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Meta-Analysis

A meta-analysis study of the association between EGFR rs2252586 mutation and the risk of glioma

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Abstract: Several studies reported the association between Epidermal growth factor receptor (EGFR) rs2252586 mutation and glioma susceptibility. However, the results of these studies were inconsistent. A computer-based search using EMBASE and PubMed databases was conducted. Odds ratios (OR) and 95% confidence interval (CI) were used to assess the strength of association between EGFR rs2252586 mutation and glioma susceptibility. The EGFR rs2252586 mutation was significantly associated with an increased risk of glioma (OR=1.16; 95%CI, 1.11–1.21; *P*<0.00001). When stratified by tumor subtype, the significantly elevated risk was observed in glioblastoma (OR=1.15; 95%CI, 1.04–1.26; *P*=0.007) but not in oligodendroglioma (OR=1.19; 95%CI, 0.97–1.46; *P*=0.10). When we excluded the studies with small sample size (case number < 1000), a significant association between EGFR rs2252586 mutation and glioma susceptibility remained (OR=1.16; 95%CI, 1.09–1.22; *P*<0.00001). In conclusion, this meta-analysis found that EGFR rs2252586 mutation was significantly associated with glioma risk.

Key words: Glioma; EGFR; Genetic.

Introduction

Glioma is a type of tumor that derives from the glial cells in the nervous system (1). The standard treatment for glioma is surgical resection followed by radiotherapy, chemotherapy, or biotherapy. Although comprehensive multimodal treatments have been adopted, the outcomes for glioma patients remain poor. The discovery of new genetic markers will help to development of novel drugs.

Epidermal growth factor receptor (EGFR) has been described in approximately 40%–50% of all glioblastomas (2). EGFR gene amplification and overexpression are a striking feature of glioblastoma but are rare in low-grade gliomas (3). EGFR signaling affects various cellular processes, including proliferation, survival, and metabolism. Thus, EGFR may play an important role in the pathogenesis of gliomas. Single nucleotide polymorphisms occurring in EGFR gene have been described. However, the role of genetic variants in EGFR on glioma susceptibility remained unknown. Several studies have showed the association between EGFR rs2252586 mutation and glioma susceptibility (4-8). However, the results of these studies were inconsistent. Therefore, we performed a meta-analysis of all eligible studies to determine the association between EGFR rs2252586 mutation and glioma susceptibility.

Materials and Methods

Publications Search

A computer-based search using EMBASE and PubMed databases was conducted. The search terms included: Epidermal growth factor receptor, EGFR, and glioma.

Publications in English until March 2017 were included. All the references of retrieved articles were also included as additional studies in this study.

Inclusion criteria

All the studies must meet the following criteria: (1) case-control study; (2) evaluating the association between EGFR rs2252586 mutation and glioma susceptibility; (3) estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Two authors extracted the data from the studies independently. The following data were collected: the first author, year, ethnicity, country, tumor subtype, minor allele frequency, and sample size.

Statistical analysis

OR corresponding to 95% CI was used to assess the strength of association between EGFR rs2252586 mutation and glioma susceptibility. The significance of the pooled OR was determined by the Z-test, and P<0.05 was considered as statistically significant. Heterogeneity in meta-analysis refers to the variation in study outcomes between different studies. Heterogeneity assumption was checked by the chi-square-based Q-test. A P>0.10 for the Q-test indicates a lack of heterogeneity among the studies, then the pooled OR estimate of each study was calculated by the fixed-effects model. Subgroup analysis was conducted by tumor subtype. Potential publication bias was examined by Egger's test and funnel plots. All statistical tests were performed with

Table 1. Characteristics of the studies.

First author	Year	Country	Ethnicity	Tumor subtype	Number of cases	Number of controls	MAF of cases	MAF of controls
Sanson 1	2011	France	Caucasian	NA	1422	1189	0.35	0.30
Sanson 2	2011	Germany	Caucasian	NA	846	1310	0.34	0.29
Sanson 3	2011	UK	Caucasian	NA	631	2698	0.33	0.29
Sanson 4	2011	USA	Caucasian	NA	1247	2236	0.31	0.29
Rajaraman	2012	Europe	Caucasian	Mixed	4954	1854	0.31	0.27
Melin	2013	Sweden	Caucasian	Mixed	107	2868	0.30	0.28
Walsh	2013	USA	Caucasian	NA	1662	1301	0.30	0.27
Wibom	2015	USA	Caucasian	Mixed	598	595	0.26	0.26

MAF, Minor allele frequency; NA, not available.

Table 2. Meta-analysis results of this study.

	OR (95% CI)	*p*
Overall	1.16 (1.11-1.21)	<0.00001
Tumor subtype		
Glioblastoma	1.15 (1.04-1.26)	0.007
Oligodendroglioma	1.19 (0.97-1.46)	0.10

the software STATA version 11.0 (Stata Corporation, College station, TX, USA) and Review Manager V.5.2 (The Cochrane Collaboration).

Results

Characteristics of the studies

We included five articles reporting the relationship between EGFR rs2252586 mutation and glioma susceptibility. One study included four case-control studies. Thus, eight case-control studies from Caucasian populations were included. A total of 11467 cases and 14051 controls were included in this meta-analysis. Table 1 summarized the main characteristics of those included studies.

Meta-analysis results

The results of the association between EGFR rs2252586 mutation and glioma susceptibility are summarized in Table 2. The EGFR rs2252586 mutation was significantly associated with an increased risk of glioma (OR=1.16; 95%CI, 1.11–1.21; P<0.00001; Figure 1). When stratified by tumor subtype, the significantly elevated risk was observed in glioblastoma (OR=1.15; 95%CI, 1.04–1.26; P=0.007; Figure 2) but not in oligodendroglioma (OR=1.19; 95%CI, 0.97–1.46; P=0.10; Figure 2). When we excluded the studies with small sample size (case number < 1000), a significant association between EGFR rs2252586 mutation and glioma susceptibility remained (OR=1.16; 95%CI, 1.09–1.22; P<0.00001). Funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plot did not reveal any evidence of

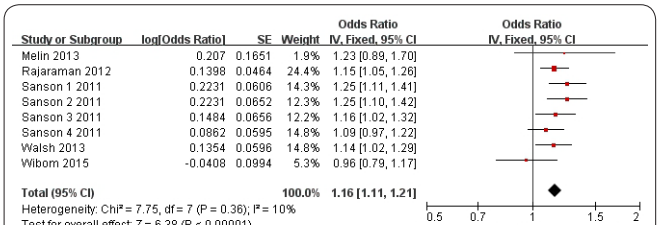

Figure 1. The association between EGFR rs2252586 mutation and glioma susceptibility.

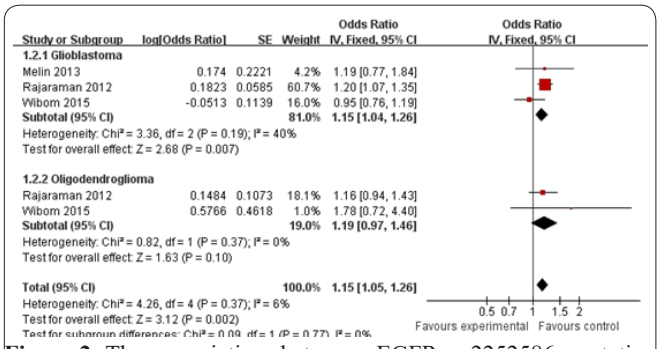

Figure 2. The association between EGFR rs2252586 mutation and glioma susceptibility in tumor subtype.

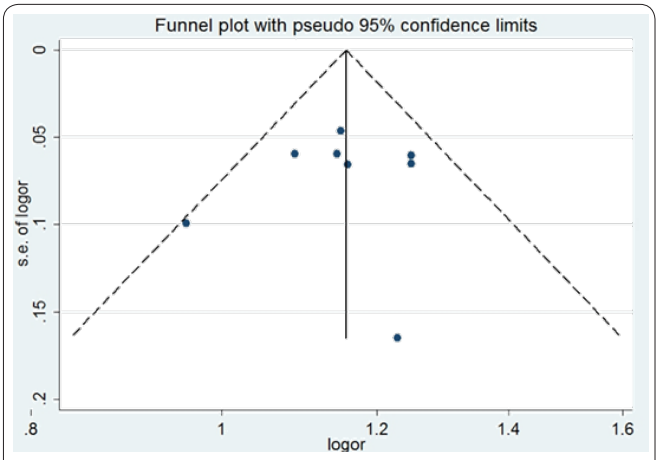

Figure 3. Funnel plot of the association between EGFR rs2252586 mutation and glioma susceptibility.

obvious asymmetry (Figure 3). Egger's test did not find the evidence of publication bias (P=0.71).

Discussion

The present meta-analysis, including 11467 cases and 14051 controls from 8 case-control studies, exploring the association of EGFR rs2252586 mutation and glioma susceptibility. We showed that EGFR rs2252586 mutation was significantly associated with an increased glioma susceptibility. Subgroup analysis stratified by tumor subtype showed individuals with EGFR rs2252586 mutation had increased glioblastoma risk but not oligodendroglioma risk. This result suggested that even the same variant in the same gene may have a different effect on the pathogenesis of glioma. However, the sample size of the subgroup analysis was small. Therefore, more studies are still needed to confirm our results. EGFR contributed to the development of glioma. Cioca *et al*. suggested that expression of EGFR in newly diagnosed GBM was significantly correlated

with EGFR expression in recurrent tumour (9) Wang *et al*. demonstrated that oncogenic activation of EGFRwt in glioma is likely maintained by a continuous EGFL7 autocrine flow line, and may be an attractive target for therapeutic intervention (10). Li *et al*. suggested that five EGFR SNPs correlated with glioma patient prognosis (11) Tsuchihashi *et al*. found a new functional role for EGFR in promoting the malignant potential of glioma cells through interaction with xCT at the cell surface (12). Phoa *et al*. demonstrated that the enhanced EGFR activity does not decrease the efficacy of tubulin inhibitors (13). Our study had some advantages. First, it was the most comprehensive meta-analysis which reported the association between EGFR rs2252586 mutation and glioma susceptibility. Second, no significant heterogeneity and publication bias were found in this meta-analysis. Some limitations in this meta-analysis should be acknowledged. First, lacking of the original data of the eligible studies limited the evaluation of the effects of the gene-environment interactions in glioma development. Second, our results were based on single-factor evaluations without adjustment for other risk factors, including tobacco, alcohol, environmental factors, or lifestyle.

In conclusion, this meta-analysis found that EGFR rs2252586 mutation was significantly associated with glioma risk. More future studies are needed to confirm this result.

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Disclosure of conflict of interest

The authors have declared that no competing interests exist.

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