Title
Mutant IDH1 and seizures in patients with glioma

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Mutant IDH1 and seizures in patients with glioma

**ABSTRACT**

**Objective:** Because the α-2-hydroxyglutarate (D2HG) product of mutant isocitrate dehydrogenase 1 (IDH1<sup>mut</sup>) is released by tumor cells into the microenvironment and is structurally similar to the excitatory neurotransmitter glutamate, we sought to determine whether IDH1<sup>mut</sup> increases the risk of seizures in patients with glioma, and whether D2HG increases the electrical activity of neurons.

**Methods:** Three WHO grade II-IV glioma cohorts from separate institutions (total N = 712) were retrospectively assessed for the presence of preoperative seizures and tumor location, WHO grade, 1p/19q codeletion, and IDH1<sup>mut</sup> status. Rat cortical neurons were grown on microelectrode arrays, and their electrical activity was measured before and after treatment with exogenous D2HG, in the presence or absence of the selective NMDA antagonist, AP5.

**Results:** Preoperative seizures were observed in 18%–34% of IDH1 wild-type (IDH1<sup>wt</sup>) patients and in 59%–74% of IDH1<sup>mut</sup> patients (p < 0.001). Multivariable analysis, including WHO grade, 1p/19q codeletion, and temporal lobe location, showed that IDH1<sup>mut</sup> was an independent correlate with seizures (odds ratio 2.5, 95% confidence interval 1.6–3.9, p < 0.001). Exogenous D2HG increased the firing rate of cultured rat cortical neurons 4- to 6-fold, but was completely blocked by AP5.

**Conclusions:** The D2HG product of IDH1<sup>mut</sup> may increase neuronal activity by mimicking the activity of glutamate on the NMDA receptor, and IDH1<sup>mut</sup> gliomas are more likely to cause seizures in patients. This has rapid translational implications for the personalized management of tumor-associated epilepsy, as targeted IDH1<sup>mut</sup> inhibitors may improve antiepileptic therapy in patients with IDH1<sup>mut</sup> gliomas. *Neurology* 2017;88:1805-1813

**GLOSSARY**

AUC = area under the receiver operating characteristic curve; CI = confidence interval; D2HG = α-2-hydroxyglutarate; GBM = glioblastoma; HR = hazard ratio; IDH1<sup>mut</sup> = mutations in isocitrate dehydrogenase 1; IDH1<sup>wt</sup> = wild-type isocitrate dehydrogenase 1; MEA = multielectrode array; NMH = Northwestern Memorial Hospital; NYU = New York University; OR = odds ratio; RR = relative risk; TAE = tumor-associated epilepsy.

WHO grade II–III gliomas are more likely to induce epilepsy than grade IV glioblastomas (GBMs), though the reason for this is unclear.1 One possible explanation is that the former group of tumors usually have mutations in isocitrate dehydrogenase 1 (IDH1<sup>mut</sup>), whereas the latter usually do not. IDH1 is a metabolic enzyme located in the cytosol and peroxisomes, catalyzing the oxidative decarboxylation of isocitrate to α-ketoglutarate. In contrast, mutant enzyme reduces α-ketoglutarate to D2HG (α-2-hydroxyglutarate). This is so efficient that the concentration of D2HG can exceed 30 mM in IDH1<sup>mut</sup> gliomas.2 IDH1<sup>mut</sup> cells release D2HG into their surroundings in culture, in vivo, and into the CSF of patients with glioma.2,3 Furthermore, infiltrative glioma cells readily migrate along axons and dendrites in the gray and white matter, forming close physical associations with neurons (figure 1, A and B). Thus, IDH1<sup>mut</sup> glioma cells can expose neurons to D2HG.

The D2HG product of IDH1<sup>mut</sup> bears a strong structural resemblance to glutamate, the most widespread excitatory neurotransmitter in the CNS (figure 1C). Because glutamate is the...
primary excitatory neurotransmitter in the brain, its baseline concentration is tightly regulated in the extracellular space around neurons. Thus, infiltrative glioma cells releasing a glutamate mimetic could disrupt the balance between inhibition and excitation, and potentially lead to seizures. In this study, we analyzed clinical data from 712 patients representing 3 separate institutions, and examined the effects of D2HG on cortical neuron activity, in order to determine whether there is a link between IDH1<sup>mut</sup> and seizures in patients with glioma.

**METHODS** Patient cohorts. This was a retrospective cohort study of WHO grade II–IV infiltrative astrocytomas, oligodendrogliomas, and GBM, from patients aged 18 years and older, with known IDH1/2 mutation status (collectively referred to as IDH1<sup>mut</sup>). Cohort 1 consisted of 159 gliomas that had been tested for IDH1<sup>mut</sup> as part of routine clinical care at the University of Kentucky (table 1). This cohort included 13 grade II astrocytomas, 14 grade II oligodendrogliomas, 16 grade III astrocytomas, 4 grade III oligodendrogliomas, and 112 GBMs from 2009 to 2014. (Some cases had originally been resected prior to 2009, but for clinical reasons required retrospective testing.) Cohort 2 consisted of 136 gliomas that had been tested for IDH1<sup>mut</sup> at New York University (NYU) from 2010 to 2014, including 4 grade II astrocytomas, 6 grade II oligodendrogliomas, 10 grade III astrocytomas, 4 grade III oligodendrogliomas, and 112 GBMs. Both of these cohorts have recently been described in a separate study. Cohort 3 consisted of 417 gliomas from 2010 to 2016, including 26 grade II astrocytomas, 14 grade II oligodendrogliomas, 70 grade III astrocytomas, 24 grade III oligodendrogliomas, and 283 GBMs with known IDH1<sup>mut</sup> status from Northwestern Memorial Hospital (NMH). In all 3 cohorts, patient charts were retrospectively reviewed for the presence of any kind of seizures as part of the documented preoperative clinical presentation. A remote history of childhood seizures, or seizures attributed to other causes (e.g., alcohol withdrawal, head trauma), were excluded. Fewer than 1% of all patients with glioma had such a seizure history. To avoid potential therapy-related confounding factors, only seizures in new patients, with no prior surgical or adjuvant therapy, were included. To avoid bias, chart reviewers were blinded to the IDH1<sup>mut</sup> status of each tumor. Average and maximal follow-up for each patient, from the time of initial surgery, in cohort 1 was 18 and 243 months, respectively. In cohort 3, average and maximal follow-up from the time of initial surgery was 13 and 141 months, respectively. Survival data were obtained in cohort 1 via the Kentucky Cancer Registry, and in cohort 3 by the Northwestern University Tumor Registry, but were not available for cohort 2.

Mutation screening was done via R132H IDH1 immunohistochemistry (Dianova, Hamburg, Germany). Immunonegative tumors were tested for less common IDH1/2 mutations via...
Multielectrode array recording in cell culture. Primary dissociated cortical cultures were prepared from postnatal day 0–1 Sprague-Dawley rat pups (Charles River, Malvern, PA) for multielectrode array (MEA) plates as previously described. \(^1\) \(1.5 \times 10^6\) neurons were plated on 12-well MEA plates (Axion Biosystems, Atlanta, GA) precoated with poly-l-lysine (0.5 mg/mL) (Sigma-Aldrich, St. Louis, MO) and laminin (20 μg/mL) (Gibco, Langley, OK). Cultures were maintained in NeuroQ basal medium supplemented with 2% GS21 (MTI-GlobalStem, Gaithersburg, MD) and GlutaMAX (Thermo Fisher Scientific, Waltham, MA) with 1% Penn/Strep (Gibco) at 37°C in 5% CO\(_2\). Cytrabine (Sigma-Aldrich) (2.5 μM) was added 4 days after plating.

MEA recordings were performed on DIV 14. Extracellular potentials were recorded at 37°C using Maestro channel amplifier with AxIS software (Axion Biosystems, Atlanta, GA) with 1,200× gain and a 12.5 kHz/channel sampling rate. Plates were placed on the amplifier and equilibrated for 30 minutes before recording. Baseline and treatment measurements were recorded for 10 minutes each, a plot of the recorded data was analyzed, while blinded to experimental groups, using AxIS software and MATLAB-based Neural Metric Tool. Recordings were passed through a Butterworth bandpass filter (300–5,000 Hz) and spikes were detected using an adaptive threshold crossing (6× SD). Bursts were classified as having a minimum of 5 spikes with a max ISI of 100 milliseconds. Raster plots were generated with Neural Metric Tool.

### Table 1  Patient cohort characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>χ²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>712</td>
<td>159</td>
<td>136</td>
<td>417</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean ± SEM age at diagnosis, y</td>
<td>—</td>
<td>54.0 ± 1.2</td>
<td>60.7 ± 1.3</td>
<td>53.4 ± 0.79</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>400 (56.2)</td>
<td>82 (51.6)</td>
<td>81 (59.6)</td>
<td>237 (56.8)</td>
<td>0.5</td>
<td>0.48</td>
</tr>
<tr>
<td>Female</td>
<td>312 (43.8)</td>
<td>77 (48.4)</td>
<td>55 (40.4)</td>
<td>180 (43.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>77 (10.8)</td>
<td>27 (17.0)</td>
<td>10 (7.4)</td>
<td>40 (9.6)</td>
<td>0.11</td>
<td>0.74</td>
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<tr>
<td>III</td>
<td>128 (18.0)</td>
<td>20 (12.6)</td>
<td>14 (10.3)</td>
<td>94 (22.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>507 (71.2)</td>
<td>112 (70.4)</td>
<td>112 (82.4)</td>
<td>283 (67.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1 status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wild-type</td>
<td>535 (75.1)</td>
<td>112 (70.4)</td>
<td>105 (77.2)</td>
<td>318 (76.3)</td>
<td>0.43</td>
<td>0.51</td>
</tr>
<tr>
<td>Mutant</td>
<td>177 (24.9)</td>
<td>47 (29.6)</td>
<td>31 (22.8)</td>
<td>99 (23.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1p/19q status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>68 (9.6)</td>
<td>18 (11.3)</td>
<td>12 (8.8)</td>
<td>38 (9.1)</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Codeleted</td>
<td>644 (90.4)</td>
<td>141 (88.7)</td>
<td>124 (91.1)</td>
<td>379 (90.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Temporal</td>
<td>191 (27.1)</td>
<td>44 (27.7)</td>
<td>30 (23.4)</td>
<td>117 (28.1)</td>
<td>0.09</td>
<td>0.76</td>
</tr>
<tr>
<td>Nontemporal</td>
<td>513 (72.9)</td>
<td>115 (72.3)</td>
<td>98 (76.6)</td>
<td>300 (71.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>276 (38.8)</td>
<td>55 (34.6)</td>
<td>54 (39.7)</td>
<td>167 (40.0)</td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td>No</td>
<td>436 (61.2)</td>
<td>104 (65.4)</td>
<td>82 (60.3)</td>
<td>250 (60.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A total of 712 patients from 3 separate institutions produced the clinical data in this study. Differences in age among the cohorts were calculated by one-way analysis of variance followed by post hoc Tukey test. All other statistical comparisons were made by χ², with Yates correction for continuity. Tumor location was unknown for 8 cases in cohort 2. *Mean patient age was higher in cohort 2 than in cohorts 1 and 3.

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Figure 2  Seizures and mutations in isocitrate dehydrogenase 1 (IDH1\textsuperscript{mut}) in patients with glioma

(A) Patients with newly diagnosed infiltrative gliomas from 3 cohorts were assessed according to whether seizures were a part of their presenting symptoms, segregated into the 3 main molecular subgroups of gliomas: wild-type isocitrate dehydrogenase 1 (IDH1\textsuperscript{wt}) (yellow), IDH1\textsuperscript{mut} (white), and IDH1\textsuperscript{mut} with 1p/19q codeletion (blue).  

(B, C) Overall survival in cohorts 1 (B) and 3 (B), according to IDH1\textsuperscript{mut} and seizures on clinical presentation.  

Values were calculated based on log-rank tests between IDH1\textsuperscript{wt} or IDH1\textsuperscript{mut} curves.  

(Cohort 2 lacked sufficient follow-up data for survival analyses.)
Statistical evaluation. Statistical significance of differences between groups was determined via 2-sided t test, one-way analysis of variance with post hoc Tukey test, Fisher exact test, or log-rank test, as appropriate, using GraphPad software (La Jolla, CA). Odds ratios (ORs) were based on exact logistic regression. Multivariable hazard ratios (HRs) were based on Cox proportional hazards models. In all analyses, the significance target was \( p \leq 0.05 \).

Standard protocol approvals, registrations, and patient consents. Institutional research board approval for the retrospective collection and analysis of deidentified patient data was obtained at University of Kentucky, NYU, and NMH prior to study initiation. Institutional Animal Care and Use Committee approval was obtained from the University of California, Davis, prior to neuronal harvesting and culture.

RESULTS To determine whether there is an association between IDH1<sup>mut</sup> and seizures in patients with glioma, we obtained clinical data from 3 separate cohorts of patients, totaling 712 newly diagnosed WHO grade II–IV infiltrative gliomas (table 1). Aside from cohort 2 having a higher mean patient age at presentation, the cohorts were similar in proportions of sex, WHO grades, IDH1<sup>mut</sup> frequency, 1p/19q codeletion, temporal lobe vs extratemporal tumor location, and patients who presented with seizures. Combining all 3 cohorts, IDH1<sup>mut</sup> frequency was 80.5% for grade II gliomas, 54.7% for grade III gliomas, and 8.9% for grade IV gliomas.

Current data indicate that testing for IDH1<sup>mut</sup> and 1p/19q effectively stratifies gliomas into 3 major clinical–pathologic groups: (1) IDH1<sup>mut</sup> with 1p/19q codeletion (i.e., oligodendroglioma), (2) IDH1<sup>mut</sup> without 1p/19q codeletion (i.e., astrocytoma), (3) neither IDH1<sup>mut</sup> nor 1p/19q codeletion (i.e., GBM).<sup>9–11</sup> Whole-arm 1p/19q codeletion does not occur in the absence of IDH1<sup>mut</sup>.<sup>12</sup> In all 3 cohorts, IDH1<sup>mut</sup> gliomas were more likely to present with seizures than gliomas with only wild-type IDH1 (IDH1<sup>wt</sup>) (figure 2A). This increase in seizure risk was 56.6% in cohort 1 (74.5% vs 17.9%, \( \chi^2 44.4, p < 0.001 \), 32.1% in cohort 2 (64.5% vs 32.4%, \( \chi^2 9.0, p = 0.003 \)), and 25.3% in cohort 3 (59.4% vs 34.1%, \( \chi^2 17.6, p < 0.001 \)). In all 3 cohorts, there was no difference in seizure frequency between IDH1<sup>mut</sup>, 1p/19q-codeleted gliomas, and IDH1<sup>mut</sup>, 1p/19q-intact gliomas (83.3% vs 69.0%, \( p = 0.32 \) in cohort 1; 66.7% vs 63.2%, \( p = 1.0 \) in cohort 2; 60.5% vs 57.4%, \( p = 0.84 \) in cohort 3). On multivariable analysis of other major factors associated with seizure risk, including 1p/19q codeletion, WHO grade, and temporal lobe location, IDH1<sup>mut</sup> was an independent correlate with seizures (OR 2.5, 95% CI 1.6–3.9, \( p < 0.001 \)) (table e-1 at Neurology.org).

We had previously created a web-based algorithm to help guide the efficient molecular workup of gliomas by providing accurate pretest probability of IDH1<sup>mut</sup>.<sup>8</sup> That model included patient age, history of glioma, and GBM diagnosis, as those were the variables that contributed to the predictive accuracy of the overall model. We found that, in the combined cohorts of that study, incorporating seizures at clinical presentation into the algorithm improved the model’s accuracy (\( \Delta \text{AUC} 0.008, 95\% \text{ CI} 0.0004–0.017 \)), further underscoring the relationship between IDH1<sup>mut</sup> and seizures in patients with glioma.

In cohorts 1 and 3, where survival data were available, there was no difference in median survival among IDH1<sup>mut</sup> gliomas without and with seizures (undefined vs undefined in cohort 1, HR 2.1, 95% CI 0.29–15.5, \( p = 0.45 \); undefined vs undefined in cohort 3, HR 0.64, 95% CI 0.17–2.4, \( p = 0.51 \)) (figure 2, B and C). Among IDH1<sup>wt</sup> gliomas, only cohort 3 showed a modest increase in median survival when patients presented with seizures (7.6 vs 12.6 months in cohort 1, HR 1.1, 95% CI 0.66–1.9, \( p = 0.25 \); 13.6 vs 18.4 months in cohort 3, HR 1.5, 95% CI 1.1–2.1, \( p = 0.01 \)). On multivariable analysis, however, only IDH1<sup>mut</sup> was an independent correlate with overall survival in both cohorts, not seizures (IDH1<sup>mut</sup> relative risk [RR] 0.027 and 0.20, 95% CI 0.006–0.12 and 0.57–1.1, \( p < 0.001 \) and <0.001; seizures RR 0.78 and 0.79, 95% CI 0.45–1.4 and 0.57–1.1, \( p = 0.39 \) and 0.15) (table 2).

We found that exogenous D2HG markedly increased the in vitro electrical activity of rat cortical neurons (figure 3, A and B, video). D2HG specifically increased the duration of synchronized bursts of firing in the neuronal networks (figure 3C), a characteristic effect of epileptogenic agents..<sup>13,14</sup> Along with an increase in network burst duration,
D2HG decreased network burst frequency (figure 3D). IDH1mut gliomas contain up to 30 mM D2HG, cells expressing IDH1mut release D2HG into their environment, and elevated D2HG has been detected in the circulating CSF of IDH1mut patients with glioma. Infiltrative glioma cells readily migrate along axons and dendrites in the gray and white matter, forming close physical associations with neurons (figure 1). Thus, IDH1mut glioma cells are poised to expose neurons to very high local concentrations of D2HG. We found a dose-response relationship between D2HG and neuronal activity, with increased activity detectable at 3 and 10 mM (figure 3E). The selective NMDA receptor antagonist, (2R)-amino-5-phosphonovaleric acid; (2R)-amino-5-phosphonopentanoate (AP5), completely blocked the excitatory effect of D2HG on neurons (figure 3F).
Seizures are a common manifestation of infiltrative gliomas. Over 50% of patients with an infiltrative glioma will experience at least one seizure during the course of their disease, and over 30% will develop tumor-associated epilepsy (TAE), defined as multiple seizures.15–16 This is a major cause of tumor-associated morbidity and greatly diminishes quality of life. At least 10% of patients with glioma will develop status epilepticus, a life-threatening condition wherein a seizure lasts longer than 5 minutes, or when multiple seizures occur without regaining consciousness.1 TAE is managed by a combination of antitumor therapies (including surgical resection, chemotherapy, and radiation), as well as antiepileptic drugs (such as lamotrigine, levetiracetam, and valproate). Even multimodal strategies fail to control seizures in up to a third of patients.17 A better understanding of the risk factors and mechanisms associated with TAE are therefore needed in order to improve patient quality of life.

The relationship between IDH1 mutant (IDH1mut) and seizures in patients with glioma has been controversial.1,10,18–20 A direct mechanistic link between the D2HG product of IDH1mut and neuronal activity strengthens the hypothesis that IDH1mut gliomas are more likely to induce TAE than IDH1 wild-type (wt) gliomas. Glutamate binds to and activates multiple receptors in neurons, including ligand-gated NMDA and AMPA ion channels, allowing influx of Na⁺, K⁺, and sometimes Ca⁺ ions. Depolarization caused by glutamate thus increases the likelihood that a neuron will fire an action potential. In an artificial model of human embryonic kidney cells expressing NMDA or AMPA receptors, D2HG bound and activated ionotropic NMDA receptors, but not AMPA receptors.21 In the current study, we directly tested the effect of D2HG on cultured neurons using MEAs, which are widely used to measure neuronal activity in vitro.22 Unlike intracellular recordings that are limited to measurement of electrophysiologic activity in a single cell for a short duration, MEAs allow for noninvasive, simultaneous, and long-term recordings of local field potentials and extracellular action potentials from a population of neurons within a millisecond time scale.23 MEAs can quantitatively measure properties of electrical activity across neuronal networks that are altered when changes in the inhibitory/excitatory balance lead to seizures.29–31 Our data demonstrate that D2HG may activate neuronal NMDA receptors, thereby promoting the same kind of heightened network synchrony that is characteristic of seizure-inducing agents (figure 3, video).

A direct excitatory role for the D2HG product of IDH1mut helps explain a number of patterns regarding epilepsy in gliomas. First, older studies reported that oligodendrogliomas are more likely to cause seizures than those of astrocytic lineage.32–34 Our data suggest that this is because the molecular profile of true oligodendrogliomas necessarily includes IDH1mut, whereas the molecular profile of astrocytic gliomas (including GBM) is more heterogeneous. Second, seizures are more common in lower-grade gliomas than in GBM, even though the latter are more invasive and destructive.35 Our multivariable data show that IDH1mut is a significant correlate of seizures, independent of WHO grade (figure 2A, table e-1). Third, presenting with seizures is commonly thought to correlate with longer overall survival in patients with glioma, possibly because such tumors are detected earlier.36 However, IDH1mut gliomas are much less aggressive than those harboring only IDH1wt,37 raising the possibility that seizures at clinical presentation only predict longer survival to the extent that they are linked with IDH1mut.

Our data suggest that the association between seizures at clinical presentation and better prognosis is driven mostly by the intrinsic biological differences between IDH1mut and IDH1wt gliomas, rather than by seizures prompting earlier clinical intervention (figure 2B and C, and table 2).

Although seizures were more common in IDH1mut gliomas, a sizeable proportion of IDH1wt gliomas also caused pretherapy seizures (figure 2A). This underscores the fact that tumors can cause seizures by a variety of mechanisms, such as abnormal regulation of excitatory and inhibitory receptors, altered expression of ion transporters, increased mTOR activity, and inflammation.37–38 Our data suggest that the production of D2HG, which is a central, defining feature of IDH1mut gliomas, may be another seizure-inducing mechanism.

While these findings suggest a mechanistic link between IDH1mut, its D2HG product, and...
glioma-induced seizures, there are some limitations to this study. First, although the clinical data consist of a large number of patients from 3 separate institutions, it is a retrospective study and the presence of seizures is based on history-taking and subjective clinical impressions, not EEG data. Second, while MEA studies firing patterns among interconnected neurons over long periods of time, and high-density in vitro neuronal networks show synapse-specific modifications similar to what is seen in vivo,59 single electrode approaches in low-density neuronal culture allow for the detailed study of D2HG-evoked currents. It will therefore be necessary to extend the current findings in future studies, using prospective patient-based analyses, single-electrode recordings, and in vivo models, in order to more fully understand the effects of D2HG on neuronal activity and epilepsy.

To date, the majority of glioma research on D2HG and IDH1mut has focused on their effects within the tumor cell. Our data indicate that IDH1mut may also exert a considerable effect on surrounding non-neoplastic cells, including neurons, through the release of its D2HG oncometabolite into the tumor microenvironment. In a preclinical model of IDH1mut glioma, pharmacologic inhibition of IDH1mut effectively lowered D2HG production and showed promising effects against tumor growth.40 Currently, there are multiple clinical trials aimed at evaluating IDH1mut inhibitors in gliomas, including AG-120 (NCT02073994), AG-881 (NCT02481154), BAY1436032 (NCT02746081), and IDH305 (NCT02381886). To our knowledge, none of these trials include seizure monitoring as a primary or secondary endpoint. Yet, even if none of these drugs effectively controls glioma growth, they might help control TAE in patients with IDH1mut gliomas, either as a monotherapy or in conjunction with other antiepileptic drugs, by directly blocking the production of D2HG (figure 4).

AUTHOR CONTRIBUTIONS
Hao Chen performed the in vitro neuronal experiments and assisted with the manuscript. Pamela Lein designed the in vitro experiments. Laith Khoury collected patient data from University of Kentucky. Choddhi Thomas, Carolina Benjamin, Donato Pacione, John Golfinos, and Matija Snuderl collected patient data from NYU. Jonathon Judkins, Farhad Ghamarsi, and Priya Kumthekar collected patient data from NMH. Meijun Wu performed biostatistical analyses on all 3 patient cohorts. Li Chen provided the IDH1mut prediction modeling. Dan Chekovich assisted with the manuscript. Craig Hubschki conceived the project, designed the study, and wrote the manuscript.

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DISCLOSURE
H. Chen, J. Judkins, C. Thomas, M. Wu, L. Khoury, C. Benjamin, D. Pacione, J. Golfinos, P. Kumthekar, F. Ghamarsi, L. Chen, P. Lein, D. Chekovich, and M. Snuderl report no disclosures relevant to the manuscript. C. Hubschki was supported by the National Cancer Institute (K08CA155764). Go to Neurology.org for full disclosures.

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REFERENCES
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The world’s leading experts on sports concussion are once again hosting the year’s premier event on sports concussion. The American Academy of Neurology’s 2016 Sports Concussion Conference, set for July 8-10 in Chicago, features a concussion boot camp and is poised to be the go-to meeting for all disciplines involved in the prevention, diagnosis, and treatment of professional, collegiate, and high school sports concussion, including neurologists, athletic trainers, and other medical professionals. Early registration discounts end June 14, so visit AAN.com/view/ConcussionConference to secure your spot—and savings—today!