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X-Ray Repair Cross-Complementing Group 1 (XRCC1) Genetic Polymorphisms and Risk of Glioma: A Meta-Analysis

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ABSTRACT Objective: To investigate the X-ray repair cross-complementing 1 (XRCC1) genetic polymorphisms and risk of glioma. **Methods:** In September, 2012, relevant articles were searched in PubMed, EMBASE, ISI Web of Knowledge, ScienceDirect database, and CNKI . ORs and 95% CIs were used to assess the strength of the associations with different genetic models. Potential sources of heterogeneity were sought out by subgroup and meta-regression analyses. **Results:** 12, 8, and 5 studies were found to be eligible for meta-analyses of Arg399Gln, Arg194Trp, and Arg280His, respectively. For Arg399Gln, the overall odds ratios (ORs) are significant under all genetic models. For Arg194Trp, the overall fixed effects ORs were significant under homozygote genetic model and recessive genetic model. No significant results were found for Arg280His. Stratified and meta-regression analyses revealed that significant risks were only observed in Asians under all genetic models for Arg399Gln, and Asians have significantly higher risk for glioma than Caucasians. Pooled risk for studies with HWE deviation in controls seems to overestimate the risk for Arg194Trp. **Discussion:** The present study suggests that the Arg399Gln is a candidate gene for glioma only for Asians, and increased risk for Arg194Trp probably due to studies deviated from HWE in controls.

Key words: Glioma; Genetic polymorphisms; DNA repair; Meta-Analysis

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Introduction

Glioma is the most common primary central nervous system (CNS) tumor which accounting for approximately 2.0-6.0% of all adults tumors in adults [1]. Although it is not common like other cancers such as breast cancer or lung cancer, glioma has attracted increased attention because of poor prognosis. More than half of this tumor is high-grade gliomas, and the survival time for patients range from 1 to 3 years after initial diagnosis [2]. Even with a low-grade glioma, 50% to 75% will eventually die[2]. A combination of multiple environmental and genetic factors has been considered to contribute to the occurence of the disease.

Many studies showed that variability in DNA repair capacity might play an important role as a modifier of cancer risk, including glioma [3,4]. XRCC1 (x-ray repair cross-complementing group 1) is a type of DNA repair gene encoding the XRCC1 complex (an enzyme), which is essential for mammalian viability and XRCC1-deficient cells are genetically unstable and sensitive to DNA damaging agents. Common polymorphisms of XRCC1 gene are associated with many cancer risks [3,5,6]. However, it is still uncertain if this gene may contribute to susceptibility to glioma.

The XRCC1 coding gene is located on chromosome 19q13.2 [7]. To date, there have been 700 polymorphisms identified in the XRCC1 gene in human (http://www.ncbi.nlm.nih.gov/SNP), most of which are nonsense mutation. Three functional polymorphisms have been most extensively studied: Arg399Gln, Arg194Trp, and Arg280His. In 2004, Wang et al.[8]. published the first study exploring the relationship between the Arg399Gln polymorphism and glioma risk. Since then, researchers had consecutively reported associations between at least 1 of those 3 polymorphisms and glioma risk, but with conflicting results [8-20], which may probably due partly to insufficient power, different source of controls or different ethnicity. Recently, a meta-analysis summarized the association of the Arg399Gln polymorphism and glioma risk, but only those studies limited to Caucasians [21]. Though Wei et al.[22]. performed a meta-analysis with 11 studies irrespective of ethnicity, and found significant associations on the basis of either a heterozygous genetic model (Gln/Arg vs. Arg/Arg) or a dominant one (Gln/Gln + Arg/Gln vs Arg/Arg), but some of the extracted data with relative large sample size studies, to our knowledge, were incorrect. For example, the reviewers mistook the group "Meningioma" with controls in one study by Kiuru et al.[11], and the number of the control in that study accounted for nearly one third of the total number of controls in the meta-analysis. In another study by Liu et al. [12], the reviewers grouped "Gln/Arg + Arg/Arg" into a group "Arg/Arg" which could be calculated according to the allele frequencies reported in the article actually. Accordingly, we aimed to carry out a meta-analysis to shed more light on the role of these 3 polymorphisms in susceptibility to glioma and to identify possible sources of heterogeneity among the eligible studies. And the

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results will help find genetic marks to prevent and treat glioma.

1 Materials and methods

1.1 Study selection

This meta-analysis followed the MOOSE guideline [23]. To identify potentially relevant articles and abstracts, two investigators independently conducted a systematically electronic search using the following terms " (glioma* or glioblastoma or astrocytomas) and (X-ray cross complementing group 1 or x-ray repair cross-complementing group 1 or XRCC1) and (polymorphism* or genotype* or variant*)" in the PubMed database (from 1966 to September, 2012). We subsequently repeated this search in the EMBASE, ISI Web of Knowledge, ScienceDirect database, CNKI and GOOGLE Scholar. Reference lists of relevant articles were reviewed manually to search for more studies.

For inclusion, studies included in the meta-analysis had to meet the following criteria: (1) case-control designed studies; (2) reported outcomes include glioma without considering the histological type; and (3) polymorphism should include at least one in our study. Studies were excluded if: (1) no detailed genotype frequency; and (2) insufficient information for data extraction; and (3) a extreme odds ratio (OR) for a single study. When multiple publications from the same patient population resource or overlapping data sets were available, only the most recent or largest sample size study was included in the meta-analysis.

1.2 Data extraction

The citations (titles and abstracts) search and data extraction were carried out independently by two reviewers (ZFF and SLL), and disagreements were resolved by consensus. The following information was collected in a predefined data collection form: article title, the first author's name, year of publication, country of origin, ethnicity, glioma diagnosis method, genotyping method, matching variable(s), source of controls, proportion of men of cases and controls, total number of cases and controls, mean age of cases and controls, and numbers of cases and controls with different genotypes. The quality of each study selected for inclusion in the meta-analysis was assessed by the Newcastle-Ottawa Quality Assessment Scale for case-control studies [24]. The instrument is a three-item checklist that provides an assessment of selection of cases and controls (0 to 4 stars), comparability of cases and controls (0 to 2 stars) and ascertainment of exposure (0 to 3 stars). The quality score ranged from 0 to 9 points[24].

2 Statistical Analysis

We used crude ORs with their 95% confidence intervals (CIs) to assess the strength of association between XRCC1 polymorphisms and glioma risks. We used additive (homozygote or heterozygote) genetic model to assess the overall and following stratified effects: Gln/Gln or Gln/Arg vs. Arg/Arg for Arg399Gln, Trp/Trp or Trp /Arg vs. Arg/Arg for Arg194Trp, His/His or His/Arg vs. Arg/Arg for Arg280His. We also performed subgroup analysis, if available, according to ethnicity, control population source, HWE in controls, and genotyping technique, respectively. The departure of frequencies in controls from expectation under Hardy-Weinberg equilibrium (HWE) was assessed by chi-square test. Ethnicity, percentage of male, source of control, mean age in cases and controls, HWE in Controls, and genotyping technique were analyzed as covariates in meta-regression for Arg399Gln. Statistical heterogeneity between studies or groups was determined by the Q-test and I2 statistic. I2 values of 25%, 50%, and 75% corresponded to cut-off points for mild, moderate, and extensive statistical inconsistencies, respectively[25], and $P<0.05$ was considered statistically significant. With lack of heterogeneity among studies, the pooled OR estimate was merged by the fixed effects model[26]. Otherwise, the random effects model was applied [27]. Publication bias was investigated with Egger regression asymmetry test and funnel plot [28]. All statistical analyses were completed using Stata Version 11.0 (College Station, TX, USA).

3 Results

3.1 Literature search and studies characteristics

A total of 61 articles were achieved by literature search from the Pubmed and Embase, ISI Web of Knowledge, ScienceDirect, CNKI and other searching methods, using different combinations of key words. We excluded one study by Yosunkaya et al.[29] with extremely large values (over four time than overall estimates for all genetic models) significantly contributing to the heterogeneity for Arg399Gln. Finally, 12 case-control studies (11 articles in English [8-13, 15-20] and 1 article in Chinese[17] were used to evaluate the association of XRCC1 polymorphisms with risk for glioma, one of which was multi-country studies (Table 1)[11]. All of the 12 articles [8-13, 15-20] (4,426 cases and 6,525 controls) were appropriate for combined analysis for the associations regarding Arg399Gln; 8 studies [11-13, 15, 16, 18-20] (3,316 cases and 5,530 controls) were relevant to the association with Arg194Trp, and 5 studies[11, 13, 16, 18, 19] (2,063 cases and 3,144 controls) were relevant to the association with Arg280His.

Table 1 shows the characteristics of these studies. Sample sizes ranged from 178 to 3,009 (median 919.1). Controls in 10 (83.3%) studies were matched at least by age and sex. The quality scores for all of these studies are ≥ 5, and 9 of 12 studies ≥ 7. Table 1 shows the XRCC1 3 polymorphisms genotype distribution, and the control groups in 3 studies [15-17] were not in HWE for Arg399Gln, 2 studies [15,16] for Arg194Trp, and 1 study [16] for Arg280His.

3.2 Quantitative synthesis

For Arg399Gln, the combined results suggest significant associations under all genetic models with moderate heterogeneity (Gln/Gln vs. Arg/Arg: OR = 1.21; 95%CI 1.07, 1.37, P = 0.002, I2 = 42.3) (Fig. 2). Stratified analyses reveal that the pooled increased ORs were significant only for Asians under all genetic models (Gln/Gln vs. Arg/Arg: OR = 1.72; 95%CI 1.31, 2.25, P <0.001). The between-studies heterogeneity reduced from moderate

Table 1 Study characteristics from included studies in the meta-analysis

First author (Year)	Ethnicity	Sample Size	Source of Controls	Cases			Controls			Quality Score	SNP(s)
				No.	Age (years)	Gender (M%)[a]	No.	Age (years)	Gender (M%)[a]		
Wang LE (2004)(1)	Caucasian	651	Population	309	44.1	54.0	342	43.8	48.8	8	Arg399Gln
Felini MJ (2007)(2)	Caucasian	793	Population	366	51.0	59.0	427	56.0	54.0	8	Arg399Gln
Cengiz SL (2008)(3)	Caucasian	222	Population	135	55.2	50.4	87	-	-	6	Arg399Gln
Kiuru A (2008)(4)	Caucasian	2,261	Population	701	48.2	60.8	1,560	51.8	45.2	8	Arg399Gln; Arg194Trp; Arg280His
Liu Y (2009)(5)	Caucasian	738	Population	373	-	56.8	365	-	43.6	9	Arg399Gln; Arg194Trp
McK-ean-Cowdin R (2009)(6)	Caucasian	3,009	Mixedb	1,015	56.3	61.0	1,994	53.6	51.1	8	Arg399Gln; Arg194Trp;
Rajaraman P (2010)(7)	Caucasian	857	Hospital	362	51.2	54.7	495	49.2	46.1	7	Arg399Gln; Arg194Trp; Arg280His
Custodio AC (2011)(8)	Hispanic	180	Population	80	45.0	65.0	100	45.0	68.0	5	Arg399Gln; Arg194Trp
Hu XB (2011)(9)	Asian	376	Hospital	127	49.5	68.5	249	48.9	66.7	8	Arg399Gln; Arg194Trp; Arg280His
Liu JM (2011)(10)	Asian	178	Hospital	89	-	58.4	89	-	58.4	6	Arg399Gln
Zhou LQ (2011)(11)	Asian	560	Hospital	271	47.8	62.0	289	46.9	62.3	7	Arg399Gln; Arg194Trp; Arg280His
Wang D (2012)(12)	Asian	1,204	Hospital	624	51.6	51.1	580	50.4	52.2	7	Arg399Gln; Arg194Trp; Arg280His

Note: a Percentage of male.

b Controls source from both hospital and general population.

(42.3%) to around mild (9.8%), indicating ethnicity significantly contributes to heterogeneity.

For Arg194Trp, the overall fixed ORs were significant under homozygote genetic model (Trp/Trp vs. Arg/Arg) (OR = 1.83; 95% CI 1.32, 2.52, P <0.001), with insignificant obvious evidence of between-study heterogeneity (I2 = 43.9%) (Figure 3). In the subgroup analysis by status of HWE in control, pooled risk for studies with HWE deviation in controls shows a significantly higher risk than studies with HWE in control a homozygote genetic model (Trp/Trp vs. Arg/Arg) (OR = 3.10; 95% CI 1.14, 8.46 vs. OR = 1.30, 95% CI, 0.85 - 1.97, P for interaction was 0.012).

For Arg280His, the combined results showed that no obvious associations were found in a fixed-effects setting (Fig. 4). No significant between sub-group heterogeneity were observed for stratified analysis (all P values >0.05).

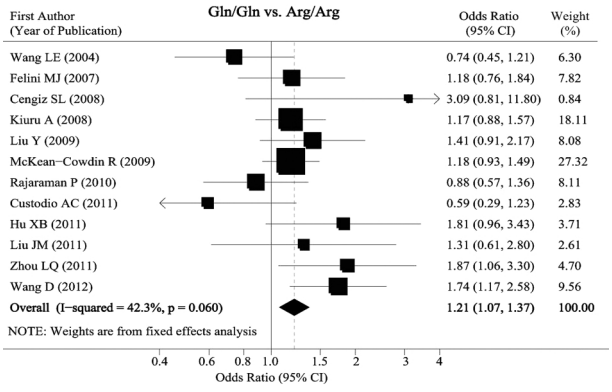

Fig.1 XRCC1 Arg399Gln polymorphism and the risk of glioma. Gln/Gln vs. Arg/Arg comparison

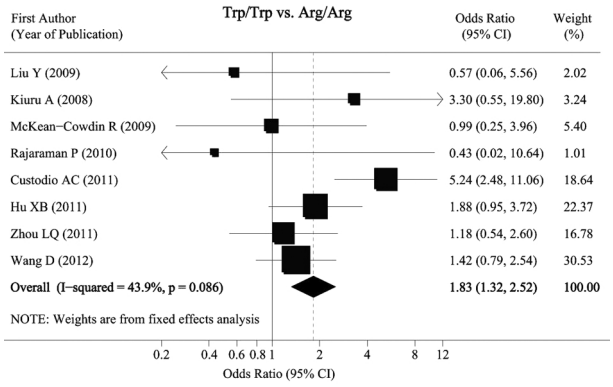

Fig. 2 XRCC1 Arg194Trp polymorphism and the risk of glioma. Trp/Trp vs. Arg/Arg comparison

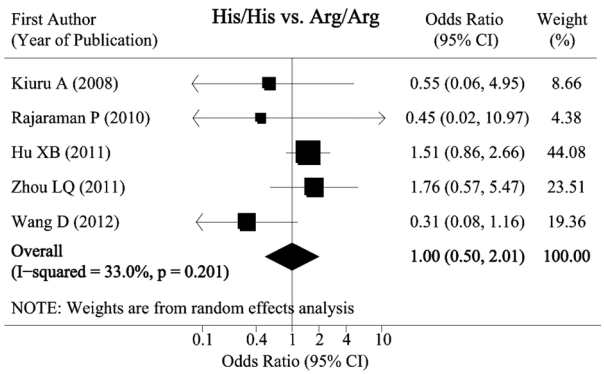

Fig. 3 XRCC1 Arg280His polymorphism and the risk of glioma. His/His vs. Arg/Arg comparison

3.3 Publication bias

The shapes of the funnel plots seemed symmetrical, and Egger's test suggested that there was no publication bias for studies of Arg399Gln, Arg194Trp and Arg280His polymorphisms associations with glioma risk in the current meta-analysis (all P values >0.05) (data not shown). These findings suggested tht bias from publications, might not have a significant effect on the results of our meta-analysis for the association between the three commonly studied XRCC1 polymorphisms and glioma risk.

4 Discussion

In this meta-analysis, the evidence of associations between the Arg399Gln, Arg194Trp, and Arg280His polymorphisms of XRCC1 and glioma susceptibility were examined. Our results provide evidence of significant risks for glioma with Arg399Gln, Arg194Trp, but not Arg280His polymorphism. Although our findings do not support the associations between the XRCC1 polymorphisms and glioma risk in all ethnic groups, our stratified analysis does reveal a significant association between the Arg399Gln polymorphism and the risk of developing glioma in Asians.

A G to A transition at position 28152 on exon 10 of XRCC1 gene, lead to a change from arginine to glutamine at codon 399, has been a research focus, due to its location within the region of the BRCT1. Mutation in Arg399Gln could influence DNA repair capability by altering the structure of the BRCT1 domain responsible for interacting with several of the key components of the base excision repair machinery [29, 30]. Epidemiologic studies indicated that the amino acid change at codon -399 resulting from a Arg- to-Gln could increase aflatoxin B1-DNA adducts and glycophorin A variant frequency which represent DNA base damage and strand breaks[31, 32]. Epidemiological evidence and meta-analyses revealed that Arg399Gln polymorphism was associated with about 3.5-fold increased risk of skin cancer[33], 1.30-fold nasopharyngeal carcinoma [34], and 1.15-fold breast cancer [33]. In our study, we also found Arg- to- Gln mutation at codon -399will increase risk of glioma.

We observed modification of the effect of the XRCC1 Gln399Arg polymorphism by ethnicity. Increased risks of giloma among Asians were persisted, but not Caucasians, which indicated a possible role of differences in genetic backgrounds, the environmental factors or the diet habits. Unfortunately, subgroup analysis was not possible in Hispanics and other ethnic population due to limited data.

XRCC1 Arg194Trp polymorphism is located in an evolutionarily conserved linker region between its DNA polymerase β domain and poly(ADP-ribose) polymerase-interacting domains, then the mutation could alter the interaction of XRCC1 with either or both of these DNA repair proteins within the base excision repair complex[35]. However, epidemiologic studies have failed to find the association between Arg194Trp and DNA repair functional outcomes [31, 36]. Arg194Trp polymorphism indeed is associated with glioma susceptibility in our study. In sub-group analysis, significant sub-group differences were found for pooled risks of studies with controls in HWE (P for interaction was 0.018). Then, the significant results in Arg194Trp probably were due to allele disequilibrium distribution in controls. More evident differences should be existed under all genetic models, because two studies with HWE deviation in controls belonging to group with Caucasians seems to overestimate the risks for studies with Caucasians. Then, we strongly recommend that researchers design genetic polymorphism association studies more rigorously and with larger number of participants in the future.

XRCC1 Arg280His polymorphism lies within the APE-binding domain [36, 37] and could interact with apurinic/apyrimidinic endonuclease (APE)[36, 38]. However, recent meta-analyses suggested that Arg280His polymorphism did not confer an increase cancer risk of stomach [7], colorectum [39], breast [40], and lung [3, 41]. In our study, we also did not found any associations between the Arg280His polymorphism and risk of glioma. But the negative results of these meta-analyses probably due to insufficient sample size (about 5000 to 10000). We calculated the sample size for one study assuming a control group incidence rate of 5% (approximately the median rate referring to Pubmed, significance level alpha of 5%, and power of 80%. A total of 10009 cases and 10009

controls were needed for detecting a 20% relative risk increase in glioma risk. Due to the heterogeneity across included studies, the meta-analysis information size additionally required adjustment for variation across studies[42]. Thus, further studies with relative large sample size were invited to yield strong evidence.

Several limitations of the present study require consideration. First, moderate to significant heterogeneity was found under most genetic models for Arg399Gln (26.0% to 50.8%) and significant for Arg194Trp (43.9% to 84.4%), which may have distorted the meta-analysis. However, after stratifying ethnicity, the heterogeneity reduced to mild (0.0% to 26.8%) for Arg399Gln. Moreover, meta-regression analyses also identified that ethnicity as a character contributing to the heterogeneity. We also found status of HWE in control was the main contributor to the heterogeneity for Arg194Trp. Second, only data from Caucasian and Asian participants was included in the ethnicity-specific analysis, and thus our results probably could not be applicable to other ethnic groups. Third, in the meta-analysis of Arg280His, we could include only five studies, and the current evidence is too limited to draw a definitive conclusion for Arg280His. Thus, further studies with large sample size are required to identify this association. Fourth, most of studies (9/12) were high-quality case-controls (Quality score was ≥ 7). Lastly, our pooled analysis based on allele frequency, it is impossible to adjust confounders such as age, sex, smoking, and alcohol consumption. However, for most studies (n = 10) in our analysis, age and sex are well matched in cases and controls. In view of the strengths and limitations, we are convinced that the results of our meta-analysis, in essence, are sound and reliable for Arg399Gln and Arg194Trp, and larger sample size or more studies were required for convincing results for Arg280His.

In conclusion, Arg399Gln and Arg194Trp polymorphisms in the XRCC1 gene are associated with the risk of glioma, but not Arg280His. With relative large number of studies combined, the present study got convinced findings. The results will help explore genetic biomarkers to find high-risk populations, and make then pay more attention to early discovery of this type of disease. In addition, it also might help develop new drugs targeting these locus to treatment or prevention of progress of glioma. Future studies are invited to work on the function of the genetic-expressed products.

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X 射线损伤修复交叉互补基因 1(XRCC1)单核苷酸多态性与神经胶质瘤易感性关系的 meta 分析

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摘要 目的:采用 meta 分析方法探讨 X 射线损伤修复交叉互补基因 1(XRCC1)单核苷酸多态性与神经胶质瘤易感性的关系。**方法:**研究检索了 PubMed、EMBASE、ISI Web of sciences、ScienceDirect 及 CNKI 数据库从建库至 2012 年 9 月关于 XRCC1 基因多态性与神经胶质瘤相关性的相关文献。合并的 OR 值及其 95%CI 用于评估不同基因模型与神经胶质瘤风险的关联强度。采用亚组分析和 meta 回归分析来探索潜在的异质性来源。**结果:** 研究最终纳入 12 篇 Arg399Gln、8 篇 Arg194Trp 和 5 篇 Arg280His XRCC1 位点多态性与神经胶质瘤关系文章用于 meta 分析。Arg399Gln 位点多态性在所有基因模型下合并 OR 值均有显著意义;Arg194Trp 位点多态性在纯合子基因模型和隐性基因模型下合并 OR 值具有显著意义; 未发现 Arg280His 位点多态性与神经胶质瘤风险相关基因模型。亚组分析和 meta 回归分析显示 Arg399Gln 位点多态性的所有基因模型风险仅在亚洲人群当中具有显著意义,亚洲人群的风险显著高于白种人群。Arg194Trp 对照组人群不符合 Hardy-Weinberg 平衡(HWE)可能高估了风险。**结论:**本研究结果显示 XRCC1 Arg399Gln 基因多态性仅为亚洲人群的神经胶质瘤风险的候选基因,Arg194Trp 基因多态性的风险可能是由于对照组不符合 HWE 的研究所导致的。

关键词:神经胶质瘤;基因多态性;DNA 修复;meta 分析

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