Meningiomi:
aspetti immunofenotipici e molecolari

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CBTRUS

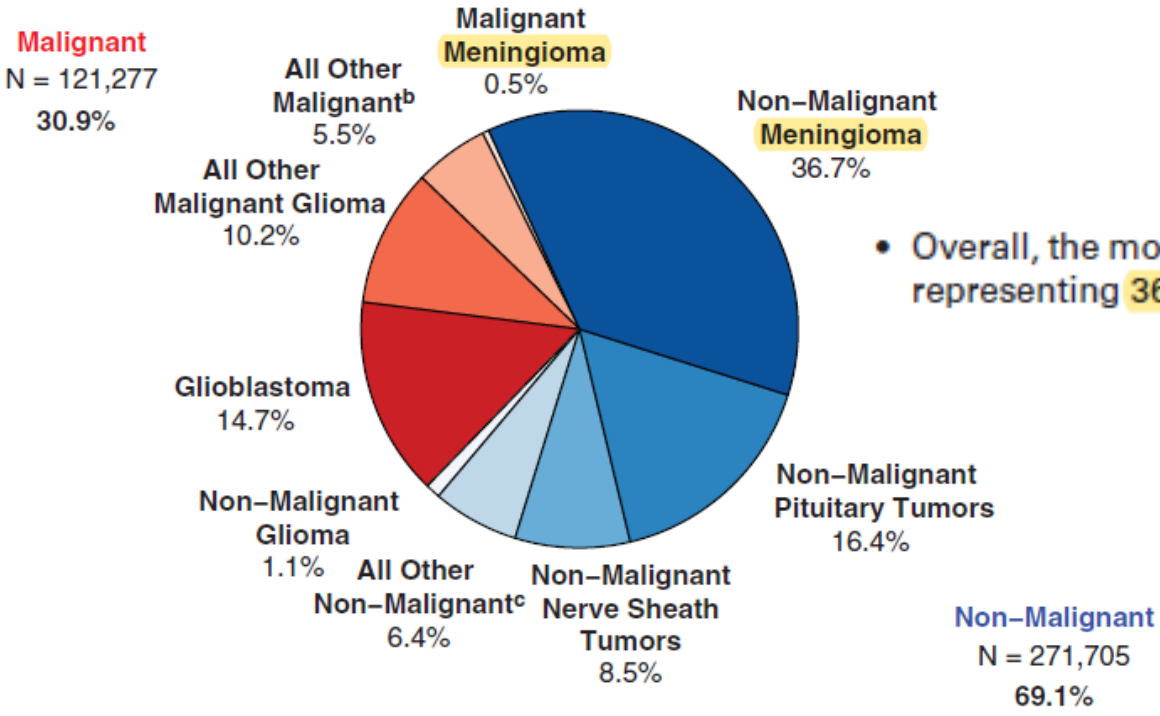
CENTRAL BRAIN TUMOR REGISTRY OF THE UNITED STATES

Neuro-Oncology
20(S4), 1–86, 2018 | doi:10.1093/neuonc/noy131

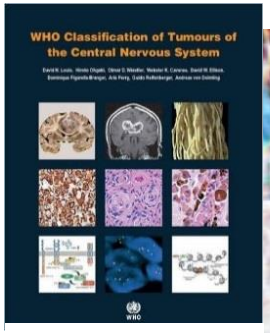
CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015

Quinn T. Ostrom, Ph.D, M.P.H.,* Haley Gittleman, M.S.,* Gabrielle Truitt, B.S., Alexander Boscia, B.S., Carol Kruchko, B.A., and Jill S. Barnholtz-Sloan, Ph.D.

Meningiomas: among the most common intracranial tumours, with an estimated incidence of 7.86 cases per 100,000 people per year



- Overall, the most common tumor site was the meninges, representing 36.8% of all tumors.

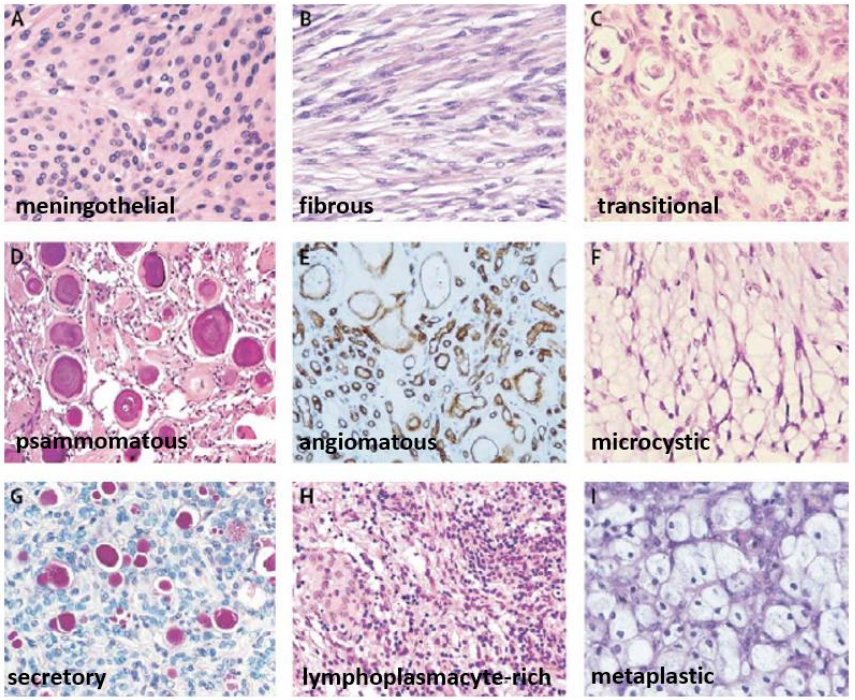


WHO Ed. 2016

CHAPTER 10

Meningiomas

Meningioma
Meningothelial meningioma
Fibrous meningioma
Transitional meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma
Chordoid meningioma
Clear cell meningioma
Atypical meningioma
Papillary meningioma
Rhabdoid meningioma
Anaplastic (malignant) meningioma



High morphologic heterogeneity!

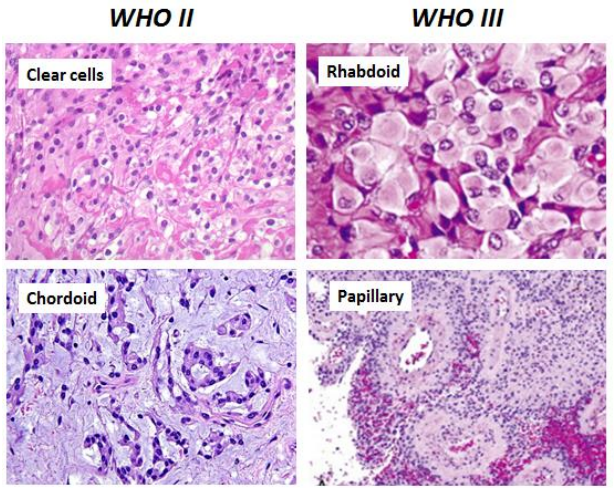
- **Clinical behaviour?**
- **Molecular heterogeneity?**
- **Responsiveness to treatment?**

Meningiomas with low risk of recurrence and aggressive growth (WHO grade I)
Meningothelial meningioma
Fibrous (fibroblastic) meningioma
Transitional (mixed) meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma

Meningiomas with greater likelihood of recurrence and/or aggressive behaviour (WHO grade II)
Atypical meningioma
Clear-cell meningioma
Chordoid meningioma

Meningiomas with greater likelihood of recurrence and/or aggressive behaviour (WHO grade III)
Anaplastic (malignant) meningioma
Rhabdoid meningioma
Papillary meningioma
Meningiomas of any type or grade with high proliferation index and/or brain invasion

WHO I : ~80%
"various histotypes"
WHO II : ~15–20%
atypical
"Chordoid" and "clear cell"
WHO III : ~1–2%
anaplastic/malignant
"Papillary" e "rhabdoid"



The introduction of improved diagnostic criteria by the 2007 WHO classification (not changed in WHO 2016) resulted in an increased recognition of grade II meningiomas, including recognition of brain-invasive tumours, and identification of a larger proportion of patients who have a high risk of tumour recurrence and need additional therapies

- **Surgery**
- **Wait & See**
- **Radiotherapy**
- **CT and/or RT**

Benign meningioma (WHO grade I)

- Histological variant other than clear-cell, chordoid, papillary, or rhabdoid
- Lacks criteria of atypical and anaplastic meningioma

> 4

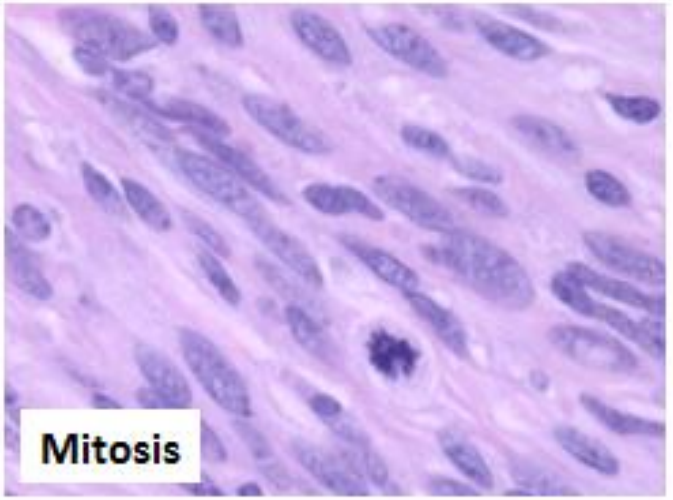
Atypical meningioma (WHO grade II) (any of three criteria)

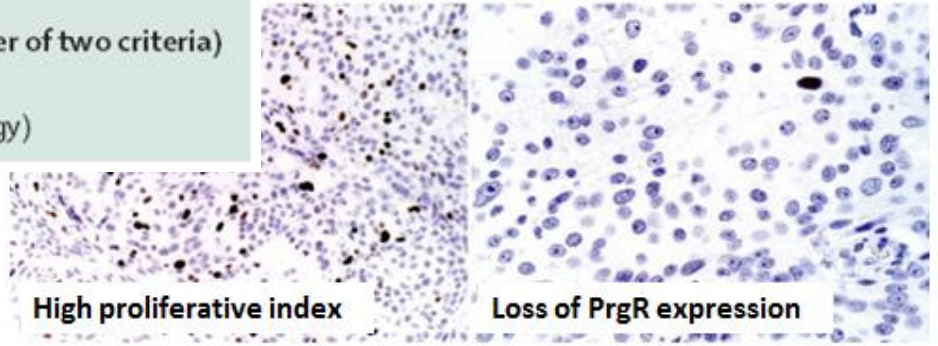
- Mitotic index ≥ four mitoses/ten high-power fields (HPF)
- At least three of five parameters:
  - Increased cellularity
  - High nuclear/cytoplasmatic ratio (small cells)
  - Prominent nucleoli
  - Uninterrupted patternless or sheet-like growth
  - Foci of spontaneous necrosis (ie, not induced by embolisation or radiation)
- Brain invasion

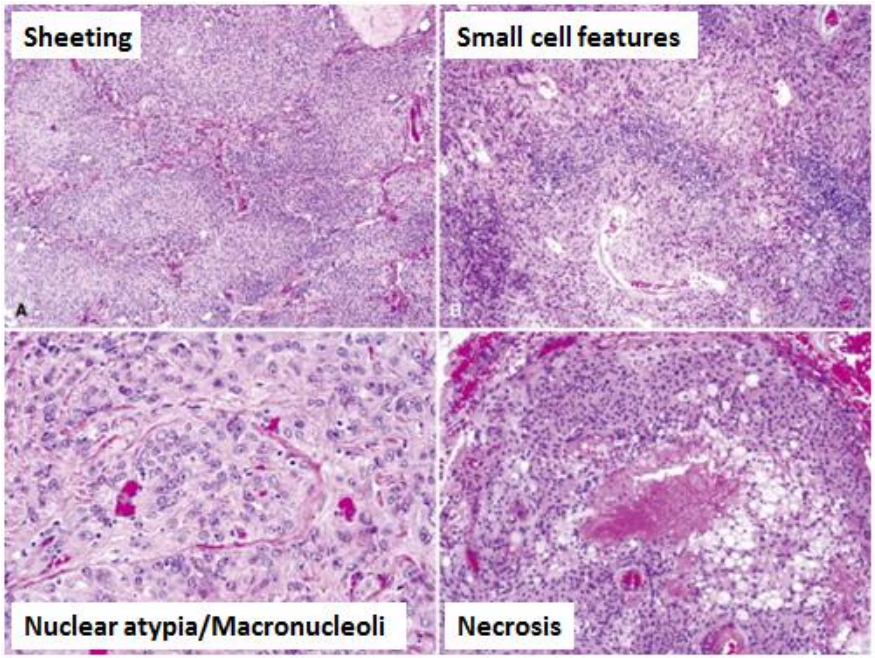
> 20

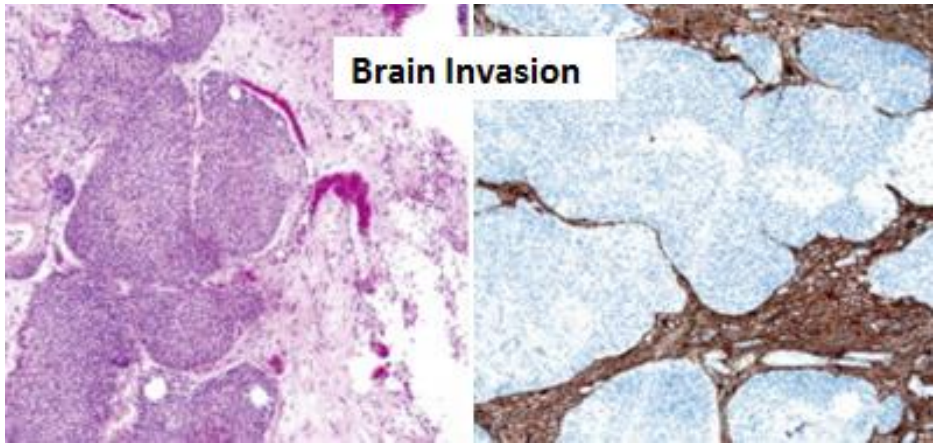
Anaplastic (malignant) meningioma (WHO grade III) (either of two criteria)

- Mitotic index ≥20 mitoses/10 HPF
- Anaplasia (sarcoma, carcinoma, or melanoma-like histology)









Neuro-Oncology
19(10), 1298–1307, 2017 | doi:10.1093/neuonc/nox071 | Advance Access

Benjamin Brokinkel, Katharina Hess, and Christian Mawrin

Department of Neurosurgery, University Hospital Münster, Münster, Germany (B.B.); Institute of Neuropathology, University Hospital Münster, Münster, Germany (K.H.); Institute of Neuropathology, Otto-von-Guericke University, Magdeburg, Germany (C.M.)

Brain invasion in meningiomas—clinical considerations and impact of neuropathological evaluation: a systematic review

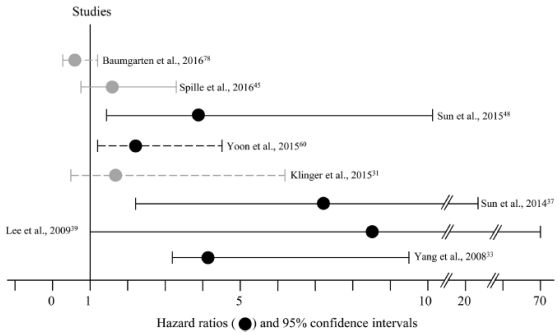


Fig. 4 **Risk of tumor recurrence comparing brain invasive and non-invasive meningiomas.** In most studies, brain invasion was significantly (black graphs) correlated with an increased hazard ratio of tumor recurrence in uni- (dashed lines) or multivariate (solid lines) analyses. However, no statistically significant correlation between tumor recurrence and brain invasion was found in some studies (gray graphs). For this figure, studies without information about hazard ratios and confidence intervals were excluded.

of brain tumors since 1993.[43] With the release of the 2016 edition, this heterogeneity gained highest clinical relevance, as microscopic evidence of brain invasion, even in the absence of further histopathological criteria of atypia, is now sufficient to impact tumor grading and therefore indirectly adjuvant therapy as well as inclusion in clinical trials.[1,46]

- Neurosurgical techniques and incomplete resection can impair neuropathological analyses and therefore grading.
- Neuropathological evaluation of brain invasion is not standardized and methods vary among published studies.
- Preoperative, imaging-based as well as intraoperative macroscopic assessment of brain invasion is not reliable.
- Microscopic evidence of brain invasion is correlated with tumor progression in most series.
- Although frequently associated with other histopathological criteria of atypia, clinical risk factors correlated with brain invasion are sparse.

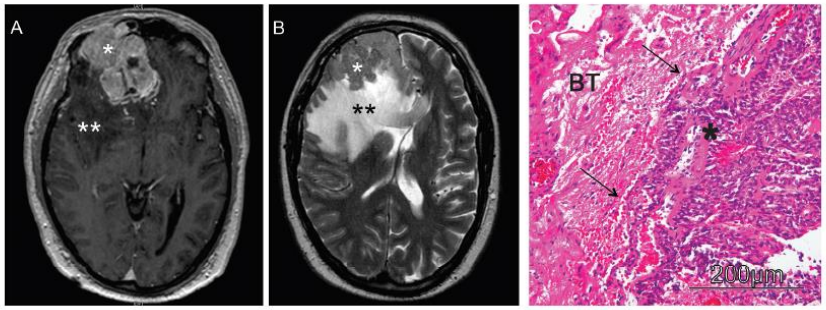


Fig. 3 **Illustrative cranial MRI of a patient with a brain invasive meningioma.** (A) Preoperative, axial post-gadolinium (GD) T1-weighted MRI revealing a large right frontal, contrast-enhancing meningioma. (B) Axial T2-weighted image shows the distinct peritumoral edema. In neuropathological analyses, the tumor showed finger-like invasion into the adjacent brain tissue (C; hematoxylin and eosin staining); *meningioma; **peritumoral brain edema; BT, brain tissue.

Panel 1: WHO 2016 grading for meningiomas[1]

Grade I
- Low mitotic rate, less than four per ten high-power fields (HPFs)
- Absence of brain invasion
- Nine subtypes

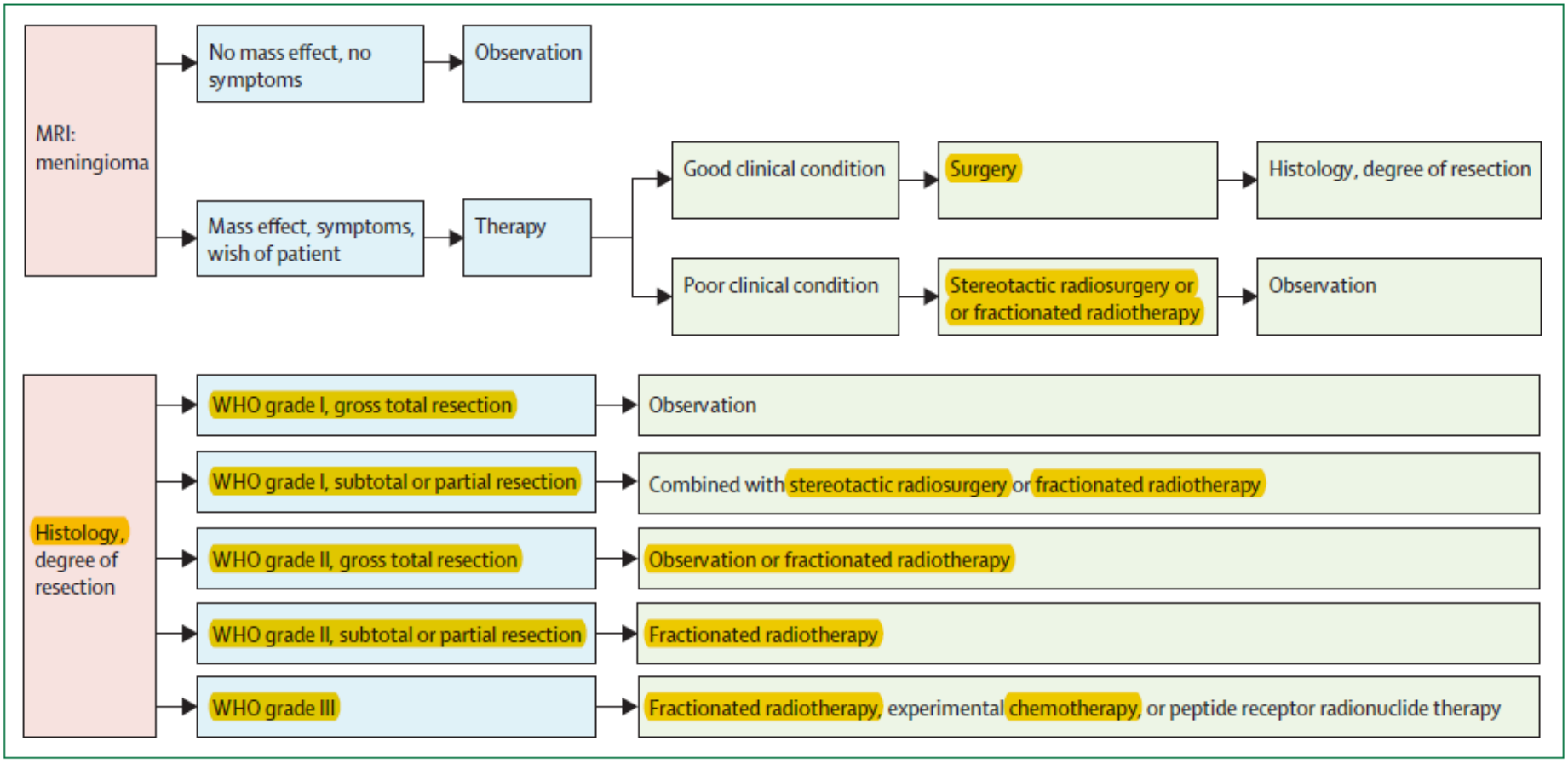
Grade II (atypical)
- Mitotic rate four to 19 per HPF
- Or brain invasion
- Or three of five specific histologies: spontaneous necrosis, sheeting, prominent nucleoli, high cellularity, and small cells

Grade III (anaplastic)
- Mitotic rate more than 20 per HPF
- Or specific histologies: papillary or rhabdoid meningioma

EANO guidelines for the diagnosis and treatment of meningiomas

Roland Goldbrunner, Giuseppe Minniti, Matthias Preusser, Michael D Jenkinson, Kita Sallabanda, Emmanuel Houdart, Andreas von Deimling, Pantelis Stavrinou, Florence Lefranc, Morten Lund-Johansen, Elizabeth Cohen-Jonathan Moyal, Dieta Brandsma, Roger Henriksson, Riccardo Soffietti, Michael Weller

www.thelancet.com/oncology **Vol 17 September 2016**



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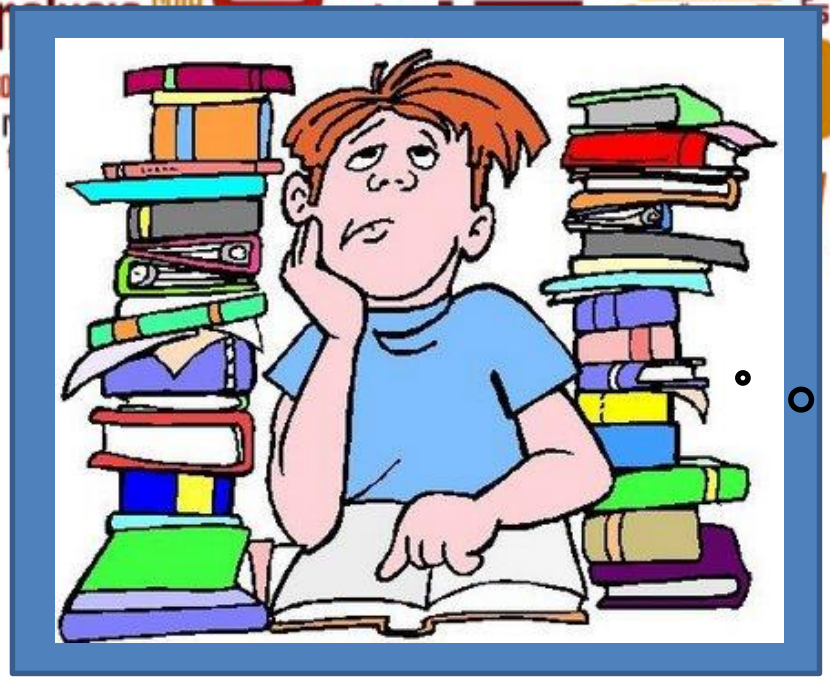
Meningiomas with similar histological features and same grade may have a different biological behaviour!
Why?

The inclusion of the newly identified recurrent molecular alterations in the diagnostic assessment might further improve accuracy in the identification of meningioma patients who need close surveillance and more-aggressive treatment

Biomarkers and Molecular features in meningiomas ?



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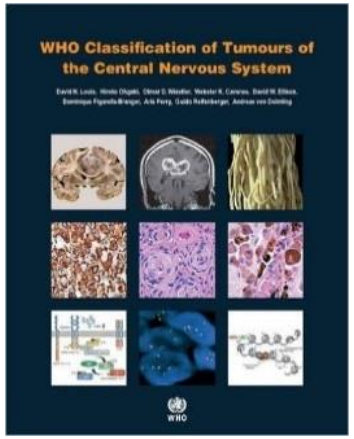
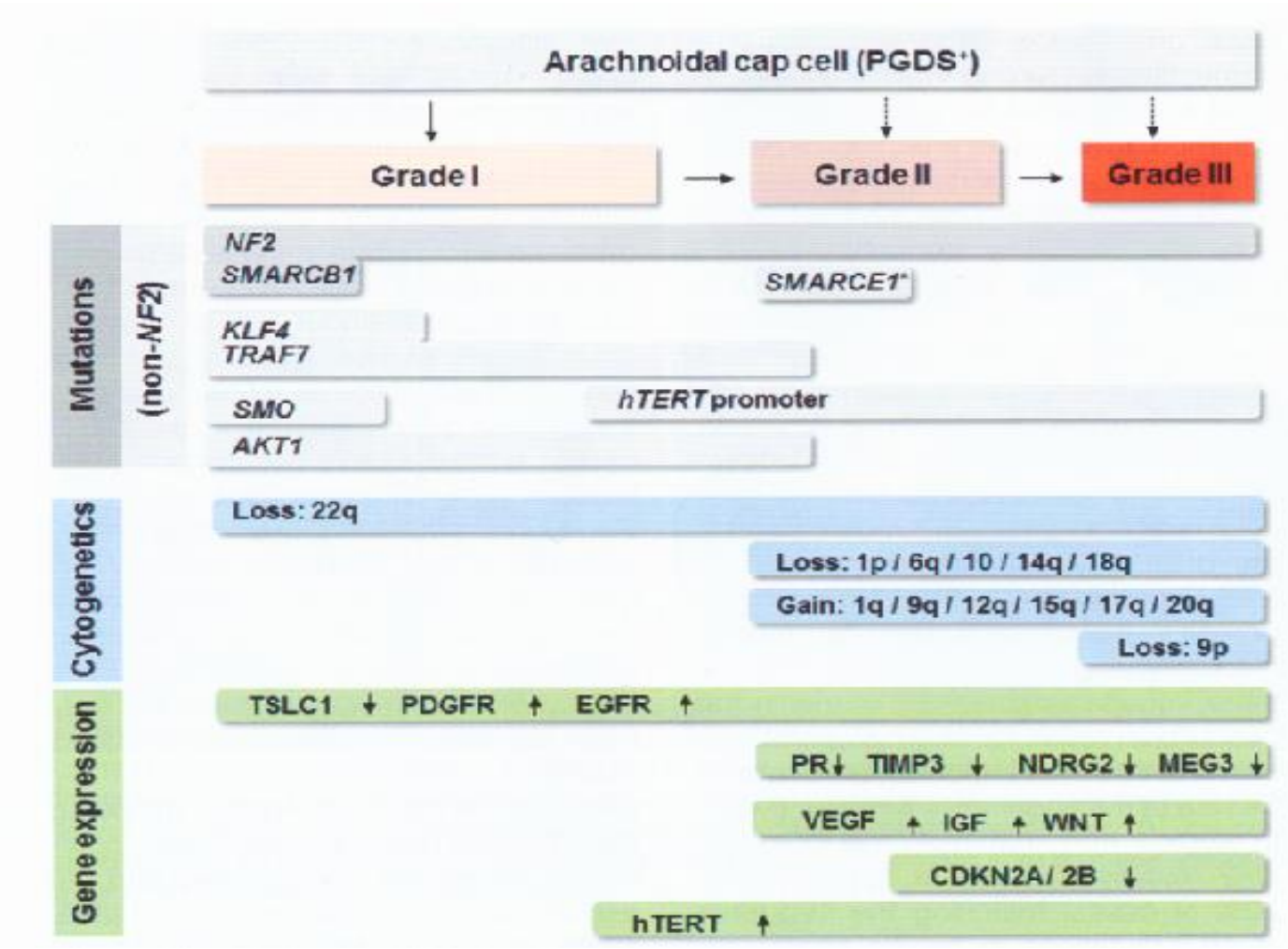
In the last few years, advances in molecular characterization of meningioma have enabled identification of genetic alterations that are responsible for an increased likelihood of tumour recurrence and could represent promising treatment targets. These information are now included within the last WHO Ed. 2016.



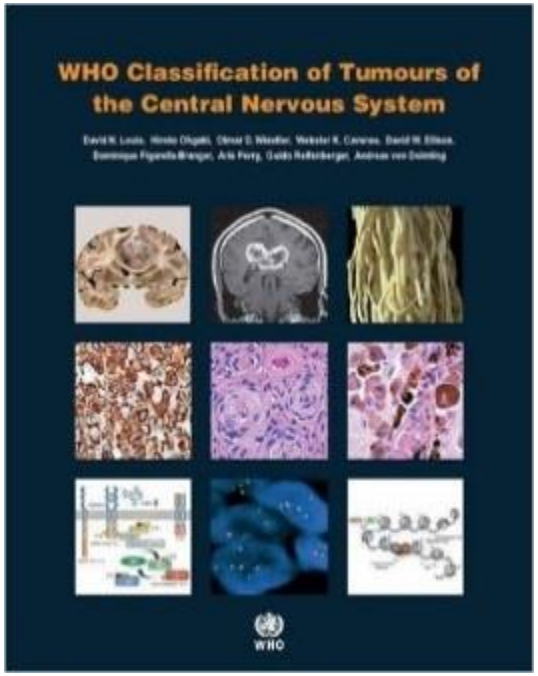
WHO Ed. 2016



Recurring genetic alterations with DIAGNOSTIC and PROGNOSTIC value

Histological subtype	WHO grade (2016 criteria)	Gene mutations
Meningothelial	I	*TRAF7*, *AKT1*, *POLR2A*, *PIK3CA*
Fibrous (fibroblastic)	I	*NF2*
Lymphoplasmacyte-rich	I	–
Metaplastic	I	–
Chordoid	II	–
Clear cell	II	*SMARCE1*
Atypical	II	*NF2*, *TRAF7*, *AKT1*
Papillary	III	–
Rhabdoid	III	*BAP1*
Anaplastic (malignant)	III	*NF2*

NF2 mutated (somatic or germline) and NF2 non-mutated (somatic !?) Meningiomas



WHO Ed. 2016

CHAPTER 16

Familial tumour syndromes

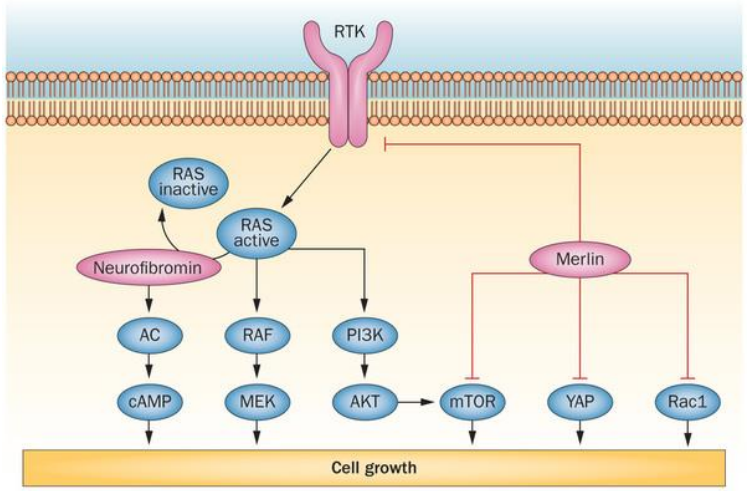
Neurofibromatosis type 1
Neurofibromatosis type 2
Schwannomatosis
Von Hippel–Lindau disease
Tuberous sclerosis
Li–Fraumeni syndrome
Cowden syndrome
Turcot syndrome
Naevoid basal cell carcinoma syndrome
Rhabdoid tumour predisposition syndrome

SYNDROMES	GENES	CHROMOSOME
Neurofibromatosis II	*NF2*	*22q12*
Nevoid basal cell carcinoma (Gorlin)	*PTCH*	*9q22.3*
Rubinstein-Taybi Syndrome or broad thumb-hallux syndrome	*CREBBP*	*16p13.3*
von Hippel-Lindau	*VHL*	*3p25*
Cowden	*PTEN*	*10q23.3*
Li Fraumeni	*TP53*	*17q (between exon 5 and 9)*

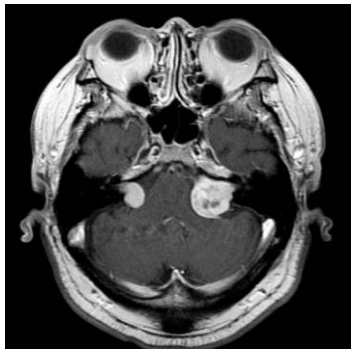
Neurofibromatosis type 2 (NF2)

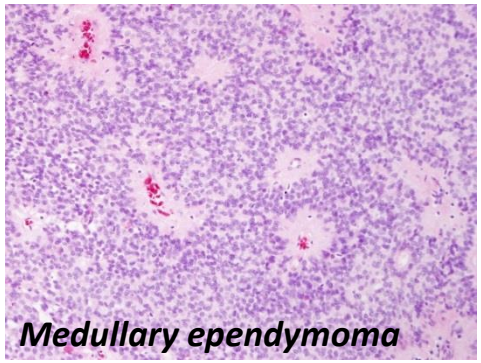
- **Vestibular schwannoma** (bilateral) are pathognomonic
- develop bilateral tumors before 30 years of age
- ≈ **60%** of pts. develop **schwannomas** from dorsal root
- **Meningiomas** found in ≈ **50%** of pts. with NF2
- **NF2-related meningiomas usually have a higher mitotic index and a more aggressive behavior than the sporadic**
- increased risk of developing other brain tumors, such as **ependymomas** and **astrocytomas** **(rare)**

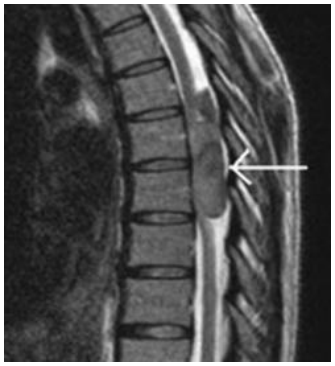
monosomy of chromosome 22 is the most common chromosomal abnormality in meningiomas, occurring in 50–70% of sporadic cases

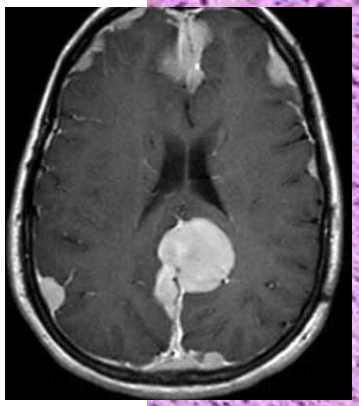


- **NF2 gene (chr. 22q12; over 110kb)**
- **merlin (or schwannomin)**
- **> mutations are truncation mutations (non-functional protein, more severe phenotype**
- **deletions (also large) or missense mutations have a milder form of NF2**

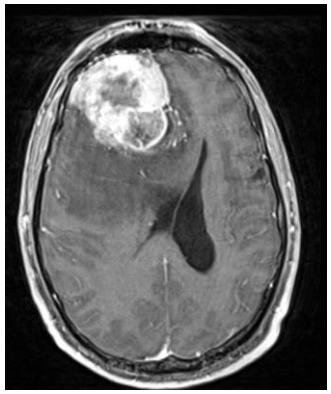


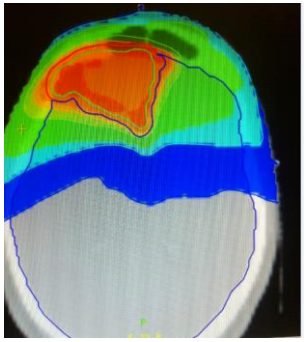






- 37 y/o; family history of NF2+ (mother and brother)
- Bilateral acoustic (VIII) schwannomas
- Meningioma dx (MRI) in FU: stable since 2009
- Slow progression from 2010.
- In 2015 rapid progression of the lesion with edema and suspect of brain invasion.
- Progression of the bilateral schwannomas.

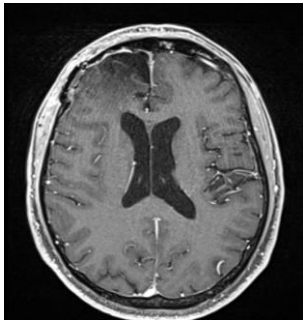


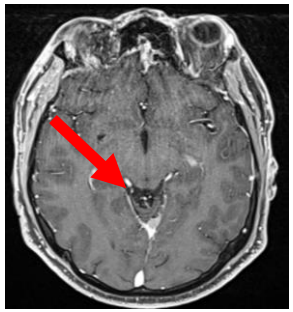


- April 28th, 2015: surgery with radical resection
- June and July 2015: Post-surgery fractionated RT (60 Gy in 30 fractions of 2 Gy/die)

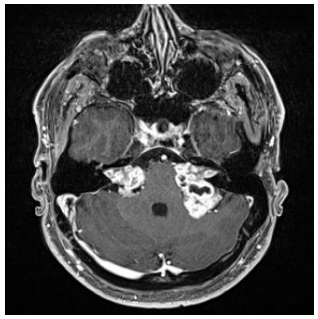
RMN October 2015:

- Not recurrence or residual disease



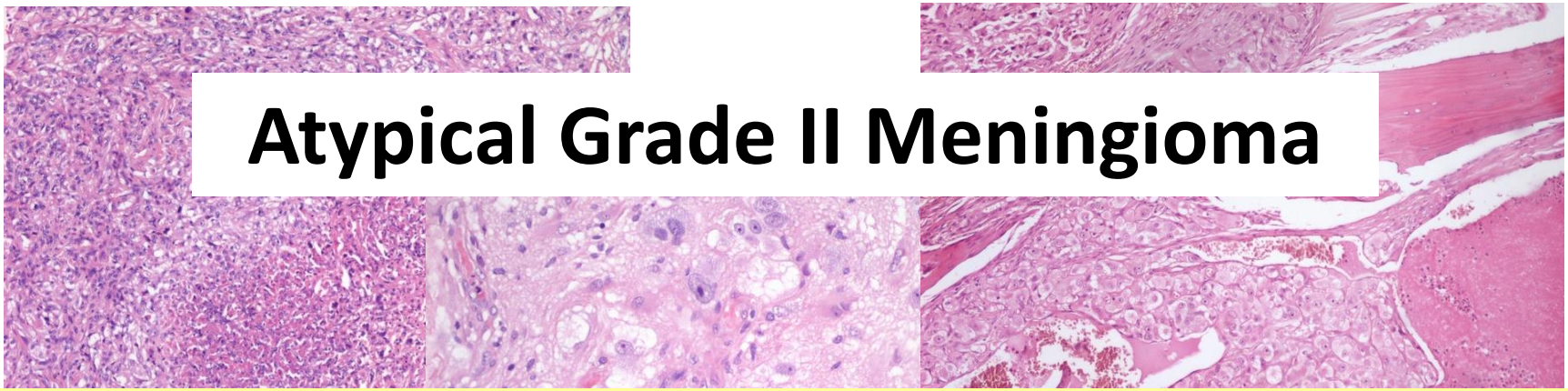


New lesion (meningioma) of about 1cm within the left falx



Progression of Scwhannomas with brainstem compression

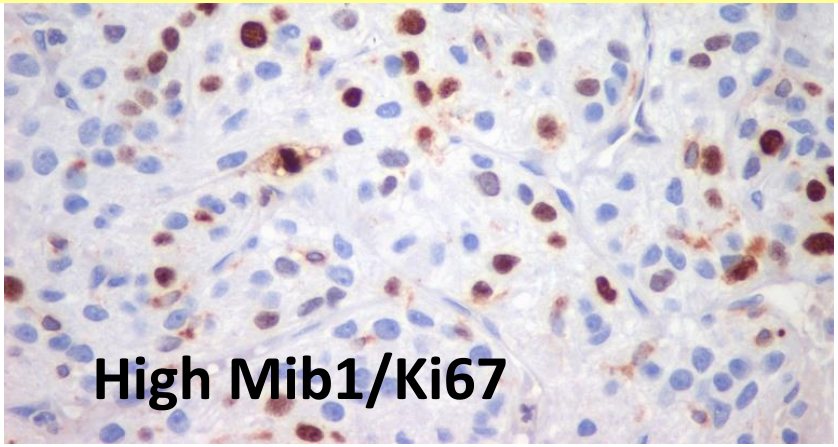
Courtesy of Dr. L. Triggiani; Radiotherapy, Brescia

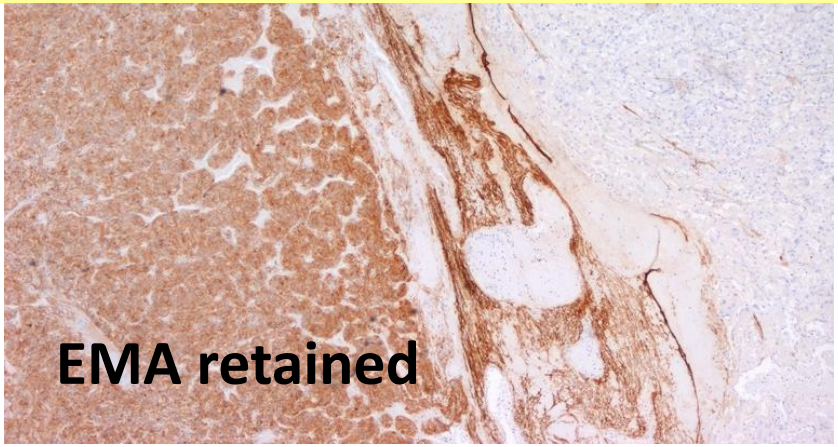


Atypical Grade II Meningioma

October 2016:

- **MRI, local recurrence**
- **Other two meningiomas**
- **Further acustic Schwannomas progression**





NF2 mutated (somatic) Meningiomas: about 50%

	AKT1	*KLF4*	*TRAF7*	*NF2*	*SMO*	*TERT*
Meningothelial meningioma WHO grade I	13%	..	8%	22%	16%	..
Transitional meningioma WHO grade I	14%	..	5%	33%	..	..
Fibroblastic meningioma WHO grade I	..	..	..	70%	..	..
Psammomatous meningioma WHO grade I	..	..	..	60%	..	..
Secretory meningioma WHO grade I	..	100%	100%	..	..	..
Metaplastic meningioma WHO grade I	25%	..	..	20%	..	..
Microcystic meningioma WHO grade I	..	..	..	..	..	..
Angiomatous meningioma WHO grade I	4%	..	..	10%	..	..
Atypical meningioma WHO grade II	4%	..	4%	70%	..	6%
Chordoid meningioma WHO grade II	..	..	..	..	..	..
Clear cell meningioma WHO grade II	..	..	..	50%	..	..
Anaplastic meningioma WHO grade III	..	..	..	70%	..	20%

- **Why Merlin drives meningiomagenesis remain poorly understood**
- **Merlin inhibits cell proliferation through contact-dependent regulation of various signaling pathways, including Hippo, Patched and Notch pathways.**
- **Activation of the mTOR pathway during meningiomagenesis**

somatic mutations in the INI1 (SMARCB1/hSNF5) gene

- Alterations in *SMARCB1*, located on chromosome 22q11.2 in close proximity to NF2, have also been reported in meningiomas and schwannomas
- SMARCB1 is part of SWI/SNF complex participating in transcriptional regulation
- Co-occurrence of recurrent SMARCB1 mutations in NF2-mutated meningiomas is frequent
- Additional SMARCB1 alterations might accelerate the growth of meningioma

INI1 mutations in meningiomas at a potential hotspot in exon 9

U Schmitz[1], W Mueller[1], M Weber[1], N Sévenet[2], O Delattre[2] and A von Deimling[1]

[1]Department of Neuropathology, Charité, Humboldt University, 13353 Berlin, Germany, [2]Laboratory of Molecular Cancer Pathology, Institut Curie, 75248 Paris, France

British Journal of Cancer (2001) **84**(2), 199–201

Germline *SMARCB1* mutation predisposes to multiple meningiomas and schwannomas with preferential location of cranial meningiomas at the falx cerebri

Pepijn van den Munckhof · Imke Christiaans · Susan B. Kenter · Frank Baas · Theo J. M. Hulsebos

Neurogenetics (2012) 13:1–7

Germline Mutation of *INI1/SMARCB1* in Familial Schwannomatosis

The American Journal of Human Genetics Volume 80 April 2007

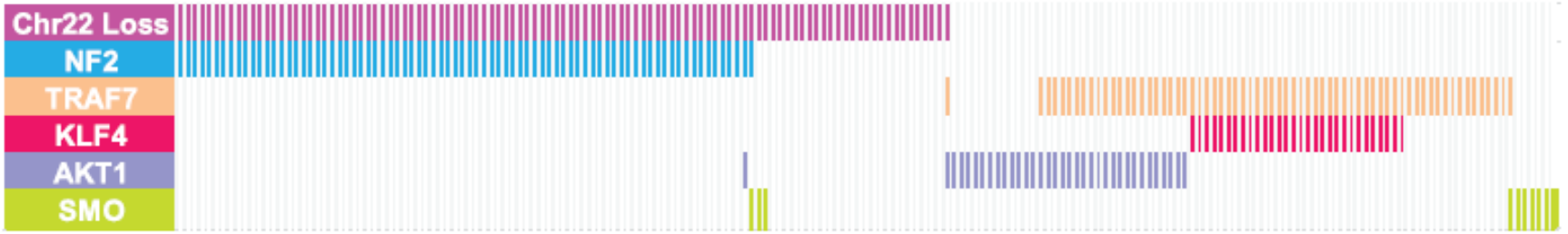
Theo J. M. Hulsebos, Astrid S. Plomp, Ruud A. Wolterman, Els C. Robanus-Maandag, Frank Baas, and Pieter Wesseling

- SMARCB1 is mutated in 50% of familial schwannomatosis (autosomal dominant with incomplete penetrance), but less than 10% of the sporadic cases
- SMARCB1^{mut} schwannomatosis lack NF2 germline mutation, but virtually all SMARCB1-schwannomatosis-related schwannomas have somatic NF2 mutations
- The relation between these two genes in the context of schwanomma development suggests a possible four-hits, three-steps mechanism of SMARCB1 and NF2 inactivation

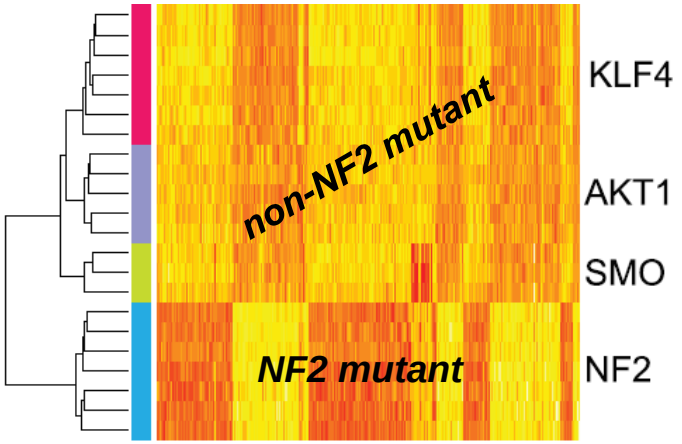
Genomic Analysis of Non-*NF2* Meningiomas Reveals Mutations in *TRAF7, KLF4, AKT1,* and *SMO*

SCIENCE VOL 339 1 MARCH 2013

Victoria E. Clark,[1] E. Zeynep Erson-Omay,[1] Akdes Serin,[1] Jun Yin,[2] Justin Cotney,[2] Koray Özduman,[3] Timuçin Avşar,[4] Jie Li,[5] Phillip B. Murray,[1] Octavian Henegariu,[1] Saliha Yilmaz,[1] Jennifer Moliterno Günel,[6] Geneive Carrión-Grant,[1] Baran Yılmaz,[7] Conor Grady,[1] Bahattin Tanrıkulu,[7] Mehmet Bakırcıoğlu,[1] Hande Kaymakçalan,[8] Ahmet Okay Caglayan,[1] Leman Sencar,[1] Emre Ceyhun,[1] A. Fatih Atik,[7] Yaşar Bayri,[7] Hanwen Bai,[1] Luis E. Kolb,[1] Ryan M. Hebert,[1] S. Bulent Omay,[1] Ketu Mishra-Gorur,[1] Murim Choi,[2] John D. Overton,[9] Eric C. Holland,[10] Shrikant Mane,[2,9] Matthew W. State,[11] Kaya Bilgüvar,[1] Joachim M. Baehring,[12] Philip H. Gutin,[6] Joseph M. Piepmeier,[13] Alexander Vortmeyer,[5] Cameron W. Brennan,[14] M. Necmettin Pamir,[3] Türker Kılıç,[15] Richard P. Lifton,[2,16] James P. Noonan,[2,17] Katsuhito Yasuno,[1] Murat Günel[1,18]*



	AKT1	*KLF4*	*TRAF7*	*NF2*	*SMO*	*TERT*
Meningothelial meningioma WHO grade I	13%	..	8%	22%	16%	..
Transitional meningioma WHO grade I	14%	..	5%	33%	..	..
Fibroblastic meningioma WHO grade I	..	..	..	70%	..	..
Psammomatous meningioma WHO grade I	..	..	..	60%	..	..
Secretory meningioma WHO grade I	..	100%	100%	..	..	..
Metaplastic meningioma WHO grade I	25%	..	..	20%	..	..
Microcystic meningioma WHO grade I	..	..	..	..	..	..
Angiomatous meningioma WHO grade I	4%	..	..	10%	..	..
Atypical meningioma WHO grade II	4%	..	4%	70%	..	6%
Chordoid meningioma WHO grade II	..	..	..	..	..	..
Clear cell meningioma WHO grade II	..	..	..	50%	..	..
Anaplastic meningioma WHO grade III	..	..	..	70%	..	20%



AKT1 gene

	AKT1
Meningothelial meningioma WHO grade I	13%
Transitional meningioma WHO grade I	14%
Fibroblastic meningioma WHO grade I	--
Psammomatous meningioma WHO grade I	--
Secretory meningioma WHO grade I	--
Metaplastic meningioma WHO grade I	25%
Microcystic meningioma WHO grade I	--
Angiomatous meningioma WHO grade I	4%
Atypical meningioma WHO grade II	4%
Chordoid meningioma WHO grade II	--
Clear cell meningioma WHO grade II	--
Anaplastic meningioma WHO grade III	--

- *AKT1* is members of the PI3K– AKT–mTOR pathway
- recurrent *Akt1* p.Glu17Lys mut with constitutive activation of AKT1
- *AKT1* p.Glu17Lys mut found in ~30% of skull-base meningiomas
- *AKT1* p.Glu17Lys mutated Men have distinct gene expression patterns compared with *NF2*-mutant meningiomas
- IHC evidence of PI3K–AKT–mTOR pathway activation

1088 Neuro-Oncology
19(8), 1088–1096, 2017 | doi:10.1093/neuonc/nox018 | Advance Access date 6 May 2017

Frequent *AKT1*^{E17K} mutations in skull base meningiomas are associated with mTOR and ERK1/2 activation and reduced time to tumor recurrence

Ümmügülsüm Yesilöz, Elmar Kirches, Christian Hartmann, Johannes Scholz, Siegfried Kropf, Felix Sahm, Makoto Nakamura, and Christian Mawrin

- 1-5% of meningiomas without alterations in *NF2* and *AKT1* harbour recurrent alterations in *SMO (*Hedgehog signaling pathway)
- *SMO* mut frequent in skull-base meningiomas (28%)
- Two hotspot mutations in *SMO* gene: Leu412Phe and Trp535Leu

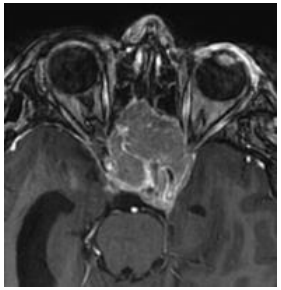
SMO gene

	SMO
Meningothelial meningioma WHO grade I	16%
Transitional meningioma WHO grade I	--
Fibroblastic meningioma WHO grade I	--
Psammomatous meningioma WHO grade I	--
Secretory meningioma WHO grade I	--
Metaplastic meningioma WHO grade I	--
Microcystic meningioma WHO grade I	--
Angiomatous meningioma WHO grade I	--
Atypical meningioma WHO grade II	--
Chordoid meningioma WHO grade II	--
Clear cell meningioma WHO grade II	--
Anaplastic meningioma WHO grade III	--

Neuro-Oncology
19(3), 345–351, 2017 | doi:10.1093/neuonc/now276 | Advance Access date 12 January 2017

SMO mutation status defines a distinct and frequent molecular subgroup in olfactory groove meningiomas

Julien Boetto, Franck Bielle, Marc Sanson, Matthieu Peyre, and Michel Kalamarides



Genomic sequencing of meningiomas identifies oncogenic *SMO* and *AKT1* mutations

Priscilla K Brastianos[1–4,11], Peleg M Horowitz[3–6,11], Sandro Santagata[3,7], Robert T Jones[1,8], Aaron McKenna[4], Gad Getz[4], Keith L Ligon[3,7], Emanuele Palescandolo[8], Paul Van Hummelen[1,8], Matthew D Ducar[1,8], Alina Raza[1,8], Ashwini Sunkavalli[1,8], Laura E MacConaill[1,8], Anat O Stemmer-Rachamimov[3,9], David N Louis[3,9,10], William C Hahn[1,3,4,8], Ian F Dunn[3,4,6] & Rameen Beroukhim[1,3–5,8]

nature genetics

VOLUME 45 | NUMBER 3 | MARCH 2013

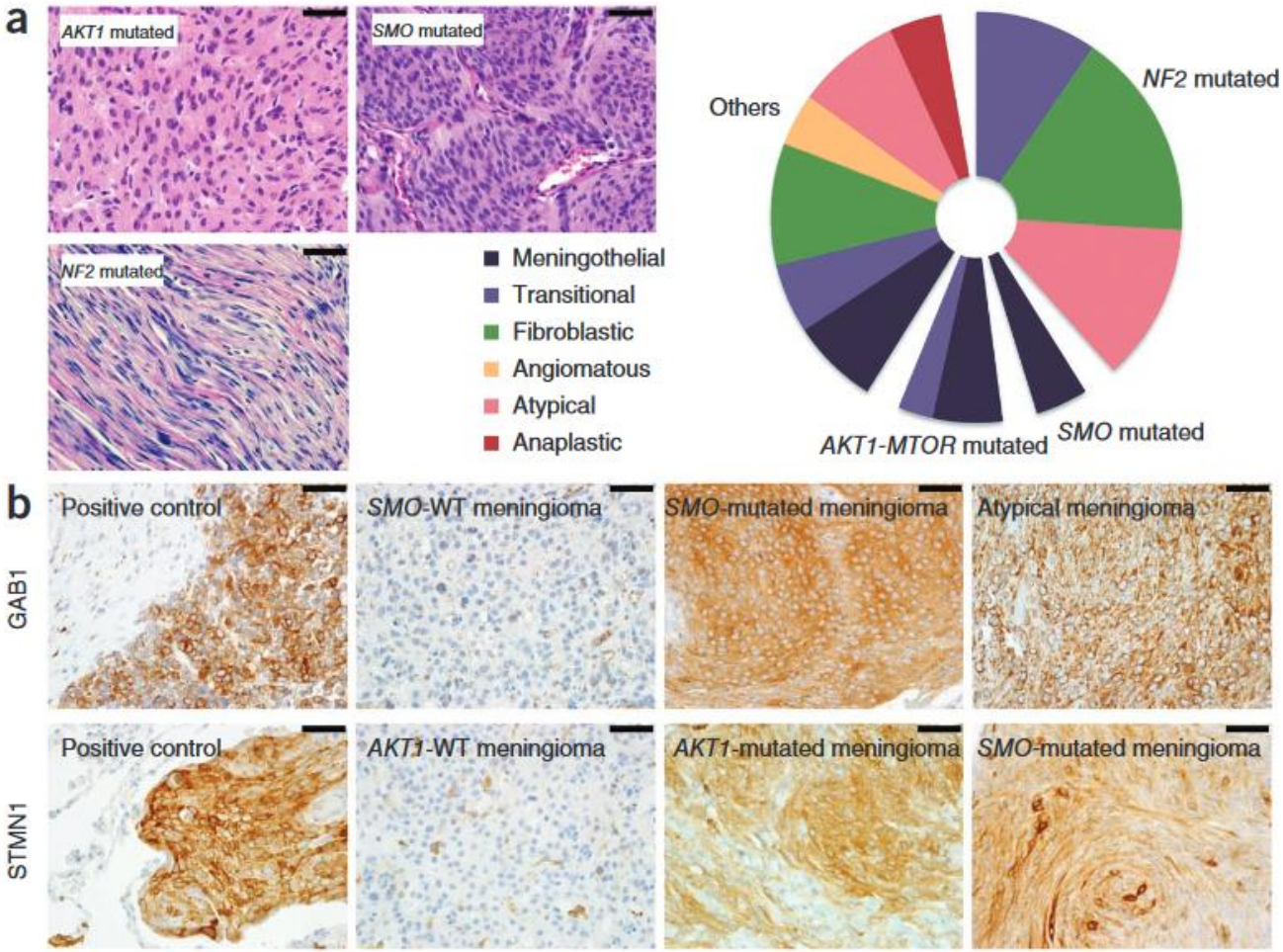


Figure 4 Associations between mutations in Hedgehog and AKT-mTOR pathways and histological findings. (**a**) Samples with mutations in *SMO* and *AKT1-MTOR* are predominantly of the meningothelial subtype ($P = 0.005$ and 0.009, respectively). *NF2*-mutated samples are predominantly fibroblastic and transitional ($P = 0.013$). Samples underwent hematoxylin and eosin staining (left). The distribution of samples within different histological subtypes is shown by pie chart (right). (**b**) Immunohistochemistry indicates activation of the Hedgehog (GAB1) and AKT-mTOR (STMN1) pathways in tumors harboring *SMO* and *AKT1* mutations, respectively ($P = 0.0008$ and 3×10^{-6}). Scale bars, 50 μm. WT, wild type.

TRAF7 gene

- *TRAF7 (*E3 ubiquitin ligase; interacts with numerous pathways, including MAP3K3)
- *TRAF7* mutations were found in up to 25% of WHO grade I and grade II Men
- > mutations mapped to WD40 domains, involved in regulation of JUN N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signaling

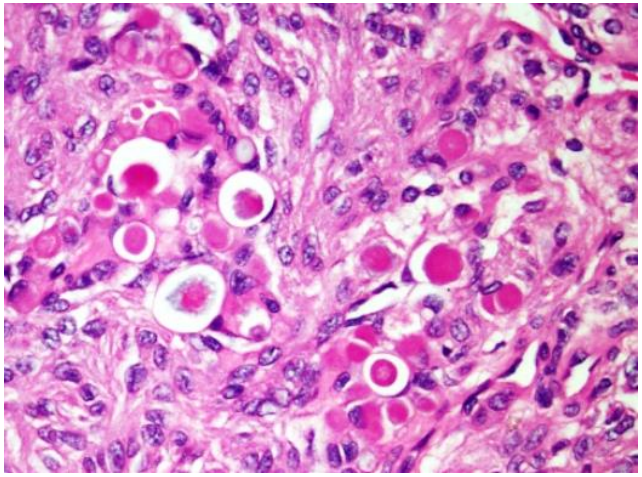
KLF4 gene

- *KLF4 (*Kruppel-like factor gene family) (transcriptional activation and repression)
- Hotspot mutation *KLF4* p.Lys409Gln in up to 50% of *NF2*-non-mutated Men
- Interestingly, have a high rate of co-occurrence with *TRAF7* mutations

Secretory meningiomas are defined by combined *KLF4* K409Q and *TRAF7* mutations

Acta Neuropathol (2013) 125:351–358

David E. Reuss · Rosario M. Piro · David T. W. Jones · Matthias Simon · Ralf Ketter · Marcel Kool · Albert Becker · Felix Sahm · Stefan Pusch · Jochen Meyer · Christian Hagenlocher · Leonille Schweizer · David Capper · Phillipp Kickingereder · Jana Mucha · Christian Koelsche · Natalie Jäger · Thomas Santarius · Patrick S. Tarpey · Philip J. Stephens · P. Andrew Futreal · Ruth Wellenreuther · Jürgen Kraus · Doris Lenartz · Christel Herold-Mende · Christian Hartmann · Christian Mawrin · Nathalia Giese · Roland Eils · V. Peter Collins · Rainer König · Otmar D. Wiestler · Stefan M. Pfister · Andreas von Deimling



	TRAF7
Meningothelial meningioma WHO grade I	8%
Transitional meningioma WHO grade I	5%
Fibroblastic meningioma WHO grade I	..
Psammomatous meningioma WHO grade I	..
Secretory meningioma WHO grade I	100%
Metaplastic meningioma WHO grade I	..
Microcystic meningioma WHO grade I	..
Angiomatous meningioma WHO grade I	..
Atypical meningioma WHO grade II	4%
Chordoid meningioma WHO grade II	..
Clear cell meningioma WHO grade II	..
Anaplastic meningioma WHO grade III	..

	KLF4
Meningothelial meningioma WHO grade I	..
Transitional meningioma WHO grade I	..
Fibroblastic meningioma WHO grade I	..
Psammomatous meningioma WHO grade I	..
Secretory meningioma WHO grade I	100%
Metaplastic meningioma WHO grade I	..
Microcystic meningioma WHO grade I	..
Angiomatous meningioma WHO grade I	..
Atypical meningioma WHO grade II	..
Chordoid meningioma WHO grade II	..
Clear cell meningioma WHO grade II	..
Anaplastic meningioma WHO grade III	..

PI3K gene

- ***AKT1* mutations in Men**, as well as previous data showing activation of the AKT protein, supports **deregulation of PI3K signaling pathway**
- Indeed, ***PIK3CA* mutations in 7% of *NF2* non-mutated Meningiomas**
- **PIK3CA-mutant Men were graded as WHO grade I (show limited chromosomal instability) and were enriched in skull base Meningiomas**
- ***PIK3CA*-mutant Men lacked mutations in *NF2*, *AKT1* and *SMO*, but they tended to harbour *TRAF7* mutations**

AKT1, SMO and PIK3CA mutations were mutually exclusive.

*AKT1, KLF4 and PIK3CA mutations often co-occurred with mutations in **TRAF7**.*

Oncogenic PI3K mutations are as common as *AKT1* and *SMO* mutations in meningioma

Neuro-Oncology

Neuro-Oncology 18(5), 649–655, 2016
doi:10.1093/neuonc/nov316
Advance Access date 28 January 2016

Malak Abedalthagafi†, Wenya Linda Bi†, Ayal A. Aizer†, Parker H. Merrill†, Ryan Brewster, Pankaj K. Agarwalla, Marc L. Listewnik, Dora Dias-Santagata, Aaron R. Thorner, Paul Van Hummelen, Priscilla K. Brastianos, David A. Reardon, Patrick Y. Wen, Ossama Al-Mefty, Shakti H. Ramkissoon, Rebecca D. Folkerth, Keith L. Ligon, Azra H. Ligon, Brian M. Alexander‡, Ian F. Dunn‡, Rameen Beroukhim‡, and Sandro Santagata‡

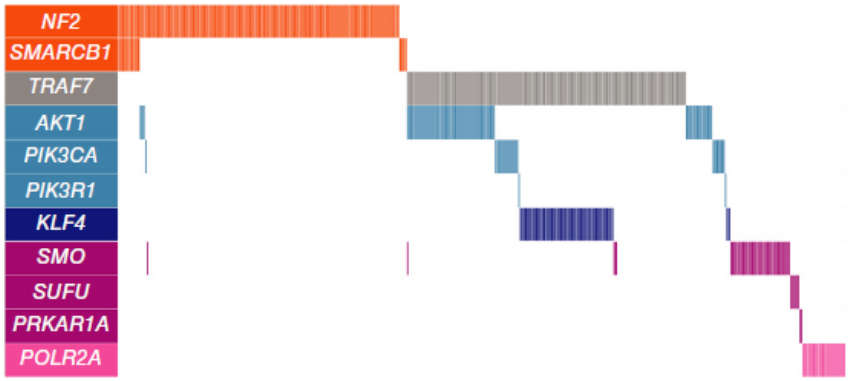
POLR2A gene

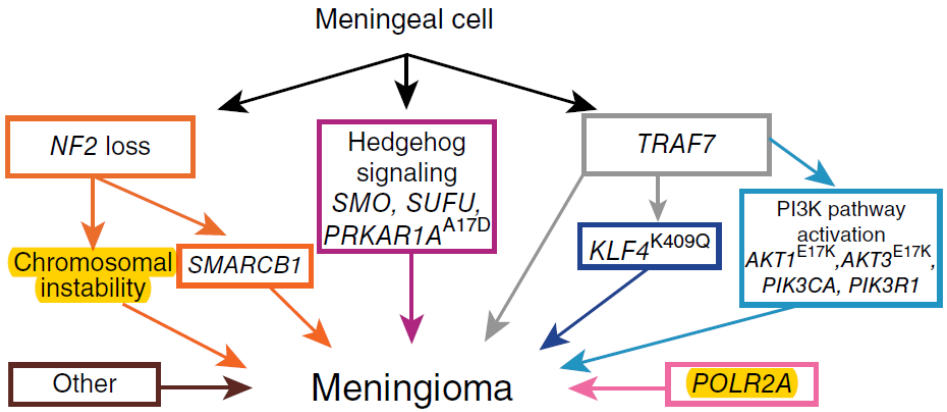
NATURE GENETICS VOLUME 48 | NUMBER 10 | OCTOBER 2016

Recurrent somatic mutations in *POLR2A* define a distinct subset of meningiomas

Victoria E Clark[1–3], Akdes Serin Harmancı[1,2], Hanwen Bai[1,3,14], Mark W Youngblood[1–3,14], Tong Ihn Lee[4], Jacob F Baranoski[1–3], A Gulhan Ercan-Sencicek[2,5], Brian J Abraham[4], Abraham S Weintraub[4], Denes Hnisz[4], Matthias Simon[6], Boris Krischek[7], E Zeynep Erson-Omay[1,2], Octavian Henegariu[1–3,5,8], Geneive Carrión-Grant[1,2], Ketu Mishra-Gorur[1–3,5,8], Daniel Durán[1–3], Johanna E Goldmann[4], Johannes Schramm[9], Roland Goldbrunner[7], Joseph M Piepmeier[2], Alexander O Vortmeyer[10], Jennifer Moliterno Günel[1,2], Kaya Bilgüvar[1,3,11], Katsuhito Yasuno[1,2], Richard A Young[4,12] & Murat Günel[1–3,5,8,13]

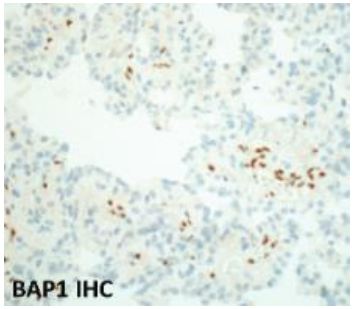
- somatic mutations of ***POLR2A*** (DNA-directed RNA polymerase II subunit RPB1) in ~6% of Meningiomas
- ***POLR2A*** mutations did not coexist with any of previously described meningioma driver mutations
- associated with meningothelial histology and location in the tuberculum sellae.
- No ***POLR2A*** mutations were present in high-grade meningiomas

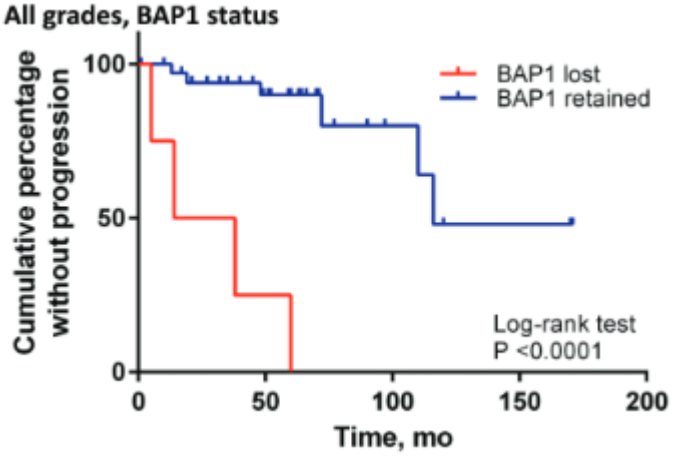


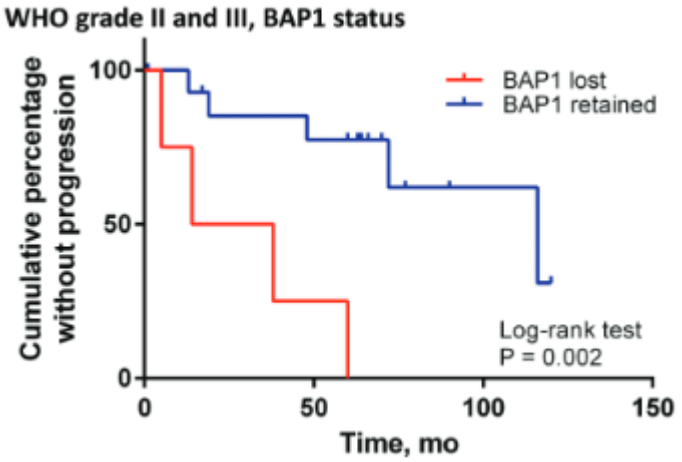


BAP1

- frequent inactivation of *BAP1* in rhabdoid meningiomas
- *BAP1* mutations are more frequent in meningiomas with >50% rhabdoid cells and a loss of BAP1 protein expression indicates early tumour recurrence.
- BAP1 immunohistochemistry could be a promising tool for risk stratification in patients with rhabdoid meningiomas (distinction of rhabdoid-appearing meningiomas into aggressive and less-aggressive tumour types)







BAP1-mutated rhabdoid meningiomas are clinically aggressive, requiring intensive clinical management.

Neuro-Oncology
19(4), 535–545, 2017 | doi:10.1093/neuonc/now235 | Advance Access date 9 November 2016

Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas

Ganesh M. Shankar,[1] Malak Abedalthagafi,[1] Rachael A. Vaubel, Parker H. Merrill, Naema Nayyar, Corey M. Gill, Ryan Brewster, Wenya Linda Bi, Pankaj K. Agarwalla, Aaron R. Thorner, David A. Reardon, Ossama Al-Mefty, Patrick Y. Wen, Brian M. Alexander, Paul van Hummelen, Tracy T. Batchelor, Keith L. Ligon, Azra H. Ligon, Matthew Meyerson, Ian F. Dunn, Rameen Beroukhim, David N. Louis, Arie Perry, Scott L. Carter, Caterina Giannini, William T. Curry Jr, Daniel P. Cahill,[2] Frederick G. Barker II,[2] Priscilla K. Brastianos,[2] and Sandro Santagata[2]

Neuro-Oncology
19(11), 1447–1456, 2017 | doi:10.1093/neuonc/nox094 | Advance Access date 8 May 2017

BAP1 mutations in high-grade meningioma: implications for patient care

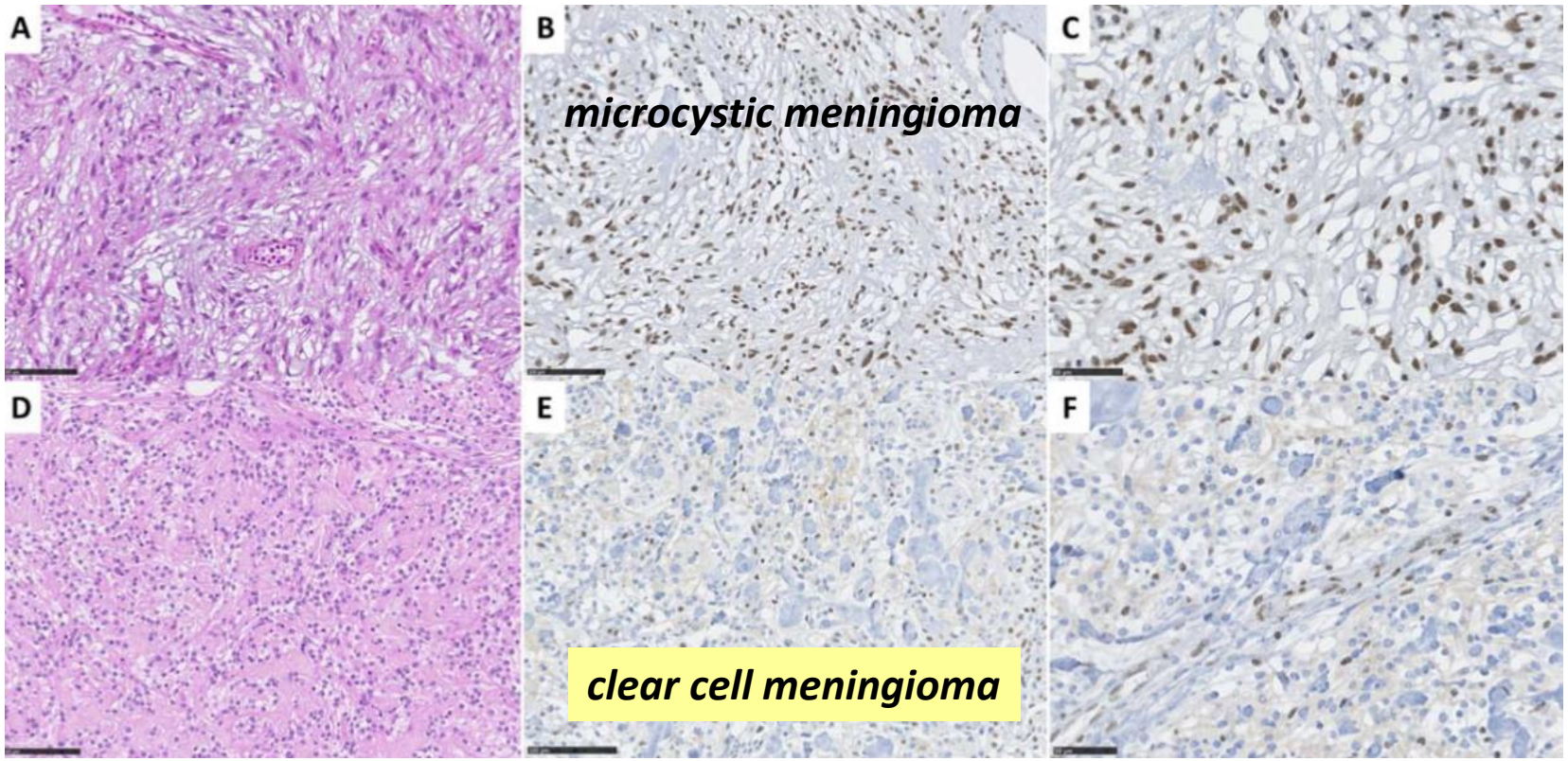
Ganesh M. Shankar and Sandro Santagata

SMARCE1

Brain Pathol. 2017 May 5

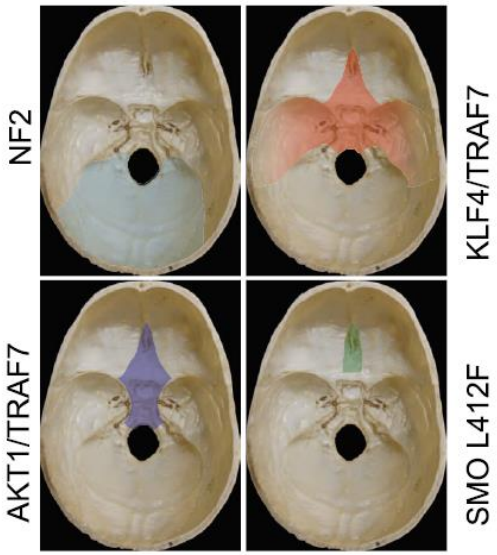
Loss of SMARCE1 expression is a specific diagnostic marker of clear cell meningioma: a comprehensive immunophenotypical and molecular analysis

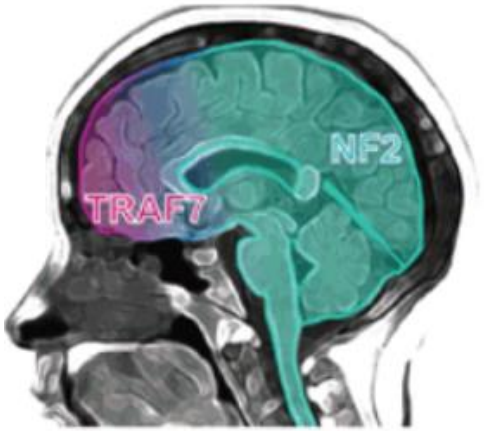
Arnault Tauziede-Espariat[1], Béatrice Parfait[2], Aurore Besnard[1], Joëlle Lacombe[1], Johan Pallud[3], Sanaa Tazi[4], Stéphanie Puget[5], Guillaume Lot[6], Benoît Terris[7], Joëlle Cohen[2], Michel Vidaud[2], Dominique Figarella-Branger[8], Franck Monnien[9], Marc Polivka[10], Homa Adle-Biassette[10], Pascale Varlet[1]

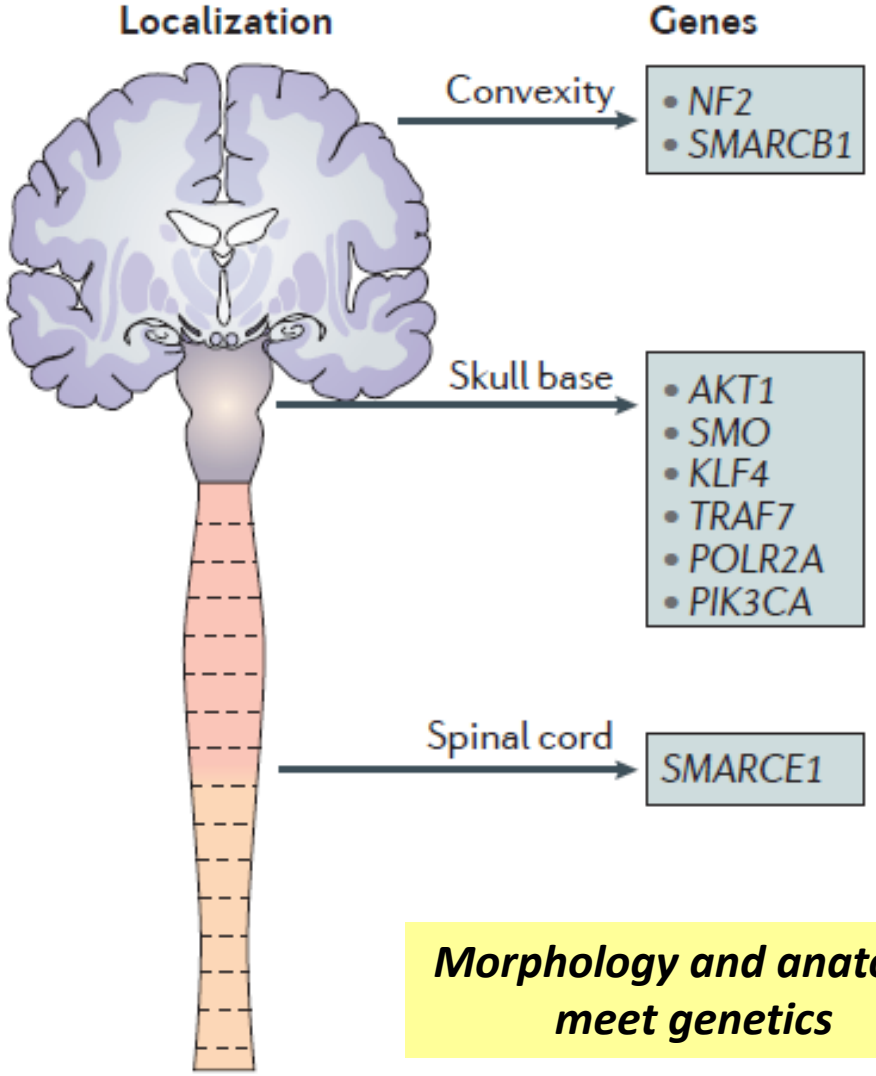


anti-SMARCE1 HPA003916 antibody

Meningioma Driver Mutations Determine Their Anatomical Site of Origin







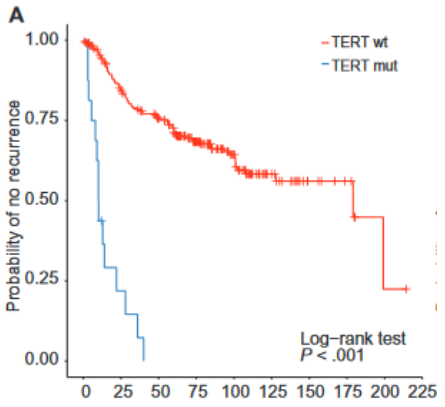
Morphology and anatomy meet genetics

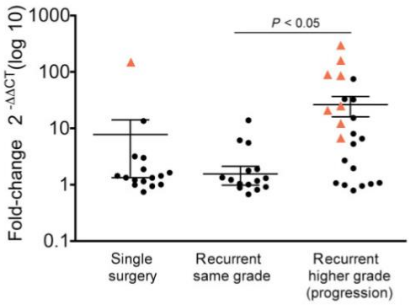
- Mutations in the *TERT* promoter have a clear effect on the prognosis of meningioma
- Increased expression of TE*RT* has been recognized in aggressive meningiomas.
- Mutations in the *TERT* promoter at the hotspot regions g.228C>T and g.250C>T were found in 6.4% of meningiomas (1.7%, 5.7% and 20% of WHO grade I, II and III meningiomas, respectively).
- The prognostic effect of this alteration was independent from histological grade

TERT Promoter Mutations and Risk of Recurrence in Meningioma

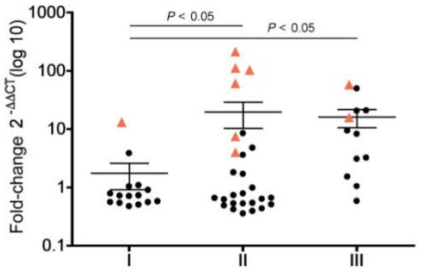
Felix Sahm*, Daniel Schrimpf*, Adriana Olar*, Christian Koelsche, David Reuss, Juliane Bissel, Annekathrin Kratz, David Capper, Sebastian Schefzyk, Thomas Hielscher, Qianghu Wang, Erik P. Sulman, Sebastian Adeberg, Arend Koch, Ali Fuat Okuducu, Stefanie Brehmer, Jens Schittenhelm, Albert Becker, Benjamin Brokinkel, Melissa Schmidt, Theresa Ull, Konstantinos Gousias, Almuth Friederike Kessler, Katrin Lamszus, Jürgen Debus, Christian Mawrin, Yoo-Jin Kim, Matthias Simon, Ralf Ketter, Werner Paulus, Kenneth D. Aldape, Christel Herold-Mende, Andreas von Deimling

JNCI J Natl Cancer Inst (2016) 108(5)





Higher TERT expression in meningioma samples undergoing histological progression



TERT expression is increased in high-grade meningioma samples

High Incidence of Activating *TERT* Promoter Mutations in Meningiomas Undergoing Malignant Progression

Stéphane Goutagny[1,2]*; Jean C. Nault[2]*; Maxime Mallet[2]; Dominique Henin[3,4]; Jessica Z. Rossi[2,5,6]; Michel Kalamarides[2,7,8]

Brain Pathology **24** (2014) 184–189

DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis

Felix Sahm, Daniel Schrimpf, Damian Stichel, David T W Jones, Thomas Hielscher, Sebastian Schefzyk, Konstantin Okonechnikov, Christian Koelsche, David E Reuss, David Capper, Dominik Sturm, Hans-Georg Wirsching, Anna Sophie Berghoff, Peter Baumgarten, Annekathrin Kratz, Kristin Huang, Annika K Wefers, Volker Hovestadt, Martin Sill, Hayley P Ellis, Kathreena M Kurian, Ali Fuat Okuducu, Christine Jungk, Katharina Drueschler, Matthias Schick, Melanie Bewerunge-Hudler, Christian Mawrin, Marcel Seiz-Rosenhagen, Ralf Ketter, Matthias Simon, Manfred Westphal, Katrin Lamszus, Albert Becker, Arend Koch, Jens Schittenhelm, Elisabeth J Rushing, V Peter Collins, Stefanie Brehmer, Lukas Chavez, Michael Platten, Daniel Hänggi, Andreas Unterberg, Werner Paulus, Wolfgang Wick, Stefan M Pfister, Michel Mittelbronn, Matthias Preusser, Christel Herold-Mende, Michael Weller, Andreas von Deimling

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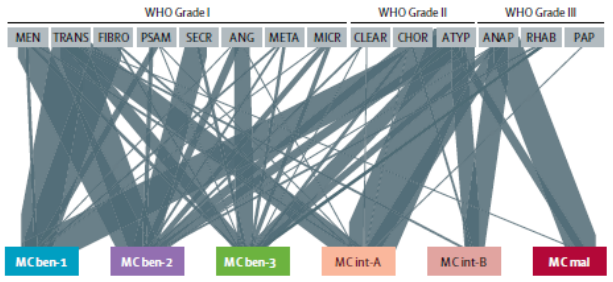
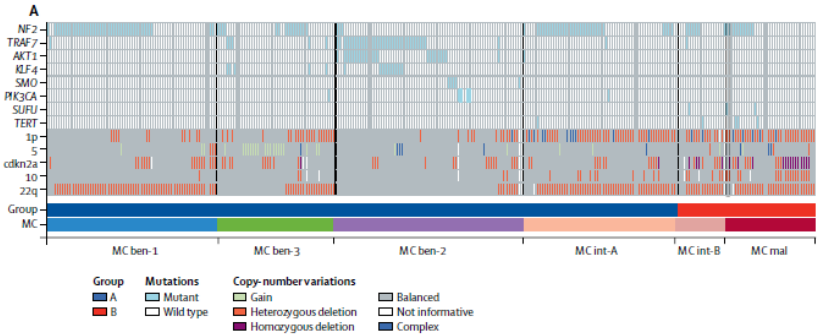
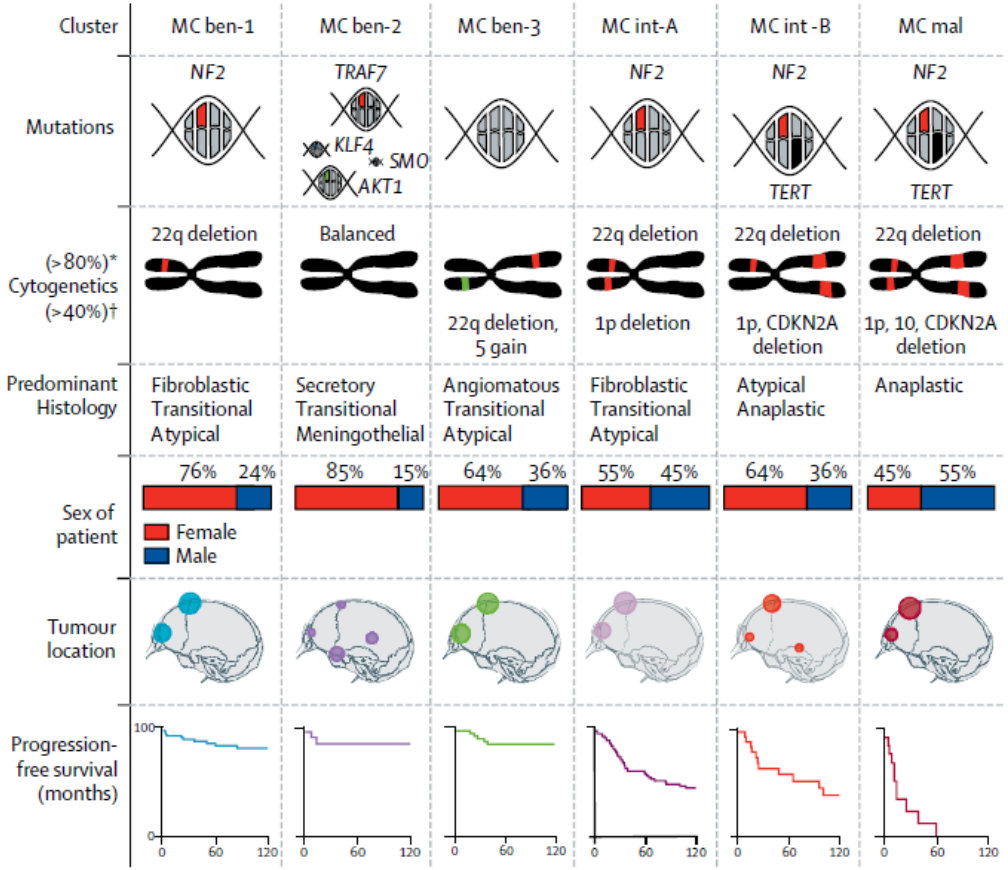
Vol 18 May 2017

Six DNA methylation classes (MC):
- benign (ben) 1–3
- intermediate (int) A and B
- malignant (mal)







Acta Neuropathologica
https://doi.org/10.1007/s00401-019-02008-w

ORIGINAL ARTICLE

Mutational patterns and regulatory networks in epigenetic subgroups of meningioma

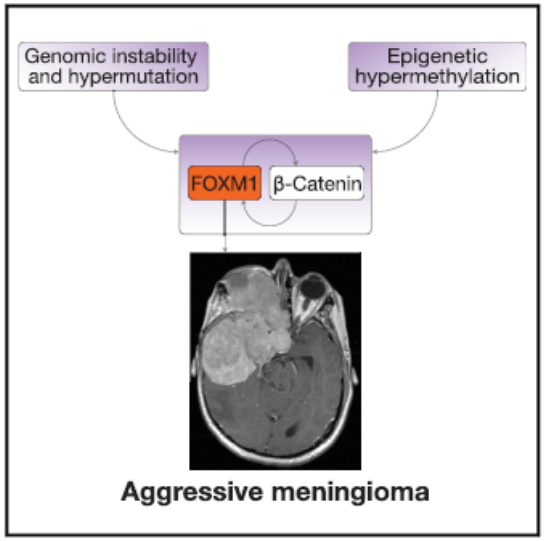
Nagarajan Paramasivam[1,2] · Daniel Hübschmann[1,3,4,5] · Umut H Toprak[6,7] · Naveed Ishaque[1,2,8] · Marian Neidert[9] · Daniel Schrimpf[10,11] · Damian Stichel[10,11] · David R… · Annekathrin Reinhardt[10,11] · Annika K. Wefers[10,11] · David T. W. Jones · Johannes Werner[1,15] · Sebastian Uhrig[16] · Hans-Georg Wirsching[17] · … · Melanie Bewerunge-Hudler[18] · Katja Beck[2] · Stephanie Brehmer[19] · … · Daniel Hänggi[19] · Christel Herold-Mende[21] · Ralf Ketter[20] · Roland Eil… · Wolfgang Wick[25,26] · Michael Weller[17] · Rachel Grossmann[23,24] · Andr… · Felix Sahm[7,10,11]

meningiomas, similar to previous reports for Mrad. Aberrations of *DMD* were found to be enriched in MCs with *NF2* mutations, and *DMD* was among the most differentially upregulated genes in *NF2* mutant compared to *NF2* wild-type cases. The mutational signature AC3, which has been associated with defects in homologous recombination repair (HRR), was detected in both sporadic meningioma and Mrad, but widely distributed across the genome in sporadic cases and enriched near genomic breakpoints in Mrad. Compared to the other MCs, the number of single nucleotide variants matching the AC3 pattern was significantly higher in the malignant MC, which also exhibited higher genomic instability, determined by the numbers of both large segments affected by copy number alterations and breakpoints between large segments. ChIP-seq analysis for H3K27ac revealed a specific activation of genes regulated by the transcription factor FOXM1 in the malignant MC. This analysis also revealed a super enhancer near the *HOXD* gene cluster in this MC, which, together with general upregulation of *HOX* genes in the malignant MC, indicates a role of *HOX* genes in meningioma aggressiveness. This data

Cell Reports

Comprehensive Molecular Profiling Identifies FOXM1 as a Key Transcription Factor for Meningioma Proliferation

Graphical Abstract



Authors

Harish N. Vasudevan, Steve E. Braunstein, Joanna J. Phillips, …, Mitchel S. Berger, Arie Perry, David R. Raleigh

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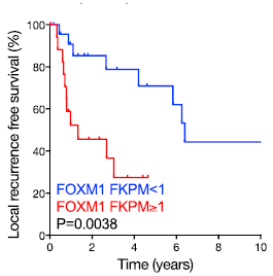
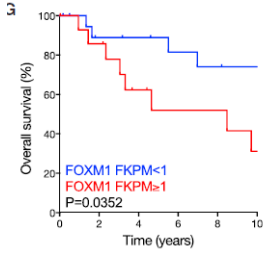
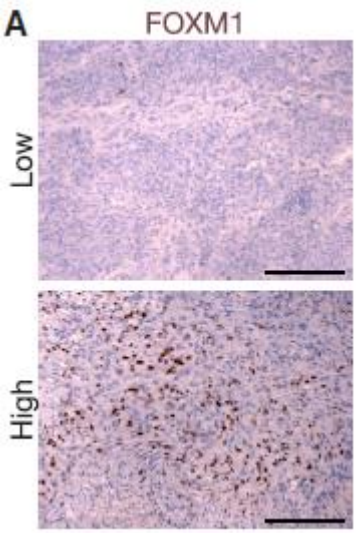
In Brief

Using multiplatform molecular profiling, Vasudevan et al. comprehensively define the molecular profile of aggressive meningioma. They identify genomic, epigenomic, and transcriptomic mechanisms that converge on a FOXM1/Wnt signaling axis in aggressive meningioma that is associated with meningioma cell proliferation and is a marker of poor clinical outcomes across molecular subgroups.







Cell Reports 22, 3672–3683, March 27, 2018

Neuro-Oncology
21(S1), 4–17, 2019 | doi:10.1093/neuonc/noy178

Molecular and translational advances in meningiomas

Suganth Suppiah,* Farshad Nassiri,* Wenya Linda Bi, Ian F. Dunn, Clemens Oliver Hanemann, Craig M. Horbinski, Rintaro Hashizume, Charles David James, Christian Mawrin, Houtan Noushmehr, Arie Perry, Felix Sahm, Andrew Sloan, Andreas Von Deimling, Patrick Y. Wen, Kenneth Aldape,* and Gelareh Zadeh*; and the International Consortium on Meningiomas†

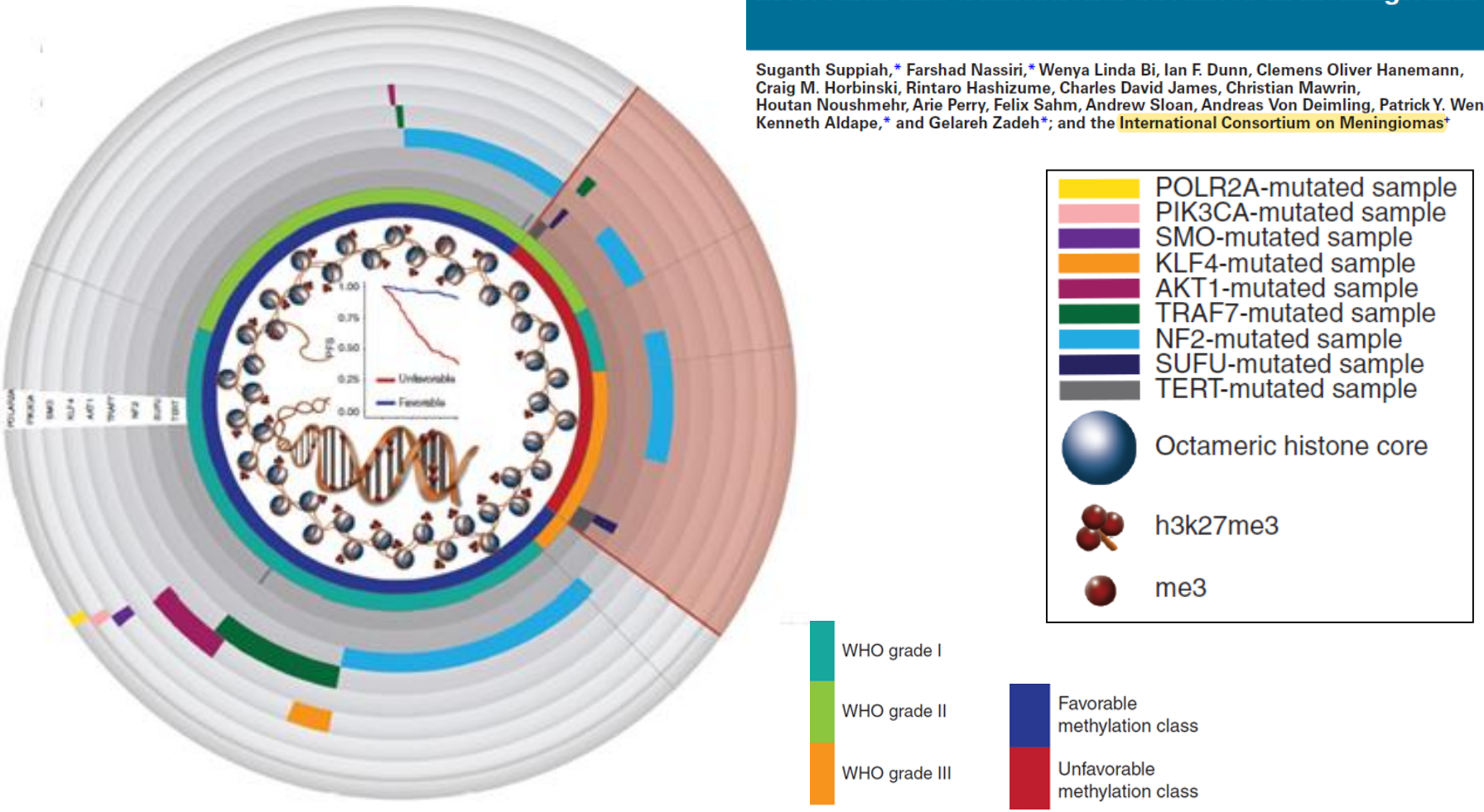


Fig. 1 Summary of established epigenomic and genomic landscape of sporadic meningiomas. DNA methylation profiling distinguishes 2 distinct tumor subgroups with distinct risk profiles that refine risk of recurrence beyond standard-of-care histopathological grading and are associated with typical known mutations.

Viaene et al. Acta Neuropathologica Communications (2019) 7:67
https://doi.org/10.1186/s40478-019-0690-x

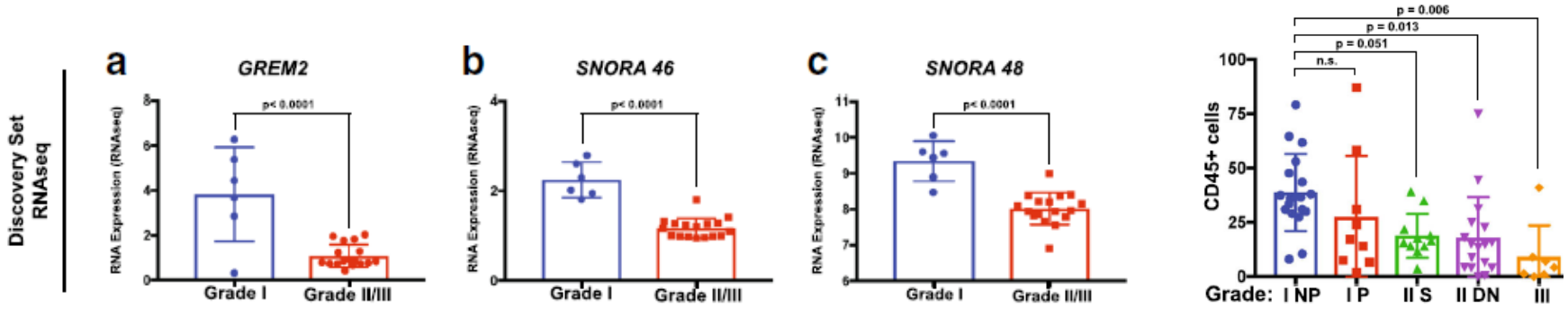
Acta Neuropathologica Communications

RESEARCH Open Access

Transcriptome signatures associated with meningioma progression

Angela N. Viaene[1,5†], Bo Zhang[2†], Maria Martinez-Lage[1,6†], Chaomei Xiang[3,7†], Umberto Tosi[4†], Jayesh P. Thawani[3], Busra Gungor[3], Yuankun Zhu[2], Laura Roccograndi[3], Logan Zhang[3], Robert L. Bailey[3,8], Phillip B. Storm[2], Donald M. O'Rourke[3], Adam C. Resnick[2], M. Sean Grady[3*] and Nadia Dahmane[3,4*]

As such, we identify *GREM2*, a regulator of the BMP pathway, and the snoRNAs *SNORA46* and *SNORA48*, as being significantly reduced in meningioma progression. Additionally, our study has identified several novel fusion transcripts that are differentially present in meningiomas, with grade I tumors that did not progress presenting more fusion transcripts than all other tumors. Interestingly, our study also points to a difference in the tumor immune microenvironment that correlates with histopathological grade.



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Taylor & Francis
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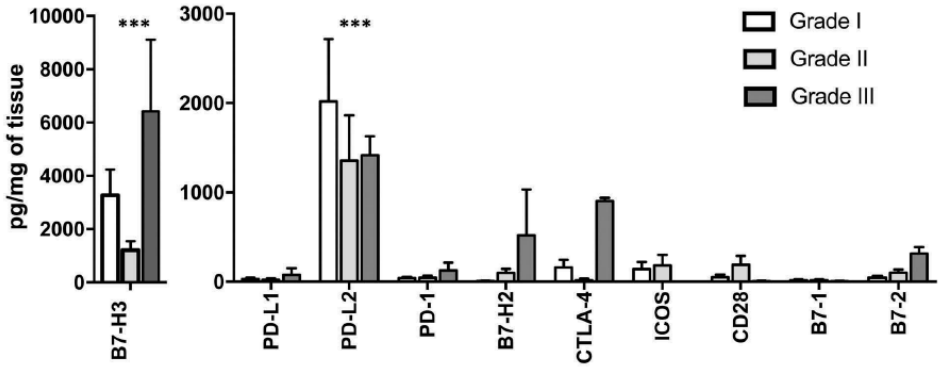
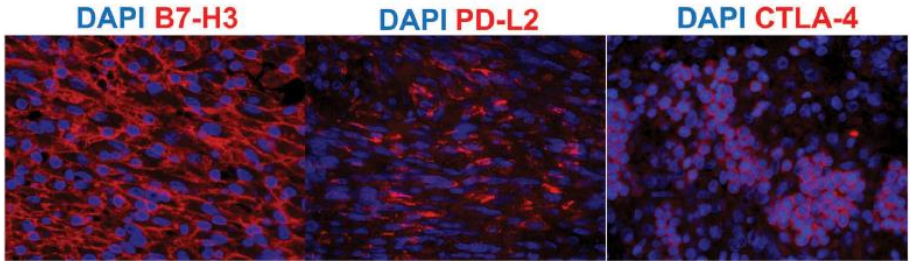
BRIEF REPORT

Identification of PD-L2, B7-H3 and CTLA-4 immune checkpoint proteins in genetic subtypes of meningioma

Dustin T Proctor[a,b,c], Zeel Patel[a,b,c], Sanju Lama[a,b,c], Lothar Resch[d], Guido van Marle[e], and Garnette R Sutherland[a,b,c]

[a]Project neuroArm, Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [b]Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada; [c]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; [d]Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, AB, Canada; [e]Department of Microbiology, Immunology and Infectious Diseases, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada





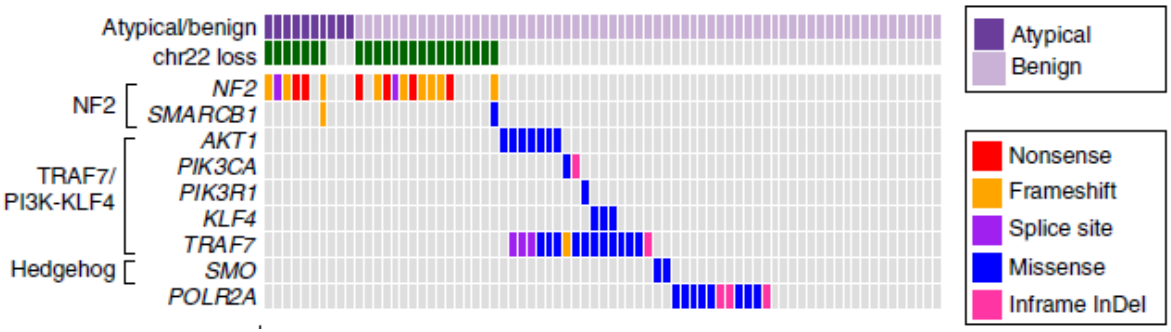
In summary, we show that meningioma invokes a diverse range of immune responses, which in part may be contributed to by common genetic changes associated with this tumor. Immune checkpoint proteins PD-L2 and B7-H3 were the most abundant proteins tested and present in all grades of meningioma, indicating that these proteins may be of more importance to immune responses than previously described immune checkpoint proteins in meningioma. Furthermore, we also describe here the presence of CTLA-4 in high grade meningiomas. It will be interesting to validate these findings in a larger study covering all morphological and genetic subtypes of meningioma and evaluate the effects of these immune markers on clinical outcome.

Progression to Atypical Meningioma

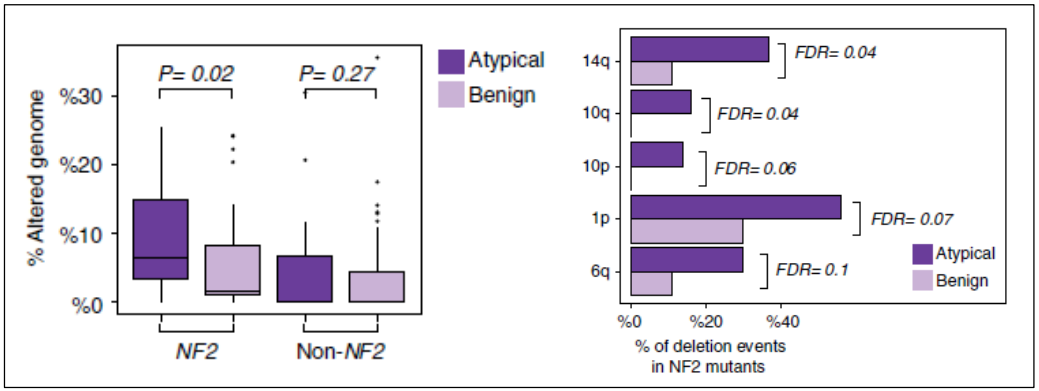
nature COMMUNICATIONS

Integrated genomic analyses of *de novo* pathways underlying atypical meningiomas

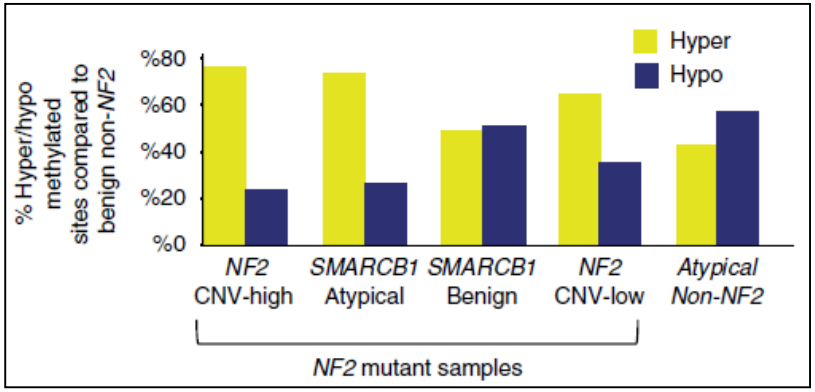
Akdes Serin Harmanci[1,2], Mark W. Youngblood[1,2,3], Victoria E. Clark[1,2,3], Süleyman Coşkun[1,2], Octavian Henegariu[1,2,3,4,5], Daniel Duran[1,2], E. Zeynep Erson-Omay[1,2], Leon D. Kaulen[1,2], Tong Ihn Lee[6], Brian J. Abraham[6], Matthias Simon[7], Boris Krischek[8], Marco Timmer[8], Roland Goldbrunner[8], S. Bülent Omay[1,2], Jacob Baranoski[1,2,3], Burçin Baran[1,2], Geneive Carrión-Grant[1,2], Hanwen Bai[1,3], Ketu Mishra-Gorur[1,2,3,4,5], Johannes Schramm[7], Jennifer Moliterno[1,2], Alexander O. Vortmeyer[9], Kaya Bilgüvar[1,3,10], Katsuhito Yasuno[1,2], Richard A. Young[6,11] & Murat Günel[1,2,3,4,5,12]

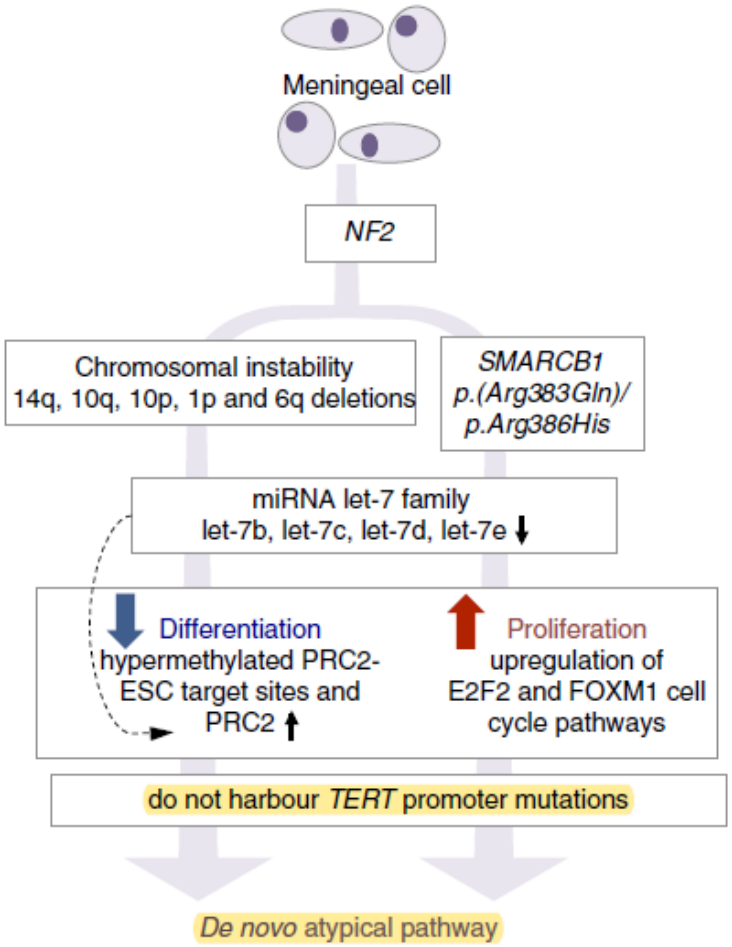


Genomic Instability



Hyper- or Hypo-methylated Phenotype





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https://doi.org/10.1007/s00401-018-1844-9

ORIGINAL PAPER

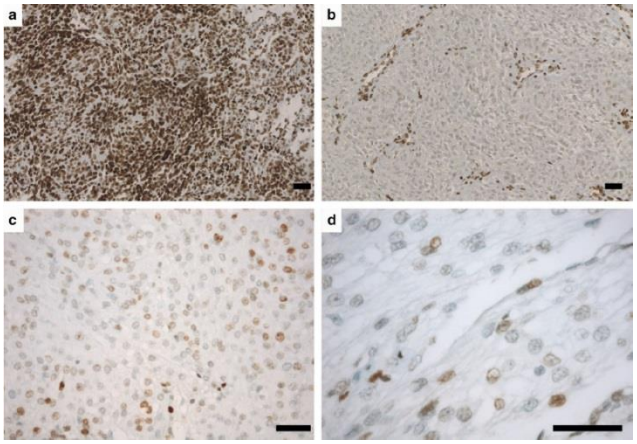
Loss of histone H3K27me3 identifies a subset of meningiomas with increased risk of recurrence

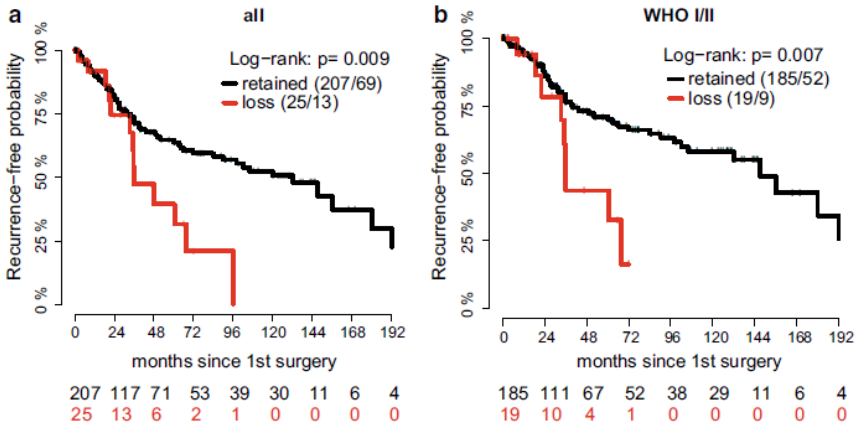
Leah M. Katz[1] · Thomas Hielscher[2] · Benjamin Liechty[3] · Joshua Silverman[1] · David Zagzag[3] · Rajeev Sen[4] · Peter Wu[1] · John G. Golfinos[4] · David Reuss[5,6] · Marian Christoph Neidert[7] · Hans-Georg Wirsching[8] · Peter Baumgarten[9] · Christel Herold-Mende[10] · Wolfgang Wick[11,12] · Patrick N. Harter[13,14,15] · Michael Weller[8] · Andreas von Deimling[5,6] · Matija Snuderl[3] · Chandra Sen[4] · Felix Sahm[5,6]

Table 3 Multivariable Cox regression model on WHO grade I/II cases

Parameter		HR	95% CI	*p* value
H3K27me3	Loss vs. retained	2.30	1.09–4.81	0.028
WHO grade	II vs. I	2.71	1.40–5.24	0.003
Extent of resection	STR vs. GTR	1.59	0.86–2.96	0.14
Age	Per 10 year increase	0.90	0.74–1.09	0.26
Sex	Male vs. female	0.99	0.57–1.71	0.96

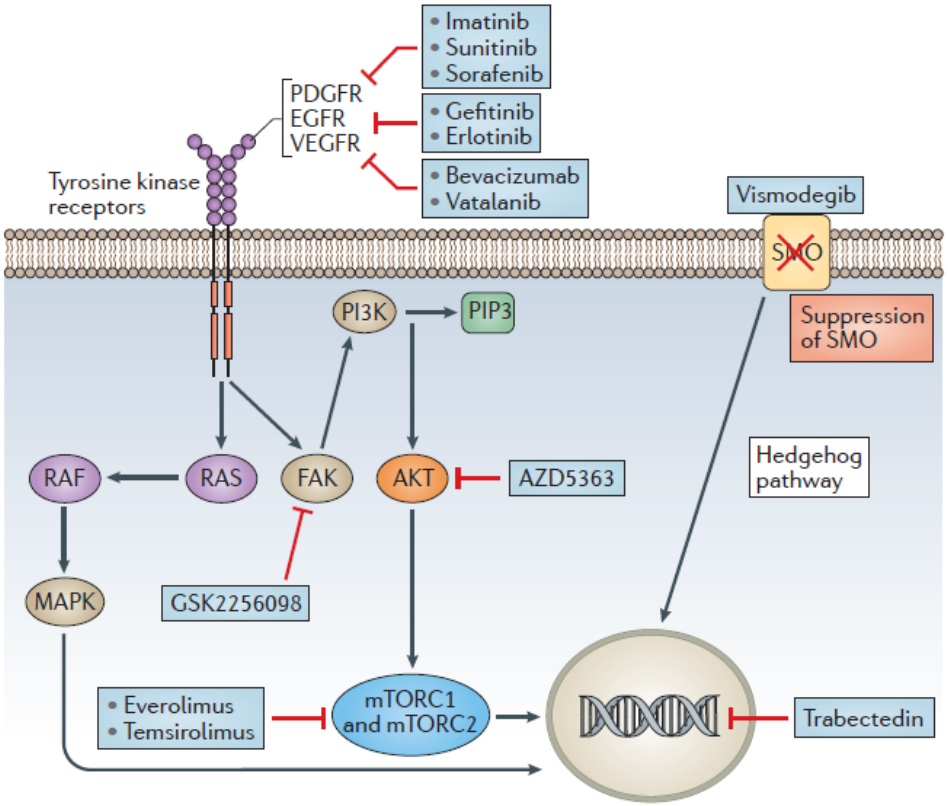
of H3K27me3 in cases with staining limited to vessels was confirmed by mass spectrometry on a subset of cases. Lack of staining for H3K27me3 in all tumor cells was significantly associated with more rapid progression ($p=0.009$). In line, H3K27me3-negative cases were associated with a DNA methylation pattern of the more aggressive types among the recently introduced DNA methylation groups. Also, *NF2* and *SUFU* mutations were enriched among cases with complete lack of H3K27me3 staining in tumor cells ($p<0.0001$ and $p=0.029$, respectively). H3K27me3 staining pattern added significant prognostic insight into WHO grade II cases and in the compound subset of WHO grade I and II cases ($p=0.04$ and $p=0.007$, respectively). However, it did not further stratify within WHO grade III cases. Collectively, these data indicate that epigenetic modifications beyond DNA methylation are involved in the aggressiveness of meningioma. It also suggests that H3K27me3 immunohistochemistry might be a useful adjunct in meningioma diagnostics, particularly for cases with WHO grade II histology or at the borderline between WHO grade I and II.





Molecular signalling pathways

- Molecular signaling pathways have been extensively studied in meningiomas
- Nearly all growth factor receptors and kinases known to be involved in tumour growth have been identified as contributing factors in meningiomas: including EGFR, PDGFRβ, VEGFR, IGFR, MET.
- Activation of these receptors drives intracellular signaling cascades involved in a plethora of cellular functions. including activation of mTOR

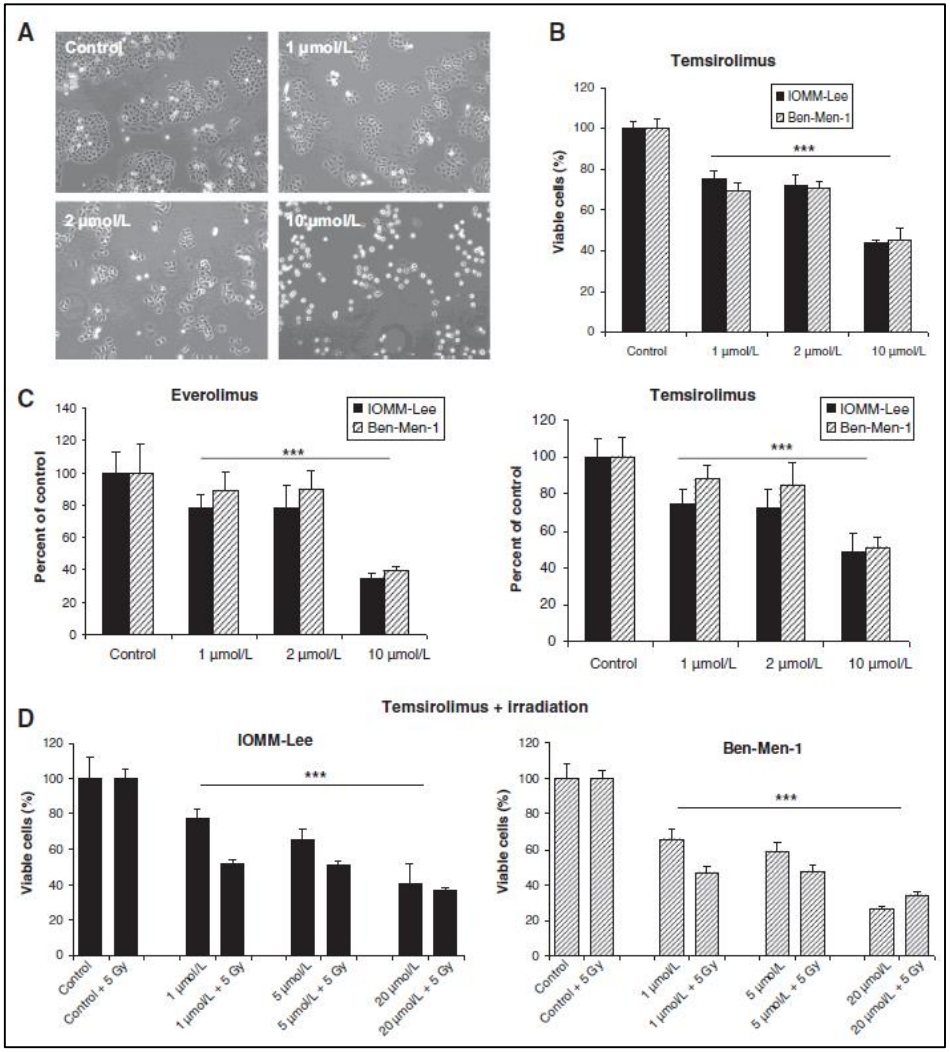


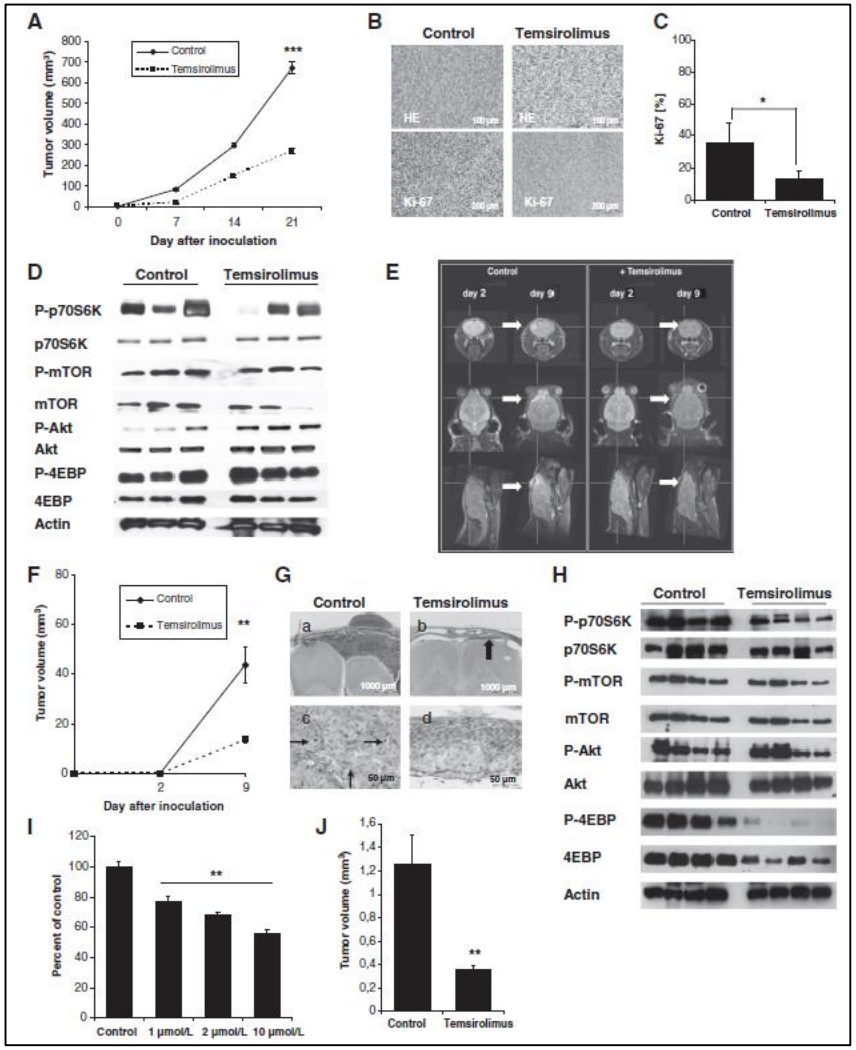
Overview of activated signaling pathways and potential drug targets in meningioma

mTORC1 Inhibitors Suppress Meningioma Growth in Mouse Models

Clin Cancer Res; 19(5); 1180–9.

Doreen Pachow[1], Nadine Andrae[1], Nadine Kliese[1], Frank Angenstein[3], Oliver Stork[2], Annette Wilisch-Neumann[1], Elmar Kirches[1], and Christian Mawrin[1]





Sample Integrated Molecular Pathology Report

Patient Name: HG

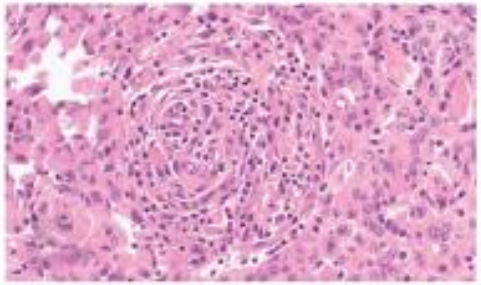
Patient Age: 54

Date of Accession: ___ / ___ / ___
mm / dd / yy

Integrated Molecular Diagnosis: **WHO grade II meningioma, methylation class unfavourable, TERTp and NF2 mutations**

Meningioma
methylation Class unfavourable
WHO Grade II
TERT promoter mutation, NF2 mutation
Amenable to recurrence risk stratification by meningioma recurrence score

2016 WHO Grade: II

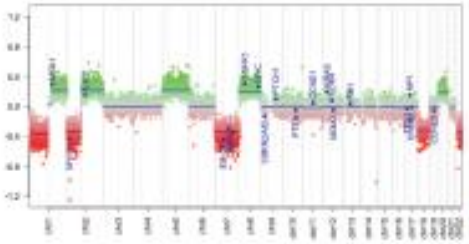


Mitoses
- ☐ <4 / 10HPF
- ☒ 4-19 / 10HPF
- ☐ >20 / 10HPF

Specific Criteria
- ☒ Brain invasion
- ☒ Hypercellularity
- ☐ Small cells
- ☐ Prominent nucleoli
- ☒ Spontaneous necrosis
- ☒ Architectural sheeting

Specific Histologies
- ☐ Clear cell
- ☐ Chordoid
- ☐ Rhabdoid
- ☐ Papillary

Methylation class: **Unfavourable**



Clinically relevant CNA

☒1p ☐4 ☐6q ☐10 ☐14q ☒18q ☒22q

Clinically relevant mutations

☒NF2 ☐AKT1 ☐SMO ☐BAP-1 ☒TERTp

This mutation makes the patient eligible for clinical trial NCT02523014

EANO guidelines for the diagnosis and treatment of meningiomas

Roland Goldbrunner, Giuseppe Minniti, Matthias Preusser, Michael D Jenkinson, Kita Sallabanda, Emmanuel Houdart, Andreas von Deimling, Pantelis Stavrinou, Florence Lefranc, Morten Lund-Johansen, Elizabeth Cohen-Jonathan Moyal, Dieta Brandsma, Roger Henriksson, Riccardo Soffietti, Michael Weller

www.thelancet.com/oncology Vol 17 September 2016

	Molecular target or biomarker
AKT inhibitor	*AKT1* (pGlu17Lys) mutation[13,14]
Hedgehog inhibitor	*SMO* (pTrp535Leu) mutation[13,15]
FAK inhibitor	*NF2* (merlin) loss[16,17]
Immune checkpoint inhibitor	PD-1 or PD-L1[18]
VEGF or VEGFR inhibitor	VEGF or VEGFR2[19-21]
PI3K inhibitors	PI3K[22]
Trabectedin	DNA, tumour-associated macrophages, angiogenesis[23]

Table 2: **Potential drug classes and their targets for future therapies**

New molecular targets in meningiomas: the present and the future

Vyshak Alva Venur[a], *Sandro Santagata*[b,c,d] *Eva Galanis*[e], *and Priscilla K. Brastianos*[a]

www.co-neurology.com
Volume 31 Number 6
December 2018

Table 1. Summary of ongoing clinical trials in meningioma

Clinical trial identifier (clinicaltrials.gov)	Drug being evaluated	Meningioma subgroups included in the study	Estimated enrollment	Mechanism of action
NCT02523014	GSK2256098 and vismodegib	Meningioma with *NF2*, *AKT1* *SMO* mutation	69	Combination of FAK and Hedgehog inhibitor
NCT03071874	Vistusertib (AZD2014)	Grade II and III	30	Dual mTORC1/mTORC2 inhibitor
NCT02831257	Vistusertib (AZD2014)'	Progressive meningioma in neurofibromatosis 2 patients	18	Dual mTORC1/mTORC2 inhibitor
NCT02933736	Ribociclib	Preoperative and postoperative treatment of meningioma	48	CDK4/6 inhibitor
NCT03279692	Pembrolizumab	Progressive high-grade meningioma	26	PD-1 inhibitor
NCT02648997	Nivolumab	Progressive high-grade meningioma	25	PD-1 inhibitor
NCT02234050	Trabectedin	Progressive high-grade meningioma	86	Preventing oncogenic factor from binding to DNA


KEEP
CALM
cause this is just the
BEGINNING


The Future
NEXT EXIT

Grazie!

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Laboratory of Experimental and Translational Pathology

Pathology Unit, DMMT, University of Brescia School of Medicine

P. L. Poliani, M.D., Ph.D.

Manuela Cominelli, Ph.D.

Francesca Pagani, Ph.D.