Evidence for Sequenced Molecular Evolution of IDH1 Mutant Glioblastoma From a Distinct Cell of Origin


ABSTRACT

Purpose
Mutation in isocitrate dehydrogenase 1 (IDH1) at R132 (IDH1R132MUT) is frequent in low-grade diffuse gliomas and, within glioblastoma (GBM), has been proposed as a marker for GBMs that arise by transformation from lower-grade gliomas, regardless of clinical history. To determine how GBMs arising with IDH1R132MUT differ from other GBMs, we undertook a comprehensive comparison of patients presenting clinically with primary GBM as a function of IDH1R132MUT mutation status.

Patients and Methods
In all, 618 treatment-naive primary GBMs and 235 lower-grade diffuse gliomas were sequenced for IDH1R132MUT and analyzed for demographic, radiographic, anatomic, histologic, genomic, epigenetic, and transcriptional characteristics.

Results
Investigation revealed a constellation of features that distinguishes IDH1R132MUT GBMs from other GBMs (including frontal location and lesser extent of contrast enhancement and necrosis), relates them to lower-grade IDH1R132MUT gliomas, and supports the concept that IDH1R132MUT gliomas arise from a neural precursor population that is spatially and temporally restricted in the brain. The observed patterns of DNA sequence, methylation, and copy number alterations support a model of ordered molecular evolution of IDH1R132MUT GBM in which the appearance of mutant IDH1 protein is an initial event, followed by production of p53 mutant protein, and finally by copy number alterations of PTEN and EGFR.

Conclusion
Although histologically similar, GBMs arising with and without IDH1R132MUT appear to represent distinct disease entities that arise from separate cell types of origin as the result of largely nonoverlapping sets of molecular events. Optimal clinical management should account for the distinction between these GBM disease subtypes.

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INTRODUCTION
Glioblastoma (GBM), also known as grade 4 astrocytoma, is the most aggressive intrinsic brain tumor in adults and continues to be associated with extremely poor outcomes. Evidence to date indicates that the cells of origin for GBM may be either neural stem cells or their more differentiated progeny. Most GBMs arise with no prior clinical history of a precursor lesion and are referred to as primary or de novo GBMs. A minority of GBM cases, known as secondary GBMs, develop from lower-grade astrocytomas or oligodendrogliomas and bear different genomic abnormalities than primary GBM. Despite recent studies suggesting that molecular subsets of GBM differ in response to current treatments, standard treatment for all patients with primary GBM is a regimen combining radiation and temozolomide. The recent identification of R132 mutations in isocitrate dehydrogenase 1 (IDH1R132MUT) in the majority of low-grade gliomas and secondary GBMs, with relative exclusion from primary GBMs, implicates IDH1R132MUT as a defining marker and key oncogenic event for GBMs...
that evolve from lower-grade glioma.\textsuperscript{11-16} Herein, we sought to develop a detailed portrait of untreated GBMs arising with \textit{IDH1}\textsuperscript{R132MUT} with the aim of gaining insights into the manner in which \textit{IDH1}\textsuperscript{R132MUT} gliomas develop and to determine whether \textit{IDH1}\textsuperscript{R132MUT} GBM is a distinct disease entity.

### PATIENTS AND METHODS

The focus of our investigation is 618 patients with newly diagnosed untreated primary (de novo) GBMs (cohorts A through F) and 235 patients with newly diagnosed untreated lower-grade diffuse gliomas (cohorts G and H). Patients with GBM included two cohorts compiled for this investigation (cohorts A and B), plus patients associated with previously reported studies\textsuperscript{17-20} (cohorts C through F). Sequence analysis of \textit{IDH1}\textsuperscript{R132MUT} and \textit{p53}\textsuperscript{R273} included 105 additional samples of diffuse glioma (cohort I). A summary of patient cohorts is provided in Table 1. Additional details regarding Methods and patient cohorts are provided in the Data Supplement.

### RESULTS

#### \textit{IDH1}\textsuperscript{R132MUT} GBMs Are Phenotypically Distinct

To characterize \textit{IDH1}\textsuperscript{R132MUT} and \textit{IDH1}\textsuperscript{R132WT}—wild type (\textit{IDH1}\textsuperscript{R132WT})—GBMs in the absence of confounding treatment effects, we pursued a comparison within treatment-naive patients with primary GBM. From 618 de novo GBMs, we identified 49 \textit{IDH1}\textsuperscript{R132MUT} tumors, all of which occurred in adults. Within adult patients, we confirmed that \textit{IDH1}\textsuperscript{R132MUT} GBMs manifest longer overall survival\textsuperscript{12,13,16,21} (Appendix Fig A1A, online only) and showed more frequent promoter methylation of \textit{O\textsuperscript{6}-methylguanine--DNA methyltransferase (MGMT)}\textsuperscript{21,22} as illustrated in Figure 1A. Histologic characterization of a sampling of \textit{IDH1}\textsuperscript{R132MUT} and \textit{IDH1}\textsuperscript{R132WT} GBMs demonstrated similar levels of cell proliferation on the basis of MIB-1 staining (Data Supplement), but revealed a lesser extent of necrosis in \textit{IDH1}\textsuperscript{R132MUT} GBMs (Fig 1A) and a nonsignificant trend toward less frequent occurrence of vascular abnormalities (Fig 1A). Consistent with a previous report,\textsuperscript{12} examination of an expanded series of samples revealed a statistically significant, albeit modest, increase in the percentage of cells with oligodendroglial morphology in \textit{IDH1}\textsuperscript{R132MUT} GBMs (Fig 1A). To examine whether tumors in our series of GBMs harbored the co-deletion of chromosome arms 1p/19q commonly observed in oligodendrogliomas, we assessed DNA copy number alterations by using array comparative genomic hybridization in a series of samples and found that a minority of \textit{IDH1}\textsuperscript{R132MUT} GBMs (two of eight) and none of the \textit{IDH1}\textsuperscript{R132WT} GBMs (zero of 13) displayed 1p/19q co-deletion (Appendix Fig A1B). There was a striking difference between the two GBM subsets regarding loss of chromosome 10; this alteration was absent in all \textit{IDH1}\textsuperscript{R132MUT} GBMs but was present in all but one sample of \textit{IDH1}\textsuperscript{R132WT} GBM (Appendix Fig A1B).

By using previously defined parameters,\textsuperscript{23} we examined available preoperative cranial magnetic resonance images. Consistent with our histologic findings, detection of necrosis was less frequent in \textit{IDH1}\textsuperscript{R132MUT} GBMs; moreover, \textit{IDH1}\textsuperscript{R132MUT} GBMs exhibited more frequent non-enhancing tumor component, larger size at diagnosis, lesser extent of edema, and increased prevalence of cystic and diffuse components (Fig 1B and Appendix Fig A1C). In addition, the \textit{IDH1}\textsuperscript{R132MUT} GBMs demonstrated greater frequency of contact with brain ventricles, although interpretation of this finding may be confounded by the larger size of \textit{IDH1}\textsuperscript{R132MUT} GBMs (Appendix Fig A1C). Overall, the radiographic and histologic features that distinguish \textit{IDH1}\textsuperscript{R132MUT} GBMs resemble characteristics of lower-grade gliomas and are consistent with a less aggressive clinical course.

### Restricted Gene Expression of \textit{IDH1}\textsuperscript{R132MUT} GBMs

By examining transcriptional signatures of both the newly diagnosed high-grade astrocytomas in this investigation and The Cancer Genome Atlas (TCGA) primary GBM data set, we found that the majority of \textit{IDH1}\textsuperscript{R132MUT} tumors express the Proneural\textsuperscript{17} subtype signature (Fig 2A and Appendix Fig A2A, online only). This Proneural signature has previously been reported as a positive prognostic indicator\textsuperscript{27} and is substantially similar to the TCGA Proneural signature associated with \textit{IDH1}\textsuperscript{R132MUT} GBMs that resembles the signature of oligodendroglia.\textsuperscript{9} A minority of \textit{IDH1}\textsuperscript{R132MUT} GBMs possessed the Proliferative signature, and none possessed the Mesenchymal signature associated with angiogenesis and poor outcome\textsuperscript{23} (Fig 2A and Appendix Fig A2A). In contrast, \textit{IDH1}\textsuperscript{R132WT} GBMs displayed all
three signatures, with a preponderance of the Mesenchymal subtype. Strikingly, evaluation of gene expression subtype in matched sample pairs from high-grade astrocytomas obtained at initial diagnosis and after recurrence (Appendix Fig A2B) showed that all IDH1R132MUT tumors maintained their original subtype, although several IDH1R132WT GBMs shifted to the Mesenchymal subtype. Thus, IDH1R132MUT tumors differ not only in their presentation but also in their pattern of disease progression and do not share the propensity of IDH1R132WT GBMs to adopt a Mesenchymal phenotype.

By using agreement of differential expression (AGDEX)34 to compare expression profiles of the human tumors with a published embryonic mouse forebrain gene expression data set,25 we found that global expression profiles of IDH1R132WT GBMs resemble mouse neural stem cells, and IDH1R132MUT GBMs resemble lineage-committed neural precursors (AGDEX, +0.147; P < .004; Data Supplement). A separate hierarchical clustering analysis that used the genes most differentially expressed between IDH1R132MUT and IDH1R132WT GBMs reveals similarity of IDH1R132MUT samples to normal fetal or adult brain parenchyma and similarity of IDH1R132WT GBMs to cultured adult neural stem cells26 (Fig 2B). Because both fetal and adult brain samples are enriched for differentiating or mature neural cell types, these findings underscore the greater similarity of IDH1R132MUT GBMs to lineage-committed neural cells than to stem cells.

**IDH1R132MUT GBMs Are Spatially and Temporally Restricted**

Tabulating the location of IDH1R132MUT and IDH1R132WT GBMs, we found a striking predominance of frontal lobe involvement of IDH1R132MUT GBMs that contrasts with the more widespread distribution of IDH1R132WT GBMs (Fig 3A). Regardless of histologic subtype, IDH1R132MUT gliomas displayed a nearly identical percentage of frontal lobe involvement (Appendix Figs A3A-A3C, online only).

Overlay of tumor areas from a series of all available IDH1R132MUT GBMs with digitized pretreatment magnetic resonance images confirmed the high frequency of frontal lobe involvement, whereas overlay of a random sampling of IDH1R132WT tumors failed to demonstrate any frequently involved regions (Appendix Fig A3D). By performing a voxel-wise Fisher’s exact test to isolate the area of differential involvement, we found that IDH1R132MUT GBMs were distributed at increased frequency in the area of the frontal lobe surrounding the rostral extension of the lateral ventricle (Fig 3B).

By examining tumor genotype as a function of age for both GBMs and grade 3 astrocytoma (anaplastic astrocytoma), we found that the relative frequency of IDH1R132MUT tumors rises sharply in the third decade of life and decreases in the fourth or fifth decade (Fig 3C). Thus, relative to IDH1R132WT tumors, IDH1R132MUT tumors appear to arise at greatest frequency within a more restricted time period. Interestingly, within adult GBMs, a significant difference in sex ratios was seen as a function of IDH1R132 status, consistent with previous reports of trends for a greater fraction of female patients with secondary versus primary GBM27,28 (Appendix Fig A3E).

**IDH1R132MUT GBMs Show Preponderance of Template Strand Mutation in IDH1 and Coding Strand Mutation in p53**

In agreement with previous reports13,16,29 our data showed a higher frequency of p53 mutation in IDH1R132MUT versus IDH1R132WT high-grade astrocytomas (Appendix Fig A4A, online only). Consistent with the well-documented propensity for C>T mutation at cytosine phosphate guanine ( CpG) sites,30 data from our sample set showed that the most common mutations in both p53 and IDH1 are at Arg residues encoded by the codon CGT (IDH1R132 and p53R273G; Figs 4A and 4B). For both IDH1R132WT and p53R273G, C>T mutations on template and coding strands will result in substitutions of His or Cys, respectively. By sequencing an expanded series of grades 2 to 4 gliomas for these codons in IDH1 and p53, we found, within IDH1R132MUT gliomas, a marked and unexpected contrast between the prevalence of Cys and His substitutions in the two proteins (P < .001 with Fisher’s exact test; Fig 4A). Given that the probability for
mutation is highest for C>T mutations, we deduce that the mutation pattern observed in tumors with mutations in both IDH1R132 and p53R273 is most likely to have occurred by strong selection for IDH1 and p53 mutations on the template versus on the coding strands, respectively (Fig 4B). These findings suggest that if both IDH1R132H and p53R273C mutations occur as C>T mutations in a nonproliferating cell, mutant IDH1 protein will be expressed immediately, whereas mutant p53 protein will not occur until after DNA replication. The predominance of p53R273C in the IDH1R132MUT tumors contrasts with the preference for p53R273H in the IDH1R132WT tumors (P < .005 with Fisher’s exact test).

**DISCUSSION**

The development of novel therapeutic regimens for human malignancies, particularly those involving targeted therapy, is greatly facilitated by methods for identifying clinically meaningful disease subsets. To gain greater understanding of the utility of IDH1R132MUT as a marker in diffuse glioma, we have conducted a comprehensive analysis of the features of newly diagnosed cases of primary GBMs arising with and without IDH1R132MUT. Our results indicate that, although histologically similar, IDH1R132MUT and IDH1R132WT GBMs differ in their demographic, anatomic, phenotypic, epigenetic, and genomic presentation and follow a different clinical course, supporting a model of two disease entities that most likely arise from separate cell types of origin as the result of largely nonoverlapping sets of molecular events (Fig 5). Increased understanding of the cell of origin and molecular evolution of IDH1R132MUT GBM may aid in development of therapeutic strategies for this tumor type by yielding insights into the biology of these lesions and facilitating the development of animal models.

Our analysis demonstrates that the phenotypic features that distinguish IDH1R132MUT from IDH1R132WT GBMs include better outcome, predominance of frontal lobe location, presentation and
A key finding of this investigation is the discovery of a constellation of restricted phenotypic, spatial, and temporal features of IDH1R132MUT GBMs that is consistent with origin from a non–stem-cell neural precursor pool. By revealing the exclusion of Mesenchymal signature as an absolute feature of IDH1R132H gliomas, our results extend earlier reports of an association between IDH1 mutation and Proneural gene expression.9,32 This observation, and the closer resemblance of IDH1R132MUT GBM transcriptional signatures to those of brain tissue rather than of stem cells suggests that IDH1R132MUT GBM cells do not retain the capability to generate progeny with a broad range of transcriptional profiles.

Although the restriction of IDH1R132MUT GBM gene expression signatures may be a consequence of the actions of IDH1R132MUT, taken with the spatial and temporal homogeneity of IDH1R132MUT GBM presentation, this finding suggests that the cell of origin for IDH1R132MUT GBMs is a neural precursor population with limited differentiation potential that is most abundant during a specific stage and location in forebrain development. Our area of differential involvement analysis demonstrates a strong propensity for IDH1R132MUT gliomas to occur in the frontal lobe, specifically in the area surrounding the rostral extension of the lateral ventricles, indicating this region as a likely location of the cell of origin for many IDH1R132MUT gliomas. Consistent with our findings, predominance of frontal lobe location has been reported in oligodendrogliomas with 1p/19q co-deletion,33,34 a tumor type now known to carry IDH1 mutation at high frequency.13,14,29 Previous studies13,15,16,21,35,36 indicate that although the median age of patients with IDH1R132MUT GBM is younger than that for IDH1R132WT GBM, IDH1R132MUT is rare in the pediatric population. By using logistic regression to overcome the limitations of patient sampling, we were able to determine that the relative probability of a tumor harboring IDH1R132MUT abruptly increases around age 20 and begins to decrease a decade later. This raises the possibility that the cell type of origin for IDH1R132MUT gliomas is most abundant and permissive during a limited developmental time window, possibly coinciding with remodeling of prefrontal cortex in adolescence.37,38 Our findings that Proneural gene expression and increased oligodendrogial histology are associated with IDH1R132MUT GBMs are consistent with an oligodendrogial progenitor cell type of origin, and several studies lend support for oligodendrogial progenitor cells as a cell type of origin for glioma.39-44

Given the strong correlation we confirmed between CIMP and IDH1 mutation, we propose that CIMP is also an early and critical event in the development of IDH1R132MUT gliomas. Recent studies45,46 indicating that IDH1 mutation acts to inhibit a class of alpha-ketoglutarate–dependent enzymes, including proteins that catalyze histone demethylation and hydroxylation of methylated DNA, support the possibility that IDH1 mutation can initiate maintenance of Proneural expression signature, lesser extent of necrosis and edema, presence of non–contrast-enhancing component, and greater oligodendrogial content. These phenotypic findings, along with our genomic and epigenetic observations, confirm and extend earlier reports that IDH1R132MUT GBMs are distinguished by features associated with lower-grade diffuse glioma and support the contention that all IDH1R132MUT GBMs arise by evolution from lower-grade IDH1R132MUT gliomas, regardless of clinical history.12,14,15,29,31 Differences in demographics (age and sex) and tumor location in patients with IDH1R132MUT and IDH1R132WT GBM add to the features that suggest different etiologies of the two disease entities.
oncogenesis by inducing an epigenetic block to differentiation in a specific population of CNS cells poised at a particular developmental state. This hypothesis explains the homogeneity in presentation of \(\text{IDH1}^{\text{R132H}}\) gliomas and suggests the possibility that these lesions might show sensitivity to therapeutic regimens with differentiating agents.

Several investigations\(^{13,16,18}\) demonstrate that most \(\text{IDH1}^{\text{R132H}}\) astrocytomas harbor mutations of \(\text{p53}^{\text{R273H}}\), and one study\(^{12}\) revealed instances in which \(\text{IDH1}^{\text{R132H}}\)-wild type \(\text{IDH1}^{\text{WT}}\) tumors, the preferred substitution at \(\text{p53}^{\text{R273H}}\) is His. (B) Schematic diagram showing that \(\text{IDH1}^{\text{R132H}}\) mutation on the template strand and \(\text{p53}^{\text{R273H}}\) mutation on coding strand can select for the expression of \(\text{IDH1}^{\text{R132H}}\) mutant protein before \(\text{p53}^{\text{R273H}}\) mutant protein if replication is delayed.

Although mutation of \(\text{IDH1}^{\text{R132H}}\) on the template strand permits immediate translation of \(\text{IDH1}^{\text{R132H}}\) mutant protein, mutation of \(\text{p53}^{\text{R273H}}\) on the coding strand allows the appearance of \(\text{p53}^{\text{R273H}}\) mutant protein only after DNA replication. Thus, in a quiescent cell, the pattern of mutations we observed at high frequency in \(\text{IDH1}^{\text{mutant}}\) glioma will result in appearance of \(\text{IDH1}^{\text{mutant}}\) protein to be followed by \(\text{p53}^{\text{mutant}}\) protein only after a cycle of DNA replication. The preferred substitutions seen in gliomas harboring mutations at both \(\text{IDH1}^{\text{R132H}}\) and \(\text{p53}^{\text{R273H}}\) stand in stark contrast to the substitution pattern in cancers with mutations in only one of these genes. Specifically, for \(\text{IDH1}^{\text{R132H}}\), the preferred substitution in acute myeloid leukemia is Cys\(^{48-50}\) and for \(\text{p53}^{\text{R273H}}\), the predominant substitution is His\(^{51}\) (including the \(\text{IDH1}^{\text{R132H}X} \text{IDH1}^{\text{mutant}}\) gliomas in this study). Our finding of the frequent co-occurrence of \(\text{IDH1}^{\text{R132H}}\) and \(\text{p53}^{\text{R273H}}\) suggests that sequential appearance of \(\text{IDH1}^{\text{mutant}}\) protein before \(\text{p53}^{\text{mutant}}\) protein may be critical for formation of \(\text{IDH1}^{\text{mutant}}\) gliomas.
Our analysis suggests a model in which IDH1R132MUT GBMs arise in a stepwise fashion as the result of a series of sequenced molecular alterations that cooperate with normal developmental events (Fig 5 and Data Supplement). We propose that although IDH1R132MUT, induction of CIMP, and p53R273MUToften occur in a quiescent neural stem cell, tumors arise only from lineage-committed progeny following a wave of proliferation related to forebrain maturation that triggers appearance of mutant p53 protein and loss of cell cycle control. This oncogenic process results in a low-grade glioma that subsequently acquires additional genomic alterations that promote malignant transformation to GBM. Previous studies provide strong evidence that PTEN loss via loss of chromosome arm 10q is an event that occurs during transition to secondary GBM. Our cytogenetic observations of focal EGFR amplification and PTEN loss in IDH1R132MUT...
GBMs are consistent with the proposal that these events occur during the evolution of lower-grade IDH1(R132MUT) glioma to GBM.

In our model, the production of IDH1 mutant protein is the initial event in an orchestrated process that leads to the stepwise emergence of a distinct GBM entity that has a less aggressive clinical course than other GBMs. In contrast to the heterogeneous presentation of most GBMs, IDH1(R132MUT) GBMs arise at high frequency in early adult life as frontal lobe lesions with a constellation of radiographic, histologic, and transcriptional features that relates these lesions to the lower-grade diffuse gliomas from which we contend they arise. This investigation adds to a growing body of data that suggests that histologically similar brain tumors may represent distinct disease entities arising as a result of vulnerability of different stem-cell and progenitor populations to particular oncogenic alterations.24,53,54 IDH1(R132MUT) glioma may be an especially interesting example of the dependence of oncogenesis on normal developmental processes, because the cell of origin we propose may be uniquely abundant in human brain.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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