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Germline rearrangements in families with strong family history of glioma and malignant melanoma, colon, and breast cancer


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Background. Although familial susceptibility to glioma is known, the genetic basis for this susceptibility remains unidentified in the majority of glioma-specific families. An alternative approach to identifying such genes is to examine cancer pedigrees, which include glioma as one of several cancer phenotypes, to determine whether common chromosomal modifications might account for the familial aggregation of glioma and other cancers.

Methods. Germline rearrangements in 146 glioma families (from the Gliogene Consortium; http://www.gliogene.org/) were examined using multiplex ligation-dependent probe amplification. These families all had at least 2 verified glioma cases and a third reported or verified glioma case in the same family or 2 glioma cases in the family with at least one family member affected with melanoma, colon, or breast cancer. The genomic areas covering TP53, CDKN2A, MLH1, and MSH2 were selected because these genes have been previously reported to be associated with cancer pedigrees known to include glioma.

Results. We detected a single structural rearrangement, a deletion of exons 1-6 in MSH2, in the proband of one family with 3 cases with glioma and one relative with colon cancer.

Conclusions. Large deletions and duplications are rare events in familial glioma cases, even in families with a strong family history of cancers that may be involved in known cancer syndromes.

Keywords: CDKN2A/B, family history, glioma, MLH1, MSH2, TP53.
Diffuse gliomas are the most common group of primary malignant brain tumors. Family history is an important risk factor for glioma, with first-degree relatives of glioma patients having an increased risk of developing the disease. Although a small percentage of these families with glioma are attributed to hereditary genetic disorders such as neurofibromatosis types I and II, Li-Fraumeni syndrome, and Turcot’s syndrome, the genes underlying the appearance of multiple gliomas in most families remain ill defined. In addition to the familial aggregation of glioma-specific risk, the risk of other cancers in first-degree relatives of glioma patients has been noted, and significantly more melanoma cases than expected have been identified. High-penetrance genes such as the tumor suppressor gene TP53 have been described in families with Li-Fraumeni syndrome; these families include persons diagnosed with glioma as well as other malignancies such as breast cancer, sarcoma, and leukemia. Moreover, these genes have also been associated with glioma and low-penetrant genetic variants in the CDKN2A (p16INK4A/p14ARF) and TP53 genomic area.

Gliomas have been observed in families with mutations in the CDKN2A and TP53 genes, but most of the studies published to date are based on small sample sizes with limited power to assess the contribution of mutations in these genes with familial glioma. In an earlier study, we used standard sequencing, which was ineffective in detecting large rearrangements of TP53 and CDKN2A in 96 unselected glioma families. Only one proband had a TP53 mutation, and no functional mutations were found in CDKN2A.

The association between glioma and melanoma has been previously reported in aggregation studies and is supported by linkage of melanoma to regions of chromosome 9. and melanoma have identified variants in chromosome 9p21 near the cyclin-dependent kinase inhibitor genes, CDKN2A, CDKN2B, and other genes. Although the variants identified for glioma and melanoma are not in the same linkage block, the results indicate the plausibility that deletions or other chromosomal modifications in the region might account for some familial aggregation of glioma and melanoma. The melanoma-neural system tumor syndrome, in which affected families have increased risk of melanoma and astrocytoma, was recently linked to loss of the CDKN2A/B genes located on chromosome 9.

The mismatch repair (MMR) genes, MLH1, MSH2, MSH6, and PMS2, play a basic role in maintaining genome integrity by correcting single-base pair mismatches after DNA replication. It is well established that the etiologic basis for Lynch syndrome is heterozygous germline mutations within one of the mismatch genes, MLH1, MSH2, MSH6 and PMS2, with MLH1 and MSH2 mutations playing a major role. Lynch syndrome patients are susceptible to colorectal, endometrial, and other cancers recognized by microsatellite instability (MSI), which is a hallmark of MMR defects. Lynch syndrome is associated with an increased risk of brain tumors. In carriers of pathogenic MLH1 or MSH2 mutations or their first-degree relatives, the cumulative risk of brain tumors to the age of 70 years was 1.7% for carriers of MLH1 mutations and 2.5% for carriers of MSH2 mutations. Mean age (38 years) at the time of brain tumor diagnosis is lower in those with Lynch syndrome than in the general population, and the most common tumor types are glioblastoma and astrocytoma. Biallelic mutations in MSH2 have been shown to be associated with childhood brain tumors. A heterozygous germline mutation in MSH2 is also known to be involved in patients with a syndrome diagnosis (e.g., Turcot’s syndrome), in which some patients have an inherited predisposition for brain tumors and colorectal cancer. The results listed above suggest the possibility that deletions or other chromosomal modifications in common chromosomal regions might account for some familial aggregation of glioma and other cancers, notably melanoma, colon, and breast cancer.

Materials and Methods

Ascertainment and Collection of Families

All families were identified through the Gliogene Consortium, and the exclusions were based on reported information obtained from the questionnaire in which we asked about the clinical criteria used for these hereditary conditions. We excluded all families with a reported or confirmed diagnosis of neurofibromatosis I, neurofibromatosis II, Turcot’s syndrome, or tuberous sclerosis. The recruitment protocol and data collection procedures for this study have been previously described. We identified 146 (34%) families meeting the criteria of having both familial glioma and associated cancers out of 428 probands recruited from 14 569 screened cases of incident glioma cases. The cases were initially screened for family history of glioma and had been diagnosed between 2007 and 2011 at one of our 14 recruitment centers. DNA was extracted from EDTA-venous blood samples and/or saliva samples. Biospecimen and clinicopathological information from probands and the above description of selected family members were collected after obtaining informed consent according to protocols approved by each center’s institutional review board in accordance with the Declaration of Helsinki. The genomic areas covering TP53, CDKN2A, MLH1, and MSH2 were selected because these genes have previously been reported to be associated with cancer pedigrees known to include glioma. Families with 2 or more verified gliomas were recruited between 2007 and 2011. Distributions of demographic characteristics of the probands, pathological characteristics of the glial tumors, and clinical variables of glioma in the families were described based on information derived from personal questionnaires (Table 1). Glioma families included from Sweden (n = 14), Denmark (n = 36), Israel (n = 10), and the United States (n = 86) (Table 2). The first category was families with at least 2 glioma cases verified and a third reported or verified in the same family (n = 67: Sweden n = 7, Denmark n = 12, Israel n = 5, United States n = 43). (International Classification of Diseases codes for oncology: low grade glioma [WHO grades I and II]: juvenile pilocytic astrocytoma [9421/3], fibrillary astrocytoma [9420/3], protoplasmic astrocytoma [9410/3], gemistocytic astrocytoma [9411/3], diffuse astrocytoma [9400/3], oligodendrogloma [9450/3], oligoastrocytoma [9382/3], ependymoma [9391/3]; high-grade glioma [WHO grades III and IV]: anaplastic astrocytoma [9401/3], anaplastic oligodendrogloma [9451/3], anaplastic oligoastrocytoma [9382/3], anaplastic ependymoma [9392/3], gliosarcoma [9442/3], gliomas cerebri [9381/3], and glioblastoma [9440/3]).
Table 1. Demographic characteristics of the probands and pathological characteristics of the glial tumors from Sweden, Denmark, Israel, and United States ascertained for multiplex ligation-dependent probe amplification analyses of TP53, CDKN2A/B, MLH1 and MSH2

<table>
<thead>
<tr>
<th>Glial Tumor (pathological characteristics)</th>
<th>Number of Affected Individuals</th>
<th>Median Age at Diagnosis (y)</th>
<th>Sex</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytic tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma, unclassified</td>
<td>3</td>
<td>43.0</td>
<td>2/1</td>
<td>2/0/1/0</td>
</tr>
<tr>
<td>Astrocytoma, fibrillary</td>
<td>1</td>
<td>43.0</td>
<td>0/1</td>
<td>1/0/0/0</td>
</tr>
<tr>
<td>Astrocytoma, gemistocytic</td>
<td>1</td>
<td>31.0</td>
<td>0/1</td>
<td>1/0/0/0</td>
</tr>
<tr>
<td>Astrocytoma, juvenile pilocytic</td>
<td>1</td>
<td>2.0</td>
<td>0/1</td>
<td>1/0/0/0</td>
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<tr>
<td>Astrocytoma, diffuse</td>
<td>9</td>
<td>29.0</td>
<td>3/6</td>
<td>8/0/1/0</td>
</tr>
<tr>
<td>Astrocytoma, anaplastic</td>
<td>18</td>
<td>47.0</td>
<td>11/7</td>
<td>18/0/0/0</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>2</td>
<td>29.0</td>
<td>0/2</td>
<td>2/0/0/0</td>
</tr>
<tr>
<td>Glioma, unclassified</td>
<td>5</td>
<td>39.0</td>
<td>2/3</td>
<td>5/0/0/0</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>64</td>
<td>56.0</td>
<td>35/29</td>
<td>61/2/0/1</td>
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<tr>
<td>Oligodendrogial tumors</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Oligodendrogloma</td>
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<td>42.0</td>
<td>9/8</td>
<td>16/0/1/0</td>
</tr>
<tr>
<td>Oligodendrogloma, anaplastic</td>
<td>10</td>
<td>51.5</td>
<td>2/8</td>
<td>10/0/0/0</td>
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<tr>
<td>Oligoastrocytoma</td>
<td>3</td>
<td>34.0</td>
<td>1/2</td>
<td>3/0/0/0</td>
</tr>
<tr>
<td>Oligoastrocytoma, anaplastic</td>
<td>3</td>
<td>45.0</td>
<td>1/2</td>
<td>3/0/0/0</td>
</tr>
<tr>
<td>Ependymal tumors</td>
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<td></td>
</tr>
<tr>
<td>Ependymoma, myxopapillary</td>
<td>2</td>
<td>24.5</td>
<td>0/2</td>
<td>2/0/0/0</td>
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<tr>
<td>Ependymoma</td>
<td>3</td>
<td>28.0</td>
<td>0/3</td>
<td>3/0/0/0</td>
</tr>
<tr>
<td>Ependymoma, anaplastic</td>
<td>1</td>
<td>60.0</td>
<td>0/1</td>
<td>1/0/0/0</td>
</tr>
<tr>
<td>Neuronal and mixed neuronal-glial tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysembryoplastic neuroependithelial tumor</td>
<td>1</td>
<td>28.0</td>
<td>0/1</td>
<td>1/0/0/0</td>
</tr>
<tr>
<td>Paraganglioma of spinal cord</td>
<td>1</td>
<td>51.0</td>
<td>0/1</td>
<td>1/0/0/0</td>
</tr>
</tbody>
</table>

Median age at diagnosis of probands.

TP53 and CDKN2A/B

Standard MLPA analysis was performed following the manufacturer’s instructions (MRC-Holland), version 31; 17-06-211. One hundred nanograms of genomic DNA were denatured and then hybridized with SALSA MLPA probe mixes that covers 6 genes in the TP53-17p13.1 region + NF2 and CHEK2 (included CHEK2*1100-delC). Probe mixes used were P056-A2 for TP53 and ME024-B1 9p21 for CDKN2A/B. Following ligation, PCR was performed in a Bio-Rad 1000series Thermal Cycler (Bio-Rad Laboratories). Fragment separation was carried out as suggested by MRC-Holland on an ABI 3100 sequencer using POP7 polymer and GeneScan-500 ROX sizing standard (Applied Biosystems). 8.75 μL of Hi-Di Formamide and 0.25 μL of GeneScan-500 ROX sizing standard were mixed with 1 μL of the MLPA PCR product per sample for a total volume of 10 μL. Data were analyzed with the SoftGenetics GeneMarker software version 1.6 from SoftGenetics LLC.

Next-generation Sequencing

Since some of the variants found in this study were not standardized and clinically validated mutations, we used massively parallel sequencing of hybrid-captured DNA to further evaluate preliminary findings from MLPA screening of genes in the 9p21 region. Agilent SureSelect probes were designed to capture the genomic regions of CDKN2A and CDKN2B, including introns and 20 kb adjacent 5' and 3' regions, which covered the regions implicated by MLPA. Paired-end sequencing 2 × 100 bp was performed on...
the Illumina HiSeq2000 instrument to an average depth of >100 reads, followed by alignment to the reference genome. Coverage over the suspected deleted/duplicated regions was not found to be different from coverage in control samples.

**Results**

We were able to successfully analyze 127 out of 146 glioma cases for TP53 and CDKN2A/B. One hundred thirty-seven out of 146 glioma cases were also successfully analyzed for MLH1 and MSH2. One mutation found was a deletion of exon 1-6 in MSH2; this mutation was present in the proband of a single family. The family included 3 glioma cases and 1 relative with colon cancer (Table 3). The proband in this family was diagnosed with an oligodendroglioma at age 70 years. The other affected relatives were the proband’s mother, who was diagnosed with a glioblastoma at age 72 years, the child of the mother’s first cousin diagnosed with a glioblastoma at age 41 years, and a maternal aunt diagnosed with breast cancer at age 38 years.

In addition, we found, a duplication at the promoter of CDKN2A prom dupl1022 before ex1 (in 3 of the families), a deletion at exon 2 of EFNB3 del ex2 (in 2 of the families) and a duplication of GLDC dupl9p24.1 (in one family) but these aberrations could not be verified by next-generation sequencing (Table 2).

**Discussion**

In this large family study of gliomas, we found one large deletion in exons 1-6 of MSH2 in one of the Swedish families with a family history of colon cancer. This mutation was originally detected in 9 apparently unrelated multigenerational kindred with Lynch syndrome. The sequence of the breakpoints of the exon 1-6 deletions and the haplotypes surrounding the mutation were identical in all 9 kindred, suggesting a common origin of the mutation. A similar mutation was reported as an American Founder Mutation in...
families with Lynch syndrome, an autosomal-dominant cancer syndrome traced back to a single couple who migrated from Germany, and settled in Pennsylvania in the early 1700s. Lynch syndrome is known to be associated with hereditary colorectal cancer \(^{33,46}\) and several extracolonic cancers including endometrial, gastric, small-bowel, renal, ovarian, and brain \(^{33,36}\). Despite a low incidence, brain tumors were the third highest cancer-related cause of death in a large Dutch cohort of patients with Lynch syndrome. \(^{45}\) Germline mutations in \(MSH2\) have also been described in families with a syndrome diagnosis such as Turcot’s syndrome, which is clinically characterized by occurrence of primary brain tumors and colorectal cancer. \(^{34,35}\) Mutations in \(MSH2\) result in production of a faulty, truncated, or absent protein, which impairs the ability of the MMR system to recognize and repair DNA mismatches. \(^{40}\) We also identified rearrangements in the promoter of \(CHEK2\), the variant \(CHEK2\) 1100delC, in one American family having a family history of breast cancer. \(CHEK2\) acts as a checkpoint gene, activated in response to DNA damage, and encodes a serine/threonine-protein kinase that phosphorylates P53. The germline 1100delC variant of \(CHEK2\) is a frameshift mutation, resulting in a truncated and nonfunctional protein. \(^{47}\) Nevertheless, \(CHEK2\) is a well-known median penetrant gene that is quite common in the population. Published data suggest that \(CHEK2\) is not involved in familial glioma. \(^{68,69}\)

In addition, a novel duplication was identified in the promoter region of \(CDKN2A\). To our knowledge, this specific aberration in the promoter has not been previously described in the literature. The aberration in \(CDKN2A\) was present in 3 families, all of which have a family history of both breast and colon cancer. Unfortunately, we were unable to confirm this aberration by additional deep-sequencing methods. Because of the unusual structure of \(CDKN2A\), mutations in this locus may affect both \(p16^{INK4a}\) and \(p14^{ARF}\) depending on the localization and type of sequence alteration. The \(p16^{INK4a}\) has been found to be inactivated in the vast majority of melanomas through mutation, deletion, or promoter hypermethylation of \(CDKN2A\). \(^{50}\) The \(CDKN2A\) has, as a low penetrant risk loci, been associated with risk of glioma and melanoma in genome-wide association studies. The aberration discovered in \(CDKN2A\) supports the finding that germline mutations in \(CDKN2A/CDKN2B\) could cause the co-occurrence of the melanoma-astrocytoma syndrome reported previously. \(^{51-53}\)

However, we did not observe the \(CDKN2A\) aberration in our families with a family history of melanoma, so it might be possible that other low-penetrance genes contributed to the melanoma-astrocytoma syndrome in this study.

In conclusion, candidate genes in known syndromes do not explain these glioma-prone families. Large rearrangements are uncommon events explaining cancer-prone glioma families, and novel strategies of exome and whole genome sequencing of glioma families with similar phenotypes are one likely strategy for the future.

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Conflict of interest statement

in this research.

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References


Conflict of interest statement

No declared.

Footnotes

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