X-ray repair cross-complementing gene 1 Arg399Gln polymorphism and glioma risk among Asians

A meta-analysis based on 2326 cases and 3610 controls

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Abstract

OBJECTIVE: Previous reports have demonstrated that X-ray repair cross-complementing gene 1 (XRCC1) Arg399Gln polymorphism is a possible risk factor for several cancers. Published data on the association of XRCC1 Arg399Gln polymorphism with glioma susceptibility have generated conflicting results. This study is designed to precisely estimate the relationship.

DATA RETRIEVAL: A computer-based online retrieval of Medline, EMBASE, OVID, ScienceDirect, and Chinese National Knowledge Infrastructure was performed to search papers regarding association of XRCC1 Arg399Gln polymorphisms with glioma published up to April 2012.

SELECTION CRITERIA: Two investigators selected data independently. Meta analysis was then performed for the selected studies using STATA 11.0 software after strict selection. Heterogeneity test, sensitivity analysis and publication bias assessments were then conducted.

MAIN OUTCOME MEASURES: Association of XRCC1 Arg399Gln polymorphism with glioma risk.

RESULTS: A total of nine case-controlled studies comprising 2326 cases and 3610 controls were selected for final analysis. The overall data failed to indicate a significant association of XRCC1 Arg399Gln polymorphism with glioma risk (Gln/Gln vs. Arg/Arg: odds ratio (OR) = 1.11; 95% confidence interval (CI) = 0.94–1.31; dominant model: OR = 1.06; 95% CI = 0.95–1.18; recessive model: OR = 1.04; 95% CI = 0.81–1.34). However, subgroup analysis regarding ethnicity showed an increased risk among Asians (Gln/Gln vs. Arg/Arg: OR = 1.70; 95% CI = 1.17–2.46; dominant model: OR = 1.40; 95% CI = 1.10–1.78; recessive model: OR = 1.46; 95% CI = 1.04–2.05) but not Caucasians or mixed ethnicities.

CONCLUSION: XRCC1 Arg399Gln polymorphism might modify the susceptibility to glioma among Asians but not Caucasians. Further large and well-designed studies are needed to confirm this conclusion.

Key Words
genetic association; XRCC1 Arg399Gln; glioma; malignancy; susceptibility; meta analysis; polymorphism; risk; case-controlled study; database; variation

Research Highlights

(1) Whether XRCC1 Arg399Gln polymorphism is a risk factor for glioma remains controversial.
(2) A meta-analysis including 2326 cases and 3610 controls were conducted.
(3) XRCC1 Arg399Gln polymorphism might confer glioma susceptibility among Asians.
INTRODUCTION

Glioma is the most common type of primary brain malignancy in adults. The prognosis for patients is generally poor, especially for older patients[1]. The etiology of glioma has been rarely understood. Evidence suggests that exposure to radiation might be a risk factor for glioma, which could explain a small proportion of glioma because the exposure is generally rare[2]. However, only a minority of people exposed to radiation eventually develop glioma, indicating that host genetic factors might play an important role in the tumorigenesis of glioma[3-4]. Radiation exposure could induce DNA damage and cell injury[5-6]. The consequences to the cell can be disastrous, ranging from single gene mutations to massive chromosomal breakdown and rearrangements. Cell instabilities may give rise to severe human disorders including cancer[7]. Repairing various types of DNA damages is important for maintenance of genomic stability and cell survival. In this process, base excision repair pathways are critical for the maintenance of the genes[8-9]. X-ray repair cross-complementing gene 1 (XRCC1), one of the most important DNA repair genes, plays a key role in the process of base excision repair[10]. The XRCC1 gene is located on chromosome 19q13.2-13.3 and is 33 kb in length, containing 17 exons and encoding a 70 kDa protein[11]. A widely studied XRCC1 single nucleotide polymorphism at the codon 399, with a Arg to Gln change, could have a reduced capacity to remove DNA adducts and oxidized DNA damage[10], therefore, Arg399Gln variation has been indicated to associate with cancer risk. Published data on the association of XRCC1 Arg399Gln polymorphism with glioma have yielded conflicting results. Whether XRCC1 Arg399Gln polymorphism is a risk factor for glioma remains largely uncertain. Thus, in this study, we conducted a quantitative meta analysis to precisely estimate the association of XRCC1 Arg399Gln polymorphism with glioma.

DATA AND METHODOLOGY

Data retrieval
A computer-based online retrieval of Medline, EMBASE, OVID, Sciedirect, and Chinese National Knowledge Infrastructure (CNKI) without a language limitation was used[13]. The significance of the pooled ORs was assessed for a homozygote comparison model (Gln/Gln vs. Arg/Arg), a dominant model (Gln/Gln + Gln/Arg vs. Arg/Arg) and a recessive model (Gln/Gln vs. Gln/Arg + Arg/Arg). For detection of any possible sample size biases, OR and 95% CI of each study was plotted against the number of participants respectively. A chi-square based Q statistic test was performed to assess heterogeneity. If the result of Q-test was P > 0.1, ORs were pooled according to the fixed-effect model (Mantel-Haenszel)[13], otherwise, the random-effect model (DerSimonian and Laird) was used[13]. The significance of the pooled ORs was determined by Z-test. The Hardy-Weinberg equilibrium was assessed by Fisher’s exact test. Sensitivity analysis was assessed by changing the effect-models. If the significance was statistically altered, the results were indicated to be unstable. In addition, one-way sensitivity analysis[14] was also used to assess the stability of the results by omitting one of the studies once. Publication bias was assessed by visual inspection of funnel plots[15], in which the standard error of log (OR) of each study was
plotted against its log (OR). An asymmetric plot indicates a possible publication bias. The symmetry of the funnel plot was further evaluated by Egger’s linear regression test[16]. Statistical analysis was performed using the program STATA 11.0 software (Stata Corporation, Texas).

RESULTS

Data retrieval
Relevant publications were retrieved and screened originally. A total of 42 publications were identified, of which 29 irrelevant papers were excluded. Thus, 13 publications were preliminarily eligible, of which one study[18] were discarded. Then, one study not providing the detailed genetic distributions[19] was excluded. Afterwards, ten case-control studies were included for data extraction and analysis. Noticeably, we found that one study[20] contributed substantially to evident heterogeneity for the overall data, thus, this study was further excluded. As a result, a total of nine case-control studies were finally selected[21-29]. All the selected publications were written in English, except for one in Chinese[28]. The relevant information is listed in Table 1. According to this table, the first author and the number and characteristics of cases and controls for each study as well as other necessary information are presented. There were three groups of Asians[22-24], four groups of Caucasians[21-22, 24-25] and two groups of mixed ethnicities[23, 26] in the present meta-analysis. The distributions of XRCC1 Arg399Gln genotype as well as the genotyping methods of the included studies are presented in Table 2. The genetic distributions of the control groups in all studies were consistent with the Hardy-Weinberg equilibrium, except for three studies[26-28].

Table 1  Characteristics of studies included in the meta-analysis

| Authors          | Publication year | Number of cases (male/female) | Number of controls (male/female) | Type of controls                       | Median (or mean) age, (range) year (cases/controls) | Racial descent | Country            |
|------------------|------------------|-------------------------------|----------------------------------|----------------------------------------|------------------------------------------------------|----------------|-------------------|
| Wang et al [21]  | 2004             | 309(167/142)                  | 342(167/175)                     | Non-cancer controls (age-, sex-, ethnicity-matched; HB) | 44.1(20-60)/43.8(20-60)                              | Caucasian      | USA               |
| Felini et al [22]| 2007             | 879(495/348)                  | 864(470/394)                     | Healthy controls (PB)                  | NA(=20)/NA(>20)                                      | Caucasian      | USA               |
| Cengiz et al [23]| 2008             | 35 (NA)                       | 87 (NA)                          | Healthy controls (PB)                  | 55.2(6-80)/NA(<18)                                    | Mixed          | Turkey            |
| Kiaru et al [24] | 2008             | 426(259/167)                  | 1,560(705/855)                   | Healthy controls (age-, sex-, geographical area-matched; PB) | 48.2(NA)/63(NA)                                      | Caucasian      | Four countries in Europe |
| Rajaraman et al [25] | 2010           | 362(198/164)                  | 495(228/267)                     | Non-cancer controls (age-, race-, sex-, hospital-, residence-matched; HB) | 51.2(18-90)/49.2(18-90)                              | Caucasian      | USA               |
| Custodio et al [26]| 2011            | 80(52/28)                     | 100(63/37)                       | Healthy controls (PB)                  | 45(1-75)/45(18-72)                                    | Mixed          | Brazil            |
| Hu et al [27]    | 2011             | 127(87/40)                    | 249(166/83)                      | Non-cancer controls (age-, sex-matched; HB) | 49.5(NA)/48.9(NA)                                    | Asian          | China             |
| Liu et al [28]   | 2011             | 89(52/37)                     | 89(52/37)                        | Non-cancer controls (age-, sex-matched; HB) | NA/NA                                                | Asian          | China             |
| Zhou et al [29]  | 2011             | 271(168/103)                  | 289(180/109)                     | Healthy controls (age-matched; PB)      | 47.8(NA)/46.9(NA)                                    | Asian          | Asian             |

Table 2  Distribution of XRCC1 Arg399Gln genotype among glioma cases and controls included in the meta-analysis

| Authors          | Publication year | Genotyping method | Glu/Gln | Glu/Arg | Arg/Arg | Glu/Gln | Glu/Arg | Arg/Arg | HWE (control) |
|------------------|------------------|-------------------|---------|---------|---------|---------|---------|---------|---------------|
| Wang et al [21]  | 2004             | PCR-RFLP          | 37      | 138     | 134     | 49      | 162     | 131     | Yes           |
| Felini et al [22]| 2007             | PCR-RFLP          | 53      | 155     | 158     | 51      | 196     | 180     | Yes           |
| Cengiz et al [23]| 2008             | PCR-RFLP          | 2       | 13      | 20      | 3       | 41      | 43      | Yes           |
| Kiaru et al [24] | 2008             | PCR-RFLP          | 91      | 324     | 284     | 176     | 728     | 645     | Yes           |
| Rajaraman et al [25] | 2010          | TaqMan            | 44      | 164     | 142     | 72      | 201     | 205     | Yes           |
| Custodio et al [26]| 2011            | PCR-RFLP          | 24      | 33      | 23      | 51      | 20      | 29      | No            |
| Hu et al [27]    | 2011             | PCR-CTPP          | 21      | 48      | 58      | 29      | 75      | 145     | No            |
| Liu et al [28]   | 2011             | TaqMan            | 29      | 37      | 23      | 27      | 34      | 28      | No            |
| Zhou et al [29]  | 2011             | TaqMan            | 37      | 113     | 121     | 24      | 118     | 147     | Yes           |

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; PCR-CTPP: polymerase chain reaction with confronting two-pair primers; XRCC1: X-ray repair cross-complementing gene 1; HWE: Hardy-Weinberg equilibrium.
Test of heterogeneity
As shown in Table 3, we analyzed the heterogeneities of the homozygote comparison model (Gln/Gln vs. Arg/Arg) and the dominant model (Gln/Gln + Gln/Arg vs. Arg/Arg) as well as the recessive model (Gln/Gln vs. Gln/Arg + Arg/Arg). The heterogeneities were absent for the overall data in the homozygote comparison (\(P = 0.128\) for \(Q\)-test) and dominant models (\(P = 0.258\) for \(Q\)-test), except for the recessive model (\(P = 0.022\) for \(Q\)-test). However, for the recessive model, heterogeneities were removed in the subgroups regarding ethnicity and reduced in the subgroups about source of controls.

Meta-analysis results
The main results of the meta-analysis are listed in Table 3. For the overall data including 2 326 cases and 3 610 controls, no significant associations of \(XRCC1\) Arg399Gln polymorphism with glioma risk were shown in the homozygote comparison (\(OR = 1.11; 95\% CI = 0.94–1.31\)), dominant (\(OR = 1.06; 95\% CI = 0.95–1.18\)) and recessive models (\(OR = 1.04; 95\% CI = 0.81–1.34\)), indicating that \(XRCC1\) Arg399Gln variations might not modify glioma susceptibility (Figure 1).

### Table 3  Main results of the pooled data in the meta-analysis of the association between \(XRCC1\) Arg399Gln polymorphism and glioma

| Item                  | Cases/controls | Gln/Gln vs. Arg/Arg | Gln/Gln+Gln/Arg vs. Arg/Arg | Gln/Gln vs. (Gln/Arg + Arg/Arg) |
|-----------------------|---------------|---------------------|-----------------------------|---------------------------------|
|                       |               | \(OR (95\% CI)\)   | \(P\)                        | \(P\) (\(Q\)-test)               | \(OR (95\% CI)\)   | \(P\)                        | \(P\) (\(Q\)-test)               |
| Total                 | 2 326/3 610   | 1.11(0.94–1.31)     | 0.214                       | 0.128                           | 1.06(0.95–1.18)     | 0.292                       | 0.258                           | 1.04(0.81–1.34)     | 0.773                           | 0.022                           |
| Ethnicity             |               |                     |                             |                                 |                     |                             |                                 |                                 |                     |                                 |                                 |
| Caucasian             | 1 724/2 796   | 1.03(0.85–1.25)     | 0.756                       | 0.328                           | 1.00(0.88–1.13)     | 0.966                       | 0.484                           | 1.02(0.82–1.27)     | 0.834                           | 0.259                           |
| Asian                 | 487/627       | 1.70(1.17–2.46)     | 0.005                       | 0.738                           | 1.40(1.10–1.78)     | 0.007                       | 0.640                           | 1.46(1.04–2.05)     | 0.030                           | 0.564                           |
| Mixed                 | 115/187       | 0.67(0.34–1.32)     | 0.244                       | 0.388                           | 0.89(0.54–1.46)     | 0.643                       | 0.536                           | 0.64(0.18–2.29)     | 0.488                           | 0.152                           |
| Source of controls    |               |                     |                             |                                 |                     |                             |                                 |                                 |                     |                                 |                                 |
| HB                    | 875/1 158     | 0.99(0.76–1.30)     | 0.964                       | 0.133                           | 1.08(0.91–1.30)     | 0.382                       | 0.060                           | 0.95(0.73–1.25)     | 0.737                           | 0.327                           |
| PB                    | 1 451/2 452   | 1.19(0.96–1.47)     | 0.106                       | 0.201                           | 1.05(0.92–1.20)     | 0.507                       | 0.626                           | 1.08(0.70–1.65)     | 0.739                           | 0.010                           |

PB: Population-based; HB: hospital-based; \(OR\): odds ratio; \(CI\): confidence interval.

Figure 1  Meta-analysis for the association of glioma risk with \(XRCC1\) Arg399Gln polymorphism (Gln/Gln + Gln/Arg vs. Arg/Arg; stratified by ethnicity).
Considering the possible effects of ethnic variation and source of controls on the results, we further conducted subgroup analyses. In subgroup analysis according to ethnicity, raised glioma risk was shown among Asians under the three genetic models (homozygote comparison model: \( OR = 1.70, 95\% CI = 1.17\text{–}2.46 \); dominant model: \( OR = 1.40, 95\% CI = 1.10\text{–}1.78 \); recessive model: \( OR = 1.46, 95\% CI = 1.04\text{–}2.05 \)), but not among Caucasians or mixed ethnicities (Figure 1). In subgroup analysis stratified by source of controls, significant associations were observed in neither the population-based subgroup nor the hospital-based subgroup under the three genetic models.

**Sensitivity analysis**

When the effect-models were changed, the significance of the overall data for the three models, respectively, was not statistically altered (data not shown). Then, we discarded the studies whose genetic distributions in controls exhibited significant deviation from the Hardy-Weinberg equilibrium\(^{[26-28]}\), given that the deviation might contribute to any bias\(^{[30]}\). The significances of the overall data in the three models, respectively, were also not statistically changed. Afterwards, one-way sensitivity analysis\(^{[14]}\) was performed to assess the stability of the meta-analysis. The statistical significance of the results was not changed when any single study was omitted (data not shown), indicating the robustness and credibility of the results.

**Bias diagnostics** (Figure 2)

![figure](image)

**DISCUSSION**

The overall data showed that \( XRCC1 \) Arg399Gln polymorphisms may not have a marked correlation with glioma risk. However, the subgroup analyses presented an increased glioma risk among Asians but not Caucasians or mixed ethnicities. Published meta-analyses about the associations of \( XRCC1 \) Arg399Gln polymorphisms with several other cancer risks have generated conflicting results. \( XRCC1 \) Arg399Gln variations have been suggested to increase risks of lung cancer and breast cancer\(^{[31\text{–}32]}\). Nevertheless, \( XRCC1 \) Arg399Gln polymorphism has been shown to have little influence on susceptibility to gastric cancer and hepatocellular cancer\(^{[33\text{–}34]}\). Therefore, \( XRCC1 \) Arg399Gln variation might play different roles in the carcinogenesis of different malignancies.

In the subgroup analysis, according to ethnicity, significant increased risks were found among Asian subgroups, indicating that variant Gln allele might elevate glioma risk among Asians but not Caucasians. This disparity might be owing to the possible effects of ethnic-specific variation and different health care and socioeconomic classes on glioma\(^{[35]}\). However, the results should be interpreted with care because of the limited number of included studies with small sample sizes. Hence, further investigations with large sample sizes are needed.

In the subgroup analysis, according to source of controls, significant increased glioma risk was not observed in either the population-based group or the hospital-based group. Since hospital-based controls might not be truly representative of the general population, any selection bias might exist. However, data of the present meta-analysis indicated little influence of the possible selection bias on the results. Noticeably, use of proper control participants with strict matching criteria and large sample sizes are important in further studies for reducing such possible selection biases.

In the present meta-analysis, evident between-study heterogeneities for the overall data were not evident in
the homozygote comparison and dominant models, respectively, and thus the fixed-effect models were utilized. For the recessive model, significant heterogeneity was presented. Thus, the random-effect models were used in this model. Nevertheless, we found that the heterogeneities were removed in the subgroup analysis concerning ethnicity. Moreover, removed heterogeneity could also be observed in subgroup regarding hospital-based controls when the data were stratified by source of controls. The data indicated that the evident heterogeneity in the recessive model might partially result from ethnicity and source of controls. Additionally, other factors such as age, pathology grade and life styles might also contribute to the heterogeneity.

Several limitations should be addressed. First, in this meta analysis, the primary articles only provided data about Caucasians, Asians and mixed ethnicities. Other ethnicities such as Africans should be concerned in the future studies. Second, subgroup analyses regarding age, gender, histological types, radiation exposure and other factors have not been performed in the present study because relevant sufficient data were not available in the primary literature. Third, only studies written in English and several other languages indexed by the common databases were searched. Thus, any bias might exist. However, the sensitivity analysis and publication bias analysis indicated the stability and credibility of the present meta analysis.

In conclusion, results of the present meta analysis suggest that XRCC1 Arg399Gln polymorphism might be a risk factor for glioma among Asians but not Caucasians. Further investigations with larger sample sizes and strict matching criteria in view of confounding factors are needed for confirmation of the associations.

Author contributions: All authors participated in conception and design of the study and review of the manuscript. Liang Zhang and Zhiqun Qiu conducted the experiments. Liang Zhang, Zhiqun Qiu and Jiaohua Luo were responsible for the analysis and interpretation of the data. Liang Zhang and Weiquan Shu wrote the manuscript.

Conflicts of interest: None declared.

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