Novelties in the WHO 2016 classification of brain tumours

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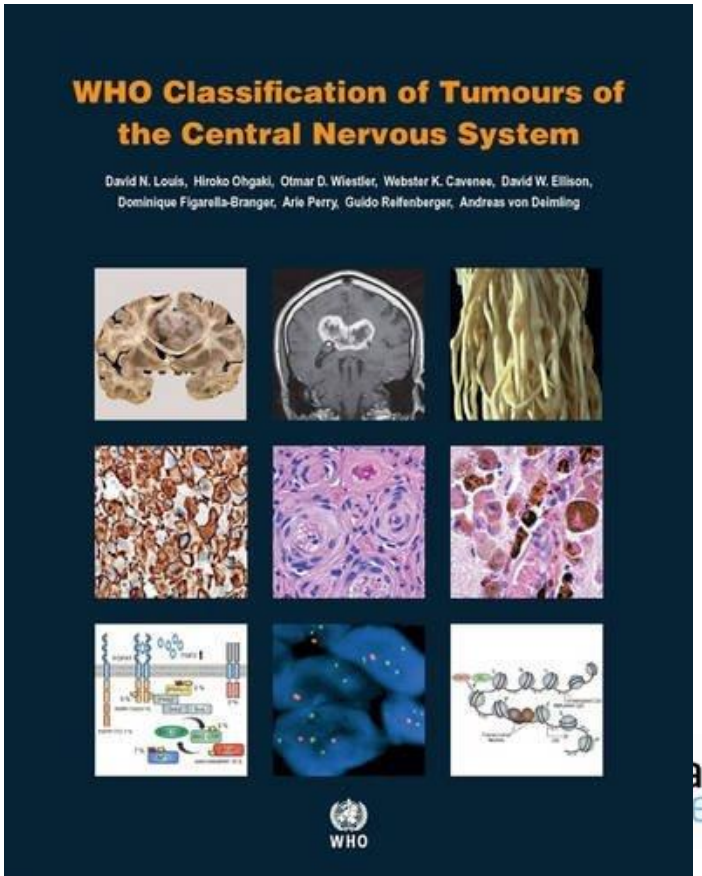
REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[4,5] · Dominique Figarella-Branger[6] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]



The 2016 WHO classification

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- A nosological shift
  - « Integrated » diagnostic
- New entities, new variants and pattern and deletion of others
- Some tumour groups have been deeply changed
  - Gliomas
  - Embryonal tumours
- Limits
- Future directions

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A nosological shift

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Before 2016

- The diagnosis was based on histological parameters only
  - Classification according to microscopic similarities with different putative cells of origin
  - Histopronostic criteria
- Discovery of cannonical genetic alterations
- How can we integrate these genetic data in the diagnosis of tumours of the SNC?

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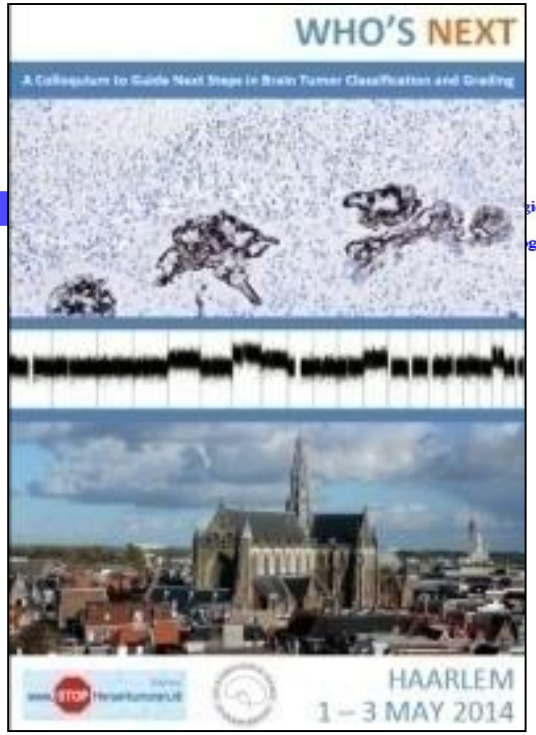
Guidelines for how to incorporate molecular findings into brain tumour diaanoses



Brain Pathology ISSN 1015-6305

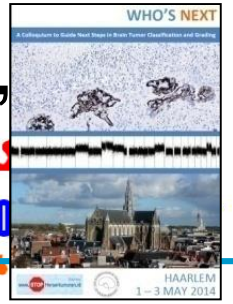
MISCELLANEOUS

International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading

David N. Louis[1]; Arie Perry[2]; Peter Burger[3]; David W. Ellison[4]; Guido Reifenberger[5,6]; Andreas von Deimling[6,7]; Kenneth Aldape[8]; Daniel Brat[9]; V. Peter Collins[10]; Charles Eberhart[3]; Dominique Figarella-Branger[11]; Gregory N. Fuller[12]; Felice Giangaspero[13,14]; Caterina Giannini[15]; Cynthia Hawkins[16]; Paul Kleihues[17]; Andrey Korshunov[6,18]; Johan M. Kros[19]; M. Beatriz Lopes[20]; Ho-Keung Ng[21]; Hiroko Ohgaki[22]; Werner Paulus[23]; Torsten Pietsch[24]; Marc Rosenblum[25]; Elisabeth Rushing[26]; Figen Soylemezoglu[27]; Otmar Wiestler[28]; Pieter Wesseling[29,30]

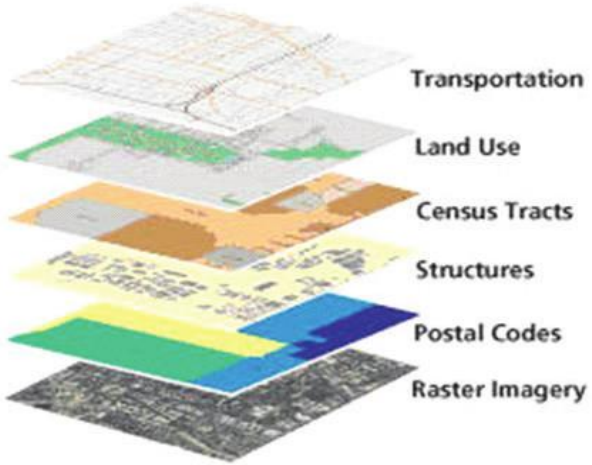
In

ISN-Haarlem format of “layered diagnoses”

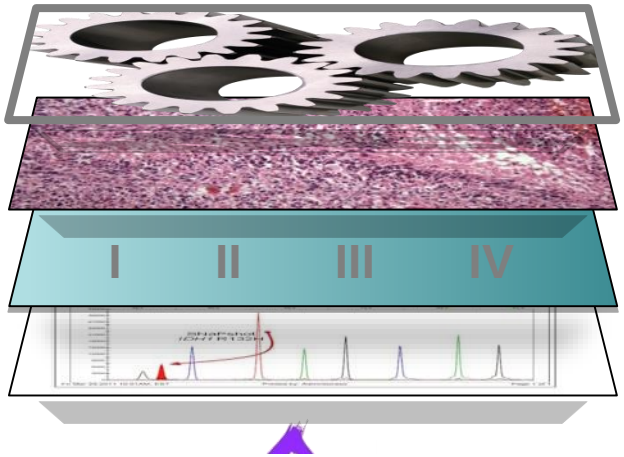


- Integrated Diagnosis (incorporated all aspects of tissue diagnosis)
- Histological Diagnosis
- WHO Grade (histological grade)
- Molecular information

Google Maps: GIS layers
Organized by Geographical Positioning



ISN-Haarlem
layered diagnosis format



Courtesy of D. Louis

A nosological shift

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2016

- Integrated diagnosis:
  - Combination of histopathological and molecular features
  - Must be performed by the pathologist
- NOS « Not Otherwise Specified » : there is insufficient information to assign a more specific code :
  - The genetic tests have not been performed
  - They have been not fully performed
  - The results does not show the diagnostic genetic alterations

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Gliomas in 2016: the major findings that have preceded the changes

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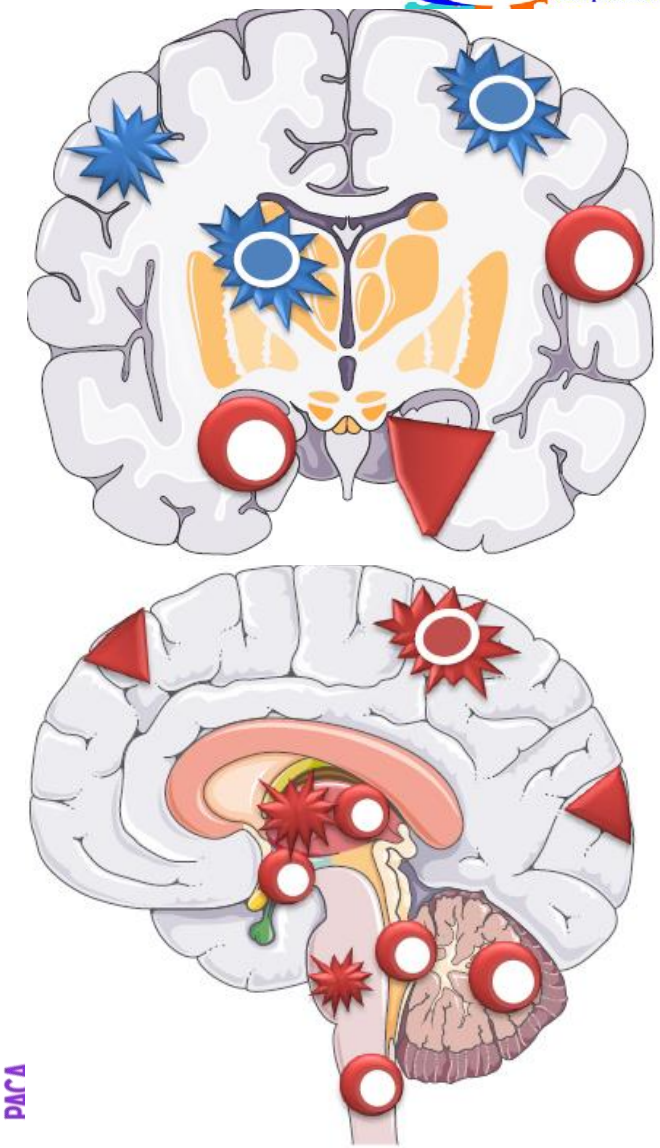
- Major advances in genetics
  - Distinction between infiltrative and circumbscribed gliomas
  - Distinction between adult and children infiltrative gliomas
- The mixed gliomas are no longer recognized
- Some histologically defined gliomas are highly heterogeneous
- Molecular alterations define three groups of adult gliomas grade II and III



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The master genes of infiltrative gliomas

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- Thanks to the whole-genome sequencing
- *IDH* mutations characterized grade II and III adult infiltrative gliomas whatever their subtype (astro, oligo, mixte)
- Histone mutations characterized infiltrative gliomas in children and young adults (midline gliomas)

Science 2008: Parson et al

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons[1,2,*], Siân Jones[1,*], Xiaosong Zhang[1,*], Jimmy Cheng-Ho Lin[1,*], Rebecca J. Leary[1,*], Philipp Angenendt[1,*], Parminder Mankoo[3], Hannah Carter[3], I-Mei Siu[4], Gary L. Gallia[4], Alessandro Olivi[4], Roger McLendon[5], B. Ahmed Rasheed[5], Stephen Keir[5], Tatiana Nikolskaya[6], Yuri Nikolsky[7], Dana A. Busam[8], Hanna Tekleab[8], Luis A. Diaz Jr.[1], James Hartigan[9], Doug R. Smith[9], Robert L. Strausberg[8], Suely Kazue Nagahashi Marie[10], Sueli Mieko Oba Shinjo[10], Hai Yan[5], Gregory J. Riggins[4], Darell D. Bigner[5], Rachel Karchin[3], Nick Papadopoulos[1], Giovanni Parmigiani[1], Bert Vogelstein[1,†], Victor E. Velculescu[1,†], and Kenneth W. Kinzler[1,†]

Nature 2012: Schwartzentruber et al

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

Nature Genet 2012: Wu et al

Somatic Histone H3 Alterations in Paediatric Diffuse Intrinsic Pontine Gliomas and Non-Brainstem Glioblastomas

Gang Wu[1,*], Alberto Broniscer[2,*], Troy A McEachron[3,*], 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,*], and Suzanne J Baker[3,*] for the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project

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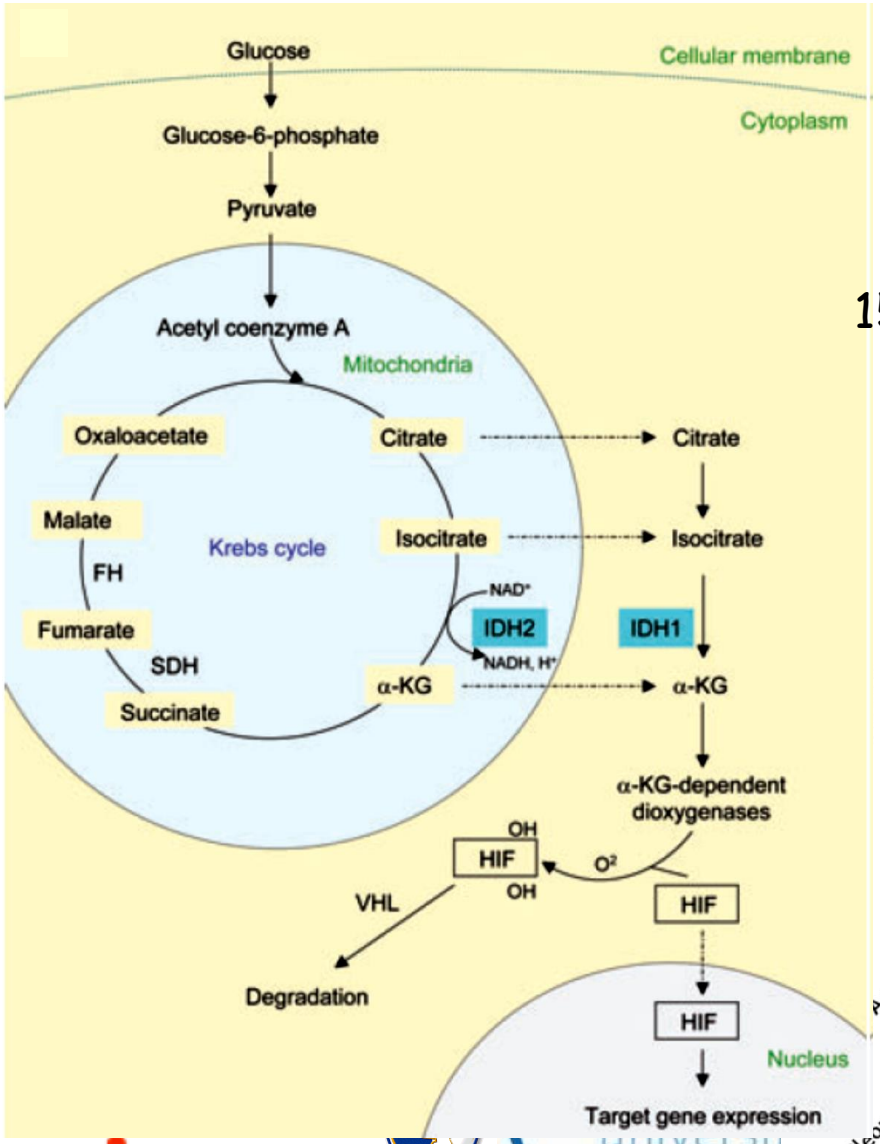
IDH genes (isocitrate deshydrogenase)



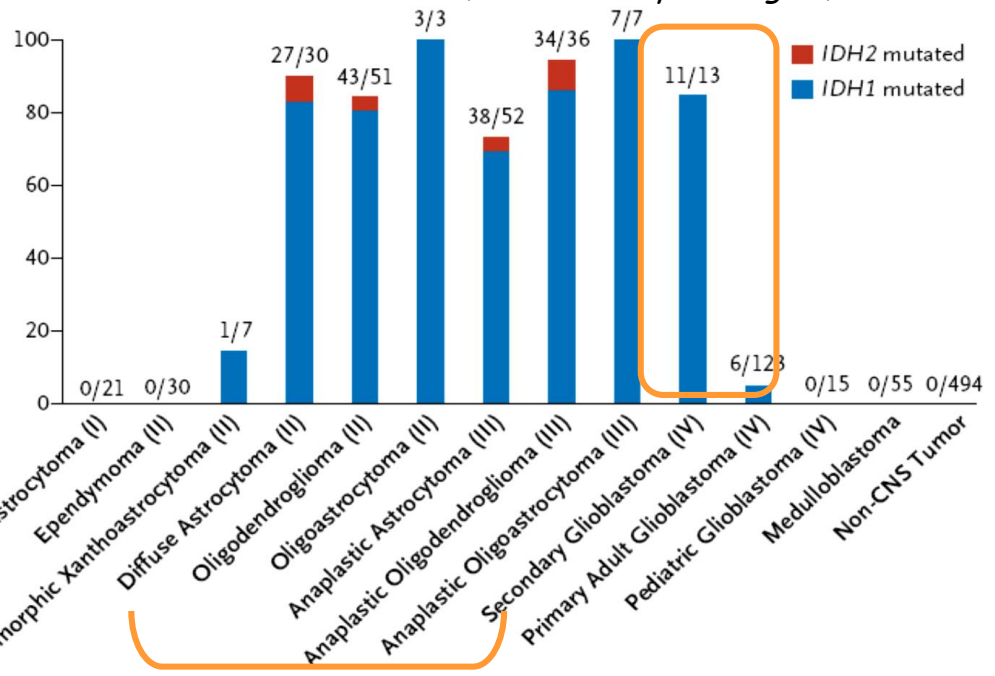
- *Ohgaki et Kleihues, Cancer Science, 2009* -

2q33

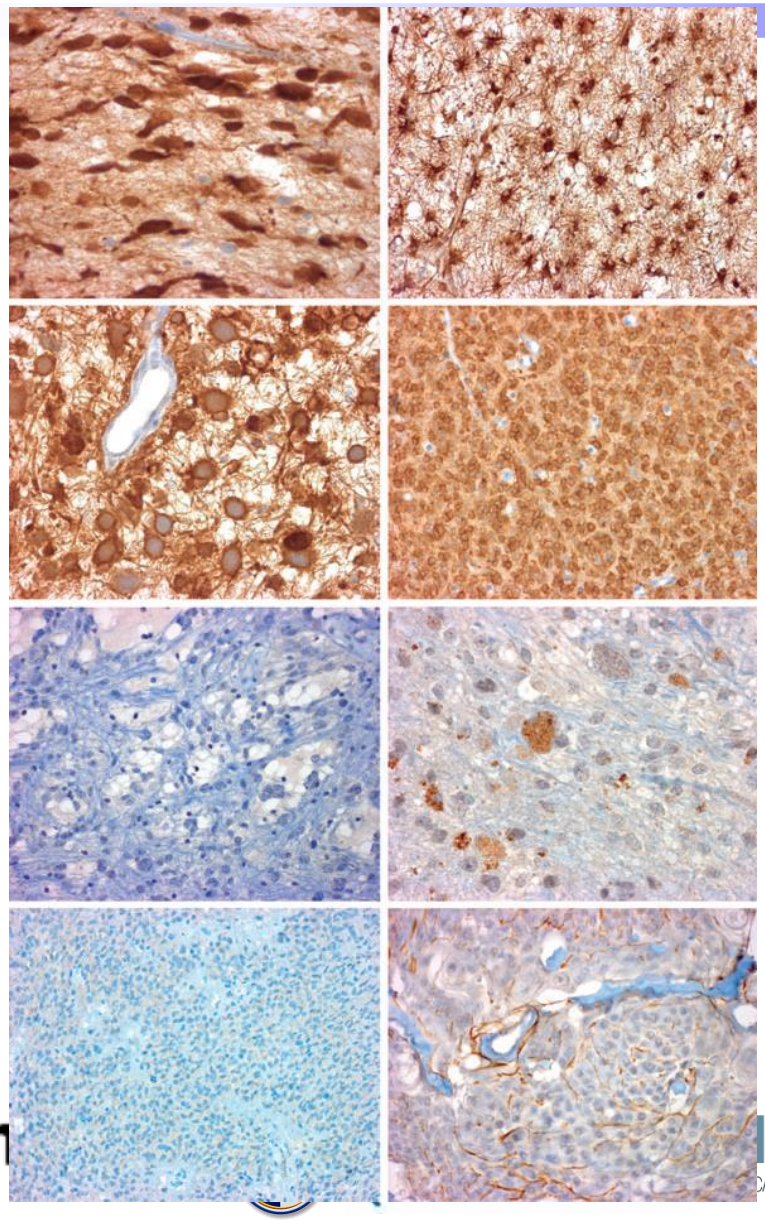
15q26.1

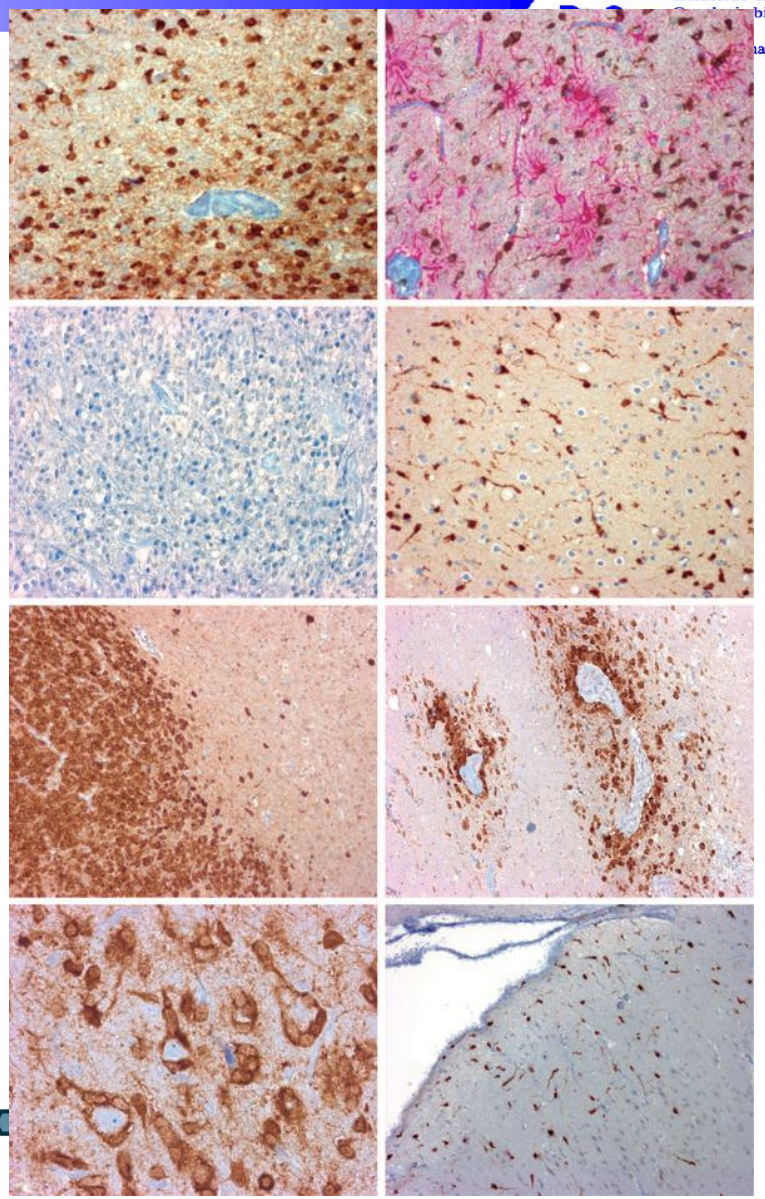
Gene	Nucleotide change	Amino acid change	*N* (%)
IDH1	G395A	R132H	664 (92.7%)
	C394T	R132C	29 (4.2%)
	C394A	R132S	11 (1.5%)
	C394G	R132G	10 (1.4%)
	G395T	R132L	2 (0.2%)
IDH2	G515A	R172K	20 (64.5%)
	G515T	R172M	6 (19.3%)
	A514T	R172W	5 (16.2%)

- *Hartmann et al., Acta Neuropathologica, 2009* -



The usefulness of IDH1R132H antibody *(Capper et al 2009)*





Histone mutations (K27M) are a common feature of midline gliomas

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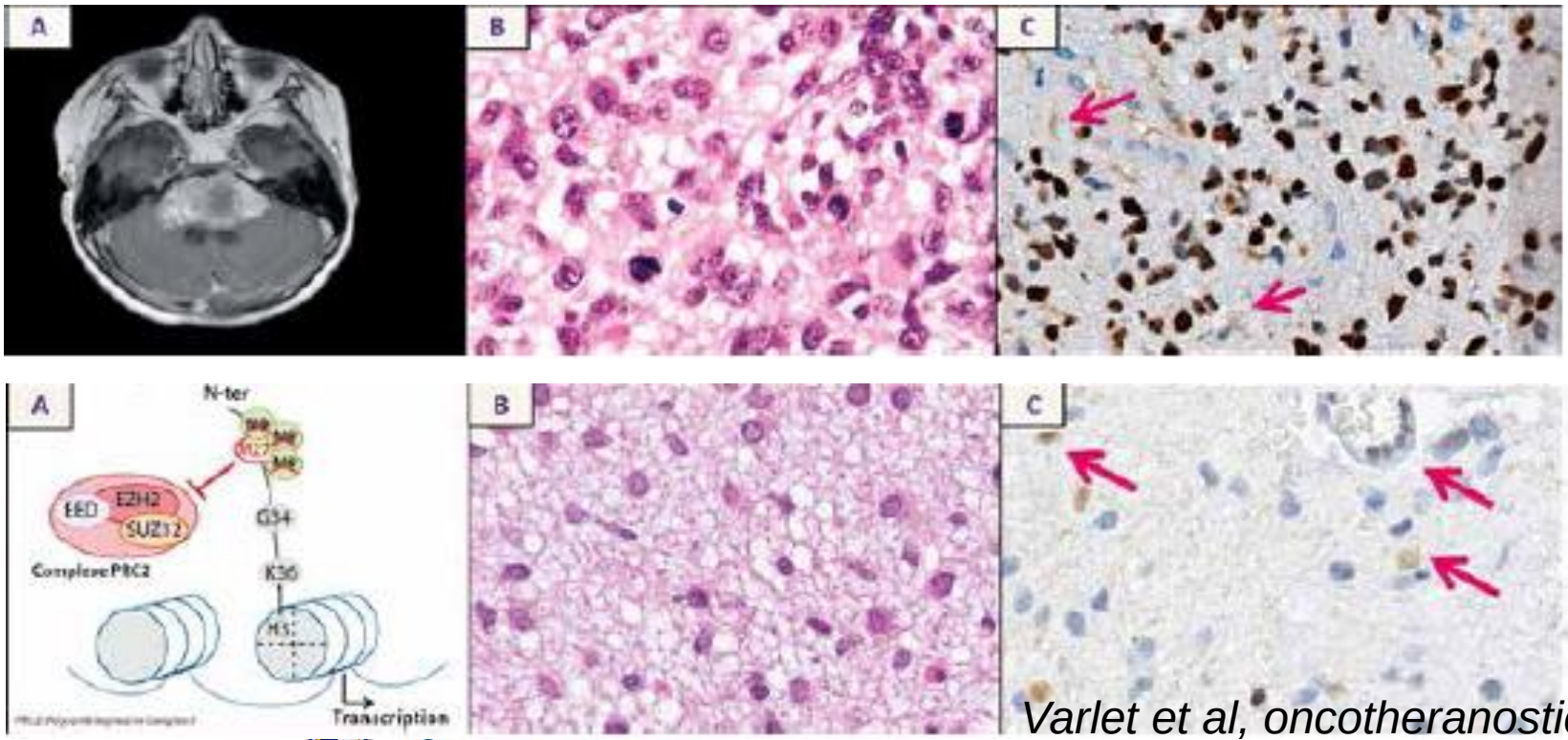
- K27M mutation *in H3F3A and HIST1H3B HIST1H3C* genes can be detect by immunohistochemistry



Varlet et al, oncotheranostic 2016

Other genetic alterations associated with IDH and histone mutations

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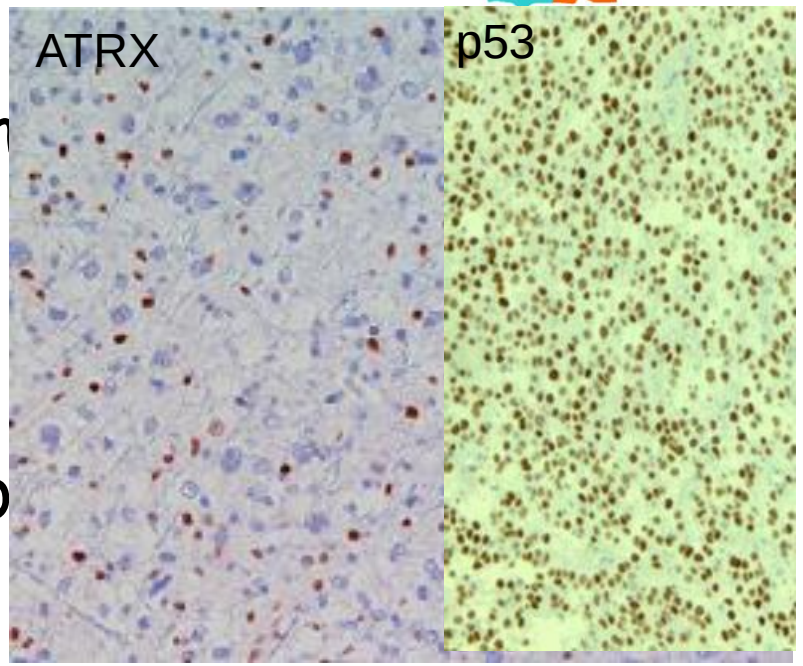
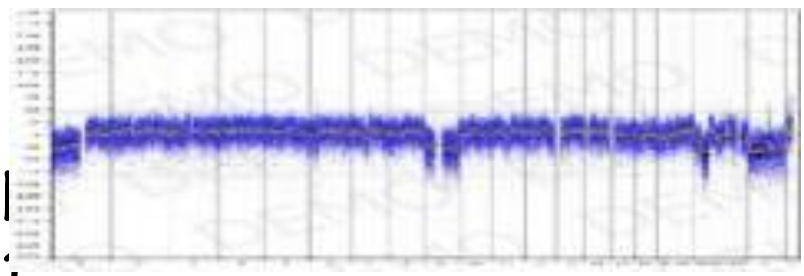
- *ATRX* and *TP53*
  - Associated with IDH and histon mutations
  - Astrocytic phenotype



- 1p19q codeletion:translocatio t(1.19)(q10;p10)
  - Associated with IDH mutations
  - Oligodendroglial phenotype
  - Other mutations associated wit 1p19q codel : CIC (19q) et FUBP1 (1p)



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MAPK pathway alterations: whole genome sequencing of 96 PA cases *(Jones et al 2013)*

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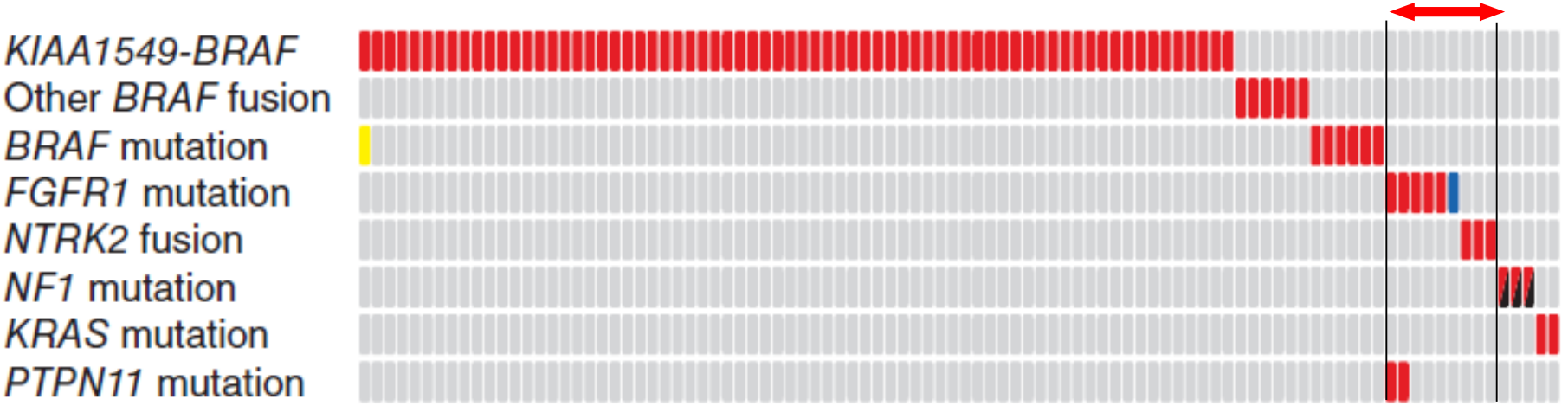
Extra cerebellar PA



- All PA demonstrated at least one alteration
- These altérations are mutually exclusive except for FGFR1 and PTPN11
- The *KIAA1549-BRAF* fusion is the most frequent one
- *FGFR1* mutation and *NTRK2* fusion are observed in extra-cerebellar PA

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Mixed gliomas

Acta Neuropathol (2014) 128:551–559
DOI 10.1007/s00401-014-1326-7

ORIGINAL PAPER

Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma

Felix Sahm · David Reuss · Christian Koelsche · David Capper · Jens Schittenhelm · Stephanie Heim · David T. W. Jones · Stefan M. Pfister · Christel Herold-Mende · Wolfgang Wick · Wolf Mueller · Christian Hartmann · Werner Paulus · Andreas von Deimling

Some histologically defined gliomas are heterogeneous exemple of anaplastic oligodendrogliomas

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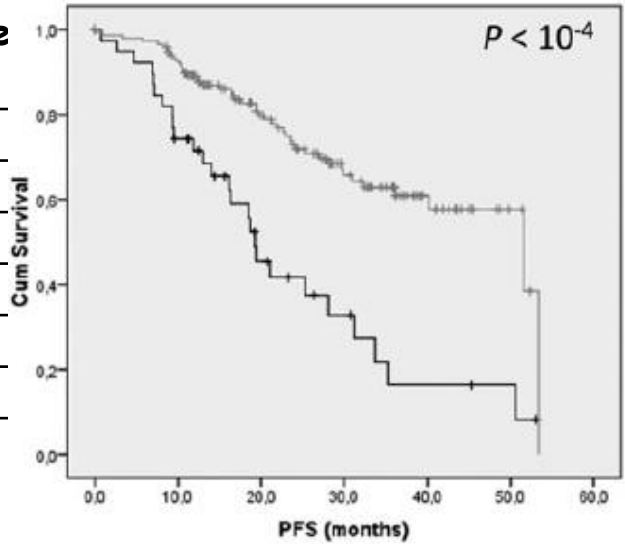
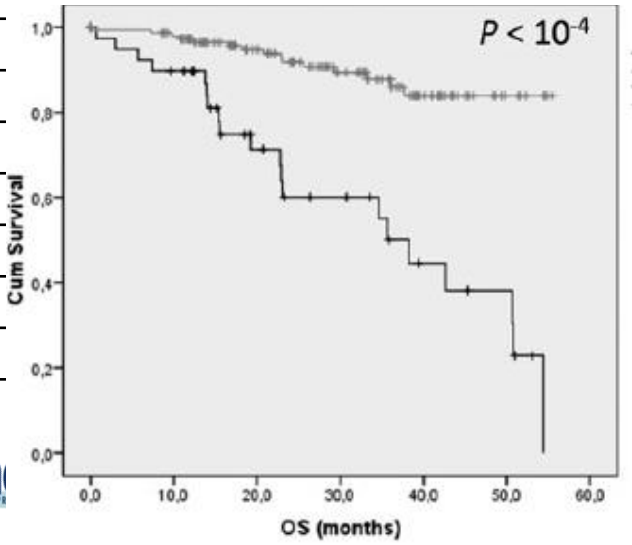
	Intact 1p19q AO	1p19q codelete AO
MPV	88%	82%
Necrosis	**44%**	28%
INA	22.5%	**88.5%**
TP53	**29%**	12%
IDH R132H	29%	**88%**
IDH1/2 mutation	44%	**97%**
Amplifications	**41%**	0
EGFR	13%	
PDGFRA	10%	
CDKN2A deletion	**24%**	<1%
Chr 4 loss	3%	**31%**
Chr 7gain	**45%**	10%
Chr 9q loss	0	**15%**
Chr 10 loss	**44%**	4%
Chr 11q gain	0	**16%**
Chr 17p loss	16%	<1%
Mean of chromosome alterations	**7.1**	4.7





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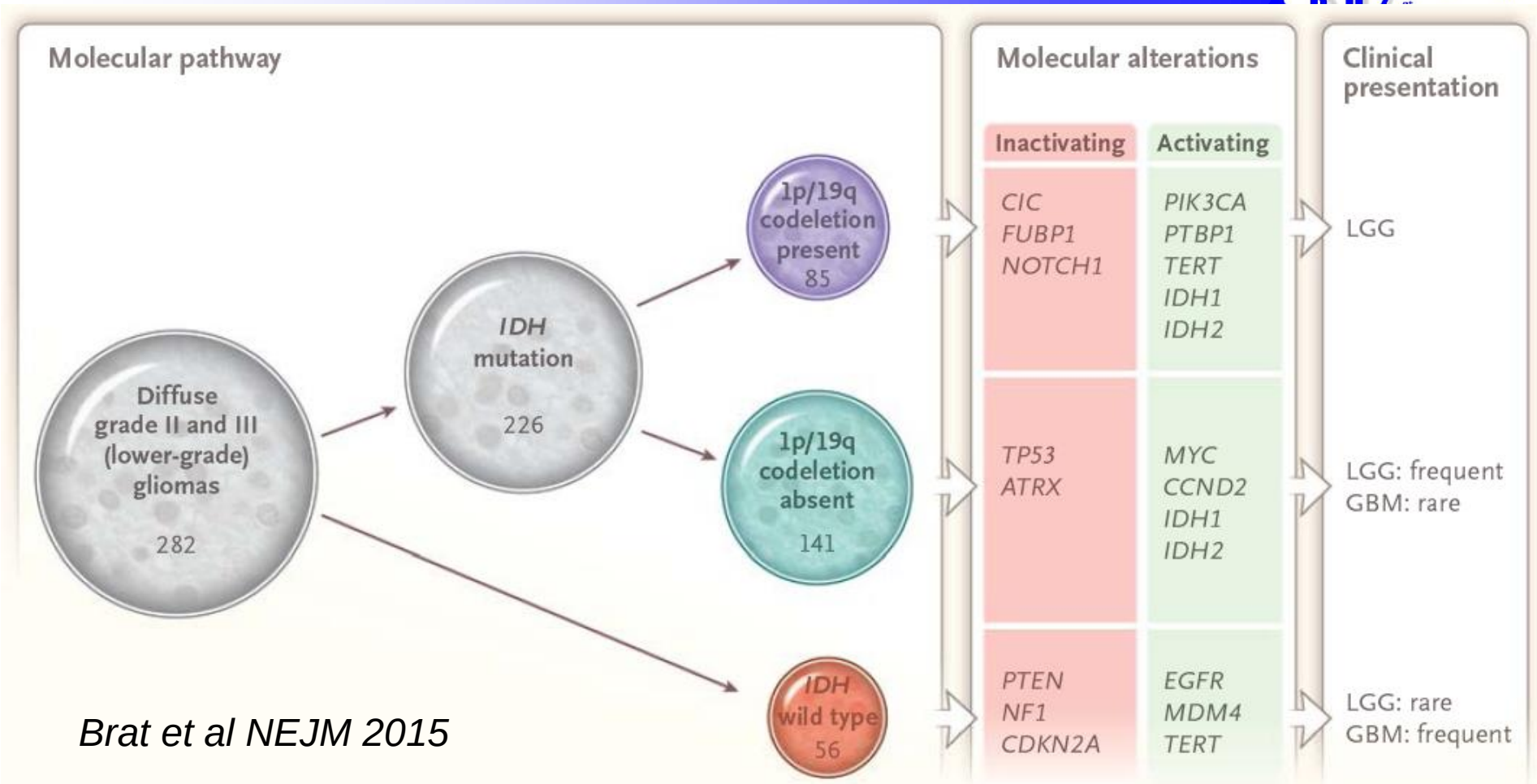
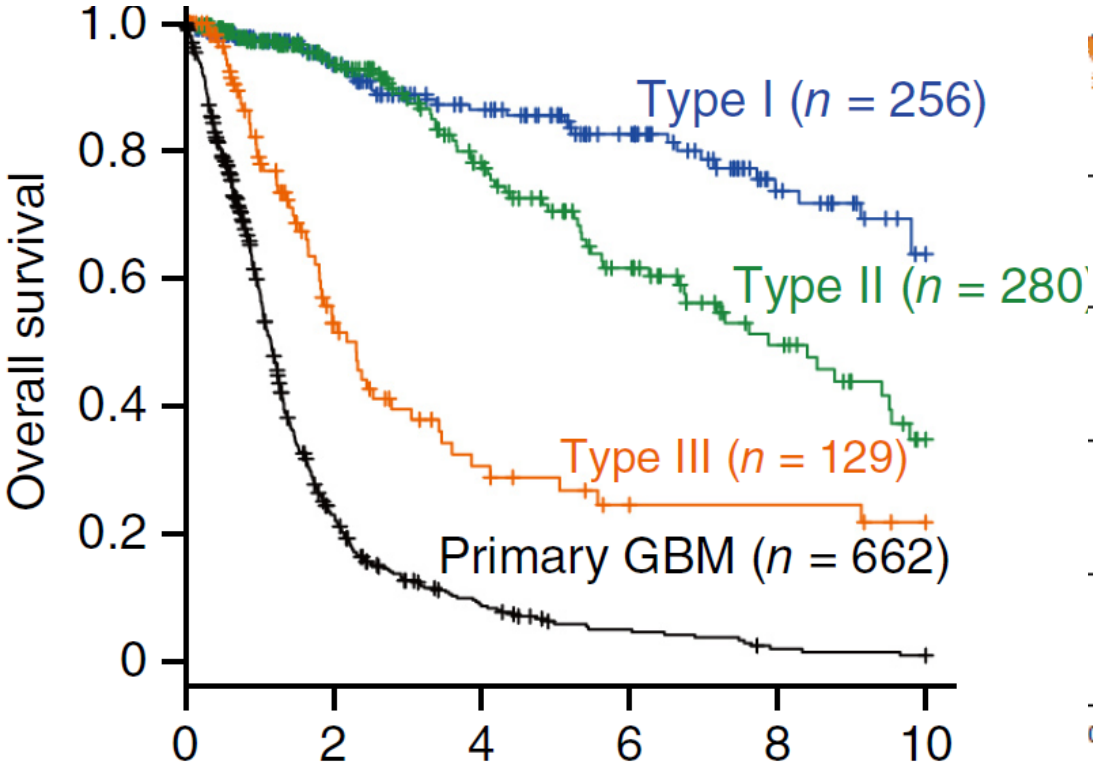
Stratification of grade II and III gliomas

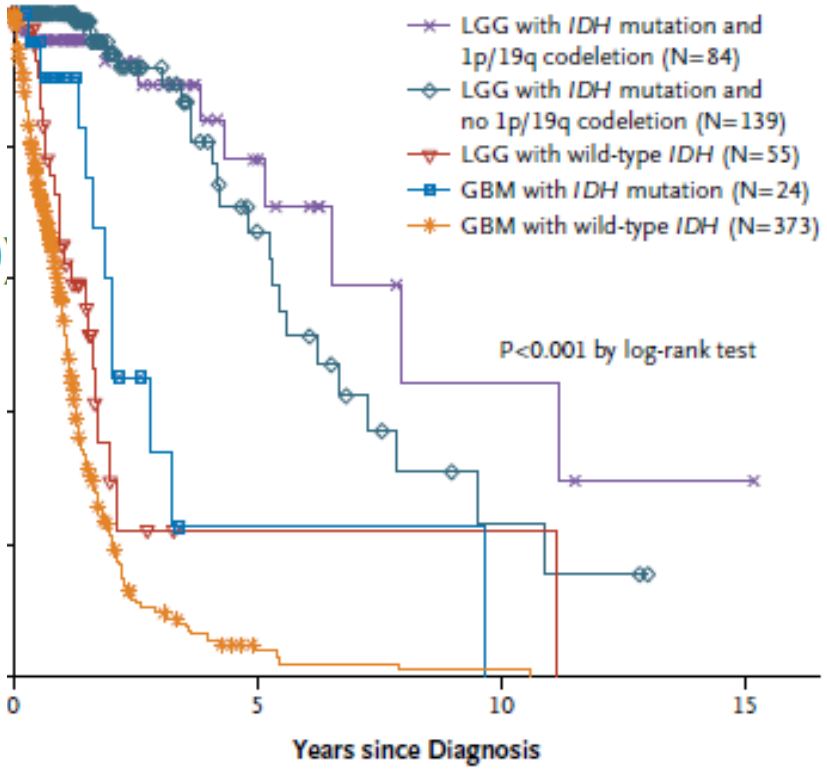


Brat et al NEJM 2015

Pronostic impact of molecular subgroups



Suzuki et al nature Genet 2015



Brat et al NEJM 2015

Gliomas in 2016

Astrocytic tumours
Pilocytic astrocytoma
Pilomyxoid astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma
Diffuse astrocytoma
Fibrillary astrocytoma
Gemistocytic astrocytoma
Protoplasmic astrocytoma
Anaplastic astrocytoma
Glioblastoma
Giant cell glioblastoma
Gliosarcoma
Gliomatosis cerebri

Oligodendroglial tumours
Oligodendroglioma
Anaplastic oligodendroglioma

Oligoastrocytic tumours
Oligoastrocytoma
Anaplastic oligoastrocytoma

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3

Diffuse midline glioma, H3K27M mutant: a new entity

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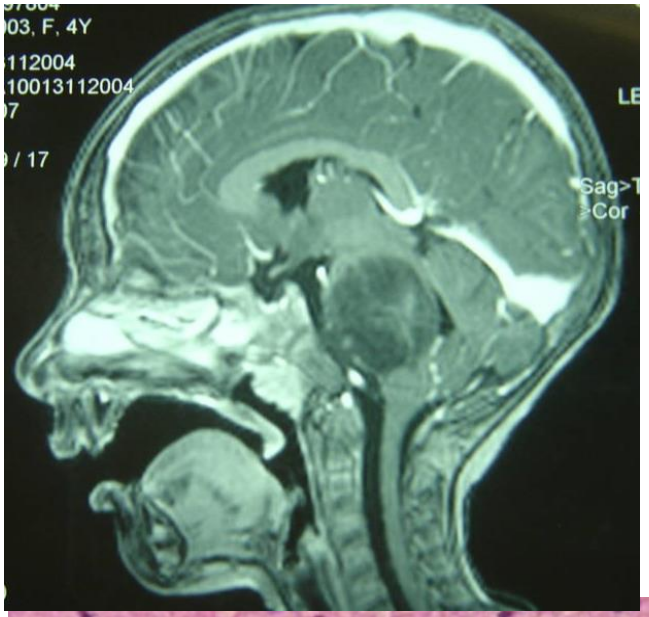
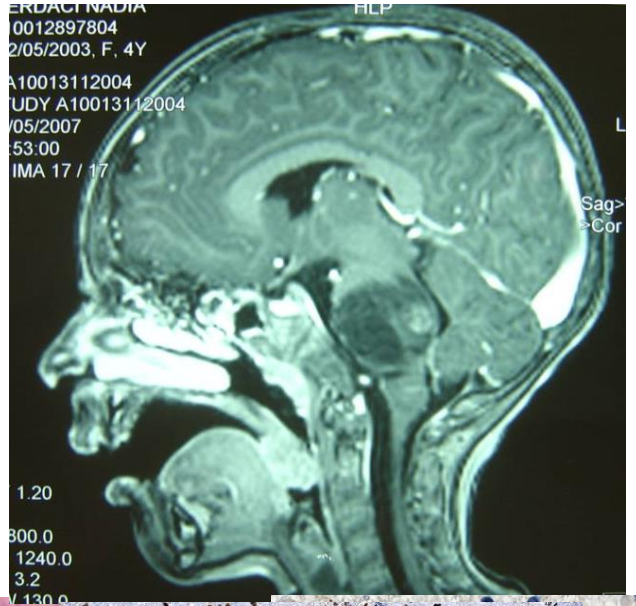
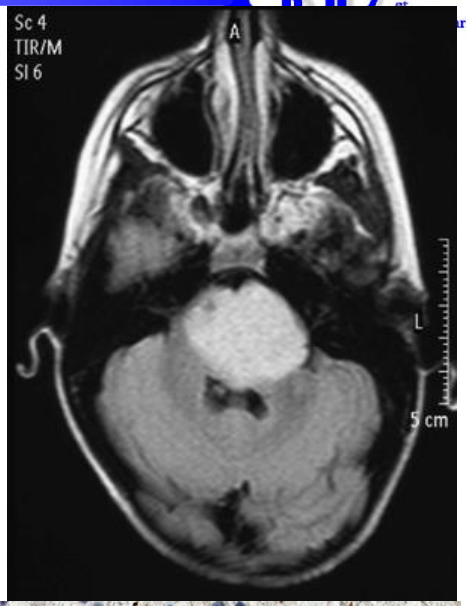
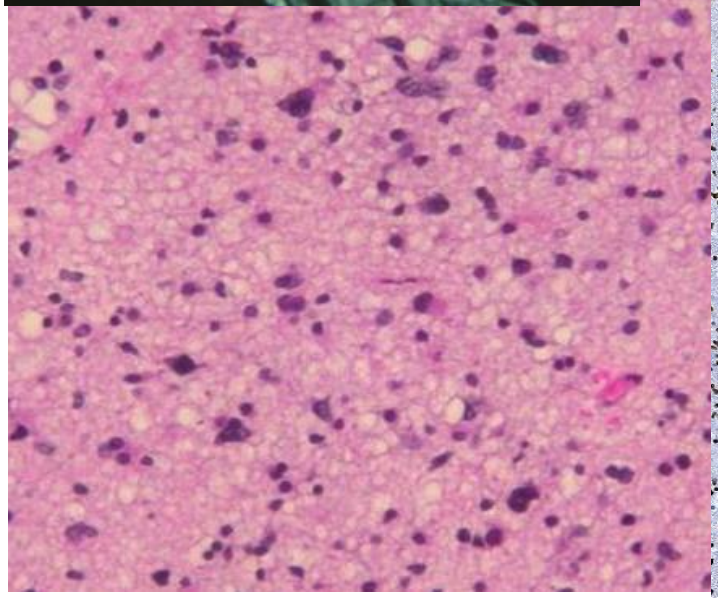
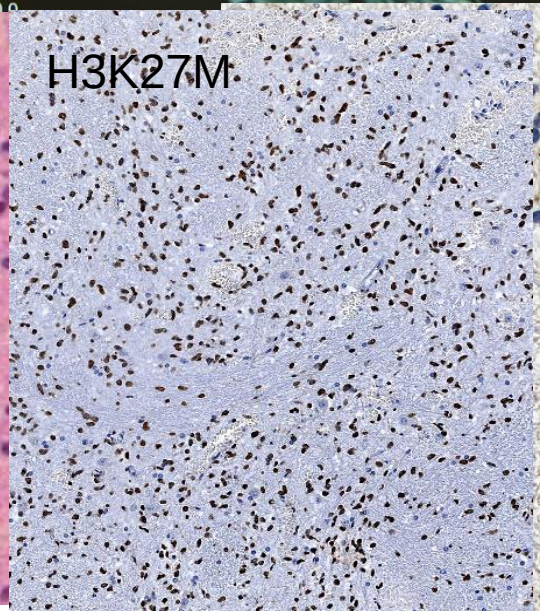
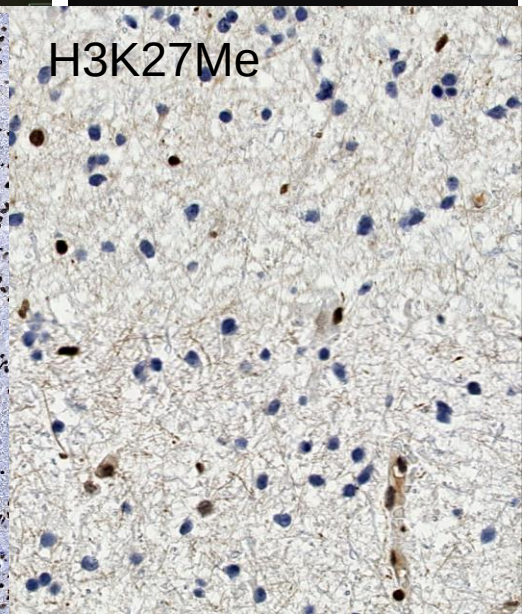


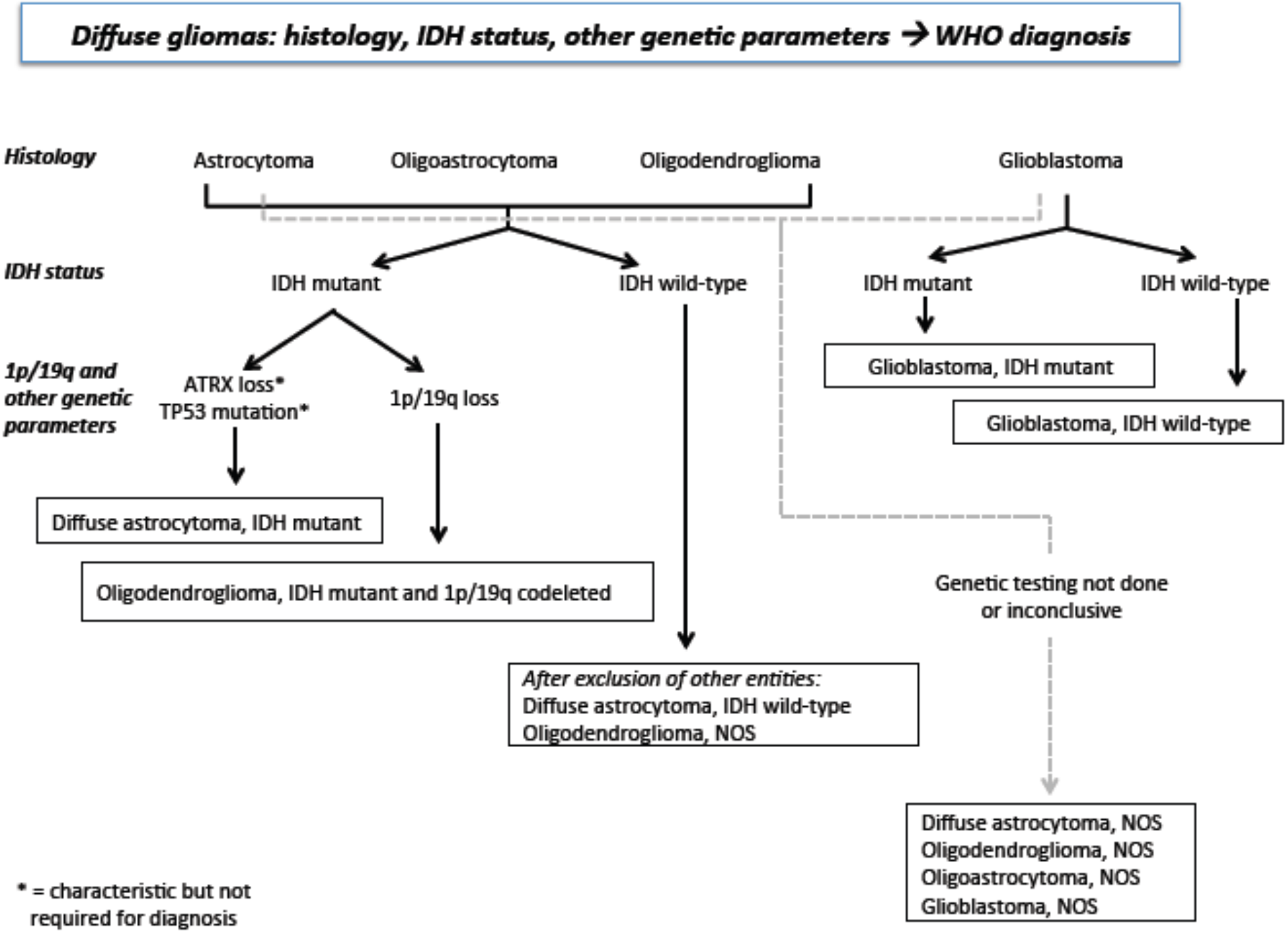






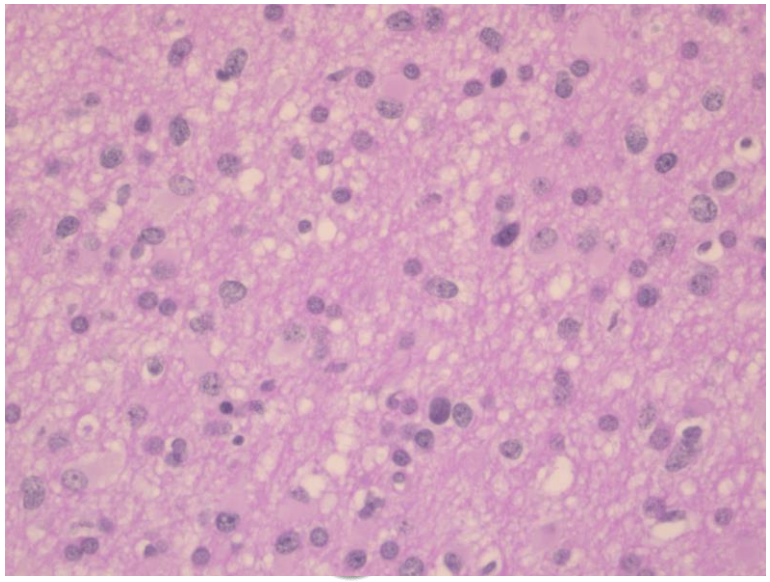


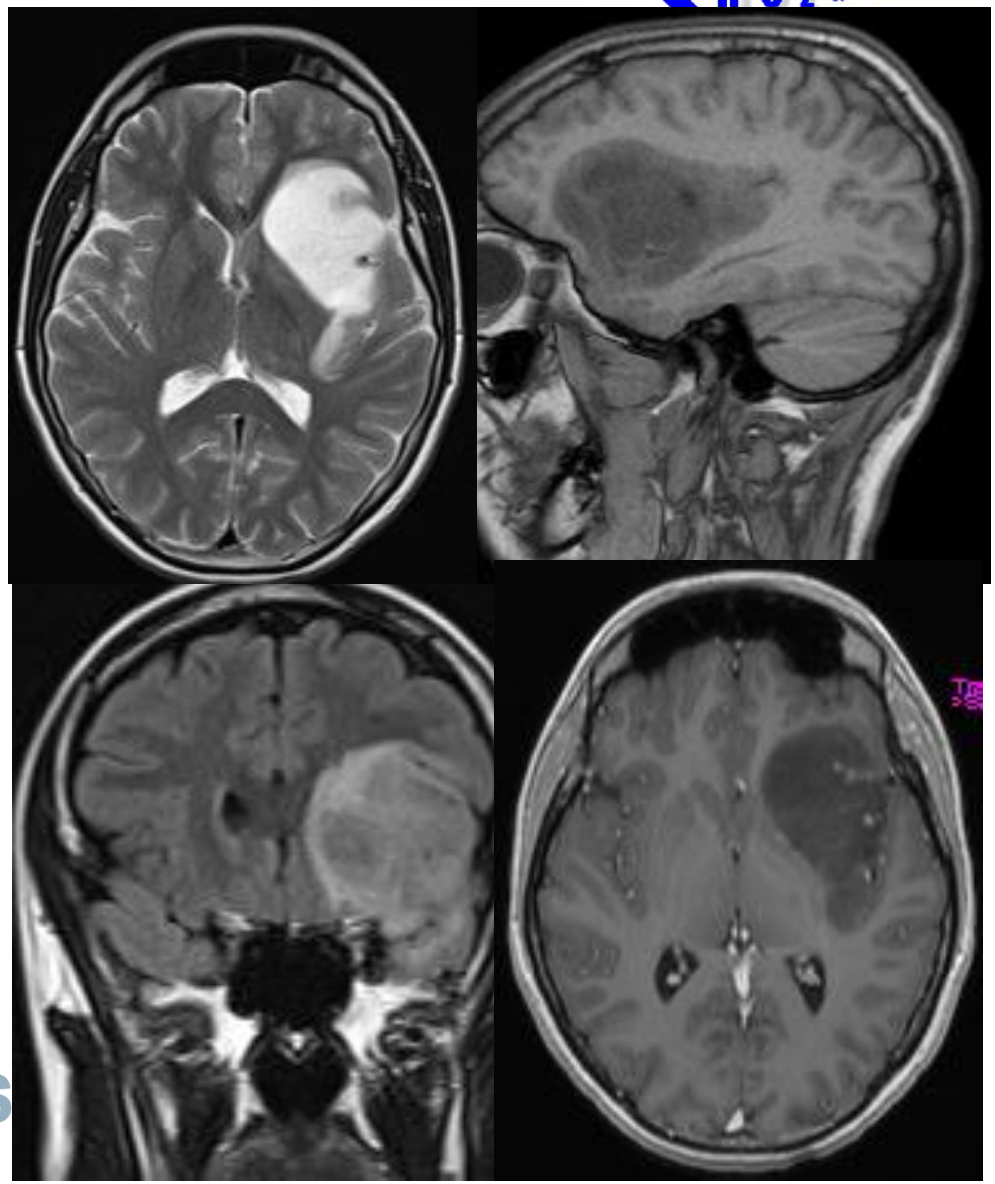



Diffuse gliomas: histology, IDH status, other genetic parameters → WHO diagnosis
Histology
Astrocytoma
Oligoastrocytoma
Oligodendroglioma
Glioblastoma
IDH status
IDH mutant
IDH wild-type
IDH mutant
IDH wild-type
1p/19q and other genetic parameters
ATRX loss*
TP53 mutation*
1p/19q loss
Glioblastoma, IDH mutant
Glioblastoma, IDH wild-type
Diffuse astrocytoma, IDH mutant
Oligodendroglioma, IDH mutant and 1p/19q codeleted
Genetic testing not done or inconclusive
After exclusion of other entities:
Diffuse astrocytoma, IDH wild-type
Oligodendroglioma, NOS
Diffuse astrocytoma, NOS
Oligodendroglioma, NOS
Oligoastrocytoma, NOS
Glioblastoma, NOS
* = characteristic but not required for diagnosis

Exemple 1: 34 year old male

- Integrated diagnosis:
  - PENDING
- Histological diagnosis
  - Diffuse astrocytoma
- Grade II
- Molecular informations
  - PENDING





Exemple 1: Final diagnosis

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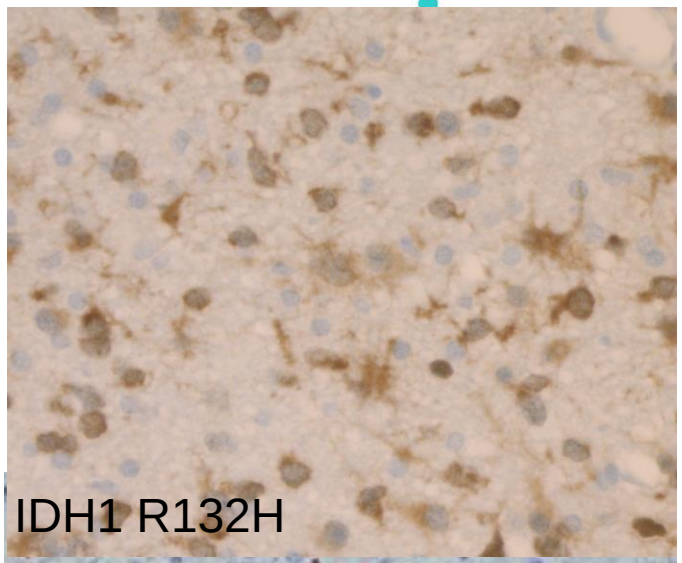
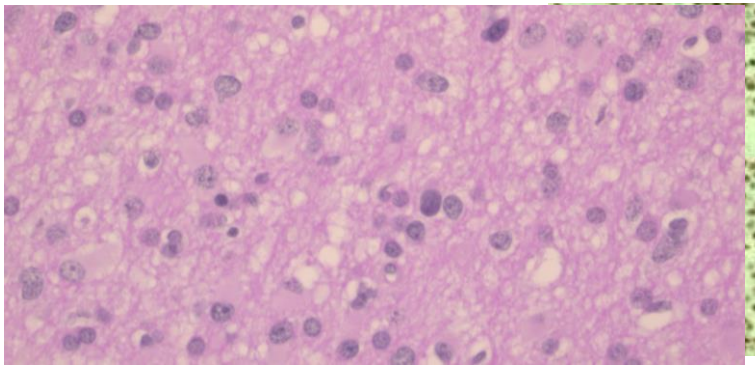
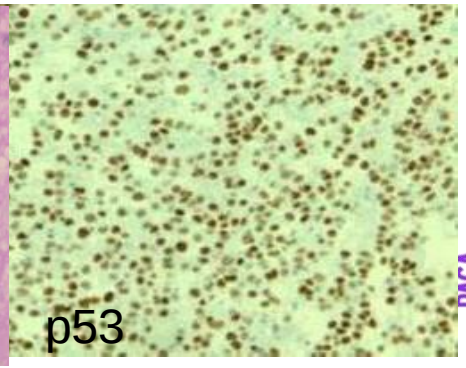
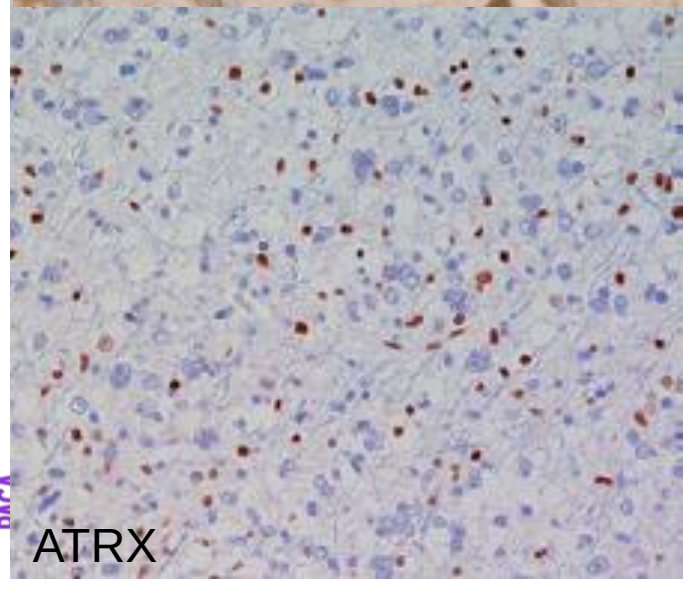
- Integrated diagnosis:
  - Diffuse astrocytoma, IDH mutant grade II
- Histological diagnosis
  - Diffuse astrocytoma
- Grade II
- Molecular informations:
  - IDH1R132H positive ATRX loss of expression (p53 positive)


IDH1 R132H




p53


ATRX

Exemple 2: 55 year old female

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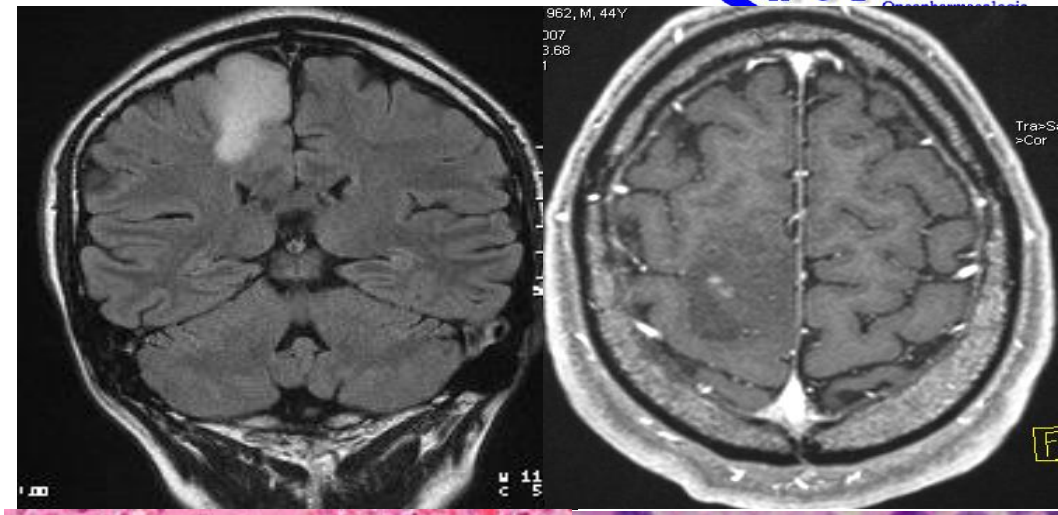
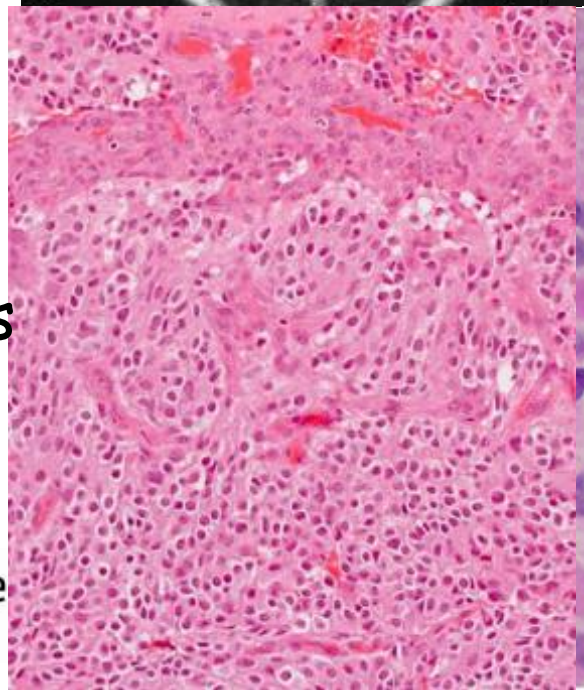
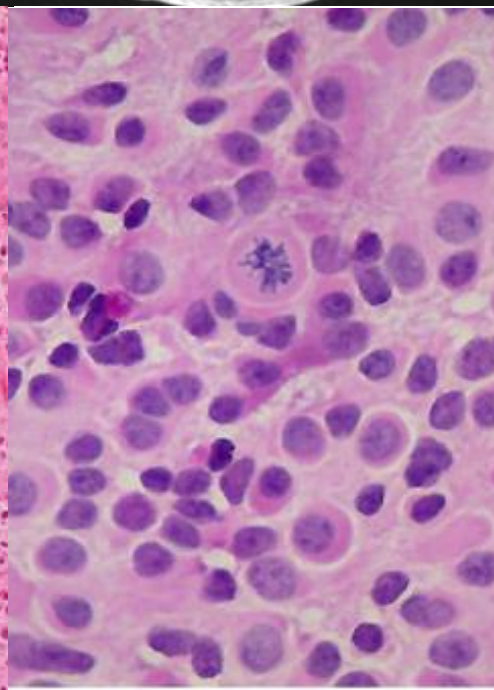
- Integrated diagnosis:
  - PENDING
- Histological diagnosis
  - Anaplastic oligodendroglioma
- Grade III ?
- Molecular informations
  - PENDING



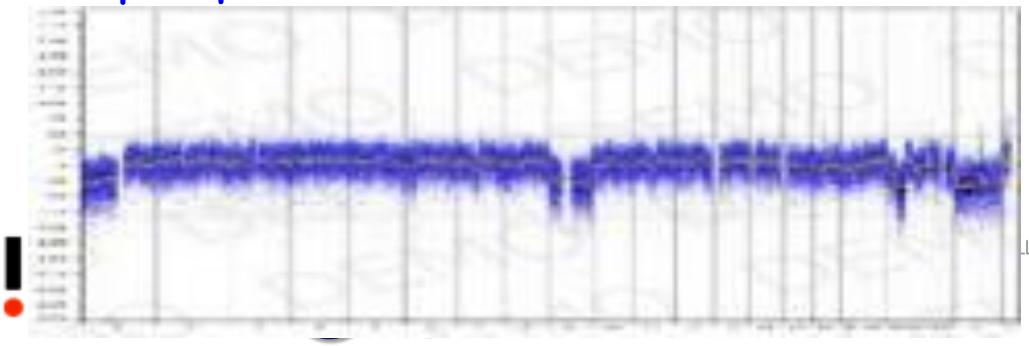


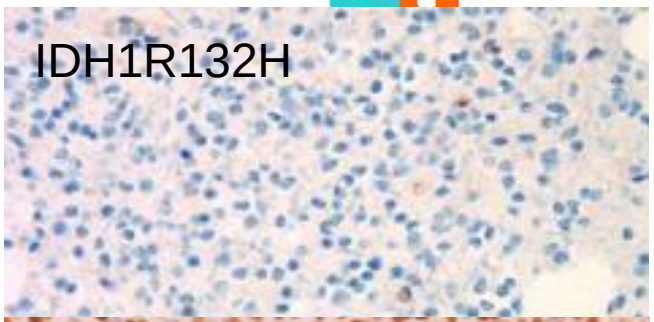


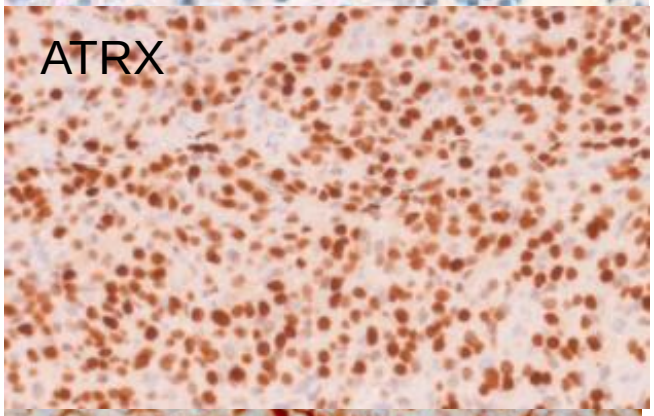
Inserm AP-HM Aix*Marseille université

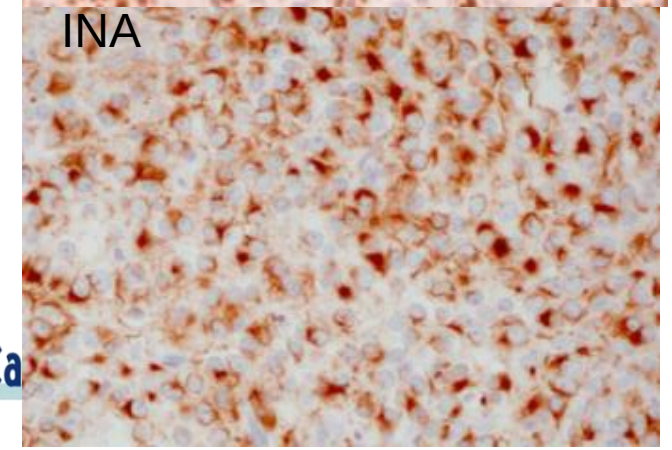
Exemple 2: Final diagnosis

- Integrated diagnosis:
  - Anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted, grade III
- Histological diagnosis
  - Anaplastic oligodendroglioma
- Grade III
- Molecular informations
  - IDH1R132H negatif, ATRX retained
  - IDH2 mutation
  - 1p19q codeletion



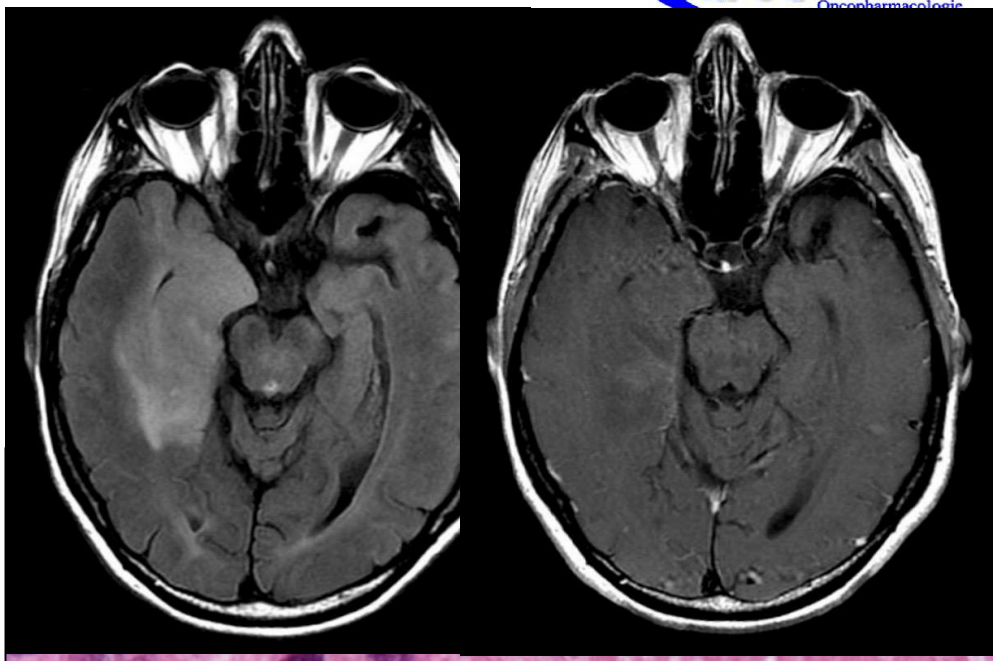


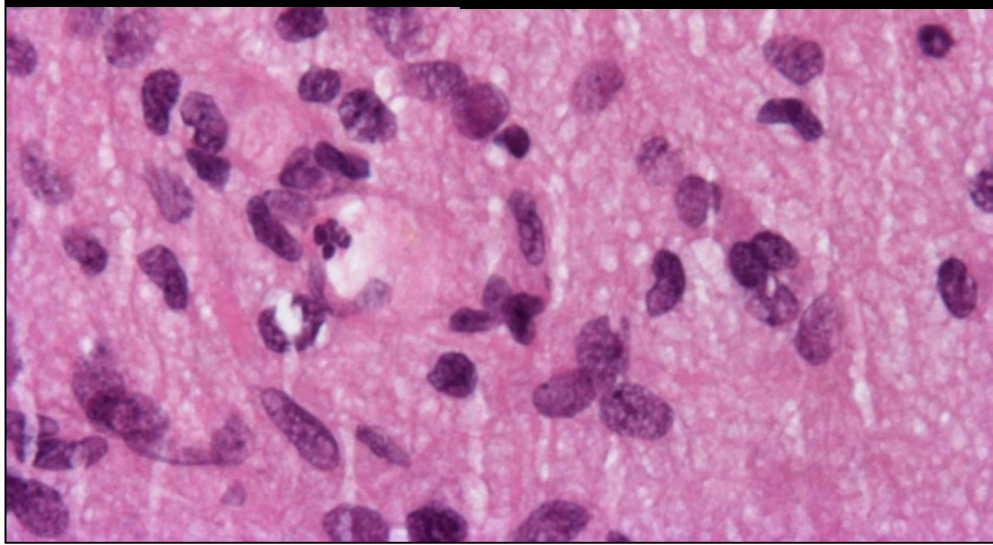




Exemple 3: 60 year old male

- Integrated diagnosis:
  - PENDING
- Histological diagnosis
  - Anaplastic astrocytoma
- Grade III ?
- Molecular informations
  - PENDING





Exemple 3: final diagnosis

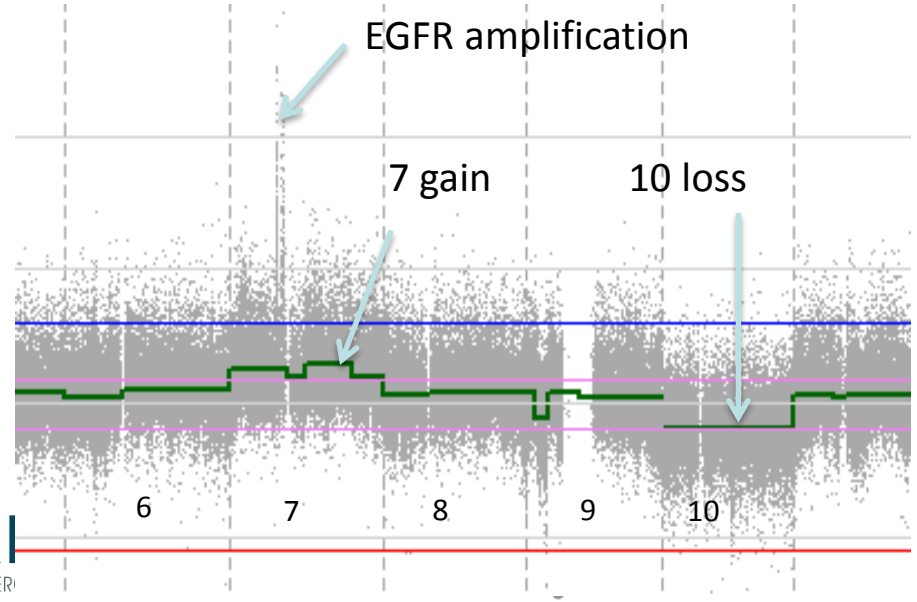
- Integrated diagnosis:
  - *Anaplastic astrocytoma IDH-wildtype*
- Histological diagnosis
  - Anaplastic astrocytoma
- Grade III
- Molecular information
  - IDH1R132H negative, lack of IDH mutation, EGFR amplification, +7 -10
- Comment:
  - Molecular feature of GBM

Acta Neuropathol (2010) 120:719–729
DOI 10.1007/s00401-010-0777-8

ORIGINAL PAPER

Absence of *IDH* mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis

Philippe Metellus · Bema Coulibaly · Carole Colin · Andre Maues de Paula · Alexandre Vasiljevic · David Taieb · Anne Barlier · Blandine Boisselier · Karima Mokhtari · Xiao Wei Wang · Anderson Loundou · Frederique Chapon · Sandrine Pineau · L'Houcine Ouafik · Olivier Chinot · Dominique Figarella-Branger



Ependymomas in 2016: the major findings that have preceded the changes

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Acta Neuropathol (2014) 127:609–611

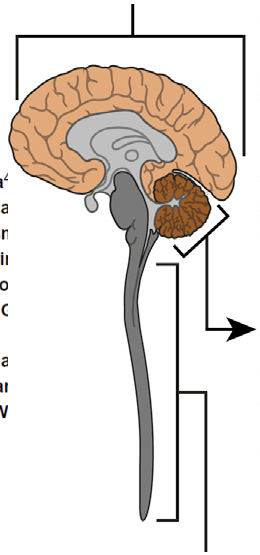
Supratentorial ependymomas of childhood carry *C11orf95–RELA* fusions leading to pathological activation of the NF-κB signaling pathway

Torsten Pietsch · Inken Wohlers · Tobias Goschzik · Verena Dreschmann · Dorota Denkhaus · Evelyn Dörner · Sven Rahmann · Ludger Klein-Hitpass

Nature. 2014 February 27; 506

***C11orf95-RELA* fusions drive oncogenic NF-κB signaling in ependymoma**

Matthew Parker[1,2,*], Kumarasamypet M. Mohankumar[3,*], Chandanamali Punchihewa[4], Ricardo Weinlich[5,*], James D. Dalton[1,4], Yongjin Li[1,2], Ryan Lee[4], Ruth G. Tatevossia[1], Timothy N. Phoenix[3], Radhika Thiruvenkatam[3], Elsie White[3], Bo Tang[1,4], Wilda Orisr[1], Kirti Gupta[4], Michael Rusch[2], Xiang Chen[2], Yuxin Li[2,6], Panduka Nagahawhatte[2], Eri[1], Hedlund[2], David Finkelstein[2], Gang Wu[2], Sheila Shurtleff[4], John Easton[1,4], Kristy Bo[1], Donald Yergeau[1], Bhavin Vadodaria[1], Heather L Mulder[1], Jared Becksford[4], Pankaj [1], Robert Huether[6], Jing Ma[1], Guangchun Song[1], Amar Gajjar[1,7], Thomas Merchant[8], Frederick Boop[9], Amy A Smith[10], Li Ding[1,11,12], Charles Lu[1,11], Kerri Ochoa[1,11,12], Da[1], Zhao[1,2], Robert S Fulton[1,11], Lucinda L Fulton[1,11,12], Elaine R. Mardis[1,11,12,14], Richar[d], Wilson[1,11,12,14], James R. Downing[1,4], Douglas R. Green[5], Jinghui Zhang[1,2], David W[ayne], Ellison[1,4], and Richard J. Gilbertson[1,3]



Cancer Cell

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Kristian W. Pajtler,[1,2,37] Hendrik Witt,[1,3,4,37] Martin Sill,[5,37] David T.W. Jones,[1] Volker Hovestadt,[6] Fabian Kratochwil,[1] Khalida Wani,[7] Ruth Tatevossian,[8] Chandanamali Punchihewa,[8] Pascal Johann,[1] Jüri Reimand,[9] Hans-Jörg Warnatz,[10] Marina Ryzhova,[11] Steve Mack,[12] Vijay Ramaswamy,[12,13] David Capper,[14,15] Leonille Schweizer,[14,15] Laura Sieber,[1] Andrea Wittmann,[1] Zhiqin Huang,[6] Peter van Sluis,[16] Richard Volckmann,[16] Jan Koster,[16] Rogier Versteeg,[16] Daniel Fults,[17] Helen Toledano,[18] Smadar Avigad,[19] Lindsey M. Hoffman,[20] Andrew M. Donson,[20] Nicholas Foreman,[20] Ekkehard Hewer,[21] Karel Zitterbart,[22,23] Mark Gilbert,[24] Terri S. Armstrong,[24,25] Nalin Gupta,[26] Jeffrey C. Allen,[27] Matthias A. Karajannis,[28] David Zagzag,[29] Martin Hasselblatt,[30] Andreas E. Kulozik,[3] Olaf Witt,[3,31] V. Peter Collins,[32] Katja von Hoff,[33] Stefan Rutkowski,[33] Torsten Pietsch,[34] Gary Bader,[9] Marie-Laure Yaspo,[10] Andreas von Deimling,[14,15] Peter Lichter,[4,6] Michael D. Taylor,[12] Richard Gilbertson,[35] David W. Ellison,[8] Kenneth Aldape,[36] Andrey Korshunov,[14,15,38] Marcel Kool,[1,38,*] and Stefan M. Pfister[1,3,4,38,*]

Molecular Subgrouping of Ependymal Tumors is Superior to Histopathological Grading for Risk Stratification

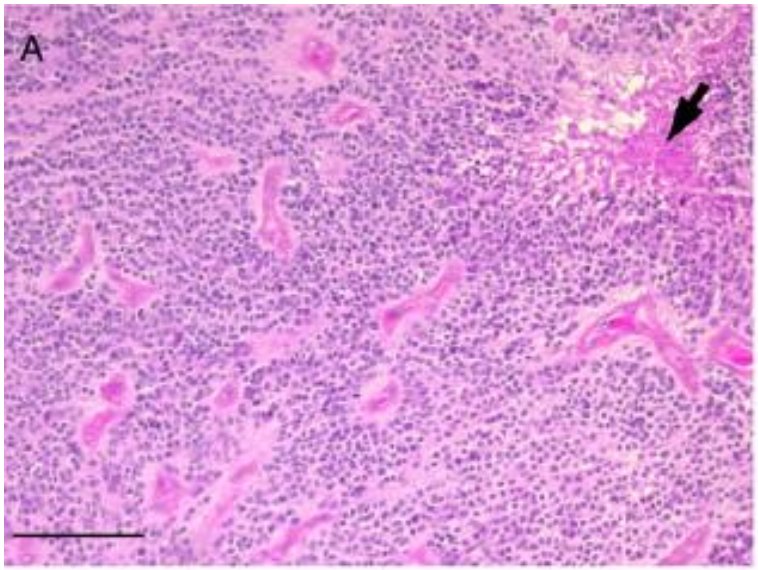
		WHO grade	Age Group	Outcome
Supratentorial (ST-)	ST-SE Subependymoma Balanced Genome	I		
	ST-EPN-YAP1 (Anaplastic) Ependymoma *YAP1*-fusion	II / III		
	ST-EPN-RELA (Anaplastic) Ependymoma Chromothripsis; *RELA*-fusion	II / III		
Posterior Fossa (PF-)	PF-SE Subependymoma Balanced Genome	I		
	PF-EPN-A (Anaplastic) Ependymoma Balanced Genome	II / III		
	PF-EPN-B (Anaplastic) Ependymoma Chromosomal Instability	II / III		
Spine (SP-)	SP-SE Subependymoma 6q deletion	I		
	SP-MPE Myxopapillary Ependymoma Chromosomal Instability	I		
	SP-EPN (Anaplastic) Ependymoma *NF2* mutation	II / III		

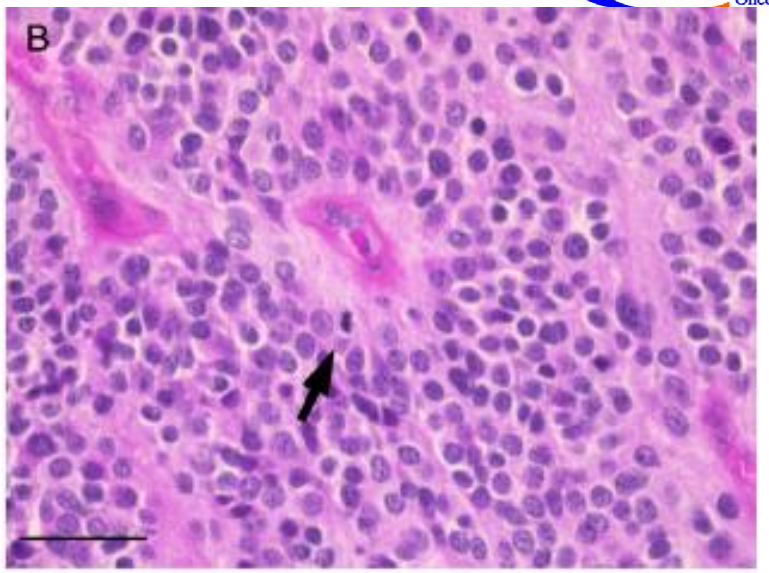
Ependymomas in 2016

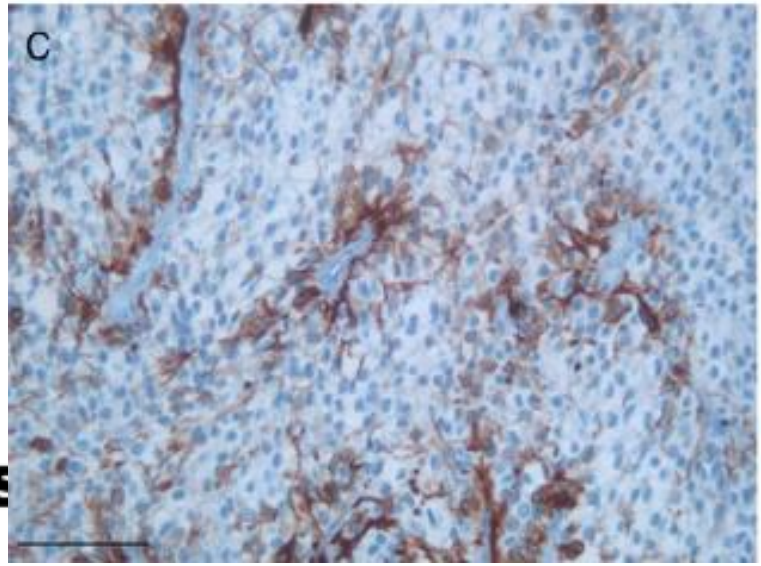
- Grade is maintained although questionable
- Cellular ependymoma is deleted
- A genetically defined ependymoma subtype has been accepted: Ependymoma, RELA fusion-positive

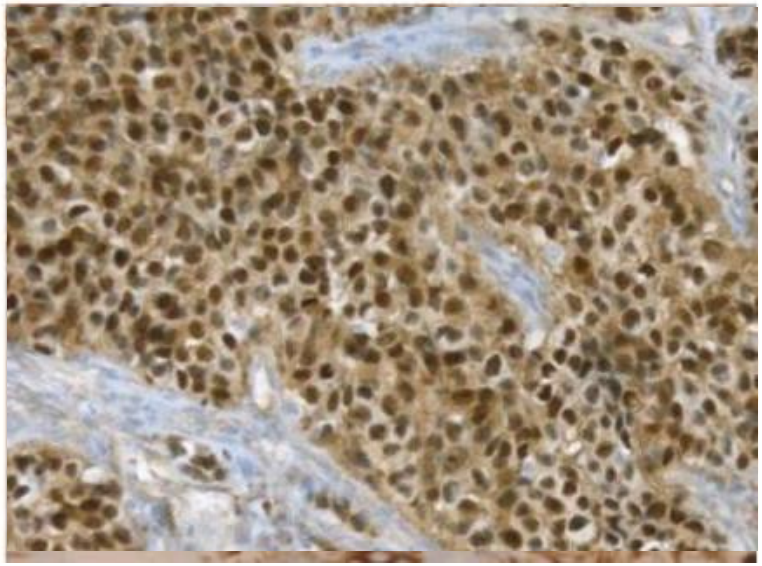
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3

Pathological features









Major advances in the genetic of medulloblastomas (summarized in Taylor et al 2012)

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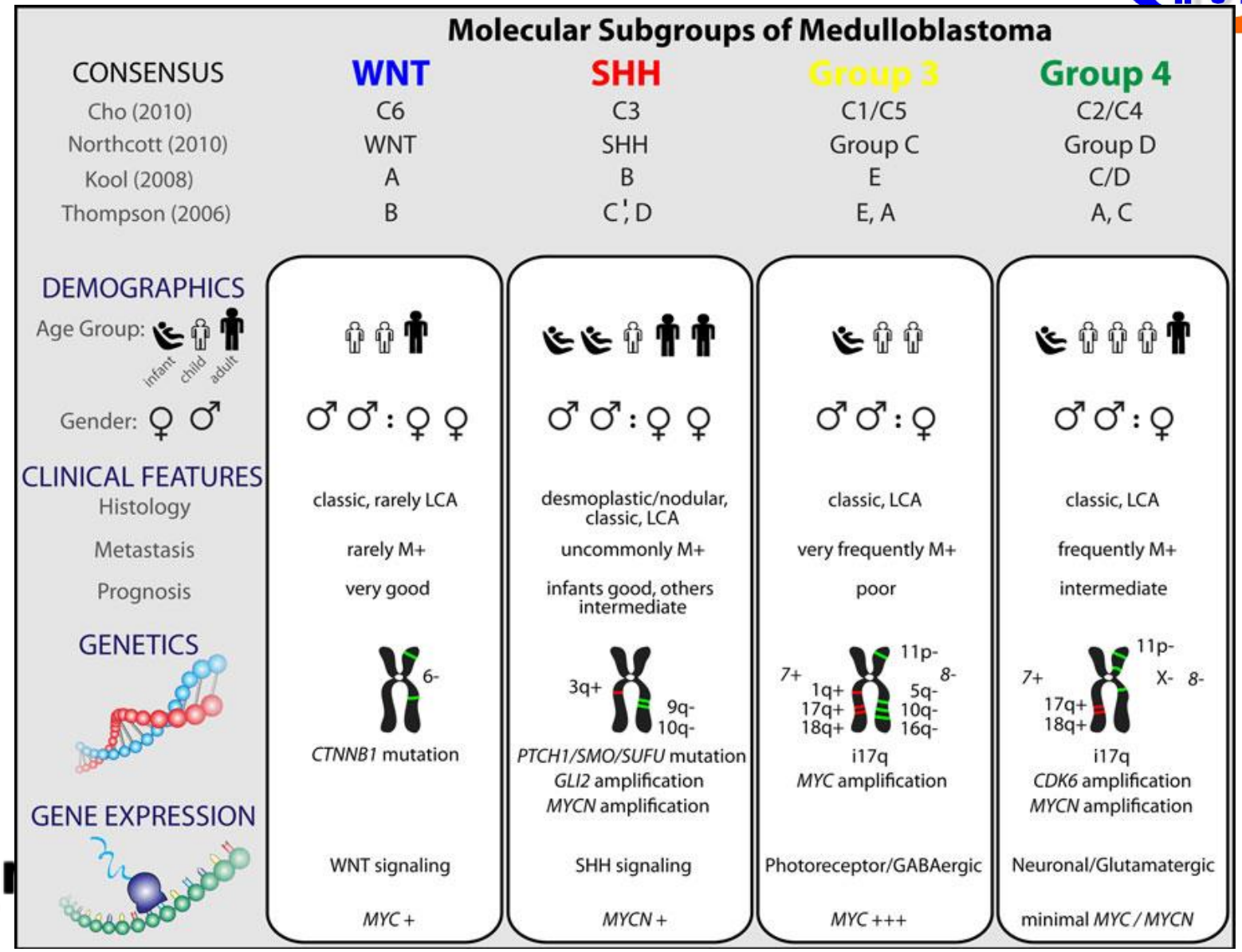


Embryonal tumours

- WHO 2016
  - Medulloblastomas:major conceptual changes in medulloblastomas: marriage of histological and molecular classification schemes
  - Other embryonal tumours
- WHO 2007

Embryonal tumours

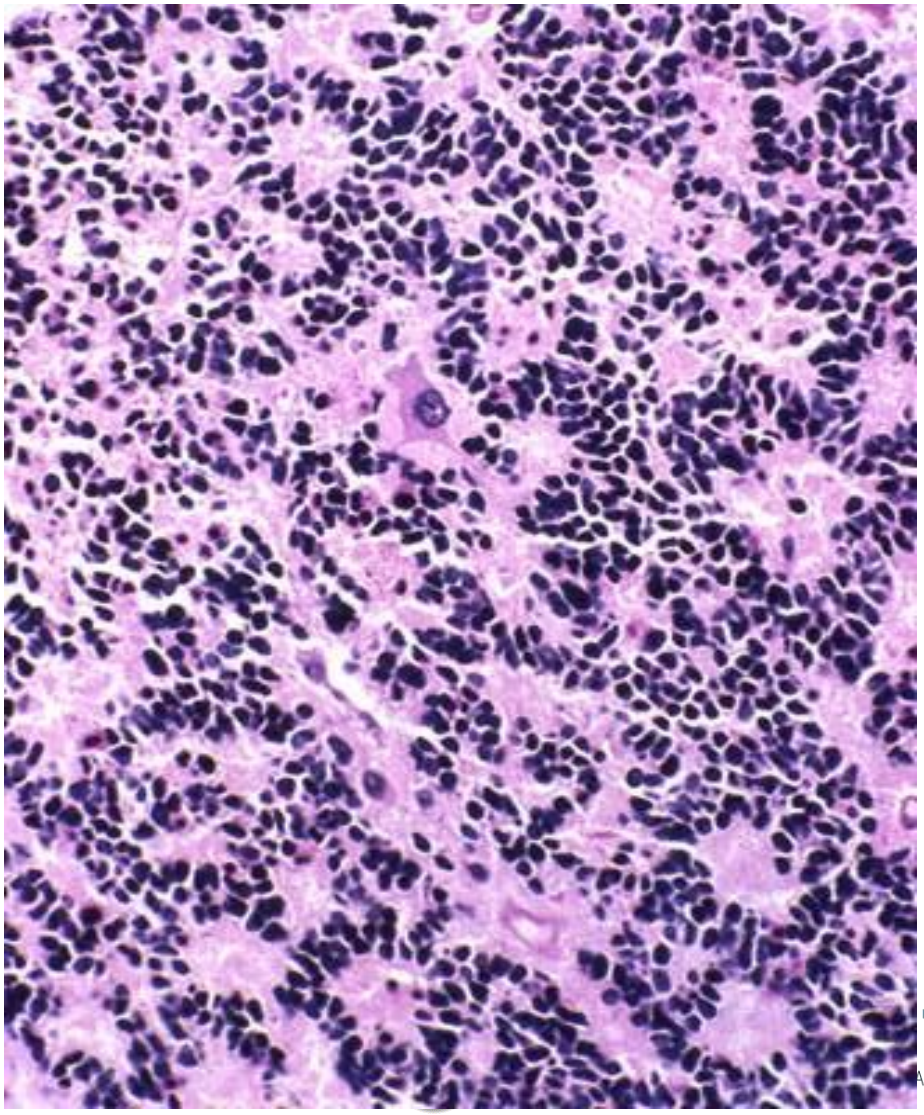
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS Neuroblastoma	9500/3
CNS Ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3

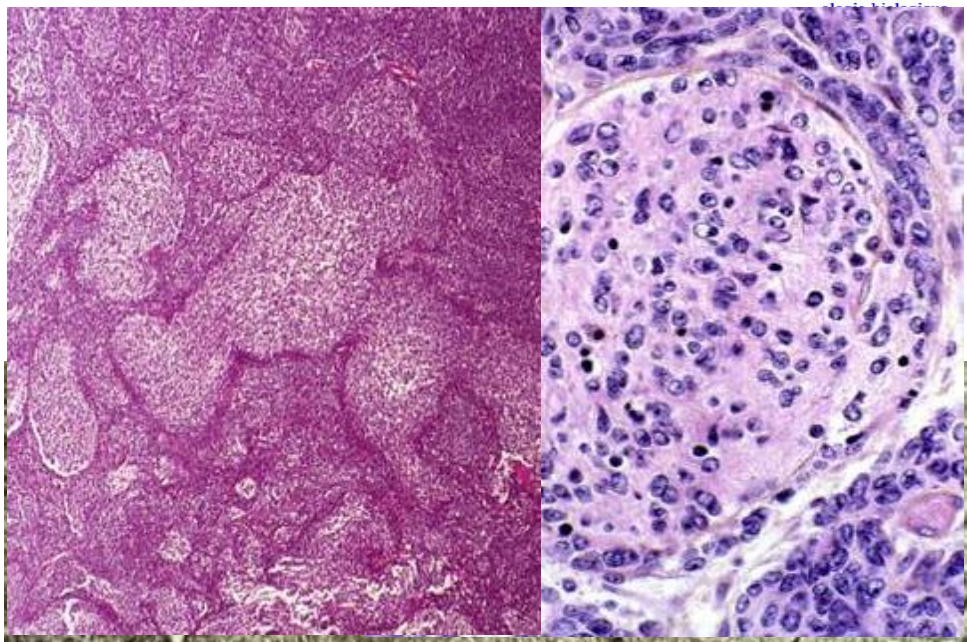
- WHO 2016

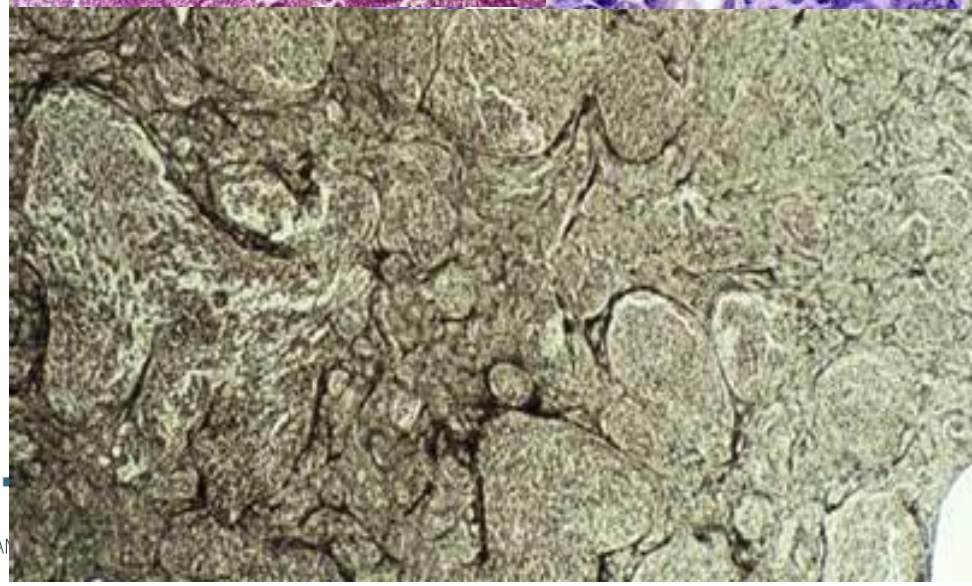
Embryonal tumours

Medulloblastoma, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and TP53-mutant	9476/3*
Medulloblastoma, SHH-activated and TP53-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastoma, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell/anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*

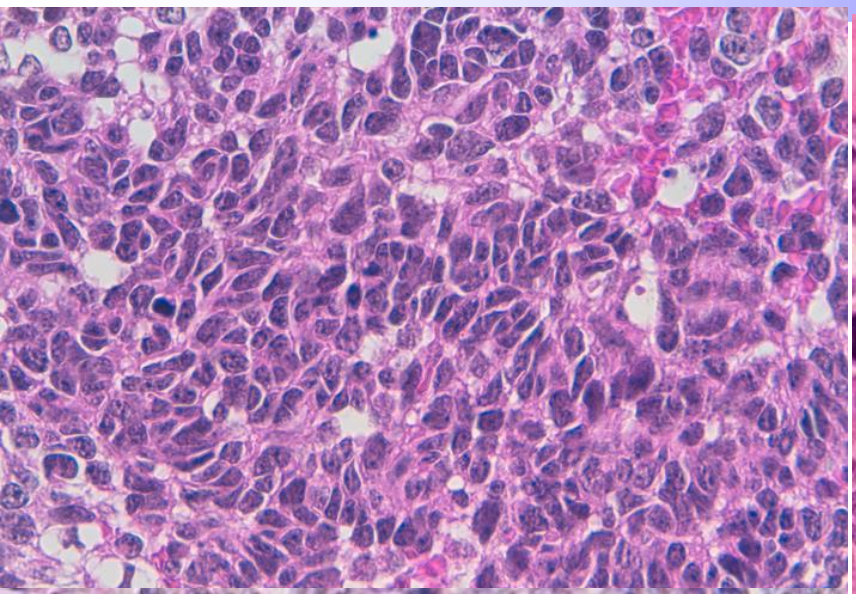
Medulloblastoma, classic and desmoplasic

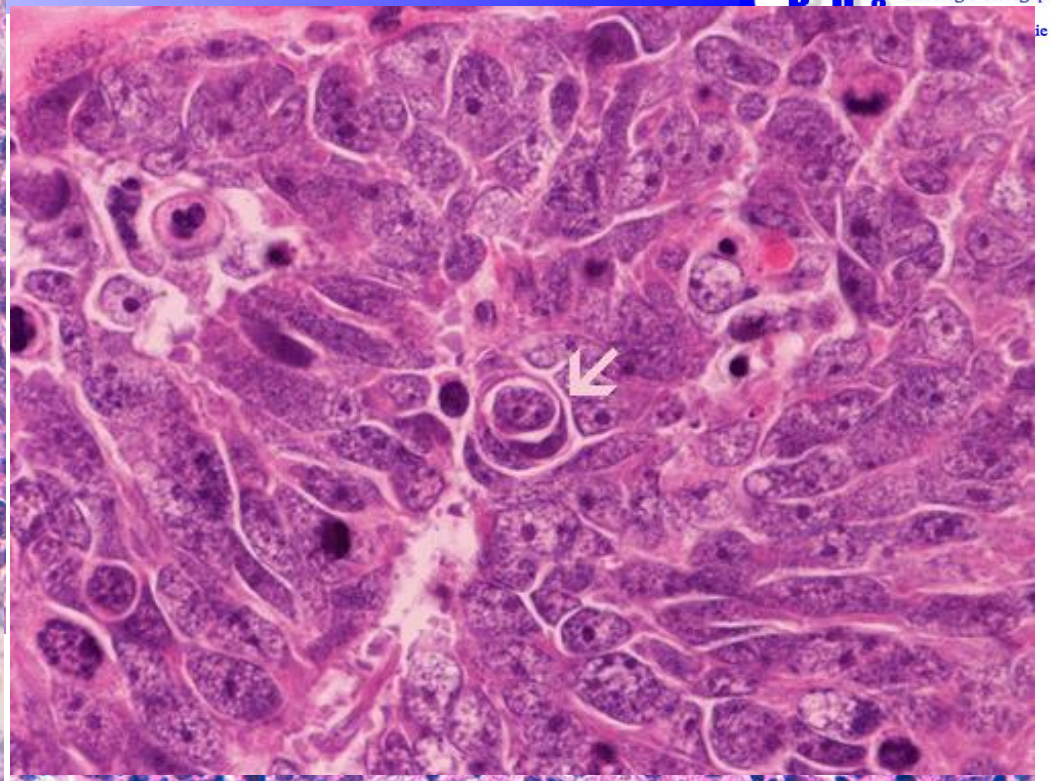


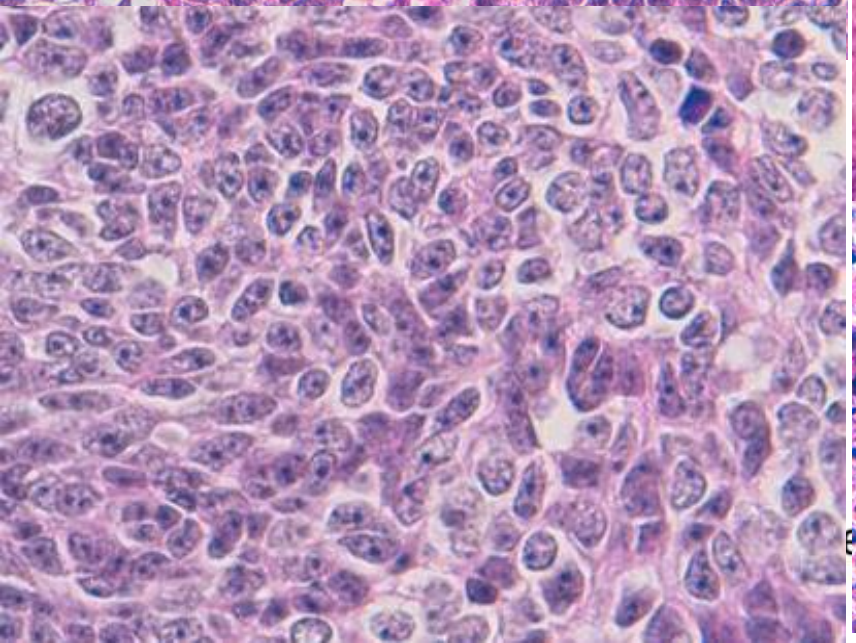


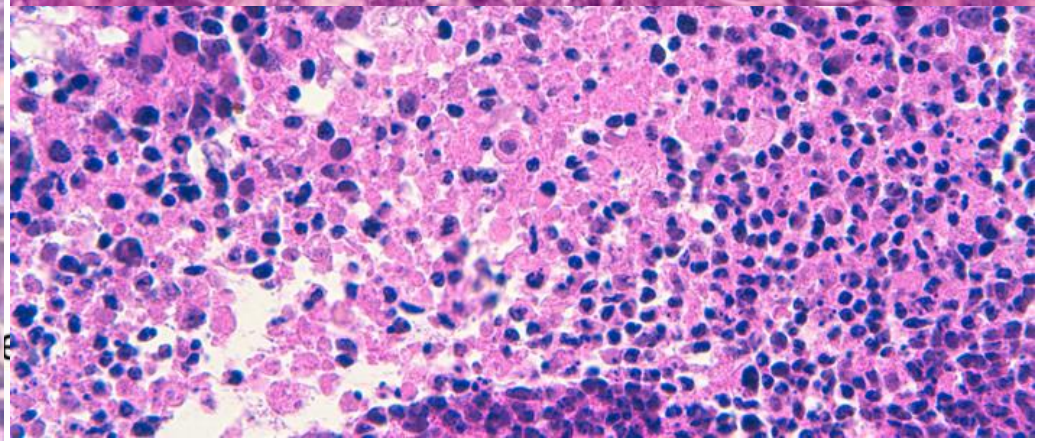


Pleiomorphism, wraping, nuclear molding, apoptotic figures and necrosis characterized anaplastic Mb









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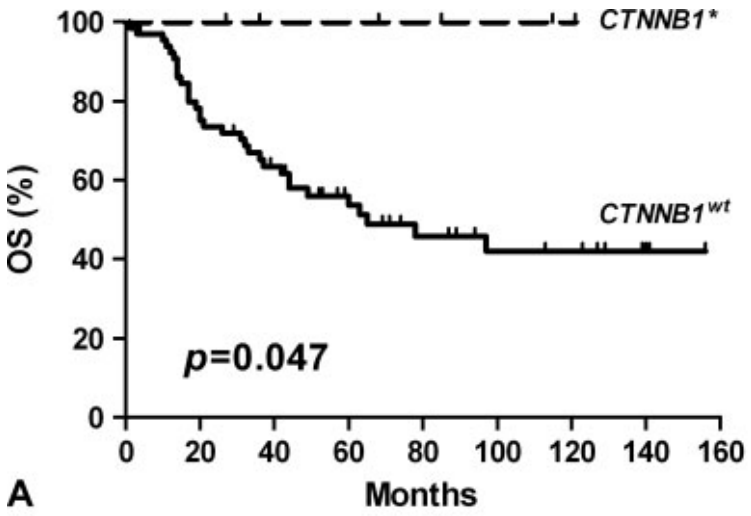
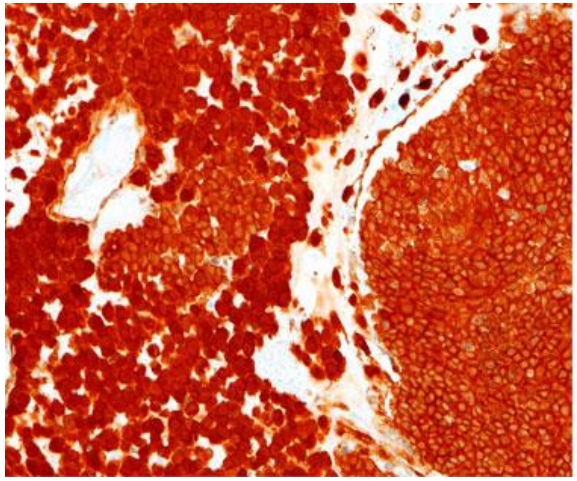
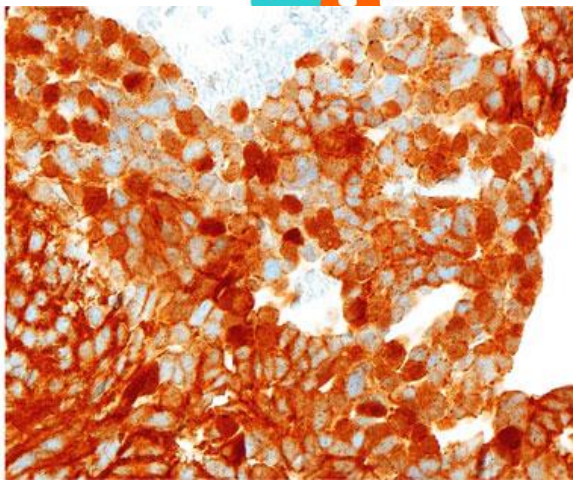
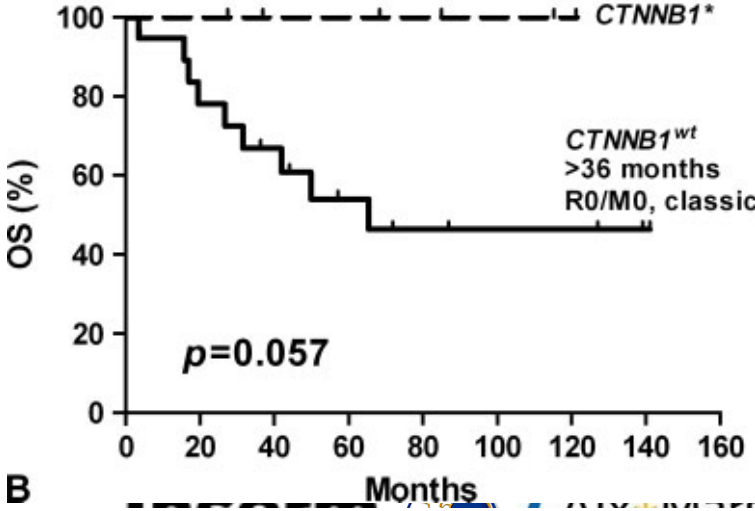
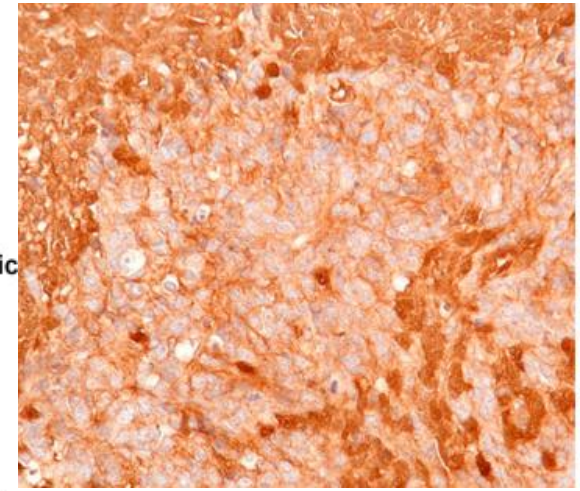
Nuclear β catenin expression characterized Wnt Mb

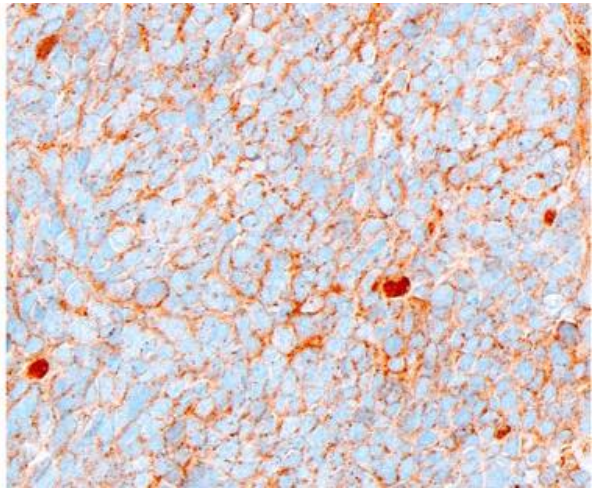












Ellisson et al Acta Neuropathol 2011; 121: 381-96

Fattey et al J. Pathol 2009

GAB1 expression in MB

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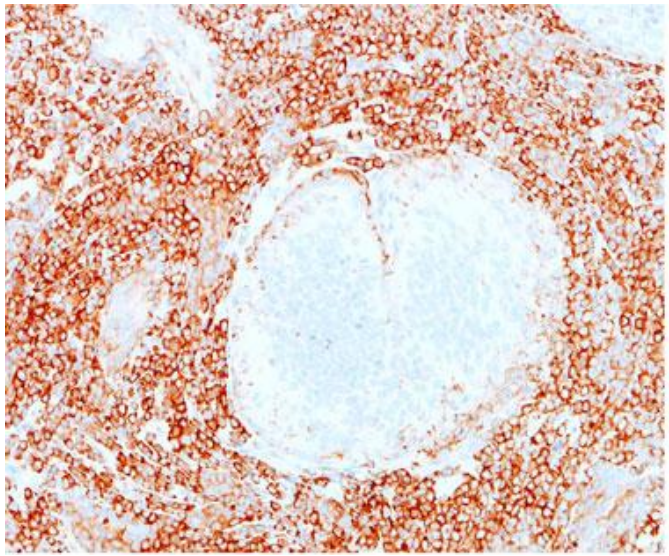
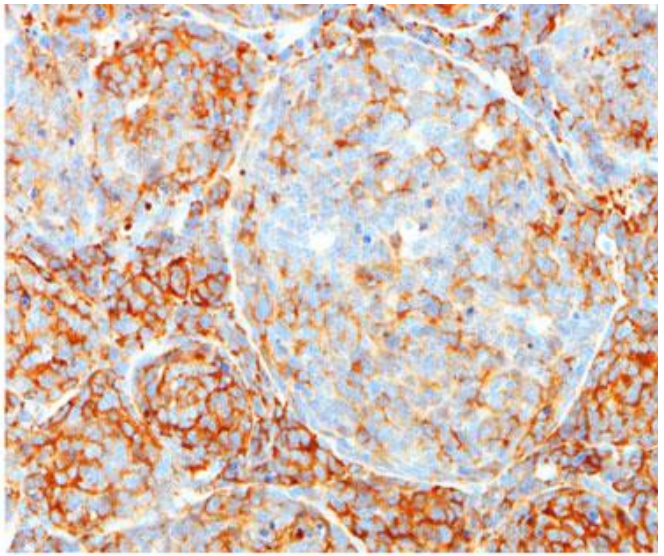
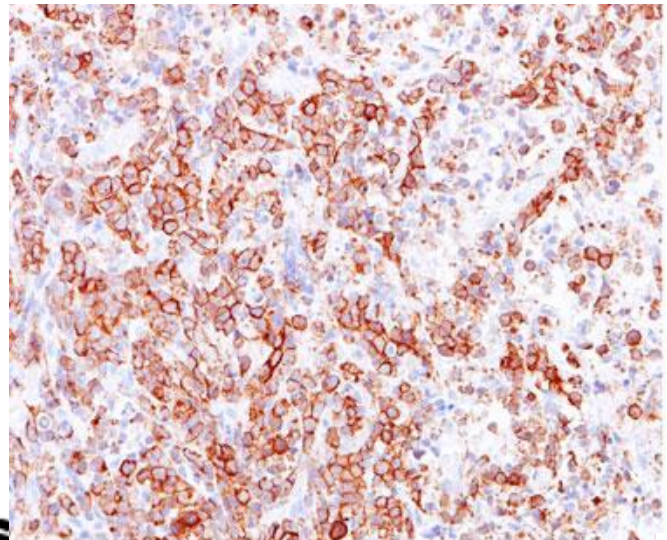
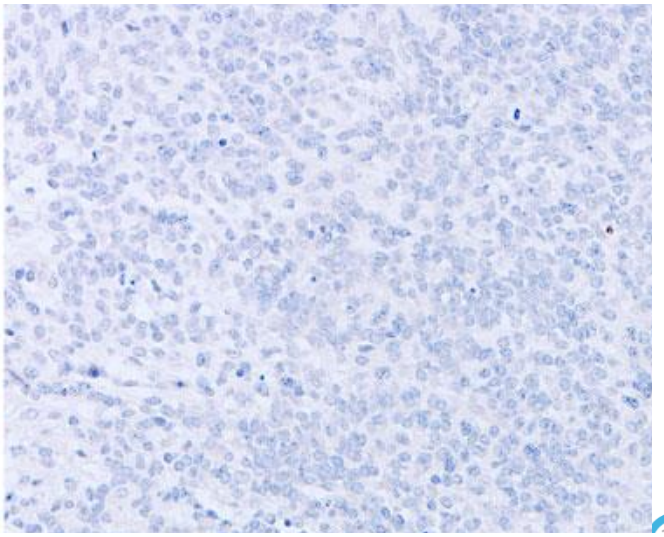




Desmoplastic

LC/A





Non SHH/Wnt

Ellisson et al Acta Neuropathol 2011; 121: 381-96

Filamin and Yap1 expression in MB

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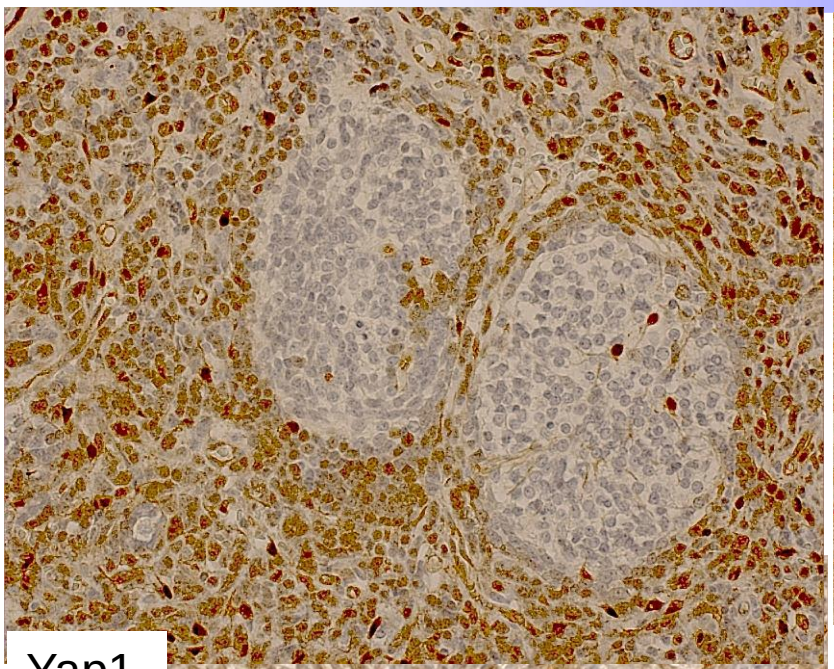
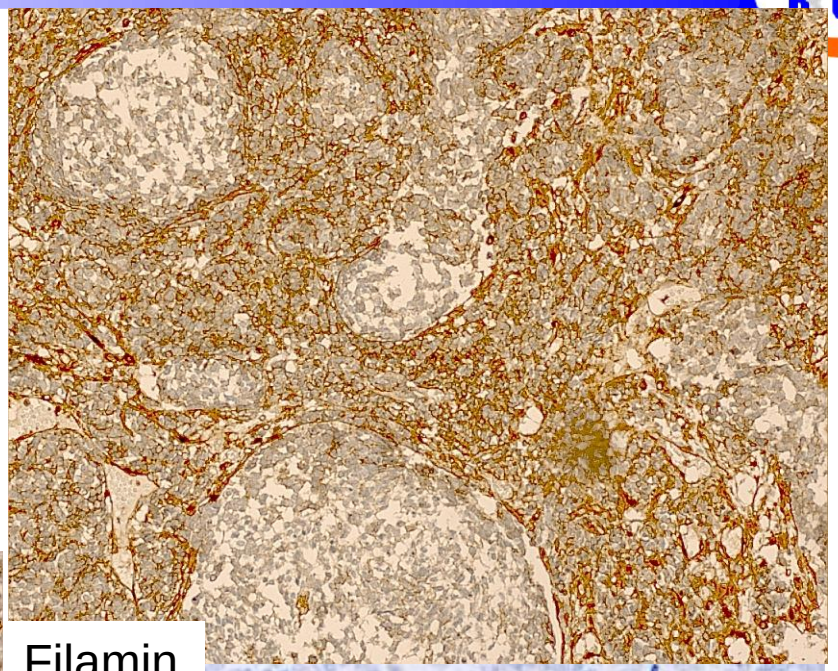
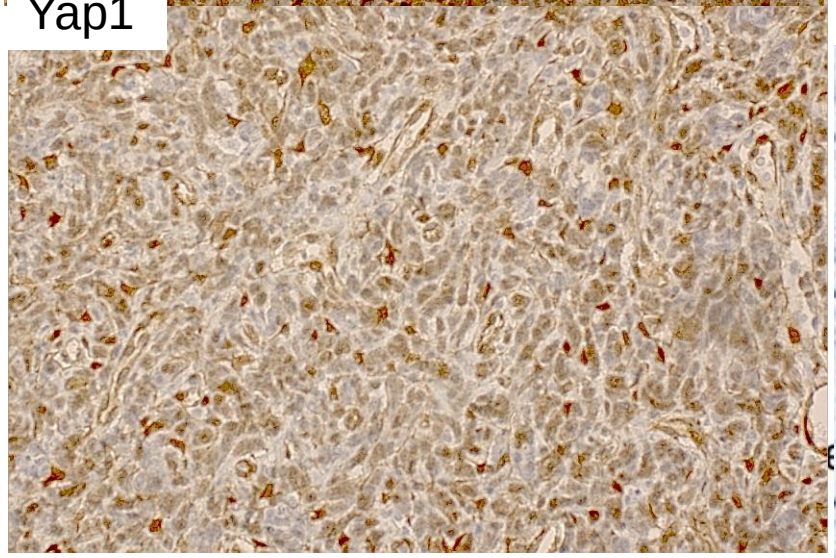


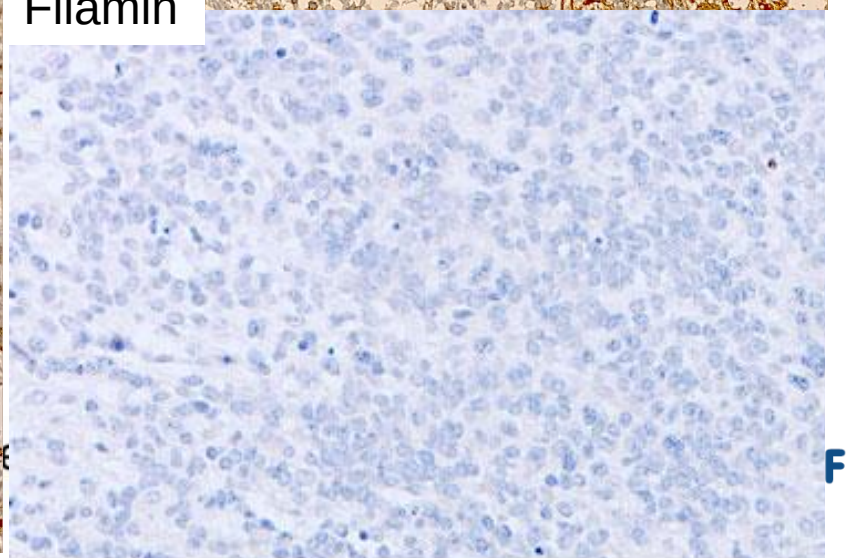
Yap1



Filamin

SHH





Non SHH/Wnt

	WNT	SHH		Non WNT/ non SHH	
		TP53 wt	TP53 mut	Group 3	Group 4
Age	Childhood	Infancy Adult	Childhood	Infancy Childhood	All ages
Pathology	Classic	Desmoplasic /nodular	LC/A	LC/A	Classic
IHC	B caténine nucléaire + et Filamine +	Gab1+ et filamine + Absence de B caténine dans les noyaux		Gab1+ et filamine - Absence de B caténine dans les noyaux	
Genetic	Monosomy 6	*PTCH1* mutation	*TP53* mutation	*PVT1-MYC*	*KDM6A*
Germline mutation	*APC*	*PTCH1* *SUFU*	*TP53*		

WHO 2016: solitary fibrous tumour /haemangiopericytoma SFT/HPC

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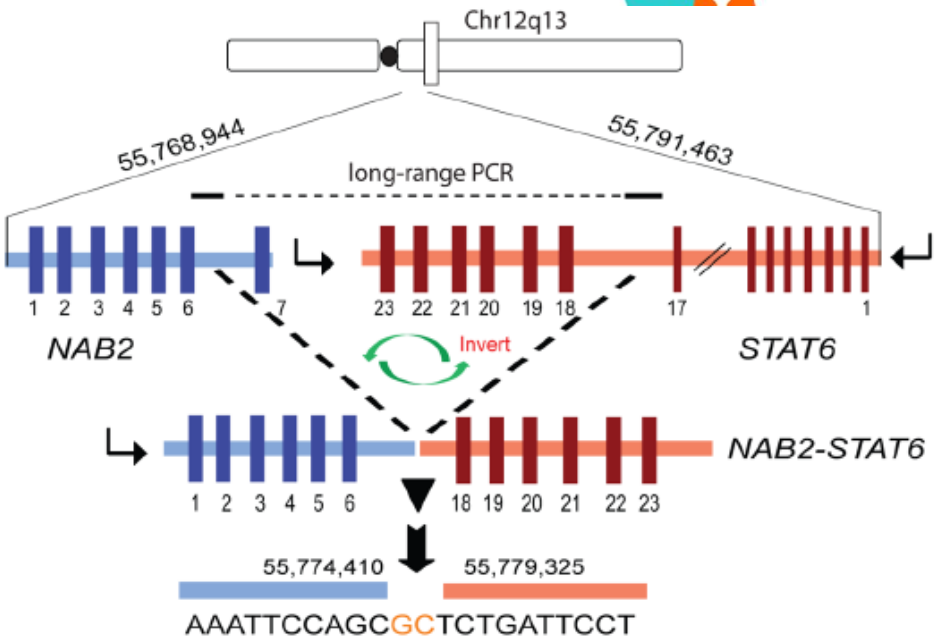
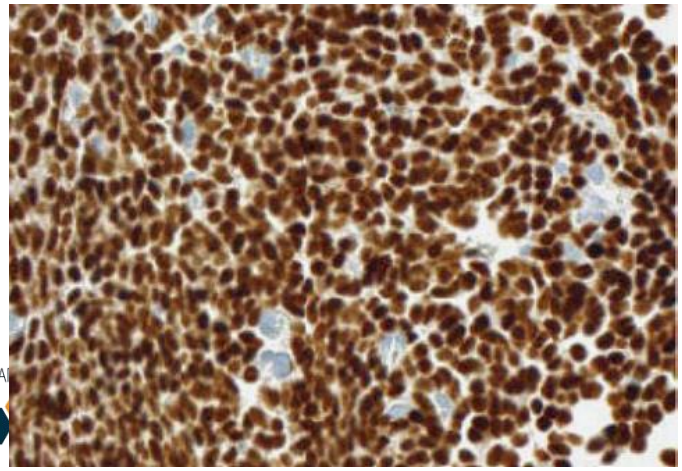
- In contrast to neuropathologists, soft tissue pathologists have removed HPC since decade



- Both SFT and HPC share inversions at 12q13 fusing the NAB2 and STAT6 gene

  Chmielecki et al Nature 2013, Robinson et al Nature Genet 2013

- This leads to strong nuclear STAT6 accumulation



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Limits 1. Adult gliomas

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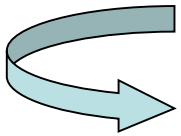
- The category of diffuse astrocytoma and *Anaplastic astrocytoma IDH -wildtype* need to be better characterized

- The grading criteria within each well defined histomolecular subgroup need to be refined



Some lessons of the POLA network

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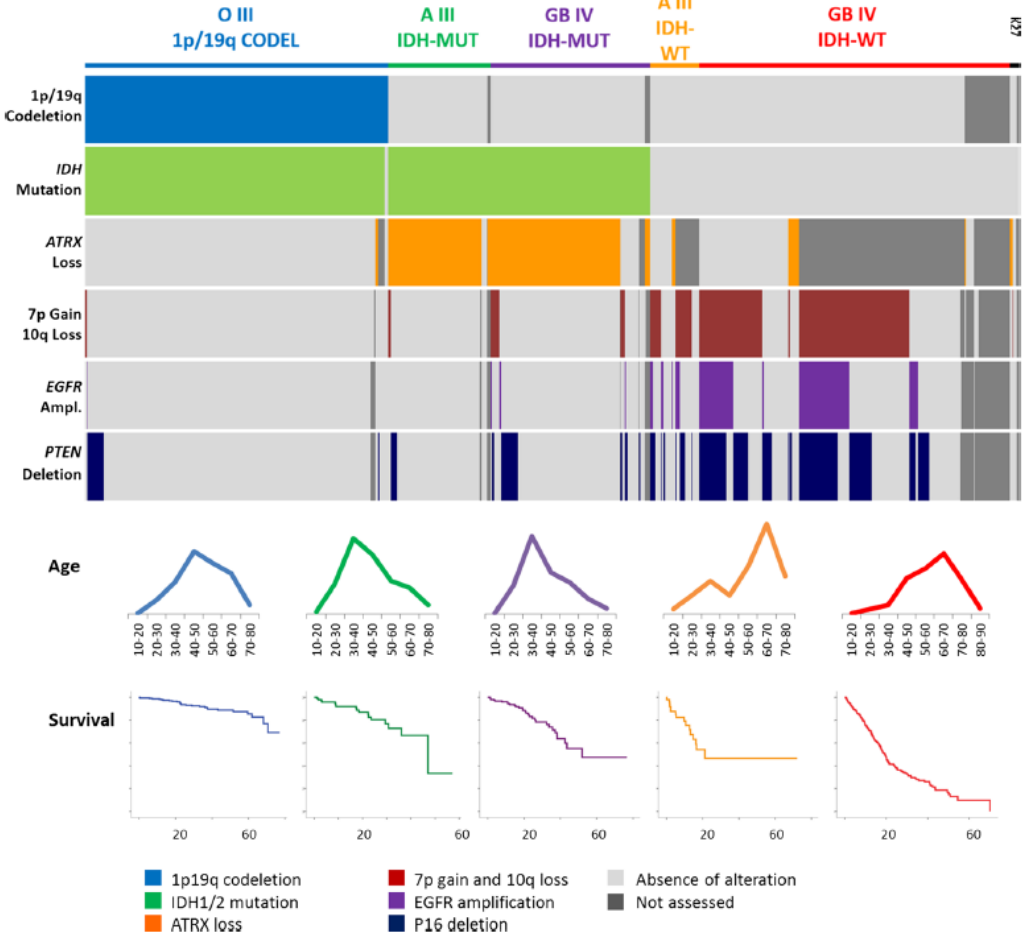
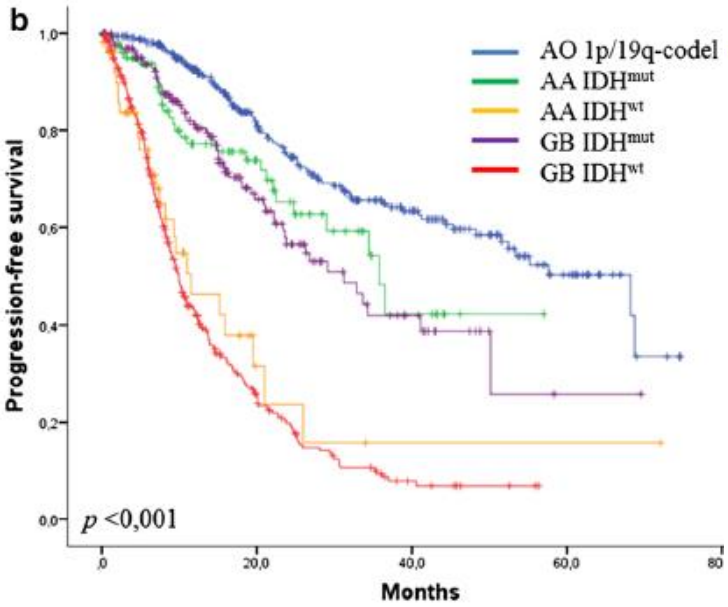
Acta Neuropathol
DOI 10.1007/s00401-016-1611-8

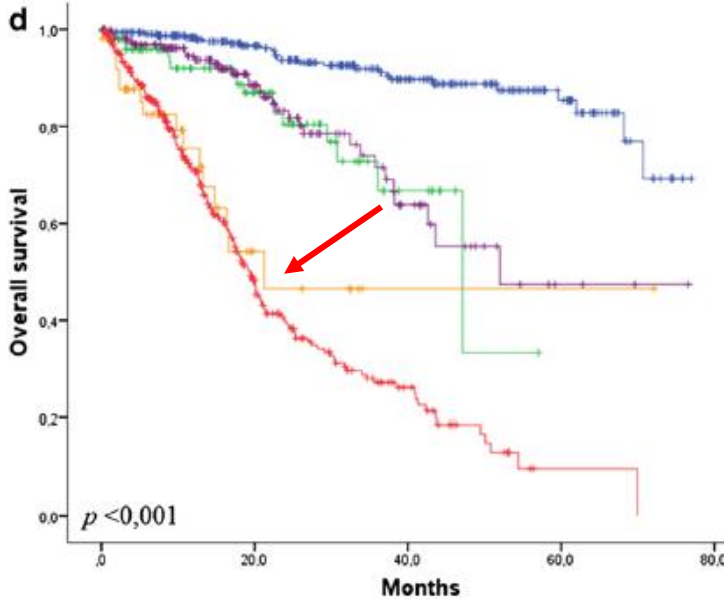
ORIGINAL PAPER

Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort

Emeline Tabouret[1,2] · Anh Tuan Nguyen[3] · Caroline Dehais[4] · Catherine Carpentier[5] · François Ducra
Ahmed Idbaih[4,5] · Karima Mokhtari[4,5,8] · Anne Jouvet[9] · Emmanuelle Uro-Coste[10,11] · Carole Colin[2] ·
Olivier Chinot[1,2] · Hugues Loiseau[12] · Elisabeth Moyal[13,14,15] · Claude-Alain Maurage[16] · Marc Polivk
Emmanuèle Lechapt-Zalcman[18,19] · Christine Desenclos[20] · David Meyronet[7,9] · Jean-Yves Delattre[4,5]
Dominique Figarella-Branger[2,3] · For POLA Network







Limits 2: diffuse gliomas and glioneuronal tumor in children

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- The diffuse gliomas in children should be better characterized according to new genetic features
- The 2016 edition contains « pediatric boxes » to highlight differences between adults but this is not sufficient

Oligodendroglioma lacking IDH mutation and 1p/19q codeletion (paediatric-type oligodendroglioma)

A small subset of histologically classic oligodendrogliomas are found to lack IDH mutation and 1p/19q codeletion on appropriate molecular testing. This group includes the majority of oligodendrogliomas in children and adolescents {1361,2057,2157}. In these cases, it is important to check carefully for and exclude histological mimics that may contain oligodendrocyte-like tumours cells, in particular dysembryoplastic neuroectodermal tumour, extraventricular neurocytoma, clear cell ependymoma

Genetic alterations in PLGG *Qaddoumi et al., 2016*

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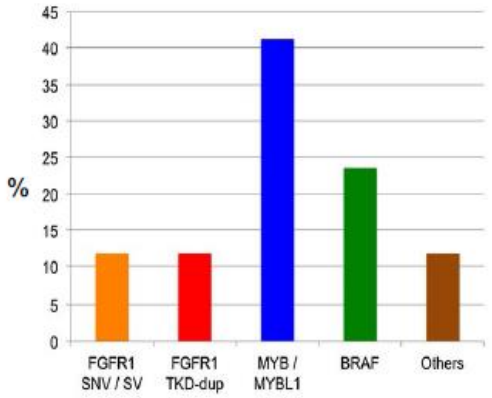
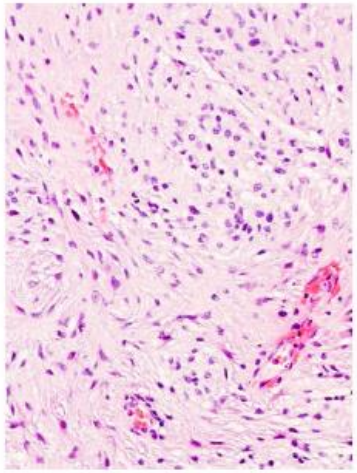
LGNTs with astrocytic phenotype

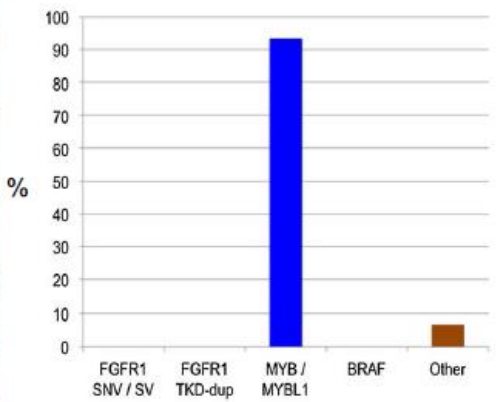
DA



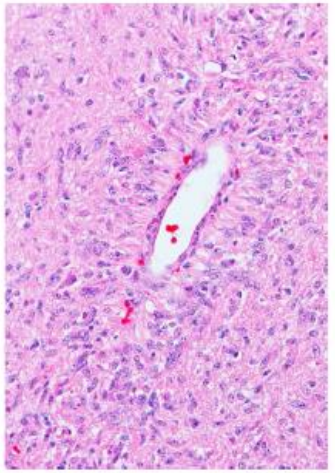
Diffuse astrocytoma



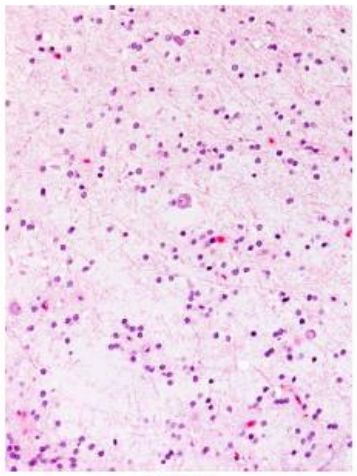
AGs



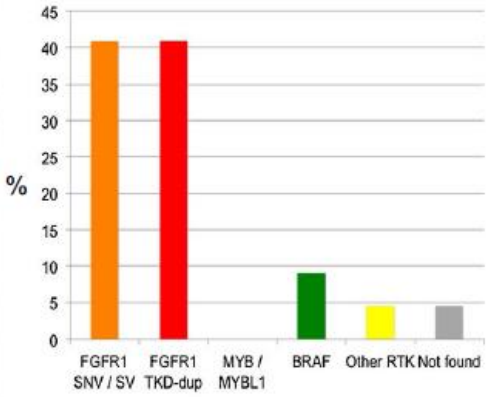
Angiocentric glioma



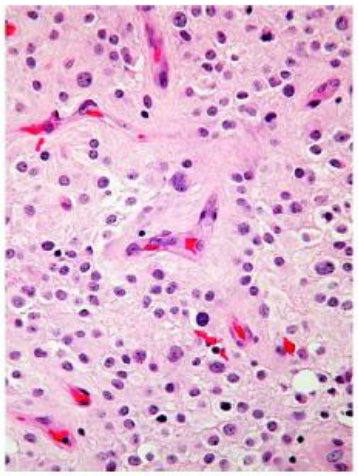
DNET



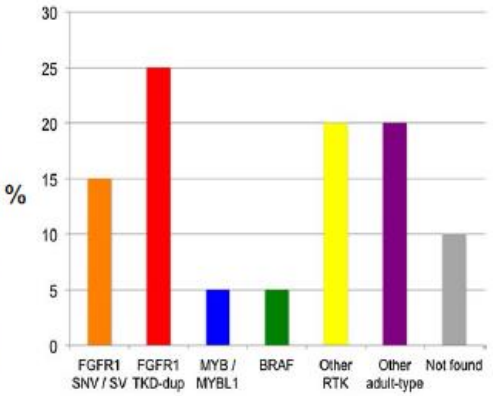
DNETs



Diffuse oligoastrocytoma



d-OTs



LGNTs with oligodendroglial phenotype

Limits 3: CNS embryonal tumors NOS (Previous CNS PNET): the future

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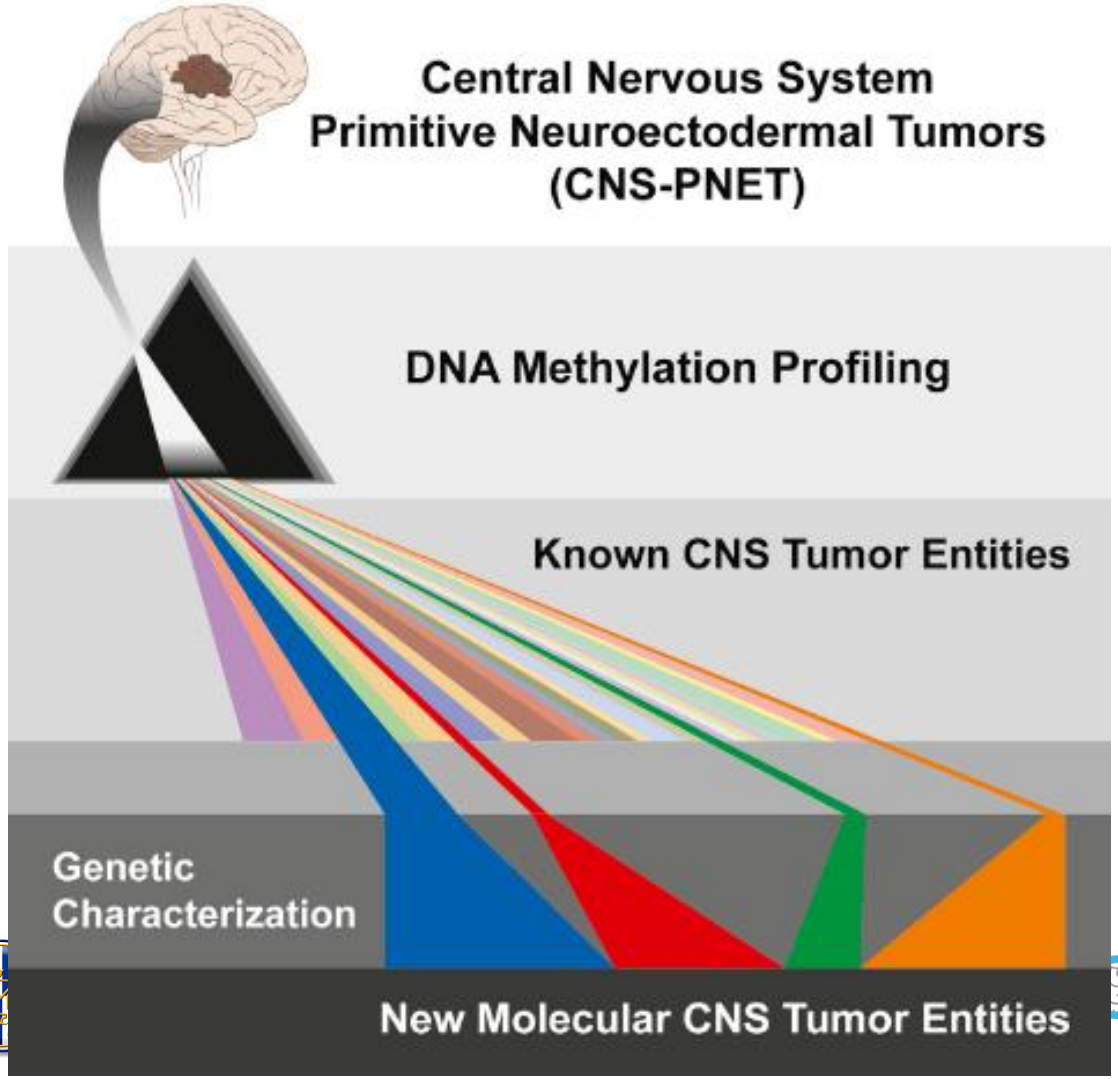
New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs

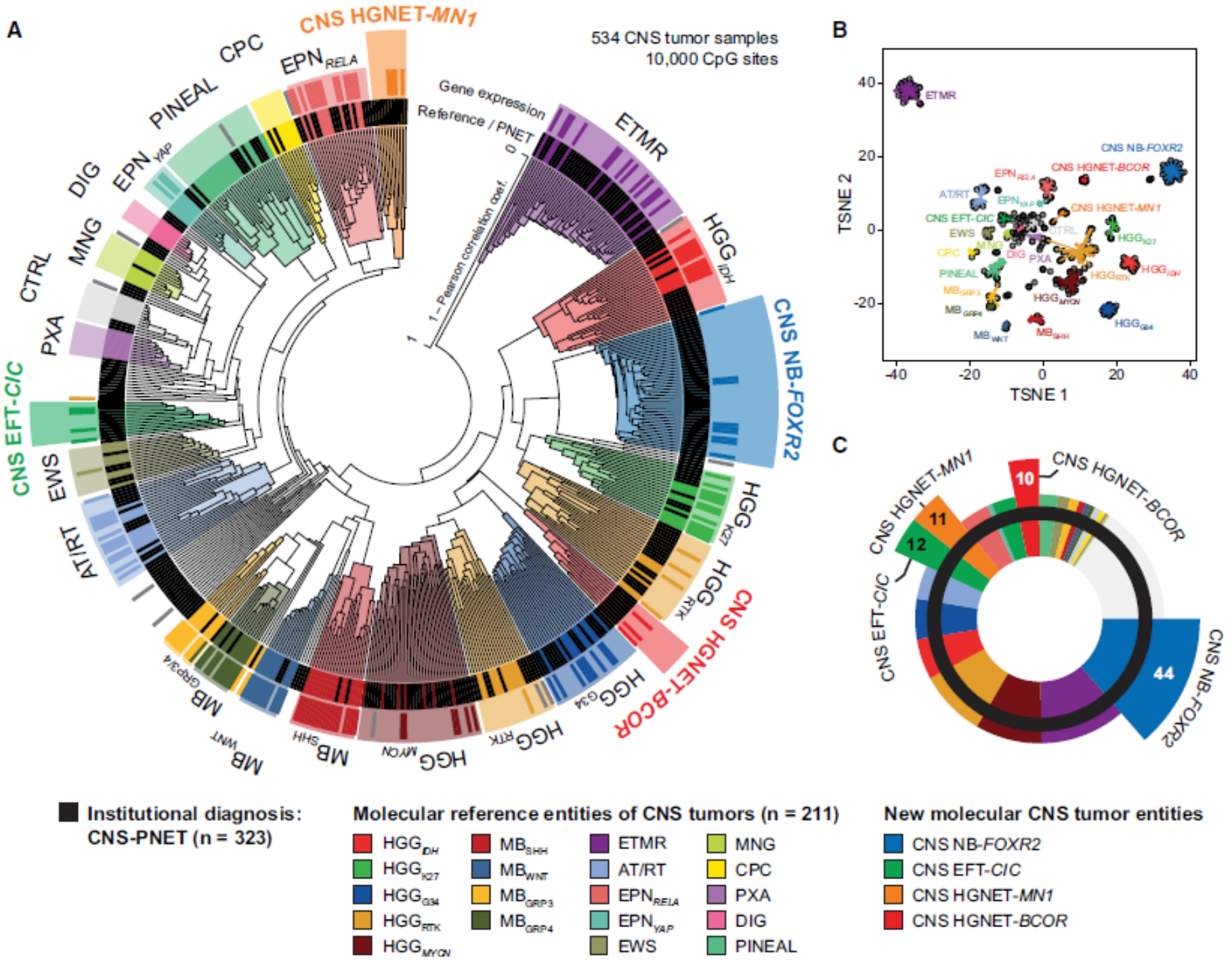
Sturm et al 2016

Cell



Inserm

CEF


A
534 CNS tumor samples
10,000 CpG sites
Gene expression
Reference / PNET
1 – Pearson correlation coef.
0
1
CNS HGNET-MN1
EPN RELA
CPC
PINEAL
EPN YAP
DIG
MNG
CTRL
PXA
CNS EFT-CIC
EWS
AT/RT
MB WNT
MB GRP3/4
MB SHH
HGG MYCN
HGG RTK
HGG G34
CNS HGNET-BCOR
HGG K27
CNS NB-FOXR2
HGG IDH
ETMR
B
TSNE 1
TSNE 2
ETMR
CNS NB-FOXR2
CNS HGNET-BCOR
EPN RELA
AT/RT
EPN YAP
CNS HGNET-MN1
CNS EFT-CIC
EWS
CTRL
HGG K27
MNG
CPC
DIG
PXA
PINEAL
HGG RTK
HGG IDH
MB GRP3
HGG MYCN
MB GRP4
HGG G34
MB WNT
MB SHH
C
CNS HGNET-MN1
CNS HGNET-BCOR
CNS EFT-CIC
CNS NB-FOXR2
10
11
12
44
Institutional diagnosis:
CNS-PNET (n = 323)
Molecular reference entities of CNS tumors (n = 211)
HGG IDH
HGG K27
HGG G34
HGG RTK
HGG MYCN
MB SHH
MB WNT
MB GRP3
MB GRP4
ETMR
AT/RT
EPN RELA
EPN YAP
EWS
MNG
CPC
PXA
DIG
PINEAL
New molecular CNS tumor entities
CNS NB-FOXR2
CNS EFT-CIC
CNS HGNET-MN1
CNS HGNET-BCOR

Future directions

cIMPACT-NOW

Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy

To provide a forum to evaluate and recommend proposed changes to future CNS tumor classifications, cIMPACT-NOW will at regular intervals facilitate input and consensus review of novel diagnostically relevant data and determine how such information can be practically incorporated into CNS tumor classifications. While it is understood that the major impact on international brain tumor classification comes about through the WHO classification update process, it is anticipated that this additional process will "see impact" in selected tumor types and in time periods between the WHO classification updates. The cIMPACT-NOW updates are not intended to supplant the existing WHO classification, but to provide possible guidelines for practicing diagnosticians and future WHO classification updates.

cIMPACT-NOW

Ken Aldape
Dan Brat
David Capper
David W. Ellison
Dominique Figarella-Branger
Cynthia Hawkins
David N. Louis
Werner Paulus
Arie Perry
Guido Reifenberger

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Tracy Batchelor
J. Gregory Cairncross
Stefan Pfister
Stefan Rutkowski
Michael Weller
Wolfgang Wick

Conclusions

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- The WHO 2016 classification of brain tumors represent an important step forward over 2007
- Introduction of genetic markers that should be widely used
- Strong impact in the daily practice
- Is likely an intermediate stage before the future fith edition of the WHO classification

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