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ORIGINAL RESEARCH

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

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growth and resistance through a novel paracrine regulation of Notch signaling, suggesting that *EFEMP1* functioned as an oncogene in glioma.[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.[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_{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 $P_{HWE} < 0.05$ 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 $P_Z < 0.05$ was considered statistically significant. The chi-square-based *Q*-test was applied to investigate the heterogeneity between studies. If the $P_H \leq 0.1$ 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*

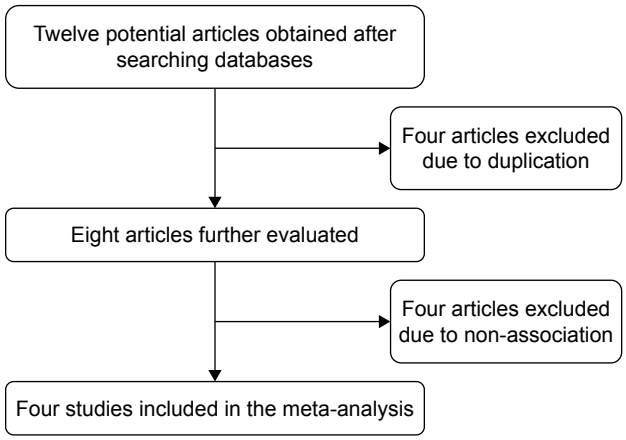

Figure 1 Acquisition process of eligible studies in the meta-analysis.

Table 1 Quality evaluation of the eligible articles

Categories	Items	Yang et al[12] study	Jiang et al[13] study	Qin et al[14] study	Zhang et al[15] 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.

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 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 al[12]	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 al[13]	2016	China	PCR-RFLP	Hospital	94	206	rs3791679	G/A	Intron 10	Yes
Qin et al[14]	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 al[15]	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	No
							rs10865291	A/G	Intron 4	No
							rs727878	A/G	Intron 4	No
							rs1344733	A/G	Intron 4	No
							rs3791661	A/G	Intron 4	No
							rs3791660	A/C	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)				P_{HWE}
	AA	AG	GG	Total	AA	AG	GG	Total	
Yang et al[12]	157	150	43	350	414	245	47	706	0.193
Zhang et al[15]	825	146	8	979	894	107	6	1,007	0.159
	rs3791679 (cases)				rs3791679 (controls)				
	GG	GA	AA	Total	GG	GA	AA	Total	
Yang et al[12]	170	139	41	350	444	225	37	706	0.228
Jiang et al[13]	14	43	37	94	13	87	106	206	0.382
Qin et al[14]	58	73	28	159	171	154	39	364	0.624
Zhang et al[15]	595	331	53	979	667	301	38	1,006	0.579
	rs1346786 (cases)				rs1346786 (controls)				
	AA	AG	GG	Total	AA	AG	GG	Total	
Qin et al[14]	51	76	32	159	129	168	67	364	0.347
Zhang et al[15]	716	241	22	979	798	193	14	1,005	0.551

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 study[13] (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.

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

SNP ID	Comparison	P_H	Model	P_Z	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: P_H, *P* value of heterogeneity; P_Z, *P* value of Z test; OR, odds ratio; SNPs, single nucleotide polymorphisms; R, random-effects model; F, fixed-effects model.

Table 5 The association of *EFEMP1* rs3791679 with glioma risk after omitting Jiang et al's study[13]

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, *P* value of heterogeneity; P_Z, *P* 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's[12] and Zhang et al's[15] 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.

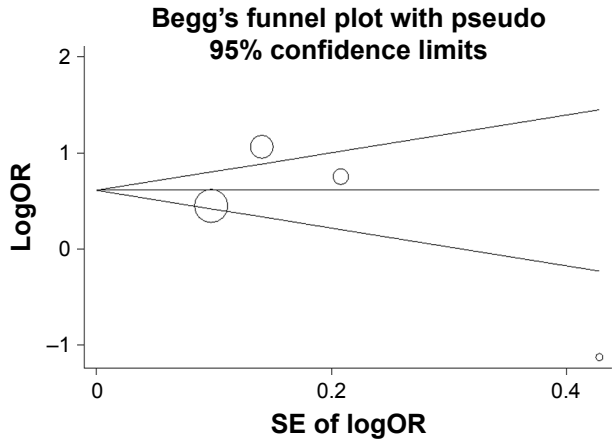

Figure 2 Begg's funnel plot assessing the publication bias for rs3791679 polymorphism under AG vs GG model.
Abbreviations: OR, odds ratio; SE, standard error.

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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