Association between common polymorphisms in ERCC gene and glioma risk
A meta-analysis of 15 studies

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Abstract

Background: A number of studies have investigated the roles of excision repair cross complementation group 1 (ERCC1), ERCC2, and ERCC5 genes polymorphisms in the development of glioma; however, the results were inconsistent. Here, we performed a meta-analysis to investigate the association between 6 polymorphisms in the ERCC genes (rs3212986, rs11615, rs13181, rs1799793, rs238406, rs17655) and glioma risk.

Methods: The PubMed, Embase, and Web of science were searched up to September 6, 2016, for studies on the association between ERCC polymorphisms and glioma risk. A fixed-effects or random-effects model was used to calculate the pooled odds ratios based on the results from the heterogeneity tests. Sensitivity and cumulative meta-analyses were also performed.

Results: A total of 15 studies were eligible for the pooled analysis, conducted in 2 populations of ethnic descent: 8 Europeans and 7 Asians. The results showed that ERCC1 rs3212986 polymorphism was positively associated with glioma [AA vs CC: odds ratio (OR) = 1.298, 95% confidence interval (95% CI) = 1.043–1.230, P = 0.025]. Association of the ERCC2 rs13181 and rs1799793 polymorphisms was only observed in Asians (CC vs AA for rs13181: OR = 1.539, 95% CI = 1.222–2.109, P = 0.007; AA vs GG for rs1799793: OR = 1.474, 95% CI = 1.090–1.994, P = 0.012). However, no association was observed between glioma risk and ERCC1 rs11615, ERCC2 rs238406, and ERCC5 rs17655 polymorphisms. Moreover, sensitivity and cumulative meta-analyses confirmed the stability of the results.

Conclusions: Our meta-analysis indicated that the ERCC1 rs3212986 polymorphism and 2 polymorphisms in ERCC2 gene (rs13181 and rs1799793) contributed to the susceptibility of glioma.

Abbreviations: CI = confidence interval, ERCC = excision repair cross complementation group, GWAS = genome-wide association studies, NER = nucleotide excision repair, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Keywords: ercc1, ercc2, ercc5, glioma, meta-analysis, polymorphism

1. Introduction

Gliomas account for more than 70% of all brain tumors, and of which, malignant gliomas, the most common primary brain tumor in adults, are generally associated with poor survival relative to other types of brain tumors. Many environmental and lifestyle factors, including several occupations, ionizing radiation, cellular phones, smoking, and diet, have been considered to be associated with an increased glioma risk. However, the exact etiology remains poorly understood. Recently, accumulating evidence suggests that inherited risks may play an important role in glioma. Genetic studies, including genome-wide association studies (GWAS), demonstrated that several genetic factors might be associated with glioma, such as CCDC26, EGFR, RTEL, GSTP1, TERT, and PHLDB1 genes. Usually, DNA damage can be induced by exogenous carcinogens, such as ultraviolet rays and ionizing radiation, and contributes to genomic instability. DNA repair, playing an important role in the maintaining genomic integrity, involves several DNA repair pathways, including base excision repair (BER), mismatch repair (MMR), and nucleotide excision repair (NER). Previous studies indicated that variants in DNA repair genes might impair the DNA repair capacity and contribute to cancer risk. Excision repair cross complementation group 1 (ERCC1), ERCC2, and ERCC5 genes are DNA repair genes, whose products are important in NER. Recently, several studies have focused on the association between polymorphisms in ERCC1 gene (rs3212986, rs11615), ERCC2 gene (rs1799793, rs13181, and rs238406), or ERCC5 rs17655 polymorphism and glioma risk. However, the results were inconclusive, which might be due
to studies with limited sample sizes or ethnic differences. To date, several meta-analyses reported the association between ERCC1 or ERCC2 polymorphisms and glioma risk, whereas these studies only focused on the 2 polymorphisms (rs3212986 in ERCC1 gene and rs13181 in ERCC2 gene). Moreover, some recent studies involving glioma risk and ERCC polymorphisms were not included. Thus, we conducted a comprehensive meta-analysis to investigate whether 6 polymorphisms in ERCC1 (rs3212986 and rs11615), ERCC2 (rs13181, rs1799793 and rs238406), and ERCC5 (rs17655) genes are risk factors to the glioma susceptibility.

2. Materials and methods

2.1. Search strategy

We performed this meta-analysis according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A comprehensive literature search was performed through the PubMed, Embase, and Web of science up to September 6, 2016. Search strategies were as follows: “glioma” or “brain tumor,” “polymorphism,” and “ERCC1,” “ERCC2,” “ERCC5,” “rs3212986,” “rs11615,” “rs13181,” “rs1799793,” “rs238406,” or “rs17655.” In addition, the reference lists of all selected articles were checked by hand-search for additional potential studies.

2.2. Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: case-control or cohort studies; association between ERCC1 (rs3212986and rs11615), ERCC2 (rs13181, rs1799793, and rs238406), or ERCC5 (rs17655) polymorphism and glioma risk; available allele and genotype frequencies. Major reasons for exclusion of studies were as follows: articles only with an abstract, review articles, and comments; articles considered overlapped with other studies; and studies that had no control group.

2.3. Data extraction

The following information from each eligible study was extracted independently by 2 investigators: first author’s name, publication year, ethnicity (Europeans and Asians), whether cases and controls were matched (for case-control studies), and genotype distribution in cases and controls. If the article did not provide sufficient genotype distribution, the corresponding author was contacted for the detailed data. Disagreements were resolved by discussion between the 2 investigators. Moreover, our analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

2.4. Quality score assessment

The quality of the studies was independently assessed by 2 authors according to the quality scoring criteria, which is modified from previous meta-analyses (Table 1). Quality scores ranged from 0 points (worst) to 13 points (best). Studies scoring less than 9 points were classified as low quality, and those scoring 9 points or higher were classified as high quality.

2.5. Statistical analysis

The strength of the association between 6 polymorphisms in ERCC1, ERCC2, and ERCC5 genes and glioma risk was estimated by odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The genetic models evaluated for the pooled OR of rs3212986 polymorphism were allele contrast (A vs C), homozgyote comparison (AA vs CC), heterozygote comparison (AC vs CC), dominant model (AA+AC vs CC), as well as recessive model (AA vs AC+CC). Similar models were analyzed for the other polymorphisms. The significance of the pooled OR was determined by the Z-test, and a P value less than .05 was considered as statistically significant. In addition, stratified analysis by ethnicity was also performed. Between-study heterogeneity was assessed by Chi-square based Q test and I² test. Heterogeneity was considered significant for I² <.10, and then the random effect model was selected; otherwise, a fixed-effects model was used. In addition, Galbraith plot was used to visualize the impact of individual studies on the overall heterogeneity, which spotted the outlier as the possible origin of heterogeneity. The Hardy–Weinberg equilibrium (HWE) in the control group was also assessed, and a P <.05 was considered as significant disequilibrium.

Sensitivity analysis was performed by sequential excluding a single study each time in an attempt to identify the potential influence of the individual data to the pooled ORs. Cumulative meta-analysis was carried out for each polymorphism in association with glioma to evaluate the trend of the genetic risk effect (OR) of the allele comparisons as evidence accumulates over time. Publication bias was assessed by funnel plots and Egger linear regression test. If significant publication bias was detected, trim and fill methods was used to adjust ORs and 95% CIs. Analyses were performed using STATA software, version 12 (StataCorp LP, College Station, TX).

3. Results

3.1. Characteristics of the included studies

A total of 166 studies were identified during our premature searches. After a review of titles and abstracts, 138 nonrelevant studies were excluded. Of the remaining 28 full-text articles, 1 article only with an abstract, 8 about other tumors, 3 review
articles, and 2 articles reported other polymorphisms. Finally, a total of 14 articles met our selection criteria. The flow chart for the study selection process is shown in Fig. 1. Among them, 1 article reported data on 2 different series, and we treated them independently. Finally, 15 studies comprising 4878 cases and 6748 controls were included in the meta-analysis. Studies were conducted in 2 populations of ethnic descent: 8 Europeans and 7 Asians. The distribution of genotypes in the control groups of all studies was in agreement with HWE except one. The characteristics of all eligible studies are summarized in Table 2.

**Table 2**

Summary characteristics for the included studies.

| Author            | Year | Polymorphisms | Ethnicity | Sample size | HWE in controls | Matching | Quality scores<sup>+</sup> |
|-------------------|------|----------------|-----------|-------------|----------------|----------|--------------------------|
| Chen et al<sup>[36]</sup> | 2000 | ERCC1          | European  | 122 159     | 0.145 Age, sex, and ethnicity | 11       | 11                       |
| Wrensch et al<sup>[41]</sup> | 2005 | ERCC1 and ERCC2 | Europeans | 472 462     | 0.204 Age, sex, and ethnicity | 13       | 13                       |
| Liu et al<sup>[41]</sup> | 2009 | ERCC1 and ERCC2 | Europeans | 401 402     | 0.310 Age, sex, and ethnicity | 13       | 13                       |
| Luo et al<sup>[41]</sup> | 2013 | ERCC1, ERCC2, and ERCC5 | Asians | 202 415     | 0.888 Age, sex, and ethnicity | 11       | 11                       |
| Chen et al<sup>[36]</sup> | 2012 | ERCC1 and ERCC2 | Asians    | 303 410     | 0.273 Age, sex, and ethnicity | 11       | 11                       |
| Zhang et al<sup>[42]</sup> | 2012 | ERCC1          | Asians    | 257 278     | 0.139 Age, sex, and ethnicity | 11       | 11                       |
| Pan et al<sup>[44]</sup> | 2013 | ERCC1          | Asians    | 443 443     | 0.075 Age, sex, and ethnicity | 9        | 9                        |
| Caggana et al<sup>[35]</sup> | 2001 | ERCC2          | Europeans | 187 171     | 0.467 Age, sex, and ethnicity | 11       | 11                       |
| Rajaraman et al<sup>[44]</sup> | 2010 | ERCC2 and ERCC5 | Europeans | 362 495     | 0.499 Age, sex, and ethnicity | 10       | 10                       |
| Dong et al<sup>[22]</sup> | 2014 | ERCC1          | Asians    | 72 302     | 0.00 Age, sex, and ethnicity | 10       | 10                       |
| Gao et al<sup>[24]</sup> | 2014 | ERCC1, ERCC2, and ERCC5 | Asians | 326 376     | 0.06 Age, sex, and ethnicity | 9        | 9                        |
| Hui et al<sup>[24]</sup> | 2014 | ERCC1 and ERCC2 | Asians    | 138 276     | 0.308 Age, sex, and ethnicity | 9        | 9                        |
| Rodriguez-Hernandez et al<sup>[22]</sup> | 2014 | ERCC1 and ERCC2 | Europeans | 115 200     | 0.524 Sex and ethnicity | 10       | 10                       |

ERCC1 = excision repair cross complementation group 1, ERCC2 = excision repair cross complementation group 2, ERCC5 = excision repair cross complementation group 5, HWE = Hardy-Weinberg equilibrium.

<sup>+</sup>Quality scores ranged from 0 points (worst) to 13 points (best). Studies scoring less than 9 points were classified as low quality, and those scoring 9 points or higher were classified as high quality.
was not significant in the subgroup analysis by ethnicity, a significant association was observed in all genetic models.

### 3.3. Association of 3 polymorphisms in ERCC2 gene (rs13181, rs1799793, and rs238406) with glioma risk

Meta-analysis findings of association between rs13181 polymorphism and glioma are summarized in Table 4. A total of 10 studies involving 3289 cases and 4718 controls were included. There was no significant association observed in the overall population. When stratified by ethnicity, a significantly increased glioma risk was found in Asians (C vs A: OR = 1.259, 95% CI = 1.095–1.466, *P* = .001) (Fig. 2B). For the rs1799793 polymorphism, significantly increased glioma risk was also observed in Asians (A vs C: OR = 1.274, 95% CI = 1.118–1.451, *P* < .001). However, nonsignificant correlation was observed between rs238406 polymorphism and glioma risk. Chi-square based Q test showed that significant heterogeneity existed in 3 genetic models for rs13181 polymorphism (C vs A: *P* = .045, CA vs AA: *P* = .070, CC+CA vs AA: *P* = .051, CC vs CA+AA: *P* = .037). Galbraith plots showed that 1 independent study was the possible origin of heterogeneity, and the heterogeneity was removed when this study was excluded (C vs A: *P* = .432, CA vs AA: *P* = .242, CC+CA vs AA: *P* = .254) (Fig. 3).

### 3.4. Association of ERCC5 rs17655 polymorphism with glioma risk

A total of 1989 patients and 3216 controls were analyzed for ERCC5 rs17655 polymorphism and glioma risk. The results showed that the risk for glioma was not significantly increased in persons carrying a C allele compared with those carrying a G allele (C vs G: OR = 1.036, 95% CI = 0.899–1.195). Similar results were observed in other genetic models (Table 5). Moreover, the Chi-square based Q test and *I*² test indicated that between-study heterogeneity was not significant in all genetic models.

### 3.5. Sensitivity analysis and cumulative meta-analysis

Sensitivity analysis was performed by sequential removal of each study, the results of which showed that the pooled ORs were consistently significant by omitting 1 study at a time (Fig. 4A, B).
In the cumulative meta-analysis, pooled ORs tended to be significant and stable with the accumulation of more data over time (Fig. 5A, B). Taken together, these results suggested that the results of this meta-analysis were highly stable.

3.6. Publication bias

Funnel plots and Egger test were carried out to assess publication bias. The shapes of the funnel plots did not reveal evidence of obvious asymmetry in all comparison models (Fig. 6). Moreover, the results of Egger test confirmed this finding ($P=.566$ for AA vs CC in rs3212986 polymorphism, $P=.163$ for TT vs CC in rs11615 polymorphism, $P=.311$ for CC vs AA in rs13181 polymorphism, $P=.973$ for AA vs GG in rs1799793 polymorphism, $P=.076$ for AA vs CC in rs238406 polymorphism, and $P=.735$ for CC vs GG in rs17635 polymorphism). Figure 6 showed the funnel plots of dominant models in the 2 polymorphisms.

4. Discussion

DNA repair plays an important role in the maintaining genomic integrity, which consists of several pathways. Recent studies showed that NER was one of the most important pathways during DNA repair.\(^4\) ERCC1, ERCC2, and ERCC5 were core factors that participated in the NER pathway.\(^5\) During NER,
the ERCC1 gene codes for a protein that makes the 5' incision by forming a complex with XPF. Moreover, Melton et al. showed that mutant cells from ERCC1-deficient mice showed NER deficiency and had an increased mutation frequency as well as an elevated level of genomic instability. The ERCC2 protein, an evolutionarily conserved helicase, is also essential for NER. Mutations in ERCC2 gene were found to affect the DNA repair proficiency. Moreover, accumulated genetic epidemiological studies have been conducted to explore the association between ERCC1, ERCC2, and ERCC5 polymorphisms and glioma risk; however, the results were inconclusive. Therefore, we performed a comprehensive meta-analysis with published studies to clarify the role of these polymorphisms in glioma.

This meta-analysis demonstrated that ERCC1 rs3212986 polymorphism was significantly associated with glioma risk under the following genetic models (AA vs CC: OR = 1.280, 95% CI = 1.083–1.514, P = .004 and AA vs AC + CC: OR = 1.263, 95% CI = 1.074–1.486, P = .005). When stratified by ethnicity, the significant association was still observed in Asians (AA vs CC: OR = 1.298, 95% CI = 1.043–1.630, P = .025), but not among Europeans in major genetic models, suggesting that the contribution of ERCC1 rs3212986 polymorphism might vary across different populations. Generally, Europeans more frequently suffered from glioma than people of African or Asian descent, which was also observed in children. In addition, the pooled OR did not change in the sensitivity analysis by excluding 1 study each time, indicating that the results of this meta-analysis were highly stable. Finally, cumulative meta-analysis indicated that pooled ORs tended to be significant and stable with the accumulation of more data over time.
The ERCC2 rs13181 polymorphism showed significant association with glioma susceptibility (CC vs AA: OR=1.539, 95% CI=1.122–2.109, P=.007) in Asians. Similar results were found in rs1799793 polymorphism. (AA vs GG: OR=1.474, 95% CI=1.090–1.994, P=.012). In the analysis of rs11381 polymorphism, significant heterogeneity existed in major genetic models when all eligible studies were pooled into analysis. However, the results of Galbraith plots analyses indicated that 1 independent study\(^{[41]}\) was the main potential origin of heterogeneity; when excluding, the heterogeneity was removed.

### Table 5

| Comparison Variables | Test of association | Test of heterogeneity |
|----------------------|---------------------|-----------------------|
|                      | OR (95% CI)         | P         | Model | I\(^2\) (%) | P  |
| C vs G               | Overall             | 1.036 (0.899–1.195) | .624   | R           | 54.4 | .087 |
|                      |                      |           |       |             |     |
| CC vs GG             | Overall             | 1.120 (1.723–1.733) | .612   | R           | 74.9 | .008 |
|                      |                      |           |       |             |     |
| CG vs GG             | Overall             | 1.017 (0.899–1.149) | .703   | F           | 0.0  | .473 |
|                      |                      |           |       |             |     |
| CC + CG vs GG        | Overall             | 1.024 (0.915–1.147) | .675   | F           | 8.8  | .349 |
|                      |                      |           |       |             |     |
| CC vs CG + GG        | Overall             | 1.131 (1.742–1.724) | .567   | R           | 75.2 | .007 |

CI=confidence interval, ERCC5=excision repair cross-complementation group 5, F=fixed-effects model, OR=odds ratio, R=random-effects model.

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**Figure 4.** Sensitivity analysis on the association between the ERCC1 rs3212986 and ERCC2 rs13181 polymorphisms and glioma risk. (A) ERCC1 rs3212986 polymorphism (A vs C); (B) ERCC2 rs13181 polymorphism (C vs A). Results were computed by omitting each study (left column) in turn.
Moreover, a sensitivity analysis showed that no single study qualitatively changed the pooled ORs. However, there was no significant association observed between rs11615, rs238406, or rs17655 polymorphism and glioma susceptibility.

Our analyses demonstrated that the \textit{ERCC1} rs3212986 and \textit{ERCC2} gene (rs13181 and rs1799793) polymorphisms had a moderate increase in glioma susceptibility. However, several limitations need to be considered for interpretation of our results. First, only 3 studies were performed in Asians for rs13181 polymorphism. Therefore, validation of association in other population is required in further studies. Second, it is clear that genetic susceptibility to cancer is complex because of interactions between genes and environmental factors. However, we could not assess gene–environment interactions due to insufficient data in most studies. Recently, Pan et al.\textsuperscript{[54]} investigated the association between language biases and selective reporting in human genome epidemiology, which demonstrated that Chinese studies showed more prominent genetic effects than non-Chinese studies, whereas the sample size of Chinese studies was always smaller. Thus, more non-Chinese studies in Asian populations were needed to confirm the significant association in Asians. In addition, GWAS have identified single nucleotide polymorphisms implicating hundreds of replicated loci for common traits and became a powerful tool to detect the susceptibility genes in cancers. Accumulated GWAS have provided strong evidences for the association between glioma risk and numerous genes, including \textit{TERT}, \textit{TERC}, \textit{EGFR}, \textit{CCDC26}, and \textit{RTEL}\textsuperscript{[10,11,15–58]}. However, to date, association of polymorphisms in \textit{ERCC} genes with susceptibility to glioma has not

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure5.png}
\caption{A cumulative meta-analysis on the association between the \textit{ERCC1} rs3212986 and \textit{ERCC2} rs13181 polymorphisms and glioma risk. (A) \textit{ERCC1} rs3212986 polymorphism (A vs C); (B) \textit{ERCC2} rs13181 polymorphism (C vs A). Pooled OR estimates with the 95% CI as information accumulates at the end of each year (left column).}
\end{figure}
been investigated in GWAS. Thus, further genetics studies, especially GWAS studies, are required to confirm the possible role of *ERCC* polymorphisms in glioma.

5. Conclusions

Future studies with larger sample size in different ethnic groups (e.g., Asians and Africans) are needed to clarify the possible roles of *ERCC1*, *ERCC2*, and *ERCC5* genes in the etiology and progression of glioma. In addition, studies investigating gene–environment may lead to a better understanding of the role of the *ERCC* gene polymorphisms in glioma.

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