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Short Communication

Association of an *ERCC1* Polymorphism with Adult-Onset Glioma[1]

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Abstract

Gliomas include several histologically distinct types of tumors whose molecular profiles suggest different etiologies. Because the ERCC1 protein is essential for nucleotide excision repair and influences genomic instability, polymorphisms in *ERCC1* may play a role in human tumors. We determined the presence of the *A versus C* polymorphism at nucleotide 8092 of *ERCC1* using a single-strand conformational polymorphism assay and DNA sequencing in adults with glioma and controls from a population-based study. Among 318 alleles from 159 controls, 27% (86) were *A* and 73% were *C*. Prevalences of the *CC* genotype were 51% (81 of 159), 48% (30 of 62), 63% (20 of 32), and 82% (23 of 28) for controls and subjects with glioblastoma multiforme, astrocytoma, and oligoastrocytoma, respectively (Fisher's exact $P = 0.009$). The age-adjusted odds ratio for genotype *CC* in all cases *versus* controls was 1.4 (95% confidence interval, 0.9–2.3), whereas that for subjects with oligoastrocytoma *versus* controls was 4.6 (95% confidence interval, 1.6–13.2). The median age at diagnosis was 46 years for glioma patients with the *CC* genotype compared with 54 years for patients with the *AA* or *AC* genotype ($P = 0.04$). This is the first study to report a significant association of a polymorphism in *ERCC1* with the risk of brain tumors. This *A/C* polymorphism, which may affect mRNA stability for ERCC1, also results in an amino acid substitution of lysine to glutamine in a recently described nucleolar protein (ASE-1) and T-cell receptor complex subunit CD3ϵ-associated signal transducer (CAST). This finding, if confirmed in other series, may provide a foundation on which to study novel mechanisms of carcinogenesis in subsets of glioma.

Introduction

An abnormal response to DNA damage resulting from endogenous or exogenous agents may contribute to genetic alterations leading to malignancy (1, 2). A wide variety of endogenous and exogenous agents cause various types of DNA damage. In the case of human brain tumors, the data on non-inherited factors from epidemiological studies designed to identify risk factors for brain tumor development are controversial. Although previous epidemiological studies indicate glioma was more common in men, in older people, and in people of white race (3), specific exposures or causative environmental agents have not been consistently identified, with the exception of therapeutic irradiation to the head (4–6), which being a relatively rare exposure, probably accounts for a relatively small proportion of cases.

Genetic factors that contribute to cancer susceptibility include both rare, highly penetrant, dominant mutations as well as more common genetic polymorphisms that influence individual response to environmental exposures. Genetic polymorphisms probably have an important role in determining cancer susceptibility and are the subject of intensive investigation for various cancer sites (7). Genetic polymorphisms are usually less penetrant than dominant mutations seen in retinoblastoma, Wilms' tumor, and cancers of the Li-Fraumeni syndrome but are important to study because they have much higher prevalence and thus may have higher attributable risk. In our population based series of nearly 500 adults with glioma, only 4 patients (<1%) had conditions known to genetically predispose to glioma (8). Given the important roles of genetic polymorphisms and DNA repair pathways in predisposition to malignancies, it is thus conceivable that polymorphisms in DNA repair genes that reduce activities of DNA repair pathways might predispose individuals to malignancies.

Here we investigated a recently discovered polymorphism in the 3′-untranslated region of ERCC1 (9), a subunit of the nucleotide excision repair complex. That no humans with a defect in *ERCC1* have been identified and that there is no known amino acid sequence altering DNA polymorphism for this gene indicate tight control through evolution and imply essential functions for viability. ERCC1, as well as XPA protein (xeroderma pigmentosum complementation group A), have been shown to be absolutely required for the incision step of nucleotide excision repair (10). Cells from *ERCC1*-deficient mice show increased genomic instability and a reduced frequency of S-phase-dependent illegitimate chromosome exchange and signs of premature aging in addition to a repair-deficient phenotype (11). Therefore, ERCC1 may be important in repairing DNA damage (removal of DNA adducts and rejoining of double-strand DNA breaks caused by X-ray irradiation) that may be important for the development of brain tumors. Furthermore, among xeroderma pigmentosum patients <40 years of age with internal cancer, there was a dispropor-

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Table 1 Comparison of the study group included in *ERCC1* genotype analysis with the overall study population of brain tumor cases and controls in the San Francisco Bay Area Adult Glioma Study, 1991–1995[a]

Factor	Total study population		ERCC1 study subset[b]	
	Cases (n = 476)	Controls (n = 462)	Cases (n = 122)	Controls (n = 159)
Gender				
Female	204 (43)	209 (45)	47 (39)	73 (46)
Male	272 (57)	253 (55)	75 (61)	86 (54)
Age (yr)	54.2 ± 0.8	53.7 ± 0.8	49.6 ± 1.3	53.2 ± 1.2
Diagnosis by cell type[c]				
Glioblastoma multiforme	281 (67)		62 (51)	
Astrocytoma[d]	89 (21)		32 (26)	
Oligoastrocytoma	47 (11)		28 (23)	
Race (white)	402 (84)	396 (86)	122 (100)	159 (100)

[a] Data are expressed as No. (%) and mean ± SE.
[b] Whites only.
[c] Percentages shown are percent of 417 tumors with astrocytic component.
[d] Includes anaplastic astrocytoma.

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tionate representation of malignant neoplasm of the brain and oral cavity compared with United States whites <40 years of age (12), supporting the idea that excision repair could be important in neuro-oncogenesis.

In this report, we examine an *A*/*C* polymorphism at 8092 of *ERCC1* (GenBank accession no. M63796) described by Shen *et al.* (9), which may affect mRNA stability, for its possible association with adult glioma.

Materials and Methods

Subjects. Cases and controls for this study were drawn from the San Francisco Bay Area adult glioma study discussed in detail elsewhere (8). We ascertained 492 incident glioma cases (ages >20 years) from August 1991 to April 1994 in six San Francisco Bay Area counties through the Northern California Cancer Center's rapid case ascertainment service. Uniform neuropathology review indicated that four cases were not glioma and that specimens could not be reviewed for 12 subjects. Thus, the parent study includes 476 cases. Four hundred sixty-two controls were contacted through a random digit dialing technique and were frequency-matched for gender, ethnicity, and age (8). We began collecting blood specimens part way through the study (13, 14), and we obtained blood from 187 cases with pathology review and 171 controls. Only white cases and controls were included in genotyping *ERCC1* because of ethnic differences in the distribution of polymorphisms (15–17) and because 84% of cases were white. The parent study consisted of 164 white controls and 161 white cases, of whom only the 129 with an astrocytic component, *i.e.,* diagnoses of glioblastoma, astrocytoma (astrocytoma and anaplastic astrocytoma), or oligoastrocytoma, were further considered. Of these subjects, DNA was insufficient for PCR amplification for two subjects with astrocytoma, five with glioblastoma, and five controls. Thus, 159 controls and 122 cases of white ethnicity were included in the present studies.

Genotyping of *ERCC1* Polymorphism. PCR-SSCP[3] assay and DNA sequencing were used to determine the frequency of the polymorphisms. The use of SSCP as a method for genotyping polymorphisms has been described (15), and we also have used this method of genotyping successfully in other polymorphic markers we are studying in the laboratory. Briefly, oligonucleotide primers 5′-TGAGCCAATTCAGCCACT-3′ and 5′-TAGTTCCTCAGTTTCCCG-3′ for PCR amplification of 255-bp fragments were synthesized by Operon Technology Inc. (Alameda, CA). PCR products were generated in a 30-μl reaction mixture, including 50 ng of DNA, 20 μM deoxynucleotide triphosphate, 10 mM Tris-HCl (pH 9.0), 1.5 mM $MgCl_2$, 0.1% Triton X-100, 10 pmol of each primer, 1 unit of Taq (Perkin-Elmer Cetus, Norwalk, CT), and 0.2 μCi of $[^{33}P]$dCTP (DuPont New England Nuclear, Boston, MA). The PCR reaction was carried out using 35 cycles (94°C for 30 s, 60°C for 30 s, and 72°C for 1 min) on a Perkin-Elmer 9600 thermal cycler. Ten μl of PCR product were diluted with 90 μl of 0.1% SDS-10 mM EDTA buffer. The diluted sample was then mixed 1:1 with gel-loading buffer solution from United States Biochemical Corp. (Cleveland, OH) and heated at 94°C for 4 min. The sample was kept on ice and loaded immediately onto 6% nondenatured polyacrylamide gel supplemented with 10% glycerol. The gel was run at room temperature for 20 h and exposed for 16 h for autoradiographic detection of bands. Direct sequencing of PCR fragments was performed on representative DNA samples of different migration patterns on SSCP gel to determine the corresponding DNA sequences using the dsDNA cycle sequencing system from Life Technologies (Gaithersburg, MD).

Statistical Analyses. ORs were computed for dichotomous factors, and means or medians were compared for continuous data. Then, 95% CIs on ORs or mean differences were used to assess precision of the estimates. We used a Fisher's exact test to compare the prevalence of *CC versus AC* or *AA* genotypes among controls and the three histological types, glioblastoma multiforme, astrocytoma, and oligoastrocytoma (18). Logistic regression was used to estimate unadjusted and age-adjusted ORs for having the *CC* genotype in each histological category *versus* controls. Wilcoxon tests were used to compare median ages of diagnosis among those with and without the *CC* genotype regardless of histological type and within each histological type. Statistical analyses were conducted with SAS software for personal computers (19).

Results

We compared the prevalence of the *ERCC1* 8092 polymorphism in 122 Caucasian adult glioma patients with 159 controls. Table 1 compares the demographic characteristics and tumor histology of cases in this genotyping study group with

[3] The abbreviations used are: SSCP, single-strand conformational polymorphism; OR, odds ratio; CI, confidence interval; ASE-1, antisense of ERCC1; CAST, CD3ϵ-associated signal transducer.

Table 2 Frequencies of *ERCC1* genotypes in white brain tumor patients and controls, stratified by tumor histopathology in the San Francisco Bay Area Adult Glioma Study, 1991–1995[a]

Group	*ERCC1* Genotypes		
	AA	*AC*	*CC*[b]
Control (n = 159)	8 (5)	70 (44)	81 (51)
All cases (n = 122)	6 (5)	43 (35)	73 (60)
Glioblastoma multiforme (n = 62)	5 (8)	27 (44)	30 (48)
Astrocytoma (n = 32)	1 (3)	11 (34)	20 (63)
Oligoastrocytoma (n = 28)	0	5 (18)	23 (82)

[a] Data are expressed as No. (%).
[b] P = 0.009 by Fisher's exact test that the frequencies of genotype *CC* are the same in controls and in the three patient groups.

the overall parent study population. The mean age of glioma cases in the ERCC1 study group was somewhat younger than that of the overall study population (49.6 years old *versus* 53.2 years old). The percentage of glioblastoma multiforme in the ERCC1 study group was lower (51% *versus* 67%), whereas the percentages of astrocytoma and oligoastrocytoma in the ERCC1 study group were higher (26% *versus* 21% and 23% *versus* 11%, respectively) than among cases with an astrocytic component in the parent study population. These factors are attributed to the fact that blood samples were collected (at times of up to 6 months) after the interview and reflect the poorer survival of the older patients and patients with glioblastoma multiforme. The case group had a slightly higher percentage of males than the control group (61% *versus* 54%), but this was not statistically significant.

The frequency distributions of the *ERCC1* genotypes *AA*, *AC*, and *CC* for cases, by histopathology, and controls are shown in Table 2. Among 159 controls, the allele frequencies were 27% (86 of 318) for *A* and 73% (232 of 318) for *C*. The frequency of *ERCC1* genotype *CC versus AA* or *AC* significantly differed among the controls and patients with glioblastoma multiforme, astrocytoma, and oligoastrocytoma (P = 0.009; Fisher's exact test of the 4×2 contingency table) and among the three subgroups of patients (P = 0.009; Fisher's exact test of the 3×2 contingency table). Prevalence of the *CC* genotype was similar in glioblastoma multiforme patients and controls (48% *versus* 51%); the *CC* genotype was more common in patients with astrocytoma (63%) and much more common in patients with oligoastrocytoma (82%). The unadjusted and age-adjusted ORs of the *CC* genotype in oligoastrocytoma subjects *versus* controls were 4.4 (95% CI, 1.6–12.2) and 4.6 (95% CI, 1.6–13.2), respectively (Table 3). In analysis of ERCC1 genotype *CC versus AA* or *AC* among patients only, the age-adjusted ORs of the *CC* genotype for patients with oligoastrocytoma *versus* glioblastoma was 4.2 (95% CI, 1.2–14.4) and for patients with astrocytoma *versus* glioblastoma was 1.6 (95% CI, 0.6–4.2); the age-adjusted OR for the *CC* genotype among patients with oligoastrocytoma *versus* either astrocytoma or glioblastoma was 3.3 (95% CI, 1.1–10.4).

Because inherited genetic factors may lead to an earlier age of onset of disease, we compared median ages at diagnosis for glioma cases with *CC versus AA*/*AC* genotypes (Table 3). Over all histologies, cases with the *CC* genotype were significantly younger than cases with *AA*/*AC* genotypes (P = 0.04). Within each of the three histological categories, the median ages at diagnosis of those with the *CC* genotype tended to be the same or younger than those with the *AA* or *AC* genotypes, but none of the differences approached statistical significance. Much of the variation in age at diagnosis of glioma occurs between histological types. That is, the median age at diagnosis for astrocytoma patients was ~15 years younger than those with glioblastoma, and for oligoastrocytoma patients, it was ~20 years younger than for those with glioblastoma. Thus, our results indicated that the *CC* genotype appears to be associated with oligoastrocytoma, the histological subtype of glioma (of the three considered here) with the youngest median age at onset.

Discussion

Our main finding was that the *ERCC1* nucleotide 8092 genotype *CC* was statistically significantly more common among patients with oligoastrocytoma compared with controls. The *CC* genotype also was somewhat more common in patients with astrocytoma compared with controls, but the genotype frequency was similar in patients with glioblastoma and controls. The potential involvement of the constitutive *ERCC1* variant with histological subtypes of glioma is consistent with multiple pathogenic mechanisms of these tumors. For example, genetic alteration models from previous molecular genetic studies of tumor DNA from glioma patients indicated the existence of at least two types of glioblastoma multiforme (20). It is thought that one type of glioblastoma multiforme results from progression from lower grades of astrocytomas, whereas the other type is *de novo* in nature. Because this series of adult glioma cases was collected through reports of only newly diagnosed cases, glioblastoma tumors of the *de novo* type likely predominate in this series. Such *de novo* tumors would be likely to have different genetic alterations than the astrocytomas from which the other type of glioblastoma multiforme may be derived. If our hypothesis is correct, we might predict that subjects with glioblastoma multiforme that progressed from lower grade tumors would have a higher prevalence of the *ERCC1 CC* genotype than the present series of glioblastoma multiforme cases.

The other interesting finding was that glioma patients with the *CC* genotype had an earlier median age at diagnosis than glioma patients with *AA* or *AC* genotypes. Although interpretation of these results is complicated by the differing median ages at onset for the different histological types of gliomas, the *CC* genotype is most frequent in those subjects with oligoastrocytoma, the histological type with the earliest median age at onset. The pattern of differences in age at diagnosis in this study is similar to that expected based on population figures. For example, the Central Brain Tumor Registry of the United States reports mean ages of diagnosis for glioblastoma, anaplastic astrocytoma, diffuse astrocytoma, and oligoastrocytoma for the period 1990–1994 of 62, 50, 47, and 40 years, respectively (21). Because survival from glioma decreases with age, blood samples were obtained somewhat disproportionately from younger patients; thus, with this sample, we cannot completely rule out the possibility of a role for the *ERCC1 CC* genotype in progression or survival *versus* etiology. It would be of interest to see if this polymorphism is associated with early onset in other cancer sites.

DNA damage responses play a central role in neoplastic transformation and are involved in both mechanisms identified as potential risk factors for brain tumors. ERCC1 may be of particular importance because it may be involved in both removal of DNA adducts caused by nitroso-compounds and rejoining of double-strand DNA breaks caused by X-ray irradiation that are important for development of brain tumors. The data presented in this study is the first to show an association of a polymorphism in *ERCC1* with the risk of brain tumor. Despite the relatively small sample sizes, the highly statistically signif-

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Table 3 Numbers and median ages of *ERCC1* genotypes *AA/AC versus CC* in white brain tumor patients and controls, stratified by tumor histopathology in the San Francisco Bay Area Adult Glioma Study, 1991–1995

Group	Genotypes and median ages		ORs	
	No. of *AA/AC* (median age)[a]	No. of *CC* (median age)	OR (95% CI)	Age-adjusted OR (95% CI)
Control (n = 159)	78 (51 yr)	81 (55 yr)	1.0[b]	
All cases (n = 122)	49 (54 yr)	73 (46 yr)[c]	1.4 (0.9–2.3)	1.4 (0.9–2.3)
Glioblastoma multiforme (n = 62)	32 (58 yr)	30 (58 yr)[c]	0.9 (0.5–1.6)	0.9 (0.5–1.6)
Astrocytoma (n = 32)	12 (43 yr)	20 (41 yr)[c]	1.6 (0.7–3.5)	1.7 (0.7–3.7)
Oligoastrocytoma (n = 28)	5 (39 yr)	23 (33 yr)[c]	4.4 (1.6–12.2)	4.6 (1.6–13.2)

[a] Age is age at diagnosis for cases and at interview for controls.
[b] Referent group.
[c] P comparing median ages at diagnosis for those with *AA/AC versus CC* genotypes from the Wilcoxon test were 0.04, 0.6, 0.7, and 0.9 for all cases, glioblastoma, astrocytoma, and oligoastrocytoma, respectively.

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icant result suggests both the need to confirm this finding in larger series of glioma cases and controls and to extend this line of investigation to polymorphisms of other DNA repair genes.

There is little other information on this polymorphism with which to compare our results. The *A* allele frequency of 27% (86 of 318) found for controls in this study is higher than the 4% observed in an initial study by Shen *et al.* (9) among 12 individuals (Fisher's exact $P = 0.02$).

Because no functional difference has yet been described for the *ERCC1* nucleotide 8092 polymorphism, it will be of interest to examine its functional consequences on confirmation of the importance of this polymorphism on larger sample sizes. If corroborated, these findings will provide a foundation on which to study this novel carcinogenesis mechanism in subsets of glioma. Further study will be necessary to determine whether the *ERCC1 CC* polymorphism affects levels of mRNA, selection of polyadenylation sites, alternative splicing of transcripts, and association with large polysomes (enhanced translation activities) as suggested by studies of *ERCC1* gene structure (22, 23).

There is a second potentially intriguing aspect of functional studies involving this polymorphism. In the course of characterizing *ERCC1*, van Duin *et al.* (24) found that its 3′ terminus overlapped with the 3′ end of another gene, designated *ASE-1*. This exceptional type of gene overlap was conserved in the mouse and even in the yeast ERCC1 homologue, RAD10, suggesting an important biological function. The *A*/*C* polymorphism in the 3′-untranslated region of *ERCC1* was located in the coding region of *ASE-1*. The ASE-1 is a nucleolar protein localized to fibrillar centers of the nucleolus and nucleolus organizer region of mitotic chromosomes (25). ASE-1 was found to contain two domains that are present in a number of nucleolar specific proteins: a glycine-, arginine-, and phenylalanine-rich putative nucleotide interaction domain and an alternating basic and acidic region (25). The polymorphism results in a change of amino acid 504 (AAG to CAG; lysine to glutamine) in the alternating charged basic/acidic region. This change results in a reduction of a lysine/arginine basic repeat at amino acid 500–504 (Lys-Lys-Arg-Lys-*Lys versus* Lys-Lys-Arg-Lys-*Gln*). This amino acid change may also affect CAST protein, a molecule encoded by the same gene as *ASE-1* but under different names. CAST serves as a component of preformed T-cell receptor complexes and transduces signals on T-cell receptor activation (26).

In conclusion, these results show that oligoastrocytoma patients are highly statistically significantly more likely than controls to have the *CC* genotype at *ERCC1* nucleotide 8092. Although no functional difference has been described for this polymorphism, confirmation of the importance of this *ERCC1* polymorphism in another series of subjects will open lines of investigation that may point to a novel mechanism of carcinogenesis in subsets of glioma. Furthermore, this polymorphism results in an amino acid substitution in the protein formed by the newly described gene *ASE-1*/*CAST* (24, 26). Further investigations may add important information for individual and population risk estimation as a result of identification of a polymorphism associated with brain tumor susceptibility. They also might eventually point to gene-environmental interactions that could provide important information on risk avoidance of environmental exposure for people with susceptible polymorphisms.

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