RESEARCH ARTICLE

The XRCC3 Thr241Met Polymorphism Influences Glioma Risk - A Meta-analysis

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Abstract

Background: Findings from previous published studies regarding the association of the XRCC3 Thr241Met polymorphism with glioma susceptibility have often been conflicting. Therefore, a meta-analysis including all available publications was carried out to make a more precise estimation of the potential relationship. Methods: By searching the electronic databases of Pubmed and Embase (up to April 1st, 2013), a total of nine case-control studies with 3,752 cases and 4,849 controls could be identified for inclusion in the current meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association. Results: This meta-analysis showed the XRCC3 Thr241Met polymorphism to be significantly associated with decreased glioma risk in the allelic model (Met allele vs. Thr allele: OR= 0.708, 95%CI= 0.631-0.795). Moreover, we also observed a statistically significant association between the XRCC3 Thr241Met polymorphism and reduced glioma risk in analyses stratified by ethnicity (Asian) and source of controls (hospital based) in the allelic model. Conclusions: Current evidence suggests that the XRCC3 Thr241Met polymorphism may be a risk factor for glioma development, especially in Asians.

Keywords: Glioma - polymorphism - meta-analysis - XRCC3 - Asian ethnicity

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Introduction

Gliomas are the most common central nervous system tumors and account for approximately 80% of primary malignant brain tumors (Schwartzbaum et al., 2006; Jemal et al., 2009). Gliomas are tumors of the neoplastic glial cells, or neuroglia, and are further classified by the World Health Organization (WHO) as a strocytoma, mixed oliogoastrocytoma, oligodendroglioma, and ependymoma (Louis et al., 2007). Up to now, the etiology of glioma remains unknown. In spite of multiple epidemiologic risk factor studies that have been performed, there are few validated associations due to most studies that are limited by small sample sizes and the differences in tumor classification. Ionizing radiation is the only established environmental risk factor with strong evidence of an association with brain tumors (Bondy et al., 2008).

It is widely accepted that the damaged DNA or lower DNA repair capacity contributes to the genetic instability and the development of cancer. DNA repair genes, which play a major role in repairing the damaged DNA, could prevent the activation of oncogenes or inactivation of tumor-suppressor genes (Abdel-Rahman et al., 2011). As a member of DNA repair genes, X-ray repair cross-complementing group 3 (XRCC3) is involved in the process of homologous recombination repair for DNA double-strand breaks so as to maintain the stability of genome (Griffin et al., 2000). The most common functional single nucleotide polymorphism (SNP) of XRCC3, Thr241Met (rs861539), is at codon 241 in exon 7 with a C to T transition (Shen et al., 1998). To date, a number of researches have shown that XRCC3 Thr241Met is a susceptible factor for several cancers, such as lung, breast, colorectal and bladder cancers (Lopez-Cima et al., 2007; Mittal et al., 2012; Romanowicz-Makowska et al., 2012; Zhao et al., 2012), and previous studies also have suggested that the XRCC3 Thr241Met polymorphism is suspected with glioma risk. However, the cumulative results are still inconclusive due to various ethnicities, age, histological types and so on. Therefore, we performed this meta-analysis based on all eligible case-control studies in order to investigate the association strength between the XRCC3 Thr241Met polymorphism and glioma risk.

Materials and Methods

Literature search strategy

We searched the databases of Pubmed and Embase (updated to April 1st, 2013) for relevant reports on the association between XRCC3 Thr241Met polymorphism and glioma risk. The search terms were used as follows: 'X-ray repair cross complementing group 3 or XRCC3', 'Thr241Met or rs861539', 'glioma or glioblastoma or astrocytoma' and 'polymorphism or polymorphisms or SNP or SNPs'. References of original studies and review articles were identified by hands-on searches for additional

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Table 1. Characteristics and Genotype Data Extracted from Eligible Studies

Study(year)	Ethnicity(country) (case/control)	Sample size of controls	Source		Genotype frequencies ThrThr	ThrMet	MetMet	Genotyping method
Liu(2012)	Asian(China)	443/443	HB	Case:	66	154	223	MassARRAY
				Control:	42	147	254	
Zhou(2009)	Asian(China)	760/708	HB	Case:	677	80	3	PCR-RFLP
				Control:	629	75	4	
Pan(2013)	Asian(China)	443/443	PB	Case:	217	198	28	MassARRAY
				Control:	234	200	9	
Luo(2013)	Asian(China)	297/414	HB	Case:	145	131	21	MassARRAY
				Control:	229	168	17	
Custodio(2012)	Mixed(Brazil)	80/100	PB	Case:	53	18	9	PCR-RFLP
				Control:	86	9	5	
Rajaraman(2010)	Caucasian(USA)	350/479	HB	Case:	135	162	53	TaqMan
				Control:	185	208	86	
Liu(2009)	Caucasian(USA)	369/360	PB	Case:	131	177	61	MassARRAY
				Control:	147	168	45	
Wang(2004)	Caucasian(USA)	309/342	HB	Case:	134	138	37	PCR-RFLP
				Control:	147	147	48	
Kiuru(2008)	Caucasian(Finland)	560/961	PB	Case:	288	319	94	PCR-RFLP
				Control:	630	761	169	

studies. No restrictions were applied on language.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) evaluation of Thr241Met (rs861539) polymorphism of XRCC3 and glioma risk; (2) sufficient data to examine an odds ratio (OR) with 95% confidence interval (CI); (3) retrospective case–control studies or prospective cohort studies; (4) conforming Hardy–Weinberg equilibrium (HWE) in the control group. Studies were excluded when: (1) case reports, letters, reviews, editorial articles, and animal studies; (2) not case-control studies; (3) duplicate or insufficient date; (4) family-based design; (5) controls were not in HWE.

Data extraction

Data from published studies were extracted independently and carefully by two reviewers (Jiang J and Quan X.F.). For each study, we collected the following information: first author, year of publication, country, ethnicity, sample size, source of controls, Genotype frequencies, and Genotyping method.

Statistical analysis

The strength of the association between the XRCC3 Thr241Met polymorphism and glioma risk was calculated by ORs with 95%CIs. We evaluated the risk of the allelic model (Met allele vs. Thr allele), the dominant model (MetMet + ThrMet vs. ThrThr), the recessive model (MetMet vs. ThrThr + ThrMet), the homozygote comparison (MetMet vs. ThrThr), the heterozygote comparison (ThrMet vs. ThrThr), respectively. We also performed the subgroup analyses including ethnicity and source of controls. The Chi-square test-based Q-statistic and I^2- statistic (Higgins et al., 2003) were used to analyze the heterogeneity (considered significant for $P \leq 0.10$). If the heterogeneity was not an issue, the fixed-effects model (Mantel-Haenszel method) was selected (Mantel et al., 1959). Otherwise, the random-effects model (DerSimonian-Laird method) was used (DerSimonian et al., 1986).

Potential publication bias was investigated with funnel plot (Begg et al., 1994), and funnel plot asymmetry was assessed by the method of Egger's linear regression test (bias considered significant for $P < 0.05$) (Egger et al., 1997). All statistical tests were performed with STATA version (Stata Corporation College Station, TX, USA). All the P values were two-sided.

Results

Study characteristics

According to the inclusion and exclusion criteria, a total of nine publications with 3,752 Cases and 4,849 Controls were included in this meta-analysis (Wang et al., 2004; Kiuru et al., 2008; Liu et al., 2009; Zhou et al., 2009; Rajaraman et al., 2010; Custódio et al., 2012; Liu et al., 2012; Luo et al., 2013; Pan et al., 2013). Among the nine studies, four studies (Zhou et al., 2009; Liu et al., 2012; Luo et al., 2013; Pan et al., 2013) were performed in Asian populations and four (Wang et al., 2004; Kiuru et al., 2008; Liu et al., 2009; Rajaraman et al., 2010) were conducted in Caucasian populations. Five of the studies (Wang et al., 2004; Zhou et al., 2009; Rajaraman et al., 2010; Liu et al., 2012; Luo et al., 2013) were hospital-based and four (Kiuru et al., 2008; Liu et al., 2009; Custódio et al., 2012; Pan et al., 2013) were population-based. The genotype distributions in the controls were conformed to the HWE in all studies. The characteristics and genotype data extracted from eligible studies were summarized in Table 1.

Meta-analysis results

Table 2 presents the results of meta-analysis and the heterogeneity test. Obviously, XRCC3 Thr241Met polymorphism was significantly associated with decreased glioma risk in the allelic model when all the available studies were pooled into the meta-analyses (Met allele vs. Thr allele: OR= 0.708, 95%CI= 0.631-0.795, P= 0.00) (Figure 1). However, no significant difference of glioma

Table 2. Summary of Pooled ORs in the Meta-analysis

Groups and subgroups(n)	Test of association			Test of heterogeneity			Model
	OR(95%CI)	Z	*P*	χ^2	*P*	I^2	
Total studies(9)							
Met allele vs. Thr allele	0.708(0.631-0.795)	5.88	0.000	17.63	0.024	54.6%	R
MetMet vs. ThrThr	1.214(0.860-1.713)	1.1	0.270	28.79	0.000	72.2%	R
ThrMet vs. ThrThr	1.047(0.909-1.207)	0.64	0.521	13.91	0.084	42.5%	R
MetMet + ThrMet vs. ThrThr	1.072(0.909-1.265)	0.83	0.408	20.81	0.008	61.5%	R
MetMet vs. ThrThr + ThrMet	1.183(0.887-1.578)	1.14	0.253	25.66	0.001	68.8%	R
Ethnicity							
Asian(4)							
Met allele vs. Thr allele	0.678(0.552-0.831)	3.74	0.000	8.38	0.039	64.2%	R
MetMet vs. ThrThr	1.296(0.496-3.387)	0.53	0.596	20.60	0.000	85.4%	R
ThrMet vs. ThrThr	1.007(0.813-1.247)	0.06	0.949	5.02	0.170	40.3%	R
MetMet + ThrMet vs. ThrThr	0.997(0.746-1.333)	0.02	0.986	9.90	0.019	69.7%	R
MetMet vs. ThrThr + ThrMet	1.365(0.623-2.990)	0.78	0.437	16.60	0.001	81.9%	R
Caucasian(4)							
Met allele vs. Thr allele	0.956(0.688-1.329)	0.26	0.791	11.48	0.003	82.6%	R
MetMet vs. ThrThr	1.088(0.837-1.414)	0.63	0.527	5.18	0.159	42.0%	R
ThrMet vs. ThrThr	1.005(0.881-1.147)	0.07	0.941	2.07	0.558	0.0%	F
MetMet + ThrMet vs. ThrThr	1.024(0.904-1.159)	0.37	0.712	2.17	0.539	0.0%	F
MetMet vs. ThrThr + ThrMet	1.067(0.817-1.394)	0.48	0.634	6.20	0.102	51.6%	R
Source of controls							
PB(4)							
Met allele vs. Thr allele	1.258(1.010-1.566)	2.05	0.041	11.06	0.011	72.9%	R
MetMet vs. ThrThr	1.747(1.123-2.717)	2.48	0.013	7.44	0.059	59.7%	R
ThrMet vs. ThrThr	1.139(0.864-1.500)	0.92	0.356	8.90	0.031	66.3%	R
MetMet + ThrMet vs. ThrThr	1.619(1.116-2.349)	2.54	0.011	6.01	0.111	50.1%	R
MetMet vs. ThrThr + ThrMet	1.226(0.943-1.594)	1.52	0.128	7.52	0.111	46.8%	R
HB(5)							
Met allele vs. Thr allele	0.640(0.563-0.727)	6.82	0.000	5.78	0.216	30.8%	R
MetMet vs. ThrThr	0.871(0.588-1.291)	0.69	0.492	9.57	0.048	58.2%	R
ThrMet vs. ThrThr	1.023(0.881-1.188)	0.3	0.764	5.01	0.287	20.1%	F
MetMet + ThrMet vs. ThrThr	0.969(0.781-1.201)	0.29	0.771	8.92	0.063	55.1%	R
MetMet vs. ThrThr + ThrMet	0.867(0.677-1.111)	1.13	0.260	5.70	0.222	29.9%	R

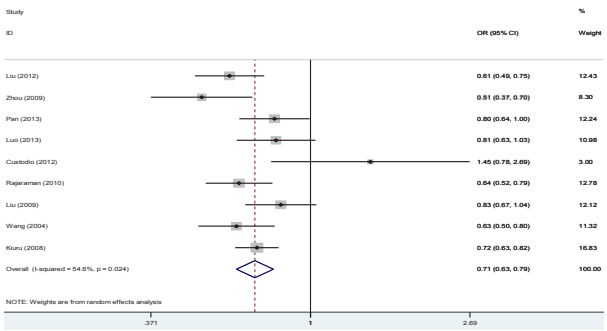

Figure 1. Forest Plot for the Overall Meta-analysis for XRCC3 Thr241Met and Glioma Risk (Met allele versus Thr allele). The squares and horizontal lines correspond to the OR and 95% CI, and the diamond represents the pooled OR and 95% CI

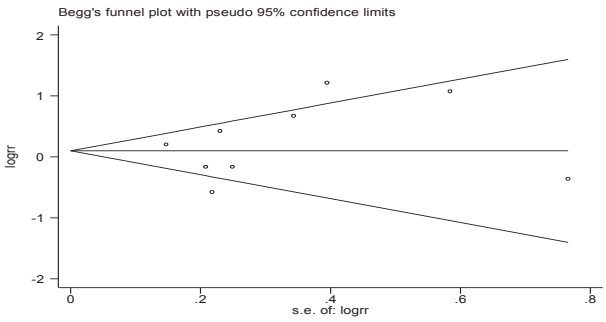

Figure 2. Begg's Funnel Plot for Publication Bias Test (MetMet versus ThrThr). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size

risk in other genotypic models (for MetMet vs. ThrThr: OR= 1.214, 95%CI= 0.860-1.713, *P*= 0.27; for ThrMet vs. ThrThr: OR= 1.047, 95%CI= 0.909-1.207, *P*= 0.521; for MetMet + ThrMet vs. ThrThr: OR= 1.072, 95%CI= 0.909-1.265, *P*= 0.408; for MetMet vs. ThrThr + ThrMet: OR= 1.183, 95%CI= 0.887-1.578, *P*= 0.253). In the further subgroup analysis by ethnicities and source of control, we also observed significant association with a decreased risk of glioma in Asian population in the allelic model (Met allele vs. Thr allele: OR= 0.678, 95%CI= 0.552-0.831, *P*= 0.00), and in hospital-based studies in the allelic model (Met allele vs. Thr allele: OR= 0.640, 95%CI= 0.563-0.727, *P*= 0.00).

Sensitivity analysis

By means of restricting the meta-analysis to studies conforming to HWE, we conducted sensitivity analysis to evaluate the robustness of the results. It turned out our meta-analysis was statistically stable since the corresponding ORs were not evidently varied (data not shown).

Publication bias

We also carried out the Begg's funnel plot and Egger's

regression test to assess the publication bias of literature. The shapes of the funnel plots did not show significant asymmetry (Figures 2), and the Egger's test was not observed any statistical evidence of publication bias (for Met allele vs. Thr allele: *P*=0.816; for MetMet vs. ThrThr: *P*=0.382; for ThrMet vs. ThrThr: P=0.804; for MetMet+ThrMet vs. ThrThr: *P*=0.871; for MetMet vs. ThrThr+ThrMet: *P*=0.149).

Discussion

Numerous studies regarding carcinogenesis have demonstrated that DNA injury and repair play an important role in the occurrence and development progress of malignant tumors. Moreover, there is evidence that SNP which occurred in the exon of DNA repair pathway genes could modify DNA repair capability, even susceptibility to cancers (Takanami et al., 2005). XRCC3 belongs to DNA double-strand break repair pathway. Therefore, XRCC3 polymorphism has received widespread attention, and many meta-analyses were reported to explore the relationship between the polymorphism and human cancers (Kiyohara et al., 2006; Saadat et al., 2009; Jacobs et al., 2012). Matullo and colleagues (Matullo et al., 2006) have realized that XRCC3 Thr241Met (rs861539) polymorphism could influence the capacity of DNA repair, and came to the conclusion that the XRCC3 Thr241Met polymorphism may be associated with cancer risks. However, the association strength of XRCC3 Thr241Met in the field of glioma susceptibility remains conflicting and is eager to be discovered.

There was no previous meta-analysis that was conducted to assess the strength of the association between the XRCC3 Thr241Met polymorphism and susceptibility to glioma. By pooling all nine eligible studies, we performed a meta-analysis including 3,752 cases and 4,849 controls to assess the impact of the polymorphisms on glioma susceptibility. The significant correlation we did notice in overall comparisons or subgroup analyses of ethnicity or source of control. For example, it is obviously that XRCC3 Thr241Met polymorphism was significantly associated with decreased glioma risk in the allelic model of the total studies (OR= 0.708, *P*<0.05). Moreover, in Asian population as well as hospital-based studies we could observe statistically significant association between the XRCC3 Thr241Met polymorphism and reduced glioma risk, which suggested that mechanisms in tumorigenesis may vary in different populations. However, no significant association we could observe in other four genetic models. For further analysis, sensitivity analysis indicated that the result was robust and no individual study influenced the statistical data, and Egger's and Begg's test proved that no obvious evidence of publication bias existed. These data and outcome suggested that the result of meta-analysis were stable and reliable. Accordingly, the XRCC3 Thr241Met polymorphism can be characterized as a susceptible factor for glioma. Among the stratified analyses by source of controls, we did observe some associations in four studies from "population-based", and this phenomenon may be due to small-study bias.

We should also be aware of some limitations in this meta-analysis. First, the overall outcomes were based on individual unadjusted ORs. The unadjusted ORs may lead to confounding bias due to lack of individual information of each study, such as joint effects of SNP-SNP or gene–environment factors. Second, there was no study of African population and only one study of mixed population. Thus, publication bias might exist. Third, the most controls were selected from healthy population in which some may have potential benign brain disease. Fourth, the recall and selection bias may exist since the meta-analysis is a type of retrospective study. Despite these above-mentioned limitations, there are some obvious advantages in our meta-analysis. On one hand, by pooling a substantial number of cases and controls, we could increase the statistical power in our result. On the other hand, the selected studies in our meta-analysis strictly fulfilled our well-designed inclusion and exclusion criteria.

In conclusion, our meta-analysis presents the first evidence that the Thr241Met polymorphism of XRCC3 gene might be a risk factor for glioma, particularly among Asians. It is indicated that XRCC3 Thr241Met variant may associated with glioma carcinogenesis. The lager and more comprehensive studies are warranted to further investigated the impact of the XRCC3 Thr241Met polymorphism on glioma risk, and other genes or environmental carcinogens regarding susceptibility to glioma should be further explored in future studies.

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