Hereditary Tumor Syndromes Associated with CNS/PNS Tumors

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Disclosures

I have no relevant financial relationships to disclose

Learning Objectives

- The attendees will be able to list multiple examples of central and peripheral nervous system neoplasms that can be seen in association with hereditary tumor predisposition syndromes.
- The attendees will be able to recognize clinical situations or morphologic features that would indicate additional IHC or molecular tests to rule/out hereditary tumor predisposition syndromes.
- The attendees will be able to identify further molecular (germline) testing and/or genetic counseling when appropriate.

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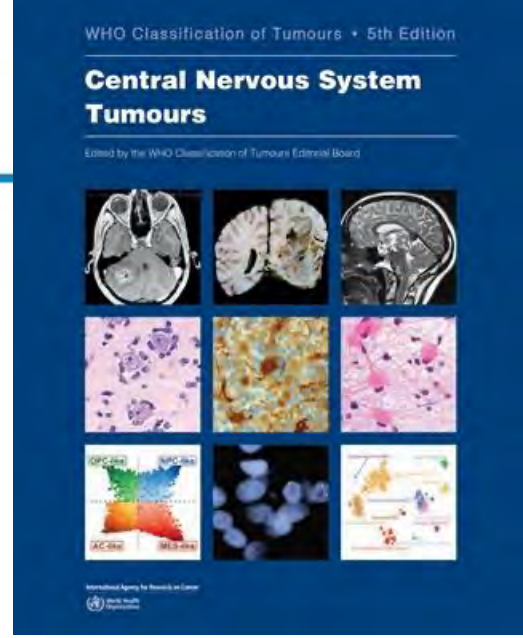
14. Genetic tumour syndromes involving the CNS

Genetic tumour syndromes of the nervous system: Introduction
Neurofibromatosis type 1
Neurofibromatosis type 2
Schwannomatosis
Von Hippel-Lindau syndrome
Tuberous sclerosis
Li-Fraumeni syndrome
Cowden syndrome
Constitutional mismatch repair deficiency syndrome
Familial adenomatous polyposis 1
Naevoid basal cell carcinoma syndrome
Rhabdoid tumour predisposition syndrome
Carney complex
DICER1 syndrome
Familial paraganglioma syndromes
Melanoma-astrocytoma syndrome
Familial retinoblastoma
BAP1 tumour predisposition syndrome
Fanconi anaemia
ELP1-medulloblastoma syndrome



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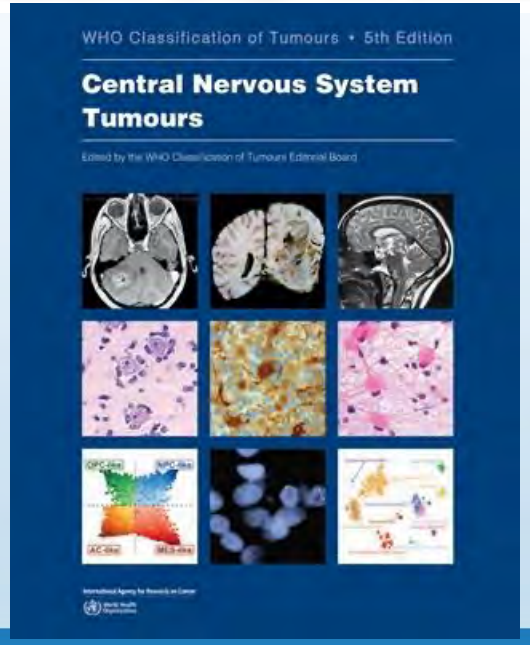
Tumour scenario	Genetic tumour syndrome(s)
Bilateral vestibular schwannomas	NF2
Choroid plexus carcinoma	Li–Fraumeni syndrome
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	Cowden syndrome
Embryonal tumour with multilayered rosettes lacking C19MC alteration	*DICER1* syndrome
Haemangioblastoma	Von Hippel–Lindau syndrome
Hybrid neurofibroma/schwannoma	NF1, NF2, and schwannomatosis
IDH- and H3-wildtype, p53-positive glioblastoma in a child	Li–Fraumeni syndrome
IDH-wildtype giant cell glioblastoma in a young patient	Constitutional mismatch repair deficiency, Lynch syndrome, and Li–Fraumeni syndrome
IDH1 p.R132C/S–mutant astrocytoma in an adult	Li–Fraumeni syndrome
Malignant melanotic nerve sheath tumour	Carney complex
Malignant peripheral nerve sheath tumour arising from a neurofibroma	NF1
Meningioma in a child	NF2
Multiple meningiomas	NF2
Multiple neurofibromas, a plexiform neurofibroma, or a massive soft tissue neurofibroma	NF1
Multiple schwannomas or one with mosaic SMARCB1 (INI1) expression	NF2 and schwannomatosis
Paraganglioma with loss of SDHB expression	Familial paraganglioma syndromes (see <<#19884>>Table 14.06, p. XXX)
Pineoblastoma	*DICER1* syndrome and familial retinoblastoma syndrome
Pituitary blastoma	*DICER1* syndrome
Primary intracranial sarcoma, *DICER1*-mutant	*DICER1* syndrome
Rhabdoid and/or papillary meningioma	*BAP1* tumour predisposition syndrome
Rhabdoid tumour(s) in an infant	Rhabdoid tumour predisposition syndrome
SHH-activated medulloblastoma	Naevoid basal cell carcinoma (Gorlin) syndrome, ELP1-medulloblastoma syndrome, and *GPR161* (Gorlin-like) syndrome
SHH-activated, *TP53*-mutant medulloblastoma (often the large cell / anaplastic histological type)	Li–Fraumeni syndrome and Fanconi anaemia
Subependymal giant cell astrocytoma	Tuberous sclerosis
WNT-activated medulloblastoma, *CTNNB1*-wildtype	Familial adenomatous polyposis



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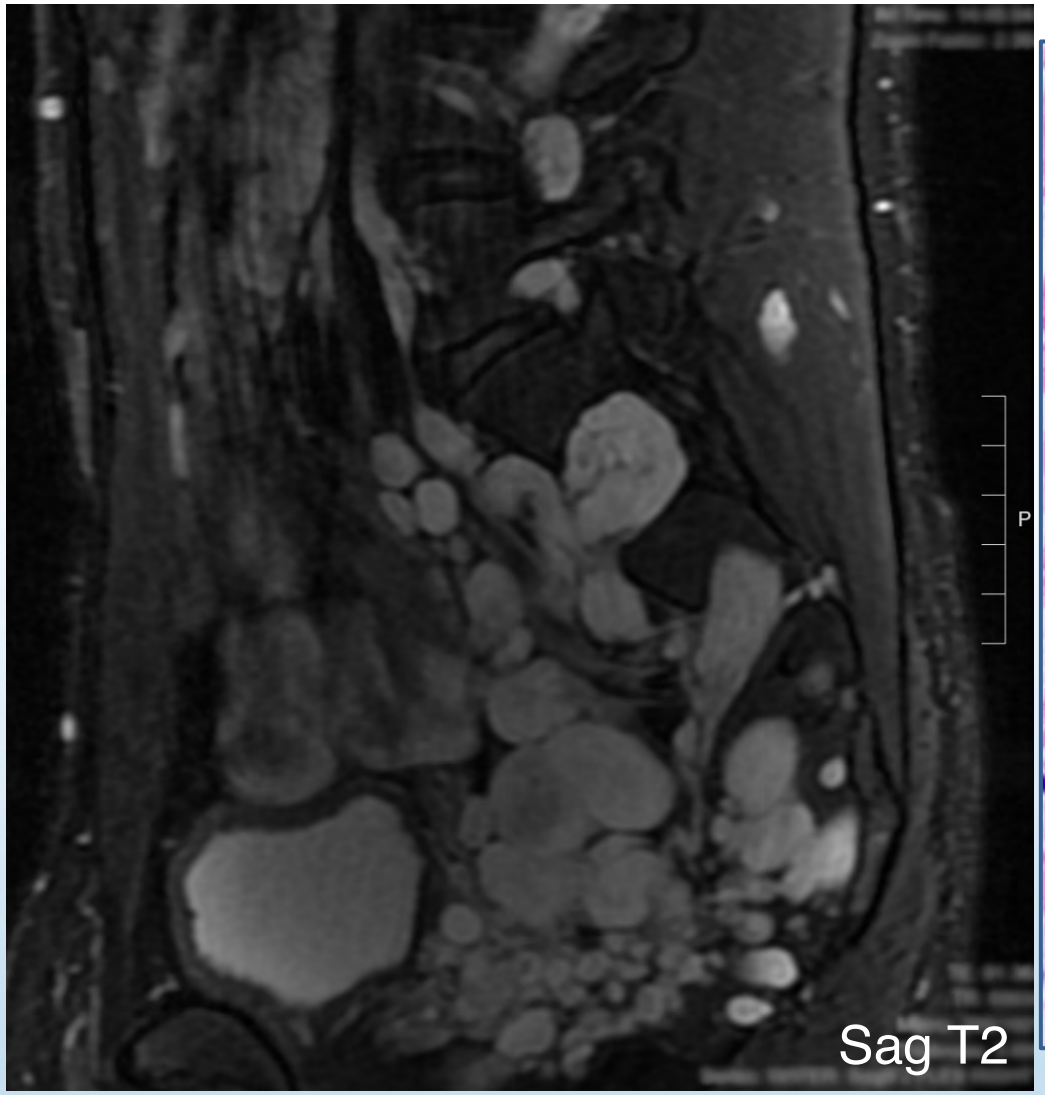
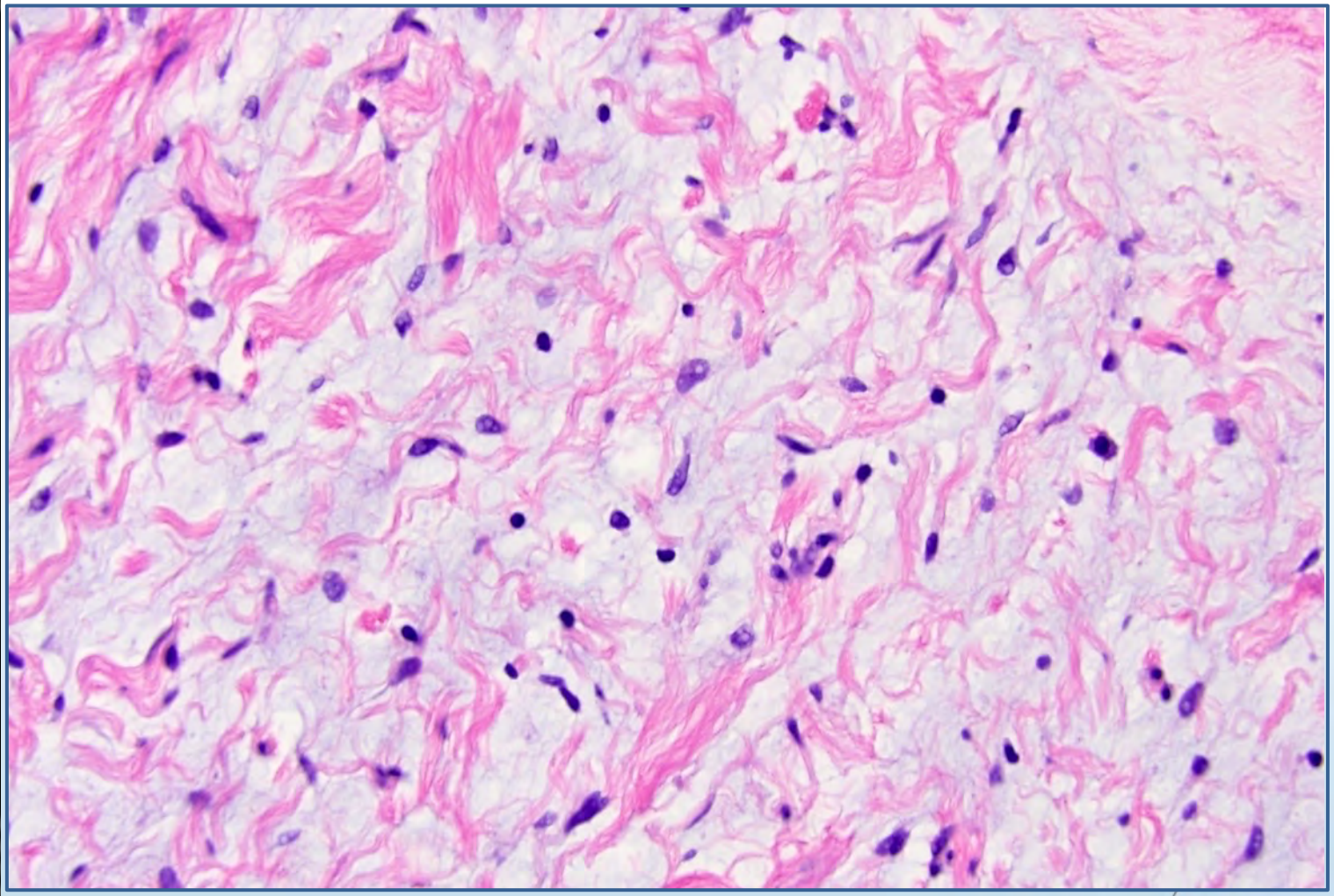
Case 1: 17-year-old with innumerable masses involving lumbosacral plexus, sciatic, intramuscular, intraabdominal nerves





Neurofibromatosis Type 1 (NF1)

NFs - PNF - ANNUBP - MPNST
Low-grade glioma – Pilocytic to diffuse
High-grade glioma – HGAP to GBM

- Autosomal dominant
- Germline *NF1* (17q11. 2)

Two or more of the following

- Café-au-lait macules (6 or more)
- Axillary/inguinal freckling
- Neurofibromas (≥2) or plexiform neurofibromas
- Optic pathway glioma
- Iris hamartomas (Lisch nodules ≥2), choroidal abnormalities
- Distinctive bony abnormalities
- *NF1* variant in normal tissues
- Parent with NF1

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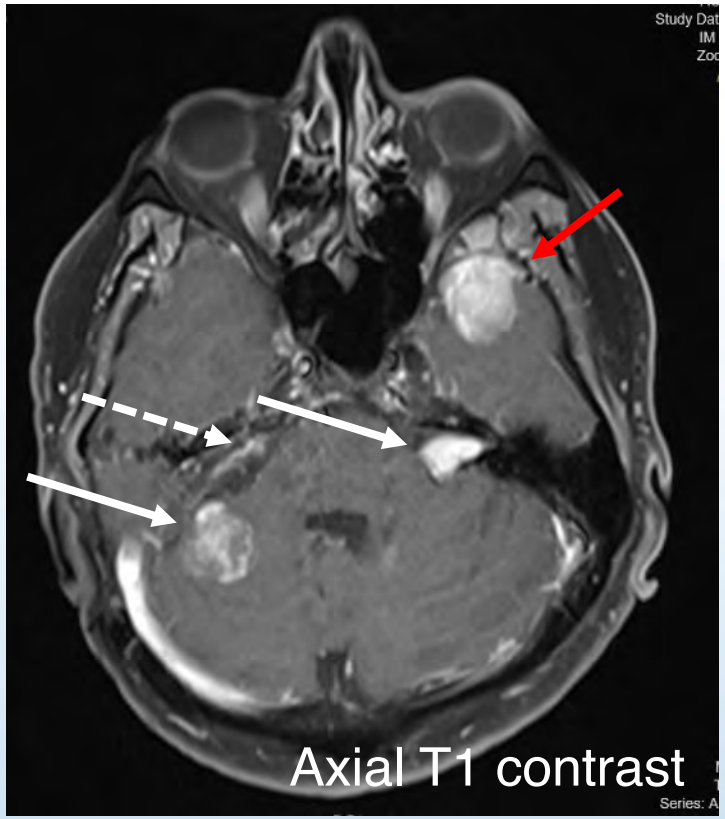
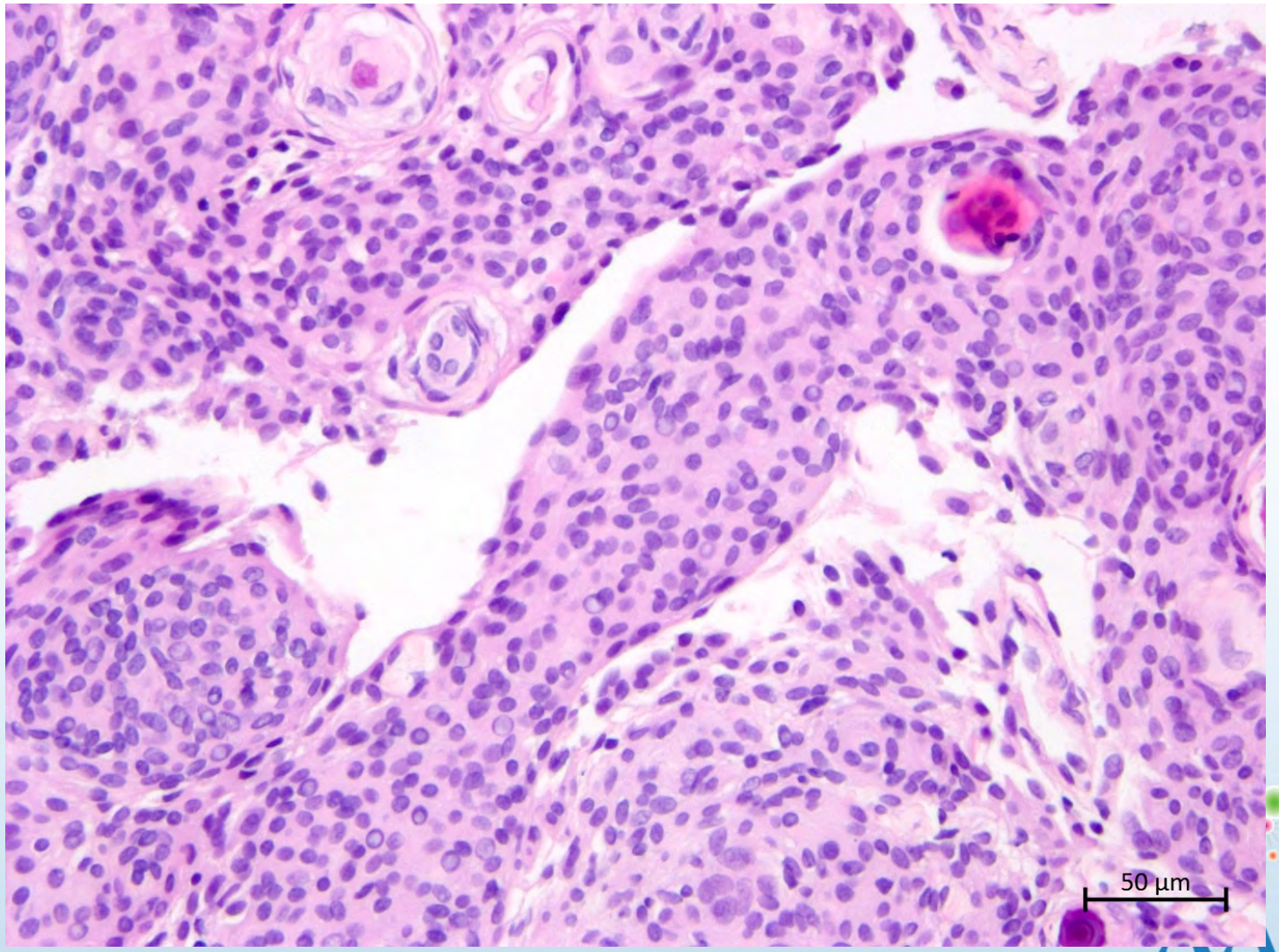
Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)

Case 2: 52-year-old man with history of multiple intracranial neoplasms





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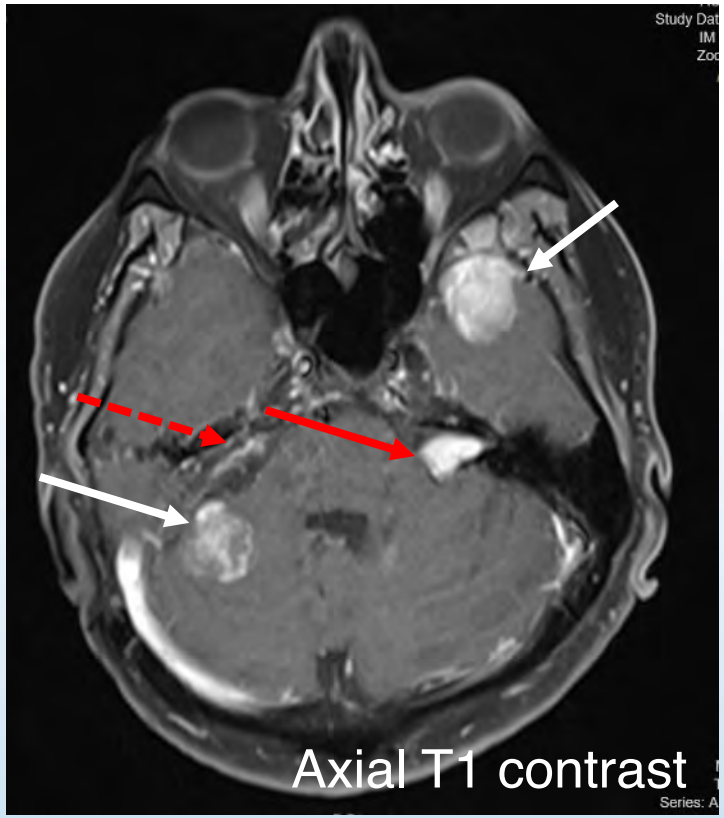
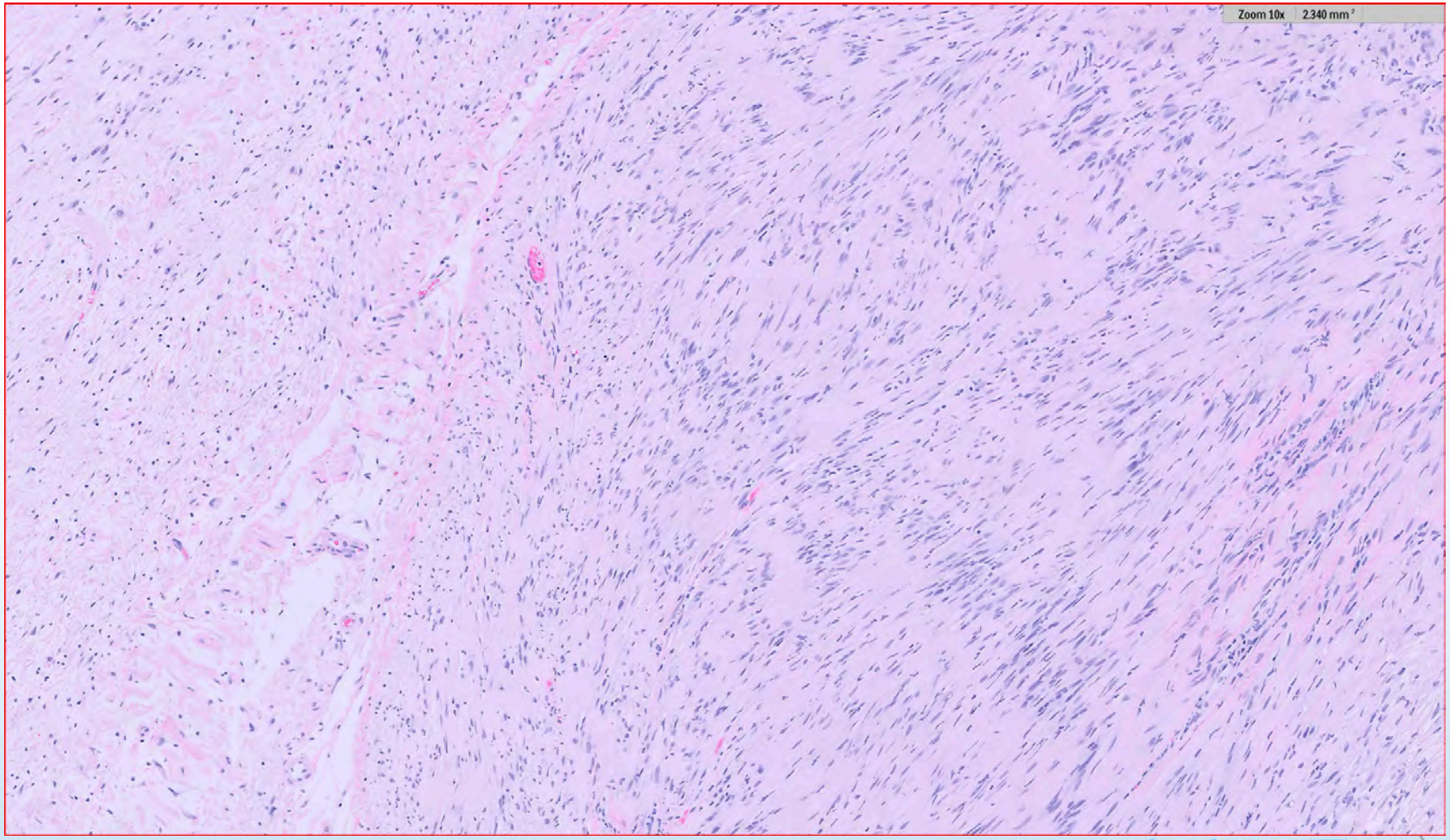




Case 2: 52-year-old man with history of multiple intracranial neoplasms – sequencing of the meningioma

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
Monosomy 22q	N/A	Pathogenic	N/A	N/A

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
NF2 p.L49* (c.146T>A:p.Lys49*)	NM_000268	Pathogenic	877/426	49%/94%

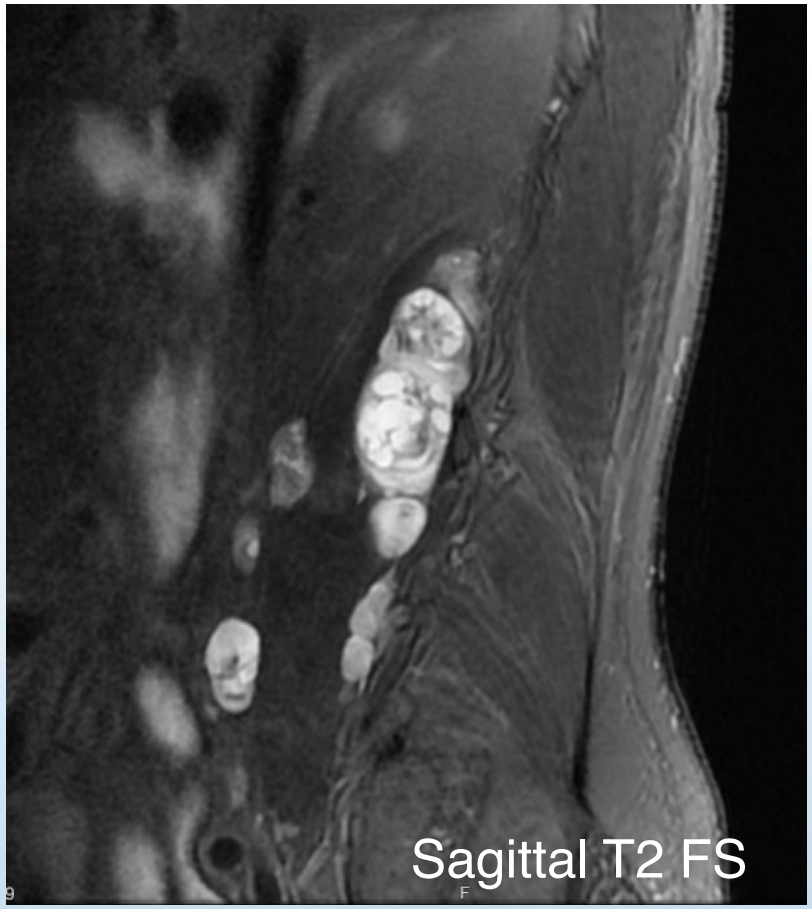
*Alterations in the normal sample are reported for cancer-related genes if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist/geneticist. For variants not classified in ClinVar, truncating or splice-site variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Alterations in the normal samples are limited to single nucleotide variants and small indels in gene coding regions. Carrier status is not reported for variants not strongly related to cancer.

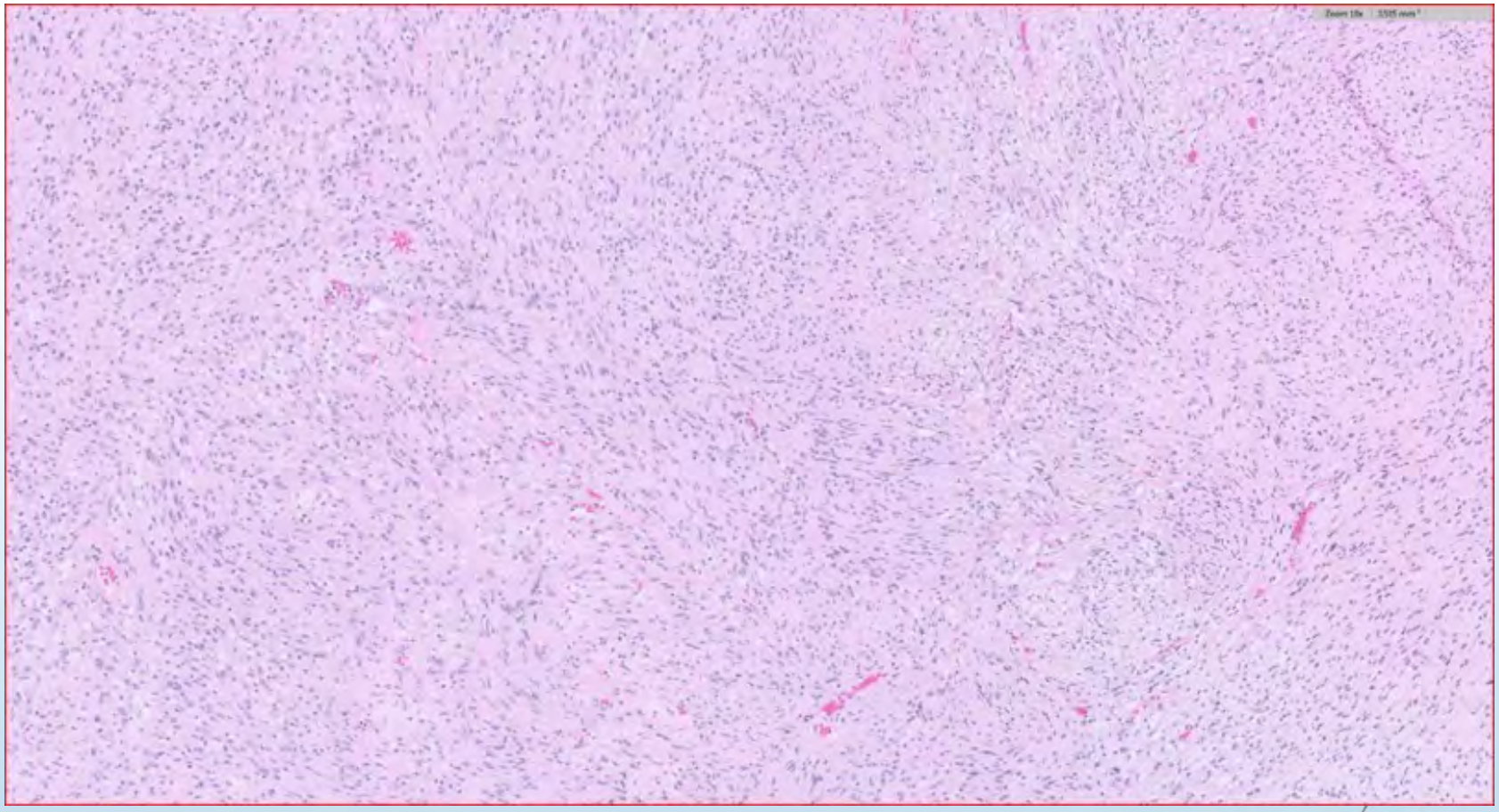
NF2-related Schwannomatosis

- Autosomal dominant
- Germline *NF2* alterations (22q12.2)
- Schwannomas, especially vestibular schwannomas, especially bilateral
- Multiple meningiomas
- (Spinal) ependymomas
- Posterior subcapsular cataract

Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis

Case 3: 37-year-old man with history of prior NSTs involving right peroneal nerve and C2-C3 nerve root now presents with right L2/L3, multinodular intradural extramedullary mass





Case 3: 37-year-old man with history of prior NSTs involving right peroneal nerve and C2-C3 nerve root now presents with right L2/L3, multinodular intradural extramedullary mass

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
NF2 p.E247*	NM_000268.3	Pathogenic	348	82%
Monosomy of 22q	N/A	Pathogenic	N/A	N/A

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
LZTR1 p.F258fs (c.774delT, p.Phe258fs)	NM_006767.3	Pathogenic	1387/305	49%/90%

*Alterations in the normal sample are reported for cancer-related genes if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist/geneticist. For variants not classified in ClinVar, truncating or splice-site variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Alterations in the normal samples are limited to single nucleotide variants and small indels in gene coding regions. Carrier status is not reported for variants not strongly related to cancer.

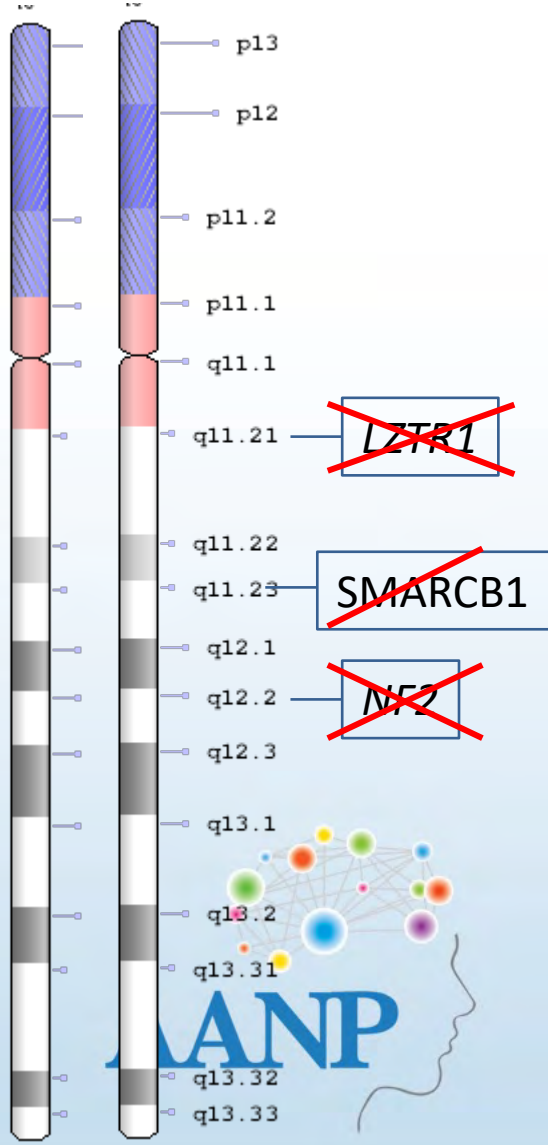
LZTR1- (or *SMARCB1- DGCR8*-) related Schwannomatosis

- Autosomal dominant
- *LZTR1, DGCR8* (22q.11.21), *SMARCB1* (22q.11.23)
- 4-hit mechanism

  LZTR1 (or *SMARCB1*) mut (#1)

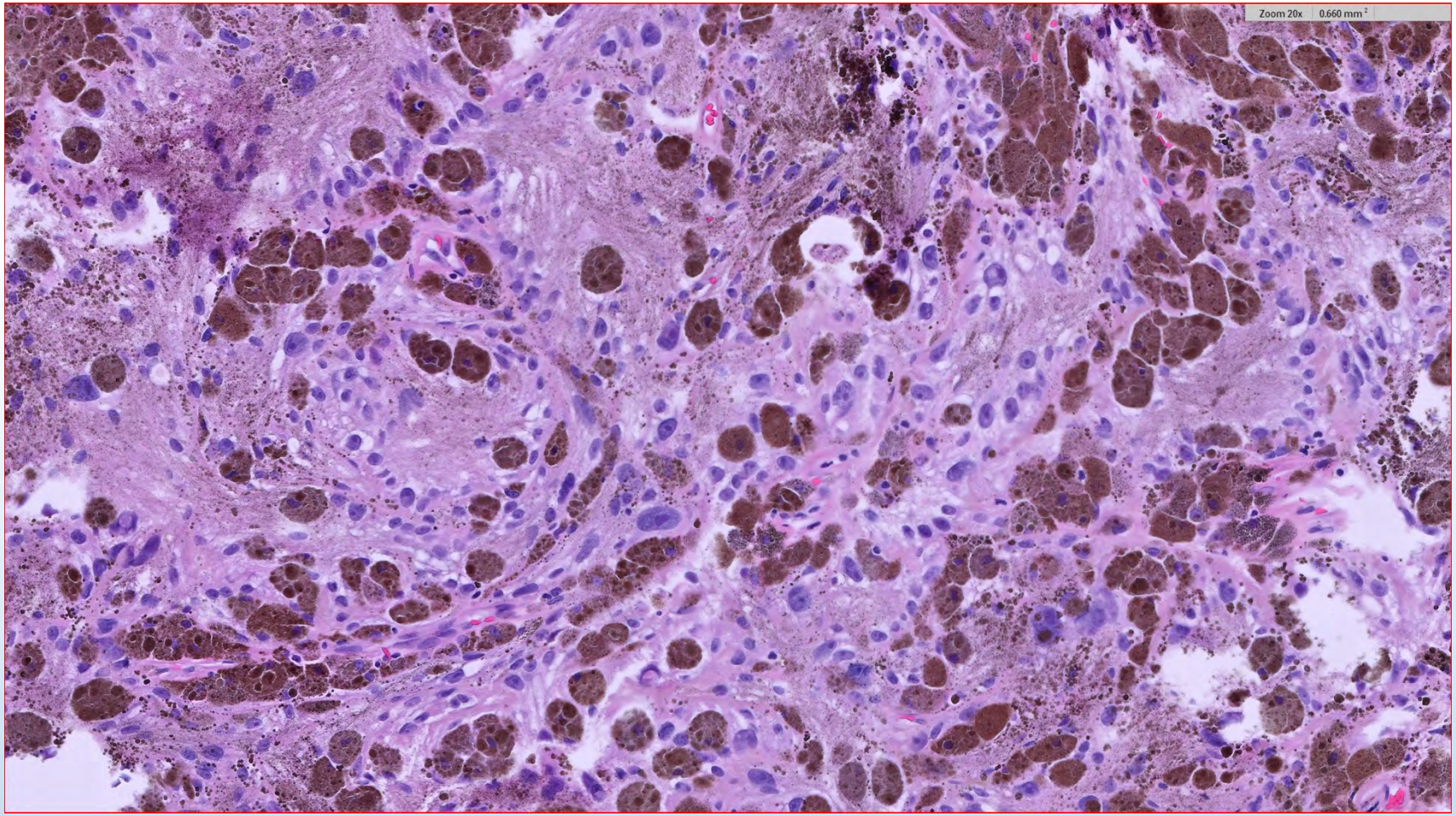
  monosomy 22q (#2&3)

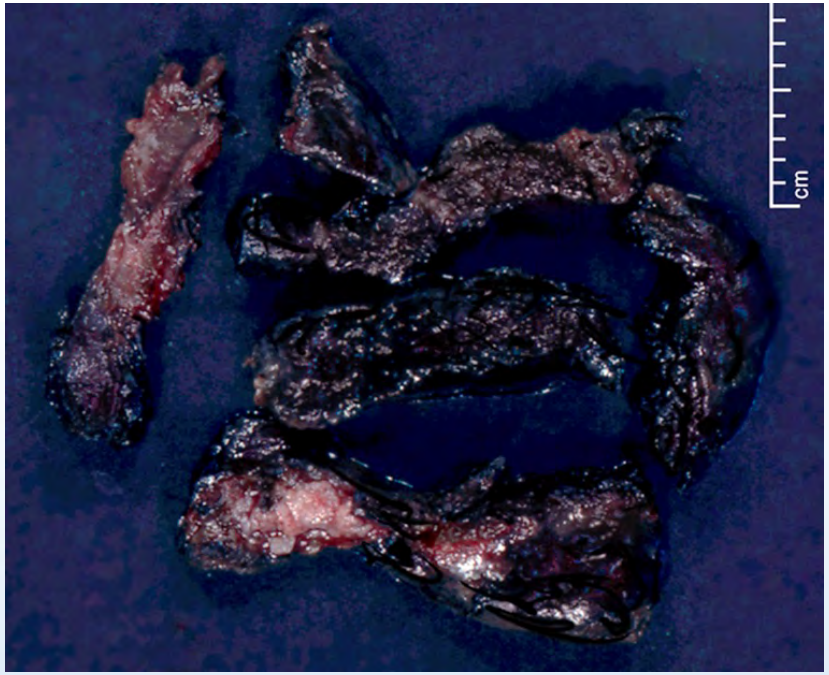
  somatic *NF2* (#4)
- Multiple schwannomas, often spinal nerve root
  - Occasionally unilateral vestibular schwannomas
- Occasionally meningiomas



Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
• Multiple schwannomas*	*LZTR1-, SMARCB1-, DGCR8-* related schwannomatosis

Case 4: 41-year-old man presented with C2/C3 intradural extramedullary, T1-hyperintense mass





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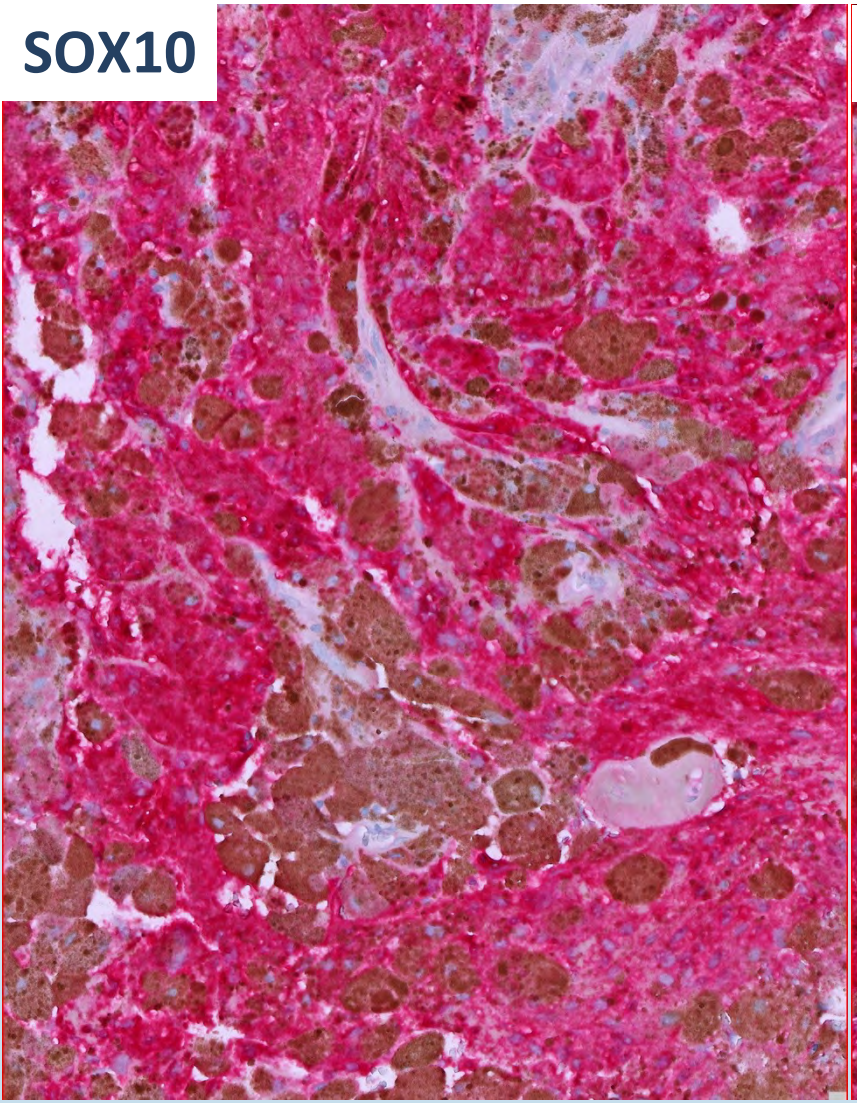
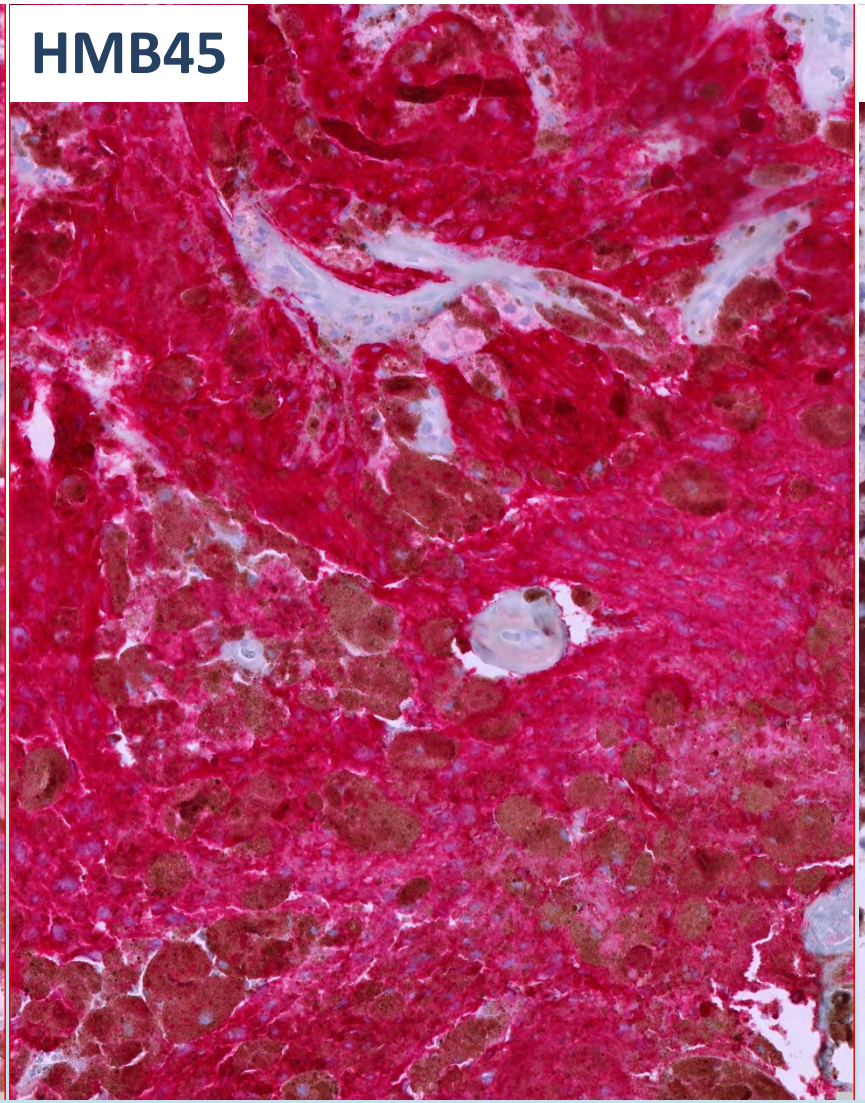
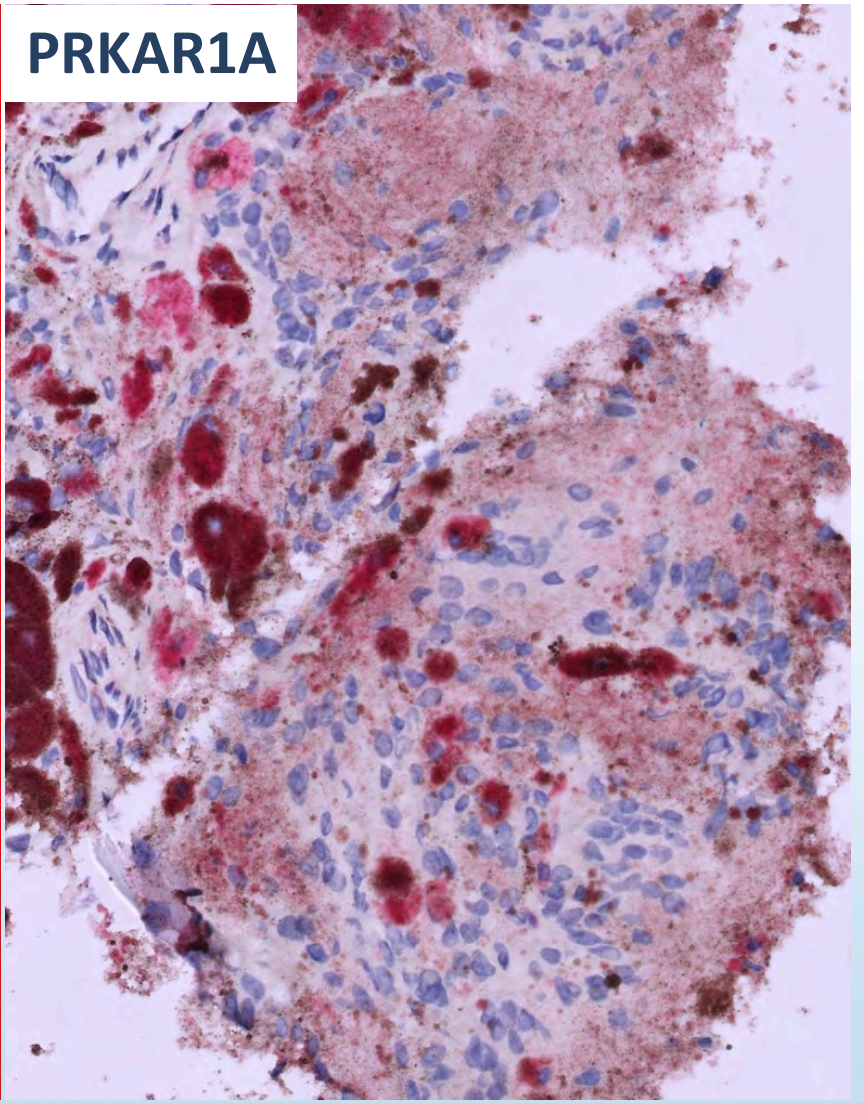
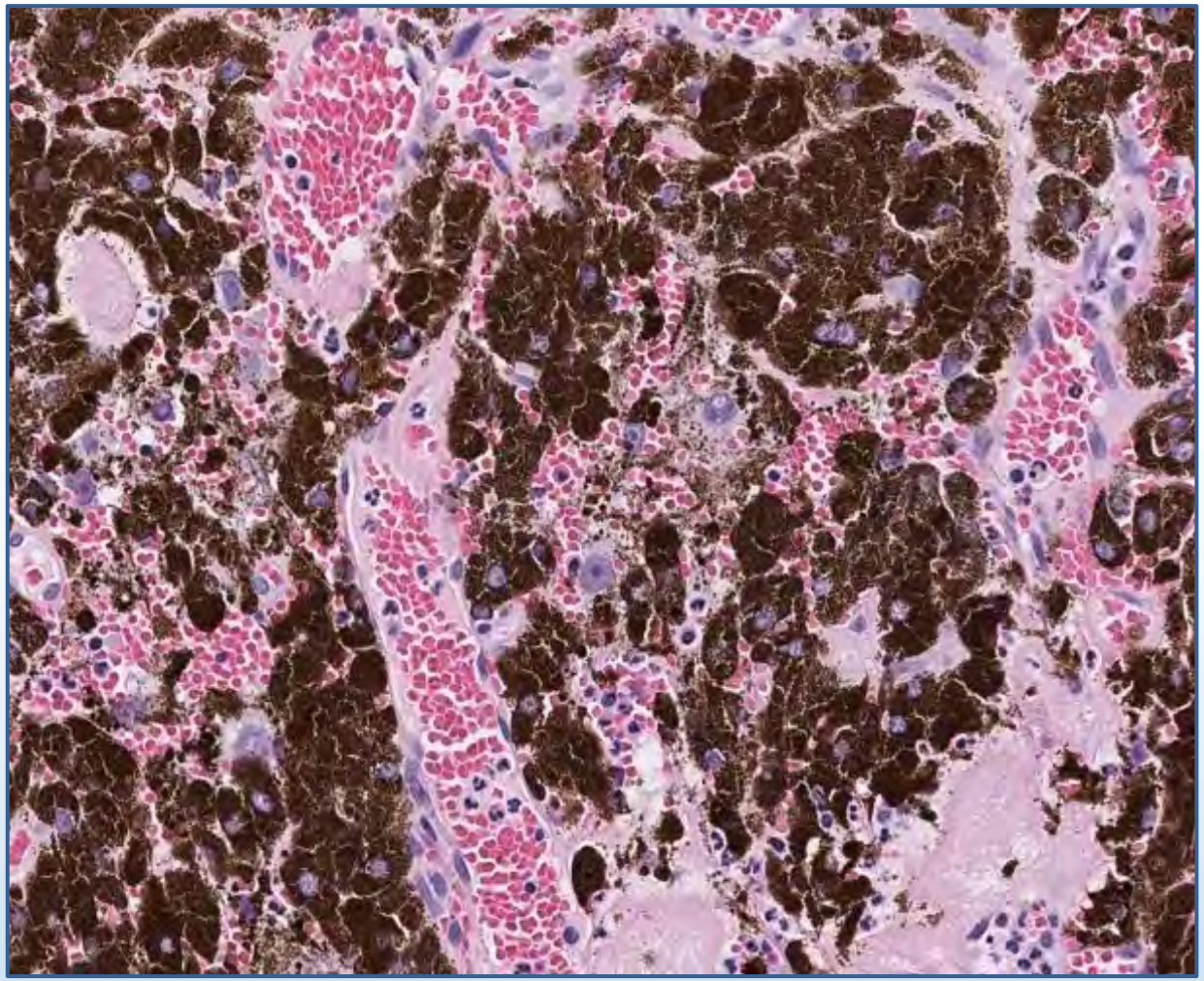
Case 4: 41-year-old man presented with C2/C3 intradural extramedullary, T1-hyperintense mass

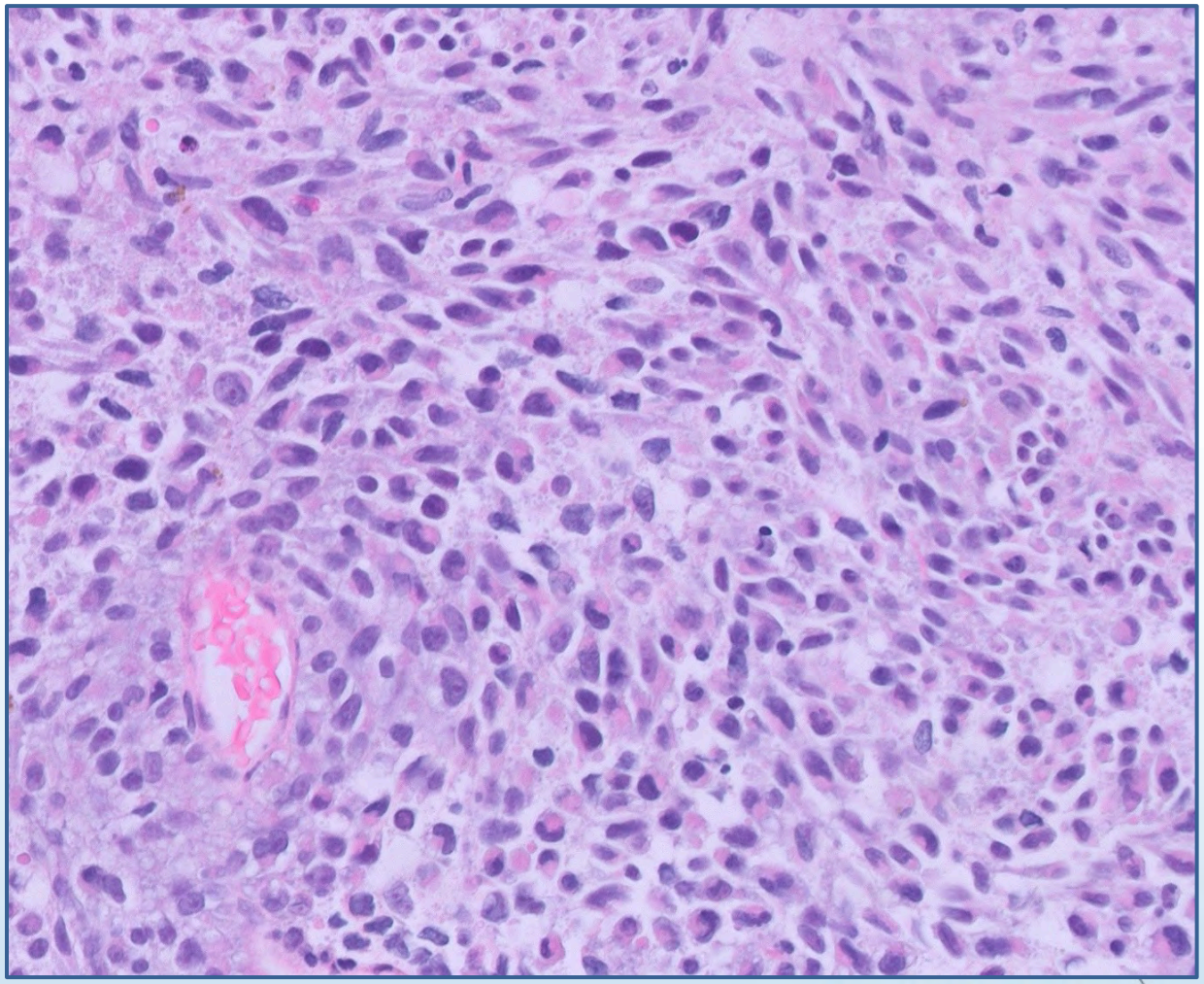






Malignant Melanotic Nerve Sheath Tumor





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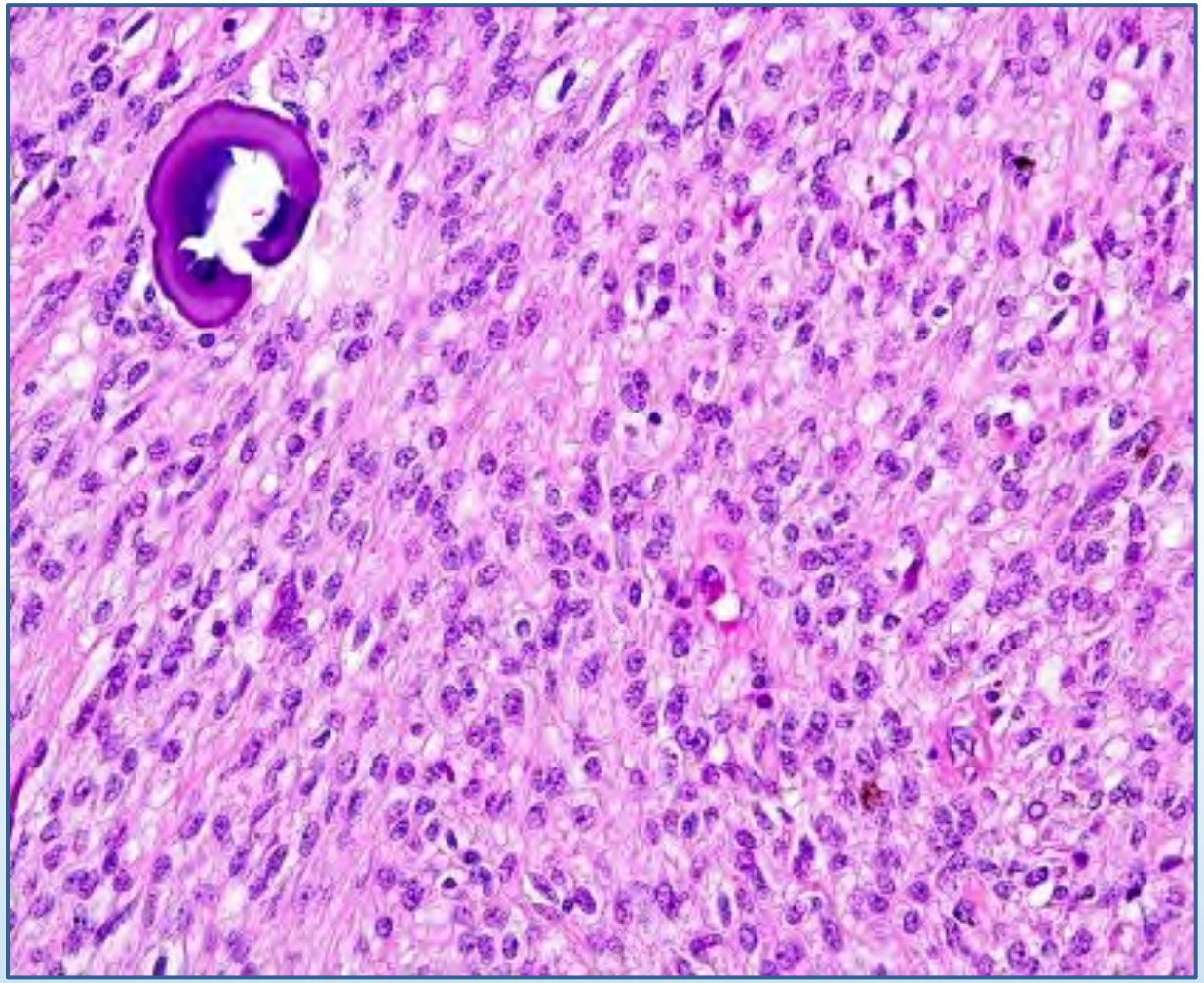

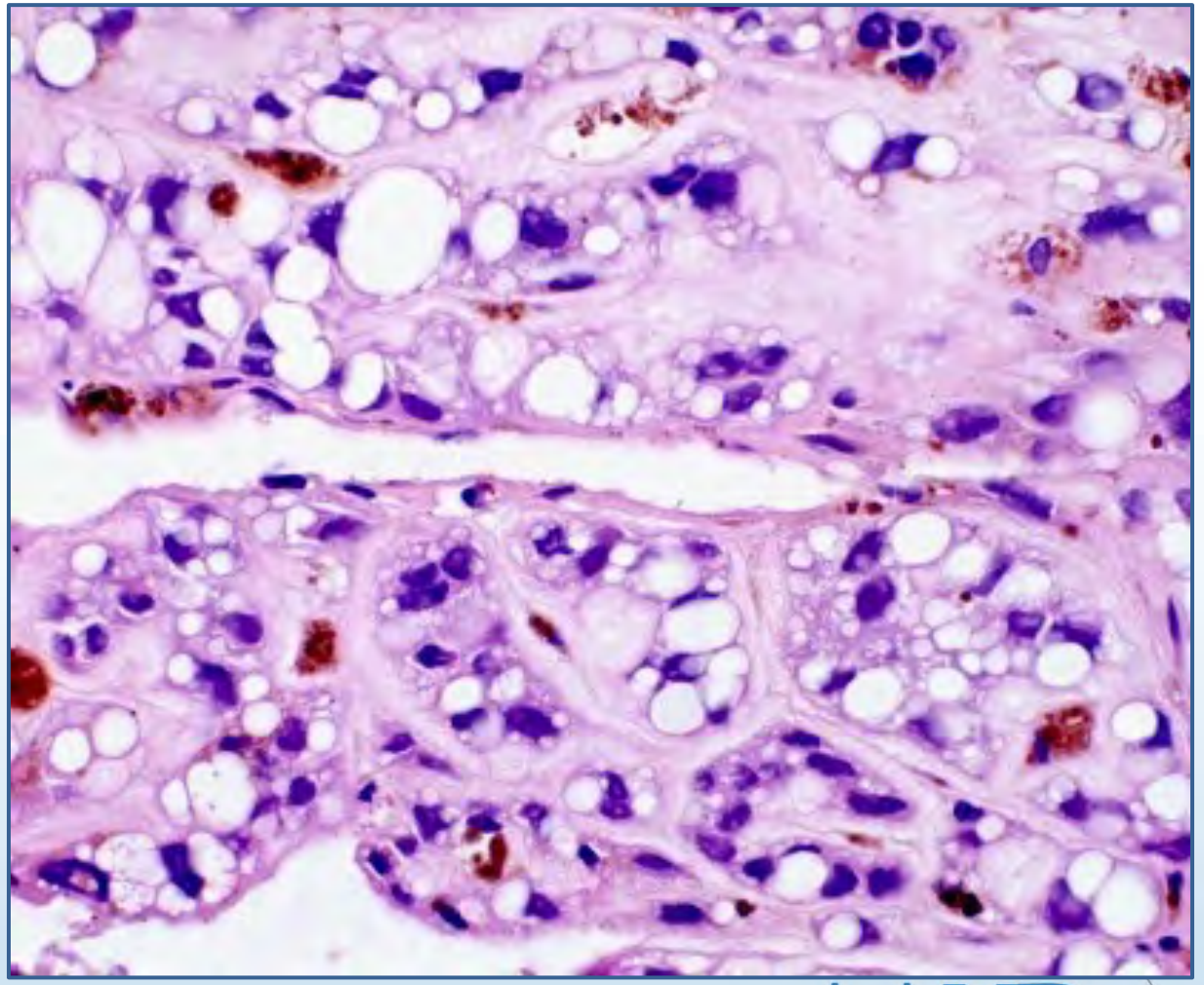

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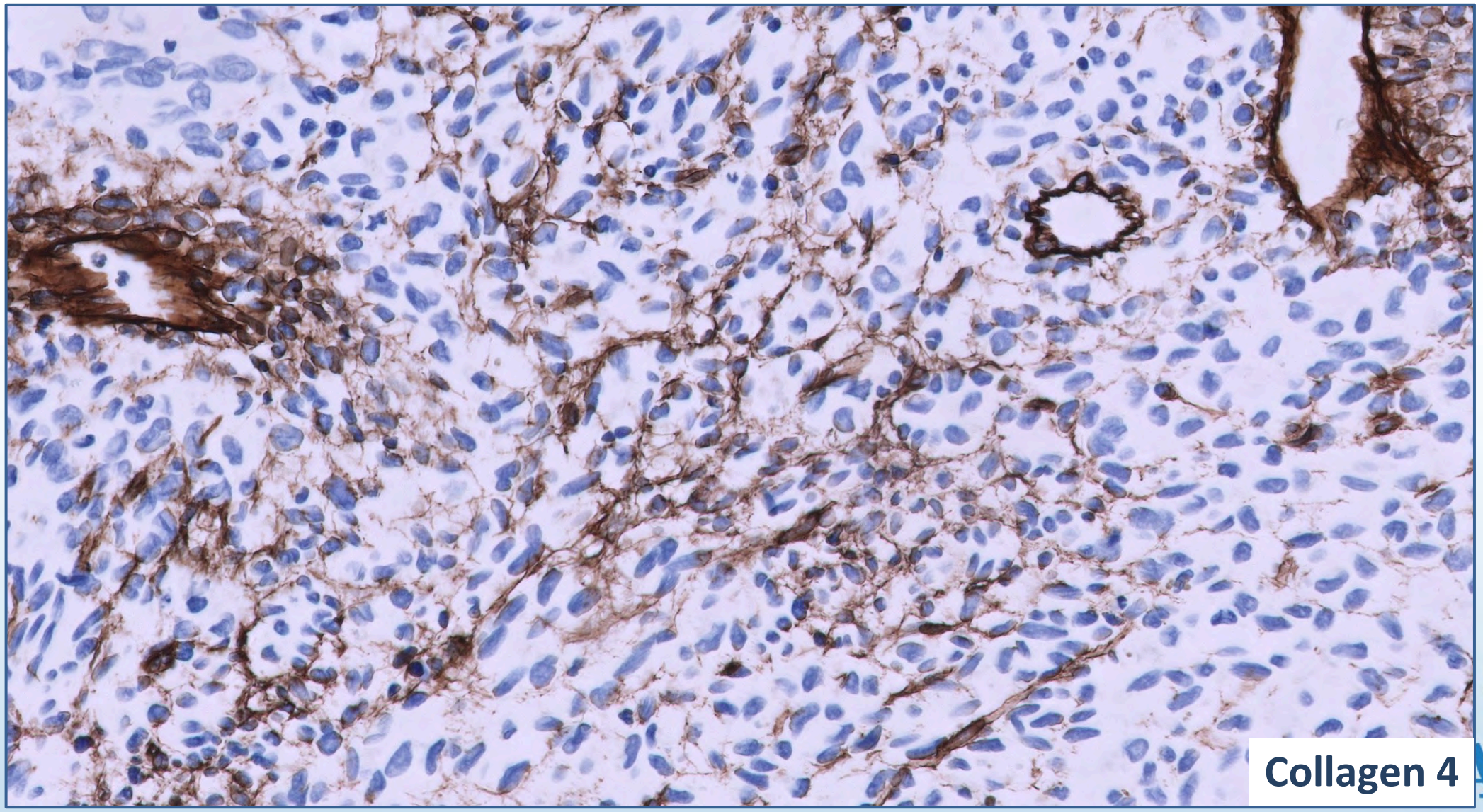


Malignant Melanotic Nerve Sheath Tumor

- "Melanotic Schwannoma" – No longer recommended
- Increased risk for local recurrence and even metastases
- SOX10, S100 +
- HMB45, MelanA, tyrosinase +
- Pericellular collagen IV +
- *PRKAR1A* mutations – Carney Complex in 5-50% of cases
  - Loss of PRKAR1A stain

Carney Complex (CNC1)

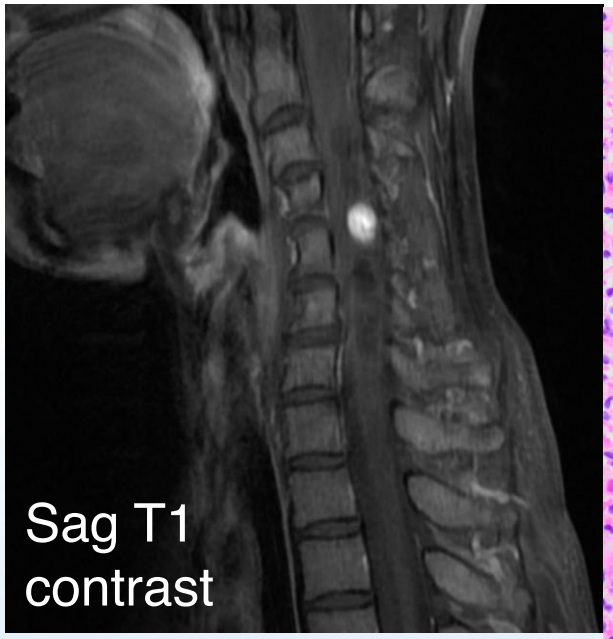
- Autosomal dominant
- *PRKAR1A* (17q24.2) germline
- Myxomas, endocrinopathy, and pigmented skin lesions

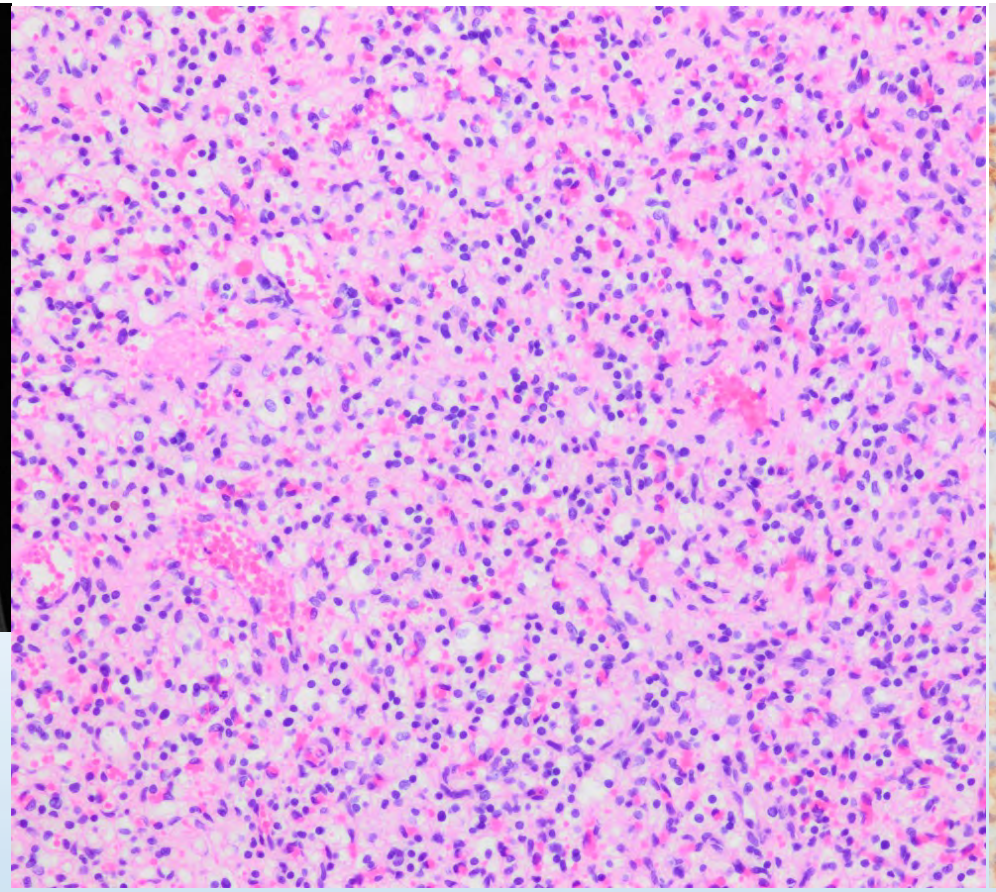
- Malignant melanotic nerve sheath tumor
- Pituitary neuroendocrine tumor (somatotroph)
- Follicular carcinoma of the thyroid

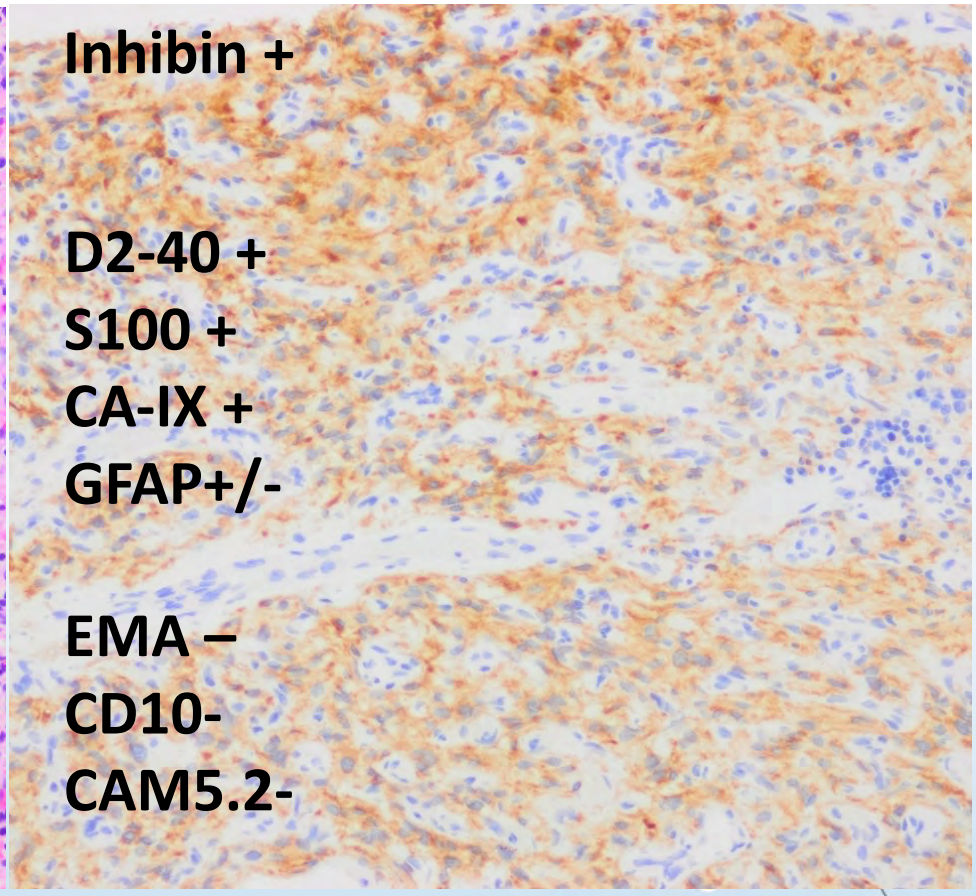
- Myxomas**
- Primary pigmented nodular adrenocortical disease (Cushing S)
- Lentigines*
- Sertoli cell tumours
- Blue nevi
- Pigmented epithelioid melanocytomas
- Breast ductal adenomas
- Osteochondromyxomas

Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
• Multiple schwannomas*	*LZTR1-, SMARCB1-, DGCR8-* related schwannomatosis
• Malignant melanotic nerve sheath tumor	Carney Complex

Case 5: 19-year-old woman with well-circumscribed spinal cord mass centered on C4-5 with avid enhancement







Hemangioblastoma

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Case 5: 19-year-old woman with well-circumscribed spinal cord mass centered on C4-5 with avid enhancement

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
Monosomy of Chromosome 3p	All	Likely Pathogenic	N/A	N/A

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Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS (Normal/Tumor)**	**MUTANT ALLELE FREQUENCY (Normal/Tumor)**
VHL p.R82H (c.245G>A, p.Arg82His)	NM_000551.3	Likely Pathogenic	708/713	53%/69%

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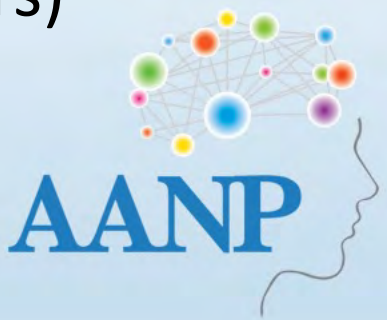
Von Hippel Lindau Syndrome

- Autosomal dominant; *VHL* gene (3q25-26)
- Retinal and CNS hemangioblastomas *
- Clear cell renal cell carcinomas (CC-RCC)
- Pheochromocytomas and paragangliomas
- Pancreatic cysts and neuroendocrine tumors
- Endolymphatic sac tumors
- ~25% of hemangioblastomas are a/w VHL syndrome
- >80% of VHL patients have CNS hemangioblastoma (33+/-10 years)
- >90% of VHL patients with hemangioblastoma have multiple



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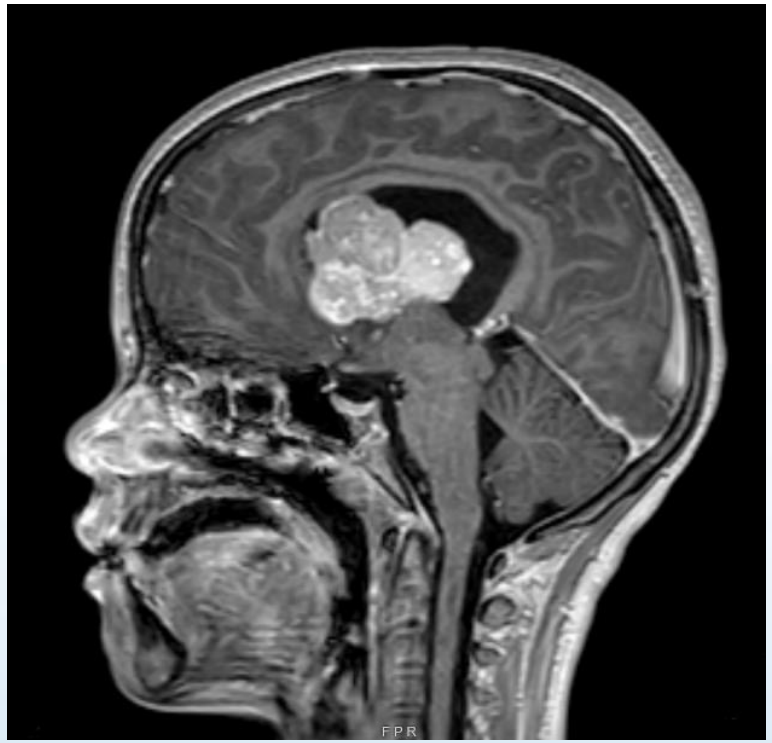
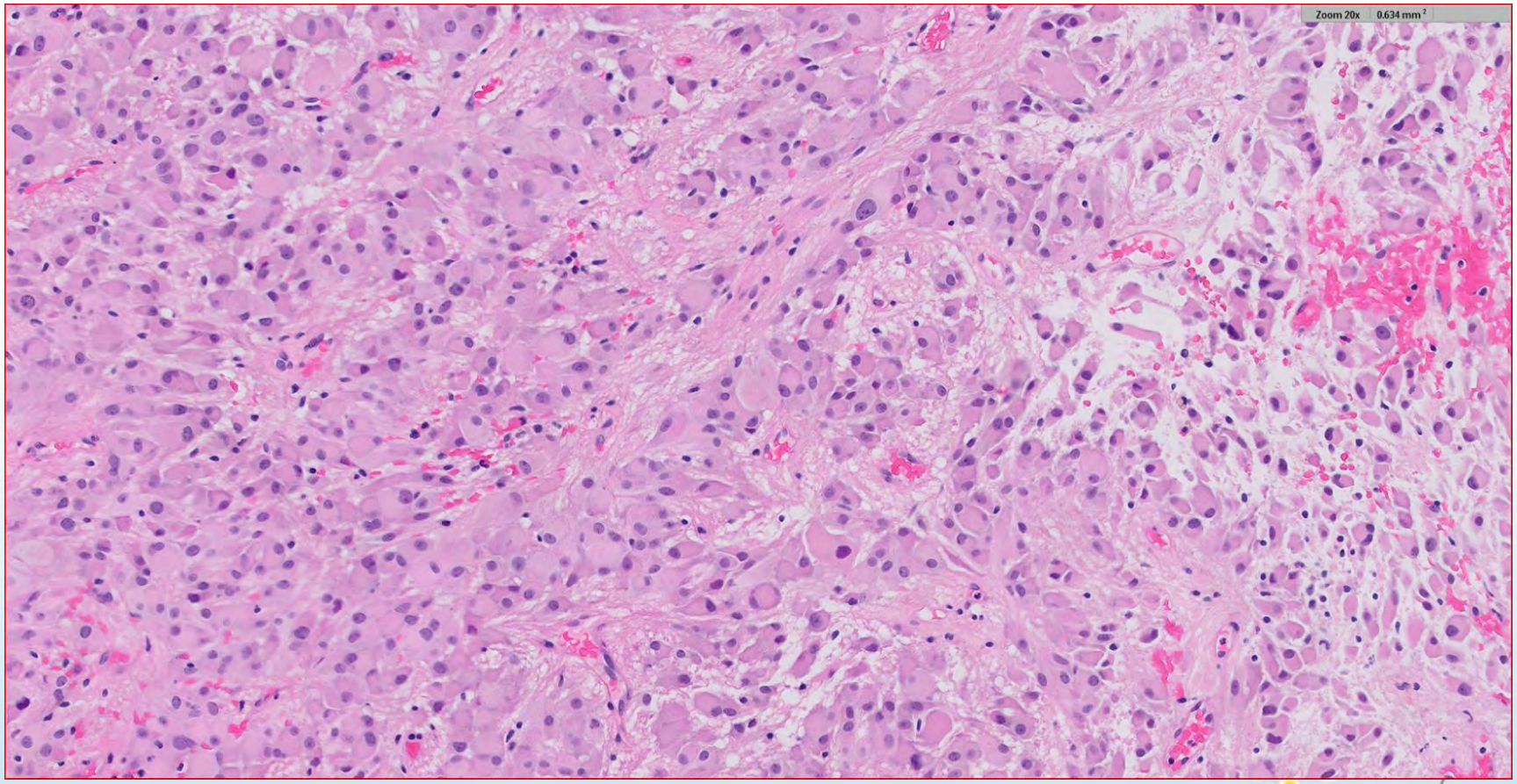
• Multiple schwannomas*	*LZTR1-, SMARCB1-, DGCR8-* related schwannomatosis
• Malignant melanotic nerve sheath tumor	Carney Complex
• Hemangioblastoma	Von Hippel-Lindau Syndrome

Case 6: 8-year-old girl with a T1-hypo, T2-hyperintense right intraventricular tumor with diffuse contrast enhancement



Sag T1 contrast



SubEpendymal Giant cell Astrocytoma

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Tuberous Sclerosis

- Autosomal dominant
- *TSC1* (9q) and *TSC2* (16p) germline mutations + LOH in tumor
- Cortical tubers
- Subependymal nodules
- SEGA
- Sporadic SEGA??

Table 1 – Diagnostic Criteria of Tuberous Sclerosis

Major Criteria	Minor Criteria
Hypomelanotic macules (≥3; at least 5 mm diameter)	"Confetti" skin lesions
Angiofibroma (≥3) or fibrous cephalic plaque	Dental enamel pits (≥3)
Ungual fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Non-renal hamartomas
Subependymal nodues (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangiomyomatosis*	
Angiomyolipomas (≥2)*	

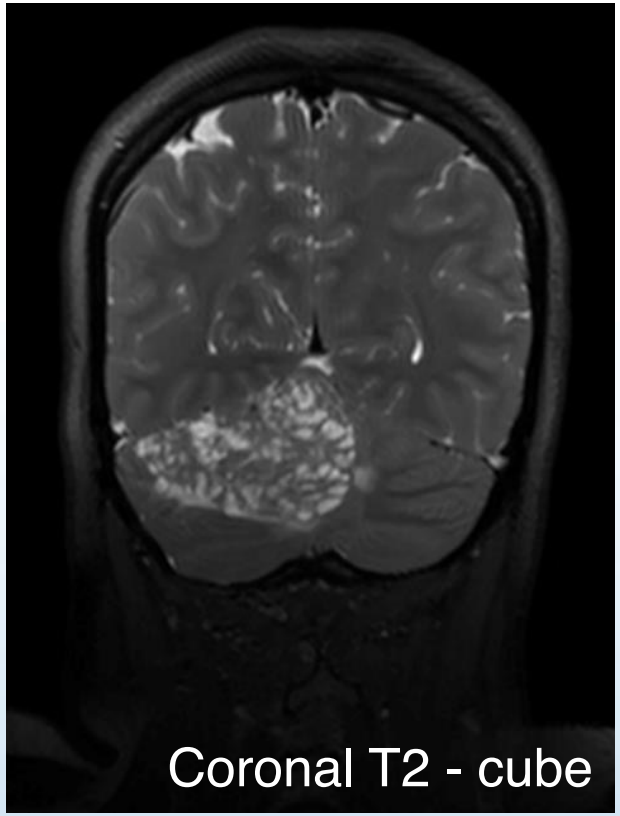
* A combination of these 2 major clinical features without other features does not meet criteria for a definite diagnosis.

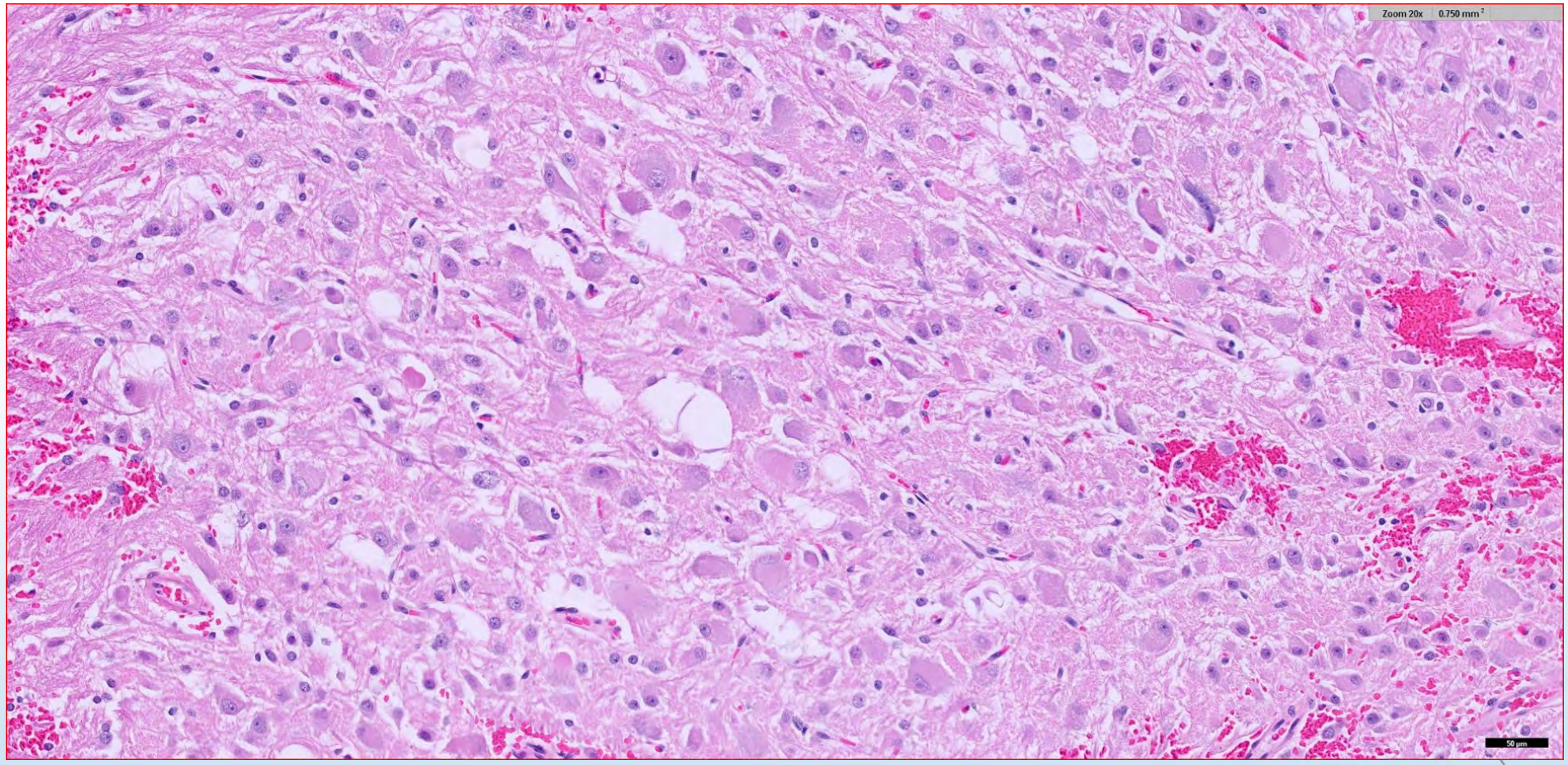
Definite TSC: 2 major features or 1 major features with 2 minor features
Possible TSC: either 1 major feature or ≥2 minor features
Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic of TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing: other variants types should be considered with caution).

WHO – Genetic tumor syndromes (5th edition) // Growth factor receptors and related signaling pathways // MTOR and PI3K pathway // Tuberous sclerosis (TSC1, TSC1)

Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
• Multiple schwannomas*	*LZTR1-, SMARCB1-, DGCR8-* related schwannomatosis
• Malignant melanotic nerve sheath tumor	Carney Complex
• Hemangioblastoma	Von Hippel-Lindau Syndrome
• Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis

Case 7: 26-year-old woman presented with headaches and MR imaging showed a right cerebellar mass extending to the vermis





Dysplastic Cerebellar Gangliocytoma / Lhermitte-Duclos Disease

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PTEN hamartoma syndrome

- Aka Cowden Disease
- Autosomal dominant
- Germline *PTEN* (10q.23) variants
- Dysplastic cerebellar gangliocytoma (~1/3 of CS)
- Mucocutaneous lesions (multiple facial trichilemmomas, acral keratoses, mucosal papillomas) and fissured tongue
- Gastrointestinal polyps (hyperplastic, hamartomatous, ganglioneuromas) and glycogenic acanthosis of esophagus
- Follicular thyroid carcinoma and breast carcinoma

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Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
• Multiple schwannomas*	*LZTR1-, SMARCB1-, DGCR8-* related schwannomatosis
• Malignant melanotic nerve sheath tumor	Carney Complex
• Hemangioblastoma	Von Hippel-Lindau Syndrome
• Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis
• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease)	PTEN hamartoma Syndrome (Cowden Syndrome)

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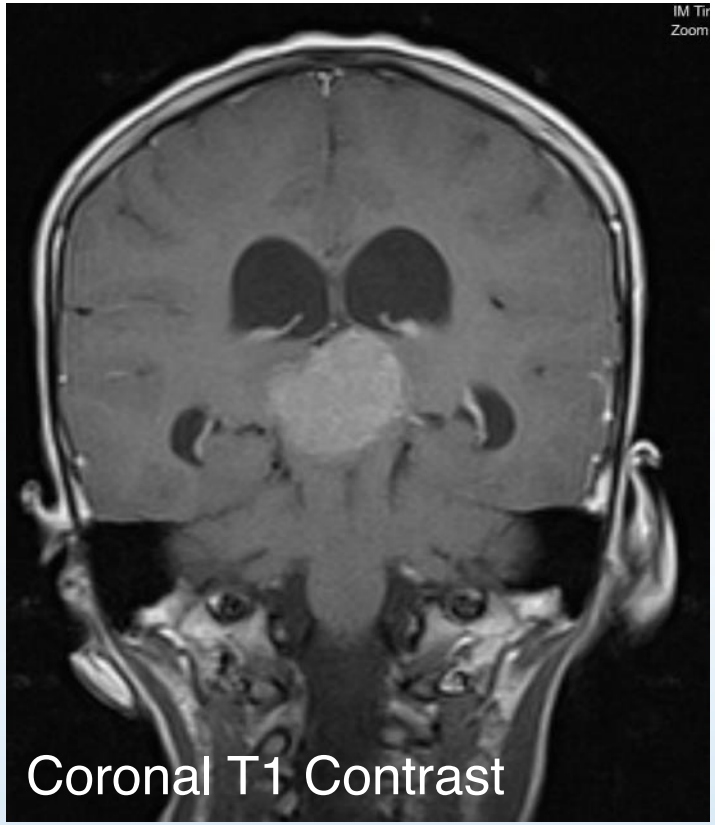
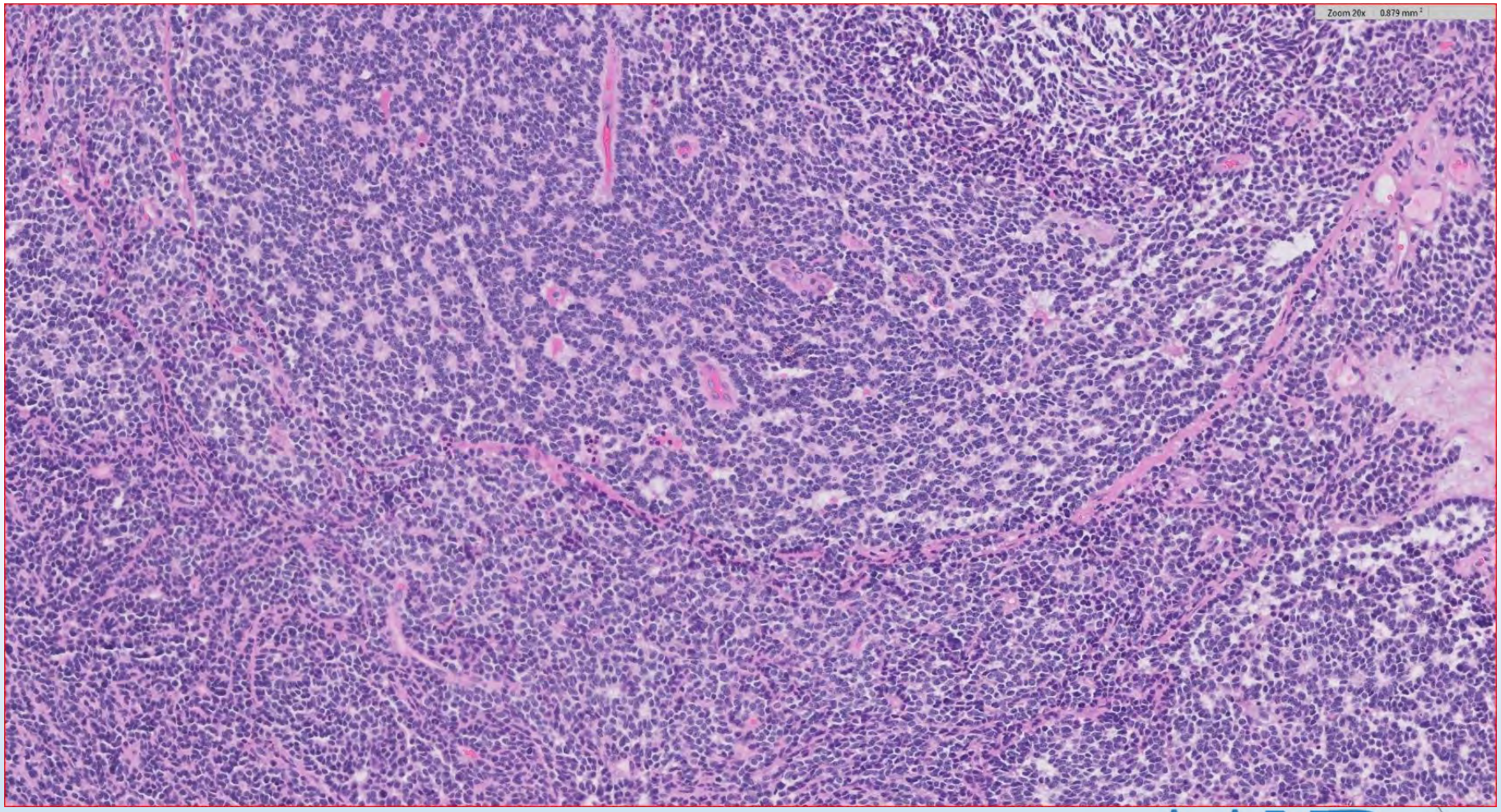
Case 8: 9-year-old girl presented with two weeks of emesis, progressing to lethargy and MRI showed a third ventricular mass





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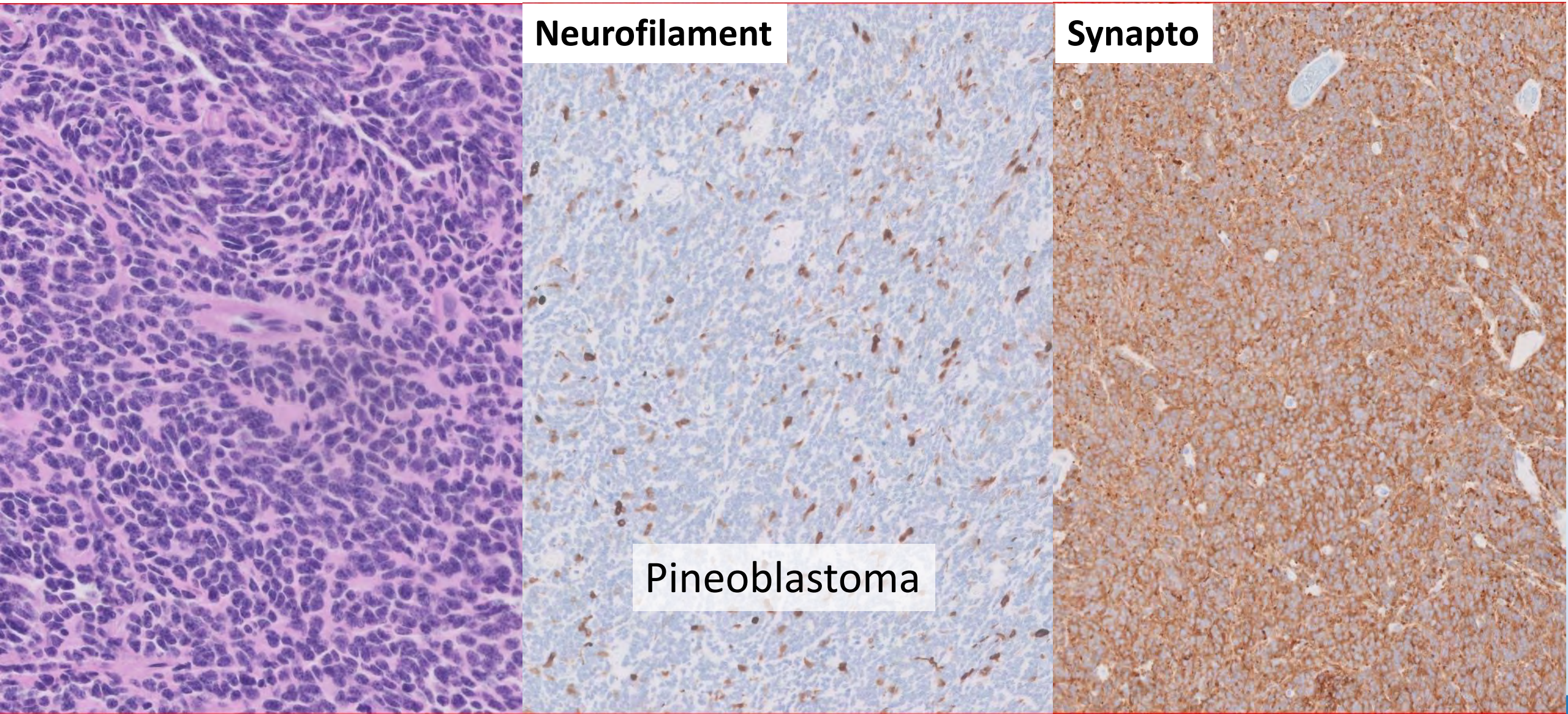

Case 8: 9-year-old girl presented with two weeks of emesis, progressing to lethargy and MRI showed a third ventricular mass

- Pineoblastoma- *MYC / FOXR2*
- Pineoblastoma- *RB1*
- Pineoblastoma – miRNA – *DICER1 / DROSHA / DHCR8*

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
ARID5B p.E132*	NM_032199.2	Pathogenic	711	26%
DICER1 p.V1080fs	NM_177438.2	Pathogenic	808	46%
DICER1 p.R1003*	NM_177438.2	Pathogenic	924	47%

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DICER1 syndrome

- Autosomal dominant
- *DICER1* (14q32.13) encoding an RNA endonuclease
- Pleuropulmonary blastoma (PPB) *
- Pineoblastoma , pituitary blastoma, thyroblastoma
- Primary intracranial sarcoma, *DICER1*-mutant
- Embryonal tumor with multilayered rosettes (ETMR) – no C19MC
- Ciliary body medulloepithelioma
- Soft tissue PPB-like tumors

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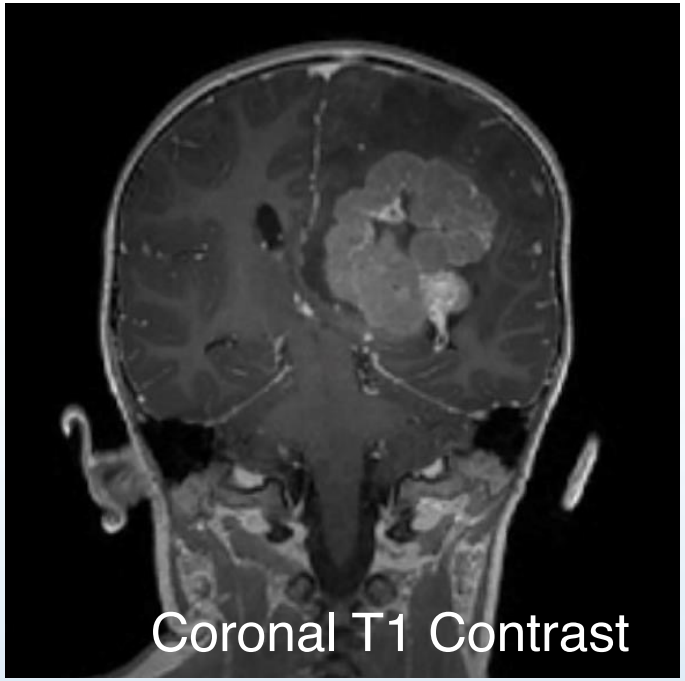
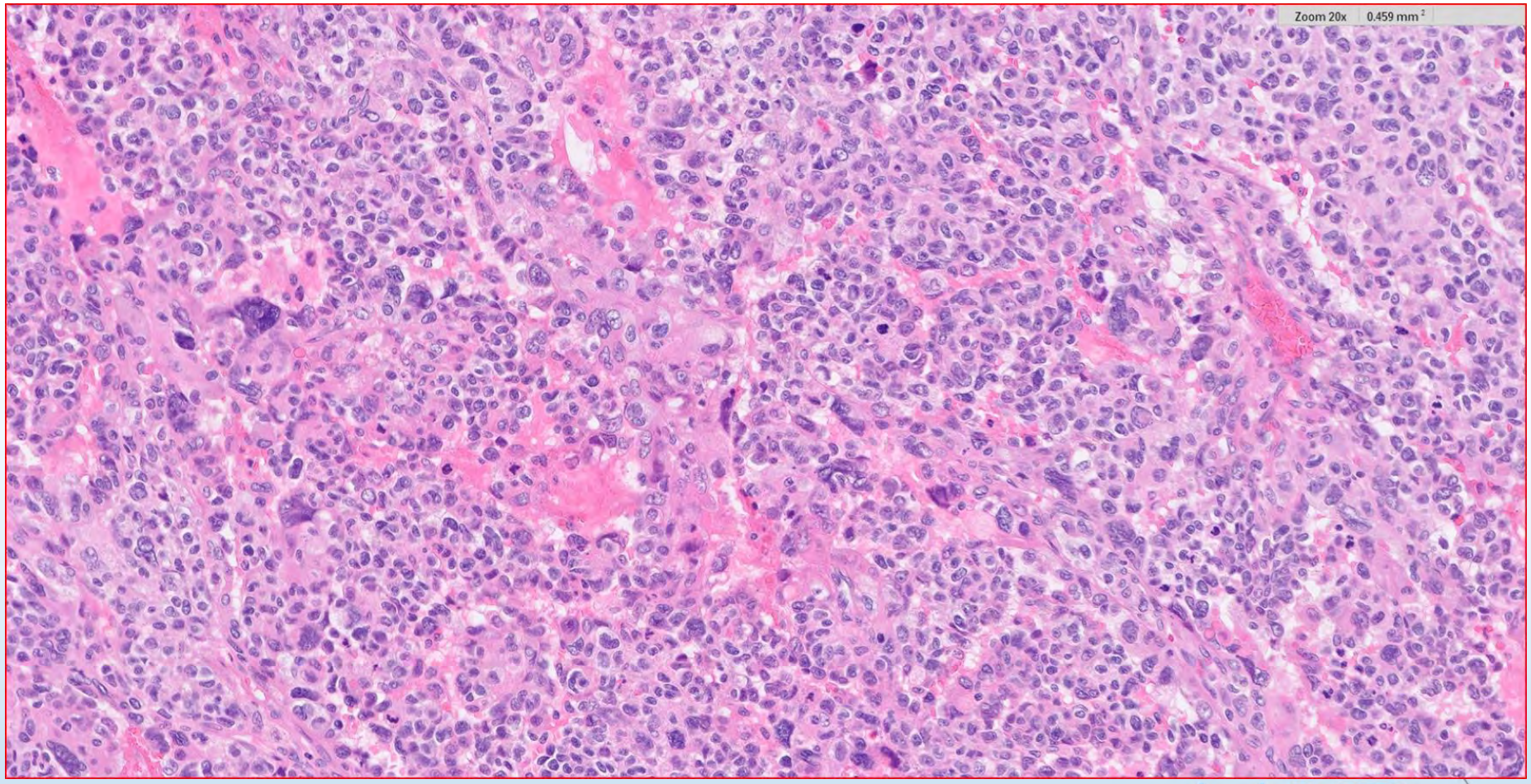
Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
• Multiple schwannomas*	*LZTR1-, SMARCB1-, DGCR8-* related schwannomatosis
• Malignant melanotic nerve sheath tumor	Carney Complex
• Hemangioblastoma	Von Hippel-Lindau Syndrome
• Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis
• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease)	PTEN hamartoma Syndrome (Cowden Syndrome)

Tumor	Syndrome
• Pineoblastoma	*DICER1* syndrome Familial Retinoblastoma syndrome
• Pituitary blastoma • Primary intracranial sarcoma, *DICER1*-mutant • Embryonal tumor with multilayered rosettes (without C19MC)	*DICER1* syndrome

Case 9: 3-year-old boy presented with new-onset seizures and MRI showed an avidly enhancing, T2 hypointense left ventricular mass





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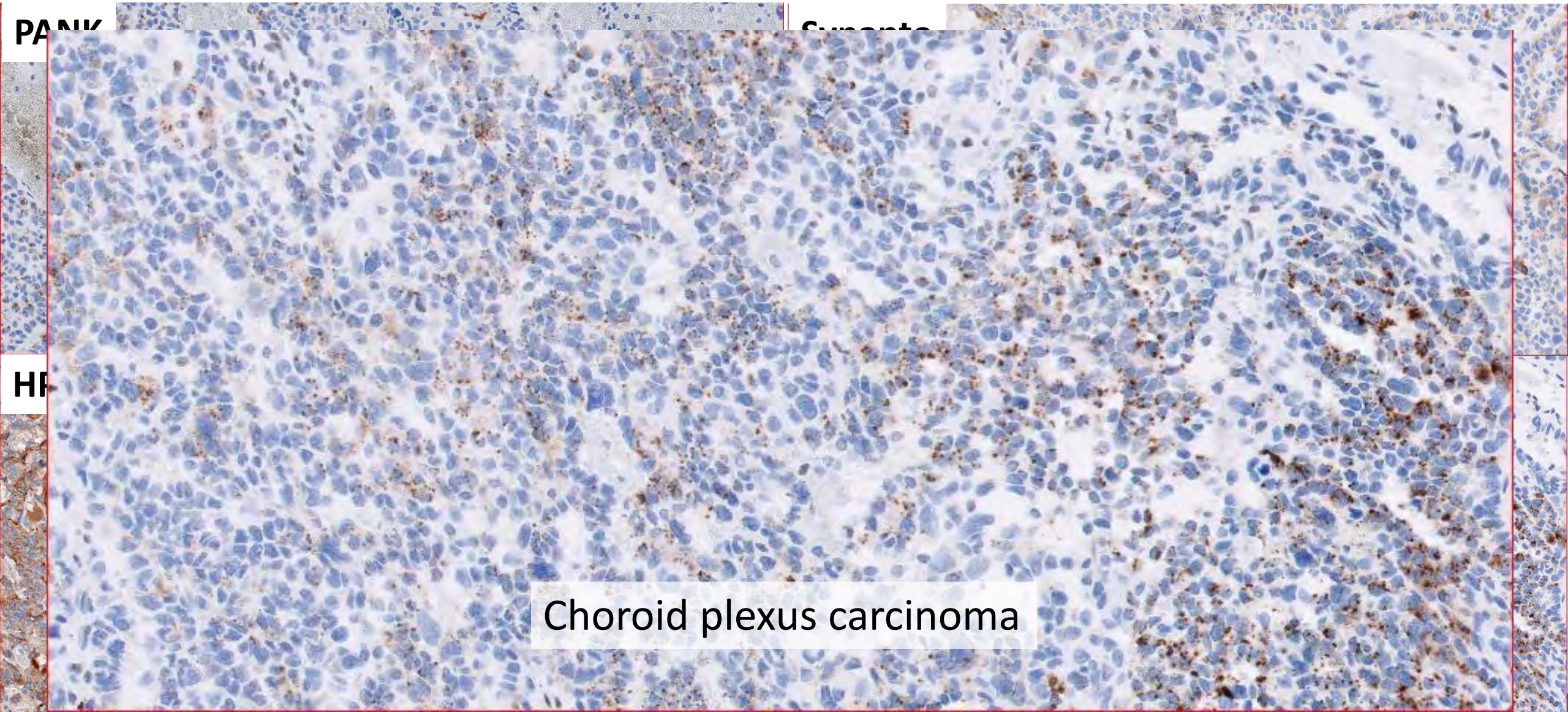

Case 9: 3-year-old boy presented with new-onset seizures and MRI showed an avidly enhancing, T2 hypointense left ventricular mass

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
TP53 intragenic deletion of exons 2-4	NM_001126112	Pathogenic	N/A	N/A
Hyperdiploid genome with numerous chromosome gains	N/A	Pathogenic	N/A	N/A
TERT promoter rearrangement with low-level TERT amplification	All	Likely Pathogenic	354 over rearrangement boundary; ~3.0 x	N/A

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

No follow-up, unclear germline testing

~40% of choroid plexus carcinomas are in the setting of germline *TP53* mutations but **ALL** patients should be offered genetic counseling and germline testing

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Li Fraumeni Syndrome

- Autosomal dominant
- *TP53* tumor suppressor gene (17p13.1)
- Breast cancer (25-30%)
- Soft tissue sarcomas (12-17%)
- Osteosarcoma (12-13%)
- Brain tumors (10-12%)
- Adrenocortical carcinoma (7-10%)

- Choroid plexus carcinoma
  - Usually infant, 40% LFS
  - High-risk, ped-type type B (mc)
- Medulloblastoma, SHH , *TP53*-mutant
  - Median age : 9 years
  - Large cell anaplastic common
- IDH&H3-wildtype HGG (+/- giant cells)
  - Young kids, often *NF1*-mutant, *MYCN* amplified
- Diffuse astrocytic glioma, IDH-mutant
  - Young adults, usually low(er) grade
  - *IDH1* p.R132C or p.R132S common

Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
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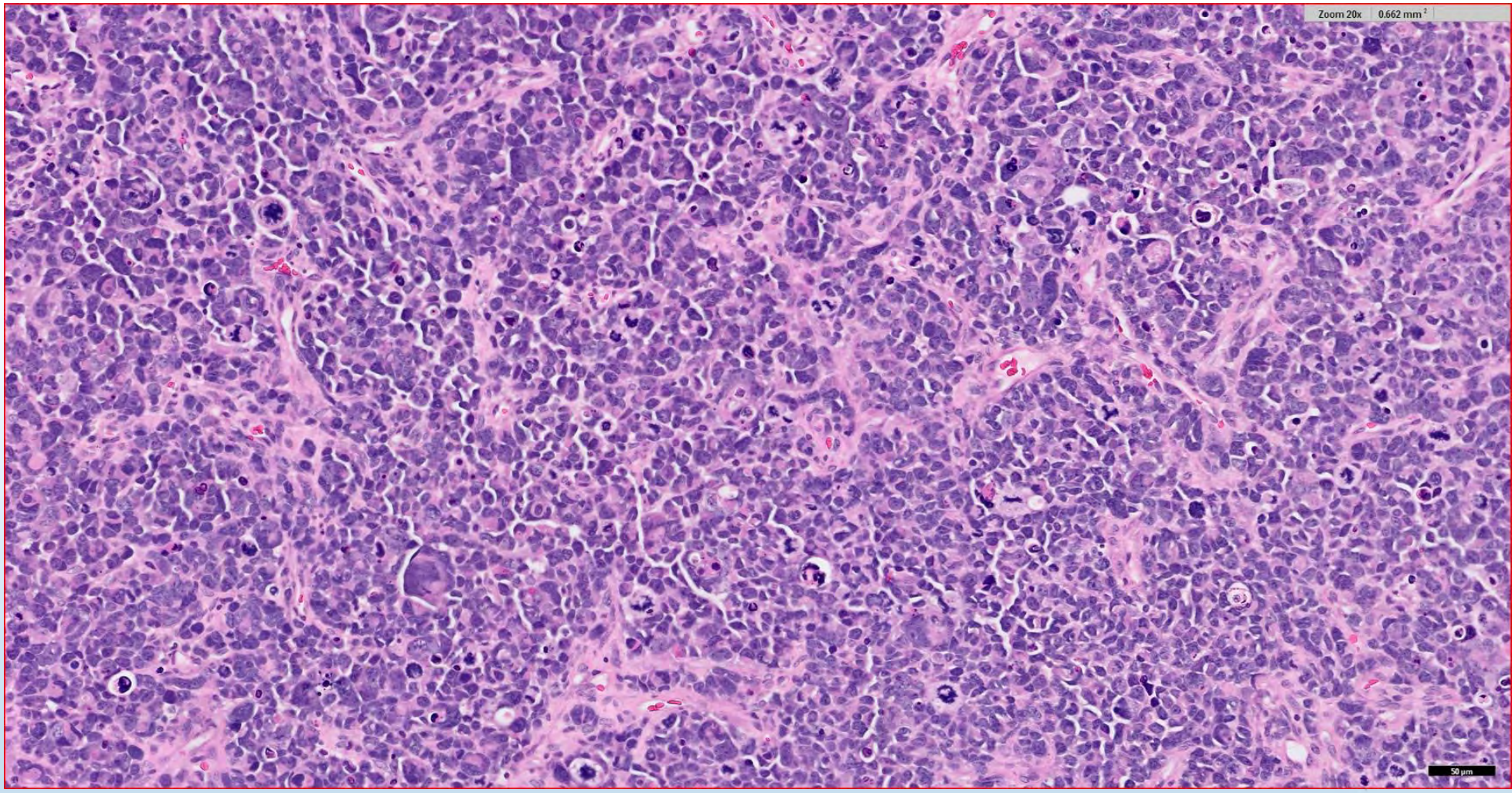
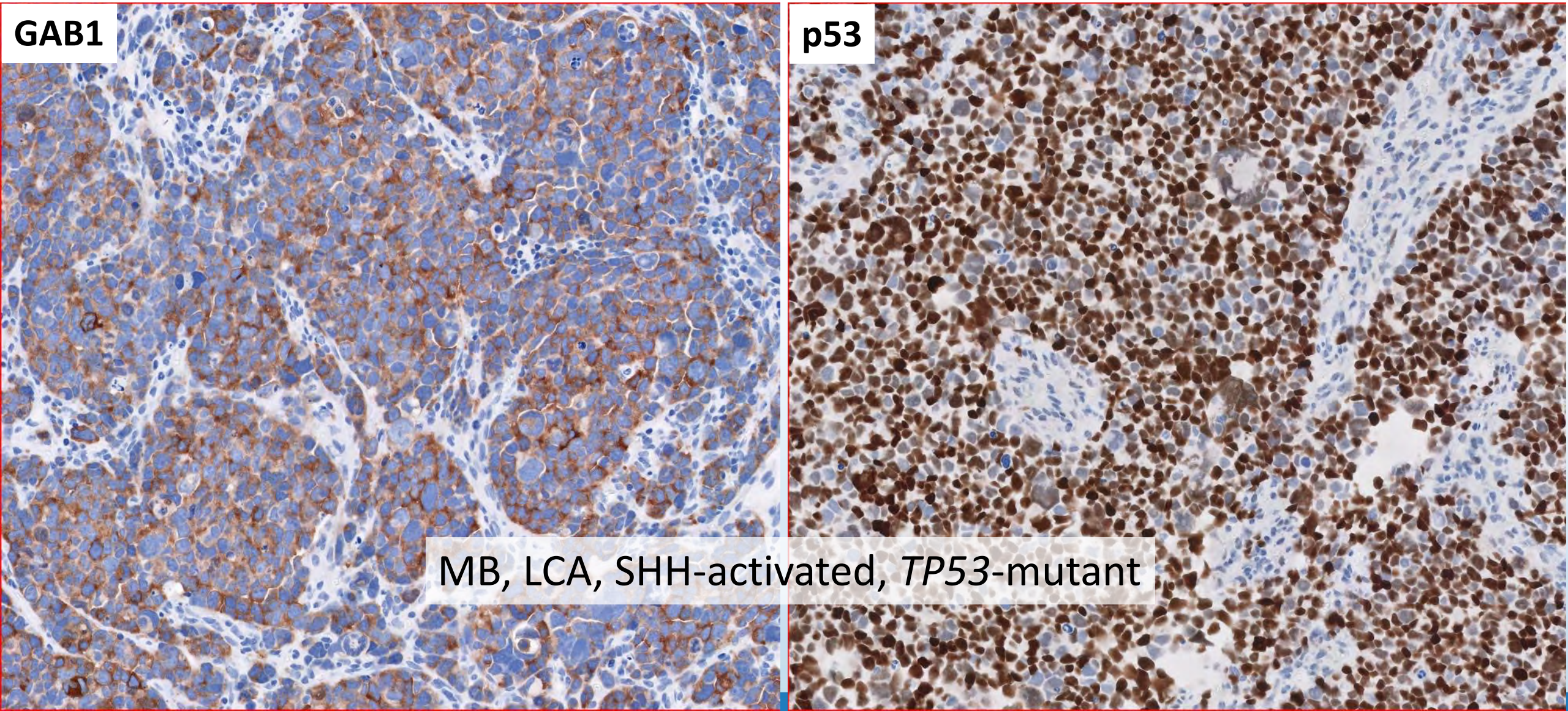
• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease)	PTEN hamartoma Syndrome (Cowden Syndrome)

Tumor	Syndrome
• Pineoblastoma	*DICER1* syndrome Familial Retinoblastoma syndrome
• Pituitary blastoma • Primary intracranial sarcoma, *DICER1*-mutant • Embryonal tumor with multilayered rosettes (without C19MC)	*DICER1* syndrome
• Choroid plexus carcinoma • IDH- and H3-wildtype HGG in a child • IDH-mutant astrocytoma in an adult (especially noncanonical *IDH1*) • Medulloblastoma, SHH-activated *TP53*-mutant, often large cell/anaplastic*	Li Fraumeni syndrome

Case 10: 7-year-old girl presented with headache, nausea, vomiting and MRI showed a diffusely enhancing left cerebellar mass



Case 10: 7-year-old girl presented with headache, nausea, vomiting and MRI showed a diffusely enhancing left cerebellar mass



Case 10: 7-year-old girl presented with headache, nausea, vomiting and MRI showed a diffusely enhancing left cerebellar mass in the setting of **Li Fraumeni Syndrome**

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
GLI2 amplification	All	Pathogenic	~21.0x (~14,000 reads)	N/A

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Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
TP53 p.T125K (c.374C>A, p.Thr125Lys)	NM_000546.5	Pathogenic	877/549	49%/90%

*Alterations in the normal sample are reported for cancer-related genes if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist/geneticist. For variants not classified in ClinVar, truncating or splice-site variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or exac65k0 datasets. Alterations in the normal samples are limited to single nucleotide variants and small indels in gene coding regions. Carrier status is not reported for variants not strongly related to cancer.

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Case 10 b: 7-year-old girl presented with headache, nausea, vomiting and MRI showed a diffusely enhancing left cerebellar mass in the setting of **Fanconi Anemia**

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
CCND2,FGF23 amplification	All	Pathogenic	~16.5x	N/A
CDK4 amplification	All	Pathogenic	~16.5x	N/A
GLI2 amplification	All	Pathogenic	~9.5x	N/A
MYCN amplification	All	Pathogenic	~13.0x	N/A
TP53 c.362_375+6del	NM_000546.5	Pathogenic	694	75%
TP53 deep deletion	All	Pathogenic	N/A	N/A

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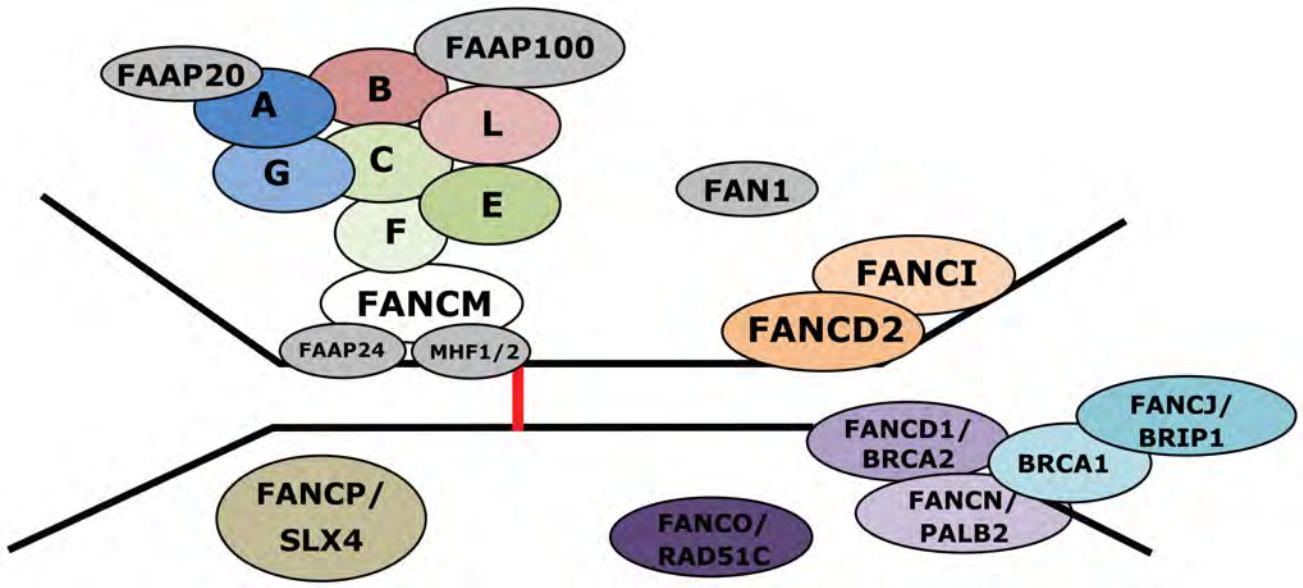
Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS (Normal/Tumor)**	**MUTANT ALLELE FREQUENCY (Normal/Tumor)**
BLM p.Q548* (c.1642C>T, p.Gln548*)	NM_000057.2	Pathogenic	511/706	46%/39%
BRCA2 p.V220fs (c.658_659delGT, p.Val220fs)	NM_000059.3	Pathogenic	384/799	38%/39%
BRCA2 p.E1953* (c.5857G>T, p.Glu1953*)	NM_000059.3	Pathogenic	345/487	56%/44%

Fanconi Anemia

- Congenital developmental abnormalities
- Progressive bone marrow failure
- Myelodysplastic syndrome+/-blasts to AML
- Solid tumors, especially oropharyngeal SCC
- Medulloblastoma (SHH-act, *TP53*-mutant >others)
- Wilms Tumor, neuroblastoma, rhabdomyosarcoma, ALL (FANC-D1/ FANC-N)

Fanconi Anemia / *BRCA* Repair pathway

- 22 genes – FA complementation groups (A, B, C, D1, D2….)
- Most are autosomal recessive – <u>homozygous or compound heterozygous</u> germline mutations
- *FANCA, FANCB, FANCC,* *FANCD2, FANCE, FANCF, FANCG,……*



Detect DNA crosslinking & Repair

Haitjema A. PLoS One. 2013 Apr 19;8(4):e62017

Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
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• Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis
• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease)	PTEN hamartoma Syndrome (Cowden Syndrome)

Tumor	Syndrome
• Pineoblastoma	*DICER1* syndrome Familial Retinoblastoma syndrome
• Pituitary blastoma • Primary intracranial sarcoma, *DICER1*-mutant • Embryonal tumor with multilayered rosettes (without C19MC)	*DICER1* syndrome
• Choroid plexus carcinoma • IDH- and H3-wildtype HGG in a child • IDH-mutant astrocytoma in an adult (especially noncanonical *IDH1*) • Medulloblastoma, SHH-activated *TP53*-mutant, often large cell/anaplastic*	Li Fraumeni syndrome
• Medulloblastoma, SHH-activated *TP53*-mutant, often large cell/anaplastic*	Fanconi Anemia

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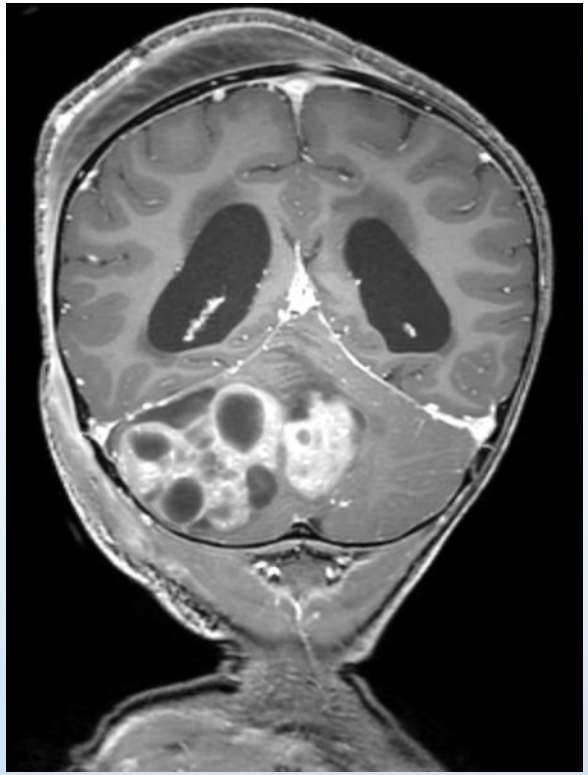
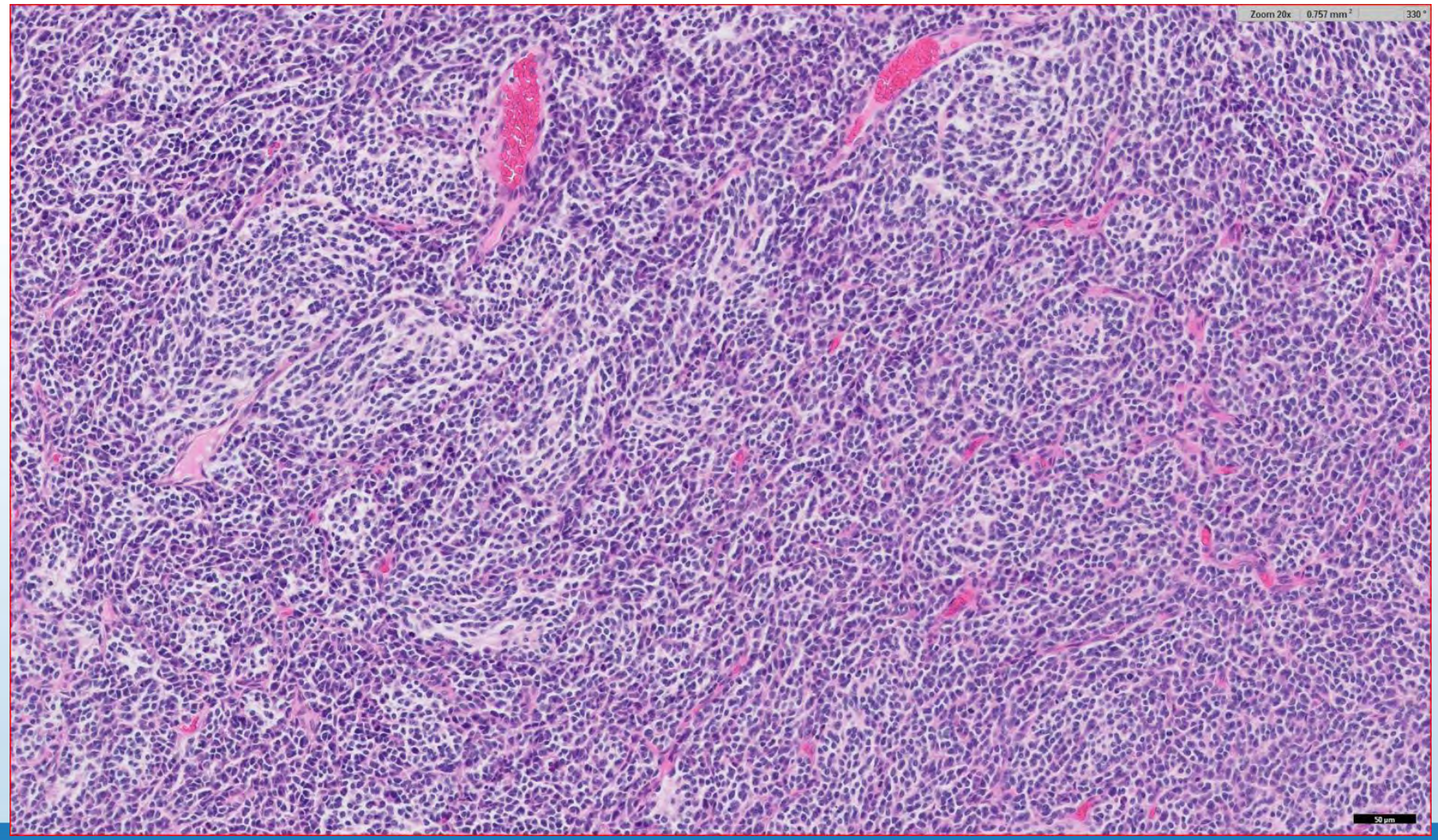
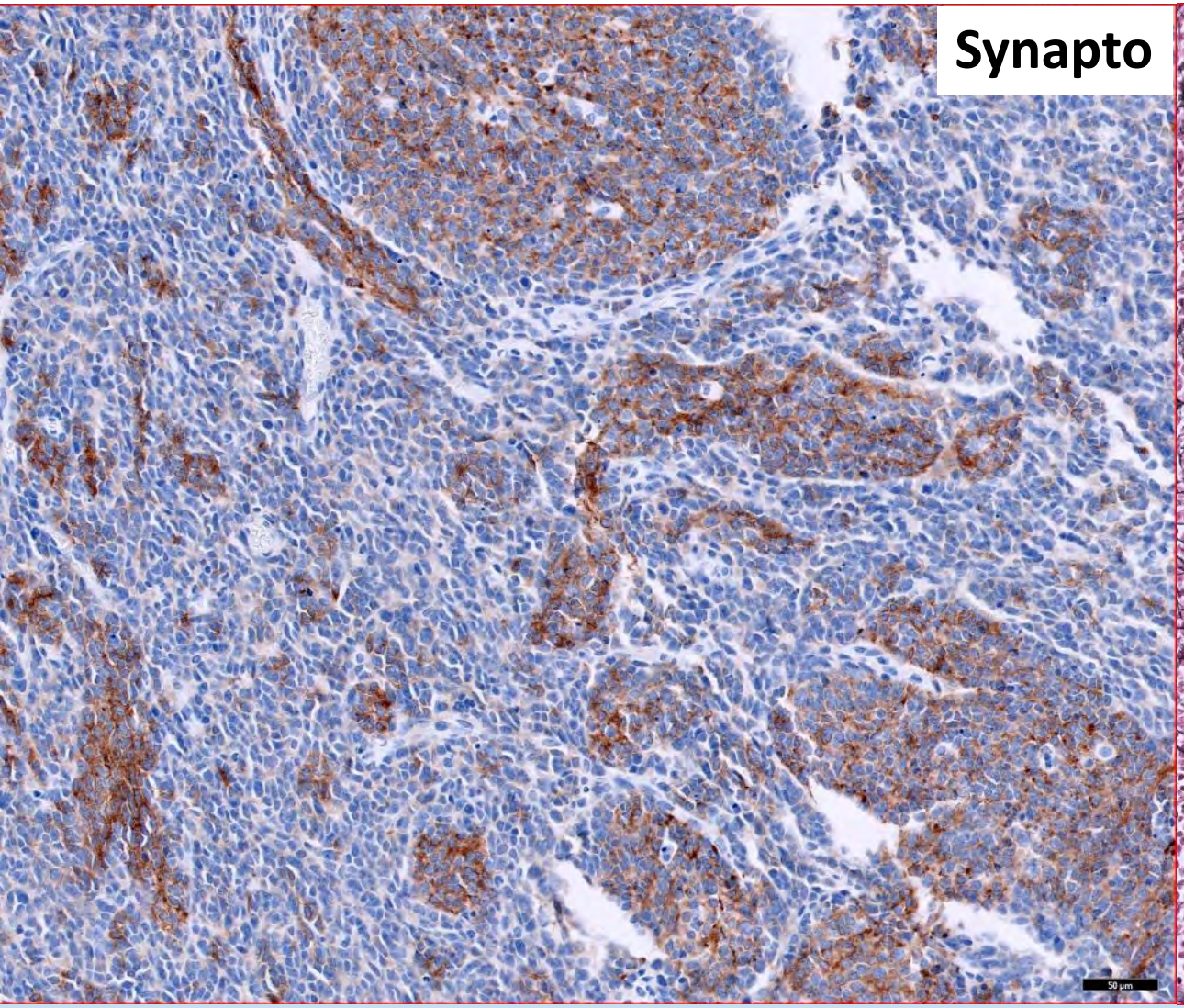
Case 11: 3-year-old girl presented with 2-month history of ataxia, headaches and intermittent vomiting and MRI showed a 6.6 cm, heterogeneous, solid and cystic, enhancing right cerebellar mass

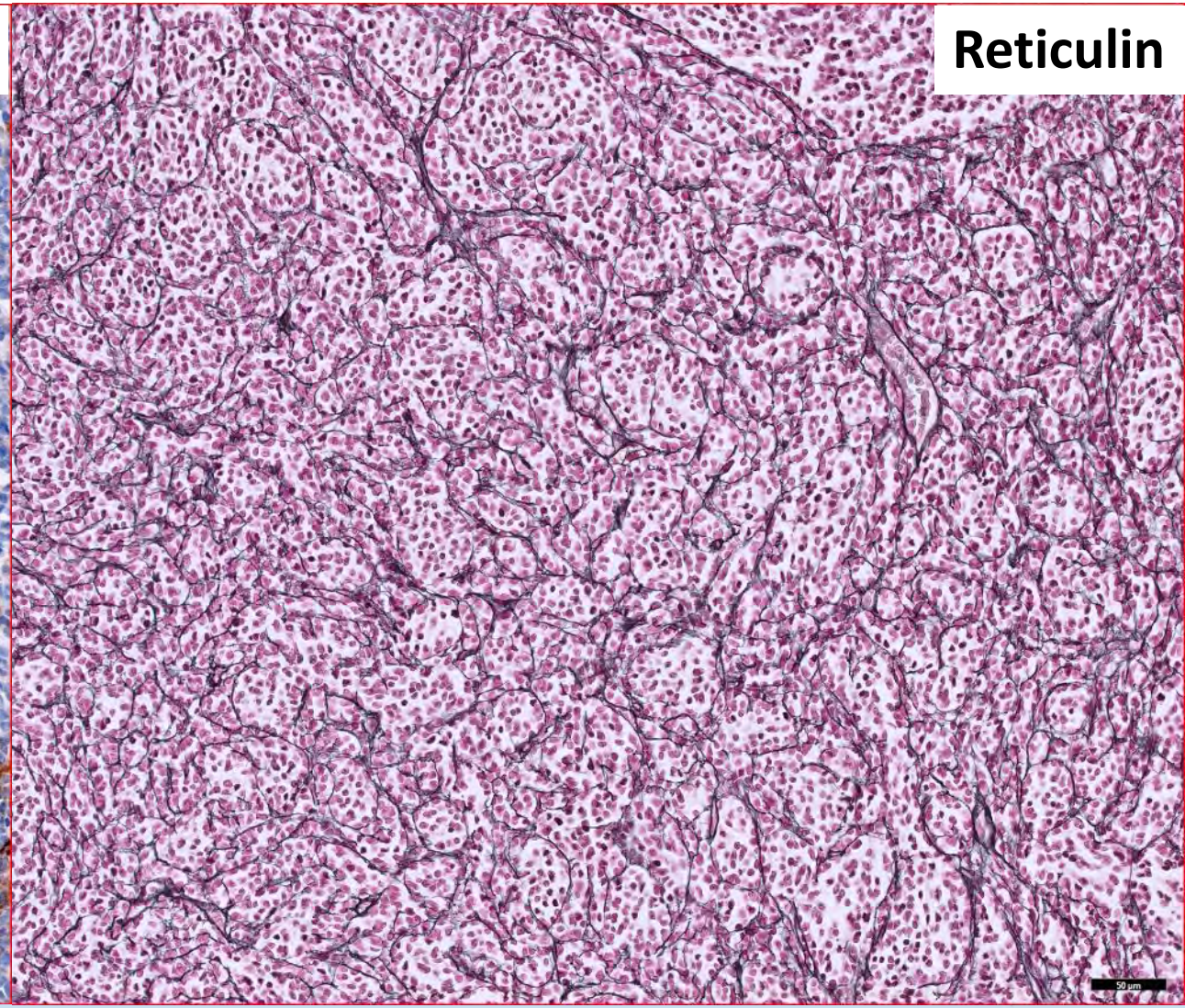


Coronal T1 Contrast

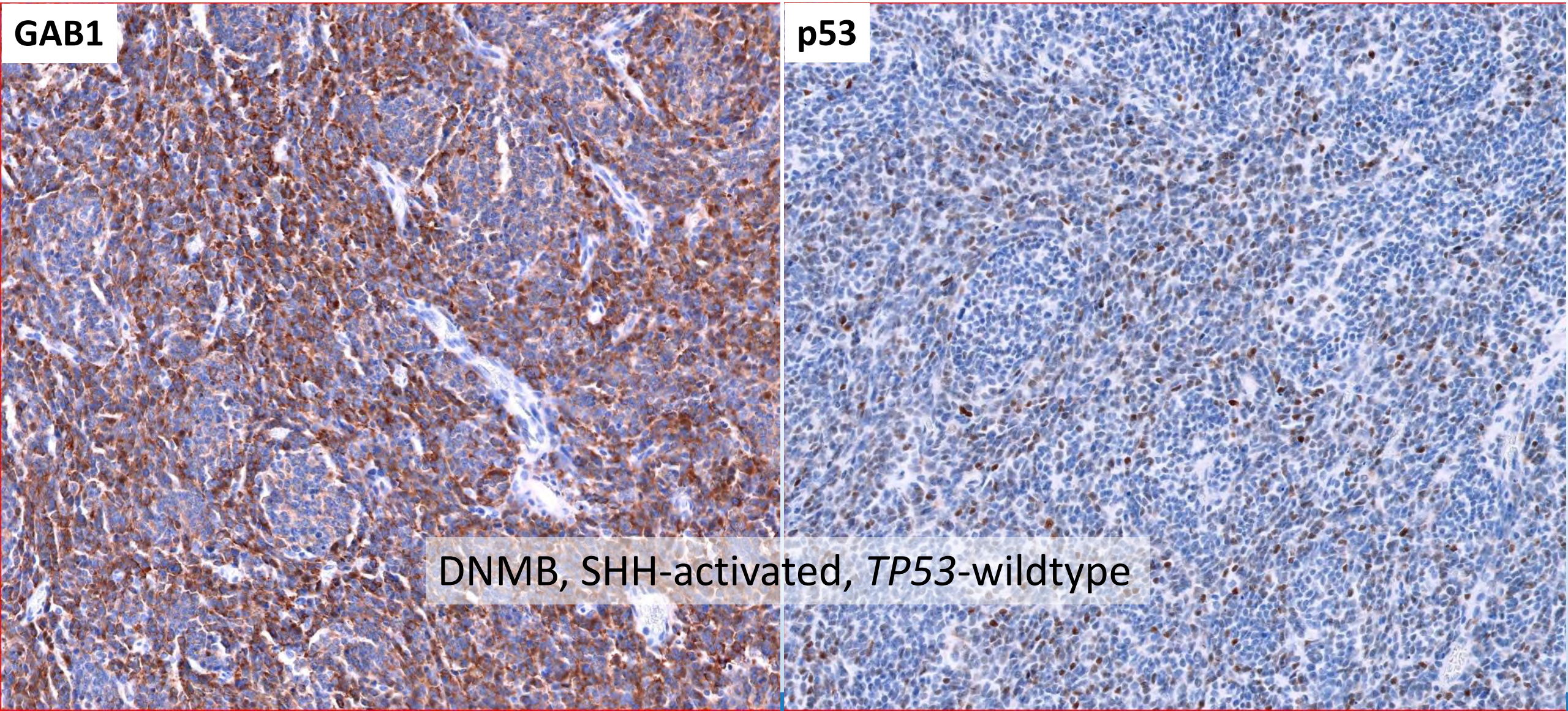


Case 11: 3-year-old girl with a 6.6 cm, heterogeneous, solid and cystic, enhancing right cerebellar mass





Case 11: 3-year-old girl with a 6.6 cm, heterogeneous, solid and cystic, enhancing right cerebellar mass



Case 11: 3-year-old girl with a 6.6 cm, heterogeneous, solid and cystic, enhancing right cerebellar mass – **Gorlin (Nevoid basal cell carcinoma) syndrome**

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
TERT c.-124C>T	NM_198253.2	Pathogenic	280	42%

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS (Normal/Tumor)**	**MUTANT ALLELE FREQUENCY (Normal/Tumor)**
PTCH1 p.G1163fs, p.Gly1163fs	NM_000264.3	Pathogenic	877/334	49%/83%

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Gorlin (Nevoid basal cell carcinoma) syndrome

- Autosomal dominant
- Germline *PTCH1 (9q22)* less likely *PTCH2* (1p34) or *SUFU* (10q24) variants
  - Germline *GPR161* (1q24.2) → Gorlin-like syndrome
- DNMB or MBEN, SHH-activated and *TP53*-wildtype (median age 2 years)
  - 2% in pts with *PTCH1* - 20% in pts with *SUFU* mutations – Might be the first presentation
- Meningioma
- Basal cell carcinomas & odontogenic keratocyst (>90% by age 40)
- Calcification of the falx cerebri, tentorium cerebelli and/or sella turcica, palmar and plantar pits, and bifid or fused ribs
- Macrocephaly, congenital facial abnormalities (e.g. cleft lip or palate, frontal bossing, and hypertelorism), skeletal abnormalities (e.g. digit syndactyly)

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Case 11 b: 3-year-old girl with a 6.6 cm, heterogeneous, solid and cystic, enhancing right cerebellar mass - **ELP1 MB Syndrome**

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
PTCH1 homozygous deletion	All	Pathogenic	N/A	N/A

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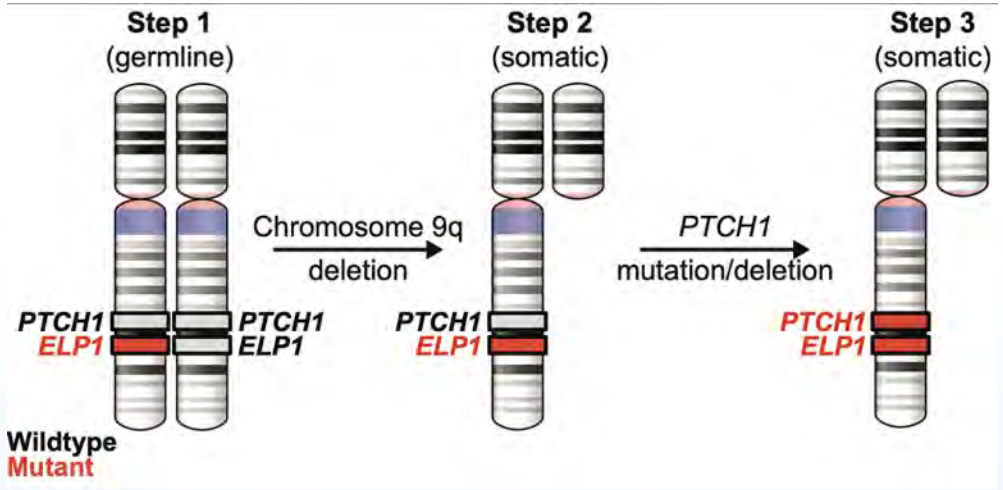
Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*						
Gene (Transcript ID)	Genomic Change (GRCh38)	Nucleotide Change	Etiology/Zygosity	Predicted Protein Change	Associated Disease/Condition	Variant Interpretation (ACMG/AMP Evidence)
ELP1 (NM_003640.5)	chr9:108931143 G>A	c.4C>T	Het	p.Arg2Ter	(AD, AR, SMu) {Medulloblastoma} (OMIM: 155255) (AR) Dysautonomia, familial (OMIM: 223900)	Pathogenic (PVS1, PM2, PS4_supporting)

NM_003640.5(ELP1):c.4C>T p.(Arg2Ter)

ELP1 Medulloblastoma Syndrome



- Autosomal dominant
- Germline *ELP1* variants (9q31.3)
- 3-step process – leading to SHH activation
- Mutually exclusive with *TP53* mutations
- *ELP1* germline mutations present in ~15% of MB-SHH
- Patients older than those with germline *PTCH1* and *SUFU* (Nevoid basal cell carcinoma syndrome), younger than those with *TP53* mutations (Li Fraumeni syndrome)
- Favorable outcome with >90% 5-year overall survival rate

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Tumor	Syndrome
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• Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis
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Tumor	Syndrome
• Pineoblastoma	*DICER1* syndrome Familial Retinoblastoma syndrome
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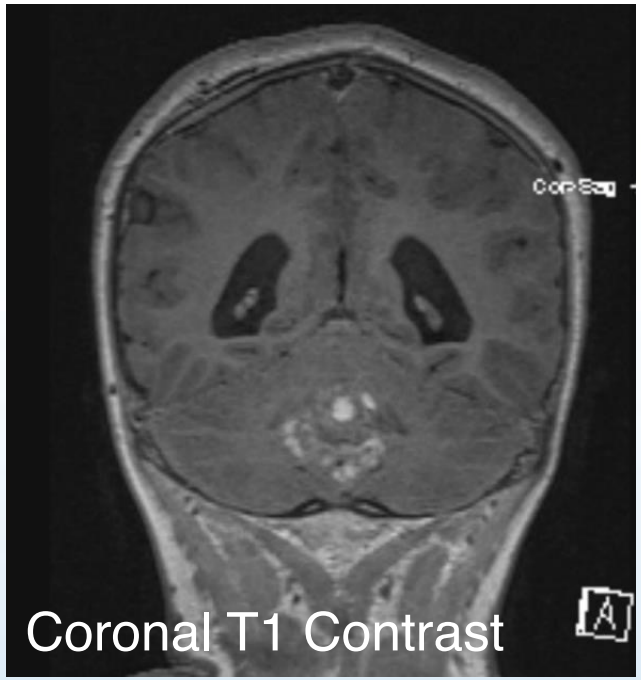
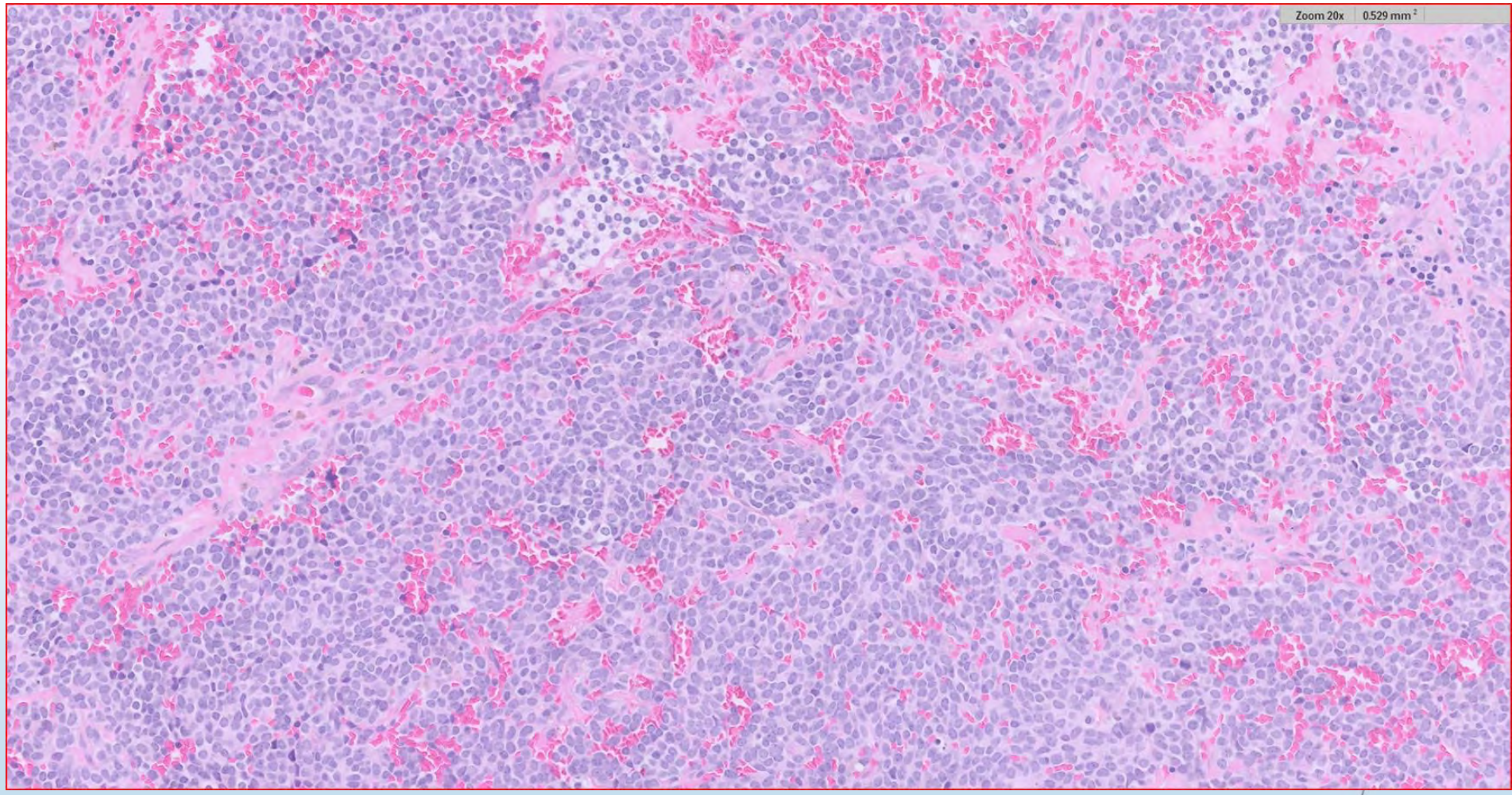
• Choroid plexus carcinoma • IDH- and H3-wildtype HGG in a child • IDH-mutant astrocytoma in an adult (especially noncanonical *IDH1*) • Medulloblastoma, SHH-activated *TP53*-mutant, often large cell/anaplastic*	Li Fraumeni syndrome
• Medulloblastoma, SHH-activated *TP53*-mutant, often large cell/anaplastic*	Fanconi Anemia
• Medulloblastoma, SHH-activated *TP53*-wildtype	•Gorlin (Nevoid basal cell carcinoma) syndrome •*GPR161* (Gorlin-like) syndrome •*ELP1*-medulloblastoma syndrome

AANP

Case 12: 11-year-old girl presented with headaches and optic disc swelling, and MRI showed a 3.7 cm, 4th ventricular mass





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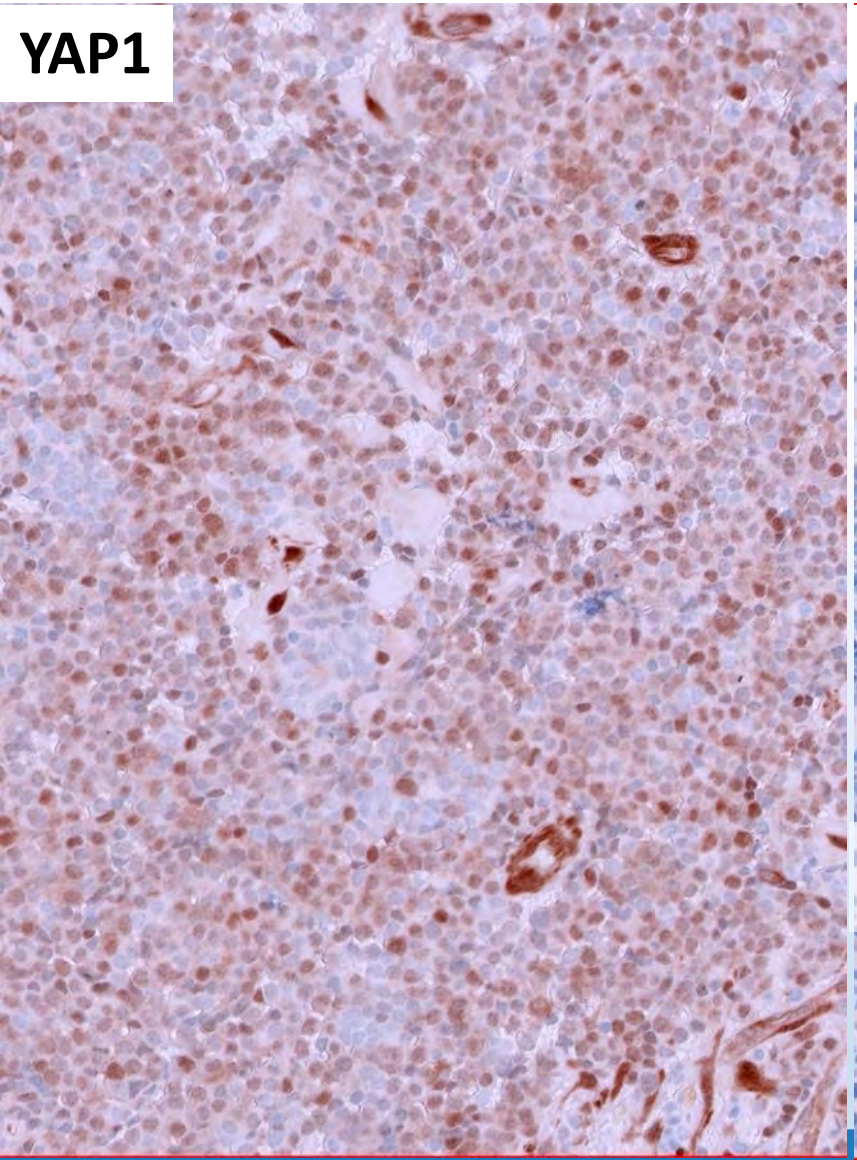
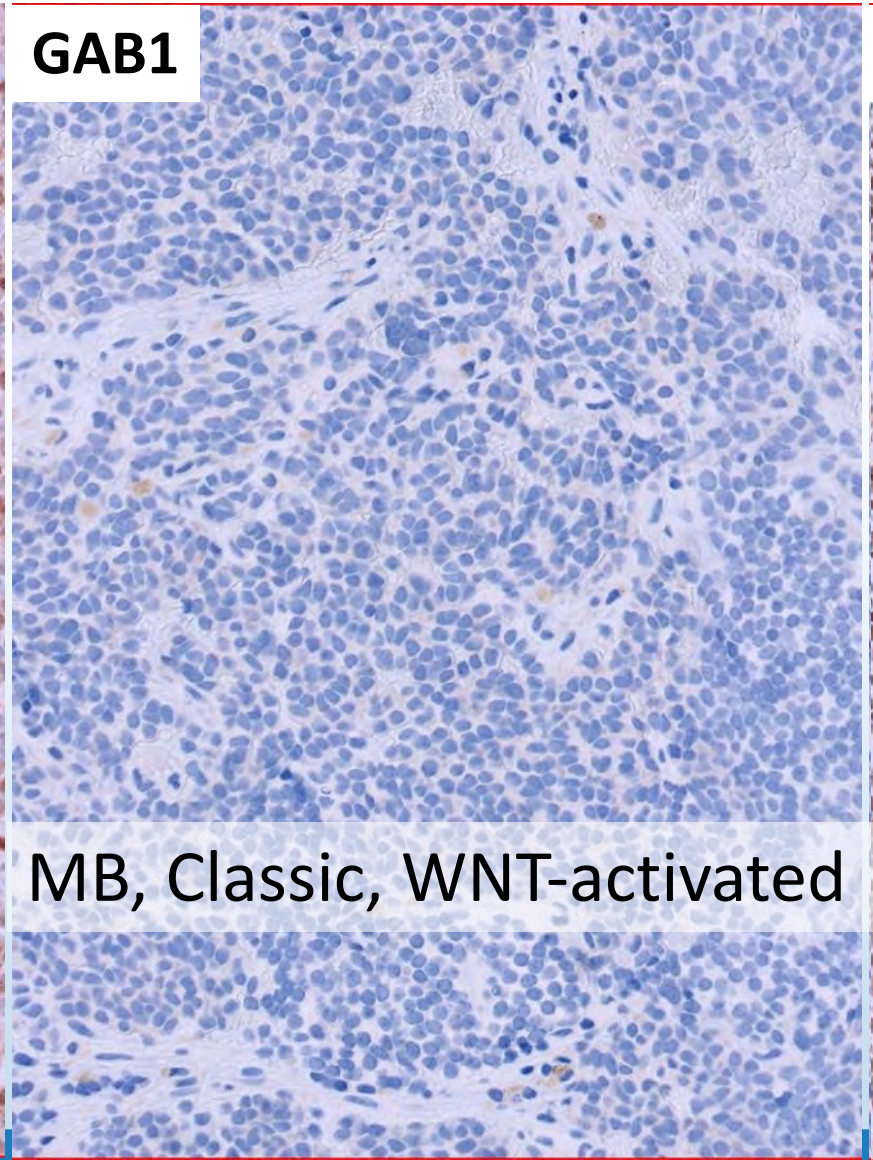
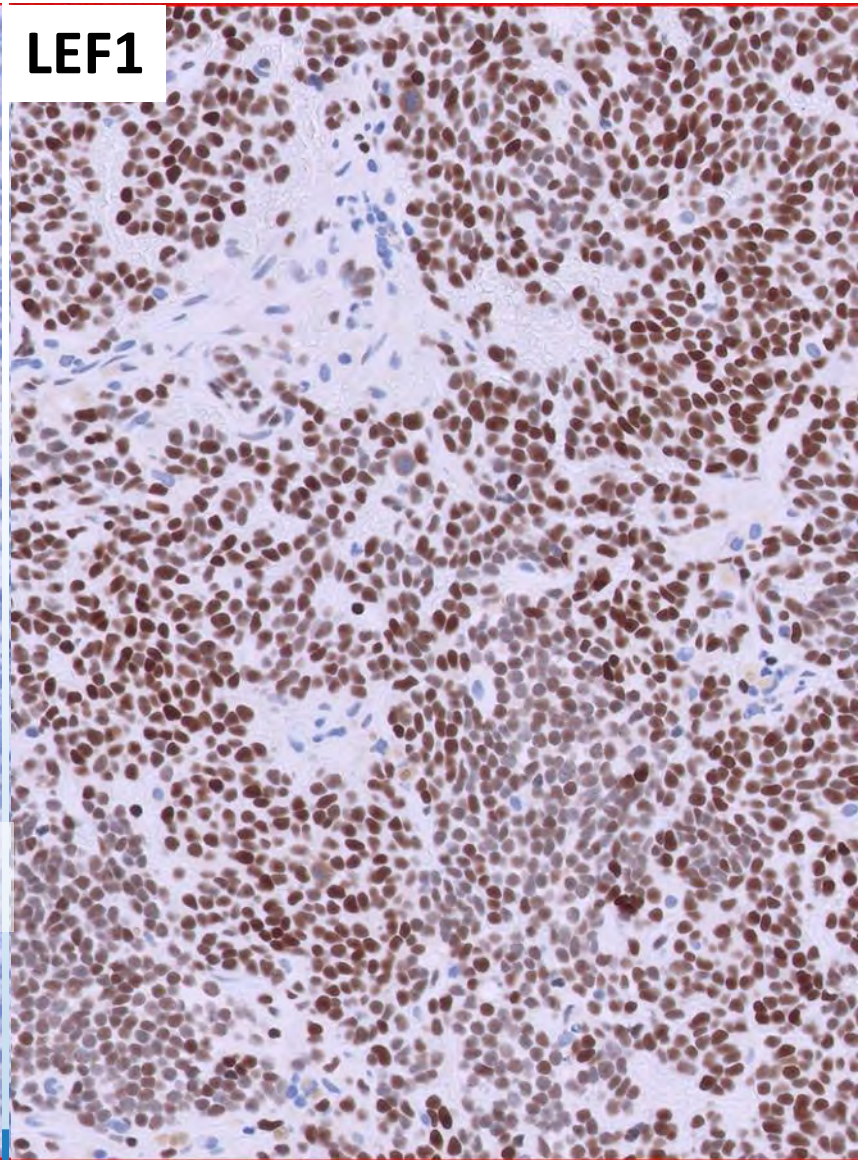




MB, Classic, WNT-activated



Case 12: 11-year-old girl presented with headaches and optic disc swelling, and MRI showed a 3.7 cm, 4th ventricular mass

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
APC p.Q1067*	NM_000038.5	Pathogenic	810	97%
DDX3X p.R351W	NM_001356.3	Pathogenic	920	46%
SMARCA4 p.T910M	NM_001128849.1	Pathogenic	1465	46%
Monosomy 6	N/A	Pathogenic	N/A	N/A

- ~90% of WNT-MB have *CTNNB1* mutations
- 70% of *CTNNB1*-wildtype WNT-MB are in the setting of germline *APC* mutations

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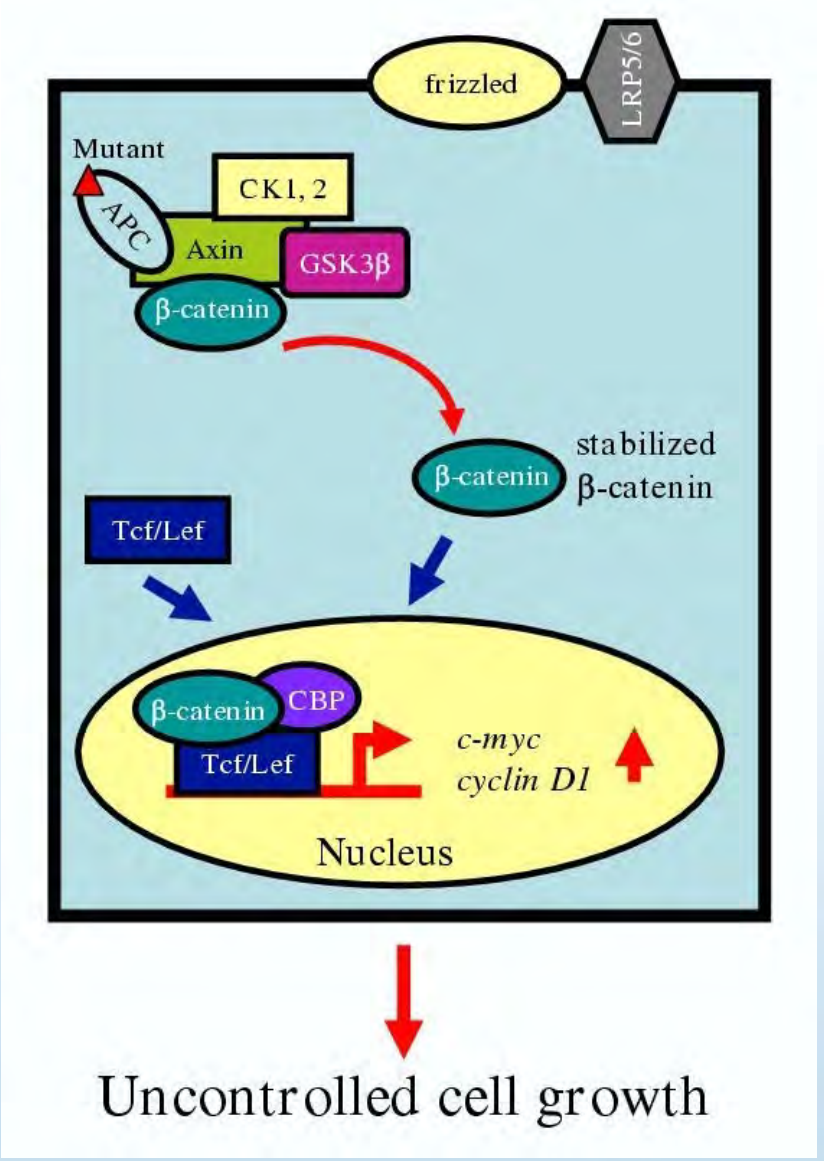
Familial Adenomatous Polyposis Syndrome

- Autosomal dominant
- Germline *APC* variants (5q22.2)
- Increased WNT signaling
- Colorectal polyps (>100-thousands)
- Colorectal adenocarcinoma (100%)
- Cribriform morular thyroid carcinoma, hepatoblastoma, adrenocortical adenoma/carcinoma, desmoid fibromatosis
- WNT-activated MB
  - 70% of *CTNNB1*-wildtype WNT-MB are a/w FAP



Tumor	Syndrome
• Multiple neurofibromas • Plexiform neurofibroma • Massive soft tissue neurofibroma • MPNST arising from a neurofibroma	Neurofibromatosis 1 (NF1)
• Multiple meningiomas • Meningioma(s) in a child • Meningioma(s) + schwannoma(s) +/- spinal ependymoma(s) • Bilateral vestibular schwannomas • Multiple schwannomas*	Neurofibromatosis 2 (NF2) *NF2*-related schwannomatosis
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• Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis
• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease)	PTEN hamartoma Syndrome (Cowden Syndrome)

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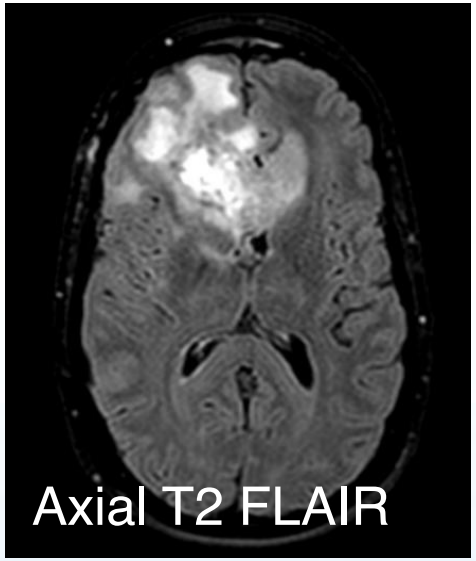
• Medulloblastoma, WNT-activated (*CTNNB1*-wildtype)	Familial adenomatous polyposis

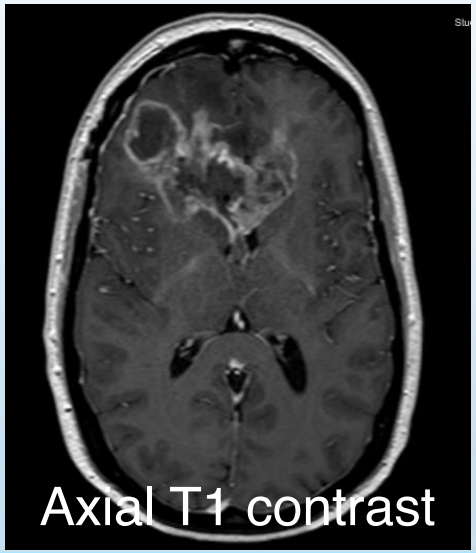
Medulloblastoma and hereditary syndromes

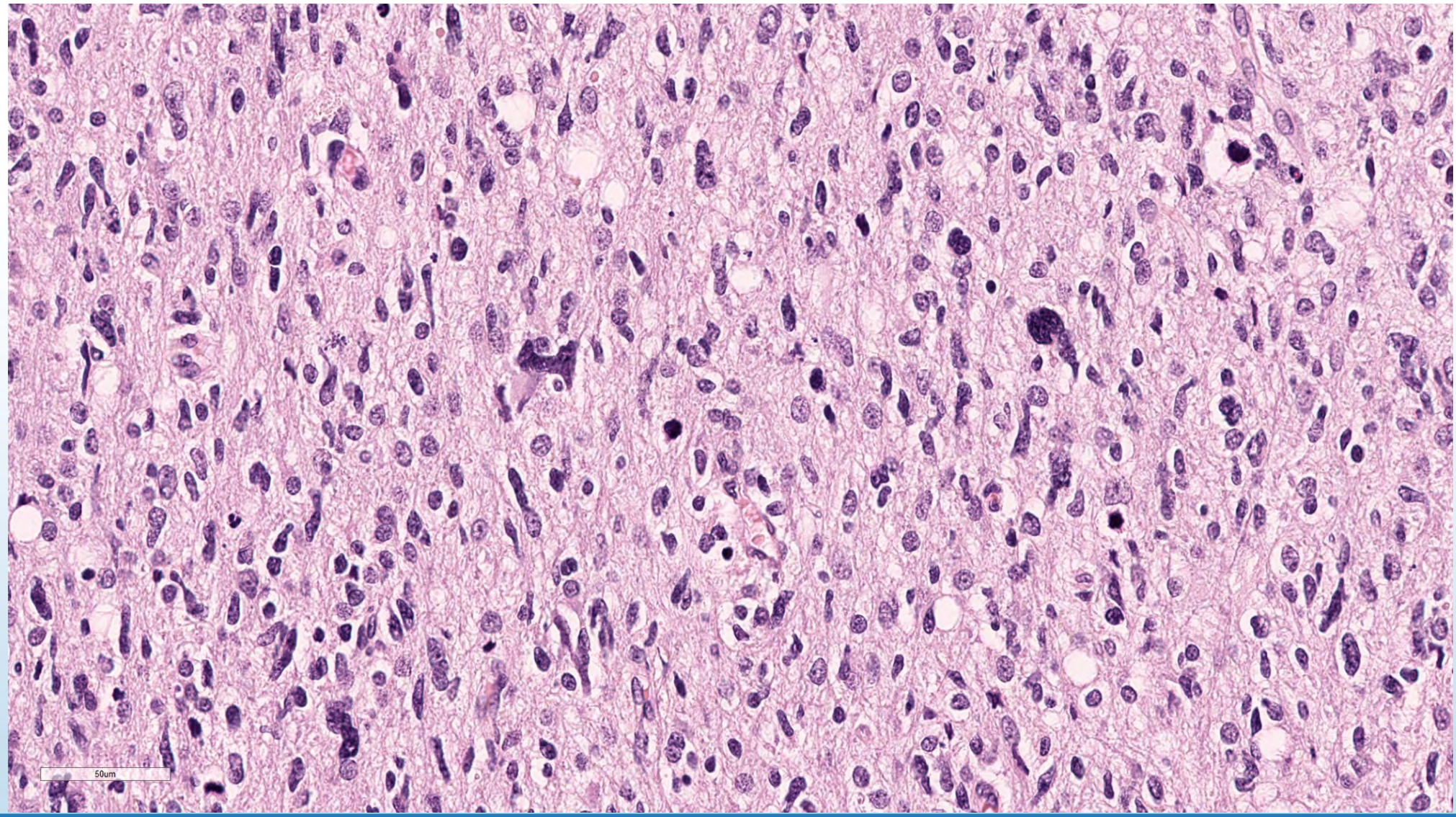
- Highest rate of germline alterations in MB-SHH group (20%)
- Clinical signs or family history to suggest a syndrome present only in 40-50% of cases
- Germline *APC* (Familial adenomatous polyposis) → MB-WNT
  - 70% of MB-WNT without somatic *CTNNB1* mutations have germline *APC* mutations
  - Median age: 9 years
- Germline *PTCH1 & SUFU* (Nevoid BCC– Gorlin- Syndrome) → MB-SHH
  - Infants, median age: 2 years
- Germline *ELP1* (ELP1 medulloblastoma syndrome) → MB-SHH, TP53-wildtype
  - Median age: 6 years
- Germline *TP53* (Li Fraumeni syndrome) → MB-SHH, TP53-mutant
  - Median age: 9 years
- Germline *PALB2, BRCA2* → MB-SHH, MB-group3, MB-group4
  - Usually childhood, but can be infancy through adulthood

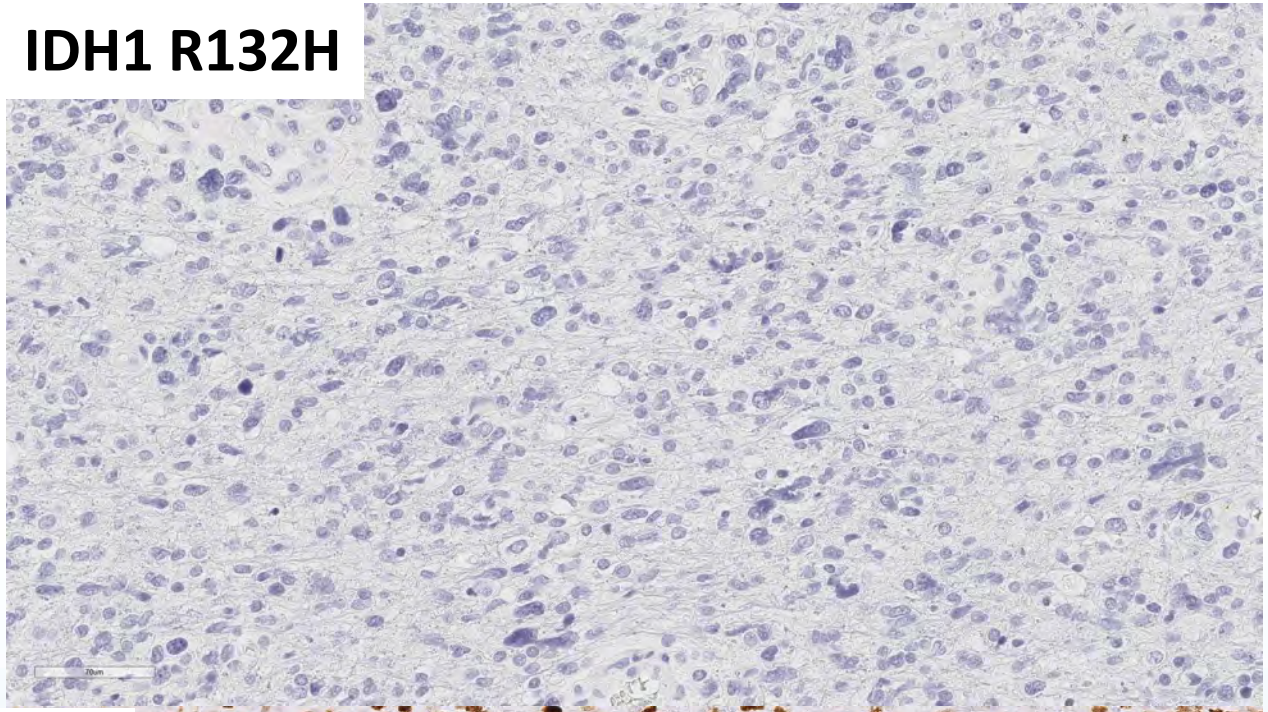
AANP

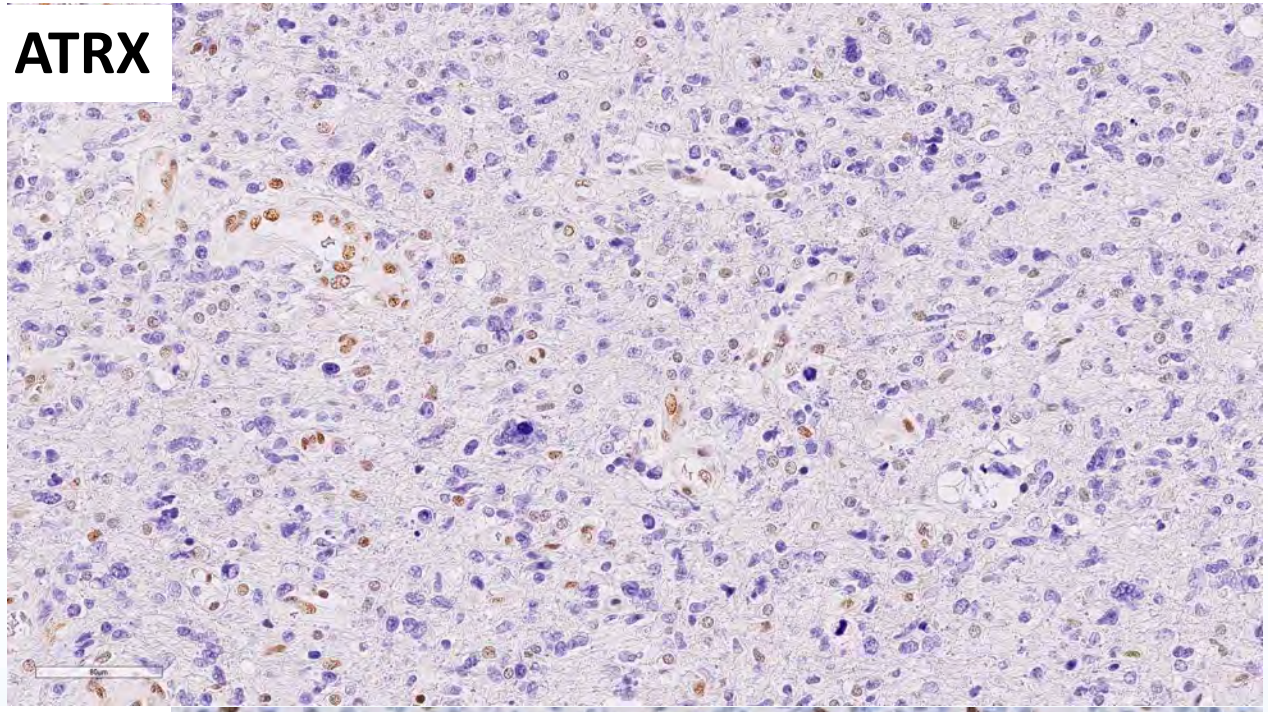
Case 13: 42-year-old woman presented with loss of consciousness and MRI a large, necrotic, peripherally enhancing mass

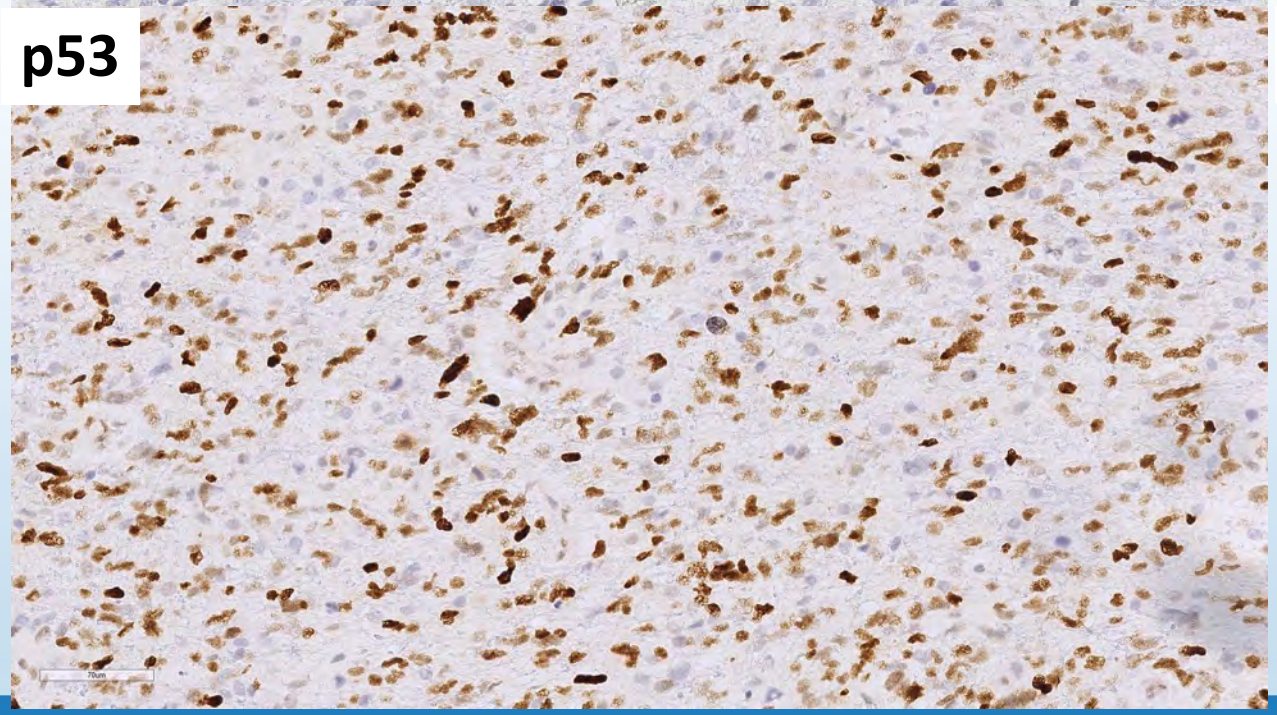


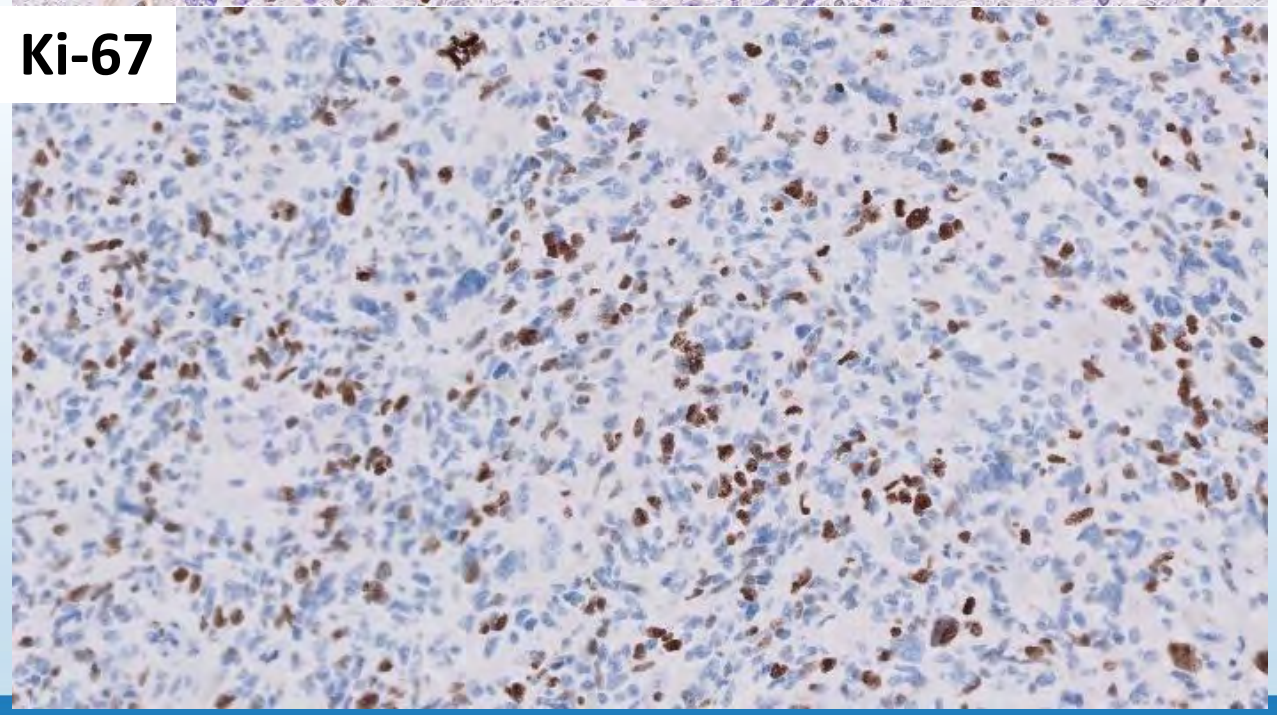


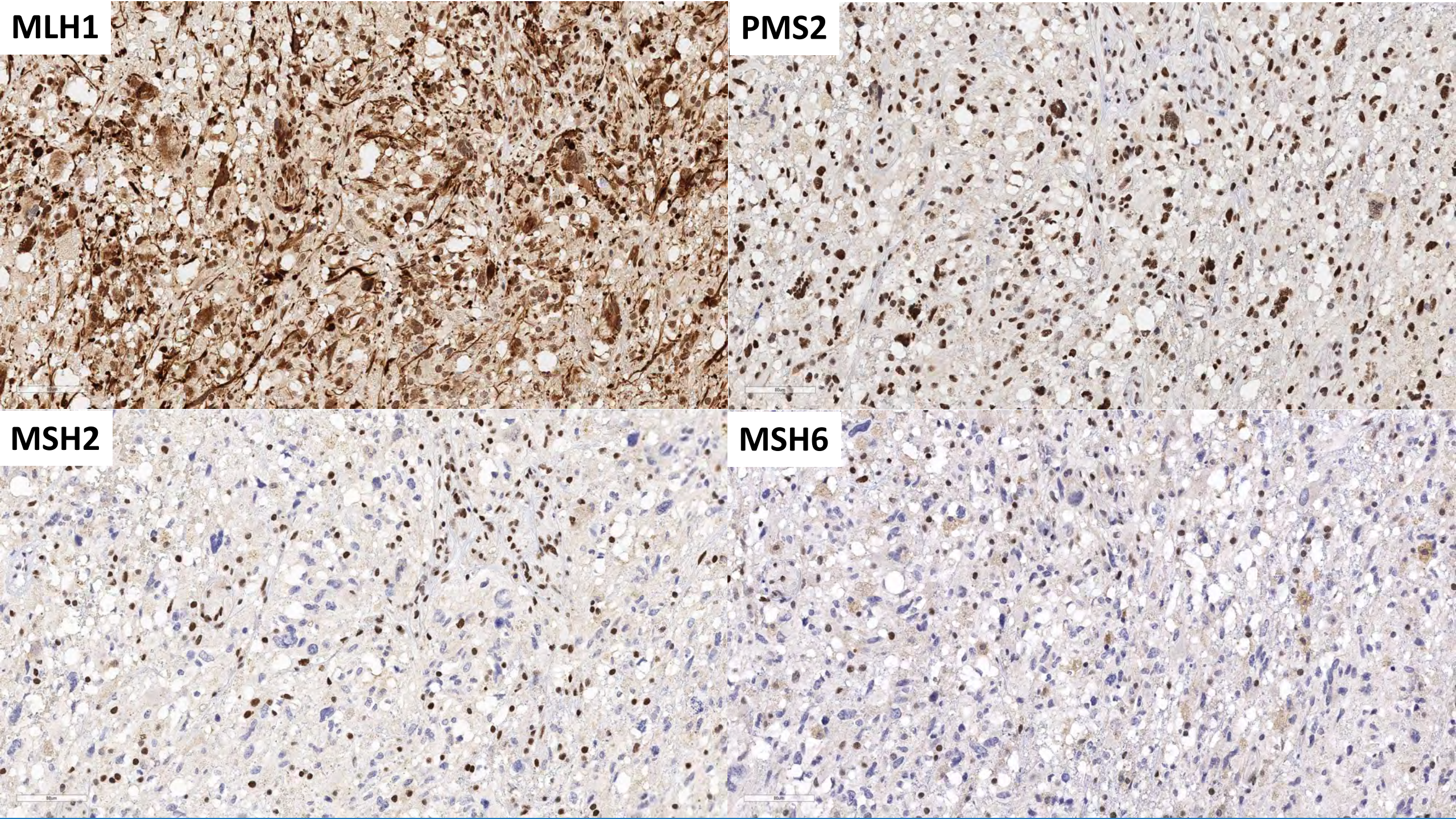



IDH1 R132H


ATRX


p53


Ki-67


MLH1
PMS2
MSH2
MSH6

Case 13: 42-year-old woman presented with loss of consciousness and MRI a large, necrotic, peripherally enhancing mass

SELECTED SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
MSH2 p.N596del homozygosity resulting from germline mutation accompanied by somatic copy-neutral loss of heterozygosity of chromosome 2	NM_000251	Pathogenic	525	82%
ATRX p.K993fs	NM_000489	Pathogenic	1031	28%
NF1 p.G629R	NM_001042492	Pathogenic	366	29%
NF1 p.R1968*	NM_001042492	Pathogenic	831	35%
PIK3CA p.R88Q	NM_006218	Pathogenic	1036	33%
PTEN p.R335*	NM_000314	Pathogenic	418	20%
RB1 p.A628fs	NM_000321	Pathogenic	719	3%
SETD2 p.R1407fs	NM_014159	Pathogenic	1091	19%
TP53 p.H214R	NM_000546	Pathogenic	799	33%
TP53 p.R175H	NM_000546	Pathogenic	521	32%
Trisomy 7, Monosomy 10q	N/A	Pathogenic	N/A	N/A
*More than 50 non-synonymous somatic mutations are present. See interpretation and see appendix for list of additional variants.				

'Reads' indicate the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal.

Pathogenic or Likely Pathogenic GERMLINE ALTERATIONS*				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
MSH2 c.1786_1788delAAT, p.N596del	NM_000251	Pathogenic	595/525	51%/82%

Lynch Syndrome

- Autosomal dominant (incomplete penetrance)
- DNA mismatch repair genes – *MLH1, MSH2, MSH6* and *PMS2*
- Colorectal, endometrium, stomach, small bowel, hepatobiliary tract, pancreas, urothelial, ovary and prostate…
- Risk of malignancy *MSH2>MLH1>MSH6>PMS2*
- De novo replication repair deficient Glioblastoma, IDH-wildtype
- Poor prognosis, decreased response to standard GBM tx
- Potential role of immune check point inhibitors

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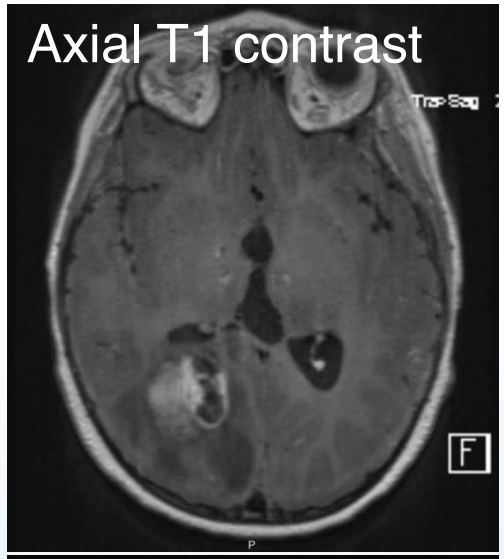
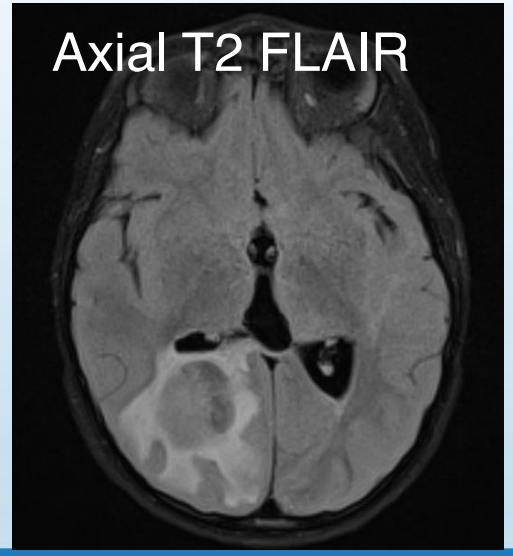
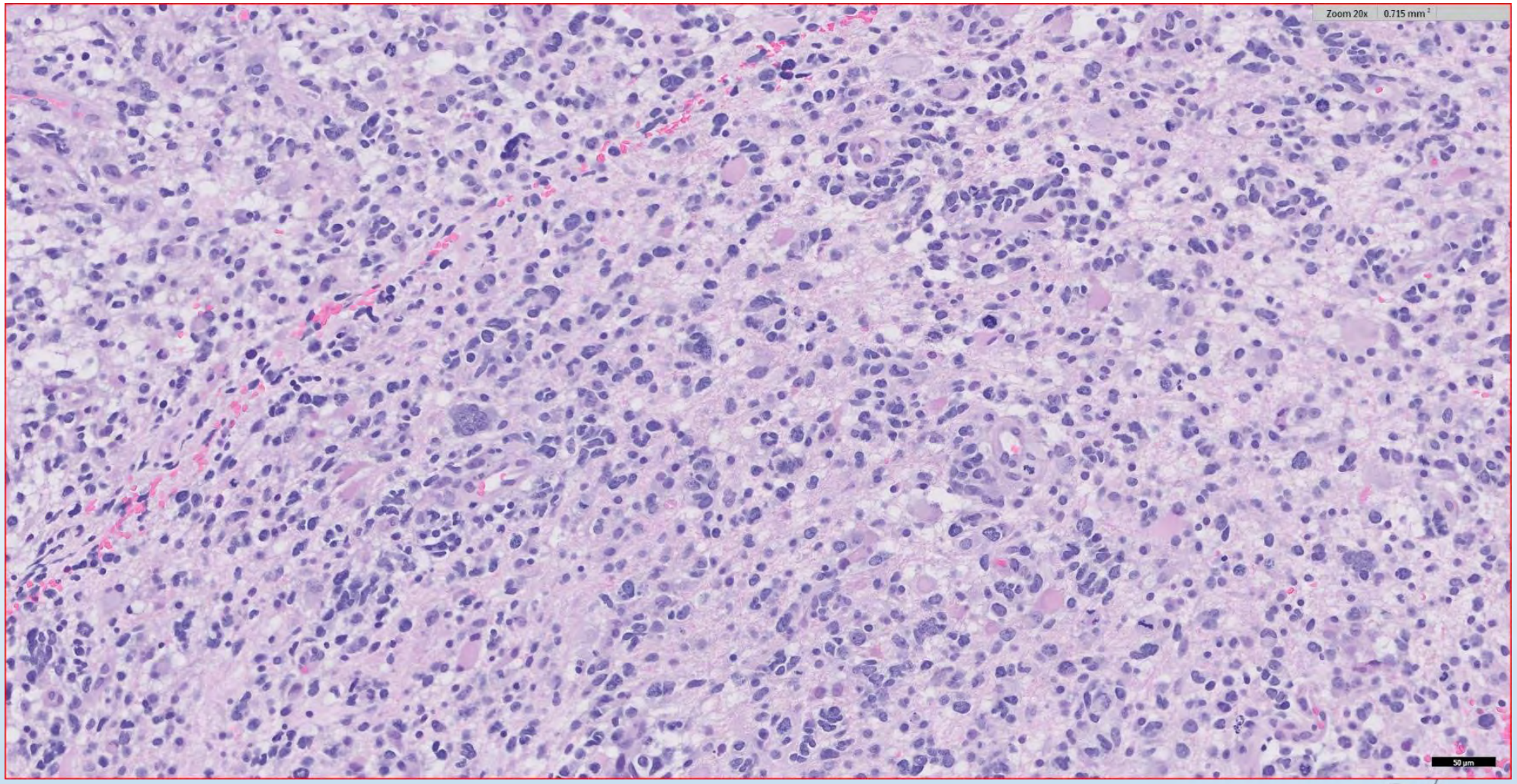
• Medulloblastoma, WNT-activated (*CTNNB1*-wildtype)	Familial adenomatous polyposis
• Giant cell-rich HGG in a young adult, often IDH-wildtype* (*PPMRDIA)	Lynch syndrome

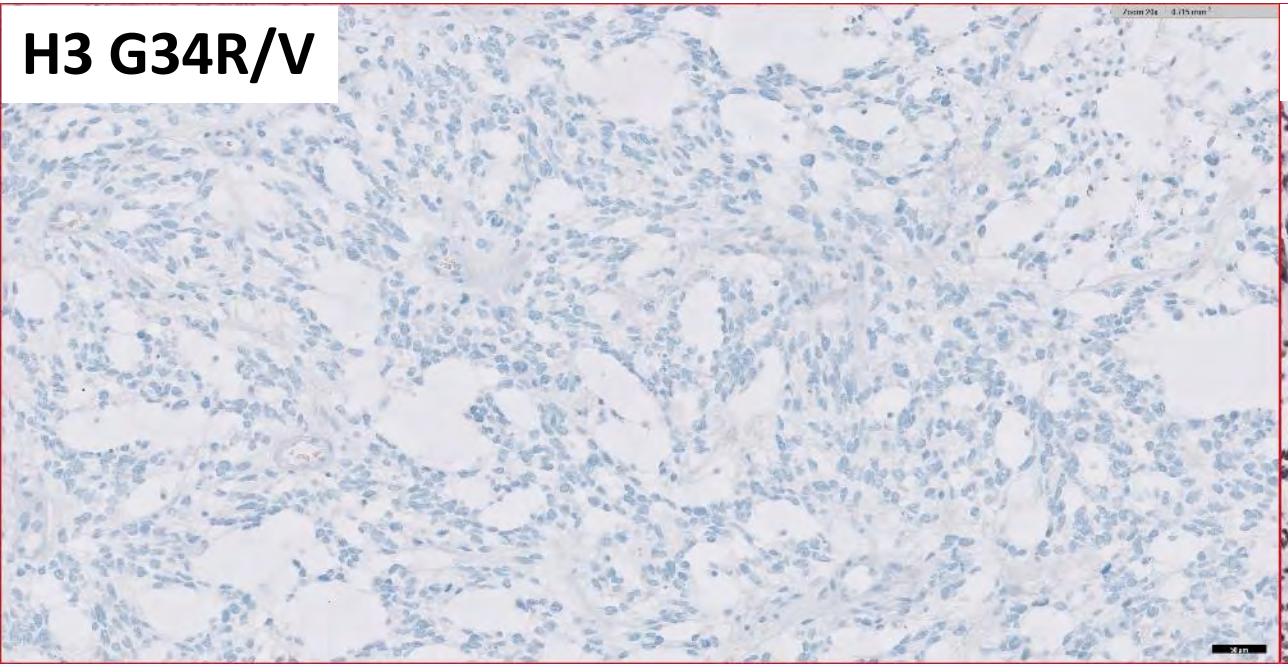
Case 14: 5-year-old boy presented with a left eye deviation and blurry vision and MR imaging showed a right parietal lobe mass

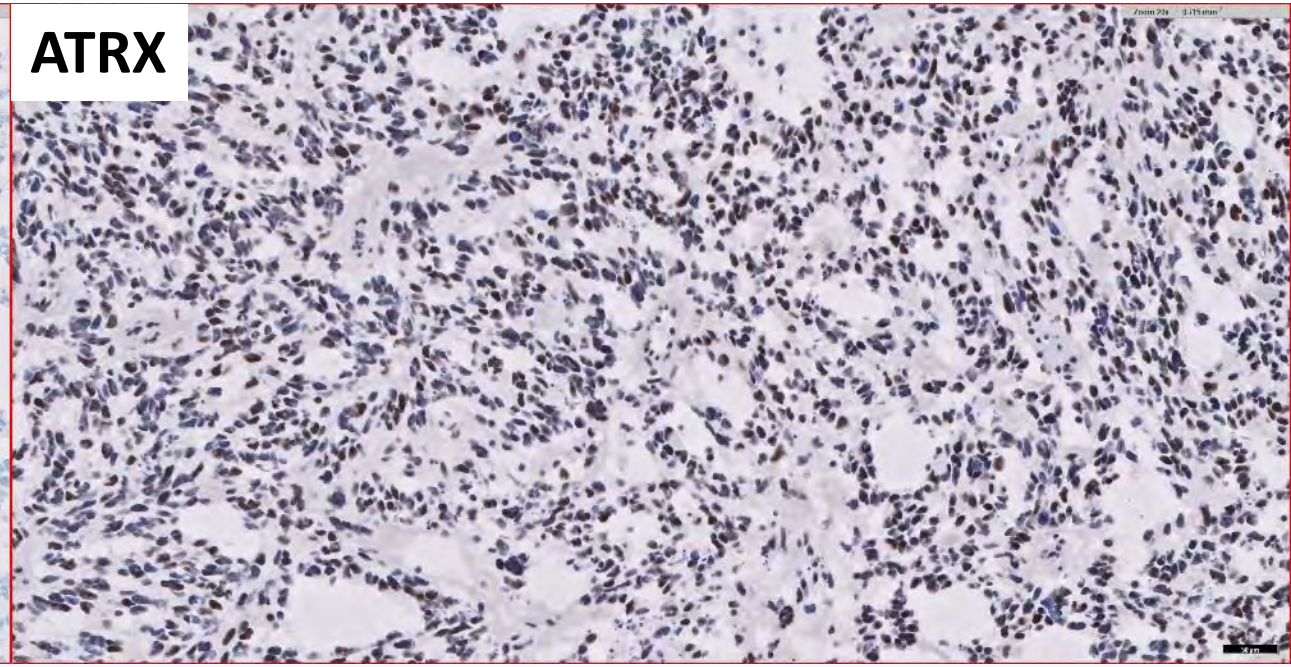


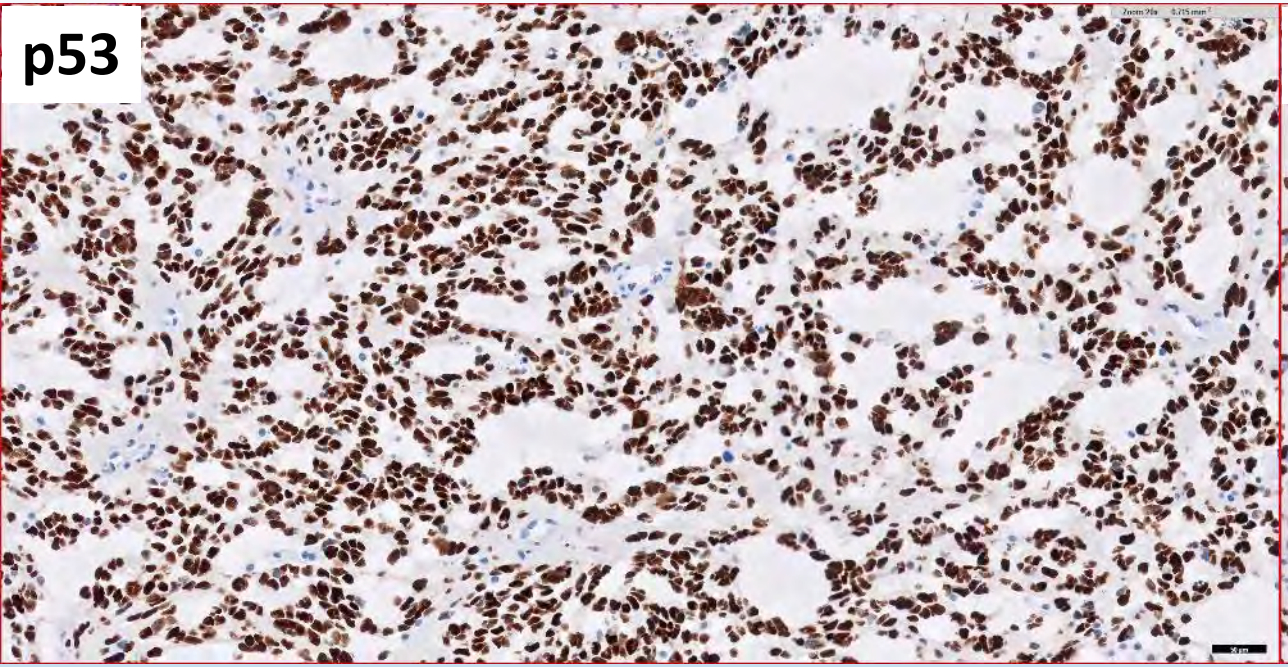


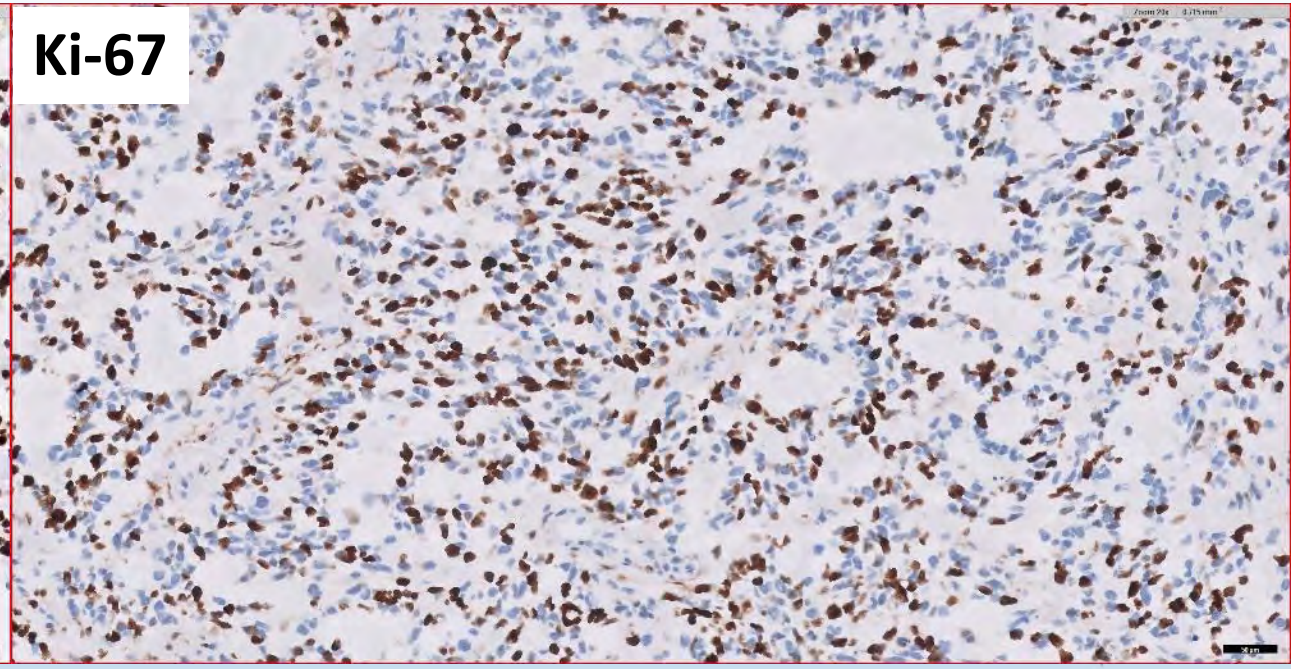


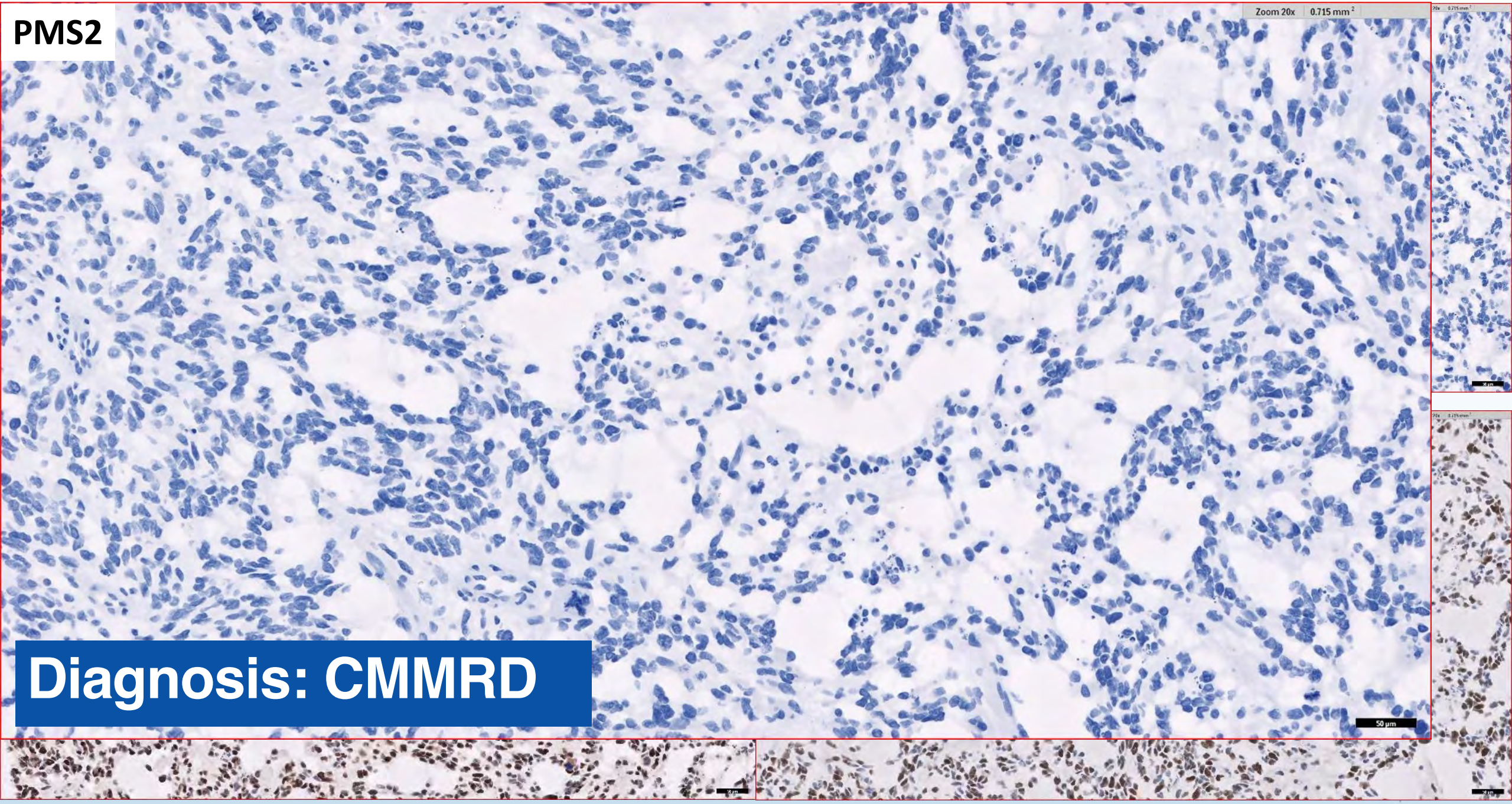
Case 14: 5-year-old boy presented with a left eye deviation and blurry vision and MR imaging showed a right parietal lobe mass


H3 G34R/V


ATRX


p53


Ki-67


PMS2
Zoom 20x
0.715 mm ²
50 µm
Diagnosis: CMMRD

Case 14: 5-year-old boy presented with a left eye deviation and blurry vision and MR imaging showed a right parietal lobe mass

SELECTED PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
Extremely high somatic mutation burden ("ultrahypermutation"), with a predominance of C>T transitions, corresponding with Mutational Signature 6 associated with defective mismatch repair		Pathogenic	N/A	N/A
ATM c.902-1G>T	NM_000051.3	Pathogenic	247	43%
PMS2 p.I611fs	NM_000535.5	Pathogenic	686	47%
PMS2 p.R211*	NM_000535.5	Pathogenic	603	40%
SMARCA4 p.R1243W	NM_001128849.1	Pathogenic	806	45%
TP53 p.R306*	NM_000546.5	Pathogenic	988	29%
TP53 p.R273C	NM_000546.5	Pathogenic	943	44%
TP53 p.P152L	NM_000546.5	Pathogenic	1052	43%
*Numerous pathogenic and likely pathogenic mutations are present. See interpretation and see appendix for list of additional variants.				

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

14 of 85 tested microsatellites (16.47%) were found to be unstable. This is interpreted as Microsatellite Stable (MSS).

Assessment of microsatellite instability (MSI) by percentage of unstable sites:
<20%: MSI absent (MSS) | 20-30%: MSI equivocal | >30%: MSI present (MSI-High)

UCSF500 tumor mutation burden: 279.9 mutations/Mb

Constitutional mismatch repair deficiency (CMMRD)

- Autosomal recessive
- Constitutional **biallelic** variants in ***PMS2,*** *MSH6, MLH1, MSH2*
- Ultrahypermutated (>100 mutations/Mb)
- Mismatch repair–deficient cells resistant to temozolomide
- May respond to immune check point inhibitors (High TMB)

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• Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos Disease)	PTEN hamartoma Syndrome (Cowden Syndrome)
• BAP1-mutant melanoma in a young patient • Rhabdoid and/or papillary meningioma	*BAP1* tumor predisposition syndrome
• Rhabdoid tumors, including AT/RT	Rhabdoid tumor predisposition syndrome
• *CDKN2A*-altered astrocytoma	Melanoma-astrocytoma Syndr
• SDH-deficient paraganglioma	Familial paraganglioma Syndr

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• IDH- and H3-wildtype HGG in a young child	Constitutional mismatch repair deficiency (CMMRD)

Take home points

- Numerous hereditary tumor syndromes have CNS and/or PNS involvement
- Sometimes these tumors might be the first/early presentation
- Neuropathologists should be aware of the (near) pathognomonic tumor-syndrome associations
- Neuropathologists should be aware of the morphologic clues for a syndrome association in other, less pathognomonic tumors
- Further clinical workup, germline testing, and/or referral to a genetic counselor should be recommended in such cases