The comprehensive taxonomic encyclopedia of the genetic alterations underlying all cancers is rapidly becoming widely available.61,85,91 To date, this molecular genomic focus has driven an evolving perspective on malignancies as lesions that are defined by (in addition to microscopic histological findings) their signature tumor genome alterations. Indeed, the lingua franca of this genome-based framework is increasingly pervasive, as is exemplified by lesions such as HER2-amplified breast cancer,83 BCR-ABL–rearranged chronic myeloid leukemia,23 EGFR-mutant55 or EML4-ALK–rearranged 48 non–small cell lung cancer, and BRAF-mutant melanoma 16 that populate the growing lexicon of molecular oncology. Importantly, the presence of these alterations is clinically significant because there are specific inhibitors that target their expressed proteins and lead to dramatic clinical response in patients with these cancers.

Several groups have used a similar approach to glioblastoma, the most common intrinsic brain tumor. 59,65 Extensive characterization of the genomic changes underlying these cancers has set the stage for a reevaluation of their clinical management. A prototypic example has been the recent identification of mutations in the IDH1 gene,65 a stunning and unexpected discovery that has led to new insights into glioma and cancer biology, has fueled new interest in studies of cancer metabolism, and has clear clinical implications.

Today, neurooncologists and neurosurgeons increasingly stratify glial neoplasms into IDH1-mutant or IDH1-wild type.24,92 Indeed, the divergent clinical characteristics of histopathologically identical primary (IDH1-WT) and secondary (IDH1-mutant) glioblastomas are lending further support to the notion that these tumors represent different diseases. Herein we review the discovery and incidence of IDH mutation in glioma and other cancers, our current understanding of mutant IDH biology, and its increasing translational implications.
Mutations of IDH1 in Cancer

Discovery of Mutant IDH1

In 2008, recurrent mutations in IDH1 were first identified through work by the Vogelstein group analyzing the DNA sequence of the protein-coding portions of the glioblastoma genome (see Parsons et al.65). In that study, 23,219 transcripts from 20,661 protein-coding genes in 22 malignant gliomas were analyzed by capillary-based Sanger sequencing. Of the 22 tumors examined, 7 were derived directly from patient tissue, and 15 were derived from xenografts of human tumors. In this initial so-called Discovery set, 5 of 22 tumors carried an identical mutation of the IDH1 gene that produced the R132H amino acid substitution of the IDH1 protein. Notably, the ages of the patients who harbored this mutation in the Discovery set were 30, 31, 32 (2 patients), and 42 years, which is considerably younger than the historically associated age at glioblastoma diagnosis (which is more typically in the 6th or 7th decade of life). Targeted sequencing analysis in a validation sample set of 127 additional tumors identified 13 IDH1 mutations, including 4 (80%) of 5 tumors known to be secondary glioblastomas. Parsons et al.65 provided 2 additional important observations that have since been corroborated by other groups. First, the median age of patients with the IDH1-mutant tumors was 33 years, whereas in the patient group with IDH1-WT tumors, the median age was 53 years. Second, patients with IDH1-mutant tumors demonstrated a significantly longer overall survival time compared with patients in the IDH1-WT group.

Of the 3 human IDH isoforms, IDH1 is located in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 are located within the mitochondria. The IDH proteins are known to catalyze the oxidative decarboxylation of isocitrate to α-KG, leading to the production of NADPH in the TCA cycle, a biochemical sequence critical in sugar, lipid, and amino acid metabolism.70 Prior to the study of Parsons et al., these proteins had not previously been linked to cancer. Although a mutation in IDH1 producing the R132C substitution had been identified previously in patients with colon cancer,84 the study of glioblastoma was the first to demonstrate that IDH1 was recurrently mutated in cancer and correlated with important clinical parameters.

In addition to mutations in IDH1, additional components of the TCA cycle are mutated in other non-CNS cancers. For example, mutations in subunits of the succinate dehydrogenase complex have been identified in paragangliomas and pheochromocytomas, and mutations in fumarate hydratase have been associated with renal cell carcinomas and leiomyomas.38-40 Together with these findings, the growing body of work revealing mutations in genes encoding canonical proteins in metabolism has lent support to Otto Warburg’s nearly century-old hypothesis that metabolic dysregulation could underlie tumor formation (reviewed in Kaelin95 and in Ward and Thompson96). The precise mechanism of tumor promotion from these mutations was unclear and awaited further study, as detailed below.

Landscape of IDH1 Mutations in Brain Tumors

The seminal observation of recurrent IDH1 muta-

G. P. Dunn, O. C. Andronesi, and D. P. Cahill

Additional Features Associated With IDH1 Mutation

Although the similar incidence of IDH1 mutation

Neurosurg Focus / Volume 34 / February 2013
Mutant IDH1/2 in glioma

**TABLE 1: Literature review of frequency of IDH1 and IDH2 mutations in CNS and non-CNS human cancers**

<table>
<thead>
<tr>
<th>Tumor Categories</th>
<th>IDH1 Mutations</th>
<th>IDH2 Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors of the CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>astrocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pilocytic (WHO Grade I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balss et al., 2008</td>
<td>1 of 41</td>
<td></td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>0 of 38</td>
<td></td>
</tr>
<tr>
<td>Jiao et al., 2012</td>
<td>0 of 9</td>
<td>0 of 9</td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>0 of 21</td>
<td>0 of 21</td>
</tr>
<tr>
<td>total</td>
<td>1 of 109 (0.01%)</td>
<td>0 of 30 (0%)</td>
</tr>
<tr>
<td>diffuse glioma (WHO Grade II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2009</td>
<td>165 of 227</td>
<td>2 of 227</td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>13 of 22</td>
<td></td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>10 of 12</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>60 of 68</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>25 of 30</td>
<td>2 of 30</td>
</tr>
<tr>
<td>total</td>
<td>273 of 359 (76%)</td>
<td>4 of 257 (1.6%)</td>
</tr>
<tr>
<td>anaplastic (WHO Grade III)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2010</td>
<td>87 of 145</td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2009</td>
<td>146 of 228</td>
<td>2 of 228</td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>32 of 62</td>
<td></td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>9 of 18</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>21 of 27</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>36 of 52</td>
<td>2 of 52</td>
</tr>
<tr>
<td>total</td>
<td>331 of 532 (62.2%)</td>
<td>4 of 280 (1.4%)</td>
</tr>
<tr>
<td>primary glioblastoma (WHO Grade IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balss et al., 2008</td>
<td>7 of 99</td>
<td></td>
</tr>
<tr>
<td>Bleeker et al., 2009</td>
<td>11 of 94</td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2010</td>
<td>17 of 237</td>
<td>1 of 237</td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>6 of 173</td>
<td></td>
</tr>
<tr>
<td>Nobusawa et al., 2009</td>
<td>14 of 377</td>
<td></td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>11 of 183</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>3 of 59</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>6 of 123</td>
<td>0 of 123</td>
</tr>
<tr>
<td>total</td>
<td>75 of 1345 (5.6%)</td>
<td>1 of 360 (0.003%)</td>
</tr>
<tr>
<td>secondary glioblastoma (WHO Grade IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balss et al., 2008</td>
<td>7 of 8</td>
<td></td>
</tr>
<tr>
<td>Bleeker et al., 2009</td>
<td>11 of 15</td>
<td></td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>5 of 10</td>
<td></td>
</tr>
<tr>
<td>Nobusawa et al., 2009</td>
<td>22 of 30</td>
<td></td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>10 of 13</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>28 of 34</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>11 of 13</td>
<td>0 of 13</td>
</tr>
<tr>
<td>total</td>
<td>94 of 123 (76.4%)</td>
<td>0 of 13 (0%)</td>
</tr>
<tr>
<td>oligodendroglioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Grade II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2009</td>
<td>105 of 128</td>
<td></td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>23 of 34</td>
<td></td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>41 of 54</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>31 of 39</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
in lower-grade astrocytic and oligodendroglial tumors points to the possibility of shared or overlapping developmental programs, cancer sequencing studies have revealed that additional molecular features characterize these histologically distinct IDH1-mutant neoplasms (reviewed in Jones et al.37). The IDH1-mutant astrocytomas often feature both IDH1 and TP53 mutations, whereas the majority of oligodendrogliomas feature the combination

TABLE 1: Literature review of frequency of IDH1 and IDH2 mutations in CNS and non-CNS human cancers (continued)

<table>
<thead>
<tr>
<th>Tumor Categories</th>
<th>IDH1 Mutations</th>
<th>IDH2 Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain tumors (continued)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oligodendroglioma (continued)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Grade II (continued)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>41 of 51</td>
<td>2 of 51</td>
</tr>
<tr>
<td>total</td>
<td>241 of 306 (78.8%)</td>
<td>8 of 179 (4.5%)</td>
</tr>
<tr>
<td>WHO Grade III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleecker et al., 2009</td>
<td>1 of 2</td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2009</td>
<td>121 of 174</td>
<td>9 of 174</td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>12 of 20</td>
<td></td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>24 of 49</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>6 of 8</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>31 of 36</td>
<td>3 of 36</td>
</tr>
<tr>
<td>total</td>
<td>195 of 289 (67.5%)</td>
<td>12 of 210 (5.7%)</td>
</tr>
<tr>
<td>oligoastrocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Grade II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2009</td>
<td>62 of 76</td>
<td>1 of 76</td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>10 of 20</td>
<td></td>
</tr>
<tr>
<td>Jiao et al., 2012</td>
<td>17 of 18</td>
<td>1 of 18</td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>26 of 34</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>16 of 17</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>3 of 3</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>134 of 168 (79.8%)</td>
<td>2 of 94 (2.1%)</td>
</tr>
<tr>
<td>WHO Grade III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann et al., 2009</td>
<td>117 of 177</td>
<td>11 of 177</td>
</tr>
<tr>
<td>Ichimura et al., 2009</td>
<td>18 of 23</td>
<td></td>
</tr>
<tr>
<td>Jiao et al., 2012</td>
<td>21 of 22</td>
<td>1 of 22</td>
</tr>
<tr>
<td>Sanson et al., 2009</td>
<td>34 of 54</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2009</td>
<td>10 of 14</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 2009</td>
<td>7 of 7</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>207 of 297 (69.7%)</td>
<td>12 of 199 (6%)</td>
</tr>
<tr>
<td>non-CNS tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figueroa et al., 2010</td>
<td>24 of 385</td>
<td>33 of 385</td>
</tr>
<tr>
<td>Marcucci et al., 2010</td>
<td>49 of 358</td>
<td>69 of 358</td>
</tr>
<tr>
<td>Mardis et al., 2009</td>
<td>16 of 188</td>
<td></td>
</tr>
<tr>
<td>Paschka et al., 2010</td>
<td>61 of 850</td>
<td>70 of 805</td>
</tr>
<tr>
<td>Schnittger et al., 2010</td>
<td>93 of 1414</td>
<td></td>
</tr>
<tr>
<td>Ward et al., 2010</td>
<td>6 of 78</td>
<td>12 of 78</td>
</tr>
<tr>
<td>total</td>
<td>249 of 3228 (7.7%)</td>
<td>184 of 1628 (11.3%)</td>
</tr>
<tr>
<td>intrahepatic cholangiocarcinomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borger et al., 2012</td>
<td>8 of 62</td>
<td></td>
</tr>
<tr>
<td>Wang et al., 2012</td>
<td>22 of 325</td>
<td>11 of 325</td>
</tr>
<tr>
<td>total</td>
<td>30 of 387 (7.8%)</td>
<td>11 of 325 (3.3%)</td>
</tr>
<tr>
<td>central/periosteal cartilaginous tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amary et al., 2011</td>
<td>74 of 145 (51%)</td>
<td>7 of 145 (4.8%)</td>
</tr>
</tbody>
</table>
Mutant IDH1/2 in glioma

of IDH1 mutation and concurrent 1p and 19q loss of heterozygosity. Although the targets of 1p and 19q loss were elusive for many years, recent work has identified candidate genes mutated within these chromosomal regions. Bettegowda et al. used whole-exome sequencing to identify novel recurrent mutations in the homolog of Drosophila capicua (CIC) and the far-upstream element (FUSE) binding protein (FUBP1) in oligodendrogliomas. When examining the findings of Bettegowda et al. together with additional work, mutations in CIC and FUBP1 are found in up to 50% and 30%, respectively, of oligodendrogliomas. Interestingly, oligoastrocytomas harbored a low incidence of CIC/FUBP1 mutations but a high incidence of alpha thalassemia/mental retardation syndrome X-linked (ATRX) alterations, which are also observed in the vast majority of low-grade IDH-mutant astrocytomas. Importantly, clusters of co-occurring mutations appear to define 2 distinct core IDH1-mutant glioma subtypes that have markedly different clinical outcomes. Specifically, IDH1/CIC/FUBP1-mutant tumors correlate with oligodendroglioidal histological features, whereas IDH1/ATRX/TP53-mutant tumors are typically Grades II and III astrocytomas and secondary glioblastomas. Further work will be necessary to determine the relative impact of molecular genetics on the histological diagnoses and subsequent treatment options of these tumor types.

Mutations of IDH in Other Neoplasms

Despite extensive searches, recurring mutations in the IDH1/2 genes seem to be restricted to select malignancies. Mutations in either IDH1 or IDH2 are found in approximately 15%–33% of AMLs, and 5%–7% of IDH2 mutations more common, as well as a smaller percentage of myelodysplastic syndromes. Mutations tend to occur in cytogenetically normal leukemias, and mutations in both genes are usually not found in the same patient. Additionally, IDH1/2 mutations occur in approximately 10%–12% of intrahepatic cholangiocarcinomas, as well as nearly 60% of central and peristeal cartilaginous tumors, with IDH1 mutations predominating in both contexts. In both of these tumor types, the R132C mutation predominated (compared with the R132H mutant in gliomas).

Somatic mosaic IDH1/2 mutations were recently found to be the likely genetic basis of Ollier disease and Maffucci syndrome. These rare, nonfamilial conditions, both characterized by the early development of multiple cartilaginous tumors, have also been reported to manifest concomitant glioma or AML, thereby providing an intriguing demonstration of a potential causal role that mutant IDH1/2 plays in these 3 distinct tumor types.

Germline Mutations in IDH Genes

Mutations of IDH2 were recently found in 50% of patients with D-2-HGA, a rare inherited neurometabolic disorder. There are 3 general classes of 2-HGAs: D-2-HGA; L-2-HGA; and combined D,L-2-HGA. Type I D-2-HGA is associated with loss-of-function mutations in the D-2-hydroxyglutarate dehydrogenase (D2HGH) gene, which encodes the enzyme that metabolizes D-2-HG to a-KG. Thus, D-2-HG accumulates to supraphysiological levels because basal levels are not cleared. Patients with D-2-HGA without D2HGH mutations harbor IDH2 mutations that encode R140 substitutions. Unlike Type I D-2-HGA, D-2-HG—the same enantiomer that is seen in IDH-mutant tumors—accumulates due to the neomorphic function of the IDH2-R140 enzyme, which is reviewed in greater detail below. Patients with D-2-HGA exhibit epilepsy, psychomotor retardation, and overall hypotonia. L-2-HGA, caused by mutations in L2HGH and associated with elevated levels of the L enantiomer of 2-HG, is characterized by epilepsy, cerebellar dysfunction, and developmental delay. The rare combined D,L-2-HGA is a more severe neurometabolic condition whose genetic basis has not yet been identified. In these conditions, it has not yet been established whether patients with 2-HGA develop a higher incidence of gliomas or AML.

Molecular and Cellular Biology of IDH Mutation

Protein Functions of WT IDH

Although a clear causal mechanism of tumor promotion has not yet been fully clarified in IDH1/2-mutant tumors, substantial progress has been made in understanding the novel functions of mutant IDH proteins in cancer. Although both WT IDH1 and IDH2 catalyze the NADP+-dependent oxidation of isocitrate to a-KG, these enzymes probably do not have completely overlapping functions (reviewed in Reitman and Yan). Located in the cytosol and peroxisome, IDH1 influences glucose sensing and lipid oxidation. Under hypoxic conditions, WT IDH1 also drives lipogenesis by reducing glutamate to a-KG. Located in the mitochondria, IDH2 is a vital component of the TCA cycle critical in sugar, lipid, and amino acid metabolism. Because IDH1 and IDH2 produce a-KG and NADPH, both proteins have also been implicated in host defense functions against insults including oxidative stress via NADPH-mediated reduction of glutathione, ultraviolet irradiation, heat shock, and exposure to pro-inflammatory cytokines.

Biological Consequences of Mutant IDH Proteins: Neomorphic Production of D-2-HG

The major finding underlying our current thinking on mutant IDH1/2 function was the discovery that these mutant enzymes gain the ability to catalyze a neomorphic function. Dang et al. used unbiased liquid chromatography-mass spectrometry profiling of WT-IDH1—expressing and mutant IDH1-R132H—expressing glioma cells to show that mutant-expressing cells expressed high levels of the metabolite 2-HG. Thus, rather than catalyze the NADP+-dependent production of a-KG, mutant IDH protein catalyzes the NADPH-dependent reduction of a-KG to produce only the D stereoisomer (or R-enantiomer) of 2-HG (Fig. 1). Although 2-HG is also found in normal cells and can be catalyzed by WT IDH1, its levels are exponentially higher in mutant cells—more than 100-fold in many cases. Primary IDH1-mutant gliomas contain extremely high levels of 2-HG, which is not present in the
were enriched in the proneural transcriptomic sub-
decreased expression between proneural G-CIMP+ and
both hypermethylated promoter regions and concomitant
survival. Interestingly, there is a subset of genes with
found, and G-CIMP status was associated with improved

domination of the mutant enzyme have
growth. Likewise, the
work has argued that these subunits probably act independ-
ently even as WT or mutant heterodimers and that
dominant negative properties of the mutant enzyme have
not been observed at physiological concentrations of iso-
citrate.

Phenotypes of 2-HG–Mediated Inhibition of Dioxygenase
Superfamily Members: DNA Hypermethylation

Work on the mechanistic consequences of elevated
2-HG production has converged on the observation that
2-HG inhibits the function of the α-KG–dependent super-
family of dioxygenases, with some exceptions (Fig. 1). These enzymes have diverse functions that modulate a
range of cellular programs that include hypoxic sensing, histone demethylation, demethylation of hypermethylated
DNA, fatty acid metabolism, and collagen modification. There is a precedent from studies of cancers with mu-
tations in succinate dehydrogenase subunits or fumarate hydratase that the accumulation of the normal metabolic
substrates for these encoded enzymes leads to the inhibi-
tion of α-KG–dependent enzymes including prolyl
hydroxylases and histone demethylases. Likewise, the
inhibition of α-KG–dependent dioxygenases by 2-HG is
the leading mechanism for mutant IDH1-mediated patho-
biology in cancer. First, a group of studies has demonstrated
increases in the hypermethylation of both DNA and
also histones that are linked to the inhibition of the biolog-
ically relevant dioxygenases. By profiling the DNA
hypermethylation status of glioblastomas in The Cancer
Genome Atlas as well as mutant LGGs, IDH1-mutant
gliomas were found to exhibit a global DNA hypermeth-
ylation state, termed G-CIMP. The G-CIMP+ gliomas were
enriched in the proneural transcriptomic sub-
type, and the subtype in which IDH1-mutant tumors are
found, and G-CIMP status was associated with improved
survival. Interestingly, there is a subset of genes with both
hypermethylated promoter regions and concomitant
decreased expression between proneural G-CIMP+ and
proneural G-CIMP+ tumors. Figueroa et al. identified a DNA hypermethylation phenotype in IDH1/2-
mutant AML and provided genetic evidence to link this
finding to the α-KG–dependent TET2 enzyme, which
converts 5-methylcytosine to 5-hydroxymethylcytosine
during the process of DNA demethylation. Of 300 AML
samples examined, 58 (19%) harbored IDH1/2 mutations
and 28 (9.3%) harbored TET2 mutations; however, these
were completely mutually exclusive, suggesting that these
mutants conferred mostly overlapping effects. Moreover, these
IDH2-mutant–expressing murine hematopoietic cells exhib-
It was concordant with that observed in IDH1-mutant gli-
os, providing further evidence that mutant IDH1 was
largely responsible for the transcriptional and epigenetic
landscapes seen in mutant tumors. Interestingly, the den-
sity of DNA methylation increased with repeated passag-
es, suggesting that remodeling of the epigenome is not an
immediate process. Ultimately, to demonstrate the tumor
promotion of 2-HG–induced epigenomic changes of the
genes identified to be hypermethylated and differentially
expressed between IDH1-WT and IDH1-mutant cells, it
will be necessary to determine which, if any, are crucial
to tumor formation and/or maintenance.

Histone Hypermethylation

The epigenomic landscape of IDH–mutant cells is also
probably influenced by the increased methylation of histone
proteins. Histones are central to the structure of eukaryotic
DNA, which is composed of nucleosomes of approximately
146-bp stretches of DNA wrapped around octamers of 4 his-
tone proteins (H2A, H2B, H3, and H4). Histone protein tails
are frequent sites for modifications such as covalent methyl
addition. The area of histone modifications within epi-
genetic biology is rapidly evolving and is well reviewed
elsewhere. Several groups have found that histone demeth-
ylates are inhibited by the 2-HG metabolite. Chow-
dhury et al. showed that (R)-2-HG inhibited recombinant
forms of the JMD2A, JMJD2C, and JHDM1A/FBXL11
histone demethylases and that the JHDM1A/KDM2A and
KDM5B/JARID1B/PU-L1 demethylases were also inhibited
by 2-HG treatment. Further studies have documented the
specific histone methylation sites that are modified in the
setting of 2-HG treatment and/or mutant IDH expression.
Specifically, increases in methylation in response to 2-HG
or mutant IDH1 expression were observed in H3K4me1, H3K4me3, H3K9me2, H3K27me2, H3K9me3, and H3K27me3.
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Significant when mutant IDH1 was expressed in immortalized astrocytes. As is the case with DNA hypermethylation, this histone mark progressively increased with increasing cell passage. Further work linked impaired cell differentiation with mutant IDH1 expression and histone methylation. Expression of mutant IDH1 impaired the differentiation of 3T3 cells into adipocytes, as did the knockdown of the H3K9 demethylase KDM4C. Furthermore, mutant IDH1-expressing murine neurospheres failed to express GFAP compared with WT neurospheres when exposed to retinoic acid. However, no clear link was established between mutant IDH1 expression and histone demethylation in this process.

Taken together, it is becoming clear that IDH1/2-mutant cells undergo changes in the epigenetic landscape that involve DNA and histone methylation, which probably leads to chromatin remodeling. At this point, it is unclear which enzymes are most critical for these processes, which chromatin modification readers modulate these changes, and what the long-term effects on gene expression programs might be. Further clarification of these mechanisms will be important to determine which nodes may represent potential therapeutic targets.

Effects on HIF-1α Biology

In addition to effects on the epigenome, mutant IDH1 proteins appear to influence the biology of the HIF. However, unlike the largely concordant studies on the epigenomic effects of the mutant IDH proteins, work on mutant IDH1 and HIF suggests that this relationship is complex and will require further clarification. First, 2-HG may stabilize HIF-1 under some conditions.\(^98,102\) Ectopic expression of mutant IDH1 or 2-HG treatment in U87 malignant glioma cells led to increased HIF protein levels, which were also modestly increased in the CNS-specific IDH1-mutant mouse model that is discussed in more detail below.\(^78\) However, IDH1-R132H and HIF expression were not entirely concordant when assessed using immunohistochemistry in glioma tissue.\(^97\) Although key biological variables are difficult to quantify in a post hoc analysis of fixed, paraffin-embedded tissue, this finding does underscore that further work is needed to un-
derstand the effects on HIF biology of mutant protein expression. A recent study provided evidence to support an alternative role for HIF in \textit{IDH1}-mutant tumors. Koivunen et al.\textsuperscript{44} showed that expression of \textit{IDH1-R132H} in the same immortalized human astrocyte model system\textsuperscript{44} used in the study by Turcan et al.\textsuperscript{65} led to more colonies formed in soft agar.

Furthermore, mutant \textit{IDH1} protein expression was correlated with decreased HIF levels; although HIF protein levels appeared to increase with cell passage, the hypoxia-induced increase in HIF was completely abolished in \textit{IDH1}-expressing astrocytes, HCT116 cells expressing physiological mutant \textit{IDH1} levels via knock-in technology, or \textit{IDH1}-mutant gliomas derived from patient samples. Moreover, HIF gene signatures were downregulated in \textit{IDH1}-mutant tumors analyzed in the data set in The Cancer Genome Atlas. Interestingly, whereas this study showed that D-2-HG inhibited some of the dioxygenases previously discussed—such as the TET1 and 2 hydroxylases, HIF asparaginyl hydroxylase, and JUM2D/KD-M4D histone demethylase—D-2-HG stimulated the HIF prolyl 4 hydroxylase EGLN1. Furthermore, knockdown of HIF alone was sufficient to increase soft agar growth of engineered normal human astrocytes, and EGLN1 was both necessary and, by itself, sufficient to drive similar in vitro colony formation. It is not clear what accounts for the differences in effects of mutant \textit{IDH1} protein expression on HIF levels across these recent studies, although differential expression or alterations in the EGLN prolyl hydroxylases could influence this biology across different in vitro model systems. Further study will be necessary to characterize the mutant \textit{IDH1}–HIF1 relationship fully and, in particular, to clarify further the HIF-dependent contributions to the tumor microenvironment.

\textbf{Cell-Based Models of Mutant \textit{IDH1} Protein}

Until recently, there has been a dearth of human cell lines that carry endogenous rather than ectopically introduced \textit{IDH1} mutations. Engineered systems such as immortalized normal human astrocytes expressing \textit{IDH1} have been tremendously useful in studying the causal effects of mutant protein expression.\textsuperscript{53,57} but the caveat remains that these lines do not harbor naturally arising somatic \textit{IDH1} mutations. One well-established mutant cell line, the HT1080 fibrosarcoma cell line expressing a naturally arising mutant \textit{IDH1-R132C} protein, was used recently in the only study to date that has demonstrated the dependency of an established \textit{IDH1}-mutant cell line on persistent mutant protein expression.\textsuperscript{35} Selective knockdown of mutant \textit{IDH1} led to decreased proliferation and clonogenic capacity of the parental cell line, suggesting that mutant cells remain dependent on the expression of mutant \textit{IDH1} protein and providing a rationale that inhibiting this enzyme may have therapeutic benefit. The \textit{IDH1}-mutant tumor—initiating cell models, or neurospheres, have traditionally been difficult to develop but have recently been reported.\textsuperscript{34} A neurosphere line from a patient with \textit{IDH1}-mutant anaplastic oligodendroglioma survived passage in vitro, was transplanted as a xenograft in vivo, and generated the expected 2-HG. Further large-scale development of these patient-derived models will be critical to generalize the dependency of these tumors on mutant protein expression and will undoubtedly serve as important preclinical models.

\textbf{Animal Models of Mutant \textit{IDH1} Protein}

Recent generation of genetically engineered mouse models of the \textit{IDH1-R132H} mutation has provided additional insights into the physiologically relevant consequences of mutant \textit{IDH1} protein expression. Both studies are from the Mak group (see Sasaki and colleagues\textsuperscript{28,79}) and use lineage-specific \textit{Cre} recombinase-driven knock-in technology. In this approach, a mutant \textit{IDH1-R132H} gene harboring an upstream transcriptional stop site flanked by \textit{Cre} recombination lox sites is introduced by homologous recombination into the endogenous WT \textit{IDH1} locus. When these heterozygously targeted mice are bred to transgenic mice expressing \textit{Cre} under distinct tissue-specific promoters, the stop site upstream of the mutant \textit{IDH1} gene is deleted, and mutant protein is expressed at physiological levels. To study the expression of \textit{IDH1-R132H} in the brain, Nes-KI mice were generated in which mutant \textit{IDH1} was expressed in the neural stem cell compartment as early as embryonic Days 10.5–12.5.\textsuperscript{58} Surprisingly, these mice were born at the expected mendelian frequency, but all died in the immediate perinatal period after birth. Necropsy of Nes-KI mice revealed uniform massive cerebral and cerebellar hemorrhage that was present in embryos prior to birth and was associated with massive apoptosis.

Three findings provided in vivo evidence for 2-HG–mediated inhibition of several dioxygenases, although not all previously reported findings in humans were observed. First, Nes-KI brains had increased levels of immature Type IV collagen that may contribute to an endoplasmic reticulum stress response, suggesting that the prolyl hydroxylases that hydroxylate these collagen forms were inhibited. Second, Nes-KI brains displayed increased levels of 5-hydroxymethylcytosine, consistent with inhibition of the TET2 hydroxylases. However, it is unclear whether this model recapitulates the extent of the global G-CIMP phenotype found in human \textit{IDH1}-mutant tumors.\textsuperscript{60} Third, the expression of HIF-1\textalpha protein and HIF-1\textalpha–regulated genes was increased in Nes-KI mice, consistent with inhibition of the prolyl hydroxylases that destabilize HIF-1\textalpha. Histones were not found to be hypermethylated, although it is unclear whether this finding may have been masked as a result of insufficient time for histone marking due to perinatal lethality. Although the Nes-KI mice died too early to assess tumor formation, GFAP-KI mice were also generated in which the \textit{IDH1-R132H} cassette was probably expressed in neurons, glia, and some neuronal precursor cells. However, GFAP-KI mice did not develop tumors, and attempts to breed GFAP-KI mice onto a \textit{p53}–, \textit{ATRX}–, and/or \textit{CIC}–deficient backgrounds proved difficult. It will be important to develop additional models in which mutant \textit{IDH1} is expressed conditionally/inducibly in relevant \textit{p53}–, \textit{ATRX}–, and/or \textit{CIC}–deficient backgrounds to develop a faithful model of \textit{IDH1}-mediated glioma development.

Sasaki et al.\textsuperscript{79} also modeled \textit{IDH1}-mutant AML by generating mice in which mutant \textit{IDH1} was expressed in all hematopoietic cells (Yav-KI mice) or in the myeloid lineage (LysM-KI mice). Unlike the CNS models, these
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mice were born at expected mendelian frequencies and had normal lifespans. Although the resulting phenotype provided critical insight into the mechanistic basis of mutant IDH1 function, these mice did not develop leukemia. As the animals aged, both Vav-KI and LysM-KI mice developed anemia and splenomegaly and accumulated increased numbers of immature cell populations, although there was no clear block in their ability to differentiate. Importantly, immature cells from LysM-KI mice displayed a DNA CpG and histone hypermethylation phenotype strikingly similar to that found in human patients with AML. However, HIF target genes were not upregulated, suggesting that the downstream effects of 2-HG–mediated modulation of the dioxygenase superfamily may be influenced by tissue context. Further study of these models should clarify the biological programs critical for mutant IDH1-mediated tumor development, especially if current models are bred onto backgrounds with additional cancer-relevant lesions.

Taken together, these data from studies of mutant IDH1/2 biology suggest that the expression of mutant enzymes influences a broad range of biological programs. However, especially in a setting wherein the production of 2-HG has the potential to exert pleiotropic effects on a large class of enzymes, it will be crucial to distinguish what can happen from what actually does happen to initiate and/or maintain the tumor phenotype by using physiologically relevant cell-based models.

Mutations in IDH1/2 Are Early Events in Brain Tumorigenesis

Several recent studies have provided evidence that mutations in IDH1/2 represent early events in brain tumor formation. Watanabe et al.66 focused on the presence of the IDH1 mutation, TP53 mutation, and 1p/19q loss in patients who had undergone multiple biopsies for Grade II or III gliomas. Interestingly, 7 patients who carried the IDH1 mutation at first biopsy had acquired either the TP53 mutation or 1p/19q loss at the second biopsy; there were no cases in which either TP53 or 1p/19q loss preceded IDH1 mutation. Although these data point to a potential temporal sequence of genetic alterations in glioma, further work in which larger sets of serial tissue samples obtained from the same patient are used will be necessary to demonstrate this possibility more definitively.

A mechanistic basis for the temporal acquisition of mutations in LGGs was proposed by Lai et al.67 By analyzing the sequences of TP53 and IDH1 in a large panel of Grades II–IV astrocytomas, these authors found that there were higher rates of Arg-to-Cys substitutions at position 273 in TP53 compared with the high rate of Arg-to-His substitutions at position 132 in the IDH1 gene. The authors proposed that this difference was caused by a strand asymmetry mechanism68 in which C→T mutations occurred on the nontranscribed DNA strand in TP53, and IDH1 mutations occurred on the transcribed strand in IDH1. Theoretically, this difference would enable IDH1 mutations to take place in nondividing clones prior to S-phase entry, which would be required for TP53 alterations on the complementary DNA strand. Further work using careful clonal analysis and appropriate clinically relevant animal models will be needed to clarify this possibility. Additionally, further in-depth analysis of serial tissue samples from the same patient will provide a deeper understanding of disease evolution and progression.

Translational Implications of Mutant IDH1/2

In the short time since the identification of IDH1 mutations in glioma, there has been a significant amount of work focused on the translational relevance of these mutations. It is already clear that IDH1 status is a major determinant of survival, and many groups have developed new ways to identify the mutations from clinical samples, as well as the oncometabolite 2-HG, by using noninvasive methods. It is likely that the determination of IDH1 status in glioma will be an early step in treatment algorithms for patients with this disease.

Clinical Consequences: Survival and Imaging Findings

Patients with IDH1 mutations in any grade of glioma exhibit increased overall survival compared with patients with IDH1-WT tumors, and patients with IDH1-mutant glioblastomas tend to be nearly 2 decades younger, on average, than patients with IDH1-WT glioblastomas. The differences in overall survival between IDH1-mutant versus IDH1-WT glioblastomas across several studies was 3.8 versus 1.1 years,65 2.6 versus 1.3 years,99 2.3 versus 1.2 years,77 and approximately 3 years versus 1 year.30 Moreover, the differences in overall survival between IDH1-mutant versus IDH1-WT anaplastic astrocytomas was 5.4 versus 1.7 years,99 6.8 versus 1.6 years,77 and approximately 7 versus 2 years.30 This survival benefit was also observed in G-CIMP+ versus G-CIMP– gliomas, wherein G-CIMP has a high association with IDH1-mutant status.65 When both histological and molecular features were taken into account, patients with IDH1-mutant glioblastoma had a median survival of nearly 3 years, whereas patients with IDH1-WT anaplastic astrocytoma had a median survival of less than 2 years. Strikingly, for patients older than 60 years, overall survival was equivalent for IDH1-WT anaplastic astrocytomas and IDH1-WT glioblastomas. The survival benefit also extended to Grade II gliomas; patients with mutant tumors had a median overall survival of 12.6 versus 5.5 years.77 Together, these data highlight the major impact IDH1 status has on survival and support the incorporation of molecular features into histopathological assessment.

Diagnostic Evaluation of IDH1 Status

There has been rapid development and clinical application of antibody and sequencing-based methods to detect IDH1 status. Monoclonal antibodies to IDH1-R132H, first described by von Deimling's group (see Capper et al.15), recognize the mutant protein with a high degree of sensitivity and specificity13,15 (Fig. 2). Beyond determination of mutant status, the histopathological utility of this antibody has extended to additional clinical scenarios such as the discrimination between diffuse astrocytoma and reactive astrocytosis when combined with a panel of key molecular features.90,91 Additional antibody reagents...
to the less common IDH1 mutations, such as R132S, have also been reported.41

Several technologies are currently in use to detect mutations in the IDH1 gene. SNaPshot22 and Oncomap,56 both of which can be used with paraffin-embedded tissue, use single base pair extension that results in an allele-specific probe that is read out by either fluorescence detection (SNaPshot) or mass spectrometry (Oncomap). Alternative approaches, such as pyrosequencing26 and next-generation sequencing,51 are also in use for the detection of mutations in tumor samples. In addition to these approaches, recent work demonstrated proof of principle in detecting IDH1 mutations from the plasma of patients with mutant gliomas.7 Although the potential application for monitoring disease noninvasively is compelling, the sensitivity attained using this assay was 60%. Further work on the nature of circulating tumor material will be necessary to determine whether it will be possible to monitor the IDH1 mutation status in the peripheral blood of all patients with mutant gliomas.

Methods to Detect the 2-HG Metabolite

Another area of investigation has focused on the detection of the 2-HG metabolite rather than on the specific sequence of the IDH1/2 gene or protein product. In theory, sensitive and specific detection of 2-HG is sequence independent in that 2-HG should be present regardless of the type of mutation in either IDH1 or IDH2. High levels of 2-HG have been detected in ex vivo tissue samples by using 2 approaches. In the first, combination gas or liquid chromatography/mass spectrometry was used to identify 2-HG in frozen59 or paraffin-embedded73 glioma tissue. However, these extraction-based approaches do not preserve the integrity of the sampled tissue. In the second approach, which is used by several groups,25,40 proton High-Resolution Magic Angle Spinning (1H HRMAS) MRS is used to determine the metabolic profiles in ex vivo tissue; this technique does not require alteration of tissue samples. This method identified 2-HG in ex vivo specimens with high degrees of sensitivity and specificity. Unlike the case with AML, wherein 2-HG can be detected in the blood of patients with IDH-mutant AML,94 its presence in peripheral blood is similar between patients with IDH1-mutant and -WT tumors.12

Detection of 2-HG by MRS represents a completely noninvasive method with which to determine the presence of IDH mutations in gliomas, irrespective of the sequence of the mutation or whether the mutation maps to IDH1 or IDH2. Importantly, this approach represents the only example in human cancer in which a genomic feature can be identified specifically by using imaging-based metabolic profiling. Prior work has demonstrated that IDH-mutant tumors display characteristic imaging findings. The IDH1-mutant tumors display reduced contrast enhancement, less surrounding edema, cystic components, and are often found in the frontal lobe compared with IDH-WT tumors.15,49 This work has been complemented by MRS-based approaches. Because it is recognized that the spectrum of 2-HG has some overlap with other commonly found metabolites such as glutamate and glutamine, the methodology for obtaining and analyzing in vivo MRS data is critical. One study to demonstrate 2-HG detection in glia by MRS used the acquisition of a point-resolved spectroscopy (PRESS) sequence.59 There was good concordance between sequence-based mutation status and 2-HG detection, although several false positives and false negatives were reported. Additional studies in which spectral editing analysis27 or 2D-correlation MRS with spectral editing5 were used demonstrated that IDH mutation status can be identified noninvasively by MRS techniques with a high level of sensitivity and specificity.

Figure 3 provides an example of the methods used by Andronesi et al.3 to detect 2-HG in glioma patients, and it demonstrates the advantages of complementing molecular identification of mutation status with imaging-based approaches. In this case of a 32-year-old patient with a nonenhancing tumor that was assessed as a WHO Grade II glioma, the tumor harbored a noncanonical IDH1-R132G mutation that was not detected by conventional anti–IDH1-R132H immunohistochemical approaches and required the additional step of DNA sequence profiling of the ex vivo tissue sample. However, the mutant status was identified unambiguously in the preoperative setting by using MRS with J-difference spectral editing (MEGA-LASER sequence3), which subtracts the signals of overlapping metabolites such as phosphocreatine, myoinositol, and lactate at or near the 4.02-ppm Hx signal of 2-HG. Ultimately, imaging-based 2-HG detection may be an important method with which to determine not only the mutant status of tumors in patients before surgery but also to monitor tumor recurrence, distinguish between treatment effect or pseudoprogression, and possibly also monitor response to treatments in the event that targeted therapies are developed for IDH-mutant tumors. 2-HG imaging could also help delineate margins of the active tumor compared with contrast enhancement or FLAIR hyperintensity.

Treatment Implications for IDH1-Mutant Tumors

The identification of IDH1/2 mutations and the rapid characterization of their protein products present a therapeutic opportunity to treat these mutant tumors. From a medical standpoint, it will be important to de-
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termine whether IDH1/2-mutant tumors would be sensitive to small molecules that inhibit the mutant enzymes. Although there are no published studies to date addressing this possibility, a recent study suggested that mutant tumor cells may be dependent on the continued expression of the mutant enzyme and/or its resultant 2-HG metabolite. As noted previously, Jin et al.35 showed that a cell line expressing endogenous mutant IDH1 required its expression for survival and anchorage-independent growth, suggesting that pharmacological inhibition of mutant IDH1 may recapitulate this result. With respect to mutant IDH1-mediated biology, this result would also suggest that 2-HG–induced cellular changes such as global DNA hypermethylation are either potentially reversible or, if not, are insufficient for tumor maintenance. Noninvasive methods of monitoring inhibitor effectiveness, such as the MRS imaging we have summarized above, would be useful in monitoring drug responses in glioma.

We anticipate that inhibition of this pathway would increase patient survival. Although there has been some discussion of whether it is prudent to inhibit mutant IDH1 because patients with mutant tumors have a better survival than patients with WT tumors, we do not expect that inhibiting the mutant enzyme would make these tumors behave like their more aggressive WT counterparts. The differences in survival most likely stem from the fact that IDH1-mutant and -WT tumors arise from distinct lineages and ontogenies and thus represent entirely different neoplastic disease processes. Because gliomas acquire the IDH1 mutation very early in their development, akin to BRAF mutations in dysplastic nevi and melanoma, we envisage that it similarly represents a targetable dependency.

From a surgical standpoint, it will be important to determine whether the mutation status of gliomas influences surgical management. In particular, it is possible that IDH1 status could have implications for the benefit of surgery.
Ongoing study is directed at assessing the radiographic features of IDH1-mutant and IDH1-WT tumors that are particularly critical targets for surgical management.

Conclusions

The identification of recurrent IDH1 mutations in glioma was a seismic discovery that has established new paradigms in cancer research and, in a short time frame, is already influencing clinical practice. From a basic research standpoint, it will be critical to determine the physiologically relevant consequences of mutant IDH1 protein function. We are beginning to understand the broad range of cellular processes that can be influenced by the production of 2-HG, but we do not yet have a clear understanding of which programs are critical for IDH1-mediated transformation and for tumor maintenance. Regarding the latter point, there are preliminary data suggesting that even established tumor cells require the continued expression of mutant enzymes, but this point must be rigorously evaluated in patient-derived mutant cell models and also disease-faithful animal models. The evaluation of persistent dependency is especially important because it is not immediately obvious that changes in the epigenetic landscape are always reversible if they are truly responsible for much of the mutant IDH phenotype. This demonstration of unequivocal and generalizable dependency of mutant tumors on mutant IDH1 expression will provide a powerful justification for accelerated efforts to develop inhibitors of the mutant enzymes, which presumably would display a large therapeutic window. The clarification of the downstream effects of mutant IDH1 expression may also reveal additional therapeutic targets. Furthermore, it is important not to overlook the fundamental mechanisms that underlie why IDH1-WT tumors are so formidable.

From a clinical standpoint, the status of a tumor’s IDH1 gene already gives the health care provider important prognostic information on overall survival that can and should be shared with patients. Across all grades of glioma, the presence of gene mutation predicts longer survival. It is such a critical piece of information that it is evaluated by immunohistochemistry and polymerase chain reaction–based DNA sequence analysis for all patients with glioma at our institution and in many others. We anticipate and agree with the incorporation of molecular profiling of important features such as IDH1 status into the current histopathological grading of all gliomas. However, further analysis is necessary to determine whether IDH1 gene mutation status should change clinical management with respect to chemotherapy/radiation and/or surgery. Nevertheless, our clinical heuristic for glioma care has already incorporated IDH1-WT or IDH1-mutant categories at the earliest stage in our approach to a patient, in large part because the biological and clinical data point to the fact that mutational status segregates otherwise histologically similar lesions into what increasingly appear to be different diseases.

Clearly, with the discovery of IDH1 mutations in glioma in the context of the ongoing characterization of the glioblastoma genome, it is an important—and exciting—era in the field. In a short period of time, we have moved from the phase of genomic “basic science” discovery in glioma to the cusp of the development of inhibitors to mutant IDH1 proteins that may offer clinical benefit to patients with these tumors. Ultimately, we hope that a critical take-home message gleaned from the story of mutant IDH1 in glioma will be a powerful demonstration that a fundamental understanding of the structure of the glioma genome was pivotal to the development of clinically meaningful therapies for patients with this disease.

Disclosure

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References

8. Borger DR, Tanabe KK, Fan KC, Lopez HU, Fantin VR, Stral-
Mutant IDH1/2 in glioma

ey KS, et al: Frequent mutation of isocitrate dehydrogenase (IDH1) and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. *Oncologist* 17:72–79, 2012


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Mutant IDH1/2 in glioma

ferlach T: IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis. Mutations occur in patients younger than 60 years and unmutated NPM1 status. Blood 116:5486–5496, 2010


References...