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Polymorphisms of DNA Repair Genes and Risk of Glioma

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Abstract

DNA repair genes play a major role in maintaining genomic stability through different repair pathways that are mediated by cell cycle control genes such as *p53*. We found previously that glioma patients were susceptible to γ-ray-induced chromosomal breaks, which may be influenced by genetic variation in genes involved in DNA strand breaks, such as *XRCC1* in single-strand break repair, *XRCC3* and *RAD51* in homologous recombination repair, and *XRCC7* in nonhomologous end joining double-strand break repair. Therefore, we tested the hypothesis that genetic polymorphisms in *XRCC1, XRCC3, RAD51, XRCC7,* and *p53* were associated with risk of glioma in 309 patients with newly diagnosed glioma and 342 cancer-free control participants frequency matched on age (±5 years), sex, and self-reported ethnicity. We did not find any statistically significant differences in the distributions of *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *RAD51* G135C, and *P53* Arg72Pro polymorphisms between the cases and the controls. However, the *XRCC7* G6721T variant T allele and TT genotype were more common in the cases (0.668 and 43.4%, respectively) than in the controls (0.613 and 38.9%, respectively), and the differences were statistically significant ($P = 0.045$ and 0.040, respectively). The adjusted odds ratios were 1.78 (95% confidence interval, 1.08–2.94) and 1.86 (95% confidence interval, 1.12–3.09) for the GT heterozygotes and TT homozygotes, respectively. The combined T variant genotype (GT+TT) was associated with a 1.82-fold increased risk of glioma (95% confidence interval, 1.13–2.93). These results suggest that the T allele may be a risk allele, and this *XRCC7* polymorphism may be a marker for the susceptibility to glioma. Larger studies are needed to confirm our findings and unravel the underlying mechanisms.

Introduction

In 2004, ~10,540 men and 7,860 women will develop a primary brain tumor, and an estimated 7,200 men and 5,490 women will die from the disease in the United States (1). Of these deaths, ~90% will result from gliomas. The etiology of gliomas remains unclear, but epidemiological studies have shown that ionizing radiation and genetic alterations are established risk factors in subsets of brain tumor patients (2–7).

Ionizing radiation induces various types of DNA damage, including single- and double-strand breaks. Dozens of genes are involved in DNA strand break repair to maintain genomic stability through different pathways mediated by cell cycle control genes (8, 9). Each DNA repair gene plays a unique role. For example, *XRCC1* is involved in single-strand break repair, *XRCC3* and *RAD51* in homologous recombination repair, and *XRCC7* in nonhomologous end joining double-strand break repair (8–11). However, genetic alterations of these genes may affect the function of their proteins and lead to diseases or cancers (12, 13). The roles of common polymorphisms, *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *RAD51* G135C, and *P53* Arg72Pro have been investigated in various cancers, and the results are mixed (14–21). There is one newly identified variant (G6721T) in *XRCC7* involved in the nonhomologous end joining, but the functional relevance is not yet known (10).

The X-ray repair cross-complementing group 7 (*XRCC7*) gene encodes the catalytic subunit of a DNA-activated protein kinase, which is involved in the nonhomologous end joining repair pathway in murine cells (22) and humans (10). Defects in the *XRCC7* gene make the DNA-activated protein kinase activity undetectable in murine mutants and these cells sensitive to ionizing radiation (23). Furthermore, the *XRCC7* gene is a strong candidate gene involved in severe combined immunodeficiency (23, 24).

Because we reported recently that glioma patients were susceptible to γ-ray-induced chromosomal breaks (6, 7), we hypothesized that the polymorphisms of these genes are associated with glioma risk. To test this hypothesis, we conducted a hospital-based case-control study using a restriction fragment length polymorphism assay to genotype for the variants of *XRCC1*, *XRCC3*, *RAD51*, *P53*, and *XRCC7* genes in 309 patients with newly diagnosed glioma and 342 cancer-free controls frequency matched on age (±5 years), sex, and self-reported ethnicity.

Materials and Methods

Study Population. In this case-control analysis, we included 309 patients with newly diagnosed and histologically confirmed glioma recruited at The University of Texas M. D. Anderson Cancer Center from 1994 to 2000. These cases included 151 glioblastoma multiforme, categorized as high-grade glioma; 70 anaplastic astrocytoma, medium-grade glioma; and 88 others in the low-grade glioma group (oligodendroglioma, not-otherwise-specified astrocytoma, or mixed glioma). The 342 controls were cancer-free participants recruited at the M. D. Anderson Blood Bank (24.9%), visitors of other patients at M. D. Anderson who were biologically unrelated to the study patients (52.0%), and others from the Houston community residing in the vicinity of M. D. Anderson (23.1%). Included among these participants were 200 patients and 220 controls who participated in a study reported previously (7) and for whom DNA was available. Because genetic susceptibility is more identifiable in young individuals, we included only study participants between the ages of 20 and 60 years. The cases and controls were frequency matched on age (by ±5 years), sex, and ethnicity (all self-reported non-Hispanic whites). Each eligible participant was interviewed to obtain data regarding age, sex, and ethnicity. Only non-Hispanic whites were included because of the small numbers of other ethnic groups. After giving informed consent, each participant donated 20 ml of blood collected in heparinized tubes. The research protocol was approved by the M. D. Anderson Institutional Review Board.

Genotyping. We used the commercially available Qiagen kit (Qiagen Inc., Valencia, CA) to extract DNA from peripheral blood leukocytes. The purified DNA was used to determine the genotypes: for the *XRCC1* Arg399Gln polymorphism at nucleotide −28152 of exon 10, the *XRCC3* Thr241Met polymorphism at nucleotide −18607 of exon 7, the *RAD51* G135C polymorphism of untranslated region, and the *p53* Arg72Pro polymorphism of exon 4, we used the published primers and the PCR-restriction fragment length poly-

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morphism method to amplify PCR fragments, then digested them with the corresponding restriction enzymes to identify the three genotypes of each gene (25–28); and for the *XRCC7* G6721T polymorphism, we designed the primers and developed a simple restriction fragment length polymorphism method. The sense primer was 5′-CGGCTGCCAACGTTCTTTCC-3′ (nucleotides 6626–6645), and the antisense primer was 5′-TGCCCTTAGTGGTTCCCTGG-3′ (complementary to nucleotides 6974–6993; GenBank accession no. L27425; Ref. 10). The primers amplified 368-bp fragment containing the G/T variant in intron 8, which was then subjected to digestion with *Pvu*II (New England BioLabs, Inc., Beverly, MA) at 37°C overnight. The homologous GG allele had only one band of 368-bp; the heterozygous allele (GT) had three bands of 368, 274, and 94 bp; and the homozygous TT allele had two bands of 274 and 94 bp because of the gain of the restriction site (Fig. 1). The 20-μl PCR mixture contained ~50 ng of genomic DNA, 5.0 pmol of each primer, 0.1 mM each deoxynucleoside triphosphate, 1 × PCR buffer [50 mM KCl, 10 mM Tris HCl (pH 9.0 at 25°C), and 0.1% Triton X-100], 1.5 mM $MgCl_2$, and 1.0 units of Taq polymerase (Sigma-Aldrich Biotechnology, Saint Louis, MO). The PCRs were performed with a PTC-200 DNA Engine (MJ Research, Inc., Watertown, MA). The PCR profile consisted of an initial melting step of 95°C for 5 min; 30 cycles of 95°C for 30 s, 61°C for 30 s, and 72°C for 45 s; and a final elongation step of 72°C for 10 min with a minor modification for each gene. The PCR products were checked on a 1% agarose gel, and the digested products were visualized on a 2% agarose gel stained with ethidium bromide and photographed using the Digital Imaging System (Model IS-1000; Alpha Innotech Co., San Leandro, CA).

Statistical Analysis. We first conducted a univariate analysis to evaluate the distribution of selected variables in the cases and controls. The χ^2 test was then computed to evaluate the differences in the frequency distributions of age; sex; and the *XRCC1*, *XRCC3*, *RAD51*, *P53*, and *XRCC7* genotypes between the cases and controls. We also evaluated the observed genotype frequencies with those calculated from the Hardy-Weinberg equilibrium theory ($p^2 + 2pq + q^2 = 1$, where p is the frequency of the variant allele and $q = 1 - p$). We applied univariate and multivariate logistic regression to calculate crude and adjusted odds ratios and 95% confidence intervals, respectively, for the association between the genotypes and risk of glioma. We stratified the data into subgroups of demographic variables and glioma histology. We used Statistical Analysis System software (Version 8; SAS Institute Inc., Cary, NC) to perform all of the statistical analyses.

Results

The mean ages were 44.1 years (SD ±11.0) and 43.8 years (SD ±10.6) for the 309 cases and 342 controls, respectively ($P = 0.686$). The frequency matching on age and sex between the cases and controls appeared to be adequate (Table 1). The genotype distributions of the *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *RAD51* G135C, and *P53* Arg72Pro between the cases and controls were not statistically significant, and their variant allele frequencies were not statistically different either between the cases and controls (Table 1). The distributions of these genotype frequencies were in agreement with those expected from the Hardy-Weinberg equilibrium model for controls ($P = 0.997$, 0.708, 0.545, and 0.986, respectively).

However, we found that the variant *XRCC7* T allele was more common in the cases (0.668) than in the controls (0.613), and the difference was statistically significant ($P = 0.045$). The *XRCC7* genotype frequencies between the cases and controls were also statistically significant ($P = 0.040$). Likewise, the difference in the distribution of combined T variant genotype (GT+TT) between the cases and controls was also statistically significant $P = 0.012$), suggesting that the T allele may be a risk allele for glioma. The distributions of the *XRCC7* genotype frequencies were in agreement with those expected from the Hardy-Weinberg equilibrium model for both the cases ($P = 0.765$) and controls ($P = 0.759$).

Table 1 *Distribution of selected variables and five genotypes in glioma patients and cancer-free controls*

Variable	Cases (n = 309) No.	(%)	Controls (n = 342) No.	(%)	P*
Age (yr)					0.536
20–45	147	(47.6)	171	(50.0)	
46–60	162	(52.4)	171	(50.0)	
Sex					0.184
Male	167	(54.0)	167	(48.8)	
Female	142	(46.0)	175	(51.2)	
XRCC1 Arg399Gln					0.375
Arg/Arg	134	(43.4)	131	(38.3)	
Arg/Gln	138	(44.7)	162	(47.4)	
Gln/Gln	37	(12.0)	49	(14.3)	
Arg/Gln + Gln/Gln	175	(56.6)	211	(61.7)	0.189
Gln allele frequency	0.343	7	0.380		0.184
XRCC3 Thr241Met					0.727
Thr/Thr	134	(43.4)	147	(43.0)	
Thr/Met	138	(44.7)	147	(43.0)	
Met/Met	37	(12.0)	48	(14.0)	
Thr/Met + Met/Met	175	(56.6)	195	(57.0)	0.922
Met allele frequency	0.343	7	0.355		0.693
RAD51 G135C					0.098
GG	265	(85.8)	301	(88.0)	
GC	40	(12.9)	41	(12.0)	
CC	4	(1.3)	0	(0.0)	
GC+CC	44	(14.2)	41	(12.0)	0.395
C allele frequency	0.078	7	0.060		0.240
P53 Arg72Pro					0.673
Arg/Arg	165	(53.4)	194	(56.7)	
Arg/Pro	126	(40.8)	128	(37.4)	
Pro/Pro	18	(5.8)	20	(5.9)	
Arg/Pro + Pro/Pro	144	(46.6)	148	(43.3)	0.394
Pro allele frequency	0.262	7	0.246		0.549
XRCC7 G6721T					0.040
GG	30	(9.7)	56	(16.4)	
GT	145	(46.9)	153	(44.7)	
TT	134	(43.4)	133	(38.9)	
GT+TT	279	(90.3)	286	(83.6)	0.012
T allele frequency	0.668	7	0.613		0.045

* Two-sided χ^2 test.

To evaluate the difference in the controls obtained from different sources (blood bank, hospital, and community), we compared these genotype distributions among the controls. There was no statistically significant difference in these five genotype distributions among these three control groups (data not shown).

As shown in Table 2, we analyzed the distribution of the *XRCC7* genotypes stratified by age, sex, and the histological type of the glioma and found that the differences in the distributions of the *XRCC7* genotypes between the cases and controls were statistically significant in the older ($P = 0.022$), males ($P = 0.034$), high-grade glioma ($P = 0.014$), and low-grade glioma subgroups ($P = 0.020$).

The odds ratios for the GT, TT, and combined GT+TT genotypes by using the GG genotype as the reference are summarized in Table

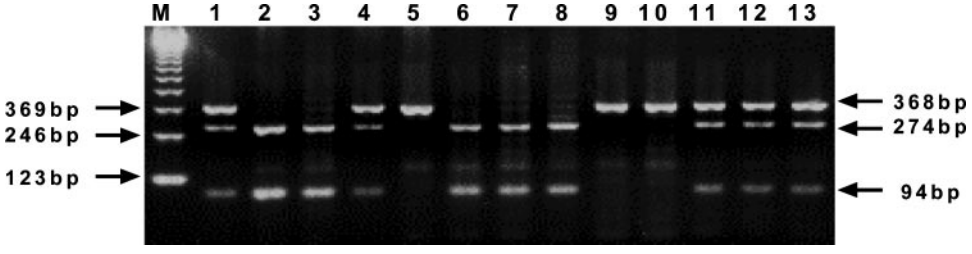

Fig. 1. PCR-based restriction fragment length polymorphism genotyping for *XRCC7* intron 8 (G6721T) polymorphism (*Pvu*II). *Lanes 5*, *9*, and *10*, GG homozygotes; *Lanes 1*, *4*, *11*, *12*, and *13*: GT heterozygotes; and *Lanes 2*, *3*, *6*, *7*, and *8*, TT homozygotes.

Table 2 *Stratification analysis of XRCC7 genotype frequencies*

	Cases (n = 309)			Controls (n = 342)			
	GG No. (%)	GT No. (%)	TT No. (%)	GG No. (%)	GT No. (%)	TT No. (%)	*P**
Age (yr)							
20–45	19 (12.9)	73 (49.7)	55 (37.4)	29 (17.0)	76 (44.4)	66 (38.6)	0.512
46–60	11 (6.8)	72 (44.4)	79 (48.8)	27 (15.8)	77 (45.0)	67 (39.2)	0.022
Sex							
Male	14 (8.4)	76 (45.5)	77 (46.1)	30 (18.0)	66 (39.5)	71 (42.5)	0.034
Female	16 (11.3)	69 (48.6)	57 (40.1)	26 (14.9)	87 (49.7)	62 (35.4)	0.536
Tumor histology†							
High-grade glioma	14 (9.3)	59 (39.1)	78 (51.7)	56 (16.4)	153 (44.7)	133 (38.9)	0.014
Medium-grade glioma	9 (12.9)	33 (47.1)	28 (40.0)				0.760
Low-grade glioma	7 (8.0)	53 (60.2)	28 (31.8)				0.020

* Two-sided χ^2 test.

† High-grade glioma: glioblastoma multiforme; medium-grade glioma: anaplastic astrocytoma; low-grade glioma: including oligodendroglioma, NOS astrocytoma, or mixed glioma.

3. After adjustment for age and sex, GT, TT, and combined (GT+TT) genotypes were all associated with a nearly 2-fold increased risk of glioma (odds ratios, 1.78; 95% confidence interval, 1.08–2.94 for GT; odds ratios, 1.86; 95% confidence interval, 1.12–3.09 for TT; and odds ratios, 1.82; 95% confidence interval, 1.13–2.93 for GT+TT). Stratifying these data by age, sex, and type of tumor histology showed that the association between the T variant genotype (GT, TT or GT+TT) and the increased risk of glioma was more pronounced in older (46–60 years; odds ratios, 2.58; 95% confidence interval, 1.23–5.43 for the GT+TT genotype) and male (odds ratios, 2.33; 95% confidence interval, 1.18–4.59 for the GT+TT genotype) participants. Additional stratification by age and sex revealed that the subgroup of males aged 46–60 years (cases/controls = 97/87) had the highest risk (odds ratios, 2.95; 95% confidence interval, 1.05–8.26; data not shown). The homozygous variant TT genotype was associated with a >2-fold increased risk of glioblastoma multiforme gliomas (odds ratios, 2.16; 95% confidence interval, 1.11–4.22), and the heterozygous GT variant genotype was associated with a nearly 3-fold risk for low-grade gliomas (odds ratios, 2.93; 95% confidence interval, 1.24–6.93; Table 3). However, significant odds ratios (2.39; 95% confidence interval, 1.04–5.53) for the GT/TT genotype was only found for the low-grade tumors.

We also investigated the effects of combined genotypes of these five polymorphisms on risk of glioma, but we did not find any significant association beyond the *XRCC7* genotype (data not shown).

Discussion

In this study, we selected five major genes involved in the single-strand break repair (*XRCC1*), homologous recombination (*XRCC3* and *RAD51*), nonhomologous end joining (*XRCC7*) repair pathways and cell-cycle control (*P53*) to investigate the associations of their common polymorphisms with risk of glioma. The data revealed that only the *XRCC7* G6721T polymorphism was associated with glioma risk. To our knowledge, this study is the first case-control analysis of the *XRCC7* intron 8 G6721T polymorphism in risk of human cancers. It provides estimates of the prevalence of the G6721T genotypes from 342 cancer-free controls. The T allele frequency of 0.613 in this non-Hispanic white population was slightly lower than that (0.667) in healthy participants from the only previously published report that included 12 cancer patients and 27 family members (10). However, we found a significantly higher frequency of the *XRCC7* T variant genotypes in the glioma patients than in the control participants, and this high frequency of the T variant genotype was associated with 1.82-fold increase in risk of glioma. The increased risk of glioma associated with the *XRCC7* variant genotypes is more pronounced in older (46–60 years), male cases and patients with high-grade and low-grade gliomas. Because the variability is always observed by strata, the results need to be verified in other hypothesis-driven studies.

Although the functional relevance of the *XRCC7* polymorphism is unknown, several lines of evidence suggest that these findings are biologically plausible. The *XRCC7* gene is located on chromosome 8q11 and encodes the catalytic polypeptide of DNA-activated protein kinase, which plays a key role in DNA nonhomologous end joining double-strand breaks (22). Studies have suggested that human chromosome 8q11 functionally corrects the hyper-radiosensitivity and variable (diversity) joining region recombination in severe combined immunodeficiency cells and complements the DNA double-strand break repair deficiency of severe combined immunodeficiency cells that are phenotypically sensitive to radiation-induced chromosome aberration (29–31). Although the functional significance of the *XRCC7* intron G6721T polymorphism is unknown, this intronic single-nucleotide polymorphism might regulate splicing and cause mRNA instability (10) or may be a haplotype with other genetic

Table 3 *Logistic regression analysis of XRCC7 genotypes stratified by selected variables and histological types*

		Adjusted odds ratio (95% confidence interval)*			
	N†	GG	GT	TT	GT/TT
All participants	309/342	1.00	1.78 (1.08–2.94)	1.86 (1.12–3.09)	1.82 (1.13–2.93)
Age (yr)					
20–45	147/171	1.00	1.48 (0.76–2.88)	1.31 (0.66–2.60)	1.40 (0.75–2.64)
46–60	162/171	1.00	2.34 (1.08–5.08)	2.87 (1.32–6.26)	2.58 (1.23–5.43)
Sex					
Male	167/167	1.00	2.42 (1.18–4.96)	2.25 (1.10–4.60)	2.33 (1.18–4.59)
Female	142/175	1.00	1.29 (0.64–2.60)	1.52 (0.74–3.12)	1.39 (0.71–2.70)
Tumor histology‡					
High-Grade Glioma	151/342	1.00	1.49 (0.75–2.93)	2.16 (1.11–4.22)	1.81 (0.96–3.43)
Medium-grade glioma	70/342	1.00	1.44 (0.64–3.23)	1.43 (0.63–3.26)	1.44 (0.67–3.09)
Low-grade glioma	88/342	1.00	2.93 (1.24–6.93)	1.78 (0.72–4.37)	2.39 (1.04–5.53)

* Adjusted for age and sex, accordingly.

† N = numbers of cases/controls.

‡ High-grade glioma: glioblastoma multiforme; medium-grade glioma: anaplastic astrocytoma; low-grade glioma: including oligodendroglioma, NOS astrocytoma, or mixed glioma.

changes in other disease-related genes through a linkage disequilibrium mechanism (12). However, these possibilities should be investigated in future studies.

We realize that population admixture is a known confounding factor for population-based association analysis, and may result in inflated type I error. In this study we only included Caucasians because >85% of our dataset were Caucasian. The ethnic distribution of our samples is similar to the distribution of gliomas reported by Surveillance, Epidemiology, and End Results and other registries. We followed the guidelines recommended by the Office of Management and Budget to respect the individual participant self-reporting their race and ethnicity (32) and also examined the consistency of the prevalence of the alleles we genotyped. The frequencies were in the ranges of frequencies published by ethnicity (12, 16, 17, 21, 33), suggesting the self-reported ethnicity was appropriate in this association study.

In conclusion, the *XRCC7* 6721T variant may contribute to risk of glioma, especially in older males, and might be associated with some glioma histologies. Although this hospital-based case-control study may have limitations resulting from bias of the case and control selection, it is unlikely that their genotypes would be influenced by this bias (34). Because this is the first report of an association between this *XRCC7* polymorphism and glioma risk, our findings need to be validated in larger studies with more rigorous study designs. It is also important to investigate the role of known polymorphisms of genes involved in the nonhomologous end joining repair pathway in the development of glioma and their gene-gene or gene-environment interactions.

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