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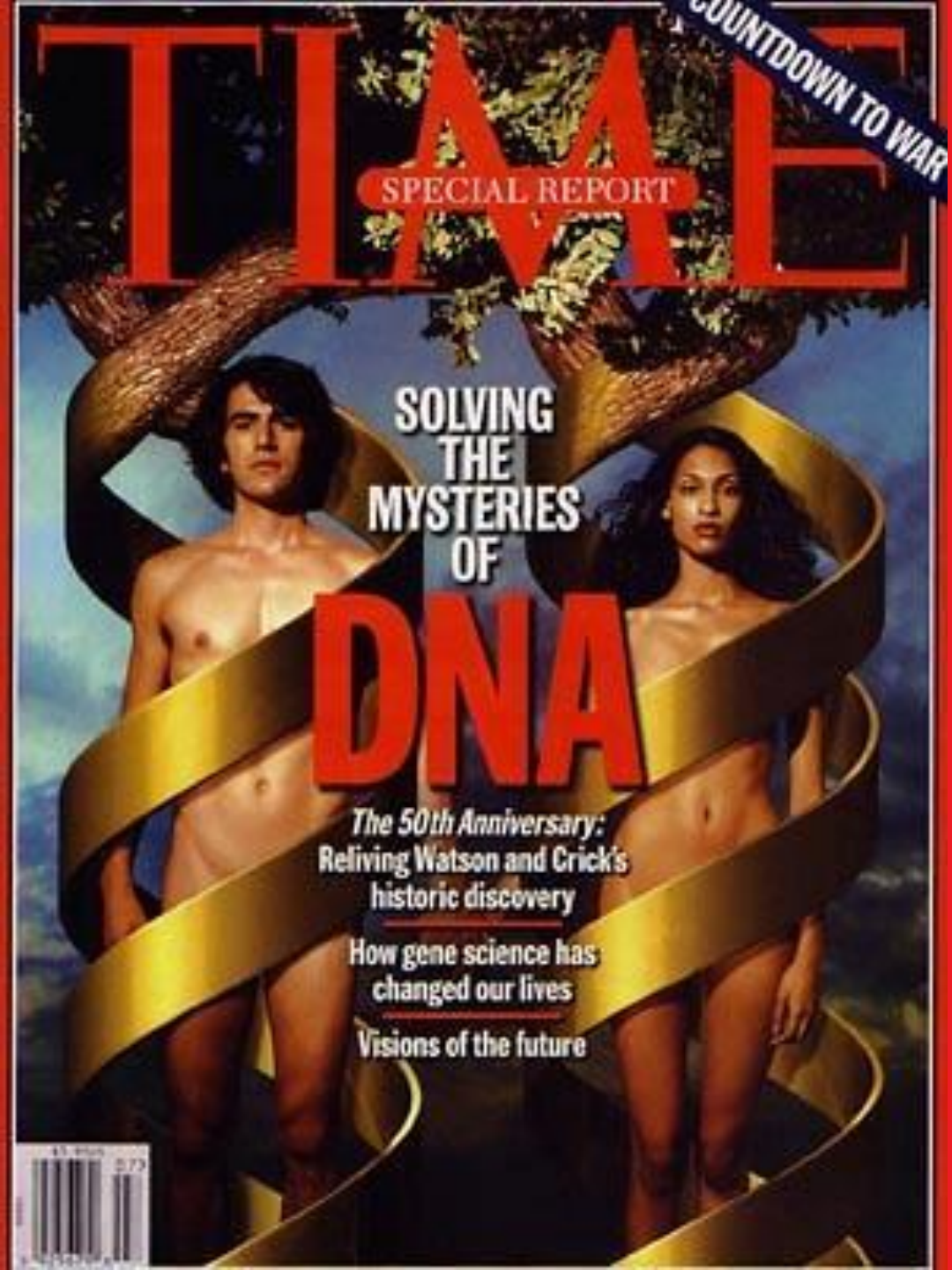
What Every Neuropathologist Needs to Know:

New Immunomarkers for Practical Diagnosis in Surgical Neuropathology

Arie Perry, M.D.
Director, Neuropathology

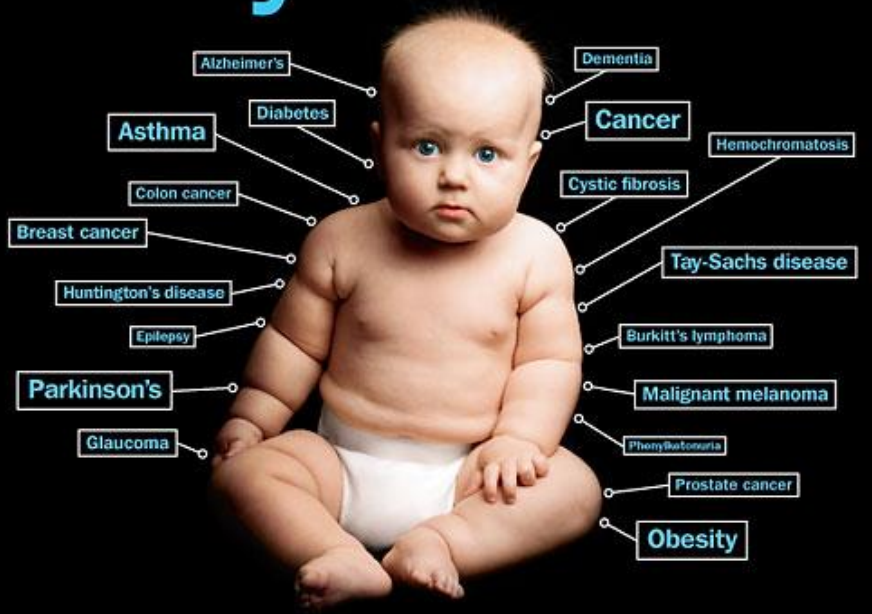


DECEMBER 24, 2012

Egypt Divided / Pot's Big Moment / Best of 2012 Movies, Music, Books & More

TIME

Want to Know My Future?



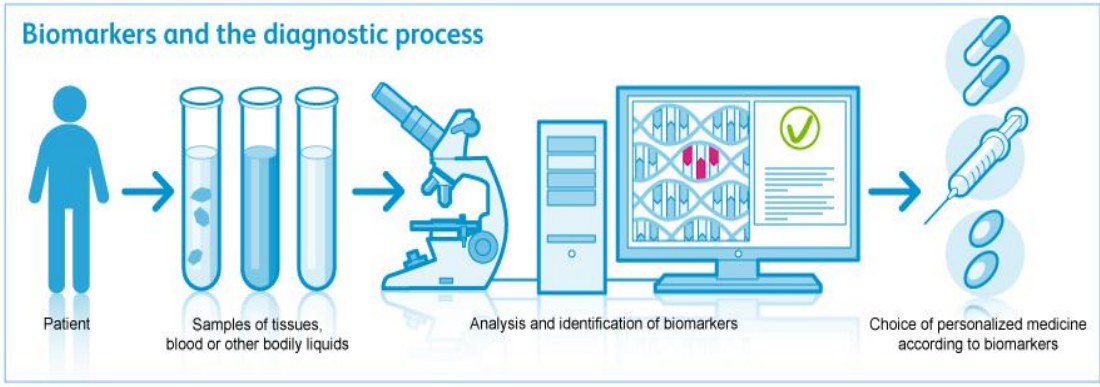
New genetic tests can point to risks—but not always a cure

BY BONNIE ROCHMAN

UCSF University of California San Francisco

BIOMARKERS

- **Types**
  - Diagnostic
  - Prognostic
  - Predictive



- **Practicality issues**
  - Cost and ease of implementation
  - **IHC** vs. FISH vs. PCR vs. genomics
  - Reimbursement

Brain Pathol, 2014
24:429-435

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]

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[15] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester MN, USA
[16] Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Canada
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[20] Department of Pathology, University of Virginia School of Medicine, Charlottesville VA, USA
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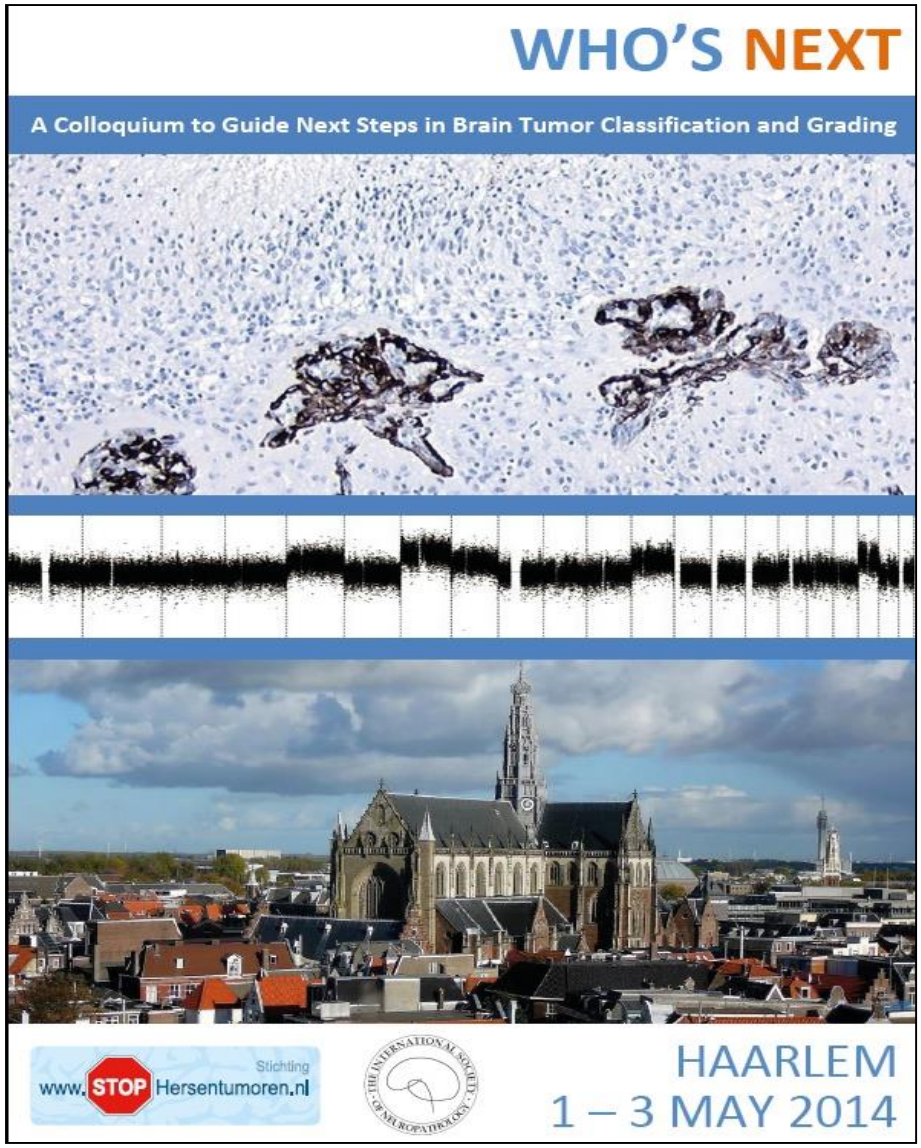
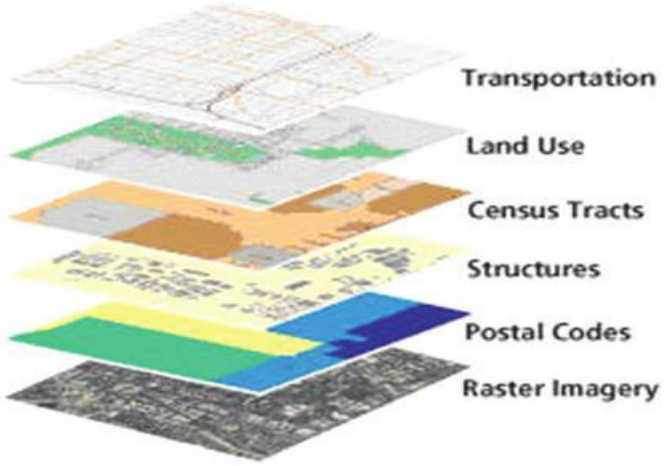
[29] Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands
[30] Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands



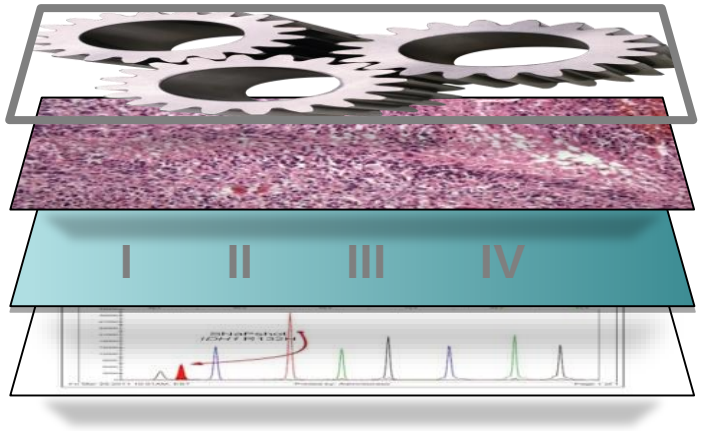
ISN-Haarlem format of “layered diagnoses”

- **Integrated Diagnosis** (incorporating all aspects of tissue diagnosis)
- Histological Classification
- WHO Grade (natural history)
- Molecular information (see parameters from previous slide)

Google Maps: GIS layers
Organized by Geographical Positioning



“ISN-Haarlem layered diagnosis format”



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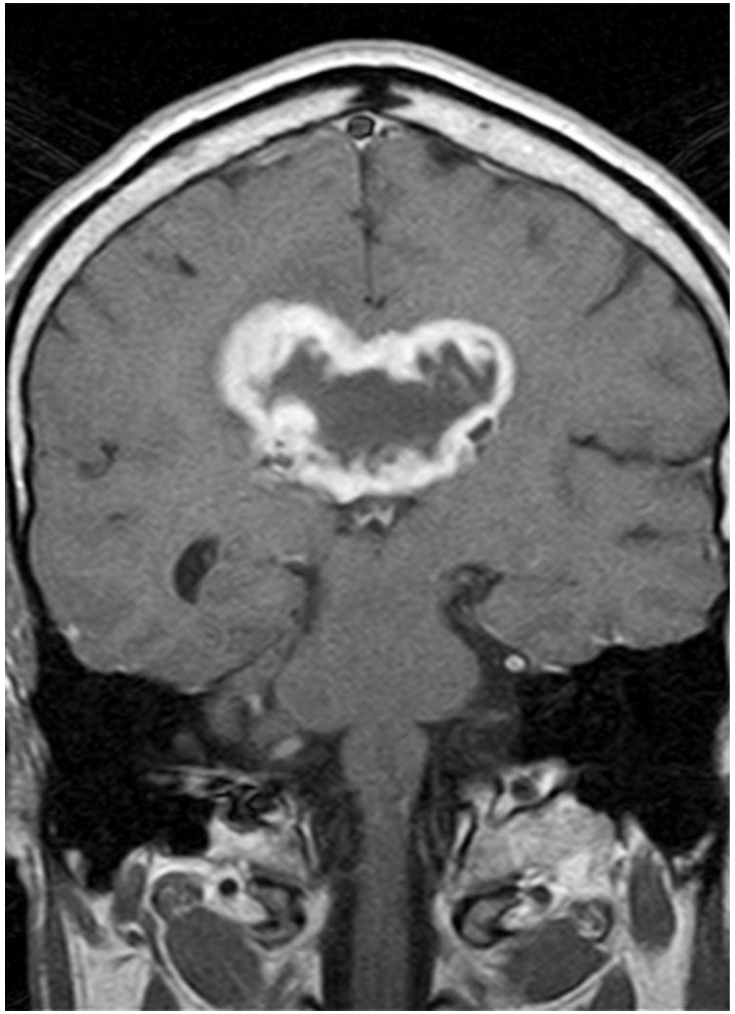
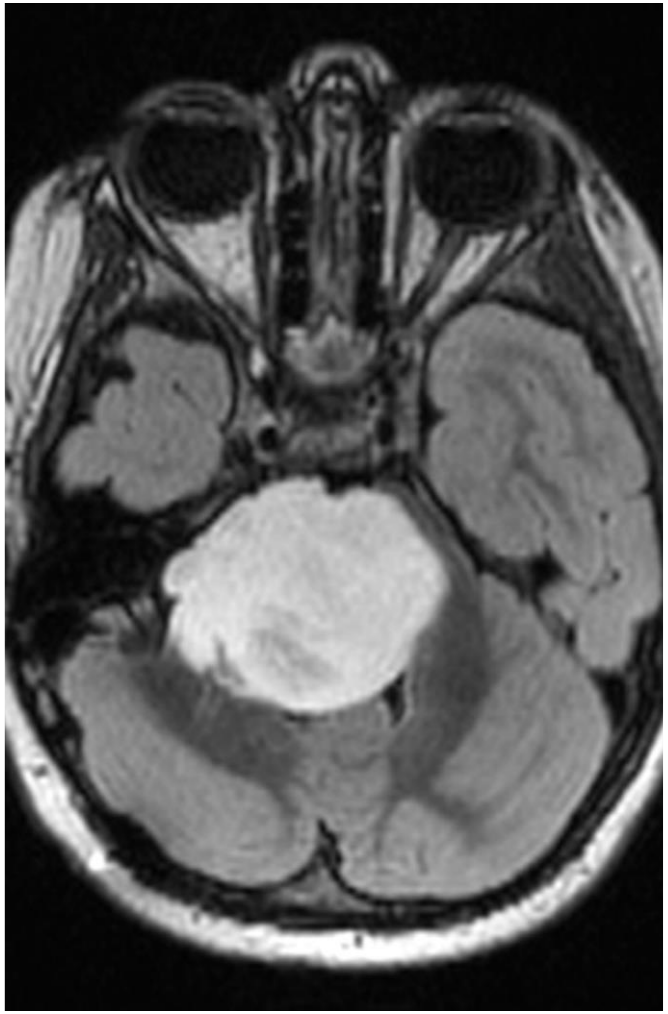
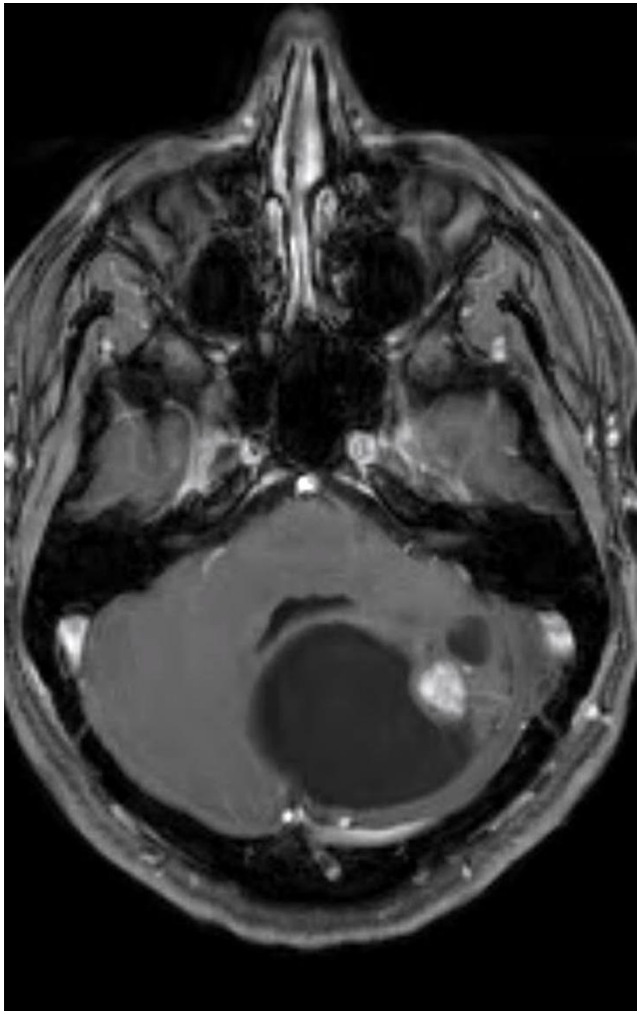
GLIOMAS







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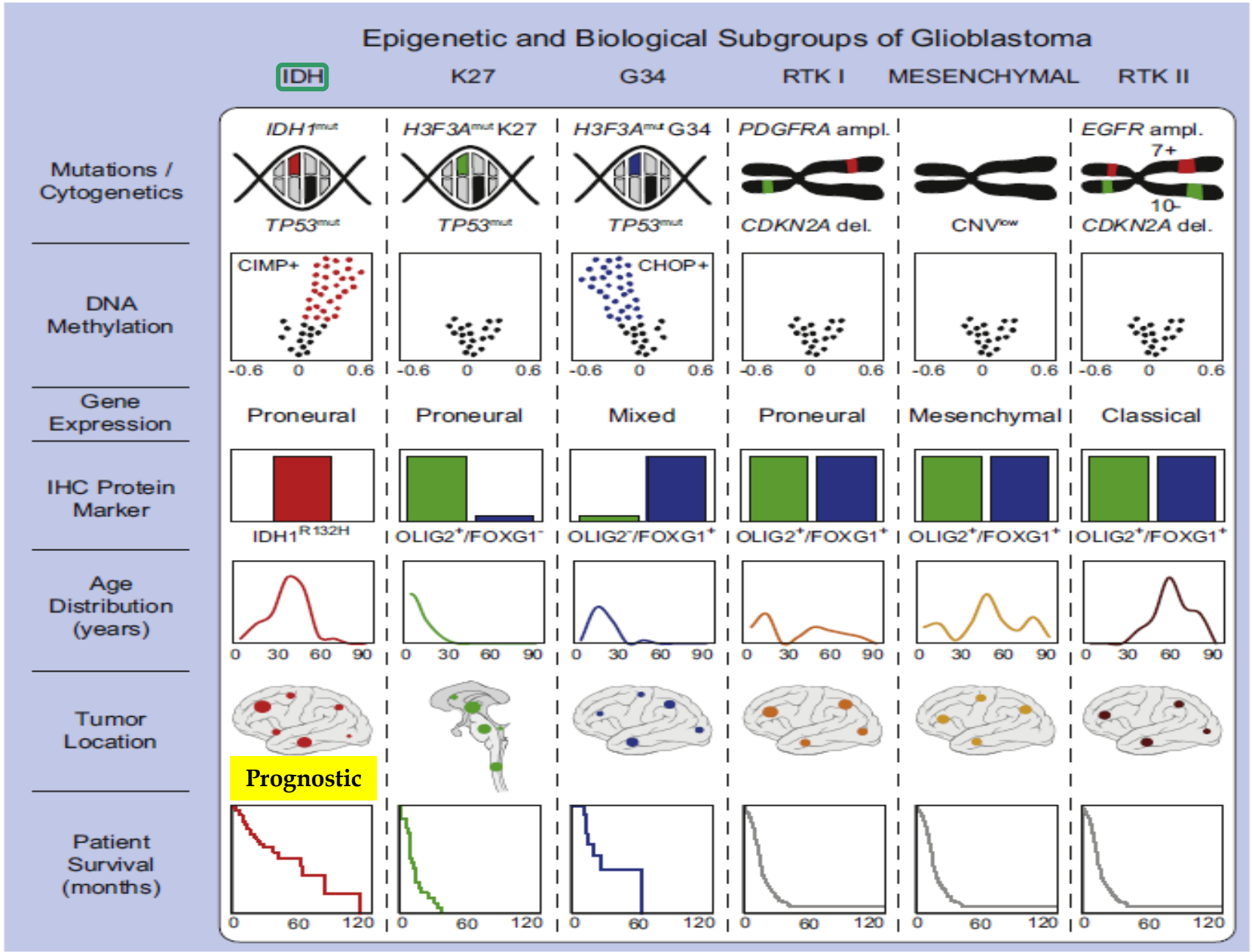
Sturm et al., Cancer Cell 2012;22:425-437



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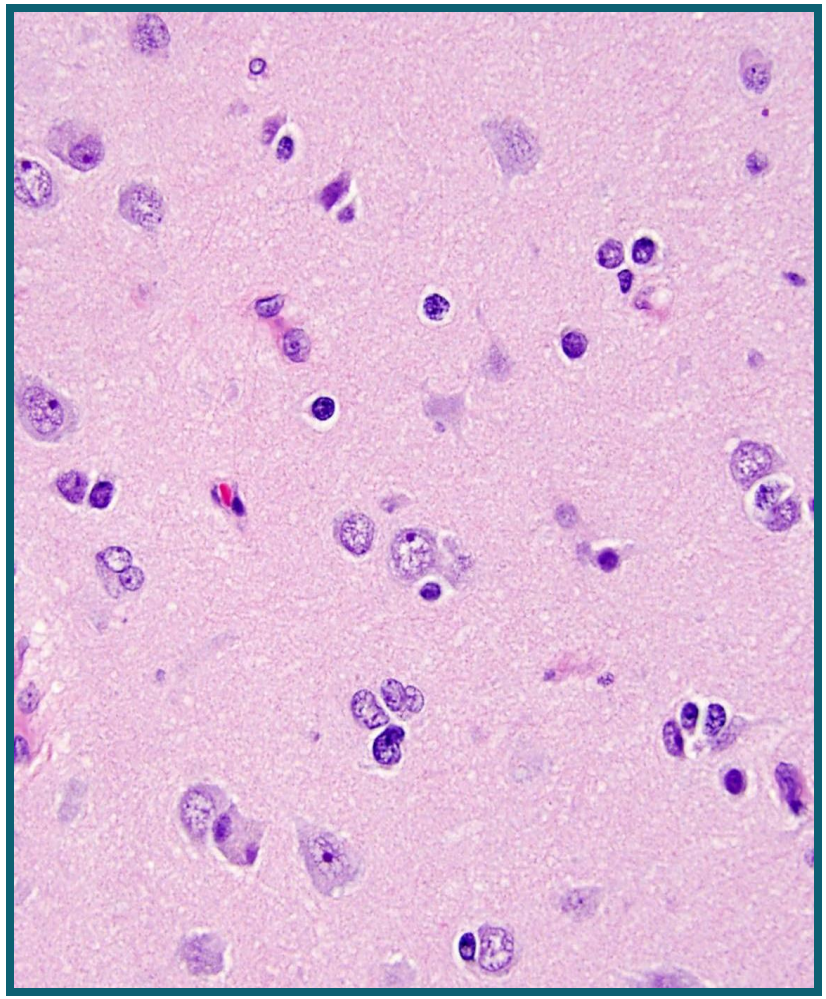
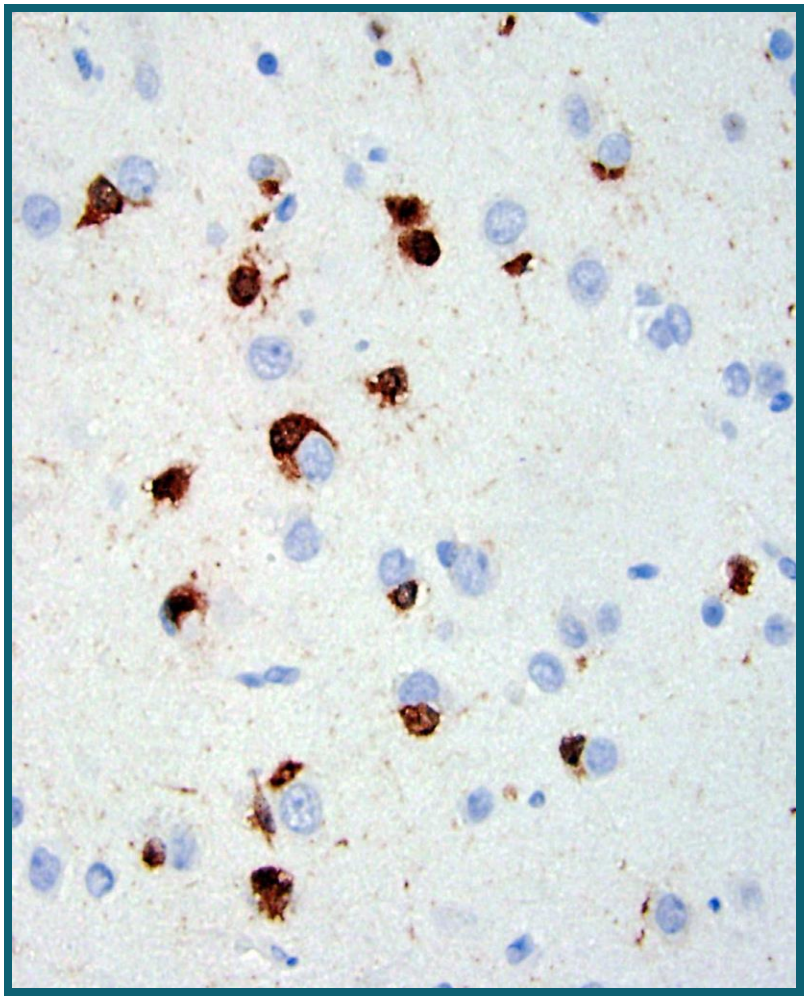
IDH-1 R132H IHC (90% of IDHm)





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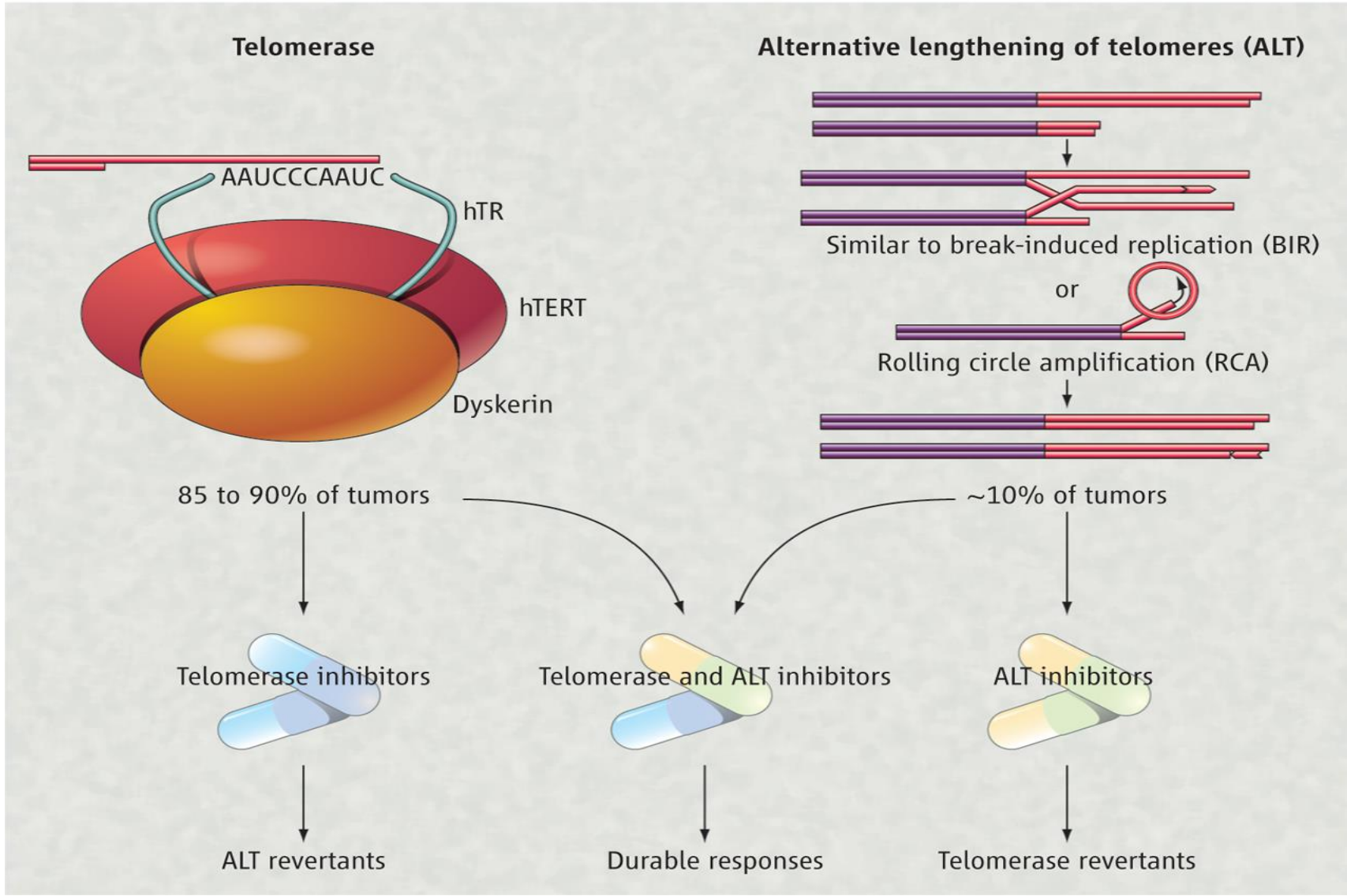
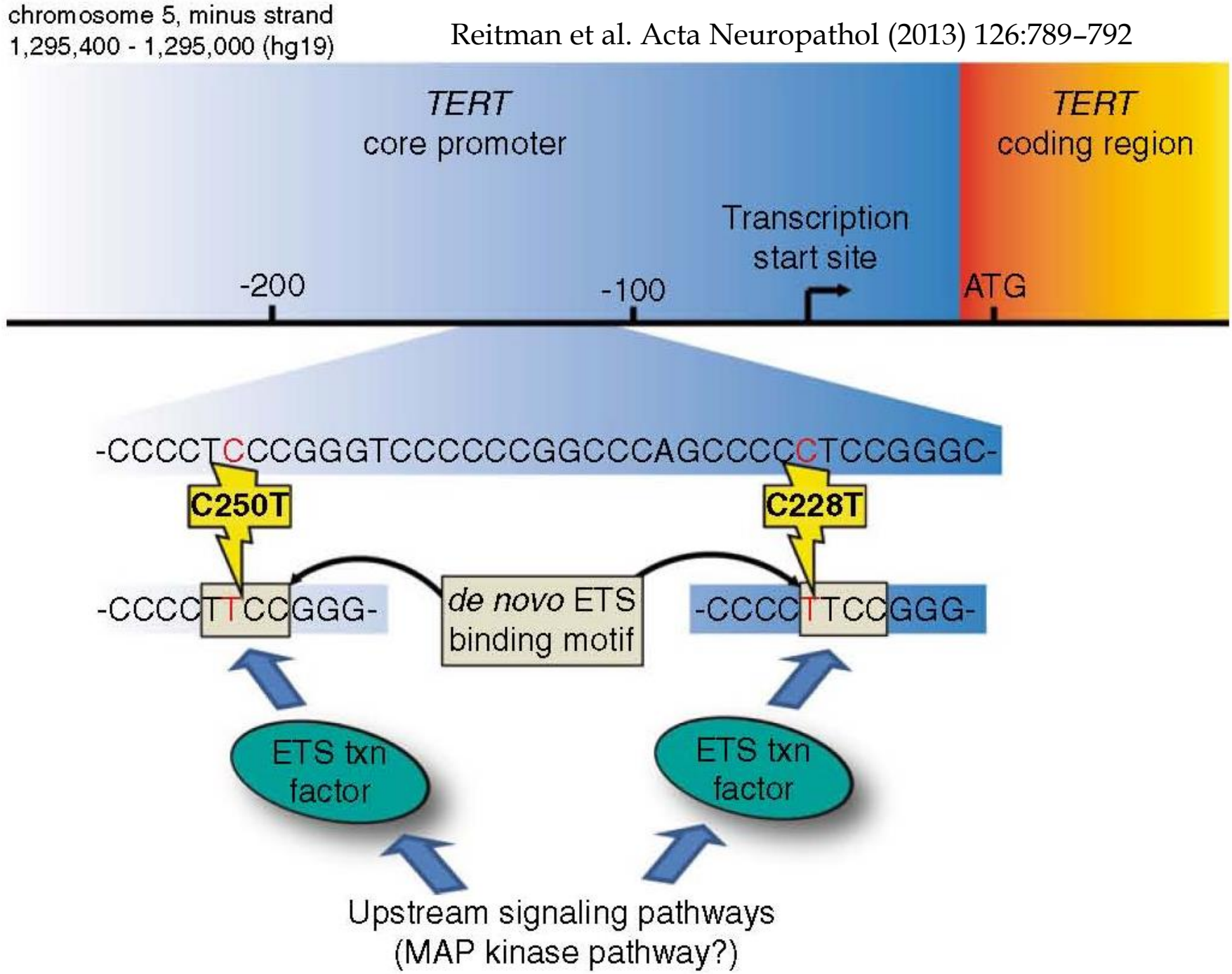
DIAGNOSTIC EXAMPLE OF HISTOLOGIC MIMICRY

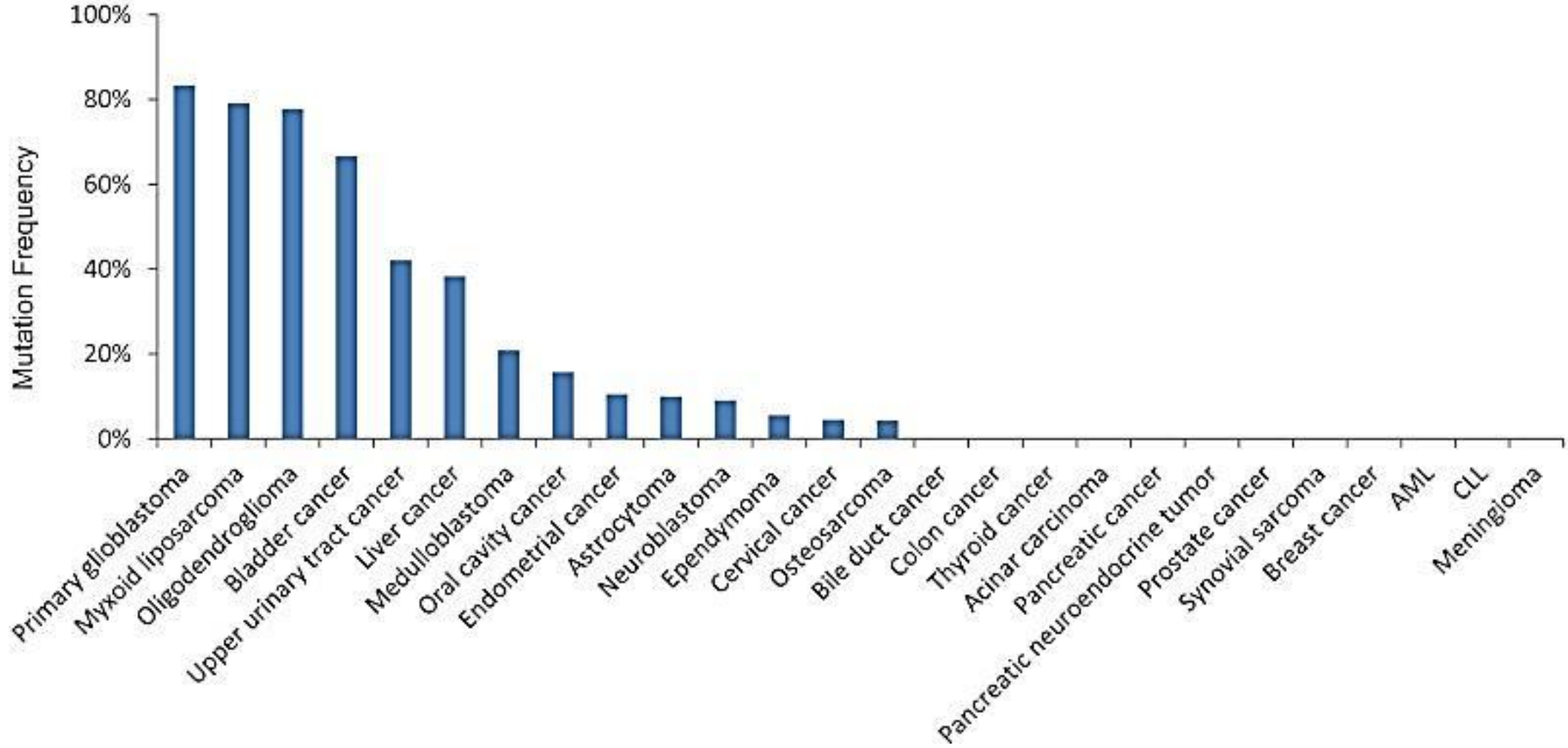
- **AO (IDHm and 1p/19q codeletion: 100%)**
  - Average survival 15 years if treated with combined chemo and radiation
  - What about chemo alone up front?
- **SC-GBM (IDHwt, EGFR-AMP 70%, -10q 95%)**
  - Average survival 1 year
  - Typically treated with combined radiochemotherapy
  - Different clinical trials than the high-grade oligodendrogliomas

CANCER CELLS ESCAPING SENESCENCE



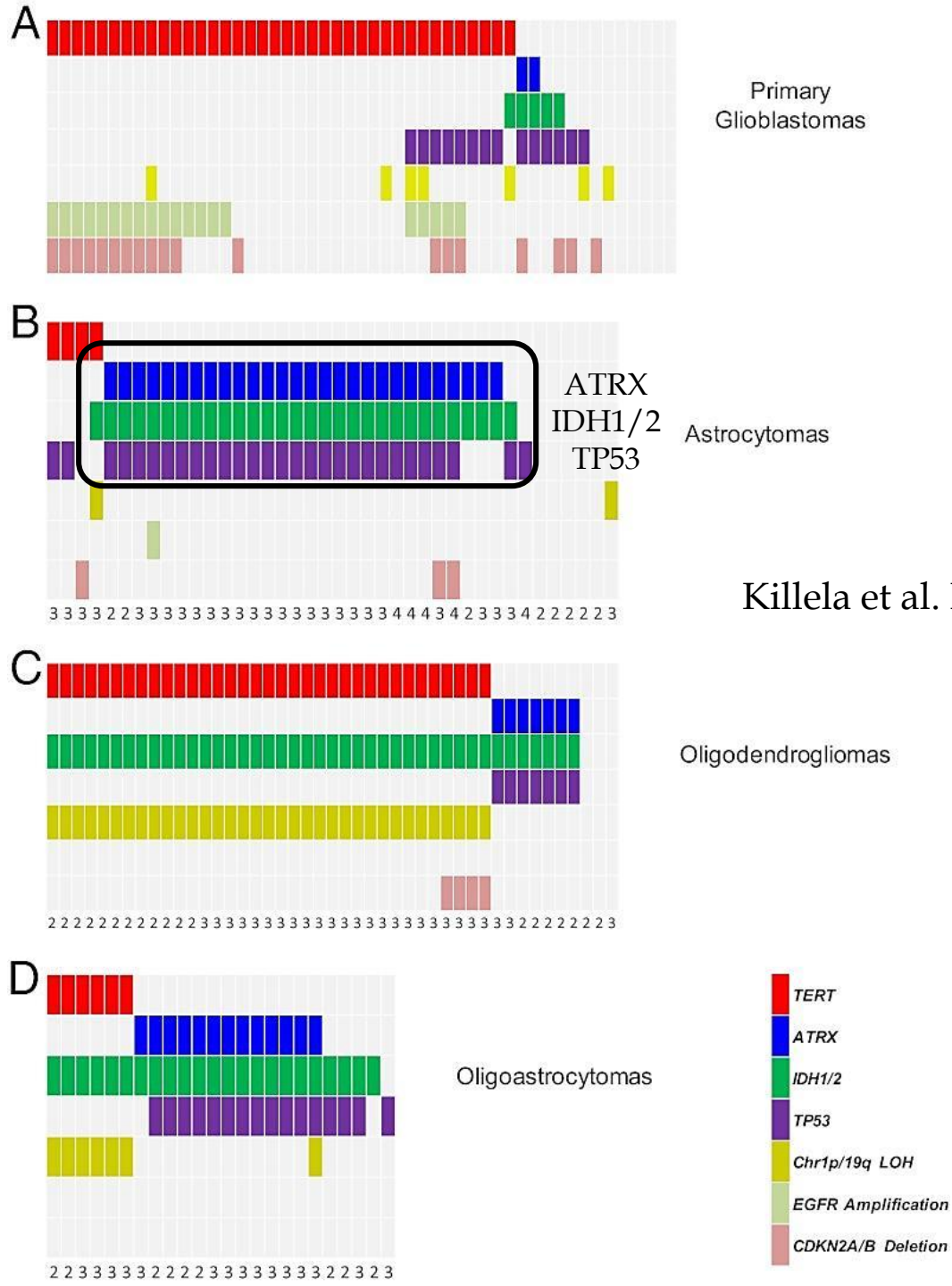
Shay JW et al. Science 15:1388-1390, 2012


chromosome 5, minus strand
1,295,400 - 1,295,000 (hg19)
Reitman et al. Acta Neuropathol (2013) 126:789–792
TERT
core promoter
TERT
coding region
Transcription
start site
-200
-100
ATG
-CCCCTCCCGGGTCCCCCCCGGCCCAGCCCCCTCCGGGC-
C250T
C228T
-CCCCTTCCGGG-
de novo ETS
binding motif
-CCCCTTCCGGG-
ETS txn
factor
ETS txn
factor
Upstream signaling pathways
(MAP kinase pathway?)



Killela et al. PNAS 2013; 110: 6021–6026

ADULT GLIOMAS



Killela et al. PNAS 2013; 110: 6021–6026

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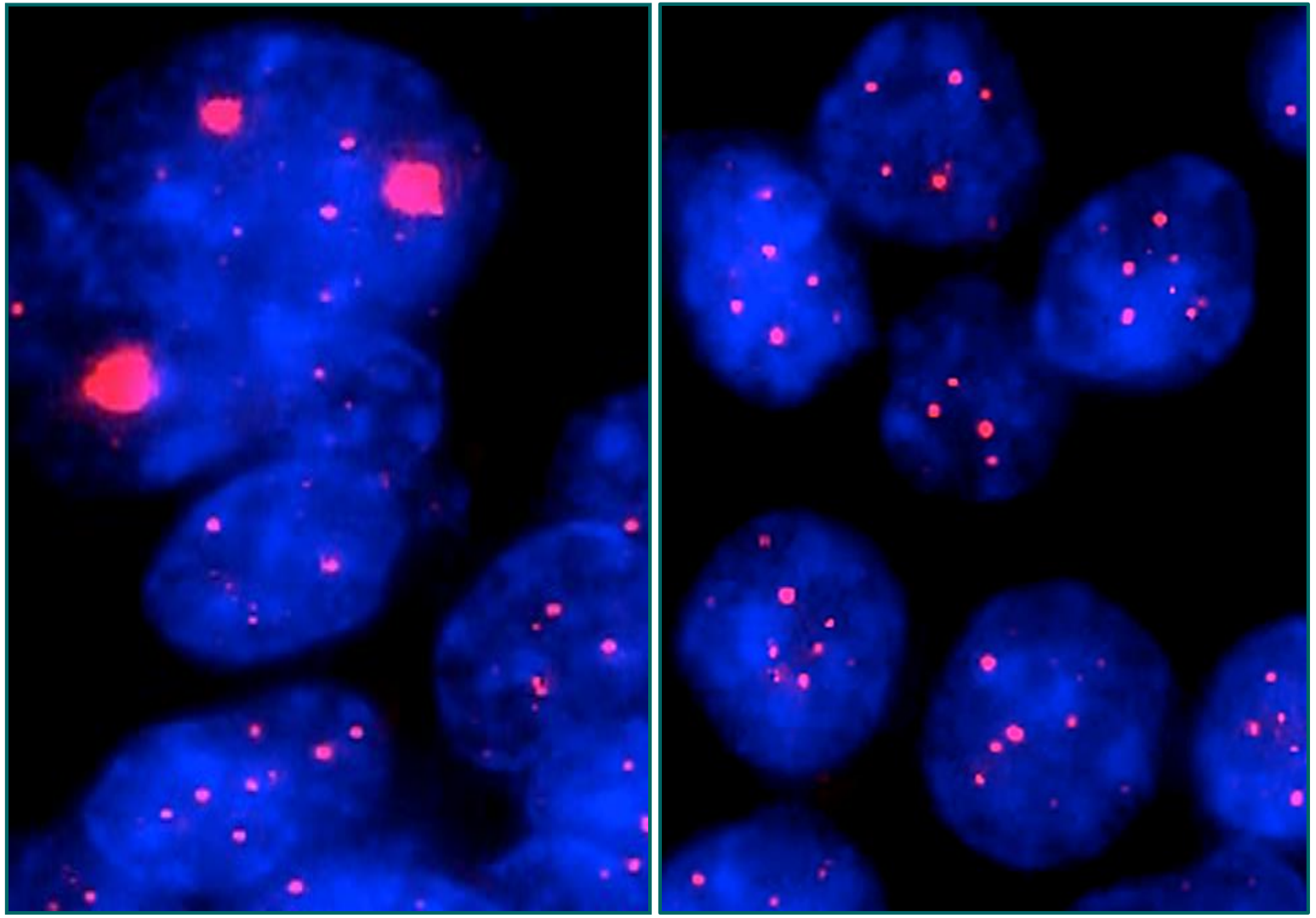
ALT FISH



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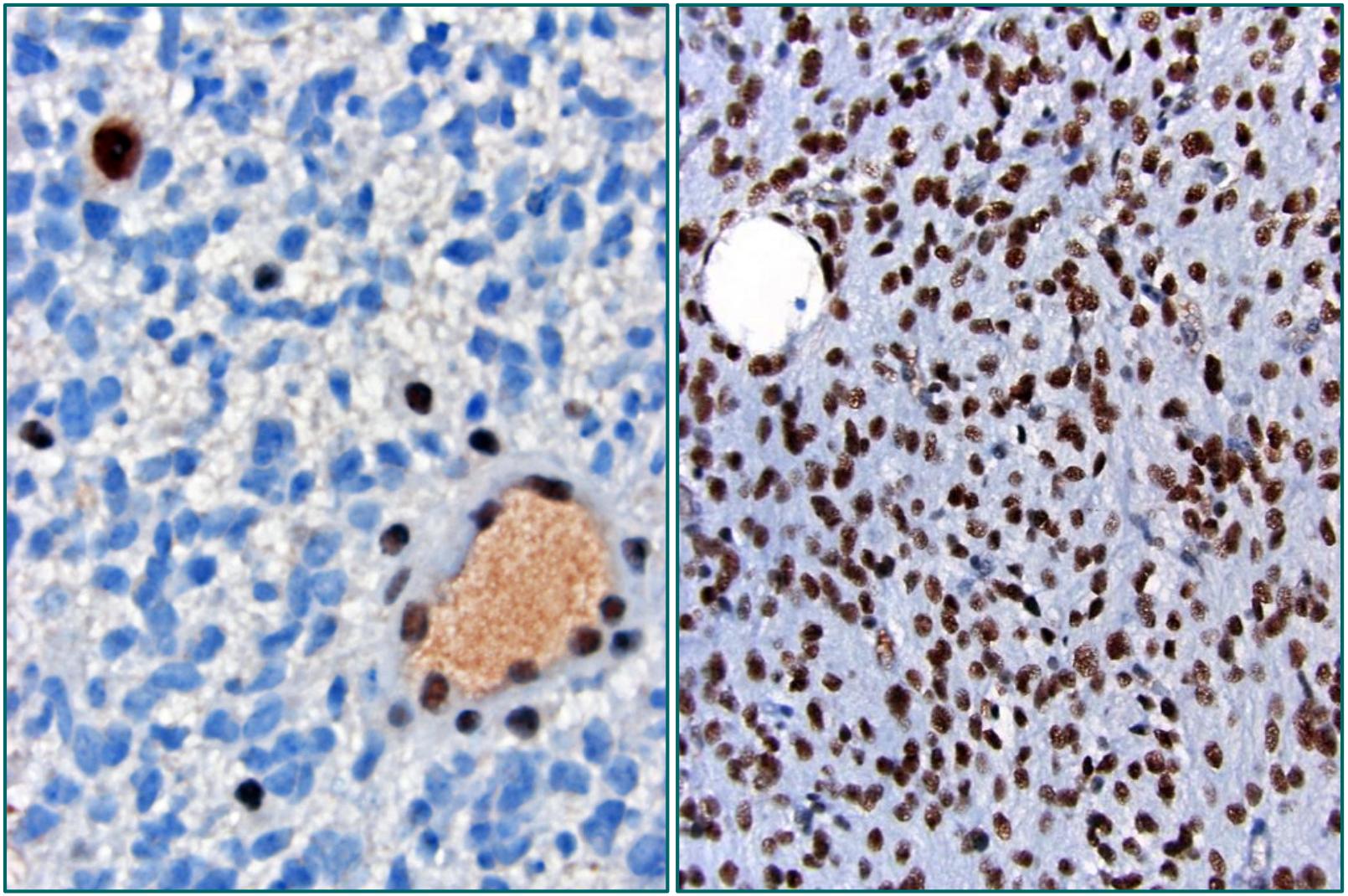
ATRX IHC



The alternative lengthening of telomere phenotype is significantly associated with loss of ATRX expression in high-grade pediatric and adult astrocytomas: a multi-institutional study of 214 astrocytomas

Malak Abedalthagafi[1,2], Joanna J Phillips[1,3], Grace E Kim[2], Sabine Mueller[4], Daphne A Haas-Kogen[5], Roxanne E Marshall[1], Sidney E Croul[6], Mariarita R Santi[7], Jing Cheng[8], Shengmei Zhou[9], Lisa M Sullivan[7], Maria Martinez-Lage[7], Alexander R Judkins[9] and Arie Perry[1,3]

[1]Division of Neuropathology, Department of Pathology, University of California, San Francisco, San Francisco, CA, USA; [2]Division of Surgical Pathology, Department of Pathology, University of California, San Francisco, San Francisco, CA, USA; [3]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA; [4]Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA; [5]Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA, USA; [6]Department of Lab Medicine and Pathobiology, University of Toronto, Toronto, Canada; [7]Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [8]Division of Epidemiology and Biostatistics, The Clinical and Translational Science Institute (CTSI), University of California, San Francisco (UCSF), San Francisco, CA, USA and [9]Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA

Loss-of-function of alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein leads to a phenotype called alternative lengthening of telomeres (ALT) in some tumors. High-grade astrocytomas comprise a heterogeneous group of central nervous system tumors. We examined a large cohort of adult (91) and pediatric ($n=88$) high-grade astrocytomas as well as lower grade forms ($n=35$) for immunohistochemical loss of ATRX protein expression and the presence of ALT using telomere-specific fluorescence *in situ* hybridization, with further correlation to other known genetic alterations. We found that in pediatric high-grade astrocytomas, 29.6% of tumors were positive for ALT and 24.5% were immunonegative for the ATRX protein, these two alterations being highly associated with one another ($P<0.0001$). In adult high-grade astrocytomas, 26.4% of tumors were similarly positive for ALT, including 80% of ATRX protein immunonegative cases ($P<0.0001$). Similar frequencies were found in 11 adult low-grade astrocytomas, whereas all 24 pilocytic astrocytomas were negative for ALT. We did not find any significant correlations between isocitrate dehydrogenase status and either ALT positivity or ATRX protein expression in our adult high-grade astrocytomas. In both cohorts, however, the ALT positive high-grade astrocytomas showed more frequent amplification of the platelet-derived growth factor receptor alpha gene (*PDGFRA*; 45% and 50%, respectively) than the ALT negative counterparts (18% and 26%; $P=0.03$ for each). In summary, our data show that the ALT and ATRX protein alterations are common in both pediatric and adult high-grade astrocytomas, often with associated *PDGFRA* gene amplification.

Modern Pathology (2013) **26**, 1425–1432; doi:10.1038/modpathol.2013.90; published online 14 June 2013

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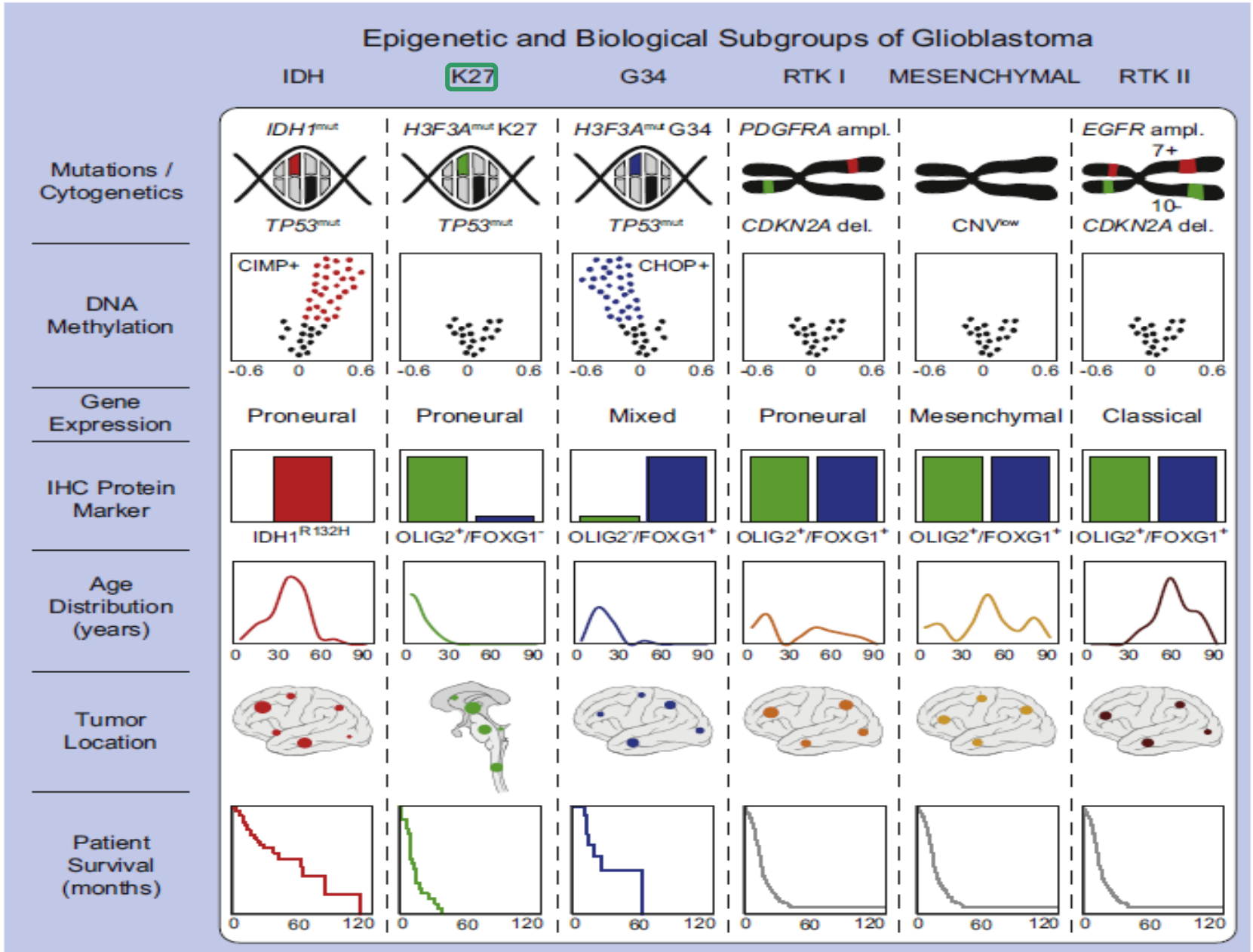
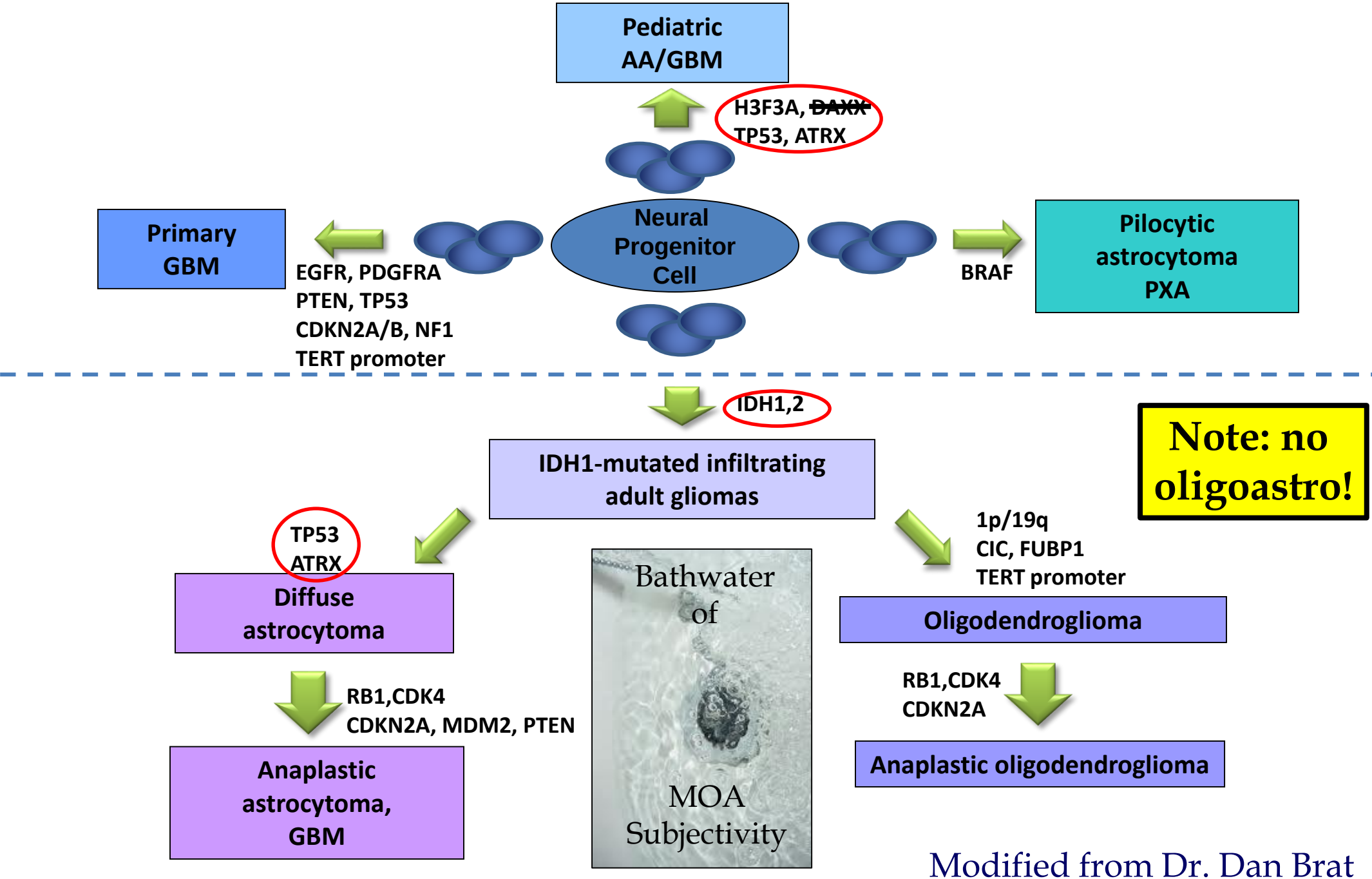
Sturm et al., Cancer Cell 2012;22:425-437





Modified from Dr. Dan Brat

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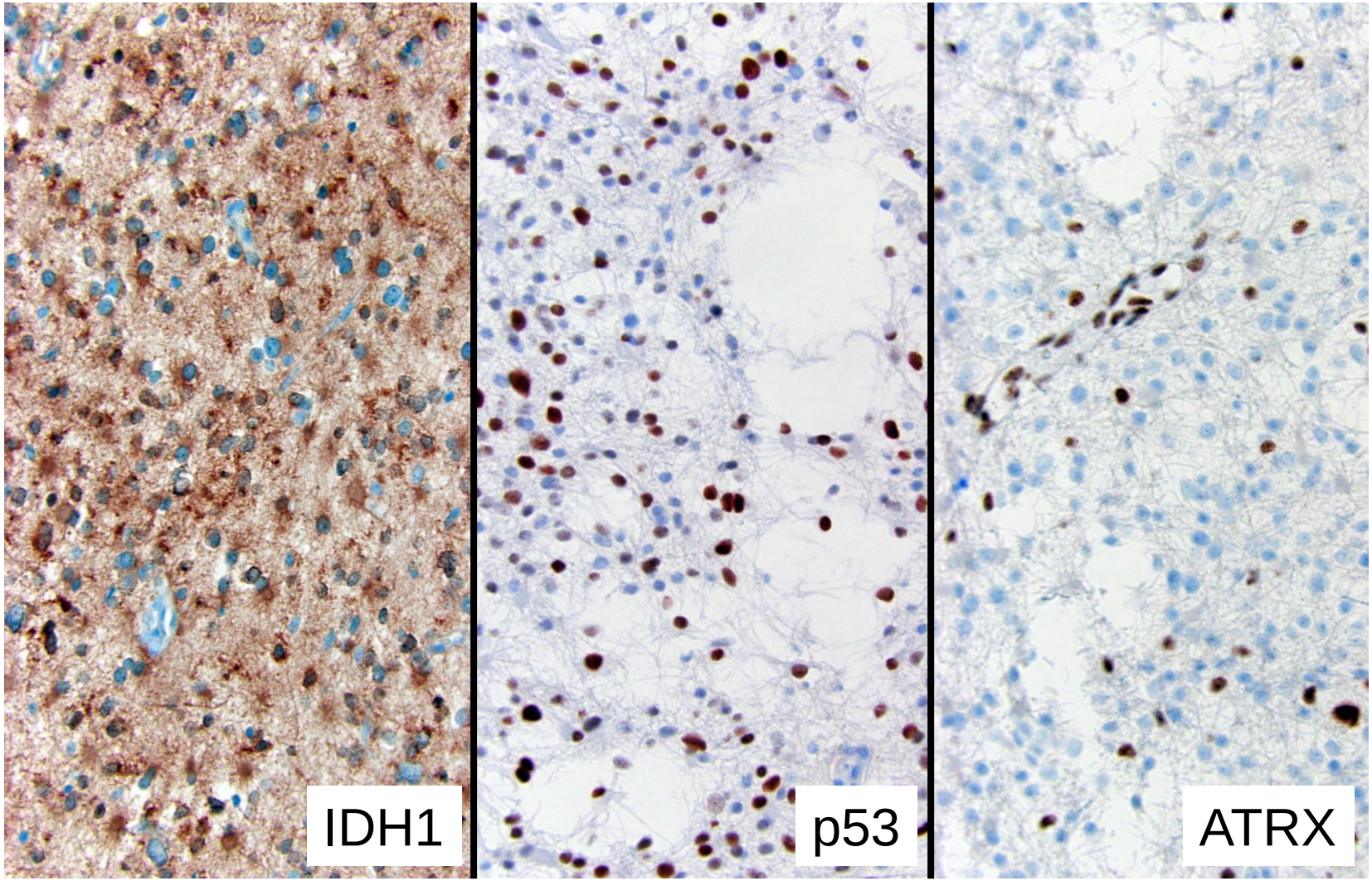
ADULT TYPE ASTROCYTOMA



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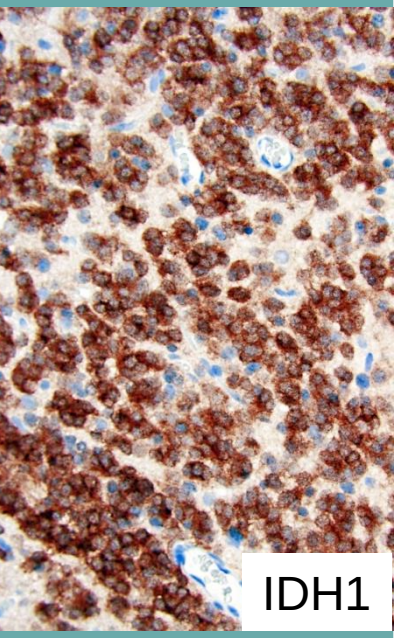
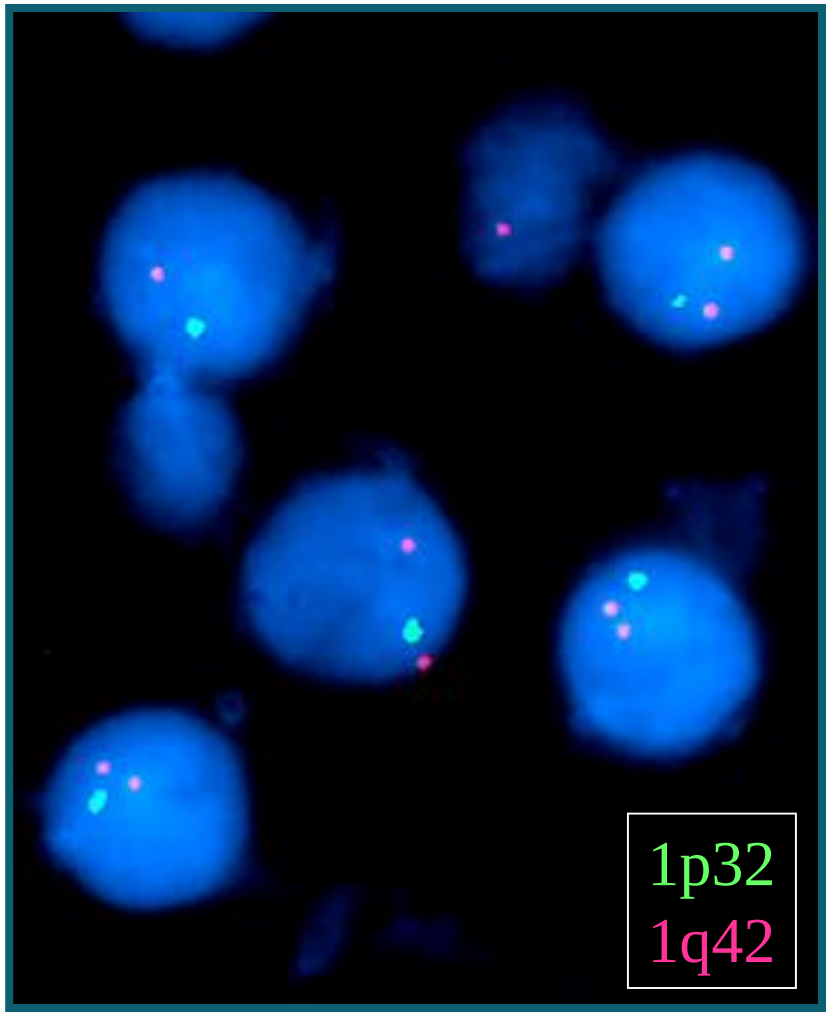
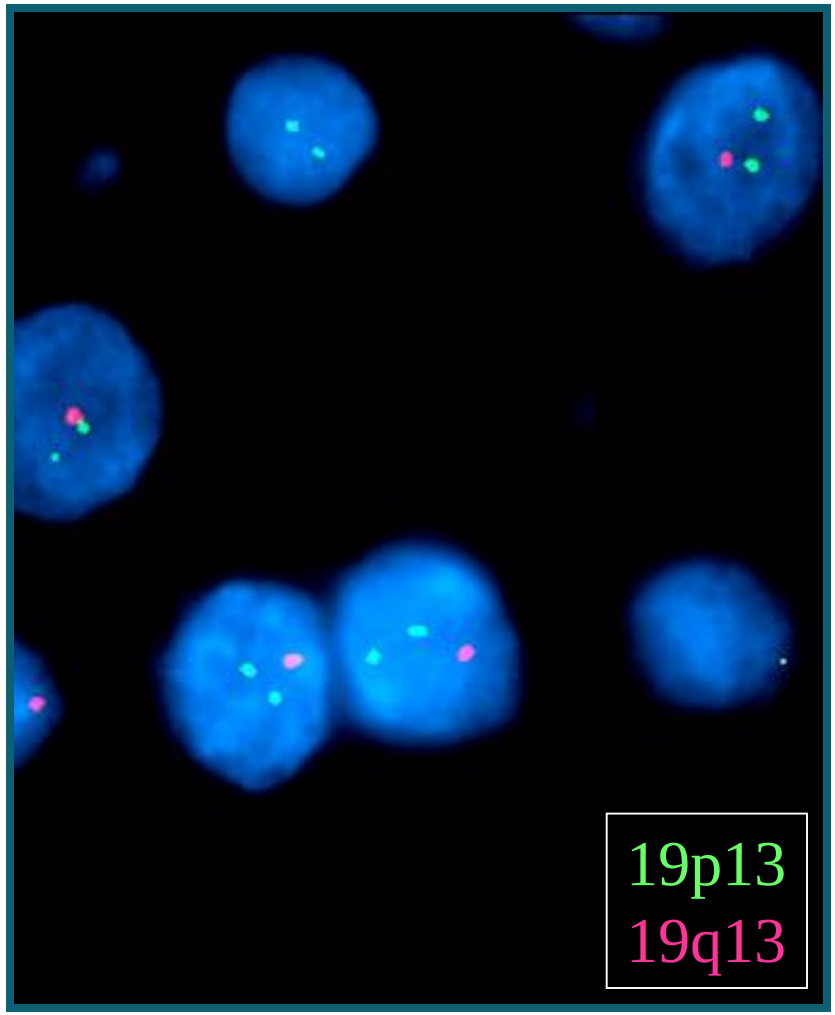
ADULT TYPE OLIGODENDROGLIOMA







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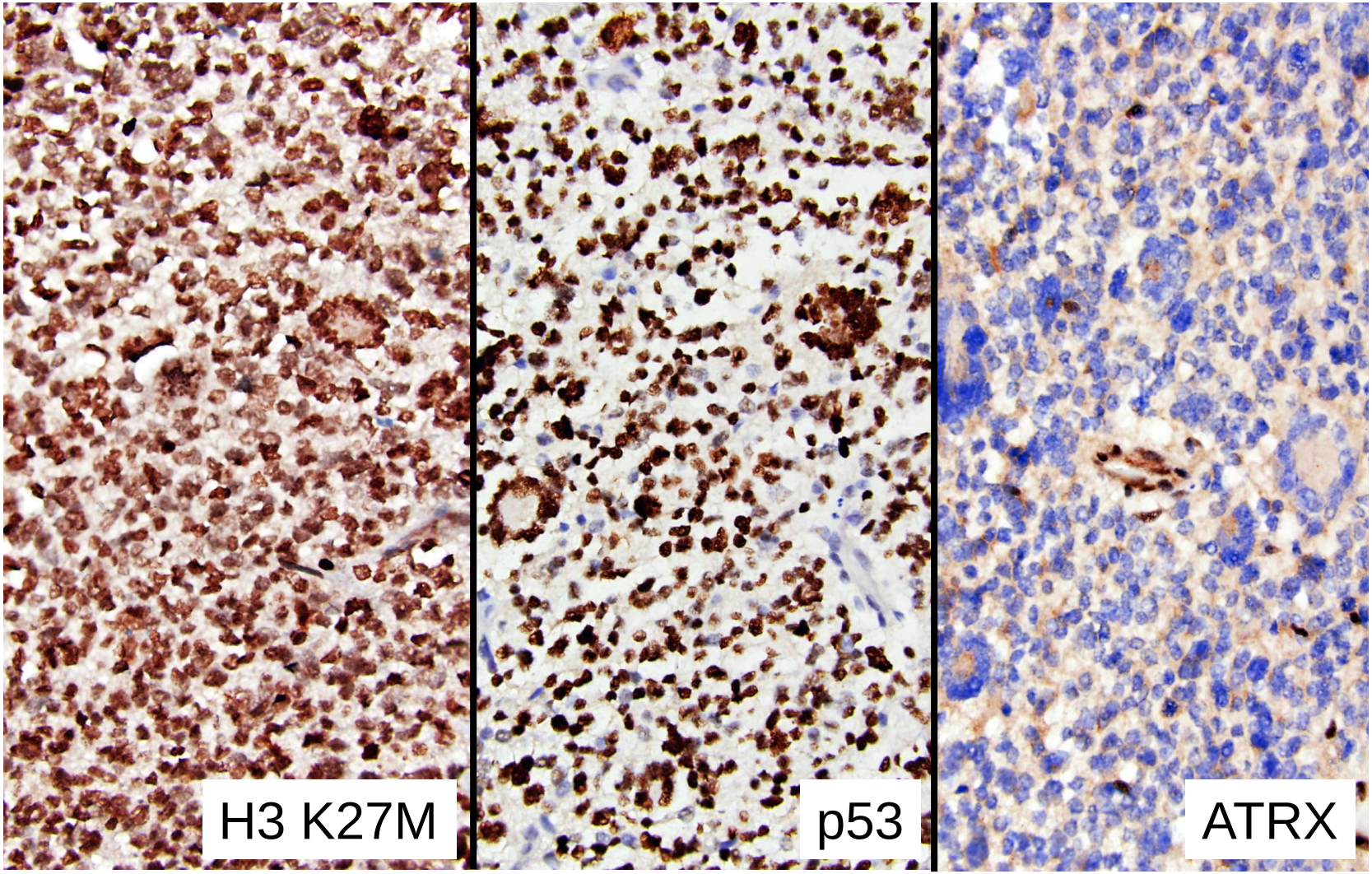
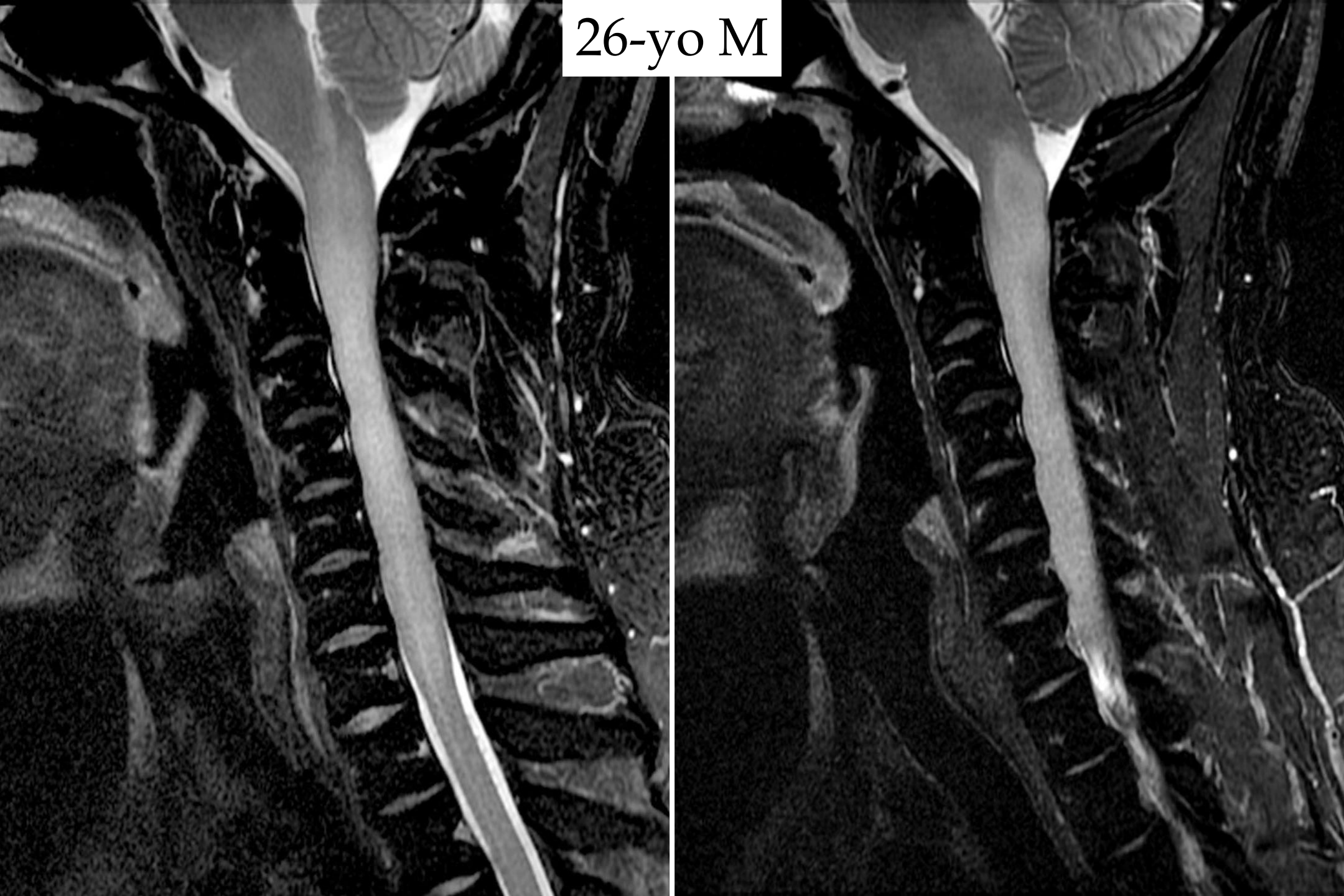
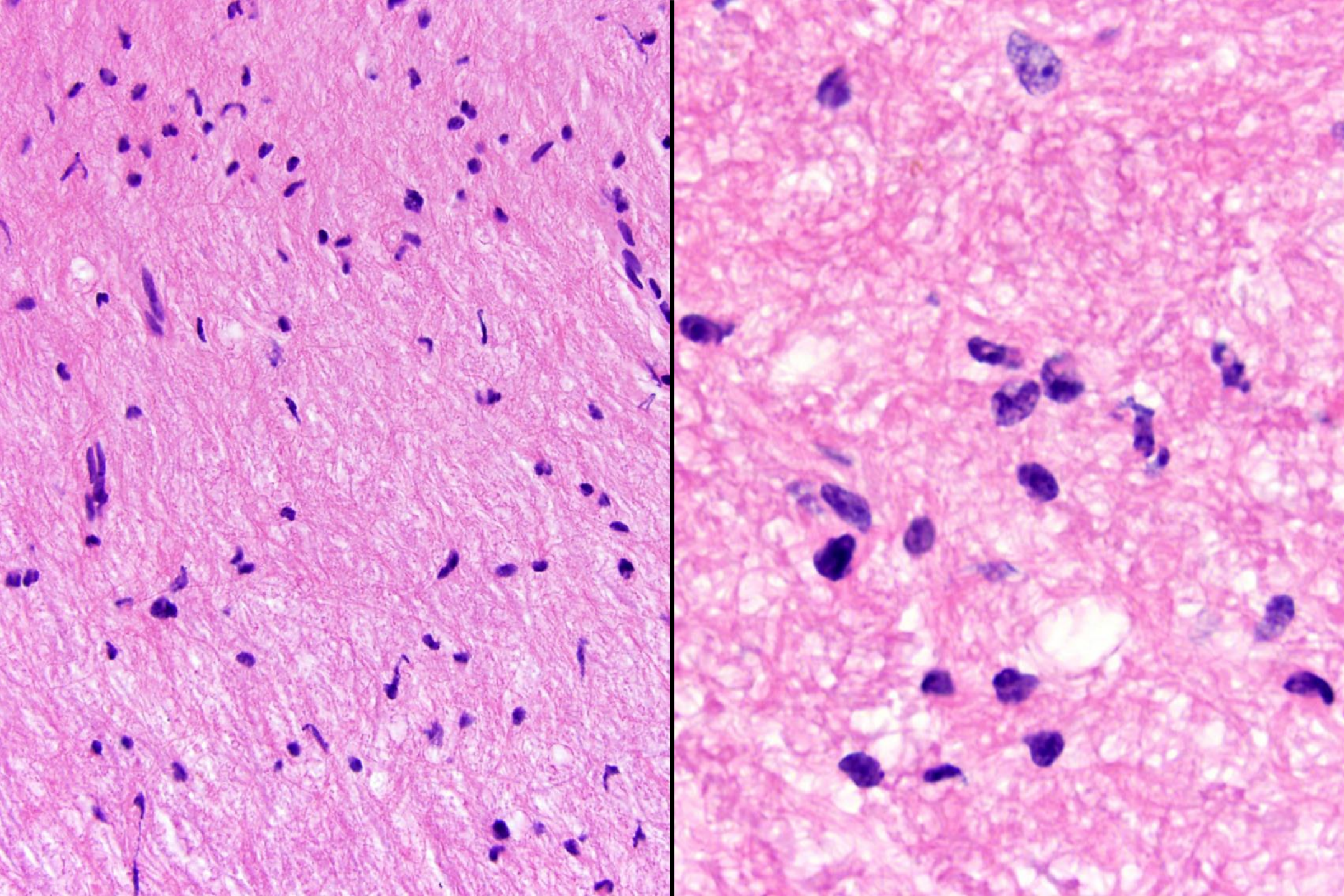
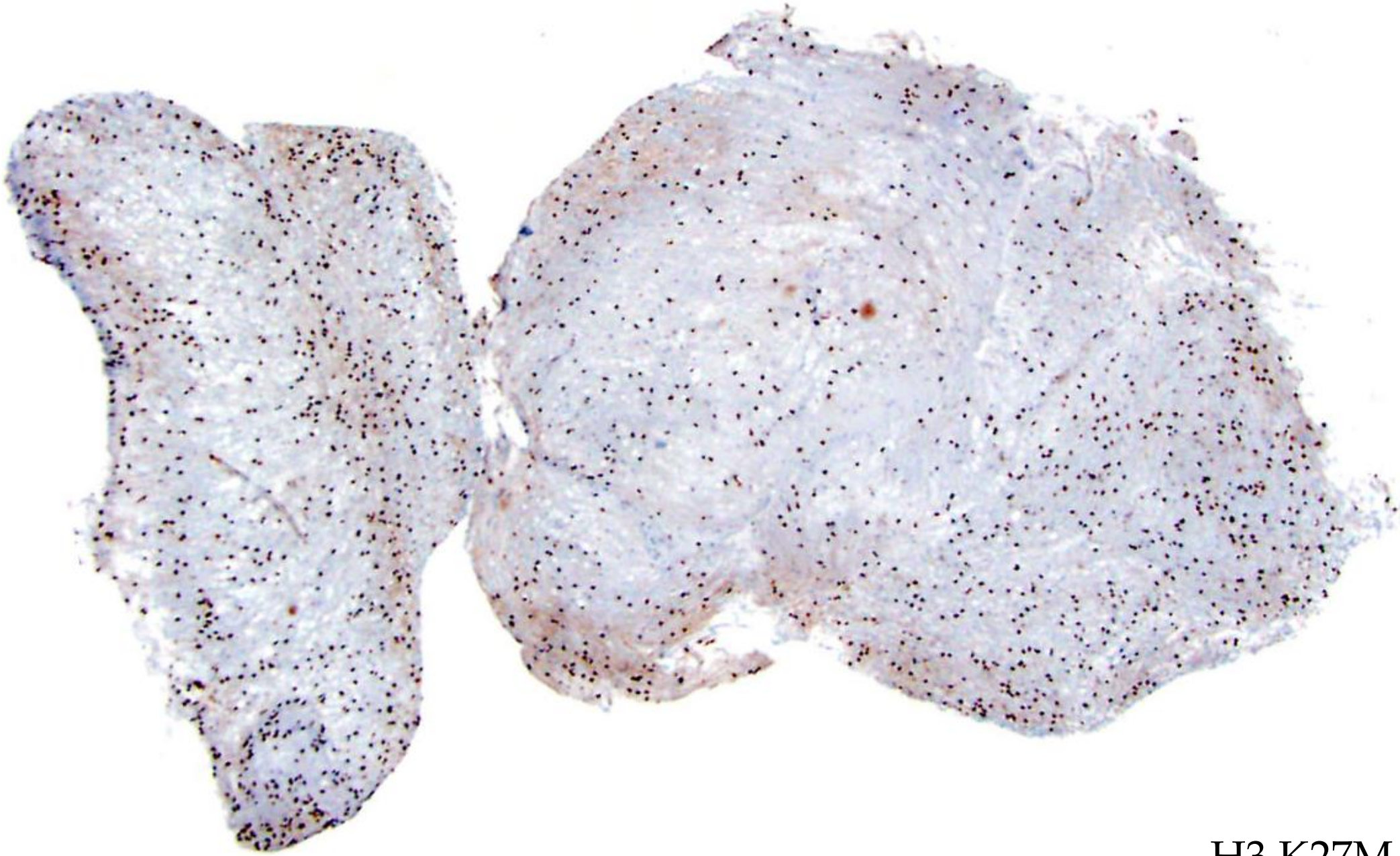
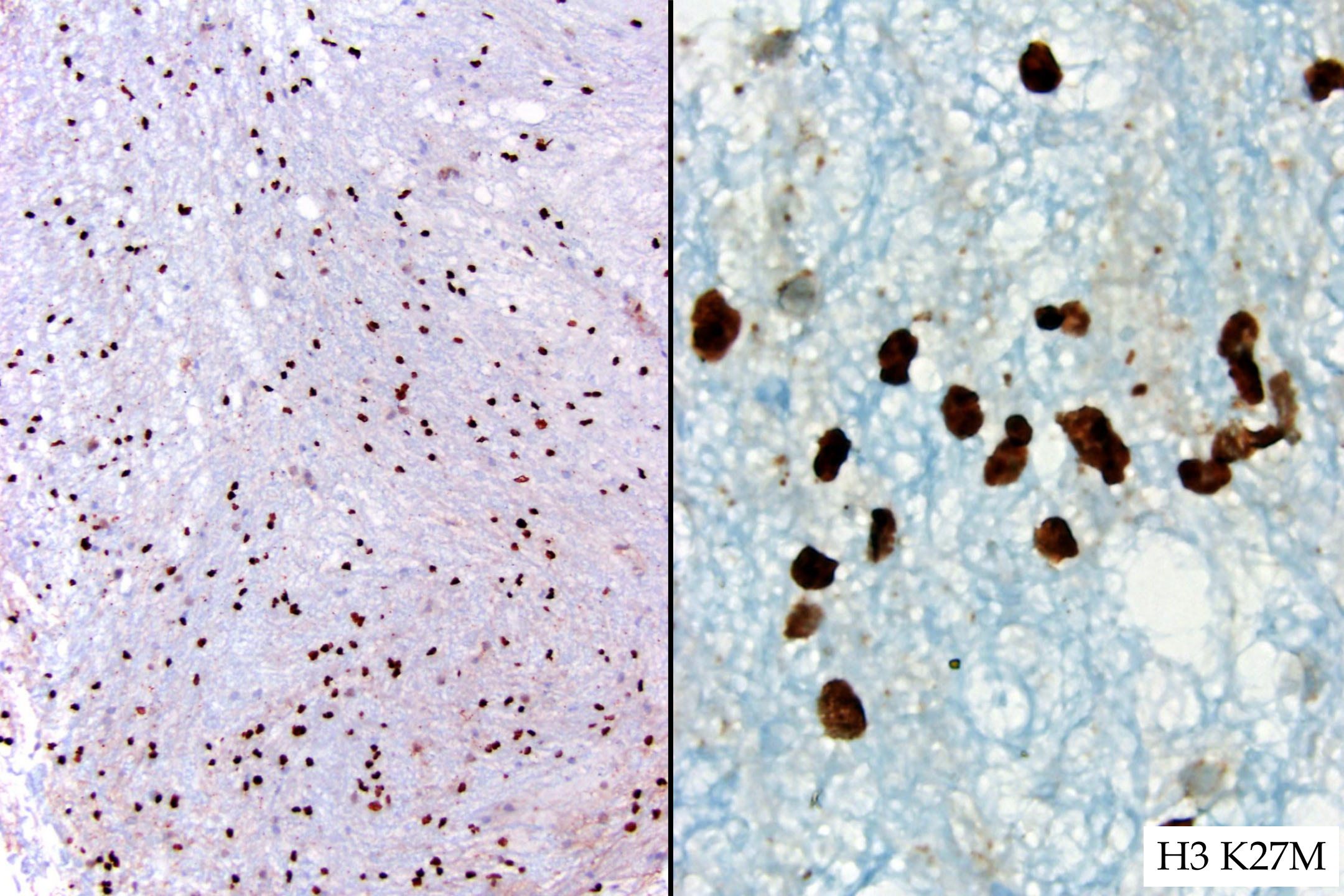
PEDI MIDLINE HGA (DIPG, THAL, SC)




26-yo M




H3 K27M


H3 K27M

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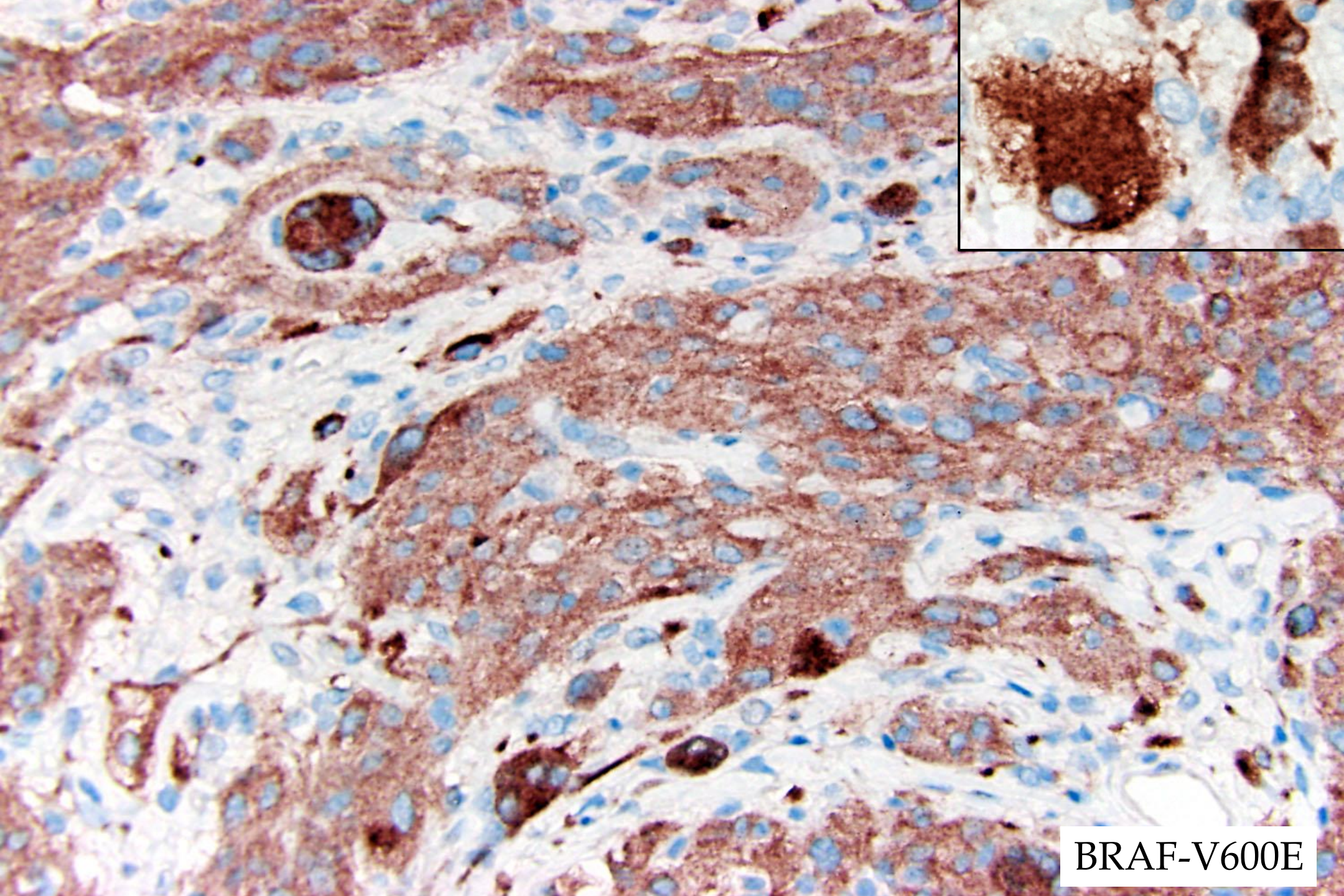
OTHER GLIOMA BIOMARKERS

- **BRAF-KIAA1549 duplication/fusion**
  - pilocytic astrocytomas (~70% in cerebellum; less in other locations)
  - Diagnostic and predictive (MEK inhibitors?)
  - FISH or PCR: No IHC surrogates
- **BRAF V600E mutation:**
  - PXA (~67%), GG (~20%), PA (~10%), HGGs (5-10%), E-GBM (50%)
  - Predictive only: BRAF inhibitors, especially in recurrent or disseminated cases?


BRAF-V600E

VIRTUALLY ‘ALL’ PEDIATRIC BRAIN TUMORS

Pediatric Neuro-Oncologist

Pediatric Pathologist/Neuropathologist

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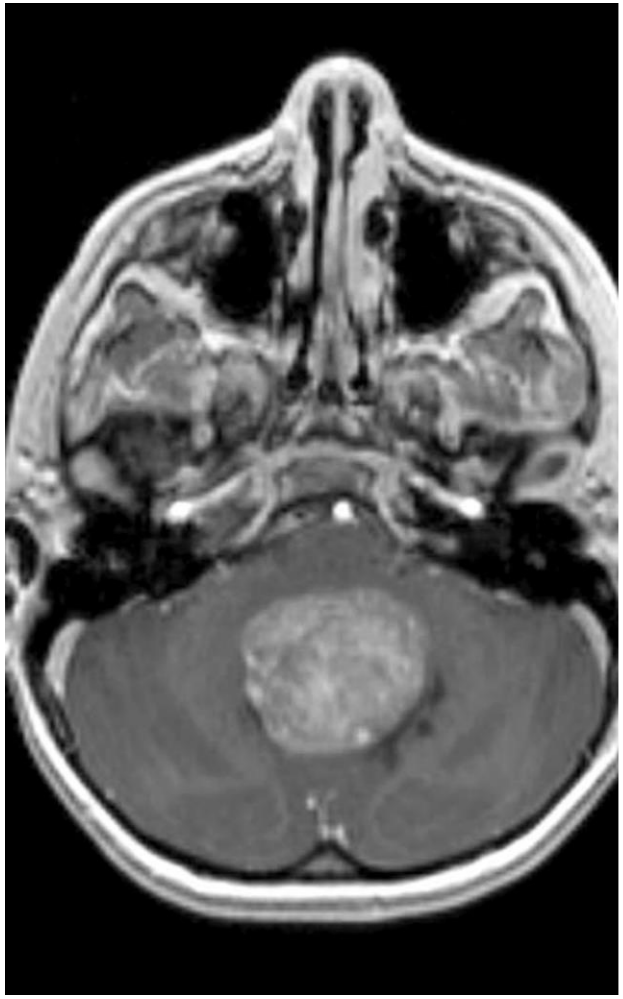
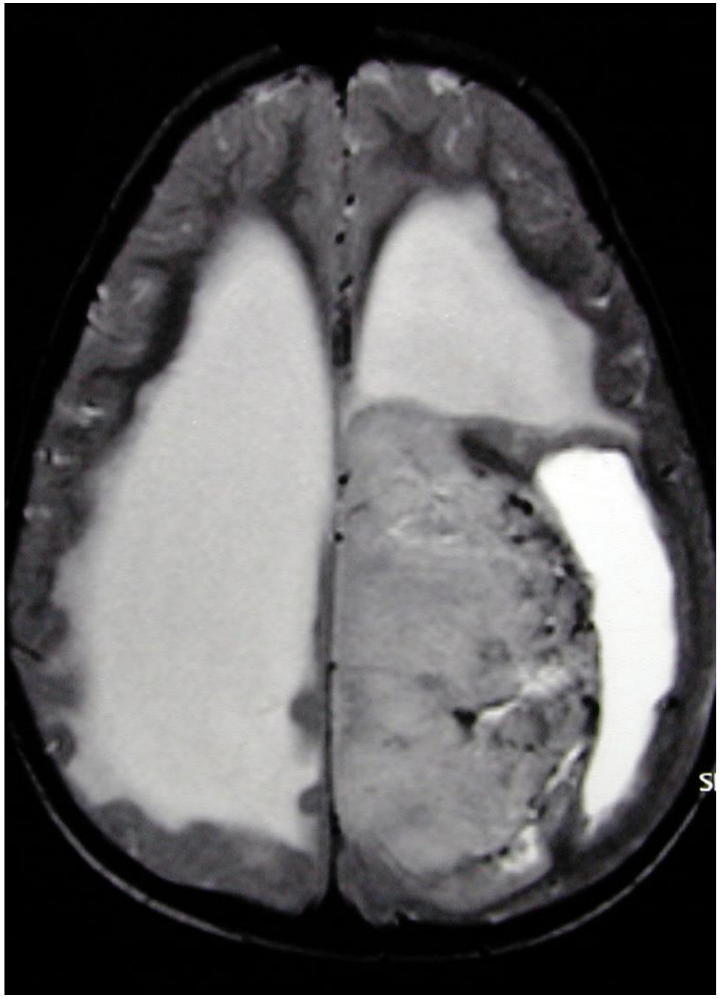
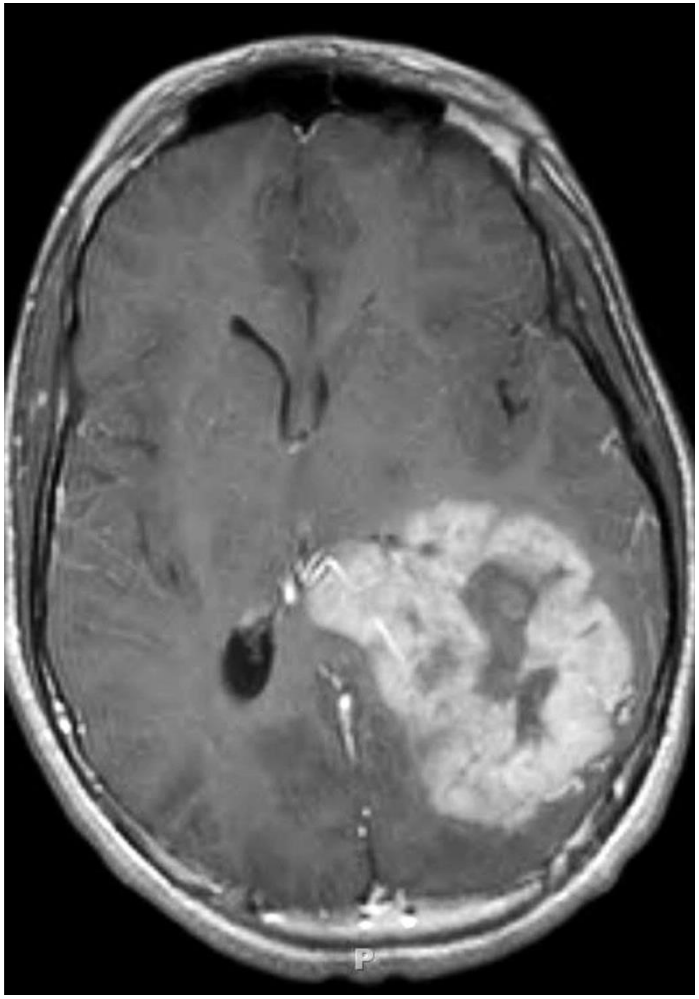
EMBRYONAL NEOPLASMS







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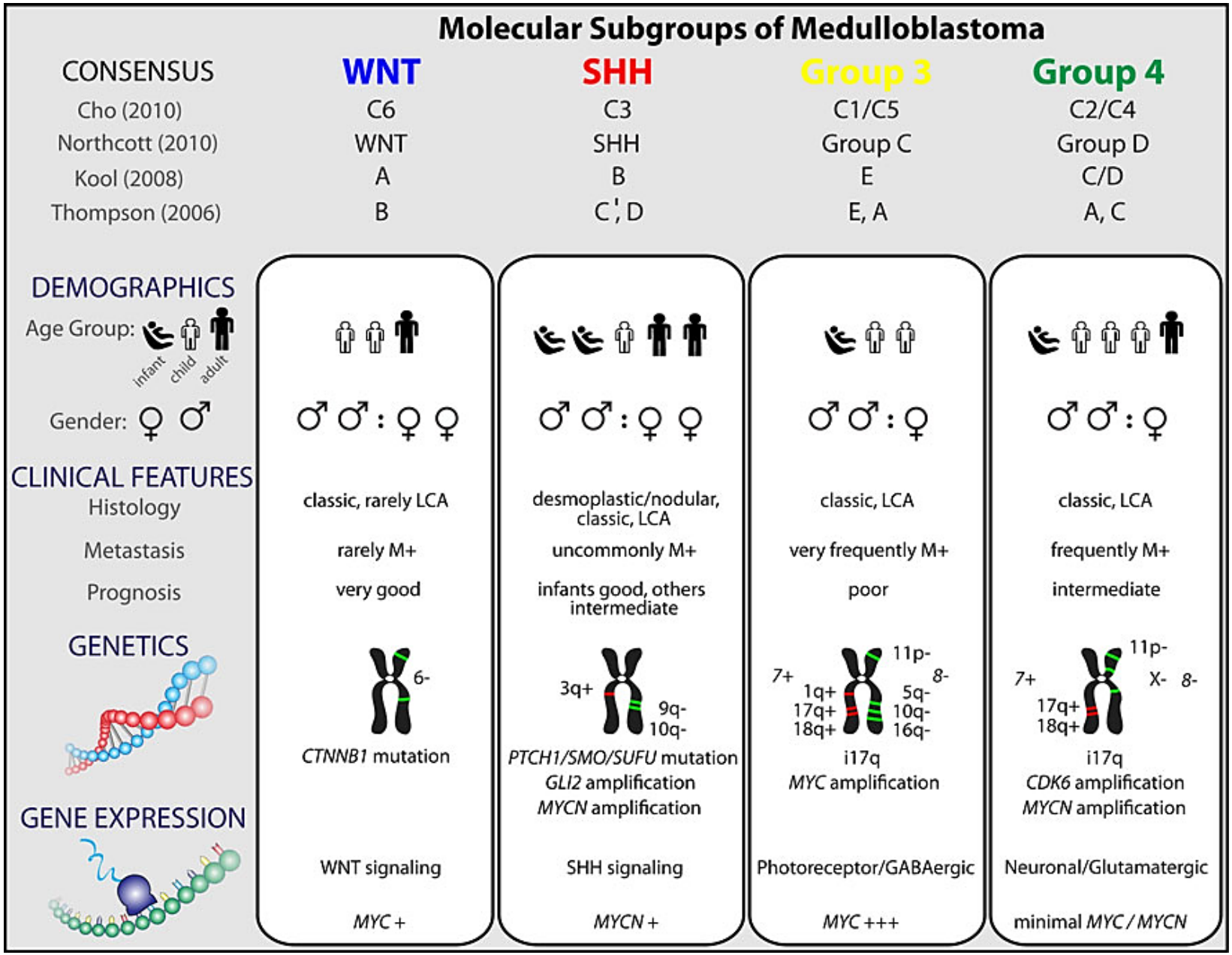
Taylor et al.,
Acta Neuropathol
2012;123:465-472



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

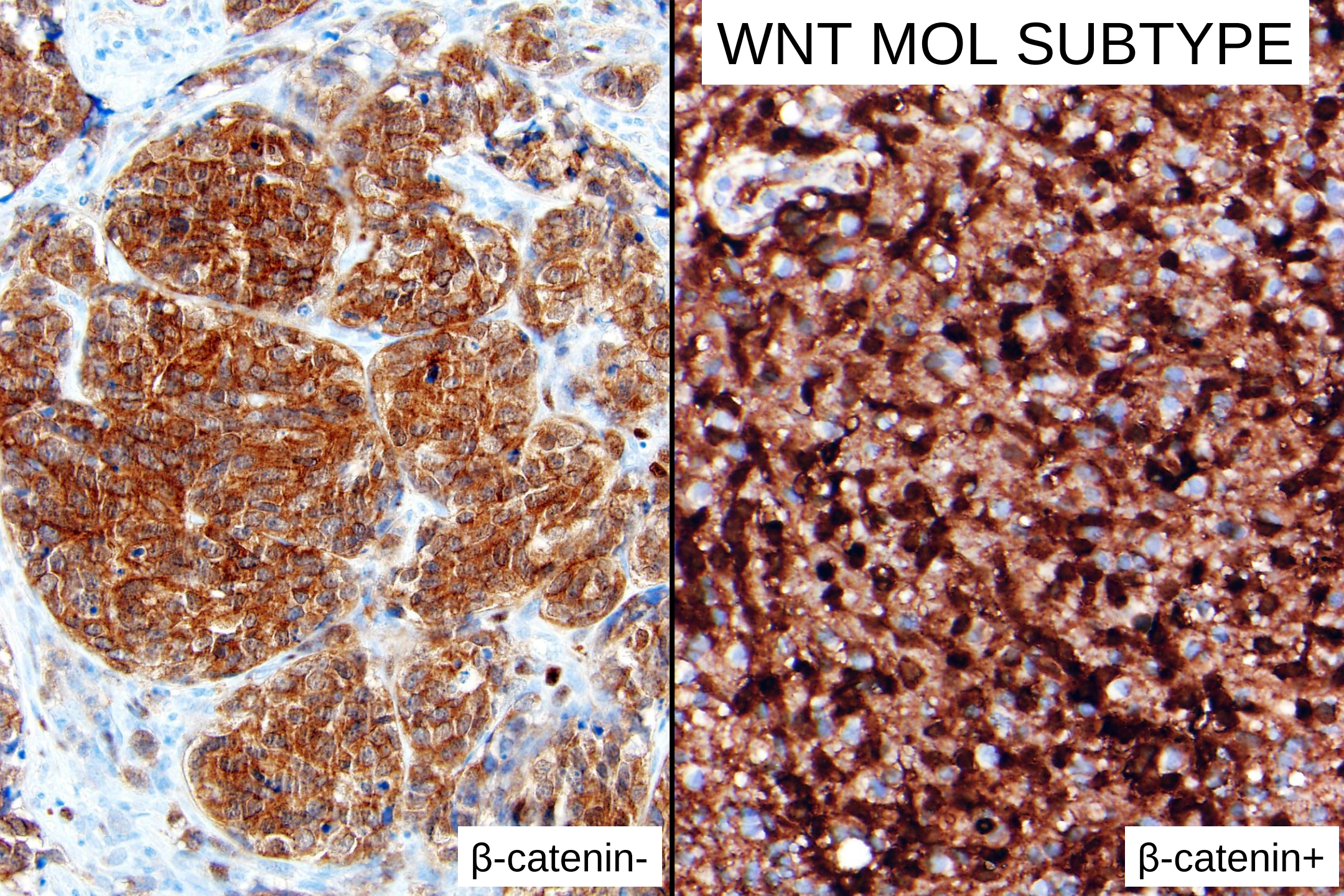
ORIGINAL PAPER

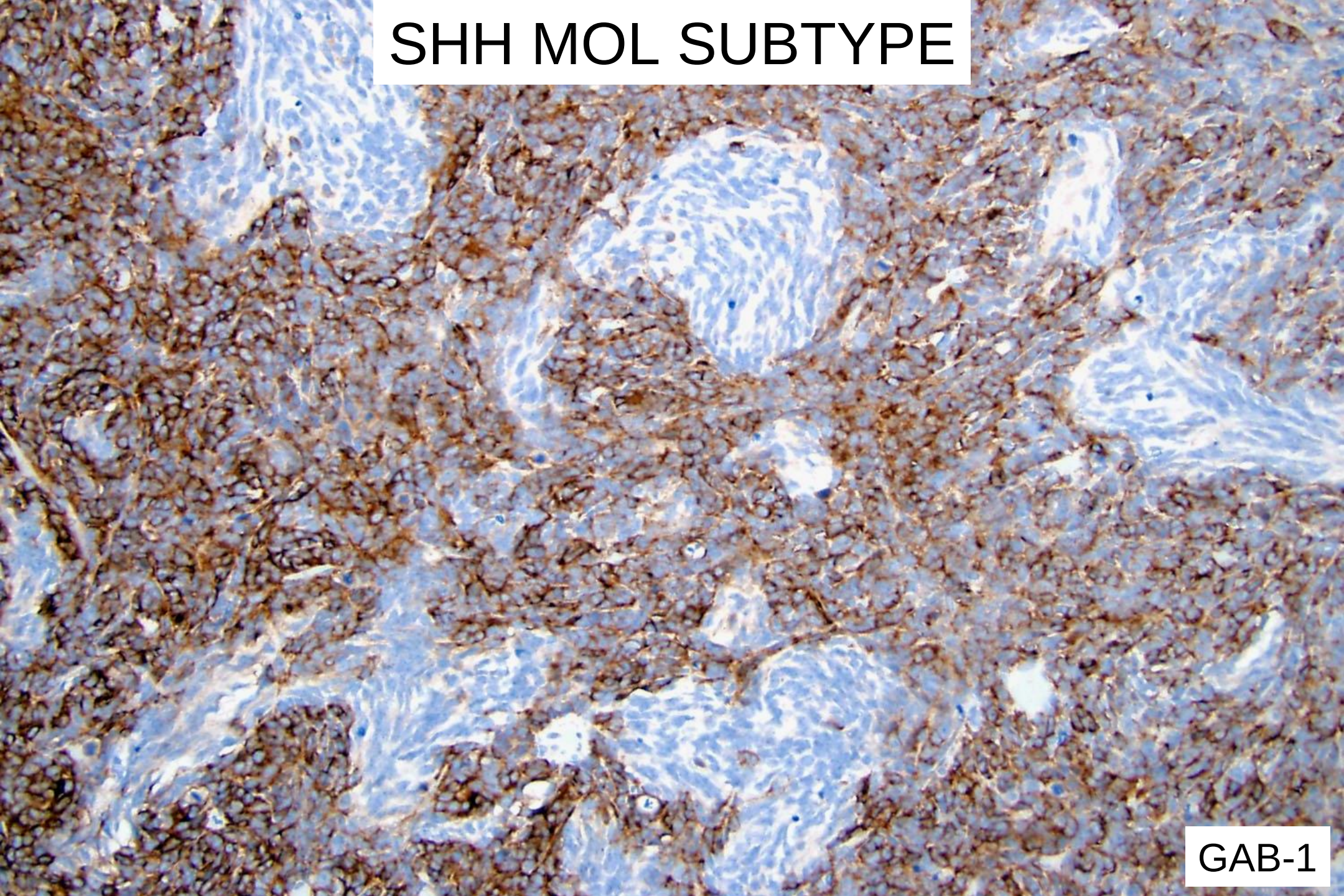
Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups

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

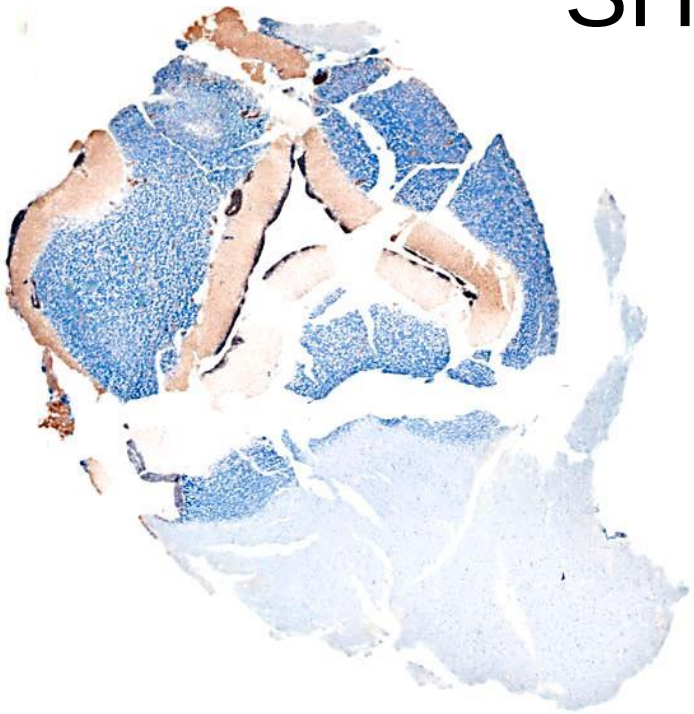
Received: 18 December 2010 / Revised: 12 January 2011 / Accepted: 13 January 2011 / Published online: 26 January 2011

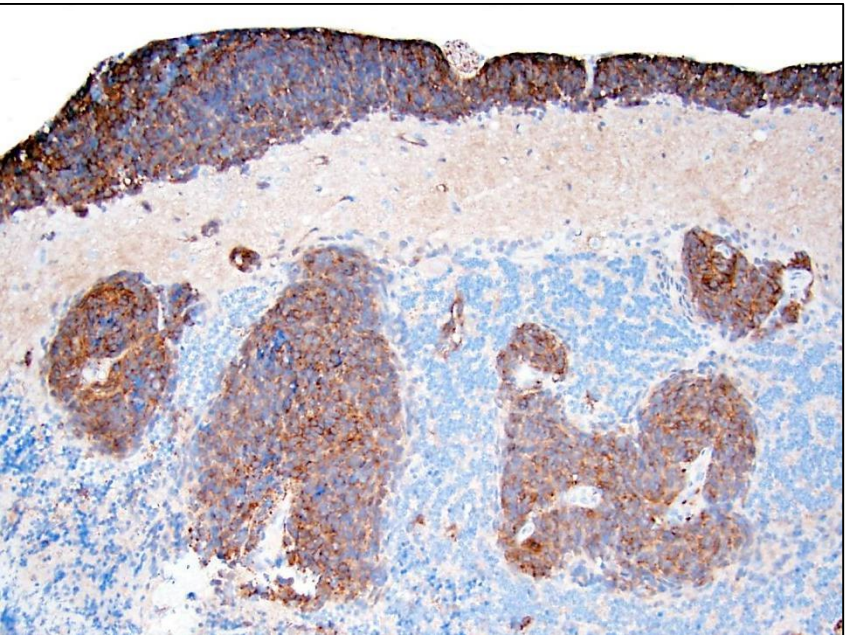
Abstract Medulloblastoma is heterogeneous, being characterized by molecular subgroups that demonstrate distinct gene expression profiles. Activation of the WNT or SHH signaling pathway characterizes two of these molecular subgroups, the former associated with low-risk disease and the latter potentially targeted by novel SHH pathway inhibitors. This manuscript reports the validation of a novel diagnostic immunohistochemical method to distinguish SHH, WNT, and non-SHH/WNT tumors and details their associations with clinical, pathological and cytogenetic variables. A cohort ($n = 235$) of medulloblastomas from patients aged 0.4–52 years was studied for expression of four immunohistochemical markers: GAB1, β-catenin, filamin A, and YAP1. Immunoreactivity (IR) for GAB1 characterizes only SHH tumors and nuclear IR for β-catenin only WNT tumors. IRs for filamin A and YAP1 identify SHH and WNT tumors. SHH, WNT, and non-SHH/WNT tumors contributed 31, 14, and 55% to the series. All desmoplastic/nodular (D/N) medulloblastomas were SHH tumors, while most WNT tumors (94%) had a classic phenotype. Monosomy 6 was strongly associated with WNT tumors, while *PTCH1* loss occurred almost exclusively among SHH tumors. *MYC* or *MYCN* amplification and

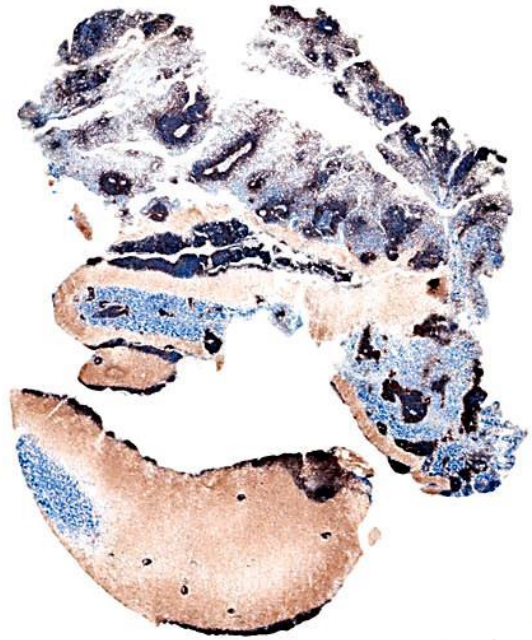

WNT MOL SUBTYPE
β-catenin-
β-catenin+

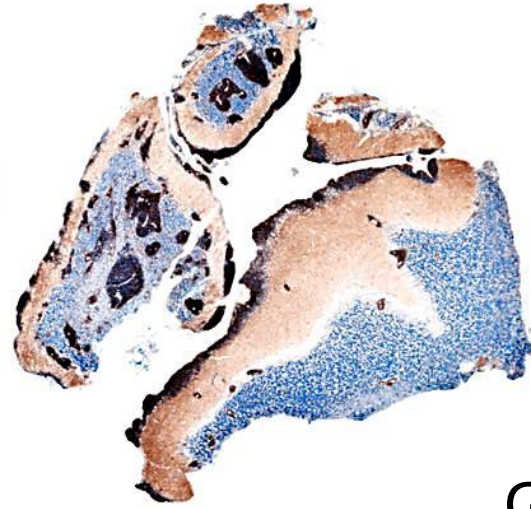

SHH MOL SUBTYPE
GAB-1

SHH MOL SUBTYPE









GAB-1

J Neurooncol (2012) 106:135–141
DOI 10.1007/s11060-011-0648-8

CLINICAL STUDY – PATIENT STUDY

p53 expression predicts dismal outcome for medulloblastoma patients with metastatic disease

Marco Gessi · André O. von Bueren · Stefan Rutkowski · Torsten Pietsch

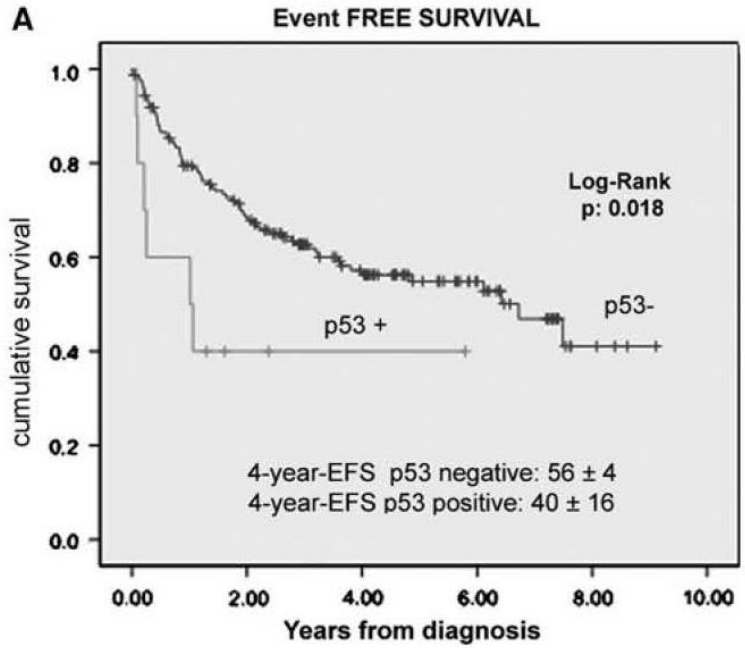
Received: 16 February 2011 / Accepted: 20 June 2011 / Published online: 28 July 2011

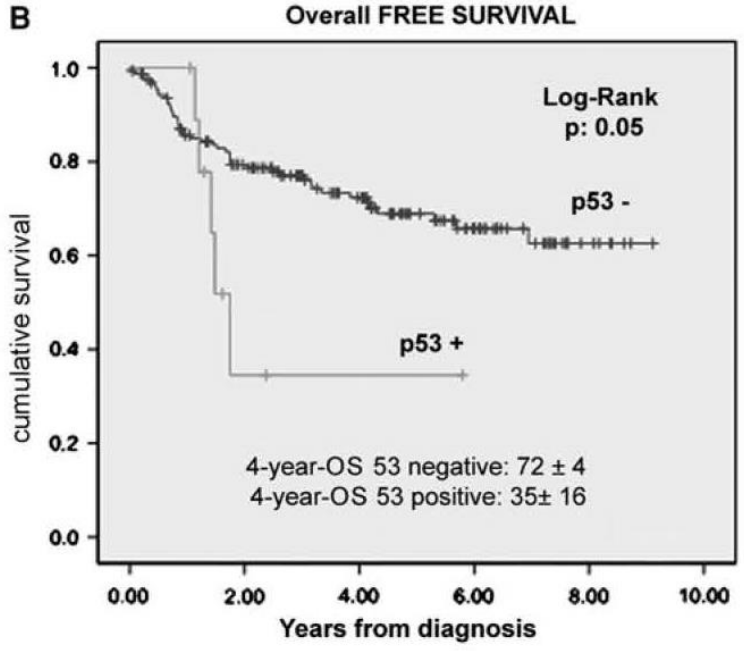
Abstract Medulloblastoma (MB) is the most common malignant primary brain tumour in childhood. Metastatic disease (M+) at diagnosis is the most important negative prognostic clinical marker and, despite craniospinal irradiation and intensive chemotherapy, it remains one of the leading causes of treatment failure. To date, few clinical and biological data have been evaluated to obtain an additional prognostic profile for these high-risk patients. In this study, 169 patients with metastatic MB registered in the multicentre HIT2000 trial of the German Society of Pediatric Oncology and Haematology (GPOH) have been investigated to determine the importance of p53 protein expression in predicting survival. At a median follow-up of 4.1 years, 159 patients with p53-negative tumours had significantly better four-year event-free survival (EFS) and progression-free survival (PFS) (56 ± 11, 59 ± 4%) than 10 patients with p53-positive tumours (40 ± 16, 40 ± 16%; $P = 0.018$ for EFS, $P = 0.007$ for PFS, respectively). Furthermore, four-year overall survival (OS) of children with p53-negative tumours was higher than for children with p53-positive tumours (72 ± 4 vs. 35 ± 18%, $P = 0.05$). Three of the p53-positive MBs harbored a point mutation in the *TP53* gene. p53 protein assessment by immunohistochemistry may be a useful tool for sub-stratification of metastatic high-risk MB patients.

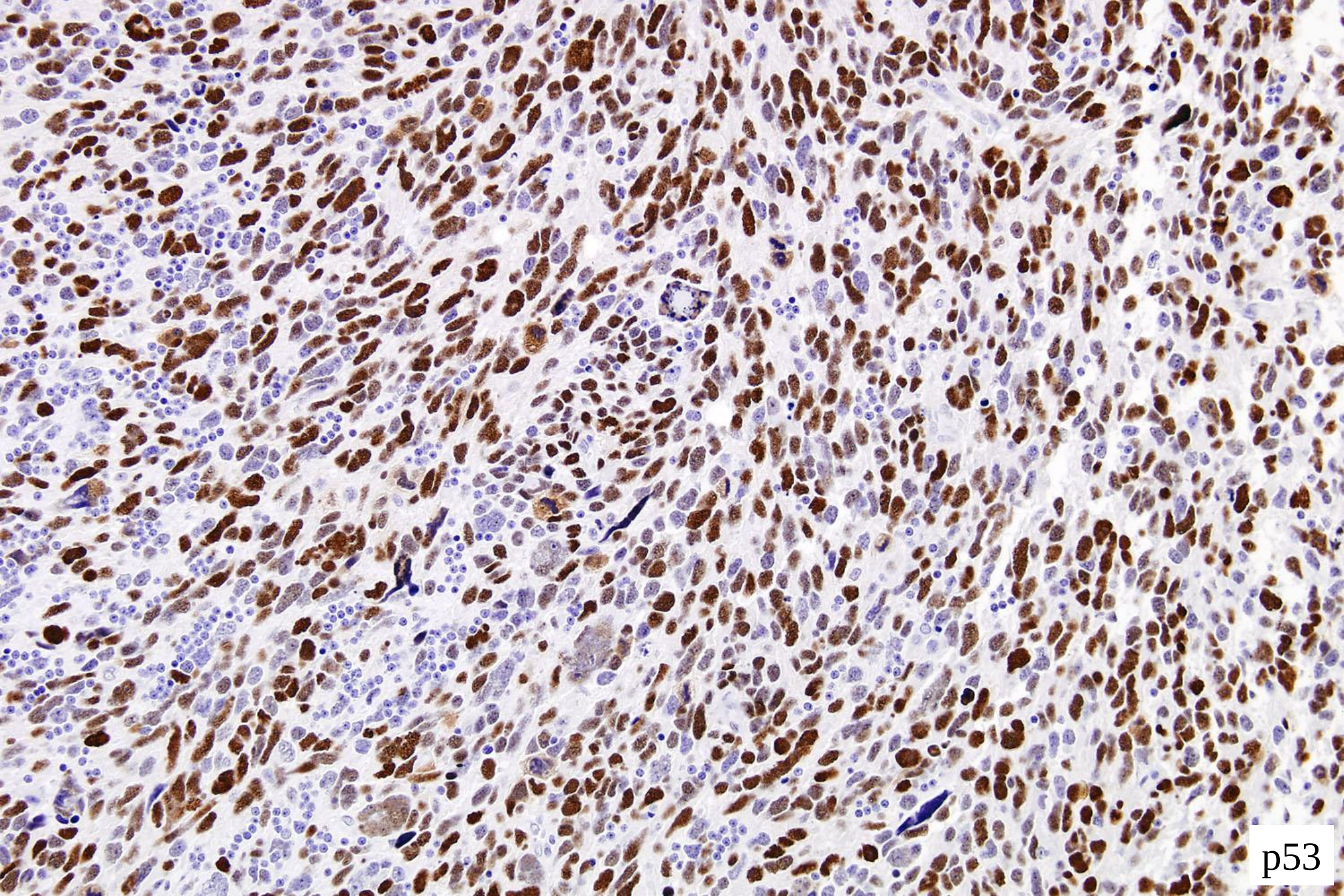
Keywords p53 · Medulloblastoma · Metastasis · Immunohistochemistry · β-catenin · TP53 mutations

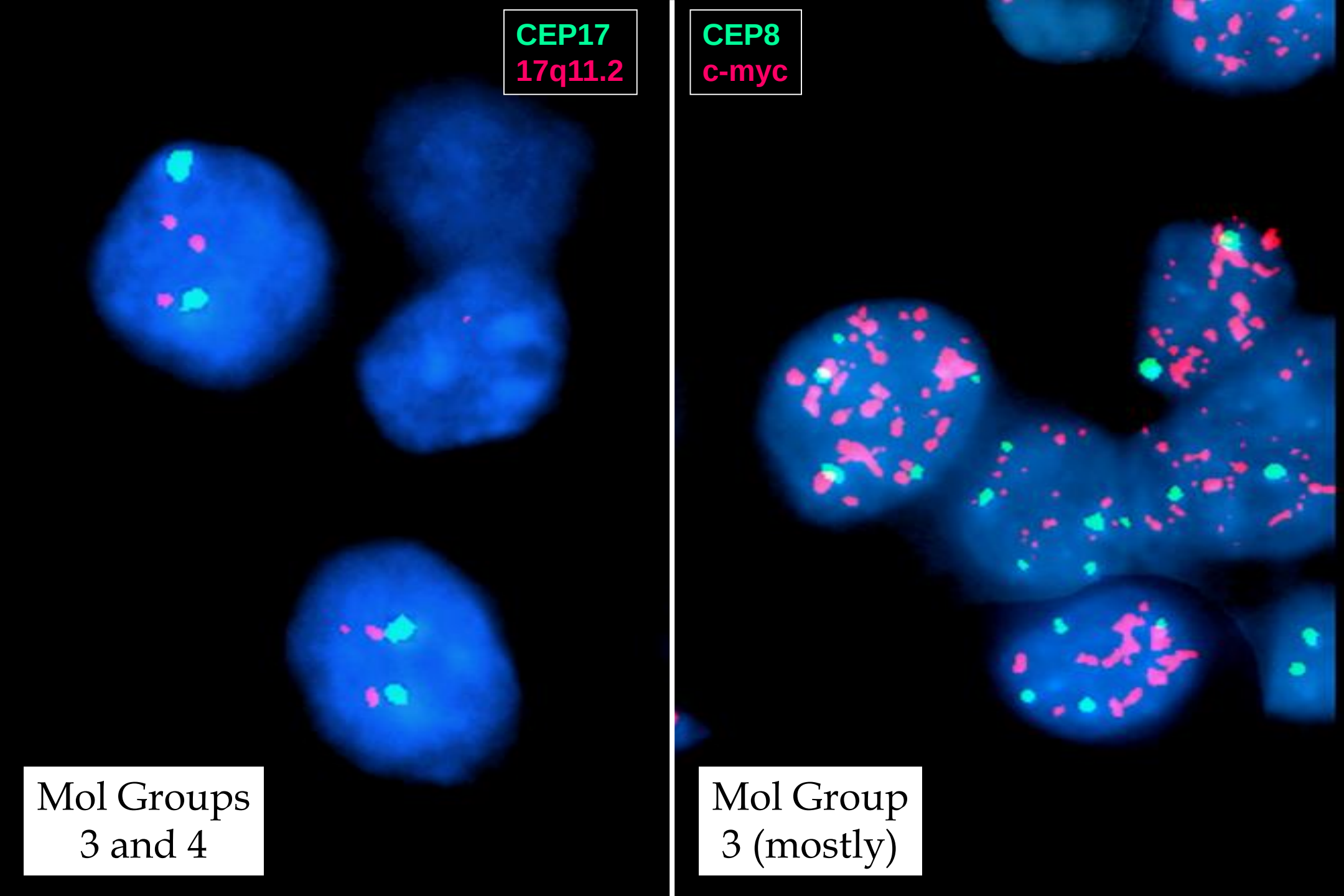
Introduction

Medulloblastoma (MB) is the most common malignant brain tumour in childhood [1]. Recent progress in understanding MB biology has indicated that this tumour is a heterogeneous disease characterized by well-defined tumour subsets with specific histological and molecular features [2]. A combination of clinical, pathological, and molecular data can be used for stratification of patients into risk groups and may lead to new risk-adapted approaches to therapy [2, 3]. Metastatic disease at diagnosis is the most important negative prognostic clinical marker for MB patients and, despite the use of craniospinal irradiation and intensive chemotherapy, is the leading clinical marker associated with treatment failure [2, 4, 5]. Approximately one-third of patients present with metastatic disease at the

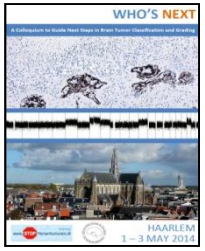





p53


CEP17
17q11.2
CEP8
c-myc
Mol Groups
3 and 4
Mol Group
3 (mostly)

Medulloblastoma



Integrated diagnosis:

Medulloblastoma, histological subtype and molecular subgroup (e.g., Wnt, SHH, non-WNT/non-SHH*), WHO grade IV

Histological classification:

Classic, anaplastic, large cell, desmoplastic/nodular, or medulloblastoma with extensive nodularity

WHO grade:

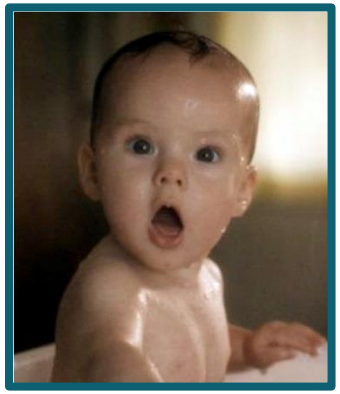
IV

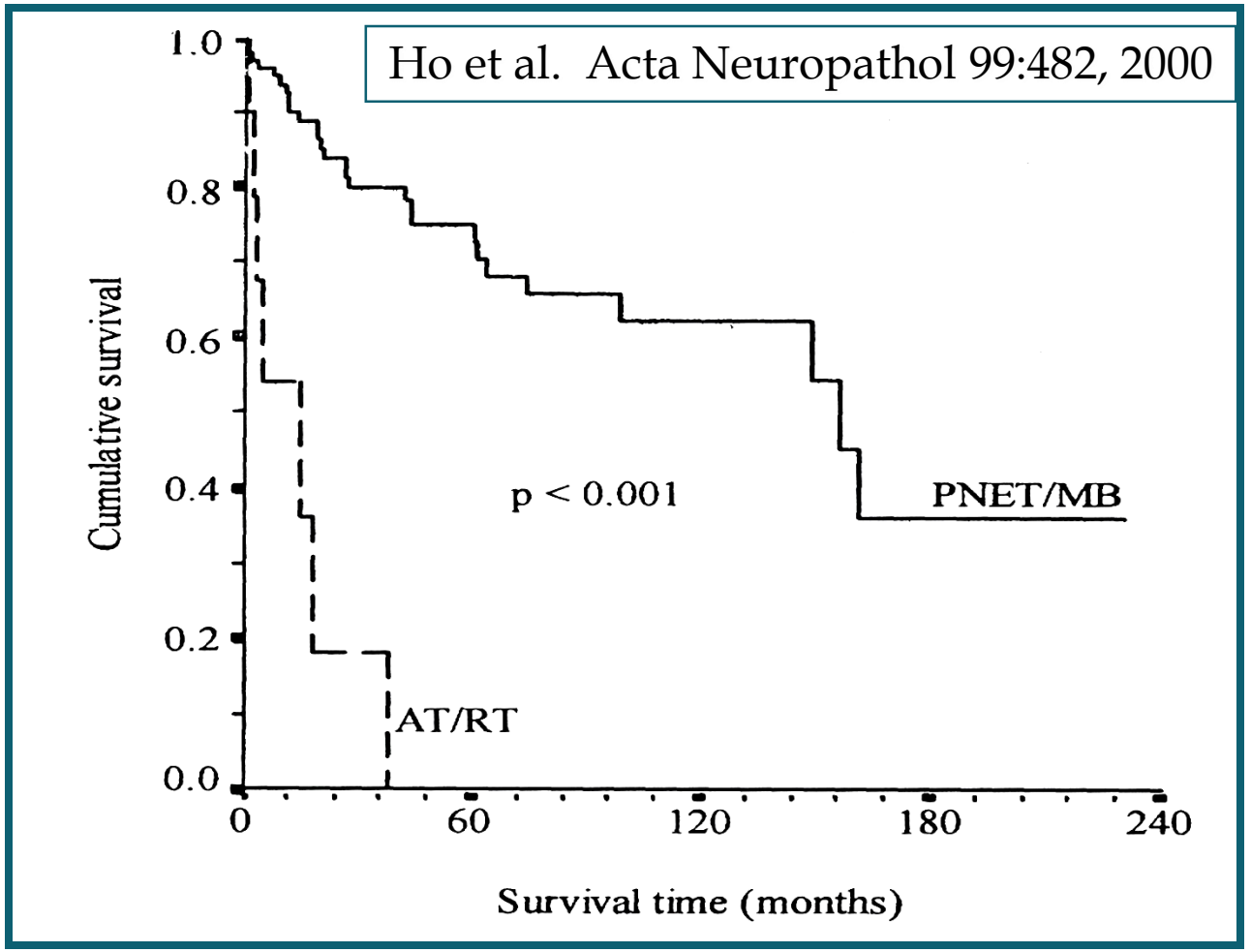
Molecular information:

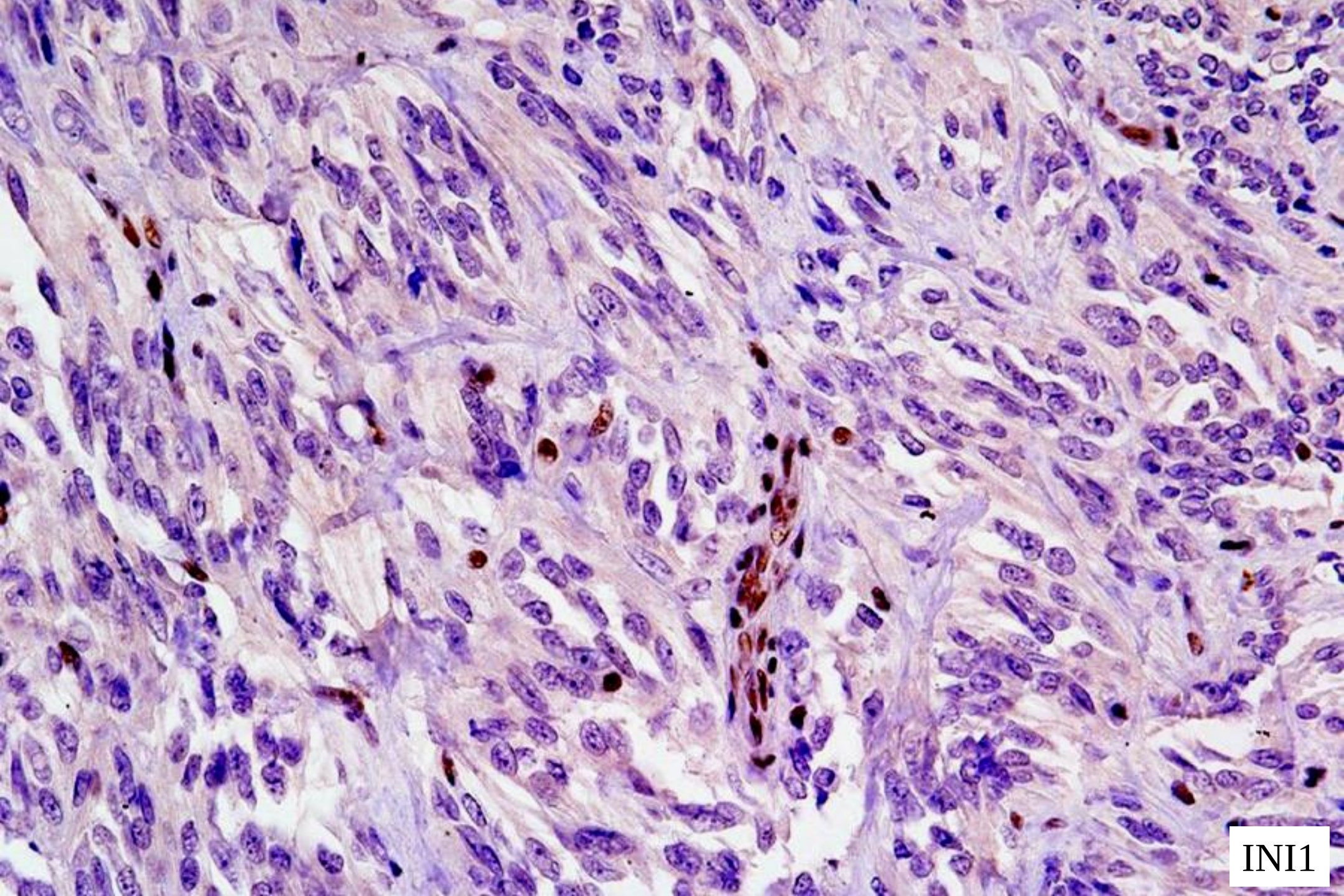
MYC amp, *NMYC* amp, *TP53* status, *CTNNB1* status, *SMO* status, *PTCH* status, i17q, monosomy 6 (list illustrative and not meant to be exhaustive)

UCSF University of California San Francisco

AT/RT






INI1

Nonsense Mutation and Inactivation of SMARCA4 (BRG1) in an Atypical Teratoid/Rhabdoid Tumor Showing Retained SMARCB1 (INI1) Expression

Martin Hasselblatt, MD, Stefan Gesk, MD,† ‡ Florian Oyen,§ Sabrina Rossi, MD,‖ Elisabetta Viscardi, MD,¶ Felice Giangaspero, MD,#** Caterina Giannini, MD, PhD, † † Alexander R. Judkins, MD,‡‡§§ Michael C. Frühwald, MD, PhD,‖‖ Tobias Obser,§ Reinhard Schneppenheim, MD, PhD,§ Reiner Siebert, MD,† ‡ and Werner Paulus, MD**

Abstract: Atypical teratoid/rhabdoid tumors (AT/RTs) are highly aggressive brain tumors of early childhood poorly responding to therapy. The majority of cases show inactivation of SMARCB1 (INI1, hSNF5, BAF47), a core member of the adenosine triphosphate (ATP)-dependent SWI/SNF chromatin-remodeling complex. We here report the case of a supratentorial AT/RT in a 9-month-old boy, which showed retained SMARCB1 staining on immunohistochemistry and lacked genetic alterations of SMARCB1. Instead, the tumor showed loss of protein expression of another SWI/SNF chromatin-remodeling complex member, the ATPase subunit SMARCA4 (BRG1) due to a homozygous SMARCA4 mutation [c.2032C > T (p.Q678X)]. Our findings highlight the role of SMARCA4 in the pathogenesis of SMARCB1-positive AT/RT and the usefulness of antibodies directed against SMARCA4 in this diagnostic setting.

Key Words: atypical teratoid/rhabdoid tumor, SMARCA4, BRG1, SMARCB1, INI1

(*Am J Surg Pathol* 2011;35:933–935)

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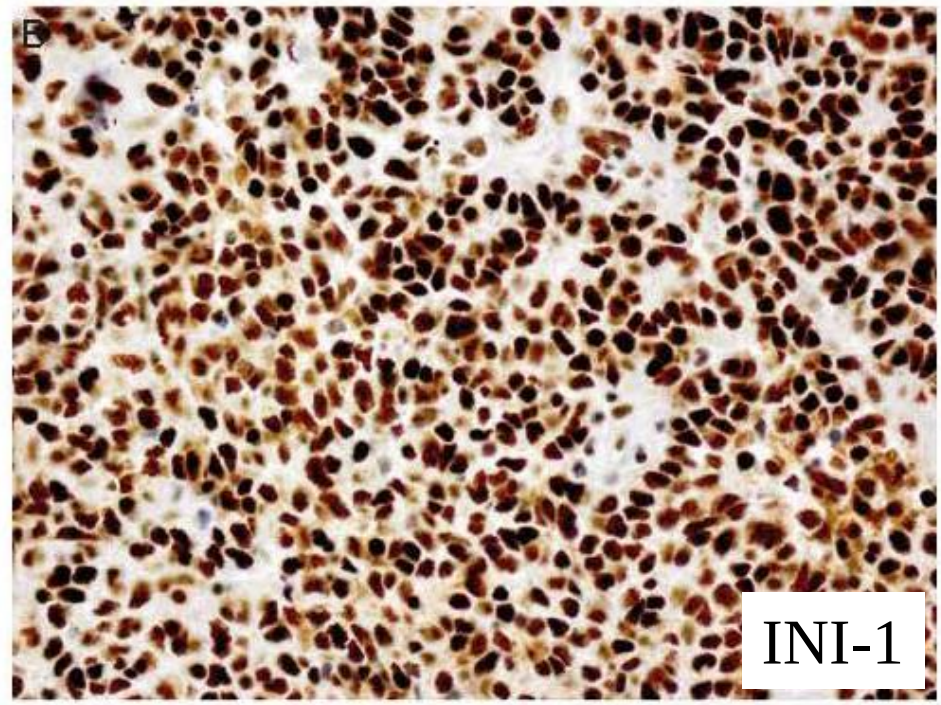
M.H.'s and W.P.'s research on the molecular pathogenesis of AT/RT was supported by IZKF Münster (HA3/016/11). R.S. was supported by KinderKrebsInitiative (KKI) Buchholz/Holm-Seppensen. The study of RSch was supported by the "Fördergemeinschaft Kinderkrebszentrum Hamburg e.V."

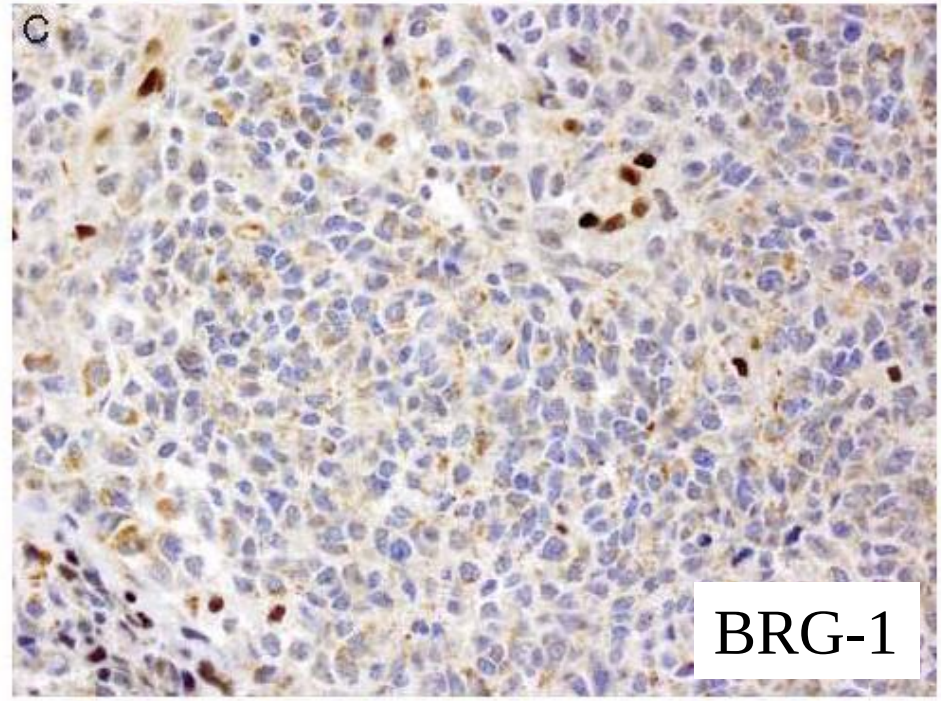
Correspondence: Martin Hasselblatt, MD, Institute of Neuropathology, University Hospital Münster Domagkstr. 19, 48129 Münster, Germany (e-mail: hasselblatt@uni-muenster.de).

Atypical teratoid/rhabdoid tumors (AT/RTs) are highly malignant rhabdoid tumors of early infancy and childhood. Despite recent therapeutic advances using aggressive multimodality approaches,[3] prognosis of many children harboring AT/RT remains dismal.[10] The vast majority of tumors show biallelic somatic inactivation of *SMARCB1* (also known as INI1, hSNF5, BAF47), a member of the adenosine triphosphate (ATP)-dependent SWI/SNF chromatin-remodeling complex, which is a key regulator of cell proliferation and differentiation.[11,12] Mechanisms involved in *SMARCB1* inactivation include gross chromosomal aberrations or loss of heterozygosity affecting the SMARCB1 locus on 22q11.2 and point mutations.[8] Mutations of the germline are observed in 20% to 35% of children[4,10] including rare familial cases described as rhabdoid tumor predisposition syndrome (MIM no. 609322). The fact that SMARCB1 constitutes only 1 component of the ATP-dependent SWI/SNF chromatin-remodeling complex raises the possibility that other members of this complex might also be implicated in the pathogenesis of AT/RT. Indeed, we could recently demonstrate genetic alterations of another SWI/SNF chromatin-remodeling complex member, the ATPase subunit SMARCA4 (also known as BRG1) in a family with rhabdoid tumor predisposition syndrome showing retained SMARCB1 expression.[13] These observations prompted us to routinely screen all cases of AT/RT for loss of SMARCA4 protein expression. We here describe the case of an AT/RT showing retained SMARCB1 staining but loss of SMARCA4 due to a homozygous mutation of the *SMARCA4* gene.

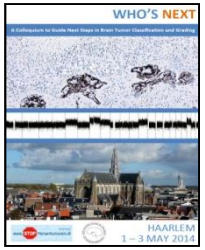
CASE REPORT

This 9-month-old boy presented with vomiting and abducens nerve palsy. The family history was noncontributory. Cranial magnetic resonance imaging disclosed hydrocephalus due to a large cystic contrast enhancing third ventricular tumor (Fig. 1). Third ventriculostomy and biopsy were performed, but the tumor could not be resected completely. After establishment of diagnosis, 4 cycles of chemotherapy (ifosfamide, carboplatin, and etoposide) were administered. Magnetic resonance imaging after the first 2 cycles showed stable disease. Unfortunately,





Proposal for ATRT



- A dx of ATRT requires typical pathological features and INI1 or BRG1 loss
- Tumors with typical pathology but no INI1 or BRG1 loss might be termed “embryonal tumor with rhabdoid features”
- A center without BRG1 and /or INI1 testing needs to send the case out

RESEARCH ARTICLE

Brain Pathol 20:441-450, 2010

Central Nervous System Primitive Neuroectodermal Tumors: A Clinicopathologic and Genetic Study of 33 Cases

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[1] Department of Pathology, Cedar Sinai Medical Center, Los Angeles, Calif.

[2] Department of Pathology and Immunology, Division of Neuropathology, Washington University School of Medicine, St. Louis, Mo.

Keywords

anaplasia, medulloblastoma, fluorescence *in situ* hybridization, primitive neuroectodermal tumor, prognosis.

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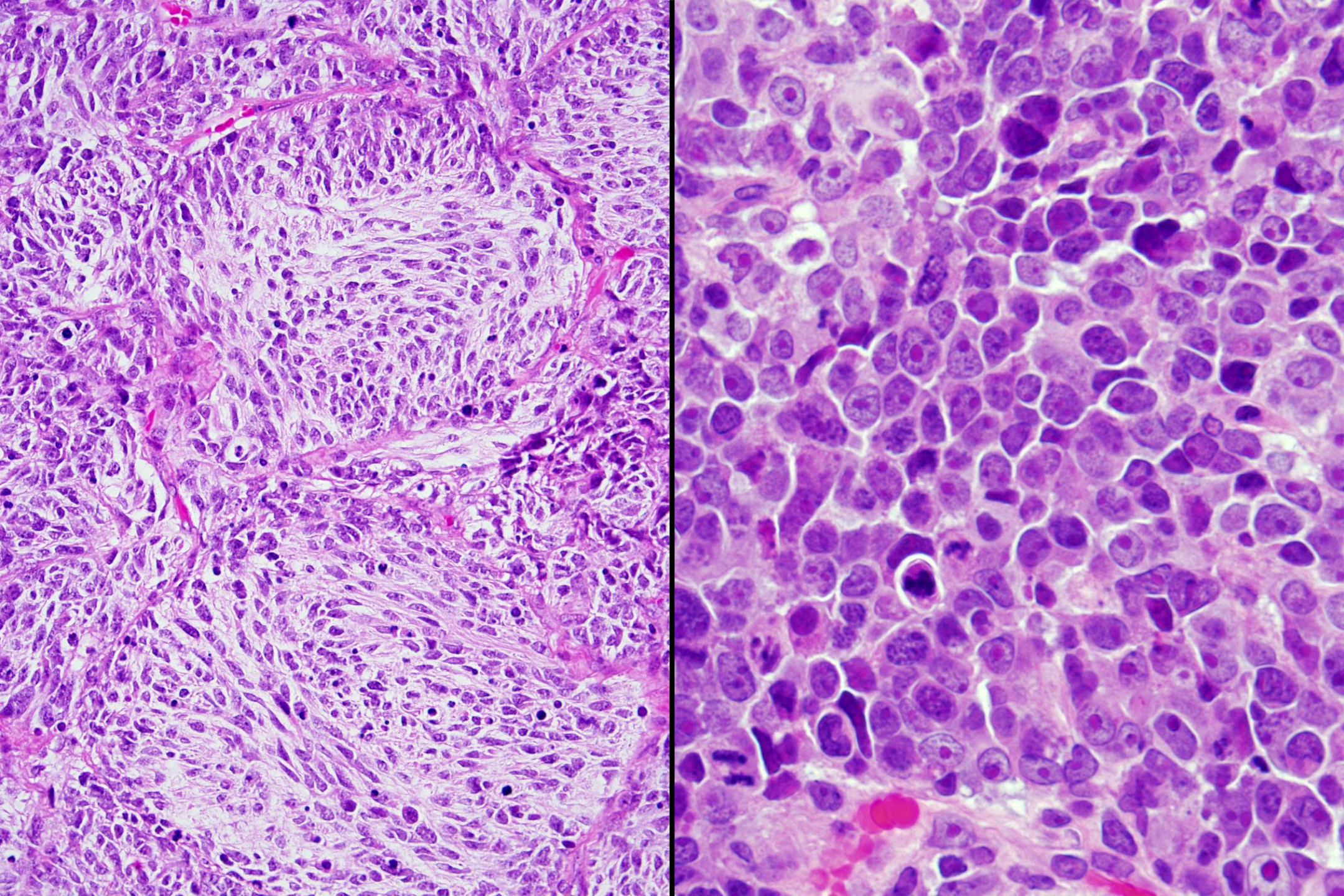
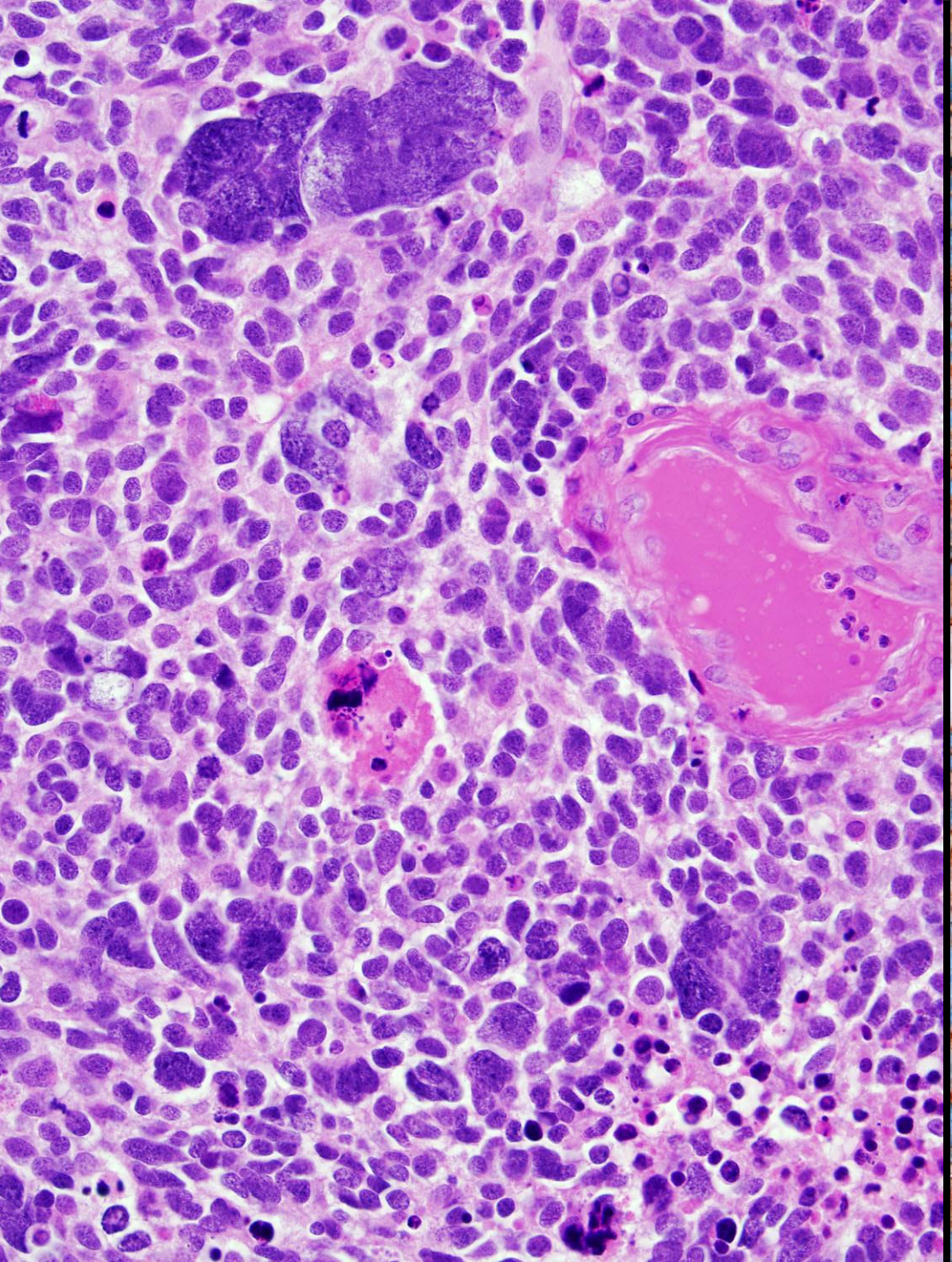
Received 22 May 2009; accepted 17 June 2009.

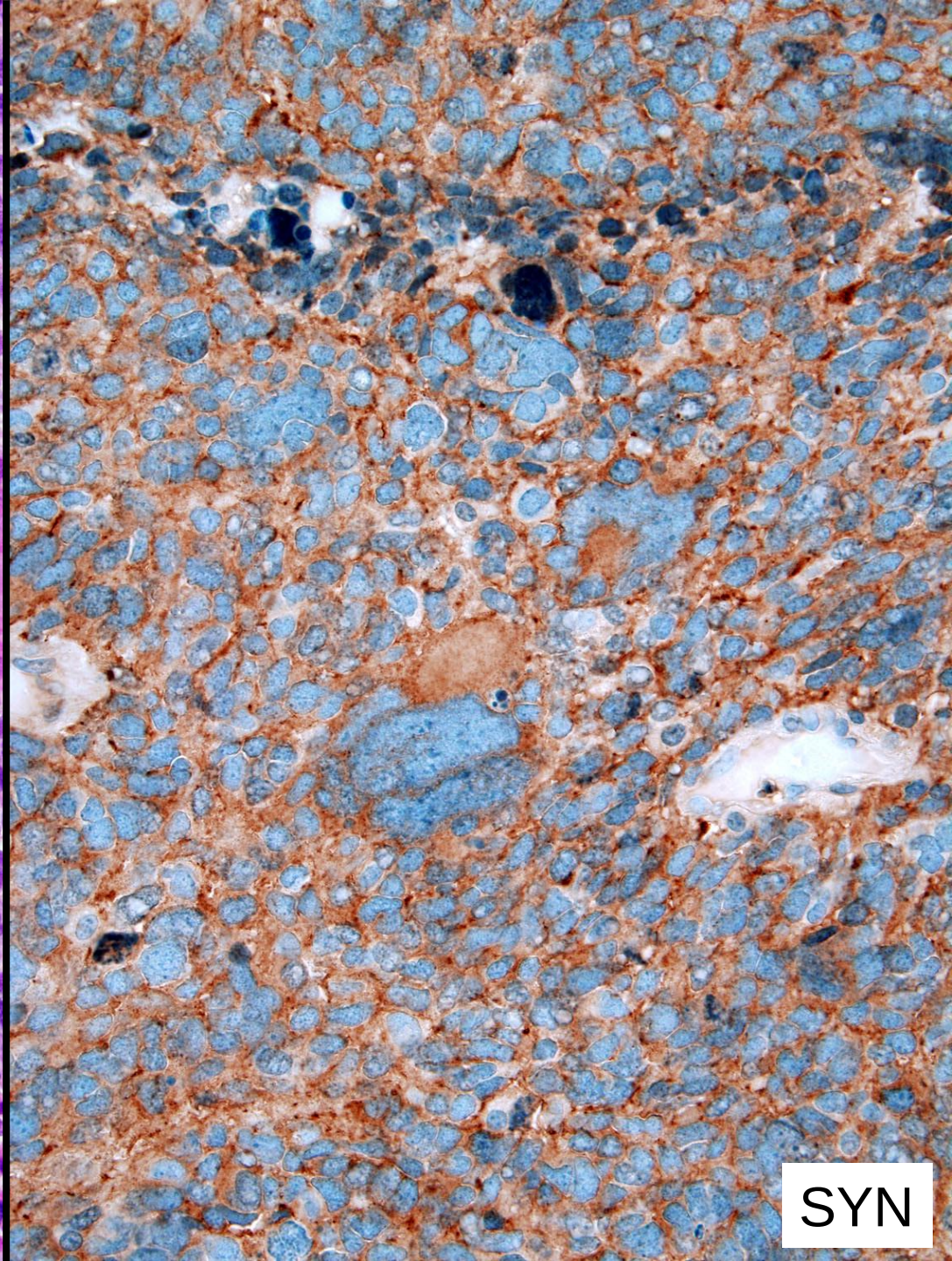
doi:10.1111/j.1750-3639.2009.00314.x

Abstract

Central nervous system (CNS) primitive neuroectodermal tumors (PNETs) include supratentorial, brain stem, and spinal cord tumors with medulloblastoma-like histopathology. The prognostic impact of various pathologic and genetic features has not been thoroughly investigated. After re-diagnosis of three infantile cases as atypical teratoid/rhabdoid tumor (AT/RT), 33 remaining CNS PNETs were retrieved for clinicopathologic and fluorescence *in situ* hybridization studies. Anaplastic and/or large cell features were seen in 18 of 33 (55%) examples and survival was decreased in these patients ($P = 0.036$). *MYCN* or *MYCC* gene amplifications were noted in about half, with a trend towards decreased survival ($P = 0.112$). Polysomies of chromosomes 2 and 8 were each individually associated with decreased survival in children, with an even stronger association when combined ($P = 0.013$). Neither *EWS* gene rearrangements, nor AT/RT-like 22q deletions were encountered. We conclude that in CNS PNET: (i) routine application of INI1 immunohistochemistry helps rule out AT/RT, particularly in infants; (ii) *MYC* gene amplifications (especially *MYCN*) are common; (iii) involvement of CNS parenchyma by Ewing sarcoma/peripheral PNET is rare enough that *EWS* gene testing is not necessary unless significant dural involvement is present; and (iv) both anaplastic/large cell features and polysomies of 2 and 8 are associated with more aggressive clinical behavior.






SYN

Markers of survival and metastatic potential in childhood CNS primitive neuro-ectodermal brain tumours: an integrative genomic analysis

Daniel Picard, Suzanne Miller*, Cynthia E Hawkins, Eric Bouffet, Hazel A Rogers, Tiffany S Y Chan, Seung-Ki Kim, Young-Shin Ra, Jason Fangusaro, Andrey Korshunov, Helen Toledano, Hideo Nakamura, James T Hayden, Jennifer Chan, Lucie Lafay-Cousin, Pingzhao Hu, Xing Fan, Karin M Muraszko, Scott L Pomeroy, Ching C Lau, Ho-Keung Ng, Chris Jones, Timothy Van Meter, Steven C Clifford, Charles Eberhart, Amar Gajjar, Stefan M Pfister, Richard G Grundy†, Annie Huang†*

Lancet Oncol 2012; 13: 838–48

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See Comment page 753

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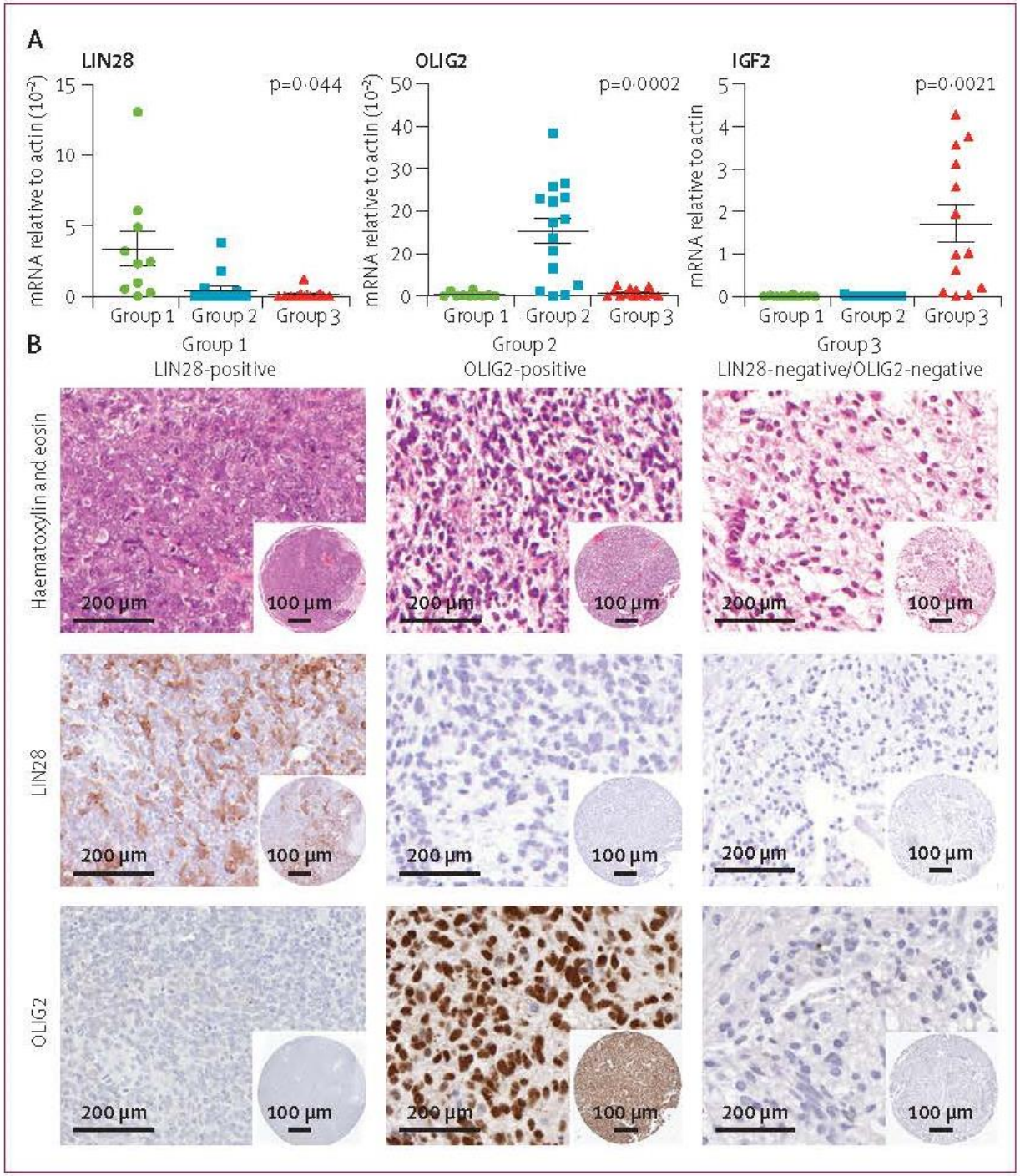
Summary

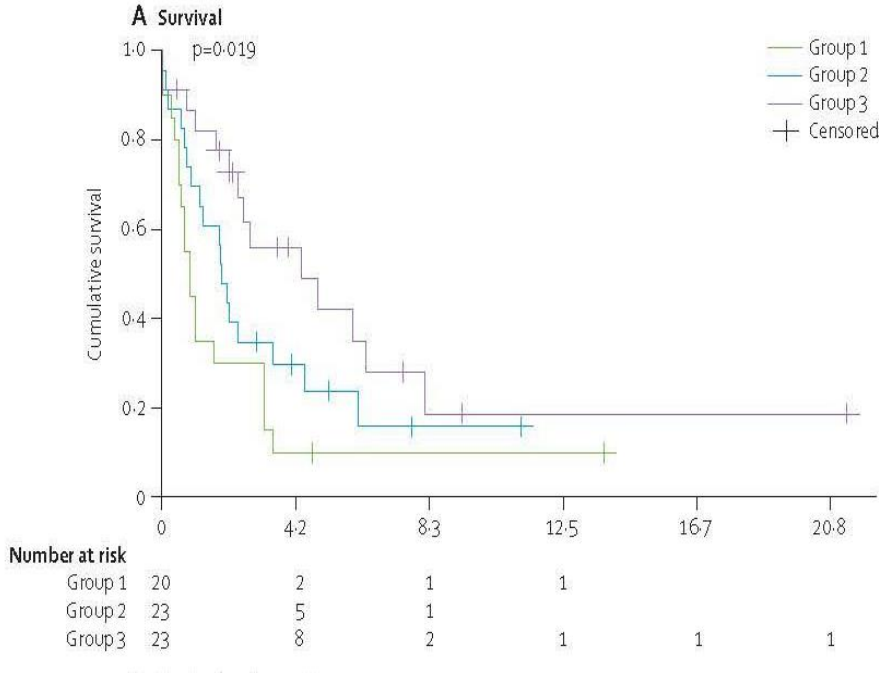
Background Childhood CNS primitive neuro-ectodermal brain tumours (PNETs) are very aggressive brain tumours for which the molecular features and best treatment approaches are unknown. We assessed a large cohort of these rare tumours to identify molecular markers to enhance clinical management of this disease.

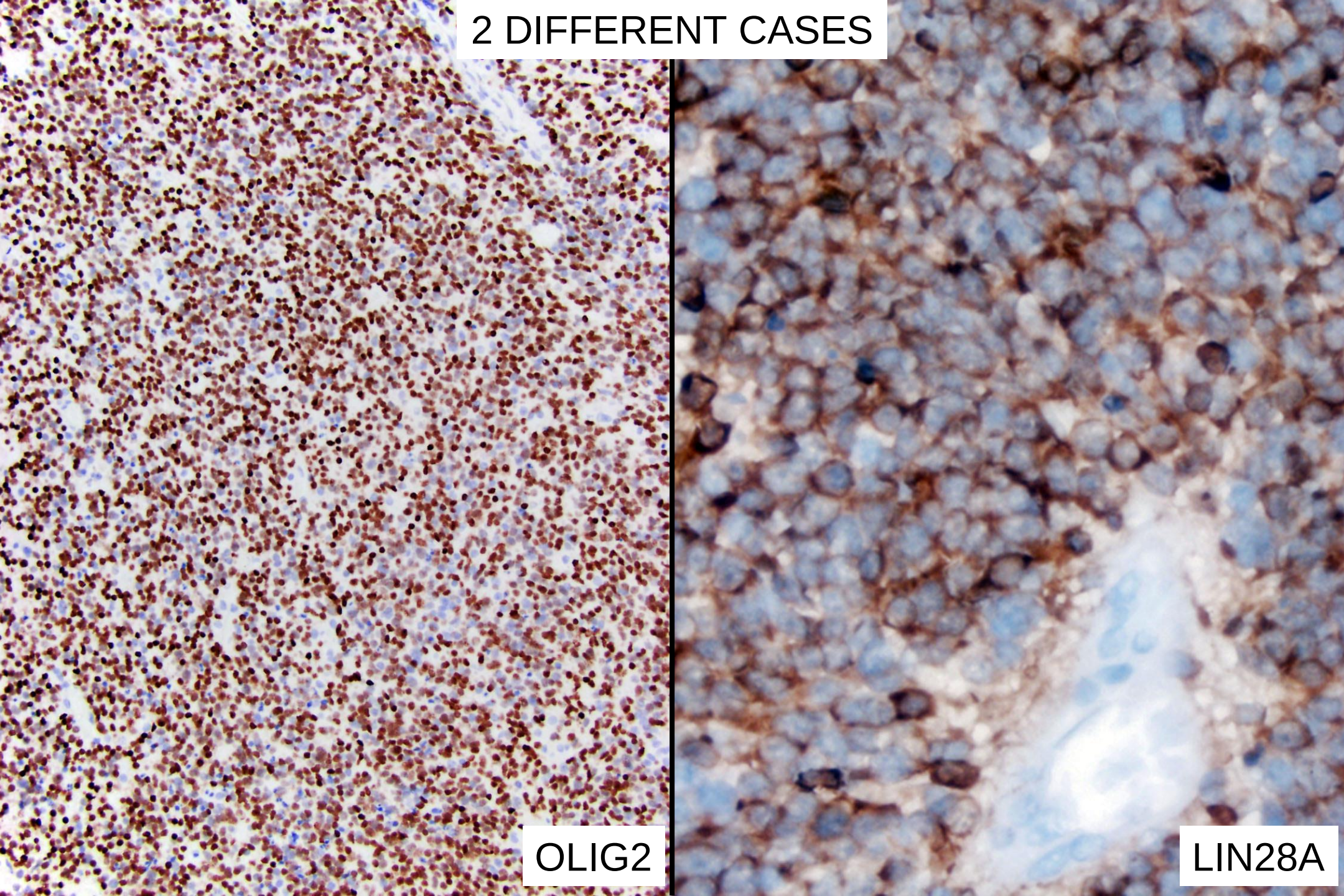
Methods We obtained 142 primary hemispheric CNS PNET samples from 20 institutions in nine countries and examined transcriptional profiles for a subset of 51 samples and copy number profiles for a subset of 77 samples. We used clustering, gene, and pathway enrichment analyses to identify tumour subgroups and group-specific molecular markers, and applied immunohistochemical and gene-expression analyses to validate and assess the clinical significance of the subgroup markers.

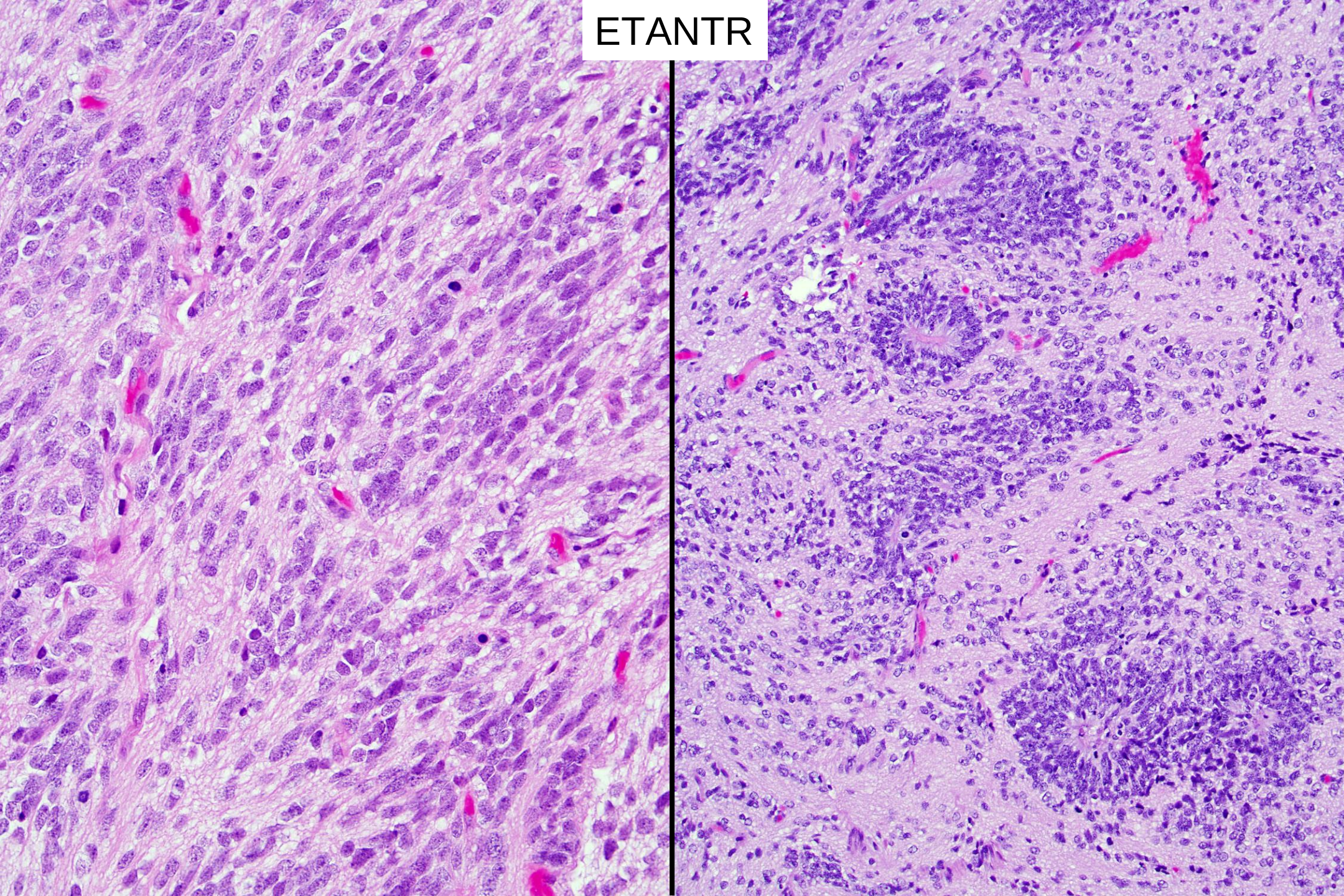
Findings We identified three molecular subgroups of CNS PNETs that were distinguished by primitive neural (group 1), oligoneural (group 2), and mesenchymal lineage (group 3) gene-expression signatures with differential expression of cell-lineage markers LIN28 and OLIG2. Patients with group 1 tumours were most often female (male:female ratio 0·61 for group 1 *vs* 1·25 for group 2 and 1·63 for group 3; p=0·043 [group 1 *vs* groups 2 and 3]), youngest (median age at diagnosis 2·9 years [95% CI 2·4–5·2] for group 1 *vs* 7·9 years [6·0–9·7] for group 2 and 5·9 years [4·9–7·8] for group 3; p=0·005), and had poorest survival (median survival 0·8 years [95% CI 0·5–1·2] in group 1, 1·8 years [1·4–2·3] in group 2 and 4·3 years [0·8–7·8] in group 3; p=0·019). Patients with group 3 tumours had the highest incidence of metastases at diagnosis (no distant metastasis:metastasis ratio 0·90 for group 3 *vs* 2·80 for group 1 and 5·67 for group 2; p=0·037).

Interpretation LIN28 and OLIG2 are promising diagnostic and prognostic molecular markers for CNS PNET that warrant further assessment in prospective clinical trials.


A
LIN28
p=0·044
mRNA relative to actin (10⁻²)
15
10
5
0
Group 1
Group 2
Group 3
OLIG2
p=0·0002
mRNA relative to actin (10⁻²)
50
40
30
20
20
0
Group 1
Group 2
Group 3
IGF2
p=0·0021
mRNA relative to actin
5
4
3
2
1
0
Group 1
Group 2
Group 3
B
Group 1
LIN28-positive
Group 2
OLIG2-positive
Group 3
LIN28-negative/OLIG2-negative
Haematoxylin and eosin
LIN28
OLIG2
200 µm
100 µm


A Survival
p=0·019
Group 1
Group 2
Group 3
Censored
Cumulative survival
1·0
0·8
0·6
0·4
0·2
0
0
4·2
8·3
12·5
16·7
20·8
Number at risk
Group 1 20 2 1 1
Group 2 23 5 1
Group 3 23 8 2 1 1 1


2 DIFFERENT CASES
OLIG2
LIN28A


ETANTR

RESEARCH ARTICLE

Brain Pathol 2010; 20:133-9

Ependymoblastoma: Dear, Damned, Distracting Diagnosis, Farewell!*

Alexander R. Judkins[1]; David W. Ellison[2]

[1] Division of Neuropathology, Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pa.

[2] Department of Pathology, St. Jude Children's Research Hospital, Memphis, Tenn.

Keywords

embryonal tumors with abundant neuropil and ependymoblastic rosettes, ependymoblastic rosettes, ependymoblastoma.

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Alexander R. Judkins, MD, Division of Neuopathology, Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Abramson Research Center, 807, 3615 Civic Center Boulevard, Philadelphia PA 19104-4318, USA (E-mail: *judkins@mail.med.upenn.edu*)

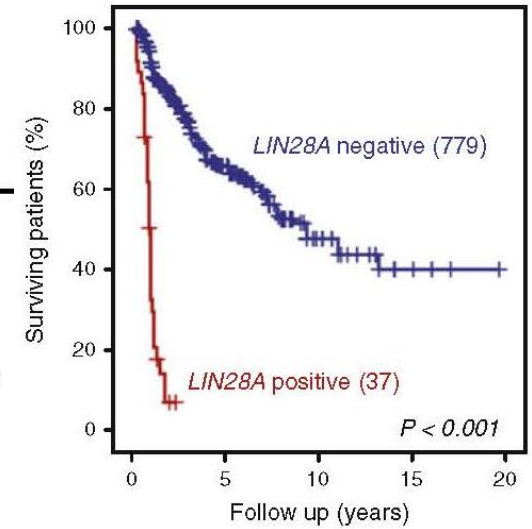
Received 15 October 2008; accepted 4 November 2008.

Abstract

Ependymoblastoma is a diagnostic label that has been applied to a variety of rare central nervous system (CNS) tumors over the last eight decades. Consequently, there is uncertainty about whether such an entity exists and what its characteristic features might be. The current study, based on 14 cases from our institutional archives and identified by the search terms "ependymoblastoma," "ependymoblastomatous," "ependymoblastic" or "PNET with ependymal differentiation," aimed to test the hypothesis that the ependymoblastoma is a distinct and recognizable entity. Ependymoblastic rosettes are a key diagnostic feature and were present in 11/14 (79%) tumors, eight (73%) of which were embryonal tumors with abundant areas of neuropil-like differentiation. Three other cases showed rare ependymoblastic rosettes in the histopathological setting of a typical primitive neuroectodermal tumor (PNET), medulloblastoma (MB) or atypical teratoid/rhabdoid tumor (AT/RT). The remaining cases were all embryonal tumors with structures that mimicked ependymoblastic rosettes. Our results indicate that ependymoblastic rosettes are most frequently encountered in embryonal tumors with abundant neuropil and less frequently in other CNS embryonal neoplasms, including PNET, MB and AT/RT. We believe that ependymoblastoma as a diagnosis is neither precise nor specific and that it is time once and for all to retire this diagnosis from the lexicon of neuropathology.

Acta Neuropathol (2012) 124:875–881
DOI 10.1007/s00401-012-1068-3

ORIGINAL PAPER



LIN28A immunoreactivity is a potent diagnostic marker of embryonal tumor with multilayered rosettes (ETMR)

Andrey Korshunov · Marina Ryzhova · David T. W. Jones · Paul A. Northcott · Peter van Sluis · Richard Volckmann · Jan Koster · Rogier Versteeg · Cynthia Cowdrey · Arie Perry · Daniel Picard · Marc Rosenblum · Felice Giangaspero · Eleonora Aronica · Ulrich Schüller · Martin Hasselblatt · V. Peter Collins · Andreas von Deimling · Peter Lichter · Annie Huang · Stefan M. Pfister · Marcel Kool

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Abstract Embryonal tumor with multilayered rosettes (ETMR, previously known as ETANTR) is a highly aggressive embryonal CNS tumor, which almost exclusively affects infants and is associated with a dismal prognosis. Accurate diagnosis is of critical clinical importance because of its poor response to current treatment protocols and its distinct biology. Amplification of the miRNA cluster at 19q13.42 has been identified previously as a genetic hallmark for ETMR, but an immunohistochemistry-based assay for clinical routine diagnostics [such as INI-1 for atypical teratoid rhabdoid tumor (AT/RT)] is still lacking. In this study, we screened for an ETMR-specific marker using a gene-expression profiling dataset of more than 1,400 brain tumors and identified

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MOLECULAR IHC SURROGATES

ADULT/PEDI GLIOMAS

- IDH1 (R132H)
- p53
- ATRX
- H3.3 (K27M)
- BRAF V600E

EMBRYONAL TUMORS

- INI1 (SMARCB1)
- BRG1 (SMARCA4)
- Beta catenin
- GAB1
- LIN28A
- OLIG2

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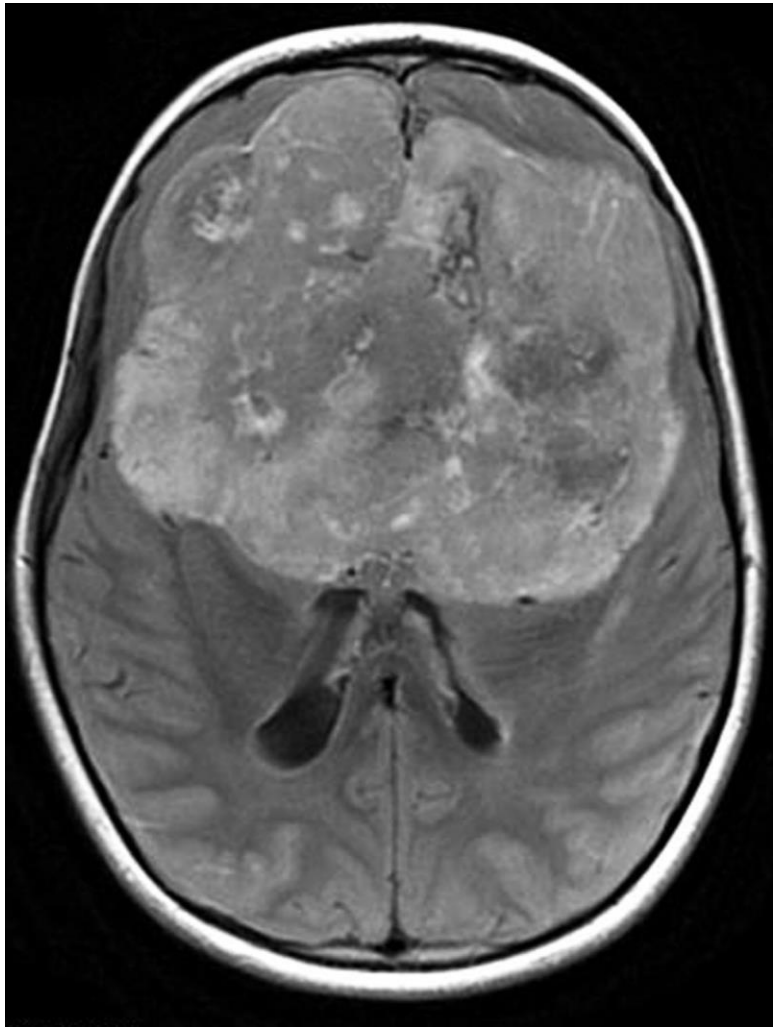
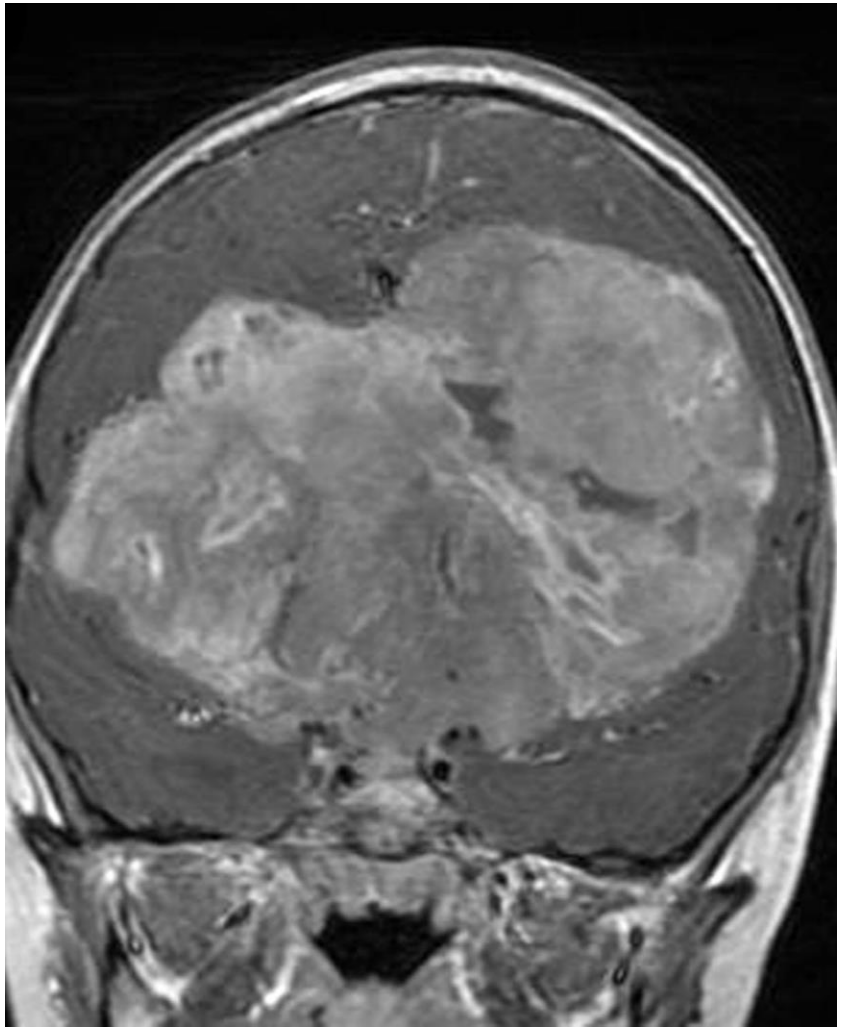
San Francisco

MENINGEAL NEOPLASMS





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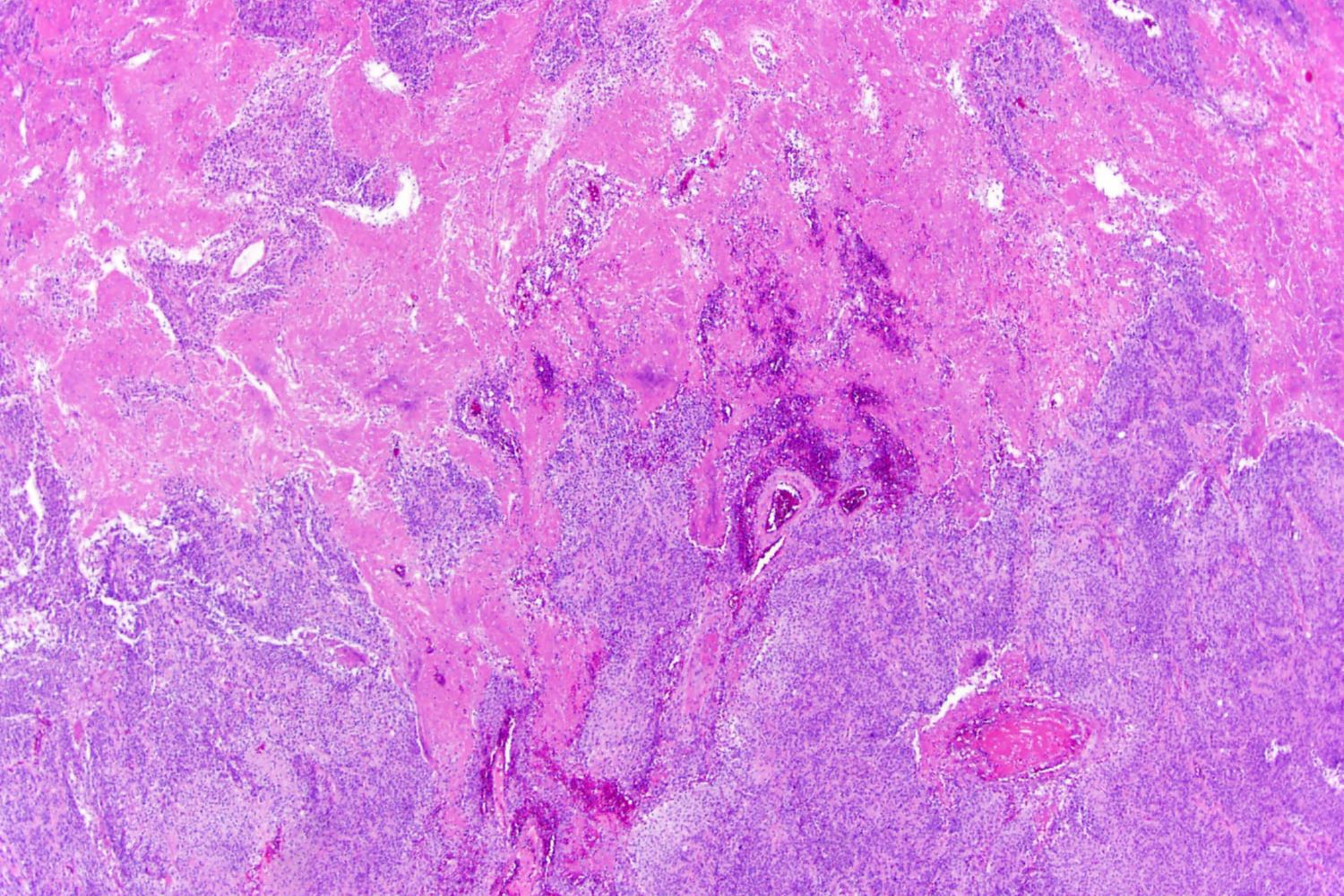
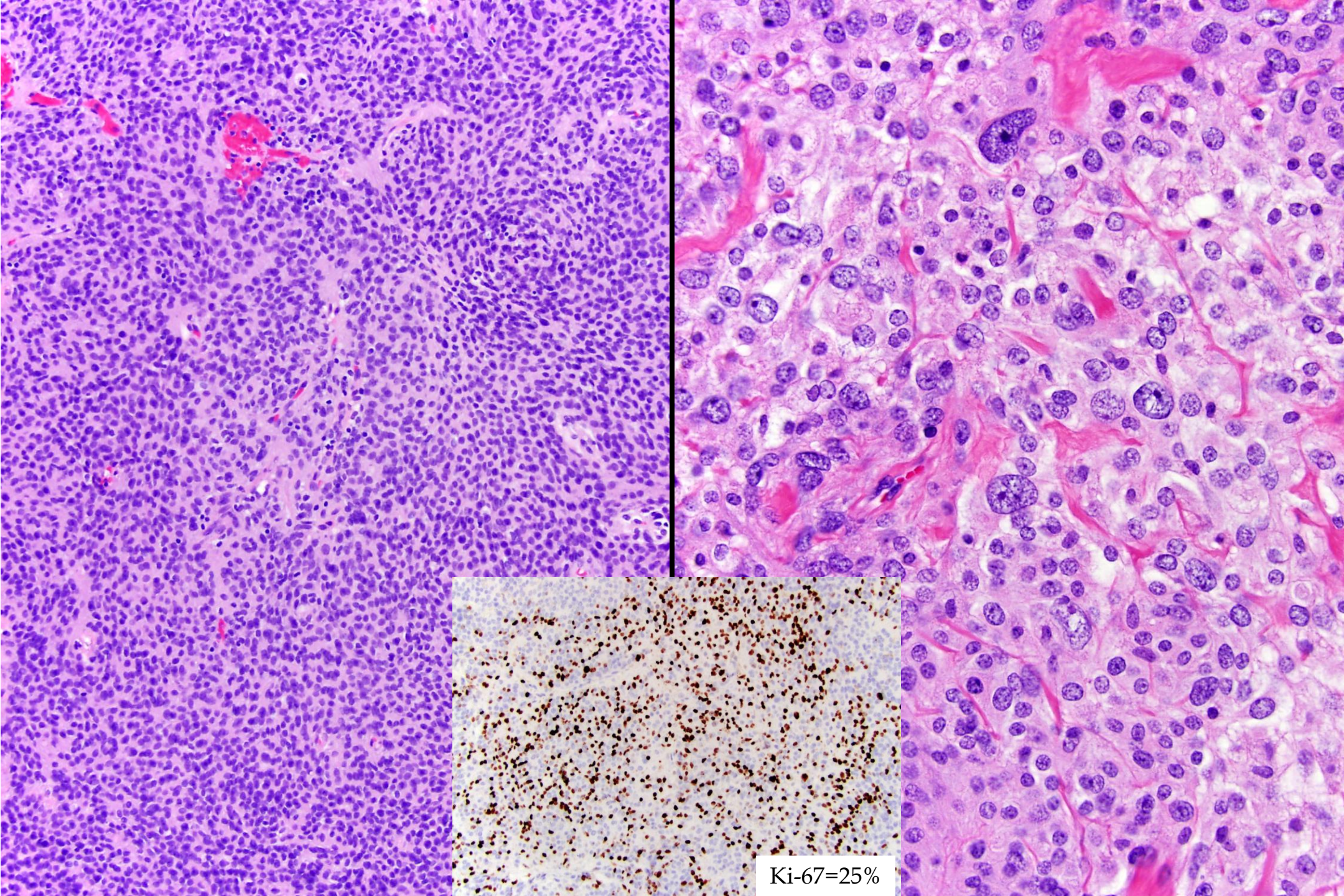
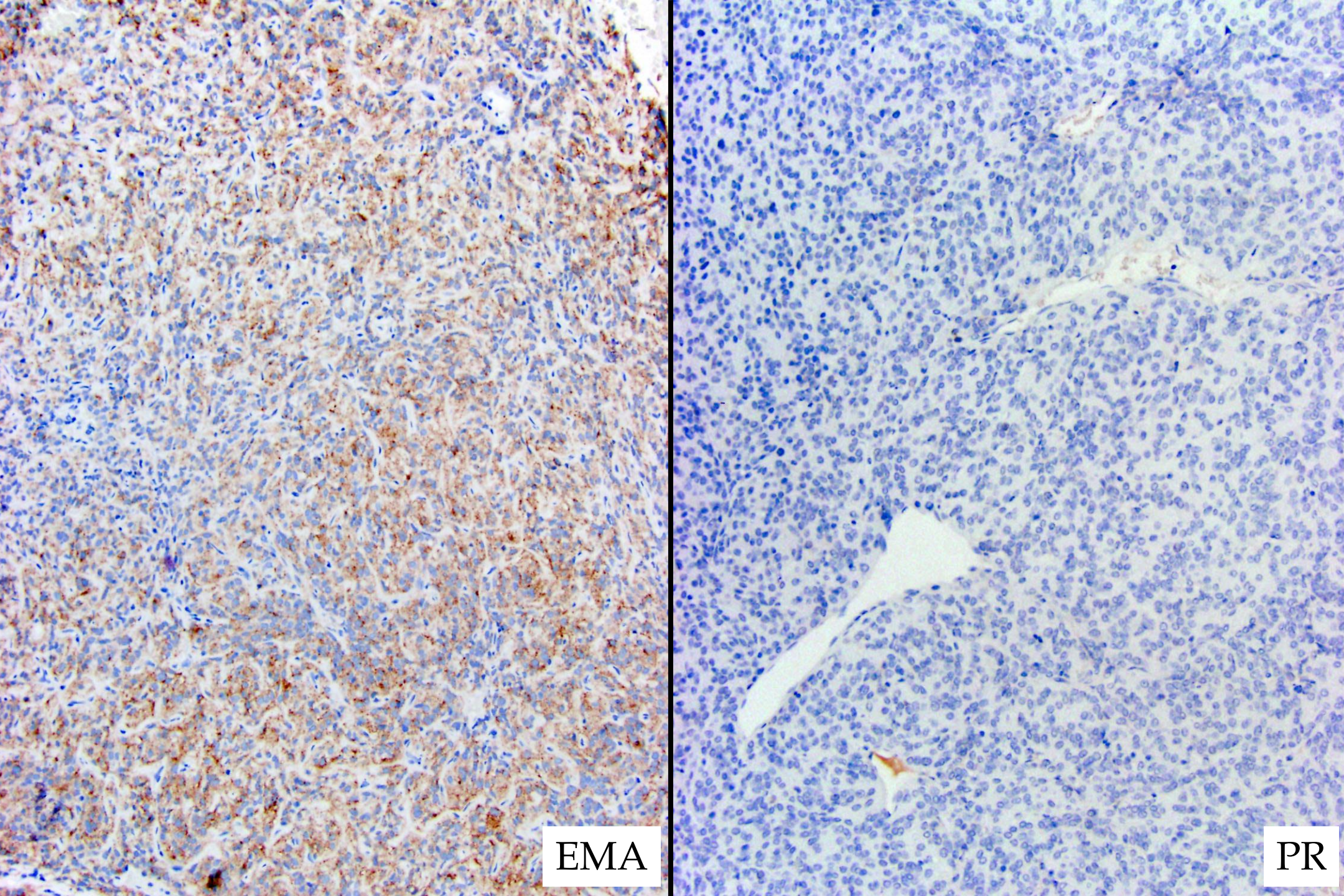
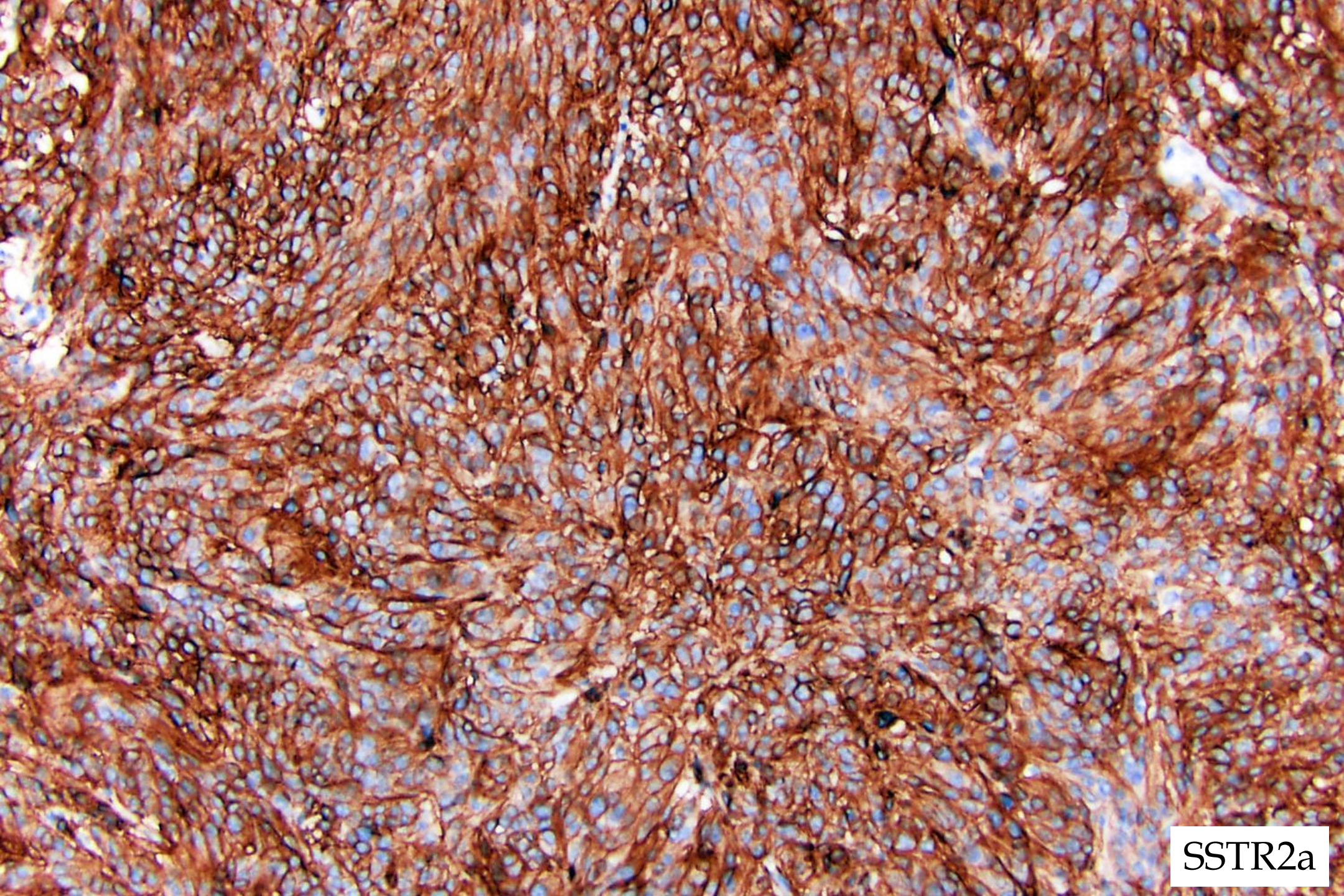



Ki-67=25%


EMA
PR


SSTR2a

[1801] Reliability of Somatostatin Receptor 2a as a Marker of Meningioma: An Immunohistochemical Study

Joshua R Menke, Allen M Gown, Sean Thomas, Arie Perry, Tarik Tihan. UCSF, San Francisco, CA; PhenoPath, Seattle, WA

Background: Meningioma is the most common extraaxial primary CNS tumor. While most meningiomas are easily diagnosed on routine stains, immunohistochemistry may become necessary for diagnosis in some tumors. However, a robust immunohistochemical marker has been elusive. Currently the most reliable meningioma markers are epithelial membrane antigen (EMA) and progesterone receptor (PR). Recent studies suggest somatostatin receptor 2a (SSTR2a) may also be a good meningioma marker.

Design: We identified cases of meningioma with an unequivocal diagnosis and WHO grade at our institution between 2002 and 2012. Small biopsy material and decalcified or frozen tissues were excluded. Slides were reviewed for diagnosis and selection of the appropriate block for microarray generation. Two 2 mm cores were taken from each block to generate microarrays along with control tissue from normal meninges, normal brain, lung adenocarcinoma and placenta. Immunohistochemical stains for SSTR2a, EMA and PR were performed following optimization of pretreatment and primary antibody dilutions. Each tissue core was assigned a score (0 to 3+) indicating signal intensity. The Mann Whitney Wilcoxon test was used determine whether each marker showed significantly different score distributions between normal meninges and meningiomas.

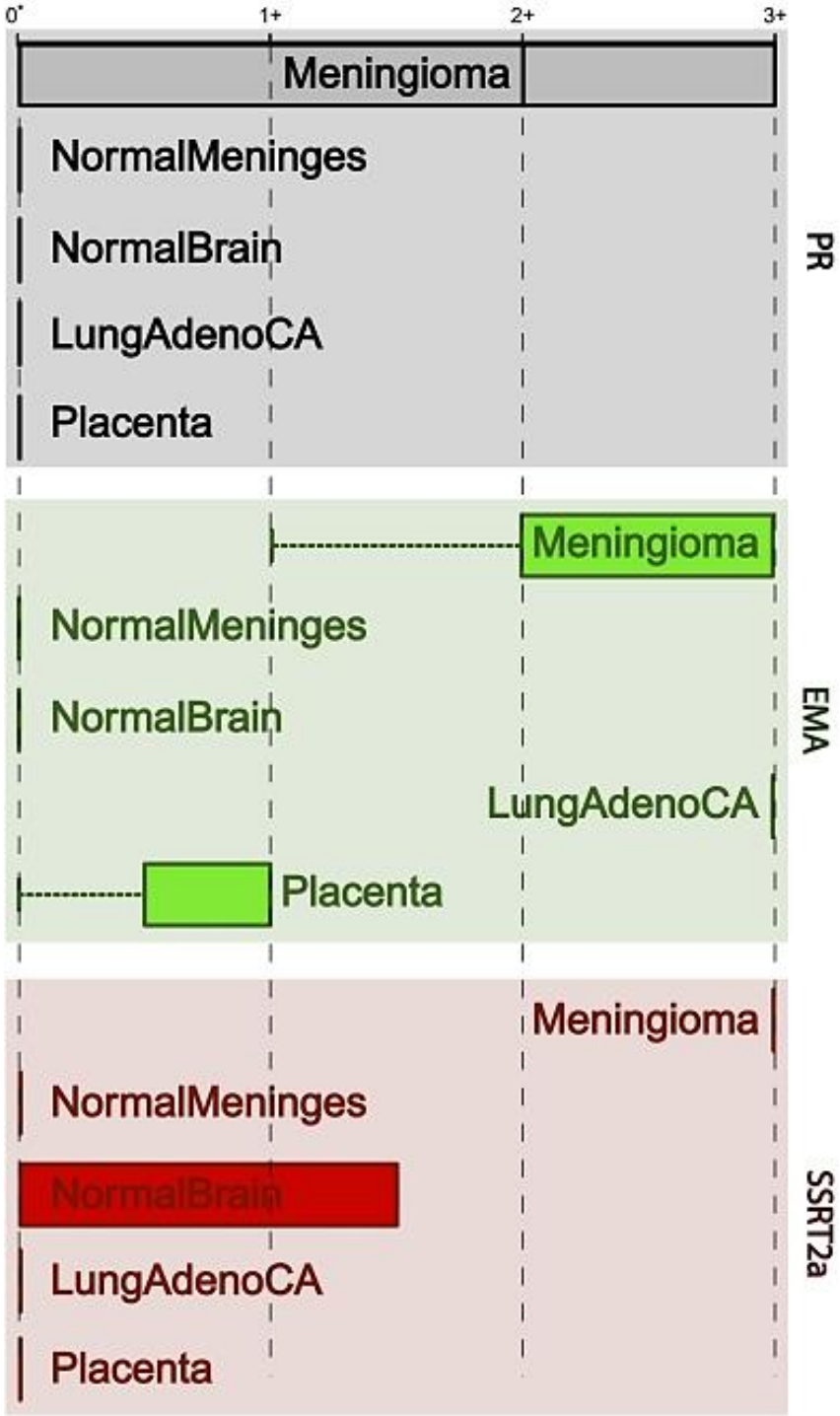
Results: 176 cases were included in the study. SSTR2a was positive in all 176 cases, EMA was positive in 168 cases and PR was positive in 171 cases. The differences in staining among normal meninges, meningioma and lung adenocarcinoma were analyzed. SSRT2a was most striking in its ability to stain positively for meningiomas as opposed to controls ($p < 6.3$ e-7), followed by EMA ($p < 4.8$ e-6) and PR ($p < 0.01$). The interquartile ranges of different factors' scores (Figure 1) showed that SSTR2a is the most reliable marker for meningiomas and that normal meninges were essentially negative for this marker.

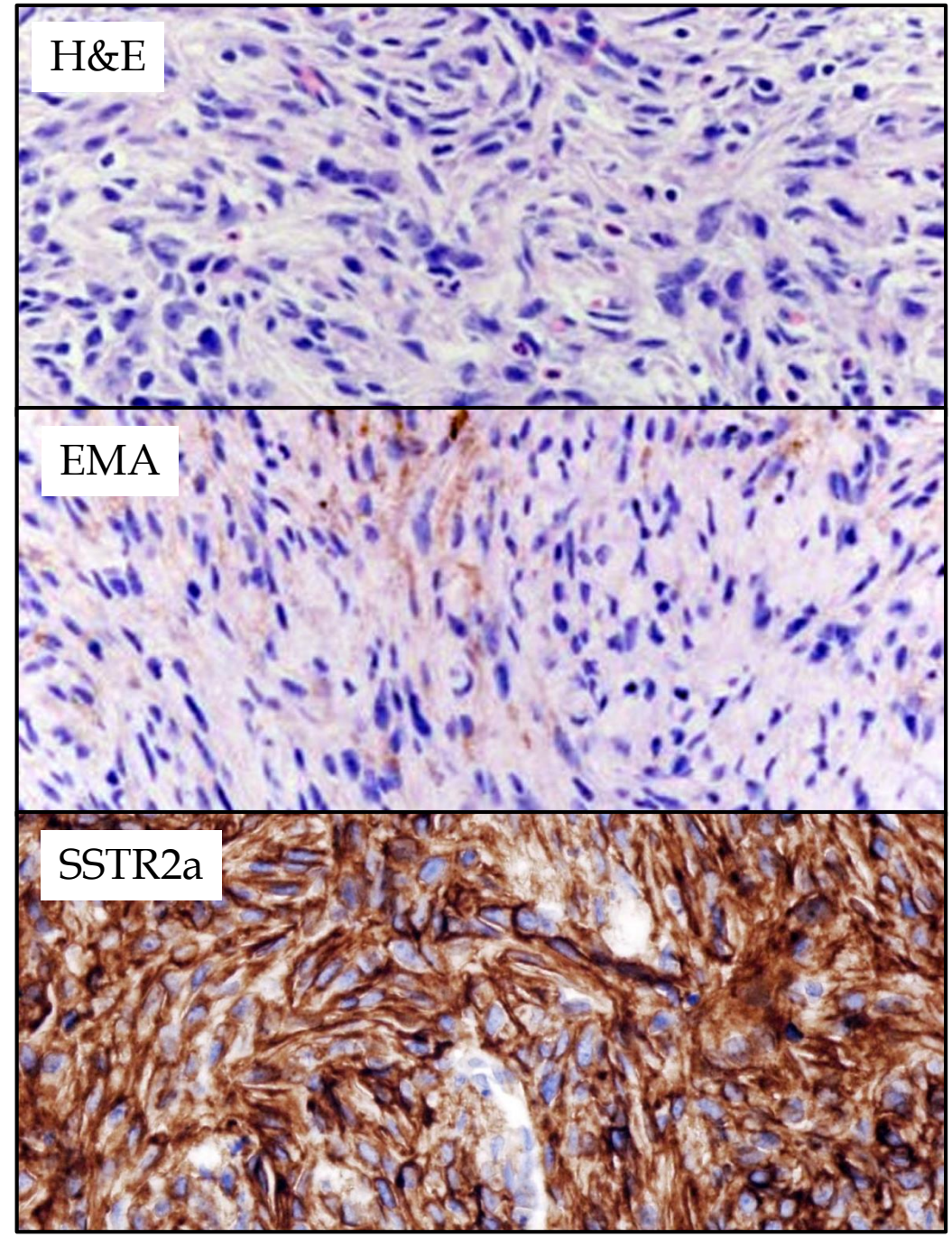
SSTR2a was positive in 5 cases, in which both EMA and PR failed to stain tumor.

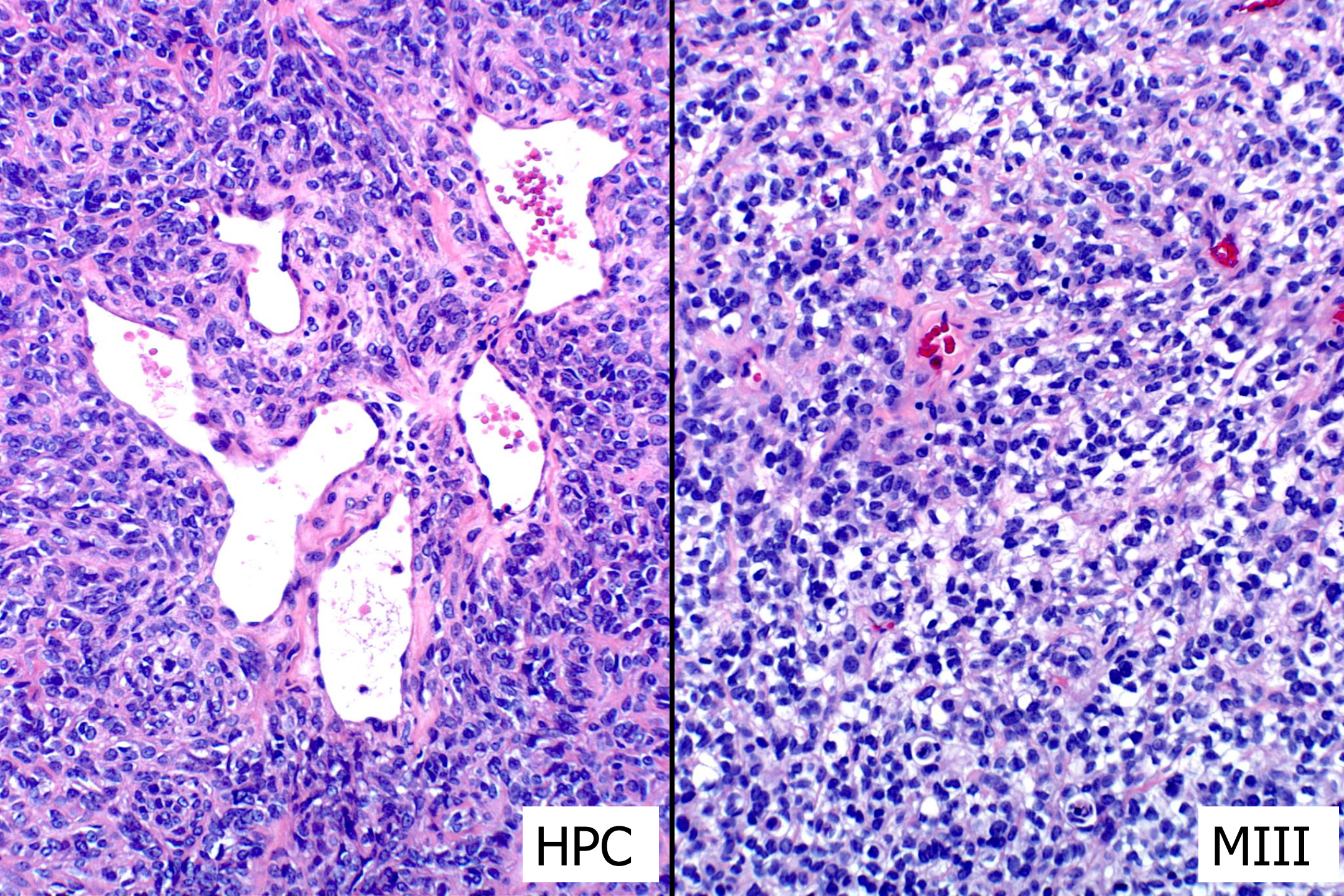
Conclusions: SSTR2a appeared to be a robust marker for meningiomas and even stained some meningiomas that classical markers did not. Studies are underway to determine SSTR2a staining in schwannomas, solitary fibrous tumors and other mesenchymal neoplasms to further characterize the specificity of this marker.

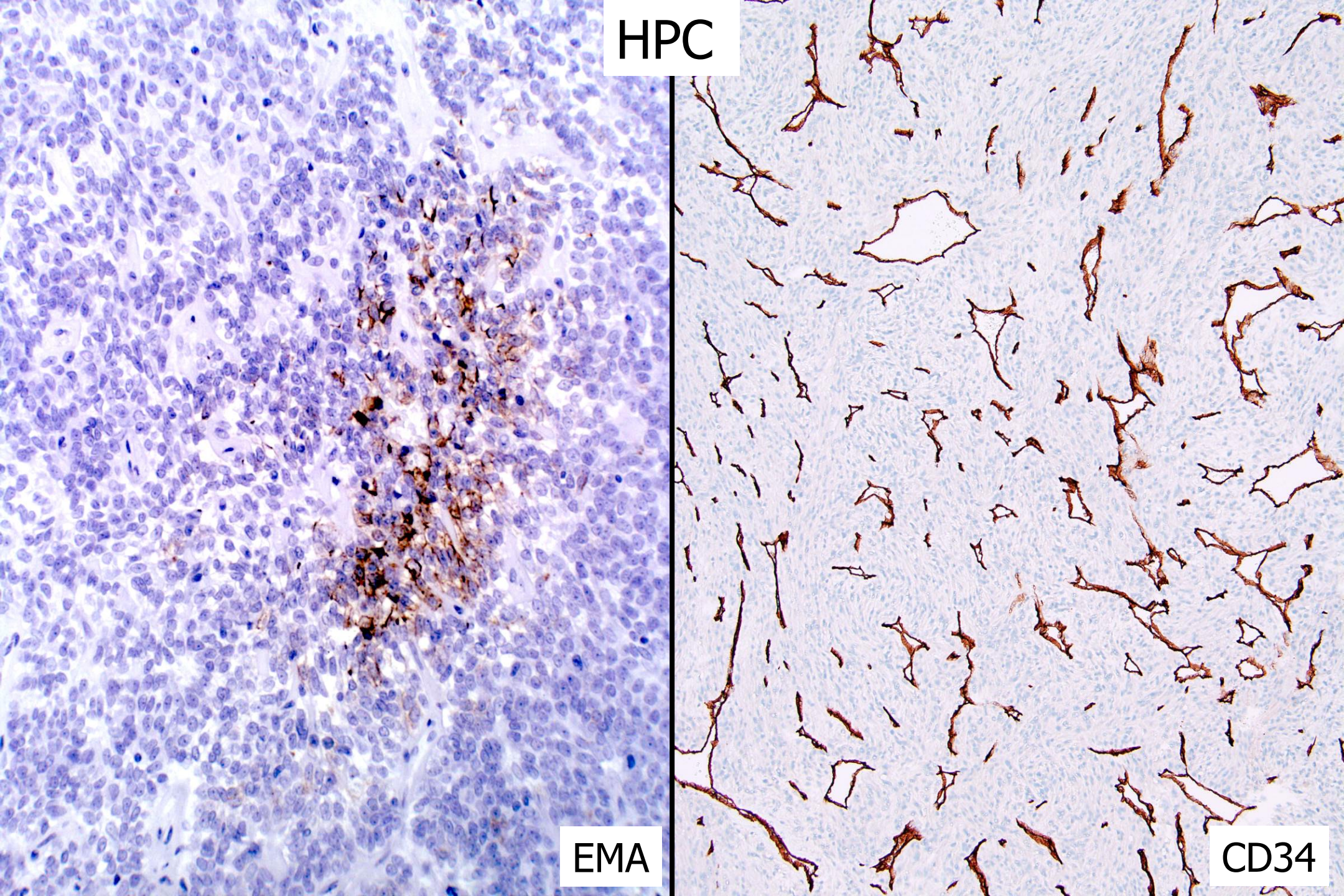
Category: Neuropathology

USCAP Meeting 2014:
Mod Pathol 27;Supp 2, 439A, 2014


0
1+
2+
3+
Meningioma
NormalMeninges
NormalBrain
LungAdenoCA
Placenta
PR
Meningioma
NormalMeninges
NormalBrain
LungAdenoCA
Placenta
EMA
Meningioma
NormalMeninges
NormalBrain
LungAdenoCA
Placenta
SSRT2a

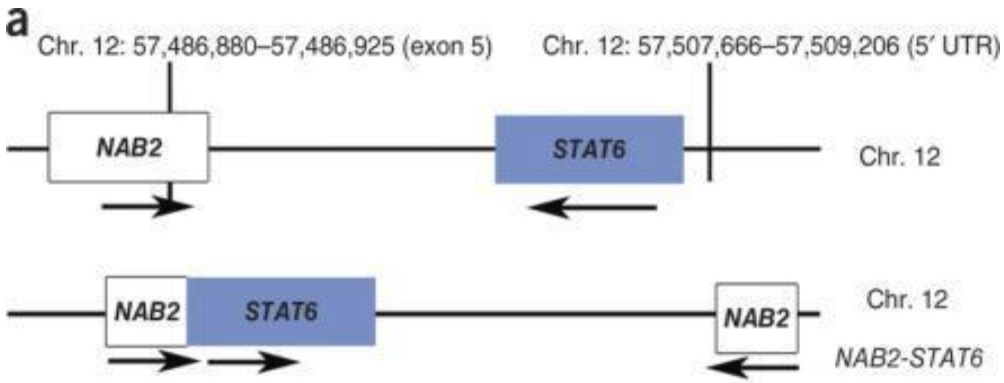

H&E
EMA
SSTR2a

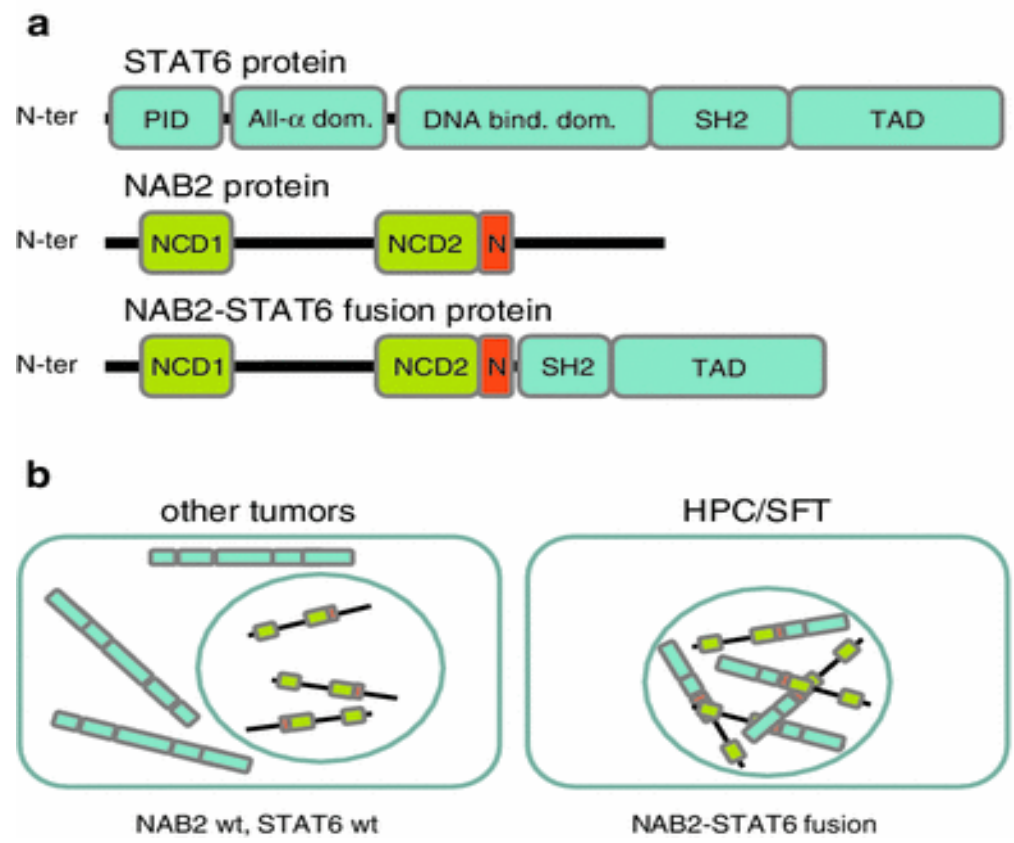

HPC
MIII


HPC
EMA
CD34

SFT/HPC Genetics

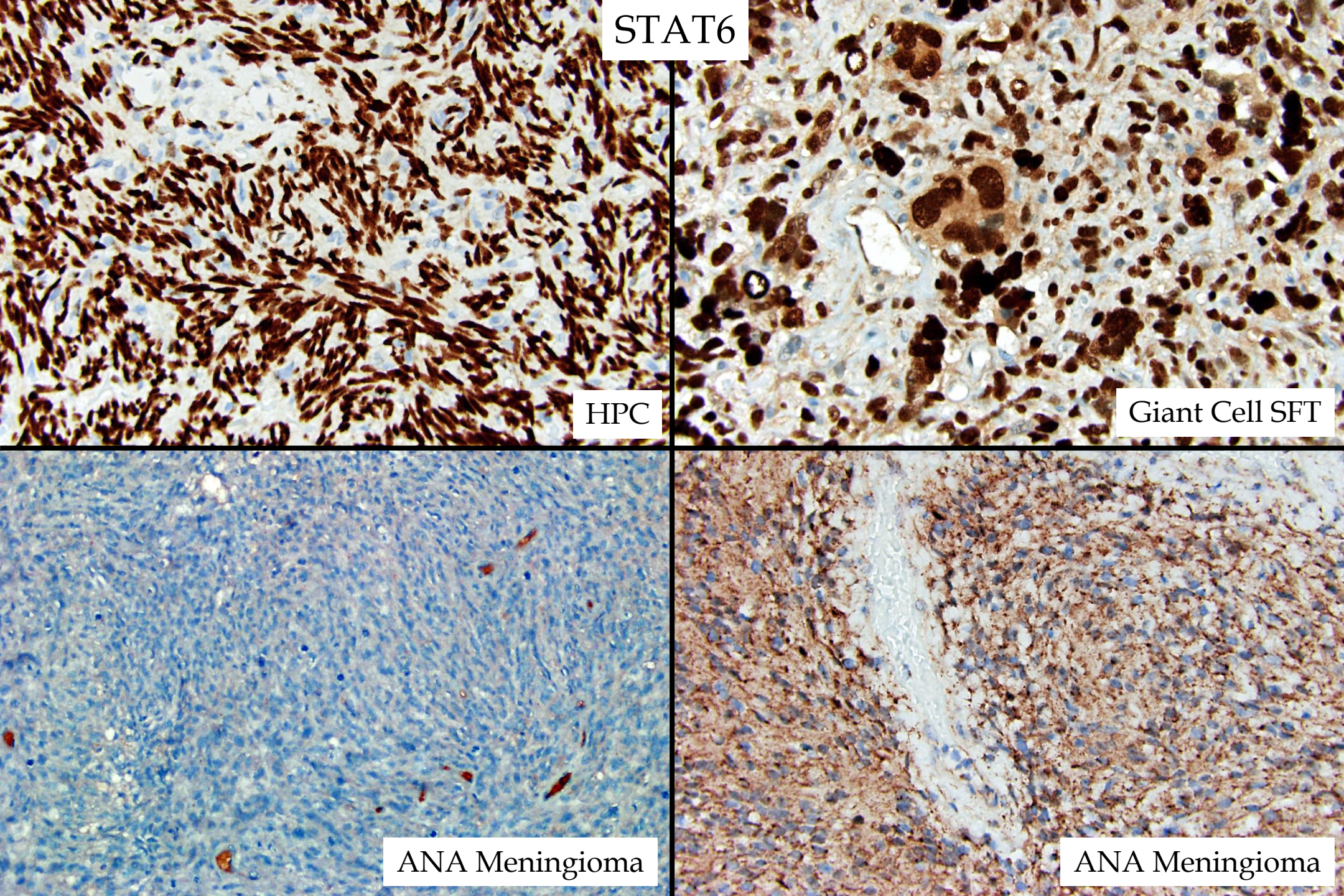
- Translocations and inversions of Chr 12q13
- *NAB2-STAT6* fusion





Nat Genet. 2013;45(2):131-2.

Acta Neuropathol. 2013;125(5):651-8.


STAT6
HPC
Giant Cell SFT
ANA Meningioma
ANA Meningioma

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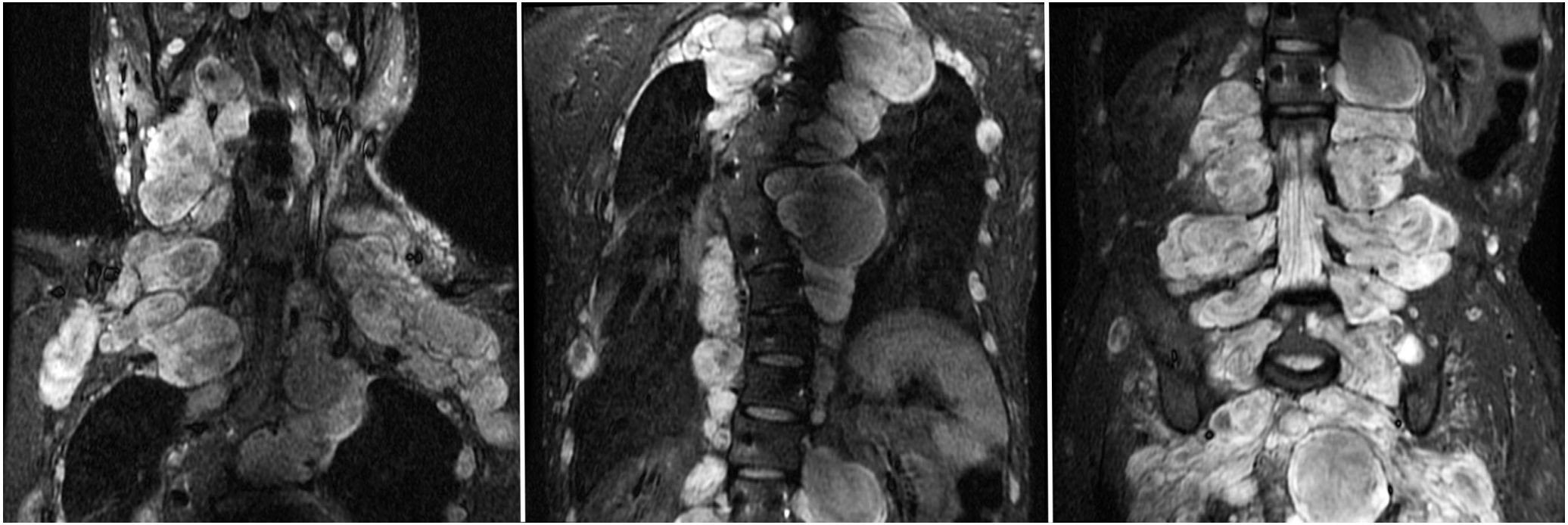
NERVE SHEATH TUMORS



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Acta Neuropathol (2014) 127:565–572
DOI 10.1007/s00401-014-1246-6

ORIGINAL PAPER

Neurofibromin specific antibody differentiates malignant peripheral nerve sheath tumors (MPNST) from other spindle cell neoplasms

David E. Reuss · Antje Habel · Christian Hagenlocher · Jana Mucha · Ulrike Ackermann · Claudia Tessmer · Jochen Meyer · David Capper · Gerhard Moldenhauer · Victor Mautner · Pierre-Olivier Frappart · Jens Schittenhelm · Christian Hartmann · Christian Hagel · Kathrin Katenkamp · Iver Petersen · Gunhild Mechtersheimer · Andreas von Deimling

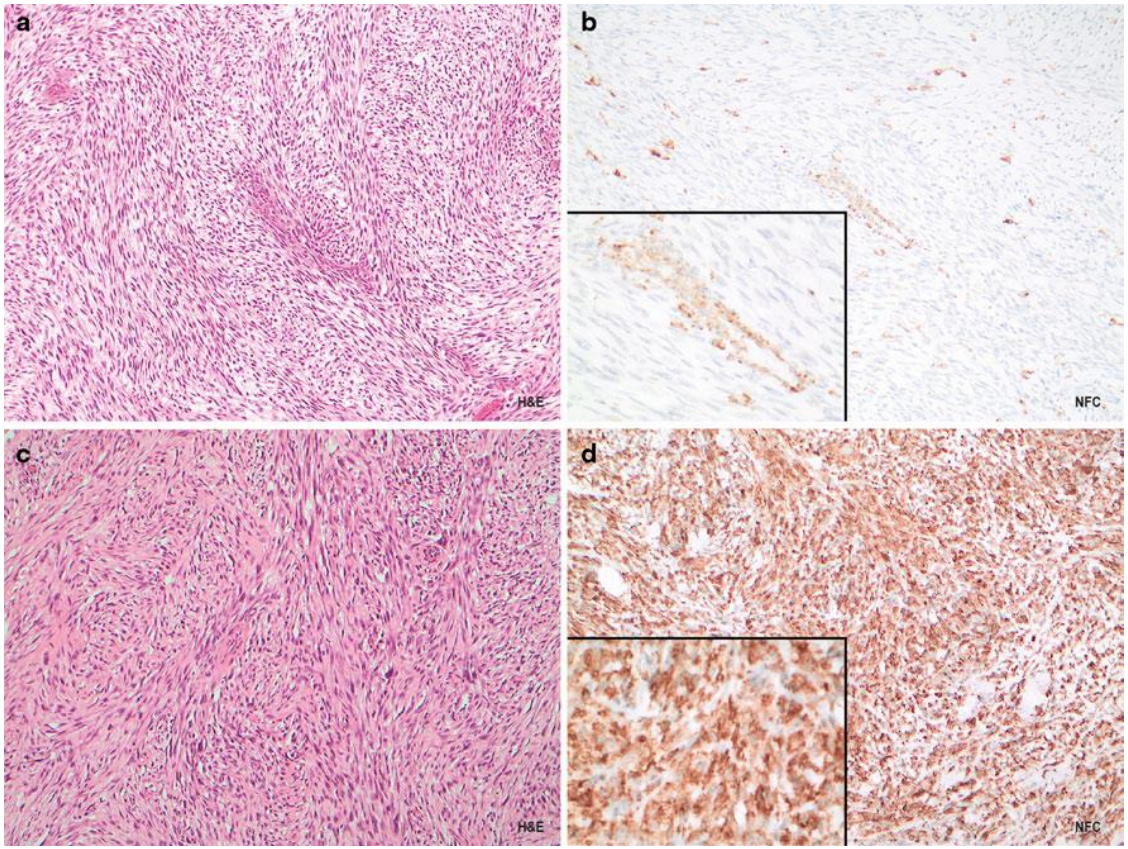


Table 2 Results of NFC immunohistochemistry in soft tissue tumors

Tumor type	*n*	NF1 loss IHC (NFC)
MPNST		
NF1	25	22 (88 %)
Sporadic	61	26 (43 %)
Synovial sarcoma	22	0
Solitary fibrous tumor	23	0
Myxofibrosarcoma	8	2
Leiomyosarcoma	16	1 (6 %)
Pleomorphic liposarcoma	12	2 (16 %)
Dedifferentiated liposarcoma	50	0
Myxoid liposarcoma	27	0
Schwannoma	27	0
Cellular schwannoma	9	0
Epitheloid sarcoma	7	0
Angiosarcoma	13	0
Low-grade fibromyxoid sarcoma	14	0
Undifferentiated pleomorphic sarcoma	28	4 (14 %)
Extraskeletal myxoid chondrosarcoma	9	0

Morphologic and immunohistochemical features of malignant peripheral nerve sheath tumors and cellular schwannomas

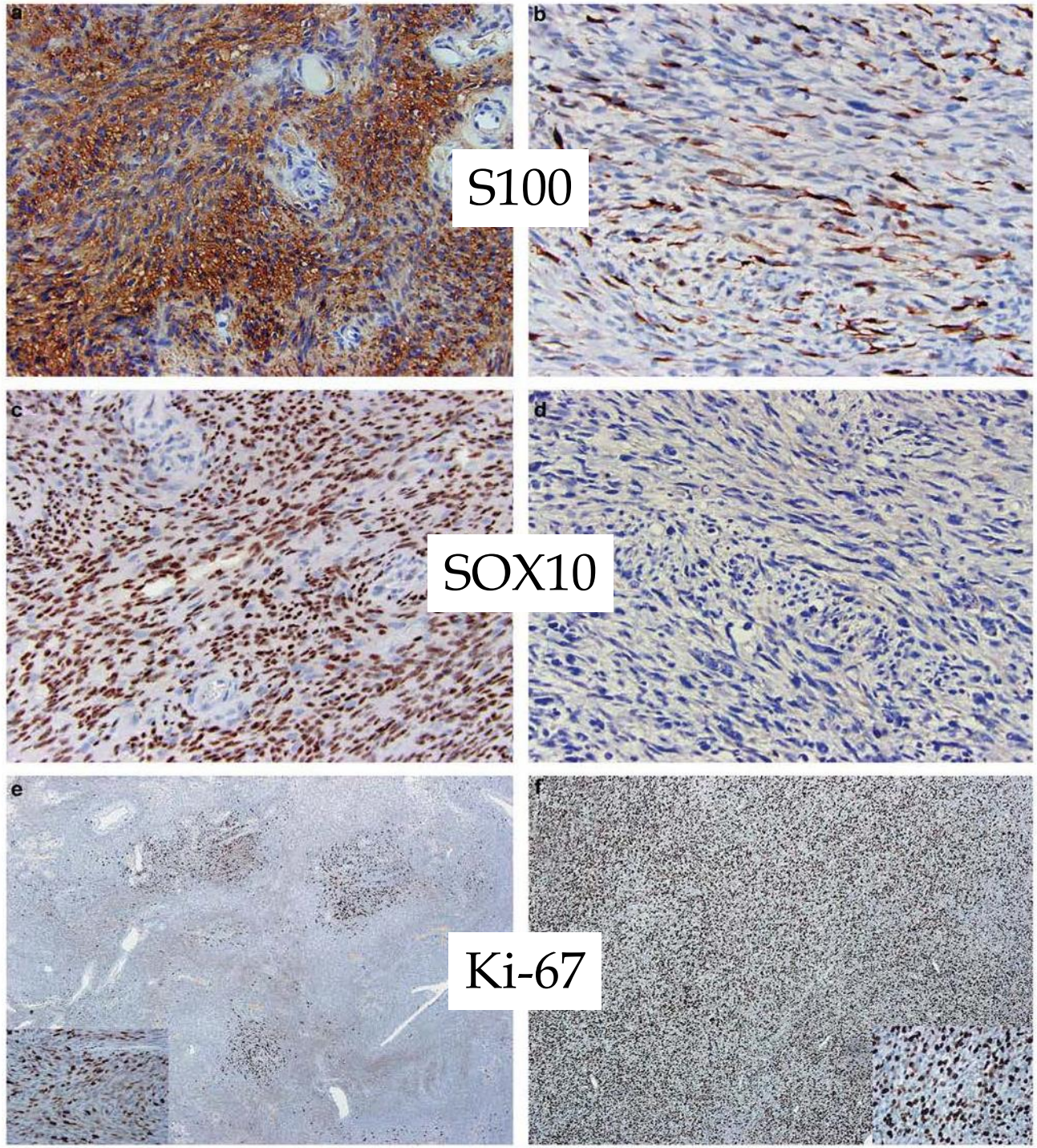
Melike Pekmezci[1], David E Reuss[2], Angela C Hirbe[3], Sonika Dahiya[4], David H Gutmann[5], Andreas von Deimling[2], Andrew E Horvai[6] and Arie Perry[1,7]

[1]Division of Neuropathology, Department of Pathology, University of California San Francisco, San Francisco, CA, USA; [2]Department Neuropathology, German Cancer Consortium (DKTK), CCU Neuropathology German Cancer Research Center (DKFZ), Institute of Pathology, University of Heidelberg, Heidelberg, Germany; [3]Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA; [4]Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO, USA; [5]Department of Neurology, Washington University School of Medicine, St Louis, MO, USA; [6]Department of Pathology, University of California San Francisco, San Francisco, CA, USA and [7]Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

Cellular schwannoma is an uncommon, but well-recognized, benign peripheral nerve sheath tumor, which can be misdiagnosed as malignant peripheral nerve sheath tumor. To develop consensus diagnostic criteria for cellular schwannoma, we reviewed 115 malignant peripheral nerve sheath tumor and 26 cellular schwannoma cases from two institutions. Clinical data were retrieved from the electronic medical records, and morphologic features, maximal mitotic counts, Ki67 labeling indices, and immunohistochemical profiles (SOX10, SOX2, p75NTR, p16, p53, EGFR, and neurofibromin) were assessed. Several features distinguish cellular schwannoma from malignant peripheral nerve sheath tumor. First, in contrast to patients with malignant peripheral nerve sheath tumor, no metastases or disease-specific deaths were found in patients with cellular schwannoma. More specifically, 5-year progression-free survival rates were 100 and 18%, and 5-year disease-specific survival rates were 100 and 32% for cellular schwannoma and malignant peripheral nerve sheath tumor, respectively. Second, the presence of Schwannian whorls, a peritumoral capsule, subcapsular lymphocytes, macrophage-rich infiltrates, and the absence of fascicles favored the diagnosis of cellular schwannoma, while the presence of perivascular hypercellularity, tumor herniation into vascular lumens, and necrosis favor malignant peripheral nerve sheath tumor. Third, complete loss of SOX10, neurofibromin or p16 expression, or the presence of EGFR immunoreactivity was specific for malignant peripheral nerve sheath tumor ($P<0.001$ for each). Expression of p75NTR was observed in 80% of malignant peripheral nerve sheath tumors compared with 31% of cellular schwannomas ($P<0.001$). Fourth, Ki-67 labeling indices $\geq$20% were highly predictive of malignant peripheral nerve sheath tumor (87% sensitivity and 96% specificity). Taken together, the combinations of these histopathological and immunohistochemical features provide useful criteria to distinguish between malignant peripheral nerve sheath tumor and cellular schwannoma with high sensitivity and specificity. Additional retrospective and prospective multicenter studies with larger data sets will be required to validate these findings.

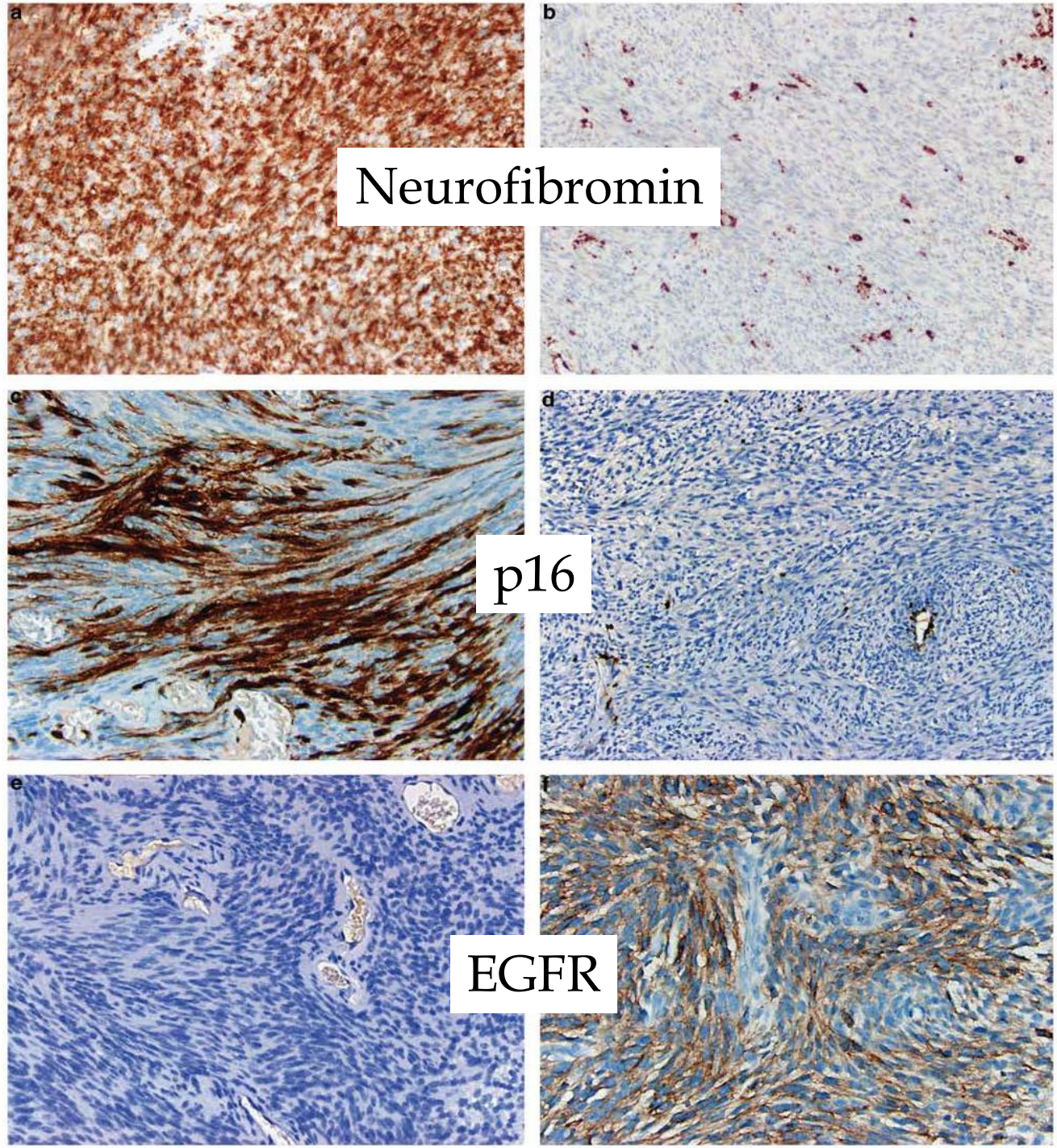
Modern Pathology (2015) **28**, 187–200; doi:10.1038/modpathol.2014.109; published online 5 September 2014

Cellular Schwannoma



MPNST

Cellular Schwannoma



MPNST

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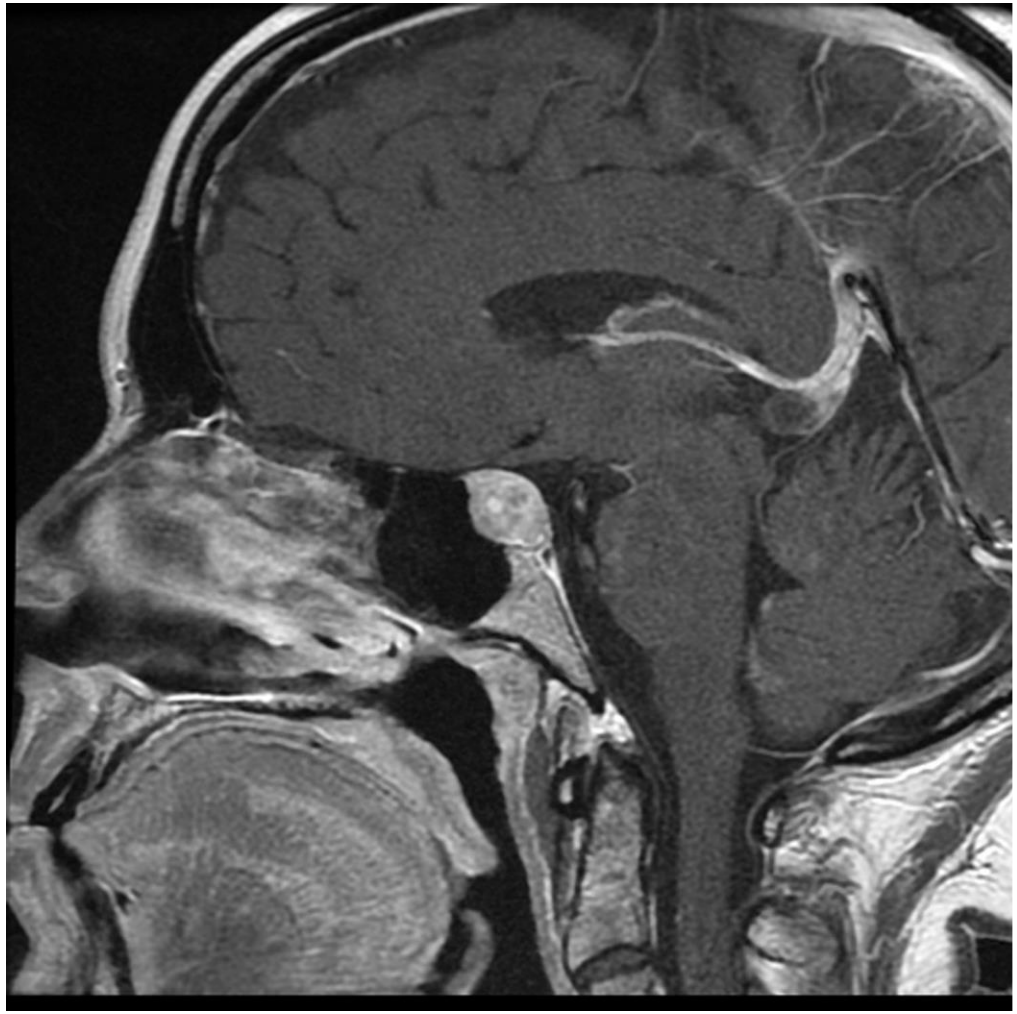
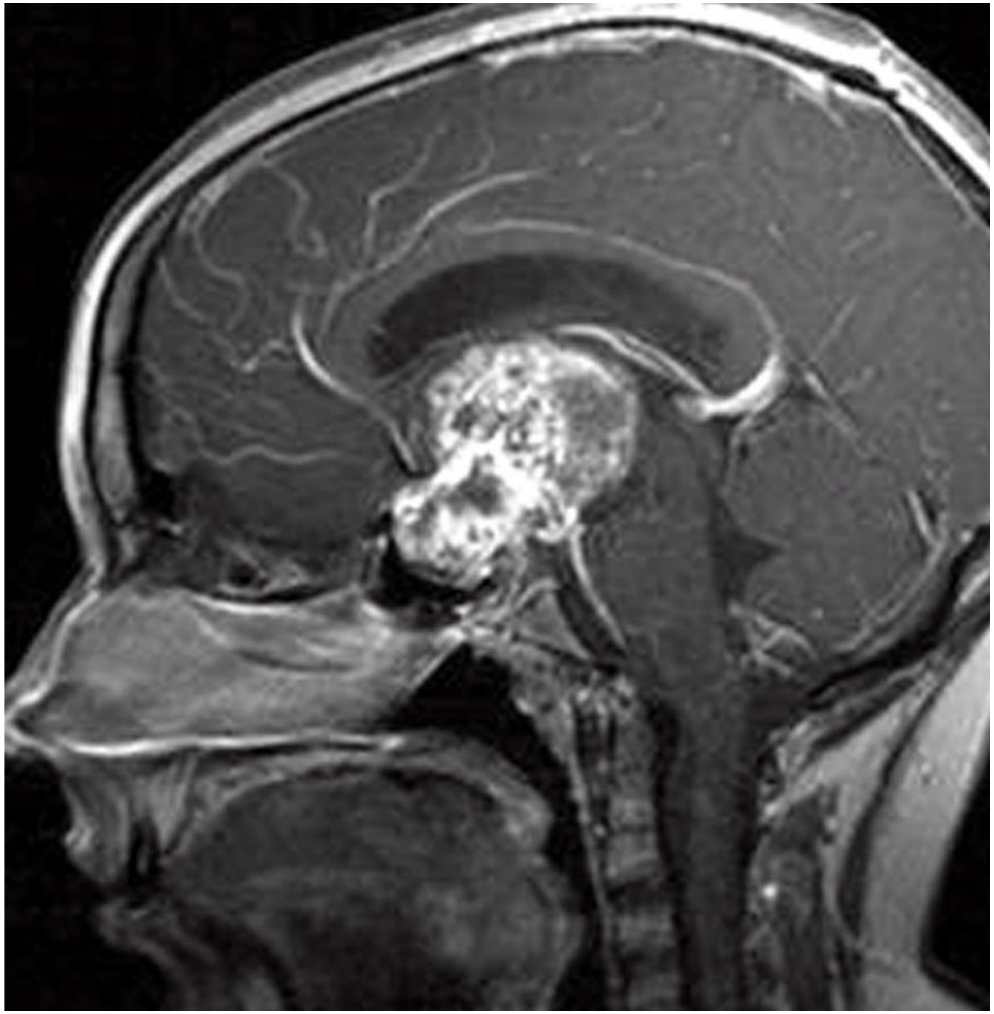
PITUITARY NEOPLASMS





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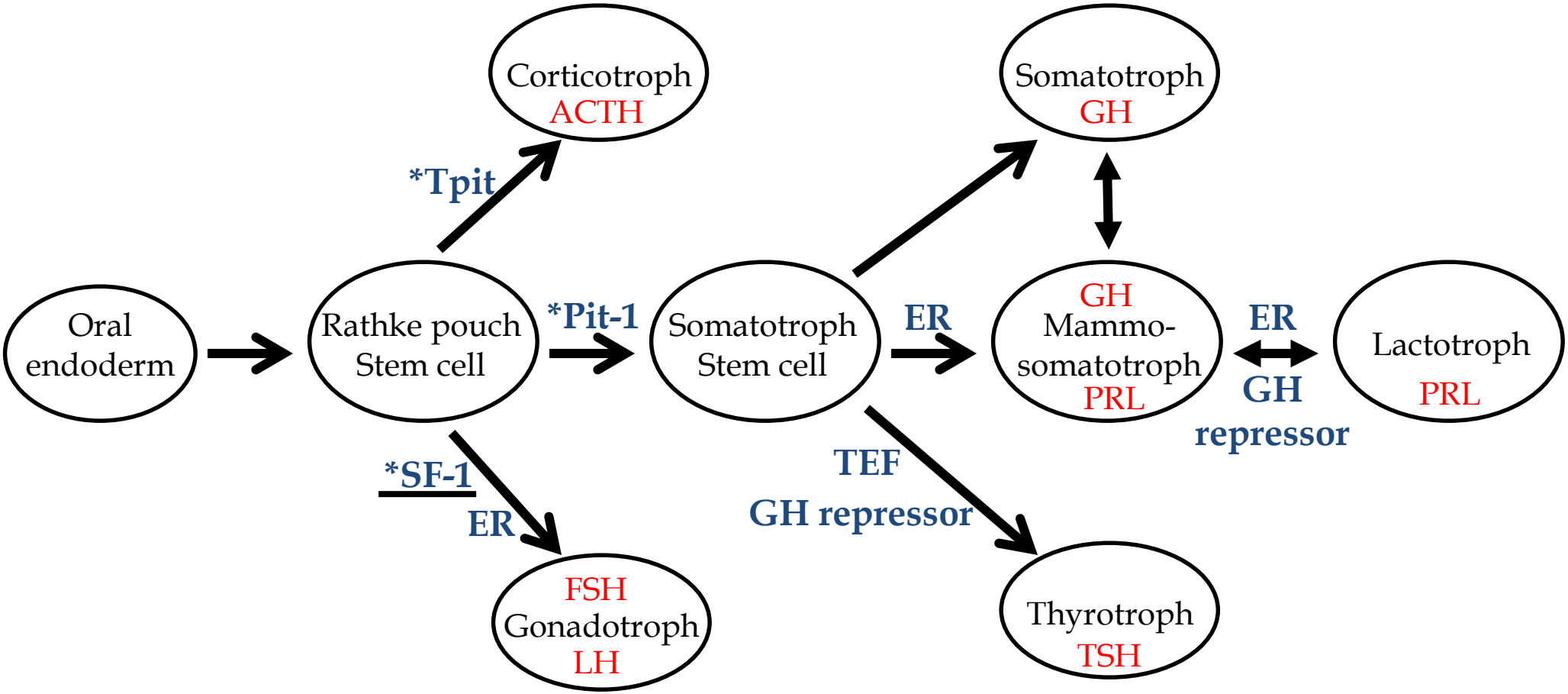
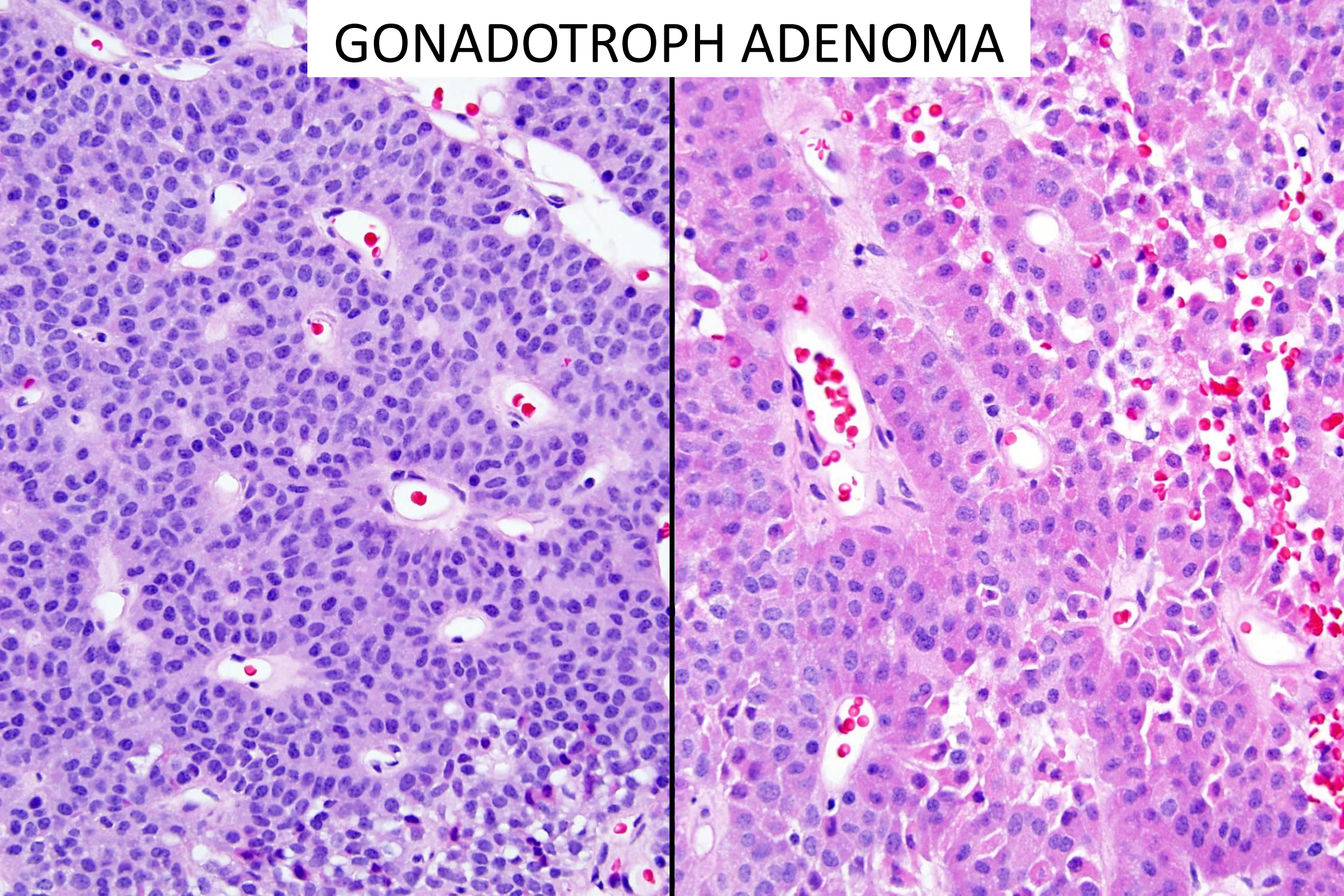
ADENOHYPOPHYSEAL DEVELOPMENT

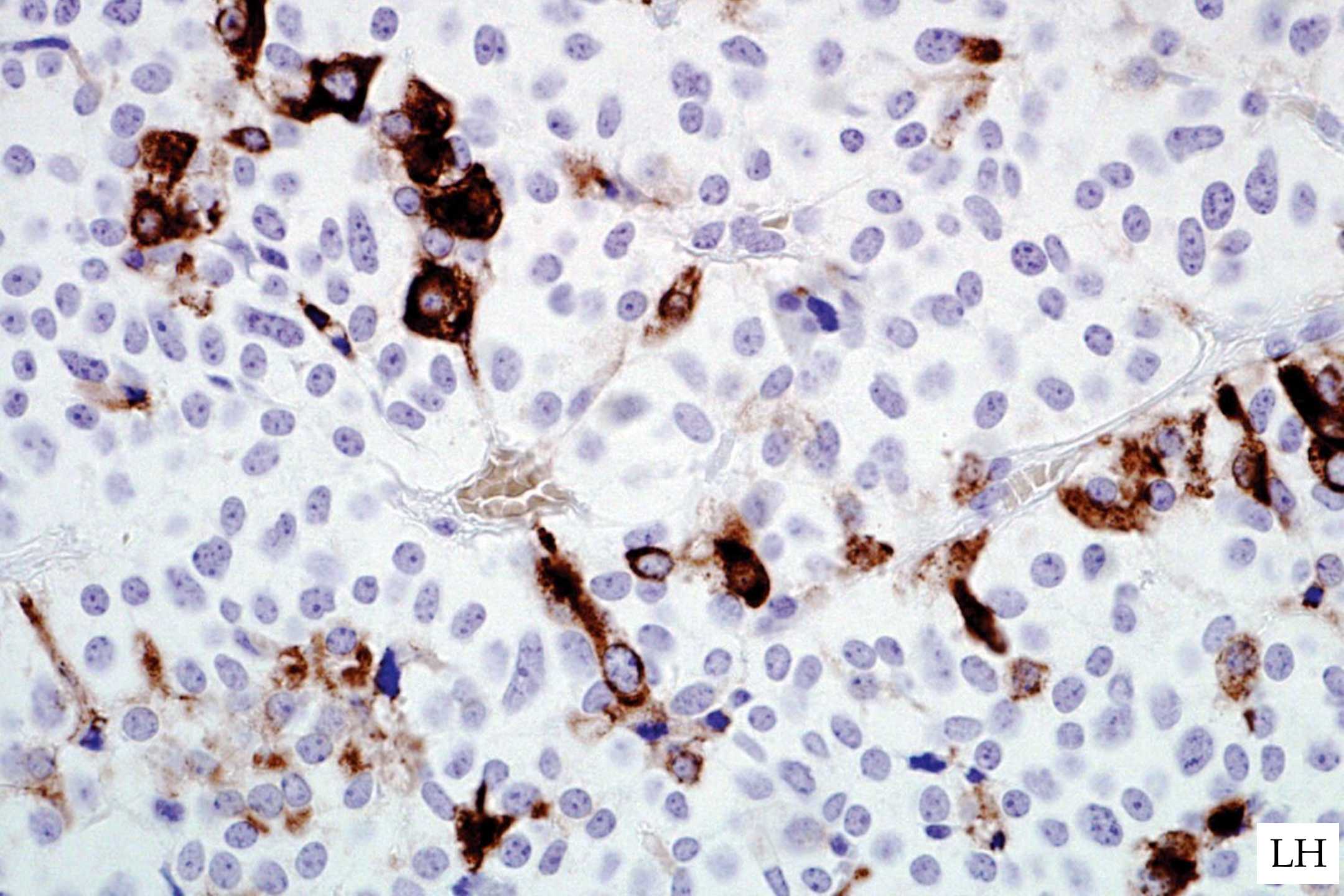


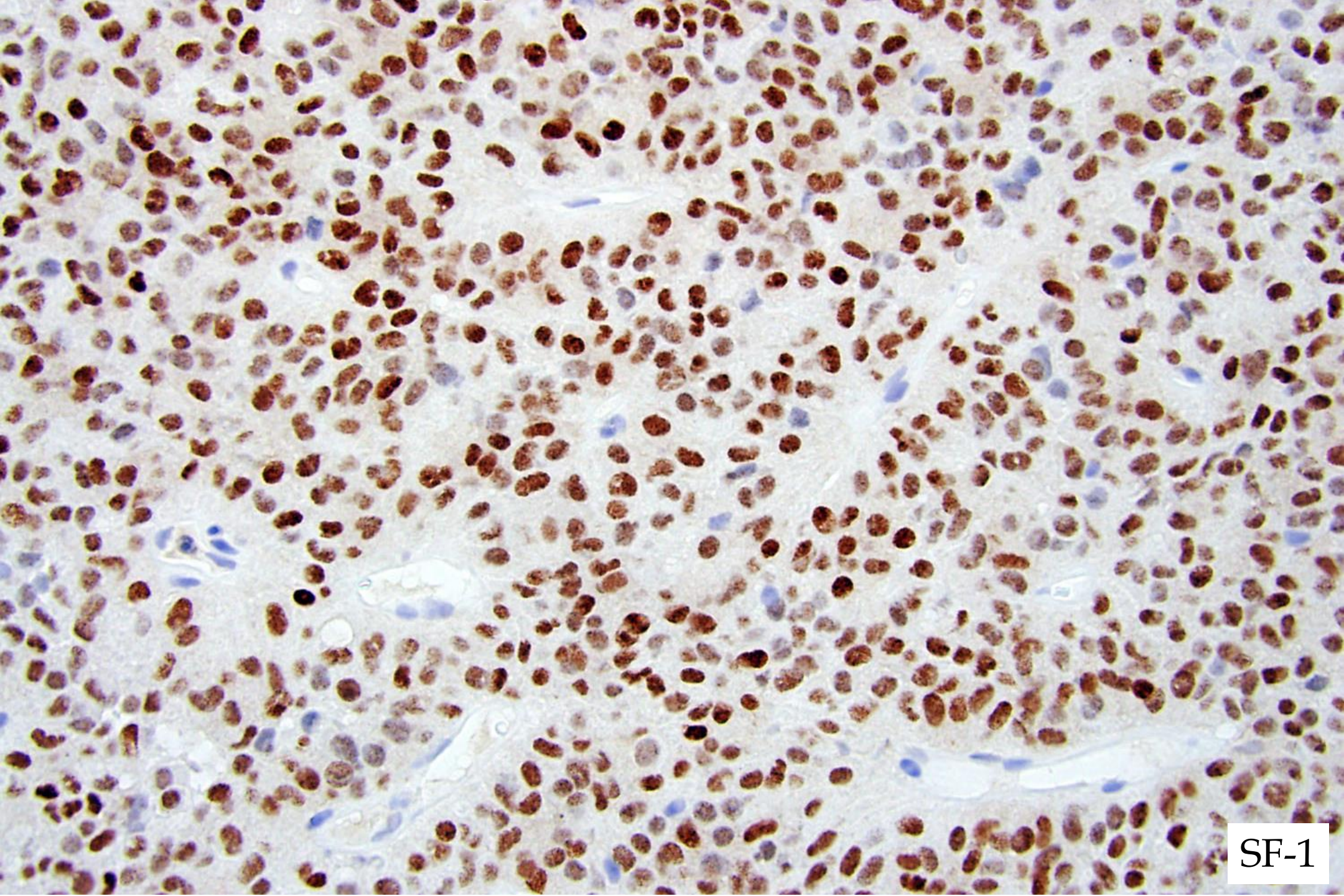
***Diagnostically useful transcription factors**

Modified from: Asa SL, Ezzat S.
Annu Rev Pathol Mech Dis 2009:4:97-126

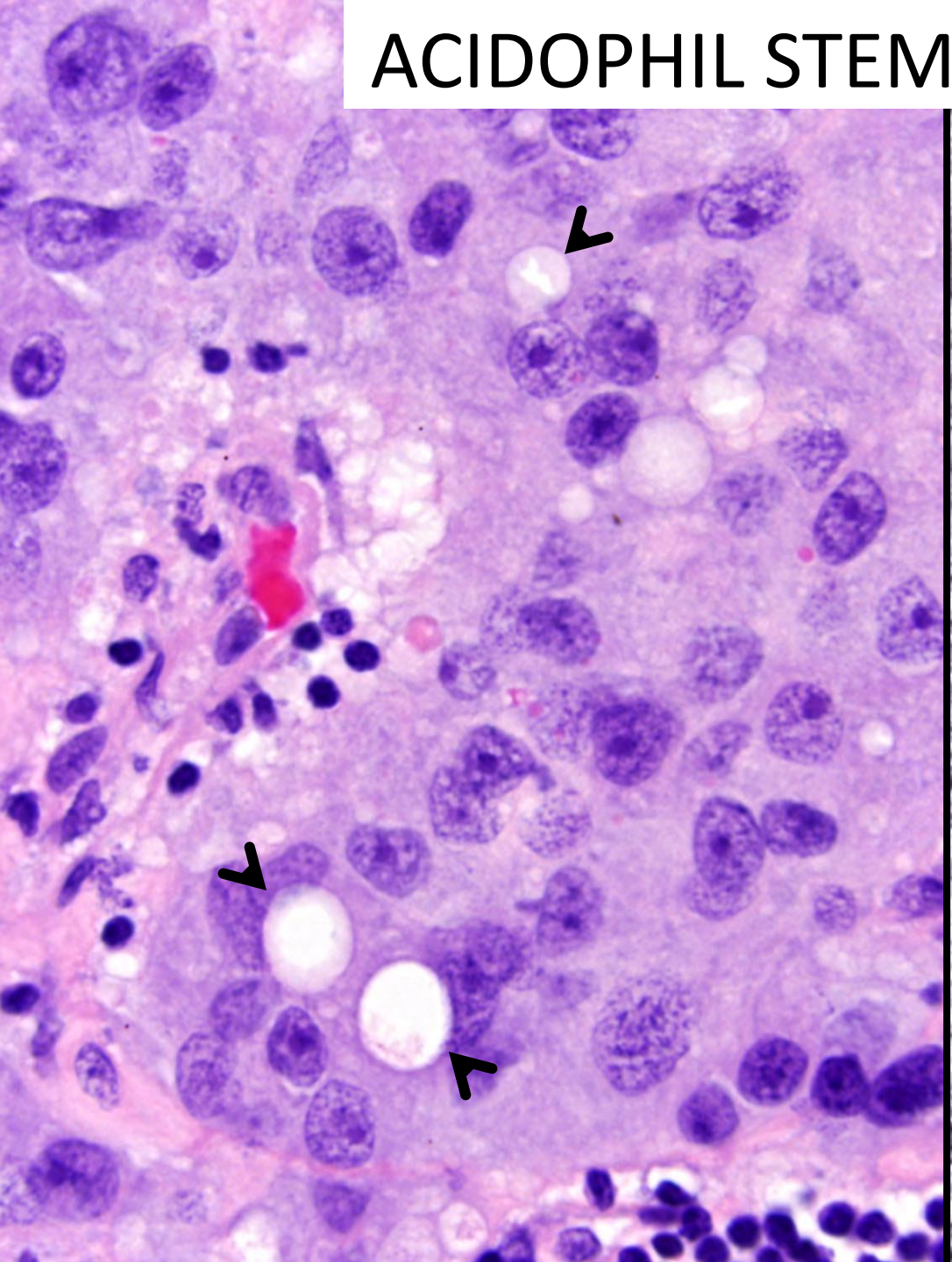
GONADOTROPH ADENOMA

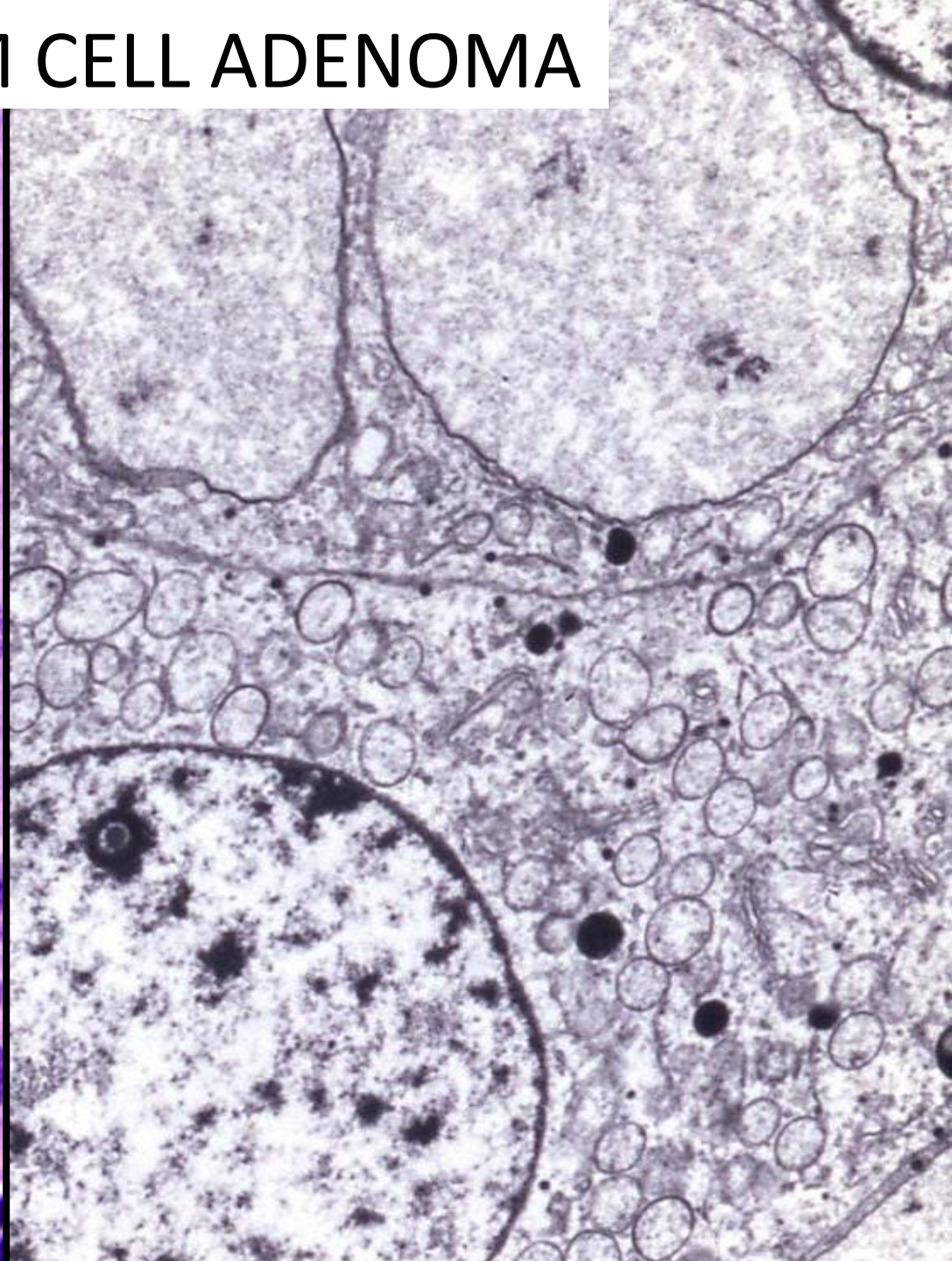



LH

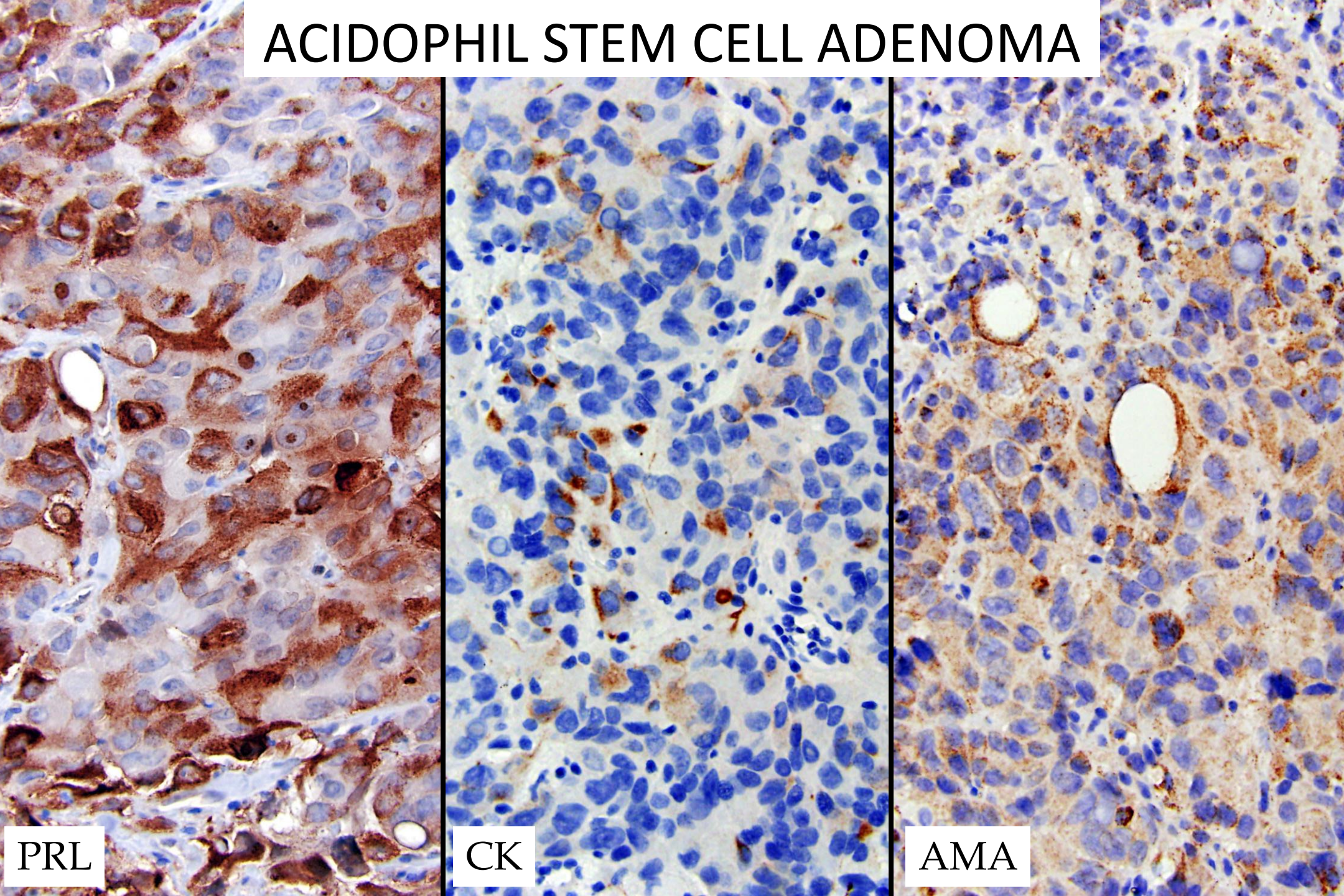

SF-1

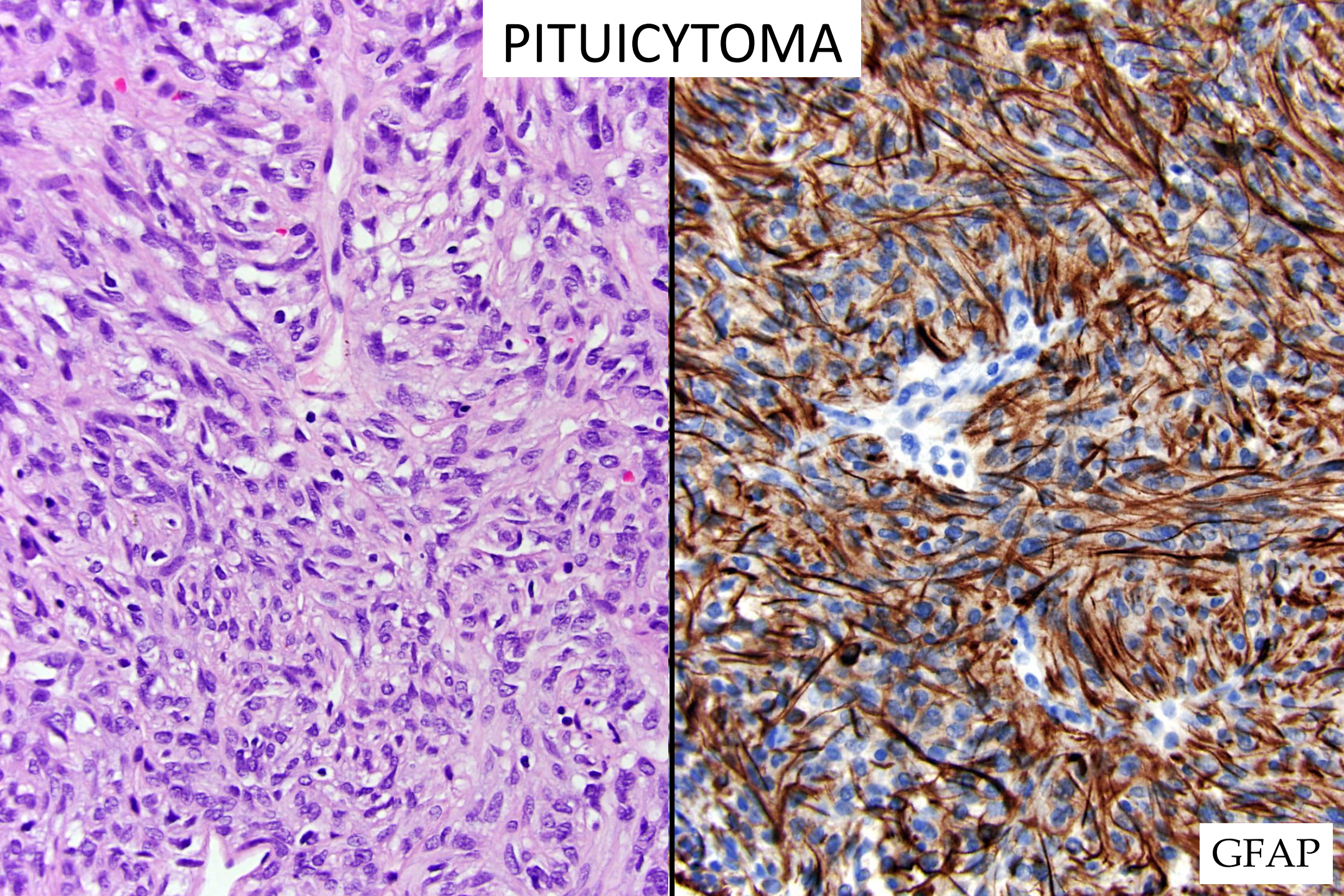
ACIDOPHIL STEM CELL ADENOMA



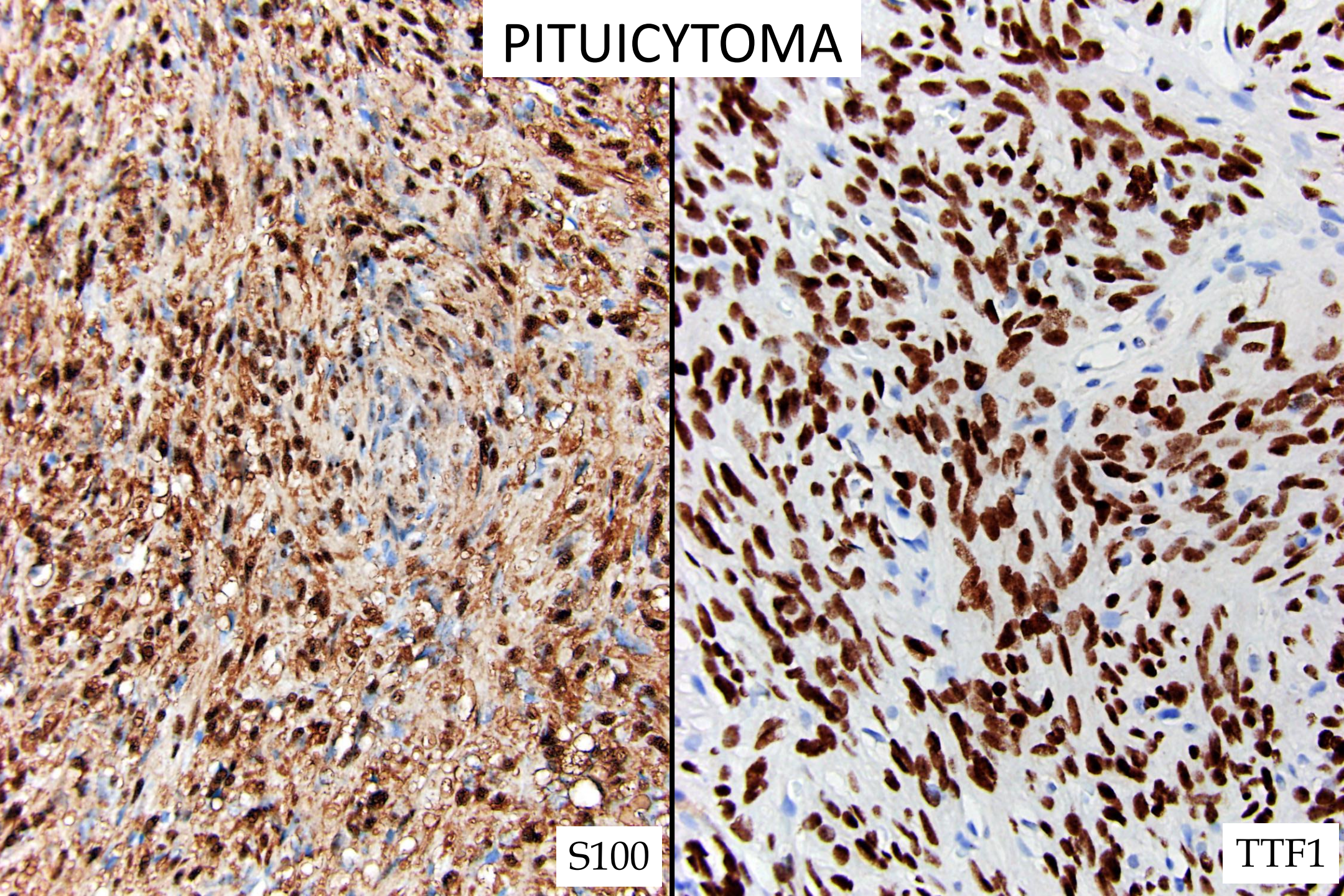


ACIDOPHIL STEM CELL ADENOMA

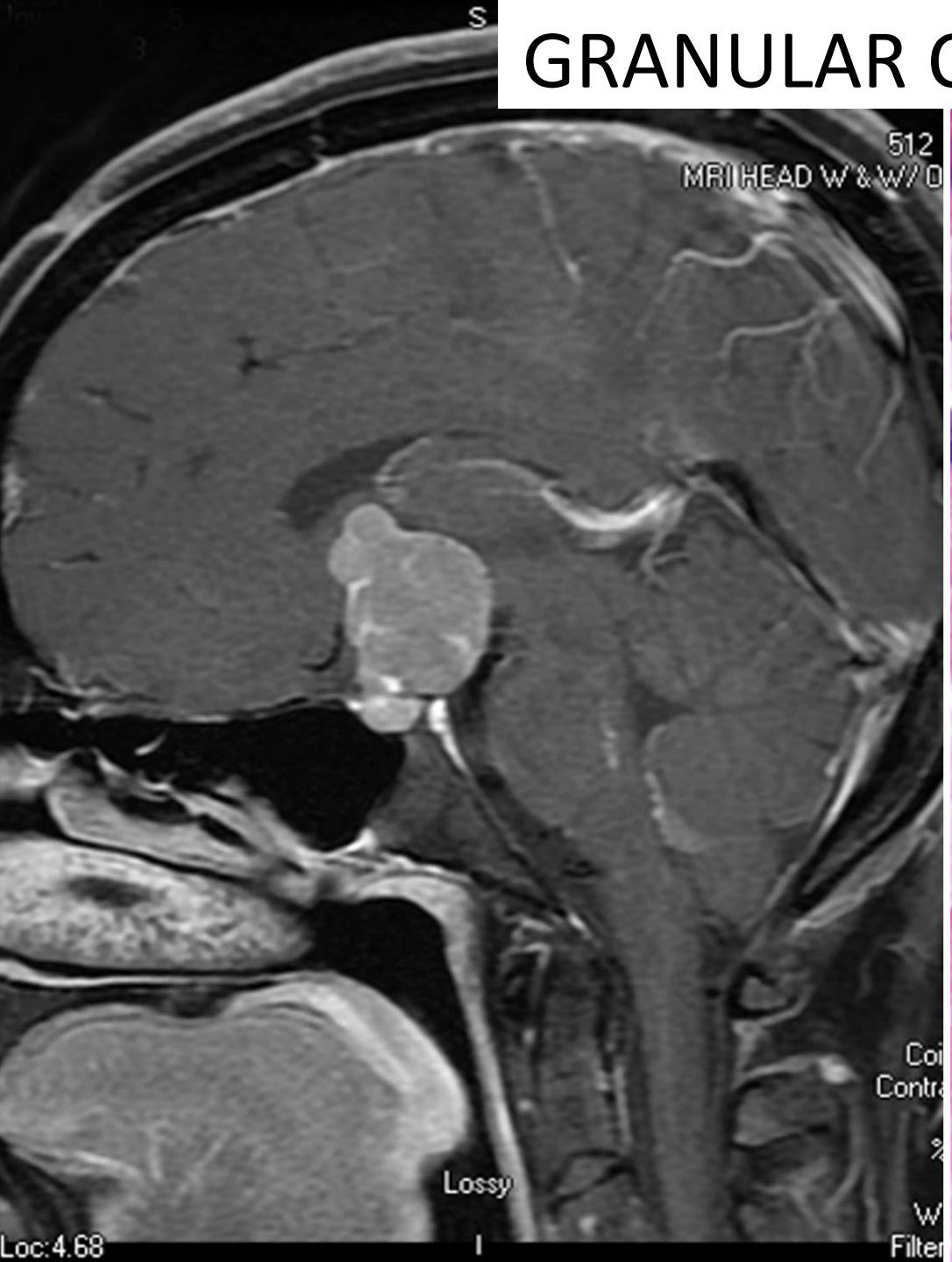


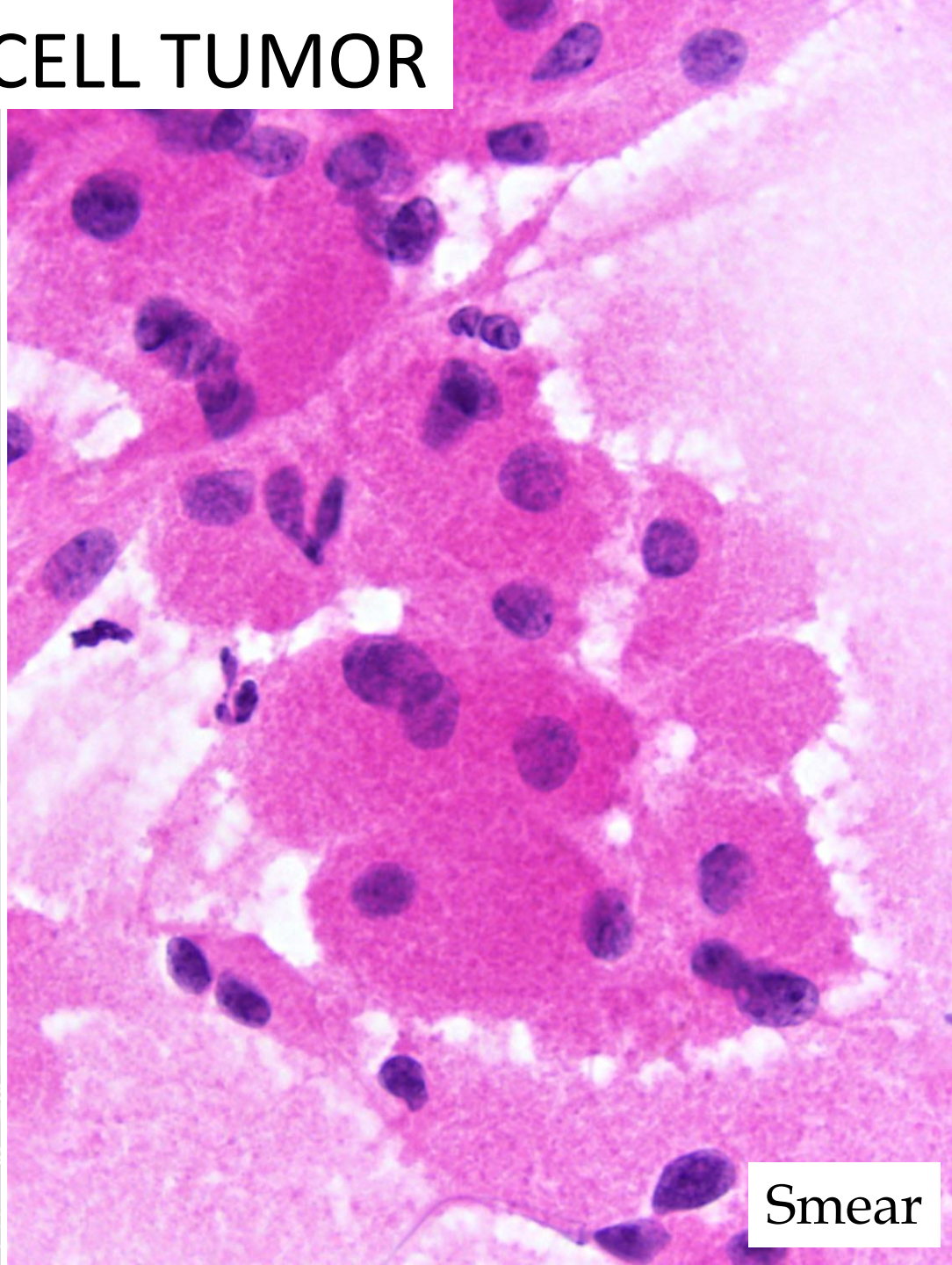

PITUICYTOMA
GFAP

PITUICYTOMA

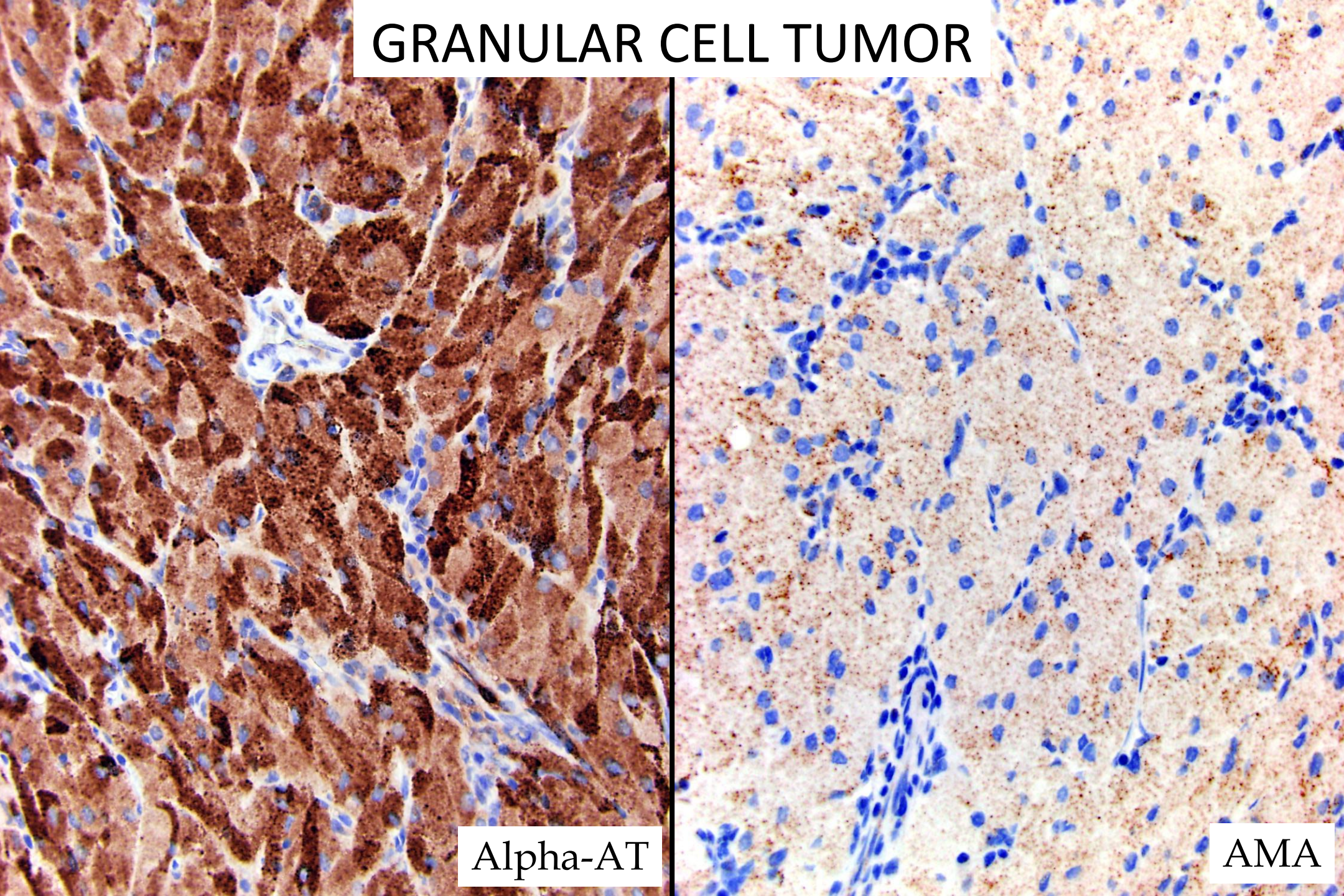


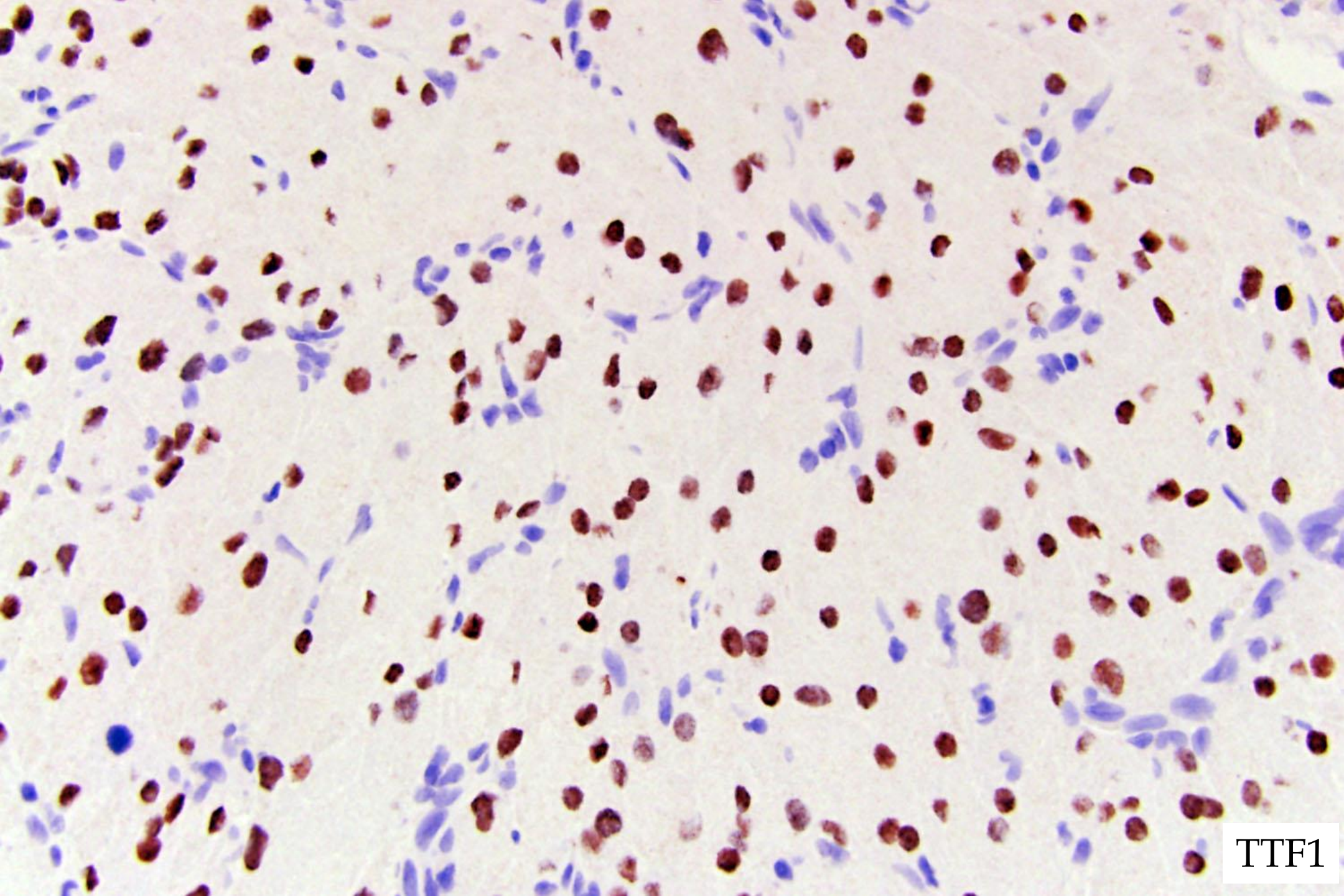
GRANULAR CELL TUMOR



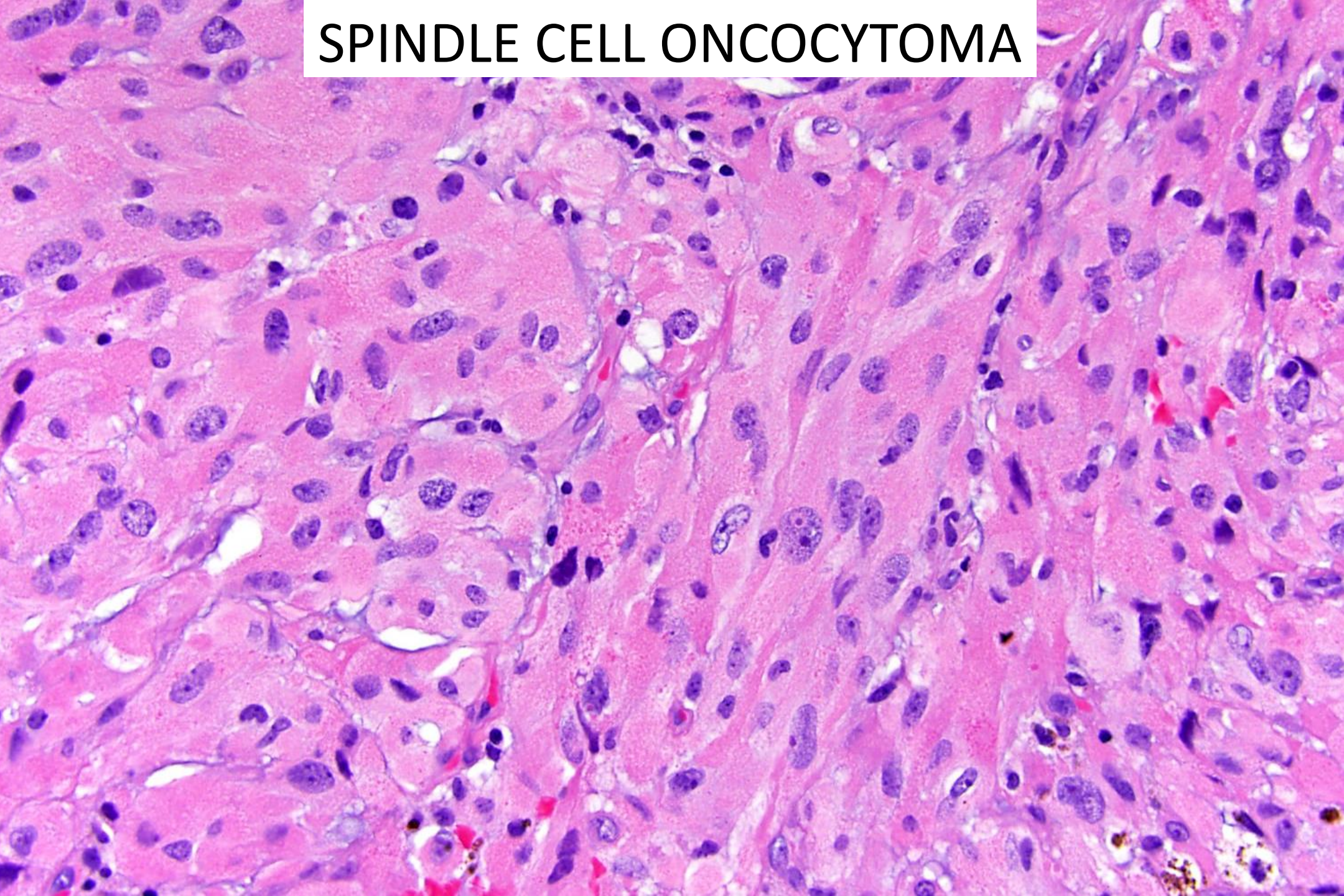


GRANULAR CELL TUMOR

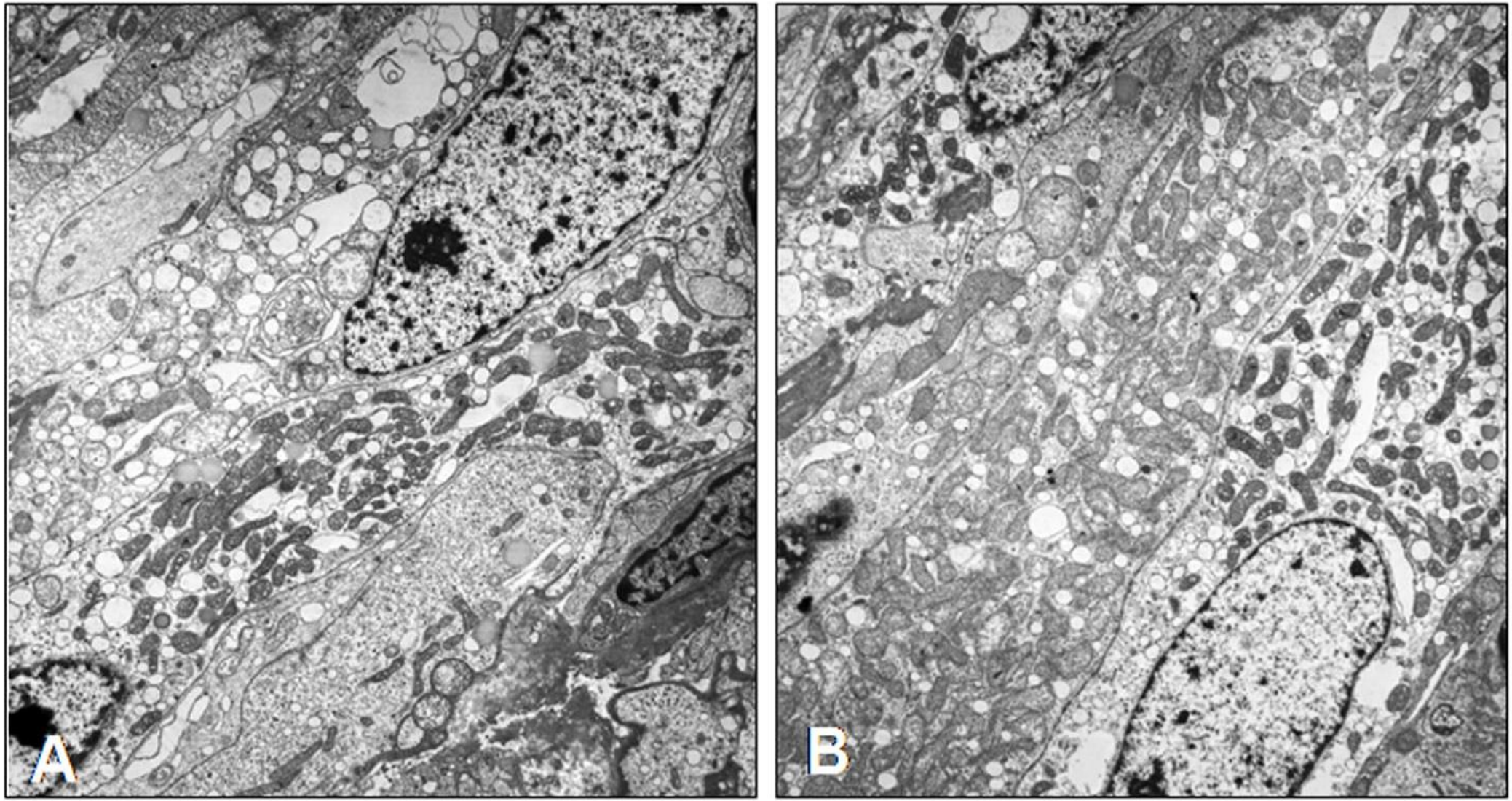



TTF1

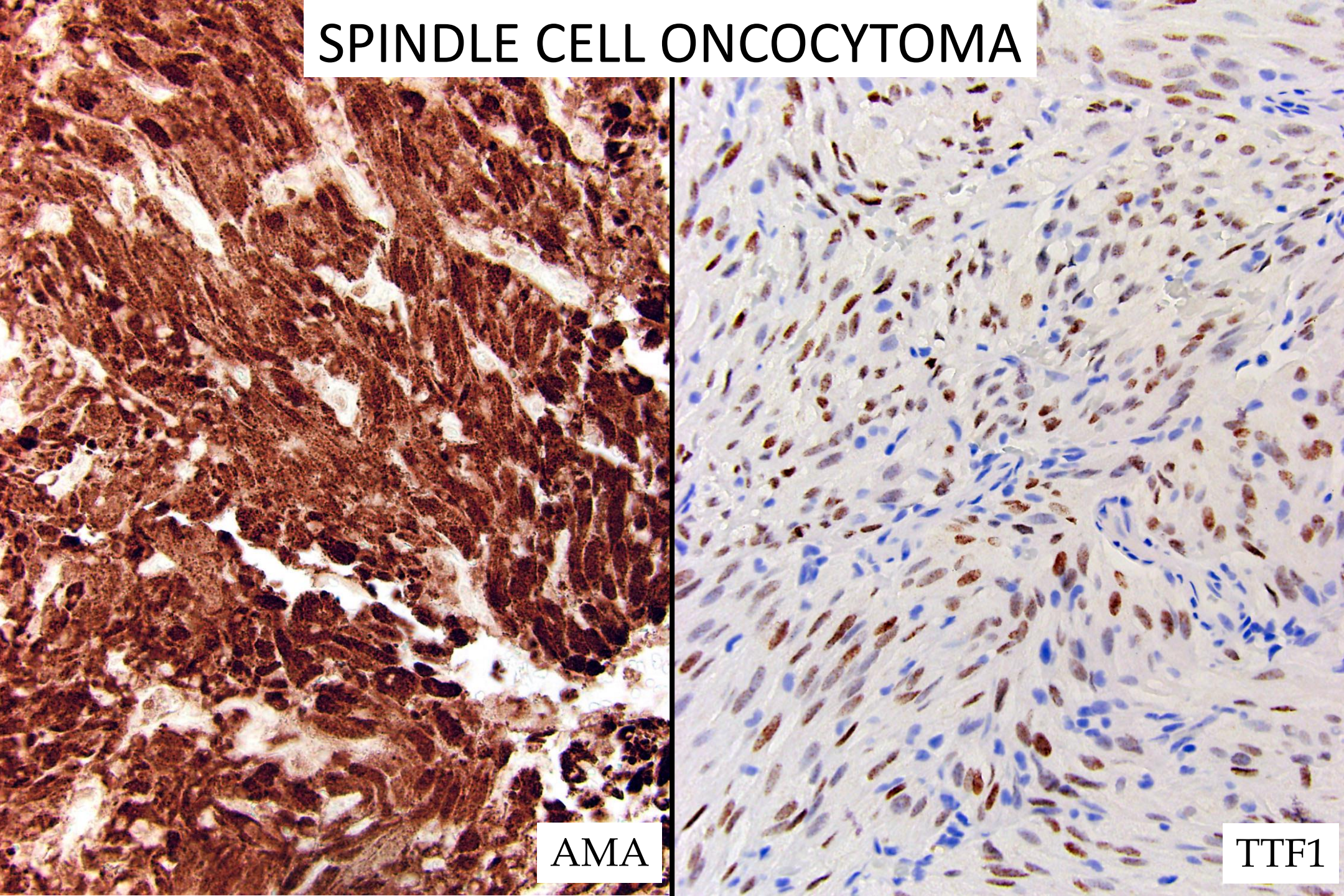
SPINDLE CELL ONCOCYTOMA



SPINDLE CELL ONCOCYTOMA



SPINDLE CELL ONCOCYTOMA



Spindle Cell Oncocytomas and Granular Cell Tumors of the Pituitary Are Variants of Pituicytoma

Ozgur Mete, MD, Maria Beatriz Lopes, MD, PhD,† and Sylvia L. Asa, MD, PhD**

Abstract: Pituicytomas are neoplasms that arise from pituicytes, which are specialized glia of the posterior pituitary. Pituicytes have 5 ultrastructural variants: light, dark, granular, ependymal, and oncocytic. Granular cell tumors of the pituitary gland are thought to arise from granular pituicytes. Spindle cell oncocytomas are considered to arise from folliculostellate cells, which are sustentacular cells of the adenohypophysis. Recent data suggest that, whereas pituicytes and all 3 tumor types are positive for TTF-1, folliculostellate cells are negative for TTF-1. We investigated 7 spindle cell oncocytomas, 4 pituicytomas, and 3 granular cell tumors for their genetic ($BRAF^{V600E}$ mutation and BRAF-KIAA fusion), immunohistochemical (GFAP, vimentin, S100 protein, olig2, IDH1-R132H, NF, galectin-3, chromogranin-A, CD56, EMA, CAM5.2, CD68, TTF-1, and bcl-2), and ultrastructural features to refine their classification. All tumors had nuclear positivity for TTF-1 and were negative for CAM5.2, chromogranin-A, and NF. GFAP, vimentin, S100, galectin-3, EMA, and CD68 were variably positive in the majority of the 3 tumor groups. Olig2 was only positive in 1 pituicytoma. Whereas granular cell tumors were negative for bcl-2 and CD56, pituicytomas and spindle cell oncocytomas showed variable positivity. All tumors were negative with the IDH1-R132H mutation–specific antibody, and none had evidence of *BRAF* alterations ($BRAF^{V600E}$ mutation and BRAF-KIAA fusion). Diffuse TTF-1 expression in nontumorous pituicytes, pituicy-

(*Am J Surg Pathol* 2013;37:1694–1699)

Historically, the term "pituicytoma" has been used to describe a number of tumors in the region of the sella turcica, including pilocytic astrocytomas, granular cell tumors, and even pituitary adenomas. Brat and colleagues formally defined pituicytoma in 2000 as a distinctive low-grade, spindle cell glial neoplasm that arises from pituicytes,[1–4] which are specialized glia that have a sustentacular function in the neurohypophysis (Fig. 1A).

Granular cell tumors of the pituitary, unlike those elsewhere that are thought to be of Schwann cell origin, are considered to be unique neoplasms of the neurohypophysis and have also been suggested to derive from pituicytes[3–5] (Fig. 1B).

Spindle cell oncocytomas of the adenohypophysis were described by Roncaroli et al[6] as mitochondrion-rich, spindle to epithelioid, nonendocrine sellar neoplasms (Fig. 1C) and proposed a folliculostellate cell origin. Folliculostellate cells are sustentacular cells of the adenohypophysis.[4,7] Others have suggested neuron-like precursors as the cell of origin of these enigmatic tumors.[8]

Recent data have uncovered that, whereas pituicytes, spindle cell oncocytomas, granular cell tumor, and

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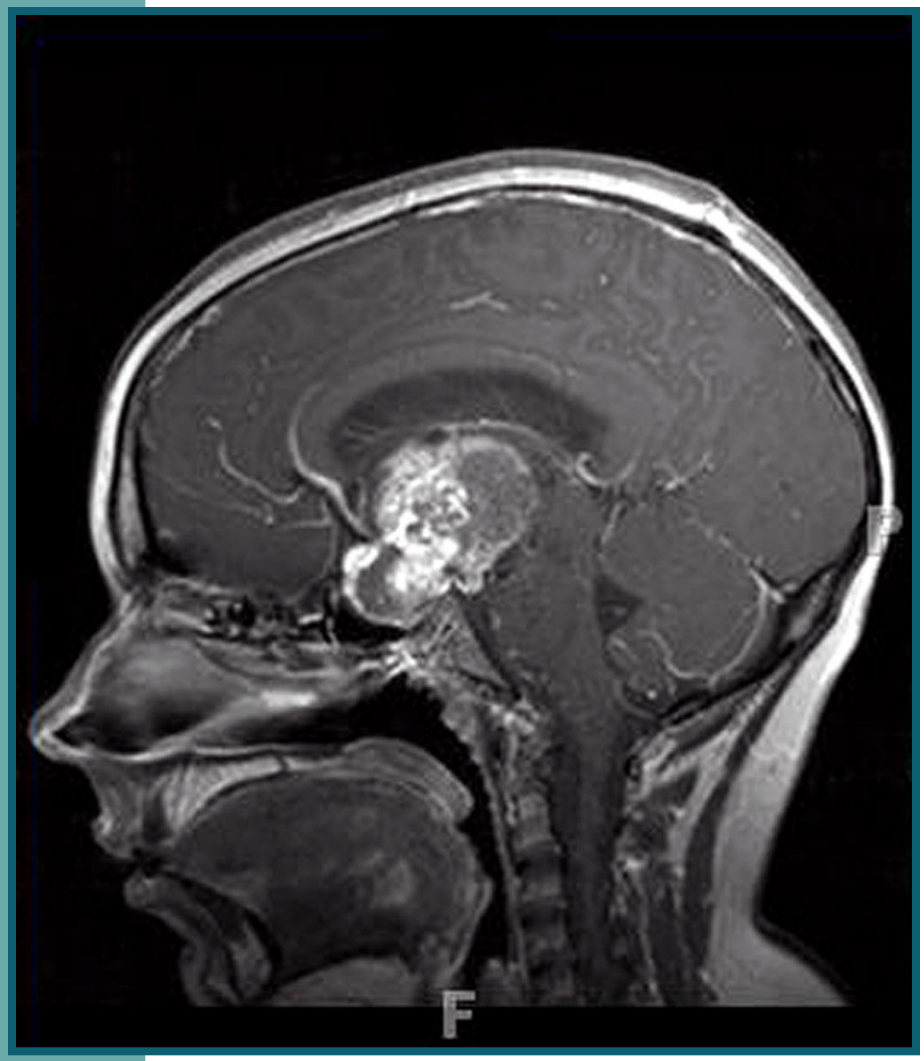
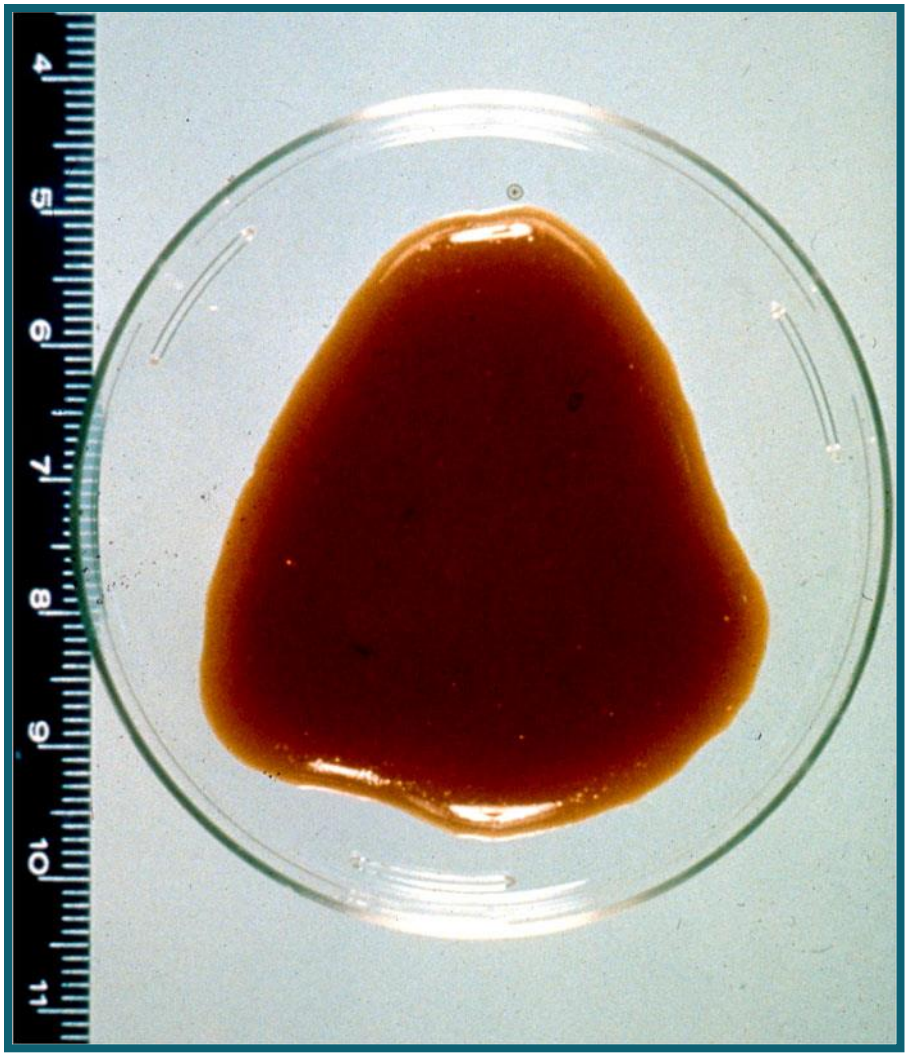
CRANIOPHARYNGIOMA





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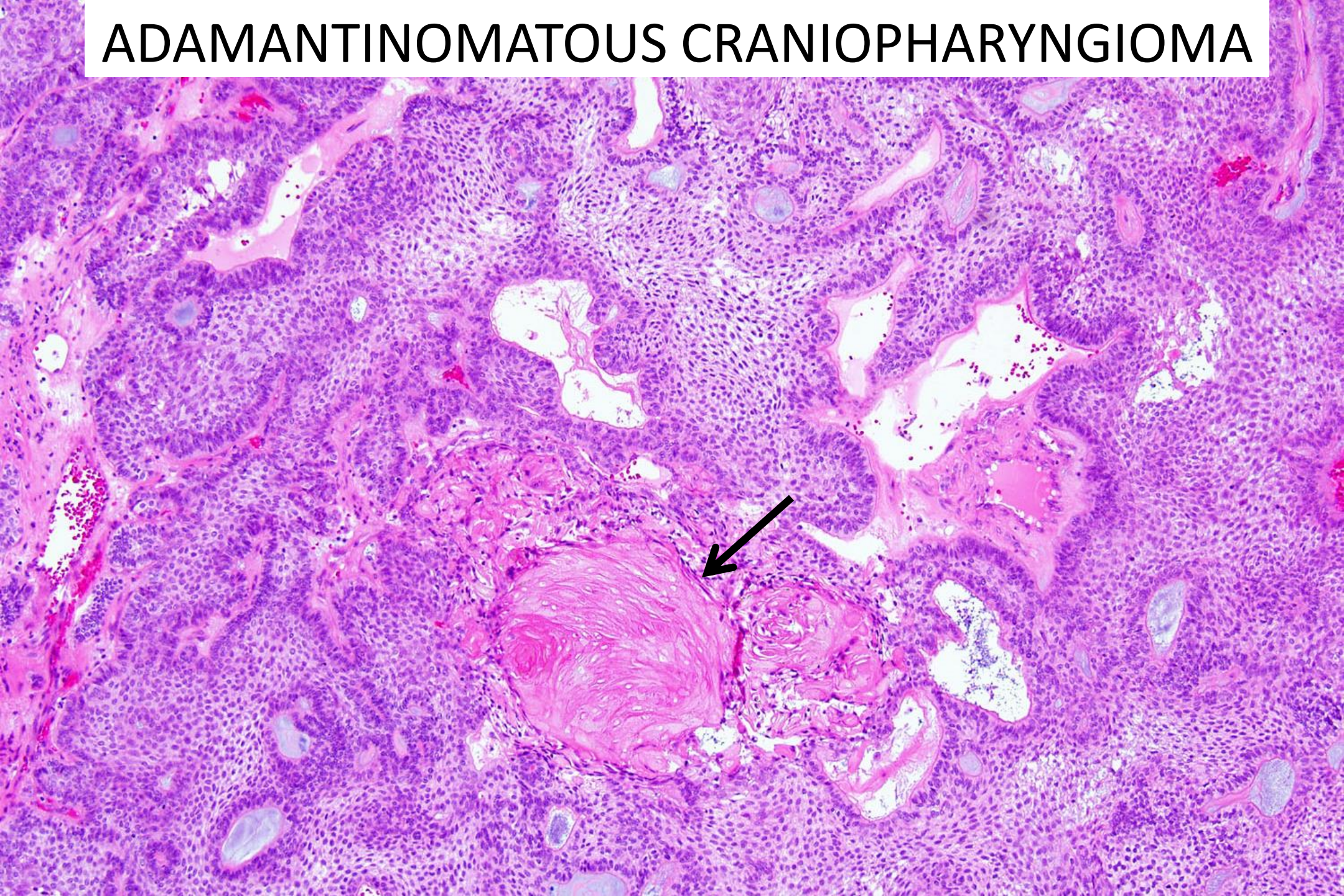
ADAMANTINOMATOUS CRANIOPHARYNGIOMA



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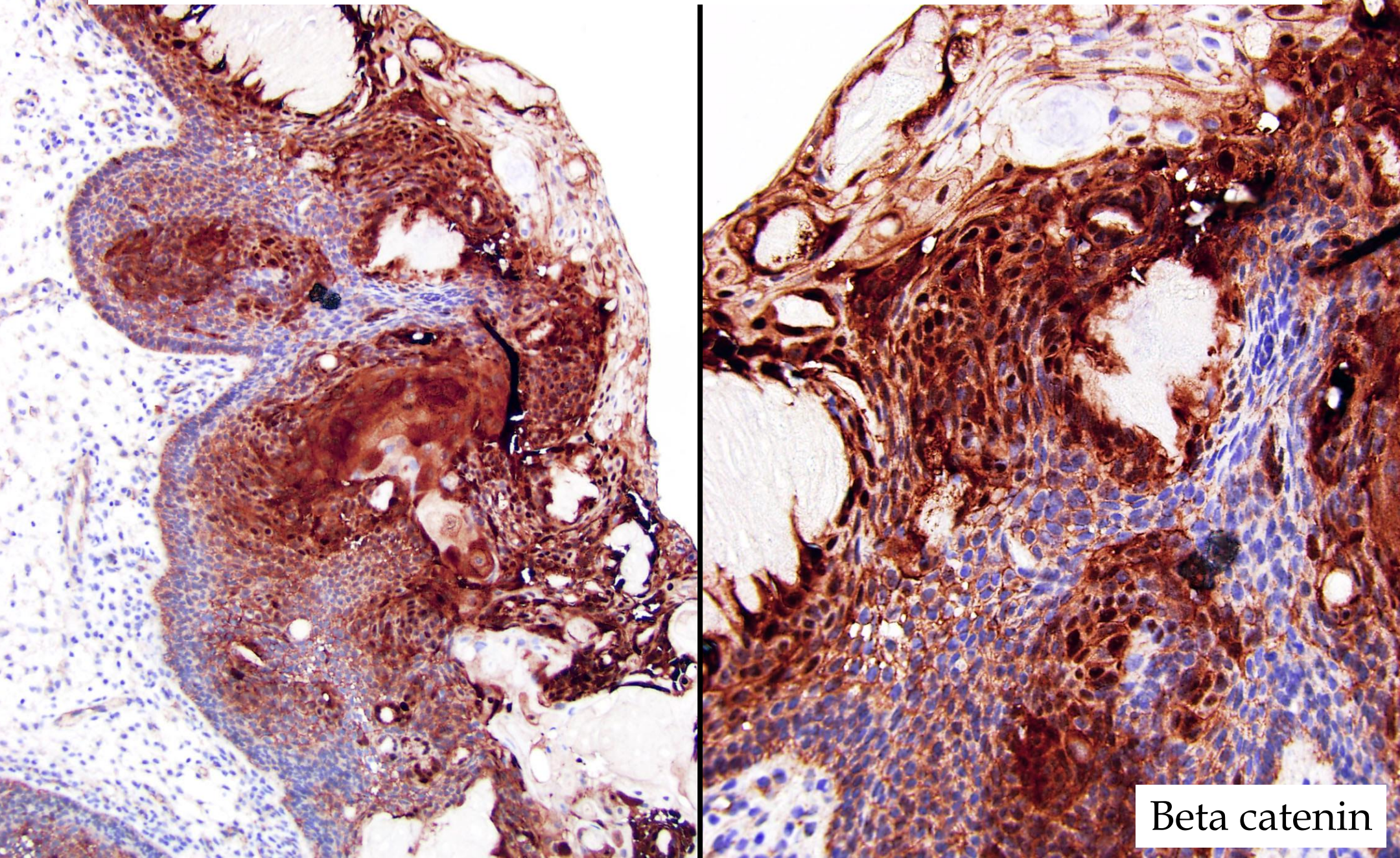
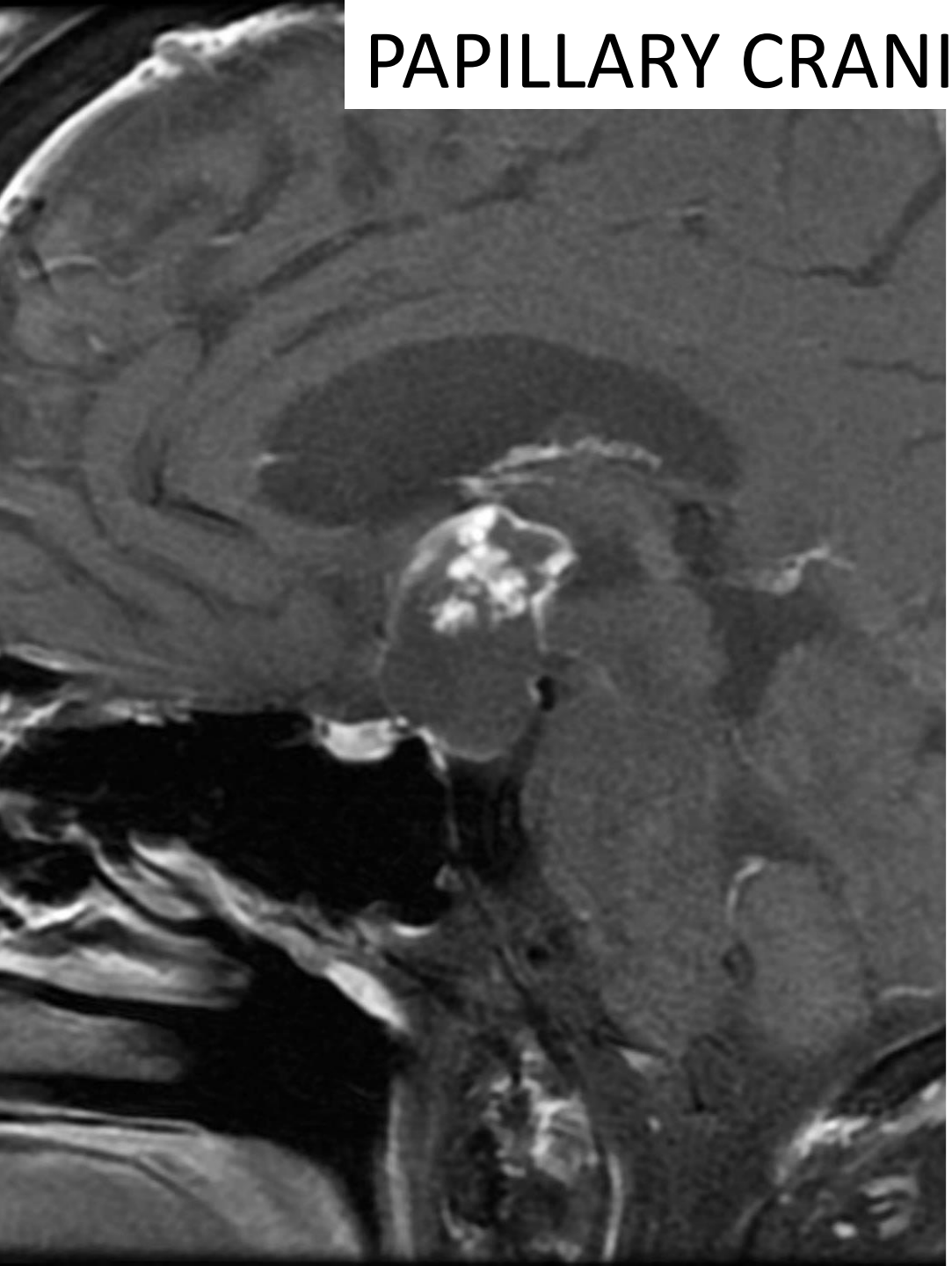
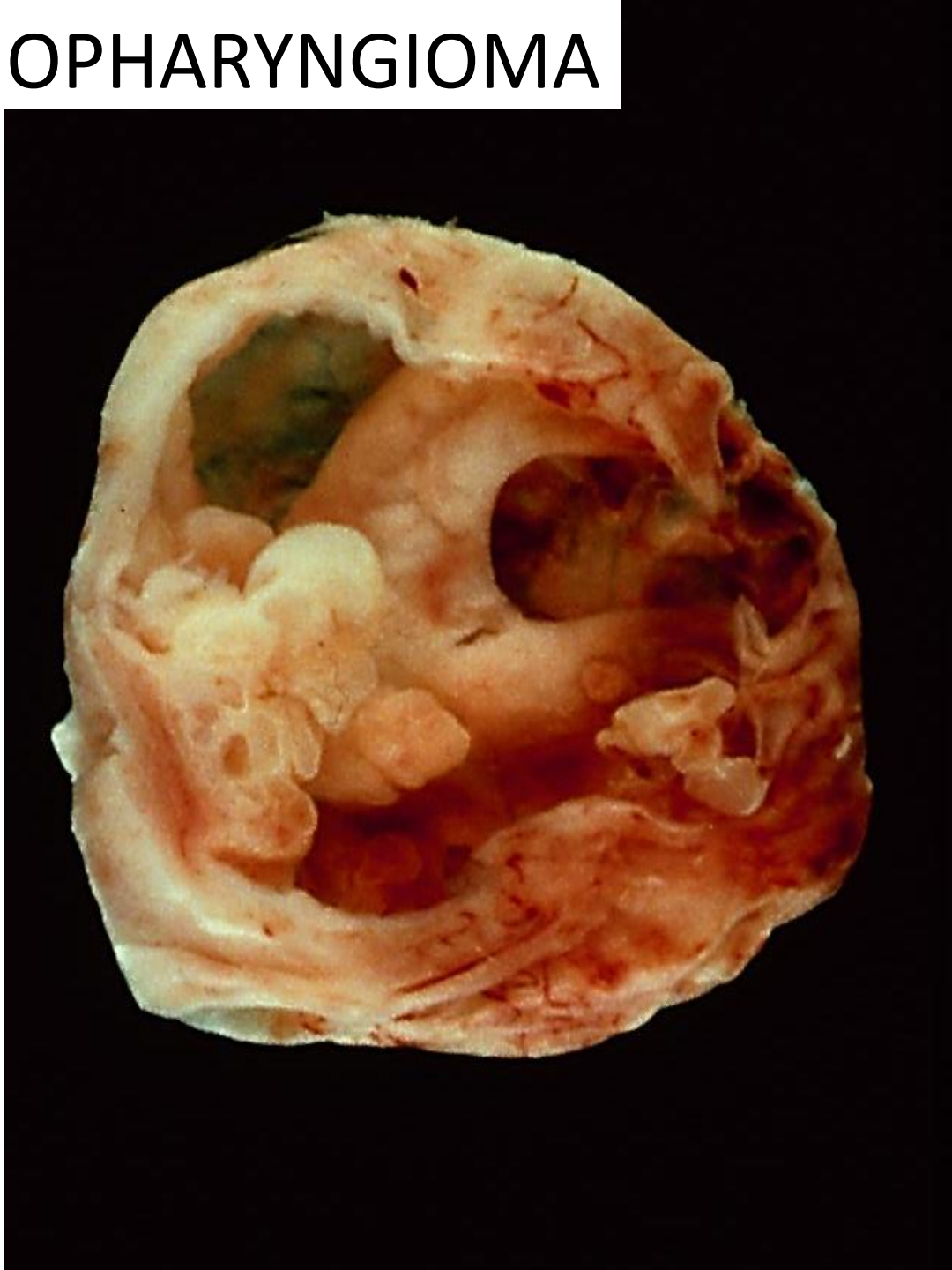


PAPILLARY CRANIOPHARYNGIOMA





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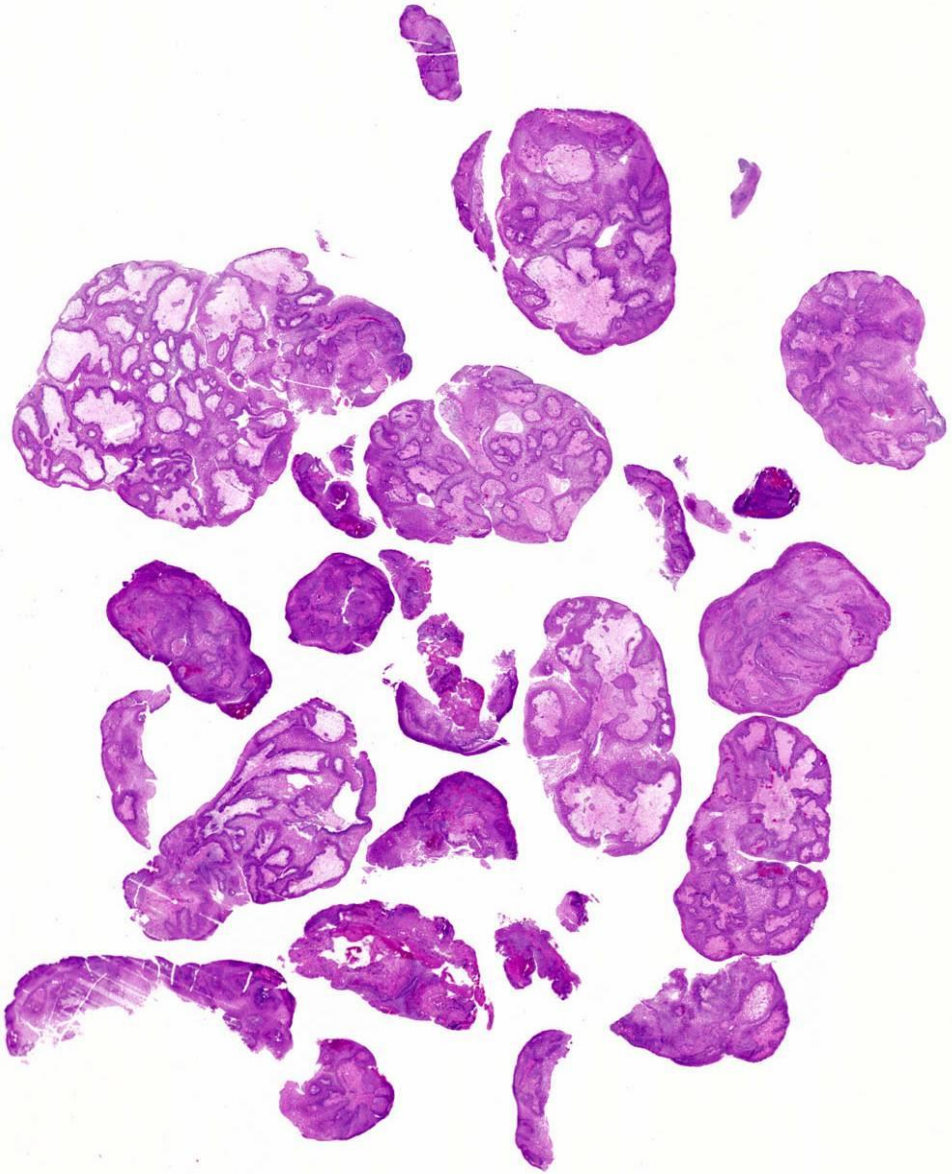

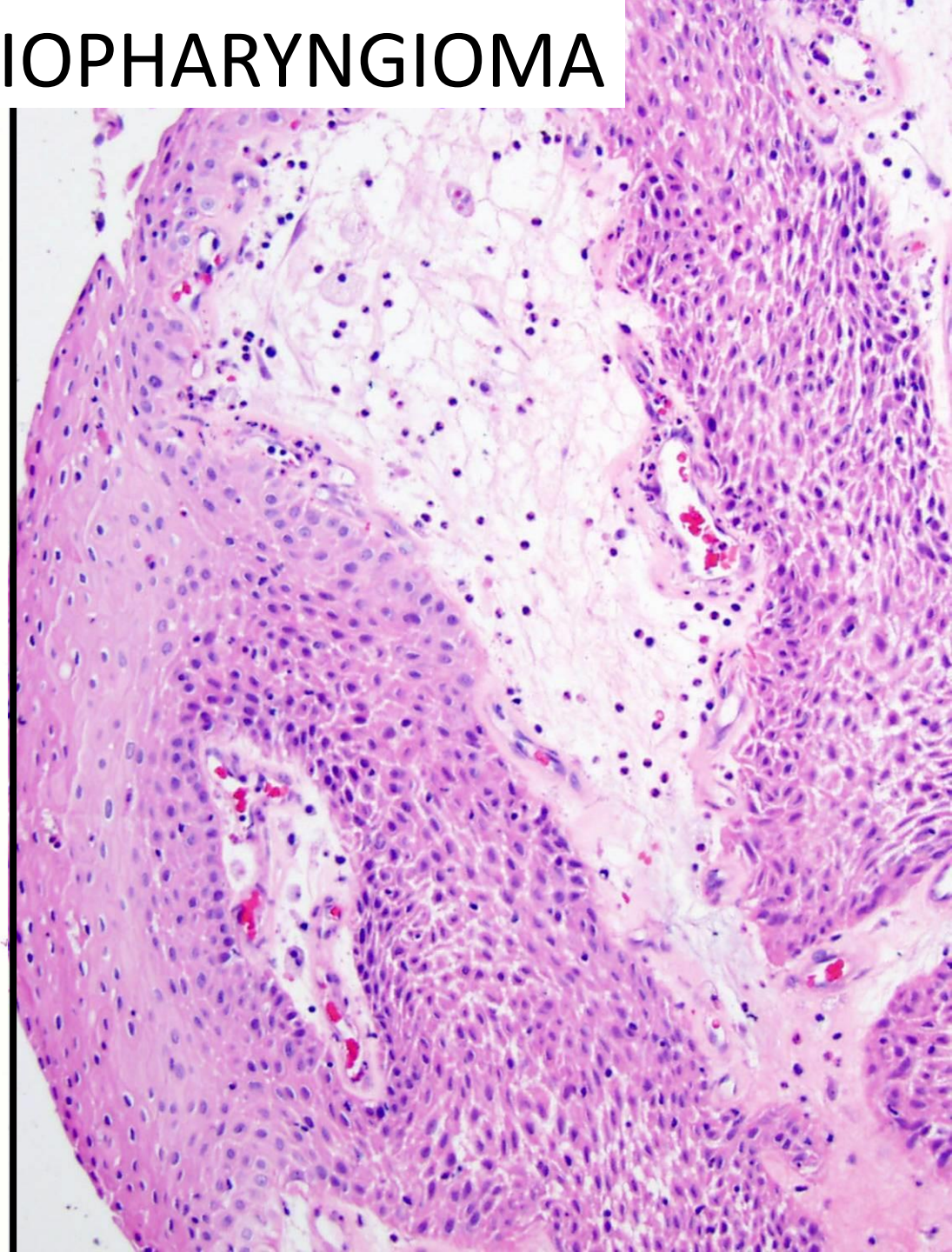

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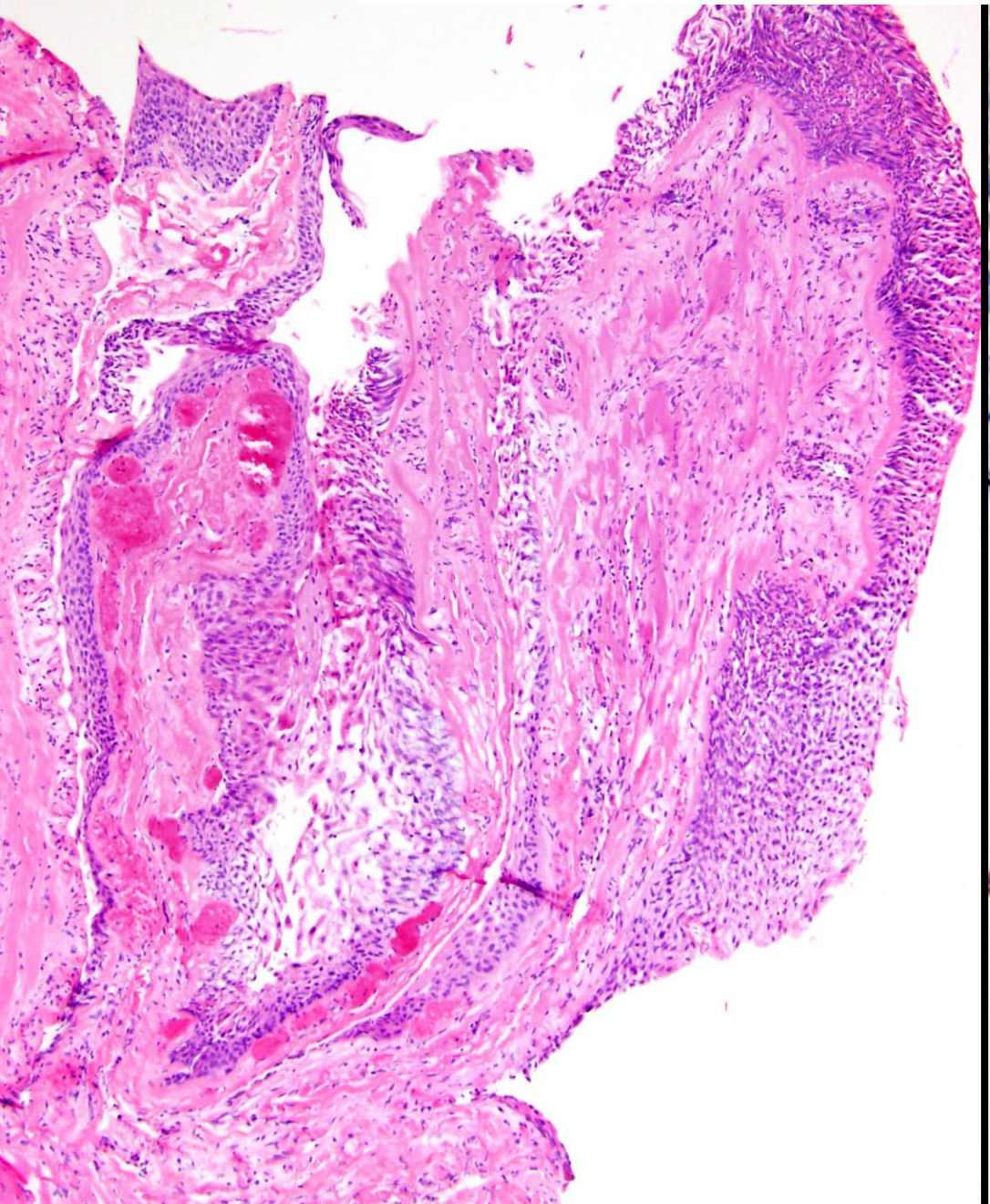

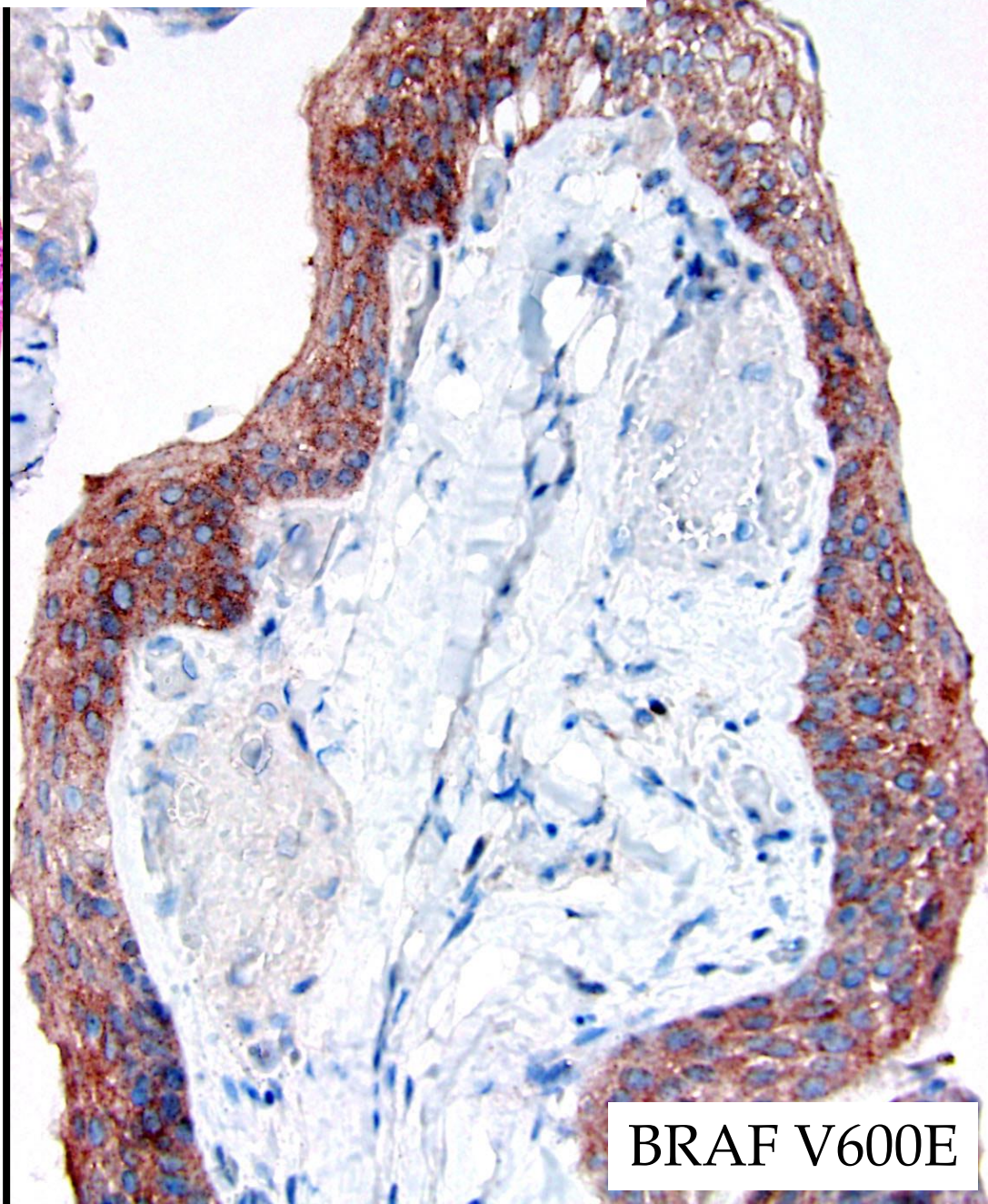


Questions/Comments?