DIPARTIMENTO DI SCIENZE
RADIOLOGICHE ONCOLOGICHE
E ANATOMO PATOLOGICHE

SAPIENZA
UNIVERSITÀ DI ROMA

NEUROMED
I.R.C.C.S.
ISTITUTO NEUROLOGICO MEDITERRANEO

Gliomi a basso grado dell'età pediatrica

Felice Giangaspero

DICHIARAZIONE

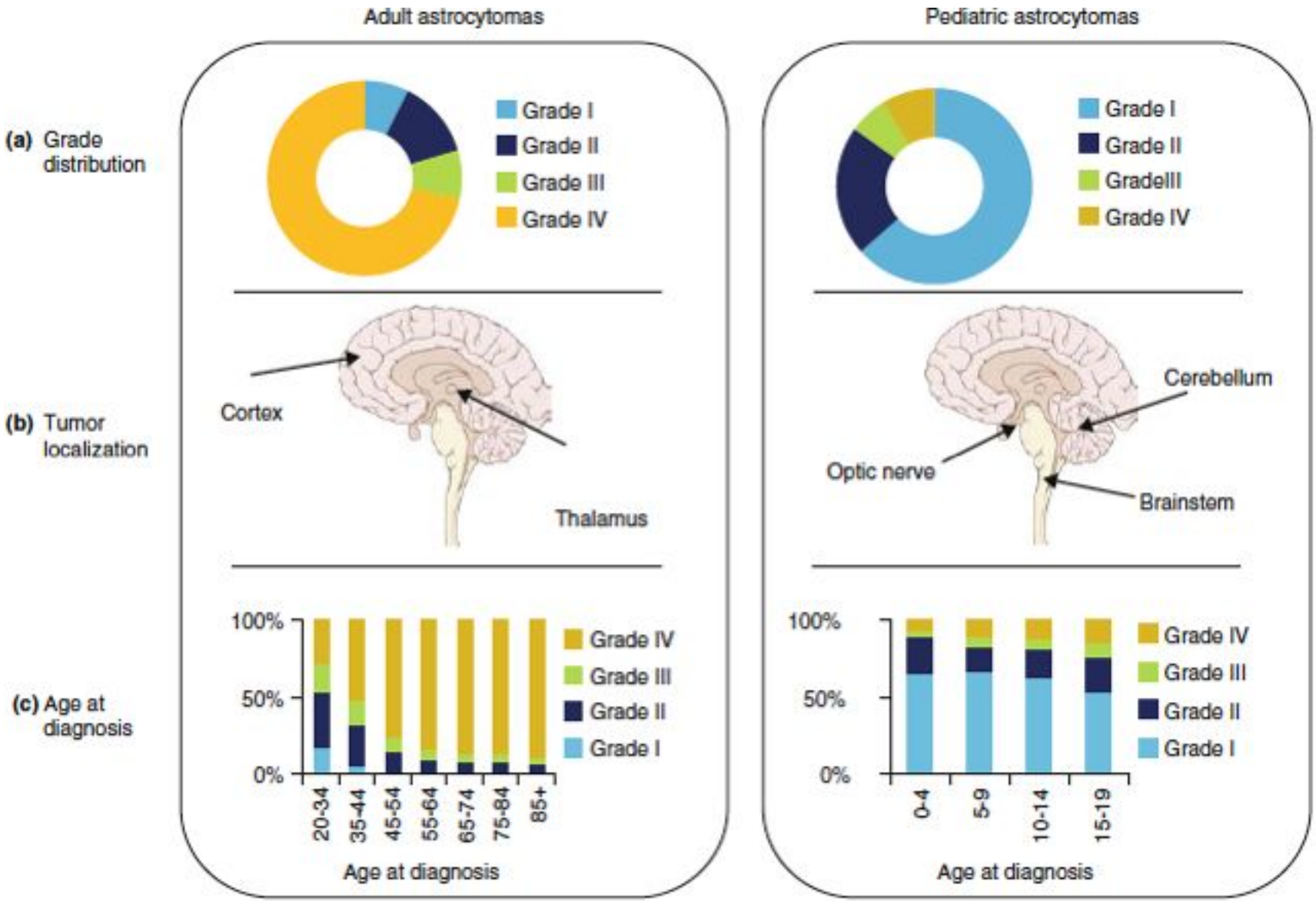
Relatore: Felice Giangaspero

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

PEDIATRIC LOW GRADE GLIOMAS

ENTITY	WHO Grade
Chordoid glioma of the third Ventricle	*II*
Angiocentric glioma	*I*
Pilocytic astrocytoma	***I***
Ganglioglioma	***I or II***
Pleomorphic xanthoastrocytoma	***II***
Diffuse astrocytoma	***II***
DNET	*I*
Ependymoma	*II*
Mixed oligoastrocytoma	*II*
Myxopapillary ependymoma	*I*
Oligodendroglioma	*II*
Subependymal giant cell astrocytoma	*I*
Subependymoma	*I*



From Gerges et al. Genome Medicine 2013, 5:66

Pediatric LGGs

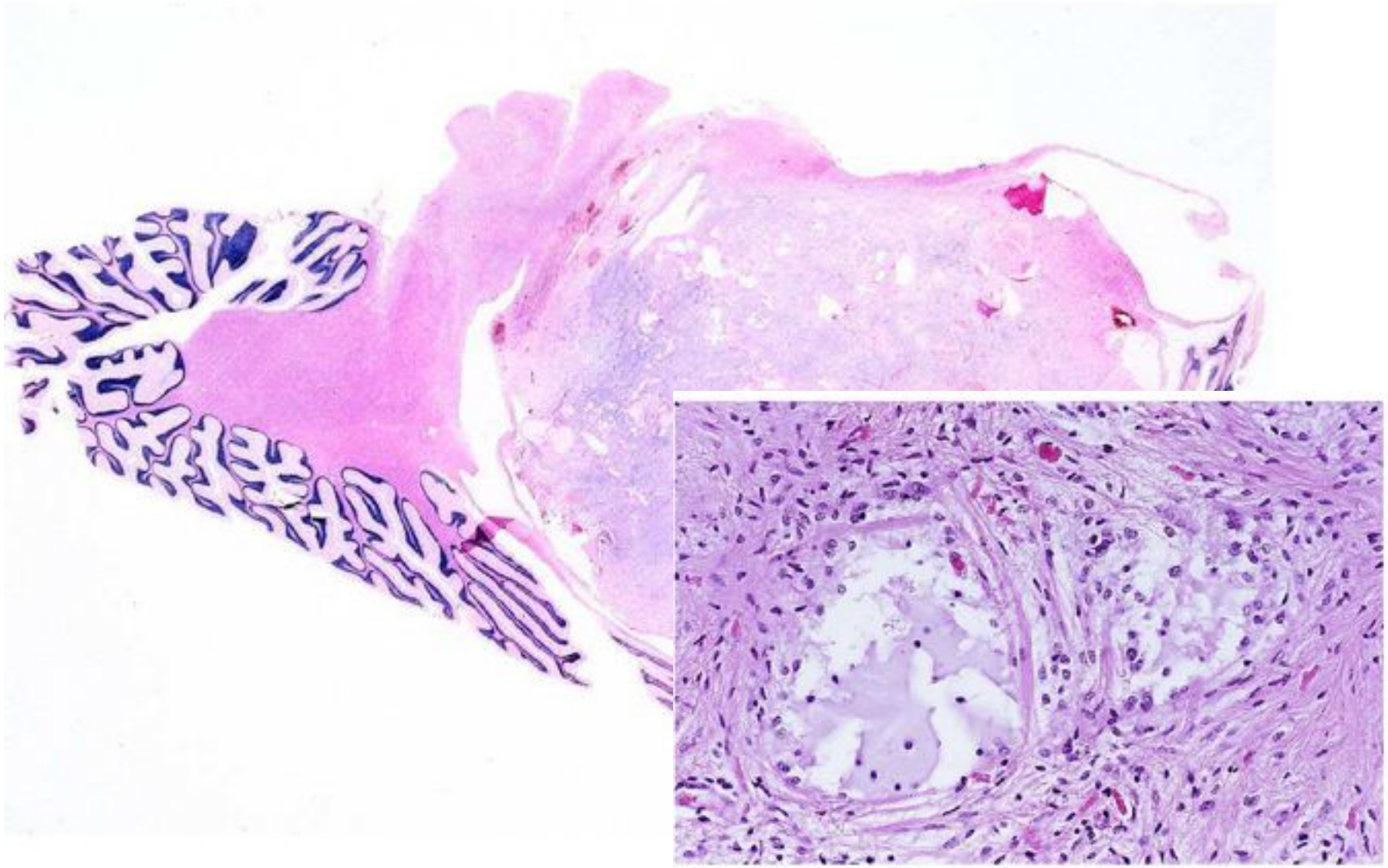
Are they benign tumors?

- Affect negatively quality of life
- Recurr even if resected completely
- Metastasize or transform in HGGs (rarely)

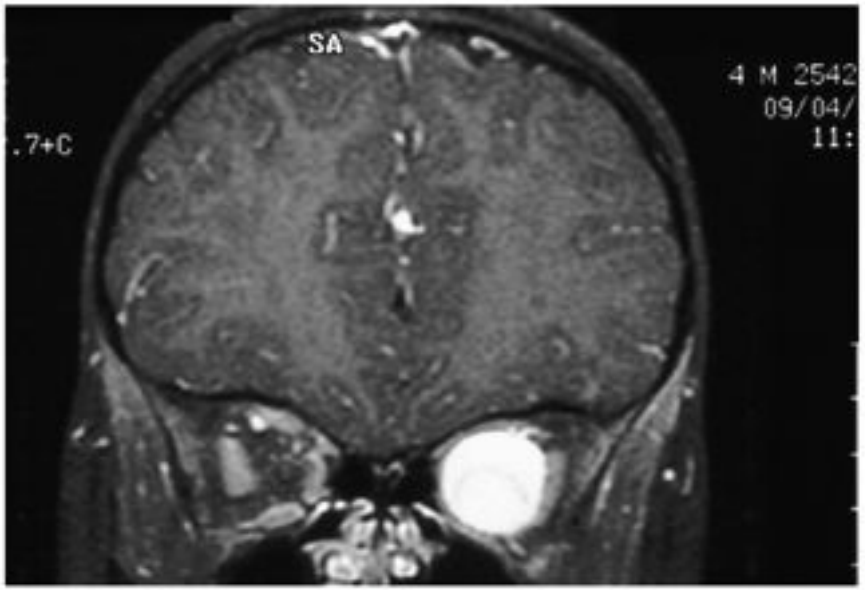
Pilocytic Astrocytoma - Distribution/Sites

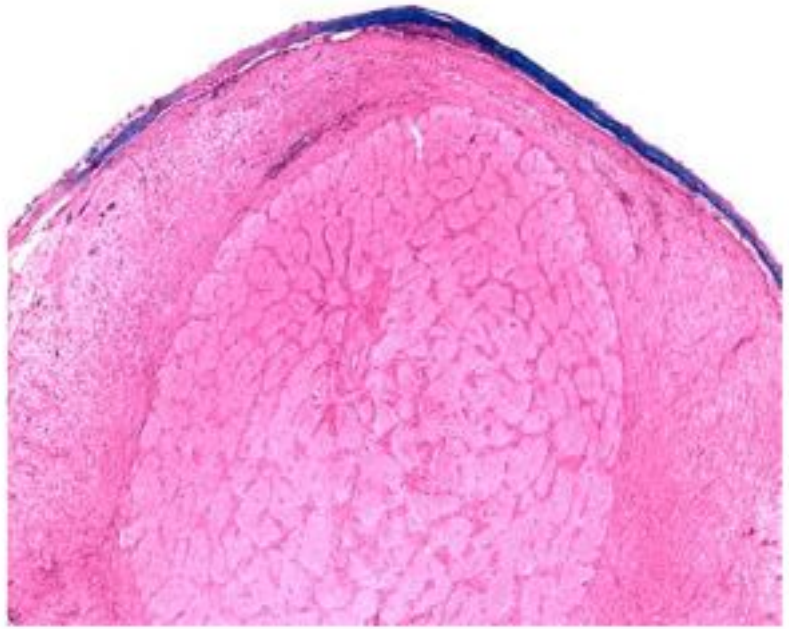
- Cerebellum
- Visual pathways
  - Optic chiasm/hypothalamus
  - Intra-orbital optic nerves
- Brain stem
- Cerebral hemispheres
- Spinal cord

Pilocytic Astrocytoma

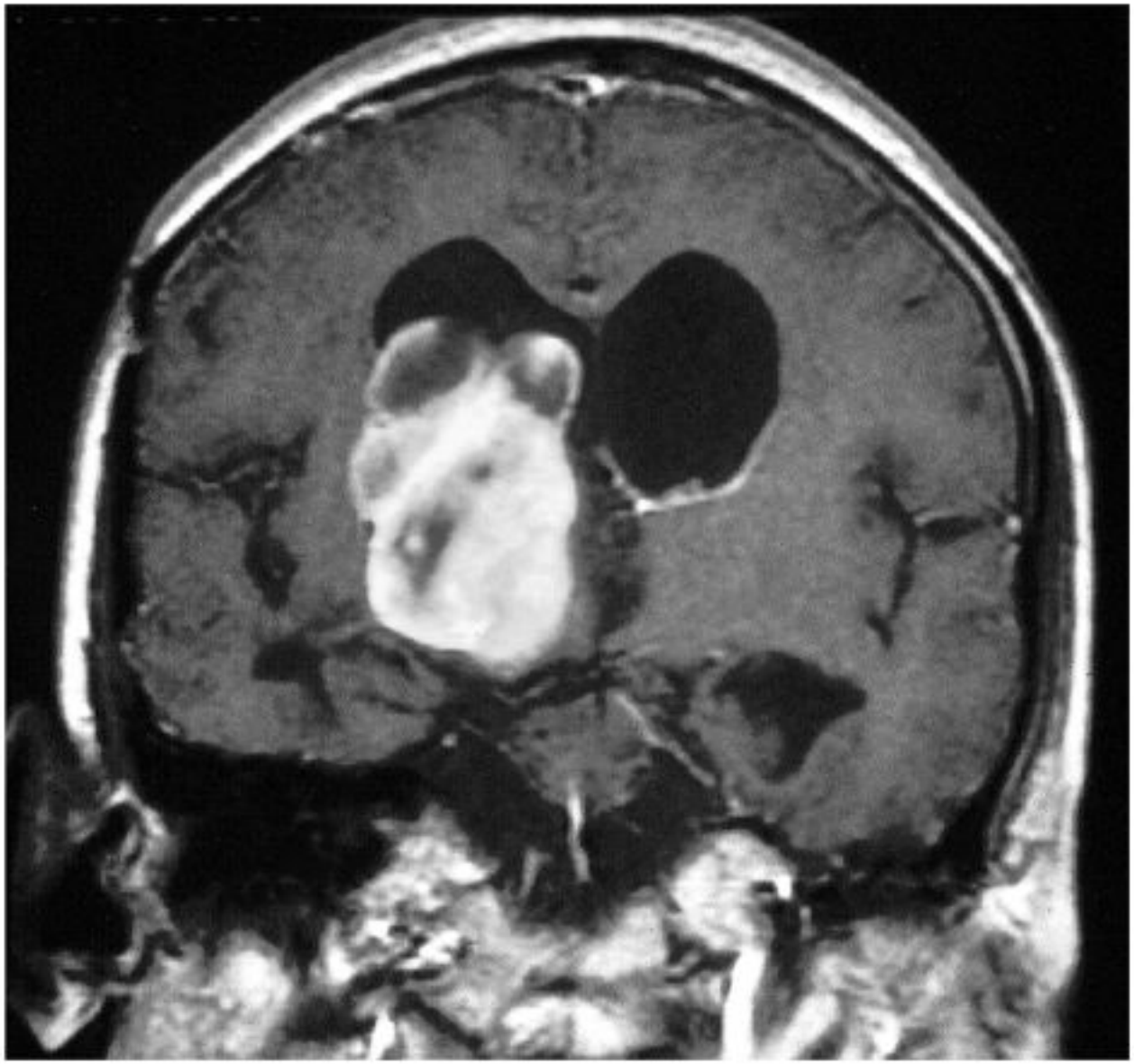


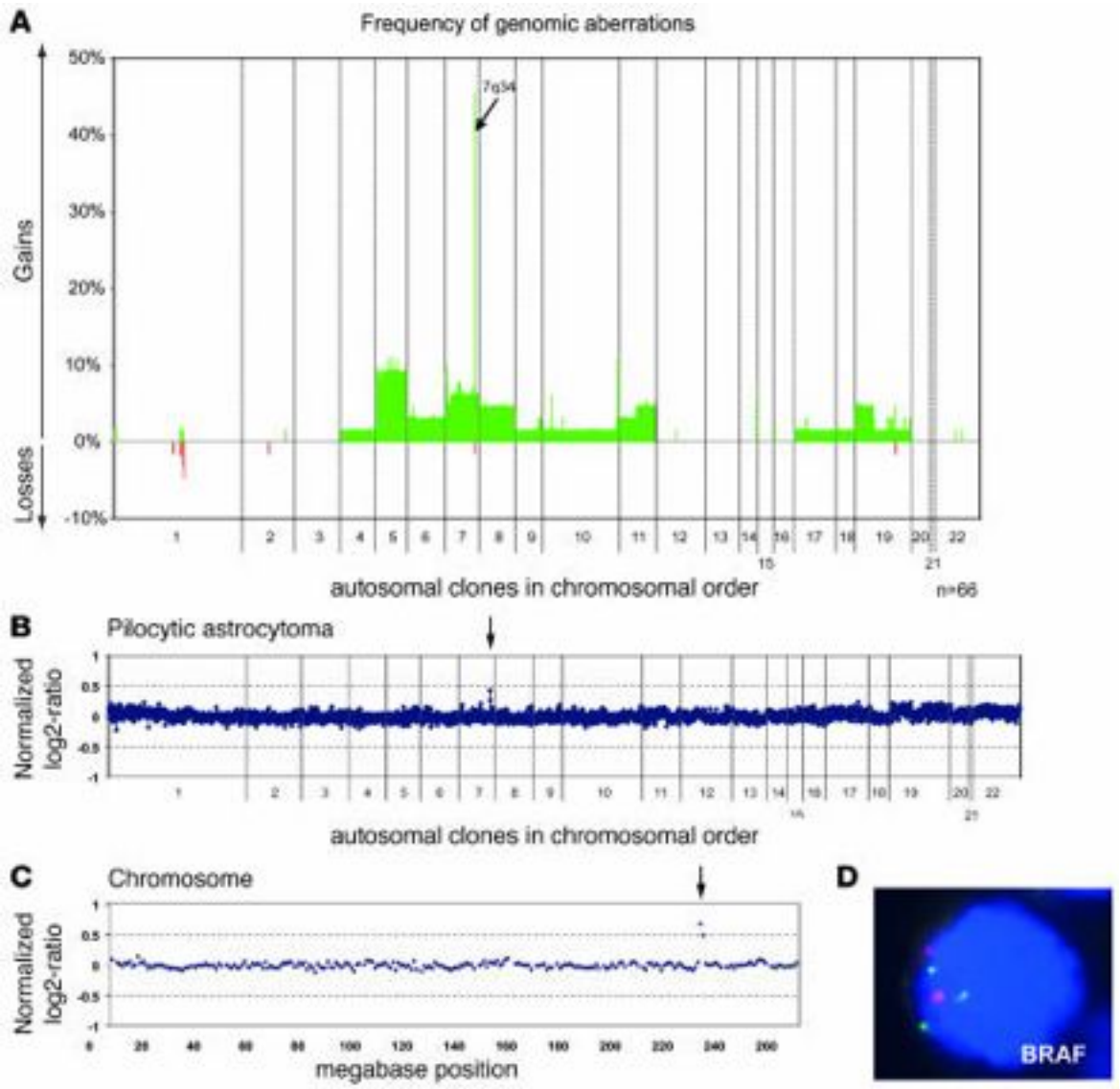
Pilocytic Astrocytoma





Pilocytic Astrocytoma



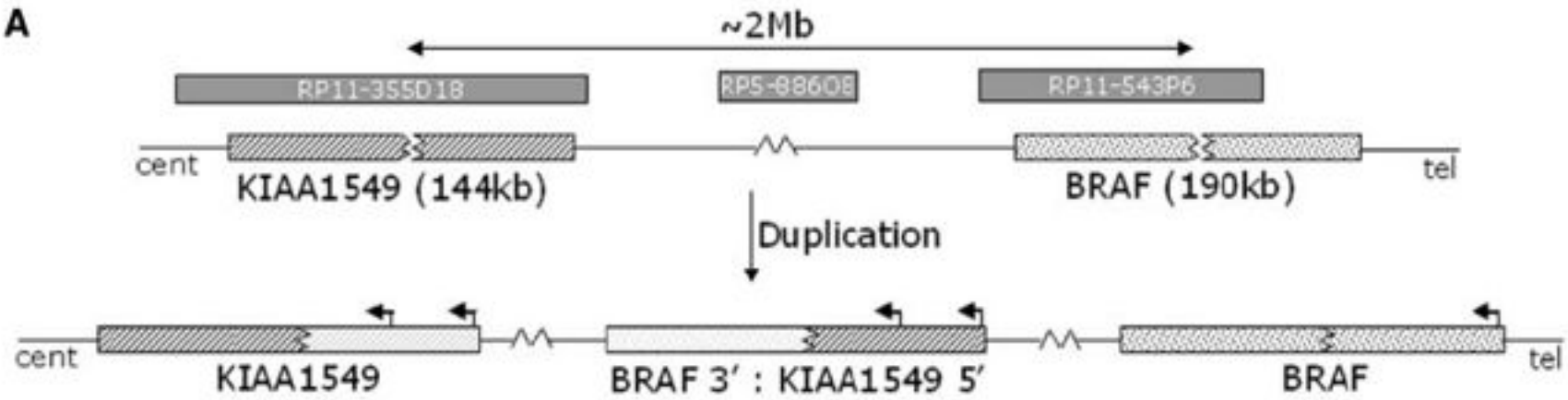


Pfister et al. J Clin Inv 118:1739, 2008

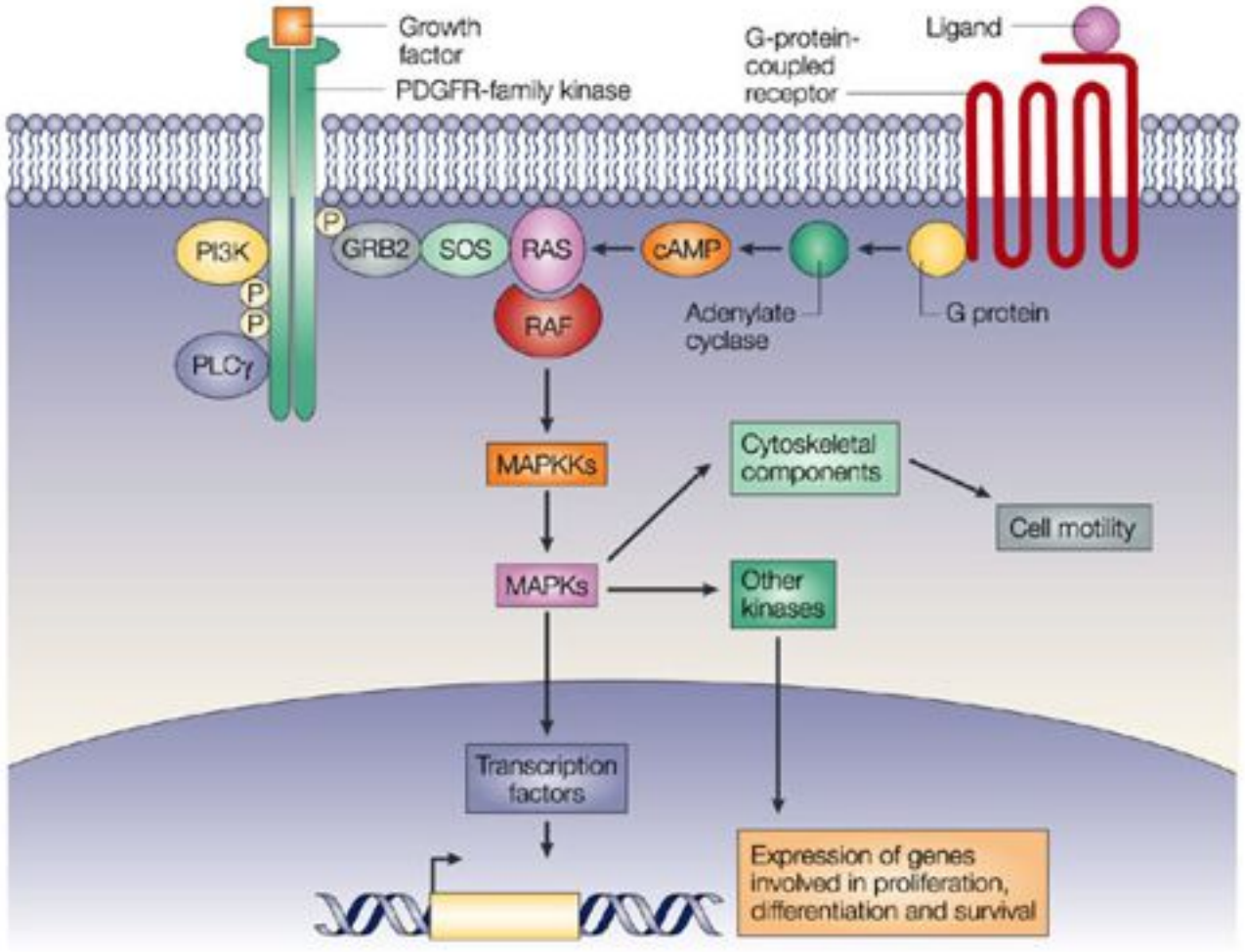
Tandem Duplication Producing a Novel Oncogenic *BRAF* Fusion Gene Defines the Majority of Pilocytic Astrocytomas

David T.W. Jones,[1] Sylvia Kocialkowski,[1] Lu Liu,[1] Danita M. Pearson,[1]
L. Magnus Bäcklund,[2] Koichi Ichimura,[1] and V. Peter Collins[1]

Cancer Res 2008;68(21):8673–7

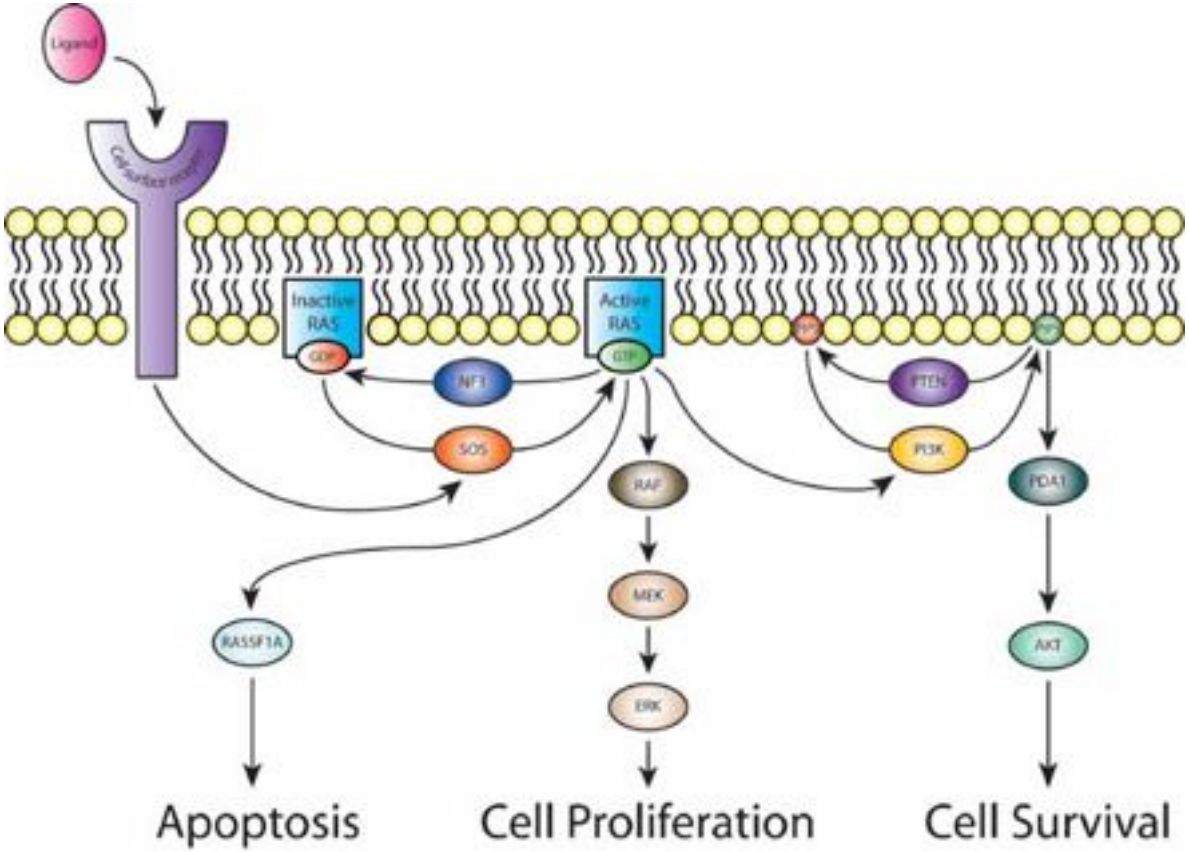


BRAF: a downstream member of the RAS signalling cascade

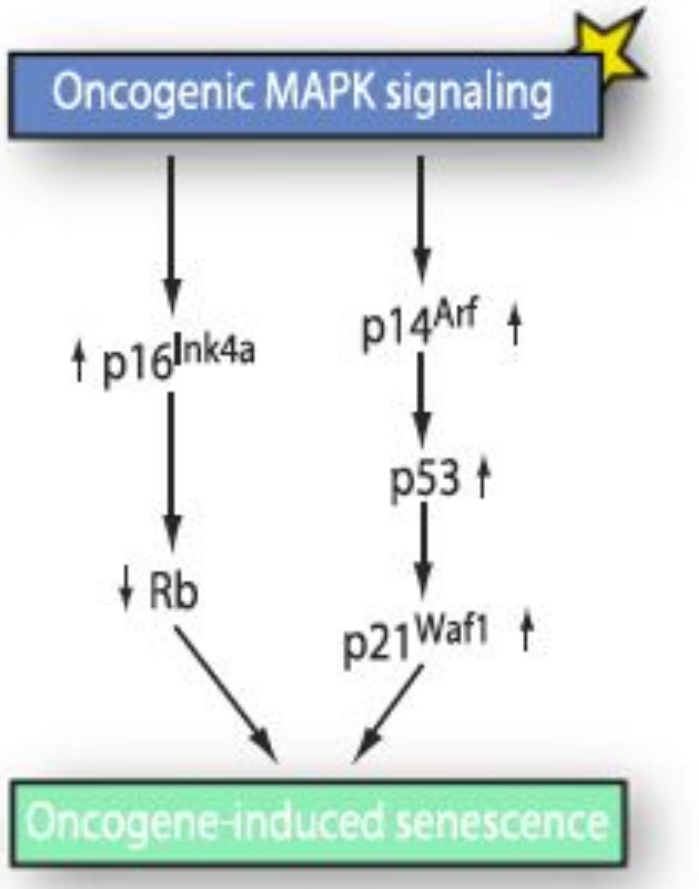


Nature Reviews | Cancer

MAPK pathway activation



Journal of Cellular Physiology
Volume 222, Issue 3, pages 509-514, 23 NOV 2009 DOI: 10.1002/jcp.21978
http://onlinelibrary.wiley.com/doi/10.1002/jcp.21978/full#fig1



OIS markers:
e.g. SAHF, SA-β-Gal, $p21^{Waf1}$, $p16^{Ink4a}$

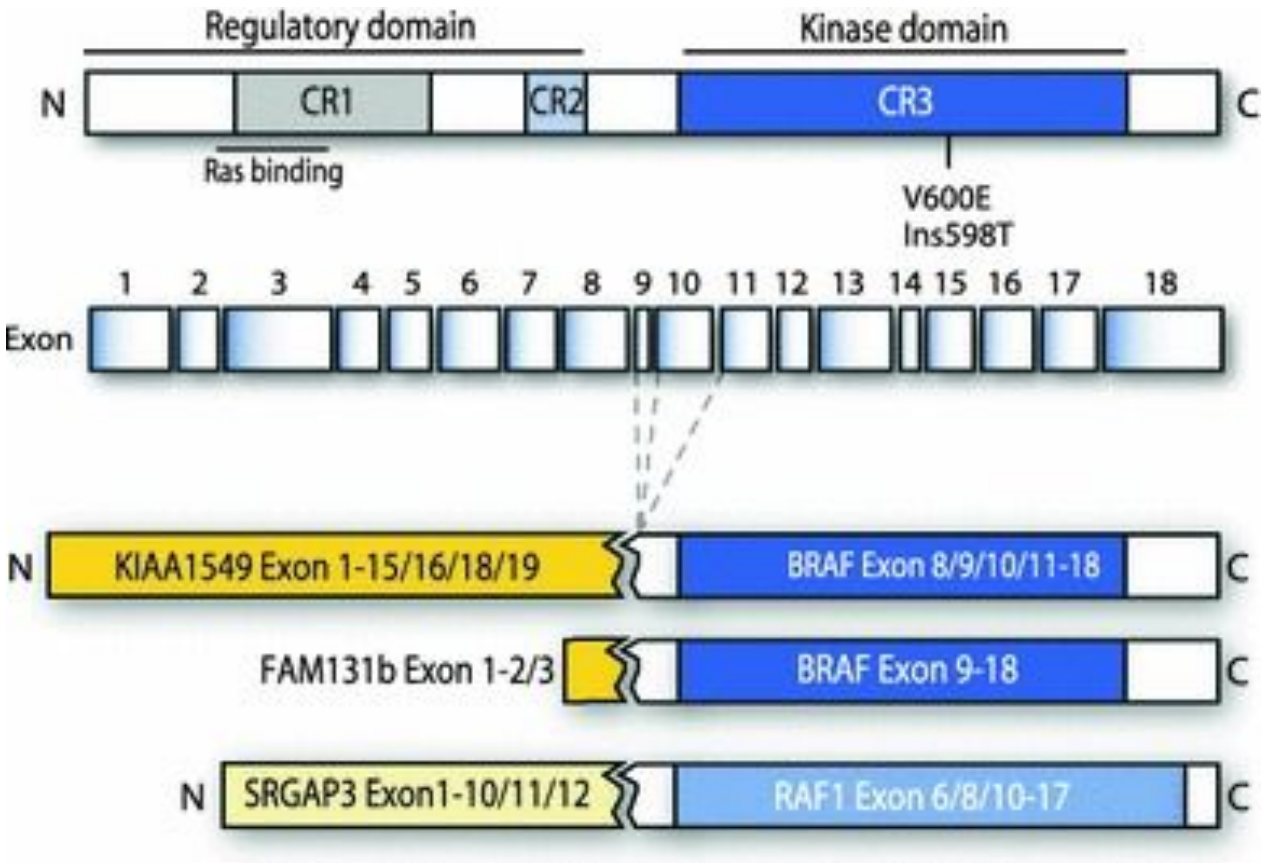
Cell. Mol. Life Sci. (2012) 69:1799–1811
DOI 10.1007/s00018-011-0898-9

Cellular and Molecular Life Sciences

REVIEW

MAPK pathway activation in pilocytic astrocytoma

David T. W. Jones · Jan Gronych · Peter Lichter · Olaf Witt · Stefan M. Pfister



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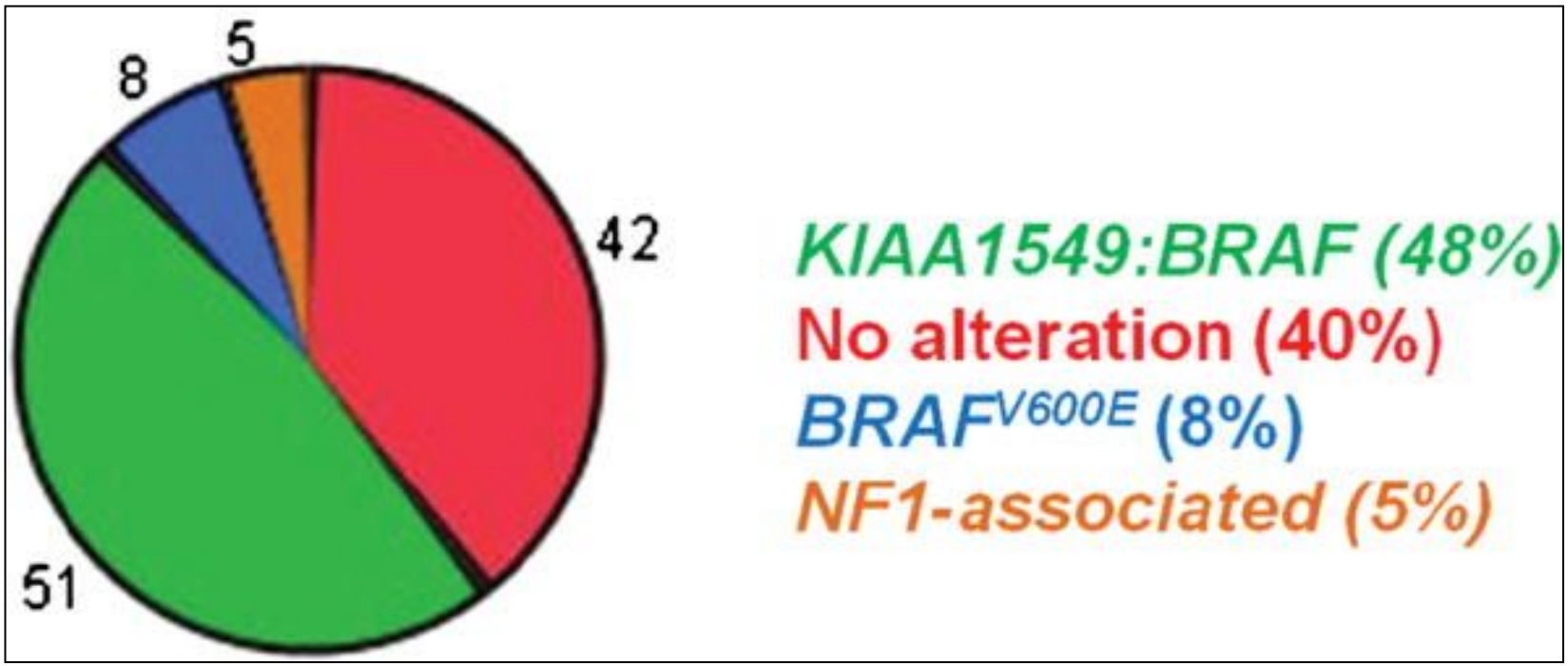
Cellular and Molecular Life Sciences

REVIEW

MAPK pathway activation in pilocytic astrocytoma

David T. W. Jones · Jan Gronych · Peter Lichter · Olaf Witt · Stefan M. Pfister

106 LGG/Glioneuronal
Mean age: 10 yrs (range 1-29 yrs)



BRAF Alterations in Primary Glial and Glioneuronal Neoplasms of the Central Nervous System With Identification of 2 Novel KIAA1549: BRAF Fusion Variants.
Lin, Alex; Rodriguez, Fausto; Karajannis, Matthias; Williams, Susan; Legault, Genevieve; Zagzag, David; MD, PhD; Burger, Peter; Allen, Jeffrey; Eberhart, Charles; MD, PhD; Bar, Eli
Journal of Neuropathology & Experimental Neurology. 71(1):66-72, January 2012.

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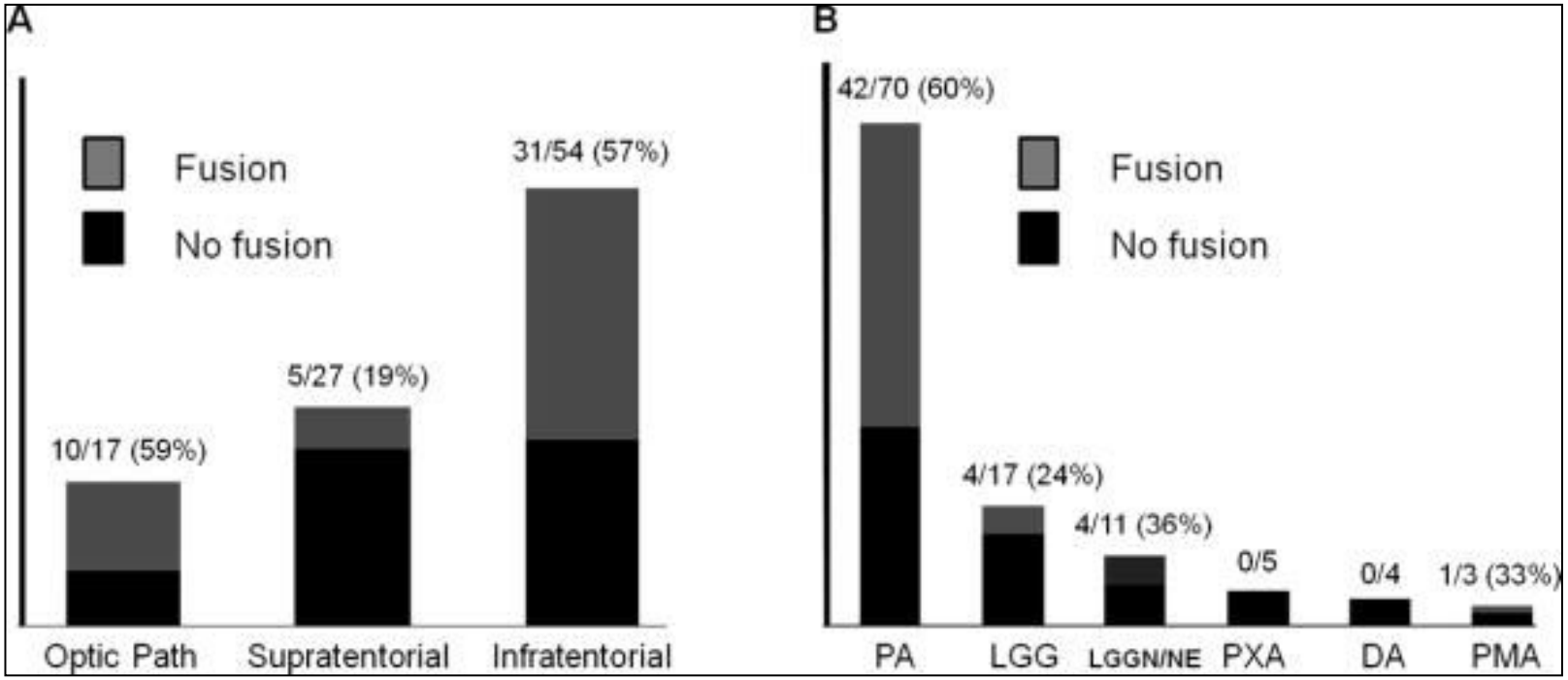

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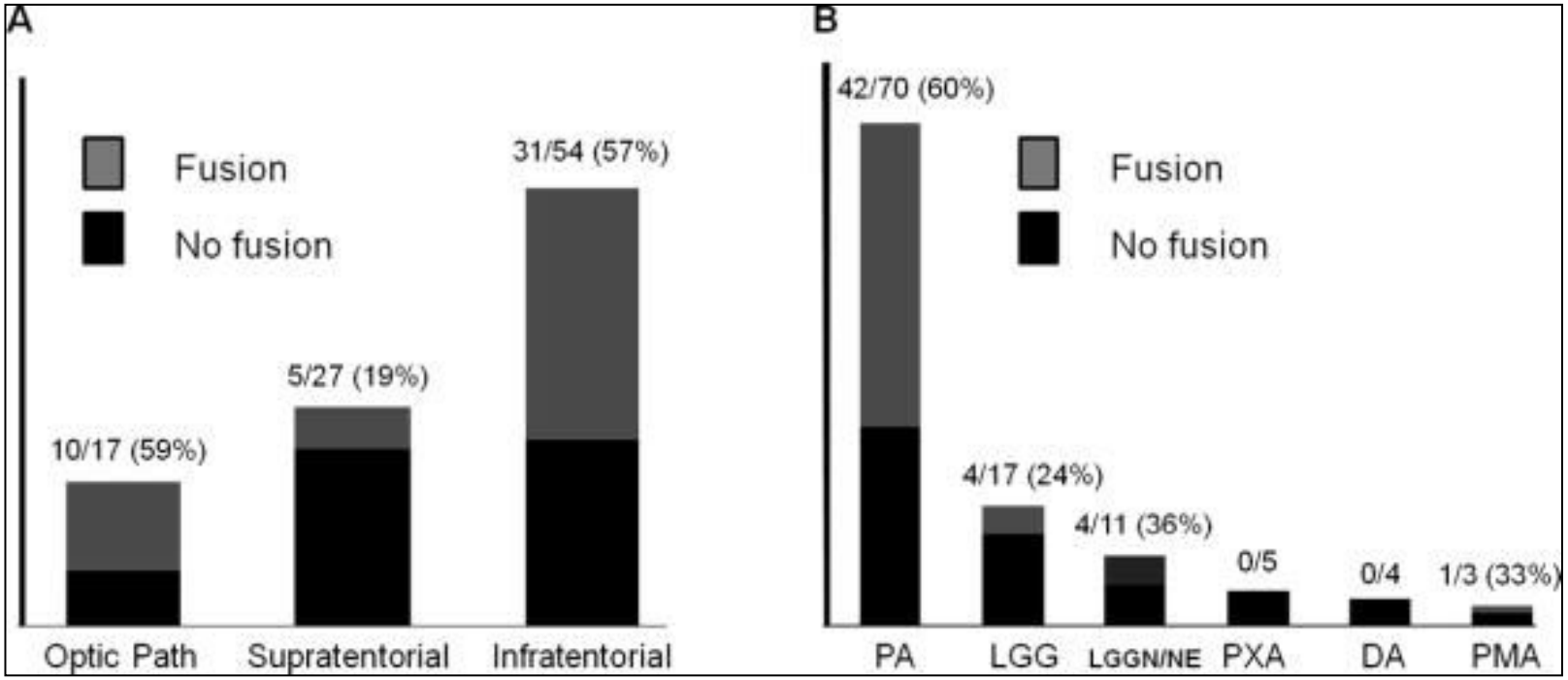

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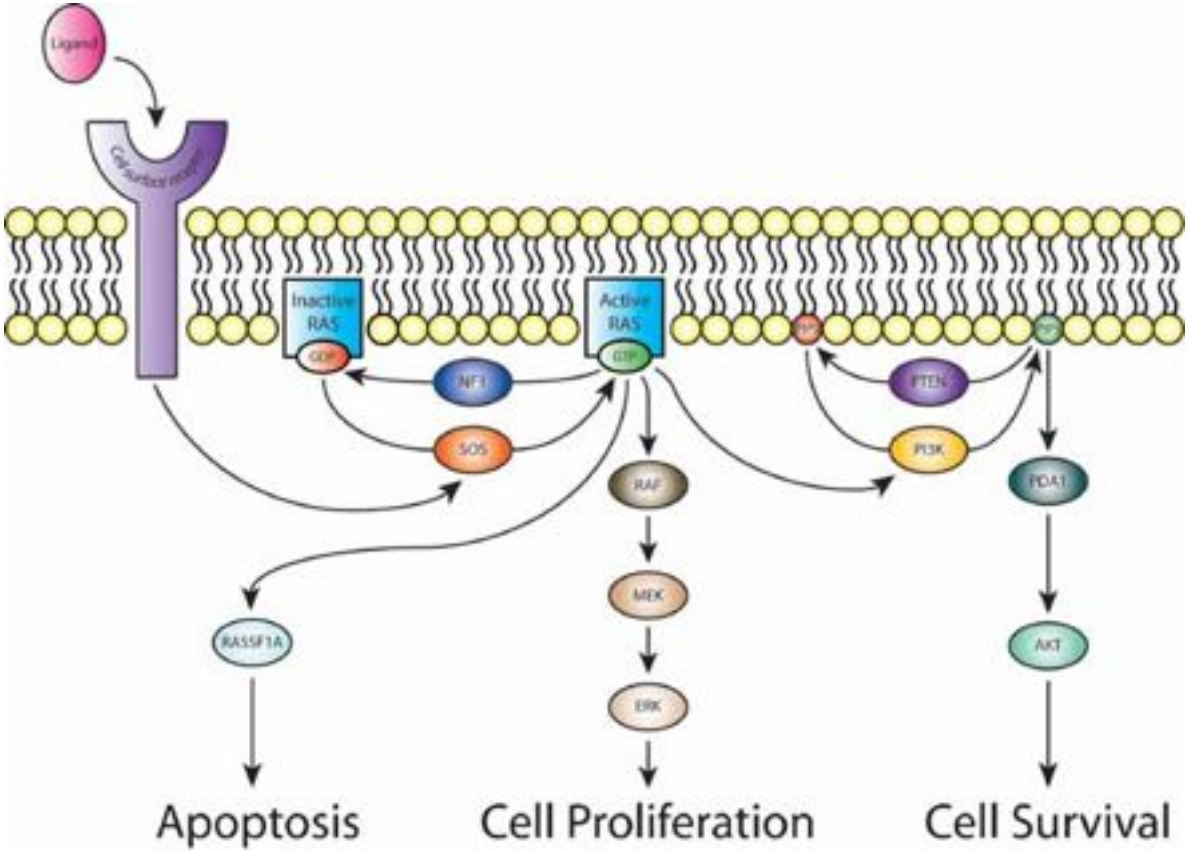
MAPK pathway activation



Journal of Cellular Physiology
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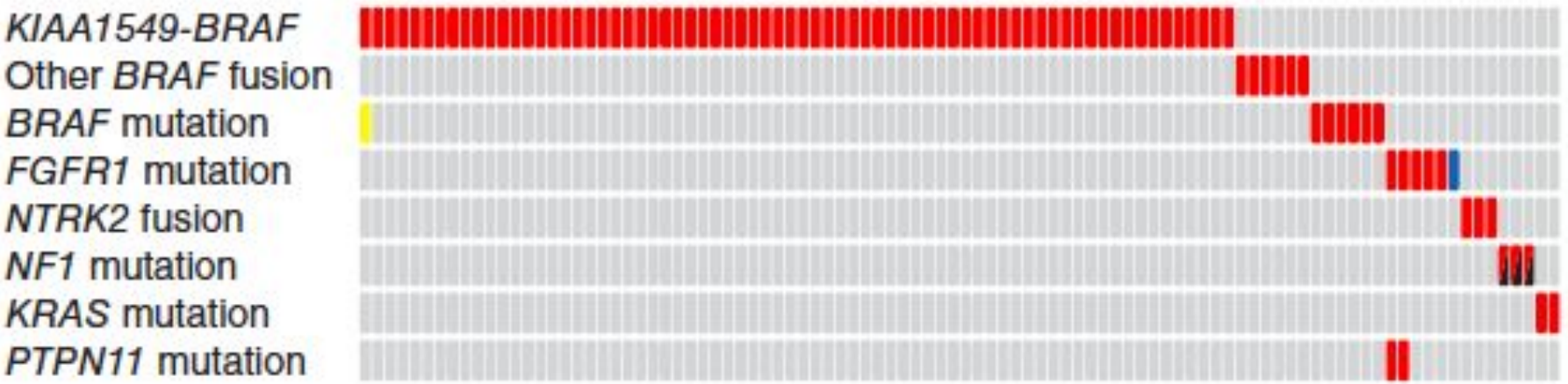
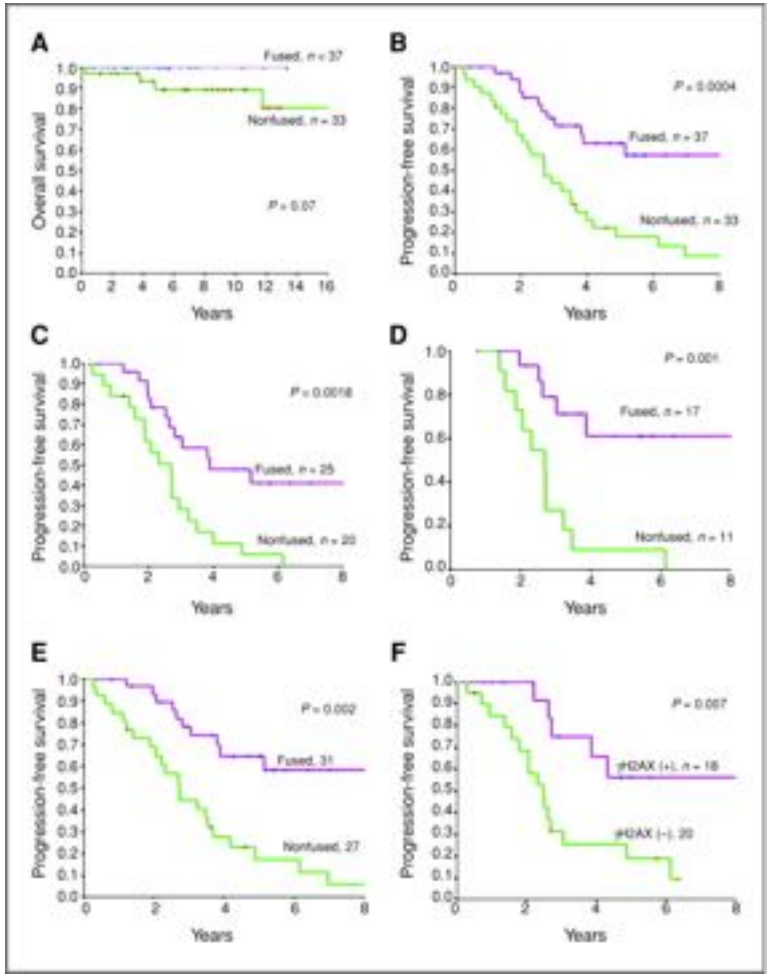


nature genetics

Recurrent somatic alterations of *FGFR1* and *NTRK2* in pilocytic astrocytoma

David T W Jones[1–3], Barbara Hutter[2,3], Natalie Jäger[2,3], Andrey Korshunov[4,5], Marcel Kool[1], Hans-Jörg Warnatz[2], Thomas Zichner[6], Sally R Lambert[7], Marina Ryzhova[8], Dong Anh Khuong Quang[9], Adam M Fontebasso[9], Adrian M Stütz[6], Sonja Hutter[2], Marc Zuckermann[10], Dominik Sturm[1], Jan Groznych[10], Bärbel Lasitschka[11], Sabine Schmidt[11], Huriye Şeker-Cin[1], Hendrik Witt[1,12], Marc Sultan[2], Meryem Ralser[2], Paul A Northcott[1], Volker Hovestadt[10], Sebastian Bender[1], Elke Pfaff[1], Sebastian Stark[2], Damien Faury[9], Jeremy Schwartzentruber[13], Jacek Majewski[13], Ursula D Weber[10], Marc Zapatka[10], Benjamin Raeder[6], Matthias Schlesner[2], Catherine L Worth[2], Cynthia C Bartholomae[14], Christof von Kalle[14,15], Charles D Imbusch[2], Sylwester Radomski[2,16,17], Chris Lawerenz[2], Peter van Sluis[18], Jan Koster[18], Richard Volckmann[18], Rogier Versteeg[18], Hans Lehrach[3], Camelia Monoranu[19], Beate Winkler[20], Andreas Unterberg[21], Christel Herold-Mende[21], Till Milde[1,2,22], Andreas E Kulozik[12], Martin Ebinger[23], Martin U Schuhmann[24], Yoon-Jae Cho[25], Scott L Pomeroy[26,27], Andreas von Deimling[4,5], Olaf Witt[12,22], Michael D Taylor[28,29], Stephan Wolf[11], Matthias A Karajannis[30], Charles G Eberhart[31], Wolfram Scheurlen[32], Martin Hasselblatt[33], Keith L Ligon[26,34,35], Mark W Kieran[30,36], Jan O Korbel[6], Marie-Laure Yaspo[2], Benedikt Brors[2], Jörg Felsberg[37], Guido Reifenberger[37], V Peter Collins[7], Nada Jabado[9,38], Roland Eils[2,15–17,40], Peter Lichter[10,15,40] & Stefan M Pfister[1,12,40], for the International Cancer Genome Consortium PedBrain Tumor Project



70 patients with incompletely resected "clinically relevant" PLGA

BRAF-KIAA1549 Fusion Predicts Better Clinical Outcome in Pediatric Low-Grade Astrocytoma

Cynthia Hawkins[1,4], Erin Walker[2,4], Nequesha Mohamed[1,4], Cindy Zhang[2,4], Karine Jacob[5], Margret Shirinian[5], Noa Alon[2], Daniel Kahn[2], Iris Fried[2], Katrin Scheinemann[6], Elena Tsangaris[2], Peter Dirks[3,4], Robert Tressler[7], Eric Bouffet[2], Nada Jabado[5], and Uri Tabori[2,4]

Clin Cancer Res 2011;17:4790-4798

BRAF mutations in human tumors

In up to 5-7% of all human tumors
~95% BRAF V600E

Carcinomas
- thyroid cancer (~30-50%) (papillary and anaplastic)
- colorectal cancer (~5-10%)
- ovarian carcinoma (~30% in serous forms)

Skin tumors
- malignant melanoma (~60%)

Hematologic tumors
- Hairy cell leukemia (>90%)
- Langerhans cell histiocytosis (~50%)

BRAF inhibitors

Selective small - molecule $BRAFV^{600E}$ inhibitors

Vemurafenib (Zelboraf™)
(FDA approval for advanced melanoma)
GSK2118436
AZD6244
Sorafenib

Acta Neuropathol (2011) 121:397–405
DOI 10.1007/s00401-011-0802-6

ORIGINAL PAPER

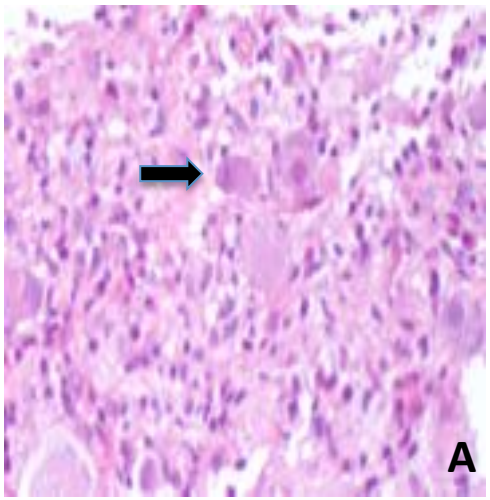
Analysis of *BRAF* V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma

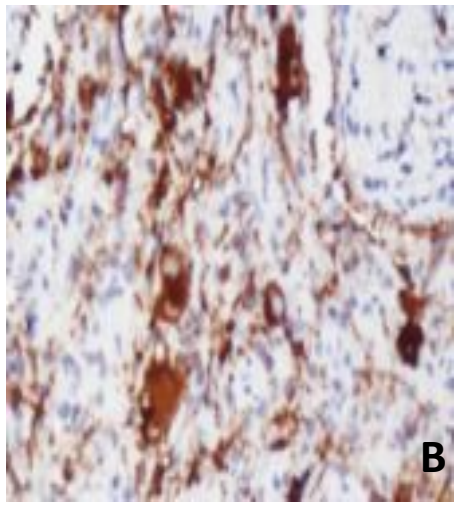
Genevieve Schindler · David Capper · Jochen Meyer · Wibke Janzarik · Heymut Omran · Christel Herold-Mende · Kirsten Schmieder · Pieter Wesseling · Christian Mawrin · Martin Hasselblatt · David N. Louis · Andrey Korshunov · Stefan Pfister · Christian Hartmann · Werner Paulus · Guido Reifenberger · Andreas von Deimling

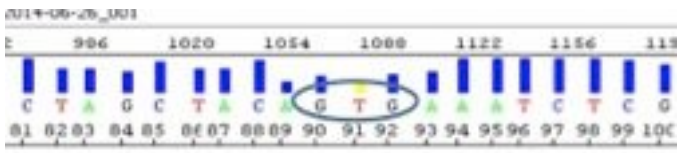
Table 1 Overview of *BRAF*^{V600E} mutations detected in 1,320 central and peripheral nervous system tumors according to tumor type

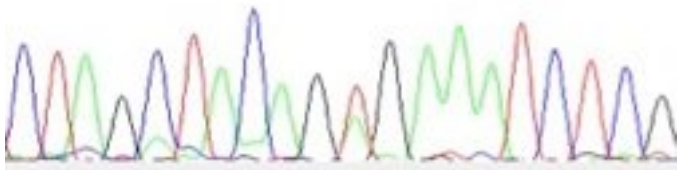
Tumor entity/variant	*N* (ad; ped)	*N* V600E (ad; ped)	% V600E (ad; ped)
Glial			
Pilocytic astrocytoma	97 (22; 75)	9 (2; 7)	9% (9%; 9%)
Diffuse astrocytoma	57 (53; 4)	0	0% (0%; 0/4)
Anaplastic astrocytoma	58 (52; 6)	2 (0; 2)	3% (0%; 2/6)
Oligodendroglioma	64 (62; 2)	1 (1; 0)	2% (2%; 0/2)
Anaplastic oligodendroglioma	70 (70; 0)	0	0%
Oligoastrocytoma	41 (41; 0)	0	0%
Anaplastic oligoastrocytoma	51 (51; 0)	0	0%
Primary glioblastoma	115 (79; 36)	2 (0; 2)	2% (0%; 6%)
Secondary glioblastoma	18 (18; 0)	1	6%
Giant cell glioblastoma	15 (15; 0)	1	7%
Gliosarcoma	16 (16; 0)	1	6%
Gliomatosis cerebri	5 (5; 0)	1	1/5
Myxopapillary ependymoma	4 (3; 1)	0	0/4 (0/3; 0/1)
Ependymoma	94 (16; 78)	0	0%
Anaplastic ependymoma	52 (5; 47)	0	0%
Subependymoma	2 (2; 0)	0	0/2
Pleomorphic xanthoastrocytoma	64 (38; 26)	42 (24; 18)	66% (63%; 69%)
Pleomorphic xanthoastrocytoma with anaplasia	23 (13; 10)	15 (5; 10)	65% (38%; 100%)
Subependymal giant cell astrocytoma	3 (3; 0)	1	1/3
Embryonal, neuronal, glioneuronal			
Medulloblastoma	141 (7; 134)	0	0%
CNS primitive neuroectodermal tumor	29 (12; 17)	0	0%
Atypical teratoid/rhabdoid tumor	14 (0; 14)	0	0%
Gangioglioma	77 (53; 24)	14 (11; 3)	18% (21%; 13%)
Anaplastic gangioglioma	6 (5; 1)	3 (2/1)	3/6 (2/5; 1/1)
Gangliocytoma	8 (8; 0)	0	0/8
Central neurocytoma	9 (8; 1)	0	0/9
Desmoplastic infantile astrocytoma/ganglioglioma	4 (0; 4)	0	0/4
Dysembryoplastic neuroepithelial tumor	4 (2; 2)	0	0/4

- 3yrs old male
- MRI: mass from medulla to C5
- Subtotal resection
- Histology: Ganglioglioma



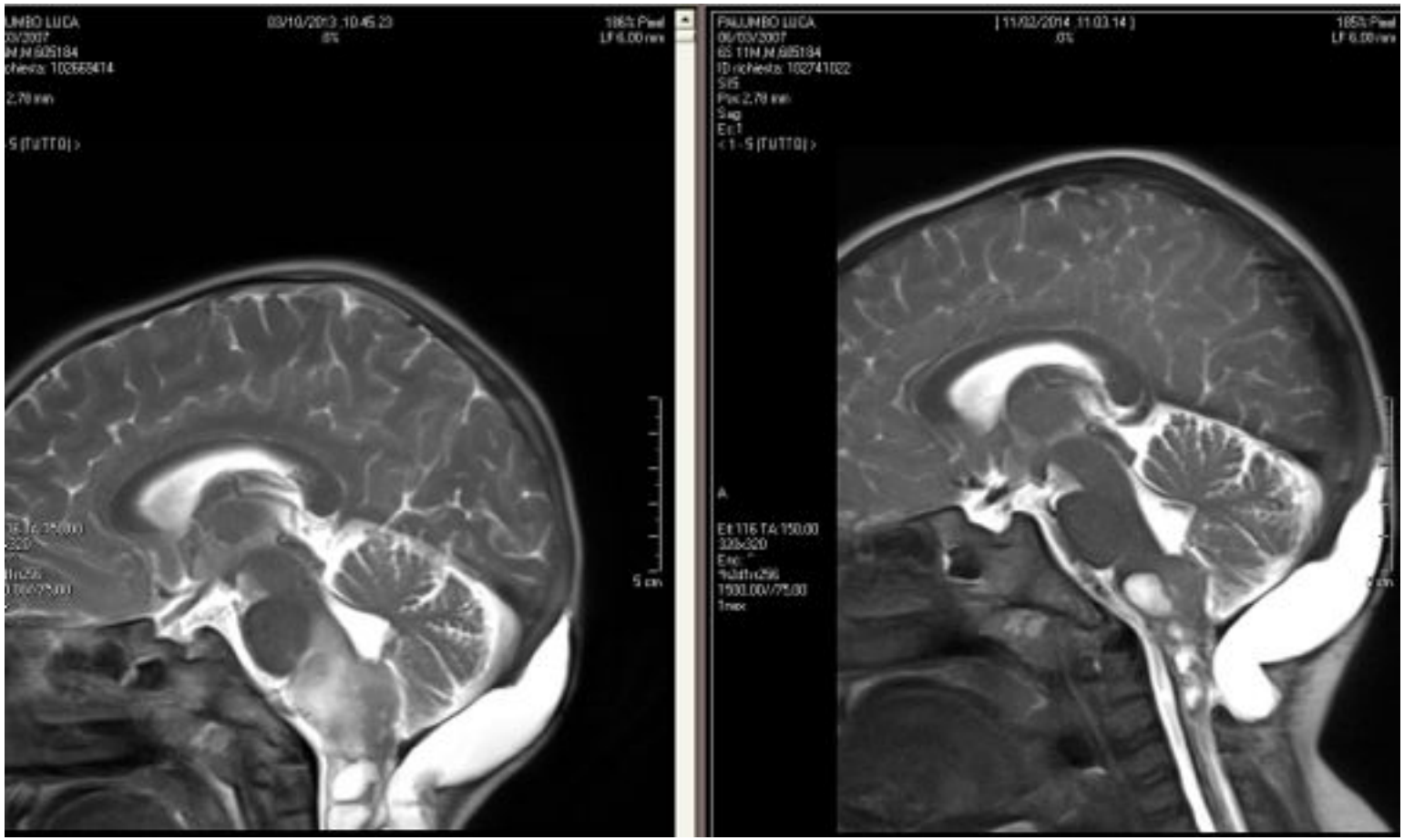






BRAF mutation V600E (GTG/GAG)

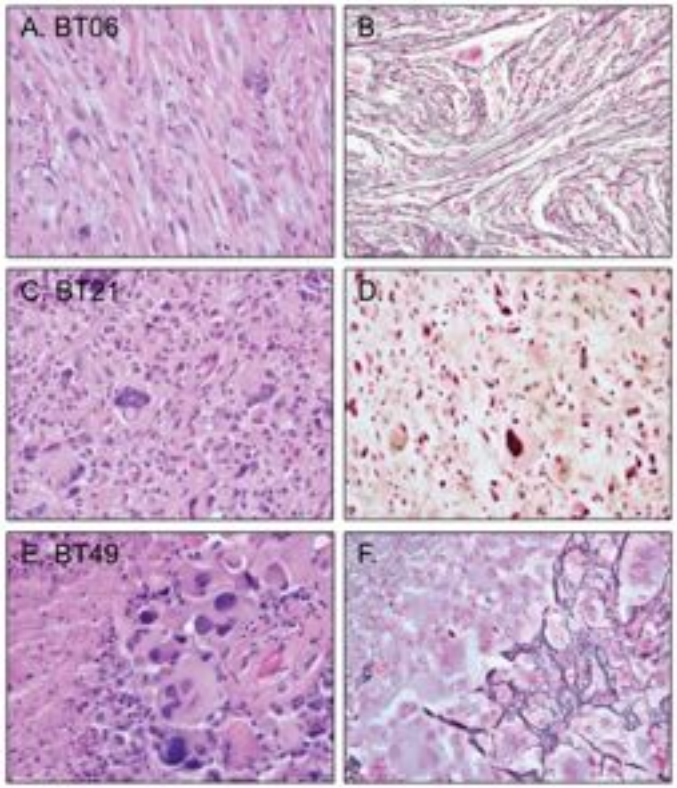
RESPONSE TO VEMURAFENIB
AFTER 3 MS OF TREATMENT

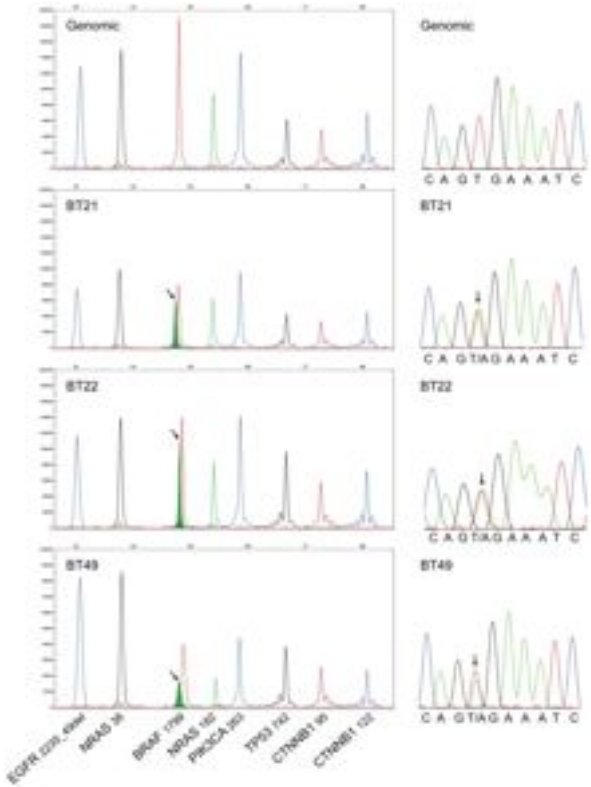


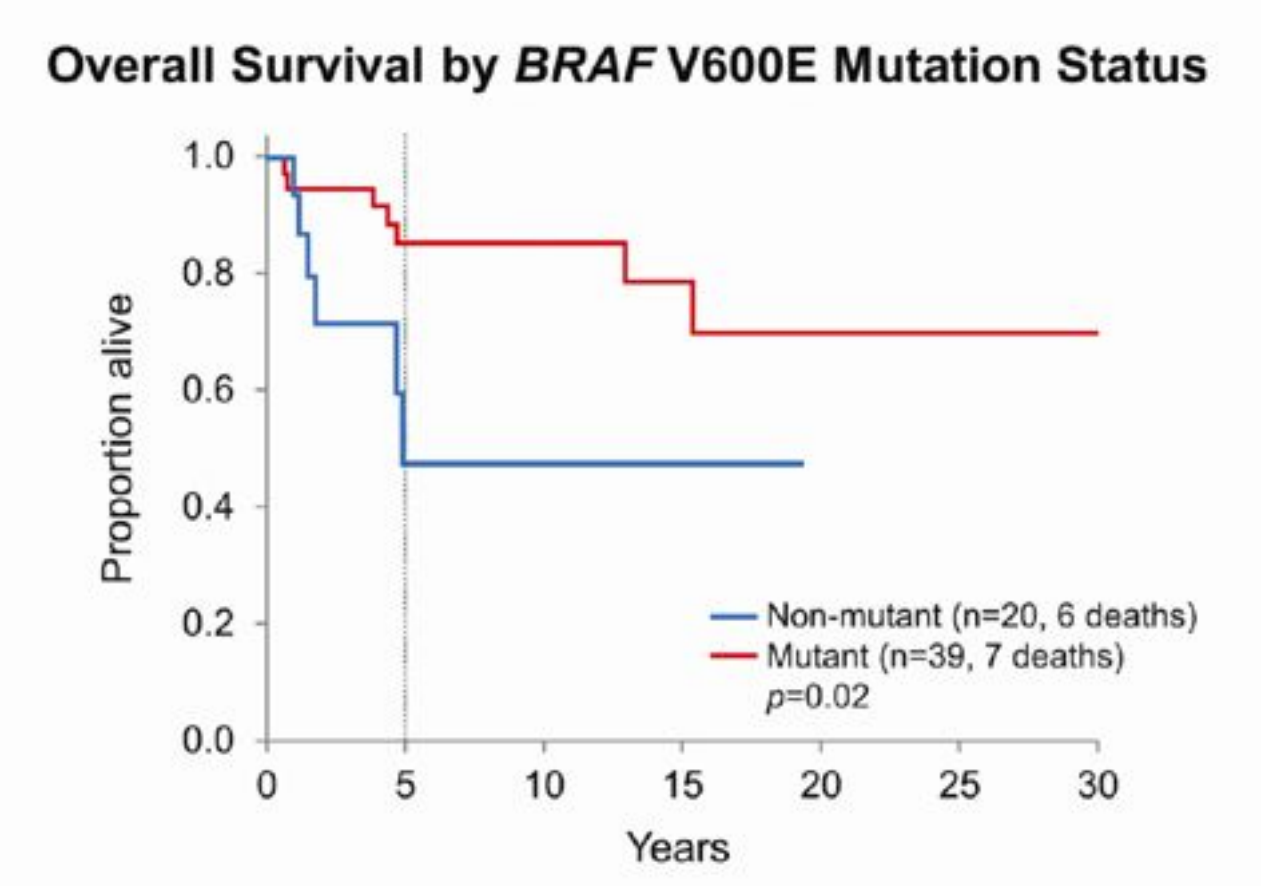
Courtesy Dr. A. Mastronuzzi Bambin Gesù Hospital, Rome, Italy

BRAF V600E Mutations Are Common in Pleomorphic Xanthoastrocytoma: Diagnostic and Therapeutic Implications

Dora Dias-Santagata[1], Quynh Lam[1], Kathy Vernovsky[2], Natalie Vena[3,4], Jochen K. Lennerz[1], Darrell R. Borger[2], Tracy T. Batchelor[2,5], Keith L. Ligon[3,4,6,7], A. John Iafrate[1], Azra H. Ligon[4,7], David N. Louis[1], Sandro Santagata[6,7]*





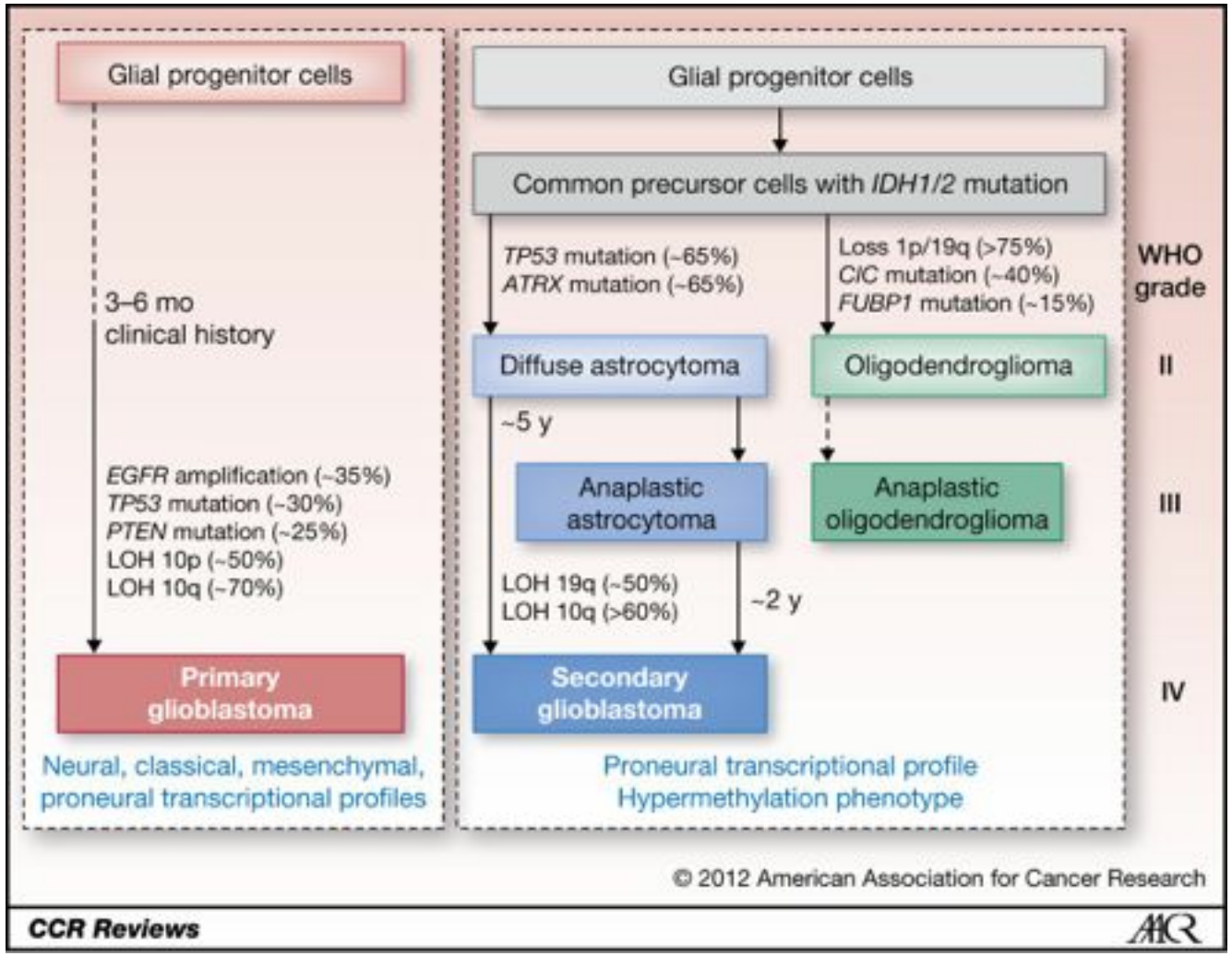


Pleomorphic Xanthoastrocytoma: Natural History and Long-term Follow-up

[1]Cristiane M. Ida, MD; [4]Fausto J. Rodriguez, MD; [4]Peter C. Burger, MD; [1]Alissa A. Caron, [3]Sarah M. Jenkins, [3]Grant M. Spears, [2]Dawn L. Aranguren, PA-C; [2]Daniel H. Lachance, MD; [1]Caterina Giannini, MD, PhD

Brain Pathol, 2014

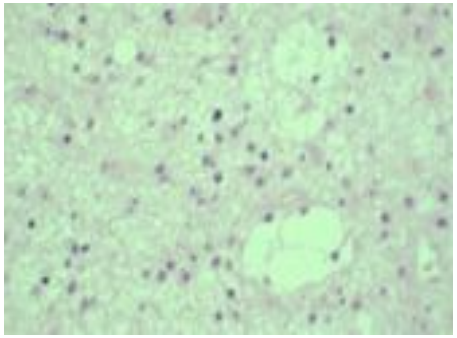
Genetic pathways diffuse gliomas in adults.



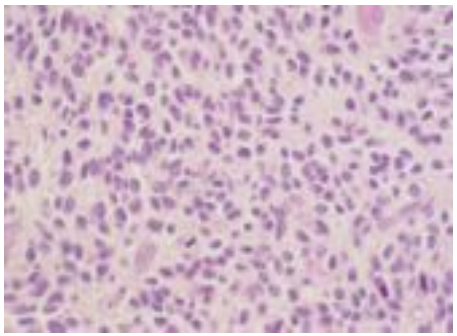
Ohgaki H , and Kleihues P Clin Cancer Res 2013;19:764-772

Pediatric Diffuse Gliomas

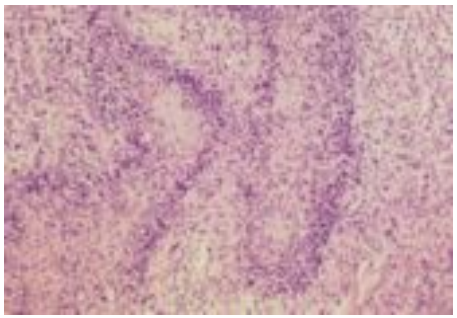
Astrocytomas



Diffuse astrocytoma (II)



Anaplastic astrocytoma (II)

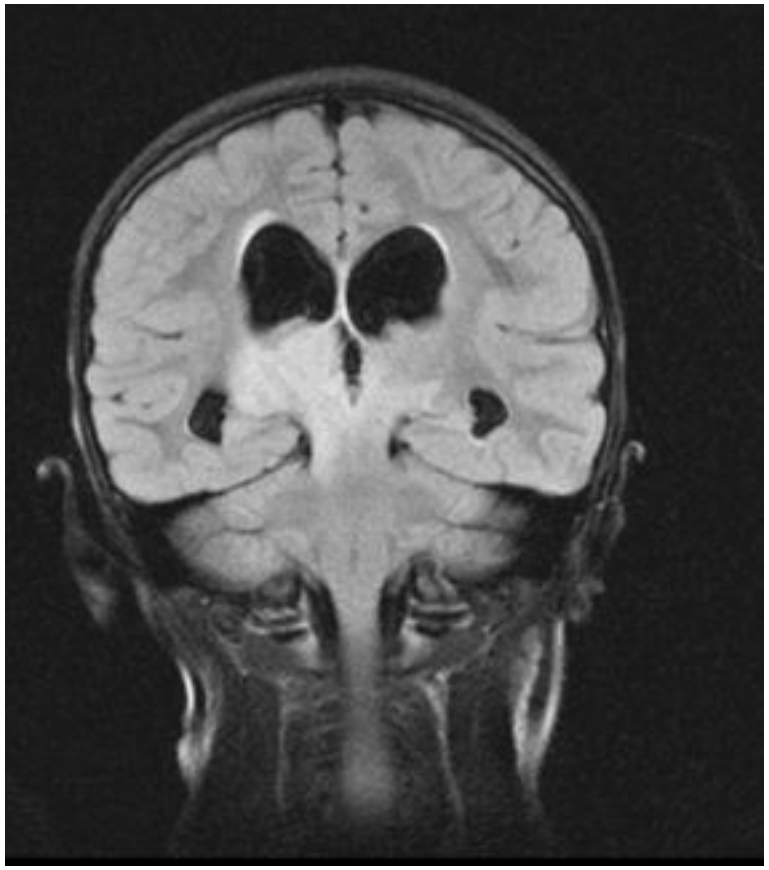


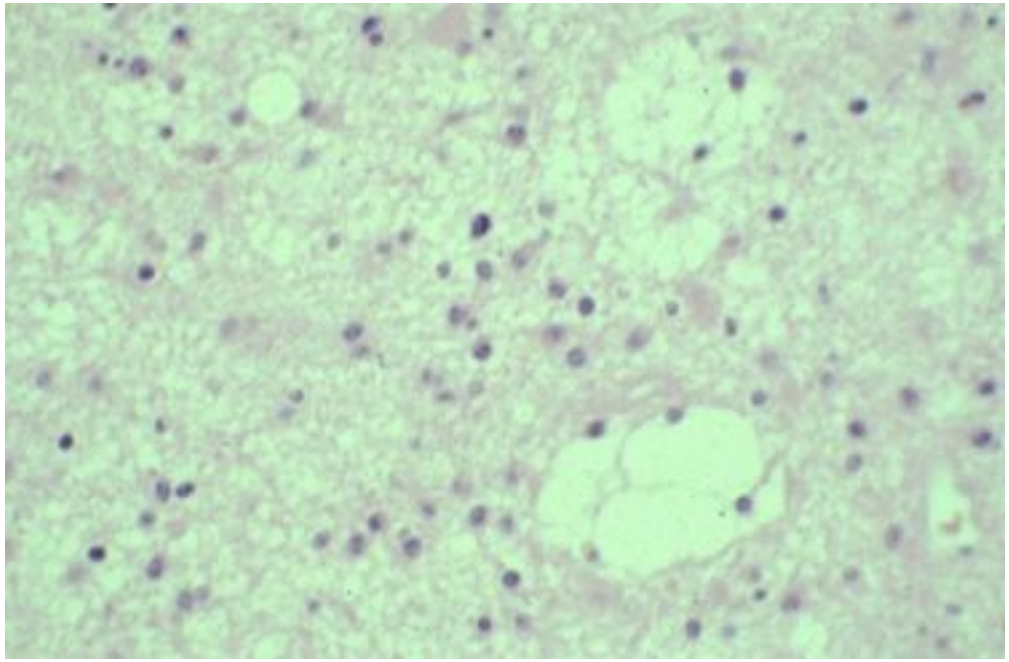
Glioblastoma (IV)

Low Grade

High Grade

Pediatric Diffuse Astrocytoma (WHO II)





Female, 10 years old

Genomic analysis of diffuse pediatric low-grade gliomas identifies recurrent oncogenic truncating rearrangements in the transcription factor *MYBL1*

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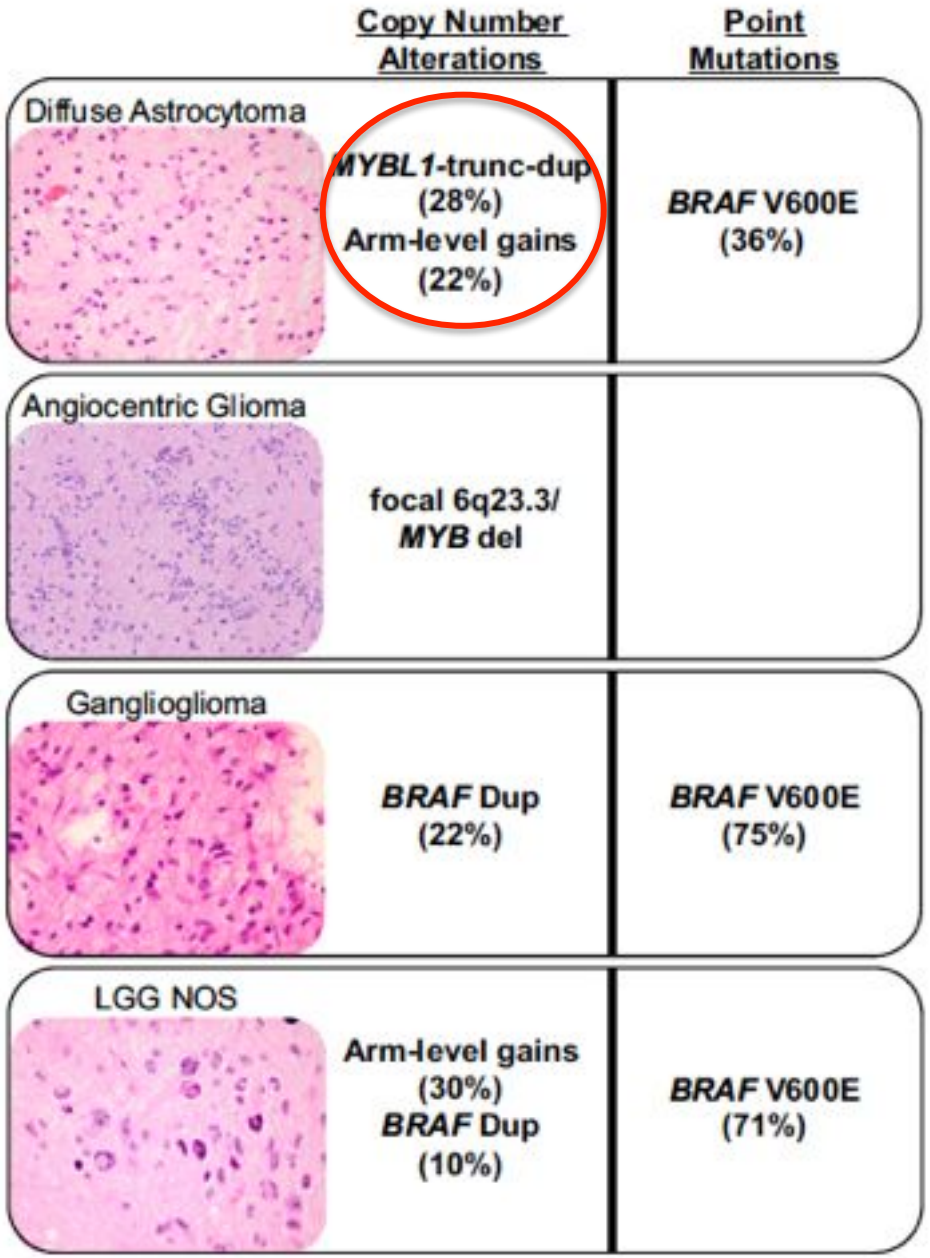
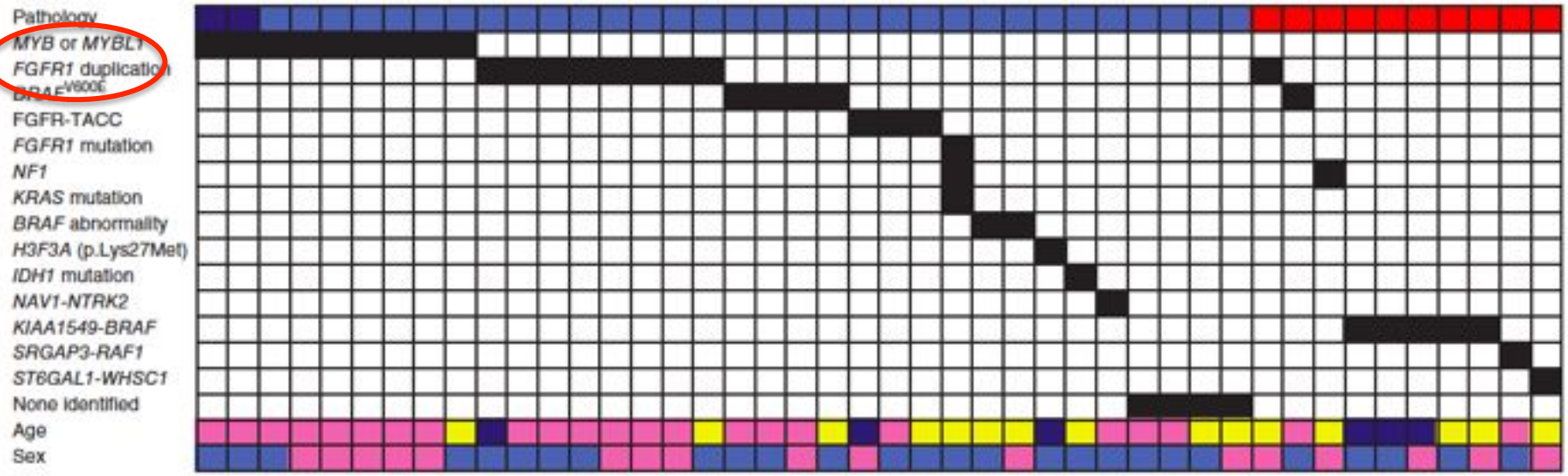


Supratentorial (hemispheric) LGG



Pathology
Age
Sex

Pilocytic or pilomyxoid astrocytoma
<3 years
Male

Diffuse glioma (DA, O, OA)
3–8 years
Female

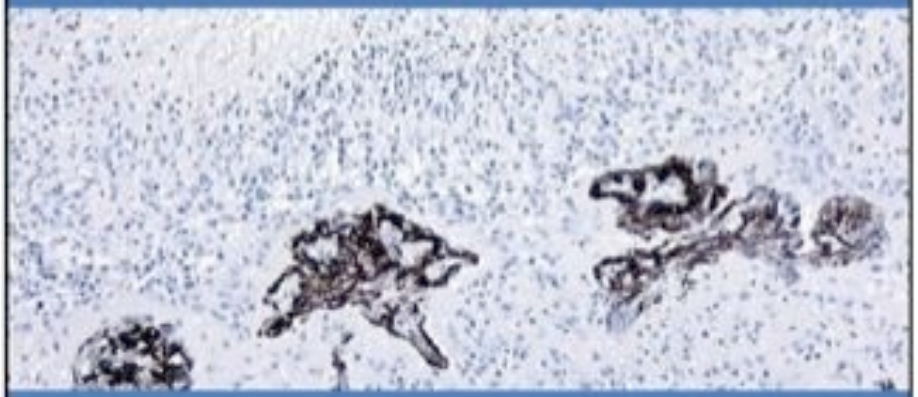
Angiocentric glioma
>8 years

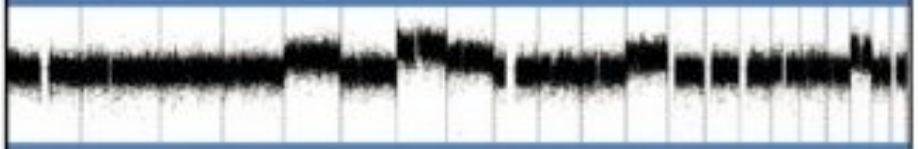
Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas

Jinghui Zhang[1], Gang Wu[1], Claudia P Miller[2], Ruth G Tatevossian[3], James D Dalton[3], Bo Tang[1], Wilda Orisme[3], Chandanamali Punchihewa[3], Matthew Parker[1], Ibrahim Qaddoumi[4], Fredrick A Boop[5], Charles Lu[6], Cyriac Kandoth[6], Li Ding[7], Ryan Lee[3], Robert Huether[2], Xiang Chen[1], Erin Hedlund[1], Panduka Nagahawatte[3], Michael Rusch[1], Kristy Boggs[8], Jinjun Cheng[3], Jared Becksfort[1], Jing Ma[3], Guangchun Song[3], Yongjin Li[3], Lei Wei[3], Jianmin Wang[8], Sheila Shurtleff[3], John Easton[8], David Zhao[1], Robert S Fulton[8], Lucinda L Fulton[8], David J Dooling[8], Bhavin Vadodaria[8], Heather L Mulder[8], Chunlao Tang[2], Kerri Ochoa[8], Charles G Mullighan[3], Amar Gajjar[4], Richard Kriwacki[10], Denise Sheer[11], Richard J Gilbertson[2], Elaine R Mardis[8], Richard K Wilson[8], James R Downing[3], Suzanne J Baker[2] & David W Ellison[3] for the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project

WHO'S NEXT

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





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HAARLEM
1 – 3 MAY 2014

Critical Question

How should clinically relevant molecular information be incorporated into nervous system tumor classification?

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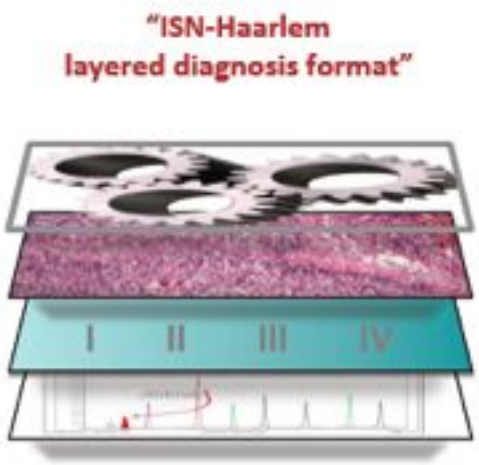
MISCELLANEOUS

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]

How to formulate a diagnosis?



Layer 1: Integrated Diagnosis (incorporating all tissue-based information)
Layer 2: Histological Classification
Layer 3: WHO Grade (reflecting natural history)
Layer 4: Molecular Information

Thank You