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

A meta-analysis based on 2 326 cases and 3 610 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 2 326 cases and 3 610 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 2 326 cases and 3 610 controls were conducted.
(3) *XRCC1* Arg399Gln polymorphism might confer glioma susceptibility among Asians.

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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, Sciencedirect, and Chinese National Knowledge Infrastructure (CNKI) without a language limitation was performed to search papers regarding association of *XRCC1* Arg399Gln polymorphisms with glioma published up to April 2012 using the key words “XRCC1, glioma, brain, neoplasm, cancer, variation and polymorphism”. All searched papers were retrieved and the bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were searched by hand to find additional eligible studies.

Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) papers regarding the association of *XRCC1* Arg399Gln polymorphism with glioma risk; (2) observational studies (case control or cohort studies); (3) papers that offer the size of the sample, odds ratio (*OR)* and their 95% confidence interval (*CI*), genetic distribution or the information that can help infer the results. Exclusion criteria include: (1) the design and definition of the experiments were obviously different from those of the selected articles; (2) not offering the source of cases and controls as well as other essential information; (3) reviews and repetitive publications.

Data extraction

Data were carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. As for conflicting evaluations, an agreement was reached following a discussion. If a consensus could not be reached, another author was asked to resolve the disputation and a final decision was made by the majority of the votes. The extracted information was input into a database.

Statistical analysis

The *OR* of *XRCC1* Arg399Gln polymorphism and glioma risk was estimated for each study. The pooled *ORs* were 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)[12], 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 review article[17] and one article not being case-control 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 finaly 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[27-29], 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
Kiuru *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	China

NA: Not available; PB: population-based; HB: hospital-based.

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

Authors	Publication year	Genotyping method	Cases			Controls			HWE (control)
			Gln/Gln	Gln/Arg	Arg/Arg	Gln/Gln	Gln/Arg	Arg/Arg	
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
Kiuru *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 v*s.* 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)	*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										
Cauca-sian	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.

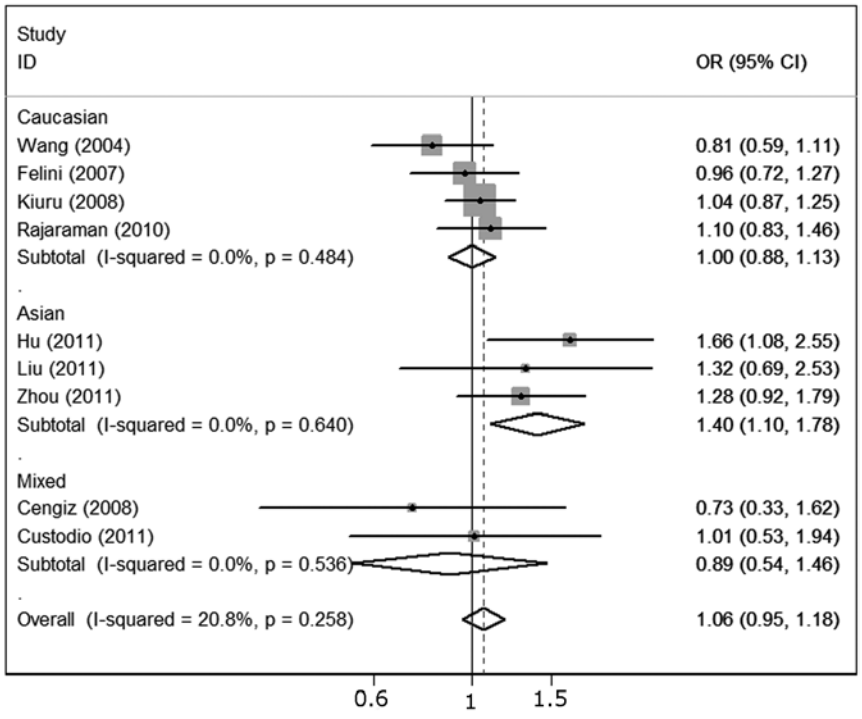

Figure 1 Meta-analysis for the association of glioma risk with *XRCC1* Arg399Gln polymorphism (Gln/Gln + Gln/Arg *vs.* Arg/Arg; stratified by ethnicity).

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* = 1.17–2.46; dominant model: *OR* = 1.40, 95%*CI* = 1.10–1.78; recessive model: *OR* = 1.46, 95%*CI* = 1.04–2.05), but not 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)

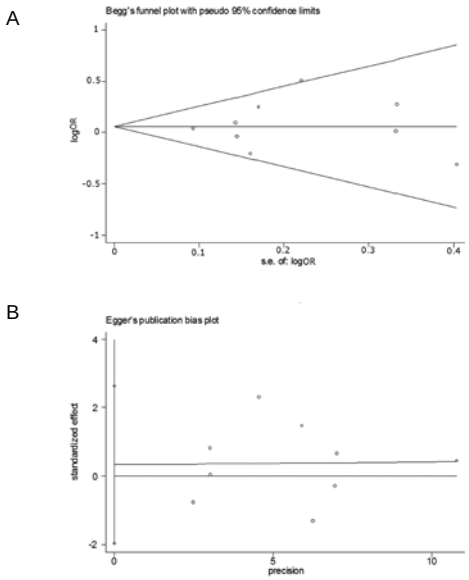

Figure 2 Publication bias test for the overall data (Gln/Gln + Gln/Arg *vs.* Arg/Arg).

(A) Funnel plot; (B) Egger's linear regression test.

Funnel plots were created for assessment of possible publication biases (Figure 2A). Then, Egger's linear regression tests were used to assess the symmetries of the plots. The funnel plots seemed symmetrical for the overall data. Additionally, results of the Egger's tests also indicate the absence of the publication bias (homozygote comparison model: $t = 0.15$, $P > 0.05$; dominant model: $t = 0.35$, $P > 0.05$; recessive model: $t = -0.12$, $P > 0.05$) (Figure 2B).

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[31-32]. Nevertheless, *XRCC1* Arg399Gln polymorphism has been shown to have little influence on susceptibility to gastric cancer and hepatocellular cancer[33-34]. 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 Weiqun Shu wrote the manuscript.

Conflicts of interest: None declared.

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