Survival and low-grade glioma: the emergence of genetic information

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Significant gaps exist in our understanding of the causes and clinical management of glioma. One of the biggest gaps is how best to manage low-grade (World Health Organization [WHO] Grade II) glioma. Low-grade glioma (LGG) is a uniformly fatal disease of young adults (mean age 41 years), with survival averaging approximately 7 years. Although LGG patients have better survival than patients with high-grade (WHO Grade III or IV) glioma, all LGGs eventually progress to high-grade glioma and death. Data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute suggest that for the majority of LGG patients, overall survival has not significantly improved over the past 3 decades, highlighting the need for intensified study of this tumor. Recently published research suggests that historically used clinical variables are not sufficient (and are likely inferior) prognostic and predictive indicators relative to information provided by recently discovered tumor markers (e.g., 1p/19q deletion and *IDH1* or *IDH2* mutation status), tumor expression profiles (e.g., the proneural profile) and/or constitutive genotype (e.g., rs55705857 on 8q24.21). Discovery of such tumor and constitutive variation may identify variables needed to improve randomization in clinical trials as well as identify patients more sensitive to current treatments and targets for improved treatment in the future. This article reports on survival trends for patients diagnosed with LGG within the United States from 1973 through 2011 and reviews the emerging role of tumor and constitutive genetics in refining risk stratification, defining targeted therapy, and improving survival for this group of relatively young patients.

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GLIOMAS are classified as Grades I to IV based on histology and clinical criteria.⁴³ Grade I tumors are generally benign and frequently curable with complete resection, occur primarily in children, and are believed to represent an entity separate from Grade II–IV tumors (seen primarily in adults). Adult Grade II tumors (low-grade gliomas [LGGs]) include: 1) astrocytomas, 2) oligo-astrocytomas or mixed gliomas, and 3) oligodendrogliomas.⁴³ Astrocytomas and oligodendrogliomas con-

sist of astrocytes or oligodendrocytes, respectively, while mixed gliomas contain a mixture of the 2 cell types. Essentially all Grade II lesions eventually progress to high-grade glioma (HGG) (Grade III/IV). Grade IV tumors (also known as glioblastomas [GBMs]) that arise from LGGs are termed “secondary GBM” to differentiate them from “primary” or “de novo” GBM, as the pathway leading to these 2 GBM types differs in a number of genetic abnormalities and clinical characteristics.⁷⁴ Most patients

ABBREVIATIONS GBM = glioblastoma; GWAS = genome-wide association study; HGG = high-grade glioma; LGG = low-grade glioma; MDA = MD Anderson Center; MGMT = *O*⁶-methylguanine-DNA methyltransferase; PCV = procarbazine, CCNU, and vincristine; RCT = randomized clinical trial; SEER = Surveillance, Epidemiology, and End Results; SNP = single-nucleotide polymorphism; TCGA = The Cancer Genome Atlas; TMZ = temozolamide; UCSF = University of California, San Francisco.

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initially undergo resection/biopsy at the time of diagnosis and then radiation therapy and/or treatment with the single chemotherapeutic agent temozolamide (TMZ) at some point. However, many of these relatively uniformly treated patients advance more quickly than others to recurrence and death. Variation in the few known prognostic factors (most of which are themselves highly correlated)—e.g., age, performance status, tumor size/location, extent of resection, and histological subtype—does not adequately explain the progression and survival differences in these patients. To date, the detection of treatment effect is limited. Gross-total resection appears associated with better survival for patients able to undergo such a procedure but has never been and is unlikely to be assessed in randomized clinical trials (RCTs);^{13,30,59} the improvement may be due to biases from differential tumor aggressiveness in nonresectable versus resectable portions of the brain and from clinician predictions of the patients likely to benefit most from resection. Randomized clinical trials suggest that radiation therapy prolongs time to recurrence but not overall survival^{36,38,62,72} and may be associated with reduction in quality of life and cognition,^{1,16,38,45} while the impact of TMZ, the primary single chemotherapeutic agent now used to treat LGG, has shown benefit primarily in RCTs of HGG but has not been fully assessed in LGG.^{5,37,50,54,68,70} For LGG, no RCT has compared TMZ (which is associated with blood disorders and leukemia)⁴¹ to other agents (trials are ongoing that compare TMZ to radiation therapy as well as the combination of TMZ and radiation therapy to radiation therapy without TMZ). A recently updated trial (RTOG 9802) comparing radiation therapy with or without procarbazine, CCNU, and vincristine (PCV) reports improved progression-free as well as overall survival with the addition of PCV, but ironically this combination has been infrequently used over the past decade to treat LGG.^{6,63} There is no comprehensive clinical prognostic or predictive classification for LGG that combines information on histology, tumor markers and constitutive/tumor genotype, and surgical treatment relative to outcome, and this has led to confusion over how to best manage these patients. The goal of this review is to examine population-based survival rates for patients with LGG within the United States by standard patient demographics and initial treatment and to then review emerging data on patient and tumor genotype relative to survival after a diagnosis of LGG.

Methods

We examined data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 1973 through 2011 (<http://seer.cancer.gov/data/>) that reflect cases involving 2825 patients diagnosed between the ages of 20 and 79 years with a histologically confirmed Grade II supratentorial (topography codes C71.0–71.4) glioma (morphology codes: mixed glioma [ICD-0 9382], oligodendroglioma [ICD-0 9450], or astrocytoma [ICD-0 9400]). In an effort to examine a homogeneous study population and to reduce the probability of including individuals with metastatic lesions, individuals

with more than 1 primary cancer (i.e., a glioma and a cancer of another site) were excluded from these analyses, as were patients diagnosed at death (autopsy only).

In addition to topography and morphology, information on patient sex, race, age, and year of diagnosis were available, as was information regarding whether the patient had been treated with resection (yes/no), radiation therapy (yes/no), or chemotherapy (yes/no) as part of the first course of treatment. Treatment parameters after the first course are not available in these data, nor are specifics of chemotherapy regimes. Race was defined according to SEER categories of white, black, and other, due to small sample sizes in the non-black, non-white categories. Age was used as a continuous variable in the proportional hazards model. The primary outcome variable was time to death as measured in years.

Comparison of cases by descriptor variables was done using a chi-square or Fisher's exact test for discrete variables and a t-test for continuous variables. Estimates of survival probabilities (with 95% confidence intervals) were calculated using Kaplan-Meier product limit methodology and compared using a Wilcoxon log-rank test. Hazard rates were computed using a Cox proportional hazards model.¹⁸ All analyses were completed using the SAS statistical software package version 9.3.

Results

Descriptive statistics for the sample are presented in Table 1. The majority (51.6%) of the cases are classified as astrocytoma, with 33.5% classified as oligodendroglioma and 14.9% as mixed glioma. The reported distributions of these 3 tumor types has changed significantly over time ($p < 0.001$), with fewer cases being classified as astrocytoma and more being identified as either oligodendroglioma or mixed glioma.²¹ The majority of patients were male (58.9%) and white (89.1%). The mean age at diagnosis was 41.4 (SD 15.6) years and did not vary by sex, race, or year of diagnosis. Persons with mixed glioma were diagnosed on average 2 years earlier than patients with other pathology. Treatment data, which include only the first course, show that the majority of LGG patients received only resection at first course; only 3.7% received chemotherapy as part of the initial treatment and the use of radiation at first course declined over time. Initial treatment did not vary by sex or race but did differ by age, with younger patients more likely to undergo resection. Treatment differed by location of the lesion (which did not vary by sex or race). As would be expected, individuals with parietal lobe lesions were more likely to receive radiation therapy and less likely to receive resection than were patients with lesions located elsewhere in the brain.

The median duration of survival for patients with astrocytoma, mixed glioma, and oligodendroglioma was 5.2, 5.6, and 7.2 years, respectively, with younger age at onset associated with an improved prognosis and use of radiation therapy at initial treatment associated with a less favorable prognosis across all 3 histological subtypes. Approximately 20% of patients survived for at least 2 decades. Female sex was associated with improved prognosis for patients with astrocytoma but not for persons di-

TABLE 1. Number of diagnoses (and deaths) for adult supratentorial LGG by histological subgroup (SEER data, 1973–2011)

Variable	Astrocytoma	Oligodendroglioma	Mixed Glioma	Total
Age (yrs)				
20–39	732 (442)	445 (153)	229 (83)	1406 (678)
40–59	538 (392)	421 (248)	161 (66)	1120 (616)
60+	188 (162)	80 (56)	31 (20)	299 (238)
Race				
White	1295 (889)	849 (317)	374 (150)	2518 (1366)
Black	92 (70)	32 (13)	18 (8)	142 (91)
Other	71 (37)	65 (27)	29 (11)	165 (75)
Sex				
Female	591 (391)	384 (131)	185 (69)	1160 (591)
Male	867 (605)	562 (226)	236 (100)	1665 (931)
Year of diagnosis				
1973–1979	143 (133)	7 (7)	3 (3)	153 (143)
1980–1989	414 (370)	28 (24)	36 (28)	478 (422)
1990–1999	346 (252)	267 (154)	92 (64)	705 (470)
2000–2009	520 (1237)	594 (171)	263 (74)	1377 (482)
2010–2011	36 (4)	59 (1)	27 (0)	112 (5)

agnosed with mixed glioma or oligodendroglioma. After controlling for race (white vs nonwhite), age at onset, sex, and initial course of treatment (surgery yes/no, radiation yes/no), there was no improvement in overall survival over time (defined as year of diagnosis before year 2000 vs diagnosis on or after the year 2000) for patients diagnosed with oligodendroglioma (HR 1.08, 95% CI 0.85–1.4), astrocytoma (HR 0.98, 95% CI 0.83–1.15), or mixed glioma (HR 0.76, 95% CI 0.54–1.07) (Figs. 1–3). Interestingly, when the time cutpoint is placed at 2005 rather than at

2000, the results are similar for astrocytoma and oligodendroglioma, but persons diagnosed with mixed glioma on or after 2005 show improved survival compared with those diagnosed prior to 2005.

Discussion

The general lack of improvement in survival for LGG patients over the past 3 decades points to the need for an intensified focus on these tumors. As for HGG, several intriguing findings have emerged, many over just the past

FIG. 1. Survival by year of diagnosis for patients with oligodendroglioma (SEER 1973–2011).

FIG. 2. Survival by year of diagnosis for patients with astrocytoma (SEER 1973–2011).

year or two, with respect to molecular tumor markers, gene expression, and constitutive genotype.

Molecular Tumor Markers

A number of molecular tumor markers have been associated with overall survival for patients with LGG, including 1) combined deletions of chromosomes 1p and 19q,^{28,31} 2) mutations in the *isocitrate dehydrogenase 1* and 2 (*IDH1* and *IDH2*) genes,^{28,80} and 3) methylation of the *O*⁶-methylguanine-DNA methyltransferase (*MGMT*)

gene.²⁸ The high rate of *p53* mutation or deletion in some gliomas, as well as the belief that this change represents an early step in glioma development, has led investigators to examine this alteration in association with LGG survival, with inconsistent results.^{21,26,28}

Codeletion of 1p and 19q

Although deletion of 1p and/or 19q occurs in all LGG subtypes, these chromosome arms are deleted in 40%–90% of Grade II oligodendrogliomas, and their deletion

FIG. 3. Survival by year of diagnosis for patients with mixed glioma (SEER 1973–2011).

is associated with increased survival as well as treatment sensitivity.^{31,35} The mechanism by which 1p/19q loss affects outcome and response is unknown, with no gene on either arm clearly defined as responsible. Recent sequencing revealed mutations in 2 tumor suppressor genes: homolog of *Drosophila* *capicua* (*CIC*) on 19q and *far-upstream binding protein 1* (*FUBP1*) on 1p in 38% and 14% of 21 Grade II oligodendrogliomas (and 0 [0%] of 15 Grade II astrocytomas and 1 [6%] of 18 Grade II mixed gliomas).³⁴ Essentially all gliomas with a *CIC* or *FUBP1* mutation in that study³⁴ also had an *IDH* gene mutation as well as codeletion of 1p and 19q. Jenkins et al.³¹ found that most 1p and 19q deletions in Grade II oligodendrogliomas were the result of an unbalanced translocation between the whole chromosomal arms of 1p and 19q and that translocation/deletion was associated with significantly improved overall survival.

IDH1 and *IDH2*

A recent notable finding is that mutations in the NADP⁺ (nicotinamide adenine dinucleotide phosphate)–dependent isocitrate dehydrogenases encoded by *IDH1* and *IDH2* occur in the majority of Grade II gliomas (all subtypes) and Grade III gliomas as well as secondary GBMs but in only a minority of primary GBMs.^{51,83} Isocitrate dehydrogenase 1 is an enzyme that catalyzes the oxidative decarboxylation of isocitrate to alpha-ketoglutarate, leading to NADPH (reduced form of NADP⁺) production, and it is thought to play a role in cellular protection from oxidative stress. *IDH* mutations are associated with a glioma CpG island DNA hypermethylator phenotype (G-CIMP)⁷¹ and with improved LGG survival⁸⁰ as well as possible LGG response to treatment.^{26,28} Such data suggest that *IDH* mutations represent an early step in the development of LGG.⁴⁴

MGMT

Methylation of *MGMT* (a DNA repair gene located on 10q) is a commonly observed change in LGG²⁶ that predicts HGG response to treatment as well as overall survival;^{8,27} this change may confer chemosensitivity in LGG^{26,28} by causing an altered response to TMZ (the primary agent used to treat LGG), although efforts to examine this are limited by small sample size.^{26,28}

TP53

There is evidence to suggest that a series of ordered genetic alterations occurs in progression from LGG to HGG, with *TP53* mutation being an early event.⁸⁰ *TP53* is the most frequently mutated gene in GBM, and its mutation is a common event in The Cancer Genome Atlas (TCGA) proneural GBM subtype (believed to include the majority of LGGs that progressed to HGG). *TP53* mutation is found in all LGG subtypes²⁶ but is highly correlated with the proportion of tumor astrocytes. Interestingly, a recent study³⁴ examined mutations in the chromatin modifier *alpha thalassemia/mental retardation syndrome X-linked* (*ATRX*) (as well as *CIC*, *FUBP1*, and *IDH1*) and noted almost complete correlation between the presence of *TP53* and *ATRX* mutations, regardless of LGG subtype.

The extent to which any of these markers are merely

indicators of the natural progression of disease or of treatment sensitivity (or both) remains ill defined. In some instances (i.e., 1p and 19q codeletion and oligodendroglioma histology), a marker and a subtype are correlated, leading to confusion about whether it is the marker or the subtype (or both) that is associated with outcome.²⁶ Similarly, correlation exists between markers (i.e., *IDH1* mutation and 1p and 19q deletion).²⁸ Adding to the confusion is the dynamic classification process of LGG subtype, with changes in the relative reported proportions of these subtypes over time reflecting an increasing awareness of the subtleties of histopathological classification for this group of tumors.^{12,43} Researchers have started to elucidate the relative roles of histology and the aforementioned markers both before treatment (thus capturing factors associated with prognosis) and after treatment (capturing factors associated with prediction). Several small studies suggest that response to TMZ³⁹ and progression-free survival²³ are associated with 1p deletion³⁹ and low *MGMT* protein expression,^{23,39} but all of these studies had a sample size of less than 70, primarily focused on Grade II oligodendrogliomas, and did not examine overall survival. Recently, several groups have presented results from larger case series. Using 271 LGGs drawn from the Groupe Hospitalier Pitié-Salpêtrière in Paris, Houillier et al.²⁸ tested whether *TP53* mutation, 1p/19q codeletion, *MGMT* promoter methylation, and *IDH1* mutation predicted natural course of disease or response to treatment with TMZ at the time of diagnosis while controlling for extent of resection. In multivariate analyses, only performance status and resection (but neither histology nor marker) was predictive of progression-free survival in the 171 untreated patients. In the 74 evaluable patients treated upfront with TMZ, *IDH1* mutation, 1p/19q codeletion, and *MGMT* promoter methylation were each associated in univariate analyses with response to TMZ, but small sample size precluded a multivariate analysis including the 3 markers simultaneously and did not allow for evaluation of overall survival. Hartmann et al.²⁶ performed a similar analysis on data from 139 LGG patients from the German Cancer Network. Again no marker was prognostic in patients who did not receive chemotherapy or radiation therapy. *IDH1* mutation and 1p and 19q codeletion were predictive of overall survival (and of progression-free survival in persons receiving treatment at diagnosis). As noted by the authors of both studies, insufficient sample size did not allow for examination of these markers by histological subtype.

Tumor Gene Expression

Recent HGG analyses from TCGA (<http://cancer.genome.nih.gov>) have used several different technology platforms, including mutation arrays, copy number arrays, expression arrays, and methylation arrays.^{9,52,74} Analysis of expression array data has identified molecular subtypes associated with grade and outcome and has shown that expression profiles are better predictors of outcome than histological subtype.^{9,14,52,74} The TCGA and other research groups^{9,24,52,74} have recently defined and validated 4 gene-expression–based classification profiles for Grade IV glioma (GBM): 1) proneural (notable for *PDGFRA* alterations, *IDH1* and *TP53* mutations, as well as oligodendro-

glioma cell type), 2) neural (associated with a variety of neuron markers and closest to normal brain), 3) classical (*EGFR* amplification and *CDKN2A* alterations), and 4) mesenchymal (*NF1* and *MET* alterations). Although this classification system was constructed using only GBM tumors, intriguing findings relative to LGG are noted: 1) the proneural profile included 3 of the 4 known secondary GBMs (believed to arise from LGG), and 2) as previously noted for LGG patients, the proneural profile was notable for young age at onset as well as longer survival, particularly when Grade II and III gliomas from validation sets were added. The absence of LGG in the TCGA data led 2 groups^{15,25} to examine the predictive value of the TCGA profiles specifically for LGG. Both groups^{15,25} used Affymetrix gene expression data for a small set of LGGs (65 Grade II astrocytomas, 4 Grade II mixed gliomas, and 30 Grade II oligodendrogliomas) from the Repository for Molecular Brain Neoplasia Data (REMBRANDT) and reported similar findings, with the TCGA profiles associated with prognostic value for LGG.¹⁵ More recently, the TCGA analyzed 293 “lower grade gliomas” (Grades II and III). Despite using a wide range of sophisticated technology platforms, the final results suggested that lower-grade tumors can be simply and better characterized solely by 2 tumor markers, *IDH1/2* and 1p/19q deletion status, than by the traditionally used histology and grade.⁷⁵ The findings are considered paradigm breaking and suggest that the decades-long classification system for glioma (focused on histology and grade) is likely inferior to a new more molecularly based (but clinically simple and cost efficient) classification scheme. With respect to outcome, these molecular findings remain untested in a pure LGG cohort and uncorrected for an additional variable of clinical import, extent of resection.^{13,33}

Constitutive Genetic Polymorphisms

Glioma Risk

Genetic polymorphisms identified in association with glioma incidence are clearly of interest when considering genes associated with glioma survival.^{2,3,7,10,17,19,20,22,29,47,48,55–57,61,84} An emerging theme in glioma research has been that the genes and pathways identified in linkage and tumor studies are also being identified in genome-wide association studies (GWASs). This demonstrates that, in addition to the rare variations associated with Mendelian disorders,⁴⁶ common genetic variations also contribute to gliomagenesis. While rare heritable loss-of-function mutations in *TP53* and *p16* cause glioma-associated familial cancer syndromes, inherited single-nucleotide polymorphisms (SNPs) near both these genes also appear to contribute to gliomagenesis. In total, GWAS of glioma patients has identified 9 independently significant SNP associations located in 8 genes (Table 2).^{32,33,60,64,66,76–78} The first two glioma GWASs,^{64,79} one of which included only HGG (from University of California, San Francisco [UCSF]/Mayo)⁷⁸ and the other (from the MD Anderson Center [MDA])⁶⁴ included HGG and some LGG, confirmed glioma risk loci in or near *TERT* (5p15), *CDKN2A/B* (9p21) (a gene region harboring p16, a tumor suppressor gene often homozygously deleted in GBM), and *RTEL1* (20q13). The MDA GWAS,⁶⁴ which included LGG cases, identified 2

additional loci: *CCDC26* (8q24) and *PHLDB1* (11q23). The top 13 SNPs in these 5 regions were further investigated by tumor subtype in 1446 cases and 1134 controls from UCSF/Mayo (with 224 Grade II/III oligodendrogliomas, 166 Grade II/III mixed gliomas, and 103 Grade II [only] astrocytomas).³² As reported in the MDA GWAS,⁶⁴ *CCDC26* (8q24) region loci were associated with Grade II/III oligodendroglioma (OR = 2.05, $p = 8.3 \times 10^{-11}$) but not GBM (Grade IV) risk, with association with Grade II/III oligodendroglioma seen regardless of 1p/19q deletion status (although the greatest risk was seen with codeletion present). In contrast, *RTEL* region polymorphisms were most strongly associated with Grade IV but less so with Grade II/III glioma risk. The *TERT* region was associated with all grades and types of glioma. The *CDKN2A/B* region SNPs were also associated with Grade IV and Grade II/III astrocytoma but not with Grade II/III oligodendroglioma. Insufficient data were available to draw conclusions about Grade II astrocytoma and Grade II oligodendroglioma independent of Grade III oligodendroglioma or about Grade II versus Grade III mixed glioma. A similar analysis was performed in the German and French replication cohorts of the MDA GWAS, again showing that *CCDC26* and *PHLDB1* loci were inversely and *RTEL1* and *TERT* loci were positively correlated with grade.⁶⁶ Data from a Chinese population agree as well.¹⁰ A pooled analysis of the US/United Kingdom/German/French data confirmed these findings and found evidence of an additional independent association for glioma (regardless of grade) risk with rs11979158 and rs2252586 at 7p11.2, which encompasses the *EGFR* gene, although interestingly this gene was not associated with survival.⁶⁰ The results listed above are remarkably confirmatory (in an era where GWAS results may vary widely) and strongly suggest that distinct germline polymorphisms underlie different glioma subtypes (i.e., *CCDC26* and *PHLDB1* loci are consistently associated with LGG while other loci are either primarily associated with HGG or with all glioma regardless of grade and histology). Jenkins et al.³³ further examined the *CCDC26* (8q24) region and found strong association for a low-frequency variant at 8q24.21 (rs55705857) associated with 1) Grade II/III oligodendroglioma regardless of *IDH* mutation status (OR 6.3, $p = 2.2 \times 10^{-23}$), and 2) Grade II–IV astrocytoma with mutated *IDH1/IDH2* (OR 5.16–6.66, $p = 4.7 \times 10^{-12}$ to 2.2×10^{-8}) but not astrocytic tumors with wildtype *IDH1/IDH2*. Their LGG-specific findings are remarkable, with increasing risk associated with decreasing astrocyte involvement (OR_{astroII} 3.82, 95% CI 2.63–5.54, $p = 1.7 \times 10^{-12}$; OR_{mixedIII} 5.01, 95% CI 3.48–7.21, $p = 3.7 \times 10^{-18}$; and OR_{oligoII} 7.06, 95% CI 5.10–9.77, $p = 6.2 \times 10^{-32}$). Two new reports^{58,75} are also of note: Using existing as well as new data from the UCSF and Mayo groups, Rice et al.⁵⁸ showed that the *PHLDB1* SNP is associated strictly with *IDH*-mutated gliomas, while Walsh et al.⁷⁵ replicated the findings that *CDKN2B* SNPs are associated with low-grade astrocytomas. In summary, 4 of the above-mentioned genes appear to contribute to the development of all glioma grades and histological types (*RTEL*, *TERT*, *EGFR*, *TP53*), whereas the other 3 genes appear to contribute only to the development of certain glioma subtypes (Table 2). *CCDC26* variants increase

TABLE 2. Glioma-associated susceptibility variants detected by GWAS and fine-mapping

Candidate Gene (chromosome location)	Risk Allele	Magnitude of Association*	Risk Allele Frequency†	Putative Functional Significance	Associated Glioma Subtypes
<i>TERC</i> (3q26.2)	rs1920116-G	+	0.72	Increased telomere length	HGG
<i>TERT</i> (5p15.33)	rs2736100-C	+	0.51	Increased telomere length	All glioma subtypes
<i>EGFR</i> (7p11.2)	rs2252586-A	+	0.27	Unknown	All glioma subtypes
<i>EGFR</i> (7p11.2)	rs11979158-A	+	0.82	Unknown	All glioma subtypes
<i>CCDC26</i> (8q24.21)	rs55705857-G	+++	0.046	microRNA site	Oligodendroglial tumors & <i>IDH</i> -mutated astrocytic tumors
<i>CDKN2B/ANRIL</i> (9p21.3)	rs1412829-G	+	0.43	Unknown	Astrocytic tumors of all grades
<i>PHLDB1</i> (11q23.3)	rs498872-A	+	0.31	Unknown	<i>IDH</i> -mutated gliomas
<i>TP53</i> (17p13.1)	rs78378222-C	++	0.014	Alteration of polyadenylation signal impairs <i>TP53</i> mRNA processing	All glioma subtypes
<i>RTEL1</i> (20q13.33)	rs6010620-G	+	0.76	Unknown	All glioma subtypes

* Magnitude of Association: +++ represents $OR \geq 5.0$, ++ represents $2.0 \leq OR < 5.0$, and + represents $1.0 < OR < 2.0$.

† Allele frequency in Caucasians, extracted from HapMap CEPH (Centre d'Etude du Polymorphisme Humain) data where available.

the risk for oligodendroglial tumors regardless of *IDH*-mutation status and also for *IDH*-mutated astrocytoma. SNPs near *CDKN2B/ANRIL* confer increased risk for astrocytic tumors of all grades, including GBM, but are not associated with oligodendroglial tumors. The histological specificity of these SNP associations remains an area of active research.

Glioma Outcome

There are few studies of genetic polymorphism and survival after diagnosis of glioma; those that exist focus on HGG (no study includes more than 50 LGG patients) with examination of SNPs in genes involved in DNA repair, cell cycle regulation, and immune function as well as in tumor markers of note.^{4,21,40,49,67,69,73,78,82}

Genome-Wide Association Studies. No data exist specific to LGG, but several informative efforts have been undertaken relative to HGG by Dr. Wrensch's group, which performed the first GBM GWAS survival analysis^{80,81} in uniformly treated patients (treated with surgery, radiation therapy, and TMZ) and found that SSBP2 (a single-stranded DNA binding protein on 5q14.1) germline variants were associated with survival (discovery [UCSF] and validation [Mayo, GliomaSE, and TCGA] sets show a combined $HR_{rs7732320}$ of 1.64, 95% CI 1.34–2.00, $p = 1.3 \times 10^{-6}$) and that expression of SSBP2 in GBMs was significantly related to reduced survival (HR 1.22, 95% CI 1.09–1.36, $p = 5.3 \times 10^{-4}$). Interestingly, among TCGA and other GBM patients, SSBP2 expression was highest among patients with the proneural signature, a group likely to include persons with secondary GBM (i.e., progressed from LGG), suggesting that SSBP2 germline variants and tumor expression (which were not linked to *IDH* mutation status) may be important independent predictors of survival for patients with LGG. Dr. Bondy also examined associations with GBM survival with the 100 top-ranking glioma susceptibility polymorphisms identified from the 2 glioma GWASs^{64,79} and found that polymorphisms in the *LIG4*, *HMG2*, *BTBD2*, and *RTEL1* genes (all involved in the double-strand break repair pathway) were associated with GBM survival in the MDA GWAS cohort (although

not confirmed in the validation set).⁴² Preliminary analyses from the UCSF/Mayo study indicate that the variant at 8q24.21 (rs55705857) associated so strongly with glioma risk appears to also be associated with survival.

The data used here to estimate survival are taken from the SEER program (<http://seer.cancer.gov/data/>). Although an important description of “real-world” LGG practice that includes persons of all ages, races, and medical status, the data are limited by 1) a lack of a uniform histological review, 2) treatment data that are restricted to first course (hence data on radiation therapy and chemotherapy are limited or absent) and not adjusted for clinical factors likely to influence treatment assignment, and 3) no information on constitutive/tumor genotype, tumor markers, or patient comorbidities.

One important reason for the lack of knowledge concerning LGG is that these patients are generally only included as a convenience subsample in studies of HGG with results driven by the much larger numbers of HGGs in these studies.^{9,11,32,60,64,65,79} Furthermore, the lack of effect in randomized clinical trials is likely also due in part to the unknowing inclusion of genetically dissimilar tumors into one study arm. In the future, clarification of the tumor markers/profiles known to be associated with outcome (both natural progression as well as response to treatment) will be required to be measured in any planned RCT to preserve randomization. The import of such markers and profiles is already recognized by organizers of the HGG trials with tumor materials retrospectively being analyzed to assess randomization. As LGG represents the first step in a multistage disease process, the need to focus efforts at the start of the disease process is clear. Large sample cohorts, which will likely require the development of consortia given the relatively small numbers of these tumors, will be necessary. As can be seen from the literature morphological and molecular subtyping is critical to cancer genetic epidemiology³³ and to date not explored specifically for LGG. Discovery of genes associated with poor outcomes will allow for improvement of randomization schemes in clinical trials of LGG as well as suggest novel biological

mechanisms for development of targeted therapy designed to improve survival. The time is right for researchers to take advantage of emerging genetic technology, statistical methodology, and computing capability to create a new clinical paradigm for LGG.

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Conception and design: Claus. Acquisition of data: Claus, Walsh, Bondy, Jenkins. Analysis and interpretation of data: Claus, Walsh, Wensch. Drafting the article: Claus, Wensch. Critically revising the article: Claus, Walsh, Molinaro, Wensch. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Claus. Statistical analysis: Claus. Administrative/technical/material support: Claus, Berger. Study supervision: Claus.

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