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DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma

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Although the etiology of primary brain tumors is largely unknown, prior studies suggest that DNA repair polymorphisms may influence risk of glioma. Altered DNA repair is also likely to affect the risk of meningioma and acoustic neuroma, but these tumors have not been well studied. We estimated the risk of glioma (n = 362), meningioma (n = 134), and acoustic neuroma (n = 69) in non-Hispanic whites with respect to 36 single nucleotide polymorphisms from 26 genes involved in DNA repair in a hospital-based, case–control study conducted by the National Cancer Institute. We observed significantly increased risk of meningioma with the *T* variant of *GLTSCR1* rs1035938 ($OR_{CT/TT}$ = 3.5; 95% confidence interval: 1.8–6.9; P_{trend} .0006), which persisted after controlling for multiple comparisons (P = .019). Significantly increased meningioma risk was also observed for the minor allele variants of *ERCC4* rs1800067 (P_{trend} .01); *MUTYH* rs3219466 (P_{trend} .02), and *PCNA* rs25406 (P_{trend} .03). The *NBN* rs1805794 minor allele variant was associated with decreased meningioma risk (P_{trend} .006). Risk of acoustic neuroma was increased for the *ERCC2* rs1799793 (P_{trend} .03) and *ERCC5* rs17655 (P_{trend} .05) variants and decreased for the *PARP1* rs1136410 (P_{trend} .03). Decreased glioma risk was observed with the *XRCC1* rs1799782 variant (P_{trend} .04). Our results suggest that common DNA repair variants may affect the risk of adult brain tumors, especially meningioma.

Keywords: acoustic neuroma, brain, case–control, DNA repair, glioma, meningioma, neoplasm, polymorphism, tumor

Tumors of the brain, meninges, and cranial nerves account for approximately 95% of all central nervous system tumors and include some of the most rapidly fatal cancer types.[1,2] In normal cells, DNA damage is recognized by cellular mechanisms, and one of the chief responses to prevent the propagation of errors and subsequent initiation and growth of tumors is the repair of damaged DNA.[3,4] Ionizing radiation, the only confirmed environmental risk factor for brain tumors in humans, produces several kinds of DNA damage, including oxidative damage to nucleotide bases, single- and double-strand breaks in DNA chains, and DNA–DNA or DNA–protein covalent cross links. Such damage also can be caused by other exogenous agents, as well as endogenous processes, such as oxidative metabolism and inflammation. The repair of

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this damage involves several molecular pathways of DNA repair, including base-excision repair, nucleotide excision repair, non-homologous end joining, and homologous recombination.[5]

Previous studies have noted that single nucleotide polymorphisms (SNPs) in DNA repair genes including *CHAF1*,[6] *LIG4*, *XRCC4*,[7] *XRCC5*, *XRCC6*,[8] *XRCC7*,[9] *MGMT*,[10] *XRCC1*,[11] *XRCC3*,[11] *ERCC1*,[12,13] *ERCC2*,[14] and *GLTSCR1*[14] may modify glioma risk. Although fewer studies have examined meningioma, results suggest that genes in DNA repair pathways could play an important part in the etiology of this tumor,[11,15,16] with increased meningioma risk for the *BRIP1* rs4968551 minor allele variant being highly statistically significant.[16] Previous studies have not examined meningioma risk with respect to variation in the *GLTSCR1*, *MUTYH*, or *PCNA* genes. To our knowledge, no previous studies have examined the risk of acoustic neuroma with respect to DNA repair polymorphisms. This study conducts an exploratory investigation of whether variation in common DNA repair genes is associated with acoustic neuroma. Using data from non-Hispanic whites in a hospital-based, case–control study conducted by the National Cancer Institute (NCI) between 1994 and 1998, we evaluated the risk of glioma ($n = 362$), meningioma ($n = 134$), and acoustic neuroma ($n = 69$) with respect to 36 SNPs from 26 genes involved in DNA repair. These genes and polymorphisms were selected based on the available data from the literature and SNP500 database (http://snp500cancer.nci.nih.gov/home_1.cfm) regarding relevance for brain tumors, common occurrence in the population, and potential functional relevance signaled by non-synonymous amino acid (AA) changes or occurrence in exonic or promoter regions of the gene (Table 1).

Materials and Methods

Study Setting and Population

A detailed description of the study methods can be found elsewhere.[17] Briefly, eligible patients were 18 years or older with a first intracranial intracranial glioma or neuroepitheliomatous tumor (ICD-O-2 codes 9380–9473 and 9490–9506), meningioma (ICD-O-2 codes 9530–9538), or acoustic neuroma (ICD-O-2 code 9560) diagnosed during 1994–1998 at 1 of 3 hospitals specializing in brain tumor treatment (in Boston, Phoenix, and Pittsburgh) within the 8 weeks preceding hospitalization. Ninety-two percent of the eligible brain tumor patients agreed to participate, and 489 patients with glioma, 197 with meningioma, and 96 patients with acoustic neuroma were enrolled, with all but 4% of acoustic neuromas being confirmed by microscopy.

Controls were admitted to the same hospitals for injuries (25%), circulatory system disorders (22%), musculoskeletal disorders (22%), digestive disorders (12%), or a variety of other non-neoplastic conditions, and were frequency-matched in a 1:1 ratio to all brain tumor patients based on age (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80–90 years); race/ethnicity (non-Hispanic white, Hispanic, African American, other), sex, hospital, and residential proximity to the hospital. Seven hundred ninety-nine control patients (86% of all contacted) were enrolled. The study protocol was approved by the Institutional Review Board of each participating institution, and written informed consent was obtained from each patient or proxy. This analysis was restricted to non-Hispanic whites (89% of all study participants) who provided blood samples. All study participants were alive at the time of interview and were therefore eligible and able to provide blood specimens. For non-Hispanic whites who had consented to provide blood samples, samples were genotyped for 362 patients with glioma (82% of all non-Hispanic whites), 134 patients with meningioma (82%), 69 patients with acoustic neuroma (78%), and 495 controls (69%). The main obstacle to obtaining blood samples was subject refusal, with non-participation in the blood draw being higher for controls (24%) than for cases (14%).

Processing of Blood Samples and Genotyping

DNA repair polymorphisms were selected based on minor allele frequency $>.05$ according to SNP500, putative functional importance, and/or evidence of an association with cancer risk. DNA was extracted using a phenol-chloroform method, and genotyping was conducted using TaqMan assays. Primer and probe sequences as well as assay conditions can be found on the SNP500 website (http://snp500cancer.nci.hih.gov).[18] Three hundred eighty-four-well plates were used, with each plate containing 368 study specimens and 16 controls (4 homozygous wild-type, 4 heterozygous, 4 homozygous variant positive controls, and 4 DNA-negative controls). Quality control (QC) specimens included 10–34 samples from 3 non-study participants and duplicates from 57 study subjects that were interspersed among all genotyping assays in a masked fashion. Three SNPs that were found to have replicate concordance of less than 95% were dropped from the analysis (*MLH1* rs1799977, *PRKDC* rs7003908, and *ERCC1* rs3212986). Results are reported for all other selected SNPs.

Statistical Analyses

Statistically significant departure from the Hardy–Weinberg equilibrium for controls was assessed using the χ^2 test. For each polymorphism, unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for each major tumor type, adjusted for the study matching factors of age, sex, hospital, and residential proximity to hospital. Since controls were frequency matched to all tumor types, all controls were used in the models for each tumor type. Models were run under the assumption of co-dominant (AA vs Aa vs aa) and dominant (AA vs Aa or aa) inheritance. A score test of linear trend was

Table 1. SNPs in DNA repair genes examined in the NCI Adult Brain Tumor Study

Gene symbol	Gene name	SNP ID	Base change	AA change	Chromosome location
Base excision repair					
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1	rs25487	A/G	Q399R	19q13.2
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1	rs25489	G/A	R280H	19q13.2
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1	rs1799782	C/T	R194W	19q13.2
OGG1	8-oxoguanine DNA glycosylase	rs1052133	C/G	S326C	3p26.2
POLB	polymerase (DNA directed), beta	rs3136794	A/G	—	8p11.2
Double-strand break repair					
XRCC2	X-ray repair complementing defective repair in Chinese hamster cells 2	rs3218536	G/A	R188H	7q36.1
XRCC3	X-ray repair complementing defective repair in Chinese hamster cells 3	rs861539	C/T	T241M	14q32.3
XRCC4	X-ray repair complementing defective repair in Chinese hamster cells 4	rs1805377	G/A	N298S (splice site)	5q13-q14
XRCC4	X-ray repair complementing defective repair in Chinese hamster cells 4	rs3734091	G/T	A247S	5q13-q14
NBN	Nibrin	rs1805794	G/C	E185Q	8q21
RAD51	RAD51 homolog (RecA homolog, *E. coli*) (*S. cerevisiae*)	rs1801320	G/C	5′UTR	15q15.1
RAD51	RAD51 homolog (RecA homolog, *E. coli*) (*S. cerevisiae*)	rs35722406	G/C	5′UTR	15q15.1
RAD52	RAD52 homolog (*S. cerevisiae*)	rs11226	C/T	3′UTR	12p13-p12.2
RAD52	RAD52 homolog (*S. cerevisiae*)	rs4987208	T/G	Y415Y	12p13-p12.2
BRIP1	BRCA1 interacting protein C-terminal helicase 1	rs4986764	T/C	S919P	17q22-q24
LIG4	Ligase 4	rs1805386	T/C	D568D	13q33-q34
LIG5	Ligase 4	rs1805388	C/T	T9I	13q33-q35
Nucleotide excision repair					
XPC	*Xeroderma pigmentosum*, complementation group C	rs2228001	C/A	K939Q	3p25
ERCC2 (XPD)	Excision repair cross-complementing rodent repair deficiency, complementation group 2	rs1799793	G/A	D312N	19q13.3
ERCC2 (XPD)	Excision repair cross-complementing rodent repair deficiency, complementation group 2	rs13181	A/C	K751Q	19q13.3
ERCC4 (XPF)	Excision repair cross-complementing rodent repair deficiency, complementation group 4	rs1800067	G/A	R415Q	16p13.3-p13.11
ERCC4 (XPF)	Excision repair cross-complementing rodent repair deficiency, complementation group 4	rs2020955	T/C	S662P	16p13.3-p13.12
ERCC5 (XPG)	Excision repair cross-complementing rodent repair deficiency, complementation group 5	rs17655	G/C	D1104H	13q22
RAD23B	RAD23 homolog B	rs1805329	C/T	A249V	A249V
Damage reversal					
MGMT	*O*-6-methylguanine-DNA methyltransferase	rs2308321	A/G	I143V	10q28
MGMT	*O*-6-methylguanine-DNA methyltransferase	rs230827	A/G	K178R	10q28
MGMT	*O*-6-methylguanine-DNA methyltransferase	rs12917	C/T	L84F	10q28
Mismatch repair					
MSH2	mutS homolog 2, colon cancer, nonpolyposis type 1 (*E. coli*)	rs4987188	G/A	G322D	2p22-p21
MUTYH	mutY homolog (*E. coli*)	rs3219466	C/T	5′UTR	1p34.3-p32.1

Continued

Table 1. *Continued*

Gene symbol	Gene name	SNP ID	Base change	AA change	Chromosome location
Multiple repair pathways					
APEX1	APEX nuclease	rs1130409	T/G	D148E	14q11.2-q12
LIG1	Ligase I	rs20579	C/T	5′UTR	19q13.2-q13.3
PARP1	poly (ADP-ribose) polymerase 1	rs1136410	T/C	V762A	1q41-q42
PCNA	Proliferating cell nuclear antigen	rs25406	C/T		20pter-p12
PCNA	Proliferating cell nuclear antigen	rs17352	A/C		20pter-p13
ZNF350	zinc finger protein 350	rs2278420	T/C	L66P	19q13.41
Other					
GLTSCR1	Glioma tumor suppressor candidate region gene 1	rs1035938	C/T		19q13.3

conducted for each SNP using a 3-level ordinal variable. In order to evaluate possible bias introduced by using disease controls, regression models were repeated for each SNP, excluding one major subset of disease controls at a time. For each major tumor type (glioma, meningioma, acoustic neuroma), trend *P* values from the 3-level ordinal model (36 contrasts per tumor) were adjusted for multiple comparisons using the false discovery rate,[19] with $\alpha = 0.05$.

Results

Percent agreement between the 3 non-study replicates ranged from 97% to 100% for all SNPs. Duplicate concordance was 93% for *GLSTCR1* rs1035938, 95% for *RAD2* rs11226, and ranged between 98% and 100% for all remaining SNPs. Hardy–Weinberg equilibrium in controls showed no significant deviation except for the *LIG4* rs1805388 ($P = .02$) and *XRCC3* rs861539 ($P = .04$) polymorphisms. Genotyped subjects, 1060 (75%) of the 1411 non-Hispanic white participants, were similar to all study subjects except for the lower proportion of those aged 70–90 and those with less education. Compared with controls, a larger proportion of glioma subjects were male, whereas subjects with meningioma and acoustic neuroma showed a female predominance and were, on average, older than controls (Table 2).

Results for dominant and co-dominant models for SNP main effects are presented in Table 3. The *GLTSCR* rs103598 T variant was associated with significantly increased risk of meningioma ($OR_{CT} = 3.5$, 95% CI: 1.8–7.0; $OR_{TT} = 3.6$, 95% CI: 1.2–11.2, $P_{trend} = .0006$), which persisted after controlling for multiple comparisons (adjusted *P* value = .019). Risk of meningioma was also significantly increased for the minor allele variants of *ERCC4* rs1800067 ($OR_{AG/AA} = 2.1$, 95% CI: 1.2–3.6; P_{trend} .01); *MUTYH* rs3219466 ($OR_{CT/TT} = 2.1$, 95% CI: 1.0–4.3; P_{trend} .02), and *PCNA* rs25406 ($OR_{CT/TT} = 2.1$, 95% CI: 1.3–3.5; P_{trend} .03). The *NBN* rs1805794 minor allele variant was associated with decreased meningioma risk ($OR_{CG/CC} = 0.5$, 95% CI: 0.3–0.8; P_{trend} .006). Decreased glioma risk was observed with the *XRCC1* rs1799782 variant ($OR_{CT/TT} = 0.7$, 95% CI: 0.4–1.0; P_{trend} .04). The small sample size for acoustic neuroma limited our ability to assess risk by genotype, particularly for homozygous variant genotypes. Nonetheless, the risk of acoustic neuroma was statistically significantly increased for the *ERCC2* rs1799793 ($OR_{AG/AA} = 2.1$, 95% CI: 1.2–3.7; P_{trend} .03) and *ERCC5* rs17655 ($OR_{CG/CC} = 1.8$, 95% CI 1.0–3.1; P_{trend} .05) variants and decreased for the *PARP1* rs1136410 ($OR_{AG/AA} = 0.5$, 95% CI: 0.3–1.0; P_{trend} .03). We observed no statistically significant associations at a *P*-level of $< .05$ between genotype and risk of meningioma, glioma, or acoustic neuroma for the remaining polymorphisms. Results remained very similar when major groups of disease controls were excluded from the analysis, one at a time.

Table 2. Demographic characteristics in non-Hispanic white participants: NCI Adult Brain Tumor Study, 1994–1998

Characteristic *n* (%)	Glioma		Meningioma		Acoustic neuroma		Controls	
	Genotyped (*n* = 362)	All, NH-White (*n* = 444)	Genotyped (*n* = 134)	All, NH-White (*n* = 163)	Genotyped (*n* = 69)	All, NH-White (*n* = 89)	Genotyped (*n* = 495)	All, NH-White (*n* = 715)
Sex								
Male	198 (54.7)	256 (57.7)	30 (22.4)	36 (22.1)	25 (36.2)	33 (37.1)	228 (46.1)	334 (46.7)
Female	164 (45.3)	188 (42.3)	104 (77.6)	127 (77.9)	44 (63.8)	56 (62.9)	267 (53.9)	381 (53.3)
Age at interview, years								
18–29	41 (11.3)	47 (10.6)	1 (0.8)	3 (1.8)	3 (4.4)	3 (3.4)	55 (11.1)	80 (11.2)
30–39	56 (15.5)	64 (14.4)	20 (14.9)	21 (12.9)	10 (14.5)	11 (12.4)	95 (19.2)	130 (18.2)
40–49	81 (22.4)	97 (21.9)	33 (24.6)	36 (22.1)	17 (24.6)	24 (27.0)	115 (23.2)	147 (20.6)
50–59	56 (15.5)	70 (15.8)	31 (23.1)	35 (21.5)	19 (27.5)	23 (25.8)	88 (17.8)	135 (18.9)
60–90	128 (35.4)	166 (37.4)	49 (36.6)	68 (41.7)	20 (29.0)	28 (31.5)	142 (28.7)	223 (31.2)
Mean, median age at interview	51.2 (50)	50.4 (50)	54.8 (54)	56.1 (55)	51.7 (53)	52.4 (53)	49.2 (48)	50.4 (50)

Discussion

Prior studies of brain tumors, mainly glioma, have indicated that common genetic variation in DNA repair genes might affect brain tumor risk.[6–16] Although very few prior studies have examined the risk of meningioma with DNA repair genes, there is some indication that meningioma may be more susceptible to common changes in DNA repair genes than glioma. In a previous large multicenter study that examined the risk of glioma and meningioma in 1127 polymorphisms of DNA repair genes, the top finding for meningioma, *BRIP1* rs4968451, was associated at a level of $P = 8.95 \times 10^{-6}$ (OR = 1.6, 95% CI: 1.3–1.9),[16] whereas the top finding for glioma, *CHAF1A* rs243356, was associated at a level of $P = 2 \times 10^{-4}$ (OR = 1.3, 95% CI: 1.1–1.5) despite having a larger sample size and therefore more power to detect an association.[6] Prior studies have not examined meningioma risk with respect to variation in the *GLTSCR1*, *MUTYH*, or *PCNA* genes. To our knowledge, the risk of acoustic neuroma with respect to DNA repair polymorphisms has not been examined in prior epidemiological studies.

The strongest association observed in our candidate gene study of 36 SNPs in the DNA repair pathway was the 3.5-fold increased risk of meningioma with the *GLTSCR1* rs1035938 T allele. This association remained statistically significant even after controlling for multiple comparisons. Although previous studies have not examined the risk of meningioma with the *GLTSCR1* rs1035938 polymorphism, one prior study has reported a 3-fold increased risk of oligodendroglioma with the T allele of *GLTSCR1* rs1035938 polymorphism.[14] Consistent with our results for glioma, the same study observed no association between the *GLTSCR1* rs1035938 polymorphism and risk of all glioma. Interestingly, individuals with gliomas and oligodendrogliomas with the TT genotype had better survival than CT/CC individuals.[14] *GLTSCR1*, which stands for glioma tumor suppressor candidate region 1, is highly conserved among humans, chimps, mice, and rats, suggesting that it may contain key genetic information. Data from MTN (multiple tissue Northern blot) hybridization suggest that the gene transcript is approximately 6.5 kb and exhibits moderate expression in the brain.[20] The *GLTSCR1* rs1035938 polymorphism is known to alter a CpG within the CpG island flanking the 5′ region of the gene. This may affect the transcription of *GLTSCR1* and other candidate genes in the region.[14]

The minor allele variants for *NBN* rs1805794, *ERCC4* rs1800067, *MUTYH* rs3219466, and *PCNA* rs25406 were also statistically significantly associated with meningioma in our study ($P < .05$). Associations between meningioma and gene variants in *GLTSCR1*, *MUTYH*, and *PCNA* have not been previously reported. However, our observation of increased risk with *ERCC4* rs1800067 is consistent with a statistically significant association observed in a multicenter European study of DNA repair genes and meningioma ($P = .02$), and

Table 3. ORs for DNA repair gene SNPs in non-Hispanic whites in the NCI Adult Brain Tumor Study, 1994–1998 (adjusted for age, sex, study site, distance of residence from hospital)

			Glioma						Meningioma						Acoustic neuroma					
Gene	rs number	Genotype	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value
APEX1	rs1130409	TT	93	118	—	—	—		39	118	—	—	—		18	118	—	—	—	
		GT	159	216	0.96	0.68	1.35		51	216	0.74	0.45	1.21		33	216	1.02	0.54	1.94	
		GG	71	115	0.81	0.54	1.22		24	115	0.66	0.36	1.21		10	115	0.52	0.22	1.23	
		GT/GG	230	331	0.91	0.66	1.25		75	331	0.71	0.45	1.13		43	331	0.85	0.46	1.57	
		P_{trend}						.32						.15						.17
BRIP1	rs4986764	CC	106	166	—	—	—		45	166	—	—	—		15	166	—	—	—	
		CT	168	213	1.29	0.94	1.78		50	213	0.83	0.52	1.34		38	213	1.93	0.99	3.77	
		TT	62	86	1.17	0.77	1.76		26	86	1.04	0.58	1.87		11	86	1.34	0.57	3.14	
		CT/TT	230	299	1.25	0.93	1.70		76	299	0.89	0.57	1.39		49	299	1.75	0.92	3.32	
		P_{trend}						.32	121					.97						.35
ERCC2	rs1799793	GG	140	214	—	—	—		56	214	—	—	—		22	214	—	—	—	
		AG	158	197	1.18	0.87	1.60		50	197	1.13	0.72	1.78		35	197	2.09	1.16	3.80	
		AA	41	57	1.07	0.67	1.69		17	57	1.30	0.67	2.50		8	57	1.94	0.78	4.80	
		AG/AA	199	254	1.16	0.87	1.54		67	254	1.17	0.76	1.78		43	254	2.06	1.16	3.66	
		P_{trend}						.50						.41						.03*
ERCC2	rs13181	AA	128	200	—	—	—		59	200	—	—	—		28	200	—	—	—	
		AC	171	215	1.19	0.88	1.62		54	215	0.96	0.62	1.49		29	215	1.08	0.60	1.94	
		CC	52	66	1.20	0.78	1.86		18	66	1.07	0.57	2.01		10	66	1.41	0.62	3.19	
		AC/CC	223	281	1.20	0.90	1.60		72	281	0.98	0.65	1.49		39	281	1.15	0.67	1.99	
		P_{trend}						.28						.93					1.71	.45
ERCC4	rs1800067	GG	280	405	—	—	—		96	405	—	—	—		58	405	—	—	—	
		AG	56	62	1.29	0.87	1.93		26	62	2.15	1.23	3.74		7	62	1.05	0.44	2.51	
		AA	**1**	**4**	**0.37**	**0.04**	**3.35‡**		**2**	**4**	**1.72**	**0.29**	**10.05**		**0**	**4**	**0.00**	**0.00**	**—**	
		AG/AA	57	66	1.24	0.83	1.83		28	66	2.11	1.23	3.60		7	66	0.97	0.41	2.31	
		P_{trend}						.42						.01*						.82
ERCC4	rs2020955	TT	330	443	—	—	—		121	443	—	—	—		62	443	—	—	—	
		CT	**1**	**1**	**1.12**	**0.07**	**18.51**		**0**	**1**	**0.00**	**0.00**	**—**		**0**	**1**	**0.00**	**0.00**	**—**	
		CT/TT	**1**	**1**	**1.12**	**0.07**	**18.51**		**0**	**1**	**0.00**	**0.00**	**—**		**0**	**1**	**0.00**	**0.00**	**—**	
		P_{trend}						.94						.99						.99
ERCC5	rs17655	GG	206	286	—	—	—		81	286	—	—	—		30	286	—	—	—	
		CG	123	156	1.10	0.81	1.49		37	156	0.71	0.44	1.13		30	156	1.75	0.99	3.08	
		CC	13	26	0.68	0.34	1.36		**3**	**26**	**0.49**	**0.14**	**1.72**		5	26	1.94	0.64	5.81	
		CG/CC	136	182	1.04	0.78	1.39		40	182	0.68	0.43	1.07		35	182	1.77	1.02	3.06	
		P_{trend}						.82						.08						.05*

GLTSCR1	rs1035938	CC	136	236	—	—	—		14	236	—	—	—		18	236	—	—	—	
		CT	86	177	0.84	0.60	1.18		31	177	3.50	1.76	6.99		14	177	1.26	0.59	2.70	
		TT	23	28	1.44	0.78	2.64		6	28	3.64	1.18	11.19		**3**	**28**	**1.05**	**0.26**	**4.21**	
		CT/TT	109	205	0.92	0.67	1.27		37	205	3.52	1.80	6.89		17	205	1.22	0.59	2.51	
		P_{trend}						.84						6×10^{-4}*						.69
LIG1	rs20579	CC	246	354	—	—	—		94	354	—	—	—		43	354	—	—	—	
		CT	74	87	1.20	0.84	1.72		25	87	1.04	0.61	1.77		15	87	1.13	0.58	2.20	
		TT	6	9	0.98	0.34	2.84		**2**	**9**	**0.89**	**0.17**	**4.55**		**3**	**9**	**2.60**	**0.63**	**10.74**	
		CT/TT	80	96	1.18	0.84	1.67		27	96	1.03	0.62	1.71		18	96	1.25	0.67	2.35	
		P_{trend}						.41						.96						.30
LIG4	rs1805386	TT	229	325	—	—	—		72	325	—	—	—		47	325	—	—	—	
		CT	102	132	1.13	0.82	1.55		44	132	1.28	0.81	2.03		15	132	0.63	0.33	1.20	
		CC	9	9	1.42	0.54	3.70		5	9	2.61	0.77	8.78		**2**	**9**	**1.08**	**0.20**	**5.76**	
		CT/CC	111	141	1.15	0.84	1.56		49	141	1.36	0.87	2.12		17	141	0.66	0.35	1.23	
		P_{trend}						.33						.10						.28
LIG4	rs1805388[†]	CC	241	307	—	—	—		86	307	—	—	—		42	307	—	—	—	
		CT	67	103	0.83	0.58	1.19		27	103	0.86	0.51	1.44		16	103	1.06	0.56	2.00	
		TT	11	18	0.71	0.33	1.55		5	18	1.13	0.38	3.37		**1**	**18**	**0.42**	**0.05**	**3.39**	
		CT/TT	78	121	0.81	0.58	1.14		32	121	0.90	0.55	1.45		17	121	0.97	0.52	1.81	
		P_{trend}						.21						.79						.71
MGMT	rs2308321	AA	254	362	—	—	—		103	362	—	—	—		47	362	—	—	—	
		AG	90	106	1.25	0.90	1.73		23	106	0.82	0.49	1.40		18	106	1.38	0.74	2.57	
		GG	5	9	0.77	0.25	2.38		5	9	2.77	0.80	9.54		**1**	**9**	**1.02**	**0.12**	**8.69**	
		AG/GG	95	115	1.21	0.88	1.67		28	115	0.95	0.58	1.56		19	115	1.36	0.74	2.49	
		P_{trend}						.37						.73						.38
MGMT	rs2308327	AA	250	357	—	—	—		97	357	—	—	—		47	357	—	—	—	
		AG	86	103	1.25	0.89	1.74		22	103	0.86	0.50	1.48		18	103	1.37	0.74	2.53	
		GG	6	9	0.97	0.33	2.79		**4**	**9**	**2.46**	**0.66**	**9.23**		**0**	**9**	**0.00**	**0.00**	**—**	
		AG/GG	92	112	1.22	0.88	1.70		26	112	0.97	0.58	1.61		18	112	1.27	0.68	2.34	
		P_{trend}						.30						.77						.67
MGMT	rs12917	CC	265	348	—	—	—		102	348	—	—	—		52	348	—	—	—	
		CT	77	117	0.85	0.61	1.19		23	117	0.75	0.44	1.27		12	117	0.73	0.36	1.45	
		TT	9	12	0.99	0.41	2.43		**4**	**12**	**1.18**	**0.34**	**4.08**		**2**	**12**	**1.54**	**0.29**	**8.22**	
		CT/TT	86	129	0.86	0.63	1.19		27	129	0.79	0.48	1.30		14	129	0.79	0.41	1.51	
		P_{trend}						.45						.50						.64
MSH2	rs4987188	GG	333	449	—	—	—		120	449	—	—	—		62	449	—	—	—	
		AG	9	17	0.64	0.28	1.48		**3**	**17**	**0.96**	**0.25**	**3.60**		**3**	**17**	**1.67**	**0.45**	**6.25**	
		AG/AA	9	17	0.64	0.28	1.48		**3**	**17**	**0.96**	**0.25**	**3.60**		**3**	**17**	**1.67**	**0.45**	**6.25**	
		P_{trend}						.30						.95						.45

Continued

Table 3. *Continued*

Gene	rs number	Genotype	Glioma						Meningioma						Acoustic neuroma					
			n, cases	*n*, controls	OR	LCI	UCI	*P* value	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value
MUTYH	rs3219466	CC	317	436	—	—	—		110	436	—	—	—		58	436	—	—	—	
		CT	23	31	0.99	0.56	1.75		12	31	1.82	0.85	3.92		6	31	1.34	0.51	3.50	
		TT	**1**	**2**	**0.53**	**0.05**	**6.00**		**2**	**2**	**9.38**	**0.88**	**100.52**		**0**	**2**	**0.00**	**0.00**	**—**	
		CT/TT	24	33	0.96	0.55	1.67		14	33	2.09	1.01	4.32		6	33	1.30	0.50	3.40	
		P_{trend}						.80						.02*						.63
NBN	rs1805794	GG	153	211	—	—	—		73	211	—	—	—		30	211	—	—	—	
		CG	145	213	0.94	0.70	1.27		37	213	0.46	0.29	0.74		27	213	0.87	0.49	1.54	
		CC	44	45	1.37	0.85	2.19		12	45	0.57	0.28	1.19		6	45	0.94	0.35	2.51	
		CG/CC	189	258	1.01	0.76	1.35		49	258	0.48	0.31	0.75		33	258	0.88	0.51	1.52	
		P_{trend}						.44						.006*						.73
OGG1	rs1052133	CC	218	274	—	—	—		72	274	—	—	—		38	274	—	—	—	
		CG	96	159	0.76	0.55	1.04		40	159	0.91	0.58	1.44		21	159	0.97	0.54	1.76	
		GG	21	25	1.08	0.58	2.01		9	25	1.56	0.65	3.73		**3**	**25**	**0.63**	**0.18**	**2.28**	
		CG/GG	117	184	0.80	0.60	1.08		49	184	0.98	0.64	1.52		24	184	0.92	0.52	1.62	
		P_{trend}						.33						.72						.60
PARP1	rs1136410	TT	242	312	—	—	—		89	312	—	—	—		51	312	—	—	—	
		CT	91	136	0.89	0.64	1.22		29	136	0.67	0.41	1.10		14	136	0.58	0.30	1.11	
		CC	7	16	0.59	0.24	1.48		**3**	**15**	**0.64**	**0.17**	**2.39**		**0**	**15**	**0.00**	**0.00**	**—**	
		CT/CC	98	152	0.86	0.63	1.17		32	152	0.67	0.42	1.07		14	152	0.53	0.28	1.00	
		P_{trend}						.23						.11						.03*
PCNA	rs25406	CC	112	167	—	—	—		25	167	—	—	—		19	167	—	—	—	
		CT	162	206	1.24	0.90	1.72		73	206	2.20	1.31	3.71		31	206	1.29	0.69	2.43	
		TT	56	83	1.03	0.68	1.58		22	83	1.88	0.97	3.65		14	83	1.57	0.72	3.43	
		CT/TT	218	289	1.18	0.87	1.60		95	289	2.12	1.28	3.50		45	289	1.37	0.75	2.48	
		P_{trend}						.64						.03*						.24
PCNA	rs17352	AA	234	322	—	—	—		89	322	—	—	—		39	322	—	—	—	
		AC	57	81	0.93	0.63	1.36		18	81	0.84	0.46	1.52		13	81	1.35	0.66	2.76	
		CC	8	5	2.15	0.68	6.84		**0**	**5**	**0.00**	**0.00**	**—**		**1**	**5**	**2.34**	**0.24**	**23.08**	
		AC/CC	65	86	1.00	0.69	1.44		18	86	0.80	0.44	1.45		14	86	1.39	0.69	2.80	
		P_{trend}						.70						.36						.31
POLB	rs3136794	AA	280	361	—	—	—		100	361	—	—	—		49	361	—	—	—	
		AG	56	100	0.70	0.49	1.01		21	100	0.80	0.46	1.38		16	100	1.17	0.62	2.20	
		GG	5	6	1.15	0.34	3.90		**2**	**6**	**1.25**	**0.22**	**7.23**		**0**	**6**	**0.00**	**0.00**	**—**	
		AG/GG	61	106	0.73	0.51	1.04		23	106	0.83	0.49	1.40		16	106	1.10	0.59	2.07	
		P_{trend}						.13						.57						.93

RAD23B	rs1805329	CC	227	296	—	—	—		79	296	—	—	—		36	296	—	—	—	
		CT	85	127	0.88	0.64	1.23		35	127	1.11	0.69	1.78		21	127	1.35	0.73	2.48	
		TT	11	21	0.66	0.31	1.41		**3**	**21**	**0.54**	**0.15**	**1.92**		**4**	**21**	**1.54**	**0.46**	**5.14**	
		CT/TT	96	148	0.85	0.62	1.17		38	148	1.02	0.64	1.62		25	148	1.37	0.77	2.46	
		P_{trend}						.23						.77						.28
RAD51	rs1801320	GG	281	392	—	—	—		110	392	—	—	—		57	392	—	—	—	
		CG	36	41	1.25	0.78	2.03		7	41	0.54	0.23	1.28		**1**	**41**	**0.15**	**0.02**	1.11	
		CC	**1**	**3**	**0.47**	**0.05**	**4.62**		**1**	**3**	**1.23**	**0.12**	**12.94**		**0**	**3**	**0.00**	**0.00**	—	
		CG/CC	37	44	1.20	0.75	1.92		8	44	0.58	0.26	1.32		**1**	**44**	**0.14**	**0.02**	1.02	
		P_{trend}						.57						.26						.06
RAD51	rs35722406	GG	327	443	—	—	—		119	443	—	—	—		60	443	—	—	—	
		CG	**1**	**4**	**0.33**	**0.04**	**3.05**		0	4	0.00	0.00	—		**1**	**4**	**1.94**	**0.19**	**19.88**	
		CG/CC	**1**	**4**	**0.33**	**0.04**	**3.05**		0	4	0.00	0.00	—		**1**	**4**	**1.94**	**0.19**	**19.88**	
		P_{trend}						.33						.99						.58
RAD52	rs11226	CC	102	150	—	—	—		36	150	—	—	—		17	150	—	—	—	
		CT	148	194	1.14	0.81	1.59		54	194	1.18	0.71	1.94		28	194	1.28	0.65	2.53	
		TT	65	76	1.28	0.84	1.95		27	76	1.34	0.73	2.45		10	76	0.97	0.40	2.32	
		CT/TT	213	270	1.18	0.87	1.61		81	270	1.23	0.77	1.96		38	270	1.18	0.62	2.26	
		P_{trend}						.24						.33						.95
RAD52	rs4987208	TT	331	445	—	—	—		121	445	—	—	—		62	445	—	—	—	
		GT	9	21	0.57	0.26	1.28		**3**	**21**	**0.69**	**0.19**	**2.47**		**2**	**21**	**0.85**	**0.19**	**3.92**	
		GT/GG	9	21	0.57	0.26	1.28		**3**	**21**	**0.69**	**0.19**	**2.47**		**2**	**21**	**0.85**	**0.19**	**3.92**	
		P_{trend}						.17						.57						.84
XPC	rs2228001	AA	103	132	—	—	—		44	132	—	—	—		18	132	—	—	—	
		AC	164	218	0.96	0.69	1.35		46	218	0.59	0.36	0.97		27	218	0.92	0.47	1.82	
		CC	46	66	0.84	0.52	1.34		20	66	0.85	0.44	1.63		10	66	1.53	0.63	3.72	
		AC/CC	210	284	0.93	0.68	1.29		66	284	0.65	0.41	1.03		37	284	1.04	0.55	1.98	
		P_{trend}						.49						.31						.48
XRCC1	rs25487	GG	142	205	—	—	—		56	205	—	—	—		31	205	—	—	—	
		AG	164	201	1.20	0.88	1.62		62	201	1.11	0.71	1.72		30	201	0.95	0.54	1.67	
		AA	44	72	0.84	0.54	1.31		14	72	0.73	0.37	1.44		6	72	0.54	0.21	1.38	
		AG/GG	208	273	1.10	0.82	1.46		76	273	1.01	0.67	1.53		36	273	0.84	0.49	1.44	
		P_{trend}						.87						.60						.27
XRCC1	rs25489	GG	312	417	—	—	—		115	417	—	—	—		57	417	—	—	—	
		AG	28	48	0.79	0.48	1.30		7	48	0.44	0.19	1.02		8	48	1.08	0.47	2.49	
		AA	0	1	5.49	0.00	—		**1**	**1**	**3.01**	**0.15**	**60.74**		**0**	**1**	**0.00**	**0.00**	—	
		AG/GG	28	49	0.77	0.47	1.27		8	49	0.49	0.22	1.09		8	49	1.06	0.46	2.44	
		P_{trend}						.26						.13						.93

Continued

Table 3. *Continued*

Gene	rs number	Genotype	Glioma						Meningioma						Acoustic neuroma					
			n, cases	*n*, controls	OR	LCI	UCI	*P* value	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value	*n*, cases	*n*, controls	OR	LCI	UCI	*P* value
XRCC1	rs1799782	CC	304	394	—	—	—		104	394	—	—	—		51	394	—	—	—	
		CT	38	73	0.66	0.43	1.01		18	73	0.90	0.50	1.62		14	73	1.75	0.89	3.44	
		TT	0	1	0.00	0.00	—		0	1	0.00	0.00	—		**0**	**1**	**0.00**	**0.00**	—	
		CT/TT	38	74	0.65	0.42	0.99		18	74	0.89	0.50	1.60		14	74	1.70	0.86	3.33	
		P_{trend}						.04*						.67						.16
XRCC2	rs3218536	GG	285	395	—	—	—		106	395	—	—	—		57	395	—	—	—	
		AG	56	70	1.12	0.76	1.65		14	70	0.65	0.35	1.24		8	70	0.78	0.35	1.75	
		AA	**1**	**3**	**0.55**	**0.06**	**5.44**		**1**	**3**	**1.02**	**0.09**	**11.13**		**0**	**3**	**0.00**	**0.00**	—	
		AG/GG	57	73	1.10	0.75	1.61		15	73	0.67	0.36	1.24		8	73	0.75	0.33	1.67	
		P_{trend}						.72						.24						.42
XRCC3	rs861539†	CC	135	185	—	—	—		47	185	—	—	—		24	185	—	—	—	
		CT	162	208	1.10	0.81	1.50		70	208	1.31	0.84	2.06		31	208	1.16	0.64	2.12	
		TT	53	86	0.89	0.59	1.35		15	86	0.66	0.34	1.28		11	86	1.00	0.45	2.21	
		CT/TT	215	294	1.04	0.78	1.39		85	294	1.12	0.73	1.71		42	294	1.12	0.64	1.96	
		P_{trend}						.80						.54						.89
XRCC4	rs1805377	GG	261	347	—	—	—		98	347	—	—	—		54	347	—	—	—	
		AG	71	115	0.85	0.60	1.20		21	115	0.69	0.40	1.18		11	115	0.59	0.29	1.20	
		AA	8	7	1.57	0.55	4.47		**2**	**7**	**1.14**	**0.22**	**5.98**		**0**	**7**	**0.00**	**0.00**	—	
		AG/GG	79	122	0.89	0.64	1.24		23	122	0.71	0.42	1.20		11	122	0.56	0.27	1.13	
		P_{trend}						.72						.28						.09
XRCC4	rs3734091	GG	326	436	—	—	—		116	436	—	—	—		62	436	—	—	—	
		GT	8	12	0.86	0.34	2.17		**2**	**12**	**0.71**	**0.14**	**3.56**		**1**	**12**	**0.55**	**0.06**	**4.68**	
		GT/GG	8	12	0.86	0.34	2.17		**2**	**12**	**0.71**	**0.14**	**3.56**		**1**	**12**	**0.55**	**0.06**	**4.68**	
		P_{trend}						.76						.67						.58
ZNF350	rs2278420	TT	242	338	—	—	—		85	338	—	—	—		41	338	—	—	—	
		CT	88	120	1.04	0.75	1.44		35	120	1.19	0.75	1.91		23	120	1.81	1.01	3.24	
		CC	13	13	1.42	0.64	3.16		**4**	**13**	**1.34**	**0.40**	**4.53**		**1**	**13**	**0.70**	**0.08**	**5.85**	
		CT/CC	101	133	1.08	0.79	1.47		39	133	1.21	0.77	1.90		24	133	1.70	0.96	3.01	
		P_{trend}						.50						.40						.15

*Significant at *P* value of <0.05.
†Controls not in Hardy–Weinberg equilibrium.
‡Estimates based on the number of exposed cases or controls <5 likely to be unstable, and given in boldface.

several SNPs in the *NBN* gene were found to be of borderline significance in that same study.[16]

Only one SNP was associated with glioma at $P < .05$, *XRCC1* rs1799782. Although previous studies have not reported on this particular polymorphism, 2 other SNPs in the *XRCC1* gene (rs3213266 and rs2854496) were associated with glioma risk in a multicenter study of glioma and DNA repair.[6] No other SNPs in *XRCC1* were associated with glioma risk in this or a previous study.[9] Our study results did not replicate previously reported findings of statistically significant or borderline associations for *ERCC2* rs13181 and glioma[13] or *XRCC1* rs25487 and glioma.[11]

To our knowledge, this is the first study to examine the risk of acoustic neuroma with respect to common variants in DNA repair genes. Given the relatively small sample size for acoustic neuroma, we underscore the exploratory nature of the findings for this tumor. We found an elevated risk of acoustic neuroma with the *ERCC2* rs1799793 and *ERCC5* rs17655 variants and decreased risk for the *PARP1* rs1136410 minor allele variant. Although these variants have not been examined previously in the context of acoustic neuroma, *ERCC2* has been reported to be down-regulated in astrocytoma compared with normal brain tissue,[21] and other polymorphisms in *ERCC2* have been associated with meningioma,[15] oligodendroglioma,[14] and certain subsets of glioma.[13] The C allele of *ERCC5* rs17655, although not associated with glioma or meningioma risk in a previous study,[6,16] has been associated with a borderline main effect association with breast cancer risk in previous studies,[22–24] with some suggestion that individuals carrying the C allele variant of this SNP are more susceptible to the effects of ionizing radiation.[24] *PARP1* rs1136410 was not associated with glioma or meningioma risk in one previous study,[6,16] but a small study in French patients reported that 21 rare genetic variants of *PARP1*, including rs1136410, were detected in 11% of patients with breast cancer.[25]

Our study had adequate statistical power to detect moderate to strong main effects ($OR \geq 1.5$) of common genetic polymorphisms for glioma and meningioma. Other strengths include standardized genotyping, high reproducibility of the genotyping results in most of the QC samples, and controls in Hardy–Weinberg equilibrium for all but 2 polymorphisms. Given that deviation from Hardy–Weinberg equilibrium was not extreme ($P < .01$) for either of these polymorphisms and that we observed no significant associations for the 2 SNPs in question, this is unlikely to affect our results. Rapid ascertainment of brain tumor cases and blood collection close to the date of diagnosis reduced the possibility that survival bias affected our results. Although there is the possibility of bias introduced by the use of hospital controls, results of the analyses were very similar after excluding major groups of disease controls, one at a time, suggesting that bias is unlikely to completely explain the findings.

Nevertheless, we underscore the need for replication of our findings given the false-positive reports frequently generated in genetic association studies, the possibility that the notable SNPs are actually in linkage disequilibrium with other causally relevant polymorphisms, and the relatively low duplicate concordance rate for *GLSTCR* rs1035938. While non-participation in the blood draw was higher among controls than cases, we believe that this is unlikely to be related to genotype, and thus unlikely to bias our results. Our results for acoustic neuroma are limited by the small sample size for this tumor.

Our findings suggest that *GLTSCR1*, *NBN*, and *ERCC4* are especially promising candidate genes to examine in terms of meningioma risk. Other genes of interest are *MUTYH* and *PCNA* in terms of meningioma risk, *XRCC1* for glioma, and *ERCC2*, *ERCC5* rs17655 and *PARP1* for acoustic neuroma. Replication of these results in large consortial studies of brain tumors is needed.

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