Minireview

GLIOGENE—an International Consortium to Understand Familial Glioma

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Abstract

Evidence for familial aggregation of glioma has been documented in both case-control and cohort studies and occurs apart from the well-described rare inherited genetic syndromes involving glioma: neurofibromatosis type 1 and 2, tuberous sclerosis, Turcot’s syndrome, and Li-Fraumeni syndrome. Nonsyndromic glioma families have been studied but no genes have been identified in the two published linkage studies of familial glioma probably due to the small number of families. Because glioma is a rare but devastating cancer, and a family history of glioma has been observed in ~5% of the cases, we initiated an international consortium to identify glioma families not affected by syndromes to better understand the inherited factors related to this disease. The international consortium GLIOGENE is an acronym for “glioma gene” and includes 15 research groups in North America, Europe, and Israel to study familial glioma. The overarching goal is to characterize genes in glioma families using a genome-wide single-nucleotide polymorphism approach and conducting linkage analysis to identify new genomic regions or loci that could harbor genes important for glioma genesis. Here, we review the rationale for studying familial glioma and our proposed strategy for the GLIOGENE study. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1730–4)

Background

Glioma is a diffusely infiltrating malignant brain tumor, with varying prognosis depending on malignancy grade (or histologic differentiation). Glioblastoma, the highest graded glioma (WHO grade 4), has a very poor prognosis with a 5-year survival of only 5% (1). To be able to find new strategies for prevention, early detection, and novel treatment, it is important to understand the underlying causes of malignant brain tumors. Presently, most cases of glioma cannot be explained by endogenous or exogenous causes. High doses of ionizing radiation (2) and rare genetic syndromes (3) are the only generally accepted well-defined risk factors, and they explain a small percentage of all glioma cases.

Evidence for Familial Aggregation of Brain Tumors

Early studies of primary brain tumor risk had small sample sizes and could not confirm a familial aggregation of brain tumors (4, 5). More recently, several large glioma case-control and nationwide cohort studies (including >200 cases) have shown statistically significant increased risks for primary brain tumors among relatives of brain
tumor patients (Table 1). Cohort studies show a standardized incidence ratio of 2 [i.e., ~2-fold increased risk of primary brain tumor or glioma (6–8)] among first-degree relatives of glioma probands compared with the population incidence data. This finding is also supported by a case-control study from the San Francisco Bay Area (9). A few cohort studies have been done. In one cohort study in Finland, Paunu et al. (10) screened 269 glioma cases and found 24 glioma families, defined with at least two gliomas among first- or second-degree relatives (8.9%) that had a family history of a primary brain tumor, which is similar to published proportions from other populations (11, 12). The Icelandic cohort study did not support a significant increased risk of primary brain tumor, which could be due to either population differences or, more likely, insufficient sample size (13). In addition, many glioma family clusters have been described in the literature. Thuwe et al. (14) found a cluster of glioma on an island outside the west coast of Sweden (Fig. 1). The inbreeding factor was higher on the island with familial glioma compared with a matched control population (14, 15). Similar patterns of related glioma families have been described in Northern Sweden (16).

Two segregation analyses have been published, with one supporting a multifactorial inheritance pattern (12) and the other supporting an autosomal recessive pattern (11). The major difference between the two segregation studies is that the study by de Andrade et al. (12) calculated risk of other cancers besides glioma in the families. The segregation analyses from Sweden (11) calculated glioma risk using only glioma because a large majority of the families included affected sib pairs. The Swedish Multi-Generation Register shows a significantly increased risk of glioma for siblings of low-grade glioma patients (standardized incidence ratio, 6.45; 95% confidence interval, 2.78-12.71; ref. 17). Two linkage studies, including small numbers of families, have been published (16, 18), and only one study has shown a significant lod score of 3.35 at the chromosomal region 15q23-q26.3 (18). Collectively, these data provide evidence for an inherited predisposition to glioma outside the context of the rare cancer-prone families but larger sample sizes are needed to identify a disease-causing locus by genetic linkage analysis.

### Family History of Other Associated Cancer Sites

In general, there is no statistically significant increased risk for other cancer sites in first-degree relatives of glioma patients (standardized incidence ratio, 6.45; 95% confidence interval, 2.78-12.71; ref. 17). Two linkage studies, including small numbers of families, have been published (16, 18), and only one study has shown a significant lod score of 3.35 at the chromosomal region 15q23-q26.3 (18). Collectively, these data provide evidence for an inherited predisposition to glioma outside the context of the rare cancer-prone families but larger sample sizes are needed to identify a disease-causing locus by genetic linkage analysis.

### Table 1. Overview of family history of cancer and specific cancer sites in recent case-control and cohort studies in chronological order with a minimum of 200 cases

<table>
<thead>
<tr>
<th>Primary brain tumor subtype</th>
<th>Type of relatives</th>
<th>Cancer site associated</th>
<th>OR/SIR (95% CI)</th>
<th>Risk of primary brain tumor</th>
<th>Risk of glioma</th>
<th>Study design</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary brain tumors</td>
<td>FDR</td>
<td>Stomach</td>
<td>3.61 (1.5-6.9)</td>
<td>1.96 (1.16-2.97)</td>
<td>NA</td>
<td>Cohort</td>
<td>Goldgar et al., 1994</td>
</tr>
<tr>
<td>Glioma</td>
<td>FDR</td>
<td>Melanoma</td>
<td>1.60 (1.1-2.2)</td>
<td>2.3 (1.0-5.8)</td>
<td>NA</td>
<td>Case/ control</td>
<td>Wrensch et al., 1997</td>
</tr>
<tr>
<td>Glioma</td>
<td>FDR</td>
<td>Cancer</td>
<td>1.0 (0.8-1.4)</td>
<td>2.3 (1.0-5.8)</td>
<td>NA</td>
<td>Cohort</td>
<td>Malmer et al., 1999</td>
</tr>
<tr>
<td>Glioma</td>
<td>Parents, offspring</td>
<td>Cancer</td>
<td>0.98 (0.85-1.3)</td>
<td>2.12 (1.18-3.49)</td>
<td>3.12 (1.42-5.92)</td>
<td>Cohort</td>
<td>Malmer et al., 2001</td>
</tr>
<tr>
<td>Glioma familial</td>
<td>FDR + SDR</td>
<td>Cancer</td>
<td>0.88 (0.72-1.07)</td>
<td>NA</td>
<td>NA</td>
<td>Cohort</td>
<td>O'Neill et al., 2002</td>
</tr>
<tr>
<td>Glioma</td>
<td>FDR</td>
<td>Cancer</td>
<td>0.98 (0.88-1.09)</td>
<td>1.69 (0.84-3.03)</td>
<td>1.46 (0.63-2.88)</td>
<td>Cohort</td>
<td>Malmer et al., 2001</td>
</tr>
<tr>
<td>Glioma</td>
<td>SDR</td>
<td>Cancer</td>
<td>0.94 (0.86-1.03)</td>
<td>0.96 (0.50-1.68)</td>
<td>1.19 (0.62-2.08)</td>
<td>Cohort</td>
<td>Paunu et al., 2002</td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>FDR + SDR + TDR</td>
<td>Melanoma</td>
<td>0.9 (1.3-1.1)</td>
<td>NA</td>
<td>NA</td>
<td>Cohort</td>
<td>Malmer et al., 2003</td>
</tr>
<tr>
<td>High-grade glioma</td>
<td>FDR</td>
<td>Cancer</td>
<td>0.97 (0.92-1.02)</td>
<td>1.76 (1.45-2.11)</td>
<td>2.30 (1.66-3.11)</td>
<td>Cohort</td>
<td>Malmer et al., 2003</td>
</tr>
<tr>
<td>Glioma</td>
<td>FDR</td>
<td>Stomach</td>
<td>2.2 (1.4-4.6)</td>
<td>NA</td>
<td>1.6 (0.5-5.3)</td>
<td>Case/ control</td>
<td>Hill et al., 2003</td>
</tr>
</tbody>
</table>

NOTE: The only cancer site, except for primary brain tumors, consistently replicated is melanoma.

Abbreviations: OR, odds ratio; SIR, standardized incidence ratio; 95% CI, 95% confidence interval; FDR, first-degree relatives; SDR, second-degree relatives; TDR, third-degree relatives; NA, not available.

*Association of astrocytoma to parents’ cancer site.

†Risk for low-grade glioma.

‡Risk for high-grade glioma.
glioma patients (Table 1), with one exception—malignant melanoma (10, 19, 20). Rare families with cases of glioma and melanoma have been reported, with single reports of families harboring p16 mutations (21).

**Glioma-Prone Syndromes**

There are rare inherited genetic syndromes predisposing to glioma, including neurofibromatosis type 1 (NF1) and 2 (NF2), tuberous sclerosis, Li-Fraumeni syndrome, and Turcot’s syndrome. Collectively, these syndromes taken together only account for ~1% of all adult glioma cases, but in children they are slightly more common (22). The most common of these rare syndromes is NF1, which has distinct skin characteristics and occurs in ~1:4,000 in the population. NF2 is characterized by less distinct skin characteristics, with its characteristic features being bilateral acoustic neuromas, which is diagnostic, and spinal gliomas, which is common. This subtype is ~10 times less common than NF1, occurring in ~1:40,000. Tuberous sclerosis is more common with an incidence of ~1 in 5,000 (23). Data from two glioma case-control studies with ~450 cases suggest that 1.7% (95% confidence interval, 0.8-3.5%) of cases can be ascribed to NF1, NF2, and tuberous sclerosis (9, 19). The Li-Fraumeni cancer family syndrome is characterized by the occurrence of several types of primary cancers: sarcoma, breast cancer, leukemia, and brain tumors. Typically, the age at onset is usually before age 45 years and ~14% of the cancers in the families are brain tumors (24). A population-based study of 297 cases of glioma suggests that the contribution of Li-Fraumeni syndrome to glioma is minimal, as only one family fulfilled the criteria of the Li-Fraumeni syndrome (7). Incidence data of Turcot’s syndrome are not available but are considered very rare.

When studying case series of the syndromes, giant cell glioma occurs in ~14% of all cases of tuberous scleroses (23). In NF1, optical pathway glioma occurs in about 15% to 20% of the children, but glioma at other locations is much less frequent (25, 26).

The genetic causes of these syndromes are in many cases identified and different genes have been observed explaining the same type of syndrome. About 70% of all Li-Fraumeni syndrome families are explained by p53 germ-line mutations (24). Although CHEK2 was suggested as a susceptibility gene in Li-Fraumeni syndrome families, it has also been discredited as studies have shown that variants such as the 1100 delC of CHEK2 function are low-penetrant alleles, primarily for breast cancer. This variant has not been linked to brain tumors (27, 28). A third Li-Fraumeni syndrome locus at chromosome 1p23 has been suggested but has not been validated (29). In summary, these glioma-predisposing syndromes support the hypothesis that high-penetrant genes can cause glioma but they only explain very few glioma cases.

**Rationale for the GLIOGENE Consortium**

Discussions for launching an international glioma linkage study began at the Brain Tumor Epidemiology Consortium biannual meeting in June 2004.18 The rationale for initiating this study was the rarity of the disorder, which necessitated multicenter collaboration to identify a large number of these rare glioma families for informative linkage analyses. We therefore have assembled an

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18 http://epi.grants.cancer.gov/btec/
international team of researchers with expertise encompassing genetic epidemiology, statistical genetics, gene mapping, brain tumor biology, cancer molecular genetics, pathology, and diagnosis and treatment of brain tumors (Fig. 2). The study includes currently 11 centers from the United States and 4 centers in Europe (Sweden, Denmark, United Kingdom, and Israel) and aims to screen 15,000 newly diagnosed glioma cases for family history of brain tumors during the time period January 2007 and December 2011. The eligibility criteria for inclusion are at least two gliomas in the family, including the proband in a first-, second-, or third-degree relative. At least two gliomas in the family must be pathologically confirmed. We estimate that 3% to 4% of all cases (n = 500) will have a family history of glioma and sufficient family members to be informative for linkage having available biological samples. The overall expectation is that 80% of these families are informative and that we will be able to identify 400 informative glioma families for linkage analyses. All screened cases will be rigorously checked for inherited genetic syndromes involving glioma and excluded if found to have one of these syndromes. We do not have estimates on how many families will have these syndromes. The pathology records and original tumor slides will be centrally reviewed by two independent study neuropathologists to have an accurate and uniform histopathologic diagnosis of all glioma. The problem is that many of the glioma cases in families are deceased and samples are not available to recreate the family for genetic analysis. We will attempt to reconstruct the genotypes for the deceased cases from their living descendants. For example, a biological specimen will be obtained from the spouse and children of the affected individual to reconstruct genotype of the affected relative. As glioma cases are affected at all ages, parents are likely to be living in many cases, so sufficient numbers of close relatives for genotyping reconstruction of deceased affected cases will be possible. All affected and unaffected individuals consenting to take part in the study will be genotyped by high-density whole genome chip arrays (Illumina platform). We will assess power and usefulness of each pedigree for linkage using software program SLINK (30, 31) before genotyping. This will help us in prioritizing families for genotyping. We will do model-based and model-free linkage analysis using software programs Allegro (30, 32), which allows complete multipoint analysis with a large number of markers but only small- to moderate-sized families. We will complement this analysis by doing model-based linkage analysis using software FASTLINK (33). The latter program can accommodate large-sized families but only four to five markers simultaneously. The families will be stratified on potential mode of inheritance, on other cancer sites observed in the families, such as malignant melanoma and histologic type of tumor of the proband (i.e., low-grade glioma versus high-grade glioma), as well as on the different populations included in the study. This is the first international collaborative study investigating familial glioma to identify genetic linkage.

As glioma is a rare, poorly understood tumor etiologically, enormous joint efforts are needed to enable researchers to gather enough cases and their respective family members to more completely understand the biology and underlying causes of malignant brain tumors.

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