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Original Article

Association between regulator of telomere elongation helicase 1 polymorphism and susceptibility to glioma

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Abstract: Background: Glioma is the most devastating type of malignant brain tumors in adults. Genetic factors play important roles in the pathogenesis of glioma. In recent years, some studies found that there were significant association between regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma susceptibility, however, the results were controversial. The aim of this study was to obtain a more exact estimation of the association between regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma through a meta-analysis. Methods: The meta-analysis included 19 published case-control studies involving 8541 cases and 14226 controls. The included papers were searched from PubMed and Embase database. Odds ratio (OR) with 95% confidence interval (95% CI) were used to evaluate the association of regulator of telomere elongation helicase 1 rs6010620 polymorphism with glioma. Results: A significant association between regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma susceptibility was observed for GG vs. AA+AG (OR=1.28, 95% CI=1.14-1.43) and G vs. A (OR=1.07, 95% CI=1.03-1.10). Further subgroup analysis based on ethnicity showed similar results in Asians and Caucasians. In the subgroup analysis of source of control, a significant association between the G allele and glioma susceptibility were found in population-based group and hospital-based group. Conclusions: The meta-analysis suggested that regulator of telomere elongation helicase 1 rs6010620 polymorphism was a risk factor for glioma. And this study also suggested that rs6010620 GG genotype and G allele may be indicators for the risk of glioma.

Keywords: Regulator of telomere elongation helicase 1, glioma, polymorphism, susceptibility

Introduction

Glioma, the most common type of brain tumors in adults, arises from glial cells and starts in the brain or spine, which accounts for about 30% of all tumors in central nervous system and 80% of malignant tumors in brain [1]. The pathogenesis of glioma involves various factors including pollution, living environment, electromagnetic radiation (cells phones), infection and genetic factor. Among the factors, genetic factors play an important role in the pathogenesis of glioma [2, 3].

Regulator of telomere elongation helicase 1 gene, located in 20q13.3, plays an important role in DNA repair, ATP-dependent DNA helicase activity, acid binding, and apotosis [4, 5]. Previous researches have suggested that RTELI contributes to genomic stability, DNA replication and telomere maintenance [4, 6]. Moreover, the inactivation of regulator of telomere elongation helicase 1 could cause chromosome breaks, fusions and telomere loss [7]. In addition, the increasing studies have showed that there exists significant association between regulator of telomere elongation helicase 1 polymorphisms and glioma susceptibility.

Among the polymorphisms, regulator of telomere elongation helicase 1 rs6010620 is the most studied single nucleotide polymorphism (SNP). However, the relationship of regulator of telomere elongation helicase 1 rs6010620 and glioma was still inconclusive. One meta-analysis conducted by Zhao et al., have suggested that regulator of telomere elongation helicase 1 rs6010620 is associated with the increased risk for glioma under four genetic models [8]. While, Li et al. have reported that the GG geno-

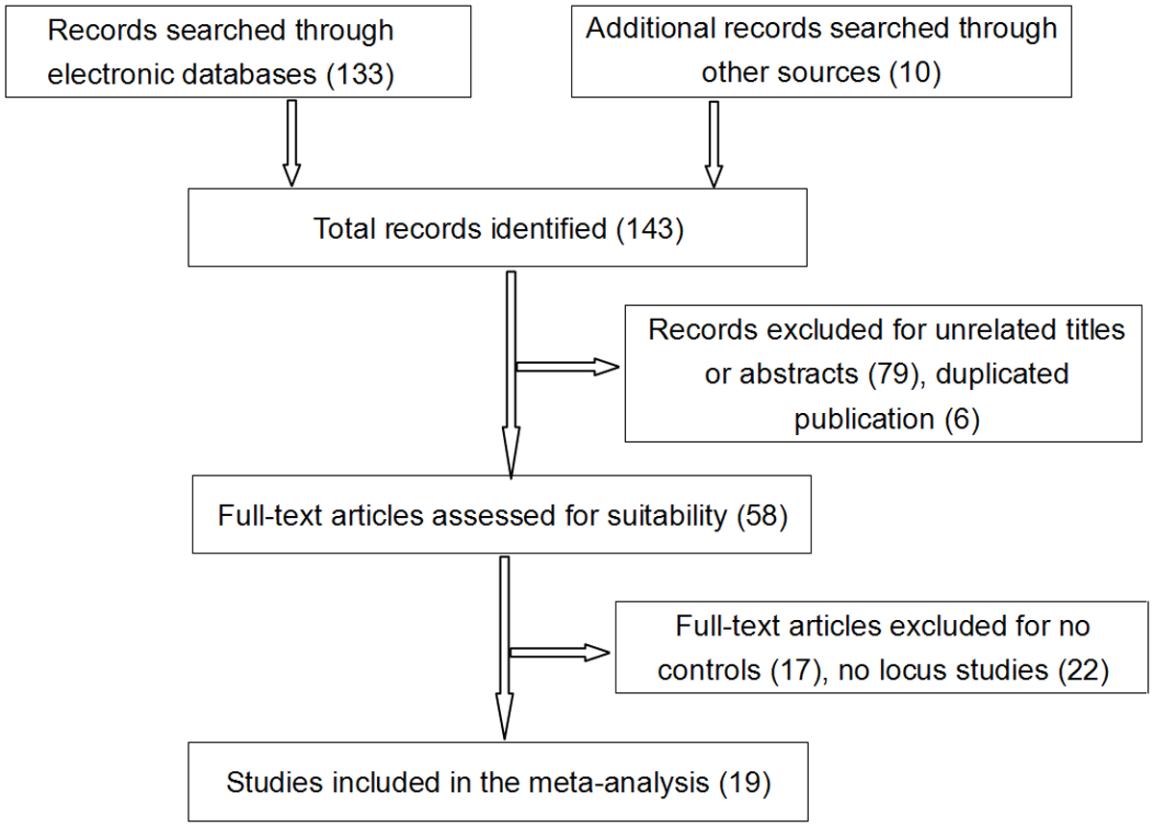

Figure 1. Flow diagram of the study selection process for the meta-analysis.

type of rs6010620 acts as the protective genotype for glioma [9]. Therefore, we conducted a meta-analysis with 8541 cases and 14226 controls to derive a more precise estimation of the correlation between regulator of telomere elongation helicase 1 rs6010620 and glioma risk.

Materials and methods

Search strategy and inclusion criteria

We searched in PubMed and Embase databases with the following key words "regulator of telomere elongation helicase 1", "*RTEL1*", "polymorphism" and "glioma".

Inclusion criteria were defined as follows: (1) case-control studies estimating the relationship of regulator of telomere elongation helicase 1 rs6010620 with glioma risk; (2) sufficient data for evaluating the odds ratio (OR) with 95% CI; (3) data collection and analysis must be statistically acceptable. If the studies with overlapping data published by the same investigators, we included the most recent or complete study.

Data extraction

The data were extracted by two investigators according to the inclusion criteria. For controversial evaluation, the investigators should discuss with other members of the team until a consensus was reached.

The data extracted from the articles included the name of first author, publication date, ethnicity, country of origin, number of cases and controls, genotyping method, genotype frequencies in cases and controls and source of the control and Hardy-Weinberg equilibrium (HWE).

Statistical analysis

Pooled ORs with 95% CIs were conducted to assess the strength of the association between regulator of telomere elongation helicase 1

Table 1. Principle characteristics of the studies included in the meta-analysis

First author	Year	Country	Ethnicity	Control source	Genotyping method	Case						Control						HWE
						Sample size	AA	AG	GG	A	G	Sample size	AA	AG	GG	A	G	
Shete (England)	2009	America	Caucasian	PB	PCR/MALDI-TOF-MS	631	26	179	426	231	1031	1433	82	533	818	697	2169	0.69
Shete (America)	2009	America	Caucasian	HB	PCR/MALDI-TOF-MS	1247	46	405	796	497	1997	2235	123	785	1327	1031	3439	0.62
Shete (France)	2009	America	Caucasian	PB	PCR/MALDI-TOF-MS	1332	34	386	912	454	2210	1545	59	508	978	626	2464	0.49
Shete (German)	2009	America	Caucasian	PB	PCR/MALDI-TOF-MS	499	16	147	336	179	819	557	28	177	352	233	881	0.35
Shete (Sweden)	2009	America	Caucasian	PB	PCR/MALDI-TOF-MS	645	20	195	430	235	1055	774	54	264	456	372	1176	0.07
Schoemaker (Denmark)	2010	England	Caucasian	PB	PCR	122	1	38	83	40	204	147	8	56	83	72	222	0.72
Schoemaker (Finland)	2010	England	Caucasian	PB	PCR	95	4	22	69	30	160	96	3	30	63	36	156	0.80
Schoemaker (Sweden)	2010	England	Caucasian	PB	PCR	200	4	52	144	60	340	371	25	116	230	166	576	0.05
Schoemaker (UK-North)	2010	England	Caucasian	PB	PCR	376	18	106	252	142	610	632	44	212	376	300	964	0.07
Schoemaker (UK-South)	2010	England	Caucasian	PB	PCR	232	8	65	159	81	383	390	28	129	233	185	595	0.09
Chen	2011	China	Asian	HBI	MassARRAY	958	411	454	93	1276	640	1040	547	438	55	1532	548	0.01
Wang	2011	America	Caucasian	Mixed	HumanHap	332	15	99	218	129	535	817	49	296	472	394	1240	0.77
Li	2013	China	Asian	PB	MassARRAY	629	293	261	75	847	411	644	337	267	40	941	347	0.18
Safaeian (NCI)	2013	America	Caucasian	PB	HumanHap	322	11	93	218	115	529	385	20	134	231	174	596	0.92
Safaeian (NIOSH)	2013	America	Caucasian	PB	HumanHap	300	12	106	182	130	470	539	25	175	339	225	853	0.69
Safaeian (PLCO)	2013	America	Caucasian	PB	HumanHap	133	0	29	104	29	237	855	51	323	481	425	1285	0.74
Safaeian (ATBC)	2013	Finland	Caucasian	PB	HumanHap	37	1	11	25	13	61	1269	51	374	844	476	2062	0.24
Safaeian (AHS)	2013	America	Caucasian	PB	HumanHap	18	2	6	10	10	26	35	1	8	26	10	60	0.69
Jin	2013	China	Asian	PB	MassARRAY	433	48	181	204	277	589	462	24	202	236	250	674	0.02

PCR: polymerase chain reaction; MALDI-TOF: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; TaqMan: TaqManSNP; NCI: the National Cancer Institute; NIOSH: the National Institute for Occupational Safety and Health; PLCO: the Prostate, Lung, Colorectal and Ovarian; ATBC: the Alpha-Tocopherol, Beta-Carotene; AHS: the Agricultural Health Study; HWE: Hardy-Weinberg equilibrium.

Table 2. Regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma risk

		GG versus AA		GG+AG versus AA		GG versus AA+AG		G versus A		AG versus AA	
		OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph
Ethnicity	Caucasian	1.04 (0.98, 1.10)	1.000	1.02 (0.98, 1.07)	1.000	1.25 (1.11, 1.41)	0.000	1.06 (1.02, 1.09)	0.998	1.04 (0.96, 1.12)	1.000
	Asian	1.31 (1.09, 1.57)	0.000	1.10 (1.00, 1.22)	0.125	1.46 (0.86, 2.45)	0.000	1.13 (1.04, 1.23)	0.005	1.09 (0.97, 1.22)	0.195
Source of control	Population	1.05 (0.98, 1.11)	0.775	1.02 (0.98, 1.07)	1.000	1.28 (1.12, 1.47)	0.000	1.06 (1.02, 1.10)	0.864	1.03 (0.95, 1.12)	1.000
	Hospital	1.11 (0.99, 1.25)	0.000	1.07 (0.99, 1.16)	0.069	1.37 (0.81, 2.31)	0.004	1.09 (1.02, 1.16)	0.010	1.11 (0.99, 1.24)	0.275
	Mixed	1.03 (0.83, 1.29)	0.000	1.02 (0.85, 1.22)	0.000	1.14 (0.93, 1.40)	0.000	1.06 (0.93, 1.22)	0.000	1.01 (0.74, 1.38)	0.000
Total		1.06 (1.00, 1.11)	0.160	1.03 (0.99, 1.08)	0.995	1.28 (1.14, 1.43)	0.000	1.07 (1.03, 1.10)	0.547	1.05 (0.99, 1.12)	0.999

Ph: *P*-value of heterogeneity test.

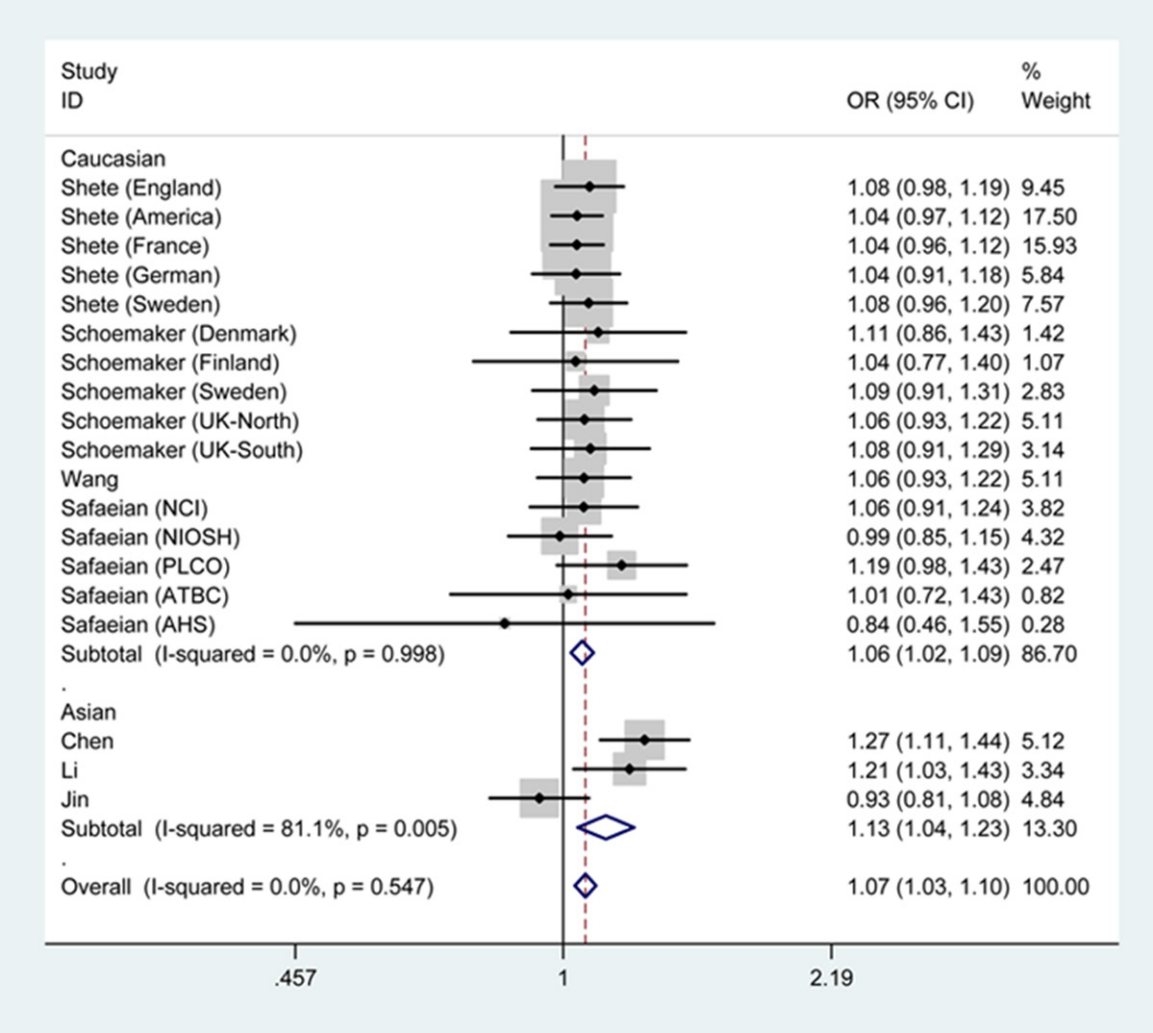

Figure 2. Forest plot of glioma risk associated with regulator of telomere elongation helicase 1 rs6010620 under G vs. A genetic model by ethnicity.

rs6010620 and glioma risk. The pooled ORs were performed for GG vs. AA, GG+AG vs. AA, GG vs. AA+AG, G vs. A, AG vs. AA. In the subgroup analysis, statistical analysis was conducted in Asians and Caucasians. Z test was used to evaluate whether the pooled ORs were significant. $P<0.05$ was considered statistically significant. Heterogeneity assumption was testified by Q test. The pooled ORs were calculated by the fixed-effects model when P (heterogenity) >0.05. Otherwise, the random-effects model was used. We adopted Begg's funnel plots and Egger's test to assess the publication bias. HWE was checked by χ^2 test. The sensitivity analysis was conducted repeatedly by precluding a single study every time in multiple genetic models. Statistical analysis was performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Articles search and the characteristics of the studies

As listed in **Figure 1**, a total of 143 relevant articles were identified. According to the inclusion criteria, 124 studies were excluded: 6 studies for overlapping data, 79 studies for unrelated research, 17 studies for no control group and 22 studies for no locus. Finally, 19 studies were considered acceptable and included into our meta-analysis. The characteristics of nineteen studies were shown in **Table 1**.

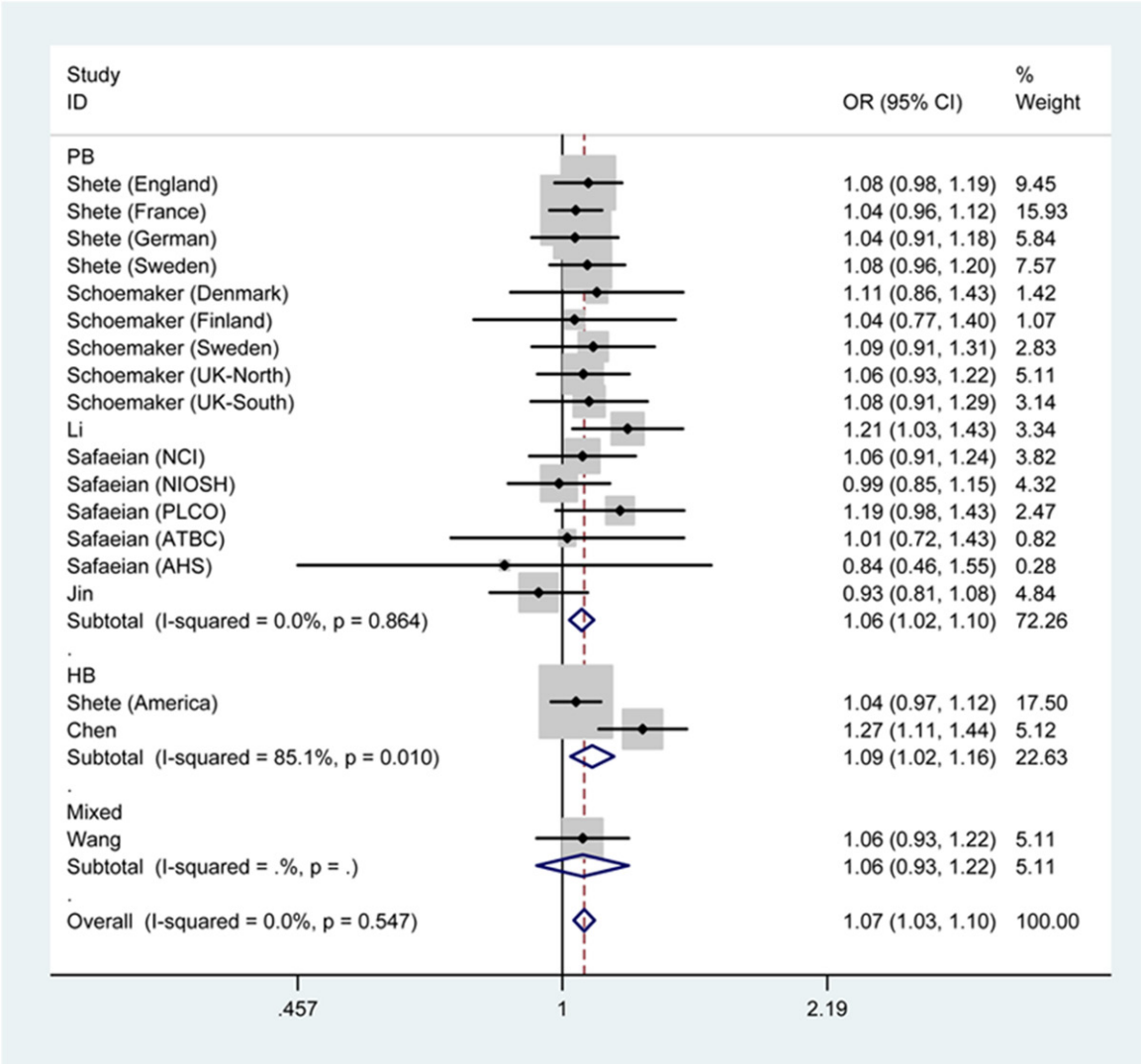

Figure 3. Forest plot of glioma risk associated with regulator of telomere elongation helicase 1 rs6010620 under G vs. A genetic model by source of control.

Meta analysis results

As shown in **Table 2**, the overall ORs with 95% CIs demonstrated that the presence of regulator of telomere elongation helicase 1 rs6010620 polymorphism with GG genotype or G allelle was an increased factor for glioma risk (GG vs. AA+AG: OR=1.28, 95% CI=1.14-1.43; G vs. A: OR=1.07, 95% CI=1.03-1.10). In the subgroup analysis by ethnicity, findings were similar in Asians (GG vs. AA: OR=1.31, 95% CI=1.09-1.57; G vs. A: OR=1.13, 95% CI=1.04-1.23) and Caucasians (GG vs. AA+AG: OR=1.25, 95% CI=1.11-1.41; G vs. A: OR=1.06, 95% CI=1.02-1.09). In the subgroup analysis by source of control, elevated risk was observed with G allele based on population (G vs. A: OR=1.06, 95% CI=1.02-1.10) and hospital (G vs. A: OR=1.09, 95% CI=1.02-1.16) (**Figures 2**, **3**).

Sensitivity analysis

The sensitivity analysis was conducted repeatedly by excluding a single study every time in multiple genetic models. The results showed that the corresponding pooled ORs were not altered, suggesting that our meta-analysis results were reliable (data not shown).

Publication bias

We used funnel plot and Egger's test to estimate the publication bias of literature. As

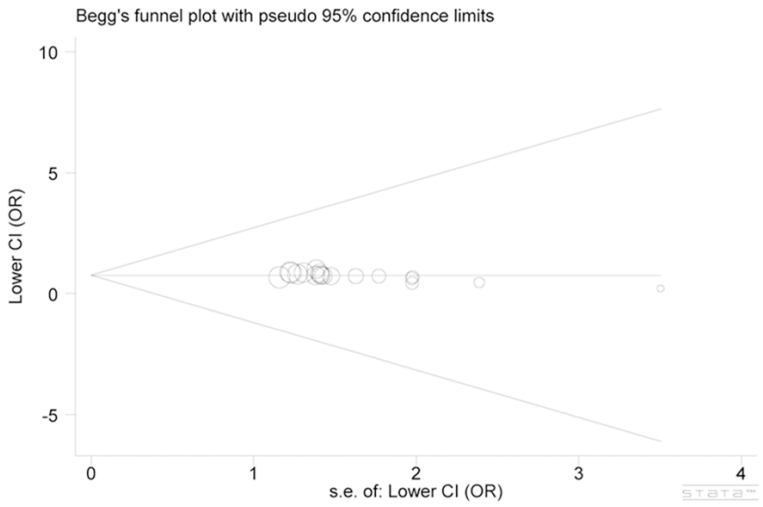

Figure 4. Begg's funnel plot of publication bias test.

shown in **Figure 4**, the shape of the funnel plot seemed symmetrical, and Egger's test had no statistical evidence for publication bias (P=0.791). Thus, there existed no apparent publication bias in the present meta-analysis.

Discussion

Glioma orginating from glial cells is the most common primary tumors of the central nervous system, and it accounts for the vast majority of the malignant brain tumors [10-14]. The incidence rate of glioma is increasing in a number of Asian countries, especially in China. According to the Health Statistics Yearbook 2009 of China, the annual mortality rate of glioma in China was approximately 3.13 per 100,000 population during 2008 [15]. For the etiology, genetic factors had strong effects on the development of glioma [16-21]. Regulator of telomere elongation helicase 1 is an essential DNA helicase that disassembles a variety of DNA secondary structures to maintain telomere integrity [22-25]. As we all know, regulator of telomere elongation helicase 1 had many polymorphic sites and rs6010620 was the most widely studied one. Regulator of telomere elongation helicase 1 polymorphisms play important roles in cancer pathogenesis, since the mutation in regulator of telomere elongation helicase 1 could cause telomere dysfunction [26] that was associated with risk of various cancers [27]. For regulator of telomere elongation helicase 1 polymorphisms, Jin et al. have reported that three locus (rs2297440, rs2853676, and rs6010620) of regulator of telomere elongation helicase 1 are associated with the increased risk of glioma [28]. Walsh et al. also have found that regulator of telomere elongation helicase 1 rs6010620 serves as risk factor for glioma based on Caucasian population [29].

The present meta-analysis, with 8541 cases and 14226 controls, was conducted to derive a more precise assessment between regulator of telomere elongation helicase 1 rs6010620 and glioma susceptibility. The results suggested that the GG genotype of regulator of telomere elongation helicase 1 rs6010620 was significantly associated with the risk for glioma under recessive model. Further subgroup analysis was based on ethnicity and source of control, and the G allele also played an important role in the pathogenesis of glioma.

Overall, our meta-analysis presented regulator of telomere elongation helicase 1 rs6010620 as the genetic-susceptibility factor for glioma. However, there were several limitations that should be addressed. Firstly, we failed to discuss how the risk G allele of rs6010620 polymorphism affect the development of glioma. Further studies are required to research this issue. Secondly, the results were based on unadjusted estimates, which might affect the validity of the association. Finally, lack of considering the effects of other genetic or environmental factors on glioma risk might make our results biased. Therefore, further well-designed investigations based on larger scales are needed to clarify this point of view.

Disclosure of conflict of interest

None.

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