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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.

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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),[6,7] occasionally in nonfamilial malignancies such as multifocal osteosarcoma,[8] in a small subgroup of young patients with 2 or more primary malignancies,[9, 10] and in patients with sporadic breast carcinoma.[11] 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).[12] 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.[13] Other studies have suggested that *p53* germline mutations may identify a subset of young adults predisposed to the development of high-grade astrocytic tumors.[14] 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.[15] 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.[16] 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.[17]

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.[18] However, a germline deletion of the *p14*(*ARF*)-specific exon 1β 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.[19] 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.[20]

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

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

Cancer Syndrome	Altered Gene	Tumors
Li–Fraumeni syndrome	*P53* gene[6–11]	Sarcoma, breast, brain, leukemia, adrenocortical carcinoma
Families with patients with multifocal glioma, glioma + second cancer	*P53* gene[12,14]	Various other tumors
Melanoma–astrocytoma syndrome	*P14* (*ARF*) gene[19,20]	Melanoma, astrocytoma
Neurofibromatosis 1	*NF1* gene[21]	Glioma, neurofibroma, pheochromocytoma, meningioma, schwannoma
Neurofibromatosis 2	*NF2* gene[75]	Bilateral acoustic schwannoma, meningioma, glioma, neurofibroma, ependymoma
Turcot's syndrome (type 1) (hereditary nonpolyposis cancer syndrome)	Mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*)[35,36]	Colorectal carcinoma, glioma
Turcot's syndrome (type 2)	*APC* gene[36]	Colorectal carcinoma, primary brain tumor
BRCA syndrome	*BRCA-1*, *BRCA-2*[26]	Breast, ovarian, prostatic, pancreatic, glioma

at risk for developing late-onset astrocytomas.[21] The Cancer Genome Atlas Network reported at least 47 somatic *NF1*, inactivating mutations or deletions among 206 glioma patient samples, suggesting that *NF1* is a human glioblastoma-suppressor gene.[2] Among them, 5 mutations have been reported as germline alterations in NF1 patients, indicating that they are probably inactivating mutations. All these recent findings are consistent with the possible role of inactivating germline *NF1* 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.[22, 23] 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.[24] Thus, either the absence of functional 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.[22] 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.[25]

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.[26] *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.[27] 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.[28]

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.[29]

In addition to Li–Fraumeni cancer family syndrome, neurofibromatosis, and melanoma–astrocytoma syndrome, familial polyposis has been also associated with CNS tumors (Table 1).[30] 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.[31] 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).[32] Further studies have indicated that homozygous mutations in *MMR* genes lead to the childhood cancer syndrome,[33] with hematological malignancies and tumors of brain and bowel early in childhood, often associated with signs similar to neurofibromatosis type 1.[34] Recognition of the inherited nature of the tumors is important for counseling these patients and their families.[35] 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.[36]

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 *OBSCN*, 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.[37]

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), 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]

Table 2. Epidemiologic studies in families with gliomas and other tumors

Studies	Patients Number	Relatives Number	Observed Cancers	Etiology of Familial Cancer
de Andrade et al.[38]	639 (under age 65 years)	5088 (first degree: 3810, second degree: 1278)	Clustering of multiple cancers in relatives of glioma patients	Multigenic action (unknown environmental exposure)
Scheurer et al.[39]	1476 (under age 75 years)	8746 (all first degree)	SIR 5.08 (FDRs < 45 years) melanoma, brain tumors, sarcoma; SIR 0.95 (FDRs > 45 years)	Unknown similar genetic contribution
Paunu et al.[46]	Multiple adult glioma patients in 17 Finnish families		SIR 1.1, 95% CI 0.8–1.4 for all cancers (melanoma: SIR 4.0, 95% CI 1.5–8.8; meningioma: SIR 5.5, 95% CI 1.1–16)	Unknown cancer susceptibility trait
Blumenthal and Cannon-Albright[47]	Utah Population Data Base in 1401 primary brain tumor cases with at least 3 generations of genealogy data	First degree: 11 498 Second degree: 36 650	RR 3.29, 95% CI: 2.33–4.51, $P < .00001$ RR 1.22, 95% CI: 0.83–1.74, $P = .15$	Heritable glioma risk and shared environment

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).[48] 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[49, 50] and that γ-radiation-induced MS of lymphocytes may be associated with an increased risk for glioma.[51]

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).[52] 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.[53] 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.[54] Similarly, a study evaluated the association of SNPs Arg194Trp, Arg280His, and Arg399Gln in the *XRCC1* 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 3. Risk assessment for glioma development based on chromosome instability of patient's lymphocytes exposed to γ irradiation

Publications	Spontaneous Chromosome Breaks of Glioma vs Control OR	Induced Chromosome Breaks of Glioma vs Control OR
El-Zein et al.[48]; Lymphocytes from: 51 untreated glioma patients and 51 controls	Mutagen sensitivity assay: OR 1.32 (95% CI = 0.49–3.58), NS FISH assay: OR 5.13 (95% CI = 2.23–12.1), $P < .001$	Mutagen sensitivity assay: OR 1.28 (95% CI = 0.59–2.80), NS FISH assay: OR 4.86 (95% CI = 2.08–11.4), $P < .001$
Bondy et al.[50]; Lymphocytes from: 45 glioma patients and 117 controls		Mutagen sensitivity assay: OR 5.79 (95% CI = 2.26–14.83), $P < .0001$
Bondy et al.[51]; lymphocytes from: 219 glioma patients and 238 controls		Mutagen sensitivity assay: OR 2.09 (95% CI = 1.43–3.06), $P < .001$

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 4. Representative recent studies describing genetic polymorphisms linked to glioma risk

	Type of Polymorphism	Genetic Locus	Glioma Risk
Bethke et al.[52]	1013 glioma cases, 1016 controls, 1127 SNPs, and 388 putative functional SNPs in 136 DNA repair genes	rs243356 (intron 3 of *CHAF1A* gene)	OR 1.32; 95% CI = 1.14–1.54
Schwartzbaum et al.[60]	217 cases, 1171 controls IL-4Rα, IL-13, *Cyclooxygenase-2*	rs1805015, rs1801275 (T-*G IL-4R*α haplotype)	OR 2.26; 95% CI = 1.13–4.52
Wiemels et al.[61]	456 cases and 541 controls IL-4 and IL-13 pathways	A *IL-4* haplotype, borderline increased risk A rare *IL-4* haplotype, decreased risk A common *IL-13* haplotype, decreased risk	OR 1.5, 95% CI = 1.0–2.3 OR 0.23, 95% CI = 0.07–0.83 OR 0.73, 95% CI = 0.53–1.00
Wang et al.[54]	309 patients with newly diagnosed glioma; 342 control subjects; *XRCC1*, *XRCC3*, *RAD51*, *XRCC7*, *p53*	*XRCC7* G6721T (GT heterozygotes) TT genotype increased in cases	OR 1.78, 95% CI = 1.08–2.94, $P = .045$ OR 1.86; 95% CI = 1.12–3.09, $P = .040$
Bethke et al.[69]	1005 glioma cases; 1101 controls; *MTHFR* C677A and A1298C, *MTRR* A66G, and *MTR* A2756G variants	*MTHFR* C677T A1298C diplotypes, increased risk	OR 1.23, 95% CI = 0.91–1.66, $P = .02$
Liu et al.[57]	771 glioma patients; 752 controls; *LIG4* and *XRCC4* SNPs	Single locus: variant *LIG4* SNP2 rs3093739:T > C, increased risk; 3 locus: *LIG4* SNP4 rs1805388:C > T, *XRCC4* SNP12 rs7734849:A > T, SNP15 rs1056503:G > T; more than additive increased risk $P = .001$	
Liu et al.[58]	373 Caucasian glioma patients; 365 Caucasian controls; *ERCC1*, *XRCC1*, *APEX1*, *PARP1*, *MGMT*, *LIG1*, SNPs	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	OR 5.95, 95% CI = 2.21–16.65
Kiuru et al.[55]	701 glioma cases; 1560 controls; *XRCC1* and *XRCC3* SNPs	Studied SNPs, not increased risk; SNP combinations: homoxygous genotypes, *XRCC1* Gln399Gln and *XRCC3* Met241Met, 3-fold glioma risk	OR 3.18, 95% CI = 1.26–8.04
Bethke et al.[62]	1005 cases; 1011 controls; *CASP8* D302H polymorphism	Carriers, 1.37 increased risk	OR 1.37, 95% CI = 1.10–1.70, $P = .004$
Rajaraman et al.[63]	*CASP8*, *CCND1*, *CCNH*, *CDKN1A*, *CDKN2A*, *CHEK1*, *CHEK2*, *MDM2*, *PTEN*, *TP53* polymorphisms	*CCND1* Ex4-1G > A and *CCNH* Ex8 + 49T > C variants, increased glioma risk; *MDM2* Ex12 + 162A > G, reduced glioma risk	
Lu et al.[68]	236 glioma patients; 366 controls; *MMP-1*, *MMP-3*, *MMP-9* polymorphisms	*MMP-1* -1607 1G/1G genotype and *MMP-1* 1G-MMP-3 6A haplotype may play protective role in the development of adult astrocytoma	OR 0.45, 95% CI = 0.29–0.67
Liu et al.[56]	771 glioma patients; 752 healthy controls *XRCC5*, *XRCC6*, *XRCC7* polymorphisms	*XRCC5* haplotype "CAGTT," 40% reduction in glioma risk	OR 0.60, 95% CI = 0.43–0.85

SNPs were not significantly associated with the risk of glioma, however, in pair-wise comparisons, carriers of both homozygous variant genotypes, i.e., *XRCC1* Gln399Gln and *XRCC3* 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 *XRCC5*, *XRCC6*, and *XRCC7* candidate genes involved in the DSB repair pathway revealed increased glioma risk of 3 *XRCC5* tSNPs (*SNP1* rs828704, *SNP6* rs3770502, and *SNP7* rs9288516), 1 *XRCC6* SNP (SNP4 rs6519265, $P = .044$), but no *XPCC7* SNPs. A haplotype-based association analysis revealed that glioma was associated with 1 protective XRCC5 haplotype "CAGTT," accounting for a 40% reduction.[56] The *LIG4* and *XRCC4* 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 *XRCC4* blocks 2 and 4. The MDR analysis suggested a significant 3-locus interaction model involving *LIG4* SNP4 rs1805388:C > T, *XRCC4* SNP12 rs7734849:A > T, and SNP15 rs1056503: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 365 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 (*ERCC1* 3'UTR, *XRCC1* 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-4Rα, IL-13, and cyclooxygenase-2 polymorphisms and glioblastoma risk reported an association between the T-G IL-4Rα 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*), C677A and A1298C, methionine synthase (*MTRR*) 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.[69]

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 α-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 (GLIOGENE) 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.

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References

1. Kyritsis AP, Zhang B, Zhang W, et al. Mutations of the p16 gene in gliomas. *Oncogene.* 1996;12:63–67.
2. The Cancer Genome Atlas (TCGA) Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature.* 2008;455:1061–1068.
3. Goussia AC, Agnantis NJ, Rao JS, Kyritsis AP. Cytogenetic and molecular abnormalities in astrocytic gliomas (review). *Oncol Rep.* 2000;7:401–412.
4. Fueyo J, Gomez-Manzano C, Yung WK, et al. Suppression of human glioma growth by adenovirus-mediated Rb gene transfer. *Neurology.* 1998;50:1307–1315.
5. Chintala SK, Fueyo J, Gomez-Manzano C, et al. Adenovirus-mediated p16/CDKN2 gene transfer suppresses glioma invasion in vitro. *Oncogene.* 1997;15:2049–2057.
6. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res.* 1988;48:5358–5362.
7. Srivastava S, Tong YA, Devadas K, et al. Detection of both mutant and wild-type p53 protein in normal skin fibroblasts and demonstration of a shared 'second hit' on p53 in diverse tumors from a cancer-prone family with Li–Fraumeni syndrome. *Oncogene.* 1992;7:987–991.
8. Iavarone A, Matthay KK, Steinkirchner TM, Israel MA. Germ-line and somatic p53 gene mutations in multifocal osteogenic sarcoma. *Proc Natl Acad Sci USA.* 1992;89:4207–4209.
9. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science.* 1990;250:1233–1238.
10. Malkin D, Jolly KW, Barbier N, et al. Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. *N Engl J Med.* 1992;326:1309–1315.
11. Sidransky D, Tokino T, Helzlsouer K, et al. Inherited p53 gene mutations in breast cancer. *Cancer Res.* 1992;52:2984–2986.
12. Kyritsis AP, Bondy ML, Xiao M, et al. Germline p53 gene mutations in subsets of glioma patients. *J Natl Cancer Inst.* 1994;86:344–349.
13. Zhou XP, Sanson M, Hoang-Xuan K, et al. Germline mutations of p53 but not p16/CDKN2 or PTEN/MMAC1 tumor suppressor genes predispose to gliomas. The ANOCEF Group. Association des NeuroOncologues d'Expression Francaise. *Ann Neurol.* 1999;46:913–916.
14. Chen P, Iavarone A, Fick J, Edwards M, Prados M, Israel MA. Constitutional p53 mutations associated with brain tumors in young adults. *Cancer Genet Cytogenet.* 1995;82:106–115.
15. Portwine C, Chilton-MacNeill S, Brown C, Sexsmith E, McLaughlin J, Malkin D. Absence of germline and somatic p53 alterations in children with sporadic brain tumors. *J Neurooncol.* 2001;52:227–235.
16. Vital A, Bringuier PP, Huang H, et al. Astrocytomas and choroid plexus tumors in two families with identical p53 germline mutations. *J Neuropathol Exp Neurol.* 1998;57:1061–1069.
17. Paunu N, Syrjakoski K, Sankila R, et al. Analysis of p53 tumor suppressor gene in families with multiple glioma patients. *J Neurooncol.* 2001;55:159–165.

18. Gao L, Liu L, van MD, et al. Lack of germ-line mutations of CDK4, p16(INK4A), and p15(INK4B) in families with glioma. *Clin Cancer Res.* 1997;3:977–981.
19. Randerson-Moor JA, Harland M, Williams S, et al. A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour syndrome family. *Hum Mol Genet.* 2001;10:55–62.
20. Tachibana I, Smith JS, Sato K, Hosek SM, Kimmel DW, Jenkins RB. Investigation of germline PTEN, p53, p16(INK4A)/p14(ARF), and CDK4 alterations in familial glioma. *Am J Med Genet.* 2000;92: 136–141.
21. Gutmann DH, James CD, Poyhonen M, et al. Molecular analysis of astrocytomas presenting after age 10 in individuals with NF1. *Neurology.* 2003;61:1397–1400.
22. Sansal I, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. *J Clin Oncol.* 2004;22:2954–2963.
23. Eng C. PTEN: one gene, many syndromes. *Hum Mutat.* 2003;22:183–198.
24. Gallia GL, Rand V, Siu IM, et al. PIK3CA gene mutations in pediatric and adult glioblastoma multiforme. *Mol Cancer Res.* 2006;4:709–714.
25. Staal FJ, van der Luijt RB, Baert MR, et al. A novel germline mutation of PTEN associated with brain tumours of multiple lineages. *Br J Cancer.* 2002;86:1586–1591.
26. Elmariah SB, Huse J, Mason B, Leroux P, Lustig RA. Multicentric glioblastoma multiforme in a patient with BRCA-1 invasive breast cancer. *Breast J.* 2006;12:470–474.
27. Pang JC, Dong Z, Zhang R, et al. Mutation analysis of DMBT1 in glioblastoma, medulloblastoma and oligodendroglial tumors. *Int J Cancer.* 2003;105:76–81.
28. Sasaki H, Betensky RA, Cairncross JG, Louis DN. DMBT1 polymorphisms: relationship to malignant glioma tumorigenesis. *Cancer Res.* 2002;62:1790–1796.
29. de Stahl TD, Hartmann C, de BC, et al. Chromosome 22 tiling-path array-CGH analysis identifies germ-line- and tumor-specific aberrations in patients with glioblastoma multiforme. *Genes Chromosomes Cancer.* 2005;44:161–169.
30. Bondy M, Wiencke J, Wrensch M, Kyritsis AP. Genetics of primary brain tumors: a review. *J Neurooncol.* 1994;18:69–81.
31. Wei Q, Bondy ML, Mao L, et al. Reduced expression of mismatch repair genes measured by multiplex reverse transcription-polymerase chain reaction in human gliomas. *Cancer Res.* 1997;57:1673–1677.
32. Leung SY, Chan TL, Chung LP, et al. Microsatellite instability and mutation of DNA mismatch repair genes in gliomas. *Am J Pathol.* 1998;153:1181–1188.
33. Kruger S, Kinzel M, Walldorf C, et al. Homozygous PMS2 germline mutations in two families with early-onset haematological malignancy, brain tumours, HNPCC-associated tumours, and signs of neurofibromatosis type 1. *Eur J Hum Genet.* 2008;16:62–72.
34. Trimbath JD, Petersen GM, Erdman SH, Ferre M, Luce MC, Giardiello FM. Cafe-au-lait spots and early onset colorectal neoplasia: a variant of HNPCC? *Fam Cancer.* 2001;1:101–105.
35. Poley JW, Wagner A, Hoogmans MM, et al. Biallelic germline mutations of mismatch-repair genes: a possible cause for multiple pediatric malignancies. *Cancer.* 2007;109:2349–2356.
36. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. *N Engl J Med.* 1995;332:839–847.
37. Balakrishnan A, Bleeker FE, Lamba S, et al. Novel somatic and germline mutations in cancer candidate genes in glioblastoma, melanoma, and pancreatic carcinoma. *Cancer Res.* 2007;67:3545–3550.
38. de Andrade M, Barnholtz JS, Amos CI, Adatto P, Spencer C, Bondy ML. Segregation analysis of cancer in families of glioma patients. *Genet Epidemiol.* 2001;20:258–270.
39. Scheurer ME, Etzel CJ, Liu M, et al. Aggregation of cancer in first-degree relatives of patients with glioma. *Cancer Epidemiol Biomarkers Prev.* 2007;16:2491–2495.
40. Hill DA, Inskip PD, Shapiro WR, et al. Cancer in first-degree relatives and risk of glioma in adults. *Cancer Epidemiol Biomarkers Prev.* 2003;12:1443–1448.
41. Fountaine T, Lind CR, Law AJ. Primary glioblastomas and anaplastic astrocytoma in a glioma family. *J Clin Neurosci.* 2006;13: 497–501.
42. Malmer B, Haraldsson S, Einarsdottir E, Lindgren P, Holmberg D. Homozygosity mapping of familial glioma in Northern Sweden. *Acta Oncol.* 2005;44:114–119.
43. Malmer B, Henriksson R, Gronberg H. Different aetiology of familial low-grade and high-grade glioma? A nationwide cohort study of familial glioma. *Neuroepidemiology.* 2002;21:279–286.
44. Paunu N, Lahermo P, Onkamo P, et al. A novel low-penetrance locus for familial glioma at 15q23-q26.3. *Cancer Res.* 2002;62: 3798–3802.
45. Hardman PD, Bell J, Whittle IR, Gregor A. Familial glioma: a report of glioblastoma in identical twins and oligo-astrocytoma in siblings. *Br J Neurosurg.* 1989;3:709–715.
46. Paunu N, Pukkala E, Laippala P, et al. Cancer incidence in families with multiple glioma patients. *Int J Cancer.* 2002;97:819–822.
47. Blumenthal DT, Cannon-Albright LA. Familiality in brain tumors B2008. *Neurology.* 2008;71:1015–1020.
48. El-Zein R, Bondy ML, Wang LE, et al. Risk assessment for developing gliomas: a comparison of two cytogenetic approaches. *Mutat Res.* 2001;490:35–44.
49. El-Zein R, Bondy ML, Wang LE, et al. Increased chromosomal instability in peripheral lymphocytes and risk of human gliomas. *Carcinogenesis.* 1999;20:811–815.
50. Bondy ML, Kyritsis AP, Gu J, et al. Mutagen sensitivity and risk of gliomas: a case-control analysis. *Cancer Res.* 1996;56:1484–1486.
51. Bondy ML, Wang LE, El-Zein R, et al. Gamma-radiation sensitivity and risk of glioma. *J Natl Cancer Inst.* 2001;93:1553–1557.
52. Bethke L, Webb E, Murray A, et al. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. *Hum Mol Genet.* 2008;17:800–805.
53. Felini MJ, Olshan AF, Schroeder JC, et al. DNA repair polymorphisms XRCC1 and MGMT and risk of adult gliomas. *Neuroepidemiology.* 2007;29:55–58.
54. Wang LE, Bondy ML, Shen H, et al. Polymorphisms of DNA repair genes and risk of glioma W2004. *Cancer Res.* 2004;64:5560–5563.
55. Kiuru A, Lindholm C, Heinavaara S, et al. XRCC1 and XRCC3 variants and risk of glioma and meningioma K2008. *J Neurooncol.* 2008;88:135–142.
56. Liu Y, Zhang H, Zhou K, et al. Tagging SNPs in non-homologous end-joining pathway genes and risk of glioma. *Carcinogenesis.* 2007;28:1906–1913.
57. Liu Y, Zhou K, Zhang H, et al. Polymorphisms of LIG4 and XRCC4 involved in the NHEJ pathway interact to modify risk of glioma L2008. *Hum Mutat.* 2008;29:381–389.
58. Liu Y, Scheurer ME, El-Zein R, et al. Association and interaction between DNA repair gene polymorphisms and adult glioma. Cancer Epidemiol Biomarkers Prev. *In press*.

59. Schwartzbaum J, Ahlbom A, Malmer B, et al. Polymorphisms associated with asthma are inversely related to glioblastoma multiforme. *Cancer Res.* 2005;65:6459–6465.
60. Schwartzbaum JA, Ahlbom A, Lonn S, et al. An international case–control study of interleukin-4Ralpha, interleukin-13, and cyclooxygenase-2 polymorphisms and glioblastoma risk. *Cancer Epidemiol Biomarkers Prev.* 2007;16:2448–2454.
61. Wiemels JL, Wiencke JK, Kelsey KT, et al. Allergy-related polymorphisms influence glioma status and serum IgE levels. *Cancer Epidemiol Biomarkers Prev.* 2007;16:1229–1235.
62. Bethke L, Sullivan K, Webb E, et al. The common D302H variant of CASP8 is associated with risk of glioma B2008B. *Cancer Epidemiol Biomarkers Prev.* 2008;17:987–989.
63. Rajaraman P, Wang SS, Rothman N, et al. Polymorphisms in apoptosis and cell cycle control genes and risk of brain tumors in adults. *Cancer Epidemiol Biomarkers Prev.* 2007;16:1655–1661.
64. Chintala SK, Sawaya R, Aggarwal BB, et al. Induction of matrix metalloproteinase-9 requires a polymerized actin cytoskeleton in human malignant glioma cells. *J Biol Chem.* 1998;273:13545–13551.
65. Kondraganti S, Mohanam S, Chintala SK, et al. Selective suppression of matrix metalloproteinase-9 in human glioblastoma cells by antisense gene transfer impairs glioblastoma cell invasion. *Cancer Res.* 2000;60:6851–6855.
66. Lakka SS, Rajan M, Gondi C, et al. Adenovirus-mediated expression of antisense MMP-9 in glioma cells inhibits tumor growth and invasion. *Oncogene.* 2002;21:8011–8019.
67. Lu Z, Wang Y, Zhang Q, et al. Association between the functional polymorphism in the matrix metalloproteinase-7 promoter and susceptibility to adult astrocytoma. *Brain Res.* 2006;1118:6–12.
68. Lu Z, Cao Y, Wang Y, et al. Polymorphisms in the matrix metalloproteinase-1, 3, and 9 promoters and susceptibility to adult astrocytoma in northern China. *J Neurooncol.* 2007;85:65–73.
69. Bethke L, Webb E, Murray A, et al. Functional polymorphisms in folate metabolism genes influence the risk of meningioma and glioma B2008A. *Cancer Epidemiol Biomarkers Prev.* 2008;17:1195–1202.
70. Costa BM, Ferreira P, Costa S, et al. Association between functional EGF + 61 polymorphism and glioma risk. *Clin Cancer Res.* 2007;13:2621–2626.
71. Vauleon E, Auger N, ouaich-Amiel A, et al. The 61 A/G EGF polymorphism is functional but is neither a prognostic marker nor a risk factor for glioblastoma. *Cancer Genet Cytogenet.* 2007;172:33–37.
72. Toepoel M, Joosten PH, Knobbe CB, et al. Haplotype-specific expression of the human PDGFRA gene correlates with the risk of glioblastomas. *Int J Cancer.* 2008;123:322–329.
73. Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. *Nat Clin Pract Neurol.* 2006;2:494–503.
74. Malmer B, Adatto P, Armstrong G, et al. GLIOGENE an International Consortium to Understand Familial Glioma. *Cancer Epidemiol Biomarkers Prev.* 2007;16:1730–1734.
75. Evans DG, Sainio M, Baser ME. Neurofibromatosis type 2. *J Med Genet.* 2000;37:897–904.