Short Communication

The Common D302H Variant of CASP8 Is Associated with Risk of Glioma

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Abstract

Caspase 8 (CASP8) is a key regulator of apoptosis or programmed cell death, and, hence, a defense against cancer. We tested the hypothesis that the CASP8 polymorphism D302H influences risk of glioma through analysis of five series of glioma case patients and controls ($n = 1,005$ and 1,011, respectively). Carrier status for the rare allele of D302H was associated with a 1.37-fold increased risk (95% confidence interval, 1.10-1.70; $P = 0.004$). The association of CASP8 D302H with glioma risk indicates the importance of inherited variation in the apoptosis pathway in susceptibility to this form of primary brain tumor. (Cancer Epidemiol Biomarkers Prev 2008;17(4):987–9)

Introduction

Glioma accounts for ~80% of malignant primary brain tumors (1). The rare susceptibility syndromes neurofibromatosis, tuberous sclerosis, retinoblastoma, Li-Fraumeni, Turcot’s, and Gorlin’s (1, 2) do not however account for the 2-fold familial risk (1, 3). Much of this genetic risk is likely to be explained by combinations of low penetrance variants, some of which may be common and, hence, detectable through association analyses. Caspase 8 (CASP8) is a regulator of apoptosis, an essential defense mechanism against hyperproliferation and malignancy. Hypermethylation of CASP8 has been linked with glioblastoma multiforme relapse (4), suggesting that CASP8 may have a role in the development of glioma. Recently, polymorphic variation in CASP8 has been reported to influence the risk of a number of cancers (5, 6). We tested the hypothesis that the single nucleotide polymorphism rs1045485 in CASP8, which generates the substitution D302H, influences glioma risk.

Materials and Methods

Our study was based on five case control studies that contributed to the Interphone Study, an international multicenter epidemiologic case control study of primary brain tumors coordinated by the IARC (7). Cases had primary gliomas [International Classification of Diseases (ICD), 10th revision, code C71; ICD-O, 2nd ed., codes 9380-9384, 9390-9411, 9420-9451, 9505] and were ages 18 to 69 y. Controls were randomly selected from population registers or general practitioner records. Eight individuals were excluded from analysis due to non-European ethnicity or unclear identity.

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The study was approved by relevant ethics committees in accordance with the tenets of the Declaration of Helsinki, and informed consent was obtained from subjects.

The distributions by sex and age of the case patients and controls in each of the five case-control series were approximately frequency matched and were not statistically different [specifically, United Kingdom North cases (230 male; 140 female; mean age at diagnosis, 49 y; SD, 12; controls: 231 male; 138 female; mean age, 51 y; SD, 11), United Kingdom Southeast cases (140 male; 71 female; mean age at diagnosis, 42 y; SD, 11; controls: 142 male; 72 female; mean age, 47 y; SD, 9), Sweden cases (121 male; 76 female; mean age at diagnosis, 50 y; SD, 13; controls: 121 male; 76 female; mean age, 52 y; SD, 12), Denmark cases (71 male; 57 female; mean age at diagnosis, 48 y; SD, 12; controls: 74 male; 57 female; mean age, 51 y; SD, 12), and Finland cases (56 male; 43 female; mean age at diagnosis, 48 y; SD, 12; controls: 37 male; 63 female; mean age, 53 y; SD, 12)]. Of the 1,005 cases, 451 had been diagnosed with glioblastoma (ICD10 codes 9440-1), 329 with astrocytoma (ICD10 codes 9400-30), 106 with oligodendroglioma (ICD10 codes 9450-1), and 119 with other glioma subtypes.

Genotyping was done using the Illumina customized GoldenGate Array (Illumina, Inc.); details available on request. Statistical analyses were undertaken using R\textsuperscript{11} and STATA Software (StataCorp). Due to low frequencies for the rare homozygote genotype, we combined the rare homozygote and heterozygote genotypes. As age and sex did not significantly alter risk estimates, we restricted adjustment to study centers. Unconditional logistic regression was used to calculate odds ratio (OR) and associated 95% confidence intervals (CI), and overall results for all five studies were calculated using logistic regression adjusted for study center and the Mantel-Haenszel method.

Results and Discussion

Of the 2,024 DNA samples submitted for genotyping, genotypes were obtained for 957 of 1,005 cases (95.2%) and 976 of 1,013 controls (96.3%). There was no evidence of any systematic bias in genotyping as single nucleotide polymorphism call rates were not significantly different between all cases and controls or between each of the 5 case control studies (93.5%-97.3%). Furthermore, there was no evidence of population stratification as the genotype distribution satisfied the criterion for Hardy-Weinberg equilibrium in each control series.

Possession of 302H was associated with risk of glioma in the five case control series, albeit nonsignificantly in four (Fig. 1). When the data were combined, carrier status for 302H was significantly associated with glioma risk (OR, 1.37; 95% CI, 1.10-1.70; \( P = 0.004 \); results were identical using logistic regression adjusting for study center or Mantel-Haenszel method). There was no evidence of heterogeneity between studies (\( P_{\text{het}} = 0.59; I^2 = 0.0\% \); Fig. 1). Sequentially omitting each of the case control series allowed us to determine the influence of individual series on the pooled estimate and served as a measure of the robustness of findings. Notably, after omitting data from the Finnish study, the risk of glioma associated with carrier status for 302H remained significant (OR, 1.31; 95% CI, 1.05-1.64; \( P = 0.018 \)).

To our knowledge, only one previous study, based on analysis of 382 cases and 550 controls, has examined the association between D302H and risk of glioma (8).

\textsuperscript{11}http://www.r-project.org/
Although nonsignificant, a higher frequency of the 302H genotype in cases was observed (Fig. 1). This finding is consistent with our results, providing increased support for the tenet that variation in CASP8 defined by D302H is a determinant of risk. On the basis of our data and the earlier study, 302H is associated with a 1.31-fold increased risk of glioma (95% CI, 1.09-1.56; \( P = 0.003 \); \( P_{\text{het}} = 0.65 \); \( I^2 = 0.0\% \); Fig. 1).

Our observation that this single nucleotide polymorphism influences risk of glioma invites speculation that the variant has a generic effect on cancer susceptibility. In contrast to breast cancer, where the 302H allele is protective (5), in glioma, it seems to be associated with an elevated risk. The cell lineage of glioma is, however, embryologically different from breast cancer. Nongenetic factors are likely to have entirely different mechanisms affecting tumorigenesis in concert with genotype; such differences have recently been documented for the CHEK2 I157T variant with the rare allele, conferring an elevated breast cancer risk but a protective effect on lung cancer (9). Although D302H may be in linkage disequilibrium with an unknown causative variant, the polymorphic site is evolutionarily conserved between mouse and man, suggesting a direct effect on CASP8. As the D302H change localizes to the external surface of the expressed protein, it is conceivable that it influences autoprocessing of procaspase-8 molecules or CASP8 interactions with the antiapoptotic FADD-like apoptosis regulator.

Our observations strengthen the hypothesis that low penetrance variants contribute to the inherited risk of glioma.

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References

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