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Original Article

DNA repair gene *XRCC3* Thr241Met polymorphism and glioma risk: a meta-analysis

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Abstract: Background: The polymorphism of *XRCC3* Thr241Met has been indicated to be correlated with glioma susceptibility, but study results are still debatable. The present meta-analysis was performed to investigate the association between *XRCC3* Thr241Met polymorphism and glioma. Methods: A total of 3754 glioma patients and 4849 controls from nine separate studies were involved. The pooled odds ratio (OR) and its corresponding 95% confidence interval (CI) was assessed by the random-effects model. Results: The association between *XRCC3* Thr241Met polymorphism and glioma was significant in the recessive model (OR = 1.36; 95% CI, 1.02 – 1.82; P = 0.03). In a stratified analysis by the ethnicity, significantly increased risk was detected in Asians (OR = 1.93; 95% CI, 1.18 – 3.17; P = 0.009). Conclusions: In conclusion, *XRCC3* Thr241Met polymorphism was implied to be associated with increased glioma risk. More studies are needed to validate this result.

Keywords: Glioma, XRCC3, meta-analysis, polymorphism

Introduction

Malignant gliomas account for approximately 70% of adult malignant primary brain tumors in the United States. These tumors are associated with median survival of only 12 to 15 months among patients with glioblastoma, the most common type of glioma [1]. Genetic factors are considered to influence the susceptibility of glioma [2, 3]. Among genetic factors, DNA repair capacity is an important factor. The reason appears to be that 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 [4, 5].

XRCC3 functions in the DNA double-strand break and cross-link repair and interacts and stabilizes Rad51, one of the key components of the homologous repair (HR) pathway [6, 7]. Thr241Met amino acid substitution due to a C18607T transition at exon 7 in the *XRCC3* gene has been found to be functionally active as it is associated with an increased number of micronuclei in lymphocytes of humans exposed to ionizing radiation [8, 9]. *XRCC3* Thr241Met polymorphism was associated with the risks of some kinds of cancers, including head and neck cancer, breast cancer [10, 11]. As for glioma, several studies were performed [12-20]. However, the results were inconsistent. So far, no quantitative summary of the evidence has ever been performed. To gain better insight into the impact of this variant on the risk of glioma, we performed this meta-analysis.

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 April 2013, 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.

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

First author	Year	Country	Ethnicity	Case number (n)	Control number (n)	Control source	Genotyping method
Wang [12]	2004	USA	Caucasian	309	342	PB	PCR-RFLP
Kiuru [13]	2008	Finland	Caucasian	701	1560	PB	PCR-RFLP
Liu [14]	2009	USA	Caucasian	373	365	PB	PCR-RFLP
Zhou [15]	2009	China	Asian	771	752	HB	TaqMan
Rajaraman [16]	2010	USA	Caucasian	350	479	HB	TaqMan
Custódio [17]	2012	Brasil	NA	80	100	PB	PCR-RFLP
Liu [18]	2012	China	Asian	312	312	HB	Sequenom MassARRAY
Luo [19]	2013	China	Asian	297	415	HB	Sequenom MassARRAY
Pan [20]	2013	China	Asian	443	443	HB	Sequenom MassARRAY

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

	Glioma			Control			Hardy-Weinberg equilibrium
Study	Met/Met	Thr/Met	Thr/Thr	Met/Met	Thr/Met	Thr/Thr	
Wang	37	138	134	48	147	147	Yes
Kiuru	94	319	288	169	761	630	No
Liu	60	179	132	44	165	151	Yes
Zhou	3	80	677	4	75	629	Yes
Rajaraman	53	162	135	86	208	185	No
Custódio	9	18	53	5	9	86	No
Liu	66	154	223	42	147	254	No
Luo	21	131	145	17	168	229	Yes
Pan	28	198	217	9	299	234	No

Inclusion criteria

The following inclusion criteria were used: (1) the study assessed the association between the glioma and *XRCC3* Thr241Met polymorphism; (2) the study population included subjects with and without glioma; (3) the study reported the genotype number.

Data extraction

The following data were recorded from each article: 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 *XRCC3* Thr241Met polymorphism and glioma risk was measured by odds ratio (OR) and 95% confidence interval (CI). OR1, OR2, and OR3 were calculated for the genotypes: Met/Met vs. Thr/Thr (OR1), Thr/Met vs. Thr/Thr (OR2), and Met/Met vs. Thr/Met (OR3). These pairwise differences were used to indicate the most appropriate genetic model as follows: if OR1 = OR3 ≠ 1 and OR2 = 1, then a recessive model was suggested; if OR1 = OR2 ≠ 1 and OR3 = 1, then a dominant model was suggested; if OR2 = 1/OR3 ≠ 1 and OR1 = 1, then a complete overdominant model was suggested; if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then a codominant model was suggested [21]. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a codominant model) and to pool the results again. Random-effects model (the DerSimonian and Laird) was used.

Hardy-Weinberg equilibrium (HWE) in controls was calculated again in our meta-analysis. The chi-square goodness of fit was used to test deviation from HWE (significant at the 0.05

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

		Sample size		Test of association			Heterogeneity		
Comparison	Study	case	control	OR (95% CI)	*Z*	*P* Value	χ^2	*P* Value	I^2 (%)
Met/Met vs. Thr/Thr	Overall	2375	2969	1.41 (1.05 – 1.87)	2.32	0.02	20.01	0.01	60.0
Thr/Met vs. Thr/Thr	Overall	3383	4524	1.06 (0.90 – 1.24)	0.68	0.50	19.50	0.01	59.0
Met/Met vs. Thr/Met	Overall	1750	2403	1.27 (0.95 – 1.72)	1.59	0.11	21.20	0.007	62.0
Met/Met vs. Thr/Met + Thr/Thr	Overall	3754	4948	1.36 (1.02 – 1.82)	2.11	0.03	22.04	0.005	64.0
Met/Met vs. Thr/Met + Thr/Thr	Asian	1943	2107	1.93 (1.18 – 3.17)	2.61	0.009	5.79	0.12	48.0
Met/Met vs. Thr/Met + Thr/Thr	Caucasian	1731	2741	1.07 (0.82 – 1.39)	0.47	0.64	6.18	0.10	51.0
Met/Met vs. Thr/Met + Thr/Thr	PB	1461	2362	1.22 (0.93 – 1.60)	1.42	0.16	4.48	0.21	33.0
Met/Met vs. Thr/Met + Thr/Thr	HB	2293	2586	1.53 (0.87 – 2.68)	1.48	0.14	17.24	0.002	77.0
Met/Met vs. Thr/Met + Thr/Thr	HWE	1737	1824	1.18 (0.81 – 1.72)	0.87	0.38	4.73	0.19	37.0

PB, population-based; HB, hospital-based; HWE, Hardy-Weinberg equilibrium.

level). A significant Q-statistic (P < 0.10) indicated heterogeneity across studies. We also measured the effect of heterogeneity by I^2 statistics. We conducted stratification analysis according to participant ethnicity and controls source in order to find the potential heterogeneity. 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 [22]. All statistical analysis were performed using the STATA statistical software (version 11.2, Stata Corporation, College Station, Texas).

Results

Characteristics of studies

Characteristics of studies included in the current meta-analysis are presented in **Table 1**. Nine studies including 3754 glioma patients and 4948 controls were included in the meta-analysis. There were 4 Caucasian and 4 Asian studies, respectively. The controls were selected from hospitals in 5 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

The estimated OR1, OR2 and OR3 were 1.41, 1.06, and 1.27, respectively (**Table 3**). These estimates suggested a recessive genetic model. The pooled OR was 1.36 (95% CI 1.02 – 1.82, P = 0.03) (**Figure 1**). In the stratified analysis by ethnicity, a significant association between *XRCC3* Thr241Met polymorphism and glioma risk was also found among Asians (OR = 1.93; 95% CI 1.18 – 3.17; P = 0.009). No significant association was found among Caucasians (OR = 1.07; 95% CI 0.82 – 1.39; P = 0.64). In the subgroup analysis stratified by the source of control, no significant association was found.

In the sensitivity analysis, the result was changed after exclusion of individual study (**Figure 2**). In addition, there was no significant association by omitting HWE-violating studies (**Table 3**).

Publication bias

Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot was prone to be symmetrical, suggesting that there was no evidence of publication bias among the studies (**Figure 3**). The Egger's test was performed to statistically evaluate funnel plot symmetry. The results suggested no publication bias (P = 0.397).

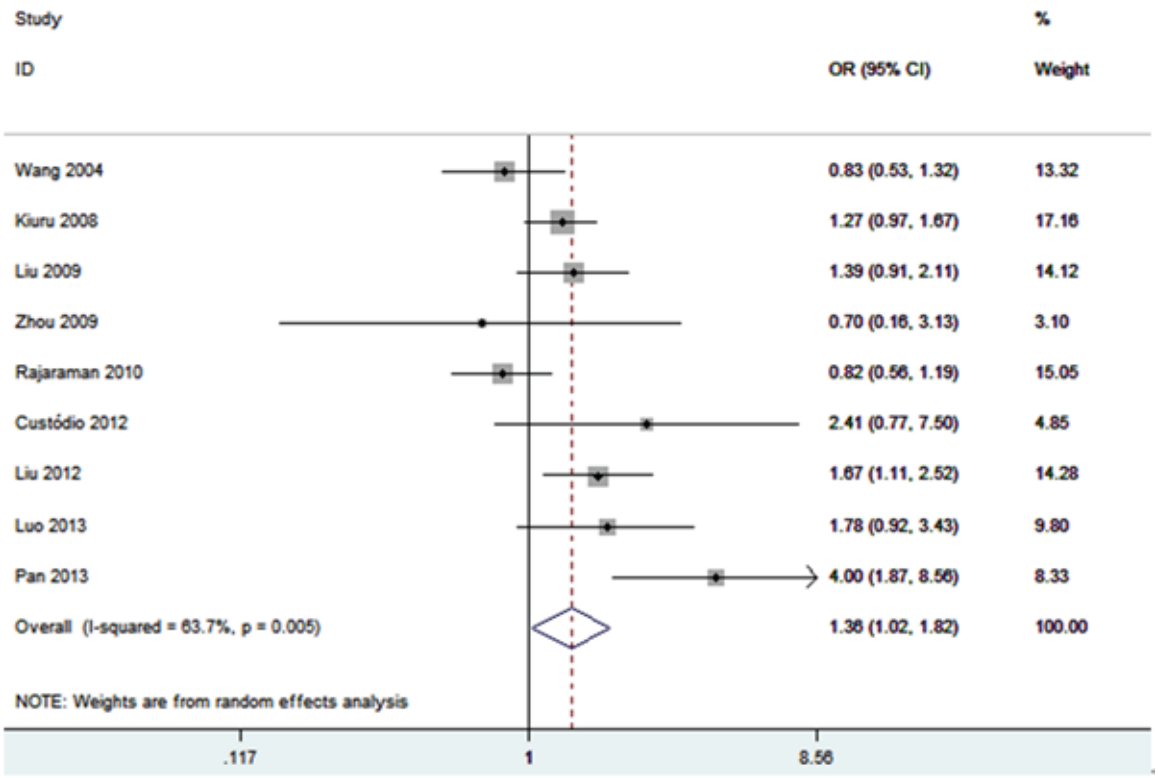

Figure 1. Meta-analysis for the association of glioma risk with *XRCC3* Thr241Met polymorphism.

Discussion

This meta-analysis, involving a total of 3754 glioma patients and 4948 controls from 9 case-control studies, investigated the association of *XRCC3* Thr241Met polymorphism with glioma risk. For *XRCC3* Thr241Met polymorphism, individuals carrying the Met/Met showed a small glioma risk compared with the individuals with the (Thr/Thr + Thr/Met) genotype. Subgroup analysis by ethnicity showed that this polymorphism was significantly associated with increased glioma risk in Asians, but not in Caucasians. This result suggested a possible influence among different genetic backgrounds. Subgroup analysis was also performed according to control source. No significant increased risk of glioma was found. The study numbers included in this subgroup meta-analysis was small. Therefore, this subgroup analysis may not have enough statistical power to explore the association of *XRCC3* Thr241Met polymorphism with glioma susceptibility. To investigate the stability of the result, we performed sensitivity analyses. Removal of each study or the studies not in HWE altered the association with glioma risk, suggesting that the result was not stable. Thus, more studies are needed to confirm our results.

Development of glioma is a multistage process, and a single polymorphism might have a limited impact on glioma susceptibility. Zhou et al. [15] reported that common genetic variants in the *XRCC3* gene, such as GGCC and AGTC, may modulate glioma risk. Thus, interactions of multiple single nucleotide polymorphisms (SNPs) in *XRCC3* might augment the effect. In addition to genetic predisposition, environmental exposure, such as smoking and alcohol consumption, is also thought to play a crucial role in the etiology of glioma [23]. However, gene-environment interactions can not be addressed because of insufficient data. Therefore, SNP-SNP and gene-environment interactions should be considered in future studies.

Significant heterogeneity was observed in this meta-analysis. We used subgroup analysis to find the sources of heterogeneity. In the subgroup analysis by ethnicity, we found heterogeneity was decreased in Asians and Caucasians. Funnel plot and Egger's test were used to find potential publication bias. However, no publica-

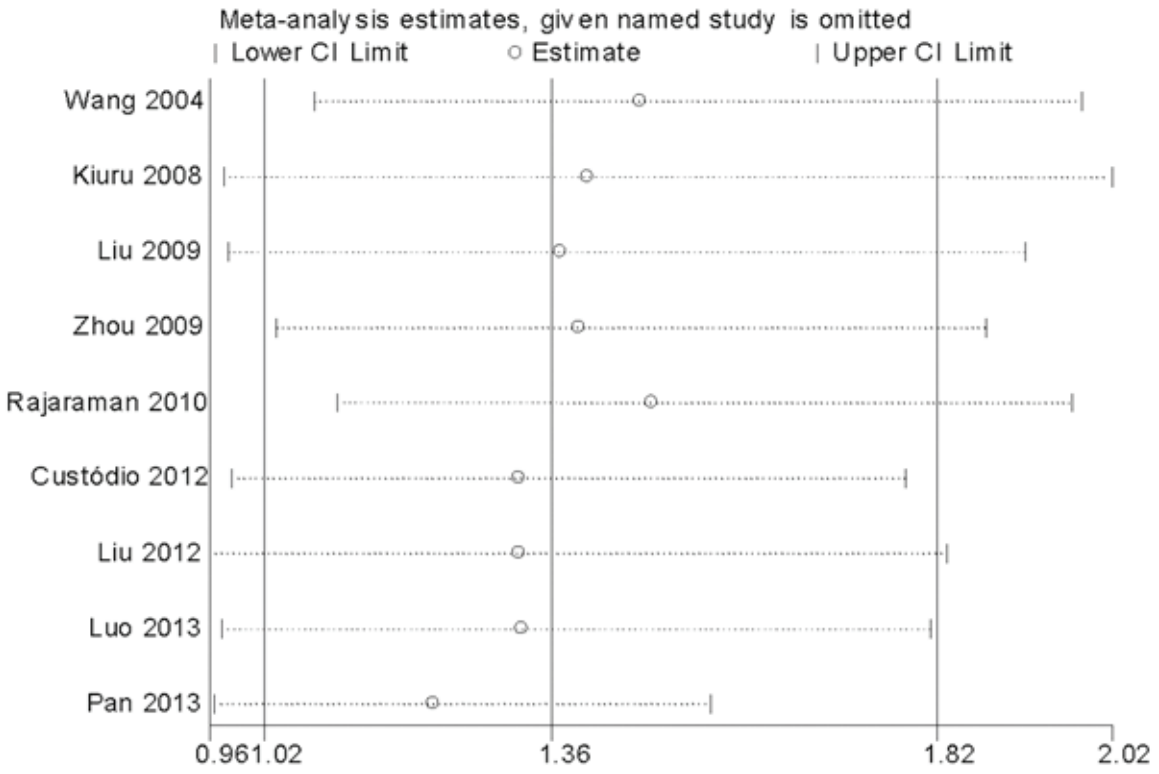

Figure 2. Sensitivity analysis through deletion of one study at a time to reflect the influence of the individual dataset to the pooled ORs.

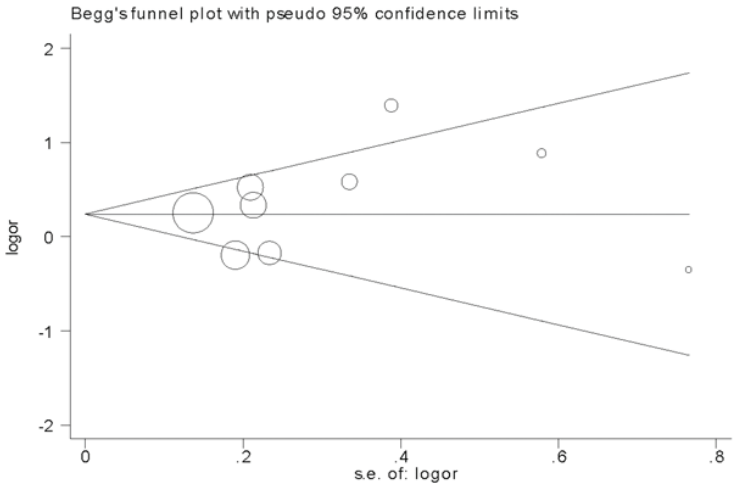

Figure 3. Funnel plot for the glioma risk with *XRCC3* Thr241Met polymorphism.

tion bias was detected; indicating that the whole pooled result might be reliable.

Certain potential limitations existed in our meta-analysis. First, these results were based on unadjusted estimates that lack the original data from the eligible studies. Second, the number of available studies that could be included in this meta-analysis was moderate. Therefore, the results could be influenced by the factors like random error. Third, most of the included studies were carried out in Asians and Caucasians. Absence of data from other ethnics made a more comprehensive evaluation of the association between this SNP and susceptibility to glioma not possible.

To the best of our knowledge, this was the first genetic meta-analysis of the association between *XRCC3* Thr241Met polymorphism and glioma. This meta-analysis suggested that *XRCC3* Thr241Met polymorphism may be a risk factor of glioma. Well-designed studies with larger sample size and more ethnic groups should be considered to further clarify the association.

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