

Original Article

The CDKN2A-CDKN2B rs4977756 polymorphism and glioma risk: a meta-analysis

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Abstract: The association between the rs4977756 single nucleotide polymorphism (SNP) and glioma risk has been studied, but these studies have yielded conflicting results. In order to explore this association, we performed a meta-analysis. A comprehensive literature search was performed using PubMed and EMBASE database. Six articles including 12 case-control studies in English with 12022 controls and 6871 cases were eligible for the meta-analysis. Subgroup analyses were conducted by ethnicity and source of controls. Our meta-analysis found that rs4977756 polymorphism was associated with glioma risks in homozygote, heterozygote, dominant, recessive and additive genetic models (GG versus AA: OR=1.55, 95% CI=1.42-1.69, $P_h=0.996$, $I^2=0.0\%$; AG versus AA: OR=1.20, 95% CI=1.12-1.28, $P_h=0.934$, $I^2=0.0\%$; recessive model: OR=1.39, 95% CI=1.28-1.50, $P_h=0.995$, $I^2=0.0\%$; dominant model: OR=1.29, 95% CI=1.21-1.37, $P_h=0.923$, $I^2=0.0\%$; additive model: OR=1.24, 95% CI=1.19-1.30, $P_h=0.966$, $I^2=0.0\%$). Moreover, our results suggested that CDKN2A-CDKN2B rs4977756 polymorphism was associated with a notable increased risk of glioma in Europeans. However, in Asians, we could not come to a conclusion because of lack of studies. Sensitivity analysis showed the omission of any study made no significant difference. No evidence of publication bias was produced. Our meta-analysis suggested that rs4977756 polymorphism was associated with increased risk of glioma. Moreover, additional studies should be further investigated to draw a more accurate conclusion.

Keywords: Glioma, CDKN2A-CDKN2B, rs4977756, polymorphism, meta-analysis

Introduction

Gliomas are the most common tumor of the central nervous system in adults accounting for more than 70% of all brain tumors, and of these, glioblastoma (GBM) is the most frequent and malignant histologic type [1]. On the basis of cellular lineage, they are classified as astrocytomas, oligodendrogliomas, oligoastrocytomas and glioblastoma, and they also can be classified into four clinical grades: World Health Organization (WHO) grade I (pilocytic astrocytomas), WHO grade II (diffuse low grade gliomas), WHO grade III (anaplastic gliomas) and WHO grade IV (GBM) [2]. The mechanisms of carcinogenesis of gliomas remain uncertain. More and more studies suggest that the number of genetic alterations play a pivotal role in glioma susceptibility [3, 4].

The rs4977756 polymorphism is in mapped 59 kb telomeric to CDKN2B within a 122-kb region

of LD at 9p21.3. This region encompasses the CDKN2A-CDKN2B tumor suppressor genes. CDKN2A encodes p16 (INK4A), a negative regulator of cyclin-dependent kinases and p14 (ARF1), an activator of p53 [5]. Previous genetic association studies, especially genome-wide association studies (GWAS), indicated that the rs4977756 polymorphism may contribute to the increased risk of glioma [6]. However, the results were inconclusive. To gain better insight into impact of rs4977756 polymorphic variants on the risk of glioma, we performed a meta-analysis from all eligible case-control studies to derive a more precise estimation of the association between the CDKN2A/B rs4977756 polymorphism and glioma risk.

Methods

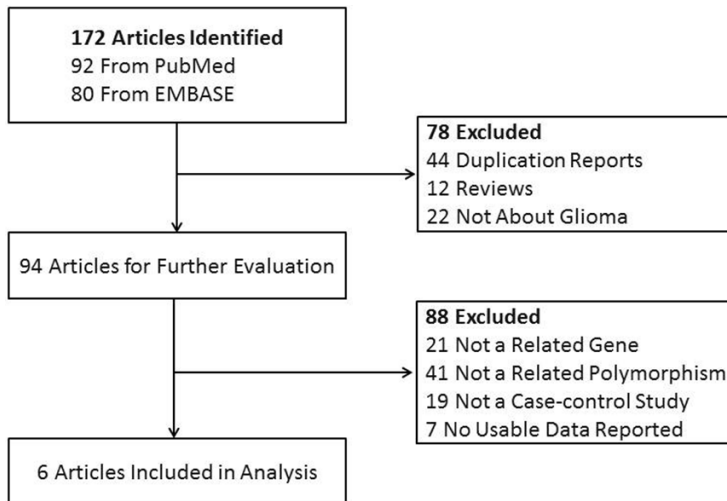
Study identification and selection

A comprehensive literature search was performed through PubMed and EMBASE using

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

First author	Year	Country	Ethnicity	Controls source	Cases/ Controls	Case			Control			A allele in controls (%)	HWE
						GG	AG	AA	GG	AG	AA		
Shete (German)	2009	German	European	PB	499/566	108	240	151	90	265	211	0.61	0.66
Shete (Sweden)	2009	Sweden	European	PB	632/770	157	325	150	168	379	223	0.54	0.77
Shete (US)	2009	US	European	HB	1247/2235	276	594	377	370	1083	782	0.59	0.88
Shete (French)	2009	French	European	PB	1352/1583	239	639	474	209	723	651	0.64	0.71
Schoemaker (Denmark)	2010	Denmark	European	PB	121/245	29	55	37	27	64	54	0.59	0.30
Schoemaker (Sweden)	2010	Sweden	European	PB	196/367	57	97	42	80	177	110	0.54	0.58
Schoemaker (UK-North)	2010	UK	European	PB	375/627	85	182	108	110	301	216	0.58	0.77
Schoemaker (UK-South)	2010	UK	European	PB	232/390	49	113	70	68	181	141	0.59	0.45
Wang	2011	US	European	PB	332/817	68	151	113	125	389	303	0.61	0.99
Stefano	2012	US	European	HB	849/1190	137	409	303	143	531	516	0.66	0.96
Li	2012	China	Asian	PB	226/251	15	72	139	15	84	152	0.77	0.46
Safaeian	2013	US	European	HB	810/3081	179	383	248	509	1460	1112	0.60	0.42

PB population-based, HB hospital-based, HWE *P* values for Hardy-Weinberg equilibrium for each study's control group.

**Figure 1.** Flow chart showing study selection procedure.

the following search terms: (CDKN2A OR CDKN2B OR CDKN2A/B OR rs4977756) AND (variant OR polymorphism OR variation OR polymorphisms) AND (glioma or glioblastoma or astrocytoma). Additional studies were identified by hand searching references. The following criteria were used for our meta-analysis: (1) a case-control study evaluating the rs4977756 polymorphism in the CDKN2A/B gene; (2) studies with full-text articles; (3) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) genotype distribution of control population must be in Hardy-Weinberg equilibrium (HWE); (5) no overlapping data. The exclusion criteria were as follows: (1) Reviews or case reports, case studies without control groups; (2) Studies that were not related to human cancer research; (3)

Studies that do not provide sufficient data; (4) Overlapping data. If studies had the same or overlapping data, only the largest study should be included in the final analysis.

Data extraction

Three investigators independently extracted the data from all the eligible studies according to the selection criteria listed above. Any disagreement was resolved by discussion. The following data were collected from each study: first author, publication year, country, ethnicity (European or Asian), source of controls, numbers of cases and

controls, genotype frequency of cases and controls, G allele frequency in controls, and *P* value for Hardy-Weinberg equilibrium.

Statistical analysis

A Chi-square test using a web-based program (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>) was applied to determine if observed frequencies of genotypes in controls conformed to HWE ($P < 0.1$ was considered significant). The crude ORs and 95% CIs in each case-control study were used to assess the strength of the associations between the CDKN2A/B rs4977756 polymorphisms and glioma risk. The pooled ORs were performed for homozygote model (GG vs. AA), a heterozygote (AG vs. AA), a dominant model (GG + AG vs. AA),

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Table 2. Results of overall and stratified analyses for the association of rs4977756 polymorphism and risk of glioma

Variables	Number	Homozygote (GG vs. AA)		Heterozygote (AG vs. AA)		Recessive model (GG vs. AG+AA)		Dominant model (GG+AG vs. AA)		Additive model (G vs. A)	
		OR (95% CI)	P _h	OR (95% CI)	P _h	OR (95% CI)	P _h	OR (95% CI)	P _h	OR (95% CI)	P _h
Total	12 (6871/12022)	1.55 (1.42, 1.69)	0.996	1.20 (1.12, 1.28)	0.934	1.39 (1.28, 1.50)	0.995	1.29 (1.21, 1.37)	0.923	1.24 (1.19, 1.30)	0.966
Ethnicity											
European	11 (6645/11771)	1.56 (1.43, 1.70)	0.999	1.21 (1.13, 1.30)	0.972	1.39 (1.29, 1.51)	0.994	1.30 (1.21, 1.38)	0.988	1.25 (1.19, 1.30)	0.997
Asian	1 (226/251)	1.09 (0.52, 2.32)	-	1.20 (1.12, 1.28)	-	1.12 (0.53, 2.34)	-	0.96 (0.66, 1.39)	-	0.99 (0.73, 1.34)	-
Source of controls											
Population-based	9 (3965/5516)	1.53 (1.35, 1.73)	0.973	1.20 (1.10, 1.32)	0.890	1.36 (1.22, 1.51)	0.976	1.28 (1.17, 1.42)	0.823	1.23 (1.16, 1.31)	0.884
Hospital-based	3 (2906/6506)	1.58 (1.38, 1.79)	0.954	1.20 (1.12, 1.28)	0.934	1.39 (1.28, 1.50)	0.993	1.29 (1.21, 1.37)	0.923	1.24 (1.19, 1.30)	0.879

P_h P-value of Q-test for heterogeneity test. Fix-effects model was used when P-value for heterogeneity test >0.05; otherwise, random-effects model was used.

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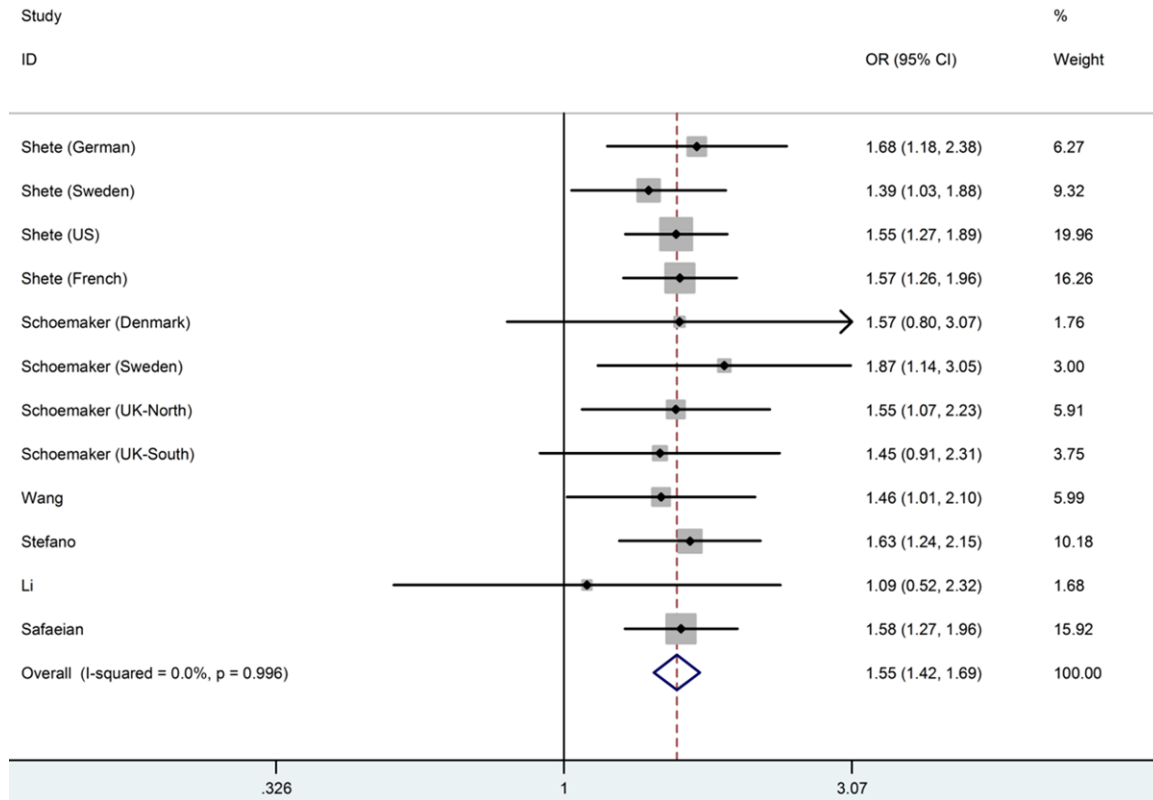


Figure 2. Meta-analysis of the association between CDKN2AB rs4977756 polymorphism and susceptibility to glioma (GG versus AA).

a recessive model (GG vs. AG + AA) and an additive model (G vs. A). Subgroup analyses were performed based on the source of controls, ethnicity and country. Heterogeneity assumption was checked by a Q-test, and I^2 ($I^2 = 100\% \times (Q - df) / Q$) statistic was calculated to quantify the proportion of the total variation across studies due to heterogeneity. If P -value < 0.05 for the Q-test indicated the existence of heterogeneity among studies, then the pooled OR estimate of each study was calculated by the random-effects model (the DerSimonian and Laird method [7]). Otherwise, the fixed-effects model (the Mantel-Haenszel method [8]) was used. An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Sensitivity analyses were performed to evaluate the stability of the results by omitting each study to reflect the influence of the individual data to the summary ORs. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test ($P < 0.05$ was considered a significant publication bias) [9]. All statistical

analyses were performed using the STATA software (version 12; Stata Corporation, College Station, TX, USA).

Results

Extraction process and study characteristics

A total of 6 articles [6, 10-14] including 12 case-control studies in English with 12022 controls and 6871 cases were eligible for the meta-analysis. The main results of this meta-analysis were listed in **Table 1**. Of all the eligible studies collected in this meta-analysis, eleven were conducted in European populations and one was in Asian. Nine studies were population-based and three were hospital-based studies. **Figure 1** shows the study selection procedure.

Meta-analysis results

Table 2 listed the main results of the meta-analysis for the CDKN2A/B rs4977756 polymorphism. And a significant association between this polymorphism and glioma risk was observed when all eligible studies were

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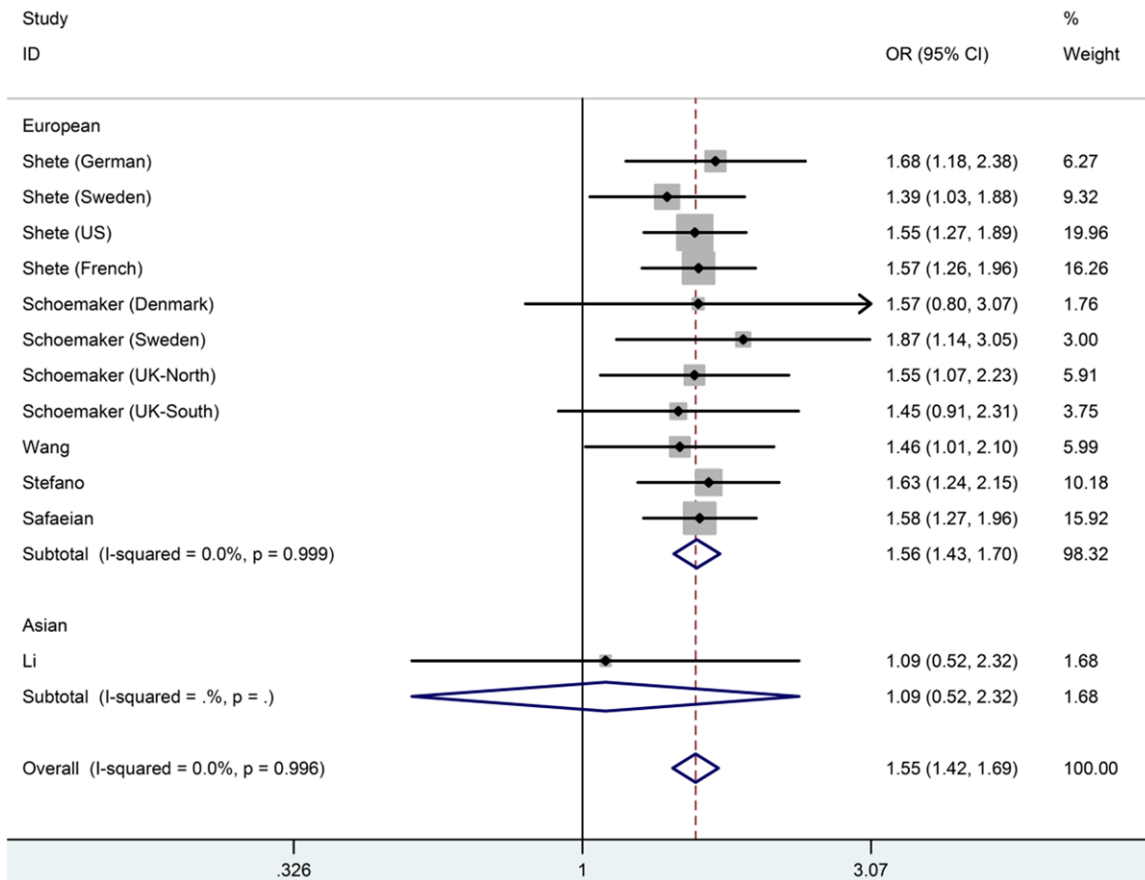


Figure 3. Forest plot from the meta-analysis of CDKN2AB rs4977756 polymorphism and the risk of glioma stratified by ethnicity using homozygote model (GG versus AA).

pooled into meta-analysis in all genetic models (GG versus AA: OR=1.55, 95% CI=1.42-1.69, $P_h=0.996$, $I^2=0.0\%$; AG versus AA: OR=1.20, 95% CI=1.12-1.28, $P_h=0.934$, $I^2=0.0\%$; recessive model: OR=1.39, 95% CI=1.28-1.50, $P_h=0.995$, $I^2=0.0\%$; dominant model: OR=1.29, 95% CI=1.21-1.37, $P_h=0.923$, $I^2=0.0\%$; additive model: OR=1.24, 95% CI=1.19-1.30, $P_h=0.966$, $I^2=0.0\%$). **Figure 2** shows the overall meta-analysis of CDKN2A/B rs4977756 polymorphism and glioma risk in homozygote model. When stratified by ethnicity, our results showed CDCC26 rs4295627 polymorphism was associated with increased risk of glioma among European population (GG versus AA: OR=1.56, 95% CI=1.43-1.70, $P_h=0.999$, $I^2=0.0\%$; AG versus AA: OR=1.21, 95% CI=1.13-1.30, $P_h=0.972$, $I^2=0.0\%$; recessive model: OR=1.39, 95% CI=1.29-1.51, $P_h=0.994$, $I^2=0.0\%$; dominant model: OR=1.30, 95% CI=1.21-1.38, $P_h=0.988$, $I^2=0.0\%$; additive model: OR=1.25, 95% CI=1.19-1.30, $P_h=0.997$, $I^2=0.0\%$), but not

among Asians. **Figure 3** shows the overall meta-analysis of CDKN2A/B rs4977756 polymorphism and the risk of glioma stratified by ethnicity in homozygote model. As for the control source, we found increased risk of glioma in hospital-based studies (GG versus AA: OR=1.58, 95% CI=1.38-1.79, $P_h=0.954$, $I^2=0.0\%$; AG versus AA: OR=1.20, 95% CI=1.12-1.28, $P_h=0.934$, $I^2=0.0\%$; recessive model: OR=1.39, 95% CI=1.28-1.50, $P_h=0.993$, $I^2=0.0\%$; dominant model: OR=1.29, 95% CI=1.21-1.37, $P_h=0.923$, $I^2=0.0\%$; additive model: OR=1.24, 95% CI=1.19-1.30, $P_h=0.879$, $I^2=0.0\%$). Studies with population-based controls also showed elevated glioma risk in all genetic models (GG versus AA: OR=1.53, 95% CI=1.35-1.73, $P_h=0.973$, $I^2=0.0\%$; AG versus AA: OR=1.20, 95% CI=1.10-1.32, $P_h=0.890$, $I^2=0.0\%$; recessive model: OR=1.36, 95% CI=1.22-1.51, $P_h=0.976$, $I^2=0.0\%$; dominant model: OR=1.28, 95% CI=1.17-1.42, $P_h=0.823$, $I^2=0.0\%$; additive model: OR=1.23, 95%

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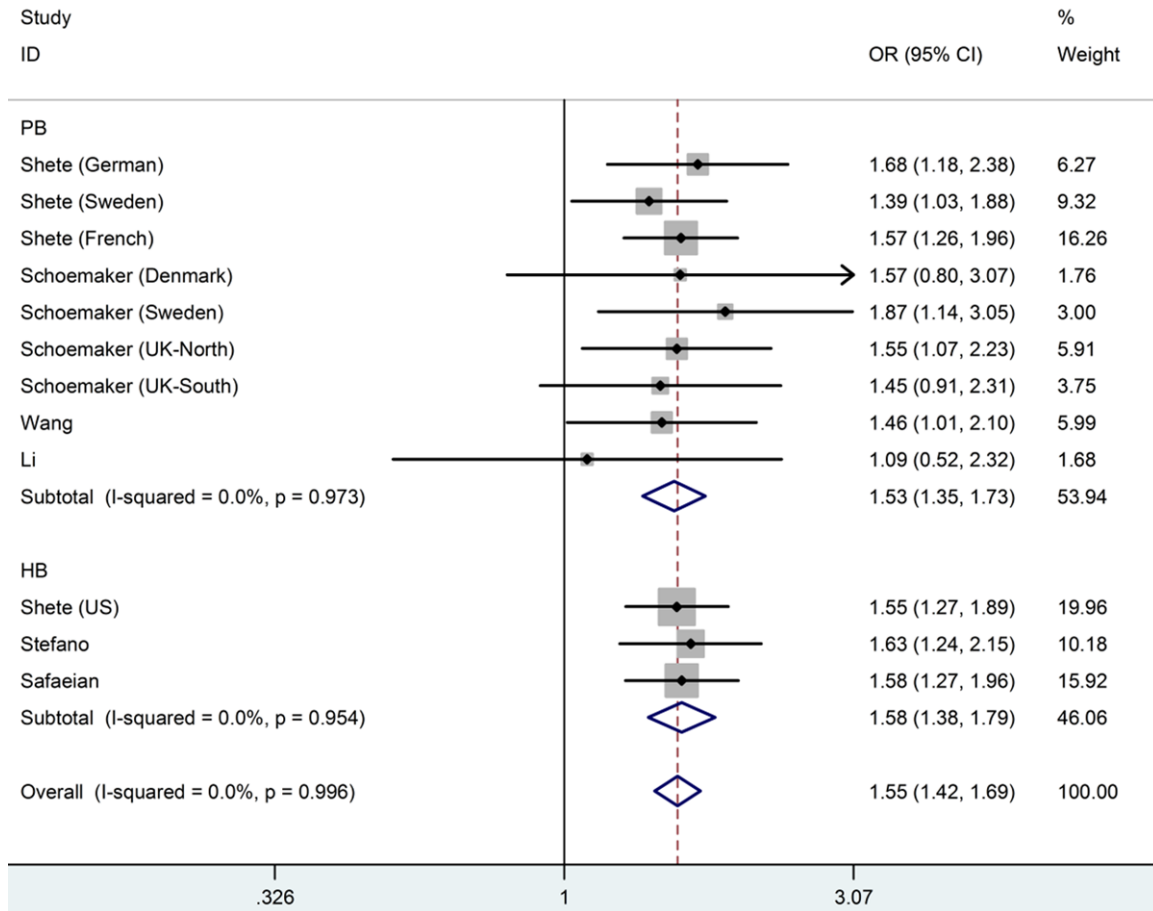


Figure 4. Forest plot from the meta-analysis of CDKN2AB rs4977756 polymorphism and the risk of glioma stratified by source of controls using homozygote model (GG versus AA).

CI=1.16-1.31, $P_h=0.884$, $I^2=0.0\%$). **Figure 4** shows the overall meta-analysis of CDKN2A/B rs4977756 polymorphism and the risk of glioma stratified by source of controls in homozygote model.

Test of heterogeneity

The heterogeneity test showed that there was no significant between-study heterogeneity in terms of the rs4977756 polymorphisms in all genetic models (GG versus AA: $P=0.996$ for heterogeneity, $I^2=0.0\%$; AG versus AA: $P=0.934$ for heterogeneity, $I^2=0.0\%$; recessive model: $P=0.995$ for heterogeneity, $I^2=0.0\%$; dominant model: $P=0.923$ for heterogeneity, $I^2=0.0\%$; additive model: $P=0.966$ for heterogeneity, $I^2=0.0\%$).

Sensitivity analysis

In the sensitivity analysis, the influence of each study on the pooled OR was examined by

repeating the meta-analysis while omitting one study each time, and the omission of any study made no significant difference. As shown in **Figure 5**, in this meta-analysis, the results of sensitive analysis showed that any single study did not influence the overall results qualitatively, indicating robustness and reliability of our results.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The polymorphism showed consistent results, indicating no publication biases. The shapes of the funnel plot did not indicate any evidence of obvious asymmetry in homozygote model (**Figure 6**), and the Egger's test suggested the absence of publication bias (GG versus AA: $P=0.457$; AG versus AA: $P=0.913$; recessive model: $P=0.297$; dominant model: $P=0.940$; additive model: $P=0.495$).

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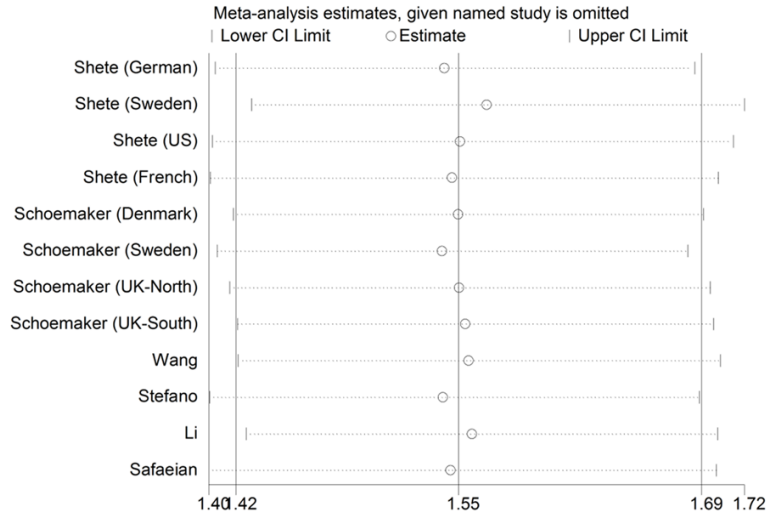


Figure 5. Sensitivity analysis of the summary OR coefficients on the association for the CDKN2AB rs4977756 polymorphism with glioma risk.

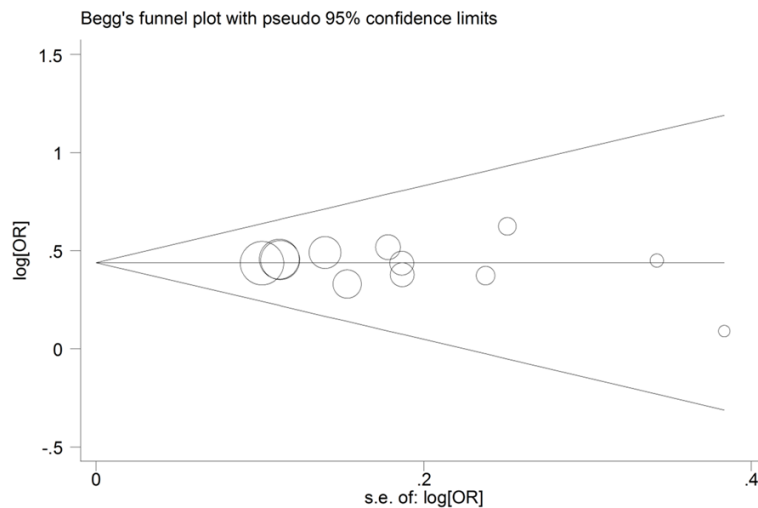


Figure 6. Begg's funnel plots of rs4977756 polymorphism and glioma risk for publication bias test in the homozygote model (GG vs. AA).

Discussion

As we know, SNPs are associated with many diseases. Genome-wide association study (GWAS) is a powerful research strategy which uses SNPs as markers to identify susceptibility genes of many complex diseases [15]. Many meta-analyses have already been made to explore the association between SNP polymorphisms and the risk of glioma [16-18]. The rs4977756 is mapped 59 kb telomeric to CDKN2B within a 122-kb region of LD at 9p21.3. CDKN2B lies adjacent to the well-

known tumor suppressor gene CDKN2A (encoding p16INK4A and p14ARF) in a region that is frequently mutated, deleted or hypermethylated in a wide variety of tumors, including high-grade glioma [19]. Researches show that germline mutation of CDKN2A-CDKN2B causes the familial melanoma and glioblastoma syndrome [20, 21]. Furthermore, Regulation of p16/p14ARF is a vital factor for sensitivity to ionizing radiation, which is the only environmental factor strongly linked to gliomagenesis [22]. Many studies provide the evidence that mutations in CDKN2A-CDKN2B may contribute to glioma predisposition.

In this meta-analysis, including a total of 12022 controls and 6871 cases from 12 studies (6 articles), we ascertained that the CDKN2A-CDKN2B rs4977756 polymorphism was significantly associated with increased glioma risk. To our knowledge, this is the first study to investigate the association between the CDKN2A/B rs4977756 polymorphism and glioma risk. In total, we found rs4977756 polymorphism was associated with increased risk of glioma in all genetic models especially in homozygote models.

As for ethnicity, rs4977756 polymorphism was associated with increased risk of glioma among Europeans. However, among Asians, there was only one study in Asians, so we could not come to a conclusion. Moreover, people should pay more attention to the risk of glioma among Asians. Ethnicity would influence tumor susceptibility by different background and environmental exposures [23]. When concerning source of controls, significantly increased risk was observed in all the genetic models in both population-based group and hospital-based group. The population-based controls might be

better to reduce biases due to the fact that the controls may be representative of the general population [16].

Some possible limitations in this meta-analysis should be discussed. First, the number of researched studies was not sufficiently large for a comprehensive analysis, especially for analyses of subgroup. Only one study in Asians was included in this meta-analysis. More studies need to be done to evaluate whether this polymorphism affects the risk of glioma in different ethnicities. Second, our results were based on unadjusted estimates, while a more accurate OR should be corrected for age, sex, drinking, smoking, and other factors that are associated with cancer risk [24]. Third, since more detailed individual information of gene-gene and gene-environment interaction was unavailable, we were not able to conduct further evaluation. Nevertheless, our meta-analysis has some advantages. First, well-designed selection methods increased the statistical power of our meta-analysis. Second, there was no evidence of between-study heterogeneity, suggesting the homogeneity of the study populations. Third, the results did not show any evidence of publication bias. Fourth, all genotypes of controls were consistent with HWE ($P>0.1$).

In conclusion, this meta-analysis suggests that CDKN2A-CDKN2B rs4977756 polymorphism was significantly associated with increased glioma risk. There was an increased risk in Europeans. But in Asians, we could not come to a conclusion. And additional studies should be further investigated to draw a more accurate conclusion.

Acknowledgements

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Disclosure of conflict of interest

None.

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