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Relationship between NAT2 polymorphisms and onset risk of acute leukemia: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This meta-analysis aims to clarify the correlation between N-acetyltransferases 2 (NAT2) polymorphisms and susceptibility of acute leukemia.

MATERIALS AND METHODS: Articles reporting the correlation between NAT2 polymorphisms and susceptibility of acute leukemia were searched from PubMed, Embase, and Cochrane. Citations in eligible articles were manually reviewed. Only cohort studies and case-control studies which provided odds ratio (OR) and 95% confidence interval (CI) of the correlation between NAT2 polymorphisms and susceptibility of acute leukemia up to December 1st, 2018 were enrolled. The included data were weighted by an inverse variance and analyzed using the fixed-effects or random-effects model. The data acquisition and the heterogeneity test were conducted. STATA 12.0 was used for statistical analysis.

RESULTS: This meta-analysis enrolled 10 independent case-control studies with 1,874 leukemia patients and 2,789 healthy volunteers. No significant difference was found between the fast-acetylator incidence of NAT2 haplotype and the onset risk of acute lymphoblastic leukemia (ALL, OR=0.70, 95% CI=0.45-1.08) or acute myeloid leukemia (AML, OR=0.79, 95% CI=0.46-1.47). The subgroup analysis was conducted based on the sources of controls (SOCs). We did not find statistical difference in population-based (PB) group (OR=0.82, 95% CI=0.47-1.42) and hospital-based (HB) group (OR=0.54, 95% CI=0.27-1.08). In addition, the fast-acetylator incidence of NAT2 haplotype was only observed to be higher in ALL patients compared with HB group (OR=0.52, 95% CI=0.33-0.83), rather than the PB group (OR=0.82, 95% CI=0.47-1.44).

CONCLUSIONS: Except for ALL patients and those hospital-based controls, no evidence has shown the relationship between NAT2 polymorphisms and the susceptibility of acute leukemia. This conclusion still needs to be further verified in multi-center hospital with a large sample size.

Key Words:
NAT2 polymorphisms, Onset risk, Acute leukemia, Meta-analysis.

Introduction

Leukemia is one of the top ten tumors in China and its mortality accounts for 10% in adult tumor death. In recent years, the incidence of leukemia has strikingly increased because of the exposure to environmental pollution[1-3]. The etiology and pathogenesis of leukemia have not been completely elucidated. Generally, it is believed that leukemia results from both genetic and environmental factors[4-6]. Environmental exposure that injuries bone marrow hematopoietic stem cells have been identified to be closely related to leukemia, such as radiation, benzene, and certain biological factors[7-9]. In addition, the incidence of leukemia varies a lot even in people exposed to the same environmental risk factors, due to individually genetic difference, that is, the polymorphism of the environmental response genes[10]. Genetic susceptibility is mainly related to exogenous compound metabolic enzyme genes, toxicant receptor genes, DNA repair genes, etc[10,11]. These genes have multiple single nucleotide polymorphisms (SNPs) sites, and the differences in SNPs lead to different activities of the gene productions[11]. Therefore, the explorations on SNPs of genetic susceptibility genes have great values in disease prevention and treatment.

N-acetyltransferases (NAT) belong to the phase II metabolic enzymes of the exogenous compound metabolizing enzymes. NAT catalyzes the acetylation of the electrophilic groups with the electrophilic groups that are catalyzed by phase I metabolic enzymes. The detoxification of various carcinogens, aromatic amines, and

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heterocyclic amines in tobacco relies on NAT enzyme-mediated N-acetylation pathway[12,13]. NAT2 exerts the protein-encoding function with evident genetic polymorphisms. It has been widely concerned in recent years[13-15]. NAT2 is located in the 8p21.3-23.1 and contains an open reading frame of 870 bp to encode a 290 amino acid protein[12,15]. The encoded protein by NAT2 has the effect of N-acetylation or O-acetylation on the exogenous compound, thereby enhancing its water solubility to detoxify[16,17]. G/A polymorphism at nucleotide position 590 (rsl799930) of the NAT2 gene coding region leads to the change of Arg/Gln at position 197. It further leads to the alterations in the structure and acetylation ability of NAT2, thereafter influencing the individual's susceptibility to tumors[17].

To date, many studies reported the relationship between NAT2 gene polymorphisms and the onset risk of acute leukemia[18,19]. Compared with people with low activity of NAT2, some reports believed that those with high activity of NAT2 present lower onset risk of leukemia[20-22]. However, the results are still inconsistent and even opposite. This study aims to clarify the potential relationship between them.

Materials and Methods

Literature Search

The articles reporting the correlation between NAT2 polymorphism and susceptibility of acute leukemia were searched from PubMed, Embase, and Cochrane by December 1st, 2018. "N-acetyltransferase-2" or "NAT2", "single nucleotide polymorphism" or "variants", or "polymorphism", and "leukemia" were used as keywords. Eligible case-control or cohort studies were reviewed, including their citations. There were no limitations on the year and region of publication. Citations in each eligible study were manually double-checked to avoid missing as much as possible, and any disagreement was solved by the third reviewer. The latest and more comprehensive articles were selected if overlapping.

Inclusion and Exclusion Criteria

Published articles on exploring the correlation between NAT2 polymorphisms and susceptibility of leukemia were enrolled. The inclusion criteria were applied as follows: (1) Independent case-control studies; (2) Explorations on the correlation between NAT2 polymorphisms and susceptibility of leukemia; and (3) Odds ratio (OR) and 95% confidence interval (CI) or relative data that could be used to calculate OR were provided.

The exclusion criteria were applied as follows: (1) Non-case-control studies; (2) Retrospective studies; (3) Raw data on the correlation between NAT2 polymorphisms and susceptibility of leukemia were not provided; (4) Repeated published and low-quality articles. Review or abstract were excluded.

Data Extraction

Baseline data acquisition included: first author, study type (cohort, case-control, prospective, or retrospective study), sample size, year of publication, region, confounding factors, OR and 95% CI. Data acquisition was independently carried out by two reviewers using accurate data acquisition table, and a third reviewer was responsible for re-evaluating the disagreements from the previous two reviewers.

Statistical Analysis

OR and 95% CI were calculated to assess the strength of the association between NAT2 polymorphism and the onset risk of leukemia. Fixed-effect model (Mantel-Haenszel method) was used when $p<0.05$. Otherwise, the random-effects model (Dersimonian-Laird method) was used. The subgroup analysis was conducted to explore the potential sources of heterogeneity based on ethnic and control sources. The sensitivity analysis reflects the stability and reliability of the results by removing one individual study each time and recalculating their ORs. Begg's funnel plot and Egger regression test were utilized for evaluating the publication bias. The statistical analysis was performed using Stata software (version 12.0, Stata Corporation, College Station, TX, USA). $p<0.05$ was considered as statistically significant.

Results

Characteristics of the Studies

This meta-analysis enrolled 10 independent case-control studies with 1,874 leukemia patients and 2,789 healthy volunteers[20-29]. The characteristics of the enrolled studies and the genotype distributions were detailed in Table I. The article search and the selection process were detailed in Figure 1. Among the selected articles, 8 studies were conducted in Caucasians, only

Table I. Characteristics of studies that investigated the association between NAT2 polymorphisms and risk of acute leukemia.

Author	Year	Country	Ethnicity	SOC	Genotyping methods	Tumor typing	No. of case	No. of control	Frequency of NAT2 haplotypes, No. of case		Frequency of NAT2 haplotypes, No. of control	
									Rapid	Slow	Rapid	Slow
Hernández-González et al	2017	Mexico	Caucasian	PB	Taqman	ALL	110	384	11	99	81	303
Kamel et al	2015	Egypt	African	HB	PCR-RFLP	ALL	93	205	8	85	23	182
Silveira et al	2012	Brazil	Mixed	HB	PCR-RFLP	ALL	186	361	11	175	27	334
Bonaventure et al	2012	France	Caucasian	PB	PCR-RFLP	ALL, AML	493	455	99	394	95	360
Zanrosso et al	2011	Brazil	Caucasian	HB	PCR-RFLP	ALL, AML	410	511	62	348	162	349
Ouerhani et al	2011	Tunisian	Caucasian	PB	PCR-RFLP	ALL	193	309	68	125	74	235
Zanrosso et al	2010	Brazil	Caucasian	HB	PCR-RFLP	ALL, AML	74	36	14	60	28	8
Müller et al	2008	Germany	Caucasian	HB	PCR-RFLP	AML	75	109	29	46	40	69
Krajinovic et al	2000	Canada	Caucasian	PB	PCR-RFLP	ALL	176	291	68	108	153	138

SOC: Source of controls; PB: Population-based controls; HB: Hospital-based controls. Rapid acetylation: NAT1*4, *11A, *12A, *12B, *12C, *13A; Slow acetylation: non-NAT1*4, *11A, *12A, *12B, *12C, *13A. ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia.

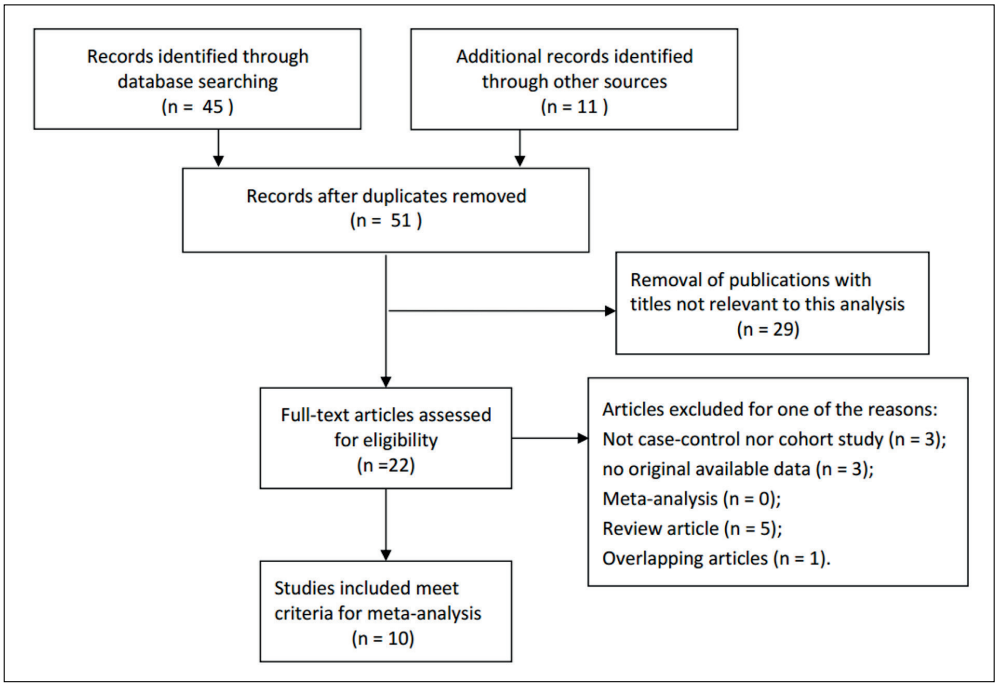

Figure 1. Flow diagram of literature search and selection process.

one study was conducted in Asian populations, and the remaining one was conducted in mixed population. 4 population-based (PB) studies and 6 hospital-based (HB) studies were utilized to distinguish different sources of controls (SOCs). The genotype determination was performed by TaqMan SNP and PCR-RFLP.

Quantitative Synthesis Results

Generally speaking, the fast-acetylator incidence of NAT2 haplotype was not associated with the onset risk of leukemia (OR=0.65, 95% CI=0.42-1.01). Next, we subdivided the pathological types of leukemia cases into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). No significant difference was found between the fast-acetylator incidence of NAT2 haplotype and onset risk of ALL (OR=0.70, 95% CI=0.45-1.08) or AML (OR=0.79, 95% CI=0.46-1.47) (Figure 2). The subgroup analyses were conducted based on the sources of controls. We did not find statistical difference in the PB group (OR=0.82, 95% CI=0.47-1.42) and HB group (OR=0.54, 95% CI=0.27-1.08) (Figure 3A).

ALL

In the random-effects model, 6 articles on the correlation between NAT2 polymorphisms and susceptibility of ALL did not show their correlation (OR=0.70, 95% CI=0.45-1.08). In addition, fast-acetylator incidence of NAT2 haplotype was only observed to be higher in ALL patients com-

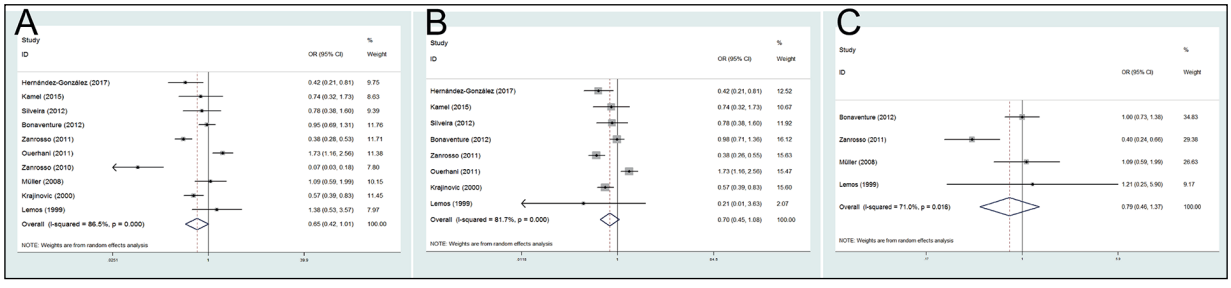

Figure 2. Forest plots of the association between NAT2 polymorphism and leukemia susceptibility in random-effects model.

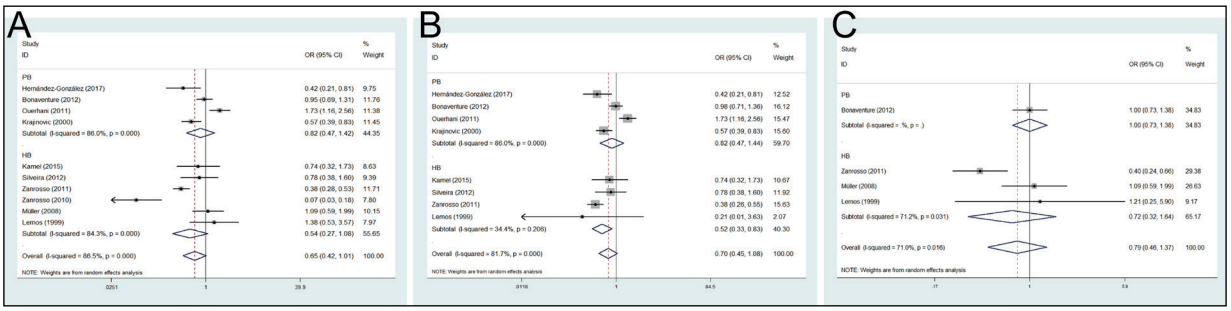

Figure 3. Forest plots of subgroup analysis by source of controls of the association between NAT2 polymorphism and leukemia susceptibility in random-effects model.

pared with HB controls (OR=0.52, 95% CI=0.33-0.83), rather than the PB group (OR=0.82, 95% CI=0.47-1.44) (Figure 3B).

AML

Fast-acetylator incidence of NAT2 haplotype was not associated with susceptibility of AML (OR=0.79, 95% CI=0.46-1.47). The subgroup analysis revealed no statistical difference either in HB group (pooled OR=0.72, 95% CI=0.32-1.64) or PB group (pooled OR=1.00, 95% CI=0.73-1.38) (Figure 3C).

Sensitivity Analysis

The sensitivity analysis was performed by reviewing each study and OR was re-calculated through regression analysis. As Figure 4 illustrated, the sensitivity analysis indicated no significant effect of the combined OR on the study conclusions. We believed that our meta-analysis results were robust and stable.

Publication Bias

Begg's funnel plot and Egger test were used to examine the publication bias of all data. Symmetrically distributed, the Funnel plot indicated that there was no remarkable publication bias in this study. Egger test further confirmed our conclusion (total: p=0.884; ALL: p=0.922; AML: p=0.872) (Figure 5).

Discussion

NAT2 is an oncogenic metabolic gene, which is able to detoxify aromatic and heterocyclic amines and their metabolites[13]. NAT2 exerts high polymorphism, and its genetic variation alters drug toxicity and tumor risk because of the imbalanced biological activity and detoxification[12,15]. NAT2 acetylated genotype is crucial in cancer susceptibility. Variant alleles in NAT2 are indicated to slow down the elimination of the oncogenic amines[15]. Several NAT2 gene variants have been identified, and among them, NAT2*4 is considered to be the most common allele involved in fast acetylation[16,17]. Previous studies[18,23,24] have indicated that fast-acetylator genotype of NAT2 leads to an increased risk of colon, bladder, and leukemia. However, slow-acetylator genotype of NAT2 decreases the colon cancer risk and increases the bladder cancer risk[23,24].

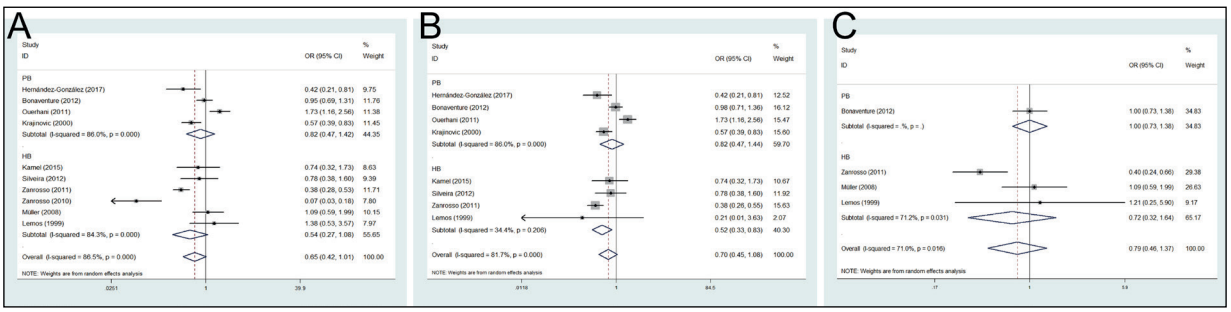

Figure 3. Forest plots of subgroup analysis by source of controls of the association between NAT2 polymorphism and leukemia susceptibility in random-effects model.

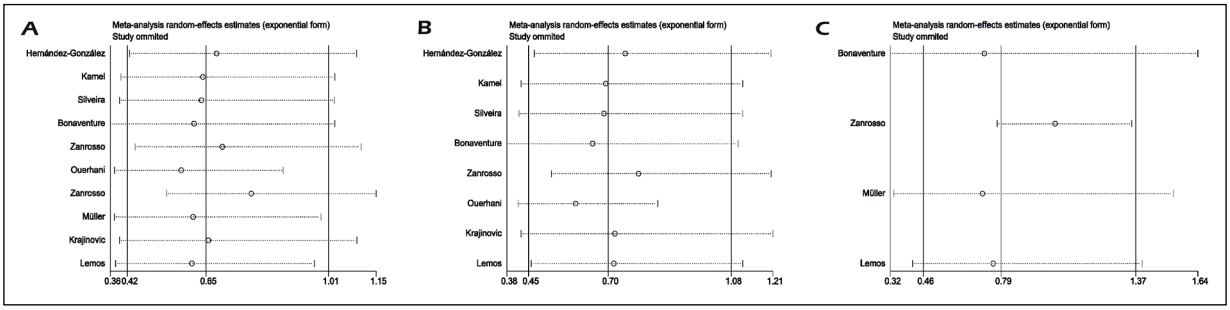

Figure 4. Sensitivity analysis in fixed model. **A,** All studies. **B,** Acute lymphoblastic leukemia. **C,** Acute myeloid leukemia.

The role of NAT2 in the etiology of leukemia has been widely explored, whereas the conclusions were controversial[20-22,25-31]. A relevant study conducted by Hernandez-Gonzalez et al[20] indicated that the slow-acetylator genotype of NAT2 increases the risk of leukemia in Japanese patients, especially in smokers. Kamel et al[21] demonstrated that the slow-acetylator genotype of NAT2 may elevate the risks of all types of childhood leukemia[21]. Silveira et al[22] pointed out that fast-acetylator genotype of NAT2 is associated with leukemia in tobacco users.

The meta-analysis contributes to make the conclusion more credible than individual studies, especially in unexplained associations[32,33]. Based on different subgroup analyses, we had a more comprehensive understanding of the relationship between fast-acetylator genotype of NAT2 and the onset risk of leukemia. In this work, a total of 10 independent case-control studies reporting 1,874 leukemia patients and 2,789 healthy volunteers were analyzed[20-22,25-31]. Our results indicated that the fast-acetylator incidence of NAT2 was not correlated to the onset risk of leukemia. Such a contradiction may be explained by various factors, including sample size difference, genotyping method, research design, and statistical methods. The subgroup analyses were then conducted based on different sources of controls. The correlation was still not observed either in the PB group or in the HB group. The onset risk of leukemia varies in different individuals, which may affect the quality of the study.

It is worth noting that we have included large-scale studies to fully explain the impact of NAT2 polymorphism on leukemia risk. The following limitations, however, should be considered. First of all, relatively small sample size in each stratified analysis may limit the statistical power. Secondly, leukemia is a multifactorial disease involving both environmental and genetic factors. Further researches are needed to explore the potential genetic factors on influencing the susceptibility of leukemia. Thirdly, the incidence of leukemia varies a lot in different ethnicities. In our study, Caucasians accounted for the majority of research subjects and the conclusion may be influenced by the subgroup analysis based on ethnicities. Large-scale case-control or prospective

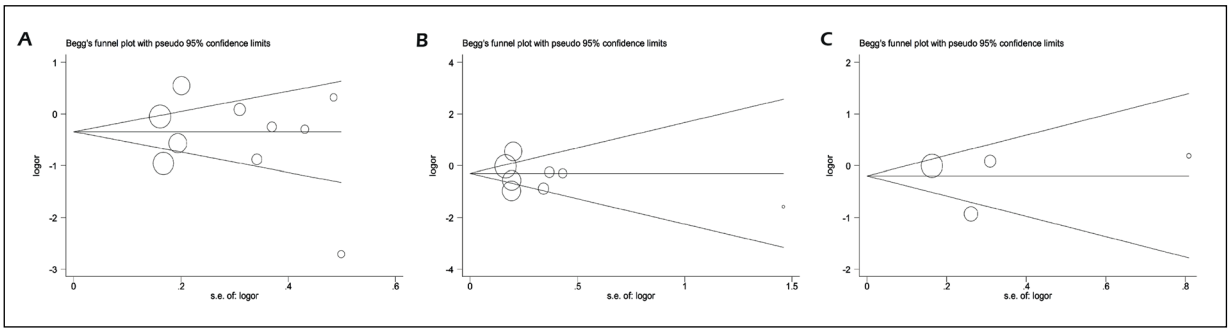

Figure 5. Begg's funnel plot of publication bias test. **A,** All studies. **B,** Acute lymphoblastic leukemia. **C,** Acute myeloid leukemia.

study in different ethnic groups are required for further verification. At the same time, the potential influences of gene-environment interaction should be taken into consideration as well.

Conclusions

Except for hospital based ALL patients, no evidence has shown the correlation between NAT2 polymorphisms and the susceptibility of acute leukemia. This conclusion still needs to be further verified in multi-center hospital with a large sample size.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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