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Association between DNA repair gene polymorphisms and risk of glioma: A systematic review and meta-analysis

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Background. Association studies of germline DNA repair single nucleotide polymorphisms (SNPs) and glioma risk have yielded inconclusive results. We therefore performed a systematic review and meta-analysis of studies investigating this association.

Methods. We identified 27 eligible studies investigating 105 SNPs in 42 DNA repair genes. Of these, 10 SNPs in 7 genes were analyzed in at least 4 studies and were therefore included in our meta-analysis. The meta-analysis was performed for homozygote comparison, heterozygote comparison, and dominant and recessive models by applying a fixed- or random-effects model. The funnel and forest plots were created using RevMan software.

Results. We found that SNPs rs3212986 (odds ratio [OR] = 1.35 (1.08–1.68), $P = .008$), rs13181 (OR = 1.18 (1.06–1.31), $P = .002$), and rs25487 (OR = 1.12 (1.03–1.22), $P = .007$) in DNA repair genes *ERCC1*, *ERCC2 (XPD)*, and *XRCC1* may increase the risk of glioma, while polymorphisms rs1136410 (OR = 0.78 (0.68–0.89), $P = .0004$) and rs12917 (OR = 0.84 (0.73–0.96), $P = .01$) in *PARP1(ADPRT)* and *MGMT* are associated with decreased susceptibility to glioma. No evidence of significant associations between *ERCC2* rs1799793, *OGG1* rs1052133, *XRCC1* rs25489, *XRCC1* rs1799782, or *XRCC3* rs861539 and risk of glioma was observed.

Conclusion. This study provides evidence that DNA repair genes *ERCC1*, *ERCC2*, and *XRCC1* might be low-penetrance glioma-risk genes, while *MGMT* and *PARP1* polymorphisms may confer protection against glioma.

Keywords: brain neoplasm, DNA repair, glioma, meta-analysis, single nucleotide polymorphism.

Although primary brain and other nervous system tumors account for only 2% of all cancer incidence, they represent a substantial burden in terms of morbidity and mortality. For example, people diagnosed with the most common primary malignant brain tumor, glioblastoma,[1,2] have a median survival time of only 14 months.

Glioma accounts for ~81% of malignant and 31% of all brain and CNS tumors.[2,3] This tumor arises from glial cells that surround and support neurons[2] and includes astrocytoma, glioblastoma, oligodendroglioma, ependymoma, mixed glioma, and malignant glioma.[2,3] The etiology of glioma is poorly understood; to date, exposure to ionizing radiation is the only clearly established environmental risk factor.[4] However, a family history of brain tumors and several inherited single gene disorders including Li-Fraumeni and Turcot's syndromes, neurofibromatosis type 1 and 2, retinoblastoma, and tuberous sclerosis are each associated with increased risk of glioma.[4,5]

Since only a minority of glioma cases are caused by inherited disorders or the effects of ionizing radiation, gliomagenesis probably results from complex interactions among germline DNA variants and interagenic and epigenetic regulatory elements in concert with the environment. These so-called gene-environment interactions may allow cells to escape from growth-regulatory mechanisms[5] and thus produce a tumor.

Ionizing radiation induces several types of DNA damage including oxidative damage to nucleotide bases, single- and double-strand breaks, and DNA-DNA or DNA-protein crosslinks. Such DNA damage, which is considered to be an important mechanism in the development of glioma, is repaired by DNA repair-pathway genes that restore genomic integrity.[6,7]

The main DNA repair pathways in humans are direct reversal, base excision, nucleotide excision,[7] mismatch, homologous recombination repair, and nonhomologous end joining. If the products of these pathways fail to repair damage because of a

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functional deficiency, the cell accumulates excessive DNA damage and induces apoptosis. Alternatively, unrepaired damage may enhance mutation, including chromosomal aberrations that can in turn alter apoptotic signals, dysregulate cell growth, and induce carcinogenesis. Therefore, it has been hypothesized that germline or somatic variations of DNA repair-related genes play an important role in the risk of cancer development.[8,9]

Epidemiological studies indicate that single nucleotide polymorphisms (SNPs) of several DNA repair-related genes are associated with risk of developing different tumor types including glioma,[7,10,11] although the results are conflicting.[7,12–14] Due to insufficient population sizes, the statistical power of each study is low, and the evidence of the risk associated with each polymorphism is inconclusive. To increase statistical power, we conducted a systematic review and meta-analysis of published studies investigating the association between SNPs in germline DNA repair genes and risk of glioma.

Materials and Methods

Search Strategy, Eligibility of Relevant Studies, Data Extraction, and Inclusion Criteria

To identify all published peer-reviewed literature on the association between germ line SNPs of DNA repair genes and brain tumor risk, we searched the PubMed database (up to December 2012) using combinations of the following keywords: "brain tumor," "single nucleotide polymorphism," "association," "gene," "risk," "case control," "susceptibility," and "polymorphism." All English-language articles that included glioma samples and contained crude odds ratios (ORs) and confidence intervals (CIs) or the raw data necessary to calculate ORs and CIs, were considered eligible. References in the selected articles were examined manually to identify additional appropriate published articles. Moreover, all genes associated with brain tumors reported by genome-wide association studies were evaluated to determine whether they belonged to DNA repair pathways to include them in our meta-analysis.

The following data were extracted from the selected articles: authors' names, year of publication, total number of cases and controls, mean age of cases and controls, source of the controls, sex and ethnicity distributions of participants, country where the study was conducted, DNA repair genes and polymorphisms investigated in the study, genotyping methods, the number of cases and controls for each polymorphism genotype, and the *P* value for Hardy-Weinberg equilibrium (HWE).

If overlapping samples were used in a series of publications for the same SNP, the most informative and complete study covering the majority of samples was included. If necessary data for each DNA repair SNP were available from at least 4 studies, that SNP was included in the meta-analysis.

Statistical Analysis

To investigate the quality of studies, HWE was assessed in the controls using the χ^2 goodness-of-fit test. A *P* value $< .05$ was considered statistically significant, and studies with deviation from HWE were defined as low-quality studies. Data pooling was performed with and without these studies to test the robustness of the estimates. When we encountered conflicts between HWE reported in publications and the one that we calculated, we used the latter. Two factors may account for the conflicting calculations: either the HWE was calculated using a method different from ours or the data used for HWE testing were not the same as the published data. Most previous studies that we investigated reported adjusted ORs and their corresponding CIs. However, because adjustment factors vary across studies, the reported ORs and CIs were not comparable. Therefore, we calculated the crude OR and 95% CI for each study, and our meta-analysis was based on these unadjusted estimates; however, we detected no conflict between the crude and corresponding adjusted ORs and CIs.

The meta-analysis was performed for homozygote and heterozygote comparisons, as well as dominant and recessive models, by applying the fixed-effects model. In the case of significant heterogeneity among studies ($P < .1$), pooled ORs were calculated using the random-effects model or omitting the heterogeneous studies. The meta-analysis was performed to test the specific hypothesis that polymorphisms in DNA-repair genes affect glioma risk; therefore, we did not adjust CIs for multiple comparisons because a Bonferroni correction is overly conservative given that each SNP is tested according to the different genotypic models. The possibility of false-positive findings is still a concern, however, and therefore we provide the reference *P* value for an experiment-wide significance with the Bonferroni' correction. Forest plots to compare ORs among studies and funnel plots to identify publication bias were created using RevMan software Version 5.2 (Cochran Collaboration). Egger's test was used to assess symmetry of the funnel plots'.[15]

Results

We identified 36 articles that evaluated the association between germline DNA-repair gene SNPs and brain tumor risk.[7,10,12–14,16–46] Twenty-seven of these studies met the eligibility criteria defined in the Materials and Methods section.[7,12–14,16–21,23,26,28–42] Overall, 105 SNPs in 42 DNA repair genes were investigated, of which 10 SNPs in 7 DNA repair genes were analyzed in at least 4 studies and evaluated for inclusion in the meta-analysis. The main characteristics of the included studies are summarized in Table S1, and the main findings for each SNP are reported below. Table 1 shows all SNPs for which significant findings were observed, and Table 2 illustrates sensitivity analyses with respect to exclusion of studies deviating from HWE. Corresponding nonsignificant findings are found in the Tables S2 and S3.

The meta-analysis suggests significant associations between *ERCC1* rs3212986, *XRCC1* rs25487, and *ERCC2* rs13181 polymorphisms and increased risk of glioma. The rs3212986 polymorphism was associated with an increased risk of glioma only in the recessive model, while an increased risk associated with SNP rs25487 was detected under all investigated genotypic models. All models, except the recessive model, showed significant associations with the rs13181 polymorphism (Table 1). As shown in Table 2, the association between the rs25487 polymorphism and glioma after exclusion from the study, which deviated from HWE, remained statistically significant only in the dominant model. Figs 1 and 2 display the forest plots of the dominant model for *XRCC1* rs25487 and *ERCC2* rs13181 polymorphisms, respectively. No publication bias was detected by the funnel plots shown in Figs 3 and 4, and Egger's test did not

Table 1. Pooled results of ERCC1-rs3212986, ERCC2-rs13181, MGMT-rs12917, PARP1-rs1136410, XRCC1- rs25487

Genotype/model	OR	95% CI	P value*	No. Cases/ Controls	Identified Studies: Included Studies, ref. no.	Identified Studies: Excluded Studies, ref. no.	Heterogeneity Between Studies	Deviation From HWE, ref. no.
ERCC1 - rs3212986				2189/3200	13[a], 17, 18, 42	19[b],33[b]	None	None
CA vs CC	0.966	0.852–1.095	.587					
AA vs CC	0.929	0.801–1.078	.332					
Dominant: CA/AA vs CC	1.006	0.892–1.136	.917					
Recessive: AA vs CA/CC	1.349	1.083–1.680	.008					
ERCC2 (XPD) - rs13181				2552/3717	7, 13[c], 17, 18, 20, 42	20[b]	None	None
AC vs AA	1.142	1.015–1.285	.027					
CC vs AA	1.239	1.044–1.471	.014					
Dominant: AC/CC vs AA	1.180	1.063–1.310	.002					
Recessive: CC vs AC/AA	1.150	0.983–1.346	.081					
MGMT - rs12917				2097/3267	7,12[d],13[c],17	–	DM	None
CT vs CC	0.929	0.801–1.078	.332					
TT vs CC	1.087	0.702–1.684	.707					
Dominant: CT/TT vs CC	0.838	0.728–0.964	.013					
Recessive: TT vs CT/CC	1.113	0.721–1.718	.629					
PARP1 - rs1136410				1818/2944	7,13[c],14,17	–	HC RM	14
TC vs TT	0.778	0.664–0.911	.002					
Dominant: TC/CC vs TT	0.779	0.684–0.888	.0002					
XRCC1 -rs25487				3995/6000	7,12,13[c],16,17, 21,29,31,37	14[e]	HC DM[f]	37
AG vs GG	1.104	1.011–1.206	.028					
AA vs GG	1.223	1.005–1.487	.044					
Dominant: GA/AA vs GG	1.143	1.019–1.283	.023					
Recessive: AA vs AG/GG	1.148	1.014–1.301	.029					

[a]Reported the data only for the recessive model.
[b]Samples overlapping.
[c]Reported the data only for the dominant model.
[d]Excluded from dominant model due to heterogeneity
[e]Excluded from all genetic models due to heterogeneity.
[f]Random-effects model was applied.
Abbreviations: DM, dominant model; HC, homozygote comparison; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; RM, recessive model.
*Bonferroni corrected reference *P* values: .0015 for an experiment-wide significance of.05;.003 for a significance of.10.

Table 2. Sensitivity analysis of PARP1 - rs1136410, XRCC1 - rs25487

Genotype/model	Ref. no. deviated from HWE	Without the Study Deviated from HWE: OR	95% CI	*P* value*
PARP1 - rs1136410	14			
TC vs TT		0.809	0.685–0.955	.012
Dominant: TC/CC vs TT		0.783	0.684–0.897	.0004
XRCC1 - rs25487	37			
AG vs GG		1.089	0.995–1.192	.063
AA vs GG		1.187	0.971–1.451	.095
Dominant: GA/AA vs GG		1.121	1.032–1.218	.007
Recessive: AA vs AG/GG		1.135	0.999–1.289	.052

Abbreviations: HWE, Hardy-Weinberg equilibrium; OR, odds ratio.
***Bonferroni corrected reference *P* values: .0015 for an experiment-wide significance of .05;.003 for a significance of .10.

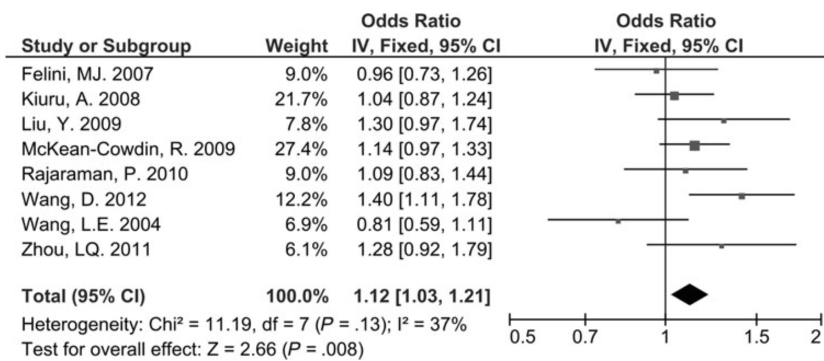

Fig. 1. Forest plot of odds ratios from the dominant model, *XRCC1* rs25487.

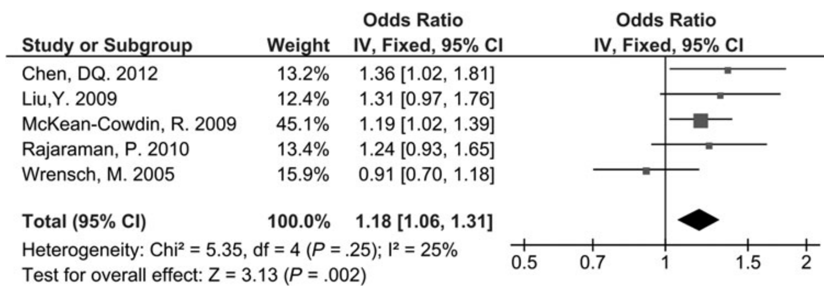

Fig. 2. Forest plot of odds ratios from the dominant model, *ERCC2* rs13181.

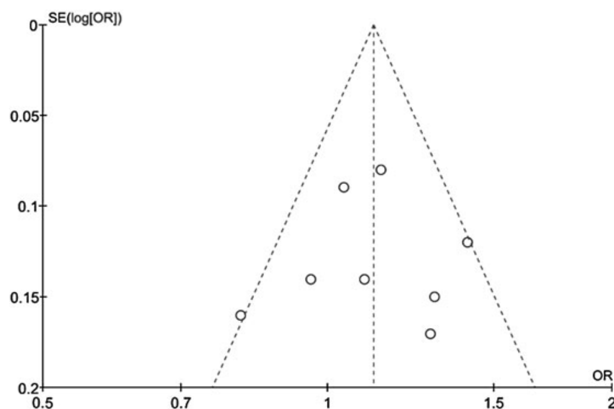

Fig. 3. Funnel plot of odds ratios from the dominant model, *XRCC1* rs25487.

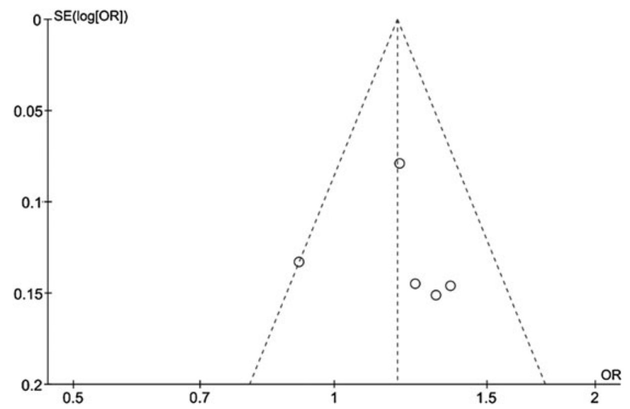

Fig. 4. Funnel plot of odds ratios from the dominant model, *ERCC2* rs13181.

provide statistical evidence of asymmetrical funnel plots' ($P_{Egger} = .93$ and $P_{Egger} = .88$, respectively).

A significantly decreased glioma risk was associated with *MGMT* rs12917 under the dominant model, as well as with *PARP1* rs1136410 under the heterozygote comparison and the dominant model (Table 1). As can be inferred from Table 2, inclusion or exclusion from the study that deviated from HWE did not alter our conclusions regarding the association between rs1136410 polymorphism and glioma risk.

No statistically significant associations were observed between SNPs rs1799793, rs1052133, rs25489, rs1799782, rs861539, and risk of glioma (Table S2). This conclusion remained unchanged after omitting the studies showing deviation from HWE (Table S3).

Overall, we performed 34 testing procedures, as described above. When the Bonferroni correction is applied, the reference *P* value is .0015 for an experiment-wide significance level of .05, and .003 for a significance level of .10. The details about

individual ORs, CIs, and HWE calculated for each study and each SNP are reported in Tables S4–S13.

Discussion

This meta-analysis of the association between germline SNPs in DNA repair genes and the risk of glioma suggests that DNA repair genes *ERCC1*, *ERCC2 (XPD)*, and *XRCC1* are low-penetrance glioma risk genes, while *MGMT* and *PARP1* polymorphisms have protective effects on glioma development. However, after Bonferroni adjustment for multiple comparisons, only the association with *PARP-1* remained statistically significant.

To date, genome-wide association and candidate gene studies have reported few inherited variations consistently associated with sporadic glioma such as polymorphisms in *RTEL1, TERT, CDKN2A, CDKN2B, EGFR, CCDC26, PHLDB1, ERCC1*, *ERCC2*, *GLTSCR1*, *XRCC7*, *MGMT*, *GSTT1-null*, and *GSTP1*.[4,5,16–18,47–50]

In the present study, we found that the absence of C allele in *ERCC1* SNP rs3212986 is significantly associated with an increased risk of glioma, while the C allele may be a risk allele in *ERCC2* rs13181; moreover, the A allele of *XRCC1* SNP rs25487 may be a marker for increased susceptibility to glioma. The *ERCC1* and *ERCC2 (XPD)* genes reside near each other in chromosome 19q13.3 and produce excision repair cross-complementing group 1 and group 2 proteins, respectively,[51] which play important roles in the DNA nucleotide excision repair pathway. Alterations in *ERCC1* and *ERCC2* result in deficiency in DNA repair, RNA transcription, and apoptosis and lead to accumulation of mutations relevant to gliomagenesis in the absence of apoptosis.[8,9,52,53]

The *XRCC1*gene, located at chromosome 19q13.3, produces an enzyme called X-ray cross-complementing group 1 that is involved in base excision repair pathway.[51] *XRCC1* polymorphisms disrupt the interaction of XRCC1 with other enzymatic proteins and consequently overwhelm DNA repair capacity, which leads to genetic instability and carcinogenesis.[54]

Our findings of a reduced risk of glioma associated with the C allele of *PARP-1* SNP rs1136410 and the T allele in SNP rs12917 of *MGMT* correlate with findings for other types of cancer and other diseases. The *PARP-1* gene located at chromosome 1q41-q42 encodes poly (ADP-ribose) polymerase family member 1, which is also one of the key molecules in the base excision repair pathway. It has been shown that, in the presence of single-strand breaks, the expression and activity of p53 and the rate of apoptosis are strongly increased in cells with PARP-1 deficiency.[55] Therefore, in the lower levels of DNA damage, PARP-1 deficiency may cause the cell to undergo apoptosis and prevent the survival of cancer-prone cells. In addition, *PARP* polymorphisms have been shown to be protective against several different diseases.[56–58] PARP inhibition can prevent chronic diseases such as cancer, stroke, myocardial infarction, and Crohn's disease and emerges as a potential therapeutic option for several diseases, including glioma.[59–64]

The *MGMT* gene, which resides in chromosome band 10q26, produces O^6-methylguanine–DNA methyl (alkyl) transferase and is involved in the mismatch repair system. There is some evidence suggesting an inverse association between SNP rs12917 and other types of cancer, which is similar to our findings.[65–68] This SNP alters the structure of MGMT,[69–72] and the recombinant structure may provide better zinc binding to MGMT and improve the DNA repair rate. Therefore, the T allele of *MGMT* SNP rs12917 has the chance of being selected by evolution.

Table S14 summarizes the functions of the genes reported by this study as being associated with the risk of glioma.

The associations between *XRCC1* rs25487 and *PARP-1* rs1136410 polymorphisms and risk of glioma have been investigated by other meta-analyses,[73–77] but these were based on fewer data or mixed evidence from germline and somatic variations. Three of the studies[73–75] reported results for *XRCC1* that are consistent with our finding, while one study was too small to reach significance.[76] One smaller meta-analysis[77] reported results for *PARP-1* and was consistent with our finding, although it was restricted to Caucasians. Meta-analyses of polymorphisms in *ERCC1* have only been performed for combinations of different cancer types which is uninformative for glioma risk.[78,79] In addition, these studies did not include all the studies that we investigated. No previous meta-analysis has investigated the associations between *MGMT* rs12917 and *ERCC2* rs13181 polymorphisms and risk of glioma.

A study by Walsh and colleagues[80] was published shortly after our closing date of the PubMed search and investigated 60 reported glioma-risk SNPs including *ERCC1* rs3212986 and *MGMT* rs12917. The results were consistent with our finding for *ERCC1* SNP rs3212986 with respect to the direction of the OR ($P = .189$), while they reported *MGMT* rs12917 as a nonsignificant glioma risk factor ($P = .202$), which is inconsistent with our finding of a reduced risk ($P = .013$). However, since they reported the associations for an allelic additive model without providing the raw data, we could not include this study in our meta-analysis to investigate whether our summary estimate would be affected.

Since most of the investigated SNPs have been evaluated in small samples, most of the individual studies did not find statistically significant associations due to low statistical power. Hence, the importance of conducting a meta-analysis for detection of clinically meaningful risk and protective factors is emphasized. This meta-analysis was conducted to test a specific hypothesis, and one might argue that Bonferroni adjustment for multiple testing is overly conservative in a meta-analysis investigating different genotypic models and may make researchers miss important findings.[81] However, to allow evaluation of the potential for false-positive findings, we provided reference *P* values with Bonferroni corrections. With these conservative estimates, only the association with *PARP-1* remained statistically significant, while the findings for *ERCC1* and *ERCC2* were of borderline significance.

Our aim was to provide evidence of the association between the SNPs and glioma risk and not to investigate the mechanisms behind these associations. Further studies, however, are needed to evaluate gene-environment interactions in DNA repair gene polymorphisms and the risk of glioma and to explore the mechanisms through which these polymorphisms influence cancer susceptibility.

In conclusion, our meta-analysis indicates that SNPs rs3212986, rs13181, and rs25487 in DNA repair genes *ERCC1, ERCC2,* and *XRCC1* may increase the predisposition to glioma, while polymorphisms rs1136410 and rs12917 in DNA repair genes *PARP-1* and *MGMT* are associated with decreased susceptibility to glioma.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. None declared.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
2. Kleihues PCW. *Pathology and genetics of tumours of the nervous system*. Lyon: IARC Press; 2000.
3. Dolecek TA, Propp JM, Stroup NE, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro Oncol*. 2012;14 (Suppl 5):v1–49.
4. Ohgaki H, Kleihues P. Epidemiology and etiology of gliomas. *Acta Neuropathol*. 2005;109(1):93–108.
5. Schwartzbaum JA, Fisher JL, Aldape KD, et al. Epidemiology and molecular pathology of glioma. *Nat Clin Pract Neurol*. 2006;2(9): 494–503. quiz 491 p following 516.
6. Friedberg EC. DNA damage and repair. *Nature*. 2003;421(6921): 436–440.
7. Rajaraman P, Hutchinson A, Wichner S, et al. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. *Neuro Oncol*. 2010;12(1):37–48.
8. Bernstein C, Bernstein H, Payne CM, et al. DNA repair/pro-apoptotic dual-role proteins in five major DNA repair pathways: fail-safe protection against carcinogenesis. *Mutat Res*. 2002;511(2):145–178.
9. Christmann M, Tomicic MT, Roos WP, et al. Mechanisms of human DNA repair: an update. *Toxicology*. 2003;193(1-2):3–34.
10. Bethke L, Webb E, Murray A, et al. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. *Hum Mol Genet*. 2008;17(6):800–805.
11. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2002;11(12):1513–1530.
12. Felini MJ, Olshan AF, Schroeder JC, et al. DNA repair polymorphisms XRCC1 and MGMT and risk of adult gliomas. *Neuroepidemiology*. 2007;29(1-2):55–58.
13. Liu Y. Association and interactions between DNA repair gene polymorphisms and adult glioma. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):204–214.
14. Yosunkaya E, Kucukyuruk B, Onaran I, et al. Glioma risk associates with polymorphisms of DNA repair genes, XRCC1 and PARP1. *Br J Neurosurg*. 2010;24(5):561–565.
15. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
16. Wang LE, Bondy ML, Shen H, et al. Polymorphisms of DNA repair genes and risk of glioma. *Cancer Res*. 2004;64(16):5560–5563.
17. McKean-Cowdin R. Associations between polymorphisms in DNA repair genes and glioblastoma. *Cancer Epidemiol Biomarkers Prevention*. 2009;18(4):1118–1126.
18. Wrensch M, Kelsey KT, Liu M, et al. ERCC1 and ERCC2 polymorphisms and adult glioma. *Neuro Oncol*. 2005;7(4):495–507.
19. Chen P, Wiencke J, Aldape K, et al. Association of an ERCC1 polymorphism with adult-onset glioma. *Cancer Epidemiol Biomarkers Prev*. 2000;9(8):843–847.
20. Caggana M, Kilgallen J, Conroy JM, et al. Associations between ERCC2 polymorphisms and gliomas. *Cancer Epidemiol Biomarkers Prev*. 2001;10(4):355–360.
21. Kiuru A, Lindholm C, Heinavaara S, et al. XRCC1 and XRCC3 variants and risk of glioma and meningioma. *J Neurooncol*. 2008;88(2): 135–142.
22. Liu Y, Zhou K, Zhang H, et al. Polymorphisms of LIG4 and XRCC4 involved in the NHEJ pathway interact to modify risk of glioma. *Hum Mutat*. 2008;29(3):381–389.
23. Liu Y, Zhang H, Zhou K, et al. Tagging SNPs in non-homologous end-joining pathway genes and risk of glioma. *Carcinogenesis*. 2007;28(9):1906–1913.
24. Semmler A, Simon M, Moskau S, et al. The methionine synthase polymorphism c.2756A>G alters susceptibility to glioblastoma multiforme. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(11):2314–2316.
25. Sadetzki S, Flint-Richter P, Starinsky S, et al. Genotyping of patients with sporadic and radiation-associated meningiomas. *Cancer Epidemiol Biomarkers Prev*. 2005;14(4):969–976.
26. Malmer BS, Feychting M, Lonn S, et al. Genetic variation in p53 and ATM haplotypes and risk of glioma and meningioma. *J Neurooncol*. 2007;82(3):229–237.
27. Yang P, Kollmeyer TM, Buckner K, et al. Polymorphisms in GLTSCR1 and ERCC2 are associated with the development of oligodendrogliomas. *Cancer*. 2005;103(11):2363–2372.
28. Zhou K, Liu Y, Zhang H, et al. XRCC3 haplotypes and risk of gliomas in a Chinese population: a hospital-based case-control study. *Int J Cancer*. 2009;124(12):2948–2953.
29. Zhou LQ, Ma Z, Shi XF, et al. Polymorphisms of DNA repair gene XRCC1 and risk of glioma: a case-control study in Southern China. *Asian Pac J Cancer Prev*. 2011;12(10):2547–2550.
30. Zhou K, Hu D, Lu J, et al. A genetic variant in the APE1/Ref-1 gene promoter-141T/G may modulate risk of glioblastoma in a Chinese Han population. *BMC Cancer*. 2011;11:1104.
31. Wang D, Hu Y, Gong H, et al. Genetic polymorphisms in the DNA repair gene XRCC1 and susceptibility to glioma in a Han population in northeastern China: a case-control study. *Gene*. 2012;509(2): 223–227.
32. Fan W. Possible association between genetic variants in the H2AFX promoter region and risk of adult glioma in a Chinese Han population. *Journal of Neurosurgery*. 2011;105(2):211–218.
33. Zhang N, Lin LY, Zhu LL, et al. ERCC1 polymorphisms and risk of adult glioma in a Chinese population: a hospital-based case-control study. *Cancer Invest*. 2012;30(3):199–202.
34. Salnikova LE, Zelinskaya NI, Belopolskaya OB, et al. Association study of xenobiotic detoxication and repair genes with malignant brain tumors in children. *Acta Naturae*. 2010;2(4):58–65.
35. Chang JS, Yeh RF, Wiencke JK, et al. Pathway analysis of single-nucleotide polymorphisms potentially associated with glioblastoma multiforme susceptibility using random forests. *Cancer Epidemiol Biomarkers Prev*. 2008;17(6):1368–1373.
36. Egan KM, Nabors LB, Olson JJ, et al. Rare TP53 genetic variant associated with glioma risk and outcome. *J Med Genet*. 2012; 49(7):420–421.
37. Hu XB, Feng Z, Fan YC, et al. Polymorphisms in DNA repair gene XRCC1 and increased genetic susceptibility to glioma. *Asian Pac J Cancer Prev*. 2011;12(11):2981–2984.
38. Biros E, Kalina I, Kohut A, et al. Allelic and haplotype frequencies of the p53 polymorphisms in brain tumor patients. *Physiol Res*. 2002; 51(1):59–64.

39. Idbaih A, Boisselier B, Marie Y, et al. TP53 codon 72 polymorphism, p53 expression, and 1p/19q status in oligodendroglial tumors. *Cancer Genet Cytogenet*. 2007;177(2):103–107.
40. Kafadar AM, Yilmaz H, Kafadar D, et al. C677T gene polymorphism of methylenetetrahydrofolate reductase (MTHFR) in meningiomas and high-grade gliomas. *Anticancer Res*. 2006;26(3B):2445–2449.
41. Malmer B, Feychting M, Lonn S, et al. p53 Genotypes and risk of glioma and meningioma. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(9):2220–2223.
42. Chen DQ, Yao DX, Zhao HY, et al. DNA repair gene ERCC1 and XPD polymorphisms predict glioma susceptibility and prognosis. *Asian Pac J Cancer Prev*. 2012;13(6):2791–2794.
43. Ciara E, Piekutowska-Abramczuk D, Popowska E, et al. Heterozygous germ-line mutations in the NBN gene predispose to medulloblastoma in pediatric patients. *Acta Neuropathol*. 2010; 119(3):325–334.
44. Bethke L, Murray A, Webb E, et al. Comprehensive analysis of DNA repair gene variants and risk of meningioma. *J Natl Cancer Inst*. 2008;100(4):270–276.
45. Idbaih A, Boisselier B, Marie Y, et al. Influence of MDM2 SNP309 alone or in combination with the TP53 R72P polymorphism in oligodendroglial tumors. *Brain Res*. 2008;10(1198):16–20.
46. Cengiz S. Deoxy-ribonucleic acid repair genes XRCC 1 and XPD polymorphisms and brain tumor risk. *Neurosciences*. 2008;13(3): 227–232.
47. Rajaraman P, Melin BS, Wang Z, et al. Genome-wide association study of glioma and meta-analysis. *Hum Genet*. 2012;131(12): 1877–1888.
48. Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. *Nat Genet*. 2009; 41(8):899–904.
49. Wrensch M, Jenkins RB, Chang JS, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nat Genet*. 2009;41(8):905–908.
50. Sanson M, Hosking FJ, Shete S, et al. Chromosome 7p11.2 (EGFR) variation influences glioma risk. *Hum Mol Genet*. 2011;20(14): 2897–2904.
51. Mohrenweiser HW, Carrano AV, Fertitta A, et al. Refined mapping of the three DNA repair genes, ERCC1, ERCC2, and XRCC1, on human chromosome 19. *Cytogenet Cell Genet*. 1989;52(1-2):11–14.
52. Wood RD. Nucleotide excision repair in mammalian cells. *J Biol Chem*. 1997;272(38):23465–23468.
53. Vermeulen W, de Boer J, Citterio E, et al. Mammalian nucleotide excision repair and syndromes. *Biochem Soc Trans*. 1997;25(1): 309–315.
54. Taylor RM, Thistlethwaite A, Caldecott KW. Central role for the XRCC1 BRCT I domain in mammalian DNA single-strand break repair. *Mol Cell Biol*. 2002;22(8):2556–2563.
55. Beneke R, Geisen C, Zevnik B, et al. DNA excision repair and DNA damage-induced apoptosis are linked to Poly(ADP-ribosyl)ation but have different requirements for p53. *Mol Cell Biol*. 2000;20(18): 6695–6703.
56. Infante J, Sanchez-Juan P, Mateo I, et al. Poly (ADP-ribose) polymerase-1 (PARP-1) genetic variants are protective against Parkinson's disease. *J Neurol Sci*. 2007;256(1-2):68–70.
57. Li C, Hu Z, Lu J, et al. Genetic polymorphisms in DNA base-excision repair genes ADPRT, XRCC1, and APE1 and the risk of squamous cell carcinoma of the head and neck. *Cancer*. 2007; 110(4):867–875.
58. Li C, Liu Z, Wang LE, et al. Genetic variants of the ADPRT, XRCC1 and APE1 genes and risk of cutaneous melanoma. *Carcinogenesis*. 2006; 27(9):1894–1901.
59. Zarghooni M, Bartels U, Lee E, et al. Whole-genome profiling of pediatric diffuse intrinsic pontine gliomas highlights platelet-derived growth factor receptor alpha and poly (ADP-ribose) polymerase as potential therapeutic targets. *J Clin Oncol*. 2010; 28(8):1337–1344.
60. Megnin-Chanet F, Bollet MA, Hall J. Targeting poly(ADP-ribose) polymerase activity for cancer therapy. *Cell Mol Life Sci*. 2010; 67(21):3649–3662.
61. Annunziata CM, O'Shaughnessy J. Poly (ADP-ribose) polymerase as a novel therapeutic target in cancer. *Clin Cancer Res*. 2010;16(18): 4517–4526.
62. Plummer R, Jones C, Middleton M, et al. Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. *Clin Cancer Res*. 2008;14(23):7917–7923.
63. Gartner EM, Burger AM, Lorusso PM. Poly(adp-ribose) polymerase inhibitors: a novel drug class with a promising future. *Cancer J*. 2010;16(2):83–90.
64. Burkle A. Physiology and pathophysiology of poly(ADP-ribosyl)ation. *Bioessays*. 2001;23(9):795–806.
65. Han J, Hankinson SE, De Vivo I. Polymorphisms in O6-methylguanine DNA methyltransferase and endometrial cancer risk. *Carcinogenesis*. 2006;27(11):2281–2285.
66. Zhang M, Huang WY, Andreotti G, et al. Variants of DNA repair genes and the risk of biliary tract cancers and stones: a population-based study in China. *Cancer Epidemiol Biomarkers Prev*. 2008;17(8): 2123–2127.
67. Huang WY, Olshan AF, Schwartz SM, et al. Selected genetic polymorphisms in MGMT, XRCC1, XPD, and XRCC3 and risk of head and neck cancer: a pooled analysis. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1747–1753.
68. Stern MC, Conti DV, Siegmund KD, et al. DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the Singapore Chinese Health Study. *Cancer Epidemiol Biomarkers Prev*. 2007;16(11): 2363–2372.
69. Sharma S, Salehi F, Scheithauer BW, et al. Role of MGMT in tumor development, progression, diagnosis, treatment and prognosis. *Anticancer Res*. 2009;29(10):3759–3768.
70. Pegg AE, Fang Q, Loktionova NA. Human variants of O6-alkylguanine-DNA alkyltransferase. *DNA Repair (Amst)*. 2007; 6(8):1071–1078.
71. Rasimas JJ, Kanugula S, Dalessio PM, et al. Effects of zinc occupancy on human O6-alkylguanine-DNA alkyltransferase. *Biochemistry*. 2003;42(4):980–990.
72. Fang Q, Kanugula S, Pegg AE. Function of domains of human O6-alkylguanine-DNA alkyltransferase. *Biochemistry*. 2005;44(46): 15396–15405.
73. Wei X, Chen D, Lv T. A functional polymorphism in XRCC1 is associated with glioma risk: evidence from a meta-analysis. *Mol Biol Rep*. 2013;40(1):567–572.
74. Sun JY, Zhang CY, Zhang ZJ, et al. Association between XRCC1 gene polymorphisms and risk of glioma development: a meta-analysis. *Asian Pac J Cancer Prev*. 2012;13(9):4783–4788.
75. Jiang L, Fang X, Bao Y, et al. Association between the XRCC1 polymorphisms and glioma risk: a meta-analysis of case-control studies. *PLoS One*. 2013;8(1):e55597.

76. Jacobs DI, Bracken MB. Association between XRCC1 polymorphism 399 G->A and glioma among Caucasians: a systematic review and meta-analysis. *BMC Med Genet*. 2012; doi: 10.1186/1471-2350-13-97.
77. Yu H, Ma H, Yin M, Wei Q. Association between PARP-1 V762A polymorphism and cancer susceptibility: a meta-analysis. *Genet Epidemiol*. 2012;36(1):56–65.
78. Li Y, Gu S, Wu Q, et al. No association of ERCC1 C8092A and T19007C polymorphisms to cancer risk: a meta-analysis. *Eur J Hum Genet*. 2007;15(9):967–973.
79. Zhang L, Wang J, Xu L, et al. Nucleotide excision repair gene ERCC1 polymorphisms contribute to cancer susceptibility: a meta-analysis. *Mutagenesis*. 2012;27(1):67–76.
80. Walsh KM, Anderson E, Hansen HM, et al. Analysis of 60 reported glioma risk SNPs replicates published GWAS findings but fails to replicate associations from published candidate-gene studies. *Genet Epidemiol*. 2013;37(2):222–228.
81. Rothman K. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43–46.