Molecular genetics of low-grade gliomas: genomic alterations guiding diagnosis and therapeutic intervention. 11th Annual Frye-Halloran Brain Tumor Symposium Meeting Report

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Object. The authors' goal was to review the current understanding of the underlying molecular and genetic mechanisms involved in low-grade glioma development and how these mechanisms can be targets for detection and treatment of the disease and its recurrence.

Methods. On October 4, 2012, the authors convened a meeting of researchers and clinicians across a variety of pertinent medical specialties to review the state of current knowledge on molecular genetic mechanisms of low-grade gliomas and to identify areas for further research and drug development.

Results. The meeting consisted of 3 scientific sessions ranging from neuropathology of *IDH1* mutations; *CIC*, *ATRX*, and *FUBP1* mutations in oligodendrogliomas and astrocytomas; and *IDH1* mutations as therapeutic targets. Sessions consisted of a total of 10 talks by international leaders in low-grade glioma research, mutant *IDH1* biology and its application in glioma research, and treatment.

Conclusions. The recent discovery of recurrent gene mutations in low-grade glioma has increased the understanding of the molecular mechanisms involved in a host of biological activities related to low-grade gliomas. Understanding the role these genetic alterations play in brain cancer initiation and progression will help lead to the development of novel treatment modalities that can be personalized to each patient, thereby helping transform this now often-fatal malignancy into a chronic or even curable disease.
(<http://thejns.org/doi/abs/10.3171/2012.12.FOCUS12349>)

KEY WORDS • glioma • meeting report • *IDH*

THE 2012 Frye-Halloran Symposium took place at the Massachusetts General Hospital on October 4, bringing together international experts to address the molecular revolution in the diagnosis and classification of low-grade gliomas. The symposium is an annual event that aims to facilitate the translation of promising innovations from the laboratory to the clinic. Noteworthy past symposia have focused on such topics as the introduction of microdialysis for real-time in situ measurement of activated drugs, the identification of novel MRI findings to track the effects of angiogenesis inhibition, the development of therapies based on viral vectors and cell-based immunizations, and racial diversity in glioma patient populations.

Gliomas represent the most common primary brain tumor, and subtypes occur along a spectrum of aggres-

siveness and therapeutic responsiveness. The WHO grading of human brain tumors provides a basis for predicting the clinical behavior of the respective neoplasm by including information beyond a strictly histological grading.¹⁶ Greater understanding of the molecular genomics of gliomas is allowing a refinement of traditional classification between low- and high-grade gliomas.

Over the past 4 years, several recurring mutations have been identified in low-grade gliomas that, together, have transformed our understanding of this disease. Recently identified gene mutations include those found in the family of *isocitrate dehydrogenase (IDH)* genes, enzymes involved in citrate metabolism. The *IDH1* mutation was first reported in 2008, when it was discovered in 12% of sequenced glioblastoma genomes.²¹ Further research has shown that *IDH* gene mutations are found in a substantial majority of lower- and intermediate-grade gliomas and are also highly prevalent in secondary glioblastomas that arise from lower-grade tumors.¹² It has also been associated with longer survival across all grades of

Abbreviations used in this paper: MGMT = O-6-methylguanine-DNA methyltransferase; PARP = poly-adenosine diphosphate-ribose polymerase; PI3K = phosphatidylinositol 3-kinase.

glioma in which it is found.^{1,25} The emerging clinical phenotype of the *IDH1* mutation is that of a younger patient (< 44 years), with frontal lobe tumor location, and a significant component of non-contrast enhancing tumor on imaging.¹⁵ Low-grade gliomas can be further subdivided into groups characterized by astrocytic or oligodendroglial histology. Recent findings have identified genetic alterations associated with these subgroups as well.

With these discoveries of specific recurrent mutations, we are now on the cusp of translating these molecular discoveries into meaningful clinical strategies for patient care. This symposium was convened to set the stage for upcoming clinical trials and opportunities for collaboration in the study and care of patients with low-grade glioma.

The meeting was divided into 3 sessions: 1) Neuropathology of *IDH1* Mutations; 2) Mutations in Low-Grade Gliomas: *ATRX*, *TP53*, *CIC*, and *FUBP1*; and 3) *IDH1* Mutations as Therapeutic Targets. The audience included clinicians and laboratory scientists in the fields of neurooncology, neurosurgery, neuropathology, radiation oncology, neuroradiology, pediatrics, nursing, and other specialties involved in the research, diagnosis, care, and treatment of patients with low-grade gliomas. This article summarizes the highlights of each of the 10 presentations. Readers are referred to the conference website (<http://fh2012.neurosuite.org/>) and the program brochure (http://www.dfhcc.harvard.edu/uploads/media/2012_Frye_Halloran.pdf) for further details.

Session 1: Neuropathology of *IDH1* Mutations

The meeting opened with a discussion of neuropathology by David Louis, M.D. (Massachusetts General Hospital, Boston, Massachusetts), who reviewed the evolving tools by which we may define low-grade gliomas. The WHO 2007 criteria were the first to include molecular and genomic analyses in brain tumor categorization, specifically recognizing the allelic losses of 1p and 19q present in 50%–70% of WHO Grade II and III oligodendrogliomas.¹⁶ Presence of this deletion has important diagnostic and therapeutic implications, as studies have shown that loss of 1p or loss of both 1p and 19q is a statistically significant predictor of good response to chemotherapeutic combination of procarbazine, lomustine, and vincristine (termed PCV).⁴ Conversely, presence of *CDKN2A* gene deletions and ring enhancement of the tumor on contrasted imaging both portend significantly worse prognosis and poor response of oligodendrogliomas to PCV. This highlights perhaps 2 tumor subtypes of oligodendrogliomas that can be distinguished almost solely on a genetic basis. With rapid advances in molecular genomics, one could imagine a future in which a molecular diagnosis replaces the traditional pathological diagnosis, so that a tumor is labeled a “*BRAF* mutant” rather than a pilocytic astrocytoma, ganglioglioma, or pleomorphic xanthoastrocytoma. However, this scenario is currently unlikely, as it seems there is a blend of genetic variations that contributes to unique tumor entities despite their distinct histological phenotypes. Further research is needed to identify the relationships between multiple genetic mutations and the disease phenotype. In the

meantime, genetic markers will continue to be powerful tools in guiding diagnosis, prognosis, and therapy.

Andreas von Deimling, M.D. (University of Heidelberg, Germany), presented his laboratory’s work on establishing the frequency, distribution, and significance of *IDH* mutations in gliomas and argued that knowledge of mutant status has allowed us to make important advances in determining the diagnosis and prognosis of gliomas. In analysis of *IDH1* and *IDH2* mutations in brain tumors,¹² the highest frequencies of *IDH1* mutations were found in diffuse astrocytomas (WHO Grade II, 72.7%), oligodendrogliomas (WHO Grade II, 82.0%), and oligoastrocytomas (WHO Grade II, 78%). *IDH2* mutations were highest in oligodendrogliomas (WHO Grade II, 4.7%), anaplastic oligodendrogliomas (WHO Grade III, 5.2%), and anaplastic oligoastrocytoma (WHO Grade III, 6.2%). Overall, *IDH1* mutation of R132C showed the strongest association with astrocytomas; conversely, *IDH2* mutations were strongly associated with oligodendroglial tumors, and patients with astrocytomas and *IDH1* mutations were on average 6 years younger than those without the mutation. A monoclonal antibody recognizing the *IDH1* R132H mutation in formalin-fixed paraffin-embedded tumor specimens has demonstrated high specificity and sensitivity,⁶ and as a result has greatly facilitated rapid determination of *IDH1* status in tumor classification.⁵ Determination of *IDH1* status has become especially important given evidence that *IDH1* status is perhaps the single most prominent prognostic factor for overall survival after histopathological grading. Sequencing of *IDH1* codon 132 in 382 patients with anaplastic astrocytoma and glioblastoma from the NOA-04 trial and from a prospective translational cohort study of the German Glioma Network showed that *IDH1* status correlated with prognosis more than age, histological diagnosis, or MGMT methylation status. As such, the combination of histological diagnosis with genomic features could be ranked from most favorable to least favorable: 1) anaplastic astrocytoma with *IDH1* mutation, 2) glioblastoma with *IDH1* mutation, 3) anaplastic astrocytoma without *IDH1* mutation, and 4) glioblastoma without *IDH1* mutation.¹¹ These findings suggest a potential guide for recategorization of WHO tumor classification to more accurately delineate tumor types in the age of molecular genomics.

Session 2: Mutations in Low-Grade Gliomas: *CIC*, *ATRX*, and *FUBP1*

Daniel Cahill, M.D., Ph.D. (Massachusetts General Hospital), discussed the potential for clinical impact of *IDH1* status on driving tumor classification and therapy. Due to the significant prognostic differences between patients harboring tumors with and without the *IDH1*-R132H mutation, we can begin to consider a tumor’s *IDH1* mutant status as having distinct biological properties that belong to a separate molecular etiological group altogether, and, as such, merit a uniquely tailored treatment strategy. The value of maximum resection in gliomas has been controversial, and there exists evidence that the prognostic significance of resection may be biased due to gross-total resections occurring more frequently

in younger patients and in noneloquent locations.²² Interestingly, there is also a predominant occurrence of *IDH1* mutations in younger patients and tumor locations in the frontal lobe. Overall, these correlations suggest that measures of resection may be difficult to isolate from other confounding molecular prognostic factors, without explicit stratification. In a study of 407 patients with malignant astrocytomas (157 anaplastic astrocytomas and 250 glioblastomas), the measures of resection associated with longer survival differed between separately analyzed *IDH1* wild-type and mutant tumors. Controlling for age, Karnofsky performance score, tumor location, and tumor grade, patients with *IDH1* wild-type tumors showed extended survival when all enhancing disease was resected, but postoperative residual nonenhancing disease was not associated with survival.³ Conversely, in patients with *IDH1* mutant tumors, both residual enhancing and nonenhancing postoperative tumor burden were associated with worse survival. These data suggest an additional survival benefit that appears to be associated with reducing nonenhancing tumor burden in *IDH1* mutant tumors. Thus, determining *IDH1* genotype may serve to uniquely guide surgical planning, which may include more aggressive resection in patients with mutant tumors.

Stephen Yip, M.D., Ph.D. (University of British Columbia, Vancouver, Canada), presented his laboratory's data on the recently discovered genetic aberration of the *CIC* gene on 19q of oligodendrogliomas. The *CIC* gene is located on 19q13.2 and encodes a transcriptional repressor that is a mammalian homolog of the *Drosophila* Capicua that plays a crucial role in development via signaling downstream of the RAS/MAPK pathway. Normal mammalian Capicua is found frequently in the brain, and *CIC* mutations have previously been identified in spinocerebellar ataxia I (SCAI) and Ewing sarcomas. In addition to the *IDH1* and *IDH2* mutations and 1p/19q loss that have already been strongly linked to oligodendrogliomas, the *CIC* gene was found to be mutated in 20 (69%) of 29 oligodendrogliomas with 1p19q codeletion that were studied with whole exome sequencing.²⁶ In contrast, deep sequencing of astrocytomas and oligodendrogliomas without 1p/19q deletion had rare loss of *CIC* (only 1 [2%] of 60). When examining 204 tumor samples, the *CIC* mutation was closely associated with classic oligodendroglioma histology and also with *IDH1/2* mutations and loss of 1p/19q. After controlling for 1p/19q status, there was a trend of association between *CIC* mutation and high-grade status, but no association with overall or progression-free survival. No *CIC* mutations were identified in 4 normal brain tissue samples. Since the prototypical oligodendroglioma involves abnormalities of *CIC*, *IDH*, and 1p/19q, this suggests that all 3 are involved in the underlying biology of this tumor class. Further research to elucidate the complex relationship and mechanisms of these genetic abnormalities is necessary to understand tumor development and help guide future therapy.

Chetan Bettegowda, M.D., Ph.D. (Johns Hopkins, Baltimore, Maryland), further discussed the *CIC* mutation and his recent work to genetically profile anaplastic oligodendrogliomas. Beyond the hallmark genetic markers of *IDH* mutation and 1p/19q codeletions, whole

exome sequencing of 7 anaplastic oligodendrogliomas also revealed common mutations of *NOTCH1* (2 tumors), *PIK3CA* (3 tumors), *CIC* (6 tumors), and *FUBP1* (2 tumors).² This high rate of *CIC* mutation was validated by analyzing 27 additional tumors, and, in total, *CIC* mutations were identified in 18 of 34 samples. While no additional *NOTCH1* mutations were found in the validation set, *FUBP1* alterations were ultimately found in 5 of 34 samples. The gene for the far-upstream element binding protein (*FUBP*) is located on 1p and encodes a protein that binds to single-stranded DNA, with a known target site within the far-upstream element of the *MYC* oncogene. All mutations identified were found to inactivate *FUBP1*. Of the 34 studied oligodendroglial tumors, 23 had either *CIC* or *FUBP1* mutations, and all of the *CIC* mutations occurred in tumors that also had loss of 19q. Additional research into these oligodendroglioma mutations will provide insight into tumor pathogenesis and diagnosis and may also inform tailored therapies. In particular, discussion centered on the yet-unclear relationship between chemosensitivity observed in the clinical studies of 1p/19q-deleted oligodendroglioma by Cairncross et al.⁴ and others and the hypothesized mechanisms of tumor promotion of these molecular genetic alterations.

Zachary Reitman, Ph.D. (Duke University, Durham, North Carolina), presented data on the *ATRX* mutation recently found in genetic profiling of 363 gliomas. The alpha-thalassemia/mental retardation syndrome X-linked (*ATRX*) was recently identified in 7% of sequenced adult glioblastomas as well as in pancreatic neuroendocrine tumors,¹³ but had not yet been examined in gliomas of all grades. It is an adenosine triphosphate-dependent helicase that maintains telomere homeostasis by incorporating histone variant H3.3 into telomeric chromatin. The mutations of gliomas cause loss of protein expression, whereby the alternative lengthening of telomeres (ALT) pathway is activated, a common pathway used by cancerous cells. Mutations of *ATRX* were found in 93 of the 363 brain tumor samples examined and occurred across 10 tumor subtypes.¹⁴ Most frequent mutations were found in Grade II diffuse astrocytomas (67%, n = 15), Grade III anaplastic astrocytomas (73%, n = 40), secondary glioblastomas (57%, n = 14), and oligoastrocytomas (68%, n = 40). Interestingly, there were no *ATRX* mutations in Grade I pilocytic astrocytomas, and there was a much lower rate in primary (or de novo) glioblastoma (4%, n = 94) when compared with secondary glioblastoma. Furthermore, *ATRX* alterations in the gliomas were found to co-occur with *TP53* and *IDH* alterations, and this constellation of mutations was significantly associated with ALT expression. Of note, *ATRX* alteration and 1p/19q loss only co-occurred in a single case. As for prognostic analysis, it was intriguing to note that survival was significantly longer in patients with Grade II–IV gliomas harboring both *IDH* and *ATRX* mutations (median 51 months) compared with *IDH* mutation alone (median 28 months). Further analysis of *CIC* and *FUBP1* alterations showed that tumor types with *IDH* mutation, combined with 1p/19q loss, *CIC* mutation, or *FUBP1* mutation, had significantly improved survival (median 96 months). Overall, while the molecular mechanisms have yet to be fully character-

ized, these data support the theory that 2 core subclasses of low-grade gliomas may be differentiated by unique genetic signatures, whereby a combination of *IDH* and *ATRX* mutations yield a different phenotype (astrocytic) than a combination of *IDH* and 1p/19q, *CIC*, or *FUBP1* mutations (oligodendroglial). Further exploration into the intricate molecular landscape of gliomas will likely contribute to more distinct tumor subtype classifications.

General Session: Mutant IDH Enzymes and Cancer Biology

Ross Levine, M.D. (Memorial Sloan–Kettering Cancer Center, New York, New York), led a general audience through Grand Rounds on how *IDH* mutations cause leukemia via aberrant epigenetic programming from DNA hypermethylation and reduced enzyme activity. Similar to gliomas, acute myeloid leukemia is one of the cancers bearing *IDH1* and *IDH2* mutant phenotypes, albeit at lower incidences.^{10,18} Moreover, AML still carries a poor overall survival under current standard treatments. Just as the *IDH1* mutant form of glioma is associated with improved survival, AML survival can also be stratified based on mutational profiling, where *IDH2* mutant AML predicts favorable outcome. The mechanisms involved in *IDH1* mutant leukemic biology have yet to be fully elucidated. Mutational and epigenetic profiling of a large cohort of patients have demonstrated that *IDH1* and *IDH2* mutant AMLs display global DNA hypermethylation and a specific hypermethylation signature.¹⁰ Follow-up studies show that *IDH* mutant gliomas also have a distinct hypermethylation signature, known as CpG island methylation profile (CIMP).^{20,23} Additionally, it is believed that the 2-hydroxyglutarate (2-HG) produced by *IDH* mutant enzymes can accumulate in cells and prevent histone demethylation that is required for lineage-specific progenitor cells to differentiate into terminally differentiated cells.^{17,24} These studies demonstrate that the neomorphic enzymatic function of the *IDH* proteins likely affects gene expression programs, at least in part, by altering the epigenome via methylation changes in both DNA and core histone proteins. The novel enzyme function of *IDH* mutants therefore represents a promising potential drug target.

Session 3: *IDH1* Mutations as Therapeutic Targets

David Schenkein, M.D. (Agiros Pharmaceuticals, Cambridge, Massachusetts), began the final session by sharing what lies on the horizon for *IDH*-related therapeutic development. There is a view that tumor-associated alterations in metabolic pathways lead to a phenotype under which tumor cells can survive and grow. To this end, targeting metabolic enzymes to treat cancer offers a promising area of oncology research. This idea has gained ground with the study of “metabolomics,” which involves rapid, high-throughput characterization of the small molecule metabolites found in tissues, biofluids, or organisms in general. Development of a “metabolome” for different tumor types offers the possibility of uncovering many novel therapeutic targets. For instance, the

IDH1-mutant metabolome is associated with high levels of 2-HG in cells expressing *IDH1*-R132H, and this onco-metabolite is detectable in brain tumor samples, in CSF, and on MR spectroscopy. Thus, levels of 2-HG could be measured during treatment in the event that mutant *IDH1* enzymes could be inhibited pharmacologically. Furthermore, studies have indicated that high levels of 2-HG can drive epigenetic changes that inhibit cell differentiation and contribute to cancer. Thus, engineering molecules to inactivate the *IDH* mutant enzymes that produce 2-HG will in theory antagonize these downstream effects, leading to tumorigenesis.^{8,9} 2-HG levels can indicate the effectiveness of such therapies. Agios Pharmaceuticals has developed potent and orally available selective inhibitors of both *IDH1* and *IDH2* mutant enzymes. Preliminary studies of in vivo tumor models have shown they are capable of lowering 2HG levels by greater than 90% and reversed the altered methylation profiles of the *IDH* mutant cells. The biology of mutant *IDH* proteins is one of a few examples of metabolic dysregulation affecting epigenetics. If clinical pharmacological development continues successfully, we may expect *IDH* mutant-selective therapies to become available soon.

Lewis Cantley, Ph.D. (Beth Israel, Boston, Massachusetts), discussed how carefully designed clinical trials using drug combinations may offer the key to developing successful cancer treatments. As previously mentioned, numerous consistent genetic mutations are known to occur within gliomas, including alterations in *IDH*, *TP53*, *PTEN*, *NF1*, and *EGFR*, to name a few. Given that tumor phenotypes are the result of the interplay among multiple aberrant molecular pathways, successful glioma treatment likely resides in the inhibition or modulation of more than one such pathway. Thus, as we explore therapeutic targets for *IDH* mutations in gliomas, coclinical trials of 2 or more therapies may be strategically advantageous. One illustration of combination molecular drug therapy development is that of a *BRCA1*-mutant mouse model treated with a PI3K inhibitor and a PARP inhibitor. The PI3K inhibitor, BKM120, alters pathways associated with cell proliferation and glucose metabolism. The PARP inhibitor olaparib prevents repair of DNA breaks, which preferentially leads to death in rapidly replicating tumor cells. In *BRCA1*-mutant mouse models, PI3K inhibition slowed tumor growth. However, the drug caused activation of PARP to help repair DNA damage. Addition of a PARP inhibitor further promoted DNA destruction and eventual cancer cell death, creating an unexpected synergistic effect. This approach to combination therapeutics may prove successful in glioma treatment as well. For instance, recent studies have indicated that there is evidence that altered glucose metabolism can affect prognosis for gliomas.¹⁹ This may warrant exploration of the synergistic effects of current standard therapies with a PI3K inhibitor or another molecular target in the glucose metabolism pathway. Ultimately, it may be important to simultaneously target different mechanisms in gliomagenesis.

Linda Liao, M.D., Ph.D. (UCLA, Los Angeles, California), gave the final presentation of the symposium by presenting data regarding the clinical implications of *IDH* gene mutations on glioma therapy. In support of the

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differing imaging characteristics and prognoses between *IDH1* mutant and wild-type gliomas, there is recent evidence to suggest that *IDH1* mutant glioblastoma evolves from a cell of origin distinct from that of glioblastomas without *IDH1* mutation.¹⁵ One of the key distinctions is that gliomas with the *IDH1* mutation have been found to harbor a distinct CpG island hypermethylation profile (*CIMP*), which is absent in *IDH1* wild-type gliomas.²⁰ It is theorized that this hypermethylation profile contributes to glioma formation by silencing tumor suppressor genes. A recent study looked at candidate tumor suppressor genes by performing bisulfate sequencing on 198 *IDH1/2* mutant and *IDH* wild-type gliomas (Grades III and IV). One particular gene that was found to be hypermethylated was that of *RBPI*, which is involved in retinoic acid metabolism. Nearly all the *IDH1* mutant (76/79) and *IDH2* mutant (3/3) tumors demonstrated *RBPI* hypermethylation, versus none of the 119 *IDH* wild-type tumors. In further analysis of the glioblastoma cohort, the patients with *RBPI* hypermethylation (n = 22) had a statistically significantly higher median overall survival compared with *RBPI* unmethylated patients (n = 102) of 36.9 months versus 20.3 months, respectively. This was expected due to the close association of *RBPI* hypermethylation and *IDH* mutation status. When controlling for clinical variables of age, sex, performance status, and extent of resection, analysis showed that either *IDH1/2* mutation or *RBPI* methylation status is an independent predictor of overall survival.⁷ MGMT promoter methylation status has already served as a valuable clinical predictor of response to standard-of-care glioblastoma therapy. As such, further research of the hypermethylation of *RBPI* and other genes may provide key insight for both identifying targets of future glioma therapy and determining prognosis.

Conclusions

The data presented at the 11th Annual Frye-Halloran Symposium highlighted the rapidly moving field of low-grade glioma molecular genetics. Recent discoveries about the underlying genetic profiles of low-grade gliomas, following the seminal discovery of *IDH* gene mutations, have led to a revolution in our understanding of the genetic alterations that are mechanistically involved in gliomagenesis. Identification of recurrent mutations in novel genes such as *CIC*, *FUBP1*, and *ATRX* certainly justifies the investment in large-scale exome-wide sequencing studies that have driven these discoveries. Low-grade gliomas, specifically, pose a unique challenge in classification, given the infiltrative nature of the tumor cells and the heterogeneity of genotypes and phenotypes. In a relatively brief period of time, there are now multiple objective mutational alterations identified that will allow for the reproducible biological subclassification of these tumors. It will be interesting to observe how rapidly these molecular features become integrated into standard diagnostic categorization and in what capacity. For instance, there now exists potential for establishing diagnostic biomarkers, whereby a tumor's genetic alterations can be identified from serum or CSF rather than a surgical procedure. Importantly, these genetic alterations

are potential targets themselves, and the possibility that these mutations or nodes in their associated biology can be therapeutically targeted in the near future offers substantial hope for improvement in the survival of patients with these cancers.

Disclosure

The Carolyn Frye-Halloran Brain Tumor Therapy Program sponsored the symposium.

Author contributions to the study and manuscript preparation include the following. Conception and design: Cahill, Jones, Barker, Curry. Acquisition of data: Jones. Analysis and interpretation of data: Jones. Drafting the article: Jones. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors.

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Manuscript submitted October 19, 2012.

Accepted December 10, 2012.

Please include this information when citing this paper: DOI: 10.3171/2012.12.FOCUS12349.

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