Int J Clin Exp Med 2016;9(6):10987-10994
www.ijcem.com /ISSN:1940-5901/IJCEM0022418

Original Article

XRCC3 T241M polymorphism is associated risk of glioma: a meta-analysis involving 4637 cases and 5854 controls

Huizhong Xu[1], Zhanliang Zhang[2], Qinghua Yan[1], Xiaohong Wu[1], Meng Zhang[1], Zhiwang Song[3]

[1]Department of Neurosurgery, Affiliated Dongtai Hospital of Nantong University, Dongtai 224200, People's Republic of China; [2]Department of Neurosurgery, Yugan People's Hospital, Yugan City, People's Republic of China; [3]Breast Cancer Center, Shanghai East Hospital, Tongji University, Shanghai 200120, People's Republic of China

Received December 21, 2015; Accepted April 3, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Background: The polymorphism of XRCC3 T241M has been indicated to be correlated with glioma susceptibility, but study results are still controversial. The aim of this study was to obtain a more exact estimation of the association between XRCC3 Thr241Met polymorphism and glioma through a meta-analysis. Methods: The meta-analysis included 11 published case-control studies involving 4637 cases and 5854 controls. Odds ratio (OR) with 95% confidence interval (95% CI) were used to evaluate the association of XRCC3 T241M polymorphism with glioma. Results: The association between XRCC3 Thr241Met polymorphism and glioma was significant in the allele model, recessive model, and co-dominant model overall. In a stratified analysis by the ethnicity, significantly increased risk was detected in Asians in the allele model, recessive model, and co-dominant model. Conclusions: In conclusion, XRCC3 Thr241Met polymorphism was implied to be associated with increased glioma risk. More studies are needed to validate this result.

Keywords: XRCC3, glioma, meta-analysis, polymorphism

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 approximately 80% of all primary malignant brain and central nervous system tumors [1, 2]. The etiology, epidemiology, and molecular mechanism of glioma are still poorly understood. Previous studies have showed that many factors, such as workplace, diet, and other personal or residential exposures might correlate with the glioma risk [3, 4]. Besides, the genetic factors including single nucleotide polymorphisms (SNPs) may also exert effects on the development of glioma.

X-ray repair cross-complementing group 3 (XRCC3), a member of DNA repair genes, is involved in maintaining the stability of genome by homologous recombination repair for DNA double-strand breaks [5]. It has been reported that a single nucleotide polymorphism (C18067T, rs861539) at the 18,067th nucleotide in exon 7 of the XRCC3 gene, with a C-to-T change, and this change leads a Thr-to-Met amino acid change at codon 241 [6]. The XRCC3 Thr241Met polymorphism may affect the enzyme's function and/or its interaction with other protein involved in DNA damage and repair, may be associated with the risk of many kinds of tumors, including gastric cancer [7], liver cancer [8], melanoma [9], prostate cancer [10] and breast cancer [11].

Over the last decade, a number of studies have been conducted to investigate the association between XRCC3 Thr241Met polymorphism and glioma risk in humans. However, these studies reported conflicting results. The reason is the possible small effect of the polymorphism on glioma risk and the relatively small sample size in each of the studies. We feel it is necessary to quantitatively summarize the evidence using

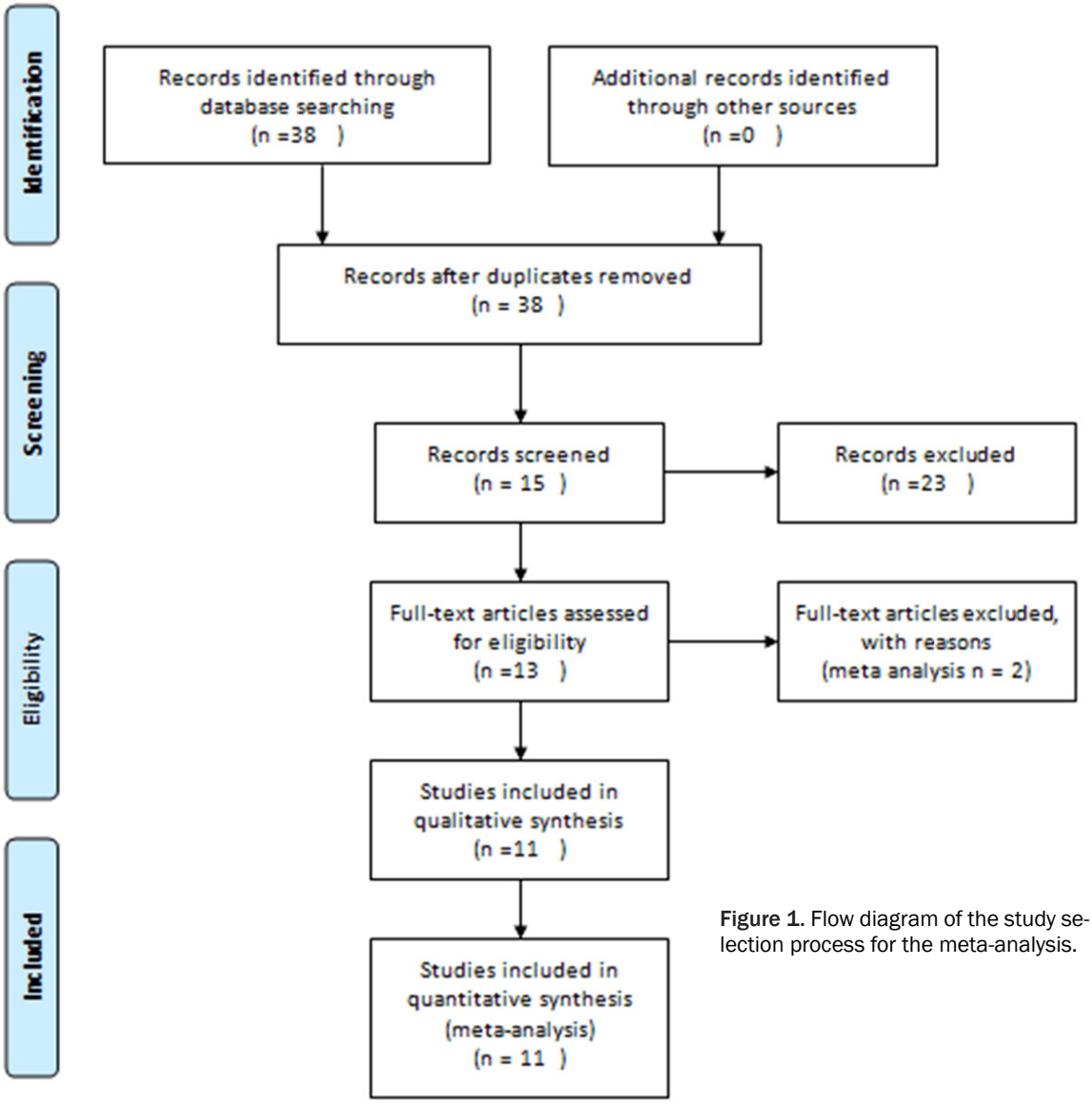

Figure 1. Flow diagram of the study selection process for the meta-analysis.

the gradually accumulated data. In this study, compared with the prior meta-analysis [12], we include several additional studies, which allowed for a larger number of subjects and more precise risk estimation.

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 November 2015, using the following keywords and subject terms: X-ray repair cross-complementing group 3, XRCC3, polymorphism, glioma, brain tumor. We expanded the scope of the computerized literature search on the basis of the reference lists of retrieved articles.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should have evaluated the association between the XRCC3 T241M polymorphism and glioma risk; (2) the study should have a case-control design; (3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) only abstracts or reviews were available, without sufficient data; (2) genotype frequencies were not reported; and (3) studies were repeated or publications overlapped.

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

First author	Year	County	Ethnicity	Case number (n)	Control number (n)	Control source	Genotyping method
Wang	2004	USA	Caucasian	309	342	PB	PCR-RFLP
Kiuru	2008	Finland	Caucasian	701	1560	PB	PCR-RFLP
Liu	2009	USA	Caucasian	373	365	PB	PCR-RFLP
Zhou	2009	China	Asian	771	752	HB	TaqMan
Rajaraman	2010	USA	Caucasian	350	479	HB	TaqMan
Custódio	2012	Brasil	NA	80	100	PB	PCR-RFLP
Liu	2012	China	Asian	312	312	HB	Sequenom MassARRAY
Luo	2013	China	Asian	297	415	HB	Sequenom MassARRAY
Pan	2013	China	Asian	443	443	HB	Sequenom MassARRAY
Xu	2014	China	Asian	886	886	HB	PCR-RFLP
Irene	2013	Spain	Caucasian	115	200	HB	TaqMan

PB, population-based; HB, hospital-based; PCR, polymerase chain reaction; RFLP, pestriction fragment length polymorphism; NA, not available.

Table 2. Distribution of XRCC3 Thr241Met genotype among patients and controls

Study	Glioma			Control			Hardy-Weinberg equilibrium
	Met/Met	Thr/Met	Thr/Thr	Met/Met	Thr/Met	Thr/Thr	
Wang, 2004	37	138	134	48	147	147	Yes
Kiuru, 2008	94	319	288	169	761	630	No
Liu, 2009	60	179	132	44	165	151	Yes
Zhou, 2009	3	80	677	4	75	629	Yes
Rajaraman, 2010	53	162	135	86	208	185	No
Custódio, 2012	9	18	53	5	9	86	No
Liu, 2012	66	154	223	42	147	254	No
Luo, 2013	21	131	145	17	168	229	Yes
Pan, 2013	28	198	217	9	299	234	No
Xu, 2014	71	343	472	45	356	485	Yes
Irene, 2013	16	56	43	21	92	87	Yes

Data extraction

The following data were extracted from each article: first author, year of publication, country, ethnicity of the participants, numbers of cases and controls, source of controls, genotyping methods. 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 the Thr-241Met polymorphism and glioma risk was measured by odds ratio (OR) and 95% confidence interval (CI).

The pooled ORs were performed for allele model (M vs. T), recessive model (MM vs. TM+TT), dominant model (MM+TM vs. TT), co-dominant model (MM vs. TT), respectively. Stratified analyses were performed by ethnicity. In consideration of the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the Q statistic. If the P>0.10 of the Q test which indicates a lack of heterogeneity among studies, the summary OR estimate of each study was calculated by the fixed effects model (the Mantel-Haenszel method). Otherwise, the random effects model (the DerSimonian and Laird method) was used. We also measured the effect of heterogeneity by I^2 statistics. Relative influence of each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis. Sensitivity analysis was also performed by omitting the HWE-violating study. Funnel plots and Egger's test were used to evaluate publication bias [13]. All statistical tests were performed with the software STATA statistical software (version 11.2, Stata Corporation, CollegeStation, Texas).

Results

Characteristics of studies

A total of eleven relevant articles on XRCC3 T241M polymorphism in glioma met the study

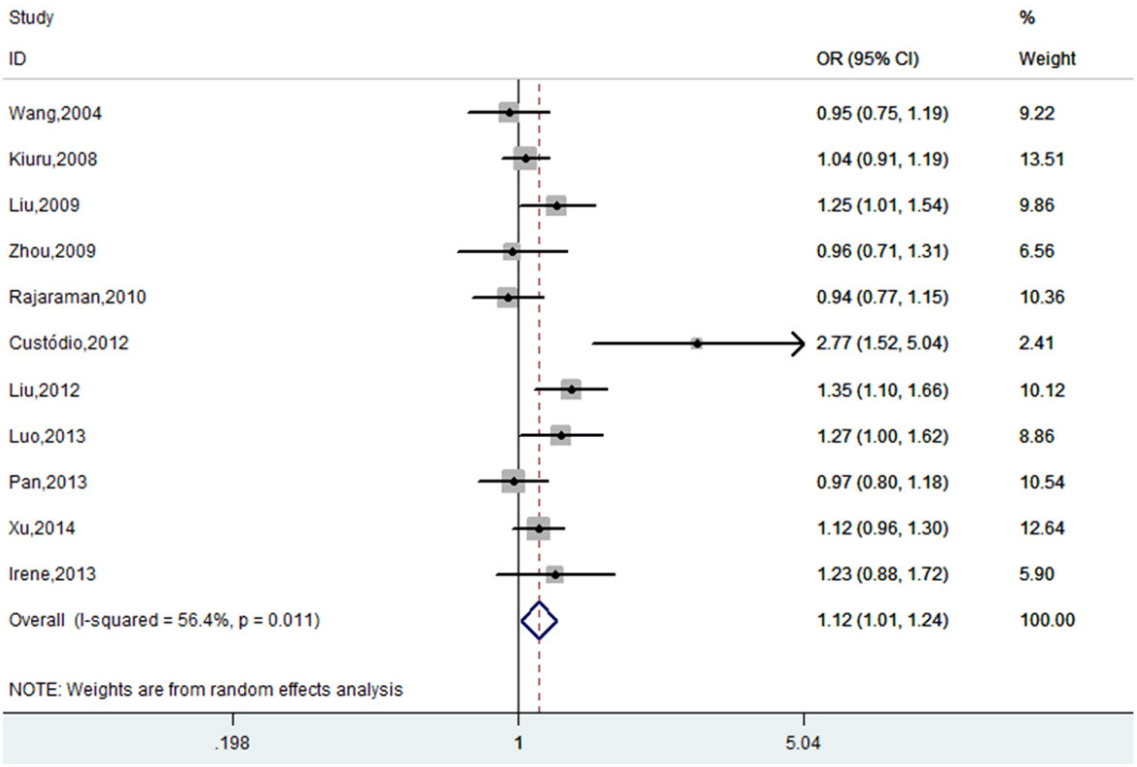

Figure 2. Forest plot of XRCC3 T241M polymorphism associated with glioma risk overall under M vs. T genetic model.

inclusion criteria (**Figure 1**) and were included in the meta-analysis [14-24]. Characteristics of studies included in the current meta-analysis are presented in **Table 1**. There were 5 Caucasian and 5 Asian studies, respectively. Besides, there is 1 not available ethnicity study. The controls were selected from hospitals in 7 studies, while the other 4 studies were selected from general population. The distribution of the genotype in case and control population is shown in **Table 2**. Five studies were not in HWE in eligible studies.

Results of meta-analyses

Eleven studies including 4637 cases and 5854 controls studied the association of XRCC3 T241M polymorphism with glioma, In allelic model, our meta-analysis showed that XRCC3 T241M polymorphism is associated with increased glioma risk overall (OR=1.12, 95% CI=1.01-1.24) (**Figure 2**), with a statistically significant between-study heterogeneity (P=0.011). When stratifying for ethnicity, we found that XRCC3 T241M polymorphism can increase glioma risk for Asian (OR=1.10, 95% CI=1.03-1.17) (**Table 3**). However, we found that there is no significant association between XRCC3 T241M polymorphism and glioma risk for Caucasians (OR=1.05, 95% CI=0.96-1.09) (**Table 3**).

In the recessive model, we found that XRCC3 T241M polymorphism can increase glioma risk overall (OR=1.38, 95% CI=1.09-1.75) (**Table 3**). When stratifying for ethnicity, we found that XRCC3 T241M polymorphisms associated with increased glioma risk for Asians (OR=1.80, 95% CI=1.42-2.29) (**Table 3**). However, we found that there is no significant association between XRCC3 T241M polymorphism and glioma risk for Caucasians (OR=1.11, 95% CI=0.93-1.32) (**Table 3**).

In the dominant model, we didn't find significant association between XRCC3 T241M polymorphism and glioma risk overall (OR=1.100, 95% CI=0.97-1.25) and for Asians (OR=1.07, 95% CI=0.89-1.28) and for Caucasians (OR=1.11, 95% CI=0.93-1.93) (**Table 2**) in the dominant model.

Sensitivity analysis

A single study was excluded each time to evaluate the effect of an individual study on the com-

Table 3. The genetic effect of XRCC3 Thr241Met polymorphism on glioma

Comparisons	Odds ratio	95% confidence interval	*P* value	Heterogeneity		Effects model
				I^2	*P* value	
M vs T						
Overall	1.12	1.01-1.24	0.026	56.40%	0.011	Random
Caucasian	1.05	0.96-1.09	0.263	23.50%	0.264	Fixed
Asian	1.10	1.03-1.17	0.007	41.20%	1.146	Fixed
MM vs TM+TT						
Overall	1.38	1.09-1.75	0.007	57.30%	0.009	Random
Caucasian	1.11	0.93-1.32	0.244	39.10%	0.161	Fixed
Asian	1.80	1.42-2.29	<0.0001	34.70%	0.190	Fixed
MM+TM vs TT						
Overall	1.10	0.97-1.25	0.142	54.80%	0.014	Random
Caucasian	1.05	0.93-1.18	0.455	0.00%	0.435	Fixed
Asian	1.07	0.89-1.28	0.485	59.60%	0.042	Random
MM vs TT						
Overall	1.43	1.13-1.81	0.003	52.60%	0.021	Random
Caucasian	1.13	0.94-1.36	0.195	35.20%	0.187	Fixed
Asian	1.82	1.43-2.33	<0.0001	8.10%	0.36	Fixed

bined ORs and 95% CIs. The omission of any single study did not significantly change the pooled effects of different models. In addition, there was no significant association by omitting HWE-violating studies. These findings confirmed that the meta-analysis results were statistically robust and that our results were reliable and stable (data not shown) (**Figure 3**).

Publication bias test results

The shape of Begg's funnel plots showed no publication bias for dominant model in the overall meta-analysis (**Figure 4**). In other genetic models, publication bias was also not detected.

Discussion

Glioma, originating from glial cells, is the most common primary tumors of the central nervous system, and it accounts for the majority of the malignant brain tumors [25, 26]. Despite significant improvements in the diagnosis and treatment for patients with glioma, this primary brain tumor remains essentially incurable. Although surgery, chemotherapy, and radiotherapy substantially improve patient survival, 95% of patients have a mean survival of less than 2 years following diagnosis [27]. Many studies demonstrated that genetic factors influence the susceptibility of glioma [28, 29]. Among genetic factors, DNA repair capacity is an important factor. DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER), and double-strand break repair (DSBR), play an important role in maintaining genetic stability through different pathways [30].

XRCC3 is the major gene involved in the restoration phase of DNA damage. To date, numerous studies have examined the association between the XRCC3 T241M polymorphism and glioma susceptibility. However, the results are inconsistent. Several individual studies reported that XRCC3 T241M polymorphism is not associated with glioma [15, 16]. On the contrary, some studies concluded that XRCC3 T241M polymorphism increased the risk of glioma [17, 19]. In addition, a meta-analysis including eight literatures failed to suggest an association of the XRCC3 T241M polymorphism with glioma risk [31]. Another meta-analysis concluded that XRCC3 T241M polymorphism is associated increased glioma risk among Asians, but have no association with overall population and Caucasians. On account of the small sample and contradictory conclusions of previous studies, we performed a meta-analysis to assess the association between XRCC3 T241M polymorphism and glioma risk.

Zhao et al conducted a meta-analysis including 3754 cases and 4958 controls showed identified XRCC3 T241M polymorphism have no significant association with glioma risk overall, but can increased glioma risk among Asians [12]. Feng et al performed a similar meta-analysis involving 3455 controls and 4435 controls demonstrated that, XRCC3 T241M polymorphism is not appreciable association with glioma risk [31].

To our knowledge, our meta-analysis had the largest sample size to date, which have altered the overall results. In this study, a total of 11 studies including 4637 cases and 5854 con-

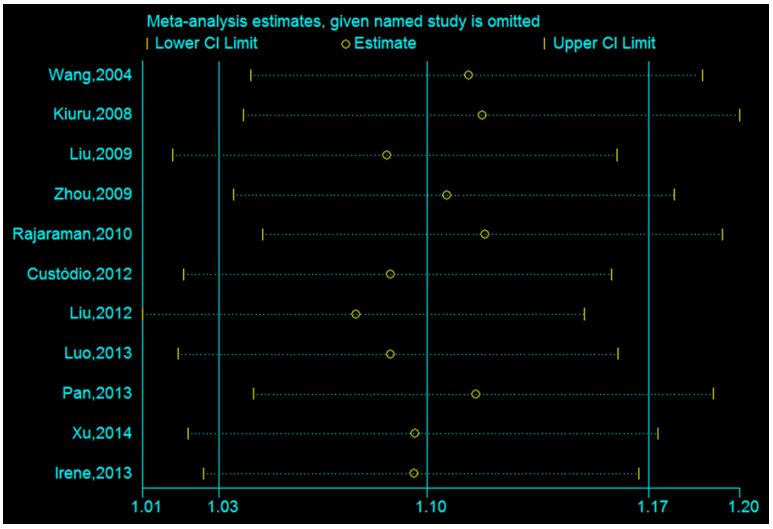

Figure 3. Sensitivity analysis of the association between the XRCC3 T241M polymorphism and glioma risk.

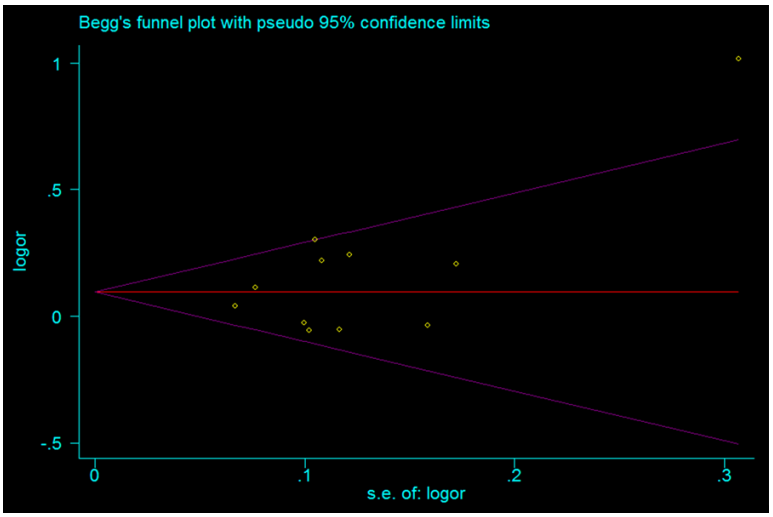

Figure 4. Begg's funnel plots of publication bias for the association between the XRCC3 T241M polymorphism and glioma risk.

trols were reviewed. Our results demonstrate that the XRCC3 T241M polymorphism can increase the risk of glioma in overall populations. In the stratified analysis by ethnicity, significant associations were found in the Asians. However, no significant associations were detected among Caucasian.

There are some possible reasons for such differences. First, the frequencies of the risk allele or genotype vary sharply between different ethnicities. Thus, more studies are needed to further investigate ethnic differences in the effect of XRCC3 T241M on glioma risk. Second, different populations usually have different linkage disequilibrium patterns. A polymorphism may be in close linkage with another nearby causal variant in one ethnic population but not in another [32]. Third, the positive association between XRCC3 T241M polymorphism and glioma among Caucasians could not be ruled out because studies with small sample size may have insufficient statistical power to detect a slight effect.

When interpreting the results of the current study, some limitations should be addressed. First, our meta-analysis is based on unadjusted estimates. A more precise analysis allowing for an adjustment by other co-variables, such as age, gender, smoking status, alcohol consumption and other variables, could be performed if individual data were available. Ideally, we would like to pool individual-level data. However, lack of individual-level data prevents us from making further analysis. Second, some heterogeneity was observed in current study as a result of uncontrolled confounding factors and internal selection bias. Heterogeneity cannot be avoided. We solved this problem by adopting sensitivity analysis and the random effects model. Third, only studies published and written in English were included this meta-analysis, which may result out some degree of publication bias. However, no evidence for publication bias was found, indicating that noticeable harm would not be caused by the potential publication bias. Finally, gene-gene and gene-environment interactions were not performed in this meta-analysis, owing to the lack of relevant data. Thus, more studies with large sample size and careful design are needed to fur-

ther identify this association more comprehensively.

Despite the limitations listed above, our meta-analysis still has several strengths that merit attention. This analysis includes the largest number of cases and controls from each included study reported to date, which significantly increases statistical power. Moreover, our results are in relatively good agreement with those observed in the previous largest study, and the results remain valid in almost every subgroup analysis.

In conclusion, our meta-analysis suggests that XRCC3 T241M polymorphism is significantly associated with an increased risk of glioma.

Acknowledgements

This research was supported in part by the National Nature Science Foundation of China (81573008), National Nature Science Foundation of China (81201798), the Fund of Pudong Health Bureau of Shanghai (PWRd-2014-01) and the Project of Key Disciplines Group Construction of Pudong Health Bureau of Shanghai (PWZxq2014-04).

Disclosure of conflict of interest

None.

Address correspondence to: Zhiwang Song, Shanghai East International Medical Center, 150 Jimo Road, Shanghai 200120, People's Republic of China. Tel: +86-13370029736; E-mail: 1866207-6641@163.com

References

[1] Mamelak AN and Jacoby DB. Targeted delivery of antitumoral therapy to glioma and other malignancies with synthetic chlorotoxin (TM-601). Expert Opin Drug Deliv 2007; 4: 175-186.

[2] Schwartzbaum JA, Fisher JL, Aldape KD and Wrensch M. Epidemiology and molecular pathology of glioma. Nat Clin Pract Neurol 2006; 2: 494-503.

[3] Chen PC, Wiencke J, Aldape K, Kesler-Diaz A, Miike R, Kelsey K, Lee M, Liu J and Wrensch M. Association of an ERCC1 polymorphism with adult-onset glioma. Cancer Epidemiol Biomarkers Prev 2000; 9: 843-847.

[4] Zong HL, Cao L, Ma C, Zhao JP, Ming X, Shang M and Xu HS. Association between the G870A polymorphism of Cyclin D1 gene and glioma risk. Tumor Biol 2014; 35: 8095-8101.

[5] Griffin CS, Simpson PJ, Wilson CR and Thacker J. Mammalian recombination-repair genes XRCC2 and XRCC3 promote correct chromosome segregation. Nat Cell Biol 2000; 2: 757-761.

[6] Shen MR, Jones IM and Mohrenweiser H. Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer Res 1998; 58: 604-608.

[7] Qin XP, Zhou Y, Chen Y, Li NN and Wu XT. XRCC3 Thr241Met polymorphism and gastric cancer susceptibility: A meta-analysis. Clin Res Hepatol Gastroenterol 2014; 38: 226-234.

[8] Liu CB and Wang HB. XRCC3 T241M polymorphism is associated risk of hepatocellular carcinoma in the Chinese. Tumor Biol 2013; 34: 2249-2254.

[9] Fan JH, Fan YH, Kang XX and Zhao LM. XRCC3 T241M polymorphism and melanoma skin cancer risk: A meta-analysis. Oncol Lett 2015; 9: 2425-2429.

[10] Xuan G, Hui Y and Fang H. The association of XRCC3 Thr241Met genetic variant with risk of prostate cancer: a meta-analysis. Afr Health Sci 2015; 15: 117-122.

[11] Chai F, Liang Y, Chen L, Zhang F and Jiang J. Association Between XRCC3 Thr241Met Polymorphism and Risk of Breast Cancer: Meta-Analysis of 23 Case-Control Studies. Med Sci Monit 2015; 21: 3231-3240.

[12] Zhao B, Ye JL, Li B, Ma Q, Su GJ and Han RZ. DNA repair gene XRCC3 Thr241Met polymorphism and glioma risk: a meta-analysis. Int J Clin Exp Med 2013; 6: 438-443.

[13] Egger M, Smith GD and Minder C. Bias in meta-analysis detected by a simple, graphical test - Reply. Br Med J 1998; 316: 470-471.

[14] Wang LE, Bondy ML, Shen HB, El-Zein R, Aldape K, Cao YM, Pudavalli V, Levin VA, Yung WK and Wei QY. Polymorphisms of DNA repair genes and risk of glioma. Cancer Res 2004; 64: 5560-5563.

[15] Kiuru A, Lindholm C, Heinavaara S, Ilus T, Jokinen P, Haapasalo H, Salminen T, Christensen HC, Feychting M, Johansen C, Lonn S, Malmer B, Schoemaker MJ, Swerdlow AJ and Auvinen A. XRCC1 and XRCC3 variants and risk of glioma and meningioma. J Neurooncol 2008; 88: 135-142.

[16] Liu YH, Scheurer ME, El-Zein R, Cao YM, Do KA, Gilbert M, Aldape KD, Wei QY, Etzel C and Bondy ML. Association and Interactions between DNA Repair Gene Polymorphisms and Adult Glioma. Cancer Epidemiol Biomarkers Prev 2009; 18: 204-214.

[17] Zhou KK, Liu YH, Zhang HS, Liu HL, Fan WW, Zhong Y, Xu ZH, Jin L, Wei QY, Huang FP, Lu DR and Zhou LF. XRCC3 haplotypes and risk of gliomas in a Chinese population: A hospital-

based case-control study. Int J Cancer 2009; 124: 2948-2953.
[18] Rajaraman P, Hutchinson A, Wichner S, Black PM, Fine HA, Loeffler JS, Selker RG, Shapiro WR, Rothman N, Linet MS and Inskip PD. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. Neuro Oncol 2010; 12: 37-48.
[19] Custodio AC, Almeida LO, Pinto GR, Santos MJ, Almeida JR, Clara CA, Rey JA and Casartelli C. Variation in DNA repair gene XRCC3 affects susceptibility to astrocytomas and glioblastomas. Genet Mol Res 2012; 11: 332-339.
[20] Liu HB, Peng YP, Dou CW, Su XL, Gao NK, Tian FM and Bai J. Comprehensive Study on Associations Between Nine SNPs and Glioma Risk. Asian Pac J Cancer Prev 2012; 13: 4905-4908.
[21] Pan WR, Li G and Guan JH. Polymorphisms in DNA Repair Genes and Susceptibility to Glioma in a Chinese Population. Int J Mol Sci 2013; 14: 3314-3324.
[22] Luo KQ, Mu SQ, Wu ZX, Shi YN and Peng JC. Polymorphisms in DNA Repair Genes and Risk of Glioma and Meningioma. Asian Pac J Cancer Prev 2013; 14: 449-452.
[23] Xu GF, Wang MD, Xie WF and Bai XB. DNA repair gene XRCC3 Thr241Met polymorphism and susceptibility to glioma: A case-control study. Oncol Lett 2014; 8: 864-868.
[24] Rodriguez-Hernandez I, Perdomo S, Santos-Briz A, Garcia JL, Gomez-Moreta JA, Cruz JJ and Gonzalez-Sarmiento R. Analysis of DNA repair gene polymorphisms in glioblastoma. Gene 2014; 536: 79-83.
[25] Walsh KM, Codd V, Smirnov IV, Rice T, Decker PA, Hansen HM, Kollmeyer T, Kosel ML, Molinaro AM, McCoy LS, Bracci PM, Cabriga BS, Pekmezci M, Zheng S, Wiemels JL, Pico AR, Tihan T, Berger MS, Chang SM, Prados MD, Lachance DH, O'Neill BP, Sicotte H, Eckel-Passow JE; ENGAGE Consortium Telomere Group, van der Harst P, Wiencke JK, Samani NJ, Jenkins RB, Wrensch MR. Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. Nat Genet 2014; 46: 731-735.
[26] Pei SJ, Zhao F, Liu JL, Fu Q and Shang PZ. Association between regulator of telomere elongation helicase 1 polymorphism and susceptibility to glioma. Int J Clin Exp Med 2015; 8: 690-697.
[27] Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K and Delattre JY. Primary brain tumours in adults. Lancet 2012; 379: 1984-1996.
[28] Holland EC. Gliomagenesis: Genetic alterations and mouse models. Nat Rev Genet 2001; 2: 120-129.
[29] Malmer B, Iselius L, Holmberg E, Collins A, Henriksson R and Gronberg H. Genetic epidemiology of glioma. Br J Cancer 2001; 84: 429-434.
[30] Wood RD, Mitchell M, Sgouros J and Lindahl T. Human DNA repair genes. Science 2001; 291: 1284-9.
[31] Feng YP, Zeng MY and Xu QS. Association between XRCC3 T241M polymorphism and glioma risk: a meta-analysis. Tumor Biol 2014; 35: 5589-5592.
[32] Xu ZQ, Ma WB, Gao L and Xing B. Association between ERCC1 C8092A and ERCC2 K751Q polymorphisms and risk of adult glioma: a meta-analysis. Tumor Biol 2014; 35: 3211-3221.