Familiality in brain tumors

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ABSTRACT

Background: Familiality in brain tumors is not definitively substantiated.

Methods: We used the Utah Population Data Base (UPDB), a genealogy representing the Utah pioneers and their descendants, record-linked to statewide cancer records, to describe the familial nature of primary brain cancer. We examined the familial clustering of primary brain tumors, including subgroups defined by histologic type and age at diagnosis. The UPDB includes 1,401 primary brain tumor cases defined as astrocytoma or glioblastoma, all with at least three generations of genealogy data. We tested the hypothesis of excess relatedness of brain tumor cases using the Genealogical Index of Familiality method. We estimated relative risks for brain tumors in relatives using rates of brain tumors estimated internally.

Results: Significant excess relatedness was observed for astrocytomas and glioblastomas considered as a group ($n = 1,401$), for astrocytomas considered separately ($n = 744$), but not for glioblastomas considered separately ($n = 658$). Significantly increased risks to first- and second-degree relatives for astrocytomas were identified for relatives of astrocytomas considered separately. Significantly increased risks to first-degree relatives, but not second degree, were observed for astrocytoma and glioblastoma cases considered together, and for glioblastoma cases considered separately.

Conclusions: This study provides strong evidence for a familial contribution to primary brain cancer risk. There is evidence that this familial aspect includes not only shared environment, but also a heritable component. Extended high-risk brain tumor pedigrees identified in the UPDB may provide the opportunity to identify predisposition genes responsible for familial brain tumors.

Neurology® 2008;71:1015-1020

GLOSSARY

GBM = glioblastoma; **GIF** = Genealogical Index of Familiality; **HGG** = high-grade gliomas; **ICD-O** = International Classification of Disease-Oncology; **LGG** = low-grade gliomas; **RR** = relative risks; **SEER** = Surveillance, Epidemiology, and End Results; **SIR** = standardized incidence ratios; **UCR** = Utah Cancer Registry; **UPDB** = Utah Population Data Base.

Although a familial component to brain tumors has been examined multiple times in the literature, the genetics underlying these observations remains undefined. Of approximately 5% of gliomas thought to be hereditary^{1,2} the majority are associated with known neoplastic syndromes. The percentage of brain tumors which are “hereditary” but not associated with one of these well-described inherited syndromes is unclear.

Access to a unique resource, the Utah Population Database (UPDB), provides the opportunity to describe the familial clustering of primary brain cancers in a large, well-defined, relatively homogenous population. This resource includes the genealogy of the Utah Pioneers and their descendants³ which has been record-linked to Utah cancer registry records from 1966,

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Data collected for this publication was assisted by the Utah Cancer Registry supported by NIH contract NO1-PC-35141, Surveillance, Epidemiology and End Results (SEER) Program, with additional support from the Utah Department of Health and the University of Utah. Partial support for all data sets within the Utah Population Database (UPDB) was provided by the University of Utah Huntsman Cancer Institute. Partial data and analysis support for this project came from NIH NLM grant RO1 LM009331 to L.A.C.-A.

Disclosure: The authors report no disclosures.

and allows definition of the genetic relationships between Utah brain tumor cases. Progress in understanding the heritable nature of cancer,⁴⁻⁶ as well as non-neoplastic disease such as intracranial aneurysm,⁷ valvular heart disease,⁸ and coronary artery disease,⁹ among others, has been made using the UPDB resource. Several predisposition genes for common cancers have been identified through the study of high-risk Utah pedigrees, including *BRCA1*,¹⁰ *BRCA2*,¹¹ *p16*,¹² and *HPC2/ELAC2*.¹³ We have analyzed 1,401 primary brain cancer cases of type astrocytoma (n = 744) or glioblastoma (GBM) (n = 658) with genealogy to describe the contribution of familial factors to brain tumor predisposition.

METHODS The Utah Genealogy was created in the 1970s^{3,14} using data made available by the Family History Library of the Church of Jesus Christ of Latter-day Saints (LDS or Mormons). Genealogy data for the Utah Mormon pioneers, both in Utah and along the pioneer trail, and their descendants, was computerized to create a genealogy of approximately 1.6 million individuals representing up to seven generations. These genealogy data have been extended to 10 generations with the triplet genealogy data (father, mother, child) available from Utah birth and death certificates. There are over 2 million individuals with at least three generations of genealogical data in what is now termed the UPDB.

The Utah Cancer Registry (UCR) was established in 1966, and became part of the NCI Surveillance, Epidemiology, and End Results (SEER) program in 1973. All cancers occurring in the state are reportable by law; follow-up rates exceed 95%. The UCR data include primary site, histology, and age at diagnosis data for each cancer. Only independent primary cancers are included in the UCR. There is an attempt to record link all UCR cancer data to the UPDB genealogy data, with approximately 60% success. There have been 3,404 individuals diagnosed with primary brain tumors recorded in the UCR since 1966. We analyzed 1,401 of these individuals who also have at least three generations of genealogy data available and who were diagnosed with either astrocytoma or GBM or both (n = 1). International Classification of Disease–Oncology (ICD-O) coding was used to identify cases. Topography codes C710–719 were used. We identified 744 cases of “astrocytoma” with histology codes 9380–9382, 9400–9401, 9410–9411, 9420, 9423–9424, 9430; and 658 cases of “glioblastoma,” using histology codes 9440–9442. (The term “astrocytoma” included low-grade [grade II], astrocytoma NOS [glioma], anaplastic astrocytoma, and may have included oligodendroglioma, mixed glioma, and inadvertently, GBM [grade IV astrocytoma] not coded as such.)

The UPDB has previously been used to define the familial nature of cancer by site with the methods reported here.^{4,5,15}

Relative risk method. Relative risks in relatives compare the rate of disease in the relatives of affecteds to the rate of disease in the population. We utilized age-, birth year-, and birthplace-specific rates calculated within the UPDB population to estimate relative risks (RR) for brain tumors in relatives of patients with

brain tumor as follows. All 2.2 million individuals in the UPDB who belong to at least three generations of genealogy were assigned membership in one of 132 birth year– (5 year), sex-, and birthplace-specific (Utah or not) cohorts. The rate of brain tumor for each cohort was estimated as the total number of individuals with a brain tumor in each cohort, divided by the total number of individuals in the cohort.

The expected number of relatives with a brain tumor was estimated by counting all relatives of the probands (by cohort, with no duplication), then multiplying the number of relatives (per cohort) by the cohort-specific rate of brain tumor, finally summing over all cohorts. Observed numbers of relatives with brain tumor were counted by cohort, without duplication. $RR = \text{observed/expected}$ is an unbiased estimator of relative risk. One-sided probabilities for the alternative hypothesis test of $RR > 1.0$ were calculated under the null hypothesis $RR = 1.0$, under the assumption that the number of observed deaths follows a Poisson distribution with mean equal to the expected number of deaths.

Genealogical Index of Familiality. The Genealogical Index of Familiality (GIF) statistic was developed to test the hypothesis of no excess relatedness within a group of individuals in the UPDB.¹⁶ The GIF statistic measures the average relatedness between all possible pairs of individuals in a group (e.g., all brain tumor cases); the GIF test compares the average relatedness of the cases to the average expected relatedness (estimated from matched controls). The relatedness measure for a pair of individuals implements the Malécot coefficient of kinship,¹⁷ defined as the probability that randomly selected homologous genes from two individuals are identical by descent from a common ancestor. For siblings the coefficient is 1/4, for grandparent/grandchild 1/8, for first cousins 1/16, and so forth. The contribution to the GIF statistic for a pair of individuals is smaller for pairs with a greater genetic distance between them. The case-GIF is defined as the average of the coefficients of kinship between all possible pairs of cases ($\times 10^5$ for ease of presentation). The significance of the hypothesis of no excess relatedness among cases is judged empirically, by comparison of the relatedness of the cases with the distribution of the relatedness measures from 1,000 matched control sets. Controls are randomly selected from all individuals with genealogy data in the UPDB, and matched to cases by birth cohort (5 year), sex, and birthplace (Utah or not).

RESULTS Relative risks. Relative risks estimated for primary brain cancers among the first-degree relatives of individuals with brain cancer, by histopathologic type (astrocytomas and GBMs together, astrocytomas separately, and GBMs separately), are shown in table 1. Table 1 shows the cancer diagnosed in the proband, the cancer diagnosed in the relative, the number of first-degree relatives of the proband, the observed number of cancers in the relatives (obs), the expected number of cancers in the relatives (exp), the RR estimate, and the one-sided significance value for the test of the alternative hypothesis of $RR > 1.0$. A significant excess risk for astrocytomas or GBM was observed in the first-degree relatives of GBM and astrocytoma cases combined ($RR = 3.29$). A significant excess risk for astrocytoma in the first-degree relatives of astrocytoma cases was observed ($RR =$

Table 1 Relative risks for brain tumor among first-degree relatives of patients with early onset brain tumor

Cancer in proband	Cancer in relative	No. relatives	Observed	Expected	RR	p Value	One-sided 95% CI
Astrocytoma/GBM	Astrocytoma/GBM	11,498	38	11.6	3.29	<0.00001	2.33,4.51
Astrocytoma	Astrocytoma	5,637	10	2.5	3.82	0.0004	1.83,7.02
GBM	GBM	5,939	8	3.5	2.29	0.026	0.99,4.51

GBM = glioblastoma.

3.82), and significantly increased risk for GBM in the first-degree relatives of GBM cases was observed (RR = 2.29; one-sided *p* value 0.026).

Table 2 shows RRs for brain tumors among second-degree relatives of cases by histopathologic type. A significant elevated RR was observed for astrocytoma in the second-degree relatives of patients with astrocytoma (RR = 1.91; *p* = 0.03). The estimated RRs for second-degree relatives were not significantly elevated for either the combined astrocytoma/GBM group (*p* = 0.15) or for the GBM subgroup (*p* = 0.30). Third-degree relative risks were not significantly elevated for astrocytoma, GBMs, or for the two types combined (data not shown).

Because cancers with a genetic contribution are often noted to occur at an earlier age than sporadic cases, we also estimated RRs for brain tumors (diagnosed at any age) among the first-degree relatives of early astrocytoma/GBM cases (diagnosed before age 20 years), and by histopathologic subgroup, defining early astrocytoma as <15 years, and early GBM as <55 years, shown in table 3. A significantly increased risk for either astrocytoma or GBM at any age was observed in the first-degree relatives of all patients with early diagnosed astrocytoma/GBM, as was a significantly increased risk for astrocytoma at any age among the first-degree relatives of the patients with astrocytoma diagnosed before age 15 years. No first-degree relatives of the patients with GBM diagnosed before age 55 years were diagnosed with GBM.

GIF analysis. Table 4 summarizes the GIF analysis of excess relatedness for astrocytomas and GBMs combined, and separately for the histopathologic subgroups, including the number of cases (n), the case average relatedness (GIF), the average control relatedness for 1,000 control sets (mean control GIF),

and the empirical *p* value. Significant excess relatedness was observed for astrocytomas and GBMs considered as a group (*p* = 0.009), and for the astrocytoma subgroup (*p* = 0.008), but the average relatedness observed for the individuals diagnosed with GBM was not significantly different from expected.

We also performed the GIF test of excess relatedness for early diagnosed brain tumors. The results are also shown in table 4. Early astrocytomas showed borderline significant excess relatedness (*p* = 0.059). There was no evidence of significant excess relatedness for the early astrocytomas/GBM cases combined, nor for the early diagnosed GBMs (age <55 years).

High-risk brain tumor pedigrees. A total of 101 high-risk pedigrees with at least three brain tumor cases (including astrocytomas or GBMs), and with a significant excess of brain tumors among the descendants of the founders (*p* < 0.01), have been identified in the UPDB. The figure shows an example of a high-risk brain tumor pedigree. The founder couple shown at the top of the pedigree had over 5,000 descendants in the Utah genealogy data. The pedigree shows only those descending lines that include a primary brain cancer case. Because the cancer registry data are only available from 1966, the brain cancer phenotype is only known with certainty for the most current (bottom) generations. The sex, histology, and age at onset of the cases are not shown, to prevent possible identification of the pedigree.

DISCUSSION It is estimated that 20,500 new primary brain tumors were diagnosed in the United States in 2005.¹⁸ Half of these are gliomas (50% of which are high-grade or anaplastic). Approximately 5% of gliomas are thought to be hereditary. Recognized autosomal dominant syndromes in which brain tumors are seen with increased incidence in-

Table 2 Relative risks for brain tumor among first-degree relatives of patients with early onset brain tumor

Cancer in proband	Cancer in relative	No. relatives	Observed	Expected	RR	p Value	One-sided 95% CI
Astrocytoma/GBM	Astrocytoma/GBM	36,650	31	25.3	1.22	0.15	0.83,1.74
Astrocytoma	Astrocytoma	17,163	12	6.3	1.91	0.03	0.99,3.33
GBM	GBM	19,940	8	6.3	1.26	0.30	0.54,2.49

GBM = glioblastoma.

Table 3 Relative risks for brain tumor among first-degree relatives of patients with early onset brain tumor

Cancer in proband	Cancer in relative	No. relatives	Observed	Expected	RR	p Value	One-sided 95% CI
Astrocytoma/GBM <20 y (n = 214)	Astrocytoma/GBM	1,059	4	0.6	6.44	0.004	1.76,16.50
Astrocytoma <15 y (n = 161)	Astrocytoma	801	3	0.3	9.65	0.004	1.99,28.20
GBM <55 y (n = 187)	GBM	1,470	0	0.7	—	—	—

GBM = glioblastoma.

clude tuberous sclerosis, neurofibromatosis, and Li-Fraumeni syndrome. The genetic changes associated with these syndromes have been largely identified.¹⁹ The p53 tumor suppressor gene may have a role in tumor development in both familial and sporadic gliomas, but not of germline origin, as seen in Li-Fraumeni syndrome. Study of affected lineages revealed germ-line mutations in the *APC* gene responsible for familial adenomatous polyposis, and likely for predisposition to brain tumors, including glioma, and possibly a separate variant which has increased incidence of medulloblastoma.²⁰ Other familial neoplastic syndromes include Turcot's,²¹ von Hippel-Lindau disease,²² Gorlin syndrome,²³ and multiple endocrine neoplasia syndromes.²⁴ There are numerous well-recognized hereditary syndromes that manifest with brain tumors as part of their phenotype. However, the incidence of brain tumors, specifically gliomas, which are hereditary in nature, but not associated with one of these well-described inherited syndromes, is less clear. The literature is mixed regarding support of a "non-syndromic" genetic component to familial brain tumors.

Thirty-eight of the 1,401 Utah astrocytoma/GBM cases analyzed have at least one first-degree relative also affected with a brain tumor. These 38 cases represent 19 different brain tumor pedigrees/clusters. These clusters might be considered more likely to represent syndromic pedigrees. A total of 101 high-risk brain cancer pedigrees were identified in the UPDB, each containing at least three cases of astrocytoma/GBM, and with a significant excess of cases observed.

Segregation studies have supported multifactorial and genetic heritability (4%) in childhood brain tumors.²⁵ Studies of patients with glioma and segregation of cancer in their first- and second-degree relatives have supported multigenic Mendelian inheritance as well as environmental influences²⁶; even patterns suggestive of autosomal recessive inheritance have been noted.²

Following several case reports suggesting familiarity in astrocytoma,²⁷⁻²⁹ the National Brain Tumor Registry was established to study the familiarity in tumors involving first-degree relatives and spouses. Results of the study of 72 families demonstrated no significantly lower age at onset; clustering in time; and a significant number of occurrences in spouses. Given these findings, the authors concluded that environmental factors might be more responsible for these familial occurrences than hereditary causes.³⁰ A study from a cohort of over 42,000 benign and malignant brain tumor cases from the Swedish Cancer Registry (1958–1997) found a significant increased risk (RR = 2.0–3.0) for brain tumors in first-degree relatives, but not in spouses, a finding which decreases the possibility of short-term shared environmental risk, but which cannot exclude the impact of environmental impact in formative years.³¹

Another descriptive study of 19 families with glial tumors in two or more related members failed to show any pattern of inheritance, but showed an almost 7% incidence of positive family history—higher than would be expected by chance occurrence.³² Some case-control studies have supported an increased risk of familiarity, with ORs

Table 4 Genealogical Index of Familiarity (GIF) test of excess relatedness among patients with brain tumor

Cases	No.	Case GIF	Mean control GIF	Empirical p value
Astrocytoma/GBM	1,401	3.01	2.68	0.009
Astrocytoma	744	3.00	2.44	0.008
GBM	658	3.09	3.04	0.409
Early brain tumors				
Astrocytoma/GBM dx <20 y	214	2.40	1.82	0.130
Astrocytoma dx <15 y	161	3.19	1.76	0.059
GBM/dx <55 y	187	1.90	2.78	0.927

GBM = glioblastoma.

Figure Sample high-risk brain tumor pedigree identified in the Utah Population Data Base

Eight individuals with primary brain cancer were observed; 2.80 were expected ($p = 0.008$).

greater than 2.0, while others show ORs near 1.0.^{33,34} Several cohort studies show increased standardized incidence ratios (SIR) in first-degree relatives of patients with brain tumors.^{35,36} The largest of these studies, from the Swedish Cancer Registry, examined familial risk in first-degree relatives of low-grade (LGG) and high-grade (HGG) gliomas. The SIR for relatives of LGG individuals was significantly elevated at 3.65 and reached 7.0 in siblings. Risk for HGG in the LGG cohort and within the HGG cohort showed a less impressive twofold increase in risk.³⁷

Studies limited to first-degree relatives are inherently unable to discern between possible environmental effects of childhood and shared genetic propensity. In a population-based retrospective study similar to ours, of 396 glioma cases from the Icelandic Cancer Registry, no excess risk for glioma was observed in the 25,546 first-, second-, and third-degree relatives of the probands.³⁸

Our analysis of the familial nature of 1,401 primary astrocytomas and GBMs is unique in both its large sample size and the availability of data on cancer and genetic relationships from a homogeneous population. Because all cancers in Utah are reported by law, estimates of cancer risk in relatives from this resource avoid the common biases of ascertainment and recall.

Our results strongly suggest a heritable contribution to astrocytoma risk, while showing only nominal support for such a hypothesis for GBMs. The GIF results for GBM suggest that these cancer cases are related, on average, as any similar group of individuals would be in this population. While the absence of a significantly elevated GIF in GBM may suggest lack of a strong genetic component, and at first glance may seem counterintuitive, it could be argued that a larger group of de novo ("primary") GBMs associated with environmental exposures of aging may mask a true genetic component in the ("secondary") GBMs which result from transformation of astrocytoma to higher grade classification. The observed significantly increased RR for GBM among first-degree relatives of patients with GBM

may suggest the presence of a minority subset of GBM that may indeed have a heritable component.

Incidence data from Sweden³⁷ show a similar pattern of increased familial risk in lower grade vs higher grade cohorts, which correlates with our observation of stronger familiarity in astrocytoma (low-grade) vs glioblastoma (high-grade). Prospective studies to identify de novo, vs transformed, GBM, both clinically and by molecular profile, are crucial to clarify this issue. Molecular discoveries show that these subsets of GBM have inherent genetic differences³⁹ and may differ in their mode of acquisition as regards heritability.

A limitation of our study is that it is retrospective in nature, and may be subject to misclassification effects in coding of malignant categories of brain neoplasms. Diagnoses of glioma were based on mandatory reporting of pathology diagnoses to the Utah Cancer Registry. These diagnoses were retrospectively collected and not subject to central review after submission.

While association with a tumor predisposition syndrome could not be definitively excluded in this retrospective analysis, it is unlikely that the majority of our familial cases were "syndromic." A closer degree of familial clustering would be expected for syndromic cases, as the inheritance patterns are more likely to be more highly penetrant.

We have previously reported an increased association of cancers of other sites in the first-degree relatives of patients with brain tumor.¹⁶ The relationship between primary brain tumors and other cancers, outside of recognized germline syndromes, needs to be further elucidated.

Our findings support the hypothesis of a genetic contribution to glioma predisposition. Prospective studies of families with higher than expected numbers of brain tumors among descendants (high-risk pedigrees) may identify brain tumor predisposition genes that are not known and not included in well-described syndromes. Brain tumors need to be categorized both histologically and molecularly for known glioma-associated chromosomal aberrations. We will prospectively study these pedigrees for phenotype, association with recognized neoplastic syndromes, and molecular genetic profile to further our understanding of the inherited contribution to risk for brain tumor. Further information from this unique and valuable resource may provide insight into the sporadic gliomas, and lead to intervention, and even prevention, of low-grade gliomas or pre-neoplastic brain tumor states. Study of the extended high-risk Utah brain tumor pedigrees could allow identification of predisposition genes for brain tumors and provide important information regarding

variations in treatment response and prognosis, and a better understanding of interactions between genes and environmental risk factors.

Received March 19, 2008. Accepted in final form June 18, 2008.

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