Rare Gliomas

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Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

• Classify rare gliomas into broad clinical, histopathological, and molecular categories
• Distinguish the various rare glioma entities from each other
• Summarize the key molecular alterations defining rare glioma subgroups
What I’m NOT going to talk about

- IDH-wildtype GBM of adults
- IDH-mutant astrocytoma
- IDH-mutant and 1p/19q codeleted oligodendrogliaoma
- Glioneuronal and neuronal tumors
- Pilocytic astrocytoma

WHO 2021 Classification
What I AM going to talk about

- Pediatric high-grade diffuse glioma
- Pediatric low-grade diffuse glioma
- "Circumscribed astrocytic gliomas"

WHO 2021 Classification
CASE PRESENTATION: 4 year-old male with a history of intractable seizures and a left sided, non contrast-enhancing temporal lobe mass

FGFR2-CTNNA3 fusion on molecular testing

CD34
Infratentorial IDH-mutant astrocytoma is a distinct subtype

Rouzbeh Banan1, Damian Stichel2, Anja Bleck1, Bujung Hong1, Ulrich Lehmann1, Abigail Suwala1, Annekathrin Reinhardt2,3, Daniel Schirripa2,3, Rolf Buslei6, Christine Stadelmann7, Karoline Ehler1, Marco Prinz9, Till Acker1, Jens Schittenhelm11, David Kaul12, Leonille Schweizer1,3,4, David Capper13,14, Patrick N. Harte13,14,17,18, Nima Etminan19, David T. W. Jones20,21,23,22, Stefan M. Pfister20,21,23,24, Chirstel Herold-Mende24, Wolfgang Wick20,26, Felix Sahm2,3, Andreas von Deimling2,5,20, Christian Hartmann1, David E. Reuss5,20.
Infratentorial IDH-mutant astrocytoma

Banan R, et al., Acta Neuropath, 2020
Core Histone Protein Mutations define Pediatric High-Grade Diffuse Gliomas

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

Jeremy Schwartzentruber1*, Andrey Korshunov2*, Xiao-Yang Liu3a, David T. W. Jones4, Elke Pfaff4, Karine Jacob5, ng6, Martje Tönjes5, Volker Hovestadt6, Steffen Albrecht6, nth8, Natalie Jäger9, Tobias Rausch10, Marina Ryzhova11, nil13, Almos Klekner14, Laszlo Bognar14, Martin Ebinger15, Michael C. Frühwald19, Wolfgang Roggendorf20, 3 Lepage1, Alexandre Montpetit1, Magdalena Zakrajšek12, Siegel16, Andreas E. Kulozik27, Marc Zapatka5, Abhijit Guha28, on Deimling2,31, Koichi Ichimura32, V. Peter Collins32, tro Castelo-Branco28, Peter Lichter*, Damien Faury3, or4,27 & Nada Jabado13,34

Nature, 2012

Nat Genet, 2012
Core Histone Protein Mutations define Pediatric High-Grade Diffuse Gliomas

Diffuse hemispheric glioma, H3 G34-mutant

Diffuse midline glioma, H3 K27-altered

Diffuse midline glioma, H3K27-altered, CNS WHO grade 4

Can arise anywhere from the basal forebrain structures to the spinal cord
Diffuse midline glioma, H3K27-altered, CNS WHO grade 4

Germline ACVR1 mutations cause Fibrodysplasia Ossificans Progressiva (FOP)

H3 K27M mutation impairs H3K27me3 genome-wide

Diffuse midline glioma, H3 K27-altered, CNS WHO grade 4

K27I mutations have the same effect!

Presence of H3K27M or lack of H3K27me3 can be assessed immunohistochemically

Do not confuse H3K27M with H3K27me3!!!

Similarly named biomarkers with diametrically opposing readouts.

Posterior fossa type A (PFA) ependymomomas also show loss of H3K27me3

Panwalkar P, et al., Acta Neuropath 2017
EZHIP overexpression mimics H3K27M mutation and is seen in both PFA ependymoma and DMG!!

**Diffuse midline glioma, H3 K27-Altered, CNS WHO grade 4**

H3 K27M mutation
H3 K27I mutation
EZHIP overexpression

Jain SU, et al., Nature Commun, 2019
Diffuse hemispheric glioma, H3 G34-mutant, CNS WHO grade 4
G34R/V mutant gliomas derive from distinct (neuronal) cells of origin and may modulate PDGFRA through abnormal epigenetic contacts

Histone H3.3G34-Mutant Interneuron Progenitors Co-opt PDGFRA for Gliomagenesis

Authors
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In Brief
Lethal pediatric glioma arises from misregulation of interneuron differentiation.

Regional identity of human neural stem cells determines oncogenic responses to histone H3.3 mutants

Raul Bardini Bressan,1,4 Benjamin Southgate,1,5 Kirsty M. Ferguson,1,6 Carla Blin,1 Vivien Grant,1 Neza Altazema,1,2 Jini C. Wills,7 Maria Angeles Marques-Torrejon,1 Gillian M. Morrison,1,7 James Ashmore,1 Faye Robertson,1,2 Charles A.C. Williams,8 Leanne Bradley,1,9 Alex von Kriegsheim,9 Richard A. Anderson,8 Simon R. Tomlinson,1,4 and Steven M. Pollard1,2,9,10

Cell Stem Cell, 2021

Diffuse hemispheric glioma, H3 G34-mutant, CNS WHO grade 4

Cell, 2020
G34R/V mutant gliomas derive from distinct (neuronal) cells of origin and may modulate PDGFRA through abnormal epigenetic contacts

Chen CCL, et al., Cell, 2020

Bressan RB, et al., Cancer Cell, 2021
Diffuse pediatric-type HGG, H3-wildtype and IDH-wildtype, CNS WHO Grade 4

Mackay A, et al., Cancer Cell, 2017
Biphasic growth pattern of pediatric HGG, MYCN-subtype
Infant-type hemispheric glioma

Clarke M, et al., Cancer Discovery, 2020
Pediatric-type diffuse low-grade glioma

- Variable histopathology (astrocytic, oligodendroglial, angiocentric)
- Overlapping palettes of molecular alterations, generally mobilizing MAP kinase signaling
- Extended survival of patients contrasts sharply with diffuse gliomas of adults
- Classification is very much a work in progress and limited by the rarity of the tumors in question
Pediatric-type diffuse low-grade glioma

Recurrent involvement of a relatively narrow group of molecular alterations across histopath patterns

- FGFR1 duplications
- FGFR1 point mutations
- FGFR1 fusions
- FGFR2 abnormalities
- BRAF V600E mutations
- MYB and MYBL1 alterations

Frequent mobilization of MAP Kinase signaling


Pediatric-type diffuse low-grade glioma

Cancer Cell
Integrated Molecular and Clinical Analysis of 1,000 Pediatric Low-Grade Gliomas

Authors
Scott Ryall, Michal Zapotocky, Kohei Fukuoka, ..., David W. Ellison, Uri Tabori, Cynthia Hawkins
DNA methylation profiling is driving brain tumor discovery and classification.
Angiocentric glioma, CNS
WHO grade 1

Supratentorial localization
Patients with intractable seizures
Unique DNA methylation signature
Angiocentric glioma, CNS WHO grade 1

MYB-QKI rearrangements in angiocentric glioma drive tumorigenicity through a tripartite mechanism

Nat Genet, 2015
Diffuse astrocytoma, MYB- or MYBL1-altered, CNS WHO grade 1

Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of MYBL1 or MYB and a benign disease course

Supratentorial localization
Patients with intractable seizures
Unique DNA methylation signature
Diffuse astrocytoma, MYB- or MYBL1-altered, CNS WHO grade 1

Wefers AK, Acta Neuropath, 2019
Polymorphous low-grade neuroepithelial tumor of the young (PLNTY), CNS WHO grade 1

Supratentorial localization
Patients with intractable seizures
Unique DNA methylation signature
Polymorphous low-grade neuroepithelial tumor of the young (PLNTY), CNS WHO grade 1

OLIG2

CD34

BRAF V600E
Diffuse low-grade glioma, MAPK pathway-altered

Broader localization pattern throughout the neuraxis
No unifying DNA methylation cluster
Common, but not invariable association with epilepsy
Diffuse low-grade glioma, MAPK pathway-altered

- IDH and H3 wildtype and no CDKN2A loss
- Indolent behavior is the rule, but no formal WHO grading as of yet, likely due to heterogeneity of this subclass


Circumscribed Astrocytic Gliomas (WHO 2021)

- Pilocytic astrocytoma
- High-grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma (PXA)
- Subependymal giant cell astrocytoma
- Chordoid glioma
- Astroblastoma, MN1-altered
Circumscribed Astrocytic Gliomas (WHO 2021)

• Pilocytic astrocytoma
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• Subependymal giant cell astrocytoma
• Chordoid glioma
• Astroblastoma, MN1-altered
Chordoid glioma, CNS WHO grade 2

Arise with symptoms of obstructive hydrocephalus and/or compression of hypothalamus/optic chiasm
Thought to arise from specialized tanycytic ependymal cells of the organum vasculosum of the lamina terminalis
Chordoid glioma, CNS WHO grade 2

A recurrent kinase domain mutation in PRKCA defines chordoid glioma of the third ventricle

Benjamin Goode¹, Gourish Mondal¹, Michael Hyun¹, Diego Garrido Ruiz², Yu-Hsiu Lin², Jessica Van Ziffle¹,², Nancy M. Joseph¹,⁴, Courtney Onodera⁴, Eric Talevich⁴, James P. Grenert¹,⁴, Iman H. Hewedi⁵, Matija Snuderl⁵, Daniel J. Brat⁶, Bette K. Kleinschmidt-DeMasters⁸, Fausto J. Rodriguez⁹, David N. Louis¹⁰, William H. Yong¹¹, M. Beatriz Lopes¹², Marc K. Rosenblum¹³, Nicholas Butowsky¹⁴, Tarik Tihan¹, Andrew W. Bollen¹, Joanna J. Phillips¹,⁴, Arun P. Willatt²,³, Iwei Yeh¹⁴, Matthew P. Jacobson⁷, Boris C. Bastian¹,⁴, Arie Perry¹,⁴ & David A. Solomon¹,⁴

Nat Commun, 2018
Astroblastoma, MN-1 altered

- Architectural pattern extends across diagnostic entities
- Variable presence of high-grade features
- Female predominance
- Most are supratentorial
Identification as a unique constituent within supratentorial PNET

New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs

MN1 alterations define a clinically distinct tumor subgroup with astroblastomatous histopathology

**Multimodal molecular analysis of astroblastoma enables reclassification of most cases into more specific molecular entities**

Matthew D. Wood 1; Tarik Tihan 1; Arie Perry 2,3; Geeta Chacko 2; Clinton Turner 4; Cunfeng Pu 5; Christopher Payne 5; Alexander Yu 5; Serguei I. Bannykh 1; David A. Solomon 1

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5 Department of Pathology, Stanford University, Stanford, CA.  

**Brain Pathol, 2018**

<table>
<thead>
<tr>
<th>Case</th>
<th>Category</th>
<th>UCSF 500 pathogenic alterations</th>
<th>MN1 FISH</th>
<th>DNA methylation profiling</th>
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<tr>
<td>1</td>
<td>MN1 breakpoint</td>
<td>CDKN2A/B deep deletion, TERT promoter mutation</td>
<td>Breakapart</td>
<td>Unclassifiable</td>
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<td>2</td>
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<td>TP53, PTEN mutations, numerous chromosome losses</td>
<td>Intact, monosomy 22q</td>
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<td>CNS-HGNET-MM1</td>
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<td>CNS-HGNET-MM1</td>
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<tr>
<td>5</td>
<td>High-grade astrocytoma</td>
<td>None identified</td>
<td>Intact</td>
<td>Unclassifiable</td>
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<tr>
<td>6</td>
<td>Unclassifiable</td>
<td>TP53 mutation, numerous chromosome losses</td>
<td>Intact, polysomy 22q</td>
<td>Unclassifiable</td>
</tr>
<tr>
<td>7</td>
<td>High-grade astrocytoma</td>
<td>BRAF p.V600E, CDKN2A/B deep deletion, TERT promoter mutation</td>
<td>Intact, monosomy 22q</td>
<td>Anaplastic PXA</td>
</tr>
<tr>
<td>8</td>
<td>MN1 breakpoint</td>
<td>ATM mutation, NF2 structural rearrangement</td>
<td>Breakapart</td>
<td>CNS-HGNET-MM1</td>
</tr>
</tbody>
</table>
High-grade astrocytoma with piloid features

Predilection for posterior fossa, but can arise across the CNS
Median age of 40 (older than standard pilocytic astrocytomas)
Most arise de novo
High-grade astrocytoma with piloid features

Anaplastic astrocytoma with piloid features, a novel molecular class of IDH wildtype glioma with recurrent MAPK pathway, CDKN2A/B and ATRX alterations

Acta Neuropath, 2018

[Graph and data analysis related to astrocytoma genetics and survival]
Summary

• IDH mutant astrocytomas can arise infratentorially
• Pediatric-type high-grade gliomas are defined by epigenetic abnormalities
• Pediatric-type low-grade gliomas feature MAP kinase pathway activation
• Pediatric-type low-grade glioma subclasses have emerged with the aid of integrated molecular profiling (including global DNA methylation analysis)
• Discrete molecular alterations characterize subsets of circumscribed astrocytic gliomas
• Unique DNA methylation signature defines HGAP
4 year-old male with a history of intractable seizures and a left sided, non contrast-enhancing temporal lobe mass

FGFR2-CTNNA3 fusion on molecular testing

PLNTY
THANKS!!

- Greg Fuller
- Leo Ballester