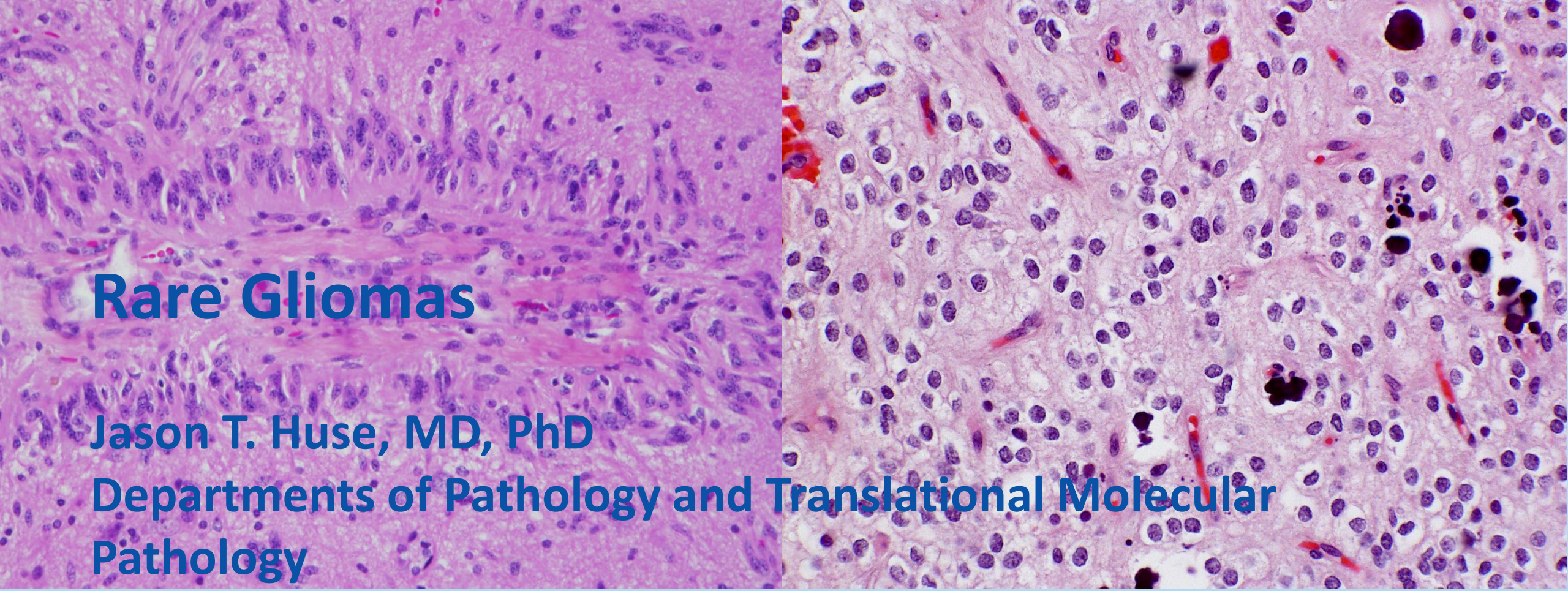


Rare Gliomas

Jason T. Huse, MD, PhD
Departments of Pathology and Translational Molecular Pathology
University of Texas MD Anderson Cancer Center

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

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 oligodendroglioma
- Glioneuronal and neuronal tumors
- Pilocytic astrocytoma

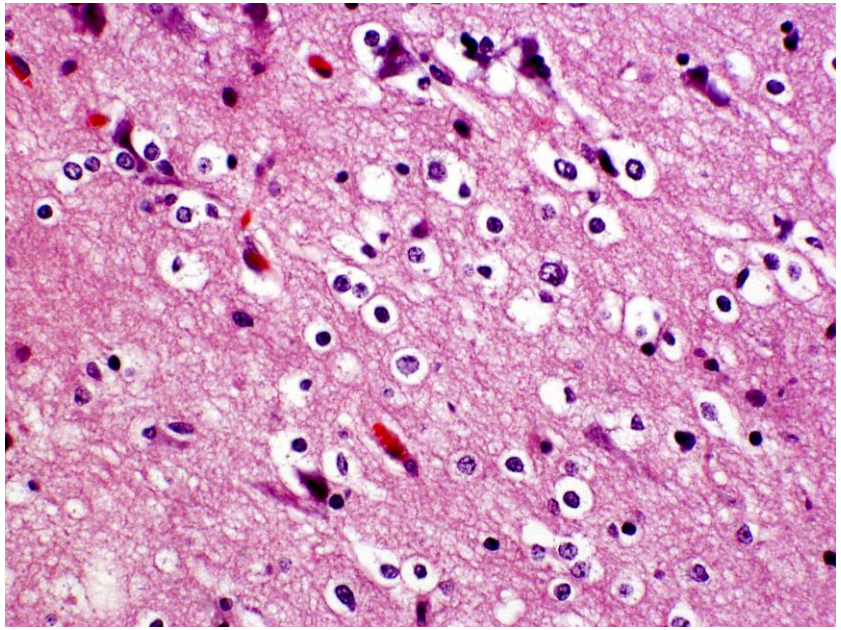
WHO 2021 Classification

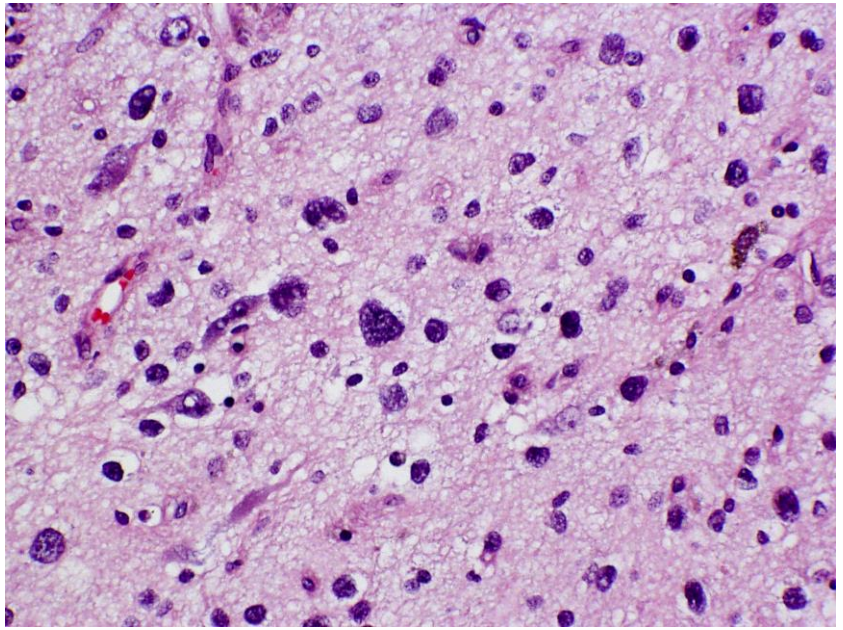
What I AM going to talk about

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

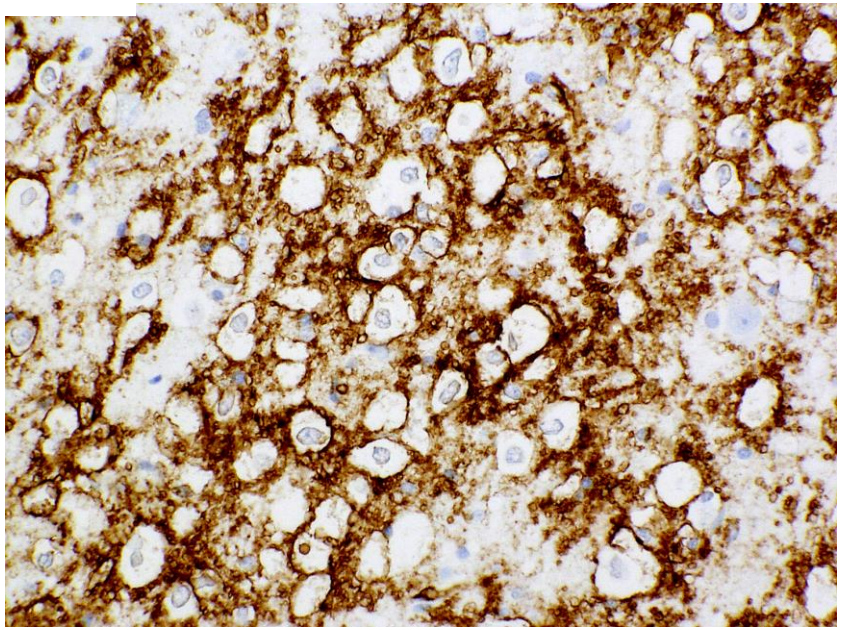
WHO 2021 Classification

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





CD34



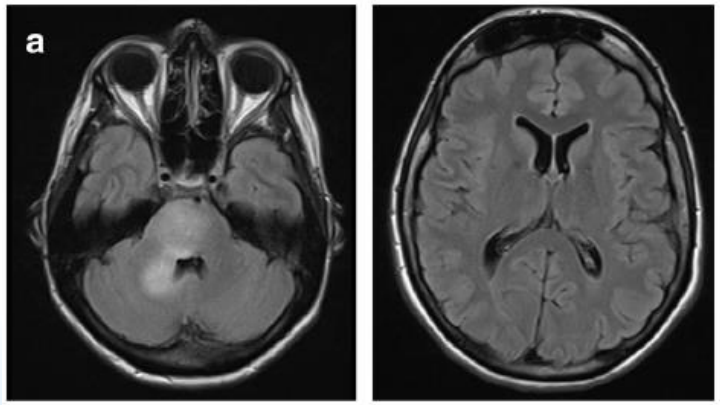
FGFR2-CTNNA3 fusion on molecular testing

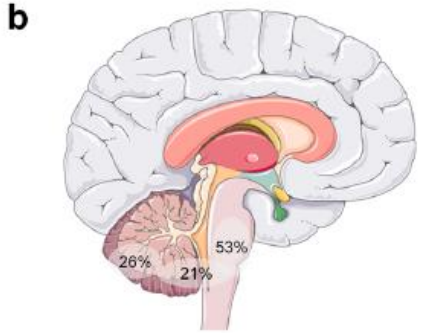
Infratentorial IDH-mutant astrocytoma

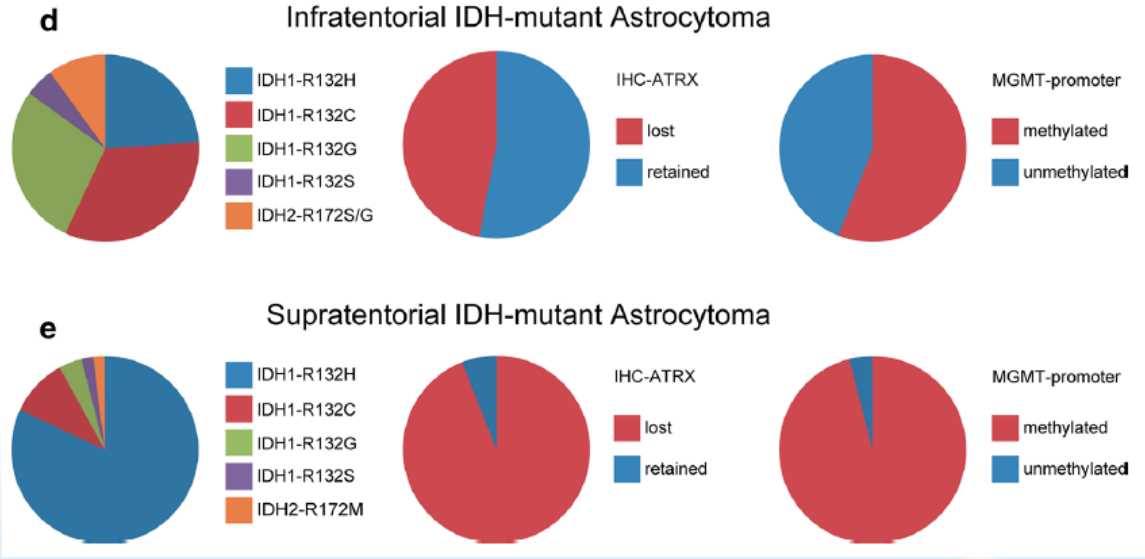
Infratentorial IDH-mutant astrocytoma is a distinct subtype

Acta Neuropath, 2020

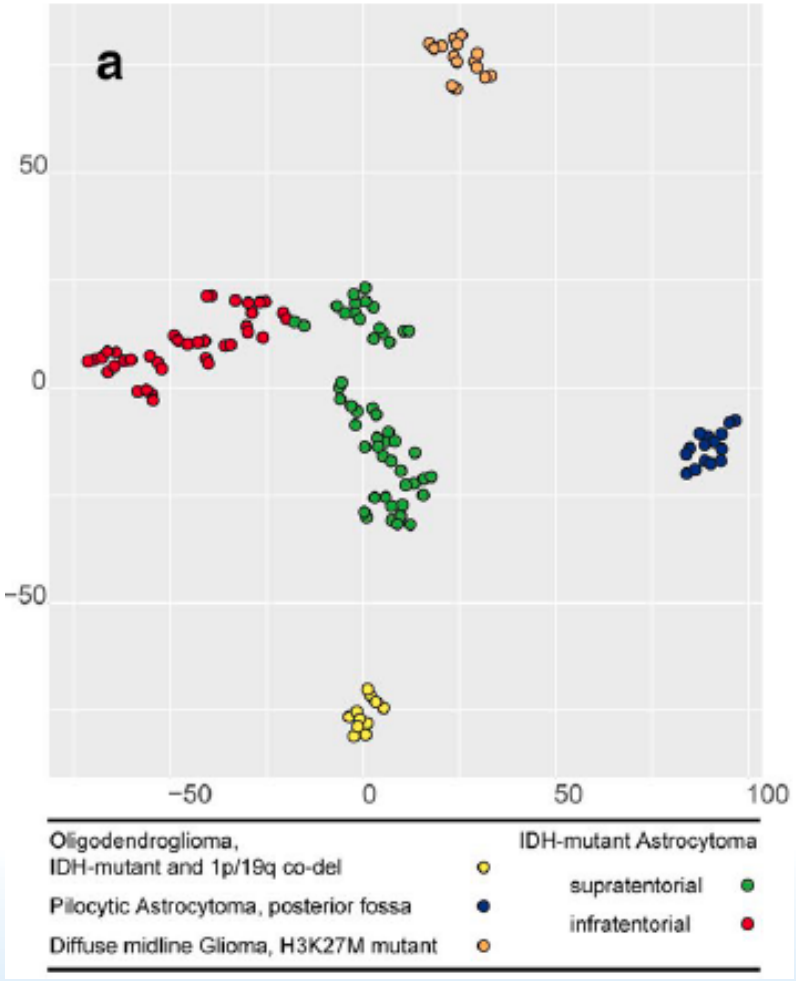
Rouzbeh Banan[1] · Damian Stichel[2] · Anja Bleck[1] · Bujung Hong[3] · Ulrich Lehmann[4] · Abigail Suwala[2,5] · Annekathrin Reinhardt[2,5] · Daniel Schrimpf[2,5] · Rolf Buslei[6] · Christine Stadelmann[7] · Karoline Ehlert[8] · Marco Prinz[9] · Till Acker[10] · Jens Schittenhelm[11] · David Kaul[12] · Leonille Schweizer[13,14] · David Capper[13,14] · Patrick N. Harter[15,16,17,18] · Nima Etminan[19] · David T. W. Jones[20,21,22] · Stefan M. Pfister[20,21,23,24] · Christel Herold-Mende[25] · Wolfgang Wick[20,26] · Felix Sahm[2,5] · Andreas von Deimling[2,5,20] · Christian Hartmann[1] · David E. Reuss[2,5]

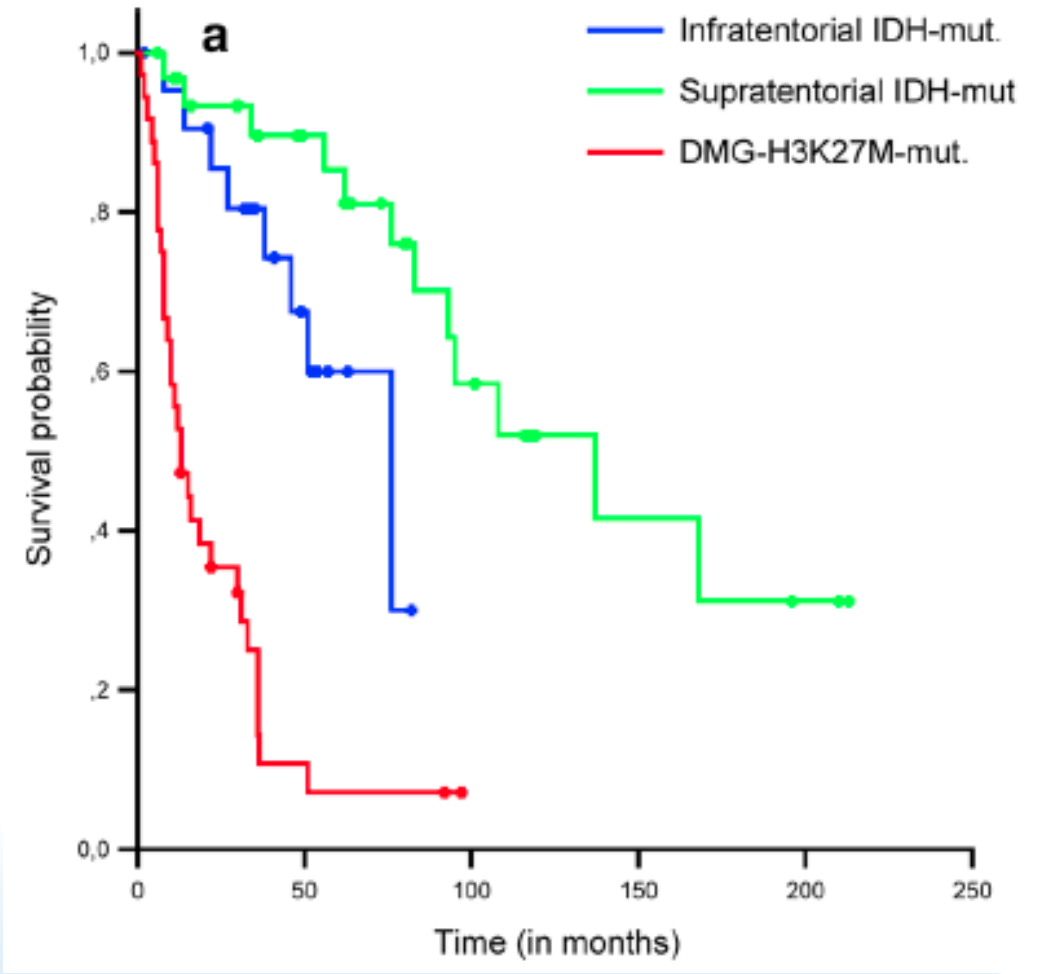






Infratentorial IDH-mutant astrocytoma





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 Schwartzentruber[1*], Andrey Korshunov[2*], Xiao-Yang Liu[3*], David T. W. Jones[4], Elke Pfaff[4], Karine Jacob[3], ...[3], Martje Tönjes[5], Volker Hovestadt[5], Steffen Albrecht[6], ...th[8], Natalie Jäger[9], Tobias Rausch[10], Marina Ryzhova[11], ...ni[13], Almos Klekner[14], Laszlo Bognar[14], Martin Ebinger[15], ...lichael C. Frühwald[19], Wolfgang Roggendorf[20], ...e Lepage[1], Alexandre Montpetit[1], Magdalena Zakrzewska[24], ... Siegel[26], Andreas E. Kulozik[27], Marc Zapatka[5], Abhijit Guha[28], ...on Deimling[2,31], Koichi Ichimura[32], V. Peter Collins[32], ...lro Castelo-Branco[28], Peter Lichter[5], Damien Faury[3], ...er[4,27] & Nada Jabado[3,34]

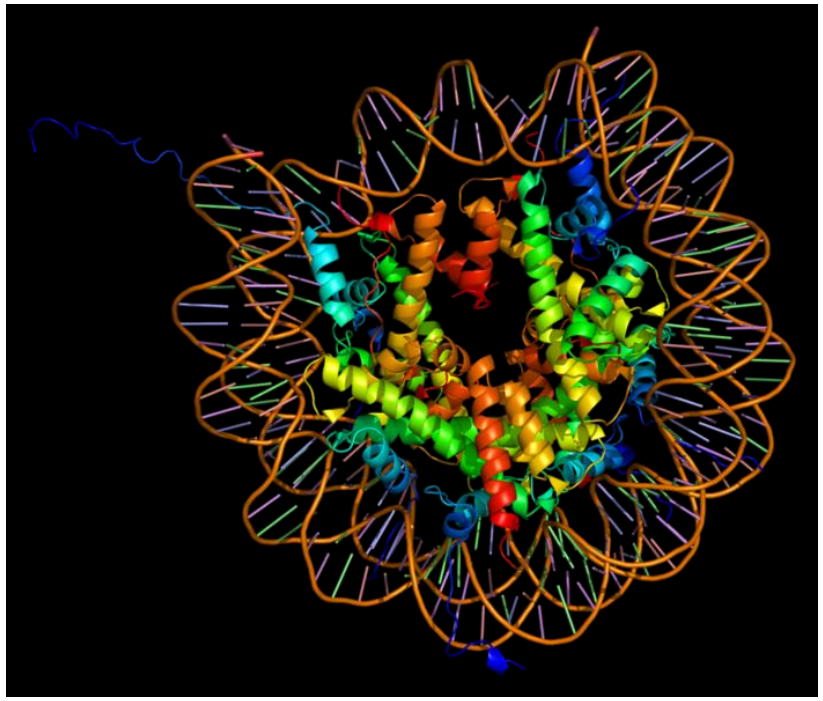
Nature, 2012

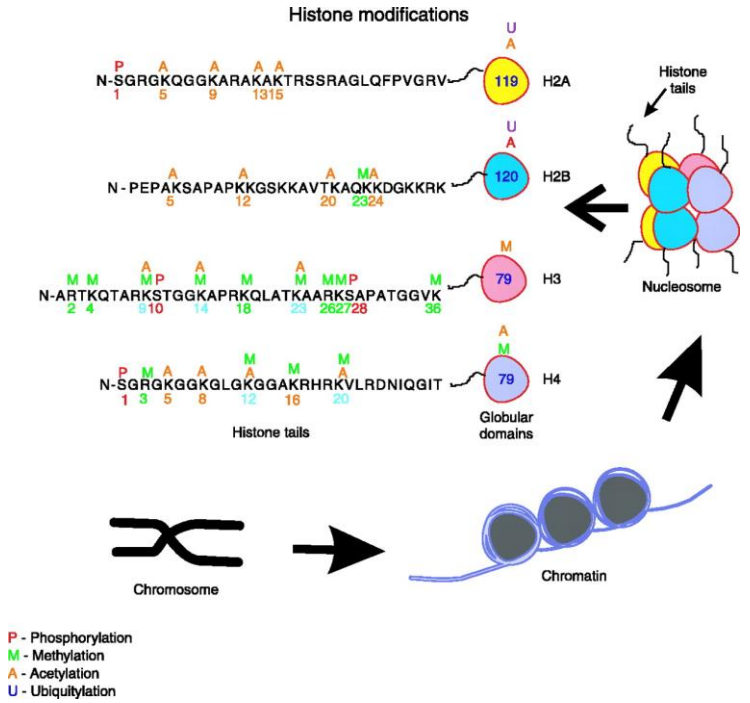
Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas

Gang Wu[1,8], Alberto Broniscer[2,8], Troy A McEachron[3,8], Charles Lu[4], Barbara S Paugh[3], Jared Becksfort[5], Chunxu Qu[5], Li Ding[4], Robert Huether[1], Matthew Parker[1], Junyuan Zhang[3], Amar Gajjar[2], Michael A Dyer[3], Charles G Mullighan[6], Richard J Gilbertson[3], Elaine R Mardis[4], Richard K Wilson[4], James R Downing[6], David W Ellison[6], Jinghui Zhang[1] & Suzanne J Baker[3] for the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project[7]

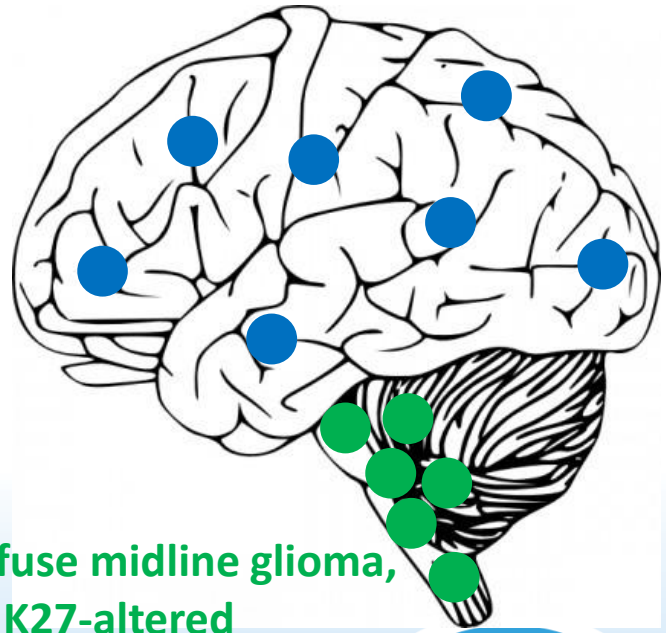
Nat Genet, 2012

Core Histone Protein Mutations define Pediatric High-Grade Diffuse Gliomas

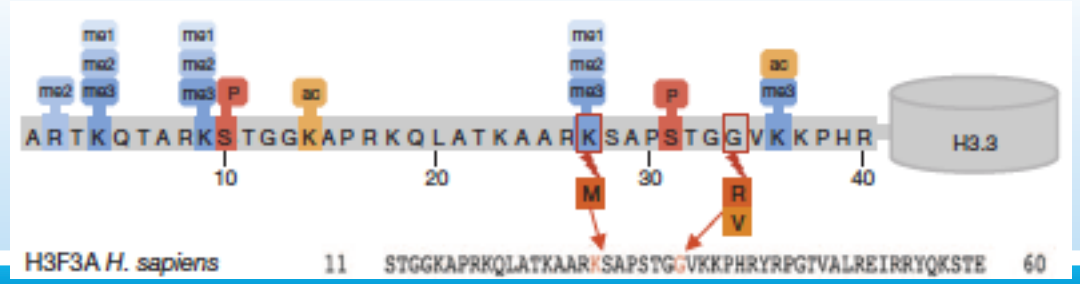




Diffuse hemispheric glioma, H3 G34-mutant

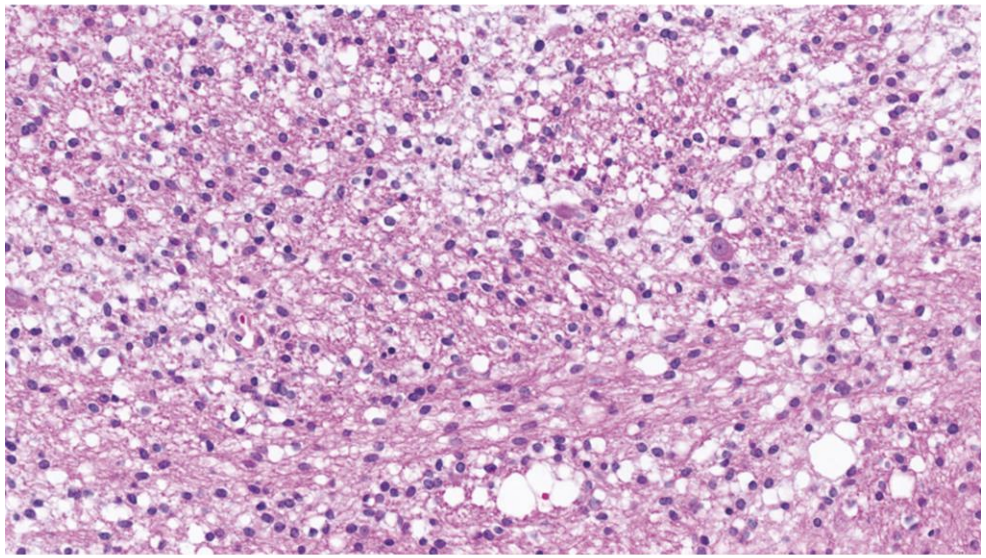


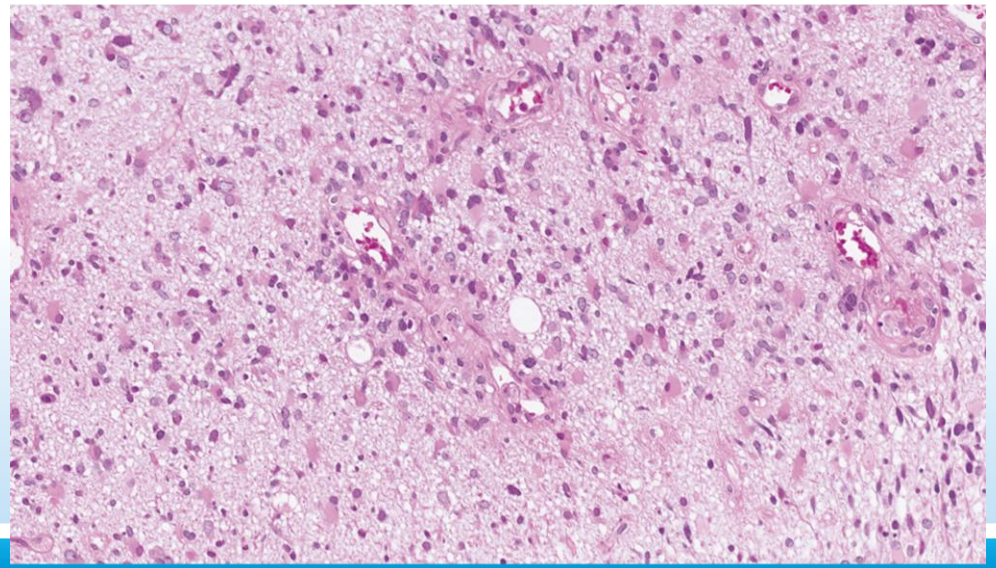
Diffuse midline glioma, H3 K27-altered



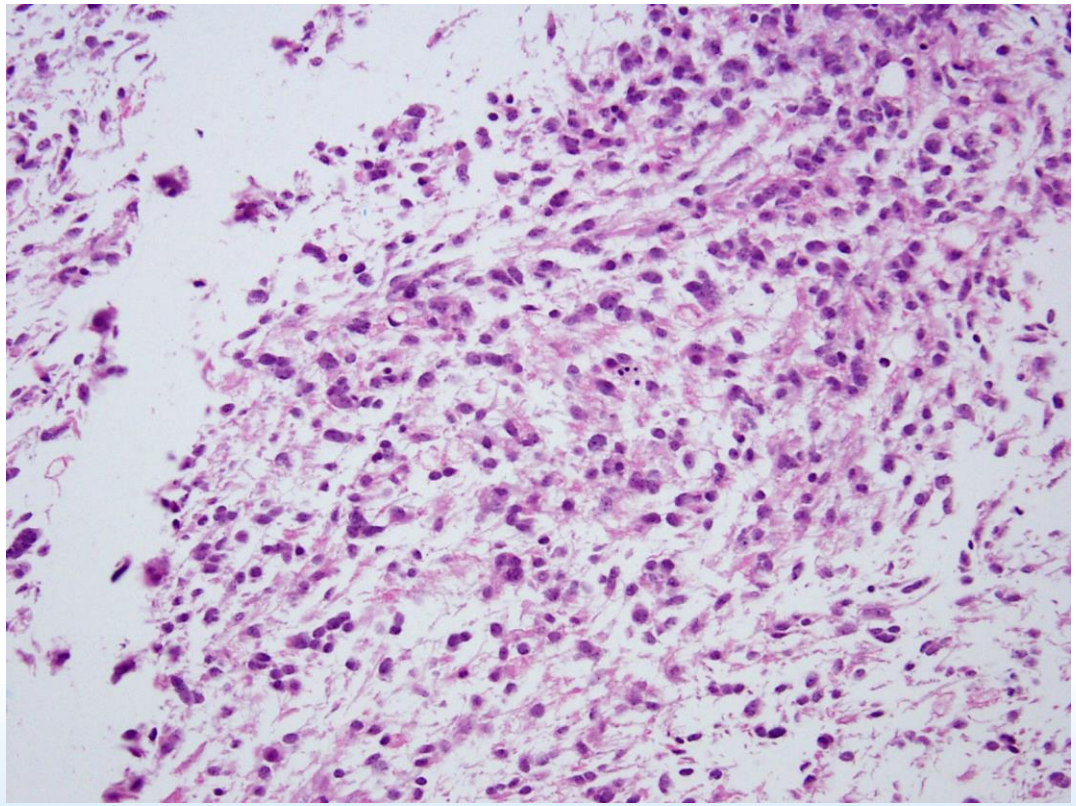
Schwartzentruber, J et. al., Nature, 2012

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

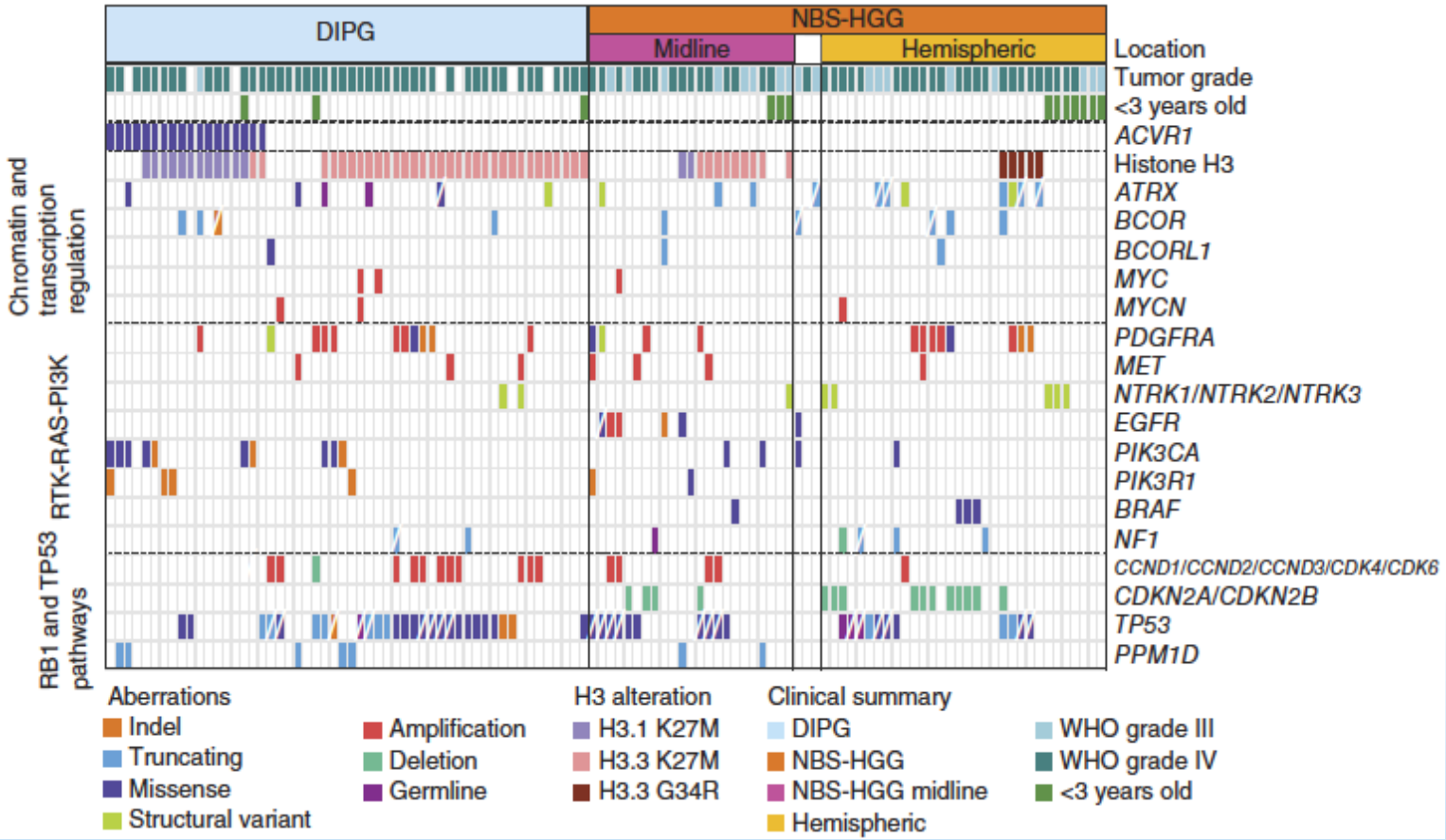




Can arise anywhere from the basal forebrain structures to the spinal cord



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

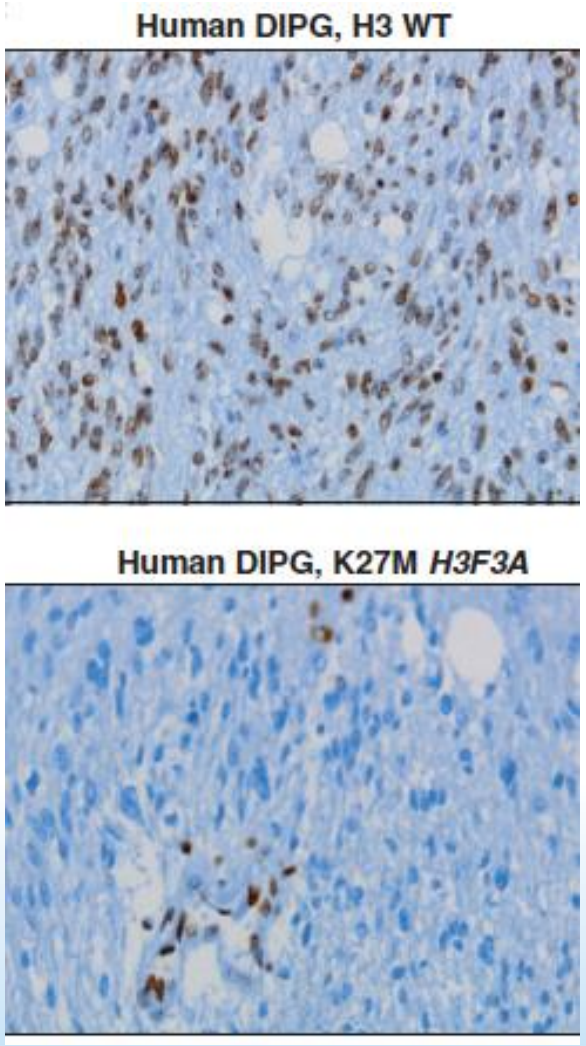


Germline ACVR1 mutations cause Fibrodysplasia Ossificans Progressiva (FOP)

Wu G, et al., Nat Genet, 2014

H3 K27M mutation impairs H3K27me3 genome-wide

Lewis P, et al., Science, 2013



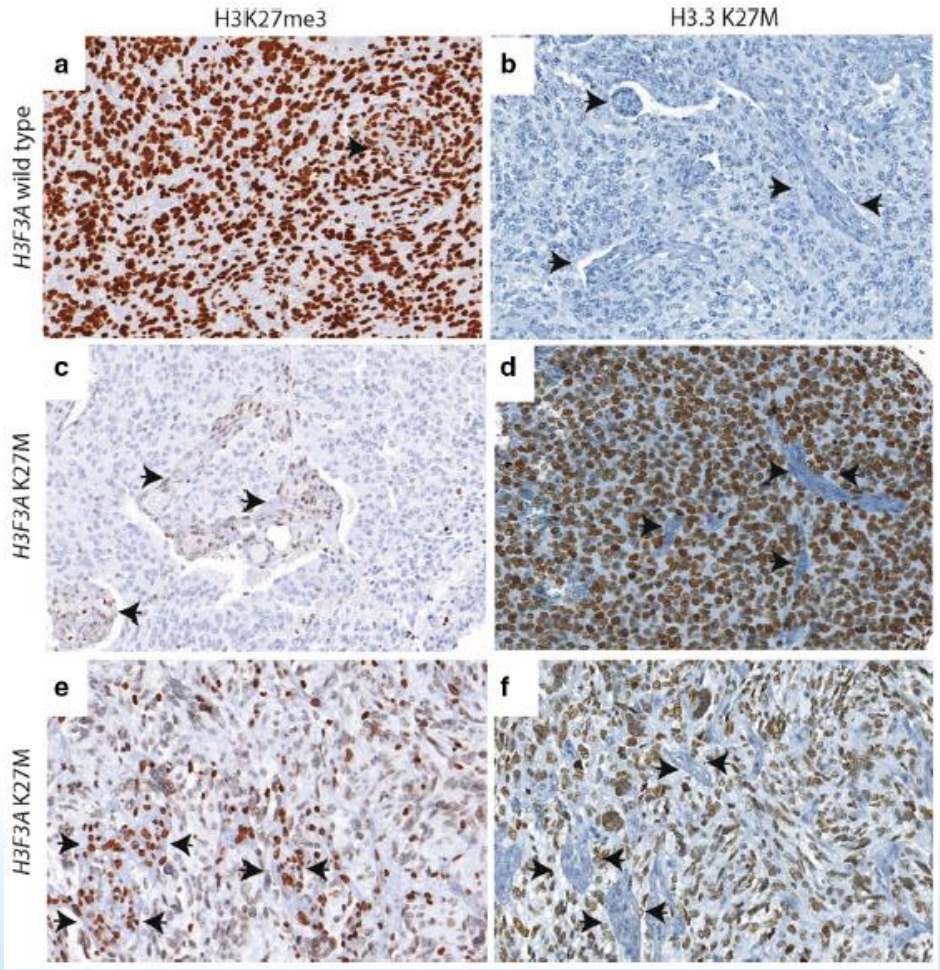
Diffuse midline glioma,
H3 K27-altered,
CNS WHO grade 4

K27I mutations have the same effect!

Presence of H3K27M or lack of H3K27me3 can be assessed immunohistochemically

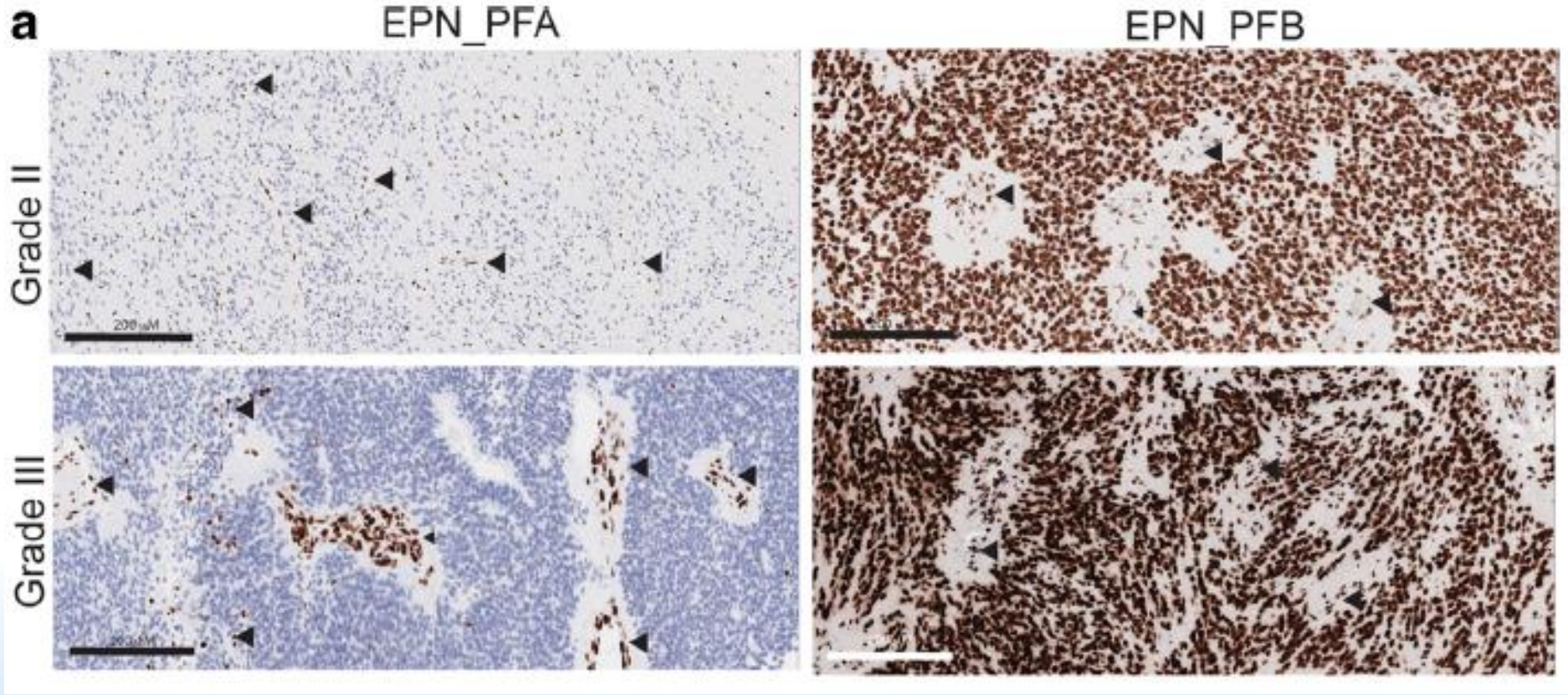
Do not confuse H3K27M with H3K27me3!!!

Similarly named biomarkers with diametrically opposing readouts.



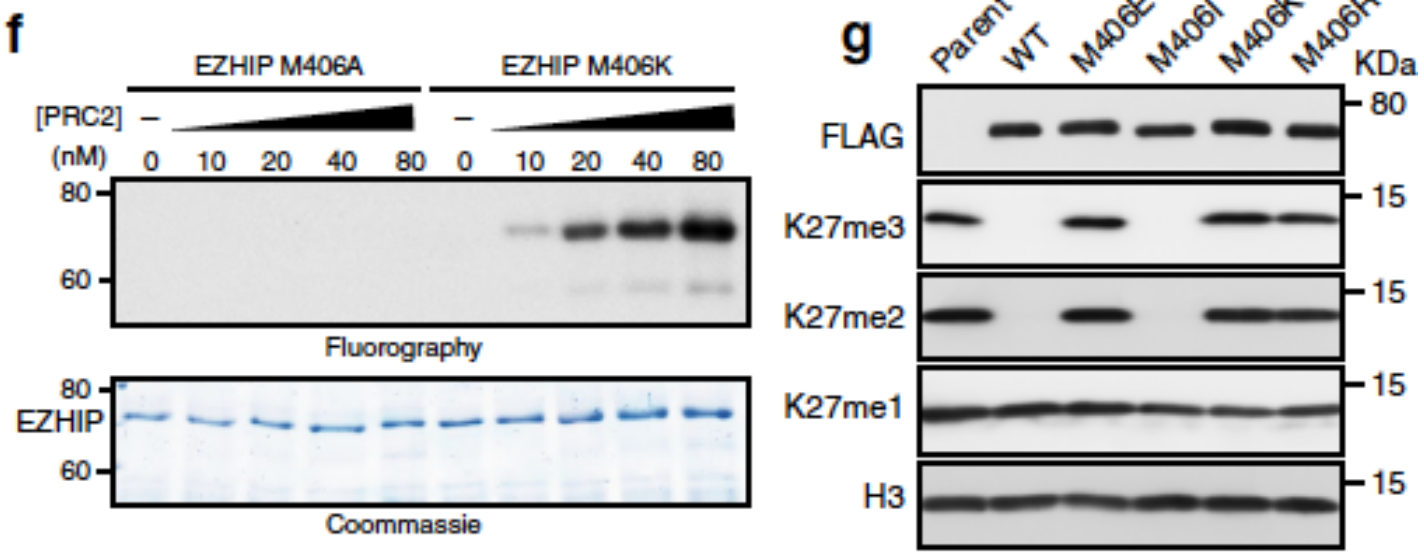
Venneti S, et al., Acta Neuropath, 2014

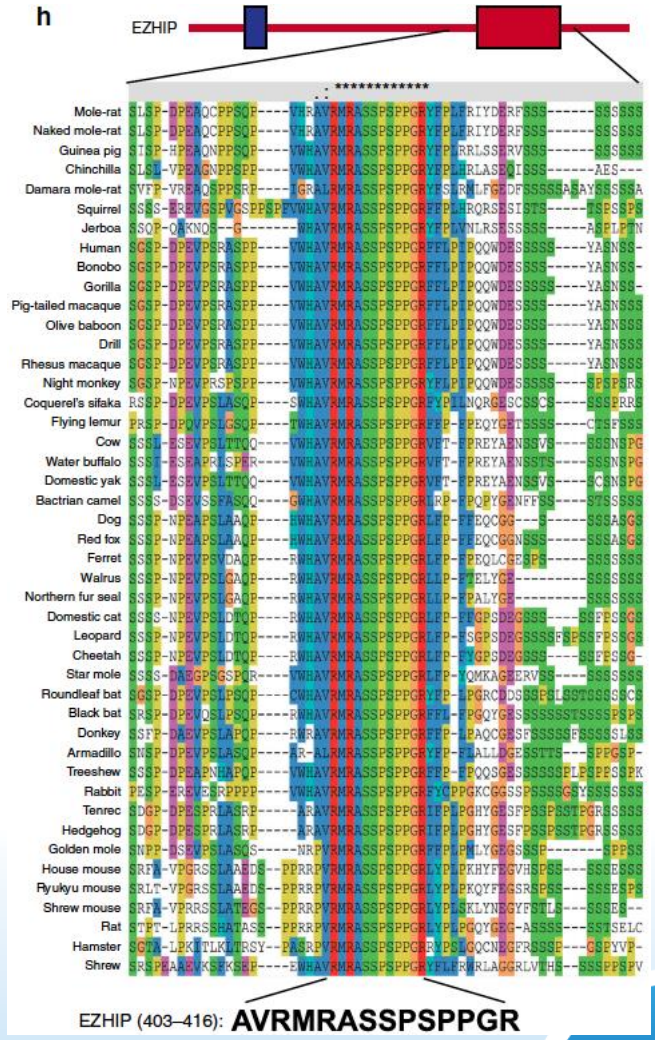
Posterior fossa type A (PFA) ependymomas also show loss of H3K27me3



Panwalkar P, et al., Acta Neuropath 2017

EZHIP overexpression mimics H3K27M mutation and is seen in both PFA ependymoma and DMG!!



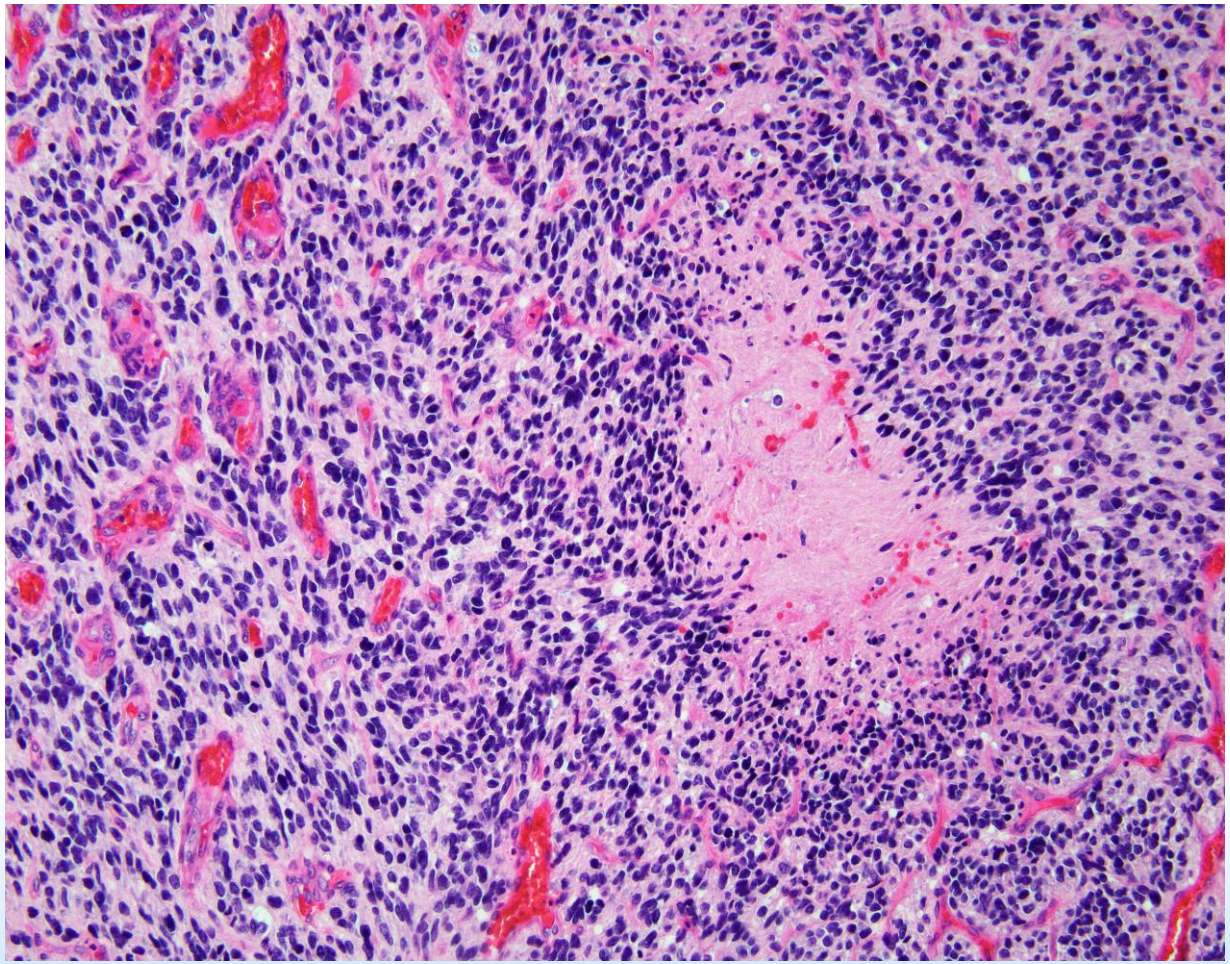


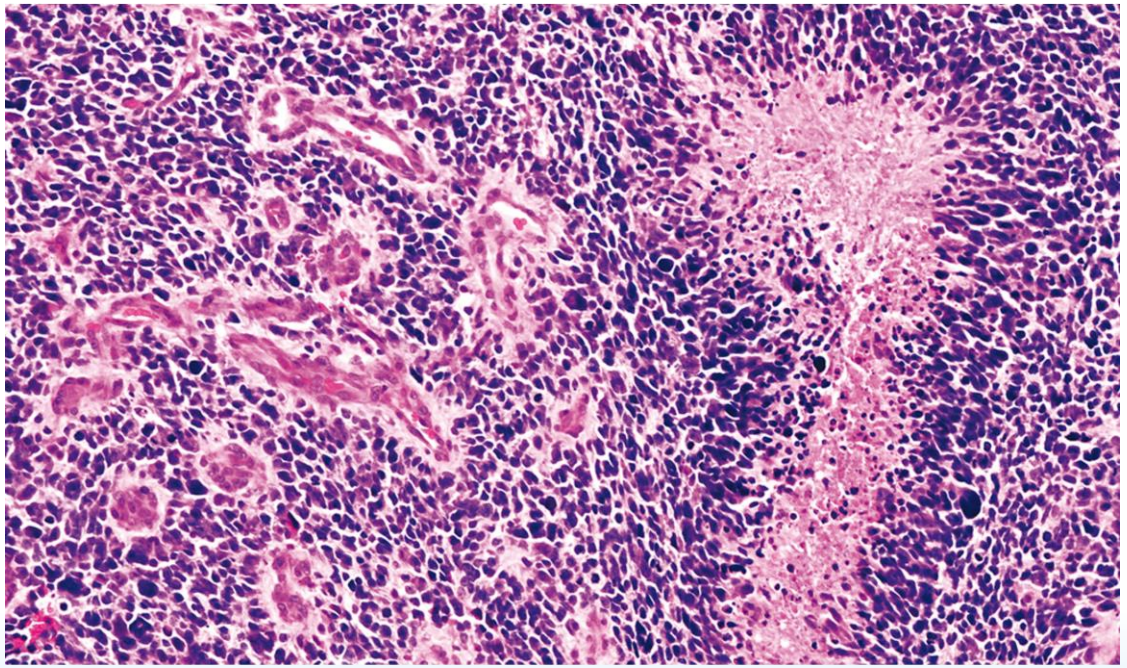
Diffuse midline glioma, H3 K27-Altered, CNS WHO grade 4

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

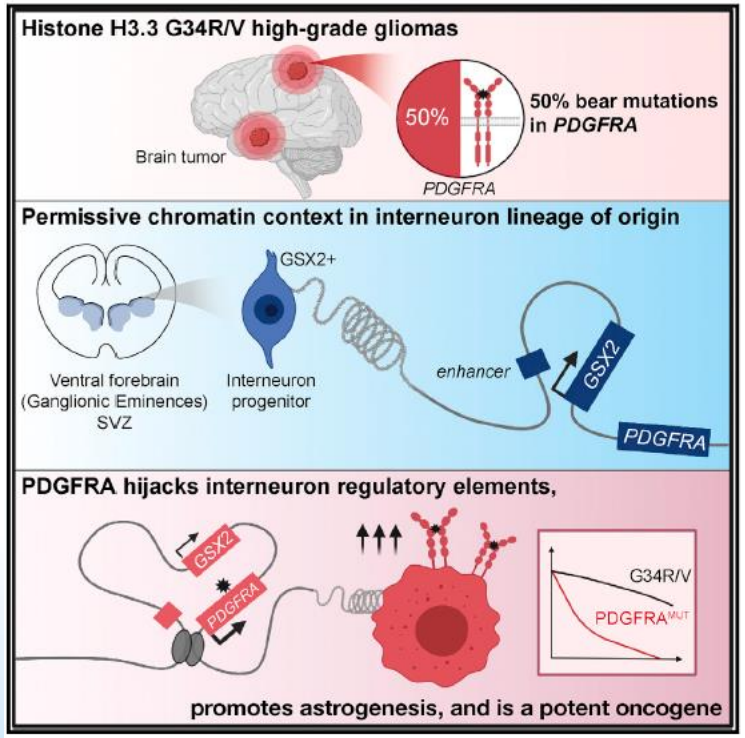




G34R/V mutant gliomas derive from distinct (neuronal) cells of origin and may modulate PDGFRA through abnormal epigenetic contacts

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

Graphical Abstract



Authors

Carol C.L. Chen, Shriya Deshmukh, Selin Jessa, ..., Paolo Salomoni, Claudia L. Kleinman, Nada Jabado

Correspondence

claudia.kleinman@mcgill.ca (C.L.K.), nada.jabado@mcgill.ca (N.J.)

In Brief

Lethal pediatric glioma arises from misregulation of interneuron differentiation.

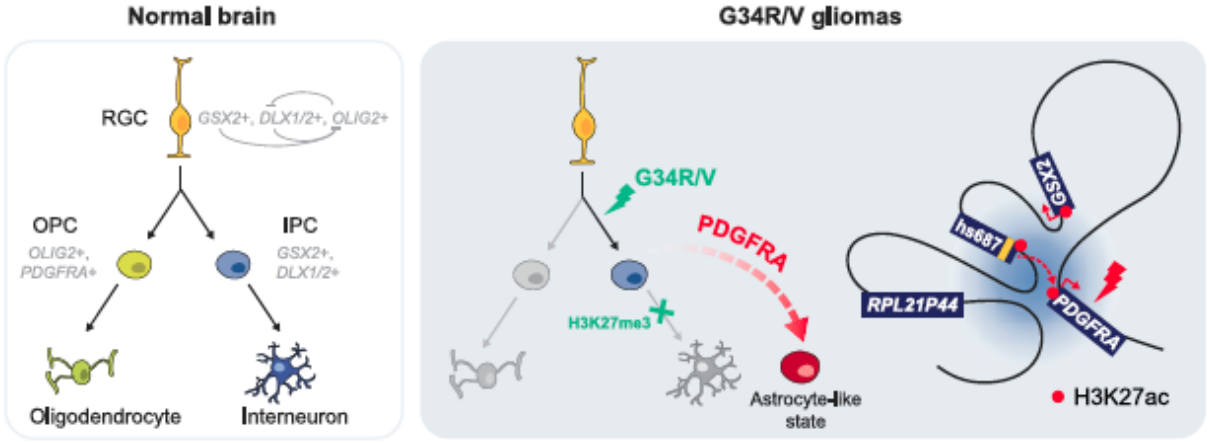
Cell, 2020

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

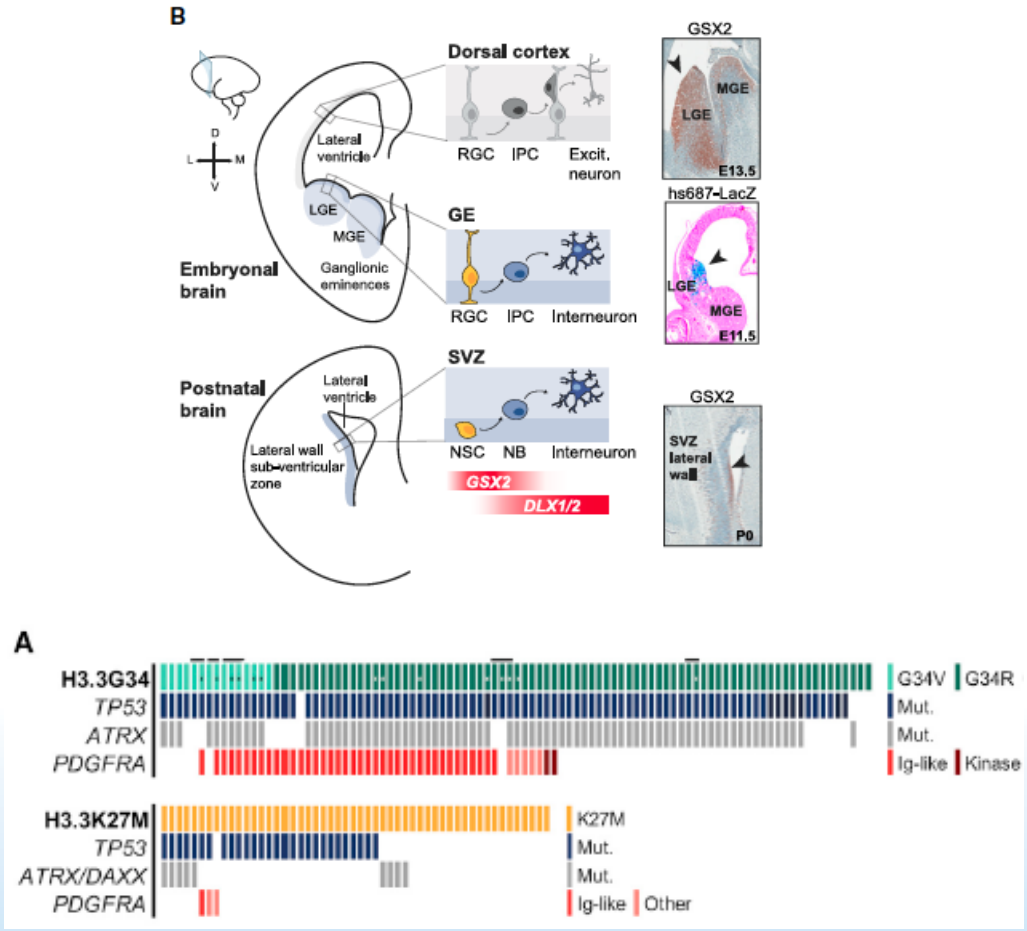
Raul Bardini Bressan,[1,4] Benjamin Southgate,[1,2] Kirsty M. Ferguson,[1,2] Carla Blin,[1] Vivien Grant,[1] Neza Alfazema,[1,2] Jimi C. Wills,[2] Maria Angeles Marques-Torrejon,[1] Gillian M. Morrison,[1,2] James Ashmore,[1] Faye Robertson,[1,2] Charles A.C. Williams,[1,2] Leanne Bradley,[1,2] Alex von Kriegsheim,[2] Richard A. Anderson,[3] Simon R. Tomlinson,[1,5] and Steven M. Pollard[1,2,6,*]

Cell Stem Cell, 2021

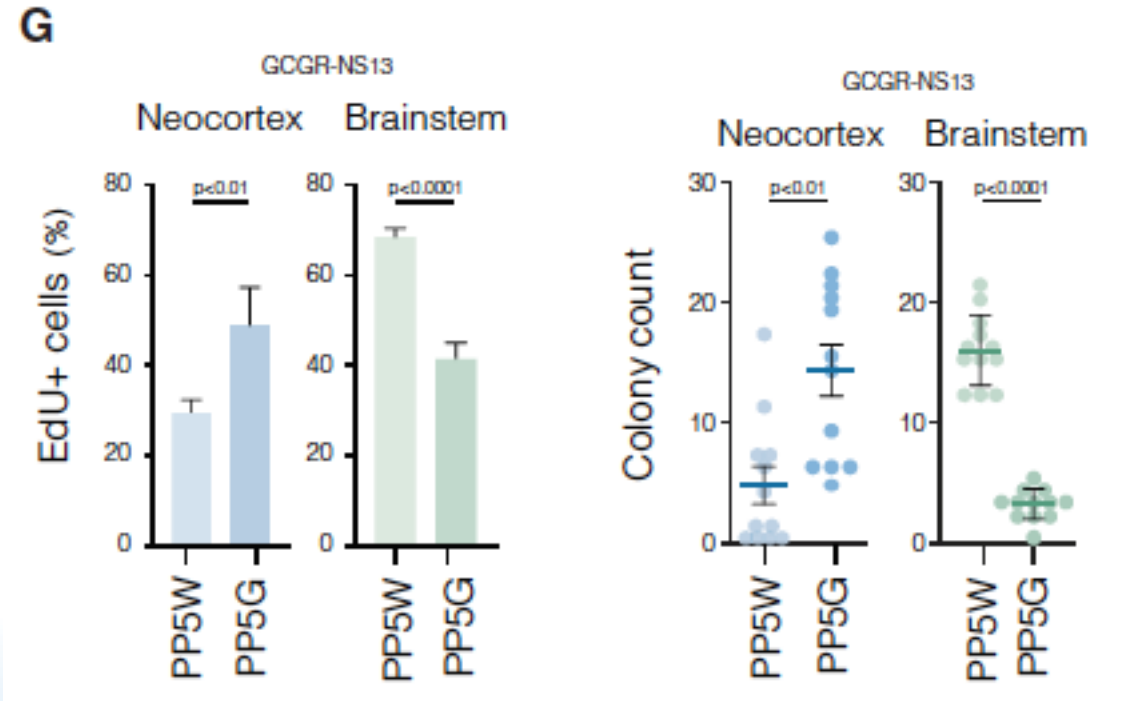
Diffuse hemispheric glioma, H3 G34-mutant, CNS WHO grade 4



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

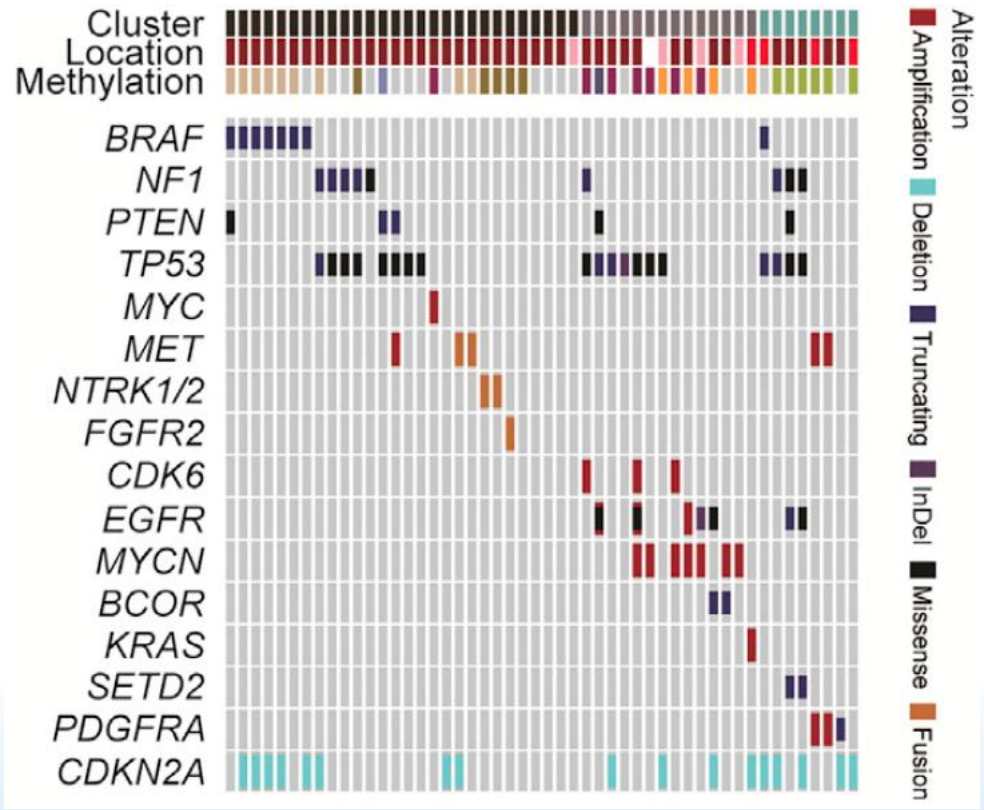


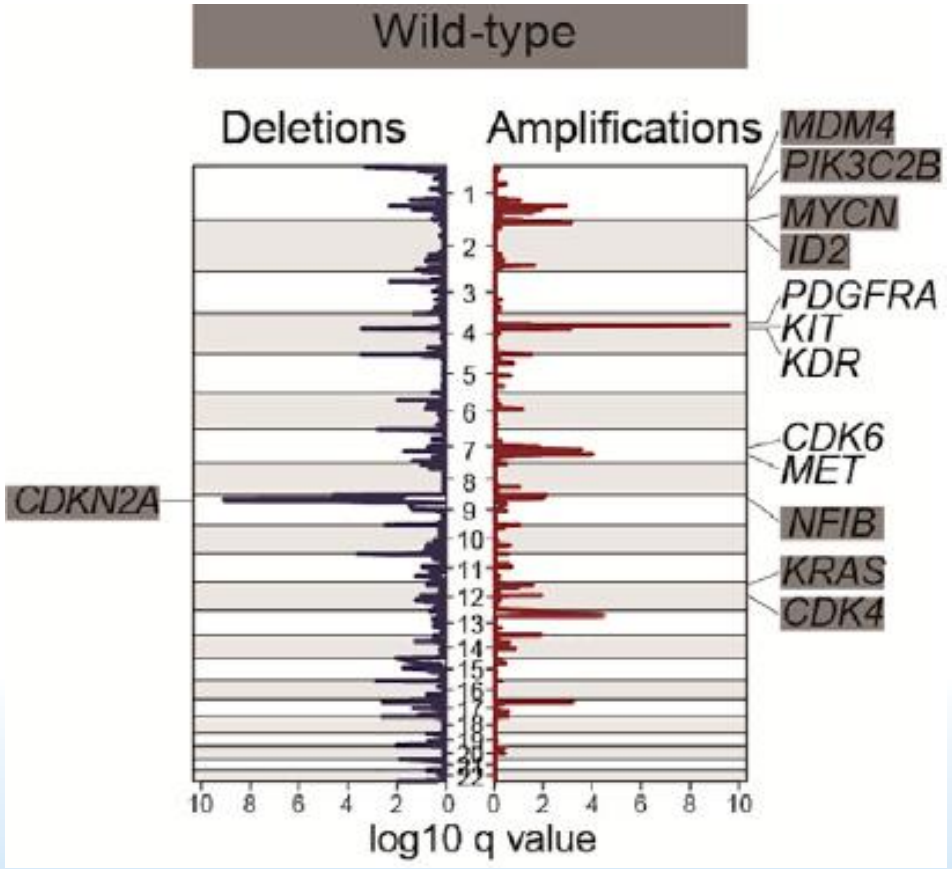
Chen CCL, et al., Cell, 2020



Bressan RB, et al., Cancer Cell, 2021

Diffuse pediatric-type HGG, H3-wildtype and IDH-wildtype, CNS WHO Grade 4





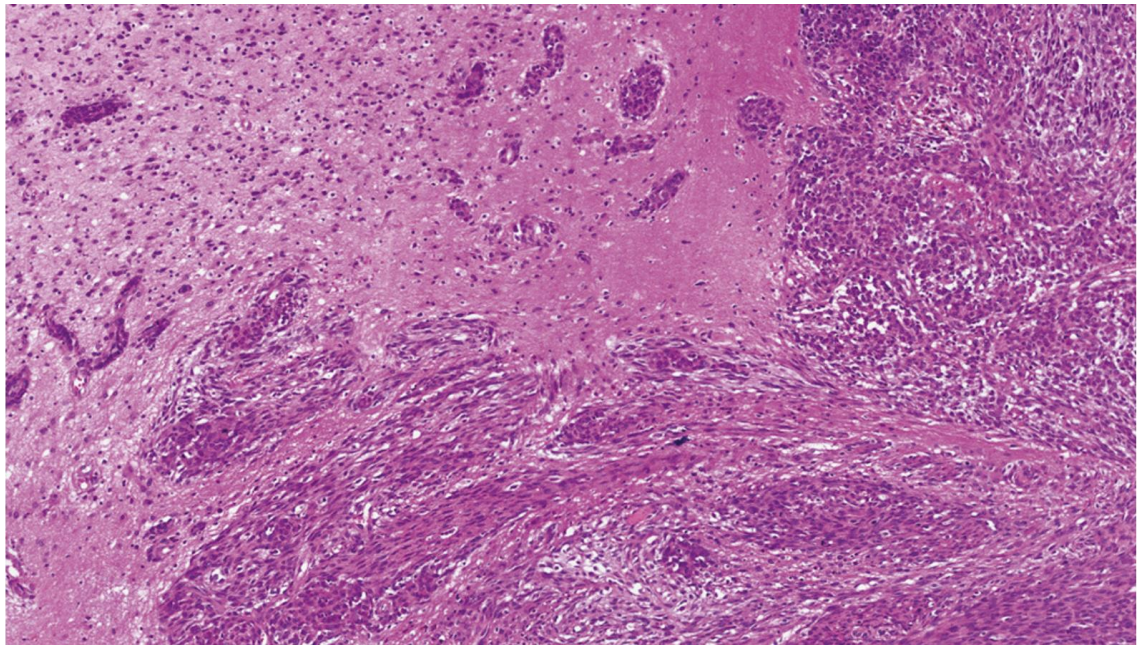
RTK1
PDGFRAamp
Lynch syndrome

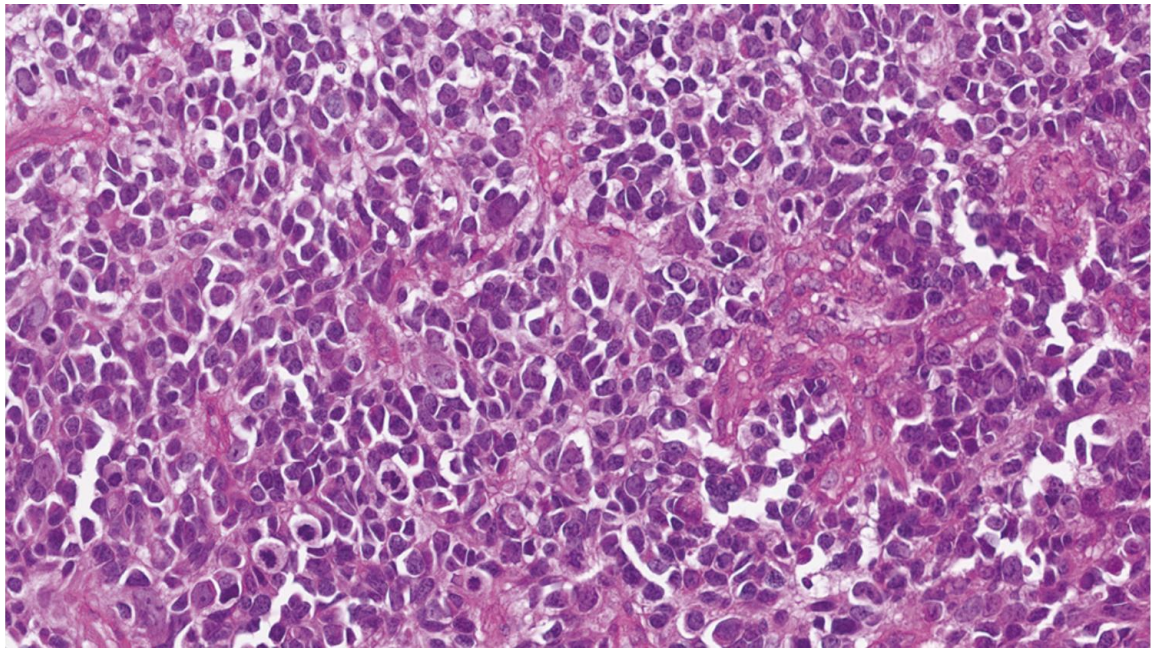
RTK2
EGFRamp/TERT mut

MYCN
MYCNamp

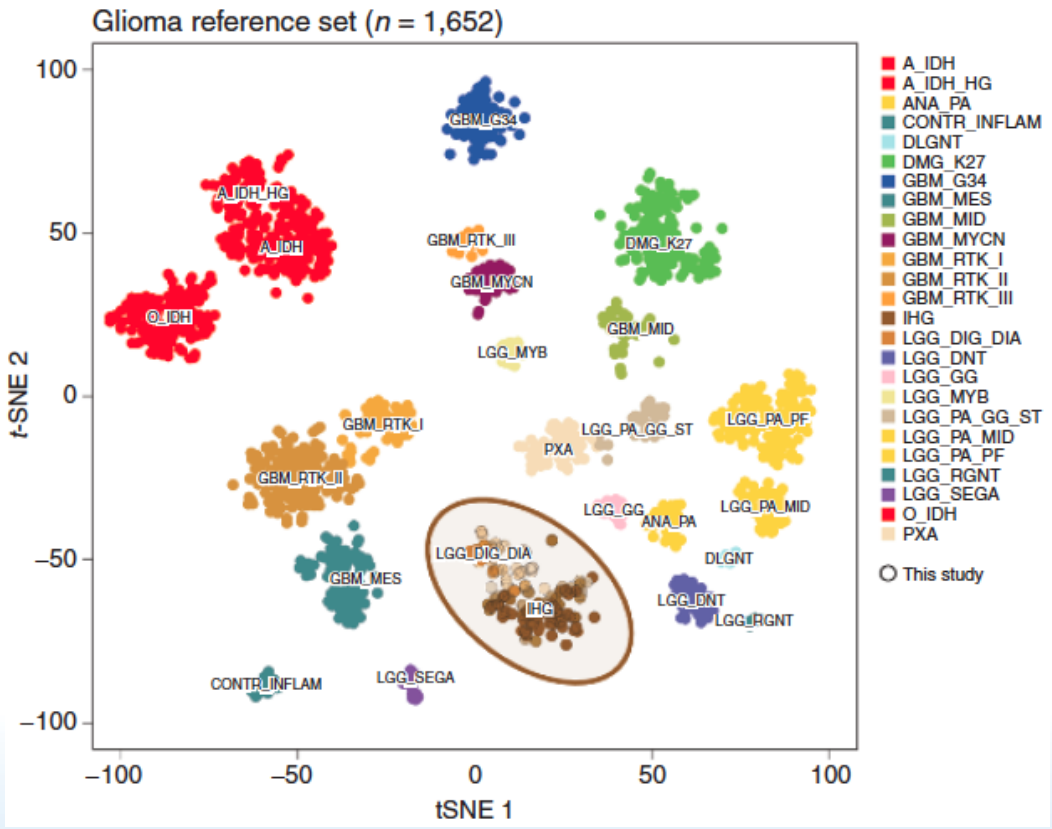
Mackay A, et al., Cancer Cell, 2017

Biphasic growth pattern of pediatric HGG, MYCN-subtype

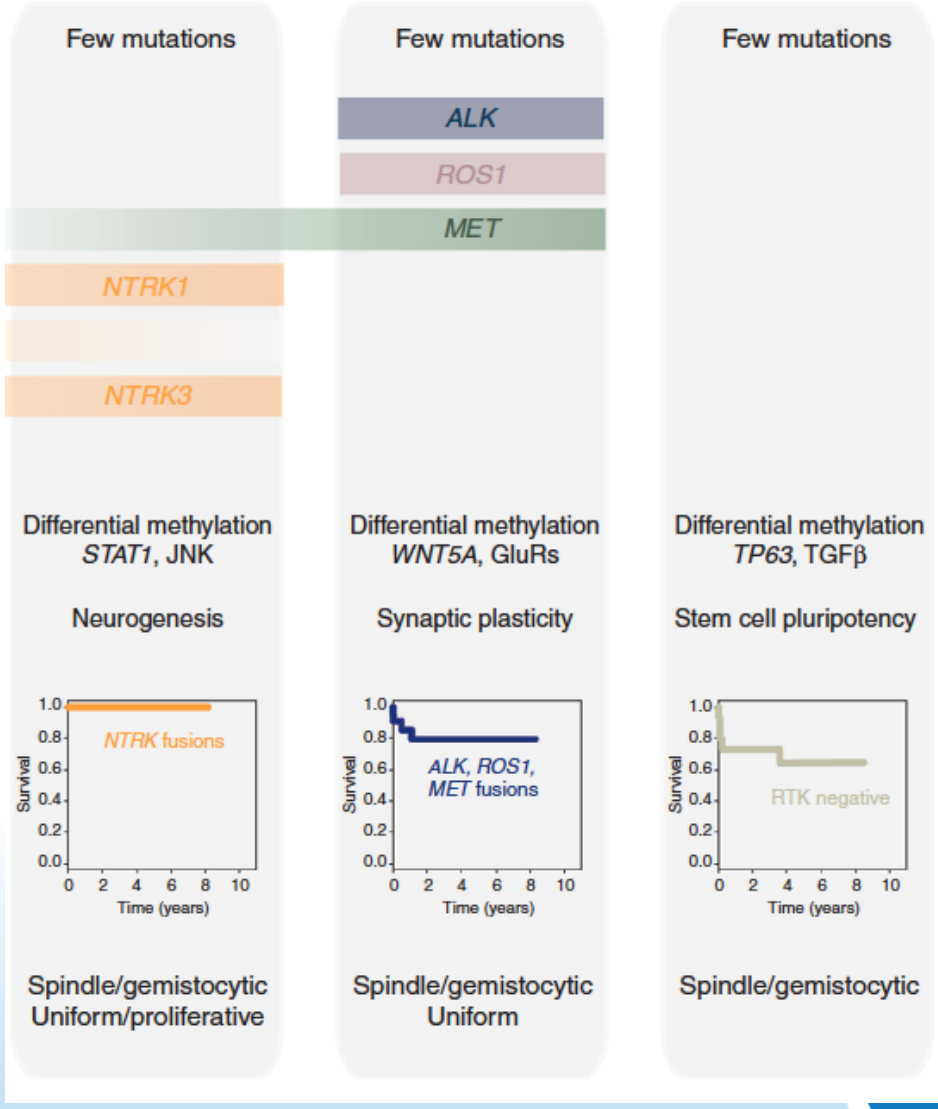




Infant-type hemispheric glioma



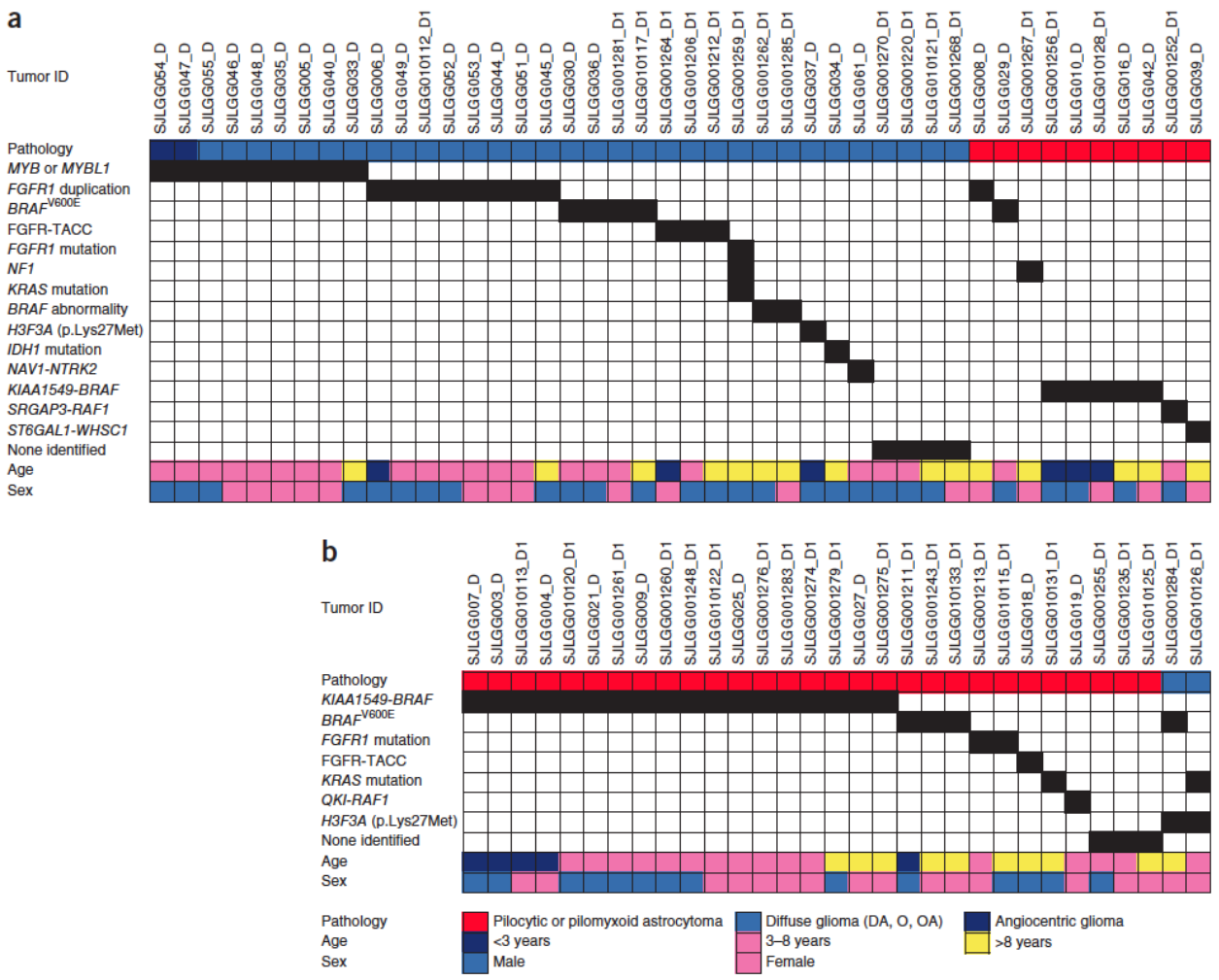
Clarke M, et al., Cancer Discovery, 2020



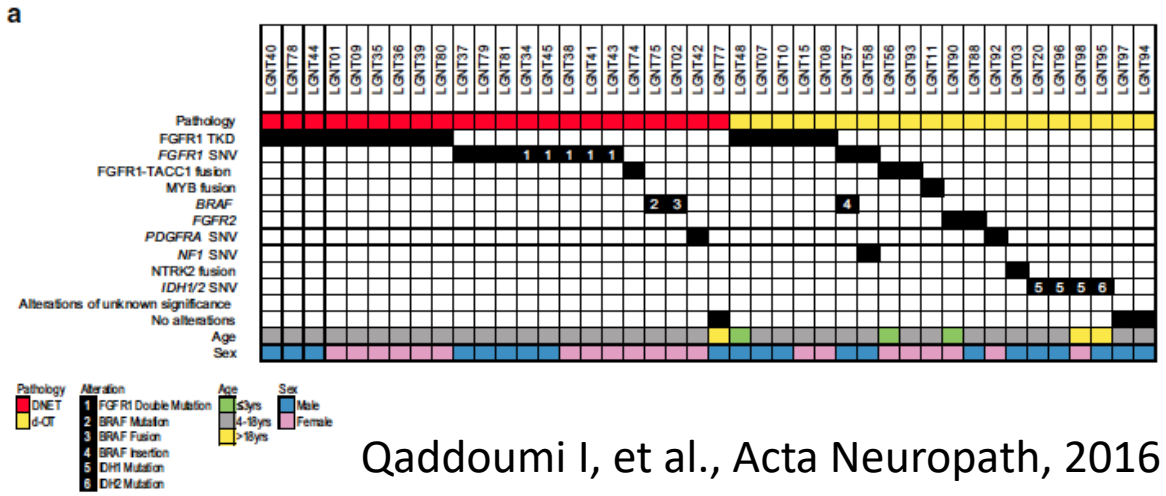
Pediatric-type diffuse low-grade glioma

- 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



Zhang J, et al., Nat Genet, 2013



Qaddoumi I, et al., Acta Neuropath, 2016

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

Article

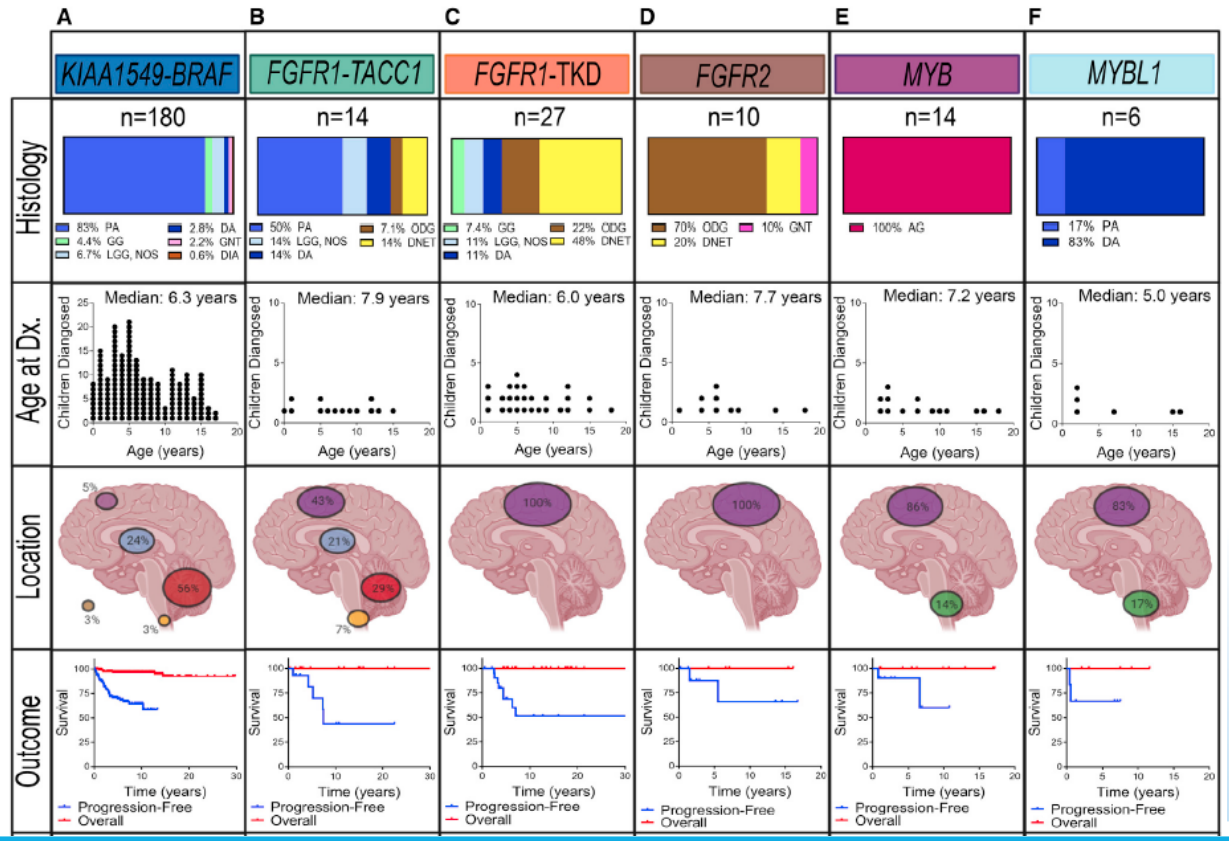
Cancer Cell

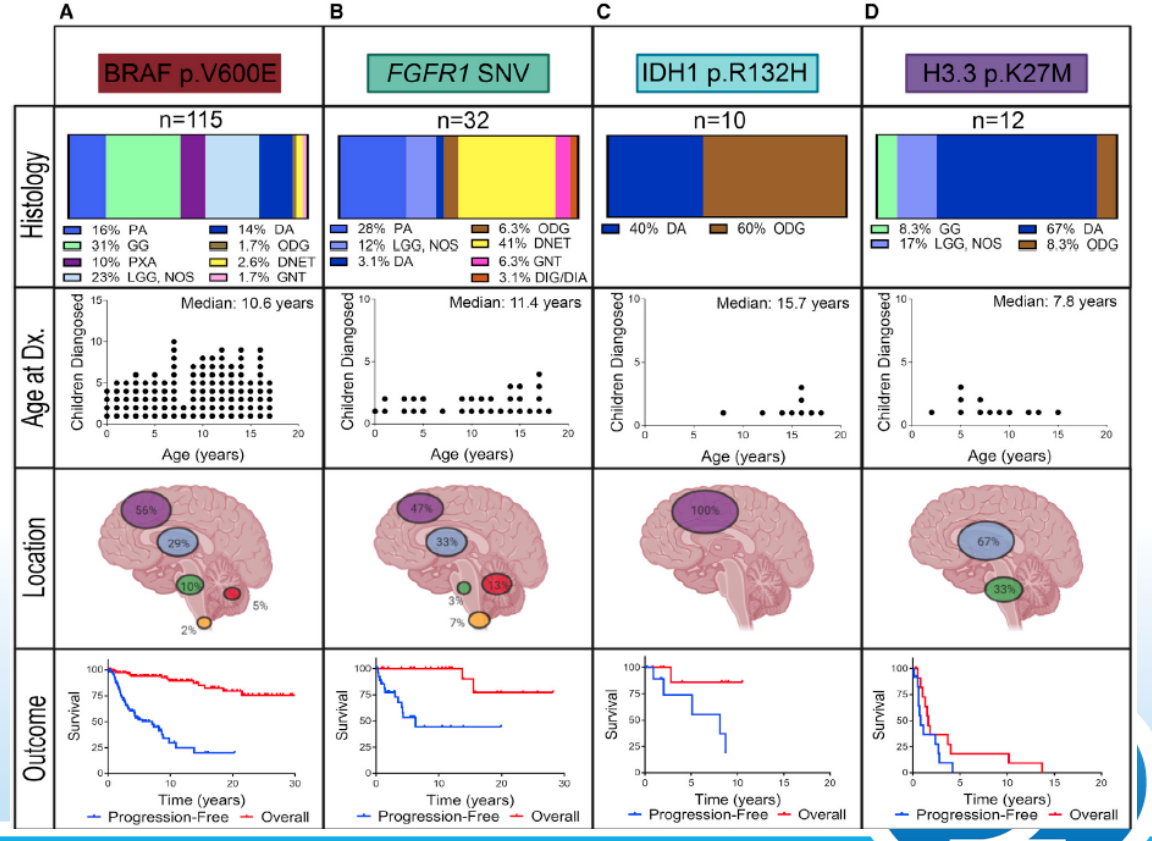
Cancer Cell, 2020

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

Authors

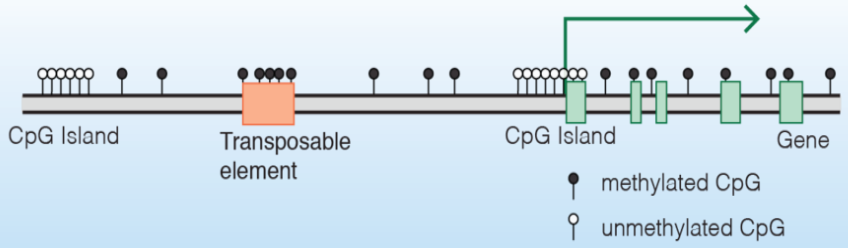
Scott Ryall, Michal Zapotocky,
Kohei Fukuoka, ..., David W. Ellison,
Uri Tabori, Cynthia Hawkins



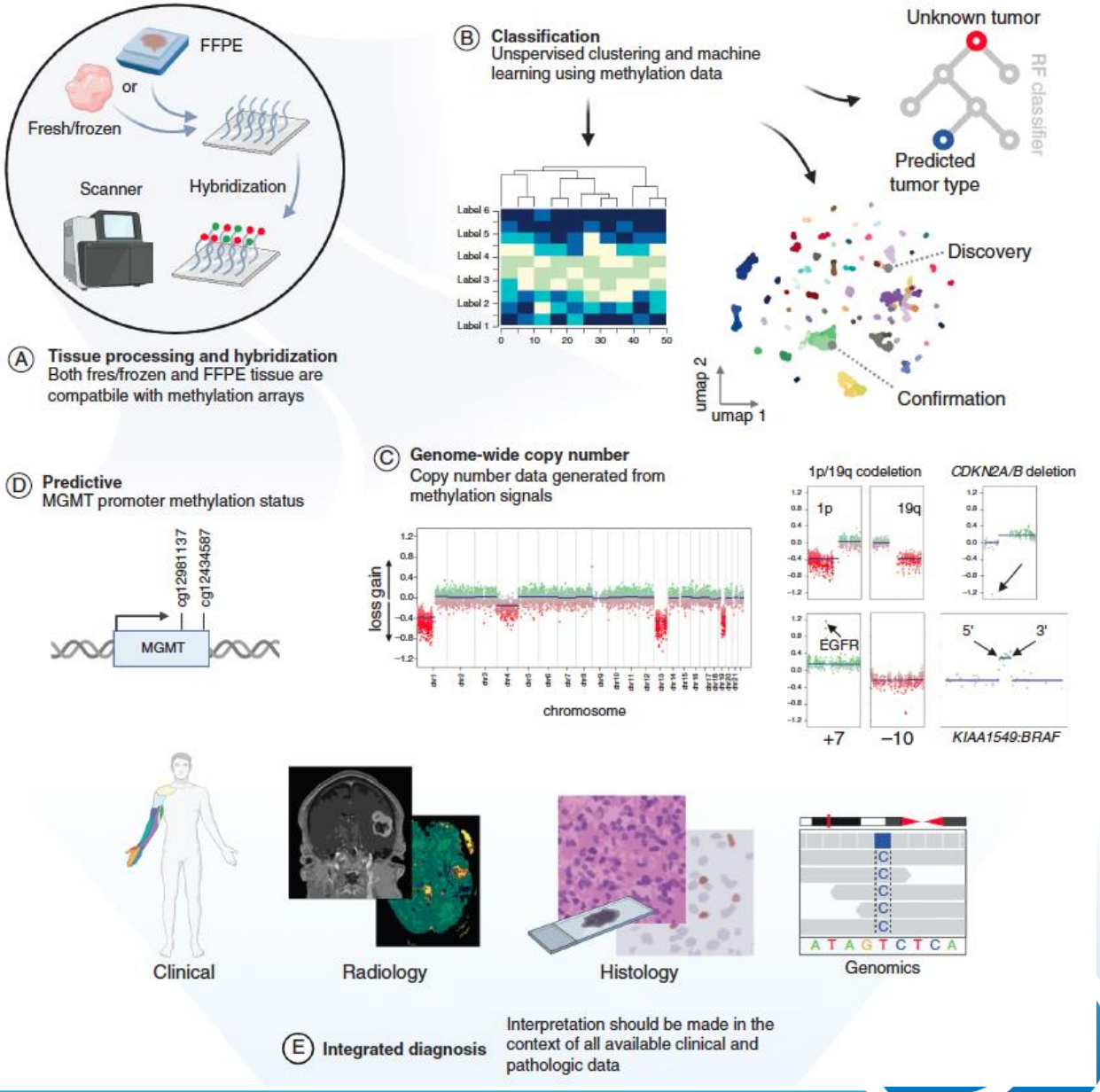


DNA methylation profiling is driving brain tumor discovery and classification

Typical mammalian DNA methylation landscape

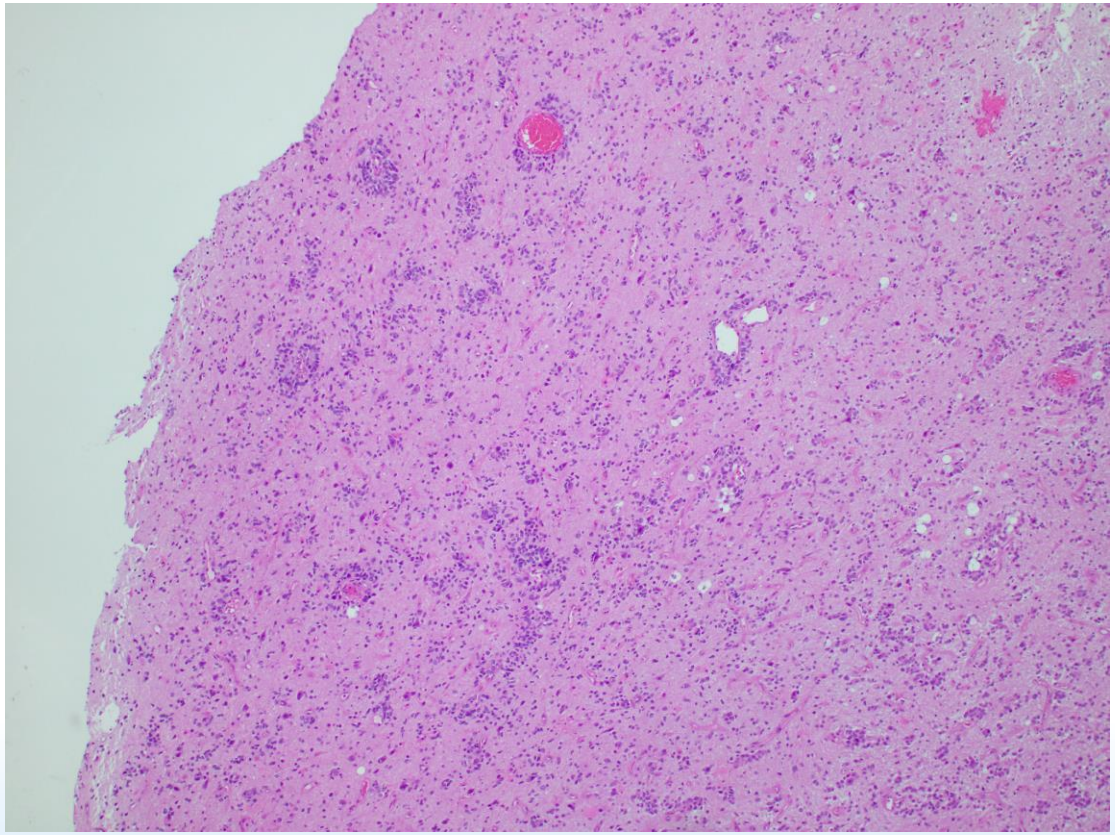


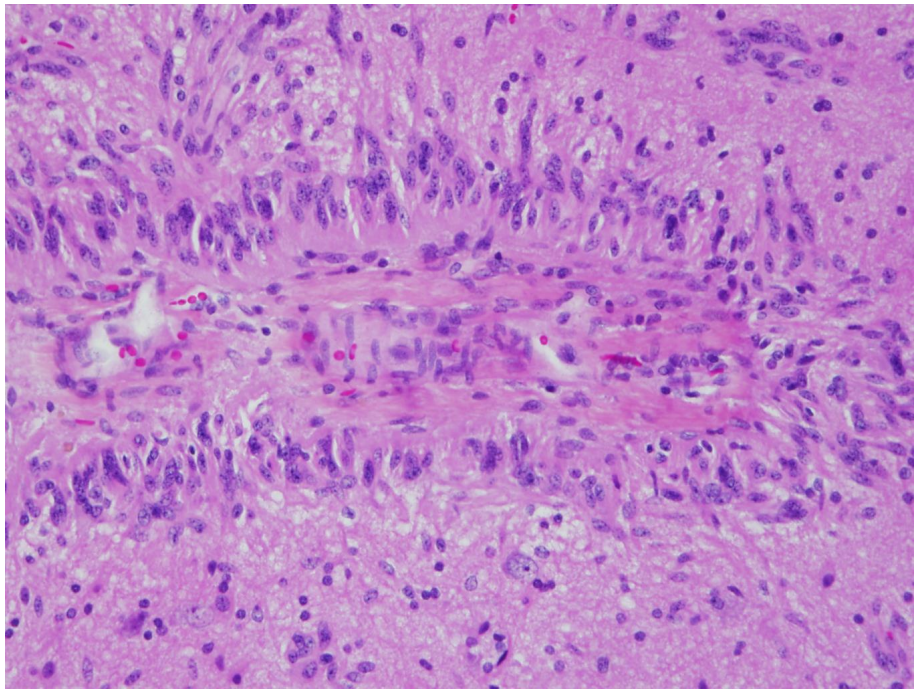
DNA methylation profiling in surgical neuropathology

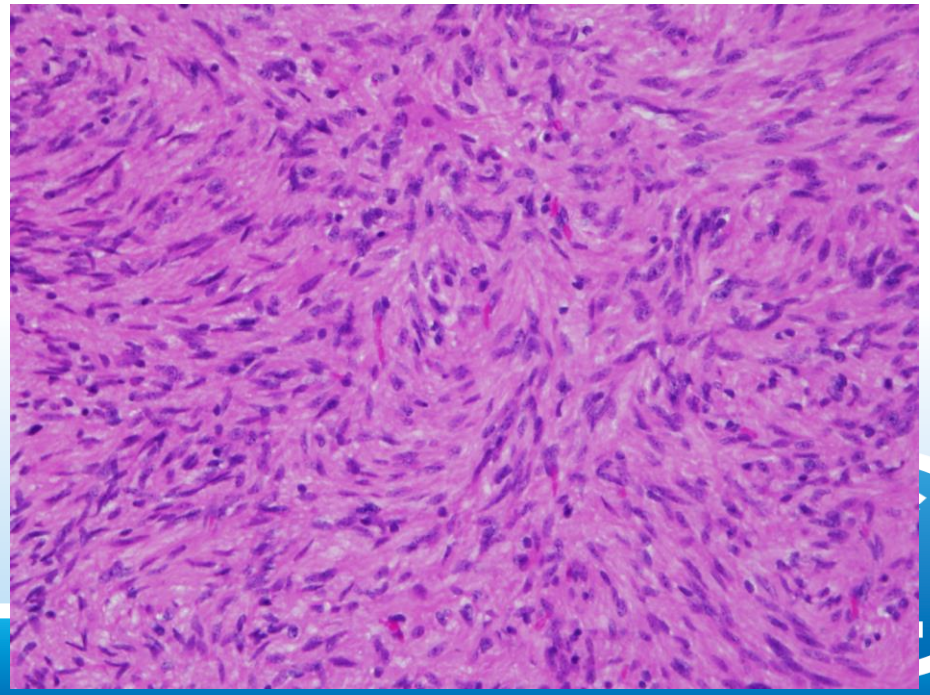


Pratt D, et al., Neuro-oncol, 2021

Angiocentric glioma, CNS WHO grade 1

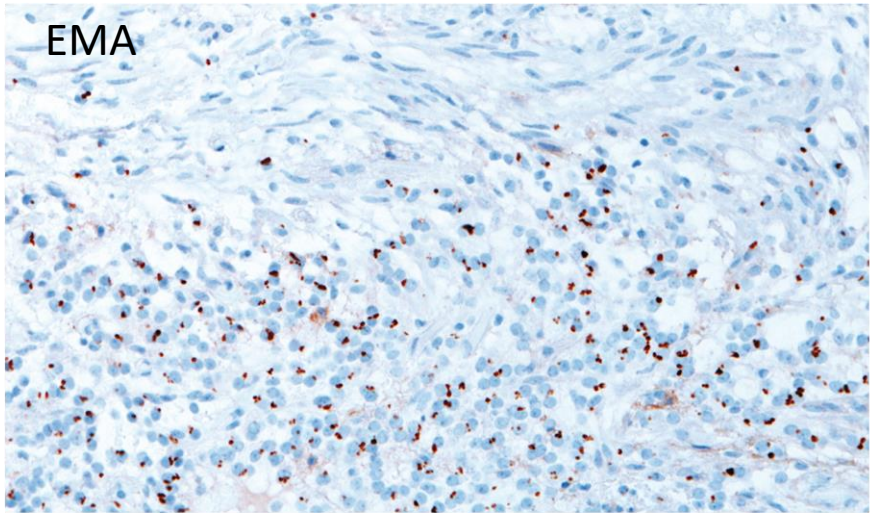


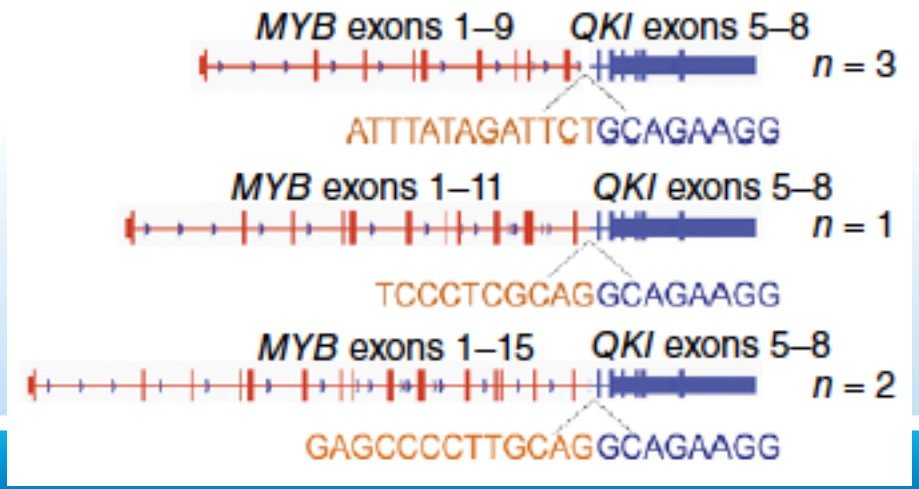




Supratentorial localization
Patients with intractable seizures
Unique DNA methylation signature

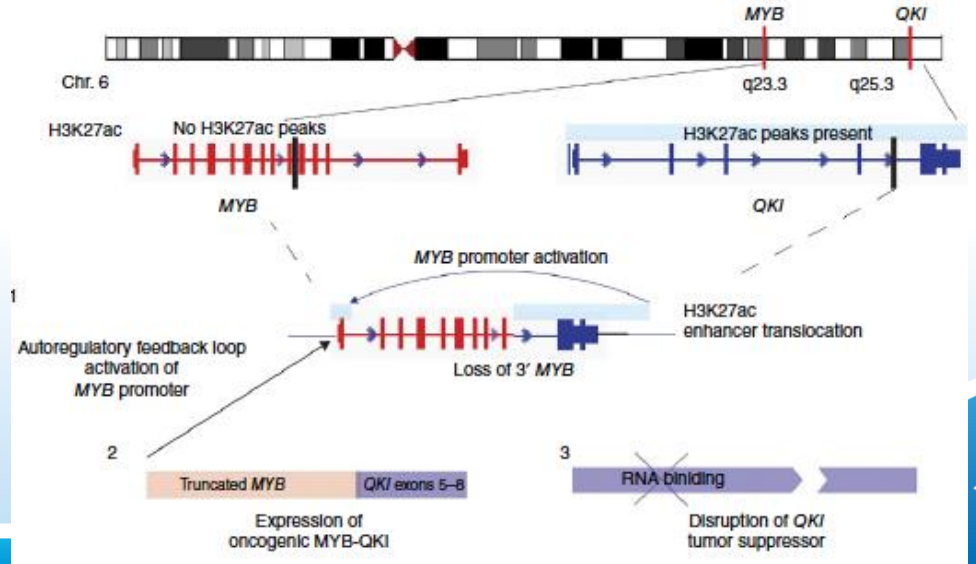
Angiocentric glioma, CNS WHO grade 1



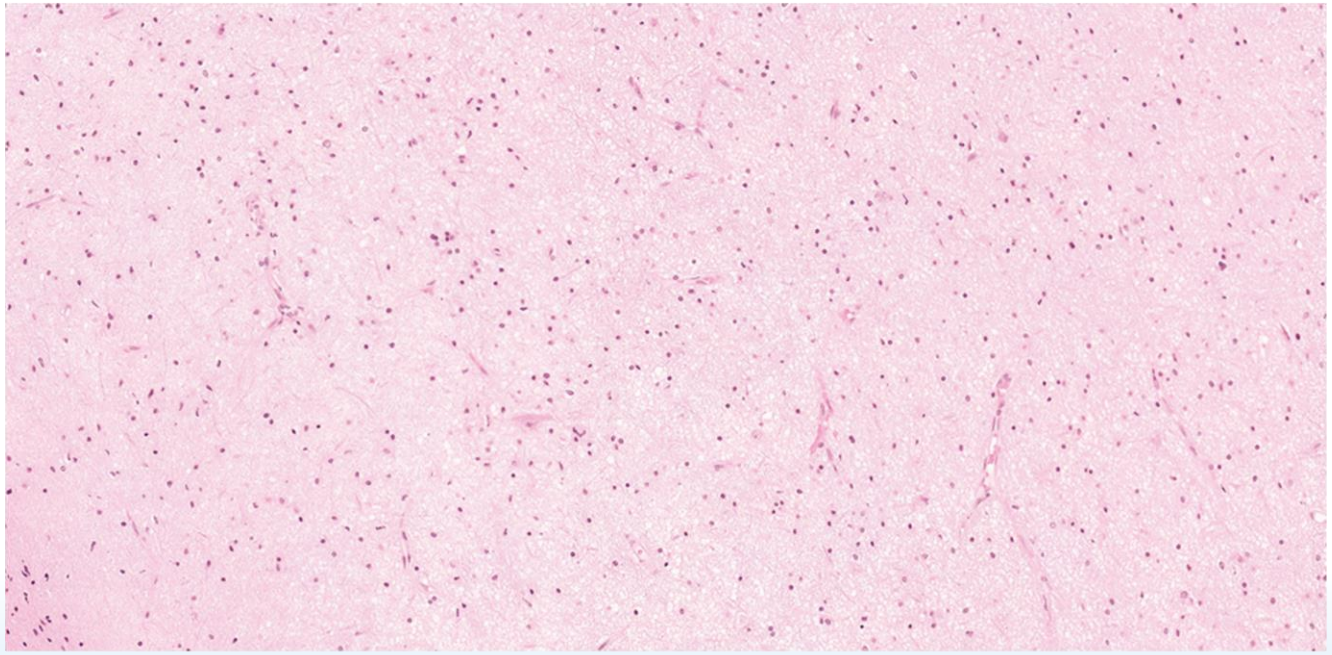


MYB-QKI rearrangements in angiocentric glioma drive tumorigenicity through a tripartite mechanism Nat Genet, 2015

Pratiti Bandopadhayay[1–4,50], Lori A Ramkissoon[5,50], Payal Jain[6–8,50], Guillaume Bergthold[1,9,50], Jeremiah Wala[1,3,4], Rhamy Zeid[4,5], Steven E Schumacher[1,3], Laura Urbanski[1], Ryan O'Rourke[1,3], William J Gibson[1,3,4], Kristine Pelton[5], Shakti H Ramkissoon[5,10–12], Harry J Han[6,7], Yuankun Zhu[6,7], Namrata Choudhari[6,7], Amanda Silva[5–7], Katie Boucher[6,7], Rosemary E Henn[6,7], Yun Jee Kang[5], David Knoff[5], Brenton R Paolella[1,3,4], Adrianne Gladden-Young[13], Pascale Varlet[14], Melanie Pages[14], Peleg M Horowitz[1,15], Alexander Federation[4,5], Hayley Malkin[2], Adam A Tracy[3], Sara Seepo[3], Matthew Ducar[10,16], Paul Van Hummelen[16], Mariarita Santi[17,18], Anna Maria Buccoliero[19], Mirko Scagnet[20], Daniel C Bowers[21], Caterina Giannini[22], Stephanie Puget[23], Cynthia Hawkins[24], Uri Tabori[25], Almos Klekner[26], Laszlo Bognar[26], Peter C Burger[27], Charles Eberhart[27], Fausto J Rodriguez[27], D Ashley Hill[28–30], Sabine Mueller[31–33], Daphne A Haas-Kogan[32,34,35], Joanna J Phillips[32,36], Sandro Santagata[1,10–12], Charles D Stiles[1], James E Bradner[3,5,37], Nada Jabado[38–40], Alon Goren[13], Jacques Grill[9], Azra H Ligon[41], Liliana Goumnerova[2,42,43], Angela J Waanders[44–46,48], Phillip B Storm[6,7,45,48], Mark W Kieran[2,4], Keith L Ligon[3,5,10–12,51], Rameen Beroukhim[1,3,5,37,49,51] & Adam C Resnick[6,7,45,47,48,51]



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

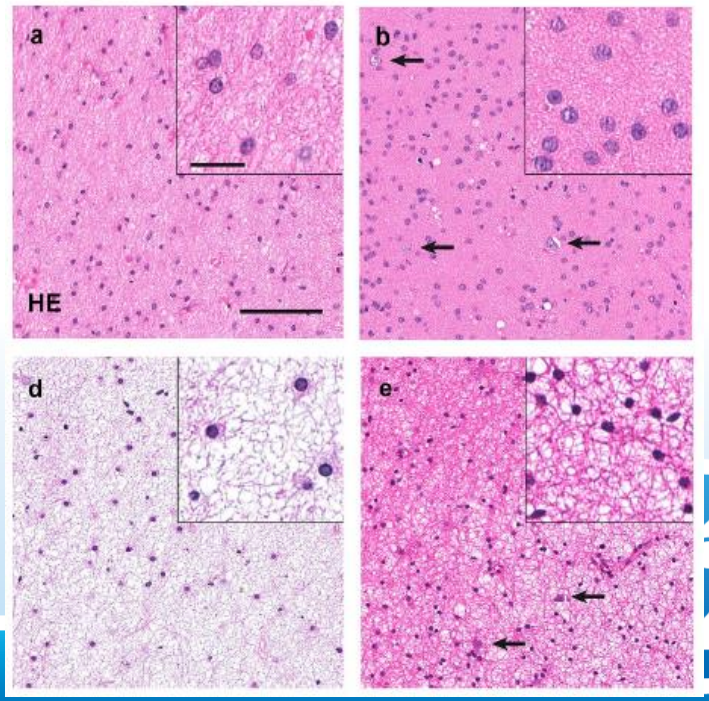


Supratentorial localization
Patients with intractable seizures
Unique DNA methylation signature

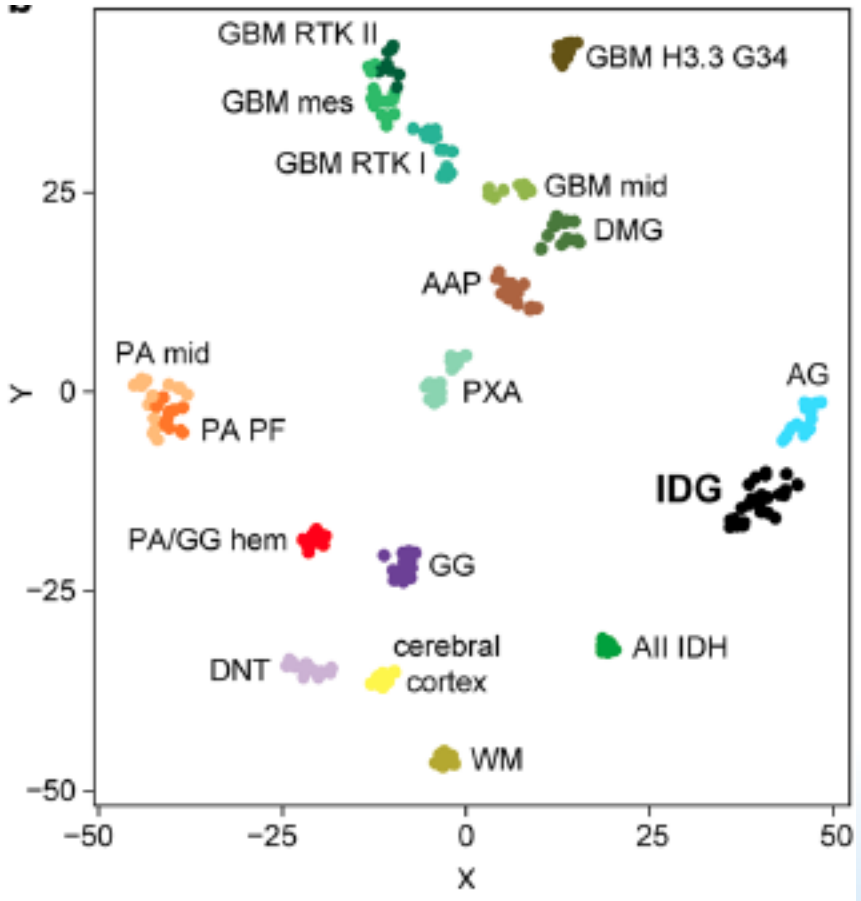
Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of *MYBL1* or *MYB* and a benign disease course

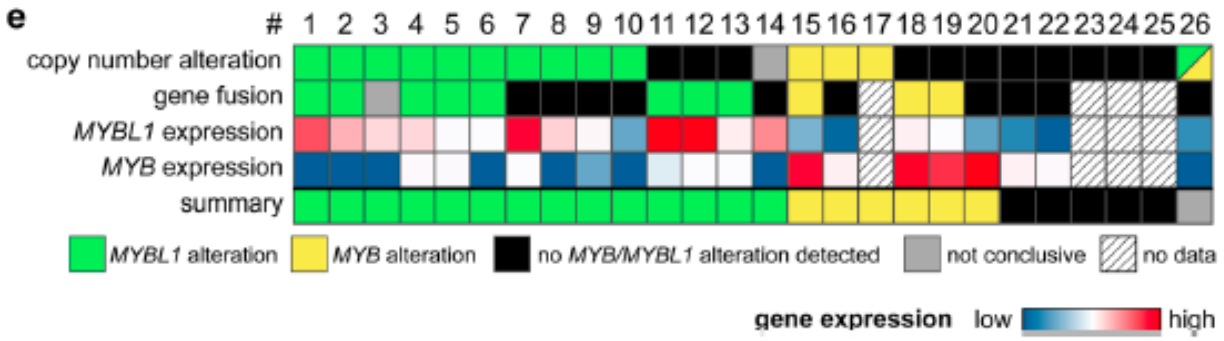
Acta Neuropath, 2019

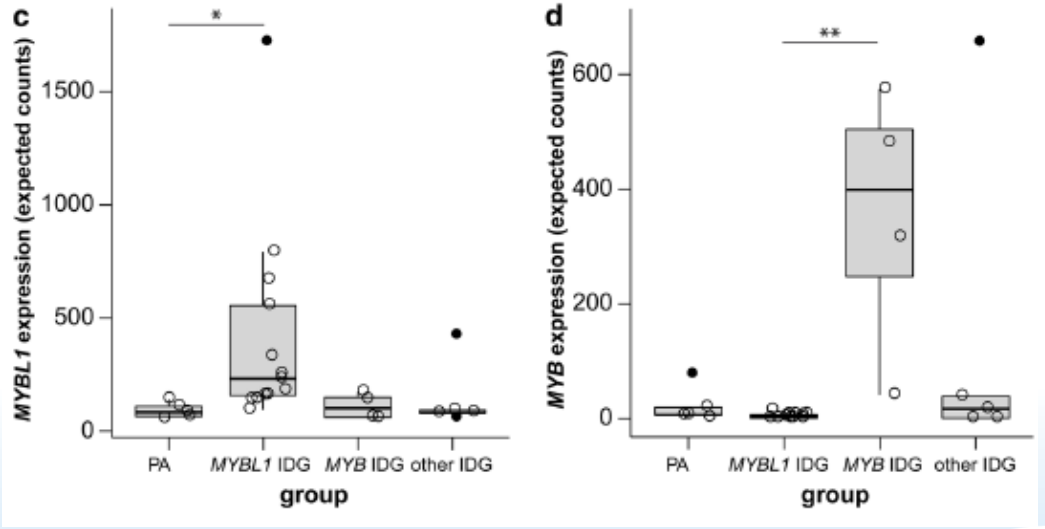
Annika K. Wefers[1,2,3] · Damian Stichel[1,2] · Daniel Schrimpf[1,2] · Roland Coras[4] · Mélanie Pages[5] · Arnault Tauziède-Espariat[5] · Pascale Varlet[5] · Daniel Schwarz[6,7] · Figen Söylemezoglu[8] · Ute Pohl[9,10] · José Pimentel[11,12] · Jochen Meyer[1,2] · Ekkehard Hewer[13] · Anna Japp[14] · Abhijit Joshi[15] · David E. Reuss[1,2] · Annekathrin Reinhardt[1,2] · Philipp Sievers[1,2] · M. Belén Casalini[1,2] · Azadeh Ebrahimi[1,2] · Kristin Huang[1,2] · Christian Koelsche[1,16] · Hu Liang Low[17] · Olinda Rebelo[18] · Dina Marnoto[18] · Albert J. Becker[14] · Ori Staszewski[19] · Michel Mittelbronn[20,21,22,23,24] · Martin Hasselblatt[25] · Jens Schittenhelm[26,27] · Edmund Cheesman[28] · Ricardo Santos de Oliveira[29] · Rosane Gomes P. Queiroz[30] · Elvis Terci Valera[30] · Volkmar H. Hans[31,32] · Andrey Korshunov[1,2] · Adriana Olar[33,34] · Keith L. Ligon[35] · Stefan M. Pfister[3,36,37] · Zane Jaunmuktane[38,39] · Sebastian Brandner[39,40] · Ruth G. Tatevossian[41] · David W. Ellison[41] · Thomas S. Jacques[42] · Mrinalini Honavar[43] · Eleonora Aronica[44] · Maria Thom[38] · Felix Sahm[1,2,3] · Andreas von Deimling[1,2] · David T. W. Jones[3,45] · Ingmar Blumcke[4] · David Capper[46,47]



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

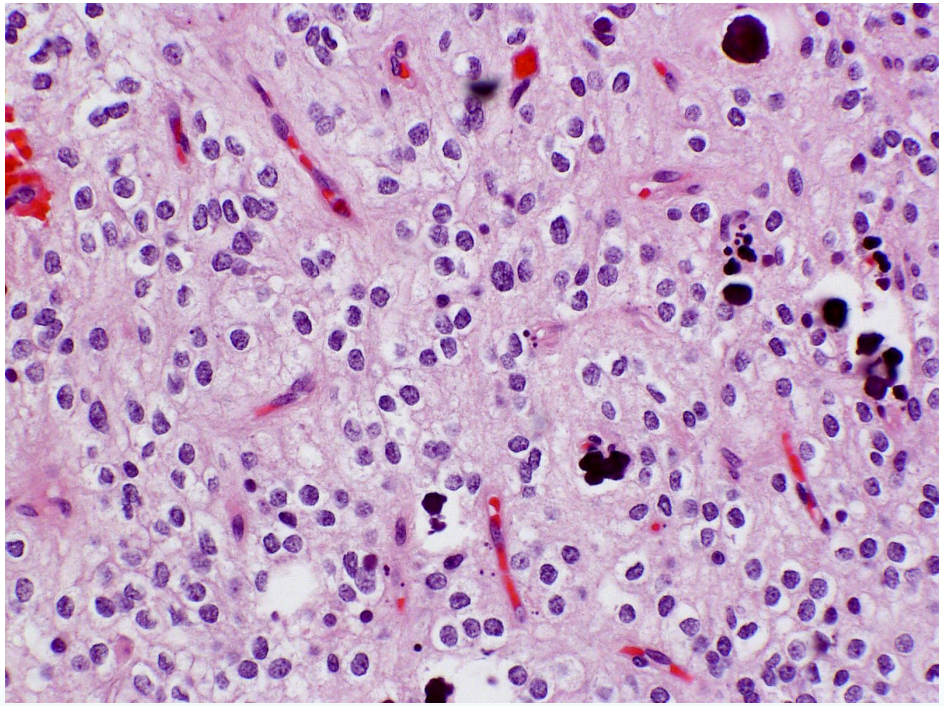


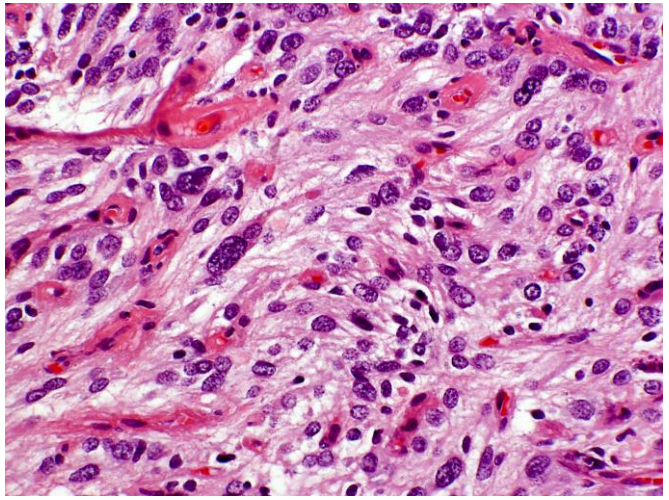


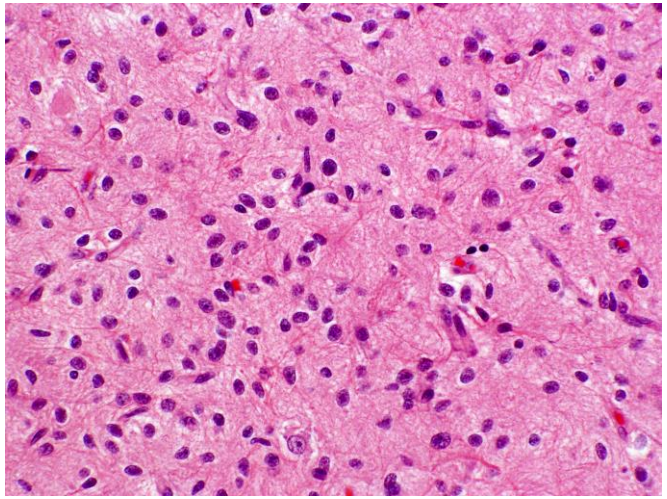


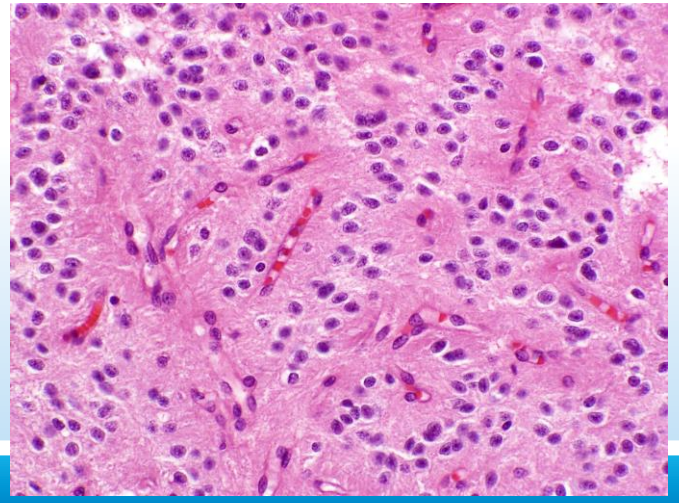
Wefers AK, Acta Neuropath, 2019

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY), CNS WHO grade 1



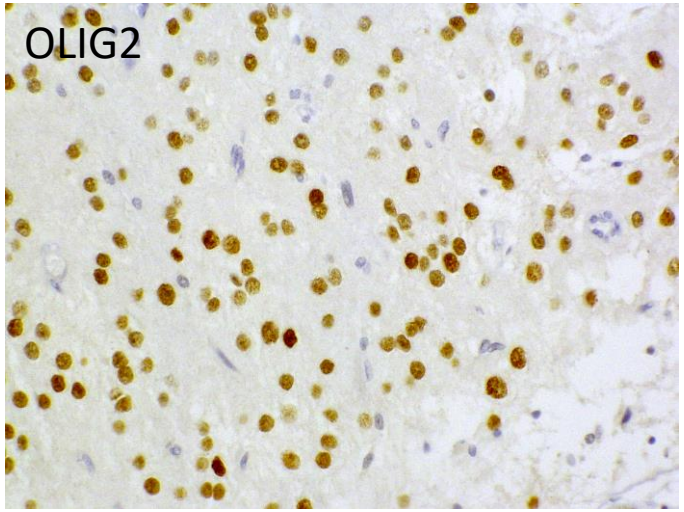


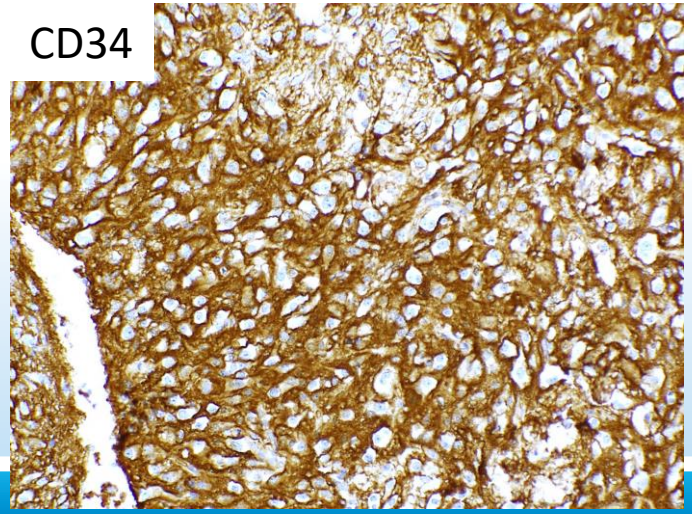


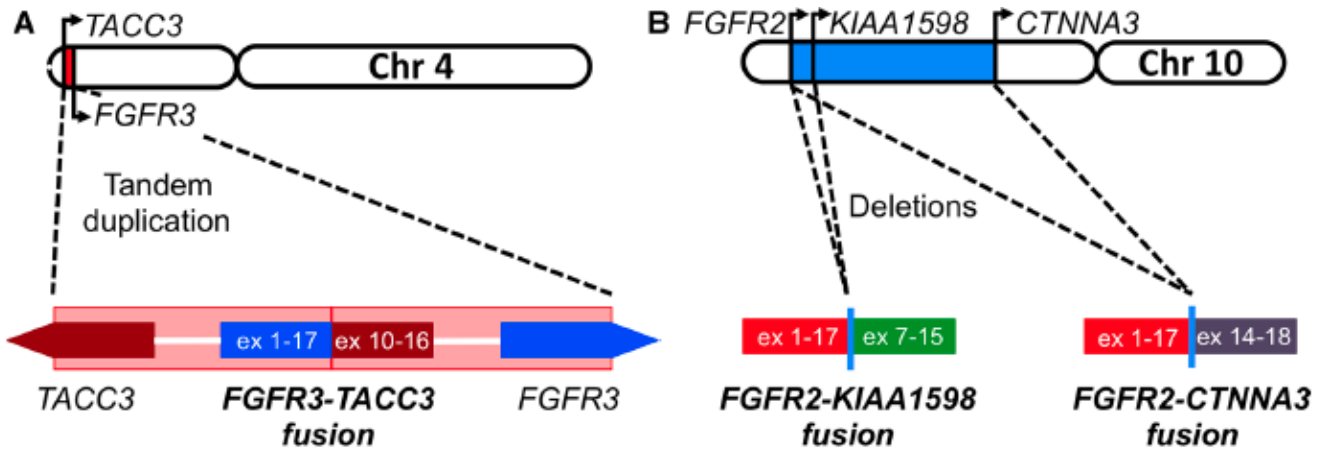


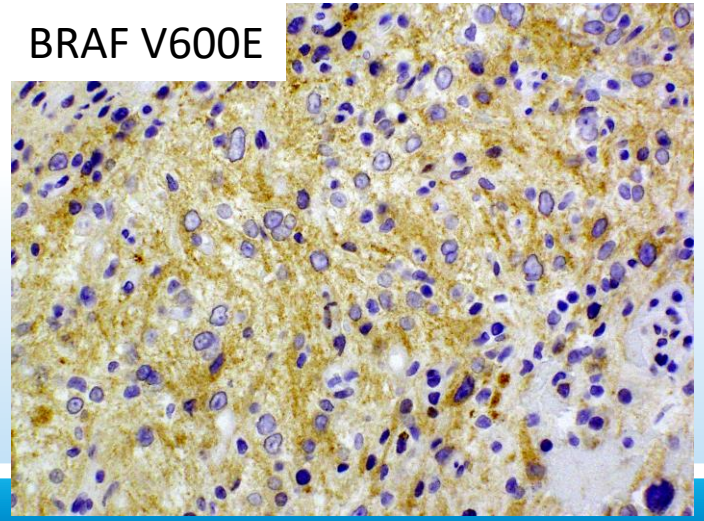
Supratentorial localization
Patients with intractable seizures
Unique DNA methylation signature

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY), CNS WHO grade 1

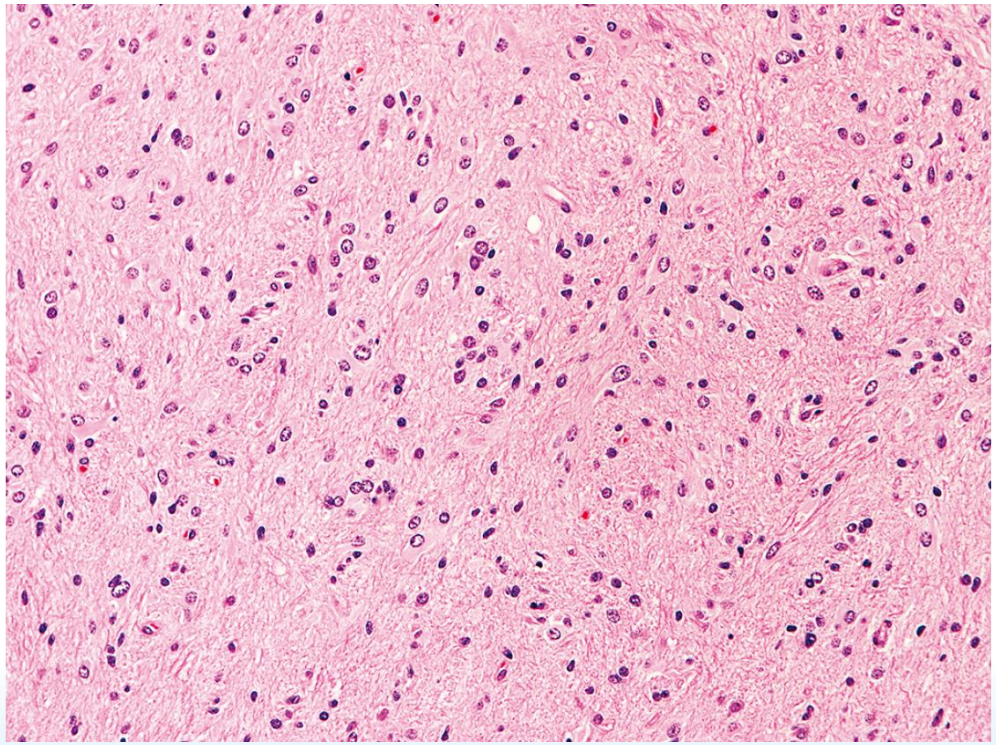


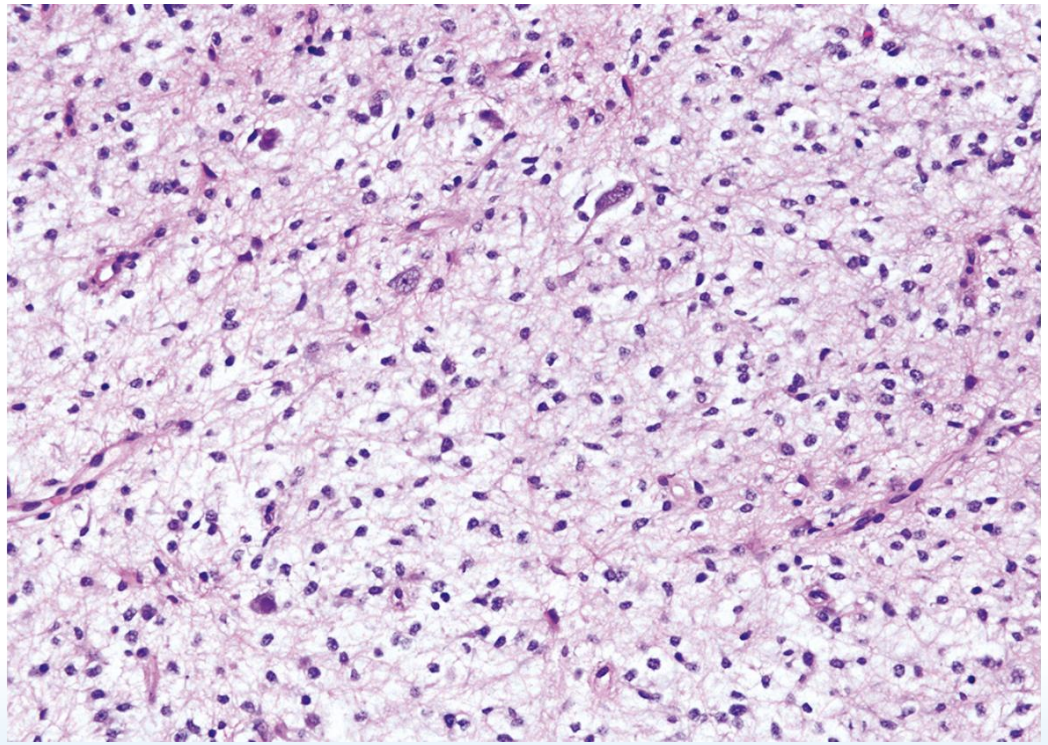






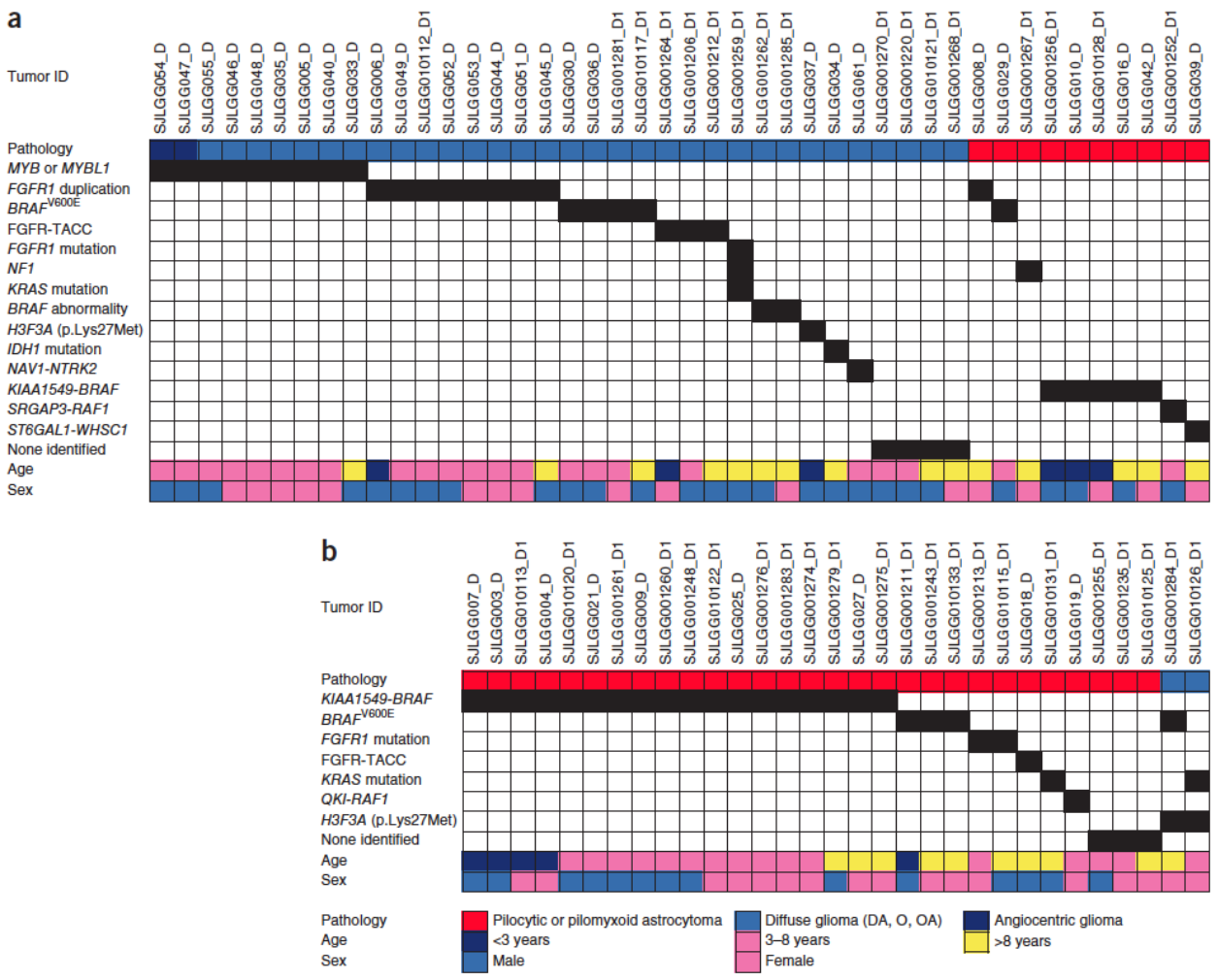
Diffuse low-grade glioma, MAPK pathway-altered

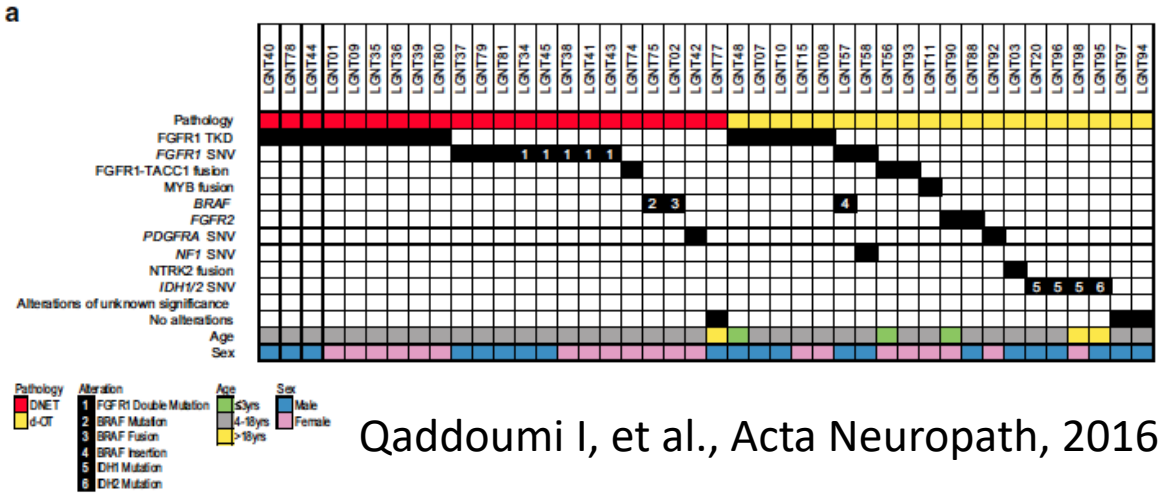




Broader localization pattern throughout the neuraxis
No unifying DNA methylation cluster
Common, but not invariable association with epilepsy

Diffuse low-grade glioma, MAPK pathway-altered





Qaddoumi I, et al., Acta Neuropath, 2016

- 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

Zhang J, et al., Nat Genet, 2013

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)

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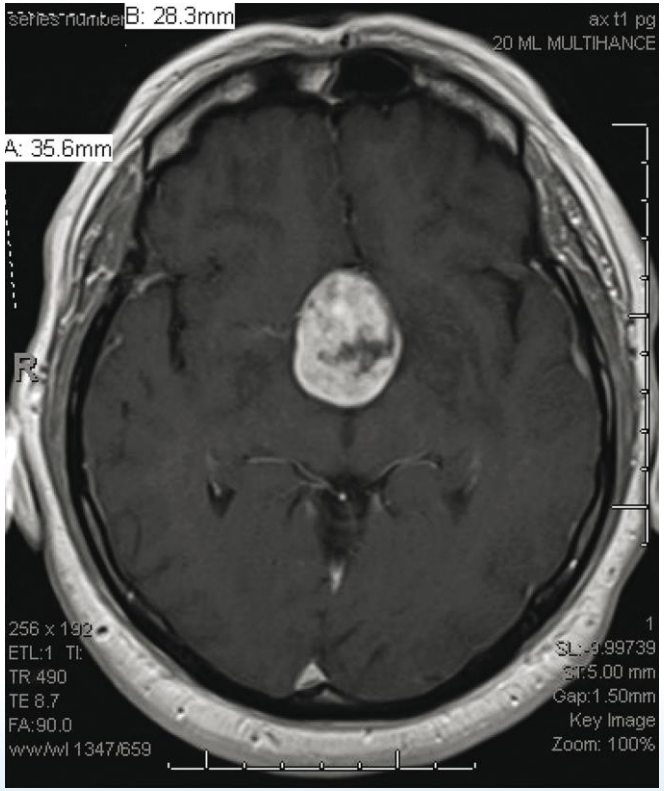
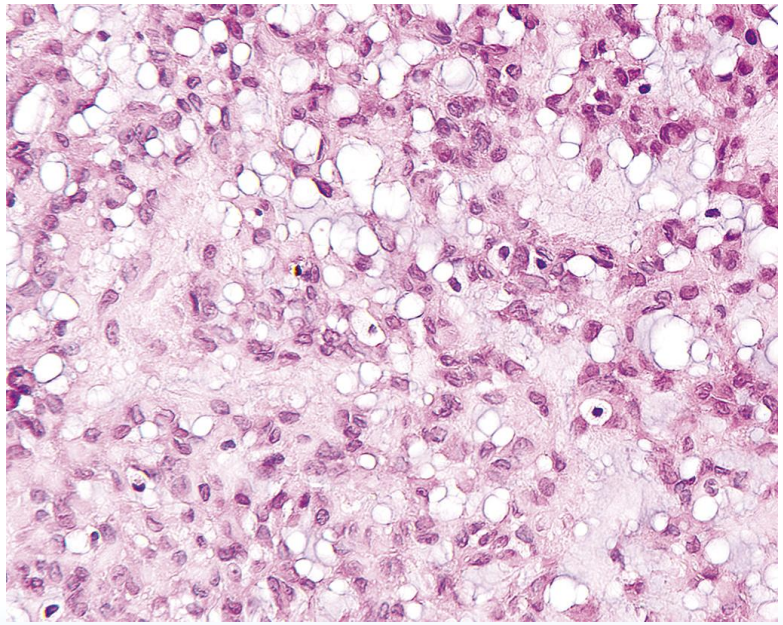
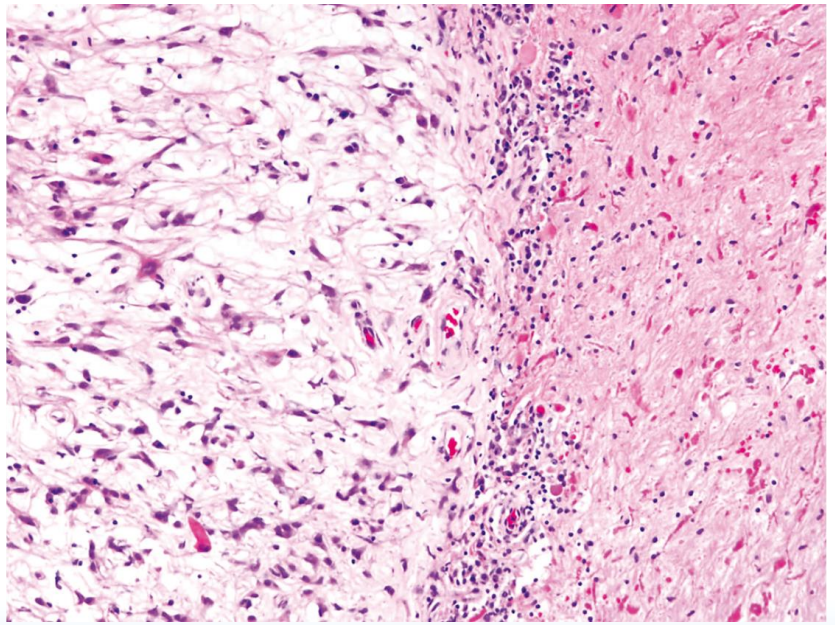
Chordoid glioma, CNS WHO grade 2

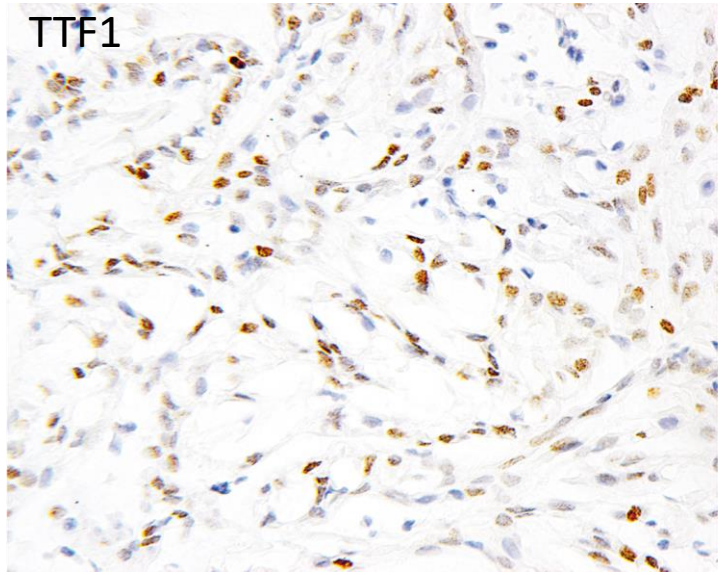


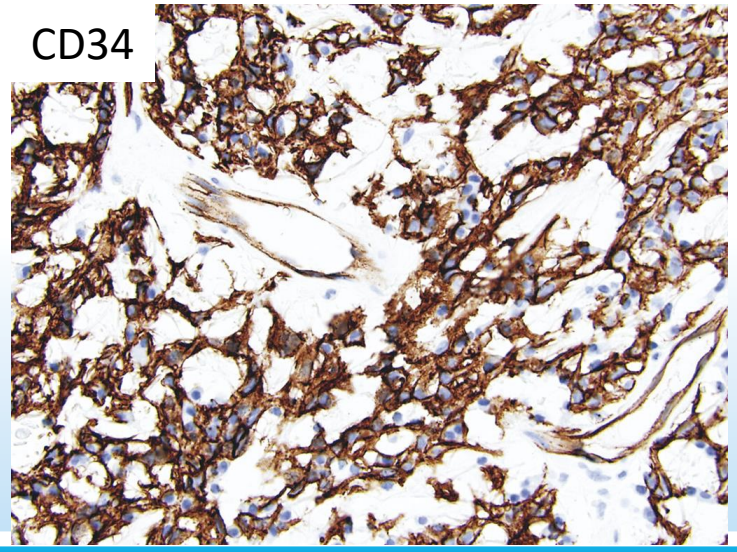




Arise with symptoms of obstructive hydrocephalus and/or compression of hypothalamus/optic chiasm
Thought to arise from specialized tanycytic ependymal cells of the organum vasculosum of the lamina terminalis

Chordoid glioma, CNS WHO grade 2

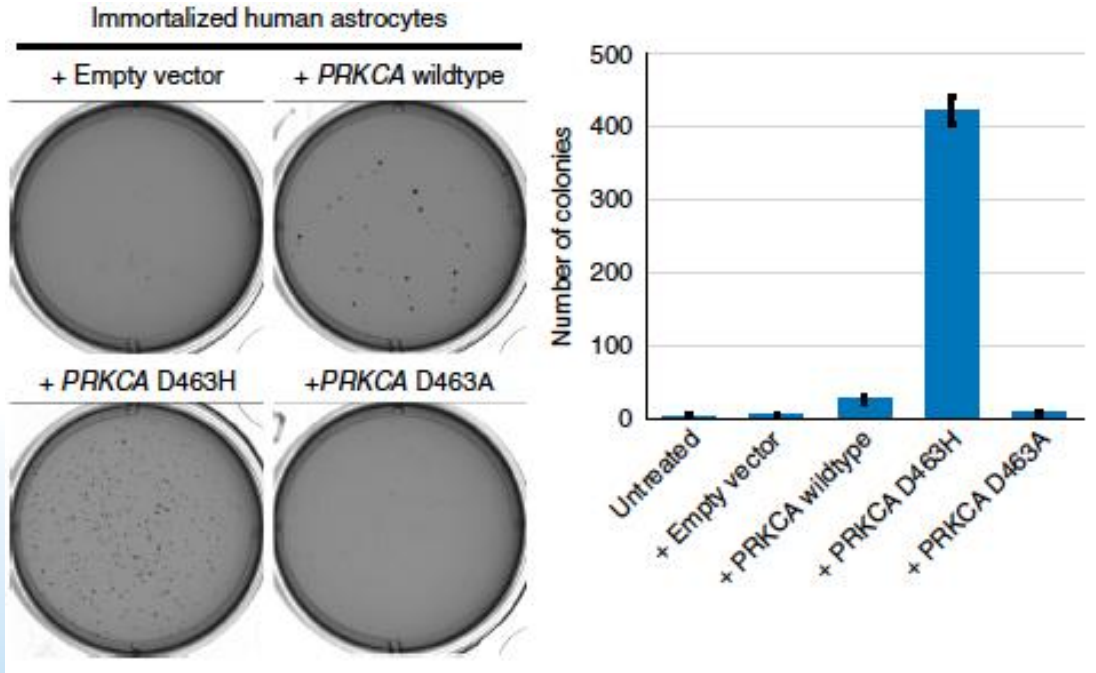




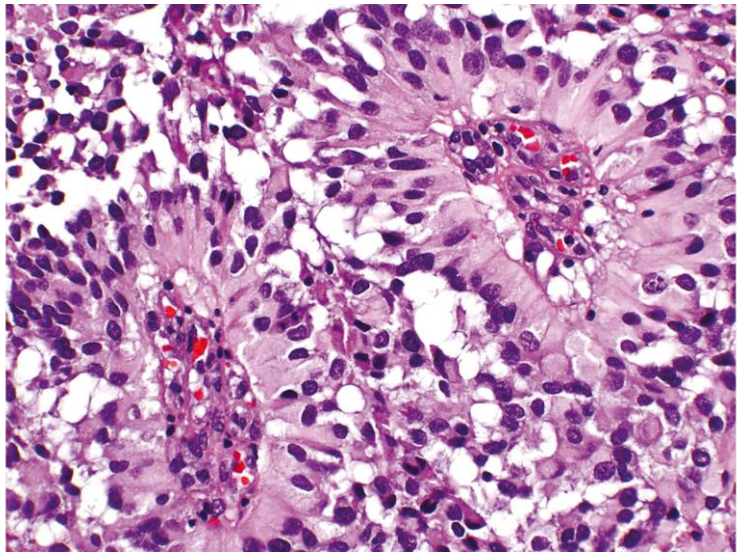
A recurrent kinase domain mutation in *PRKCA* defines chordoid glioma of the third ventricle

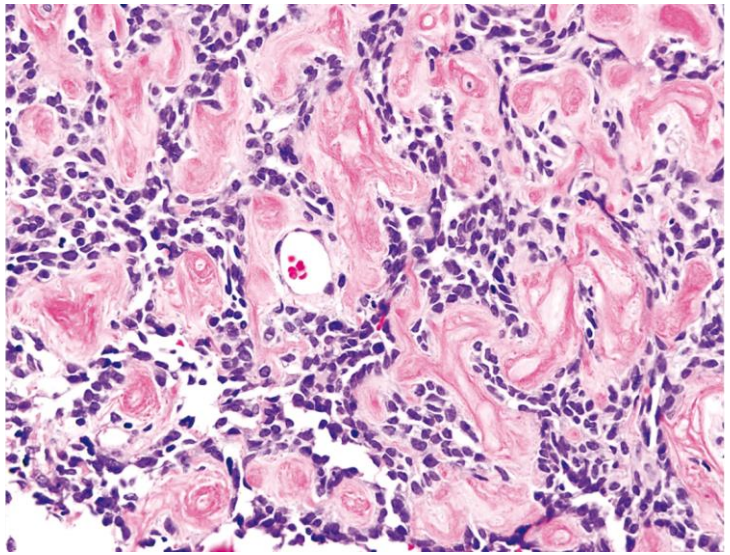
Nat Commun, 2018

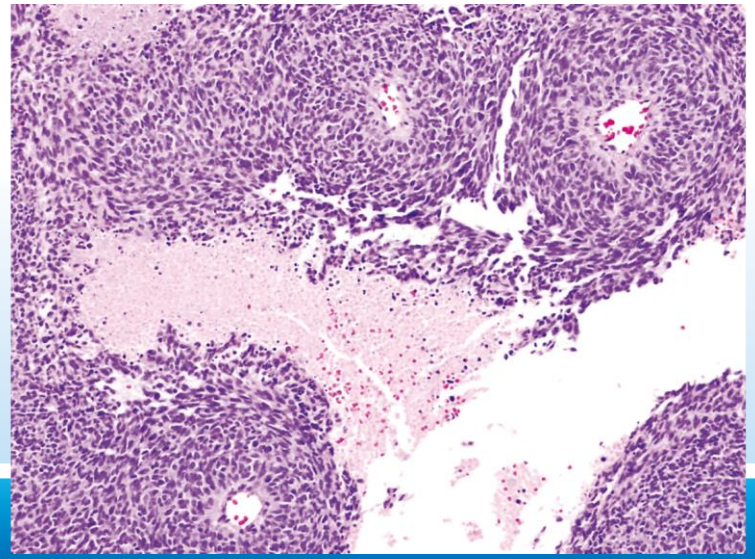
Benjamin Goode[1], Gourish Mondal[1], Michael Hyun[1], Diego Garrido Ruiz[2], Yu-Hsiu Lin[3], Jessica Van Ziffle[1,4], Nancy M. Joseph[1,4], Courtney Onodera[4], Eric Talevich[4], James P. Grenert[1,4], Iman H. Hewedi[5], Matija Snuderl[6], Daniel J. Brat[7], Bette K. Kleinschmidt-DeMasters[8], Fausto J. Rodriguez[9], David N. Louis[10], William H. Yong[11], M. Beatriz Lopes[12], Marc K. Rosenblum[13], Nicholas Butowski[14], Tarik Tihan[1], Andrew W. Bollen[1], Joanna J. Phillips[1,14], Arun P. Wiita[2,3], Iwei Yeh[1,4], Matthew P. Jacobson[2], Boris C. Bastian[1,4], Arie Perry[1,14] & David A. Solomon[1,4]

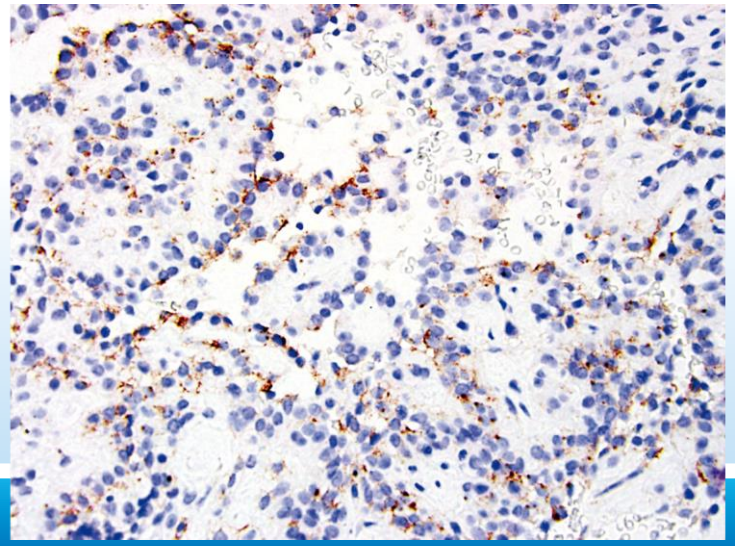


Astroblastoma, MN-1 altered









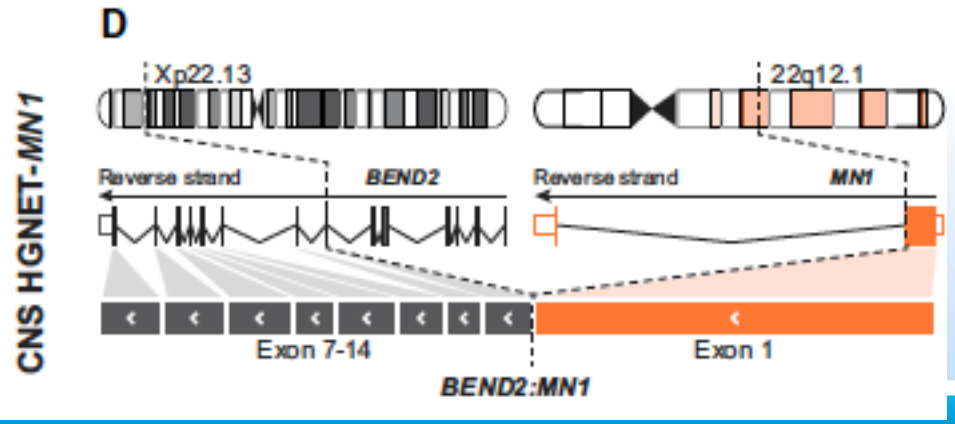
- Architectural pattern extends across diagnostic entities
- Variable presence of high-grade features
- Female predominance
- Most are supratentorial

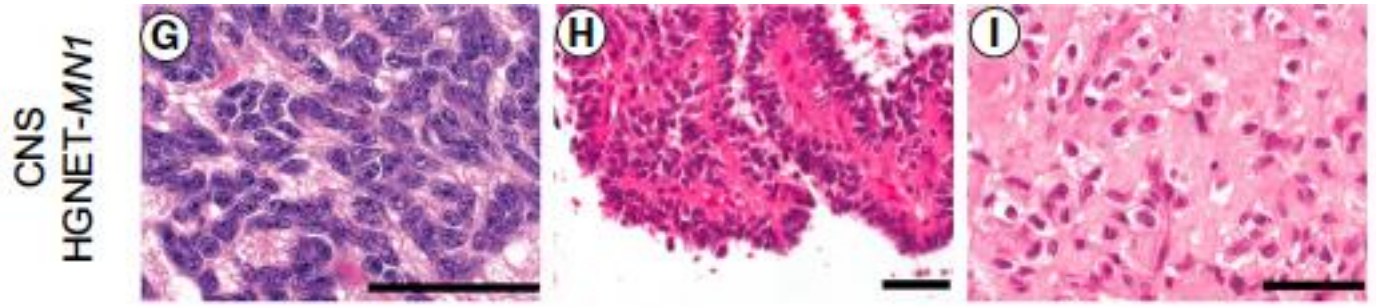
Identification as a unique constituent within supratentorial PNET

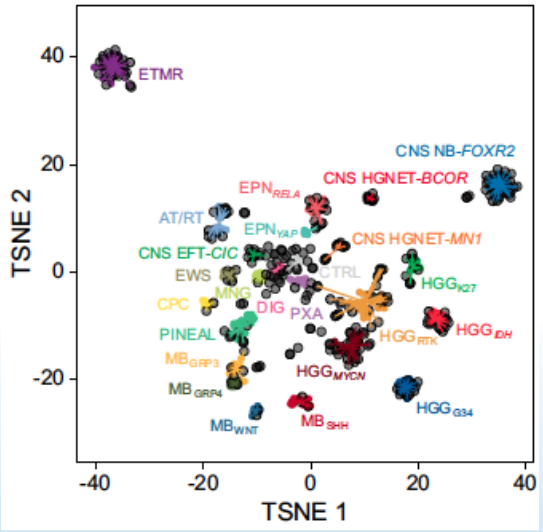
New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs

Cell, 2016

Dominik Sturm,[1,2,3,89] Brent A. Orr,[4,89] Umut H. Toprak,[2,5,89] Volker Hovestadt,[2,6,89] David T.W. Jones,[1,2] David Capper,[2,7,8] Martin Sill,[2,9] Ivo Buchhalter,[2,5] Paul A. Northcott,[1,2] Irina Leis,[7] Marina Ryzhova,[10] Christian Koelsche,[2,7,8] Elke Pfaff,[1,2,3] Sariah J. Allen,[4] Gnanaprakash Balasubramanian,[2,11] Barbara C. Worst,[1,2,3] Kristian W. Pajtler,[1,2] Sebastian Brabetz,[1,2] Pascal D. Johann,[1,2,3] Felix Sahm,[2,7,8] Jüri Reimand,[12,13] Alan Mackay,[14] Diana M. Carvalho,[14] Marc Remke,[15] Joanna J. Phillips,[16,17,18] Arie Perry,[16,17,18] Cynthia Cowdrey,[16] Rachid Drissi,[19] Maryam Fouladi,[19] Felice Giangaspero,[20,21] Maria Łastowska,[22] Wiesława Grajkowska,[22] Wolfram Scheurlen,[23] Torsten Pietsch,[24] Christian Hagel,[25] Johannes Gojo,[26,27] Daniela Lötsch,[27] Walter Berger,[27] Irene Slavc,[26] Christine Haberler,[28] Anne Jouvet,[29,30] Stefan Holm,[31] Silvia Hofer,[32] Marco Prinz,[33,34] Catherine Keohane,[35] Iris Fried,[36] Christian Mawrin,[37] David Scheie,[38] Bret C. Mobley,[39] Matthew J. Schniederjan,[40] Mariarita Santi,[41] Anna M. Buccoliero,[42] Sonika Dahiya,[43] Christof M. Kramm,[44] André O. von Bueren,[44] Katja von Hoff,[45] Stefan Rutkowski,[45] Christel Herold-Mende,[46] Michael C. Frühwald,[47] Till Milde,[2,3,48] Martin Hasselblatt,[49] Pieter Wesseling,[50,51] Jochen Rößler,[52] Ulrich Schüller,[53,54] Martin Ebinger,[55,71] Jens Schittenhelm,[56,71] Stephan Frank,[57] Rainer Grobholz,[58] Istvan Vajtai,[59] Volkmar Hans,[60] Reinhard Schneppenheim,[45] Karel Zitterbart,[61] V. Peter Collins,[62] Eleonora Aronica,[63] Pascale Varlet,[64] Stephanie Puget,[65] Christelle Dufour,[66] Jacques Grill,[66] Dominique Figarella-Branger,[67] Marietta Wolter,[68,69] Martin U. Schuhmann,[70,71] Tarek Shalaby,[72] Michael Grotzer,[72] Timothy van Meter,[73] Camelia-Maria Monoranu,[74,75] Jörg Felsberg,[68,69] Guido Reifenberger,[68,69] Matija Snuderl,[76] Lynn Ann Forrester,[77] Jan Koster,[78] Rogier Versteeg,[78] Richard Volckmann,[78] Peter van Sluis,[78] Stephan Wolf,[2,79] Tom Mikkelsen,[80] Amar Gajjar,[81] Kenneth Aldape,[82] Andrew S. Moore,[83,84] Michael D. Taylor,[15] Chris Jones,[14] Nada Jabado,[85] Matthias A. Karajannis,[86] Roland Eils,[2,5,87,88] Matthias Schlesner,[2,5] Peter Lichter,[2,6,88] Andreas von Deimling,[2,7,8] Stefan M. Pfister,[1,2,3] David W. Ellison,[4,90] Andrey Korshunov,[2,7,8,90] and Marcel Kool[1,2,90,*]







MN1 alterations define a clinically distinct tumor subgroup with astroblastomatous histopathology

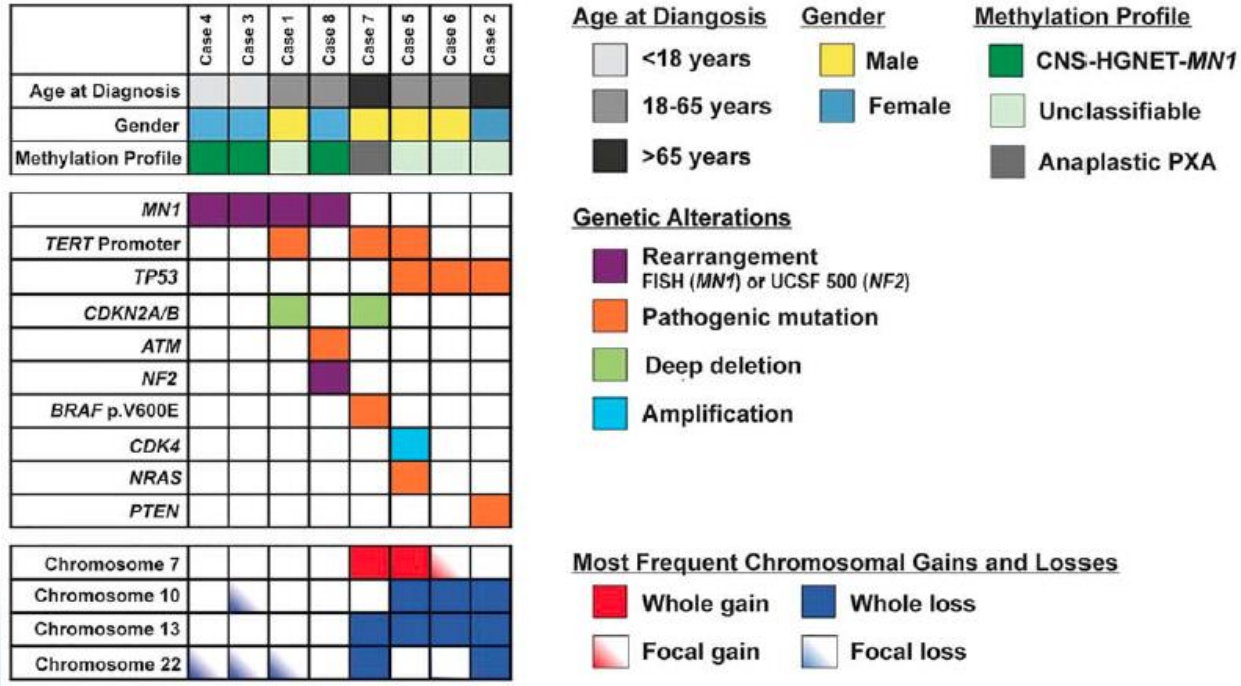
Multimodal molecular analysis of astroblastoma enables reclassification of most cases into more specific molecular entities

Brain Pathol, 2018

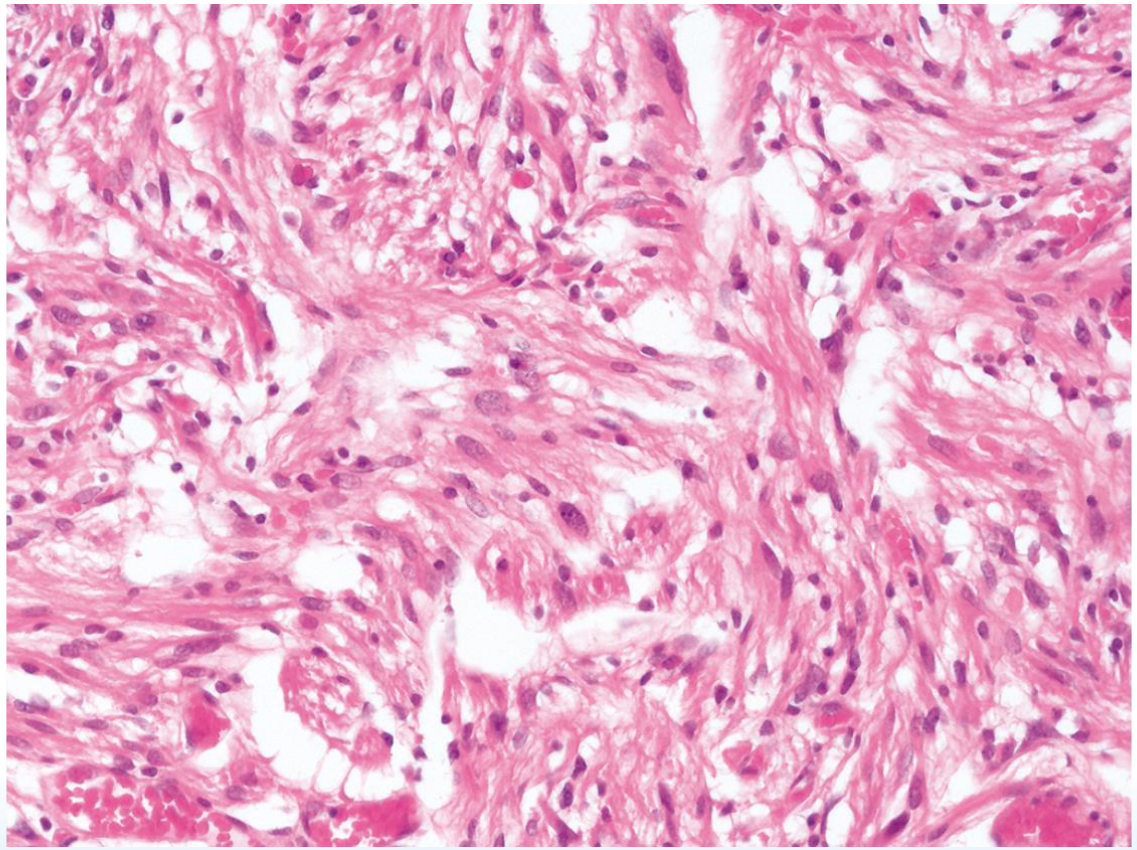
Matthew D. Wood [1]; Tarik Tihan[1]; Arie Perry[1,2]; Geeta Chacko[3]; Clinton Turner[4]; Cunfeng Pu[5]; Christopher Payne[6]; Alexander Yu[6]; Serguei I. Bannykh[7]; David A. Solomon [1]

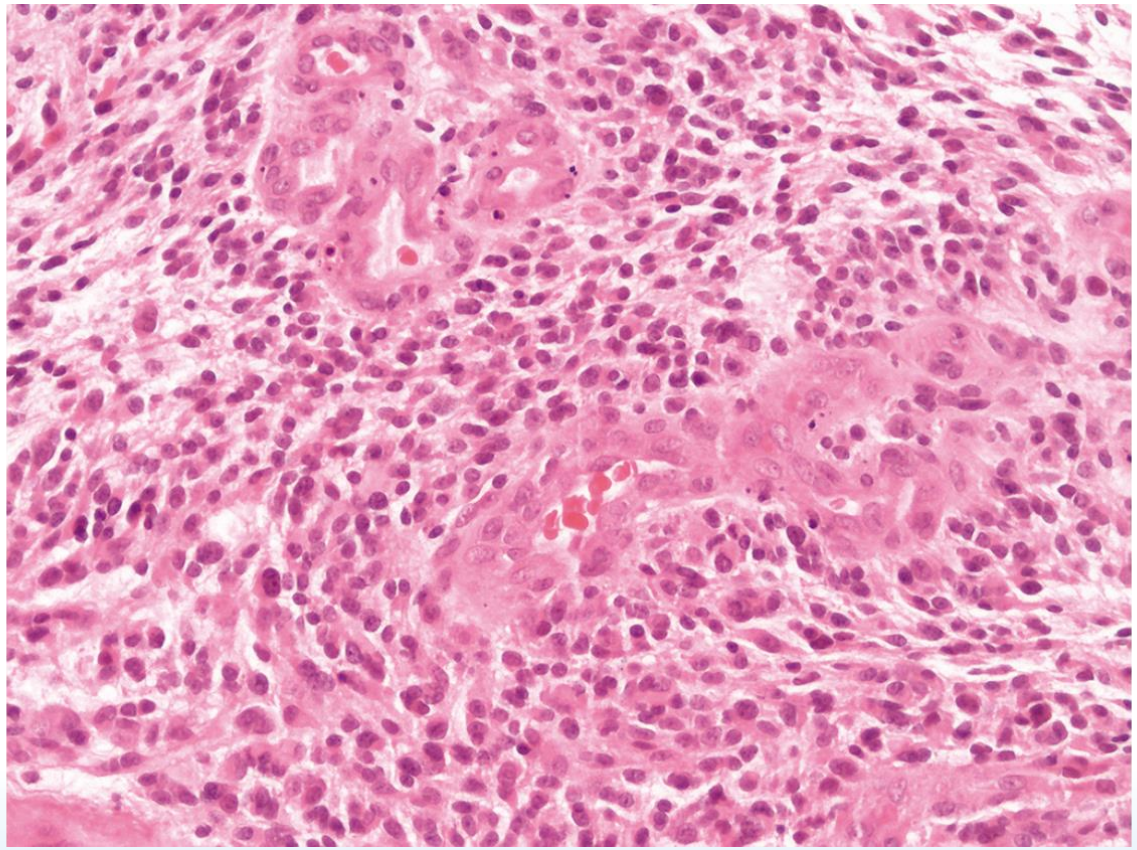
[1] Department of Pathology, Division of Neuropathology, [2] Department of Neurological Surgery, University of California, San Francisco, CA.
[3] Department of Pathology, Division of Neuropathology, Christian Medical College, Vellore, Tamil Nadu, India.
[4] Anatomical Pathology, LabPLUS Auckland City Hospital, Auckland, New Zealand.
[5] Department of Pathology, [6] Department of Neurosurgery, Allegheny General Hospital, Pittsburgh, PA.
[7] Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA.

Case	Category	UCSF 500 pathogenic alterations	*MN1* FISH	DNA methylation profiling
1	*MN1* breakapart	*CDKN2A/B* deep deletion, *TERT* promoter mutation	Breakapart	Unclassifiable
2	Unclassifiable	*TP53*, *PTEN* mutations, numerous chromosome losses	Intact, monosomy 22q	Unclassifiable
3	*MN1* breakapart	None identified	Breakapart	CNS-HGNET-*MN1*
4	*MN1* breakapart	None identified	Breakapart	CNS-HGNET-*MN1*
5	High-grade astrocytoma	*TP53*, *NRAS*, *TERT* promoter mutations, *CDK4* amplification, chromosome 7 gain/chromosome 10 loss	Intact	Unclassifiable
6	Unclassifiable	*TP53* mutation, numerous chromosome losses	Intact, polysomy 22q	Unclassifiable
7	High-grade astrocytoma	*BRAF* p.V600E, *CDKN2A/B* deep deletion, *TERT* promoter mutation	Intact, monosomy 22q	Anaplastic PXA
8	*MN1* breakapart	*ATM* mutation, *NF2* structural rearrangement	Breakapart	CNS-HGNET-*MN1*



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

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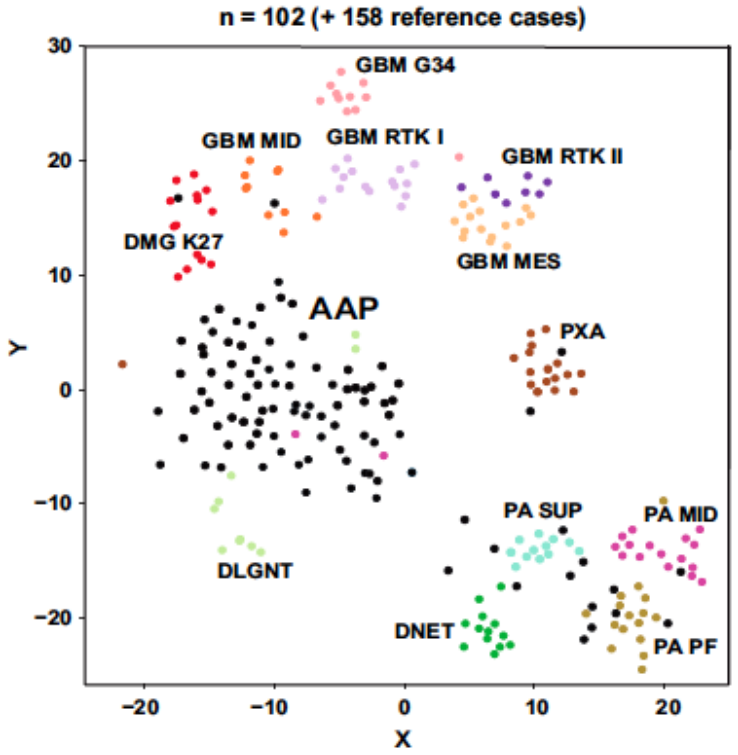
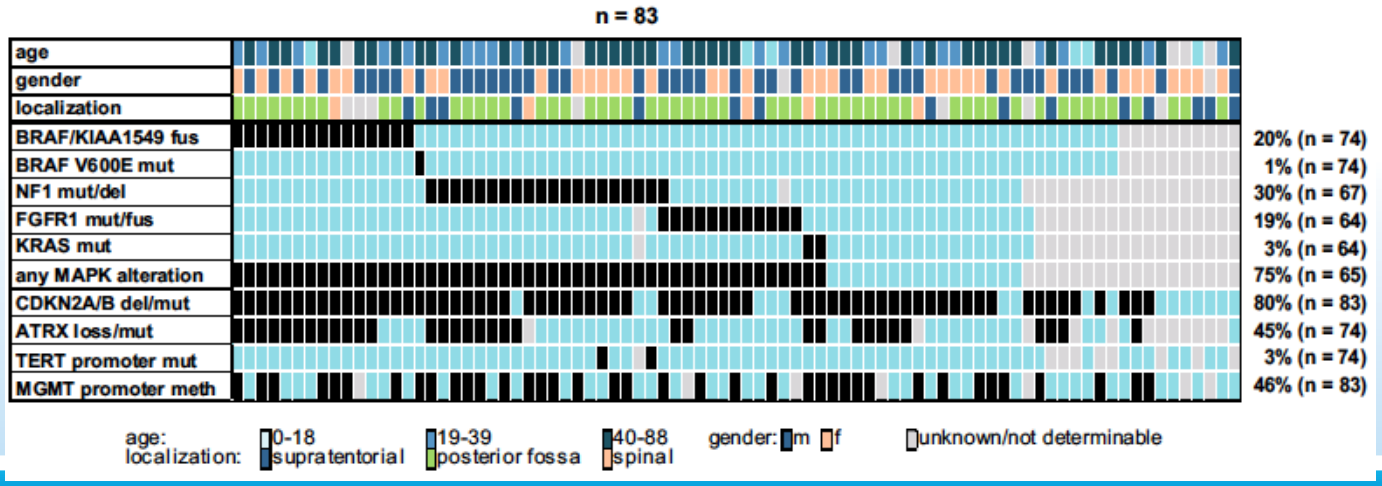
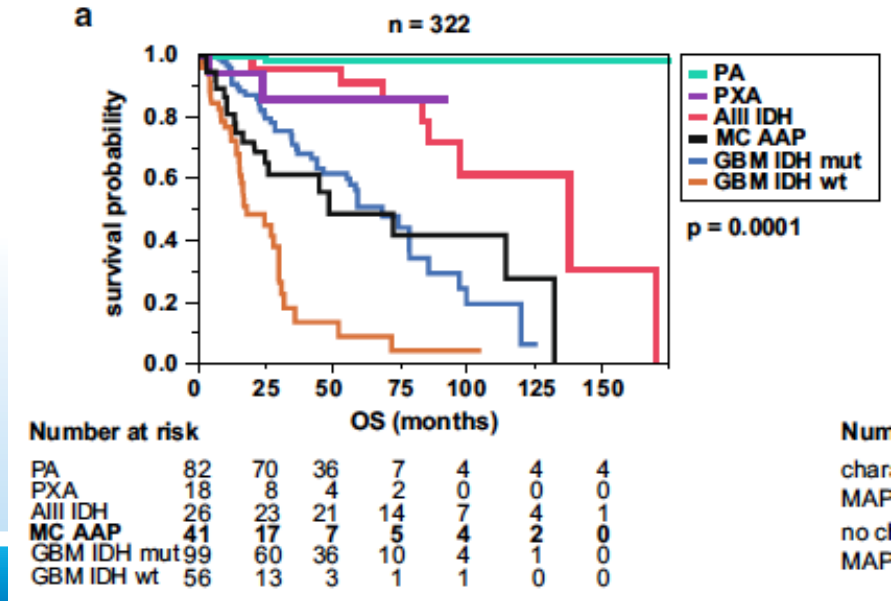
Annekathrin Reinhardt[1,2] · Damian Stichel[1,2] · Daniel Schrimpf[1,2] · Felix Sahm[1,2] · Andrey Korshunov[1,2] · David E. Reuss[1,2] · Christian Koelsche[1,2] · Kristin Huang[1,2] · Annika K. Wefers[1,2] · Volker Hovestadt[3,4] · Martin Sill[4,48] · Dorothee Gramatzki[29] · Joerg Felsberg[9] · Guido Reifenberger[9,30] · Arend Koch[7] · Ulrich-W. Thomale[35] · Albert Becker[8] · Volkmar H. Hans[10] · Marco Prinz[11,47] · Ori Staszewski[11] · Till Acker[12] · Hildegard Dohmen[12] · Christian Hartmann[13] · Wolf Mueller[14] · Muin S. A. Tuffaha[36] · Werner Paulus[15] · Katharina Heß[15] · Benjamin Brokinkel[15] · Jens Schittenhelm[16] · Camelia-Maria Monoranu[17] · Almuth Friederike Kessler[37] · Mario Loehr[37] · Rolf Buslei[18,19] · Martina Deckert[20] · Christian Mawrin[21] · Patricia Kohlhof[22] · Ekkehard Hewer[23] · Adriana Olar[24,25,26] · Fausto J. Rodriguez[27] · Caterina Giannini[28] · Amulya A. NageswaraRao[28] · Uri Tabori[38,39,40,41] · Nuno Miguel Nunes[40,41] · Michael Weller[29] · Ute Pohl[31] · Zane Jaunmuktane[32] · Sebastian Brandner[32] · Andreas Unterberg[42] · Daniel Hänggi[43] · Michael Platten[44,45] · Stefan M. Pfister[4,5,6,48] · Wolfgang Wick[33,4] · Christel Herold-Mende[34] · David T. W. Jones[4,48,49] · Andreas von Deimling[1,2,4] · David Capper[1,2,46,50]



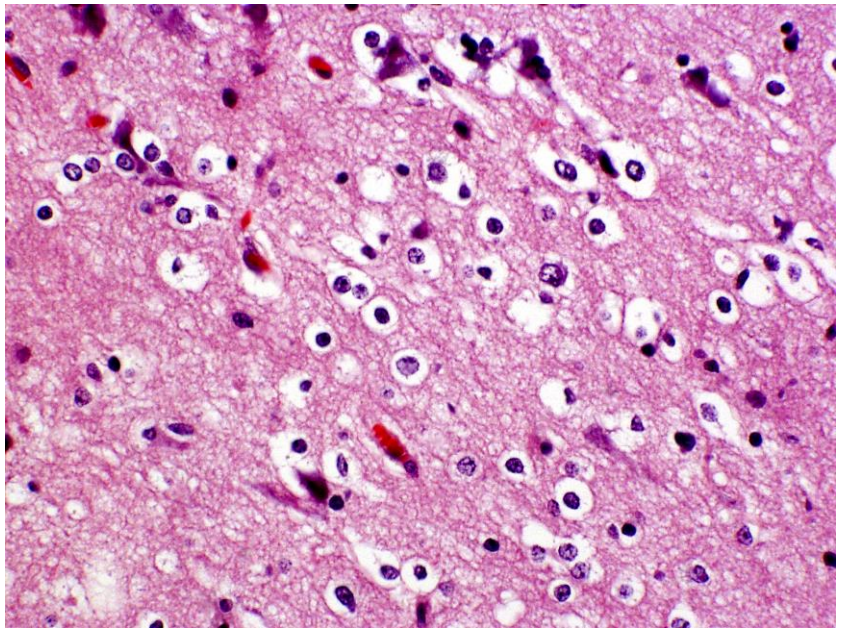


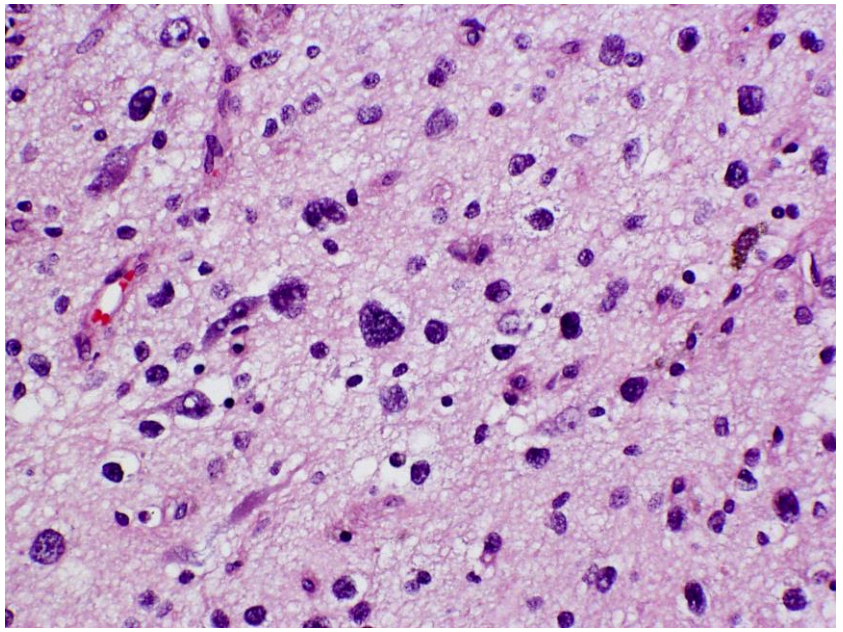


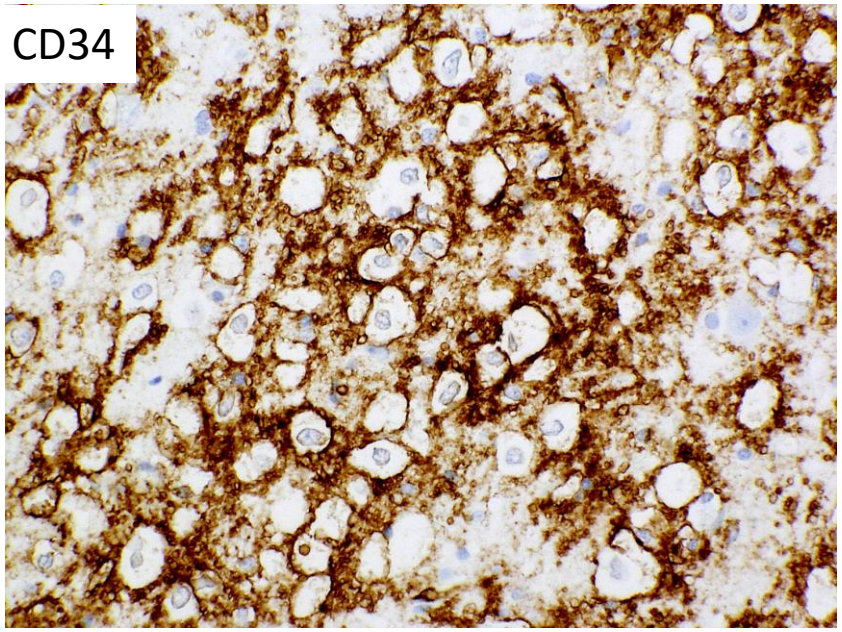
Summary

- 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

Q & A