RESEARCH ARTICLE

Association Between ERCC2 Polymorphisms and Glioma Risk: a Meta-analysis

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Abstract

ERCC2 is an essential component of the nucleotide excision repair pathway which is involved in the effective maintenance of genome integrity. Association studies on ERCC2 polymorphisms and glioma risk have yielded inconclusive results. This meta-analysis was performed to gain a better insight into the relationship between ERCC2 polymorphisms and glioma risk. A systematic literature search updated to December 2, 2013 was performed in the Pubmed and EMBASE databases. Crude pooled odds ratios (ORs) with their corresponding 95% confidence intervals (95% CIs) were used to estimate the association between ERCC2 polymorphisms and glioma risk under a suitable effect model according to heterogeneity. All analyses were performed using Review Manager 5 (version 5.2) and STATA (version 12.0). The combined results demonstrated rs13181 to be significantly associated with glioma risk (G allele versus T allele: OR=1.15, 95% CI=1.05–1.26, *P*=0.002; dominant model: OR=1.22, 95% CI=1.07–1.39, *P*=0.002; recessive model: OR=1.18, 95% CI=0.98–1.41, *P*=0.070). We also found that rs13181 acts in an allele dose–dependent manner (GG versus TT: OR=1.30, 95% CI=1.07–1.57, *P*=0.009; TG versus TT: OR=1.20, 95%=CI 1.05–1.37, *P*=0.009; trend test, *P*=0.004). However, no evidence was found in analyses for the association between other 3 ERCC2 polymorphisms (rs238406, rs1799793, and rs1052555) and susceptibility to glioma development. Our meta-analysis suggests that rs13181 is significantly associated with glioma risk in an allele dose–dependent manner, whereas, 3 other ERCC2 polymorphisms (rs238406, rs1799793, and rs1052555) may have no influence.

Keywords: ERCC2 - polymorphism - glioma - meta-analysis

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Introduction

Glioma is the most common type of primary brain tumors. Although some advances have been made in the detection and management of glioma in the past decades, most of the patients with glioma still have a poor prognosis (Schwartzbaum et al., 2006). Numerous studies have been conducted to uncover the etiology of glioma, but only ionizing radiation has so far been established firmly to be an environmental risk factor for glioma (Ohgaki et al., 2005). An important carcinogenic mechanism of ionizing radiation for glioma is inducing various types of DNA damage including single- and double-strand breaks. The accumulation of DNA damages will finally result in tumor occurrence if there is the existence of DNA repair defects. Thus, DNA repair genes are supposed to be the potential susceptibility genes of glioma.

Four major DNA repair pathways are involved in the effective maintenance of genome integrity, including the nucleotide excision repair (NER), base excision repair (BER), double strand break repair (DSBR), and mismatch repair (MMR) pathways (Wood et al., 2001). ERCC2 is an essential component of the ubiquitous NER pathway. Defects of this gene were established to result in the cancer-prone syndrome xeroderma pigmentosum group D (Lehmann, 2001). Furthermore, polymorphisms located in ERCC2 have been reported to be associated with the susceptibility of several cancers (Duan et al., 2012; Guo et al., 2012). ERCC2 is located in the chromosome 9q13.3 which has been reported to be frequently abnormal in glioma, and decreased copy number of it was also observed to be a common occurrence in glioma (Liang et al., 1995; Yong et al., 1995). Compared with normal brain tissue, down-regulated expression of ERCC2 was also observed in astrocytoma (Smith et al., 2000). Therefore, ERCC2 is considered as an important candidate tumor suppressor gene of glioma naturally.

Based on the hypothesis that polymorphisms located in ERCC2 may affect its DNA repair capacity by multiple mechanisms, several studies were conducted to investigate the association between ERCC2 polymorphisms and glioma risk. Four coding polymorphisms, rs13181 (K751Q), rs238406 (R156R), rs1799793 (D312N), and rs1052555 (D711D) were widely investigated (Caggana

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et al., 2001; Wrensch et al., 2005; Yang et al., 2005; Liu et al., 2009; McKean-Cowdin et al., 2009; Rajaraman et al., 2010; Chen et al., 2012; Luo et al., 2013; Salnikova et al., 2013). However, the results from these studies are to some extent divergent, which may be attributed partly to the limited power of individual study. Thus, we performed a meta-analysis to have a better insight into the relationship between these ERCC2 polymorphisms and glioma risk. To our knowledge, this is the most comprehensive meta-analysis conducted to date for the association between ERCC2 polymorphisms and glioma risk.

Materials and Methods

Search strategy and selection criteria

To ensure the rigour of this current meta-analysis, we designed it according to the guidelines of Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement (PRISMA) (Moher et al., 2009). Systematic literature search updated to December 2, 2013 was performed in the Pubmed and EMBASE databases, using the search terms: (ERCC2 OR "Excision repair cross-complementing group 2" OR "DNA repair gene") AND (polymorphism OR variant OR variation) AND (glioma OR "brain tumor"). References of reviews and retrieved studies were also scanned to search for additional relevant studies. The following criteria were used for the study selection: (1) case-control or cohort study design; (2) assessment of the association between ERCC2 polymorphisms and glioma risk; (3) sufficient data were provided for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) the genotype distribution of controls must be in Hardy-Weinberg equilibrium (HWE). Studies with overlapping subjects were also included if they focused on different polymorphisms. If studies had overlapping data on the same polymorphism, we just extracted data from the largest study for final analysis.

Data extraction

Data were extracted by two investigators independently complying with the selection criteria listed above. In case of discrepancies, the group discussion was conducted until a consensus was reached. The following data were extracted for each study: first author's name, publication year, origin country, ethnicity (categorized as Caucasian, Asian, or mixed descent), control source, genotyping method, total number of cases and controls, the HWE for controls, and genotype or allele frequency of cases and controls.

Statistical Analysis

Statistical analyses were performed using Review Manager 5 (version 5.2; The Cochrane Collaboration, Oxford, United Kingdom) and the STATA statistical software package (version 12.0; StataCorp, College Station, Tex). Crude pooled ORs with their corresponding 95% CIs were used to estimate the association between ERCC2 polymorphisms and glioma risk. Heterogeneity assumption was checked using the Q test and I^2 statistics. $P>0.10$ for the Q-test indicated a lack of heterogeneity among studies, while $I^2>50\%$ was considered a measure of severe heterogeneity. According to heterogeneity, pooled ORs were calculated using a fixed-effects model (the Mantel–Haenszel method) in this study. The potential publication bias was estimated by the funnel plot and Egger's linear regression test. All statistical tests were two-sided. $P<0.05$ was used as the criterion of statistical significance.

Results

Study selection and characteristics in the meta-analysis

The process of study selection was shown in Figure 1. Based on our search terms, a total of 53 articles were retrieved through Pubmed (24 articles) and EMBASE (29 articles) databases. After an initial screening of the titles and abstracts, 44 of them were excluded based on inclusion and exclusion criteria. Thus, 9 potential articles were remained for full-text view. Moreover, 1 additional study was identified from retrieved articles. After carefully reading the full articles, 2 articles were further excluded because of insufficient data or deviation from HWE. Finally, 8 eligible articles whose characteristics are listed in Table 1 were included in this meta-analysis. All eligible articles were published after 2000. Six of them were conducted in the United States (Caggana et al., 2001; Wrensch et al., 2005; Yang et al., 2005; Liu et al., 2009; McKean-Cowdin et al., 2009; Rajaraman et al., 2010), 1 in China (Chen et al., 2012), and 1 in Russian (Salnikova et al., 2013). Many kinds of genotyping methods were used, including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), allele-specific oligonucleotide hybridization (ASOH), Pyrosequencing, MassARRAY, TaqMan, and allele-specific tetraprimer PCR. Overall, there were 7 articles on rs13181 (Caggana et al., 2001; Wrensch et al., 2005; Liu et al., 2009; McKean-Cowdin et al., 2009; Rajaraman et al., 2010; Chen et al., 2012; Salnikova et al., 2013), 4 articles on rs238406 (Caggana et al., 2001; Wrensch et al., 2005; Yang et al., 2005; Liu et al., 2009), 4 articles on rs1799793 (Caggana et al., 2001; Rajaraman et al., 2010; Chen et al., 2012; Salnikova et al., 2013), and 2 articles

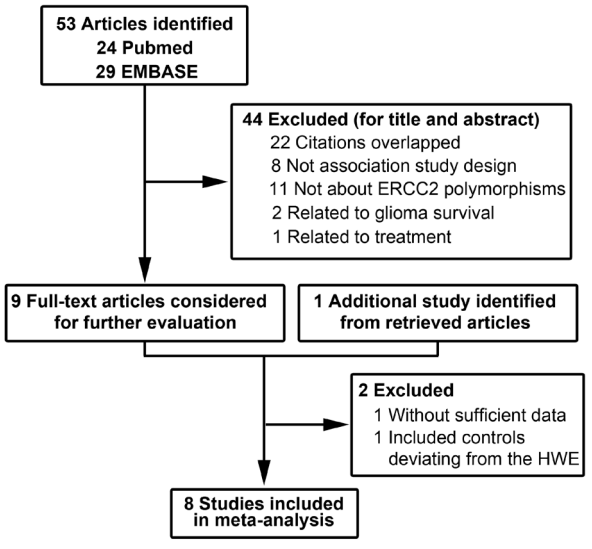

Figure 1. Flow of Included Studies

Table 1. Characteristics of Studies Included in the Meta-analysis

First author	Year	Country	Ethnicity	Cases	Controls	Control source	Genotyping method	SNPs	HWE
Caggana M	2001	USA	Caucasian	161	164	population	PCR-RFLP	rs238406	>0.05
							ASOH	rs1799793	>0.05
							ASOH	rs1052555	>0.05
							PCR-RFLP	rs13181	>0.05
Wrensch M	2005	USA	Mixed	472	558	population	PCR-RFLP	rs238406	0.72
							PCR-RFLP	rs13181	0.40
Yang P	2005	USA	Caucasian	141	108	hospital	Pyrosequencing	rs1052555	>0.05
							Pyrosequencing	rs238406	>0.05
Liu Y	2009	USA	Caucasian	373	365	population	MassARRAY	rs238406	0.34
							MassARRAY	rs13181	0.45
McKean-Cowdin R	2009	USA	Caucasian	1015	1994	mixed	TaqMan/MassARRAY	rs13181	>0.05
Rajaraman P	2010	USA	Caucasian	362	495	hospital	TaqMan	rs1799793	>0.05
							TaqMan	rs13181	>0.05
Chen DQ	2012	China	Chinese	393	410	hospital	TaqMan	rs1799793	0.36
							TaqMan	rs13181	0.18
Salnikova LE	2013	Russian	Caucasian	161	464	hospital	allele-specific tetraprimer PCR	rs1799793	0.07
							allele-specific tetraprimer PCR	rs13181	0.92

SNPs, single nucleotide polymorphisms; HWE, Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; ASOH, allele-specific oligonucleotide hybridization

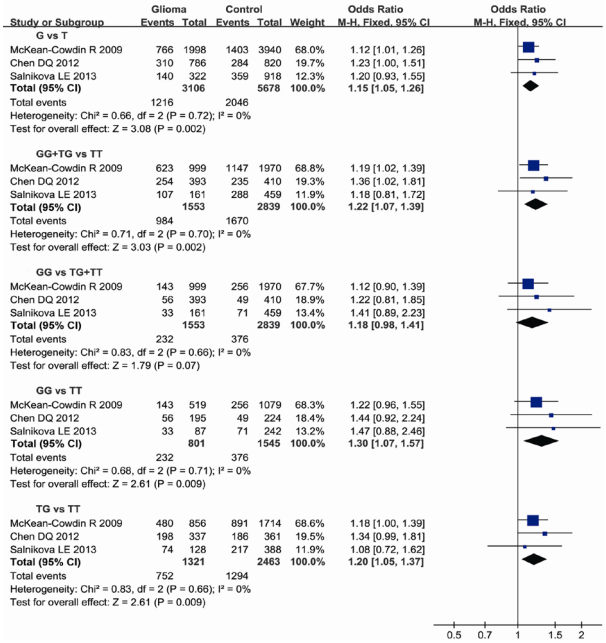

Figure 2. Forest Plots of ORs with 95% CI for rs13181 and Glioma Risk

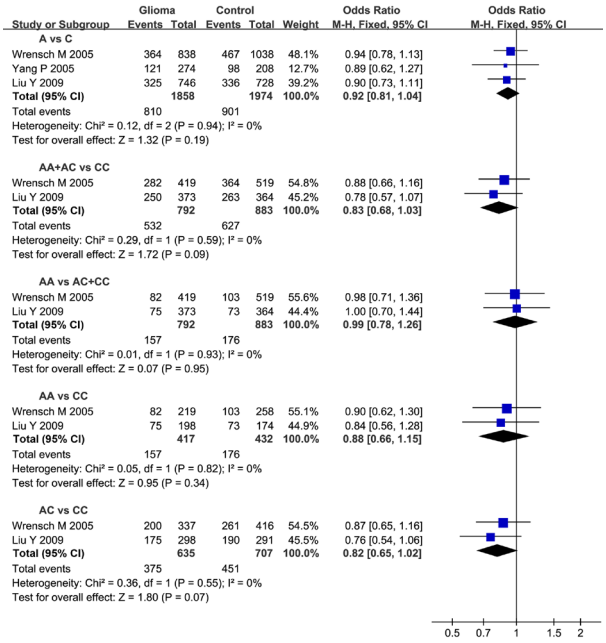

Figure 3. Forest Plots of ORs with 95% CI for rs238406 and Glioma Risk

on rs1052555 (Caggana et al., 2001; Yang et al., 2005). After carefully reading the full articles, we found that 4 studies (Caggana et al., 2001; Wrensch et al., 2005; Liu et al., 2009; Rajaraman et al., 2010) might contain partial overlapping data on rs13181 with the study by McKean-Cowdin et al (McKean-Cowdin et al., 2009). Moreover, the study by Caggana M et al (Caggana et al., 2001) may also contain partial overlapping data on rs238406 with the study by Wrensch M et al (Wrensch et al., 2005). The largest study was selected for analysis. Thus, 3 studies were included respectively for the meta-analysis on rs13181 (McKean-Cowdin et al., 2009; Chen et al., 2012; Salnikova et al., 2013) and rs238406 (Wrensch et al., 2005; Yang et al., 2005; Liu et al., 2009). For rs238406, the study by Yang et al (Yang et al., 2005) did not provide sufficient genotype data. We just extracted the allele frequency of cases and controls from this study for further analyses. Because the studies by Rajaraman et al and Salnikova et al focused on glioma and other cancers, we just extracted the data on glioma (Rajaraman et al., 2010; Salnikova et al., 2013).

Meta-analysis results

We pooled all eligible studies together for each polymorphism. Since no heterogeneity obviously existed (P>0.10 and I^2<50 % for all polymorphisms), we used fixed-effects model to evaluate the overall association between each polymorphism and susceptibility of glioma. No evidence of publication bias was found in our study even though the number of eligible studies for each polymorphism was less than 10 (data not shown). As shown in Figure 2, a total of 1, 553 glioma cases and 2, 839 healthy controls were included in the meta-analysis on rs13181, and significant association was observed

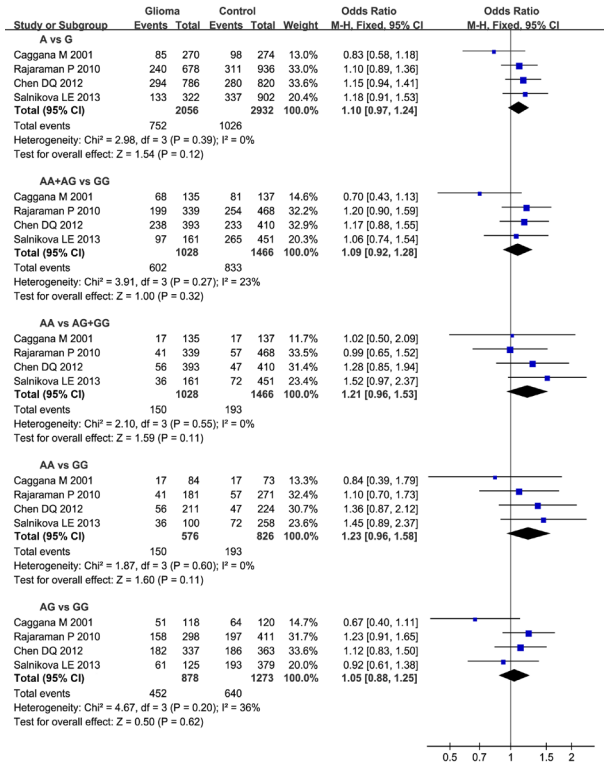

Figure 4. Forest Plots of ORs with 95% CI for rs1799793 and Glioma Risk

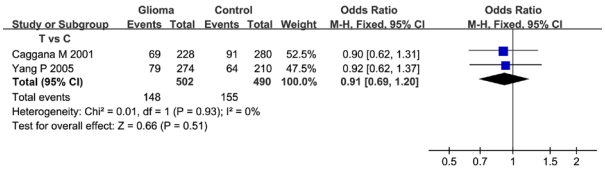

Figure 5. Forest Plots of ORs with 95% CI for rs1052555 and Glioma Risk

(G allele versus T allele: OR=1.15, 95% CI=1.05–1.26, *P*=0.002; dominant model: OR=1.22, 95% CI=1.07–1.39, *P*=0.002; recessive model: OR=1.18, 95% CI=0.98–1.41, *P*=0.070). Furthermore, compared with subjects having the TT genotype, subjects having the GG or TG genotype had an OR of 1.30 (95% CI=1.07–1.57, *P*=0.009) or 1.20 (95% CI=1.05–1.37, *P*=0.009) for developing glioma respectively. The results suggest that rs13181 acts in an allele dose–dependent manner (trend test; *P*=0.004).

Unfortunately, there was no evidence for the association between other polymorphisms and susceptibility of glioma. The results were shown in Figure 3 for rs238406 (A allele versus C allele: OR=0.92, 95% CI=0.81–1.04, *P*=0.190; dominant model: OR=0.83, 95% CI=0.68–1.03, *P*=0.090; recessive model: OR=0.99, 95% CI=0.78–1.26, *P*=0.950; AA versus CC: OR=0.88, 95% CI=0.66–1.15, *P*=0.340; AC versus CC: OR=0.82, 95% CI=0.65–1.02, *P*=0.070), Figure 4 for rs1799793 (A allele versus G allele: OR=1.10, 95% CI=0.97–1.24, *P*=0.120; dominant model: OR=1.09, 95% CI=0.92–1.28, *P*=0.320; recessive model: OR=1.21, 95% CI=0.96–1.53, *P*=0.110; AA versus GG: OR=1.23, 95% CI=0.96–1.58, *P*=0.110; AC versus GG: OR=1.05, 95% CI=0.88–1.25, *P*=0.620), and Figure 5 for rs1052555 (T allele versus C allele: OR=0.91, 95% CI=0.69–1.20, *P*=0.510).

Discussion

Although glioma accounts for almost 80% of primary brain tumors (Schwartzbaum et al., 2006), it is still a relatively rare entity. Thus, it is difficult for any single study to recruit enough patients for powerful genetic association analyses, which may partly explain the inconclusive results from previous association studies on ERCC2 polymorphisms and glioma risk. To avoid this issue, we pooled all eligible studies together to assess the association between ERCC2 polymorphisms and glioma risk in the present study. We found that rs13181 was significantly associated with glioma risk. However, no evidence was found in analyses for the association between other 3 ERCC2 polymorphisms (rs238406, rs1799793, and rs1052555) and susceptibility of glioma even though positive trend was seen for rs238406.

As an accredited environmental risk factor for glioma, ionizing radiation induces several kinds of DNA damage, including single- and double-strand breaks. Defects in cellular DNA repair pathways will lead to an accumulation of deleterious mutations in genomic DNA that result from non-repair or mis-repair DNA damage induced by endogenous or exogenous agents including ionizing radiation, and then results in the development of cancer (Hoeijmakers, 2009). NER is a ubiquitous sophisticated DNA repair mechanism which plays a predominant role in recognizing and repairing a wide range of structurally unrelated lesions such as bulky adducts and thymidine dimmers (de Laat et al., 1999). ERCC2 is an essential component of the NER pathway. It functions as an ATP-dependent DNA helicase which is an integral member of the basal transcription factor BTF2/TFIIH complex (Sung et al., 1993). Mutations in ERCC2 have been reported to reduce the activity of TFIIH complex, which may lead to repair and transcription defects (Coin et al., 1999). Decreased expression of ERCC2 has been reported to be associated with the occurrence of glioma (Liang et al., 1995; Yong et al., 1995; Smith et al., 2000). In theory, some polymorphisms located in exon can change the amino acid sequence and influence gene functions. Therefore, ERCC2 functional polymorphisms are possibly related to the susceptibility of glioma. In our study, we extracted the data from a total of 1, 553 glioma patients and 2, 839 healthy controls for the meta-analysis on rs13181, and found that a significant association between ERCC2 polymorphism rs13181 and glioma. The nonsynonymous polymorphism rs13181 locates in the exon 23 of ERCC2. It gives rise to a Lys to Gln substitution at amino acid residue 751 of ERCC2 protein, which might affect protein functions. Moreover, it was observed that the ERCC2 mRNA with rs13181G allele was less stable than the mRNA with rs13181T allele (Moisan et al., 2012). Thus, the T to G change at rs13181 may induce the downregulation of ERCC2 expression. The association of rs13181 with glioma risk is in correspondence with the above mentioned phenomenon that lower expression of ERCC2 is related to the susceptibility of glioma. Previous studies also found that individuals carrying rs13181 TT genotype are likely to have more enhanced protection ability against oxidative or UV-induced DNA damage than those with GG genotype

(Qiao et al., 2002; Wlodarczyk et al., 2012). These studies on the biologic function of rs13181 all indicates that the G allele may be a risk allele for glioma, which are consistent with our findings that rs13181G allele was significantly associated with increased risk of glioma. Furthermore, our study also found that subjects having the GG genotype had a higher OR than those having the TG genotype, and the *P* value of trend test is 0.004. The results reveal that the association of rs13181 with glioma risk is likely in an allele dose–dependent manner. Further experiments are needed to verify this phenomenon.

In published articles, there is only one meta-analysis about the relationship between rs13181 and susceptibility of glioma, in which Xu et al found no significant association in either overall population or subgroup populations (Xu et al., 2013). The discrepancy between our results and their analysis may be caused by following reasons. Data from 4 studies by Caggana et al (Caggana et al., 2001), Wrensch et al (Wrensch et al., 2005), McKean-Cowdin et al (McKean-Cowdin et al., 2009) and Rajaraman et al (Rajaraman et al., 2010) were pooled together for the meta-analysis by Xu et al (Xu et al., 2013). Subjects of the study by McKean-Cowdin et al (McKean-Cowdin et al., 2009) were enrolled from 4 centers, the National Cancer Institute (NCI), the National Institute for Occupational Safety and Health (NIOSH), the University of Texas M. D. Anderson Cancer Center (MDA), and the University of California at San Francisco (UCSF). Subjects of the other 3 studies were also from UCSF, UCSF, and NCI respectively. Thus, overlapping data existed in the study by Mckean-Cowdin et al (McKean-Cowdin et al., 2009) and the other 3 studies. They were not excluded from the meta-analysis by Xu et al (Xu et al., 2013). Furthermore, the meta-analysis by Xu et al (Xu et al., 2013) included the study by Luo et al (Luo et al., 2013) in which the genotype frequencies for rs13181 do not conform to HWE. Deviations from HWE in control subjects may bias the estimates of genetic effects in genetic association studies and meta-analysis (Zintzaras, 2010), which should be avoided when extracting the data for meta-analysis. In our study, we excluded the overlapping data from the studies by Caggana et al (Caggana et al., 2001), Wrensch et al (Wrensch et al., 2005) and Rajaraman et al (Rajaraman et al., 2010), as well as the study by Luo et al (Luo et al., 2013). Our results demonstrate that there is a significant association between rs13181 and susceptibility of glioma.

Our study also has some limitations which should be considered in interpreting the results. First, because only published studies indexed by the selected database were included for meta-analysis, publication bias may occur due to missing the unpublished studies or some relevant published studies. Second, because of the limited sample size for glioma in Asian and insufficient information on histologic types extracted from the included studies, data were not stratified by ethnicity and histologic type.

In conclusion, our current results indicate that rs13181 in ERCC2 is a genetic susceptibility factor for developing glioma. The results are consistent with the biologic function of the polymorphism and support the hypothesis that defects of ERCC2 may play a pivotal role in cancer development.

Acknowledgements

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