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The +252A/G polymorphism in the Lymphotoxin-α gene and the risk of non-Hodgkin lymphoma: a meta-analysis

C. CAO, S. LIU[2], S.-F. LOU[1], T. LIU

Department of Hematology, West China Hospital of Sichuan University and Key Laboratory of Hematology of Sichuan Province, Chengdu, China
[1]Department of Hematology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
[2]The First People's Hospital of Yibin, Yibin, China

Abstract. – BACKGROUND AND OBJECTIVES: Many studies have shown that the +252A/G polymorphism in the lymphotoxin-α gene is implicated in susceptibility to non-Hodgkin lymphoma but with considerable variance of results. This study aimed to clarify the overall association between the +252A/G polymorphism in the lymphotoxin-α gene and non-Hodgkin lymphoma (NHL) risk by performing a meta-analysis.

MATERIALS AND METHODS: The Pubmed and Embase databases were searched for all studies relating to lymphotoxin-α +252A/G gene polymorphism and NHL risk. Data were retrieved and statistical analyses were performed using the Revman 5.1 and STATA 12.0 software.

RESULTS: Fourteen case-control studies with 25,098 subjects were included. There was no significant association between lymphotoxin-α +252A/G gene polymorphism and the risk of NHL in the all-combined analysis (OR = 1.08, 95%CI: 0.98-1.19 for GG+GA vs. AA; OR = 1.05, 95%CI: 0.95-1.25 for GG vs. GA+AA). In a subgroup analysis by ethnicity, increased NHL risk was found in North Americans (OR = 1.21, 95%CI: 1.05-1.39 for GG+GA vs. AA), no significant association with NHL risk was identified in Asians or Europeans; In a subgroup analysis by NHL subtype, a significantly increased risk was identified in diffuse large B cell lymphoma patients (OR = 1.20 95%CI: 1.11-1.29 for GG+GA vs. AA), but not for follicular lymphoma.

CONCLUSIONS: This meta-analysis suggested that the lymphotoxin-α +252A/G gene polymorphism is a risk factor for NHL in North Americans, and this polymorphism may contribute to diffuse large B cell lymphoma susceptibility. Future studies that include different types of NHL and ethnicities are needed to support and extend these observations.

Key Words:
+252A/G polymorphism, Non-Hodgkin lymphoma, Meta-analysis.

Introduction

Non-Hodgkin lymphoma (NHL) is a large heterogeneous group of B-cells and T-cells lymphomas characterized with uncontrolled malignant clonal expansion, and it is an important public health burden in the worldwide with increasing caution[1]. It was estimates that 69,740 NHL patients were newly diagnosed and 19,020 deaths were occurred in 2012 in the United States according to the reports of the American Cancer Society[2]. In the Europe, about 74,000 people were diagnosed with NHL and there were more than 31,000 deaths from NHL in 2008[3]. In addition, the incidence of NHL is increasing worldwide, it places a heavy burden on patients because it reduces life quality, work ability, and increases disability. The pathogenesis of NHL has not been fully understood, and growing studies suggest that genetic factors of inflammation may play a critical role[4-5], and among them, the +252A/G polymorphism in the lymphotoxin-α gene has been highlighted.

Lymphotoxin-α is a cytokine of the tumor necrosis factor family that function as of immune and inflammation regulatory mediator. Lymphotoxin-α is a good candidate gene for lymphomagenesis because it codes for important immune-regulatory cytokines that are crucial mediators of inflammation, apoptosis, T-helper cell type 1/2 balance, and function as autocrine growth factors in the pathogenesis of NHL[6]. A polymorphism in the coding region at position +252 of the lymphotoxin-α gene (A→G) leads to different alleles of lymphotoxin-α, as lymphotoxin-α A allele for the wild-type allele and lymphotoxin-α G for the variant allele[7]. The lymphotoxin-α variant alleles has

Corresponding Author: Ting Liu, MD; e-mail: liutingscu@gmail.com

been shown to correlate with elevated circulating lymphotoxin-α level and has been associated with a more severe outcome of lymphoid malignancies[8-10]. A number of studies have examined the association of the +252A/G polymorphism in the lymphotoxin-α gene with NHL, nevertheless, these results are controversial. Since pooled estimates based on meta-analysis have proven to be useful in determining the overall risk of certain NHL polymorphisms when results of individual studies are inconsistent[11], we decided to perform the present meta-analysis in order to clarify the association between the lymphotoxin-α +252A/G polymorphism and NHL risk.

Materials and Methods

We performed this meta-analysis according to the guidelines of Systematic Reviews of Genetic Association Studies and Preferred Reporting Items for Systematic Reviews and Meta-analyses[12,13].

Literature Search Strategy

A comprehensive literature search was performed in Pubmed and Embase. The following key words were used in combination: "Non-Hodgkin lymphoma *or* NHL", "lymphotoxin-α *or* LT-α *or* LTA *or* Tumor necrosis factor-β *or* TNF-β", "polymorphism *or* variant *or* mutation" (last updated on October, 2013). Additional studies were identified by a manual search from references of original studies or review articles on the related topic.

Inclusion Criteria

Studies were included in this meta-analysis if they met the following inclusion criteria: (1) They evaluated the genetic association between the lymphotoxin-α +252A/G polymorphism and NHL risk; (2) They were case-control studies; (3) They should provide the available genotype frequency in NHL cases and controls for estimating an odds ratio (OR) with 95% confidence interval (95%CI); (4) The distribution of genotypes in the control group was consistent with Hardy-Weinberg equilibrium (HWE); and (5) They were published in English language. Reviews, conference abstracts, and studies in which genotype frequencies were not reported or could not be calculated were excluded. For studies with overlapping patients or controls, the most recent study with the greatest number of subjects was included.

Data Extraction

To minimize the heterogeneity and facilitate the appropriate interpretation and understanding of included studies, we designed a data retrieve form and the following items were retrieved: the first author's name, year of publication, country of origin, population ethnicity, number of NHL cases and controls, genotype identification method, and genotype frequencies in NHL cases and controls, HWE test etc. Two reviewers extracted data independently and the disagreements were resolved by discussion and consensus.

Data Synthesis and Meta-Analysis

OR with 95% CI were used to assess the strength of the association between the lymphotoxin-α +252A/G polymorphism and NHL risk. The heterogeneity among studies was assessed using the chi-square based Q- and I^2-statistics to choose the appropriate statistical model. Fixed-effects or random-effects models were used to pool the data according to significance of heterogeneity. Heterogeneity was considered to be significant if p values < 0.10. When the p value for heterogeneity was > 0.10, the fixed-effects model was used, otherwise, the random-effects model was used, as it is more appropriate when there is heterogeneity.

The OR and associated 95% CI were calculated by comparing the frequencies of rare alleles with that of the wild type homozygous alleles, that is GG+GA vs. AA (dominant model). Other comparative genetic models were also used to assess the association between the polymorphism and the risk of NHL, GG vs. GA+AA (recessive model), GG vs. AA (additive model), and G vs. A (allelic model). The significance of the pooled OR was determined by the Z-test, and a p value < 0.05 was considered statistically significant. To evaluate the ethnicity-specific and NHL subtype-specific effect, subgroup analyses were performed by ethnicity (Asian, North American, and European), and by NHL subtype (Diffuse large B cell lymphoma, DLBCL; and Follicular lymphoma). Publication bias in the literature was assessed using Begg's test and Egger's test[11]. Analyses were performed using RevMan 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 12.0 (StataCorp LP, College Station, TX, USA) software.

Results

After a systematic literature search and selection, a total of 14 case-control studies with

25,098 subjects were included in present meta-analysis[13-27]. Information of the 14 included articles including the first author, publication year, country and ethnicity, sample size (case/control), genotyping method was listed in Table I. There were 11,376 NHL patients and 13,722 controls. All the NHL patients were diagnosed with pathological evidence, finding as the golden standard. Four case-control studies were performed in Asian populations[17,19,20,26], three were performed in European populations[16,25,27], three were performed in North American populations[14,15,24], two were mixed populations[22,23], one of Australian[21] and one of African[18]. There were seven studies that could retrieve the data of DLBCL[15,17,21-24,27] and seven studies involved in patients of follicular lymphoma[15-17,21-24]. The results of HWE test for the distribution of the genotype in control population were in agreement in all included studies. The genotype and allele distributions for each case-control study are presented in Table II.

Quantitative Data Synthesis

The heterogeneity of GG+GA vs. AA was assessed for all 14 studies, and the chi-square value was 28.95 with 13 degrees of freedom and p = 0.007 in a random-effects model, the I-square statistic, which is another index of heterogeneity, was 55%, both suggesting moderate heterogeneity. Therefore, a random-effects model was used for synthesis of the data. The overall OR was 1.08 (95% CI: 0.98-1.19), and the Z-test value for overall effect was 1.56 (p = 0.12) for the dominant model (GG+GA vs. AA) (Figure 1). For recessive model (GG vs. GA+AA), the overall OR was 1.05 (95% CI: 0.95-1.25), and the Z-test value for overall effect was 1.29 (p = 0.20). These results did not suggest a significant association between the lymphotoxin-α +252A/G polymorphism and NHL risk. Summary results for all comparisons are presented in Table III.

Subgroup Analysis

To exclude the effect of confound factors, such as ethnicity, NHL subtype, subgroup analysis was carried out to further elucidate the relationship between the lymphotoxin-α +252A/G polymorphism and the risk of NHL. For ethnicity-specific subgroup analysis, our findings suggest a significant association between the lymphotoxin-α +252A/G polymorphism and NHL risk in North Americans with an OR of 1.21 (95%CI 1.05-1.39, p = 0.007, GG+AG vs. AA). There were no significant associations with NHL risk in Europeans and Asians (Figure 2). For NHL subtype-specific subgroup analysis, seven studies involving 17,088 subjects (3,837 cases and 13,171 controls) were focused on DLBCL, and seven studies with 14,523 subjects (2,273 cases and 12,250 controls) were focused on follicular lymphoma. A significant association between the lymphotoxin-α +252A/G polymor-

Table I. Clinical summary of included studies.

Author	Year	Country	Ethnicity	Case	Control	Genetyping method	HWE
Warzocha et al	1998	France	European	273	96	PCR-FFLP	Y
Fitzgibbon et al	1999	UK	European	121	88	PCR	Y
Rothman et al	2006	Mixed	Mixed	3085	3509	Taqman	Y
Wang et al	2006	USA	North Amiercan	1142	950	Taqman	Y
Purdue et al	2007	Australian	Australian	538	494	Taqman	Y
Cerhan et al	2008	USA	North Amiercan	440	475	PCR	Y
Aissani et al	2009	USA	North Amiercan	137	140	PCR	Y
Skibola et al	2010	Mixed	Mixed	2616	2685	Taqman	Y
Xiao et al	2011	China	Asian	160	214	PCR-FFLP	Y
Ibrahim et al	2012	Egypt	African	84	100	PCR	Y
Hosgood et al	2013	Hong Kong, South Korea, mainland China	Asian	1894	3601	PCR	Y
Liu et al	2013	China	Asian	291	300	PCR-LDR	Y
Nasiri et al	2013	Iran	Asian	61	115	PCR-FFLP	Y
Yri et al	2013	Norway	European	480	1009	PCR	Y

PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; LDR: Ligase detection reaction; HWE: Hardy-Weinberg equilibrium; Y: Yes.

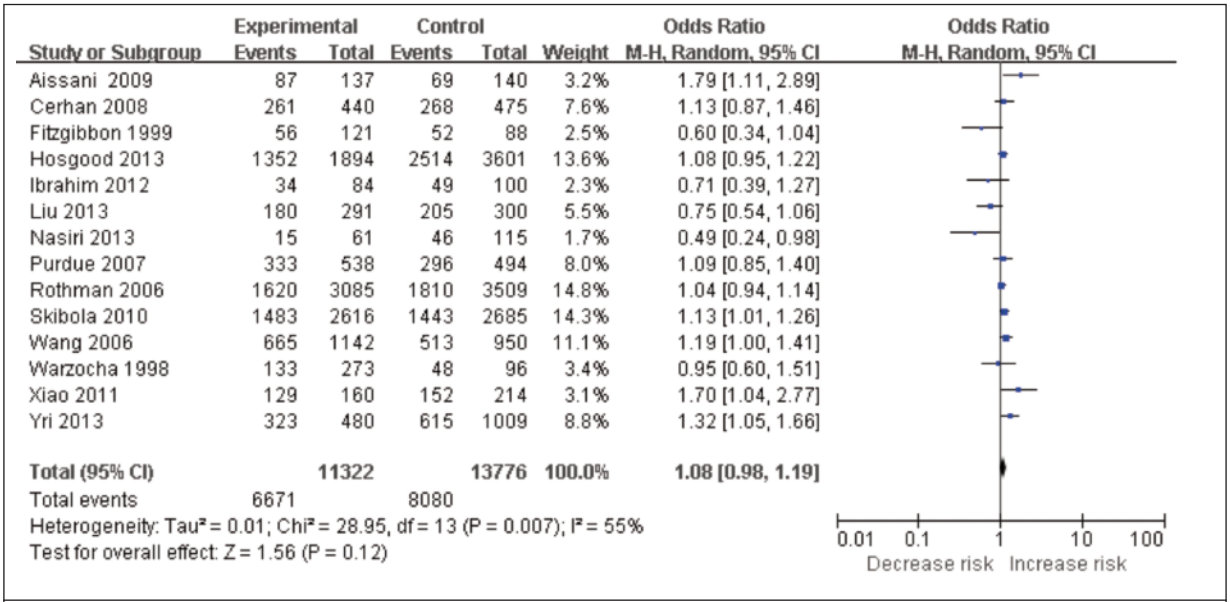
Table II. Distribution of lymphotoxin-α genotype and allele among NHL patients and controls.

	NHL			Control			NHL		Control	
Author	AA	AG	GG	AA	AG	GG	A	G	A	G
Warzocha et al	140	110	23	48	38	10	390	156	134	58
Fitzgibbon et al	65	47	9	36	37	15	177	65	109	67
Rothman et al	1465	1281	339	1699	1484	326	4211	1959	4882	2136
Wang et al	477	495	170	437	400	113	1449	835	1274	626
Purdue et al	205	265	68	198	233	63	675	401	629	359
Cerhan et al	179	208	53	207	217	51	566	314	631	319
Aissani et al	50	65	22	71	61	8	165	109	203	77
Skibola et al	1133	1172	311	1242	1148	295	3438	1794	3632	1738
Xiao et al	31	88	41	62	105	47	150	170	229	199
Ibrahim et al	50	25	9	51	42	7	125	43	144	56
Hosgood et al	542	932	420	1087	1765	749	2016	1772	3939	3263
Liu et al	111	151	29	95	149	56	373	209	339	261
Nasiri et al	46	13	2	69	44	2	105	17	182	48
Yri et al	157	247	76	394	479	136	561	399	1267	751

phism and DLBCL risk was identified (OR = 1.20, 95%CI 1.11-1.29, $p < 0.05$, GG+AG vs. AA), no association between the lymphotoxin-α +252A/G polymorphism and follicular lymphoma risk was found (Figure 3).

Sensitivity Analysis and Publication Bias

To evaluate the stability of our results, sensitivity analysis was performed by sequentially excluding each study. Similar statistically results were obtained after sequentially excluding each case-control study, revealing the stability of our findings (Figure 4). Begg's funnel plots and Egger's test were used to assessed potential publication bias. The shape of the Begg's funnel plots appeared symmetrical for the dominant model (GG+GA vs. AA) (Figure 5). Egger's test was performed to provide statistical evidence of funnel plot symmetry (p = 0.063). These data suggested that there was no evidence of publication bias among included studies.



The size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.

Figure 1. Meta-analysis to evaluate the association between the +252A/G polymorphism and NHL risk (GG+GA vs. AA).

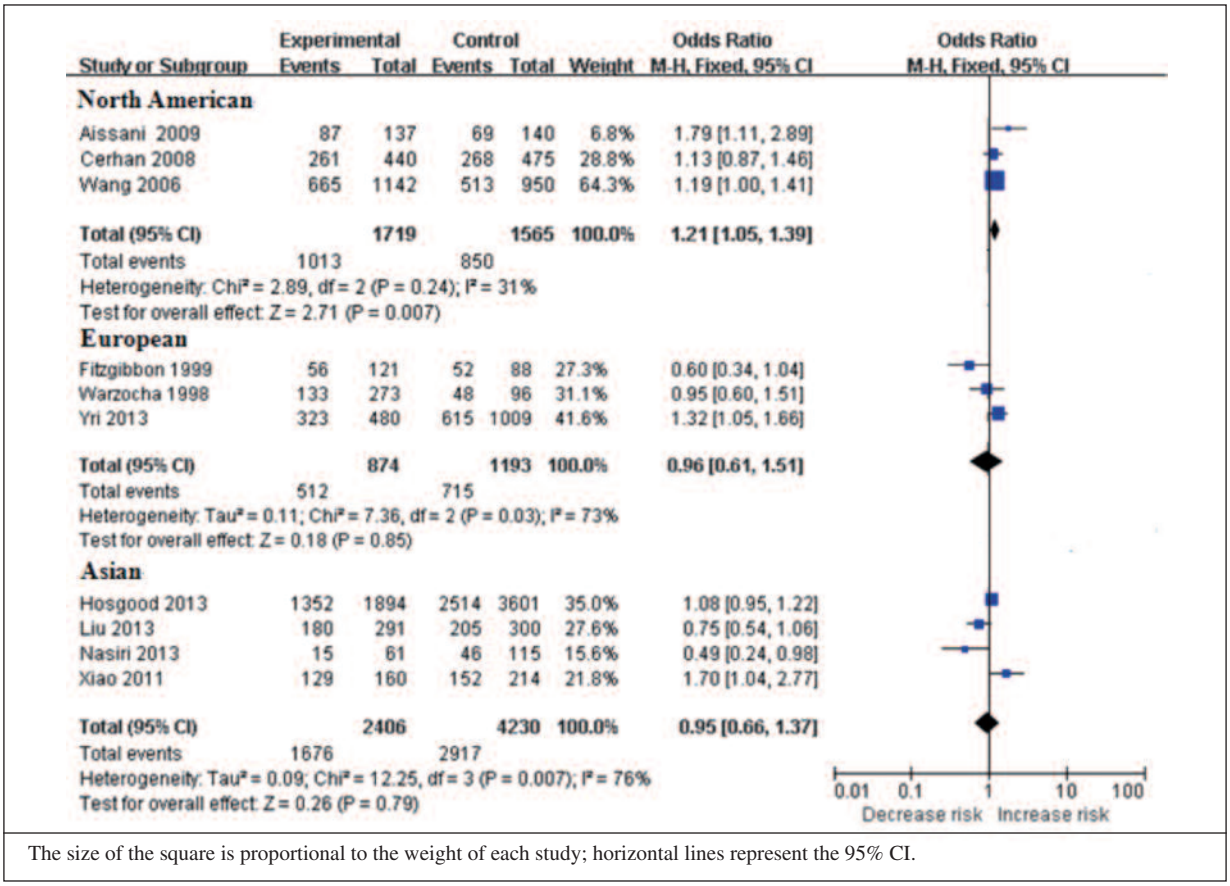
Table III. Distribution of lymphotoxin-α genotype and allele among NHL patients and controls.

	GG+AG vs. AA		GG vs. AG+AA		GG vs.AA		G vs.A	
	OR (95%CI)	*p**	OR (95%CI)	*p**	OR (95%CI)	*p**	OR (95%CI)	*p**
Total	1.08 (0.98-1.19)	0.12	1.05(0.95-1.25)	0.20	1.15(0.97-1.35)	0.10	1.06(0.98-1.14)	0.15
Subgroup by Ethnicity								
North American	1.21(1.05-1.39)	0.007	1.33(1.08-1.64)	0.007	1.58(1.00-2.49)	0.05	1.23(1.02-1.49)	0.03
European	0.96(0.61-1.51)	0.85	0.80(0.42-1.52)	0.49	0.78(0.34-1.80)	0.56	0.90(0.61-1.35)	0.62
Asian	0.95(0.66-1.37)	0.79	0.92(0.58-1.44)	0.71	0.99(0.55-1.77)	0.96	0.94(0.72-1.22)	0.64
Subgroup by NHL subtype								
DLBCL	1.20(1.11-1.29)	<0.00001	1.22(1.10-1.35)	0.0001	1.34(1.19-1.49)	<0.00001	1.16(1.10-1.22)	<0.00001
Follicular lymphoma	0.98(0.89-1.08)	0.68	1.01(0.87-1.16)	0.94	0.99(0.85-1.15)	0.88	0.99(0.92-1.06)	0.78

Note: The bold values mean that their association is significant, *p value for Z test.

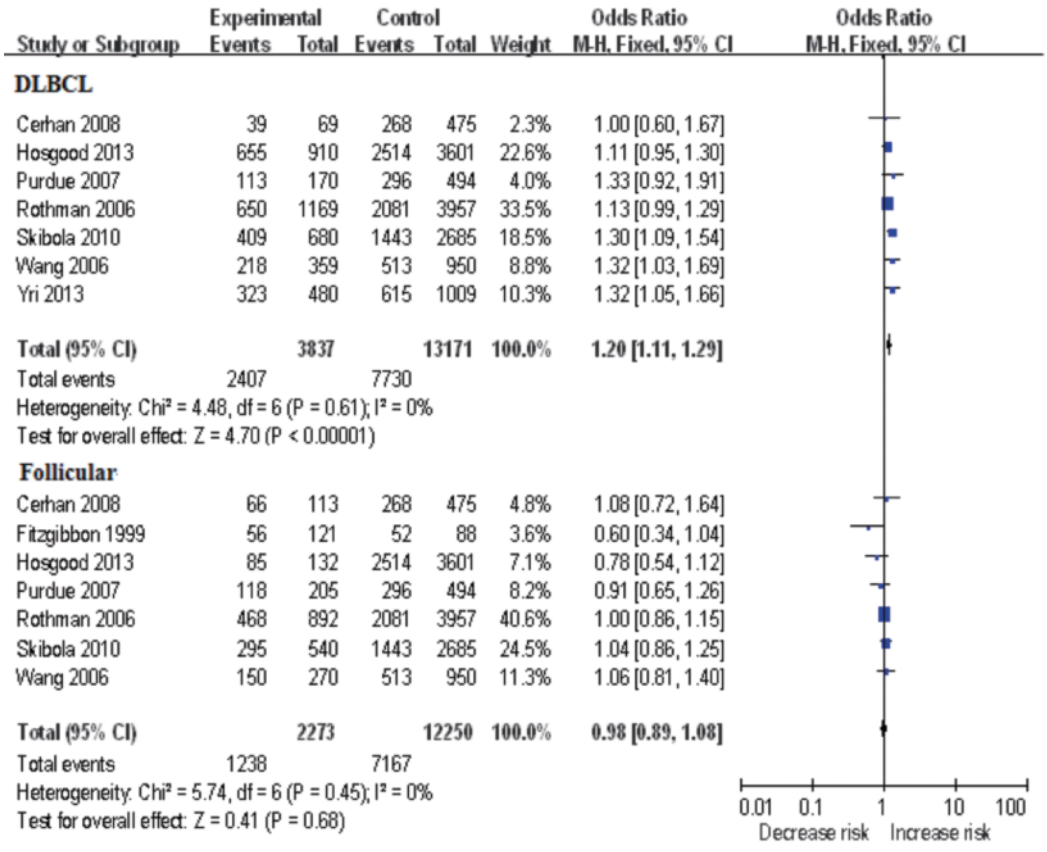
Discussion

The pathogenesis of NHL is so complicated and increasing studies have shown that genetic factors may play critical role in the development and progression of NHL[1]. Recent studies suggest that genetic variant in the +252A/G polymorphism of lymphotoxin-α may influence the expression of lymphotoxin-α, which takes part in the immune and inflammation regulation, plays a role in NHL[6,9]. Taking a consideration of variable results from different studies, we performed this



The size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.

Figure 2. Meta-analysis to evaluate the ethnicity-specific effect of +252A/G polymorphism on NHL risk (GG+GA vs. AA)



The size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.

Figure 3. Meta-analysis to evaluate the tumor subtype-specific effect of +252A/G polymorphism on NHL risk (GG+GA vs. AA).

meta-analysis to summarize the overall association between the lymphotoxin-α +252A/G polymorphism and NHL risk. To our best knowledge, this is the first meta-analysis regarding the association between the lymphotoxin-α +252A/G gene polymorphism and NHL risk.

Our studies included 14 studies with 25,098 subjects, for the overall data synthesis, there was no association between the lymphotoxin-α +252A/G gene polymorphism and NHL risk in all genetic models. Since the genetic effect on the NHL pathogenesis is so complicated, based on current available evidence, it is hard to define the accurate association between this polymorphism and NHL risk. It is possible that another polymorphism of lymphotoxin-α such as rs2239704 C > A, rs1800683 G > A play more important role in NHL. These polymorphisms in lymphotoxin-α gene may increase the synthesis and release of lymphotoxin-α, which result in activation of NF-kB signaling, constitutive NF-kB activation can promote continuous lymphocyte proliferation, survival and apoptosis, thus, takes part in the pathogenesis of NHL[15,28]. We took a subgroup analysis to exclude the effect of confound factors. Our findings suggest that lymphotoxin-α +252A/G polymorphism is associated with significant increased risk in North Americans, suggesting the effect of this polymorphism may be ethnicity-specific. In addition, subgroup analysis on NHL subtype suggests that lymphotoxin-α +252A/G polymorphism is associated with increased risk of DLBCL, not the follicular lymphoma, revealing that the effect of this polymorphism may be NHL subtype-specific. The lymphotoxin-α +252A/G polymorphism seems to play an important role in the pathogenesis of certain NHL entities or subtypes. Further studies should be performed to investigate the detailed biological mechanism of lymphotoxin-α +252A/G polymorphism on the development and progress of NHL.

In addition to providing genetic risk information, analysis of lymphotoxin-α +252A/G poly-

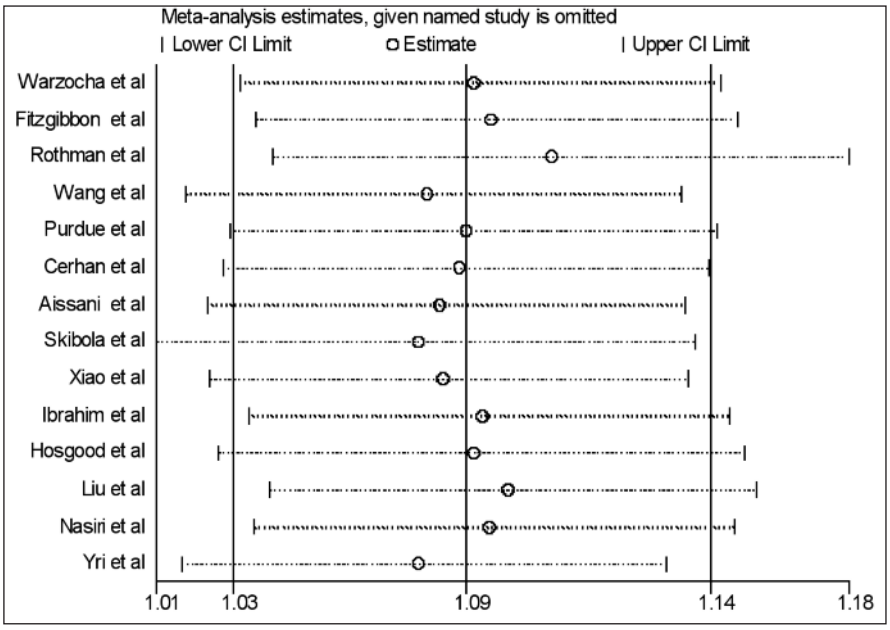


Figure 4. Sensitivity analysis of included studies (GG+GA vs. AA).

morphism can provide detailed, personalized information about patients with NHL. A study revealed that lymphotoxin-α +252A/G polymorphism is found to be a risk factor for outcome of NHL and is associated with response to first-line therapy, suggesting lymphotoxin-α+252A/G polymorphism may be function as a prognostic marker for NHL patients[29]. A recently published study[30] suggests that lymphotoxin-α rs1800683G>A was significantly associated with risk of progression or relapse in NHL patients, particularly in DLBCL cases. Kidas et al[31] reported that patients with lymphotoxin-a +252A/G polymorphism seemed to have a significant higher risk of attracting a lethal infection during induction/consolidation chemotherapy. All these studies suggest that the determination of lymphotoxin-α +252A/G polymorphism not only provides the genetic risk information, but also prognostic information.

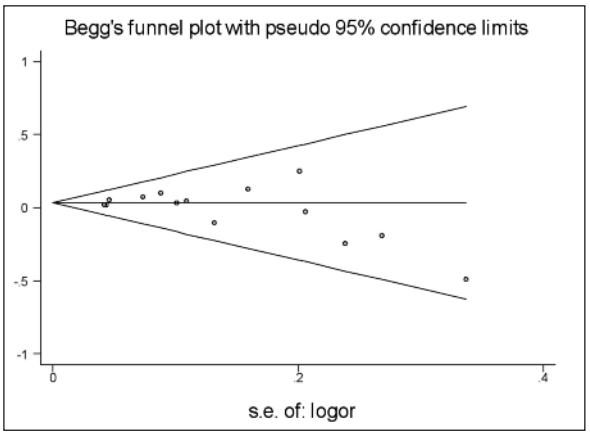


Figure 5. Begg's funnel plot to detect publication bias in studies examining the +252A/G polymorphism (GG+GA vs. AA).

The findings in this meta-analysis should be interpreted with caution. First, a relatively small number of studies were included in our meta-analysis, which may reduce the statistical power for identifying possible associations between the lymphotoxin-α +252A/G polymorphism and NHL risk. In particular, the association between this polymorphism and NHl risk should be verified in larger-scale studies. Second, the included publications were limited to Europeans, Asian and North American populations, so future work should investigate other populations, such as Latinos, especially given substantial evidence of ethnic bias in the lymphotoxin-α +252A/G polymorphism. Third, although we did not set any language restrictions for literature searching, we included only English-language publications in the meta-analysis. It is possible that our results would be different if they included the findings of relevant studies published in other languages or unpublished studies.

Conclusions

To the best of our knowledge, this is the first meta-analysis to assess the relationship between the lymphotoxin-α +252A/G polymorphism and

NHL risk. Our results suggest that the effects of lymphotoxin-α +252A/G polymorphism on NHL risk maybe ethnicity-specific and tumor subtype-specific. Large well-designed, multi-center epidemiological studies should be carried out in these and other ethnic populations to confirm our findings.

Acknowledgements

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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