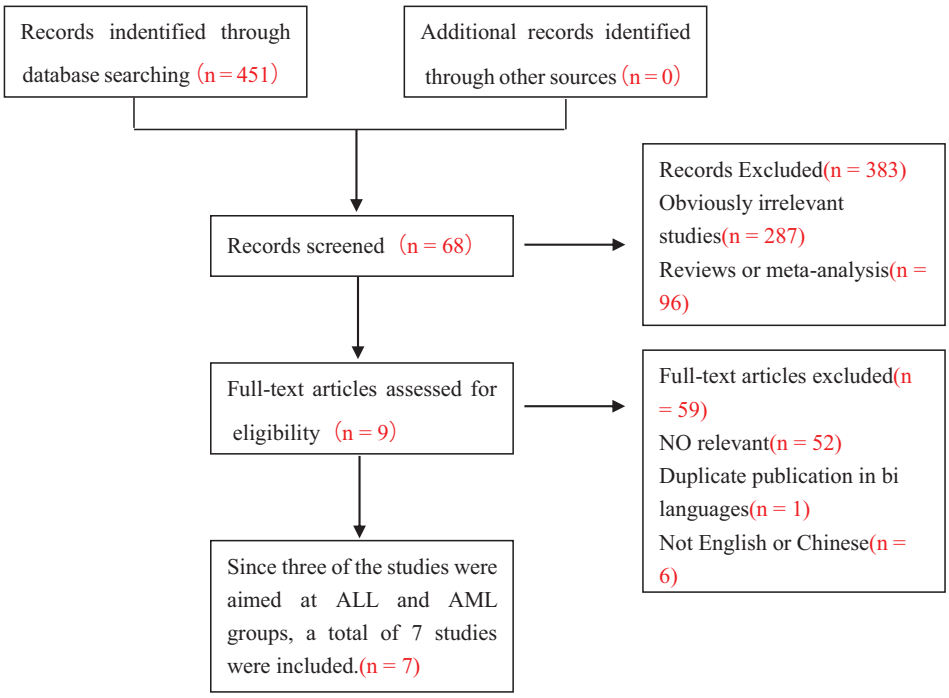

Figure 1. Flow of information through the different phases of a systematic review.

3.2. Meta-analysis results

This meta-analysis' results of association between *CYP2B6* c.516G>T variant and AL were summarized in Table 2.

Our meta-analysis results showed that *CYP2B6* c.516G>T variant was significantly related to an increased the risk of AL under four model (dominant model: RR = 0.77; 95% CI: 0.72–0.83; $P = .000$; recessive model: RR = 0.97; 95% CI: 0.95–0.99; $P = .000$; homozygote model: RR = 0.84; 95% CI: 0.80–0.89; $P = .000$; allelic model: RR = 0.88; 95% CI: 0.84–0.92; $P = .000$ (Fig. 2).

In subgroup analysis based on ALL, AML, white, Asian, and design of PB studies, there were significant associations under all models, but under the recessive model (TT vs GT + GG) in the design of HB studies, as Figure 3, no obvious associations between *CYP2B6* c.516G>T variant and AL were found (RR = 0.98, 95% CI: 0.95–1.01; $P = .118$).

3.3. Heterogeneity, publication bias and sensitivity analysis

As shown in Table 2, no significant heterogeneity was detected under each model ($I^2 < 50\%$).

The Begg funnel plot did not find any obvious publication bias ($P = .230$) under Allelic model Fig. 4, but the Egger's test shows the there are some publication bias in those studies ($P = .028$). With trim and fill method, there is no more study needed (k = 0), it means no publication bias.

Sensitivity analysis was performed by removing one single study from the studies for all models. The RRs and 95% CIs were not materially altered, suggesting this meta-analysis was robust and credible. From the fail-safe number method, >66 studies should change the conclusion. Sensitivity analysis showed that the omission of any individual study did not substantially influence the risk estimates, which supported the credibility and reliability of this meta-analysis.

Table 1

Characteristics of the included publications.

						Genotype distribution						
						Case			Control			
Study ID	Year	Racial descent	Source of control	Case	Control	GG	GT	TT	GG	GT	TT	HWE
ALL												
Berköz and Yalin[28]	2009	White	PB	44	100	18	26	0	67	33	0	0.048
Yuan et al[29]	2011	Asian	HB	96	348	55	36	5	258	83	7	0.914
Yu[30]	2010	Asian	PB	45	161	25	13	7	124	25	12	0.000
AML												
Berköz and Yalin[28]	2009	Caucasian	PB	36	100	18	18	0	67	33	0	0.048
Yuan et al[29]	2011	Asian	HB	164	348	97	61	6	258	83	7	0.914
Daraki et al[31]	2014	Caucasian	PB	572	430	297	222	53	279	128	23	0.107
Yu[30]	2010	Asian	PB	81	161	47	22	12	124	25	12	0.000

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, HB = hospital-based, HWE = Hardy-Weinberg equilibrium, PB = population-based.

Table 2

Meta-analysis of the association between *CYP2B6* c.516G>T variant and AL.

Study group	Study (n)	Dominant model TT + GT vs GG			Recessive model TT vs GT + GG			Homozygote model TT vs GG			Allelic model T vs G		
		RR (95% CI)	*P*	I^2 (%)	RR (95% CI)	*P*	I^2 (%)	RR (95% CI)	*P*	I^2 (%)	RR (95% CI)	*P*	I^2 (%)
Overall	7	0.77 (0.72–0.83)	0.000	0.0%	0.97 (0.95–0.99)	0.002	0.0%	0.84 (0.80–0.89)	0.000	0.0%	0.88 (0.84–0.92)	0.000	0.000
ALL	3	0.73 (0.64–0.85)	0.000	0.0%	0.96 (0.92–1.01)	0.088	0.0%	0.80 (0.70–0.92)	0.001	16.9%	0.85 (0.78–0.94)	0.001	0.000
AML	4	0.79 (0.73–0.85)	0.000	0.0%	0.97 (0.94–0.99)	0.020	21.9%	0.85 (0.80–0.91)	0.000	0.0%	0.89 (0.84–0.93)	0.000	0.000
White	3	0.78 (0.71–0.85)	0.000	0.0%	0.96 (0.93–0.99)	0.016	/	0.78 (0.65–0.96)	0.000	47.8%	0.89 (0.83–0.95)	0.000	0.000
Asian	4	0.77 (0.70–0.85)	0.000	0.0%	0.97 (0.94–1.00)	0.045	15.1%	0.84 (0.77–0.90)	0.000	0.0%	0.87 (0.81–0.92)	0.000	0.000
PB	5	0.77 (0.71–0.84)	0.000	0.0%	0.95 (0.92–0.98)	0.002	0.0%	0.85 (0.79–0.91)	0.000	0.0%	0.88 (0.83–0.93)	0.000	0.000
HB	2	0.79 (0.70–0.88)	0.000	0.0%	0.98 (0.95–1.01)	0.118	0.0%	0.84 (0.80–0.89)	0.000	0.0%	0.88 (0.82–0.95)	0.001	0.000

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CI = confidence interval, HB = hospital-based, PB = population-based, RR = relative risk.

4. Discussions

The molecular mechanism of AL (including ALL and AML) is not clear at present. Lan et al[32] found that the levels of single chromosome, trisomy, tetrasomy and SCA in 29 workers exposed to relatively high levels of formaldehyde were higher than those in 23 unexposed workers. The increase of these markers is common in acute myeloid leukemia.

Carlos-wallaceet al[33] performed meta-analysis and uncovered a correlation between household benzene exposure and childhood leukemia. Related studies have shown that these adverse environmental factors are closely related to the occurrence of AL. CYP2B6 enzyme can metabolize and eliminate the activity of some substances, and the decrease of its enzyme activity may result in the inactivation of harmful substances in the environment and excessive accumulation of toxic substances in the body.

Tsuchiya et al[34] found that patients with homozygous (TT) for a specific allele of the *CYP2B6* gene have significantly higher concentrations of Efavirenz. Haas et al[35] found that the negative neurological response of Efavirenz drug in patients was related to the TT genotype, whereas Gounden et al[36] found the blood concentration of Efavirenz in patients with TT type was higher

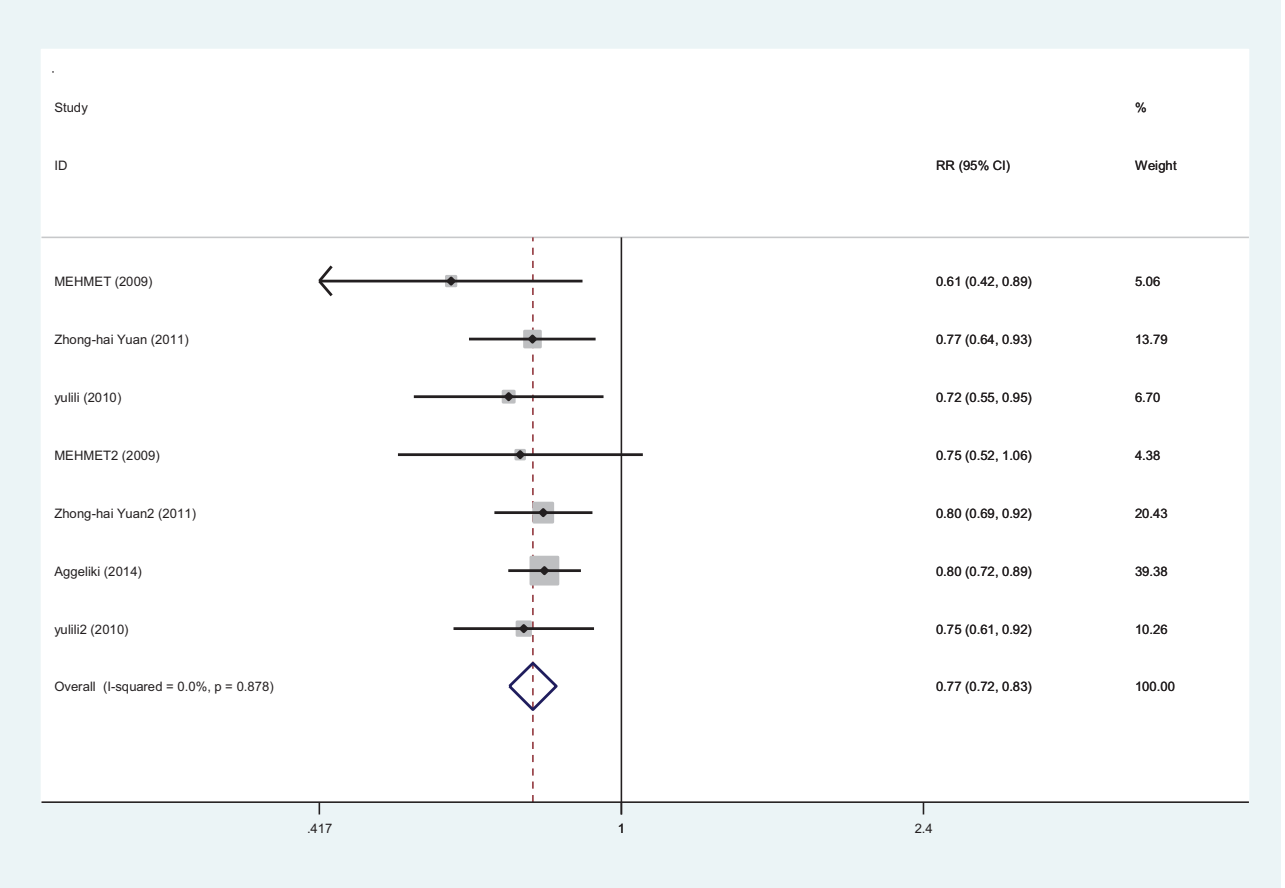

Figure 2. Forest plot showing for the relationship between *CYP2B6* c.516G>T variant and AL under dominant model.

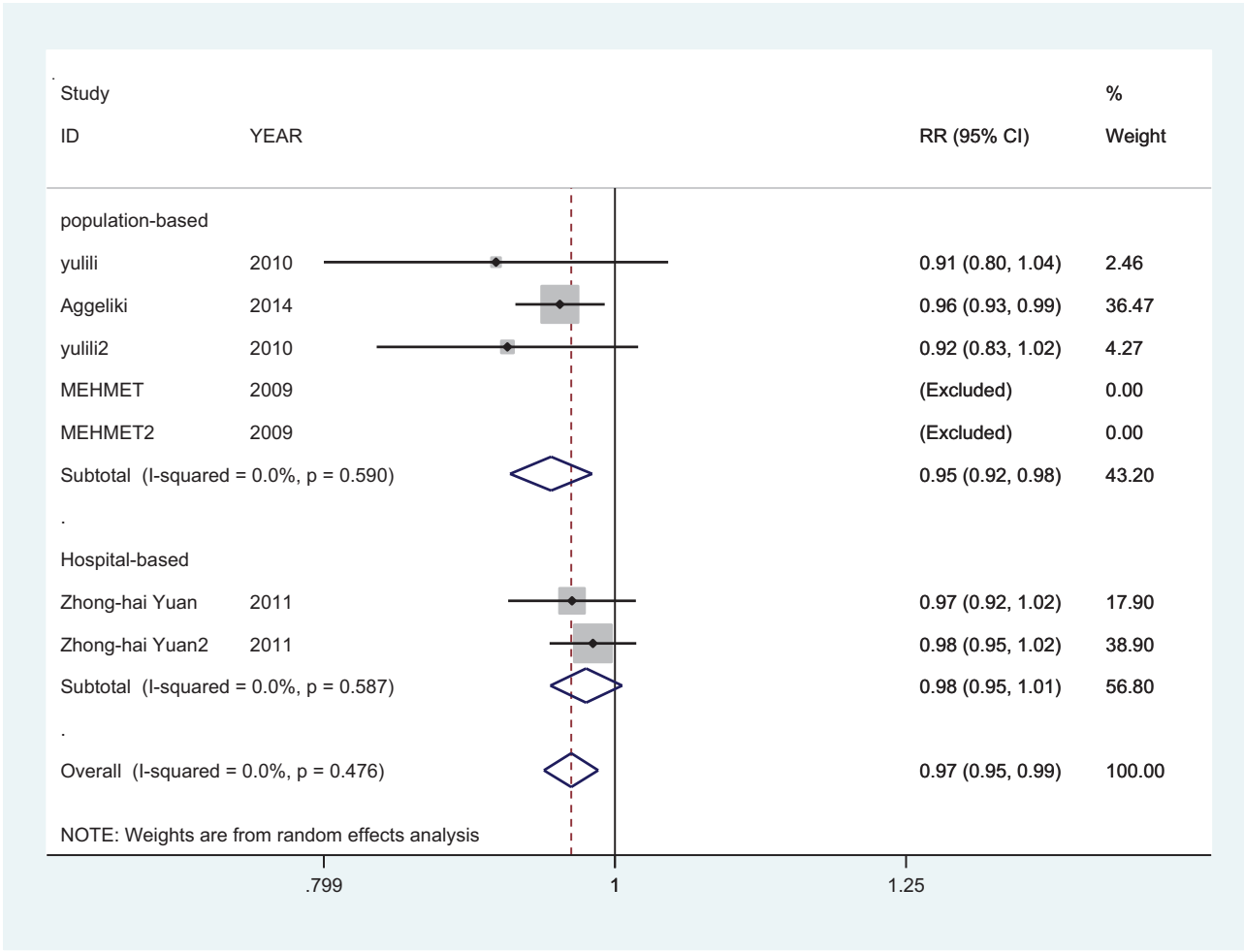

Figure 3. Forest plot showing for the relationship between *CYP2B6* c.516G>T variant and AL under recessive model in the design of HB studies.

than that of GG type in South Africans. The decrease of the clearance rate of TT genotype revealed the decrease of its metabolic ability to the substrate.

In this study, 1038 cases and 1648 controls, was analyzed by meta-analysis. The RR and *P* values of our 4 models were: dominant model: RR = 0.77, 95% CI: 0.72–0.83, *P* = .000; recessive model: RR = 0.97, 95% CI: 0.95–0.99, *P* = .000; homozygote model: RR = 0.84, 95% CI: 0.80–0.89, *P* = .000; allelic model: RR = 0.88, 95% CI: 0.84–0.92, *P* = .000; respectively. The results suggested that the *CYP2B6* c.516 G>T variant is associated with AL. The RR value under dominant model (RR = 0.77) is less than that of Recessive model (RR = 0.97), suggesting that the incidence probability of GG wild type is less than that of GT. In addition, when separating the patients with non-blood-related diseases as a subgroup we didn't find any significant relationship between incidence and gene variant under the Recessive model. Given the fact that there were only 2 studies in the subgroup and the gene distribution in the control group was not in line with HWE balance. High-quality and case control studies are needed to further assess the role of *CYP2B6* gene variant in AL.

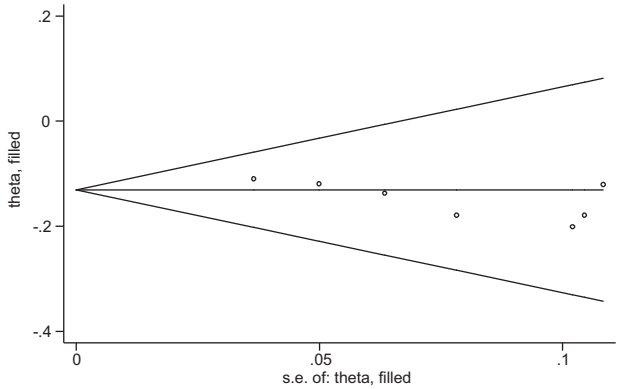

Figure 4. Filled funnel plot with pseudo 95%confidence limit.

Although present meta-analysis elicits some interesting findings, limitations still exist. First, our search was limited to the studies published in English or Chinese, which may lead to a certain level of selection bias duo to the limitation of language. Second, this study did not consider some detailed information of enrolled population, such as sex, age, and diseases. Thirdly, some studies in the control groups were not consistent with HWE, such as Yu's study, which might influence the results. Finally, there are some degrees of publication bias in this meta-analysis, the results of Egger and Begg are different. The reason is not related to publication bias, but to poor methodological quality of smaller studies.

5. Conclusions

In conclusion, our meta-analysis indicated that the *CYP2B6* c.516G>T variant is associated with the occurrence of AL under 4 models. *CYP2B6* c.516 TT, TG genotype was significantly related to an increased risk of AL. However, there were no obvious associations between the risk of AL and *CYP2B6* variants in the design of HB studies based on hospital because of the limitations of the baseline, and few studies were included. In the population with related genotypes, close attention should be paid to environmental contact factors to reduce their susceptibility factors.

Acknowledgment

The authors thank Dr. Lingling Dai, the research fellow at Dana-Farber Cancer Institute of Harvard University for its linguistic assistance during the preparation of this manuscript.

Author contributions

Conceptualization: Xuan Xiong, Hongtao Xiao.
Formal analysis: Dongke Yu.
Funding acquisition: Xuan Xiong, Rongsheng Tong.
Investigation: Qinan Yin, Xiaotao Chen.
Methodology: Xuan Xiong, Qiaoyue Gao, Yuan Zhang.
Project administration: Xuan Xiong, Hongtao Xiao.
Software: Xuan Xiong, Qiaoyue Gao.
Supervision: Rongsheng Tong.
Writing – original draft: Xuan Xiong, Qiaoyue Gao.
Writing – review & editing: Xuan Xiong, Dongke Yu.

References

[1] Wang H, Wang Y, Gao H, et al. Piperlongumine induces apoptosis and autophagy in leukemic cells through targeting the PI3K/Akt/mTOR and p38 signaling pathways. Oncol Lett 2018;15:1423–8.
[2] Organista-Nava J, Gómez-Gómez Y, Illades-Aguiar B, et al. High miR-24 expression is associated with risk of relapse and poor survival in acute leukemia. Oncol Rep 2015;33:1639–49.
[3] Takahashi K, Wang F, Morita K, et al. Integrative genomic analysis of adult mixed phenotype acute leukemia delineates lineage associated molecular subtypes. Nat Commun 2018;9:2670Published 2018 Jul 10.
[4] Zhang YY, Huang SH, Zhou HR, Chen CJ, Tian LH, Shen JZ. Role of HOTAIR in the diagnosis and prognosis of acute leukemia. Oncol Rep 2016;36:3113–22.
[5] Yue Q, Liu X, Chen L, Liu Z, Chen W. T-cell acute lymphoid leukemia resembling Burkitt leukemia cell morphology: A case report. Oncol Lett 2015;9:1236–8.
[6] Shi C, Zhang X, Li X, et al. Effects of microRNA-21 on the biological functions of T-cell acute lymphoblastic lymphoma/leukemia. Oncol Lett 2016;12:4173–80.
[7] Hernandez CP, Morrow K, Lopez-Barcons LA, et al. Pegylated arginase I: a potential therapeutic approach in T-ALL. Blood 2010;115:5214–21.
[8] Moriyama T, Relling MV, Yang JJ. Inherited genetic variation in childhood acute lymphoblastic leukemia. Blood 2015;125:3988–95.
[9] Chaber R, Gurgul A, Wróbel G, et al. Whole-genome DNA methylation characteristics in pediatric precursor B cell acute lymphoblastic leukemia (BCP ALL). PLoS One 2017;12:e0187422Published 2017 Nov 10.
[10] Ye Xiangjun, Gong Xubo,Zhou Sheng. Epidemiology, etiology and clinical characteristics of AML and ALL [EB/OL].(2018.9.16)[2019.10.16]. http://www.8888120.cn/editor/display.php?id=414t4m3341473o3g
[11] Lange BJ, Kobrinsky N, Barnard DR, et al. Distinctive demography, biology, and outcome of acute myeloid leukemia and myelodysplastic syndrome in children with Down syndrome: Children's Cancer Group Studies 2861 and 2891. Blood 1998;91:608–15.
[12] Rafieemehr H, Calhor F, Esfahani H, et al. Risk of acute lymphoblastic leukemia: results of a case-control study. Asian Pac J Cancer Prev 2019;20:2477–83.
[13] Cohen JI, Iwatsuki K, Ko YH, et al. Epstein-Barr virus NK and T cell lymphoproliferative disease: report of a 2018 international meeting. Leuk Lymphoma 2020;61:808–19.
[14] Khalade A, Jaakkola MS, Pukkala E, et al. Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. Environ Health 2010;9:31Published 2010 Jun 28.
[15] Allegra A, Spatari G, Mattioli S, et al. Formaldehyde exposure and acute myeloid leukemia: a review of the literature. Medicina (Kaunas) 2019;55:638.
[16] Lin CK, Hsu YT, Brown KD, et al. Residential exposure to petrochemical industrial complexes and the risk of leukemia: a systematic review and exposure-response meta-analysis. Environ Pollut 2020;258:113476.
[17] Leisch M, Jansko B, Zaborsky N, et al. Next generation sequencing in AML-on the way to becoming a new standard for treatment initiation and/or modulation? Cancers (Basel) 2019;11:252.
[18] Haghi A, Salami M, Mohammadi Kian M, et al. Effects of sorafenib and arsenic trioxide on U937 and KG-1 cell lines: apoptosis or autophagy? Cell J 2020;22:253–62.
[19] Krogstad V, Peric A, Robertsen I, et al. A comparative analysis of cytochrome P450 activities in paired liver and small intestinal samples from patients with obesity. Drug Metab Dispos 2020;48:8–17.
[20] Tornio A, Backman JT. Cytochrome P450 in pharmacogenetics: an update. Adv Pharmacol 2018;83:3–32.
[21] Miksys S, Lerman C, Shields PG, et al. Smoking, alcoholism and genetic polymorphisms alter CYP2B6 levels in human brain. Neuropharmacology 2003;45:122–32.
[22] He Ning. The effects of CYP2B6polymorphism and gender on pharmacokinetics of efavirenz in the healthy subjects [D]. Zhengzhou University, 2013.
[23] Abdullahi ST, Soyinka JO, Olagunju A, et al. Differential Impact of Nevirapine on Artemether-Lumefantrine Pharmacokinetics in Individuals Stratified by CYP2B6 c.516G>T Genotypes. Antimicrob Agents Chemother 2020;64:e00947–1019.
[24] Den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum Mutat 2016;37:564–9.
[25] Wang PF, Neiner A, Kharasch ED. Efavirenz Metabolism: Influence of Polymorphic CYP2B6 Variants and Stereochemistry [published correction appears in Drug Metab Dispos. Drug Metab Dispos 2019;47:1195–205.
[26] Abdullahi ST, Soyinka JO, Olagunju A, et al. Differential impact of nevirapine on artemether-lumefantrine pharmacokinetics in individuals stratified by CYP2B6 c.516G>T genotypes. Antimicrob Agents Chemother 2020;64:e00947-19Published 2020 Feb 21.
[27] Cooper H, Hedges LV, Valentine JC. The Handbook of Research Synthesis and Meta-analysis. New York: Russell Sage Foundation; 2009.
[28] Berköz M, Yalin S. Association of CYP2B6 G15631T polymorphism with acute leukemia susceptibility. Leuk Res 2009;33:919–23.
[29] Yuan ZH, Liu Q, Zhang Y, et al. CYP2B6 gene single nucleotide polymorphisms and leukemia susceptibility. Ann Hematol 2011;90:293–9.
[30] Yu LL. Association of CYO2B6 polymorphism with acute leukemia. Lanzhou: Lanzhou university; 2010.
[31] Daraki A, Zachaki S, Koromila T, et al. The $G^{516}T$ CYP2B6 germline polymorphism affects the risk of acute myeloid leukemia and is associated with specific chromosomal abnormalities. PLoS One 2014;9:e88879.
[32] Lan Q, Smith MT, Tang X, et al. Chromosome-wide aneuploidy study of cultured circulating myeloid progenitor cells from workers occupationally exposed to formaldehyde. Carcinogenesis 2015;36:160–7.
[33] Carlos-Wallace FM, Zhang L, Smith MT, et al. Parental, in utero, and early-life exposure to benzene and the risk of childhood leukemia: a meta-analysis. Am J Epidemiol 2016;183:1–14.
[34] Tsuchiya K, Gatanaga H, Tachikawa N, et al. Homozygous CYP2B6 *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. Biochem Biophys Res Commun 2004;319:1322–6.
[35] Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: An Adult AIDS Clinical Trials Group study. AIDS 2004;18:2391–400.
[36] Gounden V, van Niekerk C, Snyman T, et al. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. AIDS Res Ther 2010;7:32.