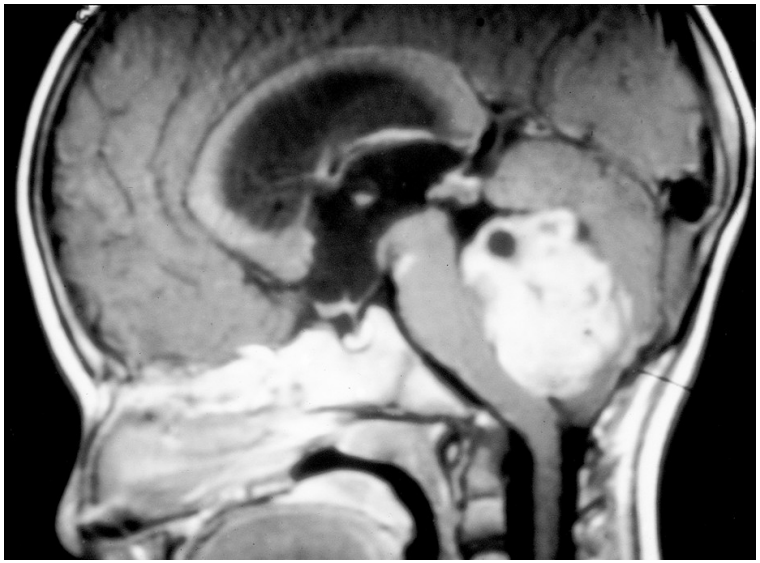
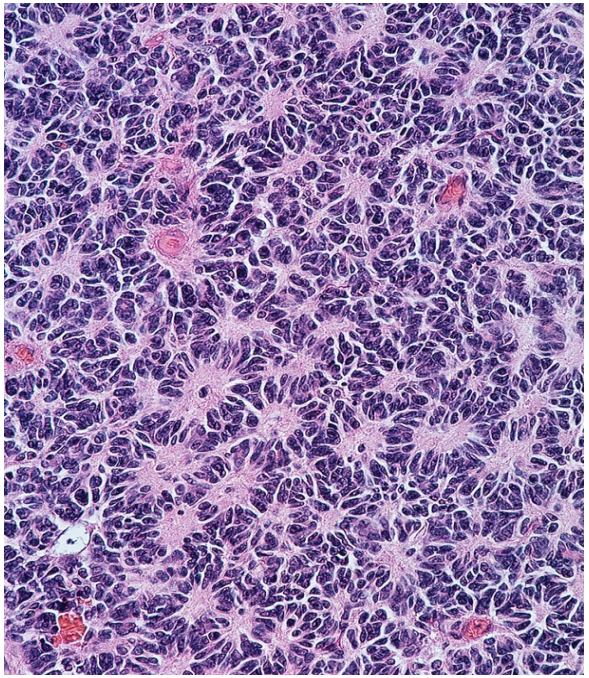
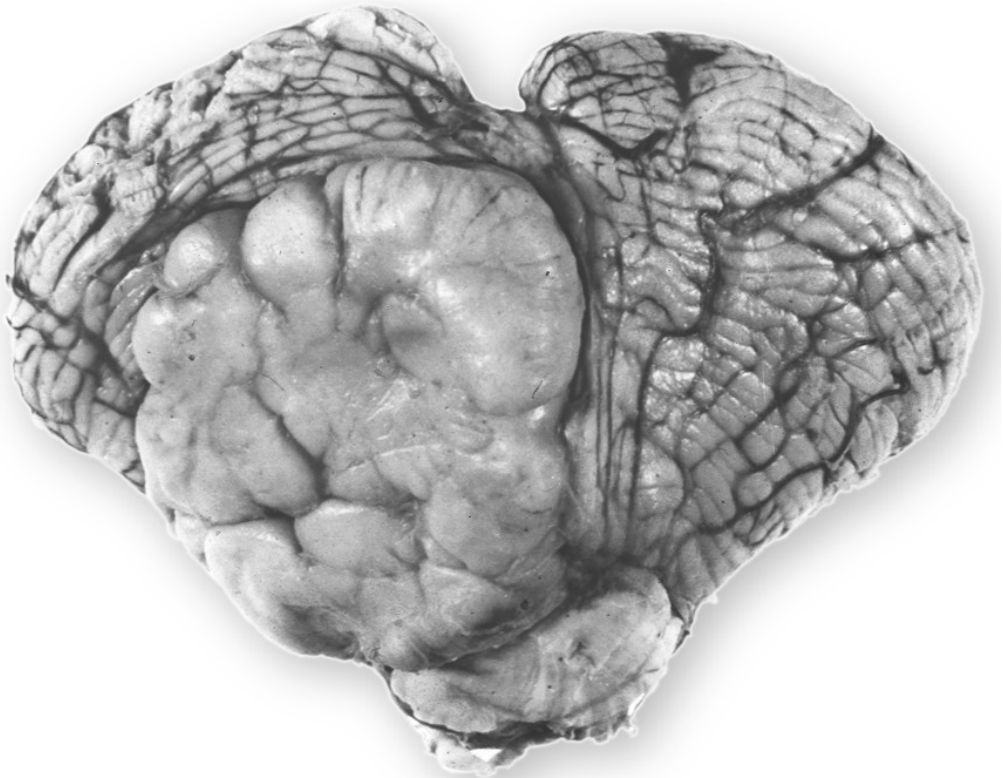
Medulloblastoma And Other Embryonal Brain Tumors





Charles G. Eberhart M.D., Ph.D.
Departments of Pathology, Ophthalmology and Oncology
Johns Hopkins University



Medulloblastoma

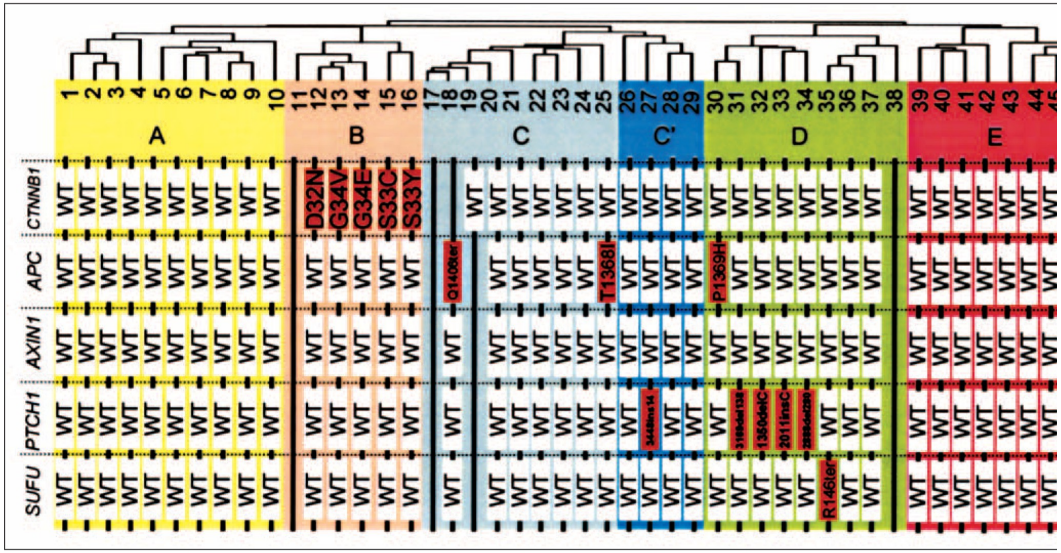
- Most common malignant pediatric CNS neoplasm
- Radiation and chemotherapy current standard
- Focus on targeted and/or reduced therapy based on emerging molecular knowledge

2004 AANP Education Day

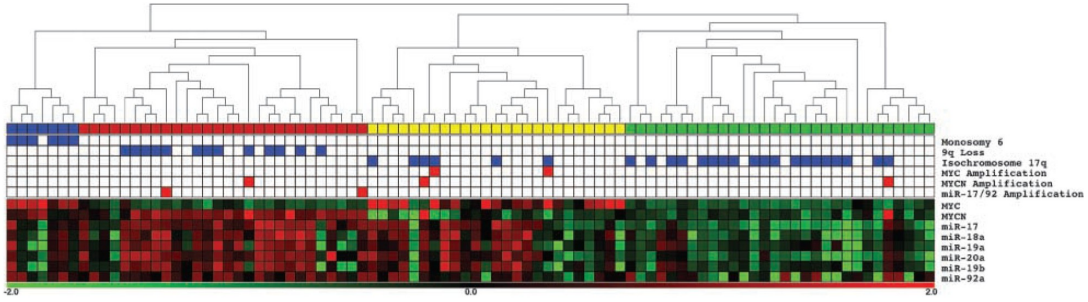
Molecular Prognostic Markers in Medulloblastoma

- ↑ TrkC mRNA = Longer Survival
- ↑ c-Myc mRNA = Shorter Survival
- ↑ Ribosomal mRNA = Shorter Survival
- ↑ ErbB2 protein = Shorter Survival

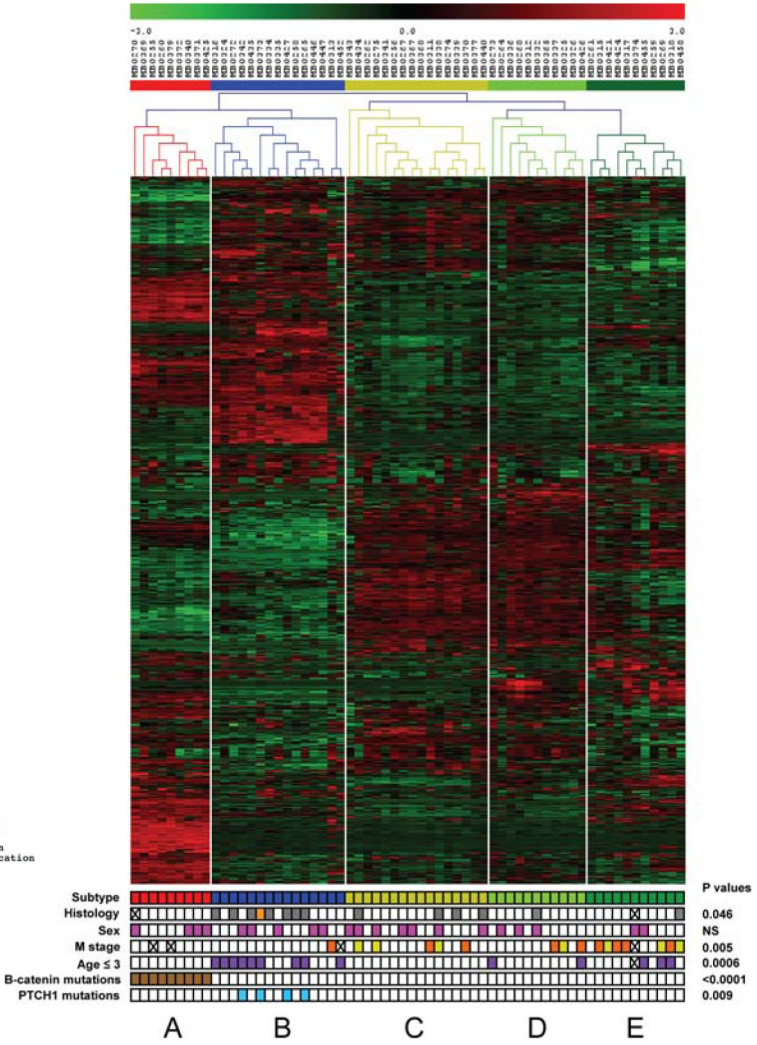
Medulloblastomas can be classified into molecular subgroups



Thompson *et al. JCO.* 2006 24: 1924-1931.



Northcott *et al. Cancer Res.* 2009 69: 3249-3255.



Kool *et al. PLOS One.* 2008 3: 1-14.

Molecular Subgroups of Medulloblastoma

CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: infant, child, adult

Gender: ♀ ♂

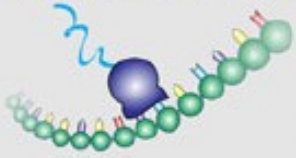
CLINICAL FEATURES

	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS

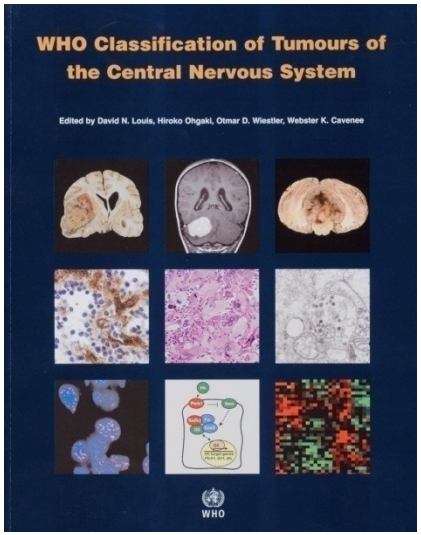
WNT	SHH	Group 3	Group 4
6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION



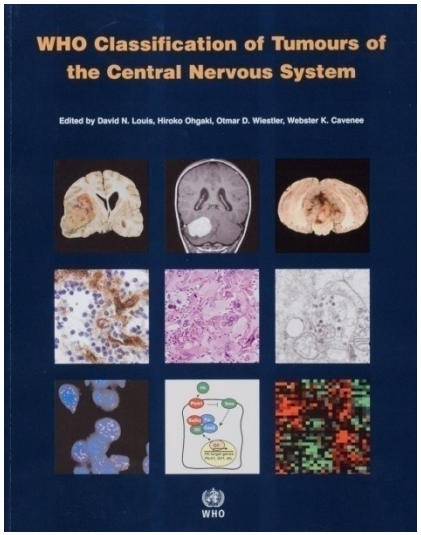
WNT	SHH	Group 3	Group 4
WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

WHO CNS Tumour Classification - 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 CNS Tumour Classification - 2007



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WHO'S NEXT

A Colloquium to Guide Next Steps in Brain Tumor Classification and Grading

Organizers: David Louis, Pieter Wesseling, Arie Perry

Program Committee: Peter Burger, David Ellison, Guido Reifenberger, Andreas von Deimling

Participating experts

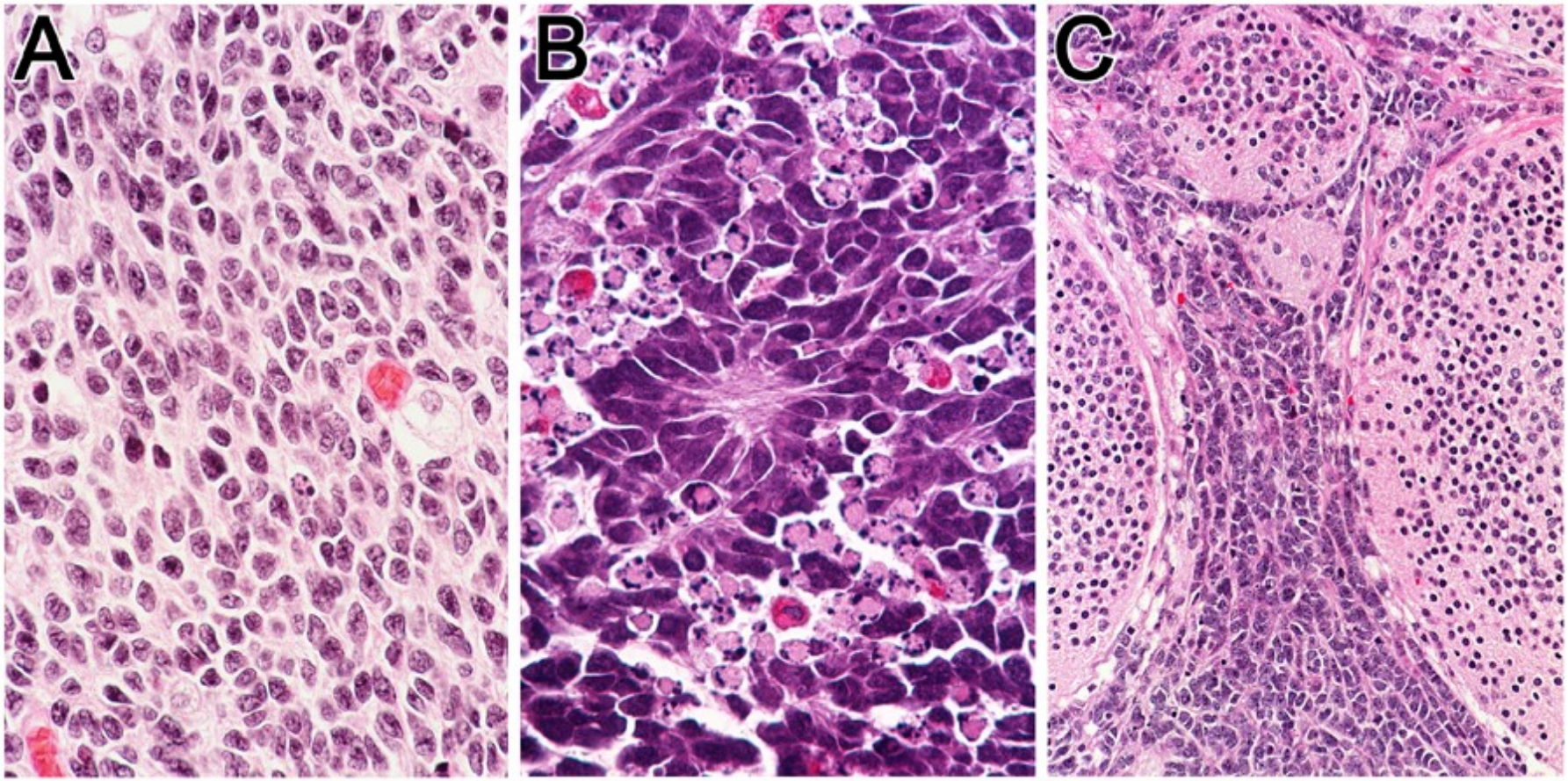
Practicing neuropathologist experts:

- Ken Aldape, Dept. of Pathology, MD Anderson Cancer Center, Houston TX, USA
- Dan Brat, Dept. of Pathology & Lab. Medicine, Emory University Hospital, Atlanta GA, USA
- Peter Burger, Dept. of Pathology, Johns Hopkins University, Baltimore MD, USA
- Peter Collins, Dept. of Pathology, University of Cambridge, Cambridge, UK
- Andreas von Deimling, Dept. of Neuropathology, Institute of Pathology, Heidelberg, Germany
- Charles Eberhart, Dept. of Pathology, Johns Hopkins University, Baltimore MD, USA
- David Ellison, Dept. of Pathology, St. Jude Children's Research Hospital, Memphis TN, USA
- Dominique Figarella-Branger, Dept. of Pathology/Neuropathology, Marseille, France
- Greg Fuller, Dept. of Pathology, MD Anderson Cancer Center, Houston TX, USA
- Felice Giangaspero, Dept. of Experimental Medicine, University of Rome, Rome, Italy
- Caterina Giannini, Dept. of Anatomic Pathology, Mayo Clinic College of Medicine, Rochester MN, USA
- Cynthia Hawkins, Div. of Pathology/Dept. of Paediatric Lab. Medicine, Hospital for Sick Children, Toronto, Canada
- Andrey Korshunov, Dept. of Neuropathology, DKFZ, Heidelberg, Germany
- Johan M. Kros, Dept. of Pathology, Erasmus Medical Center, Rotterdam, The Netherlands
- Bea Lopes, Dept. of Pathology, University of Virginia Health System, Charlottesville VA, USA
- David Louis, Dept. of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA
- Roger McLendon, Dept. of Pathology, Duke University Med. Center, Durham NC, USA
- H. K. Ng, Dept. of Anatomical Pathology and Cellular Pathology, Prince of Wales Hospital, Hong Kong, China
- Werner Paulus, Institute of Neuropathology, Univ. Hospital Munster, Munster, Germany
- Torsten Pietsch, Dept of Neuropathology, University of Bonn, Bonn, Germany
- Guido Reifenberger, Dept. of Neuropathology, Heinrich-Heine University, Dusseldorf, Germany
- Marc Rosenblum, Dept. of Pathology, Memorial Sloan Kettering Cancer Center, New York NY, USA
- Arie Perry, Dept. of Pathology, University of California San Francisco, San Francisco CA, USA
- Elisabeth Rushing, Dept. of Pathology, University Hospital Zurich, Zurich, Switzerland
- Figen Soylemezoglu, Dept. of Pathology, Haceteppe University, Ankara, Turkey
- Pieter Wesseling, Depts. of Pathology, VU Univ. Med. Ctr. Amsterdam & Radboud Univ. Nijmegen Med. Ctr., The Netherlands

Additional invited experts (including CNS WHO classification representation):

- Web Cavenee, University of California San Diego, San Diego CA, USA (not attending)
- Paul Kleihues, University of Zurich, Zurich, Switzerland
- Hiroko Ohgaki, International Agency for Research on Cancer (IARC), Lyon, France
- Otmar Wiestler, DKFZ, Heidelberg, Germany

Medulloblastoma Subtypes



Classic

Large Cell/
Anaplastic

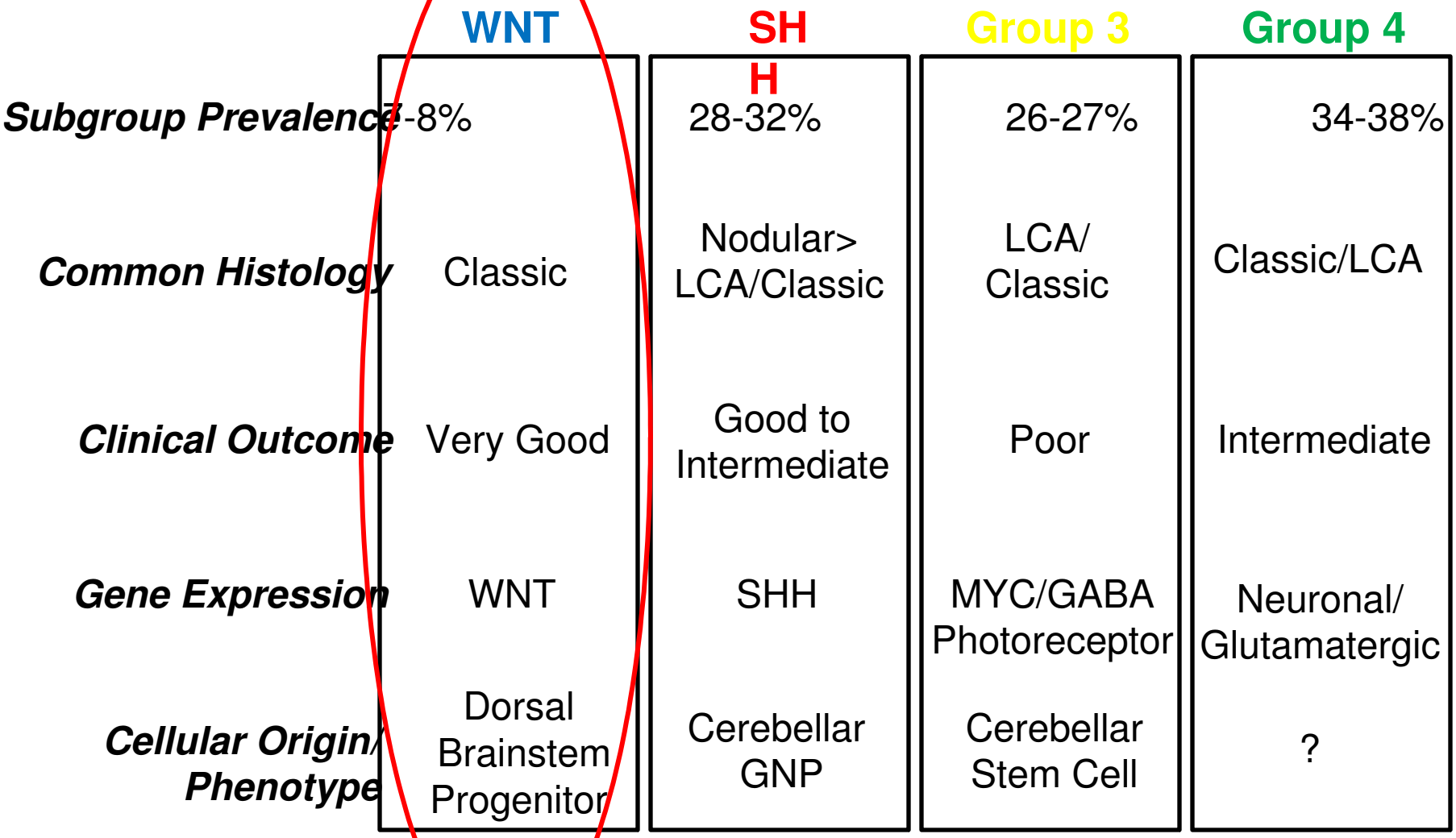
Nodular/
Desmoplastic

Medulloblastoma Subtypes

	WNT	SHH	Group 3	Group 4
Subgroup Prevalence	7-8%	28-32%	26-27%	34-38%
Common Histology	Classic	Nodular> LCA/Classic	LCA/ Classic	Classic/LCA
Clinical Outcome	Very Good	Good to Intermediate	Poor	Intermediate
Gene Expression	WNT	SHH	MYC/GABA Photoreceptor	Neuronal/ Glutamatergic
Cellular Origin/ Phenotype	Dorsal Brainstem Progenitor	Cerebellar GNP	Cerebellar Stem Cell	?

Eberhart 2012 *Cancer Cell*

Medulloblastoma Subtypes



Eberhart 2012 *Cancer Cell*

Wnt in Medulloblastoma

- Turcot's syndrome patients with inherited APC loss develop medulloblastoma
- Wnt pathway activation also occurs in sporadic medulloblastoma (generally classic ones)

[CANCER RESEARCH 58, 896–899, March 1, 1998]

Advances in Brief

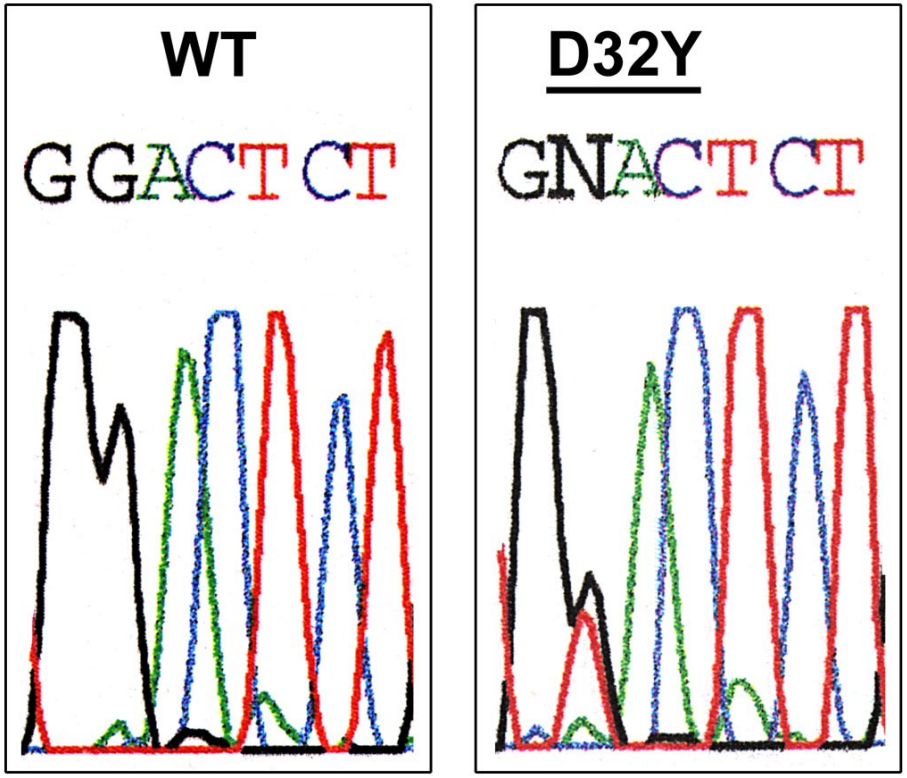
Sporadic Medulloblastomas Contain Oncogenic β-Catenin Mutations[1]

Russell H. Zurawel, Sharon A. Chiappa, Cory Allen, and Corey Raffel[2]

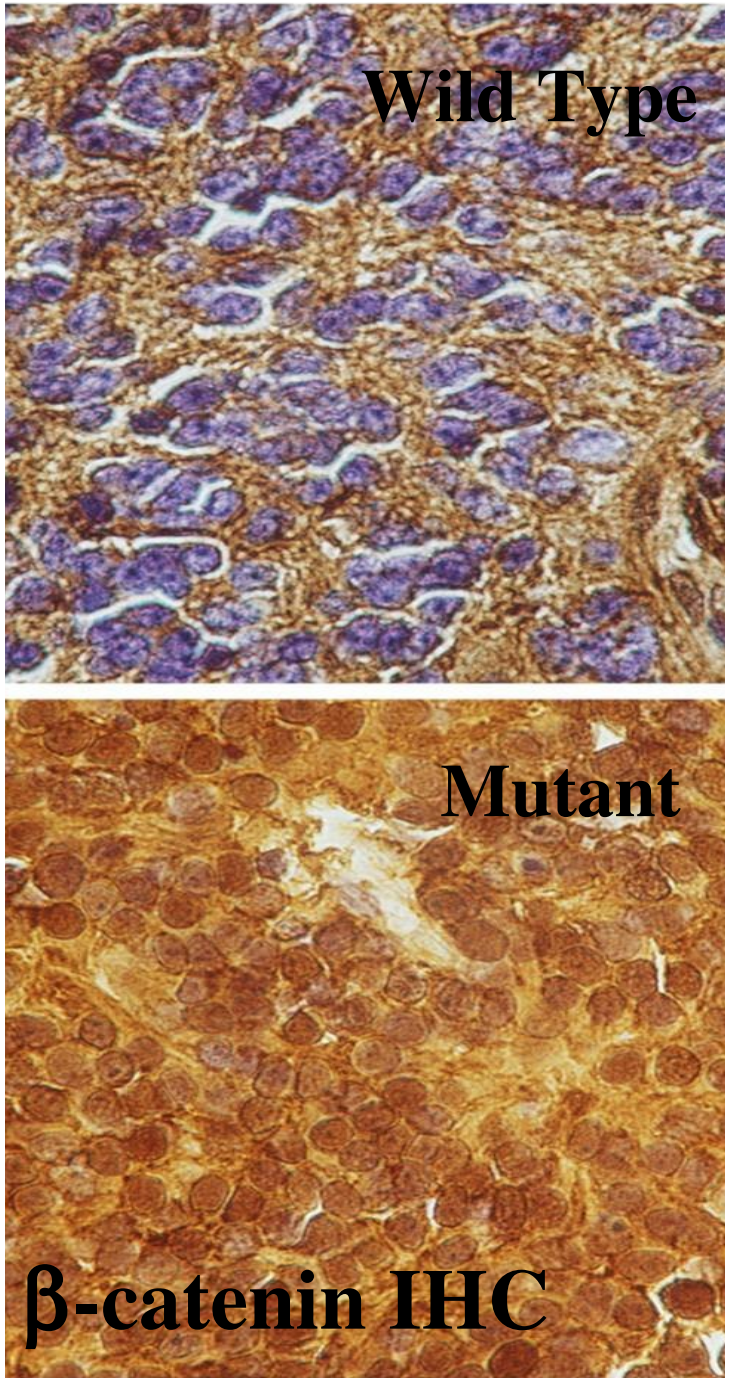
Department of Neurosurgery, Mayo Clinic and Foundation, Rochester, Minnesota 55905

Wnt Pathway Mutations

- β-catenin mutation common
- Results in nuclear translocation



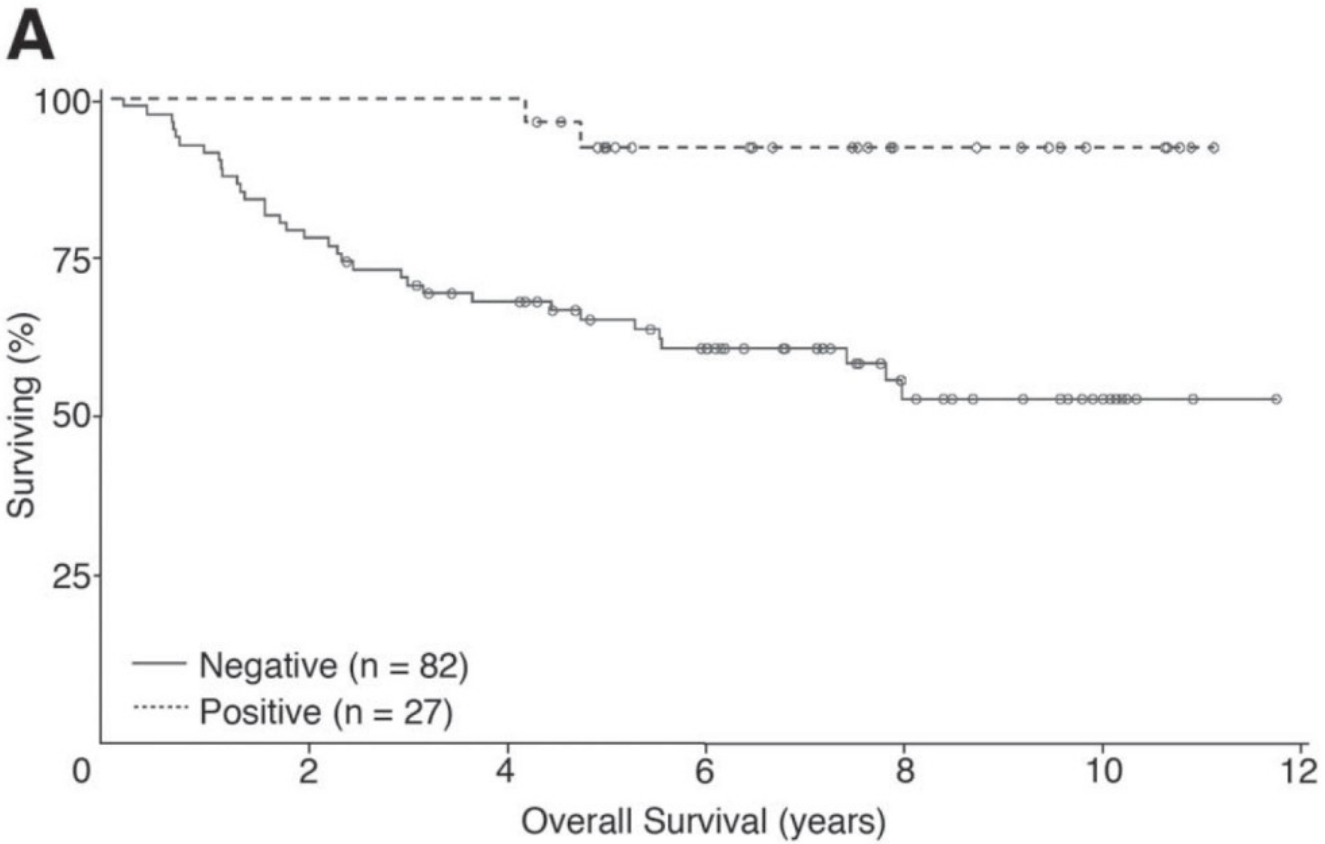
Eberhart et al JNEN 2000



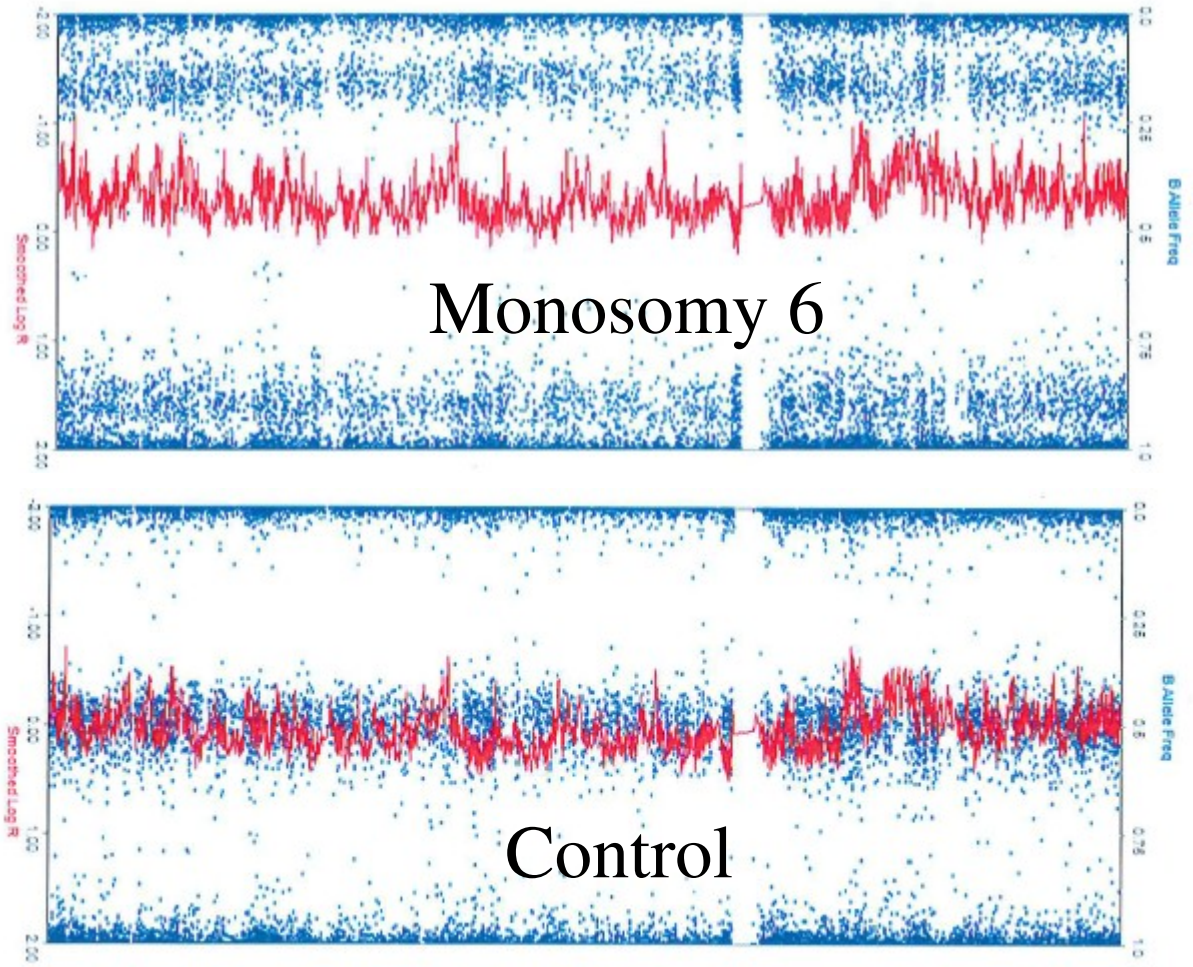
Journal of Clinical Oncology, Vol 23, No 31 (November 1), 2005: pp. 7951-7957

ß-Catenin Status Predicts a Favorable Outcome in Childhood Medulloblastoma: The United Kingdom Children's Cancer Study Group Brain Tumour Committee

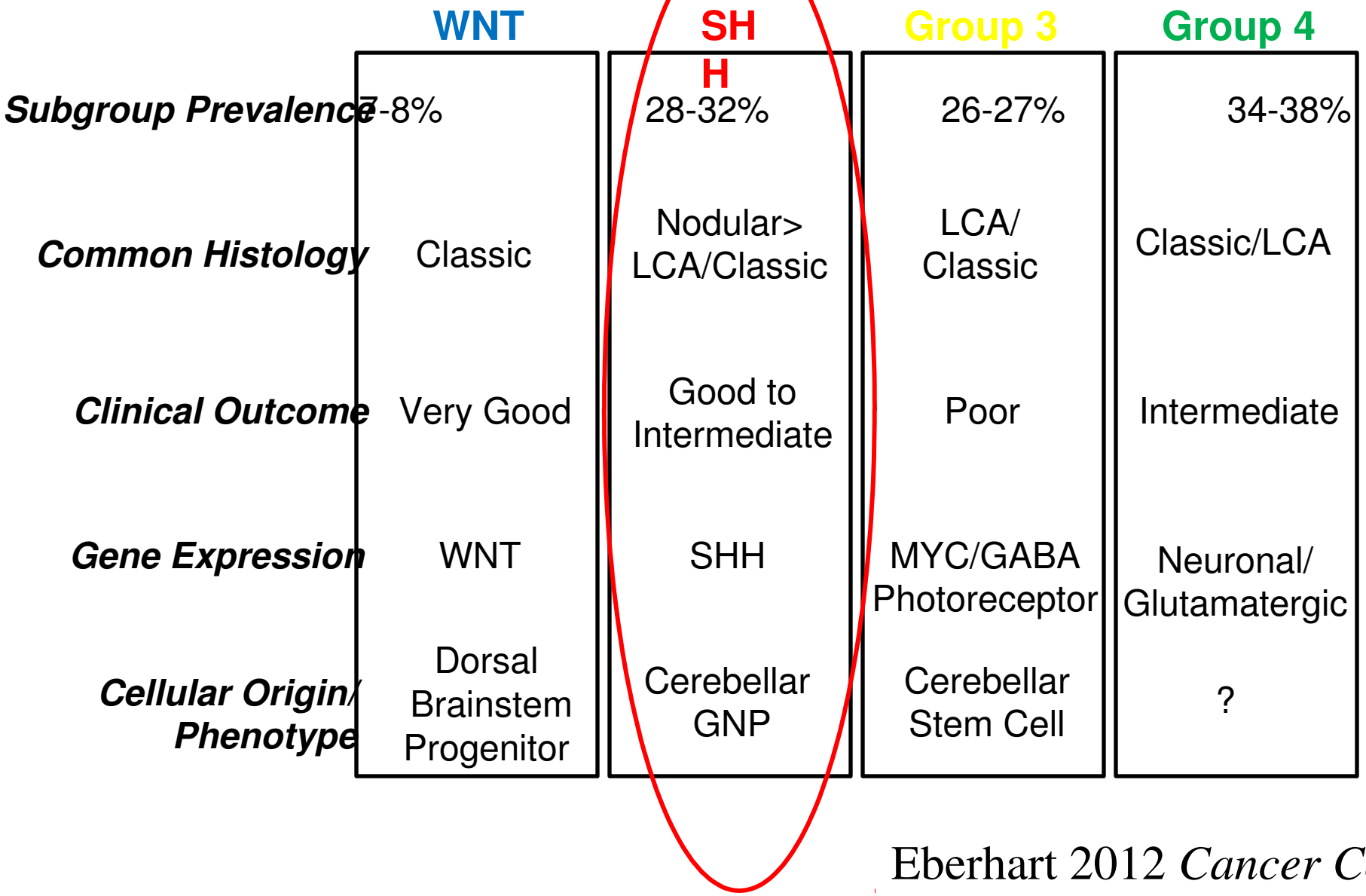
David W. Ellison, Olabisi E. Onilude, Janet C. Lindsey, Meryl E. Lusher,
Claire L. Weston, Roger E. Taylor, Andrew D. Pearson, Steven C. Clifford



Monosomy 6 is also tightly associated with Wnt medulloblastoma



Medulloblastoma Subtypes



Eberhart 2012 *Cancer Cell*

[CANCER RESEARCH 57, 2085–2088, June 1, 1997]

Advances in Brief

Medulloblastomas of the Desmoplastic Variant Carry Mutations of the Human Homologue of *Drosophila patched*[1]

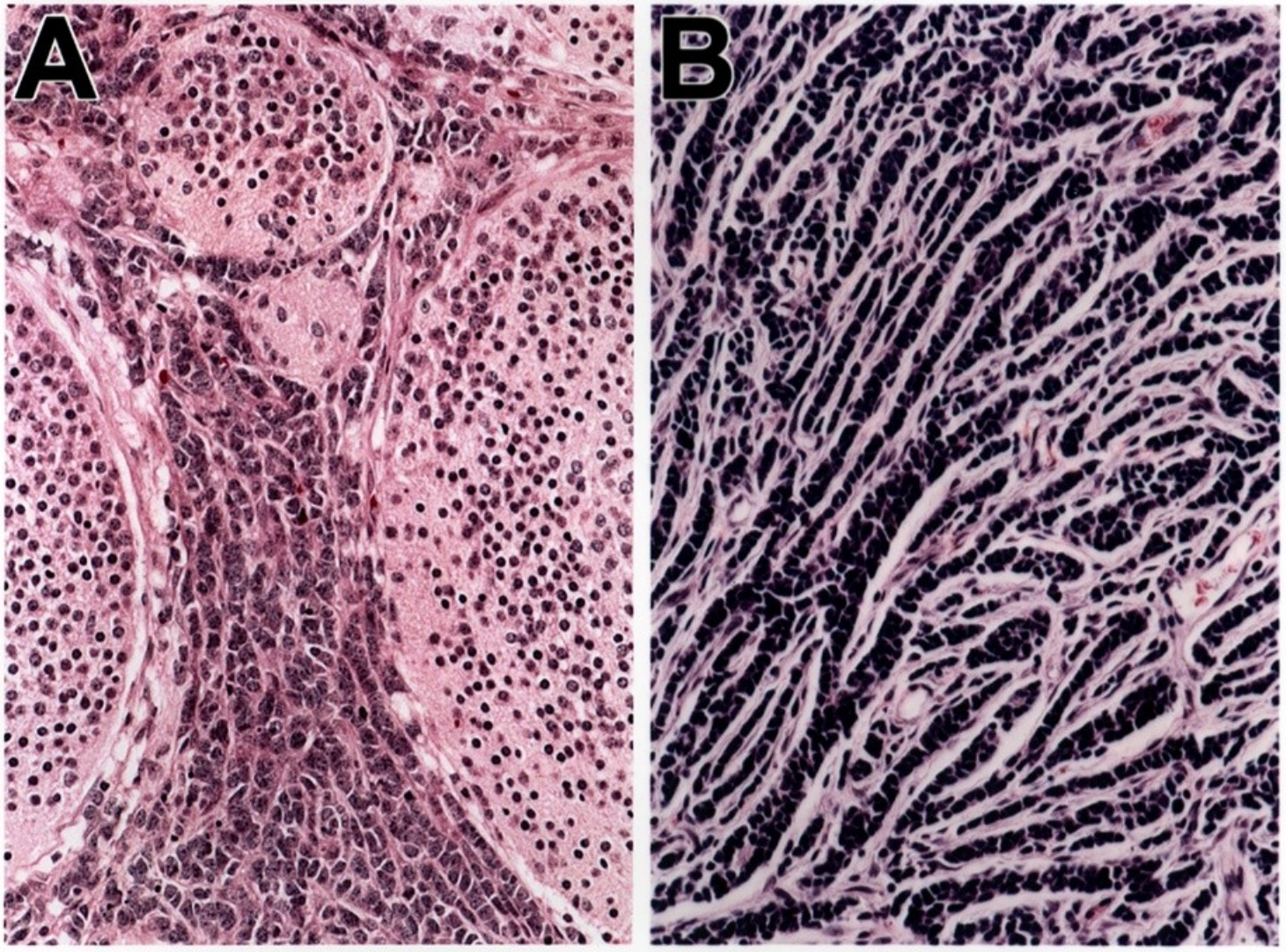
Torsten Pietsch,[2] Andreas Waha, Anke Koch, Jürgen Kraus, Steffen Albrecht, Jörg Tonn, Nils Sörensen, Frank Berthold, Bettina Henk, Nicole Schmandt, Helmut K. Wolf, Andreas von Deimling, Brandon Wainwright, Georgia Chenevix-Trench, Otmar D. Wiestler, and Carol Wicking

Department of Neuropathology, University of Bonn Medical Center, Sigmund-Freud-Strasse 25, D-53105, Bonn, Germany [T. P., A. W., A. K., J. K., B. H., N. S., H. K. W., A. v. D., O. D. W.]; Department of Pathology, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal, H3T 1E2 Canada [S. A.]; Departments of Neurosurgery [J. T.] and Pediatric Neurosurgery [N. S.], University of Würzburg, D-97080 Würzburg, Germany; Department of Pediatric Hematology and Oncology, University of Cologne, D-50925 Cologne, Germany [F. B.]; Centre for Molecular and Cellular Biology, University of Queensland, St. Lucia, QLD 4072, Australia [B. W., C. W.]; The Queensland Institute of Medical Research, Royal Brisbane Hospital, Brisbane, QLD 4029, Australia [G. C-T.]

Table 2 *Expression of the PTCH gene in MBs*

Sample no.	MB subtype	LOH on 9q	*PTCH* mutation detected by SSCP	mRNA expression ratio PTCH:GAPDH	mRNA expression ratio PTCH:β-microglobulin
D 338	Classical	NA[a]	No	5.8 (3.9–7.4)[b]	10.3 (8.2–14.2)
D 230 II	Classical	No	No	1.7	NA
D 286	Classical	NA	No	1.2	NA
D 245 II	Classical	No	No	0.7	NA
D 446	Classical	No	No	1.8 (0.8–2.8)	1.5 (1.0–1.8)
D 447	Classical	No	No	0.6	NA
D 86	Desmoplastic	Yes	Yes, exon 10	3.6 (1.4–5.4)	2.6 (1.7–3.9)
D 292	Desmoplastic	No	Yes, exon 10	0.6 (0.6–0.6)	0.3 (0.3–0.4)
D 322	Desmoplastic	Yes	Yes, exon 6	1.1	NA
D 448	Desmoplastic	Yes	No	4.3 (3.3–5.5)	2.9 (2.5–3.6)
D 398	Desmoplastic	No	No	26.5 (22.4–30.0)	18.4 (12.0–24.4)
D 444	Desmoplastic	Yes	No	4.1 (3.7–4.7)	4.5 (3.3–5.5)
D 365[c]	Desmoplastic	NA	No	0.3 (0.2–0.4)	0.1 (0.1–0.2)
Cerebellum	–	NA	NA	2.5 (1.55–3.64)	1.76 (1.42–2.09)

Nodular and Desmoplastic Medulloblastomas



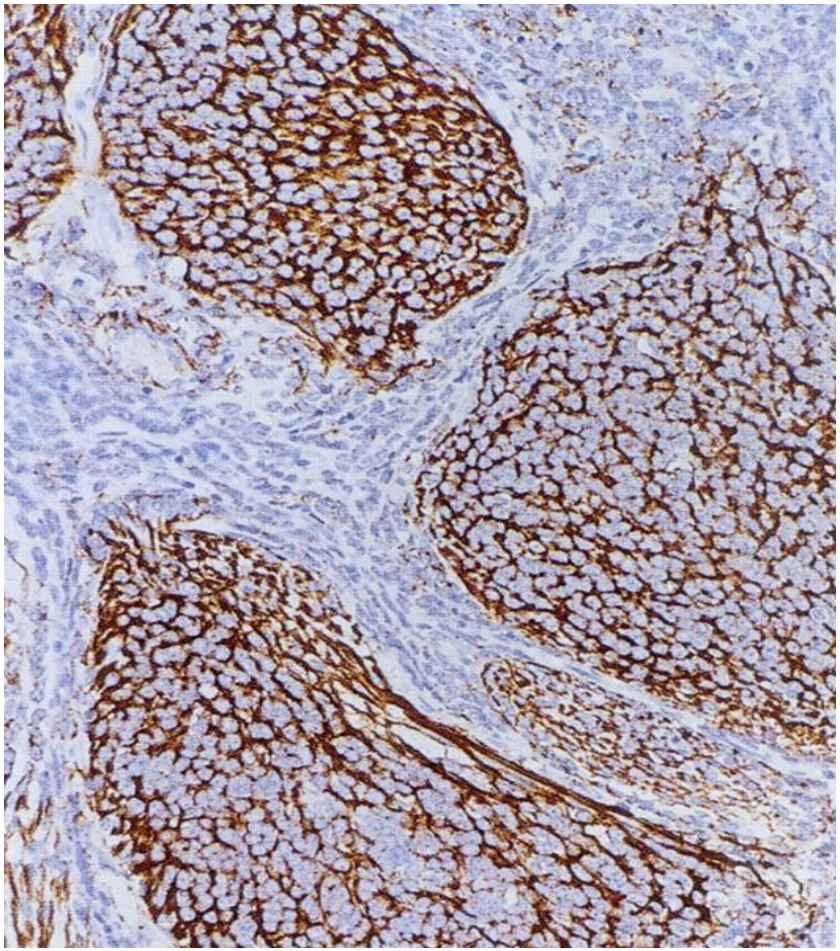
Nodular/Desmoplastic

Desmoplastic

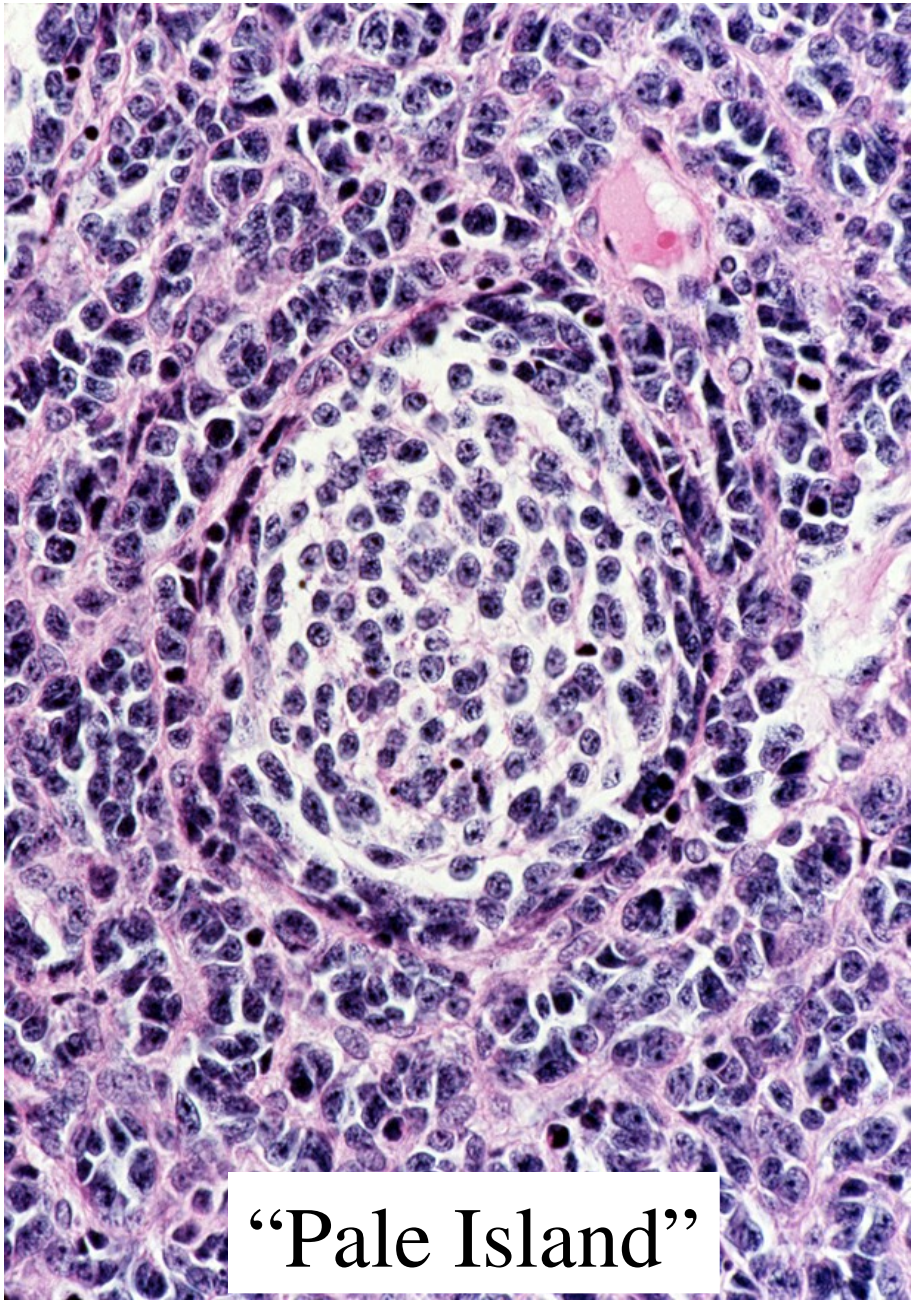
(P Burger)

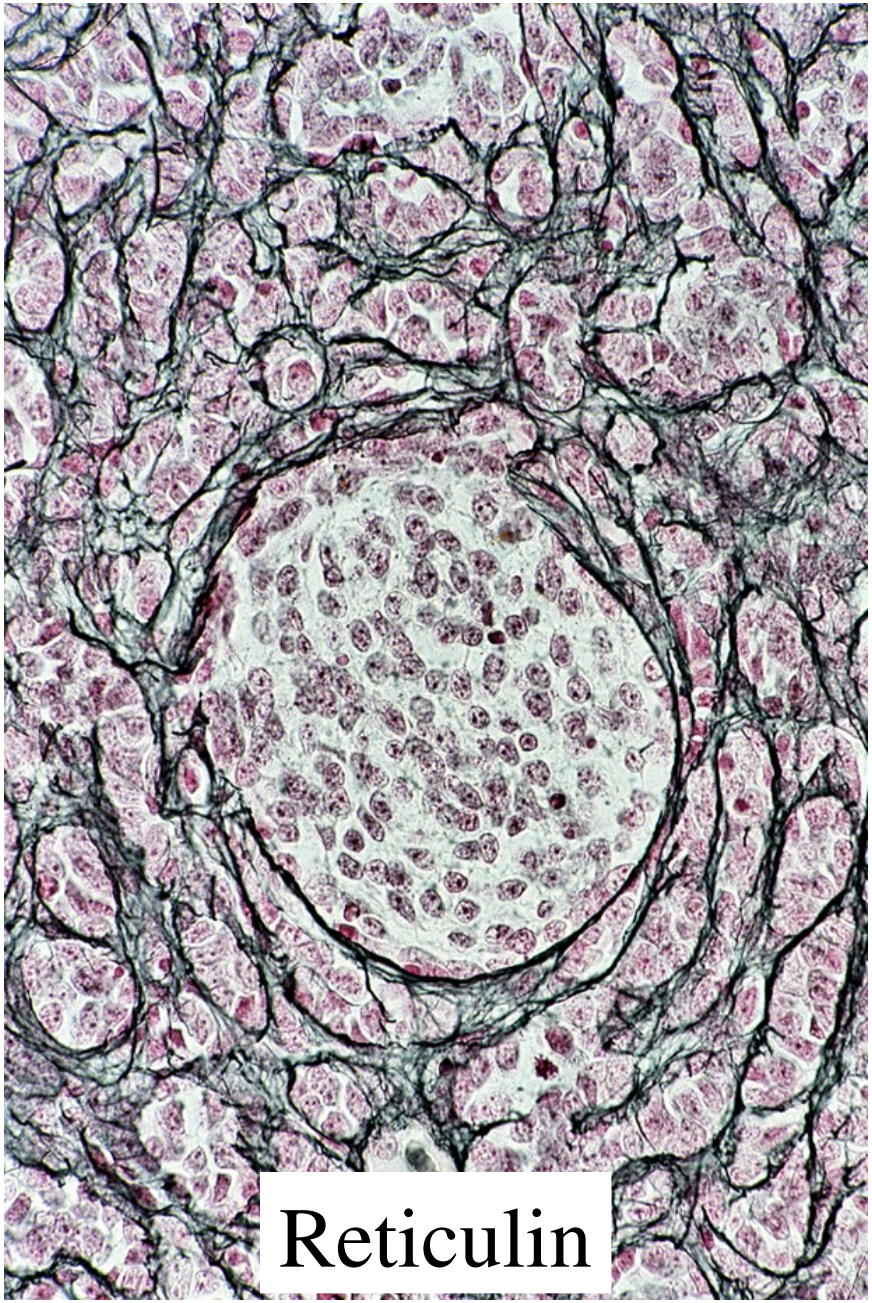
Desmoplastic/Nodular MB

- WHO requires nodules for this diagnosis
- Nodules show neuronal differentiation, decreased proliferation, increased apoptosis

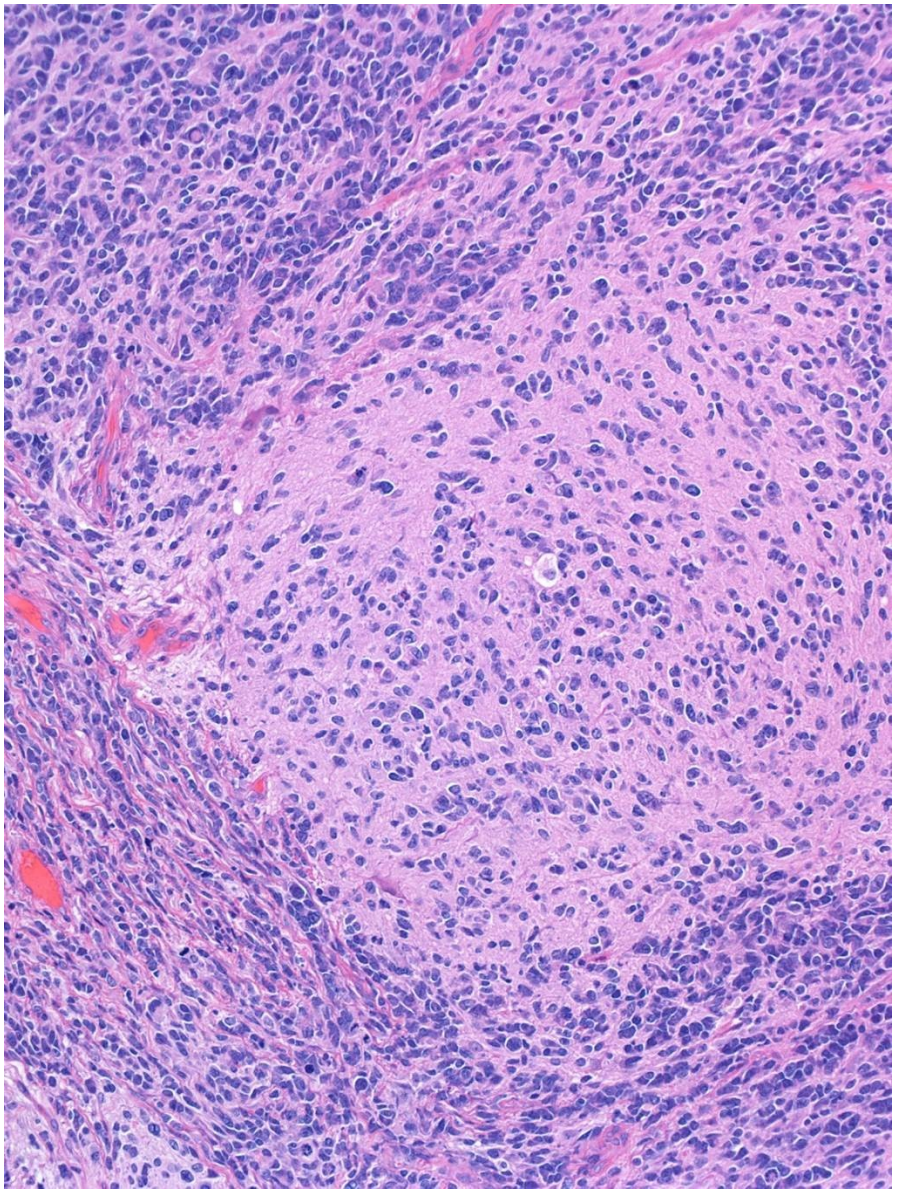


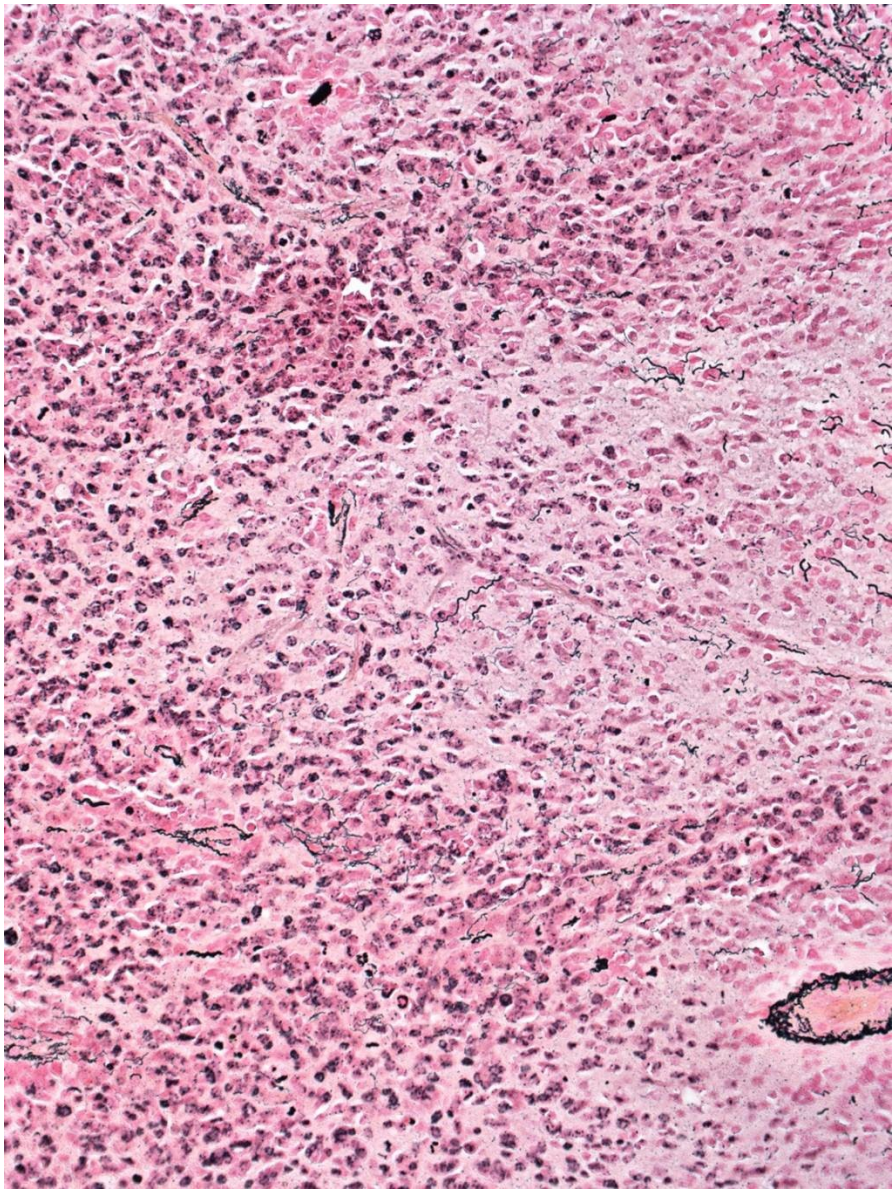
Synaptophysin


“Pale Island”


Reticulin

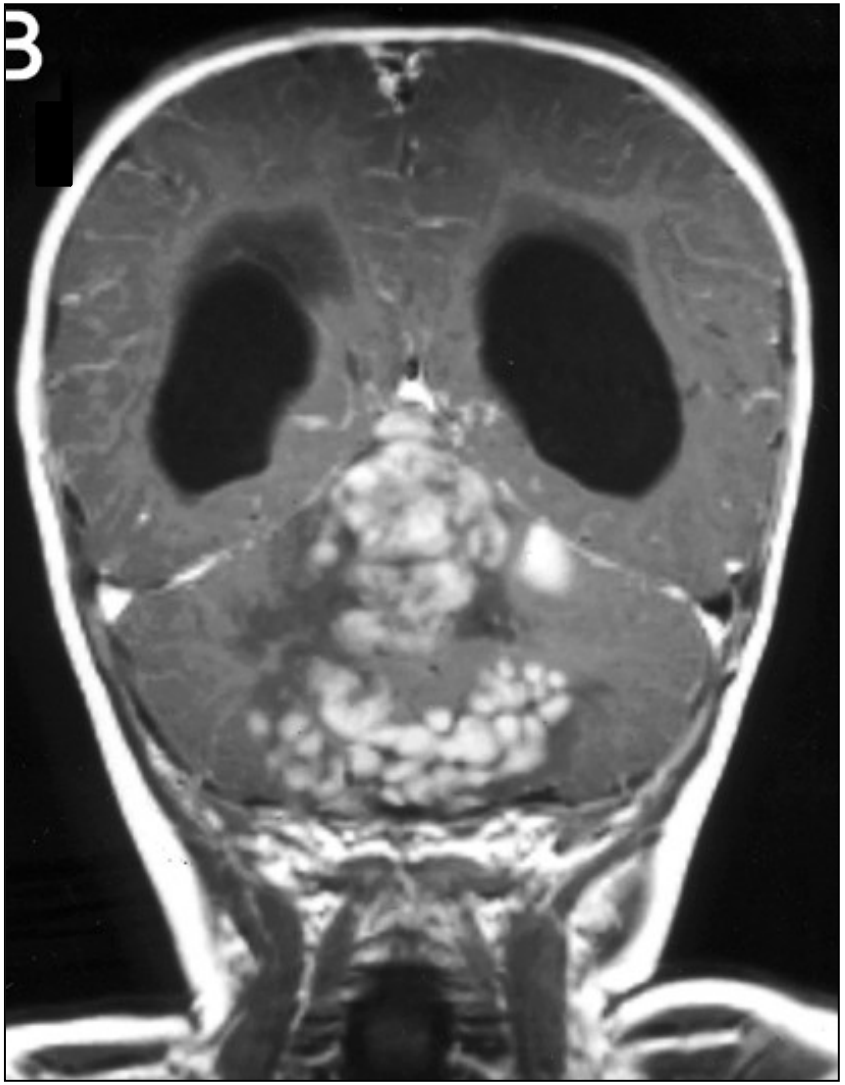
“Biphasic” Medulloblastoma

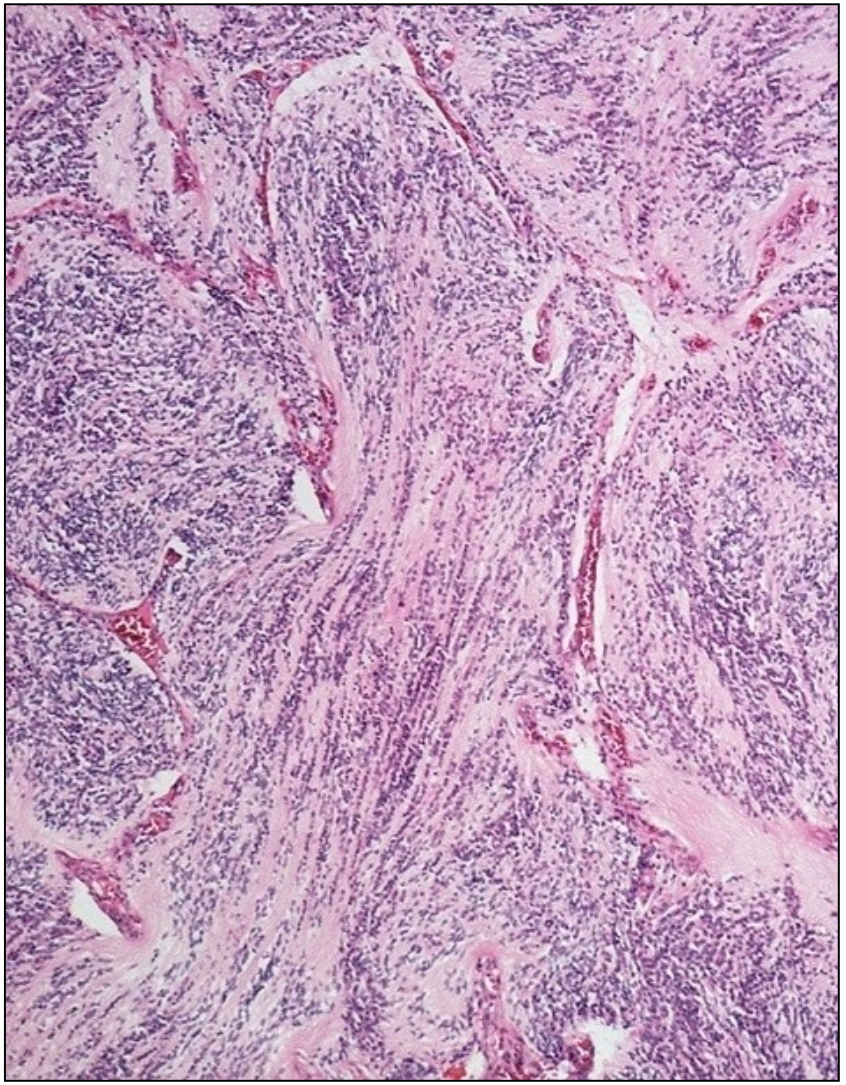




Reticulin confined to vessels

Medulloblastoma with Extensive Nodularity

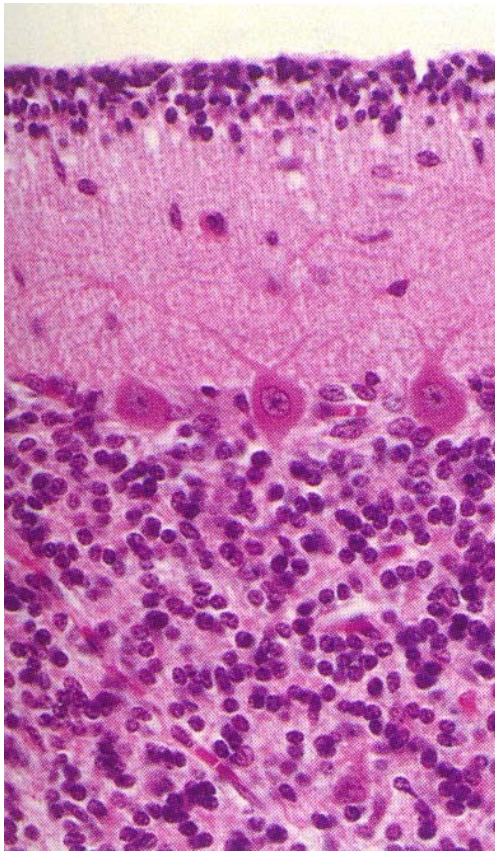




"Bunch of grapes" - T1W - post contrast

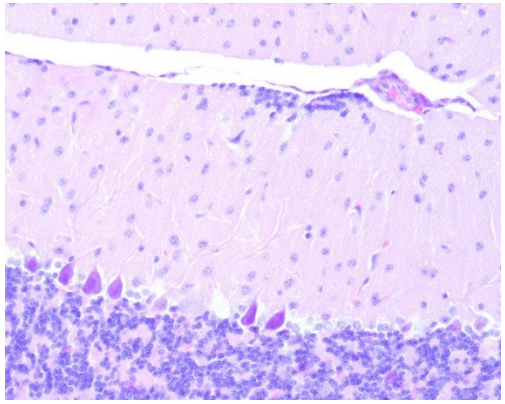
Little internodular tissue

Murine Transgenic Models Support the Concept That Medulloblastoma Can Arise From EGL Stem/Progenitor Cells

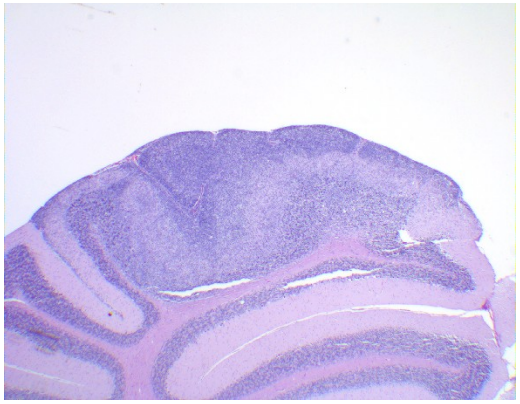


Fetal Cerebellum

Hh Activation

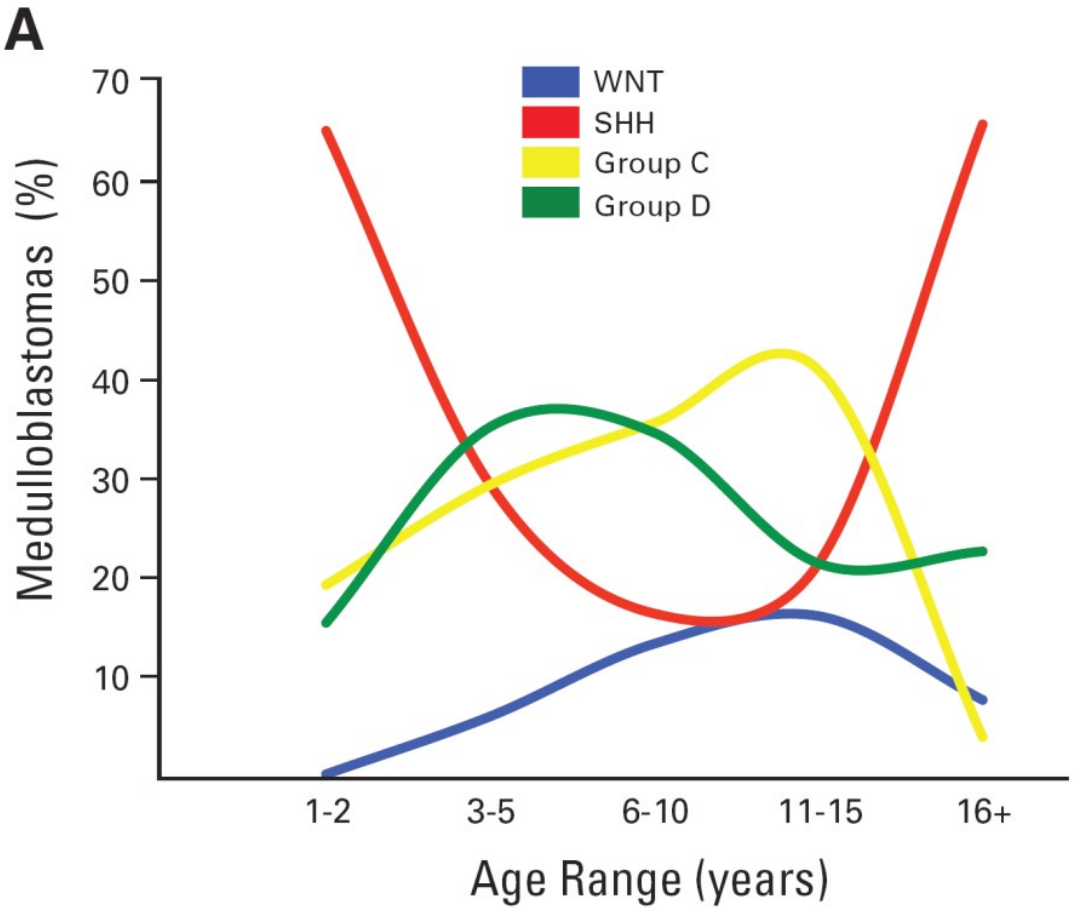


EGL Hyperplasia/
Persistent EGL



Medulloblastoma

SHH Group Medulloblastoma Are Most Common In Infants and Adolescents/Young Adults



Northcott et al. J Clin Oncol 2010

Medulloblastoma with Extensive Nodularity

TABLE 1

*Clinical characteristics of 11 children with MBENs on MR imaging**

Case No.	Age at Diagnosis (mos), Sex	"Grapelike" Appearance	Surgery	Therapy Postsurgery	Relapse	Outcome
1	<6, F	NA	total	RT (CSI)	none	alive, NED at 156 mos
2	22, F	absent	total	chemo	spinal; CSI 24 Gy, PF 42 Gy, spine 34 Gy, & 10-Gy booster	alive, NED at 39 mos, 30 mos postrelapse
3	20, F	present	partial	chemo	none	alive, NED at 72 mos
4	18, F	present	total	chemo	local; CSI 30 Gy, PF 54 Gy	alive, NED at 72 mos, 36 mos postrelapse
5	39, M	present	total	RT (CSI) & chemo	none	alive, NED at 120 mos
6	24, M	present	total	chemo	none	alive, NED at 60 mos
7†	11, M	present	total	RT (PF only)	none	alive, NED at 64 mos
8	9, M	present	total	chemo	none	alive, NED at 36 mos
9	20, M	absent‡	total	chemo	none	alive, NED at 36 mos
10	23, F	present	total	chemo	none	alive, NED at 35 mos
11	5, F	present	biopsy§	chemo	local; surgery & high-dose chemo	alive, NED at 35 mos, 9 mos postrelapse

* Chemo = chemotherapy; CSI = craniospinal irradiation; MBENs = medulloblastomas with extensive nodularity; NA = not available; NED = no evidence of disease; PF = posterior fossa; RT = radiotherapy.

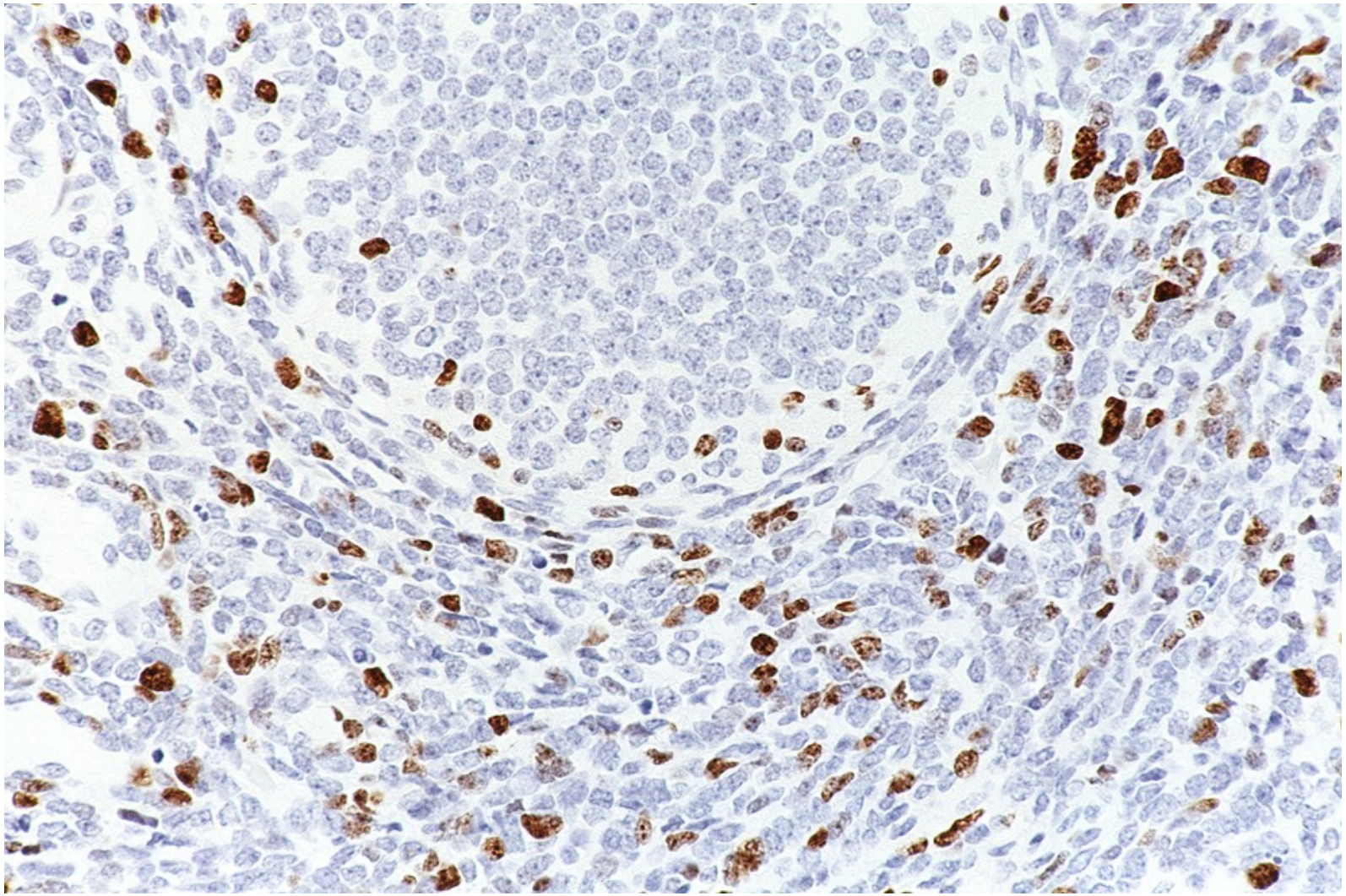
† Child affected by fragile X syndrome.

‡ Nodularity was present within the tumor mass.

§ Performed after two courses of chemotherapy.

Giangaspero et al. J. Neurosurg. 1999; 91:971-977.

Higher MIB-1 Index in Internodular Regions



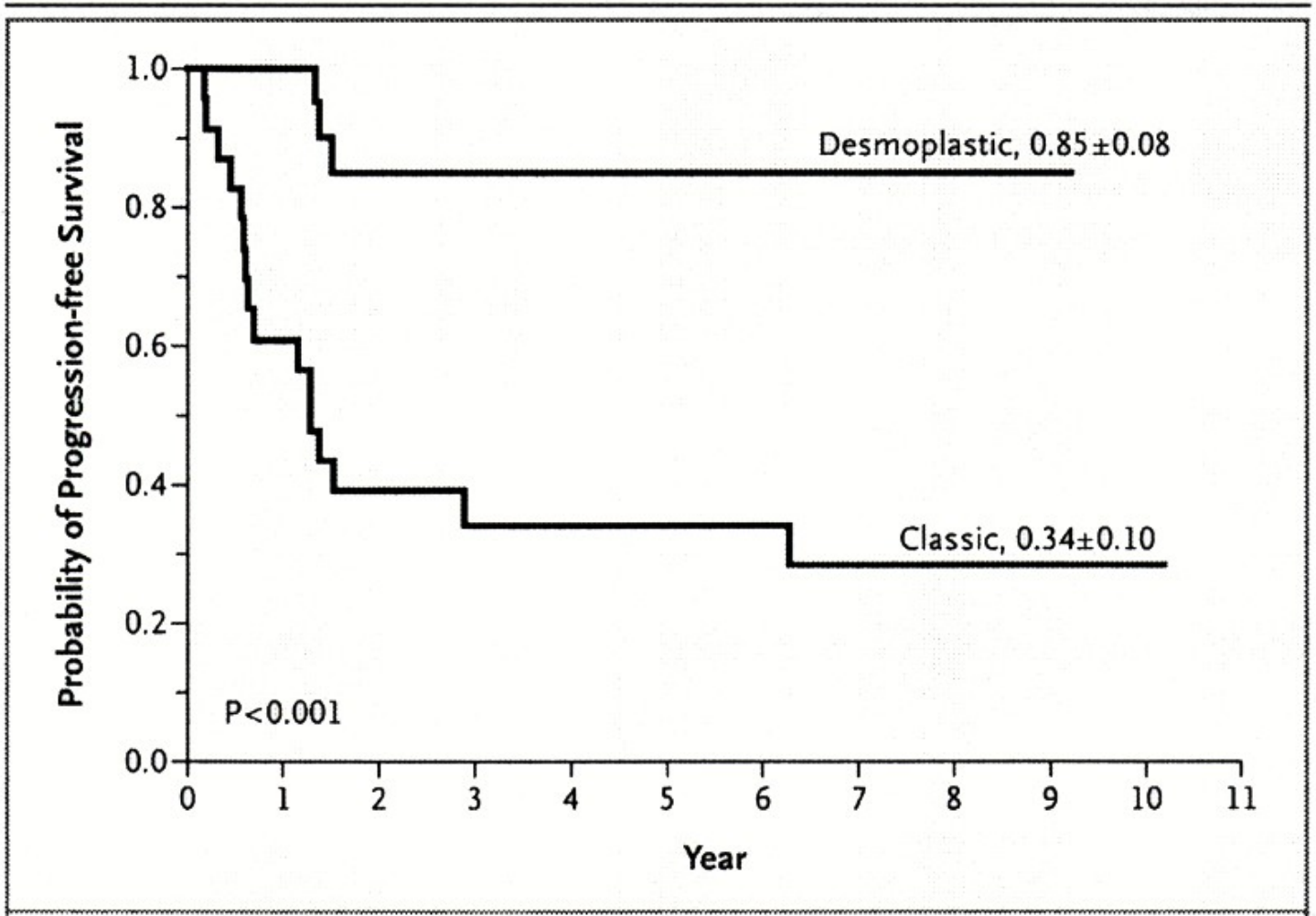


Figure 2. **Progression-free Survival among 23 Children with Classic and 20 Children with Desmoplastic Medulloblastoma.**

Rutkowski, et al., New Engl J Med 2005;352:978-986.

ACNS1221

A Phase II Study For The Treatment Of Non-Metastatic Desmoplastic Medulloblastoma In Children Less Than 4 Years Of Age

Primary Objective: Estimate of the PFS distribution for patients 0-<4 years of age with M0 desmoplastic medulloblastoma (ND or MBEN) treated with the modified HIT SKK regimen (excluding the use of intraventricular methotrexate).

Central Pathology Review For The COG ACNS1221 Trial Uses Aperio Images

- Case List
- Review List
- Demo Slides
- GOG0239 Test Cases
- User Profile
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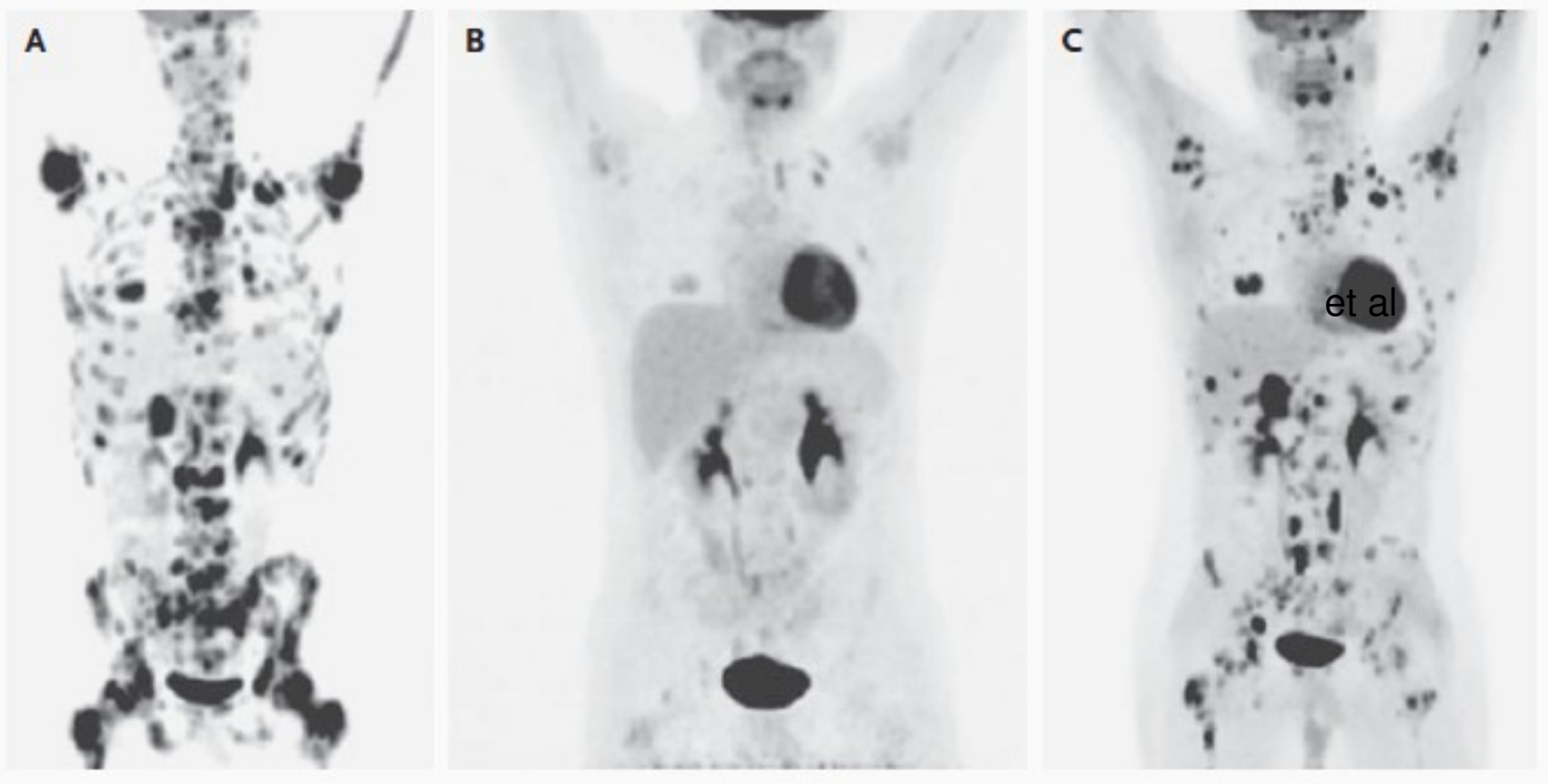
You are logged in as: **Charles Eberhart**

CASE LIST

Case Status	Case Name	Case Description
Completed	0000_02_P6583	BPC Lead: Natalie Beeler Reviewer(s):Dr. Lim Magnification Required: 20x Location of Images at OSC:T-Lymphoblastic Lymphoma Pathology Reports: No
Completed	840578	
Completed	841185	
Completed	841259	
Completed	841499	
Completed	841897	
Completed	842079	

REVIEW / GO TO REVIEW LIST

Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449



Pre Tx

2 months

3 Months

PET

Rudin, et al. New Engl J Med

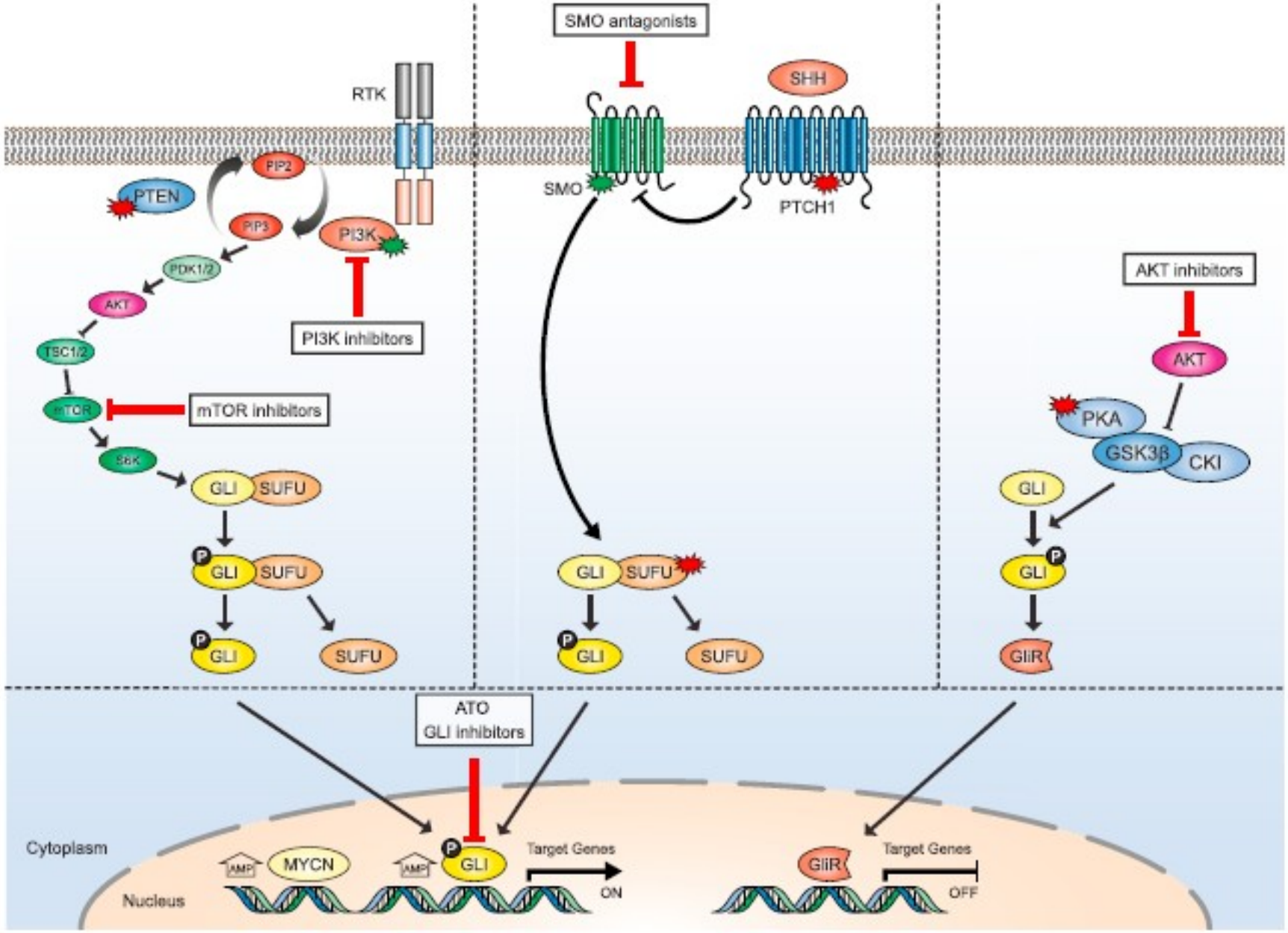
March 2014

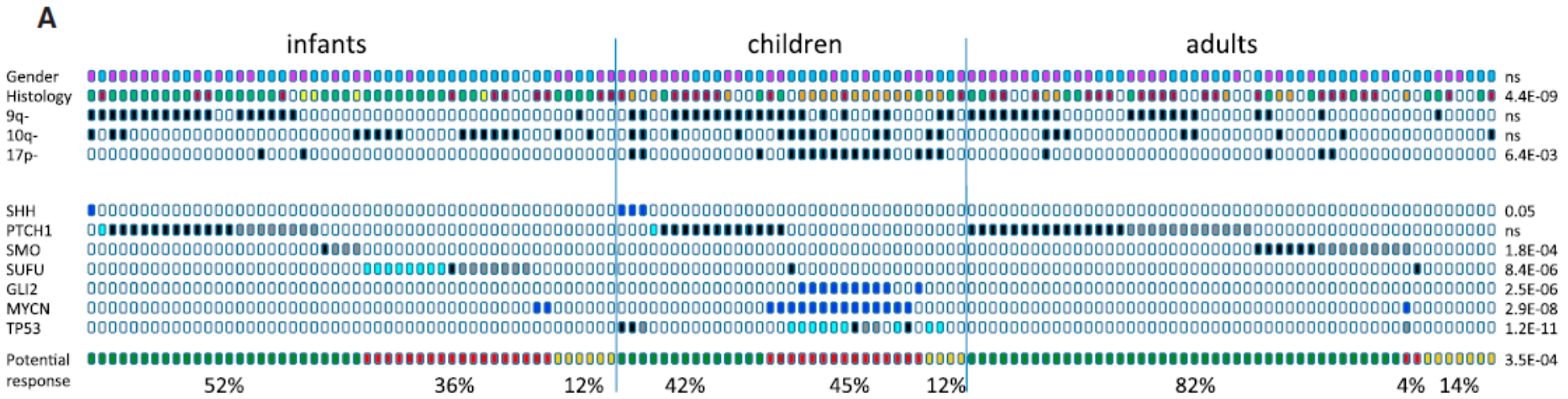
Cancer Cell
Article

Genome Sequencing of SHH Medulloblastoma Predicts Genotype-Related Response to Smoothened Inhibition

Marcel Kool,[1,*] David T.W. Jones,[1] Natalie Jäger,[2] Paul A. Northcott,[1] Trevor J. Pugh,[3] Volker Hovestadt,[4] Rosario M. Piro,[2] L. Adriana Esparza,[5] Shirley L. Markant,[5] Marc Remke,[6] Till Milde,[7] Franck Bourdeaut,[8,9] Marina Ryzhova,[10] Dominik Sturm,[1] Elke Pfaff,[1] Sebastian Stark,[1] Sonja Hutter,[1] Huriye Şeker-Cin,[1] Pascal Johann,[1] Sebastian Bender,[1] Christin Schmidt,[1] Tobias Rausch,[11] David Shih,[6] Jüri Reimand,[12] Laura Sieber,[1] Andrea Wittmann,[1] Linda Linke,[1] Hendrik Witt,[1,7] Ursula D. Weber,[4] Marc Zapatka,[4] Rainer König,[2,13,14] Rameen Beroukhim,[3,15,16] Guillaume Bergthold,[3,15,17] Peter van Sluis,[18] Richard Volckmann,[18] Jan Koster,[18] Rogier Versteeg,[18] Sabine Schmidt,[19] Stephan Wolf,[19] Chris Lawerenz,[20] Cynthia C. Bartholomae,[21] Christof von Kalle,[21] Andreas Unterberg,[21] Christel Herold-Mende,[21] Silvia Hofer,[22] Andreas E. Kulozik,[7] Andreas von Deimling,[23,24] Wolfram Scheurlen,[25] Jörg Felsberg,[26] Guido Reifenberger,[26] Martin Hasselblatt,[27] John R. Crawford,[28,29] Gerald A. Grant,[30,31] Nada Jabado,[32] Arie Perry,[33] Cynthia Cowdrey,[34] Sydney Croul,[35] Gelareh Zadeh,[35] Jan O. Korbel,[11] Francois Doz,[8,36] Olivier Delattre,[8,9] Gary D. Bader,[12] Martin G. McCabe,[37] V. Peter Collins,[38] Mark W. Kieran,[39] Yoon-Jae Cho,[40] Scott L. Pomeroy,[41] Olaf Witt,[42] Benedikt Brors,[2] Michael D. Taylor,[6] Ulrich Schüller,[43] Andrey Korshunov,[1,23,24] Roland Eils,[2] Robert J. Wechsler-Reya,[5,44] Peter Lichter,[4,44] and Stefan M. Pfister,[1,7,44] on behalf of the ICGC PedBrain Tumor Project

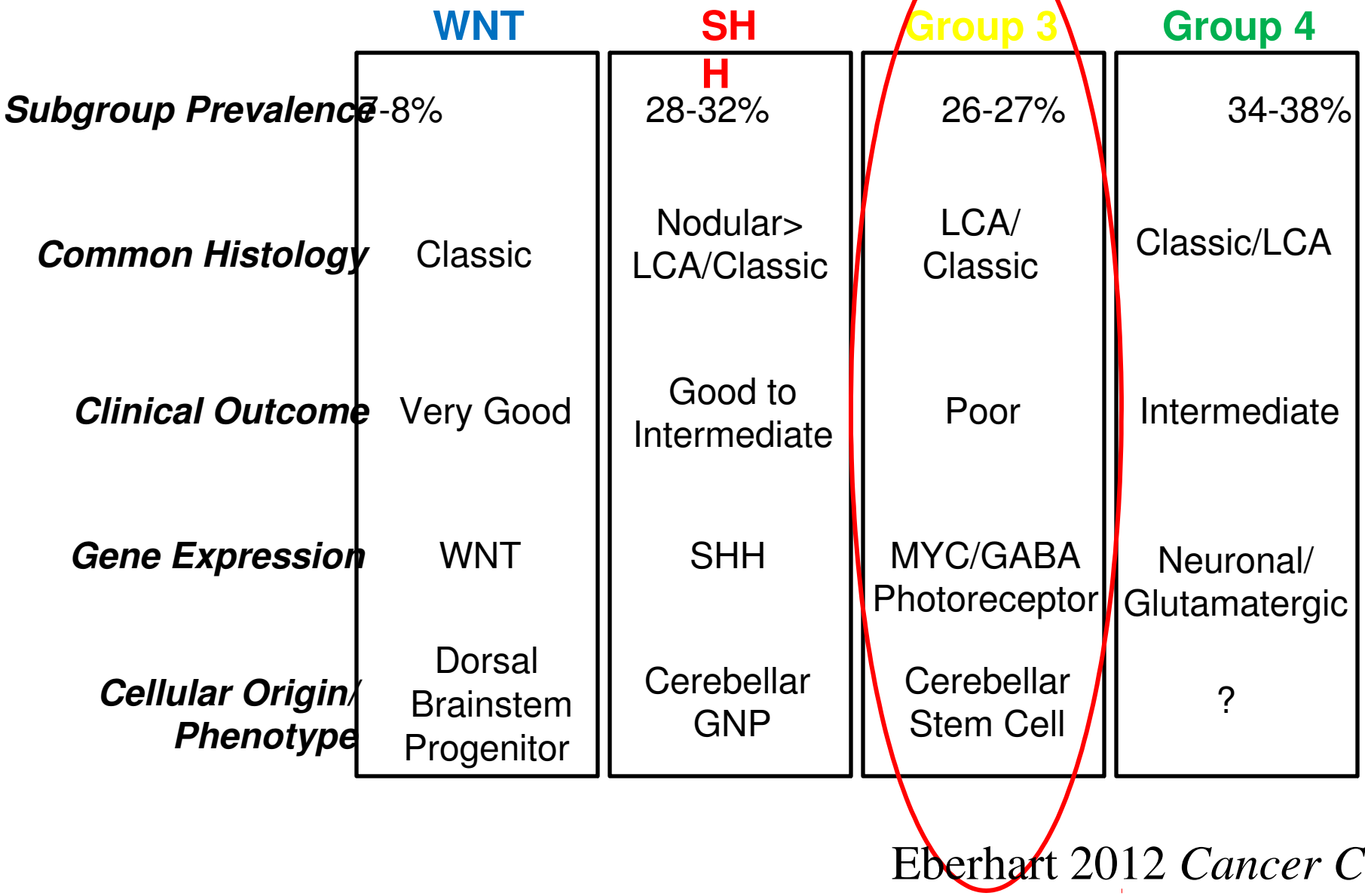
- Sequenced 50 adult and 83 pediatric MB


SMO antagonists
RTK
SHH
SMO
PTCH1
PIP2
PTEN
PIP3
PI3K
PDK1/2
AKT
PI3K inhibitors
TSC1/2
mTOR
mTOR inhibitors
S6K
GLI
SUFU
P
AKT inhibitors
PKA
GSK3β
CKI
GliR
ATO
GLI inhibitors
Cytoplasm
Nucleus
AMP
MYCN
Target Genes
ON
OFF
Amplification
Inactivating mutation
Activating mutation

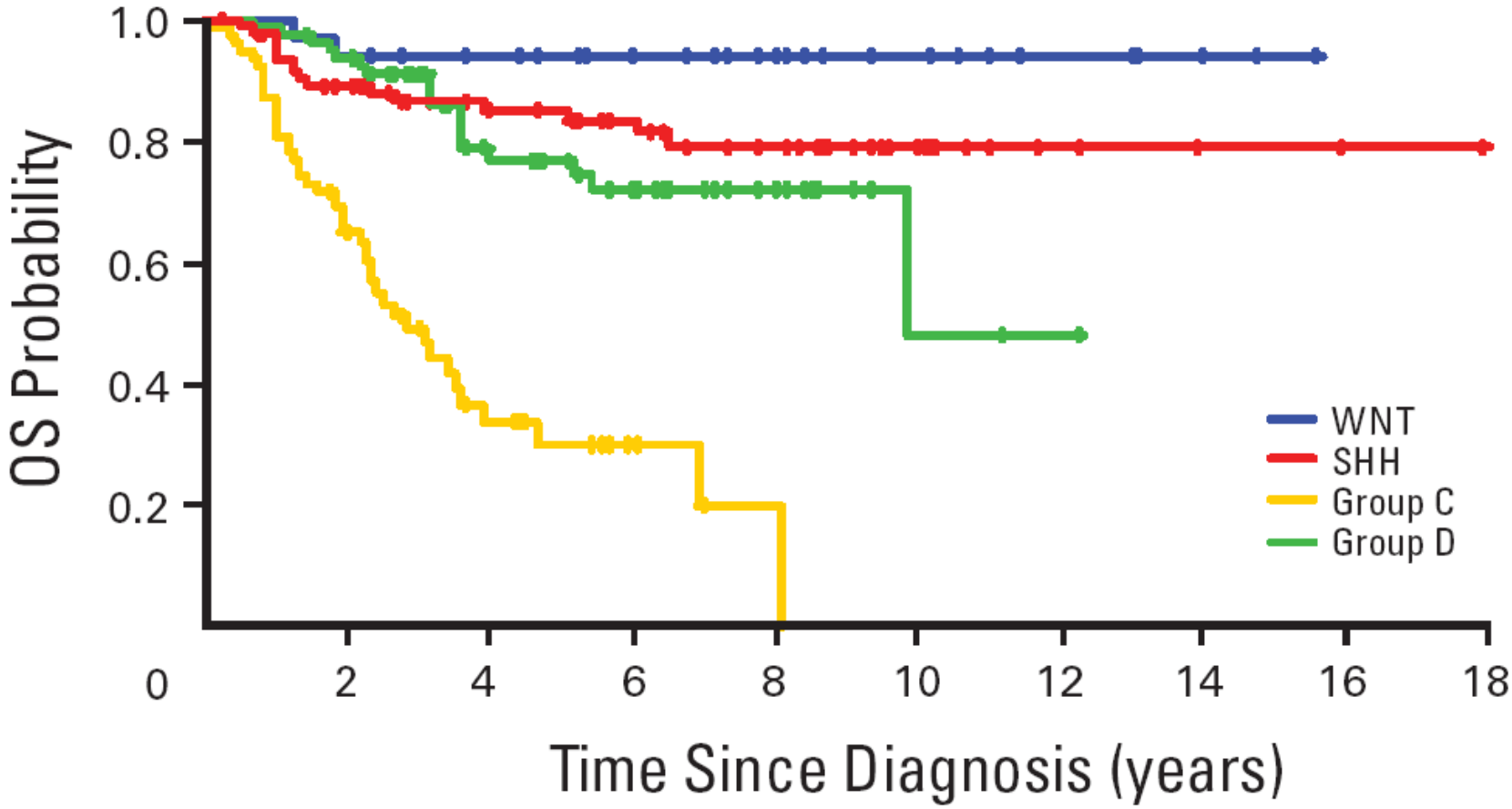


- SHH pathway mutations in 116/133 cases (87%)
- Primary alterations in downstream genes such as SUFU, GLI2, or MYCN results in resistance to SMO inhibitors.
- Data suggest that most adults, but only ~50% of children with SHH MB will respond to SMO inhibitors
- Germline p53 mutations relatively frequent in children (often with LCA tumors), and altered therapeutic approach may be required due to frequent secondary tumors

Medulloblastoma Subtypes



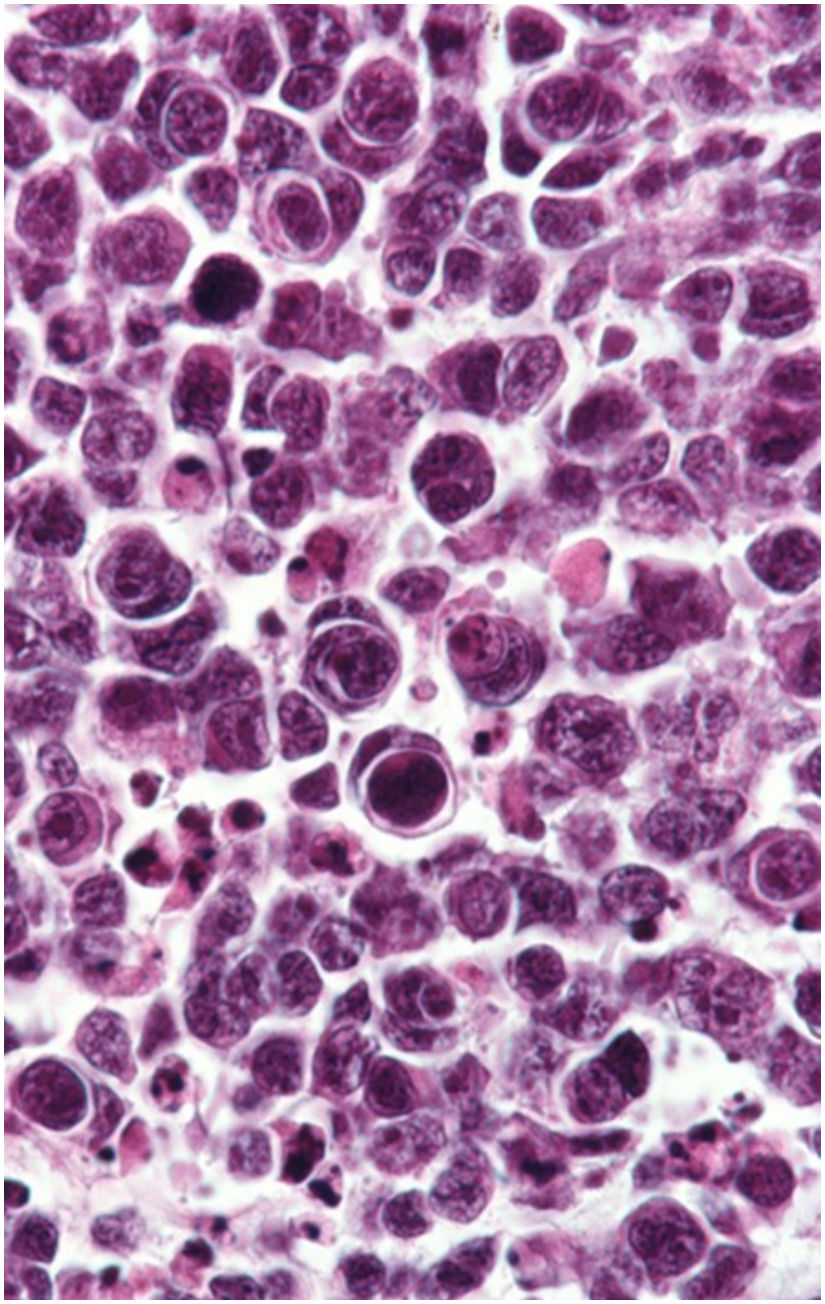
Eberhart 2012 *Cancer Cell*


1.0
0.8
0.6
0.4
0.2
OS Probability
0
2
4
6
8
10
12
14
16
18
Time Since Diagnosis (years)
WNT
SHH
Group C
Group D

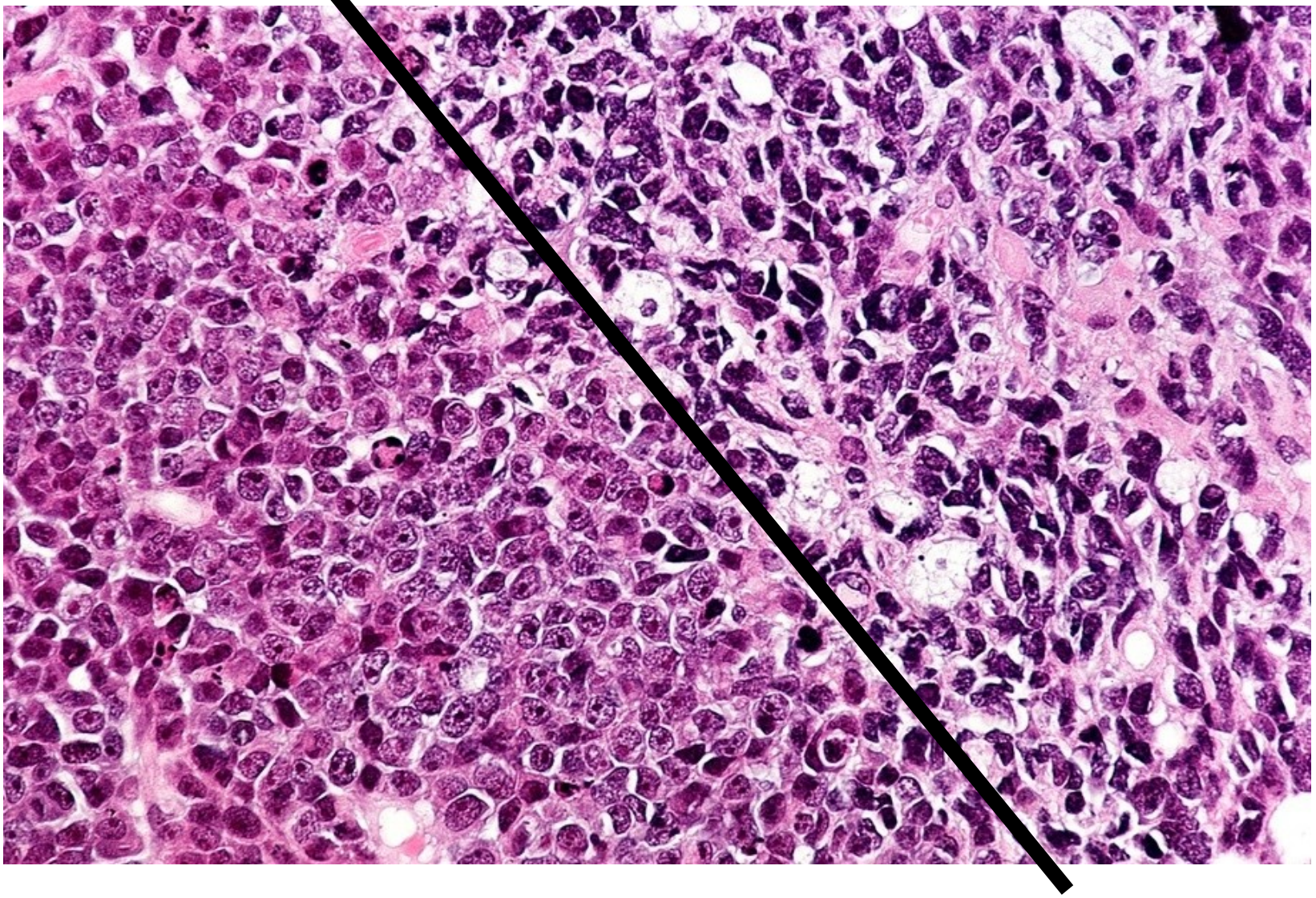
Large Cell MB

- Giangaspero 1992
 (One case *c-myc* amplified)

- Increased Cell Size
- Angularity/Engulfment
- Increased Apoptosis
- Increased Mitosis
- Prominent Nucleioli

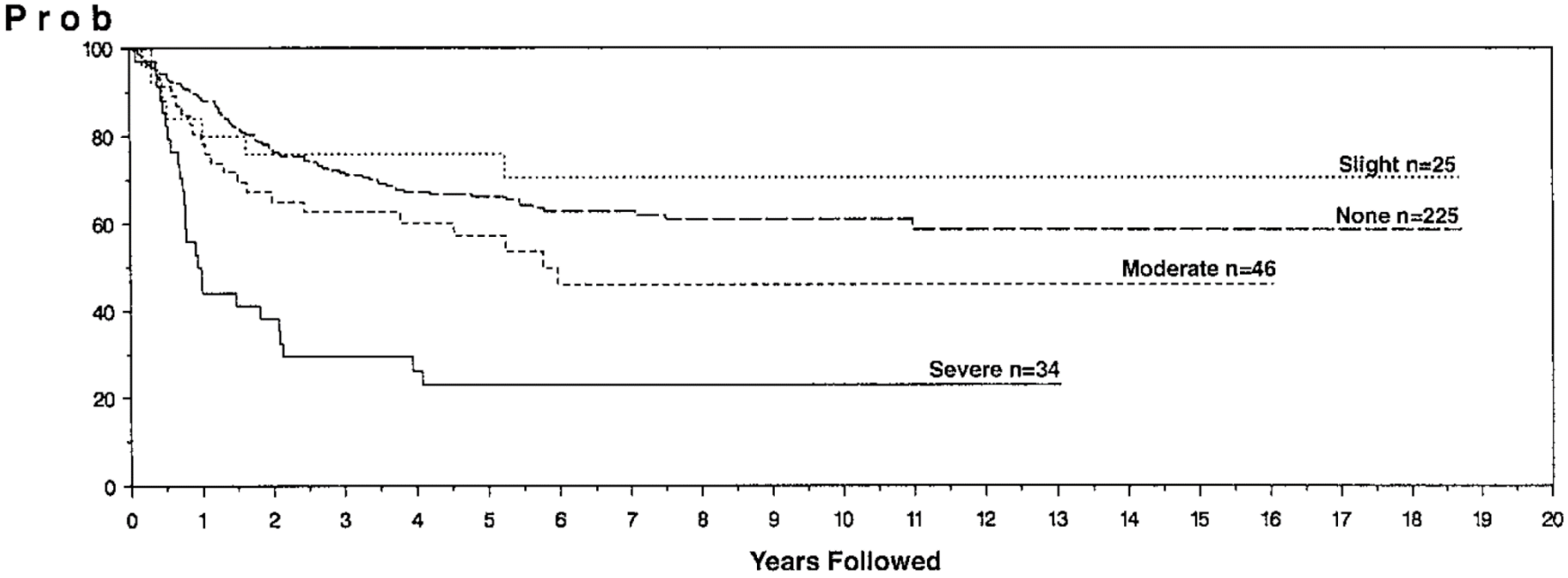


Large Cell and Anaplastic Medulloblastoma



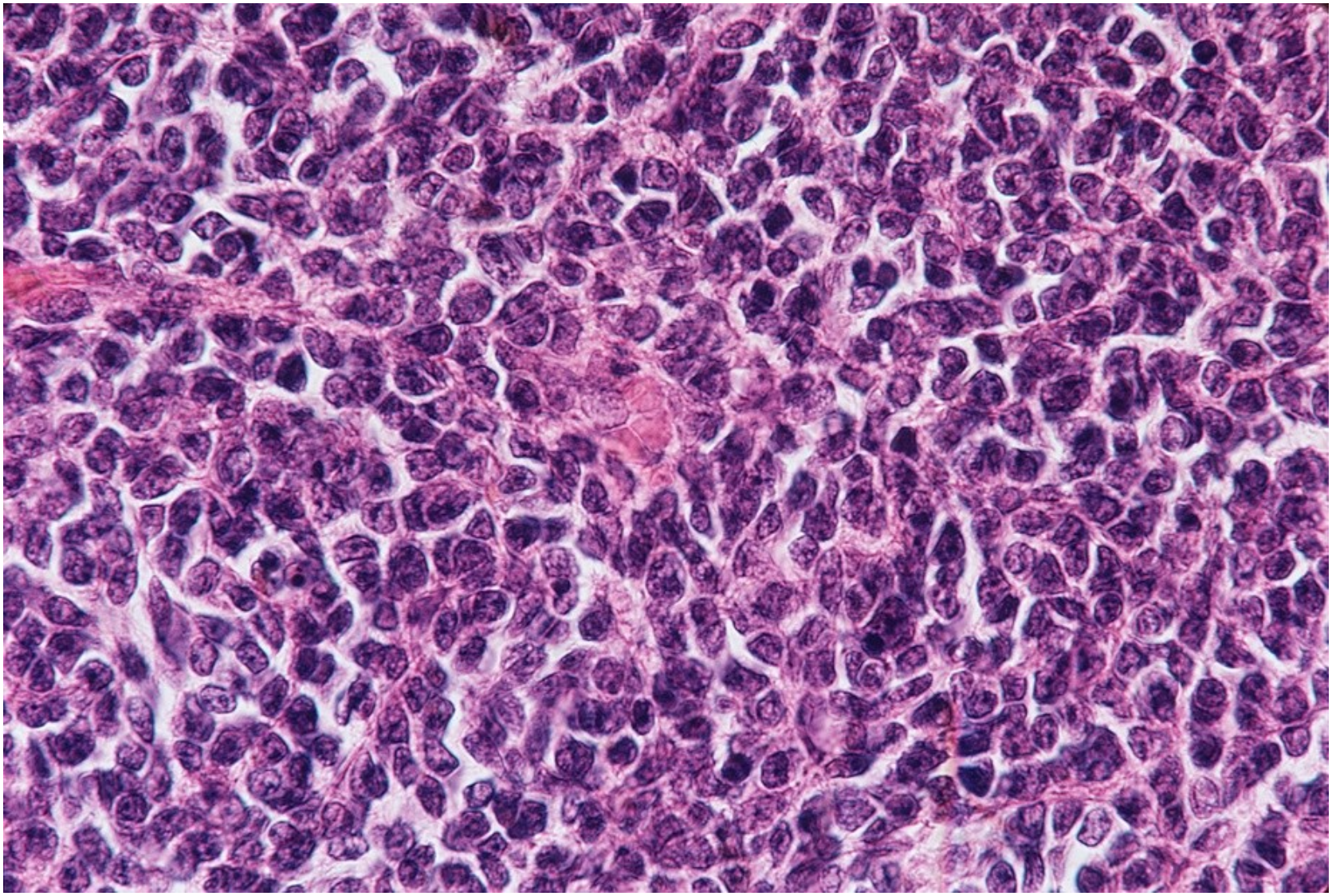
P. Burger

Effect of Degree of Anaplasia on Survival

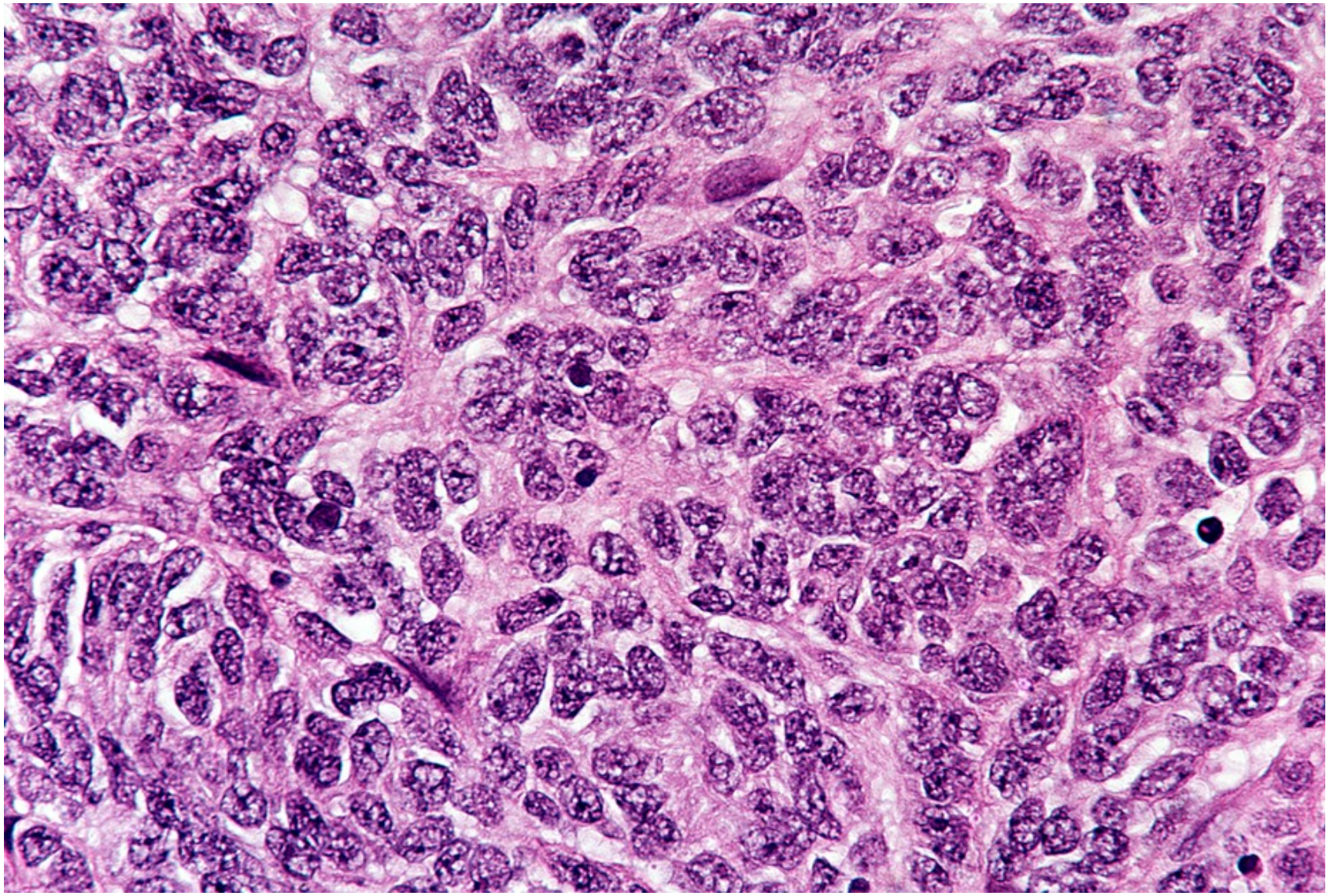


Eberhart et al. Cancer 2002;94;552-560.

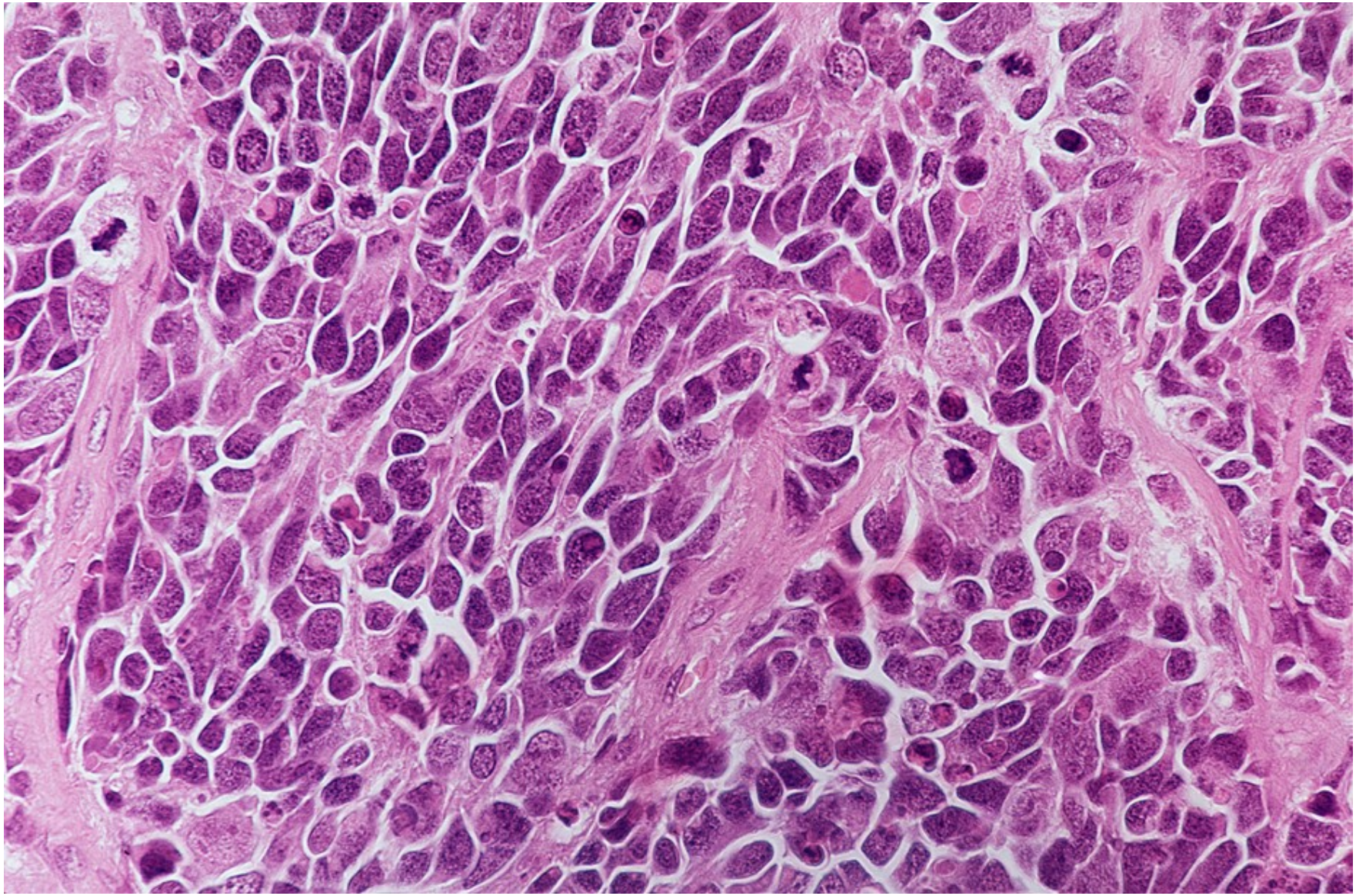
Medulloblastoma With “No Anaplasia”



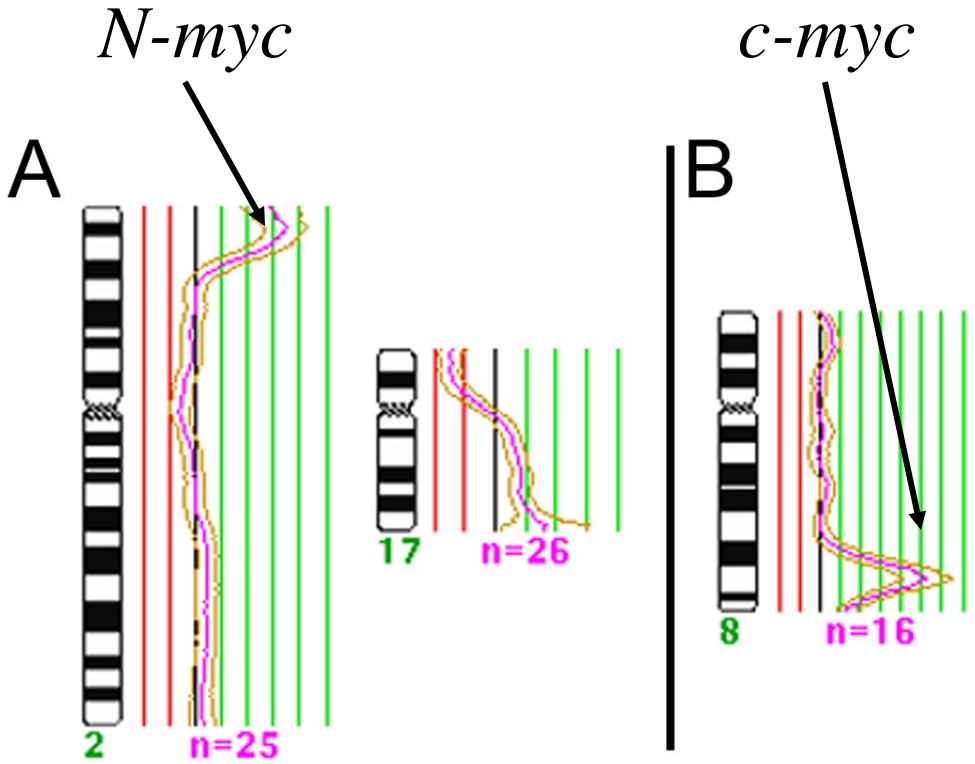
Medulloblastoma With Slight Anaplasia



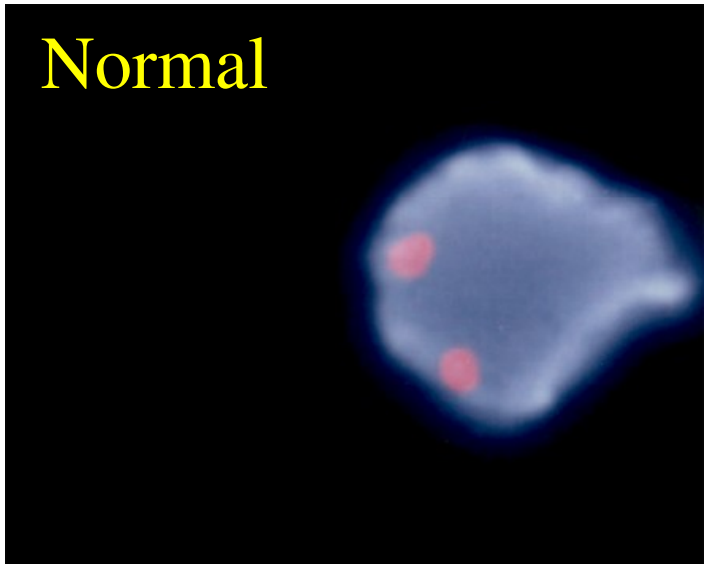
Medulloblastoma With Severe Anaplasia

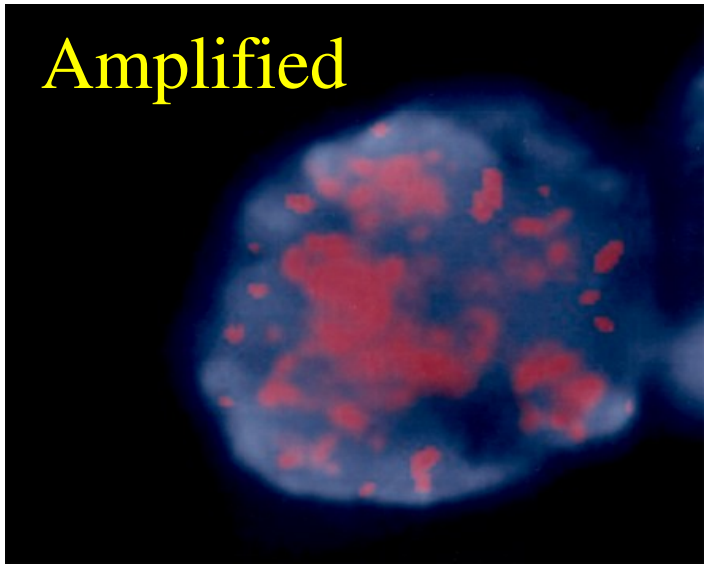


c-myc Gene Amplification Is most common in group 3



CGH



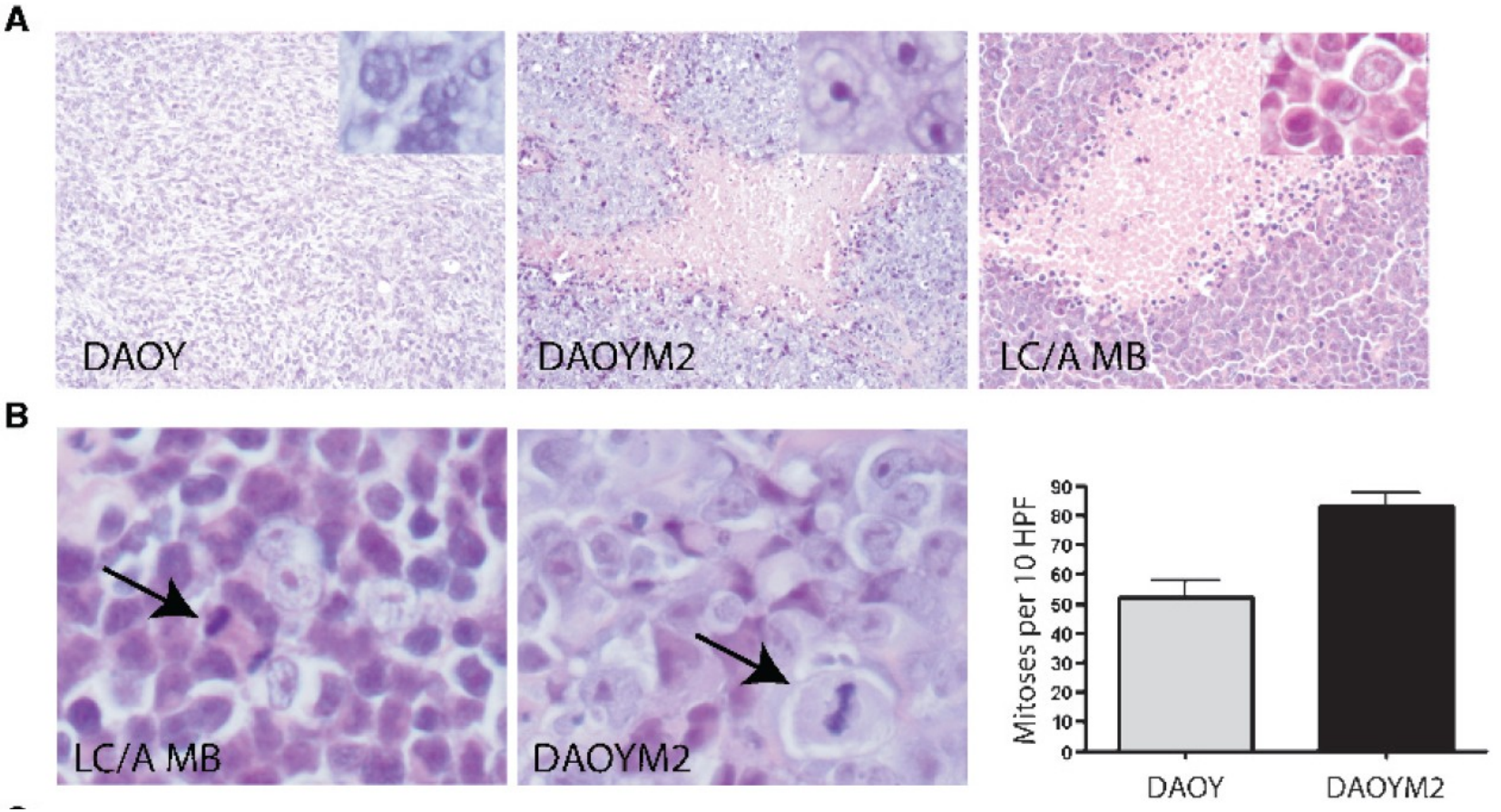


c-myc FISH

c-Myc Overexpression Causes Anaplasia in Medulloblastoma

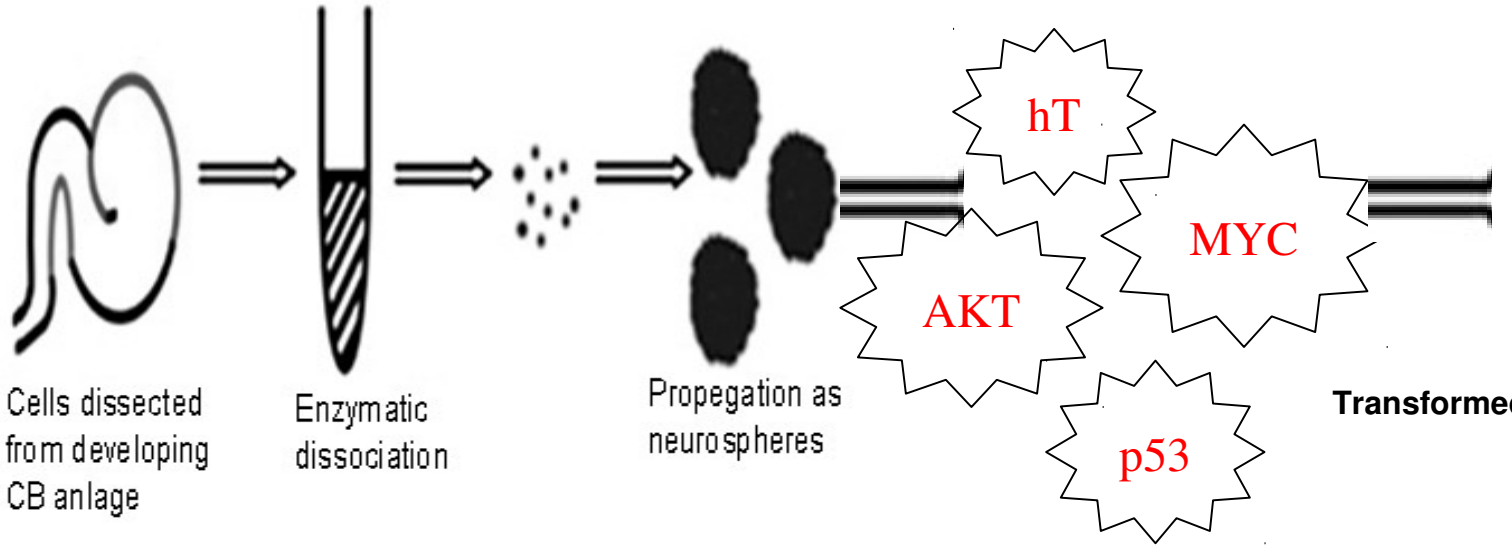
Duncan Stearns,[1,3] Aneeka Chaudhry,[1] Ty W. Abel,[1] Peter C. Burger,[1] Chi V. Dang,[2] and Charles G. Eberhart[1]

Departments of [1]Neuropathology and [2]Hematology, Johns Hopkins University School of Medicine, Baltimore, Maryland and [3]Department of Pediatrics, Drexel University School of Medicine, Philadelphia, Pennsylvania



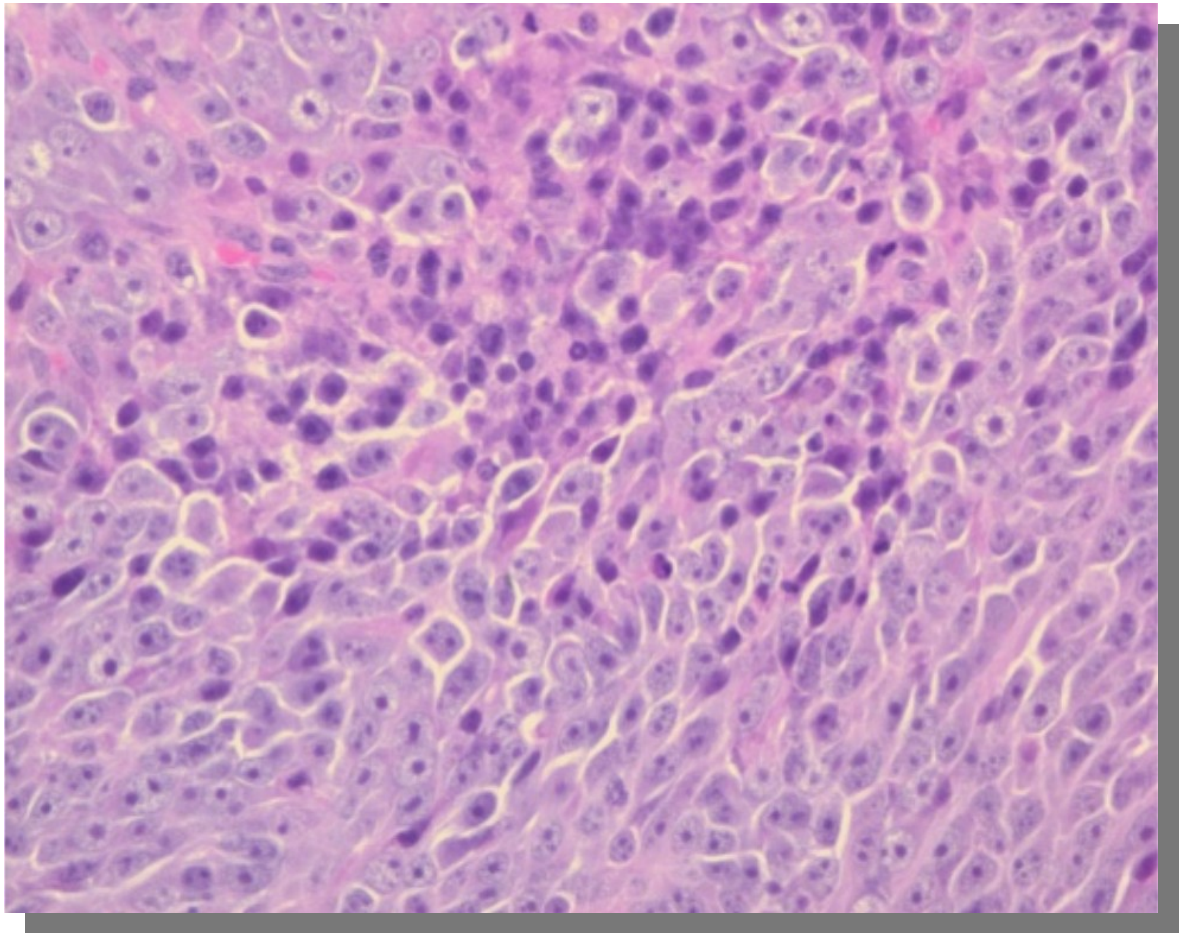
Cancer Res 2006;66:673-681

Developing a model of aggressive medulloblastoma using human neural stem cells



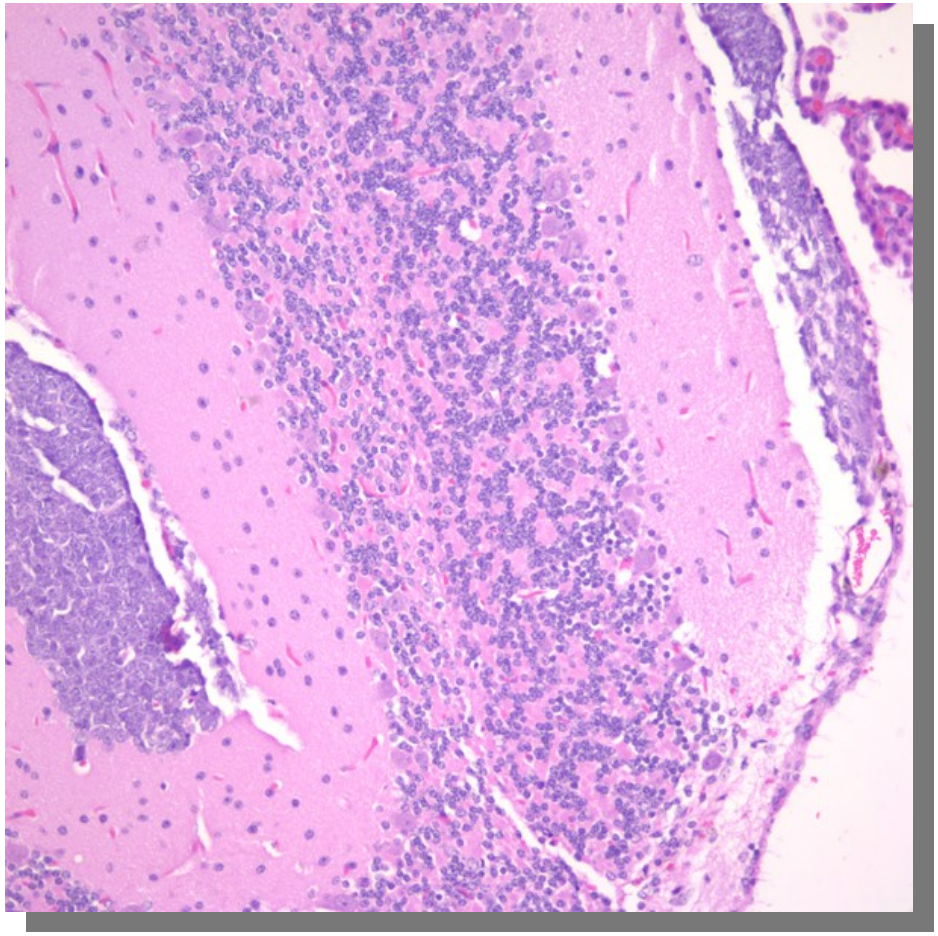
Unpublished Data

Transformed cerebellar human NSC form aggressive embryonal tumors similar to medulloblastoma

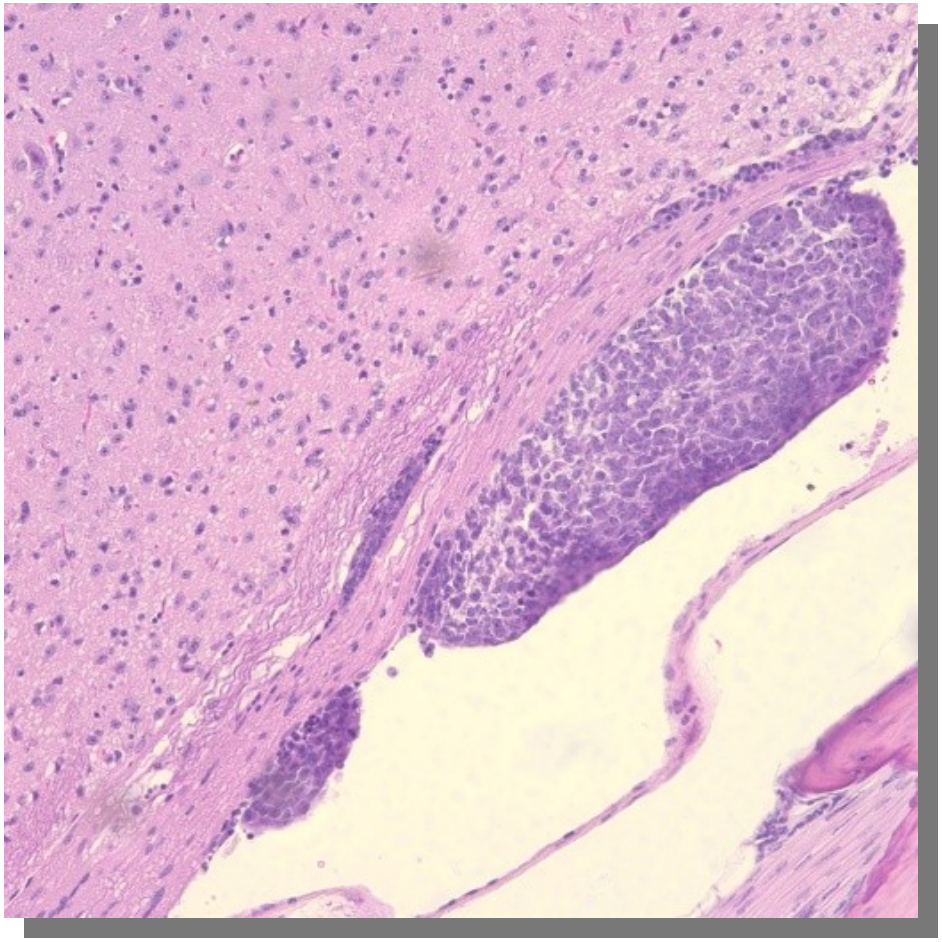


Unpublished Data

Transformed cerebellar human NSC disseminate in a fashion similar to medulloblastoma

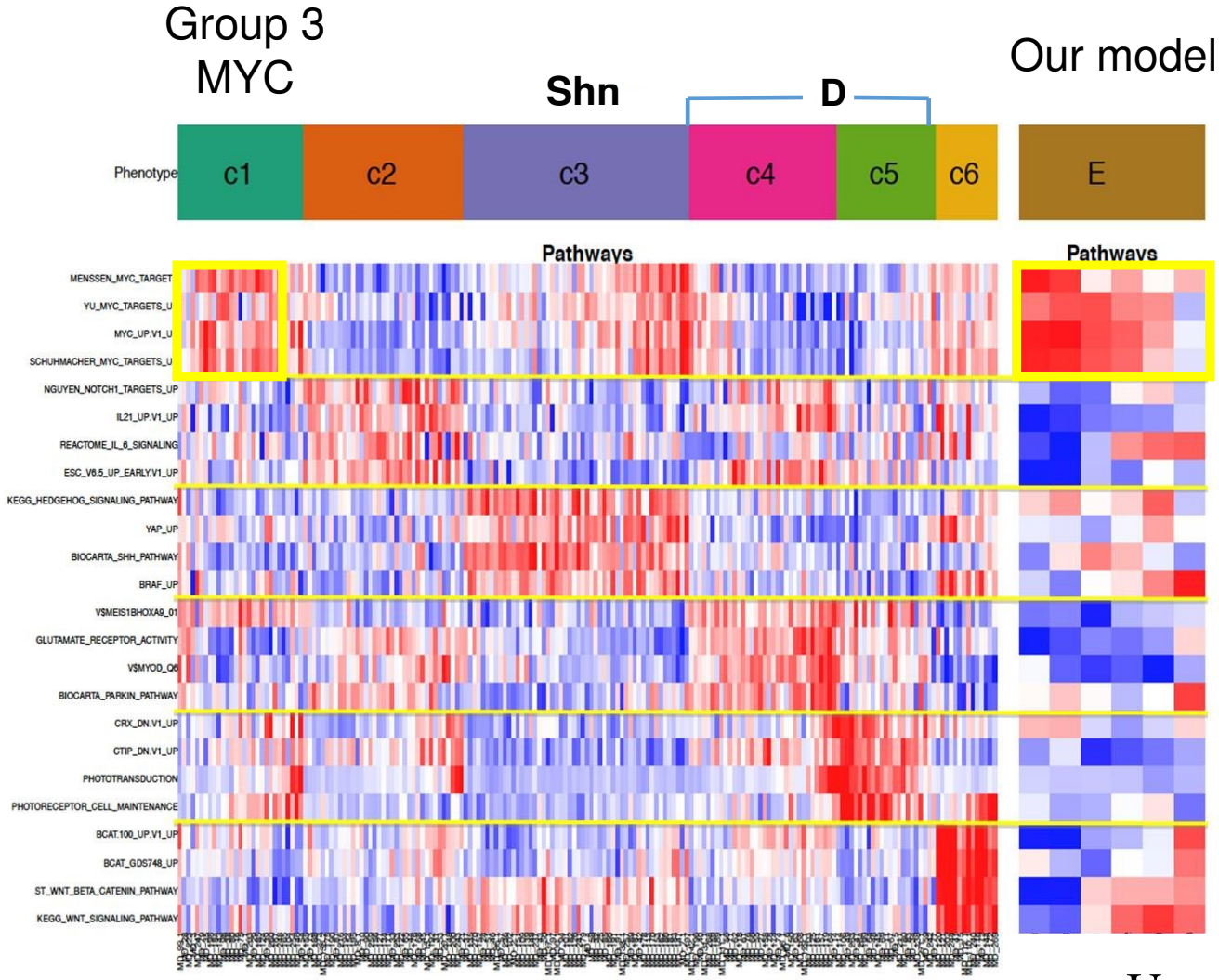


Leptomeningeal



Spinal

Neural stem cell models have expression profiles similar to group 3 high MYC medulloblastoma



Unpublished Data

Can we target high MYC MB through metabolism?

c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism

Ping Gao[1], Irina Tchernyshyov[2], Tsung-Cheng Chang[3], Yun-Sil Lee[3], Kayoko Kita[11], Takafumi Ochi[11], Karen I. Zeller[1], Angelo M. De Marzo[6,7,8], Jennifer E. Van Eyk[2,9], Joshua T. Mendell[3,4,5] & Chi V. Dang[1,3,5,6,7,10]

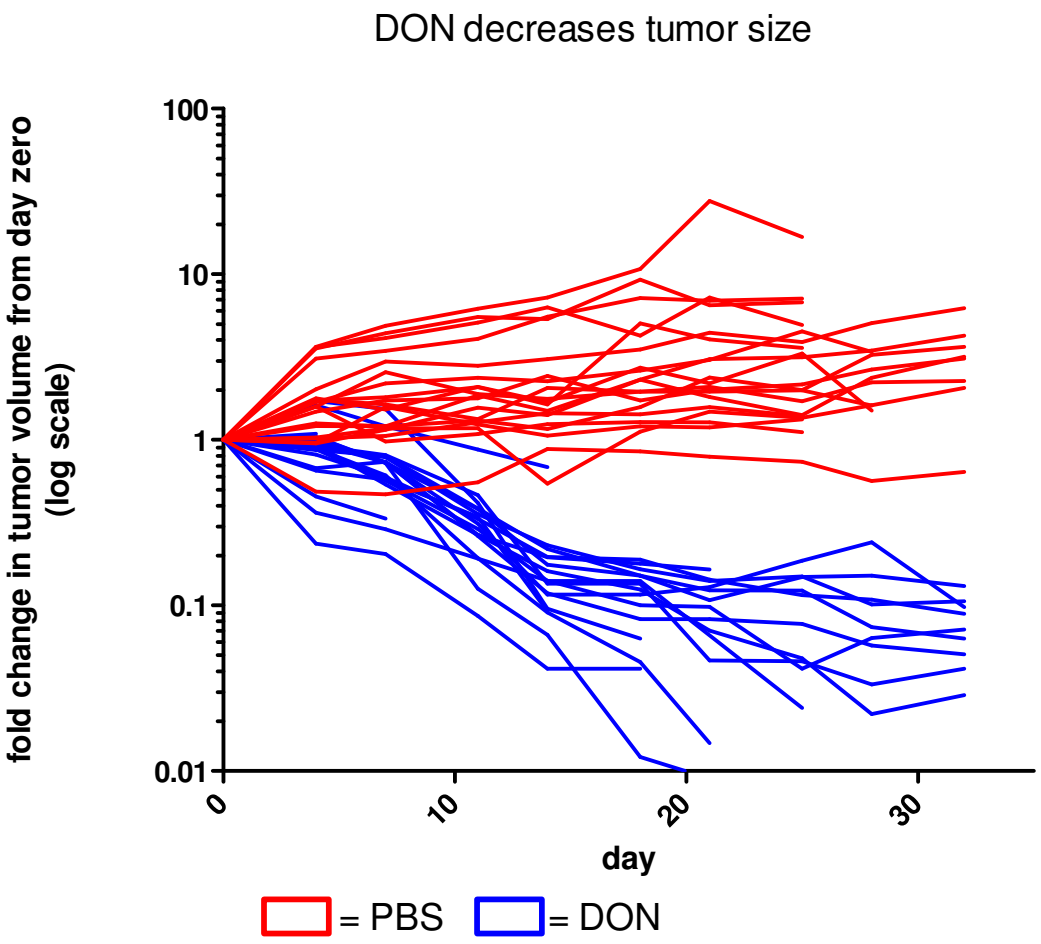
Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction

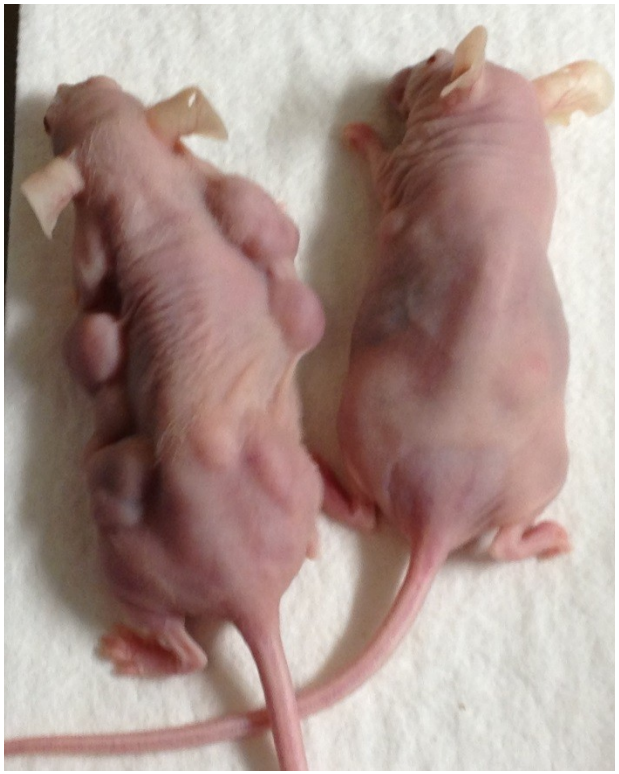
David R. Wise[a], Ralph J. DeBerardinis[b], Anthony Mancuso[a], Nabil Sayed[a], Xiao-Yong Zhang[c], Harla K. Pfeiffer[c], Ilana Nissim[d], Evgueni Daikhin[d], Marc Yudkoff[d], Steven B. McMahon[c], and Craig B. Thompson[a,1]

[a]Department of Cancer Biology, Abramson Cancer Center, University of Pennsylvania, Room 451, Biomedical Research Building II/III, 421 Curie Boulevard, Philadelphia, PA 19104-6160; [b]Department of Pediatrics and McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, TX 75390; [c]Department of Cancer Biology, The Kimmel Cancer Center, Thomas Jefferson Medical College, Philadelphia, PA 19107; and [d]Department of Pediatrics, Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104

Contributed by Craig B. Thompson, October 10, 2008 (sent for review September 12, 2008)

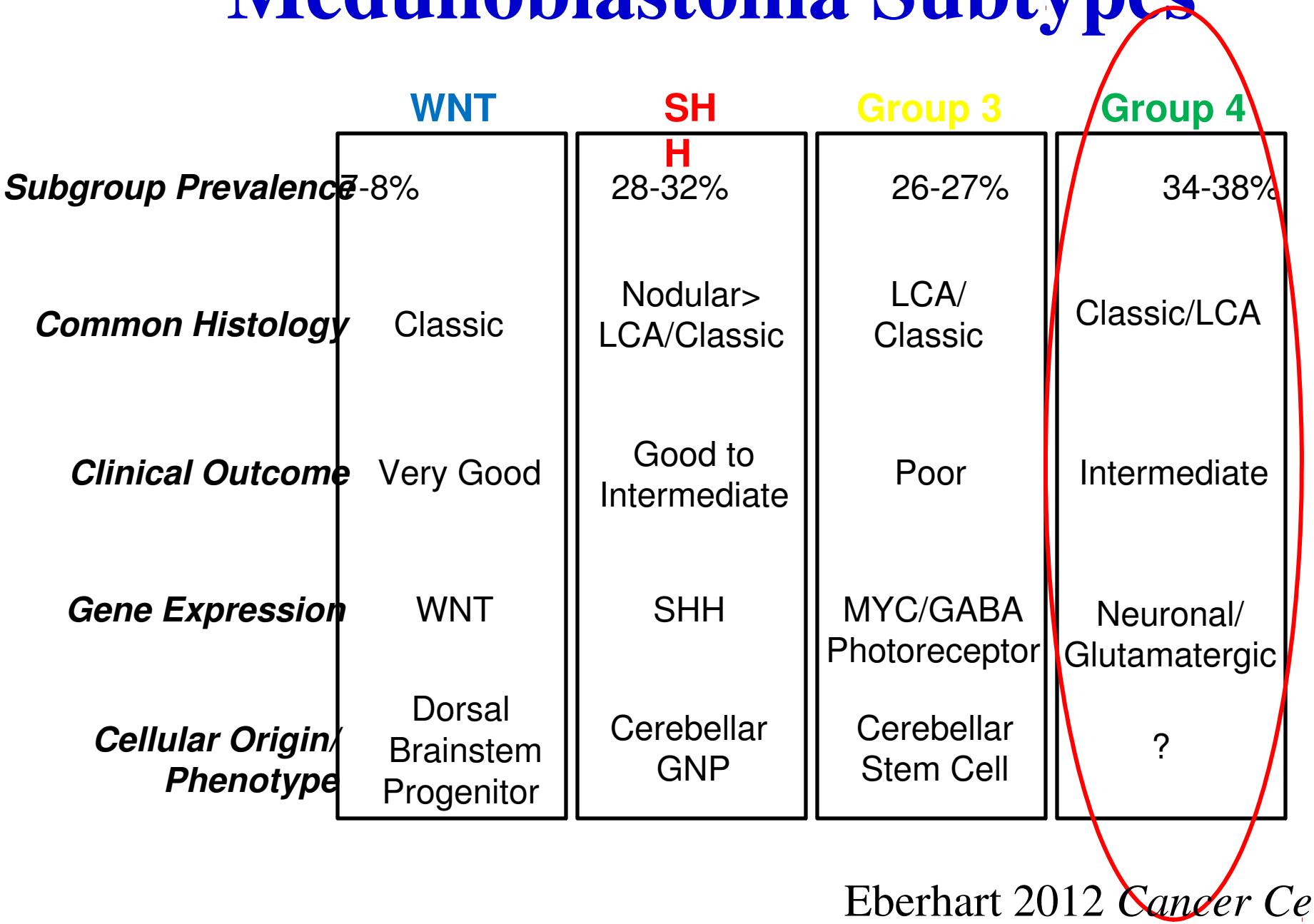
DON decreases size of medulloblastoma xenografts





Unpublished Data

Medulloblastoma Subtypes



Eberhart 2012 *Cancer Cell*

Molecular Subgroups of Medulloblastoma

CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: infant, child, adult

Gender: ♀ ♂

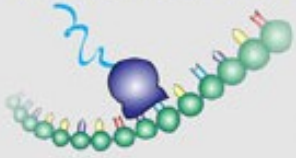
CLINICAL FEATURES

	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS

WNT	SHH	Group 3	Group 4
6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION



WNT	SHH	Group 3	Group 4
WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

Approaches To Molecular Subgroup Classification

- mRNA Expression
- Methylation
- Antibody Based
- FISH

Approaches To Molecular Subgroup Classification

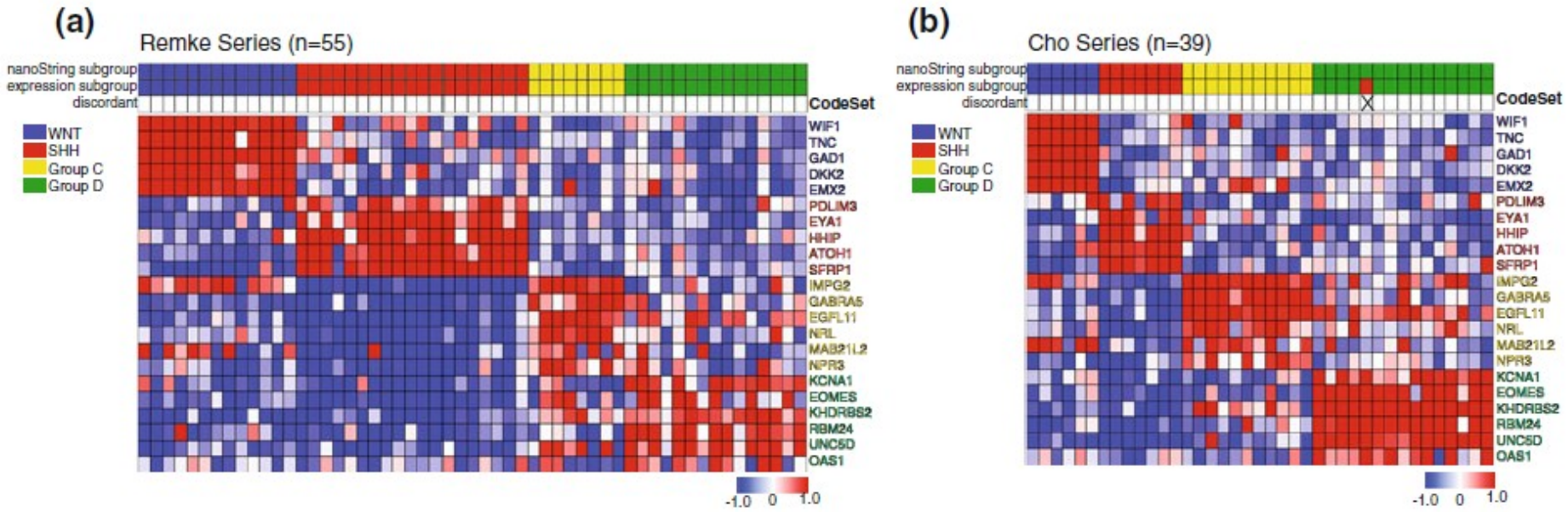
- mRNA Expression
- Methylation
- Antibody Based
- FISH

Acta Neuropathol (2012) 123:615–626
DOI 10.1007/s00401-011-0899-7

METHODS PAPER

Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples

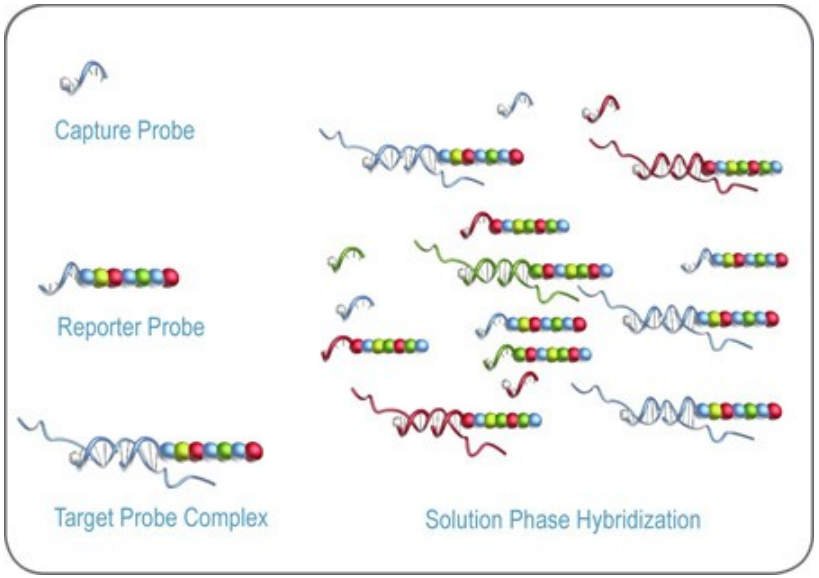
Paul A. Northcott · David J. H. Shih · Marc Remke · Yoon-Jae Cho · Marcel Kool · Cynthia Hawkins · Charles G. Eberhart · Adrian Dubuc · Toumy Guettouche · Yoslayma Cardentey · Eric Bouffet · Scott L. Pomeroy · Marco Marra · David Malkin · James T. Rutka · Andrey Korshunov · Stefan Pfister · Michael D. Taylor



Issues With Nanostring

- Need special machine
- Not designed by company for a CLIA environment
- Reagents come in multiplex packs (ie harder to run single samples)

nanoString TECHNOLOGIES



Other targeted mRNA profiling from paraffin also possible

- A 5 gene predictor set for SHH tumors developed at DFCI by Keith Ligon, Mark Kieran and colleagues
- Analyzed by real time PCR in a CLIA certified lab
- Used to support an ongoing clinial trial targeting SHH MB

Approaches To Molecular Subgroup Classification

- mRNA Expression
- Methylation
- Antibody Based
- FISH

Acta Neuropathol (2013) 125:359-

DNA methylation profiling of medulloblastoma allows robust subclassification and improved outcome prediction using formalin-fixed biopsies

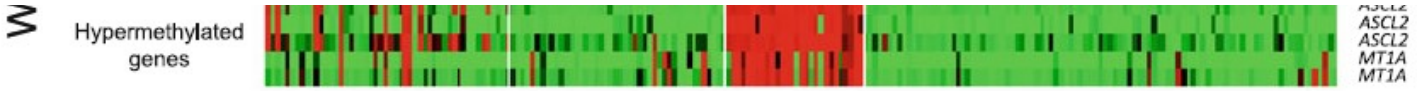
Edward C. Schwalbe · Daniel Williamson · Janet C. Lindsey · Dolores Hamilton · Sarra L. Ryan · Hisham Megahed · Miklós Garami · Peter Hauser · Bożena Dembowska-Baginska · Danuta Perek · Paul A. Northcott · Michael D. Taylor · Roger E. Taylor · David W. Ellison · Simon Bailey · Steven C. Clifford

LETTER

doi:10.1038/nature13268

Decoding the regulatory landscape of medulloblastoma using DNA methylation sequencing

Volker Hovestadt[1]*, David T. W. Jones[2]*, Simone Picelli[1], Wei Wang[1], Marcel Kool[2], Paul A. Northcott[2], Marc Sultan[3], Katharina Stachurski[4], Marina Ryzhova[5], Hans-Jörg Warnatz[3], Meryem Ralser[3], Sonja Brun[6], Jens Bunt[7,8], Natalie Jäger[9], Kortine Kleinheinz[1,9], Serap Erkek[2,10], Ursula D. Weber[1], Cynthia C. Bartholomae[11,12], Christof von Kalle[11,12], Chris Lawerenz[13], Jürgen Eils[13], Jan Koster[8], Rogier Versteeg[8], Till Milde[14,15], Olaf Witt[14,15], Sabine Schmidt[16], Stephan Wolf[16], Torsten Pietsch[17], Stefan Rutkowski[18], Wolfram Scheurlen[19], Michael D. Taylor[20,21,22], Benedikt Brors[9], Jörg Felsberg[23,24], Guido Reifenberger[23,24], Arndt Borkhardt[4], Hans Lehrach[3], Robert J. Wechsler-Reya[6], Roland Eils[9,25,26,27], Marie-Laure Yaspo[3], Pablo Landgraf[4], Andrey Korshunov[28,29], Marc Zapatka[1], Bernhard Radlwimmer[1], Stefan M. Pfister[2,14] & Peter Lichter[1,27]



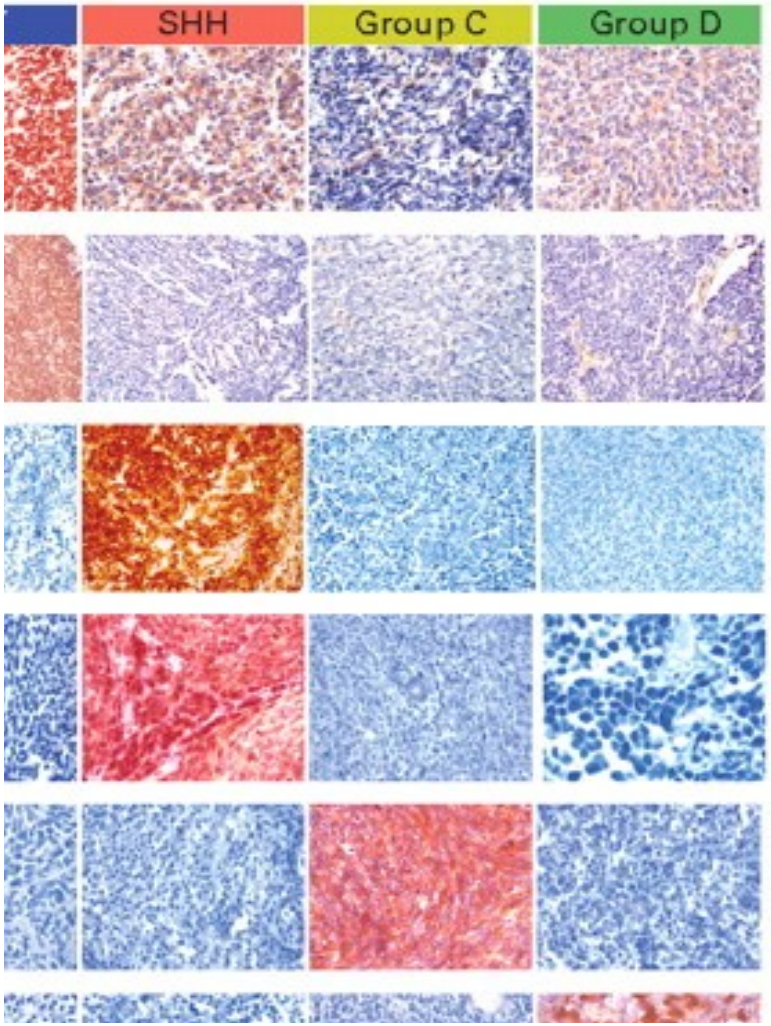
Approaches To Molecular Subgroup Classification

- mRNA Expression
- Methylation
- Antibody Based
- FISH

Medulloblastoma Comprises Four Distinct Molecular Variants

Paul A. Northcott, Andrey Korshunov, Hendrik Witt, Thomas Hielscher, Charles G. Eberhart, Stephen Mack, Eric Bouffet, Steven C. Clifford, Cynthia E. Hawkins, Pim French, James T. Rutka, Stefan Pfister, and Michael D. Taylor

JCO 2011



β-catenin (1:100)
DKK1 (1:100)
GLI1 (1:5,000)
SFRP1 (1:2,000)
NPR3 (1:200)
KCNA1 (1:2,000)

Acta Neuropathol (2011) 121:381–396
DOI 10.1007/s00401-011-0800-8

ORIGINAL PAPER

Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups

David W. Ellison · James Dalton · Mehmet Kocak · Sarah Leigh Nicholson · Charles Fraga · Geoff Neale · Anna M. Kenney · Dan J. Brat · Arie Perry · William H. Yong · Roger E. Taylor · Simon Bailey · Steven C. Clifford · Richard J. Gilbertson

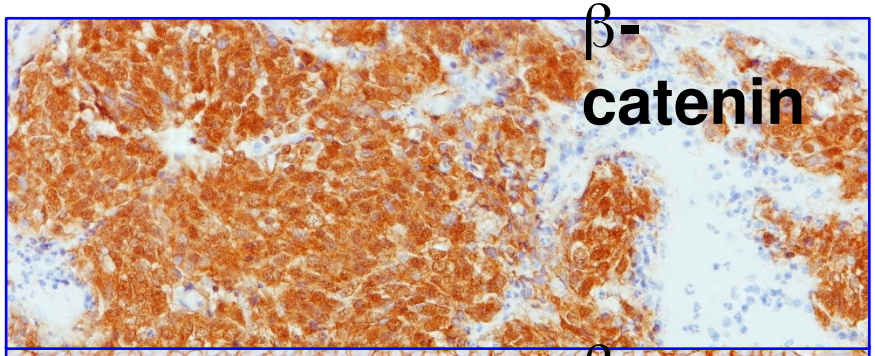
Table 2 Immunophenotypes of SHH, WNT, and non-SHH/WNT molecular subgroups

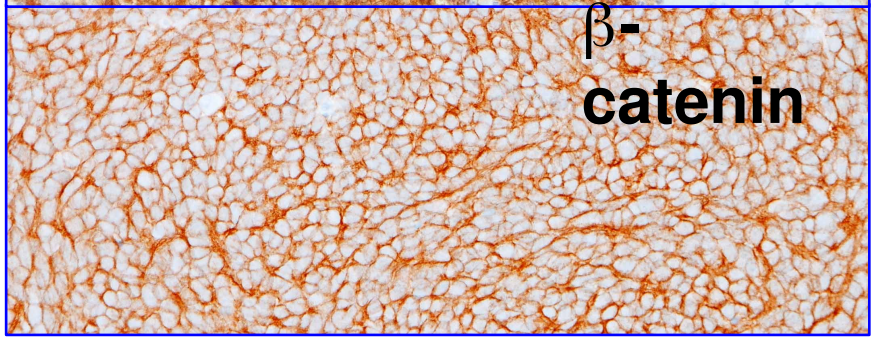
Molecular group	Immunoreactivity			
	GAB1	β-catenin	Filamin A	YAP1
SHH	Cytoplasmic	Cytoplasmic	Cytoplasmic	Nuclear + cytoplasmic
WNT	Negative	Nuclear + cytoplasmic	Cytoplasmic	Nuclear + cytoplasmic
Non-SHH/WNT	Negative	Cytoplasmic	Negative	Negative

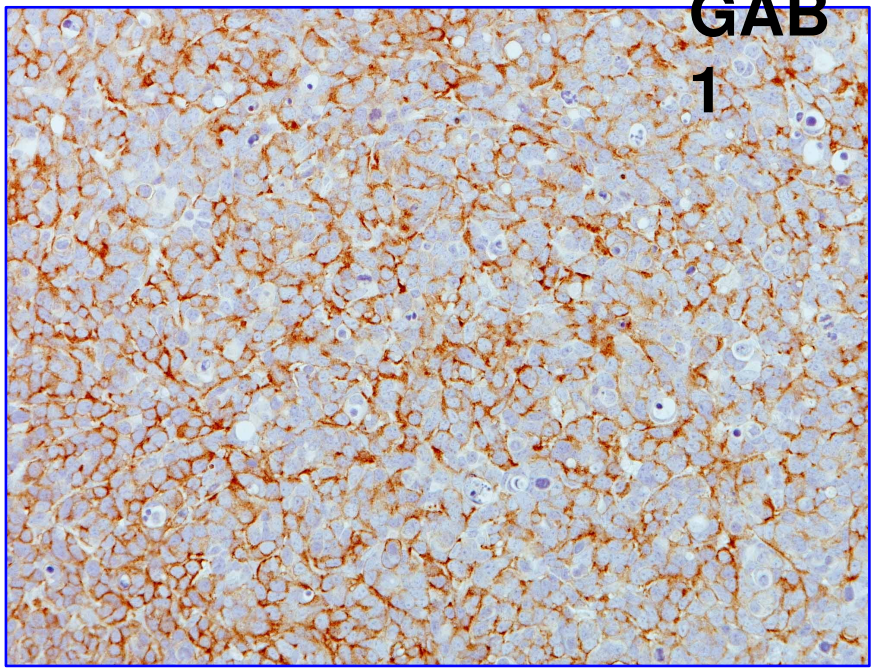
Medulloblastoma @ St. Jude (Courtesy of David Ellison)

MB molecular subgroups - IHC markers			
Antibodies to:	**SHH**	**WNT**	**non-SHH /WNT**
β-catenin	cytoplasmic	cytoplasmic / nuclear	cytoplasmic
YAP1	cytoplasmic / nuclear	cytoplasmic / nuclear	negative
GAB1	moderate / strong	negative	negative

- IHC method validated against gene expression profiling in tumors from SJMB96 / SJMB03 trial cohorts
- Molecular subgrouping service provided for St. Jude affiliates and multiple other centers


β-
catenin


β-
catenin


GAB
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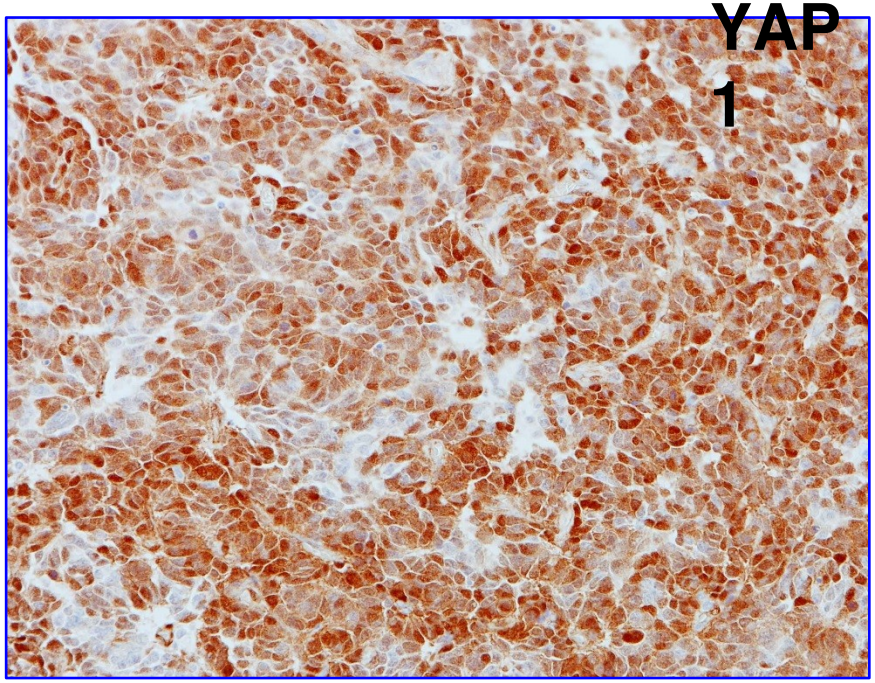
YAP
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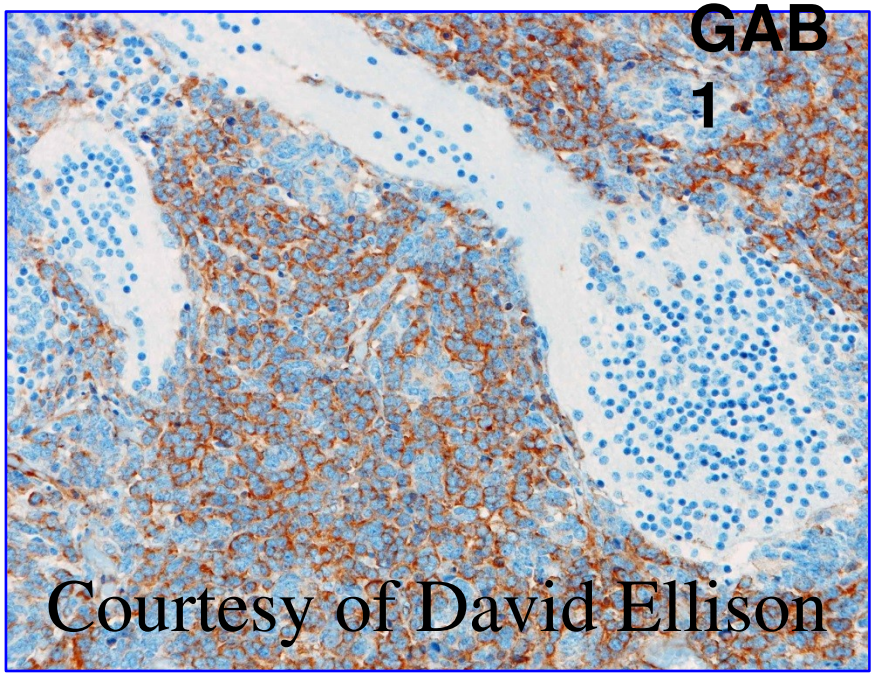

GAB
1
Courtesy of David Ellison

Approaches To Molecular Subgroup Classification

- mRNA Expression
- Methylation
- Antibody Based
- FISH

VOLUME 32 · NUMBER 9 · MARCH 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cytogenetic Prognostication Within Medulloblastoma Subgroups

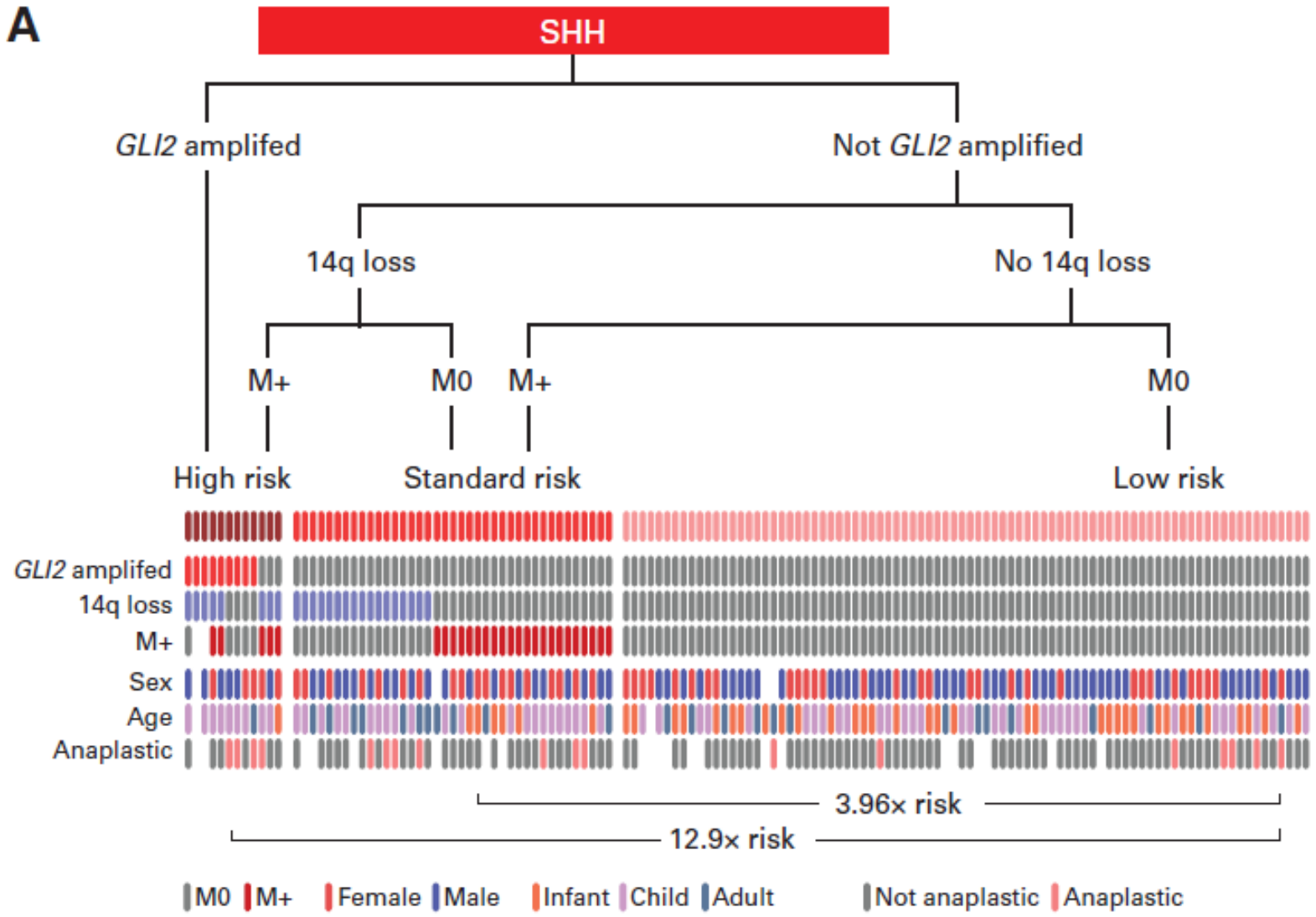
David J.H. Shih, Paul A. Northcott, Marc Remke, Andrey Korshunov, Vijay Ramaswamy, Marcel Kool, Betty Luu, Yuan Yao, Xin Wang, Adrian M. Dubuc, Livia Garzia, John Peacock, Stephen C. Mack, etc.

Results

Subgroup information improves the predictive accuracy of a multivariable survival model compared with clinical biomarkers alone. Most previously published cytogenetic biomarkers are only prognostic within a single medulloblastoma subgroup. Profiling six FISH biomarkers (*GLI2*, *MYC*, chromosome 11 [chr11], chr14, 17p, and 17q) on formalin-fixed paraffin-embedded tissues, we can reliably and reproducibly identify very low-risk and very high-risk patients within SHH, Group 3, and Group 4 medulloblastomas.

FISH for: GLI2, MYC, chr11, chr14, 17p and 17q

These combined classification schemes can be complex



Proposed COG Protocol – Medulloblastoma Classification 2014

- WNT: monosomy chromosome 6 (FISH) and nuclear translocation of Beta-catenin (IHC)
- *MYCC* and *MYCN* (FISH)
- SHH: GAB1 (IHC)

WHO'S NEXT

A Colloquium to Guide Next Steps in Brain Tumor Classification and Grading

Major question:

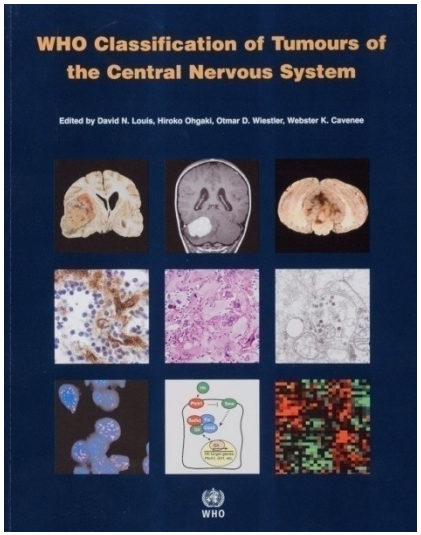
How can non-histological criteria (e.g., molecular, imaging, clinical, other?) be used to enhance typing and grading of human brain tumors?

Integrated Diagnosis	Histological subtype and molecular subgroup (e.g., Wnt, SHH, non-WNT/non-SHH*), WHO grade IV
Histopathological Diagnosis	Classic, anaplastic/large cell, desmoplastic/nodular, medulloblastoma with extensive nodularity
Histopathological Grade	WHO grade IV
Molecular Information	** MYC ampl, NMYC ampl, p53+/-, i17q, beta catenin, SMO, PTCH, monosomy 6

Conclusions

- Four main molecular MB subgroups have been identified, but these often contain additional important variation
- Implementing molecular testing for these will be complex
- In the next WHO, information on MB subgroups will be part of a new top-line integrated diagnosis

WHO CNS Tumour Classification - 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

Molecular Classification Of CNS PNET

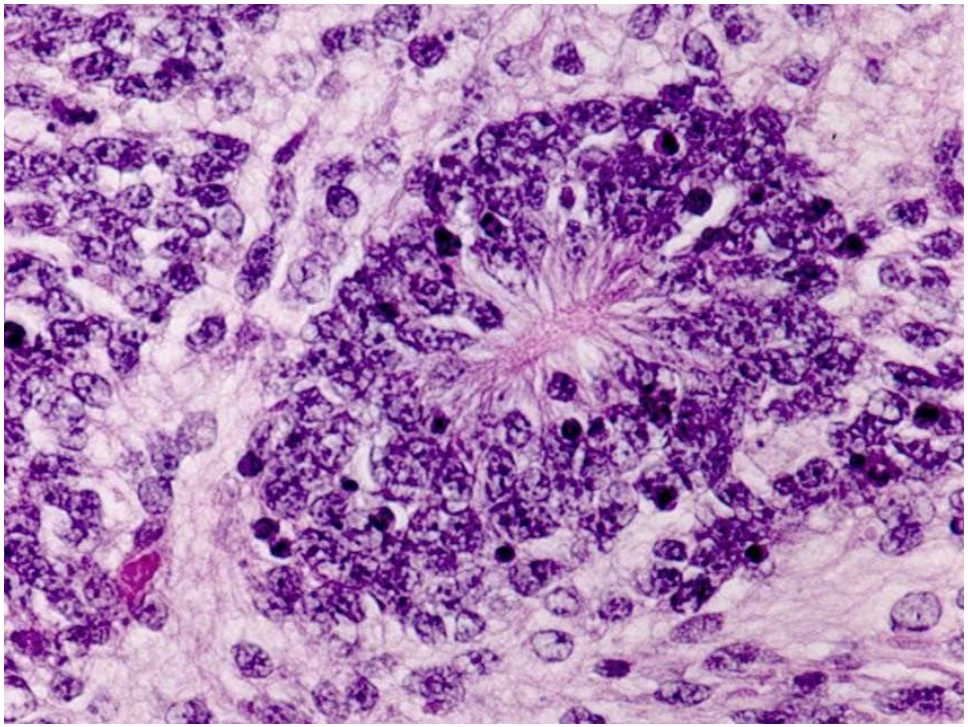
	Group 1	Group 2	Group 3
Demographics	Age < 4 years F>M	Age > 4 years M>F	All Children M>F
Histology/IHC	ETANTR/ LIN28+, OLIG2–	LIN28–, OLIG2+	LIN28–, OLIG2–
Clinical Outcome	Very Poor	Poor	Poor, Metastases Common
Chromosomal Changes	19q13 Amp +2, +3	CDKN2 loss +8p, +13, +20	CDKN2 loss –14
Gene Expression	C19MC, Lin28, WNT, Stem Cell	OLIG1/2 SOX8/10	TGFβ, PTEN Mesenchymal

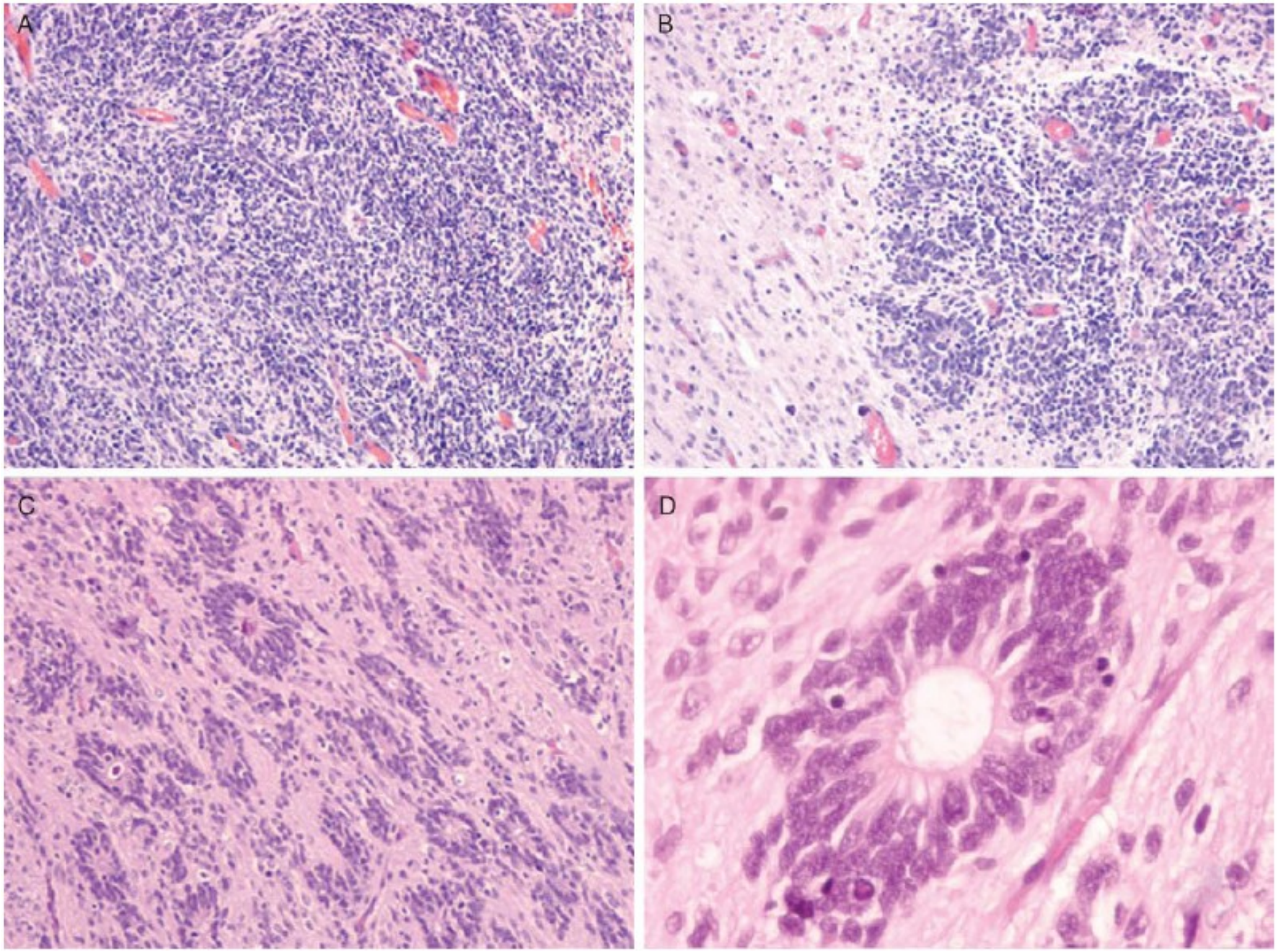
Pediatric Neuroblastic Brain Tumors Containing Abundant Neuropil and True Rosettes

CHARLES G. EBERHART,[1]* DANIEL J. BRAT,[2] KENNETH J. COHEN,[3] AND PETER C. BURGER[1]

2000

- < 10 Years Old
- Mostly supratentorial
- Synaptophysin +
- Poor clinical outcomes




A
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D

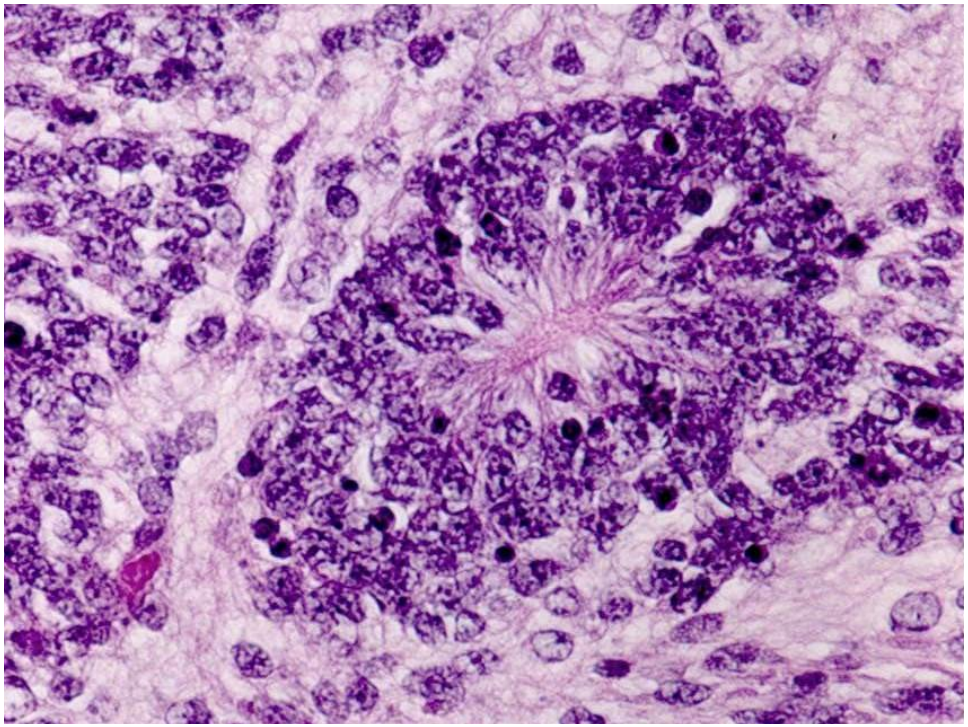
Pediatric Neuroblastic Brain Tumors Containing Abundant Neuropil and True Rosettes

CHARLES G. EBERHART,[1]* DANIEL J. BRAT,[2] KENNETH J. COHEN,[3] AND PETER C. BURGER[1]

2000

Embrynal Tumor With Abundant Neuropil And Trus Rosettes (ETANTR)

Embryonal Tumor With Multilayered Rosettes (ETMR)



Molecular Classification Of PNET

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Demographics	Age < 4 years F>M	Age > 4 years M>F	All Children M>F
Histology/IHC	ETANTR/ LIN28+, OLIG2–	LIN28–, OLIG2+	LIN28–, OLIG2–
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ETANTR
Ependymoblastoma
Medulloepithelioma (Huang 2014)

Acta Neuropathol
DOI 10.1007/s00401-013-1228-0

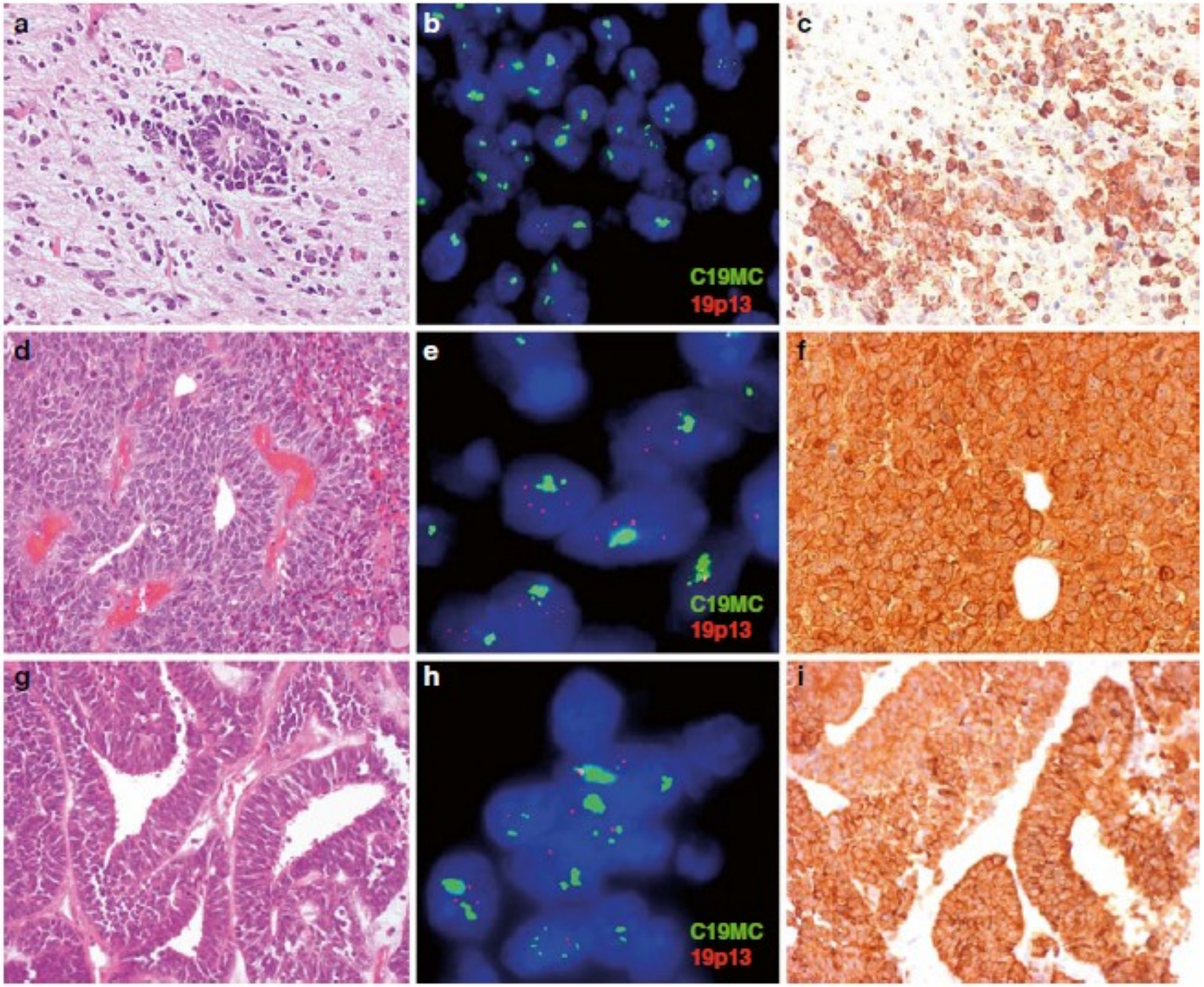
Dec 2013

ORIGINAL PAPER

Embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma share molecular similarity and comprise a single clinicopathological entity

Andrey Korshunov · Dominik Sturm · Marina Ryzhova · Volker Hovestadt · Marco Gessi · David T. W. Jones · Marc Remke · Paul Northcott · Arie Perry · Daniel Picard · Marc Rosenblum · Manila Antonelli · Eleonora Aronica · Ulrich Schüller · Martin Hasselblatt · Adelheid Woehrer · Olga Zheludkova · Ella Kumirova · Stephanie Puget · Michael D. Taylor · Felice Giangaspero · V. Peter Collins · Andreas von Deimling · Peter Lichter · Annie Huang · Torsten Pietsch · Stefan M. Pfister · Marcel Kool

Propose Embryonal Tumor With Multilayered Rosettes (ETMR) as name for new group


a
b
C19MC
19p13
c
d
e
C19MC
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C19MC
19p13
i

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Stephan Pfister
Annie Huang

Helpful Discussions
David Ellison
Mark Kieran
Keith Ligon
Chris Pierson
Torsten Pietsch
Cynthia Hawkins

Cancer Cell
Article

2009

Frequent Amplification of a chr19q13.41 MicroRNA Polycistron in Aggressive Primitive Neuroectodermal Brain Tumors

Meihua Li,[1] Kyle F. Lee,[1] Yuntao Lu,[1,11] Ian Clarke,[2] David Shih,[1] Charles Eberhart,[6] V. Peter Collins,[7] Tim Van Meter,[8] Daniel Picard,[1] Limei Zhou,[1] Paul C. Boutros,[5,8] Piergiorgio Modena,[9] Muh-Lii Liang,[10]

Acta Neuropathol (2009) 117:457–464
DOI 10.1007/s00401-008-0467-y

CASE REPORT

Novel genomic amplification targeting the microRNA cluster at 19q13.42 in a pediatric embryonal tumor with abundant neuropil and true rosettes

Stefan Pfister · Marc Remke · Mirco Castoldi · Alfa H. C. Bai · Martina U. Muckenthaler · Andreas Kulozik · Andreas von Deimling · Armin Pscherer · Peter Lichter · Andrey Korshunov

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