The WHO 2016 Classification of CNS Tumors
What the Surgical Pathologist Needs to Know

Gregory N. Fuller, MD, PhD
Professor and Chief Neuropathologist
M D Anderson Cancer Center
Houston, Texas
gfuller@mdanderson.org
WHO 2016

Over 120 entities
WHO 2016

MOST: NO SIGNIFICANT CHANGES!
WHO 2016

Example:

MENINGIOMAS
WHO 2016

• Major changes
WHO 2016

• Major changes

• What it means to you in *practical terms*
Diffuse Gliomas
Diffuse Gliomas

- Diffuse astrocytoma (II, III, IV)
- Oligodendroglioma (II, III)
Diffuse Gliomas

Incorporation of *clinically-critical* molecular signatures into the entity Definition & Name
Diffuse Gliomas

Incorporation of *clinically-critical* molecular signatures into the entity Definition & Name

Thus, the molecular signature is an *essential* diagnostic criterion!
Diffuse Gliomas
WHO 2007

• Diffuse Astrocytoma
• Oligodendroglioma
• Mixed Oligoastrocytoma
Diffuse Gliomas

WHO 2016

- Diffuse Astrocytoma
- Oligodendroglioma
- **Mixed Oligoastrocytoma**
Diffuse Gliomas

WHO 2016

• Mixed Oligoastrocytoma

In the new WHO 2016 Classification, usage of the diagnosis Oligoastrocytoma is “discouraged”
Diffuse Gliomas

WHO 2016

- Diffuse Astrocytoma
- Oligodendroglioma
Diffuse Astrocytoma

WHO 2007: 1 Diagnostic Option

• Diffuse Astrocytoma
Diffuse Astrocytoma

WHO 2016

One \textit{clinically-critical} molecular feature:

- \textit{IDH1/IDH2} mutation status
Diffuse Astrocytoma

WHO 2016

• IDH1/IDH2 mutation status

CANONICAL vs NONCANONICAL point mutations
Diffuse Astrocytoma

WHO 2016

• *IDH1/IDH2* mutation status

**CANONICAL vs NONCANONICAL** point mutations

*Canonical IDH mutation (90%):*
Diffuse Astrocytoma

*WHO* 2016 IDH1/IDH2 mutation status

**CANONICAL** vs **NONCANONICAL** point mutations

Canonical *IDH* mutation (90%): *IDH1*
Diffuse Astrocytoma
WHO 2016

• *IDH1/IDH2* mutation status

**CANONICAL** vs **NONCANONICAL** point mutations

*Canonical IDH mutation (90%):*  
*IDH1*\textsuperscript{R132H}*
Diffuse Astrocytoma

WHO 2016

• *IDH1/IDH2* mutation status

**CANONICAL** vs **NONCANONICAL** point mutations

*Noncanonical IDH1* mutations (7%):
Diffuse Astrocytoma
WHO 2016

• IDH1/IDH2 mutation status

CANONICAL vs NONCANONICAL point mutations

Noncanonical IDH1 mutations (7%):

\[ \text{IDH1}^{R132C} \quad \text{IDH1}^{R132G} \quad \text{IDH1}^{R132S} \quad \text{IDH1}^{R132L} \quad \text{IDH1}^{R132V} \]
Diffuse Astrocytoma
WHO 2016

• *IDH1/IDH2* mutation status

**CANONICAL** vs **NONCANONICAL** point mutations

*Noncanonical IDH2* mutations (3%):
Diffuse Astrocytoma

WHO 2016

• IDH1/IDH2 mutation status

CANONICAL vs NONCANONICAL point mutations

Noncanonical IDH2 mutations (3%):

$IDH2^{R172K}$  $IDH2^{R172M}$  $IDH2^{R172W}$  $IDH2^{R172S}$  $IDH2^{R172G}$
Diffuse Astrocytoma
WHO 2016

• *IDH1/IDH2* mutation status

**CANONICAL vs NONCANONICAL** point mutations

*Canonical IDH mutation (90%): IDH1*
IDH1<sup>R132H</sup> Mutant Protein IHC
Expression of mutant protein demonstrated by “surrogate immunophenotyping” is accepted by the WHO 2016 as sufficient to render a diagnosis of Diffuse Astrocytoma, IDH-Mutant.
Diffuse Astrocytoma (DA)

WHO 2016: 3 Diagnostic Options

- DA, IDH-Wildtype
- DA, IDH-Mutant
- DA, NOS
NOTE: there will ALWAYS be a Histology (H&E)-Only diagnostic option for all CNS tumors!
WHO 2016

NOTE: there will ALWAYS be a Histology (H&E)-Only diagnostic option for all CNS tumors!

e.g., Diffuse Astrocytoma, NOS
WHO 2016

NOS

“Not Otherwise Specified”
Critical molecular signature status either unknown or incomplete (H&E Dx)
Anaplastic Astrocytoma

WHO 2016: 3 Diagnostic Options

• AA, IDH-Wildtype
• AA, IDH-Mutant
• AA, NOS
Oligodendroglioma

WHO 2007: 1 Diagnostic Option

• Oligodendroglioma
Oligodendroglioma

WHO 2016

Two clinically-critical molecular features:

• *IDH1/IDH2* mutation
• 1p/19q codeletion
Oligodendrogioma
WHO 2016

• IDH1/IDH2 mutation

Canonical IDH1 point mutation (90%): \textit{IDH1}^{R132H}

Noncanonical IDH1 mutations (7%):
\textit{IDH1}^{R132C} \hspace{1cm} \textit{IDH1}^{R132G} \hspace{1cm} \textit{IDH1}^{R132S} \hspace{1cm} \textit{IDH1}^{R132L} \hspace{1cm} \textit{IDH1}^{R132V}

Noncanonical IDH2 mutations (3%):
\textit{IDH2}^{R172K} \hspace{1cm} \textit{IDH2}^{R172M} \hspace{1cm} \textit{IDH2}^{R172W} \hspace{1cm} \textit{IDH2}^{R172S} \hspace{1cm} \textit{IDH2}^{R172G}
Two **clinically-critical** molecular features:

- **IDH1/IDH2** mutation
- **1p/19q** codeletion
Oligodendroglioma
WHO 2016

Many different techniques / platforms are used to assess 1p/19 status.
Oligodendroglioma

WHO 2016

Two of the most common, FISH and LOH, do not discriminate between whole arm loss and partial (interstitial) deletions.
Oligodendroglioma

WHO 2016

The WHO 2016 does not mandate specific testing platforms/techniques, but notes that some may be superior to others in specificity for whole arm loss.
A Brief Digression

The use and misuse of molecular studies
A Brief Digression

Molecular Confusion
A Brief Digression

Molecular Confusion

• Incomplete understanding of the limitations of molecular techniques/platforms
A Brief Digression

Molecular Confusion

• Incomplete understanding of the limitations of molecular techniques/platforms

• Imprecise language for test results
A Brief Digression

Molecular Confusion

• Incomplete understanding of the limitations of molecular techniques/platforms

• Imprecise language for test results

• Lagging knowledge base currency
Example

1p/19q FISH Testing in GBM
In this issue

Molecular classification of adult diffuse gliomas: conflicting IDH1/IDH2, ATRX, and 1p/19q results

Leomar Y. Ballester MD, PhD\textsuperscript{a,b}, Jason T. Huse MD, PhD\textsuperscript{b}, Guilin Tang MD, PhD\textsuperscript{c}, Gregory N. Fuller MD, PhD\textsuperscript{b,*}

\textsuperscript{a}Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX 77030
\textsuperscript{b}Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030
\textsuperscript{c}Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030

Received 4 January 2017; revised 5 May 2017; accepted 10 May 2017
Most of the confusion surrounding these cases revolves around positive results for 1p/19q codeletion by FISH. In cases 1 and 2, FISH was performed by 2 independent laboratories with similar results. This argues against the possibility of technical or interpretation errors. Most likely, the positive results for 1p/19q codeletion in these instances represent interstitial deletions affecting the regions of probe hybridization or monosomy, rather than complete loss of 1p and 19q that is the hallmark of oligodendroglioma. The probes routinely used in FISH testing hybridize to a region comprising only 0.4% to 1.5% of the respective chromosome arms (Fig. 1E). Indiscriminate use of FISH for evaluation of 1p/19q status yields a significant number of “false-positive results.” In a study of 491 diffuse gliomas diagnosed as glioblastoma by histology, Clark
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Tumor site</th>
<th>Diagnosis</th>
<th>WHO grade</th>
<th>IDH status</th>
<th>ATRX</th>
<th>Mutation analysis</th>
<th>1P/19Q FISH</th>
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<tr>
<td>1</td>
<td>81</td>
<td>M</td>
<td>Right frontal lobe</td>
<td>GBM</td>
<td>IV</td>
<td>WT</td>
<td>Positive</td>
<td>KRAS p.G12D, PDGFRα p.Y582S</td>
<td>Codeleted</td>
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<tr>
<td>2</td>
<td>81</td>
<td>M</td>
<td>Right temporal lobe</td>
<td>GBM (small cell variant)</td>
<td>IV</td>
<td>WT</td>
<td>Positive</td>
<td>RET p.E632K</td>
<td>Codeleted</td>
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<tr>
<td>3</td>
<td>51</td>
<td>M</td>
<td>Right temporal lobe</td>
<td>GBM</td>
<td>IV</td>
<td>WT</td>
<td>Loss</td>
<td>N/A</td>
<td>Codeleted</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>F</td>
<td>Right temporal lobe</td>
<td>AO, HG-diffuse glioma with features of AO</td>
<td>III</td>
<td>Mutant</td>
<td>Loss</td>
<td>IDH1 p.R132H</td>
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<tr>
<td>5</td>
<td>68</td>
<td>M</td>
<td>SC, T10, intradural/intramedullary</td>
<td>features of AO</td>
<td>III</td>
<td>N/A</td>
<td>N/A</td>
<td>No mutations detected</td>
<td>Codeleted</td>
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<tr>
<td>6</td>
<td>19</td>
<td>M</td>
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<td>AO</td>
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**Abbreviations:** M, male; F, female; SC, spinal cord; GBM, glioblastoma; AO, anaplastic oligodendroglioma; WT, wild type; N/A, not available; HG, high grade.

* a CMA testing revealed a complex karyotype and was interpreted as negative for 1p/19q codeletion.
Bottom Line: In cases of classical glioblastoma histology in a classical clinical setting, the routine ordering of FISH testing for 1p/19q status is *inadvisable*. 
Bottom Line: In cases of classical glioblastoma histology in a classical clinical setting, the routine ordering of FISH testing for 1p/19q status is *inadvisable*.

The *false positive* incidence of 1p/19q codeletion in this setting will be *at least 6%*. 

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* CMA testing revealed a complex karyotype and was interpreted as negative for 1p/19q codeletion.
Oligodendroglioma

WHO 2016: 2 Diagnostic Options

• Oligodendroglioma, IDH-Mutant and 1p/19p-Codeleted

• Oligodendroglioma, NOS
Oligodendroglioma, IDH mut and 1p/19q codeleted

Definition
A diffusely infiltrating, slowly growing glioma with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q. Histologically, oligodendroglioma with IDH1 or IDH2 mutation and codeletion of 1p and 19q (oligodendroglioma, IDH mutant and 1p/19q codeleted) is composed of tumour cells morphologically resembling oligodendroglia with isomorphic rounded nuclei and an artificially swollen clear cytoplasm on routinely processed paraffin sections. Microcalcifications and a delicate branching capillary network are typical. An astrocytic tumour morphology is compatible with the diagnosis when molecular testing reveals the entity-defining combination of IDH mutation and 1p/19q codeletion. The vast majority of IDH mutant and 1p/19q codeleted oligodendrogliomas manifest in adult patients with preferential location in the cerebral hemispheres, most frequently in the frontal lobe.
Oligodendroglioma, NOS

A diffusely infiltrating WHO grade II glioma with classic oligodendroglial histology for which molecular testing for combined IDH mutation and 1p/19q codeletion could not be fully performed or remained inconclusive.
Oligodendroglioma

*NOTE*: There is NO OPTION to diagnose Oligo, IDH-WT
Oligodendroglioma

NOTE: There is NO OPTION to diagnose Oligo, IDH-WT

This diagnosis was available under the H&E-as-sole-gold-standard WHO 2007 Classification!
WHO 2016

NOTE: There is NO OPTION to diagnose Oligo, IDH-WT

Oligodendroglioma, IDH Wildtype
Anaplastic Oligo, IDH Wildtype
Anaplastic Oligodendroglioma

WHO 2016: 2 Diagnostic Options

• AO, IDH-Mutant, 1p/19p-Codeleted

• AO, NOS
One IHC “Shortcut” to the WHO 2016 Diagnosis of Diffuse Astrocytoma: ATRX
One IHC “Shortcut” to the WHO 2016 Diagnosis of Diffuse Astrocytoma: ATRX

ATRX Loss and 1p/19q Codeletion are MUTUALLY EXCLUSIVE
One IHC “Shortcut” to the WHO 2016 Diagnosis of Diffuse Astrocytoma: ATRX

ATRX Loss and 1p/19q Codeletion are MUTUALLY EXCLUSIVE

Thus, if normal (wildtype) ATRX protein expression is lost in glioma cells, the glioma is not an Oligodendrogioma (and 1p/19 FISH is unnecessary)
ATRX
(alpha-thalassaemia/mental retardation X-linked)


Clinical Neuropathology practice news 2-2014:
ATRX, a new candidate biomarker in gliomas

Christine Haberler and Adelheid Wöhrer

Institute of Neurology, Medical University of Vienna, Austria
Figure 1. Diffuse astrocytoma with expression of mutant IDH1 protein (A) and loss of nuclear ATRX expression (B).
ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and $IDH$ sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma

David E. Reuss, Felix Sahm, Daniel Schrimpf, Benedikt Wiestler, David Capper, Christian Koelsche, Leonille Schweizer, Andrey Korshunov, David T. W. Jones and 10 more
Integrated Diagnosis of Diffuse Gliomas

Integrated diagnosis to patients of the present series *

(82)**  (124)**  (18)  (30)  (136)  (15)**
Integrated Diagnosis of Diffuse Gliomas

Integrated diagnosis to patients of the present series:

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<td>All/AII/GBM</td>
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<td>All/AII/IDHwt</td>
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</tbody>
</table>
Glioblastoma
Glioblastoma

WHO 2007: 1 Diagnostic Option

• Glioblastoma
Glioblastoma (WHO grade IV)
# Glioblastoma: 18 Histologic Patterns

- Giant cell
- Small cell
- Spindle cell
- Bland cell
- Granular cell
- Signet-Ring cell
- Rhabdoid
- Adenoid
- Epithelioid

- Myxoid
- Inflammatory
- Lipid-Rich
- Macrophage-Rich
- GBM w/ Sarcoma-like foci
- GBM w/ Ependymoma-like foci
- GBM w/ Oligo-like foci
- GBM w/ Primitive neuronal component
- GBM w/ Neuronal phenotype

GN Fuller, Houston Area Neuropathology Review, 2018
Glioblastoma

WHO 2016

• One clinically-critical molecular feature:

IDH mutation status
Glioblastoma

WHO 2016: 3 Diagnosis Options

• Glioblastoma, IDH-Wildtype
• Glioblastoma, IDH-Mutant
• Glioblastoma, NOS
A 2nd Brief Digression

What about “Omic” Profiling for Diffuse Glioma Diagnosis and Classification?
I know a little bit about omic profiling...
First Transcriptome Profiling Study of Diffuse Gliomas: 1990s at MDACC
Advances in Brief

Reactivation of Insulin-like Growth Factor Binding Protein 2 Expression in Glioblastoma Multiforme: A Revelation by Parallel Gene Expression Profiling

Gregory N. Fuller,2 Chang Hun Rhee,2,3 Kenneth R. Hess, Laura S. Caskey, Ruoping Wang, Janet M. Bruner, W. K. Alfred Yung, and Wei Zhang4


Cancer Research 1999
First Transcriptome Profiling Study of Diffuse Gliomas: 1990s at MDACC
1st Demonstration of Genomic Classification of Diffuse Gliomas
Molecular Classification of Human Diffuse Gliomas by Multidimensional Scaling Analysis of Gene Expression Profiles Parallels Morphology-Based Classification, Correlates with Survival, and Reveals Clinically-Relevant Novel Glioma Subsets

Gregory N. Fuller¹; Kenneth R. Hess²; Chang Hun Rhee³; W. K. Alfred Yung³; Raymond A. Sawaya⁴; Janet M. Bruner¹; Wei Zhang¹

Departments of ¹Pathology, ²Biostatistics, ³Neuro-Oncology, and ⁴Neurosurgery, The University of Texas M. D. Anderson Cancer Center, Houston
* Present address: Department of Neurosurgery, Korea Cancer Center Hospital, Seoul, Korea

A preliminary report of some of the data in this study was presented at the annual meeting of the American Association of Neuropathologists in Atlanta on June 10, 2000.

the study. Survival analysis of the full data set revealed a good correlation with the molecular classification. Results of this proof-of-principle study demonstrate that molecular profiling alone can recapitulate conventional histologic classification and grading with high fidelity. In addition, results show that the molecular approach to tumor classification can generate clinically meaningful patient stratification, and, more importantly, is an efficient class-discovery tool for human gliomas, permitting the identification of previously unrecognized, clinically relevant tumor subsets.
American Association of Neuropathologists

LUCIEN J. RUBINSTEIN AWARD

presented to

G. N. Fuller, K. R. Hess, C. H. Rhee, J. M. Bruner, 
R. A. Sawaya, W. K. A. Yung, and W. Zhang

for the Best Paper on Neuro-oncology

Molecular classification of human gliomas by 
gene expression profiling

Atlanta, Georgia
June 11, 2000
1st Construction of Diffuse Glioma Tissue Microarrays for Rapid Biomarker Assay - MDACC

SYMPOSIUM: New Molecular Methodologies in Diagnostic and Investigational Neuropathology

Tissue Microarrays: Applications in Neuropathology Research, Diagnosis, and Education

Huamin Wang¹; Hua Wang²; Wei Zhang²; Gregory N. Fuller²

¹ Department of Pathology and Laboratory Medicine, The University of Texas Medical School at Houston.
² Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston.

Tissue microarrays (TMAs) are composite paraffin blocks constructed by extracting cylindrical tissue core “biopsies” from different paraffin donor blocks and re-embedding these into a single recipi-

individual human tumors. Tissue-based molecular analysis is traditionally dependent on the serial examination of candidate gene expression at the DNA, mRNA or protein level by fluorescence in situ hybridization (FISH), chromagen-based in situ hybridization (CISH) or routine immunohistochemistry (IHC) performed on individual whole-block tissue sections. Although this approach is effective, the individual analysis of hundreds of specimens is pedestrian and highly labor-intensive. Moreover, inherent variability in experimental
Tissue Microarrays: Applications in Neuropathology Research, Diagnosis, and Education

Huamin Wang¹; Gregory N. Fuller²

¹ Department of Pathology, The University of Texas M. D. Anderson Cancer Center
² Department of Pathology, The University of Texas M. D. Anderson Cancer Center

Tissue microarrays (TMAs) are a method for preparing specimens by flattening paraffin blocks containing tissue core “biopsies” from individual donor tumors. These recipient blocks are re-embedded in one large paraffin block for the serial examination of candidate gene expression at the DNA, mRNA or protein level by fluorescence in situ hybridization (FISH), chromagen-based in situ hybridization (CISH) or routine immunohistochemistry (IHC) performed on individual whole-block tissue sections. Although this approach is effective, the individual analysis of hundreds of specimens is pedestrian and highly labor-intensive. Moreover, inherent variability in experimental
1st Construction of Diffuse Glioma Tissue Microarrays for Rapid Biomarker Assay - MDACC
1st Construction of Diffuse Glioma Tissue Microarrays for Rapid Biomarker Assay - MDACC
Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis.

Heidi S. Phillips, 1,* Samir Kharbanda, 1 Ruihuan Chen, 1 William F. Forrest, 2 Robert H. Soriano, 3 Thomas D. Wu, 4 Nirgo, 5 Howard Colman, 6 Liliana Soroceanu, 1 P. Mickey Williams, 3 Zora Modrusan, 3 Ken Aldape 7

One tumor population, enriched for neural stem cell and neuroepithelial lineage markers shows longer survival, while two tumor classes enriched for neural stem cell support survival. Poor prognosis subclasses exhibit markers either of proliferation or of angiogenesis and mesenchyme. Upon recurrence, tumors frequently shift toward the mesenchymal subclass. Chromosomal locations of genes distinguishing tumor subclass parallel DNA copy number differences between subclasses. Functional relevance of tumor subtype molecular signatures is suggested by the ability of cell line signatures to predict neurosphere growth. A robust two-gene prognostic model utilizing PTEN and DLL3 expression suggests that Akt and Notch signaling are hallmarks of poor prognosis versus better prognosis gliomas, respectively.
<table>
<thead>
<tr>
<th></th>
<th>Proneural</th>
<th>Proliferative</th>
<th>Mesenchymal</th>
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<tr>
<td><strong>Histological grade</strong></td>
<td>WHO grade III or WHO grade IV with or without necrosis</td>
<td>WHO grade IV with necrosis</td>
<td>WHO grade IV with necrosis</td>
</tr>
<tr>
<td><strong>Cellular morphology</strong></td>
<td>Astrocytic or Oligodendroglial</td>
<td>Astrocytic</td>
<td>Astrocytic</td>
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<tr>
<td><strong>Evolution of signature</strong></td>
<td>Arises in 1° tumor, may persist or convert to Mes</td>
<td>Arises in 1° tumor, may persist or convert to Mes</td>
<td>Arises in 1° tumor or by conversion from other subtype</td>
</tr>
<tr>
<td><strong>Patient age</strong></td>
<td>Younger (~40 yrs.)</td>
<td>Older (~50 yrs.)</td>
<td>Older (~50 yrs.)</td>
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<tr>
<td><strong>Prognosis</strong></td>
<td>Longer survival</td>
<td>Short survival</td>
<td>Short survival</td>
</tr>
<tr>
<td><strong>Histological Markers</strong></td>
<td>Olig2, DLL3, BCAN</td>
<td>PCNA, TOP2A</td>
<td>CHI3L1/YKL40, CD44, VEGF</td>
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<td><strong>Tissue similarities</strong></td>
<td>Adult and Fetal Brain</td>
<td>HSC, lymphoblast</td>
<td>Bone, cartilage, smooth muscle, endothelium, dendritic cells</td>
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<td><strong>Biological process</strong></td>
<td>Neurogenesis</td>
<td>Proliferation</td>
<td>Angiogenesis</td>
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<td><strong>Analogous forebrain cell</strong></td>
<td>Neuroblast</td>
<td>Neural Stem Cell and/or Transit Amplifying Cell</td>
<td>Neural Stem Cell</td>
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<td><strong>Chromosome gain/loss</strong></td>
<td>None</td>
<td>Gain of 7 &amp; Loss of 10 or 10q</td>
<td>Gain of 7 &amp; Loss of 10</td>
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<tr>
<td><strong>PTEN locus</strong></td>
<td>PTEN intact</td>
<td>PTEN loss</td>
<td>PTEN loss</td>
</tr>
<tr>
<td><strong>EGFR locus</strong></td>
<td>EGFR normal</td>
<td>EGFR amplified or normal</td>
<td>EGFR amplified or normal</td>
</tr>
<tr>
<td><strong>Signaling</strong></td>
<td>Notch activation</td>
<td>Akt activation</td>
<td>Akt activation</td>
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</tbody>
</table>
Bottom Line:

• Omic profiling (transcriptome, genome, methylome, proteome, metabolome) has taught us and continues to teach us much about diffuse glioma biology, and can stratify tumors into molecular signature-based prognostically-significant subtypes,
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Bottom Line:

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Bottom Line:

- Omic profiling (transcriptome, genome, methylome, proteome, metabolome) has taught us and continues to teach us much about diffuse glioma biology, and can stratify tumors into molecular signature-based prognostically-significant subtypes,

- HOWEVER, TREATMENT DECISIONS for diffuse glioma patients are not currently (November, 2018) based on omic profiling groups; they are based on IDH and 1p/19q alteration status.
Glioblastoma

WHO 2016: 3 Diagnosis Options

• Glioblastoma, IDH-Wildtype
• Glioblastoma, IDH-Mutant
• Glioblastoma, NOS
WHO 2016

An Additional Major Change in Diffuse Glioma Classification
WHO 2016

Formal Recognition of Pediatric Diffuse Gliomas as Distinct Tumor Entities Separate From Adult Diffuse Gliomas
Diffuse Intrinsic Pontine Glioma (DIPG)
LETTER

Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma

Jeremy Schwartzentruber\textsuperscript{1,*}, Andrey Korshunov\textsuperscript{2,*}, Xiao-Yang Liu\textsuperscript{3,*}, David T. W. Jones\textsuperscript{4}, Elke Pfaff\textsuperscript{4}, Karine Jacob\textsuperscript{3}, Dominik Sturm\textsuperscript{4}, Adam M. Fontebasso\textsuperscript{3}, Dong-Anh Khuong Quang\textsuperscript{3}, Martje Tönjes\textsuperscript{5}, Volker Hovestadt\textsuperscript{5}, Steffen Albrecht\textsuperscript{6}, Marcel Kool\textsuperscript{4}, Andre Nantel\textsuperscript{7}, Carolin Konermann\textsuperscript{8}, Anders Lindroth\textsuperscript{8}, Natalie Jäger\textsuperscript{9}, Tobias Rausch\textsuperscript{10}, Marina Ryzhova\textsuperscript{11}, Jan O. Korbel\textsuperscript{10}, Thomas Hielscher\textsuperscript{12}, Peter Hauser\textsuperscript{13}, Miklos Garami\textsuperscript{13}, Almos Klekner\textsuperscript{14}, Laszlo Bognar\textsuperscript{14}, Martin Ebinger\textsuperscript{15}, Martin U. Schuhmann\textsuperscript{16}, Wolfram Scheurlen\textsuperscript{17}, Arnulf Pekrun\textsuperscript{18}, Michael C. Frühwald\textsuperscript{19}, Wolfgang Roggendorf\textsuperscript{20}, Christoph Kramm\textsuperscript{21}, Matthias Dürken\textsuperscript{22}, Jeffrey Atkinson\textsuperscript{23}, Pierre Lepage\textsuperscript{1}, Alexandre Montpetit\textsuperscript{1}, Magdalena Zakrzewska\textsuperscript{24}, Krzysztof Zakrzewski\textsuperscript{25}, Pawel P. Liberski\textsuperscript{24}, Zhifeng Dong\textsuperscript{26}, Peter Siegel\textsuperscript{26}, Andreas E. Kulozik\textsuperscript{27}, Marc Zapatka\textsuperscript{5}, Abhijit Guha\textsuperscript{28}, David Malkin\textsuperscript{29}, Jörg Felsberg\textsuperscript{30}, Guido Reifenberger\textsuperscript{30}, Andreas von Deimling\textsuperscript{3,31}, Koichi Ichimura\textsuperscript{32}, V. Peter Collins\textsuperscript{32}, Hendrik Witt\textsuperscript{4,27}, Till Milde\textsuperscript{27,33}, Olaf Witt\textsuperscript{27,33}, Cindy Zhang\textsuperscript{28}, Pedro Castelo-Branco\textsuperscript{28}, Peter Lichter\textsuperscript{5}, Damien Faury\textsuperscript{3}, Uri Tabori\textsuperscript{28,29}, Christoph Plass\textsuperscript{3}, Jacek Majewski\textsuperscript{3}, Stefan M. Pfister\textsuperscript{4,27} & Nada Jabado\textsuperscript{3,34}
Histone $H3F3A$ Gene Mutations in Young Adult High-Grade Gliomas

**Neuro-Oncology**

*Neuro-Oncology* 16(1), 140 – 146, 2014
doi:10.1093/neuonc/not144
Advance Access date 26 November 2013

**H3F3A K27M mutations in thalamic gliomas from young adult patients**

Koki Aihara, Akitaake Mukasa, Kengo Gotoh, Kuniaki Saito, Genta Nagae, Shingo Tsuji, Kenji Tatsuno, Shogo Yamamoto, Shunsaku Takayanagi*, Yoshitaka Narita, Soichiro Shibui, Hiroyuki Aburatani and Nobuhito Saito

*Department of Neurosurgery, Graduate School and Faculty of Medicine, The University of Tokyo, Tokyo, Japan (K.A., A.M., K.S., S.T.*, N.S.); Genome Science Division, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan (K.A., K.G., G.N., S.T., K.T., S.Y., H.A.); Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan (Y.N., S.S.)*

**Corresponding authors:** Akitaake Mukasa, MD, PhD, Department of Neurosurgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (mukasa-nsu@umin.ac.jp); Hiroyuki Aburatani, MD, PhD, Genome Science Division, Research Center for Advanced Science and Technology (RCAST), The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan (haburata-tky@umin.ac.jp).

**Introduction.** Mutations in $H3F3A$, which encodes histone H3.3, commonly occur in pediatric glioblastoma. Additionally, $H3F3A$ K27M substitutions occur in gliomas that arise at midline locations (eg, pons, thalamus, spine); moreover, this substitution occurs mainly in tumors in children and adolescents. Here, we sought to determine the association between $H3F3A$ mutations and adult thalamic glioma.

**Methods.** Genomic $H3F3A$ was sequenced from 20 separate thalamic gliomas. Additionally, for 14 of the 20 gliomas, 639 genes—including cancer-related genes and chromatin-modifier genes—were sequenced, and the Infinium HumanMethylation450K BeadChip was used to examine DNA methylation across the genome.

**Results.** Of the 20 tumors, 18 were high-grade thalamic gliomas, and of these 18, 11 were from patients under 50 years of age (median age, 38 y; range, 17–46), and 7 were from patients over 50 years of age. The $H3F3A$ K27M mutation was present in 10 of the 11 (91%) younger patients and absent from all 7 older patients. Additionally, $H3F3A$ K27M was not detected in the 2 diffuse astrocytomas. Further sequencing revealed recurrent mutations in TP53, ATRX, NF1, and EGFR. Gliomas with $H3F3A$ K27M from pediatric or young adult patients had similar, characteristic DNA methylation profiles. In contrast, thalamic gliomas with wild-type $H3F3A$ had DNA methylation profiles similar to those of hemispheric glioblastomas.
The Genetic Signatures of Pediatric High-Grade Glioma: No Longer a One-Act Play

Alexander K. Diaz,*† and Suzanne J. Baker, PhD*†

Advances in understanding pediatric high-grade glioma (pHGG) genetics have revealed key differences between pHGG and adult HGG and have uncovered unique molecular drivers among subgroups within pHGG. The 3 core adult HGG pathways, the receptor tyrosine kinase-Ras-phosphatidylinositol-3-kinase, p53, and retinoblastoma networks, are also disrupted in pHGG, but they exhibit a different spectrum of effectors targeted by mutation. There are also similarities and differences in the genomic landscape of diffuse intrinsic pontine glioma (DIPG) and pediatric nonbrainstem (pNBS)-HGG. In 2012, histone H3 mutations were identified in nearly 80% of DIPGs and ~35% of pNBS-HGG. These were the first reports of histone mutations in human cancer, implicating novel biology in pediatric gliomagenesis. Additionally, DIPG and midline pNBS-HGG vary in the frequency and specific histone H3 amino acid substitution compared with pNBS-HGGs arising in the cerebral hemispheres, demonstrating a molecular difference among pHGG subgroups. The gene expression signatures as well as DNA methylation signatures of these tumors are also distinctive, reflecting a combination of the driving mutations and the developmental context from which they arise. These data collectively highlight unique selective pressures within the developing brainstem and solidify DIPG as a specific molecular and biological entity among pHGGs. Emerging studies continue to identify novel mutations that distinguish subgroups of pHGG. The molecular heterogeneity among pHGGs will undoubtedly have clinical implications moving forward. The discovery of unique oncogenic drivers is a critical first step in providing patients with appropriate, targeted therapies. Despite these insights, our vantage point has been largely limited to an in-depth analysis of protein coding sequences. Given the clear importance of histone mutations in pHGG, it will be interesting to see how aberrant epigenetic regulation contributes to tumorigenesis in the pediatric context. New mechanistic insights may allow for the identification of distinct vulnerabilities in this devastating spectrum of childhood tumors.

Semin Radiat Oncol 24:240-247 © 2014 Elsevier Inc. All rights reserved.
Histone $H3F3A$ Gene Mutations in Pediatric High-Grade Gliomas

Diaz, Baker. Sem Rad Onc 2014
WHO 2016 New Entity

Diffuse Midline Glioma, H3 K27M-Mutant
Diffuse Midline Glioma, H3 K27M-Mutant

Classical Pontine Glioma (DIPG)
Histone *H3F3A* Gene Mutations – Surrogate Immunostain Markers

**A sensitive and specific histopathologic prognostic marker for H3F3A K27M mutant pediatric glioblastomas**

Sriram Veneti · Mariarita Santi · Michelle Madden Felicella · Dmitry Yarilin · Joanna J. Phillips · Lisa M. Sullivan · Daniel Martinez · Arie Perry · Peter W. Lewis · Craig B. Thompson · Alexander R. Judkins

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**Specific detection of methionine 27 mutation in histone 3 variants (H3K27M) in fixed tissue from high-grade astrocytomas**

Denise Bechet · Gerrit G. H. Gielen · Andrey Korshunov · Stefan M. Pfister · Caterina Rousso · Damien Faury · Pierre-Olivier Fiset · Naciba Benlimane · Peter W. Lewis · Chao Lu · C. David Allis · Mark W. Kieran · Keith L. Ligon · Torsten Pietsch · Benjamin Ellezam · Steffen Albrecht · Nada Jabado
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One Additional Unique Aspect of Diffuse Midline Glioma, H3 K27M-Mutant
One Additional Unique Aspect of Diffuse Midline Glioma, H3 K27M-Mutant

Conventional histologic grading (mitotic activity, vascular proliferation, necrosis) does NOT add additional prognostic information.
Diffuse Midline Glioma, H3 K27M-Mutant

WHO Classification of Tumours

Diffuse midline glioma, H3 K27M mutant

Definition
An infiltrative midline high-grade glioma with predominantly astrocytic differentiation and harbours a K27M mutation in either H3F3A or HIST1H3B/C. The tumour predominates in children but may be seen in midline locations in adults as well. Mitotic activity is present in most cases, but is not required for diagnosis; microvascular proliferation and necrosis may be seen. Tumour cells diffusely infiltrate adjacent and distant brain structures.

Additional genetic alterations are usually seen, including mutations in TP53 (50%), PPMID (15%), and ACVR1 (20%), and amplification of PDGFRA (30%), MYC/PVT1 (15%), and CDK4/6 or CCND1-3 (20%), while homozygous deletion of CDKN2A/B is infrequent (<5%). The prognosis is poor, despite current therapies, with a 2-year survival rate of <10%.
Hmmm… What about the vexing problem of separating “gray zone” WHO grade II-grade III diffuse gliomas?
Hmmm... What about the vexing problem of separating “gray zone” WHO grade II-grade III diffuse gliomas?

Often referred to in Neuropathology circles as “Grade 2.5”
An evidence-based, data-driven solution is near...
An evidence-based, data-driven solution is near…

IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO

David E. Reuss¹,² · Yasin Mamatjan³ · Daniel Schrimpf¹,² · David Capper¹,² · Volker Hovestadt⁴ · Annekathrin Kratz¹,² · Felix Sahm¹,² · Christian Koelsche¹,² · Andrey Korshunov¹,² · Adriana Olar⁵ · Christian Hartmann⁶ · Jaap C. Reijneveld⁷ · Pieter Wesseling⁸,⁹ · Andreas Unterberg¹⁰ · Michael Platten¹¹,¹² · Wolfgang Wick¹²,¹³ · Christel Herold-Mende¹⁰ · Kenneth Aldape³ · Andreas von Deimling¹,²
Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas

The Cancer Genome Atlas Research Network∗
Diffuse Glioma – Grades II & III

Molecular pathway

IDH mutation
226

1p/19q codeletion present
85

1p/19q codeletion absent
141

IDH wild type
56

Diffuse grade II and III (lower-grade) gliomas
282

Molecular alterations

Inactivating
CIC
FUBP1
NOTCH1

Activating
PIK3CA
PTBP1
TERT
IDH1
IDH2

TP53
ATRX

MYC
CCND2
IDH1
IDH2

PTEN
NF1
CDKN2A

EGFR
MDM4
TERT

Clinical presentation

LGG

LGG: frequent
GBM: rare

LGG: rare
GBM: frequent

NEJM 2015
Diffuse Glioma – Grades II & III

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PTEN
NF1
CDKN2A
EGFR
MDM4
TERT

Clinical presentation

LGG
LGG: frequent
GBM: rare
LGG: rare
GBM: frequent

NEJM 2015
Diffuse Glioma – Grades II & III

NEJM 2015
WHO 2016
Major Changes
EMBRYONAL TUMORS
Embryonal Tumors

• Medulloblastoma
• AT/RT
• ETMR
Embryonal Tumors

Incorporation of clinically-critical molecular signatures into the Entity Definition and Name (thus, essential diagnostic criterion)
However, as with the Diffuse Gliomas, there will **ALWAYS** be a Histology (H&E)-Only diagnostic option for all CNS tumors!
Medulloblastoma

- Medulloblastoma, Histologically Defined
Medulloblastoma

• Medulloblastoma, Histologically Defined

• Medulloblastoma, Genetically Defined
Medulloblastoma

Medulloblastoma, Histologically Defined
Medulloblastoma

Medulloblastoma, Histologically Defined

• Medulloblastoma, classic
Medulloblastoma

Medulloblastoma, classic
Medulloblastoma

Medulloblastoma, Histologically Defined

• Medulloblastoma, classic

• Desmoplastic / nodular medulloblastoma
Medulloblastoma

Desmoplastic / nodular medulloblastoma
Medulloblastoma

Medulloblastoma, Histologically Defined

• Medulloblastoma, classic

• Desmoplastic / nodular medulloblastoma

• Medulloblastoma with extensive nodularity
Medulloblastoma

Medulloblastoma with extensive nodularity
Medulloblastoma

Medulloblastoma with extensive nodularity

Classic Medullo

MBEN
Medulloblastoma

Medulloblastoma, Histologically Defined

- Medulloblastoma, classic
- Desmoplastic / nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large cell / anaplastic medulloblastoma
Medulloblastoma

Large cell / anaplastic medulloblastoma
Medulloblastoma

Medulloblastoma, Genetically Defined
Genetic and molecular alterations across medulloblastoma subgroups

Patryk Skowron1,2 • Vijay Ramaswamy1,3 • Michael D. Taylor1,2,4
# Medulloblastoma

## Medulloblastoma, Genetically Defined

| Table 1: Clinical and genomic characteristics of medulloblastoma subgroups [4, 17, 25, 26, 29-31] |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| **AGE DISTRIBUTION** | WNT | SHH | GROUP 3 | GROUP 4 |
| Infant | Child | Adult | Infant | Child | Adult | Infant | Child | Adult |
| **GENDER (F|M)** | | | | | | | | |
| **HISTOLOGY** | Classic, Rarely LCA | Desmoplastic, Classic, LCA | Classic, LCA | Classic, LCA |
| **METASTATIC RATE** | Low | Low | High | High |
| **PROGNOSIS** | Excellent | Intermediate | Poor | Intermediate |
| **SCNA** | - | MYCN (12%) | MYC (17%) | SNCAI (10%) |
| CTNNB1 (91%) | GLI2 (8%) | PVT1 (12%) | MYCN (6%) |
| DDX3X (50%) | TERT (60%) | PVT1 (12%) | CDK6 (5%) |
| SMARCA4 (26%) | PTCH1 (46%) | SMO (14%) | |
| MLL2 (13%) | SUFU (24%) | TP53 (13%) | |
| TPS3 (13%) | |
| **SNVS** | | | | |
| | | | | |
| **BROAD EVENTS** | 6 Loss | 3q Gain | 1q, 17q, 18q Gain | 7, 17q, 18q Gain |
| | 9q, 10q, 14q Loss | 8, 10q, 11, 16p, 17p Loss | 6, 11p, X Loss | |
| **EXPRESSION** | WNT Signaling | SHH Signaling | MYC/Retinal Signature | Neuronal Signature |
| **RECURRENCE** | - | Local | Metastatic | Metastatic |

# Medulloblastoma

**Medulloblastoma, Genetically Defined**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and genomic characteristics of medulloblastoma subgroups [4, 17, 25, 26, 29–31]</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td>Infant</td>
<td>Child</td>
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<tr>
<td>WNT</td>
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<tr>
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<tr>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>GLI2 (8%)</td>
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<td><strong>SNVS</strong></td>
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<td></td>
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## Medulloblastoma

**Medulloblastoma, Genetically Defined**

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<td>Infant: 100</td>
<td>Infant: 185</td>
<td>Infant: 185</td>
<td>Infant: 180</td>
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<tr>
<td></td>
<td>Adult: 50</td>
<td>Adult: 95</td>
<td>Adult: 95</td>
<td>Adult: 90</td>
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<tr>
<td>**GENDER (F</td>
<td>M)**</td>
<td>Female: 50</td>
<td>Female: 90</td>
<td>Female: 90</td>
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<tr>
<td></td>
<td>Male: 50</td>
<td>Male: 90</td>
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<td>7, 17q, 18q Gain 6, 11p, X Loss</td>
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*Skowron P et al. J Molec Med 2015*
# Medulloblastoma

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<td>MYCN (12%)</td>
<td>MYC (17%)</td>
<td>SNCAIP (10%)</td>
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<td>GLI2 (8%)</td>
<td>PVT1 (12%)</td>
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<td>PTCH1 (46%)</td>
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<td>MLL2 (16%)</td>
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<td>SMO (14%)</td>
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<td>TP53 (13%)</td>
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<td>6 Loss</td>
<td>3q Gain</td>
<td>1q, 7, 17q, 18q Gain</td>
<td>7, 17q, 18q Gain</td>
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<tr>
<td></td>
<td>9q, 10q, 14q Loss</td>
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<td>8, 10q, 11, 16p, 17p Loss</td>
<td>6, 11p, X Loss</td>
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<tr>
<td>EXPRESSION</td>
<td>WNT Signaling</td>
<td>SHH Signaling</td>
<td>MYC/Retinal Signature</td>
<td>Neuronal Signature</td>
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</table>

Medulloblastoma

Medulloblastoma, Genetically Defined

• MB, WNT activated
Medulloblastoma

Medulloblastoma, Genetically Defined

• MB, WNT activated

• MB, SHH activated
Medulloblastoma

Medulloblastoma, Genetically Defined

• MB, WNT activated

• MB, SHH activated, *TP53-Mutant*
• MB, SHH activated, *TP53-Wild-Type*
Medulloblastoma

Medulloblastoma, Genetically Defined

- MB, WNT activated
- MB, SHH activated, *TP53*-Mutant
- MB, SHH activated, *TP53*-Wild-Type
- MB, non-WNT / non-SHH
Medulloblastoma

Medulloblastoma, Genetically Defined

• MB, WNT activated

• MB, SHH activated, \textit{TP53-Mutant}

• MB, SHH activated, \textit{TP53-Wild-Type}

• MB, non-WNT / non-SHH
  \begin{itemize}
  
  \item \textit{MB, group 3}
  
  \item \textit{MB, group 4}
  
  \end{itemize}
Medulloblastoma, Genetically Defined

- MB, WNT activated
- MB, SHH activated, *TP53-Mutant*
- MB, SHH activated, *TP53-Wild-Type*
- MB, non-WNT / non-SHH
  - MB, group 3
  - MB, group 4
- MB, NOS (Not Otherwise Specified)
Medulloblastoma

Medulloblastoma, Genetically Defined

*Practical Clinical Classification using Immunophenotype Surrogate Markers*
Medulloblastoma

Medulloblastoma, Genetically Defined

Kaur K et al. Brain Pathology 2015
Medulloblastoma

WHO 2016: Diagnostic reporting of BOTH the Histologic subtype AND the Genetic subtype will be encouraged.
Molecular Signature-Based Reduction in Complexity!

ETMR
3 Rare and Unusual Embryonal Tumors

- Medulloepithelioma
- Ependymoblastoma
- **ETANTR** (Embryonal Tumor with Abundant Neuropil and True Rosettes)
Medulloepithelioma, Ependymoblastoma, and Embryonal Tumor with Abundant Neuropil and True Rosettes (ETANTR) share the same unique molecular signature: Amplification of C19MC (chromosome 19 microRNA cluster; 19q13.41-42)
What to call it?
What to call it?
Multiple proposed names in the literature...
What to call it?

Multiple proposed names in the literature...

• Embryonal tumor with ependymoblastic rosettes?

• Embryonal tumor with multilayered rosettes?

• Embryonal tumor with abundant neuropil and true rosettes?
WHO 2016 Working Group
Besides the **Diffuse Gliomas** and **Embryonal Tumors**, are there any other WHO 2016 tumors with molecular signatures incorporated into their name?
Just one.
Just one.

Ependymoma, *RELA* Fusion-Positive
Recognition of a Genetically Defined Ependymoma Variant

C11orf95–RELA fusions drive oncogenic NF-κB signalling in ependymoma

Matthew Parker1,2, Kumarasamy M. Mohankumar3*, Chandanamali Punchihewa4*, Ricardo Weinlich5*, James D. Dalton1,4, Yongjin Li1,2, Ryan Lee4, Ruth G. Tatevossian1,4, Timothy N. Phoenix3, Radhika Thiruvenkatam3, Elsie White3, Bo Tang1,4, Wilda Orisme1,4, Kirti Gupta4, Michael Rusch2, Xiang Chen2, Yuxin Li2,6, Panduka Nagahawatte2, Erin Hedlund2, David Finkelstein2, Gang Wu2, Sheila Shurtleff4, John Easton1,4, Kristy Boggs1, Donald Yergeau1, Bhavin Vadodaria1, Heather L. Mulder1, Jared Becksfort1, Pankaj Gupta2, Robert Huether6, Jing Ma1, Guangchun Song1, Amar Gajjar1,7, Thomas Merchant8, Frederick Boop9, Amy A. Smith10, Li Ding1,11,12, Charles Lu1,11, Kerri Ochoa1,11,12, David Zhao1,2, Robert S. Fulton1,11, Lucinda L. Fulton1,11,12, Elaine R. Mardis1,11,12,13, Richard K. Wilson1,11,12,13, James R. Downing1,4, Douglas R. Green5, Jinghui Zhang1,2, David W. Ellison1,4 & Richard J. Gilbertson1,3
Ependymoma: Clinicogenetic Subtyping

Supratentorial ependymoma
- Adolescents, adults
- Intermediate prognosis
- Few chromosomal defects
- Intrachromosomal translocation (C11orf95–RELA fusion)

Posterior fossa ependymoma
Type A
- Infants, adolescents
- Intermediate prognosis
- Few chromosomal defects
- No gene mutations
- Epigenetic changes

Type B
- Adolescents, adults
- Good prognosis
- Extensive chromosomal defects
- No gene mutations
- No epigenetic changes
And one that came close.
Atypical Teratoid/Rhabdoid Tumor (AT/RT)

Genetic studies show mutation/deletion of the putative rhabdoid tumor suppressor gene:

\[ \text{INI1 (hSNF5) on chromosome 22q11.2} \]

INI1 gene product loss detectable as absence of BAF47 immunoreactivity
Medulloblastoma
INI1 (BAF47)
Reactive lymphocytes are positive. ATRT tumor cells are negative.
WHO 2016

Atypical Teratoid / Rhabdoid Tumor DEFINITION

A malignant embryonal CNS tumour composed predominantly of poorly differentiated elements and frequently including rhabdoid cells, with inactivation of SMARCB1/INI1 or, extremely rarely, SMARCA4/BRG1. The atypical teratoid/rhabdoid tumour occurs most frequently in young children. Neoplastic cells demonstrate histological and immunohistochemical evidence of polyphenotypic differentiation along neuroectodermal, epithelial and mesenchymal lines. Diagnosis of atypical teratoid/rhabdoid tumour requires demonstration of inactivation of SMARCB1/INI1 or, if intact, SMARCA4/BRG1 genes by either routine immunohistochemical staining for the proteins or other appropriate means. Tumours lacking this molecular genetic confirmation should be designated as "CNS embryonal tumour with rhabdoid features".
Summary
What Does a WHO 2016 Surgical Pathology Report Diagnosis Look Like?
Five outside slides, brain, left frontal lobe, biopsy:

**DIFFUSE ASTROCYTOMA, IDH-MUTANT**
**WHO GRADE II**

Mitotic index (H&E): <1 mitosis / 10 HPF  
Ki67 index (MIB1): 4.1% (maximum); 3.2% (average)

IDH1 protein status (IHC): POSITIVE for IDH1 p.R132H expression in glioma cells (by report)  
ATRX protein status (IHC): LOSS in glioma cells (by report)  
TP53/p53 status: Unknown  
CDKN2A/B status: Unknown

(SEE COMMENT)
DIAGNOSIS

Twelve slides, brain, right parietal lobe, craniotomy with resection:

**ANAPLASTIC OLIGODENDROGLIOMA, IDH-MUTANT, 1p/19q CODELETED WHO GRADE III**

- IDH1 protein status (IHC): **POSITIVE** for IDH p.R132H expression in glioma cells
- 1p/19q status (FISH): **POSITIVE** for codeletion (by report)
- ATRX protein status (IHC): Retained wildtype expression

(SEE COMMENT)

COMMENT

H&E-stained sections show a diffusely infiltrating glioma with characteristic morphologic features of oligodendroglial differentiation. Cortical ribbon microcalcifications are focally prominent, correlating with preoperative MR imaging studies performed at the referring institution (available on MDACC Epic), which show curvilinear susceptibility, consistent with calcification. Mitotic figures and apoptotic bodies are easily identified, and the Ki67 antigen (MIB1) labeling index ranges up to approximately 10%. Per referring institution pathology report, vascular proliferation was noted on the cytologic smear preparation (not received for review). This correlated with the avid heterogeneous contrast enhancement present on preoperative MR imaging studies.
DIAGNOSIS

Twelve slides, brain, right parietal lobe, craniotomy with resection:

ANAPLASTIC OLIGODENDROGLIOMA, IDH-MUTANT, 1p/19q CODELETED WHO GRADE III

IDH1 protein status (IHC): POSITIVE for IDH p.R132H expression in glioma cells
1p/19q status (FISH): POSITIVE for codeletion (by report)
ATRX protein status (IHC): Retained wildtype expression

(SEE COMMENT)

COMMENT

H&E-stained sections show a diffusely infiltrating glioma with characteristic morphologic features of oligodendroglial differentiation. Cortical ribbon microcalcifications are focally prominent, correlating with preoperative MR imaging studies performed at the referring institution (available on MDACC Epic), which show curvilinear susceptibility, consistent with calcification. Mitotic figures and apoptotic bodies are easily identified, and the Ki67 antigen (MIB1) labeling index ranges up to approximately 10%. Per referring institution pathology report, vascular proliferation was noted on the cytologic smear preparation (not received for review). This correlated with the avid heterogeneous contrast enhancement present on preoperative MR imaging studies.
A. BRAIN, RIGHT OCCIPITAL LOBE, STEREOTACTIC BIOPSY:

GLIOBLASTOMA, IDH-MUTANT (GLIOMATOSIS CEREBRI PRESENTATION)  
WHO GRADE IV

**IDH1** protein status (IHC): POSITIVE for IDH1 p.R132H expression  
**ATRX** protein status (IHC): LOSS of expression in tumor cells  
**p53** protein status (IHC): POSITIVE nuclear expression in glioma (strong, diffuse)  
1p/19q status (FISH): Negative for codeletion (19q13 locus deleted; 1p36 locus intact)  
**BRAF** protein status (IHC): Negative for mutant BRAF V600E expression  
**MGMT** status (PCR): Negative for promoter methylation

(SEE COMMENT)
The patient has a history of Anaplastic Astrocytoma diagnosed by stereotactic biopsy.

H&E-stained sections of the present biopsy show a high-grade diffuse astrocytoma with epithelioid morphologic features, elevated mitotic activity and vascular proliferation, diagnostic of glioblastoma; necrosis is NOT identified.

Molecular signature determination studies are shown in the Diagnosis section above. This glioma exhibits the characteristic molecular signature triad of IDH-mutant diffuse astrocytic disease, comprising *IDH* mutation, *ATRX* loss, and strong diffuse nuclear expression of p53 protein indicative of likely *TP53* mutation (1).

The diagnosis of glioblastoma is congruent with preoperative MR imaging studies, which showed interval development of multiple foci of contrast enhancement in the context of an initially non-enhancing (at the time of initial biopsy in July, 2017) gliomatosis cerebri presentation.

Reference

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The diagnosis of glioblastoma is congruent with preoperative MR imaging studies, which showed interval development of multiple foci of contrast enhancement in the context of an initially non-enhancing (at the time of initial biopsy in July, 2017) gliomatosis cerebri presentation.

Reference

A Glimpse of the Future...

Beyond the WHO 2016
Novel, improved grading system(s) for IDH-mutant astrocytic gliomas

Mitsuaki Shirahata¹,² · Takahiro Ono¹,³ · Damian Stichel⁴ · Daniel Schrimpf¹,⁴ · David E. Reuss¹,⁴ · Felix Sahm¹,⁴ · Christian Koelsche¹,⁴ · Annika Wefers¹,⁴ · Annekathrin Reinhardt¹,⁴ · Kristin Huang¹,⁴ · Philipp Sievers¹,⁴ · Hiroaki Shimizu³ · Hiroshi Nanjo⁵,⁶ · Yusuke Kobayashi² · Yohei Miyake² · Tomonari Suzuki² · Jun-ichi Adachi² · Kazuhiko Mishima² · Atsushi Sasaki⁷ · Ryo Nishikawa² · Melanie Bewerunge-Hudler⁸ · Marina Ryzhova⁹ · Oksana Absalyamova⁹ · Andrey Golanov⁹ · Peter Sinn¹⁰ · Michael Platten¹¹ · Christine Jungk¹² · Frank Winkler¹³,¹⁴ · Antje Wick¹³,¹⁴ · Daniel Hänggi¹⁵ · Andreas Unterberg¹² · Stefan M. Pfister¹⁶,¹⁷,¹⁸ · David T. W. Jones¹⁶,¹⁷ · Martin van den Bent¹⁹ · Monika Hegi²⁰,²¹ · Pim French¹⁹ · Brigitta G. Baumert²² · Roger Stupp²³ · Thierry Gorlia²⁴ · Michael Weller²⁵ · David Capper¹,²⁶,²⁷,²⁸ · Andrey Korshunov¹,⁴ · Christel Herold-Mende¹² · Wolfgang Wick¹³,¹⁴ · David N. Louis²⁹ · Andreas von Deimling¹,⁴,³⁰

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Abstract
According to the 2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 CNS WHO), IDH-mutant astrocytic gliomas comprised WHO grade II diffuse astrocytoma, IDH-mutant (AII_{IDHmut}), WHO grade III anaplastic astrocytoma, IDH-mutant (AIII_{IDHmut}), and WHO grade IV glioblastoma, IDH-mutant (GBM_{IDHmut}). Notably, IDH gene status has been made the major criterion for classification while the manner of grading has remained unchanged: it is based on histological criteria that arose from studies which antedated knowledge of the importance of IDH status in diffuse astrocytic tumor prognostic assessment. Several studies have now demonstrated that the anticipated differences in survival between the newly defined AII_{IDHmut} and AIII_{IDHmut} have lost their significance. In contrast, GBM_{IDHmut} still exhibits a significantly worse outcome than its lower grade IDH-mutant counterparts. To address the problem of establishing prognostically significant grading for IDH-mutant astrocytic gliomas in the IDH era, we undertook a comprehensive study that included assessment of histological and genetic approaches to prognosis in these tumors. A discovery cohort of 211 IDH-mutant astrocytic gliomas with an extended observation was subjected to histological review, image analysis, and DNA methylation studies. Tumor group-specific methylation profiles and copy number variation (CNV) profiles were established for all gliomas. Algorithms for automated CNV analysis were developed. All tumors exhibiting 1p/19q codeletion were excluded from the series. We developed algorithms for grading, based on molecular, morphological and clinical data. Performance of these algorithms was compared with that of WHO grading. Three independent cohorts of 108, 154 and 224 IDH-mutant astrocytic gliomas were used to validate this approach. In the discovery cohort several molecular and clinical parameters were of prognostic relevance. Most relevant for overall survival (OS) was CDKN2A/B homozygous deletion. Other parameters with major influence were necrosis and the total number of CNV. Proliferation as assessed by mitotic count, which is a key parameter in 2016 CNS WHO grading, was of only minor influence. Employing the parameters most relevant for OS in our discovery set, we developed two models for grading these tumors. These models performed significantly better than WHO grading in both the discovery and the validation sets. Our novel algorithms for grading IDH-mutant astrocytic gliomas overcome the challenges caused by introduction of IDH status into the WHO classification of diffuse astrocytic tumors. We propose that these revised approaches be used for grading of these tumors and incorporated into future WHO criteria.
Table 2  Genes with amplifications or homozygous deletions found in 211 IDH-mutated astrocytomas in the discovery set and their association with OS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>n</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>CCND1</td>
<td>Amplification (cutoff 0.35)</td>
<td>1</td>
<td>0.17</td>
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<td>CCND2</td>
<td>Amplification (cutoff 0.35)</td>
<td>27</td>
<td>0.15</td>
</tr>
<tr>
<td>CDK4</td>
<td>Amplification (cutoff 0.35)</td>
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<td>Amplification (cutoff 0.35)</td>
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<td>0.13</td>
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<tr>
<td><strong>CDKN2A/B</strong></td>
<td><strong>Homo del (cutoff − 0.415)</strong></td>
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<td>0.0001</td>
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<td>EGFR</td>
<td>Amplification (cutoff 0.35)</td>
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<td>NF1</td>
<td>Homo del (cutoff − 0.415)</td>
<td>4</td>
<td>0.52</td>
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<td>SMARCB1</td>
<td>Homo del (cutoff − 0.415)</td>
<td>2</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Univariate analysis

*homo del* homozygous deletion
## Table 2

**Proposed Update to WHO Classification of IDH-Mutant Diffuse Astrocytomas**

### Diffuse astrocytic tumours

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytic glioma, IDH-mutant, CDKN2A/B-intact, WHO grade II</td>
</tr>
<tr>
<td>Diffuse astrocytic glioma, IDH-mutant, CDKN2A/B-intact with necrosis, WHO grade III</td>
</tr>
<tr>
<td>Diffuse astrocytic glioma, IDH-mutant, CDKN2A/B-deleted, WHO grade IV</td>
</tr>
</tbody>
</table>
Five outside slides, brain, left frontal lobe, biopsy:

**DIFFUSE ASTROCYTOMA, IDH-MUTANT**

**WHO GRADE II**

Mitotic index (H&E): <1 mitosis / 10 HPF  
Ki67 index (MIB1): 4.1% (maximum); 3.2% (average)

IDH1 protein status (IHC): POSITIVE for IDH1 p.R132H expression in glioma cells  
ATRX protein status (IHC): LOSS in glioma cells  
CDKN2A/B status: Unknown

*(SEE COMMENT)*
H&E-stained sections show a diffuse glioma composed of relatively small cells with round-to-oval nuclei. Occasional gemistocytic cells are seen; cytoplasmic clearing (“perinuclear halos”) are not a prominent feature. Mitotic figures are not readily identified on H&E-stained sections. Similarly, computer-assisted automated quantitation shows a correspondingly low maximum single field Ki67 antigen (MIB1) labeling index of 4.1% (1,648 nuclei counted), with an average index of 3.2% over six hotspot fields quantitated (9,664 total nuclei counted).

Molecular signature determination by surrogate immunophenotyping was performed at a consultant institution, with results shown in the Diagnosis section above.

The morphologic differential diagnosis would include diffuse astrocytoma and oligodendroglioma; however, the reported demonstration of ATRX loss in the glioma cells militates against oligodendroglioma and indicates that this is a diffuse astrocytic neoplasm.

This diffuse astrocytoma is classified as WHO grade II based on the relatively low degree of cell proliferation, which is in accordance with the traditional histologic criteria espoused in the current WHO 2016 Classification. However, traditional concepts and criteria for diffuse astrocytoma classification and grading are being challenged. In the most recent thorough examination of prognostic factors for IDH-mutant diffuse astrocytomas (1), no prognostic significance was found for mitotic indices (H&E, pHH3), and the Ki67 antigen labeling index that was associated with poorer overall survival was relatively high, 14.5% (significantly higher than that of the present glioma). The only traditional histologic grading feature that retained prognostic significance was the presence of necrosis, which warranted a grade III (anaplastic) designation, NOT grade IV as in the traditional WHO grading scheme. Beyond this, the principle determinant of response to therapy is molecular signature (2-4). Specifically, CDKN2A/B deletion status has been identified as a highly significant predictor of overall survival, with CDKN2A/B homozygously-codeleted tumors having a worse prognosis (1).
H&E-stained sections show a diffuse glioma composed of relatively small cells with round-to-oval nuclei. Occasional gemistocytic cells are seen; cytoplasmic clearing (“perinuclear halos”) are not a prominent feature. Mitotic figures are not readily identified on H&E-stained sections. Similarly, computer-assisted automated quantitation shows a correspondingly low maximum single field Ki67 antigen (MIB1) labeling index of 4.1% (1,648 nuclei counted), with an average index of 3.2% over six hotspot fields quantitated (9,664 total nuclei counted).

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H&E-stained sections show a diffuse glioma composed of relatively small cells with round-to-oval nuclei. Occasional gemistocytic cells are seen; cytoplasmic clearing (“perinuclear halos”) are not a prominent feature. Mitotic figures are not readily identified on H&E-stained sections. Similarly, computer-assisted automated quantitation shows a correspondingly low maximum single field Ki67 antigen (MIB1) labeling index of 4.1% (1,648 nuclei counted), with an average index of 3.2% over six hotspot fields quantitated (9,664 total nuclei counted).

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Diffuse astrocytic glioma, IDH-mutant, CDKN2A/B-intact with necrosis, WHO grade III
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**Diffuse astrocytic glioma, IDH-mutant, CDKN2A/B-deleted, WHO grade IV**
The CDKN2A/B status of the present glioma is unknown.

References

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References

ANAPLASTIC ASTROCYTOMA, IDH-MUTANT, CDKN2A/B-INTACT
GEMISTOCYTIC MORPHOLOGIC SUBTYPE
WHO GRADE III

**IDH1** status (NGS): POSITIVE for IDH1 c.394C>G p.R132G
**CDKN2A/B** status (NGS): NEGATIVE for deletion

**EGFR** status (NGS): POSITIVE for c.1562G>A p.R521K
**PDGFRa** status (NGS): POSITIVE for c.1432T>C p.S478P
**MUC17** status (PCR): POSITIVE for c.864C>T p.A2882V
**ATRX** protein status (IHC): LOSS of expression
**p53** protein status (IHC): POSITIVE nuclear staining (strong, diffuse)

(SEE COMMENT)
H&E-stained sections show a diffusely infiltrating composed of classical gemistocytic astrocytoma. Mitotic figures are present. Vascular alterations are present that correlate with and can explain the contrast enhancement seen on the preoperative MR imaging studies performed at the referring institution (available on MDACC Epic). Microscopic foci of necrosis are present. The hypercellularity of the glioma is sufficient to account for the restricted diffusion noted on preoperative imaging.

Preoperative MR imaging studies performed at the referring institution show a 9.0 cm AP x 6.0 cm TR x 7.0 cm CC complex mass with solid and cystic components centered in the left paramedian frontal lobe. A majority of the mass is nonenhancing or minimally enhancing, with an approximately 5.0 cm x 2.1 cm x 2.8 cm enhancing component.

Molecular signature determination studies (next generation sequencing) were performed by the referring institution, with salient results listed in the Diagnosis section above.

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References

Summary
Thank You!

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gfuller@mdanderson.org