RESEARCH ARTICLE

The *CCND1 G870A* Gene Polymorphism and Brain Tumor Risk: a Meta-analysis

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Abstract

Background: In recent years, numerous studies have been performed to investigate the *CCND1 G870A* gene polymorphism impact on brain tumors susceptibility. Unfortunately, the results of previous studies were inconsistent. Therefore, we performed a meta-analysis to derive a more precise estimation of any association. Materials and Methods: We conducted a search in PubMed, Embase and CNKI covering all published papers up to November, 2013. Odds ratios (ORs) and their 95% confidence intervals (95%CIs) were applied to assess associations. Results: A total of 6 publications including 9 case-control studies met the inclusion criteria. The pooled ORs for the total included studies showed significant association among comparison A *vs* G (OR= 1.246, 95%CI= 1.092-1.423, *p*= 0.001), homozygote comparison AA *vs* GG (OR= 1.566, 95%CI= 1.194-2.054, *p*= 0.001), heterozygote comparison AG *vs* GG (OR= 1.290, 95%CI= 0.934-1.782, *p*= 0.122), dominant model AA/GA *vs* GG (OR= 1.381, 95%CI= 1.048-1.821, *p*= 0.022) and recessive model AA *vs* GA/GG (OR= 1.323, 95%CI= 1.057-1.657, *p*= 0.015) especially in glioma. Conclusions: *CCND1 G870A* polymorphism may increase brain tumor risk, especially for gliomas. However, more primary large scale and well-designed studies are still required to evaluate the interaction of *CCND1 G870A* polymorphism with brain tumor risk.

Keywords: Brain tumors - cyclin D1 gene - polymorphism - meta-analysis

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Introduction

According to the estimates of WHO, cancer was a leading cause of death worldwide and accounted for 7.6 million deaths (13% of all deaths) in 2008 (http://www.who.int/gho/ncd/mortality_morbidity/cancer/en/index.html). The incidence of primary brain tumors and nervous system is estimated at 3.5 per 100,000 persons for all ages, and the mortality is 2.5. The incidence and mortality of men are higher than women (http://globocan.iarc.fr/factsheet.asp#BOTH). According to the classification of pathology (WHO), three common types of brain tumors are glioma, meningioma, and pituitary adenomas. Glioma and meningioma are the two commonest primary brain tumors with approximately 50% and 20% proportion respectively (Inskip et al., 1995), and prolactinoma is the commonest pituitary tumors in adults, occupying more than 60% of all functioning pituitary adenomas (Daly et al., 2006). According to the research, primary brain tumors mostly appear familial aggregation, suggesting an important genetic basis for its tendency. Thus, many studies related to SNP are used to clarify the molecular in disease (Bondy et al., 2008). Regulatory genes of cell cycle mainly detect DNA damage through preventing error propagation and stimulating the cell cycle check points. Hereditary alterations of the critical genes are associated with numerous malignancies including brain tumors (Vogelstein et al., 2004).

CCND1 gene, which is a cell cycle regulatory gene, locating at 11q13 and encoding a protein (cyclin D1), is crucial 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 was found in a variety of tumors (Diehl et al., 2002). The *CCND1* gene exists a common 870 G>A polymorphism (rs603965) at the junction of the fourth exon and intron. It has two transcriptions (transcription A and transcription B). The two transcriptions can code two protein subtypes, cyclin D1a and cyclin D1b. The different proteins exist in the 55 amino acids of C-terminal domain. Some studies suggest that 870 G>A polymorphism and cyclin D1b affect the risk of malignant tumors (Betticher et al., 1995; Bala et al., 2001; Qiuling et al., 2003; Wang et al., 2003). Another study indicates that an A allele may bypass the G1/S checkpoint more easily than those carrying a G allele (Kong et al., 2000). The significant association between the *CCND1* A genotype (AA or AG) and early onset and progression has been reported in various tumors, like hepatocellular carcinoma (Akkiz et al., 2010), colorectal cancer (Yang et al., 2012), and lung cancer (Liu et al., 2012). Given the background, we performed

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this meta-analysis on all published case-control studies to derive a more precise estimation of *CCND1 G870A* gene polymorphism with brain tumors 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 brain tumor risk published up to November, 2013. 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 "brain tumor" or "glioma" or "meningioma" or "pituitary adenomas." 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 Xu Chen).

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 brain tumor risk; (b) supplied the number of individual genotypes for the *CCND1 G870A* gene polymorphisms in brain tumor 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. Ethnic backgrounds were categorized as Caucasian and Mixed. If a study showed the Asian descendent or it was not possible to separate participants according to such phenotype, the group reported was termed as "mixed ethnicity." 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 brain tumors, and significance of the pooled OR was determined by Z test. *P* value of less than 0.05 was considered significant. 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 ethnicity and types of brain tumors.

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. To further investigate the heterogeneity, the Galbraith plot was used in our meta-analysis (Galbraith et al., 1988).

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 31 potentially relevant articles through PubMed, Embase, and CNKI. After screening the title, abstract, or content, seven publications studies were selected. However, a genetic locus of one study did not meet the inclusion criteria, and the study was excluded (Sadetzki et al., 2005). Manual search of references did not cite in any additional article. Finally, a total of six publications including nine case-control studies met the inclusion criteria for the meta-analysis (including a total of 1, 402 brain tumors cases and 1, 504 controls) (Simpson et al., 2001; Gazioglu et al., 2007; Rajaraman et al., 2007; Cander et al., 2012; Chen et al., 2012; Zeybek et al., 2013). There were five studies of Caucasian, four studies of mixed ethnicity. As the two studies reported the results on different brain tumors, each subpopulation was treated as a separate study in our meta-analysis (Rajaraman et al., 2007; Zeybek et al., 2013). There are 3 studies of glioma (Rajaraman et al., 2007; Chen et al., 2012; Zeybek et al., 2013), 3 studies of pituitary adenomas (Simpson et al., 2001; Gazioglu et al., 2007; Cander et al., 2012), 2 studies of meningioma (Rajaraman et al., 2007; Zeybek et al., 2013), and 1 study of Acoustic neuroma (Rajaraman et al., 2007). 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 (Figure 1, Table 1).

Quantitative synthesis of data

The summary results for the association of *CCND1 G870A* gene polymorphism with brain tumors risk are

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

First author	Year	Country	Ethnicity	Tumor type	Source of control	Method of Genotyping	Sample size case/control		HWE of controls
Zeybek (2013a)	2013	Turkey	Caucasian	meningioma	PB	PCR-RFLP	42	155	0.471
Zeybek (2013b)	2013	Turkey	Caucasian	glioma	PB	PCR-RFLP	57	155	0.471
Cander (2012)	2012	Turkey	Caucasian	prolactinoma	PB	PCR-RFLP	113	108	0.092
Chen (2012)	2012	China	Mixed	glioma	PB	PCR-RFLP	170	170	0.447
Gazioglu (2007)	2007	Turkey	Caucasian	pituitary adenomas	PB	PCR-RFLP	130	129	0.956
Rajaraman (2007a)	2007	USA	Mixed	glioma	HB	TaqMan	374	528	0.266
Rajaraman (2007b)	2007	USA	Mixed	meningioma	HB	TaqMan	151	528	0.266
Rajaraman (2007c)	2007	USA	Mixed	acoustic neuroma	HB	TaqMan	71	528	0.266
Simpson (2001)	2001	Mixed	Caucasian	pituitary adenomas	PB	PCR-RFLP	294	414	0.586

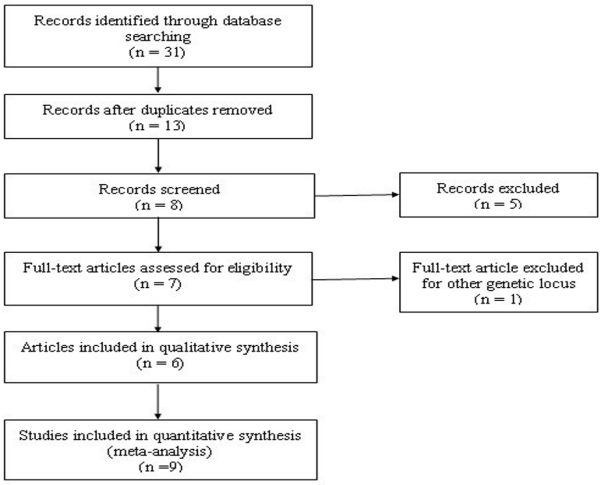

Figure 1. Flow Diagram for Identification of Eligible Studies for This Meta-analysis

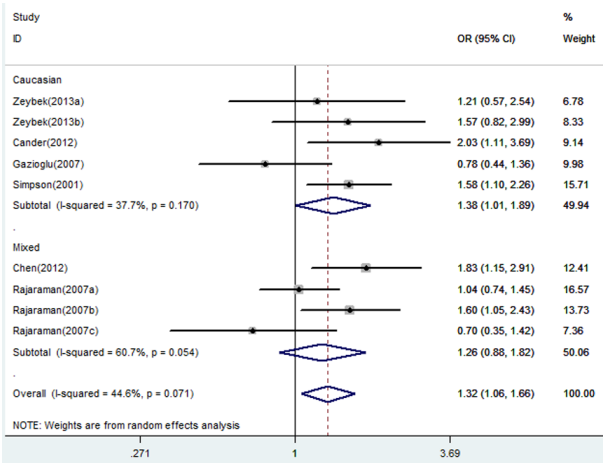

Figure 2. Forest Plot of CCND1 G870A Polymorphism with Brain Tumors Risk (Recessive model AA *vs* AG/GG)

shown in Table 2. After all of the eligible studies were pooled into the meta-analysis, significant association between *CCND1 G870A* gene polymorphism and brain tumors risk were found in comparison A *vs* G: OR=1.246, 95%CI=1.092-1.423, *p*=0.001; homozygote comparison AA *vs* GG: OR=1.566, 95%CI=1.194-2.054, *p*=0.001; dominant model AA/GA *vs* GG: OR=1.381, 95%CI=1.048-1.821, *p*=0.022; and recessive model AA *vs* GA/GG: OR=1.323, 95%CI=1.057-1.657, *p*=0.015 (Figure 2, Figure 3, Table 2).

In further stratified analyses, the increased risk was observed in the subgroups of glioma (comparison A *vs* G: OR=1.227, 95%CI=1.056-1.426, *p*=0.007; homozygote comparison AA *vs* GG: OR=1.420, 95%CI=1.056-1.911, *p*=0.020; dominant model AA/GA *vs* GG: OR=1.301, 95%CI=1.029-1.644, *p*=0.028; and recessive model AA *vs* GA/GG: OR=1.304, 95%CI=1.016-1.672, *p*=0.037), and Caucasian ethnicity (comparison A *vs* G: OR=1.338, 95%CI=1.054-1.700, *p*=0.017; homozygote comparison AA *vs* GG: OR=1.926, 95%CI=1.191-3.116, *p*=0.008; recessive model AA*v*GA/GG: OR=1.404, 95%CI=1.110-1.776, *p*=0.005) (Figure 2, Table 2).

Heterogeneity analysis

Heterogeneity existed in our current study. To explore the sources of heterogeneity, we performed meta-regression and subgroup analysis. After assessing the source of heterogeneity for all genetic models by subgroup analysis on ethnicity, the heterogeneity was partly decreased in different types of brain tumors (Table 2). What's more, Galbraith plot found the outlier in the study Cander et al. (Cander et al., 2012). After removal, the heterogeneity disappeared in all of comparisons (comparison A *vs* G: P_Q=0.278, I^2=19.2; homozygote comparison AA *vs* GG: P_Q=0.437, I^2=0; heterozygote comparison AG *vs* GG: P_Q=0.958, I^2=0; dominant model AA/GA *vs* GG: P_Q=0.850, I^2=0; and recessive model AA *vs* GA/GG: P_Q=0.265, I^2=20.8). It revealed that the study Cander et al. mainly contributed the between-study heterogeneity (Figure 3).

Sensitivity analyses

Sensitivity analysis was performed by sequential omission of individual studies. Our analysis indicated that the results of the overall population and subgroup were 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 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 possible low-penetrant susceptibility allele for a variety of cancers. Cell

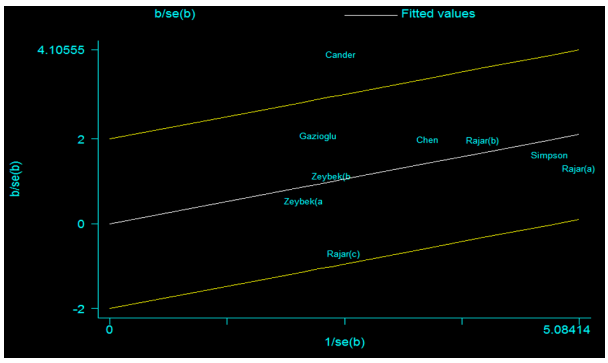

Figure 3. Galbraith Plot of CCND1 G870A Polymorphism with Brain Tumors (Homozygote Comparison AA *vs* GG)

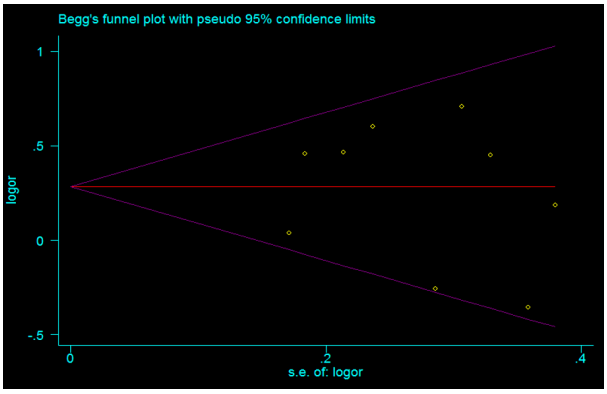

Figure 4. Funnel plot CCND1 G870A Polymorphism with Brain Tumors (Recessive Model AA *vs* AG/GG)

cycle regulator gene is a key factor to cell proliferation, differentiation and apoptosis (Evan et al., 2001). Although *CCND1 G870A* polymorphism is a silent mutation (Pro 241 Pro), an A allele has been shown to have a longer half-life than a G allele encoded protein (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 brain tumors contained the inconsistency. Given the background, we therefore performed this meta-analysis. Interestingly, we found a crucial association between *CCND1 G870A* polymorphism and brain tumors, especially glioma.

In the stratified analyses based on ethnicity and tumor type, the results showed that increased tumor risk was significantly associated with Caucasian population and glioma. The present findings indicated that *CCND1 G870A* polymorphism played an important role in brain tumors, especially in glioma, which showed a distinct correlation (comparison A *vs* G: OR=1.227, 95%CI=1.056-1.426, *p*=0.007; homozygote comparison AA *vs* GG: OR=1.420, 95%CI=1.056-1.911, *p*=0.020; dominant model AA/GA *vs* GG: OR=1.301, 95%CI=1.029-1.644, *p*=0.028; and recessive model AA *vs* GA/GG: OR=1.304, 95%CI=1.016-1.672, *p*=0.037). In other types of brain tumors, the associations were not very obvious, but might induct a risk development of brain tumors (for meningioma, AA *vs* GA/GG: OR=1.488, 95%CI=1.032-2.144, *p*=0.033; for pituitary adenomas, AA *vs* GG: OR=2.379, 95%CI=1.095-

Table 2. Meta-analysis of CCND1 G870A polymorphism and Brain Tumors

Comparison	Population	N	Test of association			Model	Test of heterogeneity		Pegger
			OR	95% CI	*P*		*P*	I^2(%)	
A vs. G	Overall	9	1.246	1.092-1.423	0.001	R	0.090	41.6	0.488
	Caucasian	5	1.338	1.054-1.700	0.017	R	0.058	56.1	0.529
	Glioma	3	1.227	1.056-1.426	0.007	F	0.575	0	-
	Meningioma	2	1.235	0.984-1.549	0.068	F	0.667	0	-
	pituitary adenomas	3	1.422	0.979-2.067	0.065	R	0.013	77.2	-
	prolactinoma	2	1.558	0.792-3.063	0.199	R	0.013	83.6	-
AA vs. GG	Overall	9	1.566	1.194-2.054	0.001	R	0.078	43.4	0.436
	Caucasian	5	1.926	1.191-3.116	0.008	R	0.069	54.1	0.446
	Glioma	3	1.420	1.056-1.911	0.020	F	0.664	0	-
	Meningioma	2	1.510	0.982-2.322	0.060	F	0.635	0	-
	pituitary adenomas	3	2.379	1.095-5.168	0.029	R	0.019	74.7	-
	prolactinoma	2	2.436	0.660-8.990	0.181	R	0.017	82.4	-
AG vs. GG	Overall	9	1.290	0.934-1.782	0.122	R	0.001	70.6	0.302
	Caucasian	5	1.603	0.775-3.317	0.203	R	0	83.7	0.229
	Glioma	3	1.225	0.954-1.573	0.112	F	0.337	8.0	-
	Meningioma	2	1.009	0.690-1.475	0.963	F	0.936	0	-
	pituitary adenomas	3	2.184	0.656-7.271	0.203	R	0	91.6	-
	prolactinoma	2	1.810	0.478-6.858	0.383	R	0.005	87.2	-
AA/GA vs. GG	Overall	9	1.381	1.048-1.821	0.022	R	0.004	64.8	0.205
	Caucasian	5	1.727	0.917-3.253	0.090	R	0.000	81.0	0.230
	Glioma	3	1.301	1.029-1.644	0.028	F	0.876	0	-
	Meningioma	2	1.162	0.819-1.647	0.400	F	0.906	0	-
	pituitary adenomas	3	2.277	0.789-6.576	0.128	R	0	90.3	-
	prolactinoma	2	1.996	0.520-7.660	0.314	R	0.003	88.9	-
AA vs.GA/GG	Overall	9	1.323	1.057-1.657	0.015	R	0.071	44.6	0.75
	Caucasian	5	1.404	1.110-1.776	0.005	F	0.170	37.7	0.722
	Glioma	3	1.304	1.016-1.672	0.037	R	0.127	51.6	-
	Meningioma	2	1.488	1.032-2.144	0.033	F	0.521	0	-
	pituitary adenomas	3	1.363	0.820-2.263	0.232	R	0.046	67.5	-
	prolactinoma	2	1.682	1.083-2.610	0.021	F	0.345	0	-

5.168, p=0.029). As the observed increase in risk of brain tumors might be due to small-study bias, considering the limited sample size and ethnicity 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 brain tumors risk. Although the limitation existed in our study, the risked result was similar to previous study in other cancers (Catarino et al., 2012; Chen et al., 2012; Yang et al., 2012; Bedewy et al., 2013; Wang et al., 2013).

In subgroup of ethnicity, the increased association also found in Caucasian population (comparison A *vs* G: OR=1.338, 95%CI=1.054-1.700, p=0.017; homozygote comparison AA *vs* GG: OR=1.926, 95%CI=1.191-3.116, p=0.008; recessive model AA *vs* GA/GG: OR=1.404, 95%CI=1.110-1.776, p=0.005). Our results indicate that ethnicity might be a critical effect of the polymorphic allele on susceptibility to brain tumors. Because different ethnicities have different genetic backgrounds, life styles, dietary habits and environmental exposures. Considering small amount of studies in African and Asian, more studies needed to evaluate the interaction of *CCND1 G870A* polymorphism with brain tumors risk in various ethnicities.

Heterogeneity between studies was common in meta-analysis. To explore the sources of heterogeneity, we performed meta-regression and stratified analyses. Although we found that the types of brain tumors contributed substantial heterogeneity to our results, some heterogeneity can not be explained by several possible sources of heterogeneity, such as types of brain tumors, ethnicity, and source of control. 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 analyses using the random effects model. In order to further evaluate the between-study heterogeneity, we performed a Galbraith plot to explore the outliers. Subsequently, the study Cander et al. contributed a significant heterogeneity to the overall. With omitting the outlier, heterogeneity disappeared in our meta-analysis.

In the present study, 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 show any obvious publication bias. This suggests that the publication bias did not make substantial negative 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 brain tumors, there are still some limitations that should be pointed out. Firstly, the primary studies included in our meta-analysis mainly investigated the Caucasian population. Since *CCND1 G870A* polymorphism substantially vary across different ethnicities, more primary studies which focused on other ethnicities such as Asian and African population should be carried out. Secondly, we should be cautious to unscramble the result in our study because the included studies of tumor 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. A meta-analysis of the association of *CCND1 G870A* polymorphism on cancer 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 brain tumors risk, especially glioma. However, more primary large scale and well-designed studies are still required to evaluate the interaction of *CCND1 G870A* polymorphism with brain tumors risk.

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