Int J Clin Exp Med 2016;9(2):2590-2594
www.ijcem.com /ISSN:1940-5901/IJCEM0016221

Original Article

CDKN2A/B rs4977756 and glioma risk: a meta-analysis

Dongsheng Wang, Hongqiang Zhang, Zhongbo Yuan, Zhikuan Yu, Ting Yang, Bo Zhang, Yang Liu, Xiaoxue Jia

Department of Neurosurgery, Second Affiliated Hospital of Dalian Medical University, 467 Zhong Shan Road, Dalian 116023, Liaoning, People's Republic of China

Received September 15, 2015; Accepted December 5, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Several studies were performed to investigate the association between CDKN2A/B rs4977756 polymorphism and the risk of glioma. However, the results were inconsistent. Thus, we performed this meta-analysis. Methods: Eleven studies including 12814 glioma patients and 21140 controls were included in the meta-analysis. The pooled odds ratio (OR) and its corresponding 95% confidence interval (CI) was assessed. Results: CDKN2A/B rs4977756 polymorphism was significantly associated with an increased risk of glioma (OR=1.25; 95% CI, 1.21-1.30; P<0.00001). In the subgroup analysis by race, CDKN2A/B rs4977756 polymorphism was significantly associated with an increased risk of glioma in Caucasian (OR=1.27; 95% CI, 1.22-1.31; P<0.00001). However, no significant association between CDKN2A/B rs4977756 polymorphism and glioma risk was found in Asian (OR=1.05; 95% CI, 0.92-1.21; P=0.45). Conclusions: This meta-analysis suggested that DKN2A/B rs4977756 polymorphism may be a risk factor of glioma.

Keywords: Glioma, CDKN2A/B, meta-analysis, polymorphism

Introduction

Gliomas make up about 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors [1]. Despite the growing number of preclinical and clinical trials focused on the treatment of malignant gliomas, the prognosis for this disease remains grim [2]. Therefore, several molecular markers have been proposed to predict risk of glioma, including gene polymorphisms. The CDKN2A/B gene is located in the chromosome 9p21 region, which has been highlighted as the strongest genetic susceptibility locus for cardiovascular disease and diabetes [3, 4]. Several studies were performed to investigate the association between CDKN2A/B rs4977756 polymorphism and the risk of glioma [5-15]. However, the results were inconsistent. Thus, we performed this meta-analysis.

Materials and methods

Search for publications

We conducted a literature search of the PubMed and EMBASE databases, without a language limitation, covering all papers published up to Aug 2015, using the following keywords and subject terms: CDKN2A/B, polymorphism, glioma, brain tumor. We expanded the scope of the computerized literature search on the basis of the reference lists of retrieved articles.

Inclusion criteria

The following inclusion criteria were used: (1) the study assessed the association between CDKN2A/B rs4977756 polymorphism and the risk of glioma; (2) the study population included subjects with and without glioma; (3) the study reported the odds ratio (OR) and 95% confidence interval (CI).

Data extraction

The following data were recorded from each article: author, year of publication, country, ethnicity of the participants, age, gender, numbers of cases and controls. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Statistical analysis

The strength of association between CDKN2A/B rs4977756 polymorphism and the risk of glio-

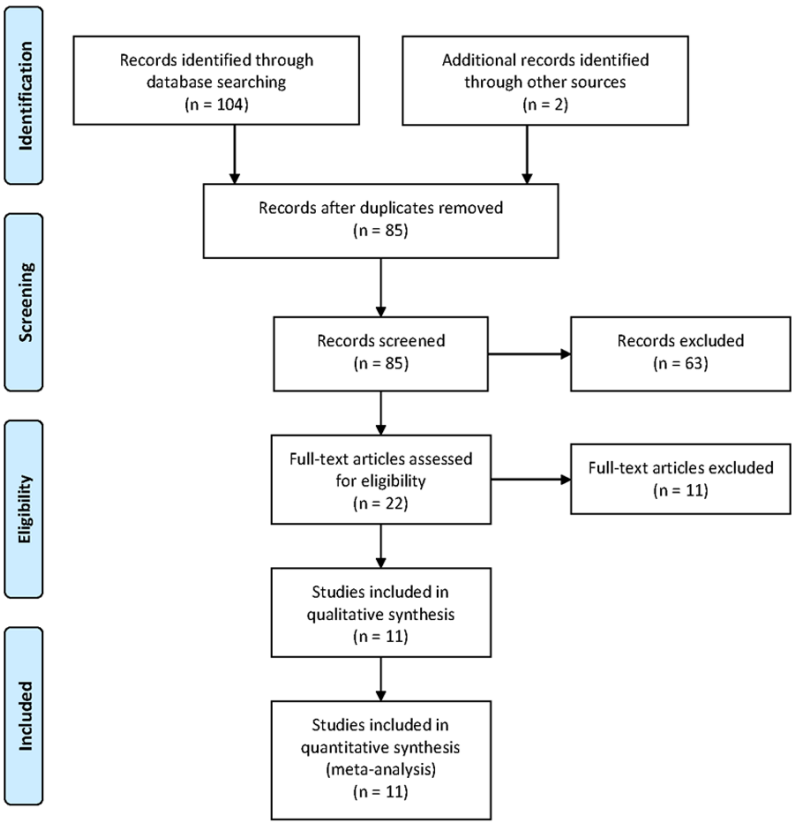

Figure 1. Flow chart of the literature search.

ma was measured by OR and 95% CI. Random-effects model or fixed-effects model was used if possible. Hardy-Weinberg equilibrium (HWE) in controls was calculated again in our meta-analysis. The chi-square goodness of fit was used to test deviation from HWE (significant at the 0.05 level). A significant Q-statistic (P<0.10) indicated heterogeneity across studies. We also measured the effect of heterogeneity by I^2 statistics. We conducted stratification analysis according to participant ethnicity. Relative influence of each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis. Funnel plots and Egger's test were used to evaluate publication bias. All statistical analyses were performed using the STATA statistical software (version 11.2, Stata Corporation, College Station, Texas).

Results

Characteristics of studies

As shown in **Figure 1**, 11 studies including 12814 glioma patients and 21140 controls were included in the meta-analysis. Characteristics of studies included in the current meta-analysis are presented in **Table 1**. There were 9 Caucasian and 2 Asian studies, respectively. One study included pediatric patients and one study included females. All studies were in HWE.

Results of meta-analyses

CDKN2A/B rs4977756 polymorphism was significantly associated with an increased risk of glioma (OR=1.25; 95% CI, 1.21-1.30; P<0.00001; **Figure 2**). In the subgroup analysis by race, CDKN2A/B rs4977756 polymorphism was significantly associated with an increased risk of glioma in Caucasian (OR=1.27; 95% CI, 1.22-1.31; P< 0.00001). However, no significant association between CDKN2A/B rs4977756 polymorphism and glioma risk was found in Asian (OR=1.05; 95% CI, 0.92-1.21; P=0.45). In the sensitivity analysis, the result was changed after exclusion of individual study (**Figure 3**).

Publication bias

Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot was prone to be symmetrical, suggesting that there was no evidence of publication bias among the studies (**Figure 4**). The Egger's test was performed to statistically evaluate funnel plot symmetry. The results suggested no publication bias (P=0.436).

Discussion

To the best of our knowledge, this is the most comprehensive meta-analysis of the association between CDKN2A/B rs4977756 polymorphism and glioma risk. This study with 12814 glioma patients and 21140 controls revealed a significant result. The subjects with CDKN2A/B rs4977756 polymorphism might have higher glioma risk than the one without this polymorphism. In addition, subgroup analysis by ethnic-

Table 1. Characteristics of the case-control studies included in meta-analysis

First author	Year	Country	Ethnicity	Age group	Gender	Number of Case	Number of Control	HWE
Shete	2009	Europe	Caucasian	Adult	Mixed	4661	6587	Yes
Schoemaker	2010	Europe	Caucasian	Adult	Mixed	1029	1668	Yes
Wang	2010	USA	Caucasian	Adult	Women	332	817	Yes
Jenkins	2011	USA	Caucasian	Adult	Mixed	1056	1134	Yes
Chen	2011	China	Asian	Adult	Mixed	968	1052	Yes
Egan	2011	USA	Caucasian	Adult	Mixed	639	649	Yes
Li	2012	China	Asian	Adult	Mixed	226	251	Yes
Safaeian	2013	Europe	Caucasian	Adult	Mixed	2182	1571	Yes
Melin	2013	Europe	Caucasian	Adult	Mixed	104	5732	Yes
Stefano	2013	Finland	Caucasian	Adult	Mixed	1372	1190	Yes
Adel Fahmideh	2015	Europe	Caucasian	Pediatric	Mixed	245	489	Yes

HWE, Hardy-Weinberg equilibrium.

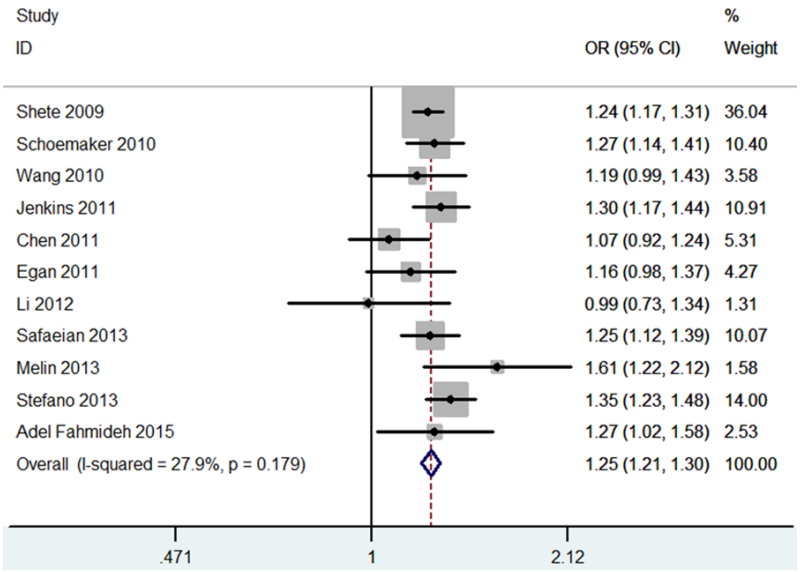

Figure 2. Meta-analysis for the association of CDKN2A/B rs4977756 polymorphism and glioma risk.

ity showed that this polymorphism was significantly associated with increased glioma risk in Caucasians, but not in Asians. This result suggested a possible influence among different genetic backgrounds.

CDKN2A/B gene encodes cyclin-dependent kinase inhibitors and block cell cycle division during the G1/S phase. Therefore, CDKN2A/B rs4977756 polymorphism might have a role in the context of cellular proliferation, andits alterations result in abnormal self-renewing capabilities typicalof cancer cells. The polymorphisms of CDKN2A/B also played an important role in the development of other diseases. Wei et al. suggested that significant associations were found between CDKN2A/B gene SNPs and type 2 diabetes [16]. Zhang et al. suggested that polymorphism of CDKN2A/B was associated with myocardial infarction risk in a Chinese population [17].

Several limitations should be addressed as follows. First, only summarized data rather than individual patient data were pooled in our study, which might preclude us from conducting a more in-depth analysis. Second, due to lack of appropriate data, the association of CDKN2A/B rs4977756 polymorphism, and other clinical parameters were not explored. Thus, more worldwide studies are required to confirm the value of the CDKN2A/B rs4977756 polymorphism test for glioma risk in the future.

This meta-analysis suggested that DKN2A/B rs4977756 polymorphism may be a risk factor of glioma.

Disclosure of conflict of interest

None.

Address correspondence to: Bo Zhang, Department of Neurosurgery, Second Affiliated Hospital of Dalian Medical University, 467 Zhong Shan Road, Dalian 116023, Liaoning, People's Republic of China. Tel:

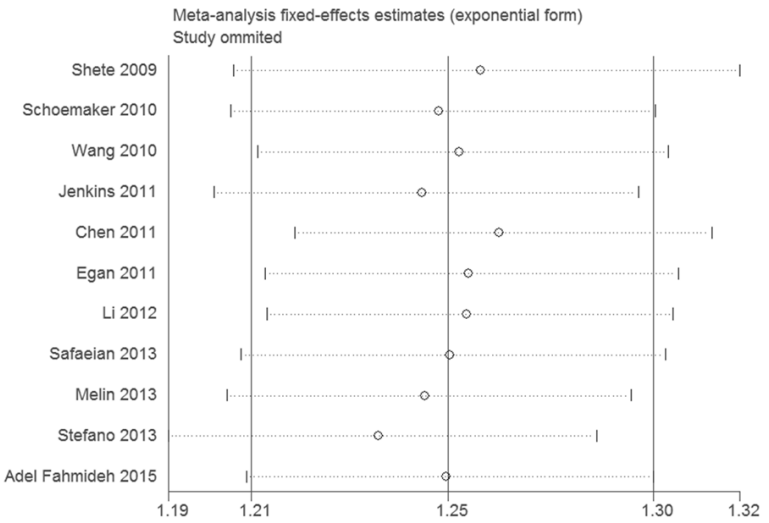

Figure 3. Sensitivity analysis through deletion of one study at a time to reflect the influence of the individual dataset to the pooled ORs.

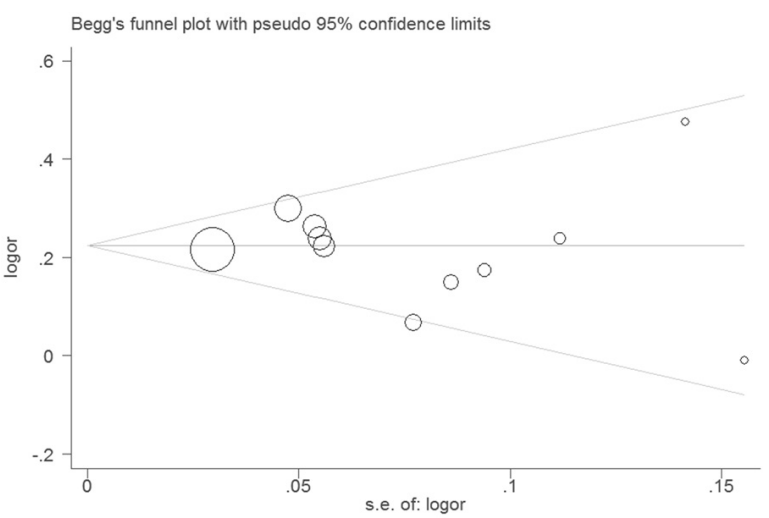

Figure 4. Funnel plot for the glioma risk with CDKN2A/B rs4977756 polymorphism and glioma risk.

86-0411-84671291; E-mail: 15541178350@126.com

References

[1] Wen PY and Kesari S. Malignant gliomas in adults. N Engl J Med 2008; 359: 492-507.

[2] Ohgaki H, Kleihues P. Epidemiology and etiology of gliomas. Acta Neuropathol 2005; 109: 93-108.

[3] Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447: 661-78.

[4] Cugino D, Gianfagna F, Santimone I, de Gaetano G, Donati MB, Iacoviello L, Di Castelnuovo A. Type 2 diabetes and polymorphisms on chromosome 9p21: a meta-analysis. Nutr Metab Cardiovasc Dis 2012; 22: 619-25.

[5] Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, Simon M, Marie Y, Boisselier B, Delattre JY, Hoang-Xuan K, El Hallani S, Idbaih A, Zelenika D, Andersson U, Henriksson R, Bergenheim AT, Feychting M, Lönn S, Ahlbom A, Schramm J, Linnebank M, Hemminki K, Kumar R, Hepworth SJ, Price A, Armstrong G, Liu Y, Gu X, Yu R, Lau C, Schoemaker M, Muir K, Swerdlow A, Lathrop M, Bondy M, Houlston RS. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet 2009; 41: 899-904.

[6] Schoemaker MJ, Robertson L, Wigertz A, Jones ME, Hosking FJ, Feychting M, Lönn S, McKinney PA, Hepworth SJ, Muir KR, Auvinen A, Salminen T, Kiuru A, Johansen C, Houlston RS, Swerdlow AJ. Interaction between 5 genetic variants and allergy in glioma risk. Am J Epidemiol 2010; 171: 1165-73.

[7] Wang SS, Hartge P, Yeager M, Carreón T, Ruder AM, Linet M, Inskip PD, Black A, Hsing AW, Alavanja M, Beane-Freeman L, Safaiean M, Chanock SJ, Rajaraman P. Joint associations between genetic variants and reproductive factors in glioma risk among women. Am J Epidemiol 2011; 174: 901-8.

[8] Jenkins RB, Wrensch MR, Johnson D, Fridley BL, Decker PA, Xiao Y, Kollmeyer TM, Rynearson AL, Fink S, Rice T, McCoy LS, Halder C, Kosel ML, Giannini C, Tihan T, O'Neill BP, Lachance DH, Yang P, Wiemels J, Wiencke JK. Distinct germ line polymorphisms underlie glioma morphologic heterogeneity. Cancer Genet 2011; 204: 13-8.

[9] Chen H, Chen Y, Zhao Y, Fan W, Zhou K, Liu Y, Zhou L, Mao Y, Wei Q, Xu J, Lu D. Association of sequence variants on chromosomes 20, 11, and 5 (20q13.33, 11q23.3, and 5p15.33)

with glioma susceptibility in a Chinese population. Am J Epidemiol 2011; 173: 915-22.
[10] Egan KM, Thompson RC, Nabors LB, Olson JJ, Brat DJ, Larocca RV, Brem S, Moots PL, Madden MH, Browning JE, Ann Chen Y. Cancer susceptibility variants and the risk of adult glioma in a US case-control study. J Neurooncol 2011; 104: 535-42.
[11] Li S, Jin T, Zhang J, Lou H, Yang B, Li Y, Chen C, Zhang Y. Polymorphisms of TREH, IL4R and CCDC26 genes associated with risk of glioma. Cancer Epidemiol 2012; 36: 283-7.
[12] Safaeian M, Rajaraman P, Hartge P, Yeager M, Linet M, Butler MA, Ruder AM, Purdue MP, Hsing A, Beane-Freeman L, Hoppin JA, Albanes D, Weinstein SJ, Inskip PD, Brenner A, Rothman N, Chatterjee N, Gillanders EM, Chanock SJ, Wang SS. Joint effects between five identified risk variants, allergy, and autoimmune conditions on glioma risk. Cancer Causes Control 2013; 24: 1885-91.
[13] Melin B, Dahlin AM, Andersson U, Wang Z, Henriksson R, Hallmans G, Bondy ML, Johansen C, Feychting M, Ahlbom A, Kitahara CM, Wang SS, Ruder AM, Carreón T, Butler MA, Inskip PD, Purdue M, Hsing AW, Mechanic L, Gillanders E, Yeager M, Linet M, Chanock SJ, Hartge P, Rajaraman P. Known glioma risk loci are associated with glioma with a family history of brain tumours--a case-control gene association study. Int J Cancer 2013; 132: 2464-8.
[14] Di Stefano AL, Enciso-Mora V, Marie Y, Desestret V, Labussière M, Boisselier B, Mokhtari K, Idbaih A, Hoang-Xuan K, Delattre JY, Houlston RS, Sanson M. Association between glioma susceptibility loci and tumour pathology defines specific molecular etiologies. Neuro Oncol 2013; 15: 542-7.
[15] Adel Fahmideh M, Lavebratt C, Schüz J, Röösli M, Tynes T, Grotzer MA, Johansen C, Kuehni CE, Lannering B, Prochazka M, Schmidt LS, Feychting M. CCDC26, CDKN2BAS, RTEL1 and TERT Polymorphisms in pediatric brain tumor susceptibility. Carcinogenesis 2015; 36: 876-82.
[16] Wei F, Cai C, Feng S, Lv J, Li S, Chang B, Zhang H, Shi W, Han H, Ling C, Yu P, Chen Y, Sun N, Tian J, Jiao H, Yang F, Li M, Wang Y, Zou L, Su L, Li J, Li R, Qiu H, Shi J, Liu S, Chang M, Lin J, Chen L, Li WD. TOX and CDKN2A/B Gene Polymorphisms Are Associated with Type 2 Diabetes in Han Chinese. Sci Rep 2015; 5: 11900.
[17] Zhang LW, Li JP, Duan FF, Liu ZK, Zhan SY, Hu YH, Jiang J, Zhang Y, Huo Y, Chen DF. Interaction of type 2 diabetes mellitus with chromosome 9p21 rs10757274 polymorphism on the risk of myocardial infarction: a case-control study in Chinese population. BMC Cardiovasc Disord 2014; 14: 170.