

RESEARCH ARTICLE

The *CCND1* G870A Gene Polymorphism and Leukemia or Non-Hodgkin Lymphoma Risk: a Meta-analysis

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Abstract

In recent years, mounting evidence has indicated that the *CCND1* G870A gene polymorphism, which impacts the mitotic cell cycle, may influence leukemia or non-Hodgkin lymphoma risk. Unfortunately, the previous results were inconsistent. Therefore, a meta-analysis was performed to obtain a more precise estimation of any association. We conducted a search in PubMed, Embase and CNKI covering all published papers up to March, 2014. A total of 9 publications including 10 case-control studies met the inclusion criteria. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were applied to assess association. The pooled ORs showed significant association in non-Hodgkin lymphoma (comparison A vs G: OR= 1.114, 95% CI=1.053-1.179, $p=0.000$; homozygote comparison AA vs GG: OR=1.245, 95% CI=1.110-1.396, $p=0.000$; heterozygote comparison AG vs GG: OR=1.095, 95% CI=1.000-1.199, $p=0.05$; dominant model AA/GA vs GG: OR=1.137, 95% CI=1.043-1.239, $p=0.003$; and recessive model AA vs GA/GG: OR=1.177, 95% CI=1.066-1.301, $p=0.001$). However, there was no association between the *CCND1* G870A polymorphism and leukemia risk. In conclusion, the *CCND1* G870A polymorphism may increase risk of non-Hodgkin lymphoma, but not leukemia. However, more primary large scale and well-designed studies are still required to evaluate the interaction of *CCND1* G870A polymorphism with leukemia and non-Hodgkin lymphoma risk.

Keywords: Leukemia - non-Hodgkin lymphoma - *CCND1* gene - polymorphism - meta-analysis

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Introduction

Leukemia and non-Hodgkin lymphoma have been selected in our study because of their high incidence rates and mortality rates. Based on observation of WHO, incidence rates of them are estimated at 8.8 and 9.8 per 100,000 persons in Europe, respectively, and the mortality is 5.1 and 3.5. The incidence and mortality of men are higher than women (<http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=968>). According to the degree of cell differentiation and the length of the natural course of the disease, leukemia is classified as acute leukemia and chronic leukemia in general. Acute leukemia is a malignant tumor of the hematopoietic system. With respect to the cell affected, the disease can be subdivided into two major groups as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), respectively. ALL, with a high degree of malignancy, recurrence rate, poor prognosis features and multiple drug resistance, is a greater difficulty in its treatment. The etiology is not yet fully understood. ALL is the most common diseases of children malignant tumor (Advani et al., 2009; Stieglitz et al., 2013). Non-Hodgkin lymphoma (NHL), a heterogeneous disease, results from the malignant transformation of lymphocytes and contains multiple subtypes, each with specific

molecular and clinical characteristics. The etiology of NHL, which includes many factors, environmental factors and genetic factors, is not clear (Morton et al., 2008; Bassig et al., 2012).

CCND1 gene, which is a cell cycle regulatory gene, locating at 11q13 and encoding a protein (cyclin D1), is important in control of the cell cycle at the G1 to S phase transition of the cell cycle checkpoint (G1/S checkpoint) (Sherr et al., 1995; Donnellan et al., 1998; Gijtenbeek et al., 2005). Its dysregulation exists in a variety of tumors (Diehl et al., 2002). The *CCND1* gene has a common 870 G>A polymorphism (rs603965) at the junction of the fourth exon and intron. It exists two transcriptions, transcription A and transcription B, coding two protein subtypes (cyclin D1a and cyclin D1b). Two proteins are different in the 55 amino acids of C-terminal domain. Some studies indicate that the *CCND1* gene has a G to A polymorphism, and the *CCND1* 870A allele expresses transcript B (cyclin D1b), which affects the risk of malignant tumors (Betticher et al., 1995; Bala et al., 2001; Qiuling et al., 2003; Wang et al., 2003). *CCND1* gene has been reported in various tumors (Akkiz et al., 2010; Yang et al., 2012; Wang et al., 2014). Similarly, the *CCND1* G870A gene polymorphism also has been reported in various tumors in Asian Pacific journal of cancer prevention (APJCP) during the last two

years, but the results of previous studies were inconsistent (Li et al., 2012; Zeybek et al., 2013). What is more, there are some studies about the gene polymorphism and leukemia or non-Hodgkin lymphoma risk, but the results of previous studies were also inconsistent. Given the background, we performed this meta-analysis on all published case-control studies to derive a more precise estimation of *CCND1 G870A* gene polymorphism with leukemia or non-Hodgkin lymphoma risk. In addition, a meta-analysis was robust to detect the overall effects and the inconsistency of previous studies.

Materials and Methods

Search strategy

All case-control studies about the *CCND1 G870A* polymorphism and leukemia or non-Hodgkin lymphoma risk published up to March, 2014. Systematic searches were identified by PubMed, Embase and China National Knowledge Infrastructure (CNKI), using the terms “*CCND1*” or “cyclin D1” in combination with “polymorphism” or “polymorphisms” or “variant” or “mutation” in combination with “leukemia” or “non-Hodgkin lymphoma”. Concurrently, the reference lists of reviews and retrieved articles were searched manually. No language or country restrictions were applied. Review articles were also examined to find additional eligible studies. The literature retrieval was performed in duplication by two independent reviewers (Lingyan Qin and Ligang Zhao).

Inclusion and Exclusion Criteria

Studies included in the meta-analysis must meet the following criteria: they (a) evaluated the association between *CCND1 G870A* polymorphism and leukemia or non-Hodgkin lymphoma risk; (b) supplied the number of individual genotypes for the *CCND1 G870A* gene polymorphisms in leukemia or non-Hodgkin lymphoma cases and controls, respectively; and (c) were case-control studies. The exclusion criteria were as follows: they were (a) not case-control studies; (b) studies that were based on incomplete raw data and those with no usable data reported; (c) conference abstracts, case reports, reviews, letters, and editorial articles; and (d) studies that contained overlapping data.

Data extraction

From each eligible study, the following information were extracted by two investigators independently with the standard protocol: the first author's surname, year of publication, country of origin, ethnicity, tumor type, source of control, method of genotyping, numbers of cases and controls, Hardy-Weinberg equilibrium (HWE) of controls, and the frequency of genotypes in both cases and controls. We did not contact the author of the primary study to request the information.

Statistical analysis

The odds ratio (OR) and its 95% confidence interval (95%CI) were calculated to assess the association strength between *CCND1* polymorphism and leukemia or non-

Hodgkin lymphoma risk. Significance of the pooled OR was determined by Z test. P value of less than 0.05 was considered as significance. Pooled ORs were calculated under comparison (A vs G), homozygote comparison (AA vs GG), heterozygote comparison (AG vs GG), dominant model (AA/AG vs GG), and recessive model (AA vs AG/GG) for each polymorphism, respectively. Subgroup analysis was done by clinical types of leukemia.

The heterogeneity between the studies was assessed by the χ^2 -test based Q-statistic and I^2 statistics. If the results of the Q test was $P_Q \geq 0.1$ and $I^2 < 50\%$, the fixed-effects was performed to pool the results (Mantel et al., 1959). Otherwise, random-effects model was considered when the result of the Q test was $P_Q < 0.1$ or $I^2 \geq 50\%$ (DerSimonian et al., 1986). If heterogeneity was observed, logistic meta-regression analysis was applied to both general analyses and subgroup analyses to find the source of heterogeneity.

Sensitivity analysis was performed to assess the stability of the results and identify potentially influential studies. It was performed by sequential omission of a single study (Tobias et al., 1999). Funnel plots and Egger's linear regression test were used to detect the potential publication bias ($p < 0.05$ was considered a statistically significant publication bias) (Egger et al., 1997; Stuck et al., 1998). All calculations were performed using Stata, version 12.0 (Stata Corporation, College Station, TX), and all the P values were two sided.

Results

Eligible studies

The literature search identified 45 potentially relevant articles through PubMed, Embase, and CNKI. After screening the title, abstract, or content, 10 publications studies were selected. However, one publication contained overlapping data, then was excluded (Wang et al., 2006). Manual search of references did not cite in any additional article. Finally, a total of 9 publications including 10 case-control studies met the inclusion criteria for the meta-analysis (including a total of 6085 leukemia and non-Hodgkin lymphoma cases and 5460 controls) (Howe et al., 2001; Hou et al., 2005; Wang et al., 2006; Morton et al., 2009; Fernberg et al., 2010; Rong et al., 2010; Wang et al., 2011; Qian et al., 2012; Bedewy et al., 2013). There were 6 studies of leukemia (containing 4 of ALL, 1 of CLL and 1 of CML), and 4 of non-Hodgkin lymphoma. Among these 10 studies, seven studies were English and three were Chinese. The distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium ($p > 0.05$) in all studies. The main characteristics of the studies were presented in Table 1.

Quantitative synthesis of data

The summary results for the association of *CCND1 G870A* gene polymorphism with leukemia and non-Hodgkin lymphoma risk are shown in Table 2. After 6 studies of leukemia and 4 studies of non-Hodgkin lymphoma were pooled into the meta-analysis separately, significant association were found in non-Hodgkin lymphoma (comparison A vs G: OR=1.114, 95%CI=1.053-

1.179, $p=0.000$; homozygote comparison AA vs GG: OR=1.245, 95%CI=1.110-1.396, $p=0.000$; heterozygote comparison AG vs GG: OR= 1.095, 95%CI= 1.000-1.199, $p= 0.05$; dominant model AA/GA vs GG: OR=1.137, 95%CI=1.043-1.239, $p=0.003$; and recessive model AA vs GA/GG: OR=1.177, 95%CI=1.066-1.301, $p=0.001$) (Figure 1, Table 2). But there was no association between *CCND1 G870A* polymorphism and leukemia risk in any model (comparison A vs G: OR=1.174, 95%CI=0.818-1.687, $p=0.384$; homozygote comparison AA vs GG: OR=1.38, 95%CI=0.694-2.744, $p=0.359$; heterozygote comparison AG vs GG: OR=1.08, 95%CI=0.849-1.375, $p=0.53$; dominant model AA/GA vs GG: OR=1.186, 95%CI=0.752-1.870, $p=0.462$; and recessive model AA vs GA/GG: OR=1.276, 95%CI=0.780-2.088, $p=0.332$) (Figure 2, Table 2).

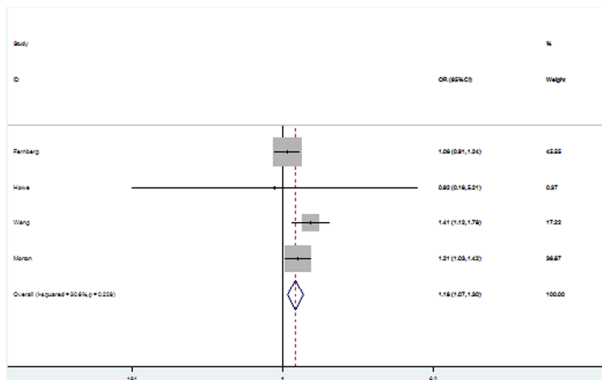


Figure 1. Forest Plot Showed That *CCND1 G870A* Gene Polymorphism was Not Associated with NHL Susceptibility under Recessive Model (AA vs GA/GG)

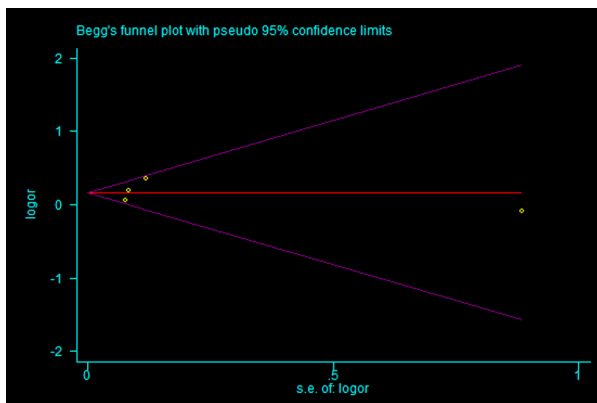


Figure 3. Funnel Plot did Not Indicate any Evidence of Obvious Asymmetry in NHL under Recessive Model (AA vs GA/GG)

In further stratified analyses, association between *CCND1 G870A* polymorphism and ALL was not observed (comparison A vs G: OR=1.415, 95%CI=0.978-2.046, $p=0.065$; homozygote comparison AA vs GG: OR=1.921, 95%CI=0.923-3.998, $p=0.081$; heterozygote comparison AG vs GG: OR=1.133, 95%CI=0.882-1.456, $p=0.328$; dominant model AA/GA vs GG: OR=1.44, 95%CI=0.906-2.291, $p=0.123$; and recessive model AA vs GA/GG: OR=1.56, 95%CI=0.921-2.645, $p=0.098$) (Table 2).

Heterogeneity analysis

Heterogeneity existed in leukemia, rather than non-Hodgkin lymphoma (Table 2). To explore the sources of heterogeneity of leukemia, we performed meta-regression and subgroup analysis. After assessing the source of heterogeneity for all genetic models by subgroup analysis

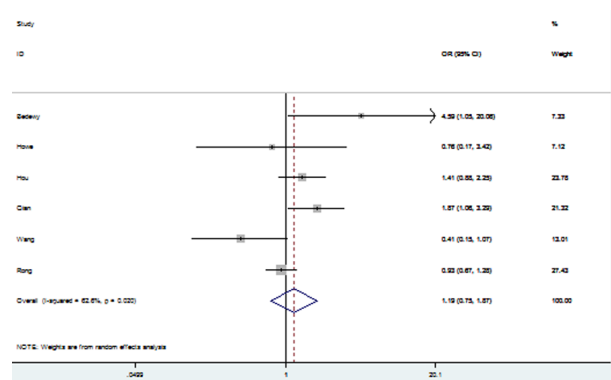


Figure 2. Forest Plot Showed that *CCND1 G870A* Gene Polymorphism was Associated with leukemia Susceptibility under Dominant Model (AA/GA vs GG)

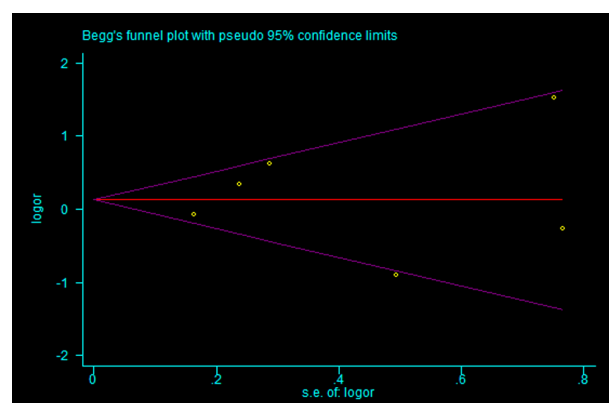


Figure 4. Funnel Plot did not Indicate any Evidence of Obvious Asymmetry in Leukemia under Dominant Model (AA/GA vs GG)

Table 1. Main Characteristics of All Case-control Studies Included in Meta-analysis

first author	year	country	ethnicity	clinical type	source of control	Method of Genotyping	Sample size case	control	HWE of Controls
Fernberg	2010	DS	Caucasian	NHL	HP	MassArray assay	2258	1780	Yes
Morton	2009	Australia	Caucasian	NHL	HP	GoldenGate assay	1946	1808	Yes
Wang	2006	USA	Caucasian	NHL	HP	Taqman	1111	928	Yes
Howe	2001	UK	Caucasian	NHL	HP	RFLP-PCR	42	13	Yes
Bedewy	2013	Egypt	African	ALL	HP	RFLP-PCR	25	15	Yes
Qian	2012	China	Asian	ALL	HP	RFLP-PCR	115	160	Yes
Wang	2011	China	Asian	CML	HP	RFLP-PCR	40	46	Yes
Rong	2010	China	Asian	ALL	HP	RFLP-PCR	346	520	Yes
Hou	2005	China	Asian	ALL	HP	RFLP-PCR	183	190	Yes
Howe	2001	UK	Caucasian	CLL	HP	RFLP-PCR	19	13	Yes

*DS: Denmark and Sweden; PB: Population-based; HB: Hospital-based. HWE: Hardy-Weinberg equilibrium.

Table 2. Meta-analysis of CCND1 G870A Polymorphism and Leukemia or Non-Hodgkin Lymphoma

Comparison	Population	N	Test of association			Model	Test of heterogeneity		<i>P</i> _{egger}
			OR	95% CI	<i>P</i>		<i>P</i>	I ² (%)	
A vs G	NHL	4	1.114	1.053-1.179	0.000	F	0.132	46.6	0.905
	leukemia	6	1.174	0.818-1.687	0.384	R	0	77.5	0.752
	ALL	4	1.415	0.978-2.046	0.065	R	0.003	78.7	0.092
AA vs GG	NHL	4	1.245	1.110-1.396	0.000	F	0.114	49.6	0.875
	leukemia	6	1.380	0.694-2.744	0.359	R	0.001	74.5	0.646
	ALL	4	1.921	0.923-3.998	0.081	R	0.004	77.2	0.118
AG vs GG	NHL	4	1.095	1.000-1.199	0.050	F	0.583	0	0.948
	leukemia	6	1.080	0.849-1.375	0.530	F	0.294	18.4	0.785
	ALL	4	1.133	0.882-1.456	0.328	F	0.250	27	0.082
AA/GA vs GG	NHL	4	1.137	1.043-1.239	0.003	F	0.302	17.8	0.939
	leukemia	6	1.186	0.752-1.870	0.462	R	0.020	62.6	0.766
	ALL	4	1.440	0.906-2.291	0.123	R	0.038	64.4	0.075
AA vs GA/GG	NHL	4	1.177	1.066-1.301	0.001	F	0.228	30.6	0.846
	leukemia	6	1.276	0.780-2.088	0.332	R	0.011	66.3	0.616
	ALL	4	1.560	0.921-2.645	0.098	R	0.016	70.8	0.148

*OR: odds ratio; CI: confidence intervals; Random: random effects model; Fixed: fixed effects model.

on clinical type, we found that heterogeneity mainly came from ALL (Table 2). What's more, Galbraith plot was used to found the outlier in overall studies, and the result showed that there was not an obvious outlier study.

Sensitivity analyses

Sensitivity analysis was performed by sequential omission of individual studies. Our analysis suggested that the results of the overall population and subgroup were quite robust and reliable.

publication bias

Begg funnel plot was used to assess the publication bias of selected literatures. The shapes of the funnel plots did not show any evidence of obvious asymmetry (Figure 3, Figure 4). The Egger test was used to provide statistical evidence of funnel plot symmetry. The results also suggested the absence of publication bias (Table 2).

Discussion

In recent years, *CCND1 G870A* (rs603965) polymorphism has been widely viewed as a low-penetrant susceptibility allele for various cancers. Cell cycle regulator gene is crucial to differentiation, cell proliferation, and apoptosis (Evan et al., 2001). *CCND1 G870A* polymorphism is a silent mutation (Pro 241 Pro), but an A allele, encoding cyclin D1a, has been shown to have a longer half-life than a G allele, encoding cyclin D1b (Gijtenbeek et al., 2005). It was suggested that *CCND1 870A* allele was more likely to contribute to cancer development (Betticher et al., 1995; Solomon et al., 2003). Previous studies of leukemia or non-Hodgkin lymphoma and *CCND1 G870A* polymorphism contained the inconsistency. Given the background, we therefore performed this meta-analysis. Interestingly, we found a crucial association between *CCND1 G870A* polymorphism and non-Hodgkin lymphoma.

The present finding indicated that *CCND1 G870A* polymorphism played an important role in non-Hodgkin lymphoma, which showed a correlation (comparison A vs G: OR=1.114, 95%CI=1.053-1.179, $p=0.000$; homozygote

comparison AA vs GG: OR=1.245, 95%CI=1.110-1.396, $p=0.000$; heterozygote comparison AG vs GG: OR=1.095, 95%CI=1.000-1.199, $p=0.05$; dominant model AA/GA vs GG: OR=1.137, 95%CI=1.043-1.239, $p=0.003$; and recessive model AA vs GA/GG: OR=1.177, 95%CI=1.066-1.301, $p=0.001$). This positive result suggested *CCND1 870A* allele might be crucial to develop disease. The increased risk of non-Hodgkin lymphoma with *CCND1 G870A* polymorphism was observed in a relative large sample size. What is more, no heterogeneity was found in any model. Therefore, our analysis indicated that the results of the non-Hodgkin lymphoma population were robust and reliable. Although the limitation of small amount of studies existed in our study, the risked result was still similar to previous study in other cancers (Catarino et al., 2012; Yang et al., 2012; Bedewy et al., 2013).

Based on our study, correlation between leukemia and *CCND1 G870A* polymorphism was not observed in any model (Table 2). As the result might be due to small-study bias, considering the limited sample size included in our meta-analysis, more primary large scale and well-designed studies are still needed to further evaluate the interaction of *CCND1 G870A* polymorphism with leukemia risk. In addition, different clinical types could increase the negative result. So it was necessary to do further clinical subtype study and analysis.

In the stratified analysis of clinical type, we considered ALL population as the only subgroup on account of the number of articles. The result showed that no association was found in ALL (Table 2). However, when the *P* value in ALL was compared with *P* value in overall leukemia, it decreased obviously to certain degree and tended to have statistical significance. Our result indicated that clinical type might be a critical effect on the association. Furthermore, more studies needed to evaluate the interaction of *CCND1 G870A* polymorphism with ALL risk in various ethnicities.

Heterogeneity between studies was common in meta-analysis. To explore the sources of heterogeneity, we performed meta-regression and stratified analysis. Although we found that leukemia contributed substantial heterogeneity to our results, some heterogeneity can

not be explained by possible source of heterogeneity, such as clinical type of leukemia. What is more, many factors could affect the genomic polymorphism spectrum in populations, such as habits, geographical location, type of diet etc. The ethno-genetic status, the radiation background, age, and bad habits strongly influence on mutagenic processes. Hence, we conducted analysis using the random effects model except heterozygote comparison. In order to further evaluate the between-study heterogeneity, we performed a Galbraith plot to explore the outliers. Subsequently, no outlier was found in our meta-analysis.

Funnel plot, Begg's and Egger's test were used to assess the publication bias of our included studies. Both the shape of funnel plot and statistical results did not reveal any obvious publication bias. This suggests that the publication bias did not make substantial effect on our results and that results of our meta-analysis are relatively stable.

Although comprehensive meta-analysis was conducted to demonstrate the association between *CCND1 G870A* polymorphism and risk of leukemia or non-Hodgkin lymphoma, there are still some limitations that should be pointed out. Firstly, *CCND1 G870A* polymorphism substantially varies across different ethnicities, more primary studies which focused on ethnicities should be carried out. Secondly, we should be cautious to unscramble the result in our study because the included studies of clinical type were limited. Thirdly, as some studies included in our meta-analysis are based on unadjusted estimates, so that some risk factors such as gender, age, family history and environment factors might cause confounding bias.

In spite of the limitations above, our meta-analysis had also several advantages. Firstly, a meta-analysis of the association of *CCND1 G870A* polymorphism on diseases risk is statistically more powerful than any other single study. Secondly, the majority of the eligible studies included in our meta-analysis were population-based. It has been accepted that population-based studies were more representative of the general population than hospital-based studies, and the quality of our eligible studies met our inclusion criteria. Besides, the sensitivity analysis and publication bias analysis showed the stability and credibility of the meta-analysis, and the process of literature selection, data extraction and data analysis in the meta-analysis was well designed and conducted.

In conclusion, *CCND1 G870A* polymorphism may increase non-Hodgkin lymphoma risk, but not leukemia. However, more primary large scale and well-designed studies are still required to evaluate the interaction of *CCND1 G870A* polymorphism with leukemia and non-Hodgkin lymphoma risk.

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