XRCC1 Gene Polymorphisms and Glioma Risk in Chinese Population: A Meta-Analysis

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Abstract

Background: Three extensively investigated polymorphisms (Arg399Gln, Arg194Trp, and Arg280His) in the X-ray repair cross-complementing group 1 (XRCC1) gene have been implicated in risk for glioma. However, the results from different studies remain inconsistent. To clarify these conflicts, we performed a quantitative synthesis of the evidence to elucidate these associations in the Chinese population.

Methods: Data were extracted from PubMed and EMBASE, with the last search up to August 21, 2014. Meta-analysis was performed by critically reviewing 8 studies for Arg399Gln (3062 cases and 3362 controls), 8 studies for Arg194Trp (3419 cases and 3680 controls), and 5 studies for Arg280His (2234 cases and 2380 controls). All of the statistical analyses were performed using the software program, STATA (version 11.0).

Results: Our analysis suggested that both Arg399Gln and Arg194Trp polymorphisms were significantly associated with increased risk of glioma (for Arg399Gln polymorphism: Gln/Gln vs. Arg/Arg, OR = 1.82, 95% CI = 1.46–2.27, P = 0.000; Arg/Gln vs. Arg/Arg, OR = 1.25, 95% CI = 1.10–1.42, P = 0.001 and for Arg194Trp polymorphism: recessive model, OR = 1.78, 95% CI = 1.44–2.19, P = 0.000), whereas the Arg280His polymorphism had no influence on the susceptibility to glioma in the Chinese population.

Conclusions: This meta-analysis suggests that there may be no association between the Arg280His polymorphism and glioma risk, whereas the Arg399Gln/Arg194Trp polymorphisms may contribute to genetic susceptibility to glioma in the Chinese population. Nevertheless, large-scale, well-designed and population-based studies are needed to further evaluate gene-gene and gene–environment interactions, as well as to measure the combined effects of these XRCC1 variants on glioma risk.

Introduction

Glioma is the most common and aggressive malignant primary brain tumor in humans, especially in adults, accounting for approximately 30% of all brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors [1,2]. Currently, the therapy for glioma is a combined approach, using surgery, radiation therapy, and chemotherapy. The prognosis for glioma patients is still poor, except for pilocytic astrocytomas (WHO grade I). Fewer than 3% of glioblastoma patients are still alive at 5 years after diagnosis, with an older age being the most significant and consistent prognostic factor for poorer outcome. Despite decades of research, the etiology of glioma is poorly understood. Many environmental and lifestyle factors including several occupations, environmental carcinogens, and diet have been reported to be associated with an elevated glioma risk, but the only factor unequivocally associated with an increased risk is high dose exposure to ionizing radiation [3,4]. However, only a minority of those exposed to ionizing radiation eventually develop glioma, suggesting that genetic factors, such as single nucleotide polymorphisms (SNPs), may be crucial to modify the risk for glioma [5,6].

DNA repair genes play a major role in the DNA mismatch repair pathway, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double strand break repair (DSBR), and are essential for maintaining the integrity of the genome [7,8]. The X-ray repair cross-comple-
menting group 1 (XRCC1) gene is an important component of DNA repair and encodes a scaffolding protein that participate in the BER pathway [9–11] for repairing small base lesions derived from oxidation and alkylation damage [12]. Several non synonymous coding polymorphisms were identified in this gene, and the three which are most extensively studied are Arg399Gln on exon 10 (rs25487, G/A), Arg194Trp on exon 6 (rs1799782, C/T), and Arg280His on exon 9 (rs25489, G/A) [13]. These polymorphisms, which involve amino acid changes at evolutionarily conserved sequences, could alter the function of XRCC1, which may diminish repair kinetics in individuals with the variant alleles and increase the risk of glioma in humans.

To date, several epidemiologic studies have been performed to elucidate the effect of these SNPs on glioma risk. However, the results are to some extent divergent, but nevertheless intriguing. The inconsistency of these studies may be explained by differences in population background, source of controls, sample size, and also by chance. Actually differences in the allele frequencies of these three polymorphisms in Asians and Caucasians have been reported [14,15]. Since most of the previous association studies focused on Caucasians [16–25], few, if any, large-scale studies have been performed in Chinese populations. The genetic effect of XRCC1 polymorphisms on glioma risk in Chinese populations remains largely inconclusive. In addition, several new related studies of glioma risk in Chinese populations [26–28] have since been published. Therefore, in the present study, we performed a meta-analysis to elucidate the relationship between XRCC1 polymorphisms and glioma risk in Chinese populations by combining all available studies.

Materials and Methods

Search strategy

We performed a comprehensive literature search of PubMed and EMBASE for relevant studies that tested the association between XRCC1 polymorphisms and the risk of glioma up to August 21, 2014. The following search terms and keywords were used: (“DNA repair gene” OR XRCC1 OR “X-ray repair cross-complementation group 1”) AND (polymorphism OR variant OR OR variation OR mutation) AND (glioma OR “brain tumor”). In addition, references cited in the retrieved articles were reviewed to trace additional relevant studies missed by the search.

Inclusion criteria

Included studies were considered eligible if they met all of the following criteria: 1) studies with full text articles; 2) a case–control study evaluating at least one of these three polymorphisms in the XRCC1 gene; 3) enough data to estimate an odds ratio (OR) with 95% confidence interval (CI); 4) no overlapping data. For the studies with the same or overlapping data by the same authors, we selected the ones with the most subjects.

Data extraction

Data were extracted independently by three investigators. For conflicting evaluations, an agreement was reached following discussion. For each study, the following characteristics were collected: first author, publication year, source of controls, genotyping method, numbers of cases and controls, genotype frequency of cases and controls, and the results of the Hardy–Weinberg equilibrium test.

Quality score evaluation

The quality of the included studies was independently assessed by three investigators (LWH, RS and LJ) according to the quality assessment criteria (shown in Table S1) that was amended from previous published meta-analyses [29,30]. All disagreements were resolved by consensus after discussion. Study quality was evaluated on a numerical score ranging from 0 to 12. If the score was ≥7, the study was categorized as “high quality”; otherwise, the study was categorized as “low quality”.

Statistical analysis

We assessed the deviation from HWE for the genotype distribution in controls using a chi-squared goodness-of-fit test (P<0.05 was considered significant). ORs with the corresponding 95% CI were used as the common measures of assessing the strength of association between XRCC1 polymorphisms (Arg399Gln, Arg194Trp, and Arg280His) and glioma risk for each study. To calculate the pooled ORs, we selected the studies with the same or overlapping data by the same authors, we performed an additive model (A allele versus A allele, a was for the minor allele and A was for the major allele), a dominant model (aa versus AA), a recessive model (aa versus Aa) and a codominant model (aa versus Aa) and OR3 (aa versus Aa) were explored with a designated as the risk allele. The above pairwise differences were used to determine the most appropriate genetic model. If OR1 = OR2 = OR3 = 1, then a recessive model was indicated. If OR1 = OR2 = 1 and OR3 = 1, then a dominant model was indicated. If OR1 = 1/ OR2 = 1 and OR1 = 1, then a complete over-dominant model was indicated. If OR1 = OR2 = 1 and OR1 = OR2 = 1, or OR1 = OR2 = 1, then a co-dominant model was indicated [31]. The significance of the pooled ORs was determined using a Z-test, and the level of statistical significance was established as P<0.05. The heterogeneity among studies was checked by the Q test [32]. The I2 statistic, which is a quantitative measure of the proportion of the total variation across studies due to heterogeneity [33], was also calculated. If the P value for the heterogeneity test was greater than 0.05, the Mantel–Haenszel method-based fixed effects model [34] was used to calculate the pooled OR. Otherwise, the DerSimonian and Laird method-based random effects model [35] was performed. Sensitivity analysis was performed by limiting the meta-analysis to studies conforming to HWE and omitting each study in turn to assess the stability of results, respectively. Potential publication bias was evaluated by visual inspection of the Begg funnel plots in which the standard error of log (OR) of each study was plotted against its log (OR). We also performed an Egger’s linear regression test (P<0.05 was considered a significant publication bias) [36]. All of the statistical analyses were performed using a software program, STATA version 11.0 (Stata, College Station, TX, USA).

Results

Extraction process and study characteristics

According to our search criterion, 132 articles were retrieved. Among them, the majority were excluded after the first screening based on abstracts or titles, mainly because they were overlapping citations, not relevant to the XRCC1 polymorphisms and glioma risk, reviews, conference abstracts, or not a related gene polymorphism. Afterwards, a total of 19 full-text articles [16–28,37–42] were preliminarily identified for further detailed evaluation (Figure 1). Of these, 10 studies were excluded [16–25] because the country of source was not from China. Eventually, nine case-control studies [26–28,37–42] were selected, including 8 studies for the Arg399Gln polymorphism (3062 cases and 3362 controls), 8 studies for the Arg194Trp polymorphism (3419 cases and 3680 controls), and 5 studies for the Arg280His polymorphism.

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(2234 cases and 2380 controls). With respect to the assessment of study quality, the vast majority of the included studies were high quality (shown in Table S2) except for the study by Liu et al. [41]. The characteristics of these included studies and the genotype distribution and allele frequency of XRCC1 polymorphisms in case and control subjects is shown in Table 1.

Meta-analysis results
The main results of the meta-analysis are shown in Table 2. According to the principle of genetic model selection by Thakkinstian et al. [31], the most appropriate genetic model for the Arg399Gln/Arg194Trp polymorphisms was the codominant model and the recessive model, respectively. Our results revealed that the Arg399Gln polymorphism was significantly associated with an increased risk of glioma in the Chinese population (Gln/Gln vs. Arg/Arg: OR = 1.82, 95% CI = 1.46–2.27, P = 0.000; Arg/Gln vs. Arg/Arg: OR = 1.25, 95% CI = 1.10–1.42, P = 0.001; recessive model: OR = 1.63, 95% CI = 1.32–2.01, P = 0.000; dominant model: OR = 1.34, 95% CI = 1.18–1.51, P = 0.000; additive model: OR = 1.31, 95% CI = 1.19–1.44, P = 0.000; Figure 2, Table 2). For the Arg194Trp polymorphism, a significant association between this polymorphism and glioma risk was also observed (Trp/Trp vs. Arg/Arg: OR = 1.82, 95% CI = 1.48–2.25, P = 0.000; recessive model: OR = 1.78, 95% CI = 1.44–2.19, P = 0.000; dominant model: OR = 1.17, 95% CI = 1.06–1.30, P = 0.001; additive model: OR = 1.23, 95% CI = 1.13–1.33, P = 0.000; Figure 3, Table 2), with the exception of the heterozygote comparison model (OR = 1.08, 95% CI = 0.97–1.20, P = 0.169, Table 2). But, for the Arg280His polymorphism, we did not detect any significant association with glioma risk in any genetic model (Table 2). Since several original papers depart from the HWE which could cause unreliable results, we performed stratification analysis according to the status of HWE. Because ethnicity of all studies was Chinese and the source of controls was hospital-based, we did not carry out subgroup analysis. In addition, the subgroup analysis according to quality assessment scores is not shown because only one included study was low quality which did not materially change the corresponding pooled ORs.
| Polymorphism   | First author | Year | Design | Sample size (case/control) | Case AA | Case Aa | Case aa | Control AA | Control Aa | Control aa | HWE in control | MAF  |
|---------------|--------------|------|--------|----------------------------|---------|---------|---------|------------|------------|------------|----------------|------|
| Arg399Gln     | Gao          | 2014 | HB     | 326/375                    | 126/155 | 45      | 178/168 | 0.215      | 0.301      |            |                |      |
|               | Xu           | 2013 | HB     | 886/886                    | 451/365 | 70      | 469/372 | 0.008      | 0.261      |            |                |      |
|               | Pan          | 2013 | HB     | 443/443                    | 226/190 | 27      | 244/178 | 0.108      | 0.248      |            |                |      |
|               | Luo          | 2013 | HB     | 296/415                    | 111/134 | 51      | 189/181 | 0.866      | 0.327      |            |                |      |
|               | Wang         | 2012 | HB     | 624/580                    | 270/279 | 75      | 300/232 | 0.739      | 0.283      |            |                |      |
|               | Zhou         | 2011 | HB     | 271/289                    | 121/113 | 37      | 147/118 | 0.963      | 0.287      |            |                |      |
|               | Hu           | 2011 | HB     | 127/249                    | 58/48   | 21      | 145/75  | <0.001     | 0.267      |            |                |      |
| Arg194Trp     | Gao          | 2014 | HB     | 326/376                    | 235/73  | 18      | 279/84  | 0.041      | 0.146      |            |                |      |
|               | Xu           | 2013 | HB     | 886/886                    | 525/301 | 60      | 540/311 | 0.236      | 0.215      |            |                |      |
|               | Pan          | 2013 | HB     | 444/443                    | 301/116 | 27      | 327/101 | 0.045      | 0.148      |            |                |      |
|               | Luo          | 2013 | HB     | 297/415                    | 204/63  | 30      | 297/96  | <0.001     | 0.169      |            |                |      |
|               | Liu          | 2012 | HB     | 444/442                    | 294/105 | 45      | 334/89  | <0.001     | 0.144      |            |                |      |
| Arg280His     | Wang         | 2012 | HB     | 624/580                    | 376/218 | 30      | 355/205 | 0.143      | 0.211      |            |                |      |
|               | Zhou         | 2011 | HB     | 271/289                    | 145/112 | 14     | 159/117 | 0.138      | 0.247      |            |                |      |
|               | Hu           | 2011 | HB     | 127/249                    | 71/38   | 18     | 163/64  | <0.001     | 0.217      |            |                |      |
|               | Gao          | 2014 | HB     | 326/376                    | 250/66  | 10     | 313/57  | 0.079      | 0.092      |            |                |      |
|               | Xu           | 2013 | HB     | 886/886                    | 618/177 | 91     | 621/178 | <0.001     | 0.199      |            |                |      |
|               | Wang         | 2012 | HB     | 624/580                    | 506/115 | 3      | 473/98  | 0.140      | 0.100      |            |                |      |
|               | Zhou         | 2011 | HB     | 271/289                    | 218/45  | 8      | 240/44  | 0.085      | 0.093      |            |                |      |
|               | Hu           | 2011 | HB     | 127/249                    | 72/28   | 27     | 153/58  | <0.001     | 0.269      |            |                |      |

Abbreviations: HWE, Hardy-Weinberg equilibrium; HB, hospital-based; MAF, minor allele frequency; A, the major allele; a, the minor allele.

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Test of heterogeneity and sensitivity analyses

The results of heterogeneity test indicated that there was no significant heterogeneity for the Arg399Gln/Arg194Trp polymorphisms across studies. However, we found heterogeneity for the Arg280His polymorphism only in an additive model ($P_h = 0.002$, $I^2 = 77.1\%$). To explore the potential sources of heterogeneity across studies, we determined that the study by Zhou et al. [40] could contribute to substantial heterogeneity because heterogeneity was significantly decreased, in the additive model ($P_h = 0.117$, $I^2 = 49.0\%$), after exclusion of this study. Although there were 3 and 2 studies that deviated from HWE for the Arg399Gln/Arg280His polymorphisms, respectively, the corresponding pooled
ORs were not materially altered by including or not including these studies (Table 2). Similarly, the results of the Arg194Trp polymorphism remained practically unchanged in a recessive model and a codominant model when excluding the 5 studies that departed from HWE. Nevertheless, this polymorphism was no longer associated with the risk of glioma in a dominant model (OR = 1.06, 95% CI = 0.93–1.21, \(P = 0.392\)) and an additive model (OR = 1.10, 95% CI = 0.99–1.23, \(P = 0.089\)). Additionally, we also assessed the influence of each individual study on the pooled ORs by sequential omission of individual studies. The results showed the pooled ORs of these three polymorphisms were not materially altered by the contribution of any individual study, suggesting that the results of this meta-analysis are credible (data also not shown).

Publication bias
Publications were assessed by performing Funnel plot and Egger’s regression tests under all contrast models. All of these genetic polymorphisms showed consistent results, indicating no publication bias. Using the Arg399Gln polymorphism as an example; the shapes of the funnel plot did not indicate any evidence of obvious asymmetry in a codominant model (Figure 4), and the Egger’s test also suggested that there was no evidence of publication bias (\(P = 0.185\) for a dominant model, \(P = 0.296\) for a recessive model, \(P = 0.300\), or for an additive model, \(P = 0.108\) for Arg/Gln vs. Arg/Arg and \(P = 0.552\) for Gln/Gln vs. Arg/Arg, respectively).

Discussion
DNA damage, which leads to gene deletions, amplifications, rearrangements, and translocations occurs very frequently and results in the formation of a tumor [7,43]. Many of these mutations may lead to less effective DNA repair than normal. It is acknowledged that glioma is appreciably associated with specific mutations causing by exposure to ionizing radiation in the DNA mismatch repair pathway. XRCC1 is an essential DNA repair gene involved in BER pathway and the vast majority of previous studies have been focused on three polymorphisms (Arg399Gln, Arg194Trp, and Arg280His) in this gene. Genetic variations in this gene confer a susceptibility to tumorigenesis through the alteration of base excision repair functions [44]. At present, several systematic reviews and meta-analyses have been carried out as preliminary studies to determine the association between XRCC1 variants and glioma risk based on previous published studies [45–54]. However, none of these studies collected sufficient data to draw a solid conclusion in a Chinese population and some results remain contradictory. Thus, Zhang et al. [52] reported that XRCC1 Arg194Trp polymorphism was not a risk factor for glioma risk in a Chinese population, which was the opposite of the conclusions made in a previous study [51]. Considering the paradoxical and underpowered conclusions of the individual studies, we conducted the most comprehensive meta-analysis using available eligible data to provide more reliable results to determine the association between the variants of the XRCC1 gene and glioma risk in the Chinese population.

Overall, our combined results based on available data from all the studies revealed that the Arg399Gln polymorphism in XRCC1 gene was associated with increased risk of glioma among Chinese people in all genetic models, which was consistent with the conclusion of individual studies involving the Arg399Gln polymorphism [26–28,37–41]. Meanwhile, we also detected that individuals harboring the Trp/Trp genotype of the Arg194Trp polymorphism might have an increased risk of developing glioma, which was in line with the majority, but not all, previous studies [26–28,37,38,51]. As for the Arg280His polymorphism, our results did not provide any evidence of such an association with glioma risk in any genetic model, which coincided with the conclusions of

![Figure 3. Forest plots of ORs with 95% CI for XRCC1 Arg194Trp polymorphism and the risk of glioma observed in recessive model among Chinese (fixed effects).](https://doi.org/10.1371/journal.pone.0111981.g003)
Table 2. Results of meta-analysis for Arg399Gln, Arg194Trp and Arg280His polymorphisms and the risk of glioma in Chinese population.

| Genetic model | Recessive model | Dominant model | Homozygote | Heterozygote | Additive model |
|---------------|----------------|----------------|------------|--------------|---------------|
|               | n              | Gln/Gln vs. Arg/Arg | Gln/Gln vs. Arg/Arg | Gln/Gln vs. Arg/Arg | Gln/Gln vs. Arg/Arg |
| Arg399Gln     | n              | Gln/Gln vs. Arg/Arg | Gln/Gln vs. Arg/Arg | Gln/Gln vs. Arg/Arg | Gln/Gln vs. Arg/Arg |
|               | OR(95%CI)      | p             | p             | OR(95%CI)      | p             |
|               | p               |               |               | p             |               |
| Total         | 5(2062/3326)   | 1.57(1.32–1.86) | 0.000 0.0 | 0.506 1.74(1.46–2.08) | 0.000 0.0 |
| All in HWE    | 5(1900/2102)   | 1.63(1.32–2.01) | 0.000 0.0 | 0.842 1.62(1.46–2.01) | 0.000 0.0 |
| Not in HWE    | 3(1102/1224)   | 1.46(1.10–1.96) | 0.010 0.0 | 0.194 1.60(1.18–2.18) | 0.003 0.0 |
| Arg194Trp     | n              | Trp/Trp vs. Arg/Trp | Trp/Trp vs. Arg/Trp | Trp/Trp vs. Arg/Trp | Trp/Trp vs. Arg/Trp |
|               | OR(95%CI)      | p             | p             | OR(95%CI)      | p             |
|               | p               |               |               | p             |               |
| Total         | 5(3419/3680)   | 1.78(1.44–2.19) | 0.000 0.0 | 0.782 1.08(0.97–1.20) | 0.169 0.0 |
| All in HWE    | 3(1781/1755)   | 1.54(1.13–2.11) | 0.006 0.0 | 0.641 1.01(0.88–1.16) | 0.920 0.0 |
| Not in HWE    | 2(1638/1925)   | 1.98(1.50–2.62) | 0.000 0.0 | 0.852 1.17(1.00–1.30) | 0.049 0.0 |
| Arg280His     | n              | His/His vs. Arg/His | His/His vs. Arg/His | His/His vs. Arg/His | His/His vs. Arg/His |
|               | OR(95%CI)      | p             | p             | OR(95%CI)      | p             |
|               | p               |               |               | p             |               |
| Total         | 5(2234/2380)   | 1.14(0.89–1.46) | 0.306 0.0 | 0.424 1.14(0.89–1.47) | 0.295 0.0 |
| All in HWE    | 3(1221/1245)   | 1.11(0.60–2.05) | 0.740 0.0 | 0.090 1.15(0.62–2.12) | 0.059 0.0 |
| Not in HWE    | 2(1013/1135)   | 1.14(0.87–1.50) | 0.331 0.0 | 0.460 1.14(0.87–1.50) | 0.343 0.0 |

P<sub>OR</sub> values for pooled OR from Z-test. P<sub>p</sub> values for heterogeneity from Q test. I<sup>2</sup>, the percentage of variability in OR attributable to heterogeneity. Random-effects model was used when P<sub>value for heterogeneity test</sub> < 0.05; otherwise, fixed-model was used.

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all previous studies [28,37,39,40]. For example, Xu et al. [28] suggested that the Arg280His polymorphism was unlikely to be associated with the risk of glioma.

It is generally agreed that departures from HWE in controls may be due to genotyping error, chance, nonrandom mating, genetic drifting, population stratification, and selection bias. Although there were 3, 2 and 5 studies that deviated from HWE for the Arg399Gln, Arg280His, and Arg194Trp polymorphisms, respectively, the studies that appeared to deviate from HWE should not be excluded mechanically in the meta-analysis unless there are other convincing grounds for doubting the quality of the study [55]. Also, there is no consensus on what to do with studies that are not in HWE in the meta-analysis of genetic association studies. Some authors suggest performing sensitivity analyses, pooling both with and without the studies that appear not to be in HWE and assessing whether studies classified as not being in HWE provide a different estimate of the genetic effect [56,57]. Furthermore, Mao et al. [58] emphasized that authors of gene-disease association meta-analyses may need to pay more attention to HWE issues, and sensitivity analyses including and excluding the HWE-violating studies may need to be routinely performed in meta-analyses of genetic association studies. In this study we performed sensitivity analyses by excluding the HWE-violating studies to check the robustness of our conclusions, and the corresponding pooled ORs were not materially altered. In addition, we comprehensively assessed the publication bias using several means including the Begg’s and Egger’s tests as well as funnel plot tests, indicating no publication bias for all these three genetic polymorphisms. In view of this, we are strongly convinced that the methods are appropriate and well described and the results or data of our meta-analysis, in essence, are sound and reliable.

Figure 4. Begg’s funnel plots of Arg399Gln polymorphism and glioma risk for publication bias test. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size. (A) Gln/Gln vs. Arg/Arg. (B) Arg/Gln vs. Arg/Arg.

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Additionally, there is still a lack of uniform and standardized quality score methods for evaluating case-control gene association studies although it is crucial for a meta-analysis to assess the quality of the individual included studies. Here we used a self-made rating scale for study quality assessment, which was modified based on two previously published meta-analyses [29,30]. The quality score assessment results showed that almost all of individual studies were high quality except for the study by Liu et al. [41], indicating that the quality of the included studies was generally high, which lends support to our conclusions. However, considering that high-quality studies may offer quite different outcomes from that of low-quality studies [59], we recommend that researchers carry out study quality assessment and stratification analysis based on the quality appraisal scores when performing the quantitative synthesis of the genetic polymorphism association studies.

When interpreting the results of the current study, some limitations should be addressed. First, lacking the original data for the included studies limited our further evaluation of the association between glioma risk and other risk factors, such as age, gender, smoking status, alcohol consumption and other variables, which might have caused a serious confounding bias. Second, we did not estimate the potential interactions among gene–gene, gene–environment, or even between various polymorphic loci of the same gene, which may alter the risk of cancer. Although the analysis of haplotypes can increase the power to detect disease associations, our study was limited to analyzing a single SNP site owing to only one study [37] focused on determining the XRCC1 haplotype. Third, selection bias should be considered because the controls from the primary literatures were all hospital-based which may not be very representative of the general population. Finally, some inevitable publication bias might exist in the results because only published studies were retrieved although the funnel plot and Egger’s test indicated no remarkable publication bias.

In summary, this meta-analysis provides evidence that both the Arg399Gln and Arg194Trp polymorphisms may contribute to genetic susceptibility to glioma risk in the Chinese population, whereas Arg280His polymorphism may have no impact. Nevertheless, large-scale, well-designed and population-based studies are needed to investigate the combined effects of these variants within XRCC1 gene or other BER genes in the Chinese population, which may eventually lead to better comprehensive understanding of their possible roles in gliomagenesis.

Supporting Information
Table S1 Scale for Quality Assessment.  
(DOC)
Table S2 Quality score assessment results.  
(DOC)
Checklist S1 Prisma 2009 Checklist for this meta-analysis.  
(DOC)

Author Contributions
Conceived and designed the experiments; JYZ. Performed the experiments: LWH RS LJ. Analyzed the data: LWH RS LJ. Contributed reagents/materials/analysis tools: LWH RS LJ. Wrote the paper: LWH RS LJ. Revised manuscript: JYZ YZ WLM.

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