The associations between common SNPs of EFEMP1 gene and glioma risk in Chinese population

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Background: Although the associations between common single nucleotide polymorphisms (SNPs) of EFEMP1 gene and glioma risk have been investigated in Chinese population-based case-control studies, investigation results for several SNPs are inconsistent. In addition, the single-center study has a poor statistical power due to finite sample size. Therefore, a meta-analysis was conducted to comprehensively determine the associations.

Methods: All eligible case-control studies were obtained by searching PubMed, EMBASE, Web of Science, and Chinese National Knowledge Infrastructure. Pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of the associations in fixed- or random-effects model.

Results: EFEMP1 rs1346787 polymorphism was significantly associated with glioma risk in Chinese population under all genetic models (GG vs AA, OR = 2.22, 95% CI = 1.46-3.36; AG vs AA, OR = 1.54, 95% CI = 1.27-1.87; (GG+AG) vs AA, OR = 1.60, 95% CI = 1.34-1.93; GG vs (AG+AA), OR = 1.86, 95% CI = 1.24-2.78; G vs A, OR = 1.54, 95% CI = 1.32-1.79). However, the significant association of EFEMP1 rs1346786 with glioma risk in Chinese population was observed only under heterozygous model of AG vs AA (OR = 1.34, 95% CI = 1.10-1.62), dominant model of (GG+AG) vs AA (OR = 1.36, 95% CI = 1.13-1.63), and allelic model of G vs A (OR = 1.28, 95% CI = 1.10-1.50).

Conclusion: Our study demonstrated that EFEMP1 polymorphisms, especially rs1346787 and rs1346786, might predict glioma risk in Chinese population. However, high-quality case-control studies with larger sample sizes are warranted to confirm the above-mentioned findings.

Keywords: polymorphism, glioma, risk, meta-analysis

Introduction

As one of the most common primary brain tumors, glioma poses a serious threat to human health. Although the pathogenesis mechanism of glioma is not perfectly illustrated, previous studies have provided substantial evidence that individual’s genetic factors, besides external environmental factors, play an important role in the occurrence of glioma.1-4

EGF containing fibulin like extracellular matrix protein 1 (EFEMP1) gene, located on chromosome 2p16.1, encodes a member of the fibulin family of extracellular matrix glycoproteins, which contain tandemly repeated epidermal growth factor-like repeats followed by a C-terminus fibulin-type domain. EFEMP1 plays important roles in the development of many types of cancer, such as ovarian carcinoma, endometrial carcinoma, cervical cancer, osteosarcoma, and glioma.5-9 As for glioma, Hu et al found that EFEMP1 was consistently upregulated in malignant glioma tissue and promoted tumor cell motility and invasion. Furthermore, EFEMP1 could promote glioma...
growth and resistance through a novel paracrine regulation of Notch signaling, suggesting that EFEMP1 functioned as an oncogene in glioma.\textsuperscript{10,11}

Due to the fact that single nucleotide polymorphisms (SNPs) in cancer-related genes have an effect on the occurrence of cancer, the role of EFEMP1 SNPs in glioma risk has been widely investigated in recent years.\textsuperscript{10–15} However, investigation results for several SNPs (rs3791679 G/A and rs1346786 A/G) were inconsistent. In addition, the single-center study on the association of EFEMP1 rs1346787 A/G with glioma risk had a poor statistical power due to finite sample size. In order to get a more precise conclusion, a meta-analysis of the associations between common SNPs (rs3791679, rs1346786, and rs1346787) of EFEMP1 gene and glioma risk was conducted in the present study.

Methods

Literature search

PubMed, EMBASE, Web of Science, and Chinese National Knowledge Infrastructure were searched for published articles that assessed the associations of EFEMP1 SNPs with glioma risk. The cutoff date for searching was April 15, 2017. The search keywords were as follows: (“EGF containing fibulin like extracellular matrix protein 1” OR “EFEMP1”) and (“polymorphism” OR “SNP” OR “variant”), and (“glioma” OR “brain tumor”). Only English and Chinese languages were applied in the search process. Furthermore, the reference lists of the obtained articles were also manually screened to identify more potential studies.

Selection criteria and data extraction

Two authors independently searched and selected the eligible articles. Eligible articles should meet the following criteria: 1) studies were of case–control design; 2) studies evaluated the associations between EFEMP1 polymorphisms and glioma risk; 3) studies contained the available data for calculating the odds ratio (OR) and 95% confidence interval (CI); 4) the genotype distribution of the control groups in each study should conform to the Hardy–Weinberg equilibrium (HWE). After obtaining the eligible articles, two authors independently extracted the following data: the first author’s surname, year of publication, country, detection method, source of the control group, number of cases and controls, allele and genotype frequencies, and \( P \)-values for HWE \( (P_{\text{HWE}}) \). Finally, any disagreements were resolved by discussion.

Quality evaluation for the eligible articles

Two authors independently assessed the quality of each eligible article according to the Newcastle–Ottawa Scale (NOS). The NOS contained three assessment categories, including selection, comparability, and exposure. In the selection and exposure categories, each eligible item was awarded one star. In the comparability category, each eligible item was awarded no more than two stars.

Statistical analysis

HWE was examined by goodness-of-fit chi-square test, and \( P_{\text{HWE}} < 0.05 \) was considered as a deviation from HWE. The strength of associations between EFEMP1 polymorphisms and glioma risk were evaluated by pooled OR and 95% CI. The significance of the pooled OR was assessed by the Z-test, and \( P_{\text{Z}} < 0.05 \) was considered statistically significant. The chi-square-based \( Q \)-test was applied to investigate the heterogeneity between studies. If the \( P_{\text{Q}} = 0.1 \) indicated the existence of between-study heterogeneity, the random-effects model was applied to calculate the pooled OR; otherwise, the fixed-effects model was used in the analysis. As for EFEMP1 rs3791679 polymorphism, sensitivity analysis was conducted by sequentially omitting one study at a time to assess the stability of the result. Furthermore, publication bias for EFEMP1 rs3791679 polymorphism was determined by Begg’s funnel plots and Egger’s test. All statistical tests were implemented in the Review Manager (version 5.2; Cochrane Collaboration, London, UK) or Stata 12.0 (version 12.0; StataCorp, College Station, TX, USA).

Results

Characteristics of the included studies

A total of 12 potential articles were obtained after searching databases (Figure 1). Further analysis found that four studies with the same quality could be included in the present meta-analysis (Table 1). These eligible studies contained 1,582 cases and 2,283 controls, and were conducted in the Chinese population. A total of 14 SNPs were investigated in EFEMP1

![Figure 1](image-url) Acquisition process of eligible studies in the meta-analysis.
gene (Table 2). Among these SNPs, significant associations of rs1346787, rs3791679, rs1346786, and rs3791675 with glioma risk were observed in at least one study. However, detection methods for EFEMP1 SNPs, including TaqMan, polymerase chain reaction-restriction fragment length polymorphism, and MassARRAY, were not exactly the same in these studies. Considering that rs1346787, rs3791679, and rs1346786 polymorphisms might affect individual risk of developing glioma and were assessed in more than one study, we extracted genotype frequencies of these polymorphisms (Table 3).

**Meta-analysis results**

Table 4 shows the main results of the overall meta-analysis. No significant heterogeneity was observed for rs1346787 and rs1346786 polymorphisms. Thus, fixed-effects model was used to assess the strength of the association. Results showed that rs1346787 polymorphism was significantly associated with glioma risk under all genetic models (GG vs AA, OR = 2.22, 95% CI = 1.46–3.36; AG vs AA, OR = 1.54, 95% CI = 1.27–1.87; (GG+AG) vs AA, OR = 1.60, 95% CI = 1.34–1.93; GG vs (AG+AA), OR = 1.86, 95% CI = 1.24–2.78; G vs A, OR = 1.54, 95% CI = 1.32–1.79). However, the significant association of rs1346786 polymorphism with glioma risk was only observed under heterozygous model of AG vs AA (OR = 1.34, 95% CI = 1.10–1.62), dominant model of (GG+AG) vs AA (OR = 1.36, 95% CI = 1.13–1.63), and allelic model of G vs A (OR = 1.28, 95% CI = 1.10–1.50). For rs3791679 polymorphism, random-effects model was adopted due to the existence of heterogeneity. When all

**Table 1 Quality evaluation of the eligible articles**

| Categories   | Items                                      | Yang et al12 study | Jiang et al13 study | Qin et al14 study | Zhang et al15 study |
|--------------|--------------------------------------------|--------------------|--------------------|------------------|---------------------|
| Selection    | Adequacy of case definition               | *                  | *                  | *                | *                   |
|              | Representativeness of the cases           | *                  | *                  | *                | *                   |
|              | Selection of controls                     | *                  | *                  | *                | *                   |
|              | Definition of controls                    | *                  | *                  | *                | *                   |
| Comparability|                               |                    |                    |                  |                     |
|              | Comparability of cases/controls           | *                  | *                  | *                | *                   |
| Exposure     | Ascertainment of exposure                 | *                  | *                  | *                | *                   |
|              | Same method of ascertainment for cases and controls | *                  | *                  | *                | *                   |
|              | Non-response rate                         | –                  | –                  | –                | –                   |

Note: Eligible item according to the Newcastle–Ottawa scale.

**Table 2 The main characteristics of the eligible studies**

| Study        | Year of publication | Country | Detection method | Source | Cases | Controls | SNPs | Base change | Gene location of SNPs | Association with glioma risk |
|--------------|---------------------|---------|------------------|--------|-------|----------|------|-------------|------------------------|-----------------------------|
| Yang et al12 | 2017                | China   | TaqMan           | Hospital | 350  | 706      | rs1346787 | A/G         | 3′near gene          | Yes                          |
|              |                     |         |                  |         |       |          | rs3791679 | G/A         | Intron 10            | Yes                          |
|              |                     |         |                  |         |       |          | rs17047290 | A/G         | Intron 5             | No                           |
| Jiang et al13| 2016                | China   | PCR-RFLP         | Hospital | 94   | 206      | rs3791679 | G/A         | Intron 10            | Yes                          |
| Qin et al14  | 2015                | China   | PCR-RFLP         | Hospital | 159  | 364      | rs3791679 | G/A         | Intron 10            | Yes                          |
|              |                     |         |                  |         |       |          | rs1346786 | A/G         | Intron 5             | No                           |
|              |                     |         |                  |         |       |          | rs1344733  | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs727878   | A/G         | Intron 5             | No                           |
| Zhang et al15| 2015                | China   | MassARRAY        | Hospital | 979  | 1,007    | rs1346787 | A/G         | 3′near gene          | Yes                          |
|              |                     |         |                  |         |       |          | rs3791679 | G/A         | Intron 10            | Yes                          |
|              |                     |         |                  |         |       |          | rs17047290 | A/G         | Intron 5             | No                           |
|              |                     |         |                  |         |       |          | rs1346786 | A/G         | Intron 5             | Yes                          |
|              |                     |         |                  |         |       |          | rs3791675  | A/G         | Intron 4             | Yes                          |
|              |                     |         |                  |         |       |          | rs10496055 | A/G         | Intron 4             | Yes                          |
|              |                     |         |                  |         |       |          | rs10865291 | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs727878   | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs1344733  | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs3791661  | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs1430195  | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs7559906  | A/G         | Intron 4             | No                           |
|              |                     |         |                  |         |       |          | rs4233964  | A/G         | Intron 4             | No                           |

**Abbreviations:** PCR, polymerase chain reaction; SNPs, single nucleotide polymorphisms; RFLP, restriction length polymorphism.
Table 3 The genotype frequencies of EFEMP1 rs1346787, rs3791679, and rs1346786 polymorphisms

| Study                        | rs1346787 (cases) | rs1346787 (controls) | rs3791679 (cases) | rs3791679 (controls) | rs1346786 (cases) | rs1346786 (controls) |
|------------------------------|------------------|----------------------|-------------------|----------------------|------------------|----------------------|
|                              | Total            | AA                   | AG                | GG                   | Total            | AA                   | AG                | GG                   |
| Yang et al12                 | 157              | 150                  | 43                | 350                  | 414              | 245                  | 47                | 706                  |
| Zhang et al13                | 825              | 146                  | 8                 | 979                  | 894              | 107                  | 6                 | 1,007                 |
|                              |                  |                      |                   |                      |                  |                      |                   |                      |
|                              |                  |                      |                   |                      |                  |                      |                   |                      |

Abbreviation: HWE, Hardy–Weinberg equilibrium.

The eligible studies were pooled into the meta-analysis of rs3791679 polymorphism, no significant association was observed under all genetic models (AA vs GG, OR = 1.42, 95% CI = 0.69–2.92; AG vs GG, OR = 1.26, 95% CI = 0.94–1.69; (AA+AG) vs GG, OR = 1.26, 95% CI = 0.88–1.82; AA vs (AG+GG), OR = 1.40, 95% CI = 0.80–2.46; A vs G, OR = 1.21, 95% CI = 0.88–1.68).

Sensitivity and publication bias analysis for rs3791679 polymorphism

Sensitivity analysis for rs3791679 polymorphism was performed by omitting one study at a time (Table 5). Results showed that the overall effect changed noticeably after omitting Jiang et al.’s study13 (AA vs GG, OR = 2.05, 95% CI = 1.55–2.71; AG vs GG, OR = 1.35, 95% CI = 1.17–1.56; (AA+AG) vs GG, OR = 1.49, 95% CI = 1.18–1.89; AA vs (AG+GG), OR = 1.81, 95% CI = 1.38–2.37; A vs G, OR = 1.45, 95% CI = 1.18–1.78).

Begg’s funnel plots and Egger’s test were used to assess the publication bias for rs3791679 polymorphism. As shown in Figure 2, Begg’s funnel plots did not show any obvious asymmetry. In addition, P-values of Egger’s test were more than 0.05 under all genetic models (AA vs GG, P = 0.254; AG vs GG, P = 0.624; (AA+AG) vs GG, P = 0.611; AA vs (AG+GG), P = 0.789; A vs G, P = 0.492). These results suggested lack of publication bias.

Table 4 Meta-analysis of the associations between EFEMP1 SNPs and glioma risk

| SNP ID       | Comparison | PH | Model | Pz  | OR (95% CI) |
|--------------|------------|----|-------|-----|-------------|
| rs1346787    | GG vs AA   | 0.38 | F     | <0.001 | 2.22 (1.46–3.36) |
|              | AG vs AA   | 0.65 | F     | <0.001 | 1.54 (1.27–1.87) |
|              | (GG+AG) vs AA | 0.38 | F     | <0.001 | 1.60 (1.34–1.93) |
|              | GG vs (AG+AA) | 0.54 | F     | 0.003 | 1.86 (1.24–2.78) |
|              | G vs A     | 0.48 | F     | <0.001 | 1.54 (1.32–1.79) |
| rs3791679    | AA vs GG   | <0.001 | R     | 0.34 | 1.42 (0.69–2.92) |
|              | AG vs GG   | 0.03 | R     | 0.13 | 1.26 (0.94–1.69) |
|              | (AA+AG) vs GG | 0.002 | R     | 0.21 | 1.26 (0.88–1.82) |
|              | AA vs (AG+GG) | <0.001 | R     | 0.24 | 1.40 (0.80–2.46) |
|              | A vs G     | <0.001 | R     | 0.24 | 1.21 (0.88–1.68) |
| rs1346786    | GG vs AA   | 0.40 | F     | 0.12 | 1.40 (0.92–2.12) |
|              | AG vs AA   | 0.42 | F     | 0.003 | 1.34 (1.10–1.62) |
|              | (GG+AG) vs AA | 0.39 | F     | 0.001 | 1.36 (1.13–1.63) |
|              | GG vs (AG+AA) | 0.37 | F     | 0.23 | 1.27 (0.86–1.86) |
|              | G vs A     | 0.19 | F     | 0.001 | 1.28 (1.10–1.50) |

Note: Bold values indicate statistical significance.

Abbreviations: PH, P value of heterogeneity; Pz, P value of Z test; OR, odds ratio; SNPs, single nucleotide polymorphisms; R, random-effects model; F, fixed-effects model.

Discussion

In recent years, the associations between common SNPs within EFEMP1 gene and glioma risk have been investigated in the Chinese population. However, only rs1346787, rs3791679, and rs1346786 polymorphisms might play an important role in glioma risk. Considering that inconsistent results were reported in rs3791679 and rs1346786 polymorphisms, we applied a meta-analysis, which was a powerful tool for analyzing cumulative data of studies, to get more precise estimation. Results of meta-analysis showed that EFEMP1 rs1346786 polymorphism was significantly associated with an increased risk of glioma in Chinese population under heterozygous model of AG vs AA, dominant model of (GG+AG) vs AA, and allelic model of G vs A. However, the association of EFEMP1 rs3791679 with glioma risk was not observed in overall meta-analysis. Interestingly, the overall effect of EFEMP1 rs3791679 polymorphism on glioma risk changed noticeably after omitting Jiang et al.’s study.13 The phenomenon might be due to the fact that sample sizes were...
Table 5  The association of EFEMP1 rs3791679 with glioma risk after omitting Jiang et al’s study13

| SNP ID | Comparison     | \( P_{H} \)  | Model | \( P_{Z} \) | OR (95% CI) |
|--------|----------------|------------|-------|------------|-------------|
| rs3791679 | AA vs GG       | 0.17       | F     | <0.001     | 2.05 (1.55–2.71) |
|          | AG vs GG       | 0.29       | F     | <0.001     | 1.35 (1.17–1.56) |
|          | (AA+AG) vs GG  | 0.10       | R     | <0.001     | 1.49 (1.18–1.89) |
|          | AA vs (AG+GG)  | 0.30       | F     | <0.001     | 1.81 (1.38–2.37) |
|          | A vs G         | 0.05       | R     | <0.001     | 1.45 (1.18–1.78) |

Abbreviations: \( P_{H} \), value of heterogeneity; \( P_{Z} \), value of Z test; OR, odds ratio; SNP, single nucleotide polymorphism; R, random-effects model; F, fixed-effects model.

small in Jiang et al’s study compared with those in the three other studies, which could make allele and genotype frequency distribution of rs3791679 polymorphism more easily deviate from the actual distribution. The change hinted that the overall results of rs3791679 polymorphism were unstable and needed to be treated cautiously. Although the consistent results of EFEMP1 rs1346787 polymorphism were observed in Yang et al’s12 and Zhang et al’s13 studies, single-center study had a poor statistical power due to finite sample size. Thus, meta-analysis was used to further assess the role of EFEMP1 rs1346787 polymorphism in glioma risk. Results indicated that EFEMP1 rs1346787 polymorphism was significantly associated with an increased risk of glioma.

Several limitations of the present meta-analysis should be considered. Firstly, the unadjusted estimates were used in the present meta-analysis, while a more precise analysis should be performed if individual lifestyle and environmental factors are available. Furthermore, our meta-analysis was restricted to the Chinese and English languages, which might result in potential language bias. Last but not least, the function of these risk alleles was not identified in traditional epidemiology research. As a promising direction, a molecular pathologic epidemiology approach could be used to find the function of these risk alleles. For example, risk alleles could be hypothesized to regulate the expression of EFEMP1 gene. Thus, the relationship between risk alleles and EFEMP1 gene expression in glioma tissue could be examined.

Conclusion
We found significant associations between rs1346787 and rs1346786 polymorphisms within EFEMP1 gene and glioma risk in Chinese population. However, more case–control studies need to be conducted in the Chinese population to verify the above-mentioned findings.

Disclosure
The authors report no conflicts of interest in this work.

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