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Review Article

MTRR A66G polymorphism and non-Hodgkin lymphoma risk: a meta-analysis

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Abstract: Background: Several studies have explored the relationship between methionine synthase reductase (*MTRR*) A66G polymorphism and non-Hodgkin lymphoma (NHL) risk, however, the published results were controversial. Thus, a meta-analysis was performed to provide a more precise estimate of the association of *MTRR* A66G polymorphism with NHL risk. Methods: The PubMed, Elsevier, China National Knowledge Infrastructure and Wanfang Databases were searched (up to February 01, 2015) to collect case-control studies investigating the relationship between *MTRR* A66G polymorphism and NHL risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were applied to assess the strength of association. Results: Finally, five case-control studies, bearing 1357 cases and 3374 controls, were included in this meta-analysis. The results of overall comparisons suggested that there was no significant association between *MTRR* A66G polymorphism and NHL risk under all four genetic models (AG vs. AA: OR=0.97, 95% CI=0.84-1.11, P=0.65; GG vs. AA: OR=1.06, 95% CI=0.85-1.31, P=0.62; GG vs. AA+AG: OR=1.02, 95% CI=0.85-1.23, P=0.84; AG+GG vs. AA: OR=0.99, 95% CI=0.87-1.13, P=0.90). In the subgroup analyses by ethnicity and NHL subtype, significant association was found in Asians (GG vs. AA: OR=1.32, 95% CI=1.01-1.72, P=0.04; GG vs. AA+AG: OR=1.34, 95% CI=1.03-1.73, P=0.03) and diffuse large B-cell lymphoma (DLBCL) in overall population (GG vs. AA: OR=1.46, 95% CI=1.05-2.03, P=0.02; GG vs. AA+AG: OR=1.46, 95% CI=1.06-2.00, P=0.02). Conclusion: The present meta-analysis suggested that *MTRR* A66G polymorphism was associated with an increased risk for NHL in Asian populations and for DLBCL in whole population. Further well-designed studies based on larger sample sizes are required to confirm these findings.

Keywords: Methionine synthase reductase, polymorphism, non-Hodgkin lymphoma, meta-analysis

Introduction

Non-Hodgkin lymphoma (NHL) is a complex group of heterogeneous disease containing multiple subtypes, each with specific morphologic, immunophenotypic and clinical characteristics [1]. NHLs can be broadly divided into two major groups: B-cell lymphomas and T-cell lymphomas, and each of these can be further classified based on clinical features, pathology, histology and genetic indicators [2]. Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma are the two major subtypes of B-cell lymphomas, which make up approximately 85% of all NHL cases. The incidence of NHL has increased steadily in the last few decades [3]. It was estimated that 70,800 NHL patients were newly diagnosed and 18,990 deaths were occurred in 2014 in the United States [4]. However, the etiology of NHL remains largely unknown [5, 6]. Environmental exposure to some chemicals, family history, dietary factors, immune dysfunction, and viral infection, have all been associated with the risk for NHL [7, 8]. In addition, individual genetic susceptibility may also play an important role in the pathogenesis of NHL as the host polymorphisms may modify the individual's ability to maintain an intact genome in face of genotoxic stress. Genetic variants could also interact with exogenous exposures and contribute to lymphomagenesis [9-11]. Moreover, studies have showed that deficiencies in one-carbon metabolizing nutrients (e.g., folate, vitamin B12 and methionine) can lead to impaired immune responses, and various immune deficiencies are well-established risk factors for NHL [12-14]. Increasing studies suggest that genetic polymorphisms in

genes encoding folate-metabolizing enzymes may cause interindividual differences and have been associated with the risk of malignant lymphoma [15-17].

Folate metabolism network not only provides essential cofactors in the production of primary methyl donor for DNA methylation, it also supplies the methyl group for DNA synthesis [18, 19]. Folate metabolism is regulated by folate-metabolizing pathway genes. Methionine synthase (MTR) is one of the most critical enzymes involved in folate metabolism, which is responsible for synthesis of methionine through irreversible transfer of a methyl group from 5-methyltetrahydrofolate. The enzymatic active form of MTR is maintained by methionine synthase reductase (MTRR), an enzyme that regenerates functional MTR by reductive methylation [20]. The A66G polymorphism at codon 22 is the most common functional polymorphism in *MTRR* and the variant enzyme has a lower affinity for MTR [21, 22]. Changes in MTRR activity may significantly influence DNA methylation and synthesis, and altered DNA synthesis and methylation have been linked to human cancer risk, including lymphoma [23, 24]. *MTRR* A66G polymorphism has been widely investigated in a variety of diseases, such as Down syndrome, breast cancer, and leukemia [25-27]. Several studies have focused on the relationship between this polymorphism and NHL risk, but the published results remain controversial. The discrepancies among investigations may be ascribed to the relatively small sample size in each study and ethnicity difference. Therefore, we performed a meta-analysis to provide a more precise evaluation of the association of *MTRR* A66G polymorphism with NHL risk.

Materials and methods

Studies identification

A systematic literature search in the PubMed, Elsevier, China National Knowledge Infrastructure platform and Wanfang databases was conducted to identify studies that explored the relationship between *MTRR* A66G polymorphism and NHL risk. The search terms and keywords were as follows: "methionine synthase reductase" or "*MTRR*", "polymorphism" or "variant" or "variation", and "NHL" or "non-Hodgkin lymphoma" or "non-Hodgkin's lymphoma". There were no restriction to the language and the latest search was undertaken on February 01, 2015. The references cited in the eligible studies were also examined to find additional studies.

Inclusion criteria

All studies included in this meta-analysis must have met the following criteria: (a) case-control studies assessing the relationship between *MTRR* A66G polymorphism and NHL risk; (b) the case group had confirmed diagnosis; (c) genotype frequencies for both cases and controls were available; (d) the distribution of genotypes in the control group was in consistent with Hardy-Weinberg equilibrium (HWE). The case reports, meta-analysis, reviews, letters and editorial articles were excluded.

Data extraction

Two reviewers independently extracted information from each eligibility study and disagreement was addressed by discussion. The following data were extracted from each study: first author's name, year of publication, country, ethnicity, controls source, genotyping methods, sample size of cases and controls, genotype frequencies of the *MTRR* A66G polymorphism for cases and controls, and HWE of control group.

Statistical analysis

The strength of association between *MTRR* A66G polymorphism and NHL risk was assessed by odds ratios (ORs) with corresponding 95% confidence intervals (CIs) under the heterozygote model (AG vs. AA), homozygote model (GG vs. AA), recessive model (GG vs. AA+AG) and dominant model (AG+GG vs. AA). The significance of combined OR was determined by the *Z*-test. The Q-test was used to evaluate the between-study heterogeneity. If $P>0.05$, indicating that there was no significant heterogeneity, the fixed-effects model (Mantel-Haenszel) was applied to combine the data, otherwise, the random-effects model (DerSimonian-Laird) was selected. Subgroup analyses were performed according to ethnicity and NHL subtype. Funnel plot was applied to evaluate publication bias. HWE of genotypes distribution in the control group was checked using the χ^2-test and $P<0.05$ was designated as deviations from HWE. All the tests were two-sided and $P<0.05$ was considered as statistically significant. The data analyses were performed using the soft-

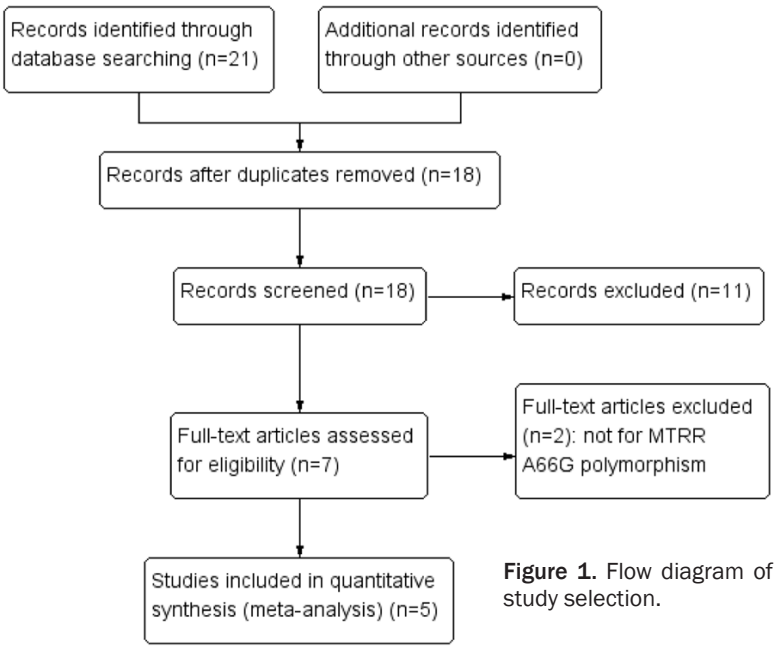

Figure 1. Flow diagram of study selection.

ware STATA v12.0 (Stata Corporation, College Station, TX) and Review Manager v5.2 (The Cochrane Collaboration, Oxford, UK).

Results

Study characteristics

A flow diagram showing the process of study selection was illustrated in **Figure 1**. According to the literature search strategy, a total of 18 potentially relevant publications were identified. 11 articles were excluded firstly because of irrelevant research; under the included criteria, two studies were excluded as not for *MTRR* A66G polymorphism research [28, 29]. Finally, five case-control studies were included in this meta-analysis, bearing 1357 cases and 3374 controls [30-34]. Among these publications, there were three studies for Caucasians [30-32], two studies for Asians [33, 34]. The controls were healthy populations and blood bank donors and mainly matched for age, gender and ethnicity. Genotypes distribution in the controls of all included studies were in consistent with HWE. **Table 1** showed the detailed characteristics of included studies.

Meta-analysis results

The main results of meta-analysis and heterogeneity test were listed in **Table 2**. As shown in **Table 2**, there was no significant heterogeneity among the included studies in overall populations (P_h=1.00, I^2=0%; P_h=0.13, I^2=44%; P_h=0.05, I^2=57% and P_h=0.91, I^2=0% for heterogeneity test of AG vs. AA, GG vs. AA, GG vs. AA+AG and AG+GG vs. AA, respectively), in which case the fixed-effects model was applied to combine the ORs and 95% CIs. The combined results suggested that there was no significant association between *MTRR* A66G polymorphism and NHL risk in overall comparisons under all four genetic models (AG vs. AA: OR=0.97, 95% CI=0.84-1.11, P=0.65; GG vs. AA: OR=1.06, 95% CI=0.85-1.31, P=0.62; GG vs. AA+AG: OR=1.02, 95% CI=0.85-1.23, P=0.84; AG+GG vs. AA: OR=0.99, 95% CI=0.87-1.13, P=0.90) (**Table 2**). In the subgroup analyses by ethnicity and NHL subtype, *MTRR* A66G polymorphism was significantly associated with an increased risk for NHL in Asian populations (GG vs. AA: OR=1.32, 95% CI=1.01-1.72, P=0.04; GG vs. AA+AG: OR=1.34, 95% CI=1.03-1.73, P=0.03), and for DLBCL in whole population (GG vs. AA: OR=1.46, 95% CI=1.05-2.03, P=0.02; GG vs. AA+AG: OR=1.46, 95% CI=1.06-2.00, P=0.02) (**Table 2**).

Publication bias

Funnel plots were applied to assess the publication bias in the overall meta-analysis and the results showed that all points were symmetrically distributed and the shape of funnel plots revealed no obvious asymmetry, suggesting the absence of publication bias (**Figure 2**).

Discussion

Human *MTRR* is a housekeeping gene and locates at chromosome 5 (5p15.2-p15.3) [35]. MTRR enzyme is responsible for the regeneration of the active form of MTR by reductive methylation and plays a key role in folate and vitamin B12-dependent homocysteine metabolism [36]. The enzyme has three characteristic sites which bind FMN, FAD, and NADPH. The most common polymorphism in *MTRR* is A66G

Table 1. Main characteristics of studies included in the meta-analysis

Reference	Year	Country	Ethnicity	Control source	Genotyping method	Sample size		Case			Control			HWE	Quality score
						Case	Control	AA	AG	GG	AA	AG	GG		
Gemmati [30]	2004	Italy	Caucasian	Blood donor	PCR-RFLP	200	257	51	106	43	59	122	76	0.46	8
Gra [31]	2008	Russia	Caucasian	Blood donor	Biochip	76	177	16	40	20	33	92	52	0.49	7
Kim [33]	2008	Korea	Asian	Population-based	Pyrosequencing	584	1700	292	235	57	857	718	125	0.13	9
Suthandiram [34]	2015	Malaysia	Asian	Blood donor	Sequenom MassARRAY	372	722	178	153	41	353	306	63	0.77	7
Weiner [32]	2011	Russia	Caucasian	Blood donor	Real-time PCR	125	518	26	64	35	97	259	162	0.72	9

HWE, Hardy-Weinberg equilibrium; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

Table 2. Results of meta-analysis for methionine synthase reductase (*MTRR*) A66G polymorphism and NHL risk

Variables	No.	AG vs. AA			GG vs. AA			GG vs. AA+AG			AG+GG vs. AA		
		OR (95% CI)	*P*	P_h*	OR (95% CI)	*P*	P_h*	OR (95% CI)	*P*	P_h*	OR (95% CI)	*P*	P_h*
Overall	5	0.97 (0.84-1.11)	0.65	1.00	1.06 (0.85-1.31)	0.62	0.13	1.02 (0.85-1.23)	0.84	0.05	0.99 (0.87-1.13)	0.90	0.91
Ethnicity													
Asian	2	0.97 (0.83-1.14)	0.72	0.85	1.32 (1.01-1.72)	0.04	0.90	1.34 (1.03-1.73)	0.03	0.85	1.03 (0.88-1.19)	0.74	0.87
Caucasian	3	0.95 (0.70-1.30)	0.76	0.95	0.73 (0.52-1.04)	0.08	0.85	0.77 (0.58-1.01)	0.06	0.63	0.87 (0.65-1.16)	0.35	1.00
Subtype													
DLBCL	2	1.01 (0.83-1.24)	0.91	0.35	1.46 (1.05-2.03)	0.02	0.41	1.46 (1.06-2.00)	0.02	0.56	1.08 (0.89-1.31)	0.42	0.30
T-cell NHL	2	0.99 (0.70-1.38)	0.94	0.76	0.97 (0.57-1.65)	0.91	0.50	0.97 (0.62-1.52)	0.89	0.54	0.99 (0.72-1.37)	0.95	0.64

DLBCL, diffuse large B-cell lymphoma; No. number of studies; P_h value used to test the heterogeneity; *If P_h>0.05, the fixed-effects model was applied to combine the data, otherwise, the random-effects model was selected.

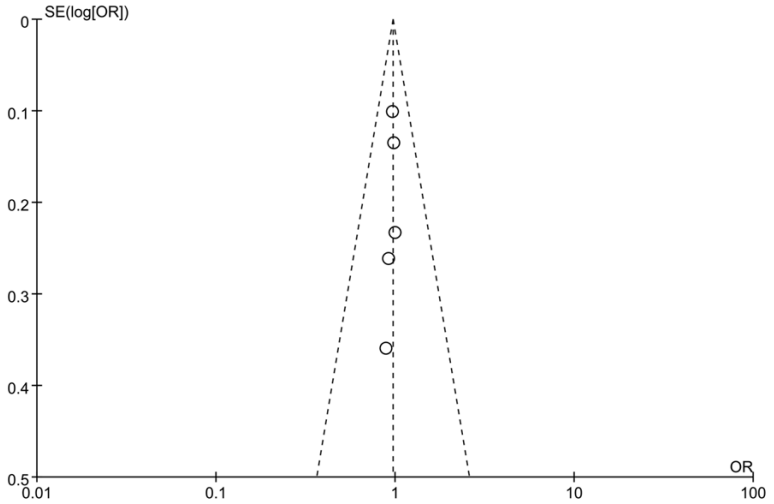

Figure 2. Funnel plot for publication bias test under heterozygote model (AG vs. AA). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of odds ratio.

substitution, which results in an amino acid substitution from isoleucine to methionine at codon 22 (I22M). The I22M variant is located in the putative FMN-binding domain of the MTRR enzyme that is suggested to interact with MTR. Substitution of an isoleucine by a methionine in this part of the enzyme might disrupt the binding of MTRR to the MTR-cob(I) alanine-complex, thereby decreasing the rate of homocysteine remethylation [22, 37]. The variant enzyme has a 3- to 4-fold lower affinity for MTR [21]. Thus, DNA methylation and synthesis may be influenced by alterations in this enzyme activity, which lead to tumorigenesis. Some studies have investigated the association between the *MTRR* A66G polymorphism and risk of cancers. This polymorphism has been associated with a decreased risk for acute lymphoblastic leukemia [27], and an increased risk for adult meningioma [38]. However, there are controversial findings about the role of *MTRR* A66G polymorphism in the development risk of NHL. Weiner et al. [32] found that the genotype frequencies of *MTRR* A66G polymorphism in NHL patients were similar to those in the controls, suggesting a lack of association between this variant and NHL risk. While the *MTRR* 66GG genotype was associated with increased risk for DLBCL (OR=1.56, 95% CI=1.03-2.38) in study reported by Kim et al. [33].

To investigate the effect of *MTRR* A66G polymorphism on NHL risk through a more robust analysis, a meta-analysis of five case-control studies was carried out. By pooling five studies with 1357 cases and 3374 controls, the present meta-analysis suggested that there was no significant association between *MTRR* A66G polymorphism and NHL risk in overall comparisons under all four genetic models. The subgroup analysis by ethnicity revealed that significant association only existed in Asian populations, but not in Caucasians. The racial differences in NHL incidence could partly be attributed to differences in genotype frequencies between different populations at *MTRR* loci. In the subgroup analysis according to NHL subtype, significant association was found in DLBCL under homozygote model and recessive model, but not in T-cell lymphomas in any comparison models, which may be explained that the effect of genetic polymorphisms on cancer risk is various to different clinical subtypes.

However, some limitations need to be addressed in interpreting the results of this meta-analysis. Our analysis largely used unadjusted estimates without adjustment for other potential confounders such as folate intake status, lifestyles and exposures, which may influence the combined results. Due to the limited number of relevant included studies, the pooled results in some subgroups may have insufficient statistical power to detect a slight effect. In addition, folate intake status has an important impact on DNA methylation and synthesis, which may influence cancer risk by potential gene-nutrition interactions. Due to the limited original data, potential gene-environment interactions were not evaluated in this study.

In summary, the present meta-analysis found that *MTRR* A66G polymorphism was associated with an increased risk for NHL in Asian populations and for DLBCL in whole population. Since limited relevant studies were included in this meta-analysis, larger sample sizes and well-designed studies are required in the future to confirm these findings. Moreover, gene-gene

and gene-environment interactions should also be considered in further analysis.

Disclosure of conflict of interest

None.

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