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

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

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Age group</th>
<th>Gender</th>
<th>Number of Case</th>
<th>Number of Control</th>
<th>HWE</th>
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<tr>
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<td>1668</td>
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<tr>
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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, and its alterations result in abnormal self-renewing capabilities typical of 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.

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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.

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References

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