Inherited predisposition to glioma

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In gliomas, germline gene alterations play a significant role during malignant transformation of progenitor glial cells, at least for families with occurrence of multiple cancers or with specific hereditary cancer syndromes. Scientific evidence during the last few years has revealed several constitutive genetic abnormalities that may influence glioma formation. These germline abnormalities are manifested as either gene polymorphisms or hemizygous mutations of key regulatory genes that are involved either in DNA repair or in apoptosis. Such changes, among others, include hemizygous alterations of the neurofibromatosis 1 (NF1) and p53 genes that are involved in apoptotic pathways, and alterations in multiple DNA repair genes such as mismatch repair (MMR) genes, x-ray cross-complementary genes (XRCC), and O6-methylguanine-DNA methyltransferase (MGMT) genes. Subsequent cellular changes include somatic mutations in cell cycle regulatory genes and genes involved in angiogenesis and invasion, leading eventually to tumor formation in various stages. Future molecular diagnosis may identify new genomic regions that could harbor genes important for glioma predisposition and aid in the early diagnosis of these patients and genetic counseling of their families.

Keywords: genetic predisposition, glioma, glioblastoma, polymorphism

Introduction

Malignant gliomas are tumors of glial origin of the central nervous system (CNS), exhibiting various degrees of differentiation inside the same tumor. Thus, a glioblastoma multiforme may have areas of anaplastic astrocytoma, or low-grade glioma. Mixed gliomas have some areas of astrocytic differentiation and others of oligodendrocytic or ependymal differentiation. The same heterogeneity is noted between the gene alterations that exist in gliomas. For example, inside the same tumor, some cells exhibit alterations of the CDKNA gene although other cells do not.1 This heterogeneity could be either due to tumor evolution or related to a possible origin of glioma from a primitive glial stem cell capable of partial differentiation into various immature cell types observed in the CNS. Development of human gliomas involves a complex combination of cancer-predisposing constitutive genetic alterations in association with known or unknown environmental risk factors and somatic genetic alterations that ultimately drive the pre-existing glial stem cells to abnormal proliferation and malignant transformation. Most of the somatic genetic alterations that exist in gliomas have been characterized over the last few years and involve inactivation of the p53 and retinoblastoma (Rb) tumor-suppressor gene pathways, activation of the phosphatidylinositol-3OH kinase pathway either through inactivation of the PTEN tumor-suppressor gene or mutations of the PIK3CA, and amplification of the receptor tyrosine kinase genes.2 In the present study, we review earlier and recent information on the role of various germline genetic alterations that contribute to the risk of development of gliomas.

Germline Alterations in Tumor Suppressors/Oncogenes and Hereditary Cancer Syndromes

During malignant transformation and progression of astrocytic tumors, several tumor-suppressor genes are inactivated, such as p53, p16, Rb, and PTEN, and numerous growth factors and oncogenes are overexpressed progressively, such as CDK4, EGFR, and VEGF genes.3–5 Heritable germline mutations of the p53 gene initially
were described in patients with Li–Fraumeni syndrome (Table 1), occasionally in nonfamilial malignancies such as multifocal osteosarcoma, in a small subgroup of young patients with 2 or more primary malignancies, and in patients with sporadic breast carcinoma. Previous work from our laboratory in glioma patients has demonstrated that germline p53 mutations are frequent in patients with multifocal glioma, glioma and another primary malignancy, and glioma associated with a family history of cancer, particularly if these factors are combined (Table 1). Constitutional DNA analysis from 44 selected patients suspected of being genetically predisposed to develop astrocytic tumors showed 6 missense mutations of the p53 (13.6%), but no mutations of the p16 and PTEN genes, suggesting that germline p53 mutations contribute to a small portion of astrocytic tumors. Other studies have suggested that p53 germline mutations may identify a subset of young adults predisposed to the development of high-grade astrocytic tumors. In the contrary, the frequency of germline and somatic p53 mutations in sporadic childhood brain tumors is very low, probably less than 1%, and there is no need to screen these patients routinely for their germline p53 status. Interestingly, 2 families in France with an identical p53 germline mutation in codon 248 were described with a clustering of CNS tumors, consisting of gliomas and choroids plexus tumors. Another study in 18 families with 2 or more family members with glioma revealed no germline p53 mutations in any of the 18 families. Thus, in families with aggregation of selective gliomas, p53 may not be a common susceptibility gene and possibly other genes are also involved.

Early studies found no evidence that germline mutations in the coding region of p16 (INK4A), p15 (INK4B), or CDK4 genes could predispose to inherited glial tumors. However, a germline deletion of the p14 (ARF)-specific exon 1B of the CDKN2A gene has been described in families with melanoma–astrocytoma syndrome, suggesting either loss of p14 (ARF) function, which is the critical abnormality associated with this syndrome or disruption of expression of p16 by an unknown mechanism. Similarly, a study in 15 glioma patients with a family history of brain tumors described a p53 germline point mutation in 1 family with some findings of Li–Fraumeni syndrome, and a hemizygous germline deletion of the p16 (INK4A)/p14 (ARF) tumor-suppressor region in a family with a history of both astrocytoma and melanoma. Thus, although germline mutations of PTEN, p53, p16 (INK4A)/p14 (ARF), and CDK4 are not common events in familial glioma, occasionally they may account for a subset of familial glioma cases.

To investigate the genetic basis for glioma development in patients with NF1 beyond the first decade of life, molecular genetic analyses of 10 NF1-associated astrocytomas showed NF1 inactivation, supporting a direct association with NF1 rather than a chance occurrence. In addition, genetic changes observed in high-grade sporadic astrocytomas, including TP53 mutation and CDKN2A/p16 deletion, were also seen in NF1-associated high-grade astrocytomas, suggesting that patients with germline NF1 deletions may be

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**Table 1.** Known germline gene mutations and cancer syndromes that include gliomas

<table>
<thead>
<tr>
<th>Cancer Syndrome</th>
<th>Altered Gene</th>
<th>Tumors</th>
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<tbody>
<tr>
<td>Li–Fraumeni syndrome</td>
<td>p53 gene</td>
<td>Sarcoma, breast, brain, leukemia, adrenocortical carcinoma</td>
</tr>
<tr>
<td>Families with patients with multifocal glioma, glioma + second cancer</td>
<td>p53 gene</td>
<td>Various other tumors</td>
</tr>
<tr>
<td>Melanoma–astrocytoma syndrome</td>
<td>p16 (INK4A) / PTEN gene</td>
<td>Melanoma, astrocytoma</td>
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<tr>
<td>Neurofibromatosis 1</td>
<td>p14 (ARF) gene</td>
<td>Glioma, neurofibroma</td>
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<tr>
<td>Neurofibromatosis 2</td>
<td>p14 (ARF) gene</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Turcot’s syndrome (type 1) (benignitary nonpolyposis cancer)</td>
<td>p14 (ARF) gene</td>
<td>Turcot’s syndrome</td>
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<tr>
<td>Turcot’s syndrome (type 2)</td>
<td>mismatch repair genes (MLH1, MSH2, MSH6, PMS2)</td>
<td>BRCA syndrome</td>
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<td>BRCA syndrome</td>
<td>mismatch repair genes (MLH1, MSH2, MSH6, PMS2)</td>
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<td>BRCA syndrome</td>
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at risk for developing late-onset astrocytomas. The Cancer Genome Atlas Network reported at least 47 somatic NFI, inactivating mutations or deletions among 206 glioma patient samples, suggesting that NFI is a human glioblastoma-suppressor gene. Among them, 3 mutations have been reported as germline alterations in NFI patients, indicating that they are probably inactivating mutations. All these recent findings are consistent with the possible role of inactivating germline NFI mutations in the risk of glioma development.

Genetic alterations targeting the PTEN tumor-suppressor gene have been noted in cancers of the prostate and endometrium and in glioblastoma multiforme (GBM), among many others. Germline mutation of PTEN leads to the development of hereditary cancer predisposition syndromes, Cowden disease, and Bannayan–Zonana syndrome, wherein breast and thyroid cancer incidence is elevated. The protein product, PTEN, is a lipid phosphatase, the enzymatic activity of which primarily serves to remove phosphate groups from key intracellular phosphoinositide signaling molecules. This activity normally serves to restrict growth and survival signals by limiting the activity of the phosphoinositide-3 kinase (PI3K) pathway. Somatic mutations of the PIK3CA, which encodes the p110α catalytic subunit of class IA PI3K, were found in 17% of adult gliomas, confirming its involvement in gliomas.

Thus, either the absence or inactivation of PTEN in cancer cells or mutations of the PIK3CA lead to constitutive activation of downstream components of the PI3K pathway including the Akt and mTOR kinases. These data raise the possibility that drugs targeting these kinases, or PI3K itself, might have significant therapeutic activity in PTEN-null cancers. Although germline mutations of the PTEN gene are not common in glioma patients, identification of a novel germline mutation in the PTEN gene (Arg234Gln) in a patient with a glioma and meningioma suggested that this particular missense mutation may have oncogenic properties and predisposed the patient to brain tumors of multiple lineages.

Germline mutations in BRCA-1 and BRCA-2 significantly increase the risk of developing breast and ovarian cancers and are also associated with an increased incidence of primary cancers at other sites including multicentric GBM. DMBT1, a tumor-suppressor gene on chromosome 10q, has been implicated in brain, gastrointestinal, and lung cancer. Some studies suggest that the intragenic homozygous deletion of DMBT1 is common in gliomas and is likely a result of a germline deletion of 1 allele followed by a loss of the second allele during tumor development. However, other studies indicate that DMBT1 polymorphisms are not likely primary targets of 10q loss in malignant gliomas and do not support a major role for DMBT1 in gliomagenesis.

Recurrent allelic losses of chromosome 22 have been reported in gliomas, indicating tumor-suppressor genes at this location. However, the target genes are still unknown. Employment of a high-resolution tiling-path chromosome 22 array to a series of 50 glioblastoma samples detected hemizygous deletions in 28% of the gliomas, with monosomy 22 being the predominant pattern. The distribution of overlapping hemizygous deletions delineated 2 putative tumor-suppressor loci (11.1 and 3.08 Mb in size) across 22q, of germline origin. Analysis of these 2 regions revealed 2 candidate genes, TOP3B, involved in the unlinking of parental strands at the final stage of DNA replication, and TAFA5, which encodes a novel family of proteins with similarity to chemokines.

In addition to Li–Fraumeni cancer family syndrome, neurofibromatosis, and melanoma–astrocytoma syndrome, familial polyposis has been also associated with CNS tumors (Table 1). Microsatellite instability (MIN) is frequently observed in hereditary nonpolyposis colon cancer and in other sporadic cancers. Abnormalities in at least 1 of 5 mismatch repair (MMR) genes are implicated in the development of cancers in hereditary nonpolyposis colon cancer and the associated MIN. Reduced expression of MMR genes is frequent in human gliomas, and aberrant expression of more than 1 MMR gene may be associated with an increased risk of second primary malignancies in glioma patients. MIN and germline MMR gene mutations are present in a subset of young glioma patients, and these patients and their relatives are at risk of developing other hereditary nonpolyposis colorectal cancer syndrome-related tumors, such as colorectal carcinomas (Table 1). Further studies have indicated that homozgyous mutations in MMR genes lead to the childhood cancer syndrome, with hematological malignancies and tumors of brain and bowel early in childhood, often associated with signs similar to neurofibromatosis type 1. Recognition of the inherited nature of the tumors is important for counseling these patients and their families. Turcot’s syndrome is characterized clinically by the concurrence of a primary brain tumor and multiple colorectal adenomas. Thus, the association between brain tumors and multiple colorectal adenomas can result from either 1 of 2 distinct types of germ-line defects: either mutation of a mismatch-repair gene (Turcot’s syndrome type I) or the APC gene (Turcot’s syndrome type II) (Table 1). Molecular diagnosis may contribute to the appropriate diagnosis and management of these patients and counseling of their families.

A recent systematic sequence analysis of well-annotated human protein coding genes identified 189 genes with somatic mutations in breast and colorectal cancers. A subset of these genes was identified as cancer candidate genes and their mutational profiles were evaluated in glioblastoma, melanoma, and pancreatic carcinoma. In this study, a germline nucleotide variant of OBSCN was found, suggesting that OBS-CN, a gene that encodes, RhoGEF protein part of the sarcomeric signaling family of myosin light chain kinases, may be also be involved in glioblastoma predisposition.

### Risk of Glioma in Families with Increased Frequency of Cancers

The epidemiologic evidence is suggestive but inconclusive for an association between brain tumors and
cancers in other family members, including cancers of the breast, lung, and colon. In a large study that included 5088 relatives of 639 probands (3810 first- and 1278 second-degree) diagnosed with a glioma under age 65 years, it was found that familial cancer in relatives of glioma patients are probably a result of multigenic action, and familial clustering of cancer among relatives of glioma patients may involve unknown environmental exposures (Table 2).38

In another epidemiologic study in 1476 glioma patients under age 75 years, the number of observed cancers among 8746 first-degree relatives (FDRs) was compared with the number expected from age-, sex-, and calendar year-specific rates from the Surveillance, Epidemiology, and End Results Program using standardized incidence ratios (SIRs). Among FDRs under 45 years, the overall SIR was 5.08, but for relatives >45 years, the overall SIR was 0.95. The SIRs were significantly elevated for brain tumors (2.14), for melanoma (2.02), and sarcoma (3.83), suggesting similar genetic contributions for these malignancies.39 Similarly, another study in FDRs of patients with gliomas showed that individuals with a family history of specific cancers such as stomach, colon, prostate, or Hodgkin disease may have an increased glioma risk.40 Several other studies reported excess of various types of gliomas in FDRs of glioma patients,41–45 pointing to an unknown yet predisposing gene.

The overall cancer risk in family members with multiple adult glioma patients in 12 Finnish families was equal to that of the reference population, whereas the risk of skin melanoma and meningioma was significantly increased, suggesting that the presence of meningiomas and skin melanomas in glioma families may indicate a novel association as a cancer susceptibility trait.46 However, another study using the Utah Population Data Base examined the familial clustering of primary brain tumors in 1401 primary brain tumor cases defined as astrocytoma or glioblastoma, all with at least 3 generations of genealogy data. The results of that study showed significant excess for astrocytomas and glioblastomas considered as a group for astrocytomas considered separately but not for glioblastomas considered separately. There were increased risks to FDR and second-degree relatives for astrocytomas in relatives of astrocytomas and increased risks to FDRs, but not second-degree relatives, to astrocytoma and glioblastoma when both were considered together and glioblastoma cases were considered separately (Table 2). The authors concluded that the increased familial risk suggests not only a shared environment, but in addition a heritable component.47

**Chromosome Instability and Glioma Risk**

Chromosome instability (CIN) measured as chromosome aberrations may be a cancer susceptibility biomarker. Conventional cytogenetic approaches may improve by combining molecular methods, which increase the sensitivity and specificity of the findings. In a study that
examined both spontaneous and γ-ray-induced CIN in lymphocyte cultures from 51 previously untreated glioma patients and 51 age-, sex- and ethnicity-matched controls, 2 parallel methods were applied, the mutagen sensitivity (MS) assay and the multicolor fluorescence in situ hybridization (FISH) assay. In this study that included a rather small number of patients, the frequency of spontaneous and induced breaks was significantly higher in glioma patients than in controls using the FISH assay but not the MS assay. By combining both methods, an estimated risk of 7.0 was observed, suggesting that each method is a measure of a different event (Table 3). Similar findings were observed in other studies, suggesting that CIN can be detected in the peripheral blood lymphocytes of glioma patients and may be a marker for identifying individuals at risk and that γ-radiation-induced MS of lymphocytes may be associated with an increased risk for glioma.

Genetic Polymorphisms and Inherited Glioma Risk

The variation in inherited risk of glioma could be related to combinations of multiple risk variants. DNA repair genes play a major role in maintaining genomic stability through multiple repair pathways. A recent study in 1127 haplotype-tagging single-nucleotide polymorphisms (SNPs) and 388 putative functional SNPs in 136 DNA repair genes identified 16 SNPs associated with glioma risk at the 1% significance level. The highest association involved rs243356 mapped to intron 3 of CHAF1A gene. This gene encodes a protein that is part of the chromatin assembly factor-1 complex involved in DNA replication and repair. These findings, although the significance at the 1% level was not remarkable, suggested that a genetic variant located in or around the CHAF1A gene may contribute to disease risk (Table 4). DNA repair genes, such as x-ray cross-complementing group 1 (XRCC1), which is associated with repair from ionizing radiation, and O6-methylguanine-DNA methyltransferase (MGMT), which is involved in the removal of alkyl groups from DNA may be linked to gliomas. However, a study reported no evidence of an association between XRCC1 genotypes and glioma but a weak positive association for the MGMT Leu84Phe polymorphism and the MGMT Ile143Val polymorphism. Another study in 309 patients with newly diagnosed glioma and 342 cancer-free control participants reported that the XRCC7 G6721T variant T allele and TT genotype were more common in the cases than in the controls, suggesting that the T allele may be a risk allele and the XRCC7 polymorphism may be a marker for the susceptibility to glioma. Similarly, a study evaluated the association of SNPs Arg194Trp, Arg280His, and Arg399Gln in the XRCCI and Thr241Met in the XRCC3 DNA repair genes and glioma risk in 701 glioma cases, and 1560 controls in a prospective population-based case–control study conducted in Denmark, Finland, Sweden, and the UK. The studied

<table>
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<th>Table 3. Risk assessment for glioma development based on chromosome instability of patient’s lymphocytes exposed to γ irradiation</th>
<th>Publication</th>
<th>Spontaneous Chromosome Breaks of Glioma vs Control OR</th>
<th>Induced Chromosome Breaks of Glioma vs Control OR</th>
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<tr>
<td>El-Zein et al.48; Lymphocytes from: 51 untreated glioma patients and 51 controls</td>
<td>Mutagen sensitivity assay: OR 1.28 (95% CI = 0.99–1.63), NS</td>
<td>Mutagen sensitivity assay: OR 1.28 (95% CI = 0.49–2.80), NS</td>
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<tr>
<td>Bondy et al.50; Lymphocytes from: 45 glioma patients and 117 controls</td>
<td>Mutagen sensitivity assay: OR 5.79 (95% CI = 2.26–14.83), P &lt; .001</td>
<td>Mutagen sensitivity assay: OR 5.79 (95% CI = 2.26–14.83), P &lt; .001</td>
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<tr>
<td>Bondy et al.51; lymphocytes from: 219 glioma patients and 238 controls</td>
<td>Mutagen sensitivity assay: OR 2.09 (95% CI = 0.99–4.43), NS</td>
<td>Mutagen sensitivity assay: OR 2.09 (95% CI = 0.99–4.43), NS</td>
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Spontaneous and induced chromosome breaks refer to either no use or use of γ irradiation. The combination of MS and FISH assays in the El-Zein et al. study resulted in OR of 7.0 (95% CI = 1.7–25.6) for spontaneously induced chromosome breaks. There was no correlation between the breaks detected by the 2 methods, suggesting that each method is a measure of a different event.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Cases</th>
<th>Number of Controls</th>
<th>Number of SNPs and Genes</th>
<th>Genetic Locus</th>
<th>Glioma Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethke et al. 52</td>
<td>1013 glioma cases</td>
<td>1016 controls</td>
<td>1127 SNPs, 388 functional SNPs in 136 DNA repair genes</td>
<td>rs243356 (intron 3 of CHAF1A gene)</td>
<td>OR 1.32; 95% CI = 1.14–1.54</td>
</tr>
<tr>
<td>Schwartzbaum et al. 60</td>
<td>217 cases, 1171 controls</td>
<td>IL-4Rα, IL-13, Cyclooxygenase-2</td>
<td>1805015, 1801275</td>
<td>T-G IL-4Rα haplotype</td>
<td>OR 2.26; 95% CI = 1.13–4.52</td>
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<tr>
<td>Wiemels et al. 61</td>
<td>456 cases and 541 controls</td>
<td>IL-4, IL-13, Cyclooxygenase-2</td>
<td>rs1805015, rs1801275</td>
<td>T-G IL-4Rα haplotype</td>
<td>OR 2.26; 95% CI = 1.13–4.52</td>
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<tr>
<td>Wang et al. 54</td>
<td>309 patients with newly diagnosed glioma; 342 control subjects</td>
<td>IL-4 and IL-13 pathways</td>
<td>XRCC7 G6721T (GT heterozygotes)</td>
<td>OR 1.78; 95% CI = 1.08–2.94, P = .045</td>
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<tr>
<td>Bethke et al. 69</td>
<td>1005 cases; 1011 controls</td>
<td>MTHFR C677T and A1298C, MTRR A66G, and MTR A2756G variants</td>
<td>OR 1.23, 95% CI = 0.91–1.66, P = .02</td>
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<tr>
<td>Liu et al. 57</td>
<td>771 glioma patients; 752 controls</td>
<td>LIG4 and XRCC4 SNPs</td>
<td>Single locus: variant LIG4 SNP2 rs3093739:T &gt; C, increased risk; 3 loci: LIG4 SNP4 rs1805388:C &gt; T, XRCC4 SNP12 rs7734849:A &gt; T, SNP15 rs1056503:G &gt; T; more than additive increased risk P = .001</td>
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<tr>
<td>Liu et al. 58</td>
<td>373 Caucasian glioma patients; 365 Caucasian controls</td>
<td>ERCC1, XRCC1, APEX1, PARP1, MGMT, LIG1, SNPs</td>
<td>6 SNPs (ERCC1 3'UTR, XRCC1 R399Q, APEX1 E148D, PARP1 A762V, MGMT F84L, and LIG1 5'UTR) increased glioma risk; MGMT F84L, main risk factor; MGMT F84L plus PARP1 A762V, dramatic increase glioma risk</td>
<td>OR 5.95, 95% CI = 2.21–16.65</td>
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<tr>
<td>Kiuru et al. 55</td>
<td>701 glioma cases; 1560 controls</td>
<td>XRCC1 and XRCC3 SNPs</td>
<td>Studied SNPs, not increased risk; SNP combinations: homozygous genotypes, XRCC1 Gln399Gln and XRCC3 Met241Met, 3-fold glioma risk</td>
<td>OR 3.18, 95% CI = 1.26–8.04</td>
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<tr>
<td>Bethke et al. 62</td>
<td>1005 cases; 1011 controls</td>
<td>CASP8 D302H polymorphism</td>
<td>Carriers, 1.37 increased risk</td>
<td>OR 1.37, 95% CI = 1.10–1.70, P = .004</td>
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<tr>
<td>Rajaraman et al. 63</td>
<td>CASP8, CCND1, CCNH, CDKN1A, CDKN2A, CHEK1, CHEK2, MDM2, PTEN, TP53 polymorphisms</td>
<td>CCND1 Ex4-1G &gt; A and CCNH Ex8 + 49T &gt; C variants, increased glioma risk; MDM2 Ex12 + 162A &gt; G, reduced glioma risk</td>
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<tr>
<td>Lu et al. 68</td>
<td>236 glioma patients; 366 controls</td>
<td>MMP-1, MMP-3, MMP-9 polymorphisms</td>
<td>MMP-1 -1607 1G/1G genotype and MMP-1 1G-MMP-3 6A haplotype may play protective role in the development of adult astrocytoma</td>
<td>OR 0.45, 95% CI = 0.29–0.67</td>
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<tr>
<td>Liu et al. 56</td>
<td>771 glioma patients; 752 healthy controls</td>
<td>XRCC5, XRCC6, XRCC7 polymorphisms</td>
<td>XRCC5 haplotype “CAGTT,” 40% reduction in glioma risk</td>
<td>OR 0.60, 95% CI = 0.43–0.85</td>
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</table>
SNPs were not significantly associated with the risk of glioma, however, in pair-wise comparisons, carriers of both homozygous variant genotypes, i.e., XRCCI Gin399Gln and XRC3 Met241Met, were associated with a 3-fold increased risk of glioma.55

Exposure to ionizing radiation, which can cause single-strand and double-strand DNA breaks (DSBs), is a risk factor for gliomas. An investigation in 771 glioma patients and 752 healthy controls for SNPs of XRC5, XRC6, and XRC7 candidate genes involved in the DSB repair pathway revealed increased glioma risk of 3 XRC5 rSNPs (SNP1 rs828704, SNP6 rs3770502, and SNP7 rs9288516), 1 XRC6 SNP (SNP4 rs6519265, P = .044), but no XPC7 SNPs. A haplotype-based association analysis revealed that glioma was associated with 1 protective XRC5 haplotype, "CAGTT," accounting for a 40% reduction.56 The LIG4 and XRC4 genes encode proteins that form a complex functionally linked to the repair of double-stranded DNA breaks. A case–control analysis of 771 glioma patients and 752 cancer-free controls assessed the associations between glioma risk and 20 tagging SNPs of these genes and evaluated their potential gene–gene interactions using the multifactor dimensionality reduction (MDR), interaction dendrogram, and entropy analysis. In a single-locus analysis, the LIG4 SNP2 rs3093739:T > C was significantly associated with the risk of developing glioma. A haplotype analysis revealed an association of glioma risk with genetic variants in LIG4 block 1 and XRC4 blocks 2 and 4. The MDR analysis suggested a significant 3-locus interaction model involving LIG4 SNP4 rs1805388:C > T, XRC4 SNP12 rs7734849:A > T, and SNP15 rs10565030:G > T. Further analysis indicated a more-than-additive effect among these 3 loci, suggesting that these variants may add to glioma susceptibility.57 Similarly, a study in 373 Caucasian glioma cases and 363 cancer-free Caucasian controls was performed to determine possible associations between glioma risk and 18 functional SNPs in DNA repair genes, using a multi-analytic strategy combining logistic regression, MDR, and classification and regression tree (CART) approaches.58 This study demonstrated 6 SNPs (ERCCI 3′UTR, XRCCI R399Q, APEX1 E148D, PARP1 A762V, MGMT F84L, and LIG1 5′UTR) with a significant association with glioma risk. Furthermore, employing both the MDR and CART analyses identified MGMT F84L as the predominant risk factor for glioma, which was dramatically increased in ionizing radiation, exposed individuals who had the wild-type genotypes of both MGMT F84L and PARP1 A762V (Table 4).

A repressed immune system may be another mechanism predisposing to glioma formation. Previous studies have reported an association between interleukin (IL)-4Ra, IL-13, and glioblastoma that are independent of their role in allergic conditions.59 An international case–control study of IL-4Ra, IL-13, and cyclooxygenase-2 polymorphisms and glioblastoma risk reported an association between the T-G IL-4Ra haplotype and glioblastoma risk, indicating a role of immune factors in glioblastoma development.60 Similarly, there is evidence of different frequencies of polymorphisms in the IL-13 and IL-4 pathways than controls in glioblastomas, suggesting a role for IL-4, IL-4R, and IL-13 haplotypes on case–control status.61

Abnormal apoptosis is a major contributor to glioma formation. Caspase 8 (CASP8) represents one of the key regulators of apoptosis. An analysis of 5 series of glioma case patients and controls found that the carrier status for the rare allele of CASP8 polymorphism D302H was associated with a 1.37-fold increased risk indicating the importance of inherited variation in the apoptosis pathway in susceptibility to glioma.62 Ten genes (CASP8, CCND1, CCNH, CDKN1A, CDKN2A, CHEK1, CHEK2, MDM2, PTEN, and TP53) involved in apoptosis and cell cycle control pathways were evaluated in 388 glioma patients with respect to 12 SNPs. The CCND1 Ex4-1G > A variant was associated with increased risk for glioma, and the Ex8 + 49T > C variant of CCNH was associated with increased risk of glioma and acoustic neuroma. However, the MDM2 Ex12 + 162A > G variant was associated with significantly reduced risk of glioma. The authors concluded that future research should include more detailed coverage of genes in the apoptosis/cell cycle control pathways.63

The diffuse and extensive infiltration of malignant gliomas into the surrounding normal brain is believed to rely on modifications of the proteolysis of extracellular matrix components.64 Similarly, increased matrix metalloproteinases,65 such as metalloproteinase 9 (MMP-9) levels, are associated with human glioma tumor progression.66 Recently, an association between the A to G transition at the −181-bp position in the promoter of matrix metalloproteinase-7 gene (MMP-7-181A/G) and susceptibility to adult astrocytoma was described.67 In order to investigate the association of the SNPs in MMP-1, MMP-3, and MMP-9 promoters with glioma risk, genotyping for the MMP-1 -1607 2G/1G, MMP-3 -1171 5A/6A, and MMP-9 -1562 C/T SNPs were performed among 236 adult Chinese glioma patients and 366 healthy controls. The results showed that compared with the 2G/2G MMP-1 genotype, the 1G/1G genotype significantly decreased the risk of astrocytoma development. No association between MMP-3 -1171 5A/6A or MMP-9 -1562 C/T SNPs and astrocytoma was observed; however, MMP-1 1G-MMP-3 6A haplotype significantly reduced the risk of astrocytoma development when using MMP-1 2G-MMP-3 6A haplotype as a reference. Thus, in this population sample, the MMP-1 -1607 1G/1G genotype and MMP-1 1G-MMP-3 6A haplotype may play a protective role in the development of adult astrocytoma.68

Folate metabolism plays an important role in carcinogenesis. A recent study in 1005 glioma cases and 1101 controls for the 5,10-methylenetetrahydrofolate reductase (MTHFR), C677T and A1298C, methionine synthase (MTR) A66G, and methionine synthase reductase (MTR) A2756G variants showed that MTHFR C677T-A1298C diplotypes were associated
with risk of glioma ($P = .02$) and reduced MTHFR activity.$^{59}$

A polymorphism in the epidermal growth factor ($EGF$) gene ($EGF + 61$, located in the 5'UTR of the $EGF$) may be a susceptibility factor for the development of gliomas and influence their aggressive behavior.$^{70}$ However, other studies have indicated that although this polymorphism is functional, it is not a significant risk factor for glioblastoma development or overall survival.$^{71}$ Aberrant expression of the platelet-derived growth factor $\alpha$-receptor ($PDGFRA$) gene, especially $PDGFRA$ promoter haplotypes, may predispose to gliomas.$^{72}$

Because of these findings, the Brain Tumor Epidemiology Consortium has been recently formed to coordinate research focused on identifying various germline polymorphisms associated with the risk of glioma and using molecular markers to classify glial tumors into more homogenous groups.$^{73}$ Furthermore, an international consortium (GLOGENE) was also formed in order to characterize genes in glioma families using a genome-wide SNP approach and conduct linkage analysis to identify new genomic regions or loci that could harbor genes important for gliomagenesis.$^{74}$

Conclusions

Germline genetic abnormalities that influence glioma formation involve the $NF1$ gene, $p53$ gene, $MMR$ genes, $APC$ gene, and only rarely the $PTEN$, $p16$($INK4A$)/$p14$($ARF$), and $CDK4$. In addition, genetic polymorphisms that predispose to glioma formation involve heavily multiple genes that regulate various DNA repair pathways. Thus, although not clearly established yet, initial predisposing events that involve genes regulating DNA repair and apoptosis may eventually lead to further somatic events and the formation of glial tumors. These predisposing alterations are more frequent in families with a history of multiple cancers and occasionally in random gliomas. Ongoing and future research may identify additional germline polymorphisms associated with the risk of glioma and classify glial tumors into more homogenous groups using molecular markers. In such cases, the approximate risk for developing glioma could be estimated and family members could be closely monitored to avoid potential environmental risk factors and enroll into chemopreventive trials.

Conflict of interest statement. None declared.

Funding

This research was supported by National Cancer Institute grants CA 75557, CA 92393, CA 95058, and CA 116708 (to JSR), and CA119215 and CA 070917 (to MLB).

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