AANP Diagnostic Slide Session Case 8

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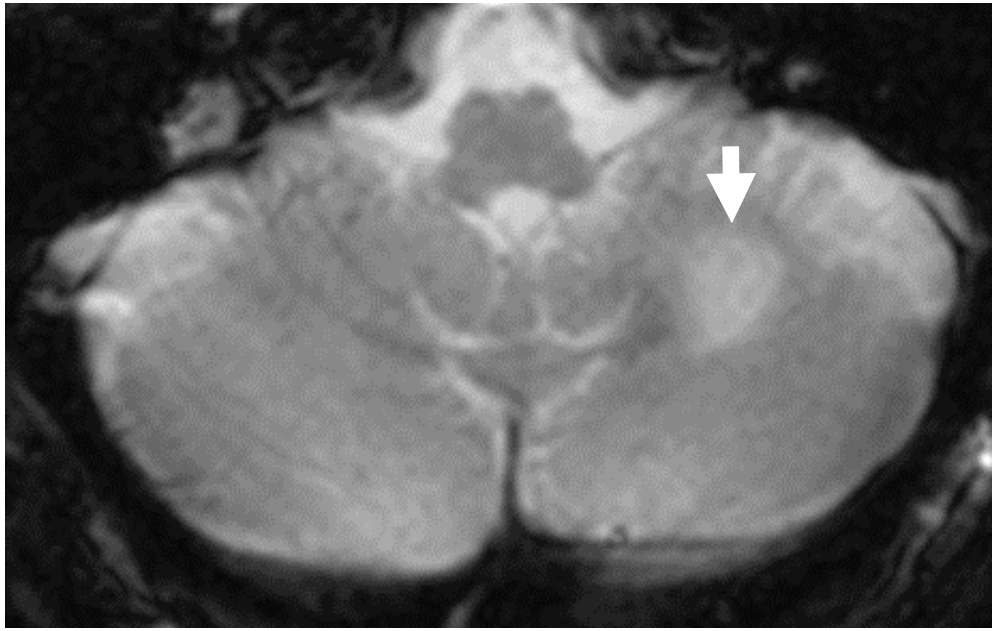
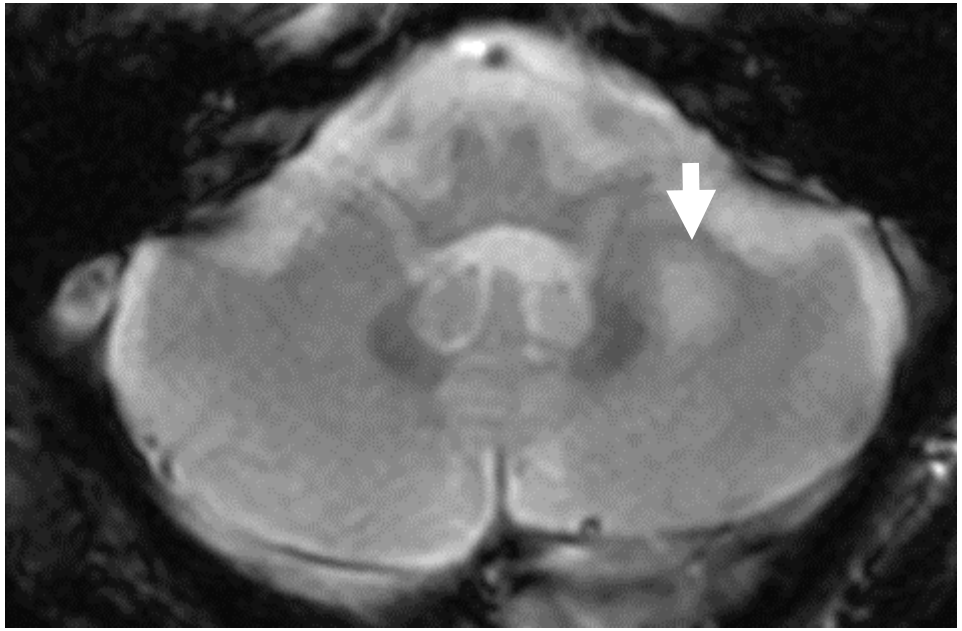
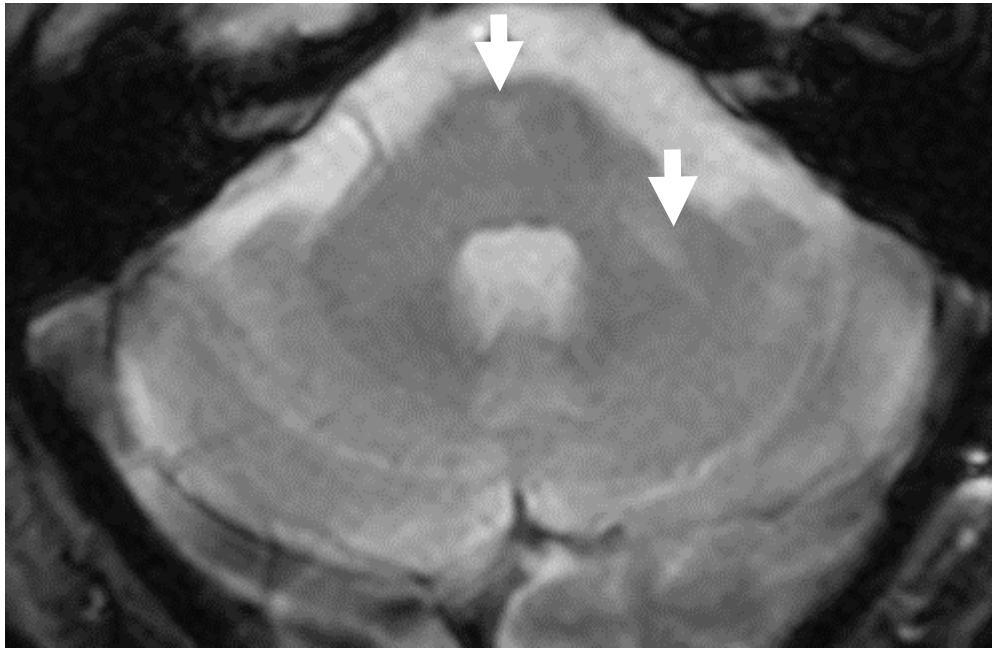
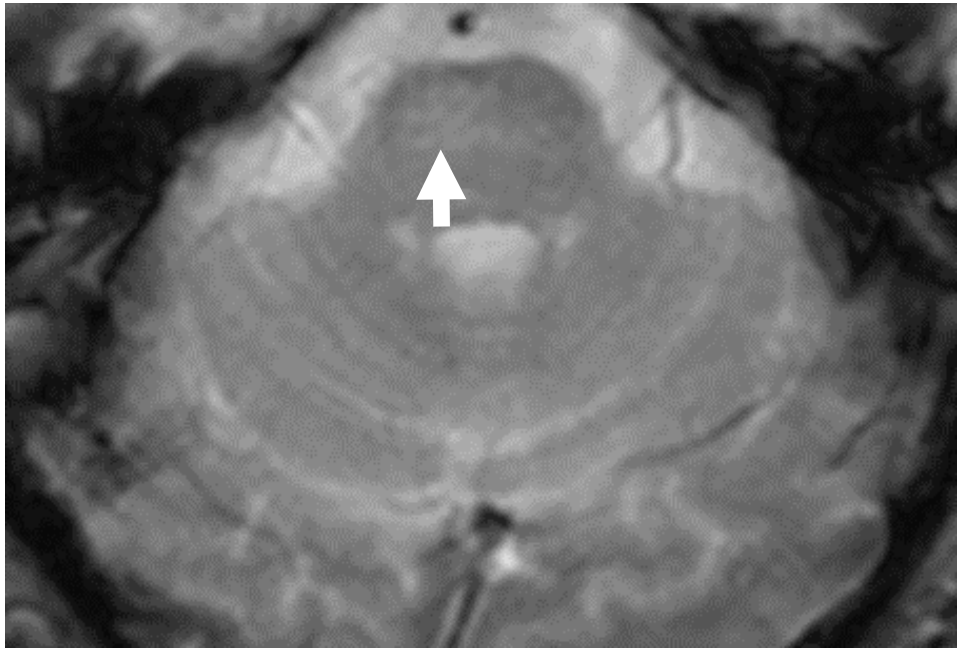
Clinical history

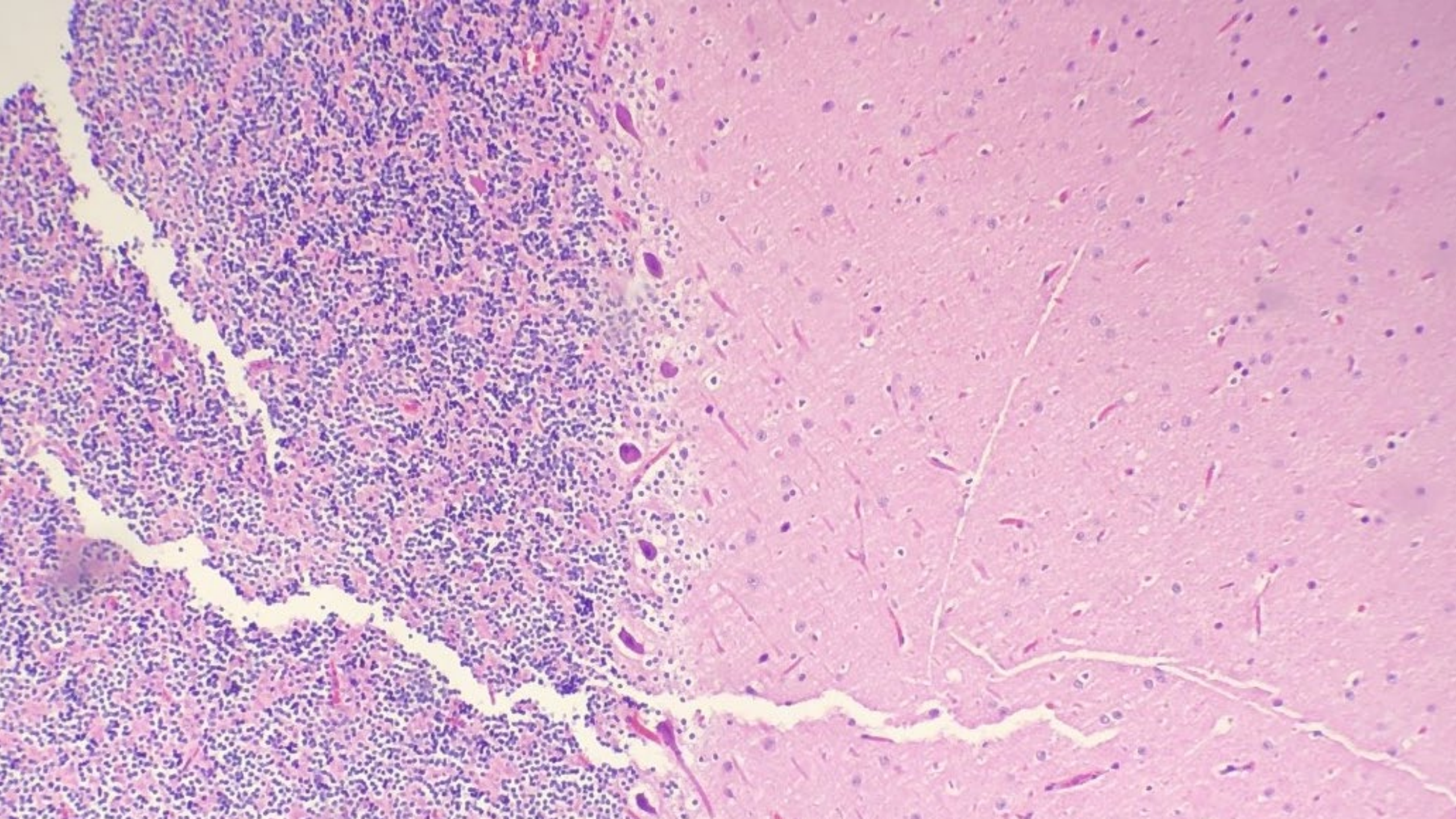
- 58-year-old man with a four-year history of bilateral essential tremor, right hand greater than left, for which thalamic deep brain stimulators were placed. Subsequent MR imaging noted a 0.6 cm, non-enhancing, T2-hyperintense lesion in the left cerebellar hemisphere.
- MRI surveillance of the lesion documented a tripling in size. MRI report stated: "…contiguous involvement of the left middle cerebellar peduncle and brainstem, including the pons, extending across the midline."
- Concomitant with the lesion growth, the patient's tremors returned and became refractory to DBS.
- Patient was referred to neurosurgery for biopsy of left cerebellar mass.

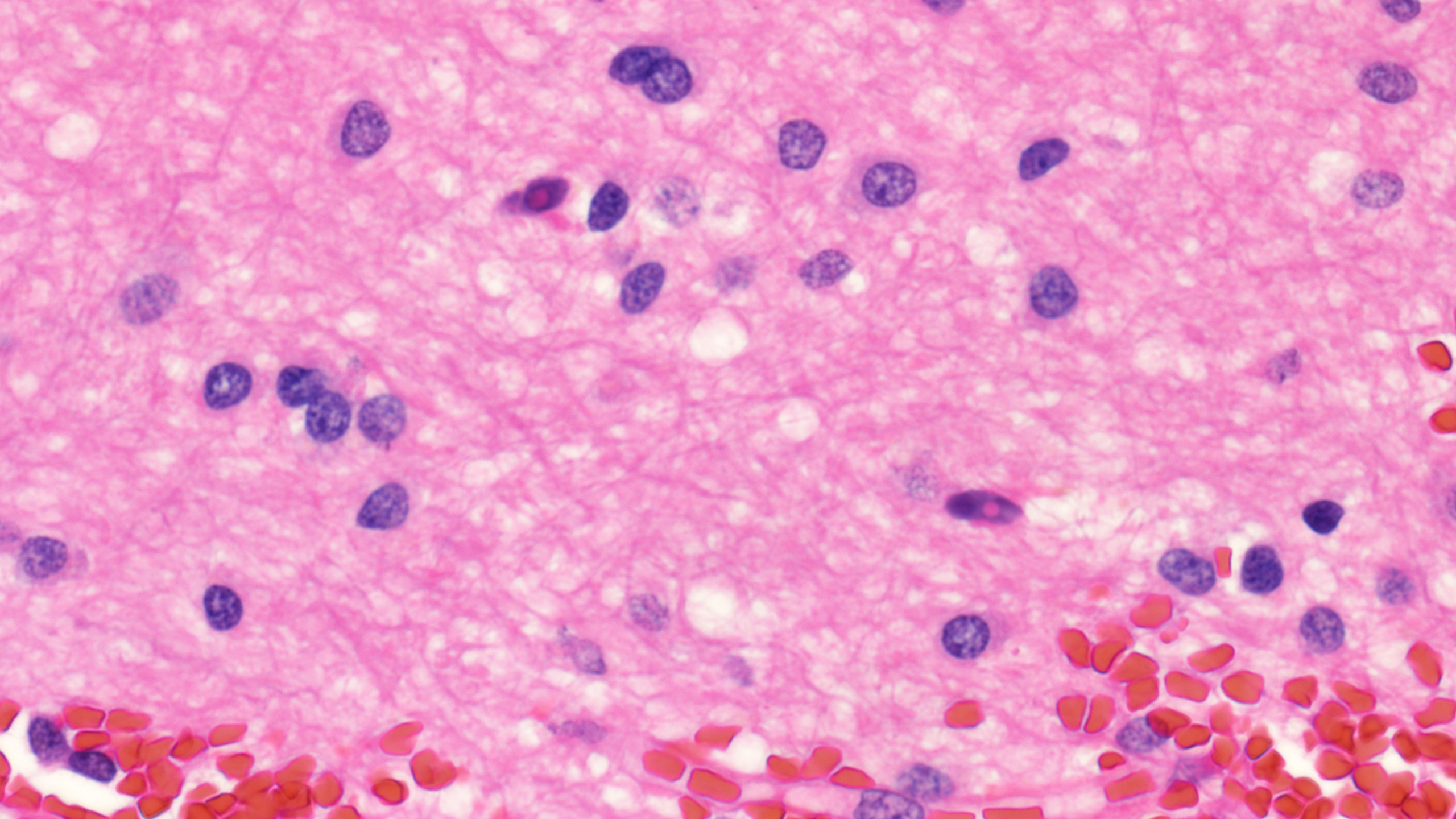


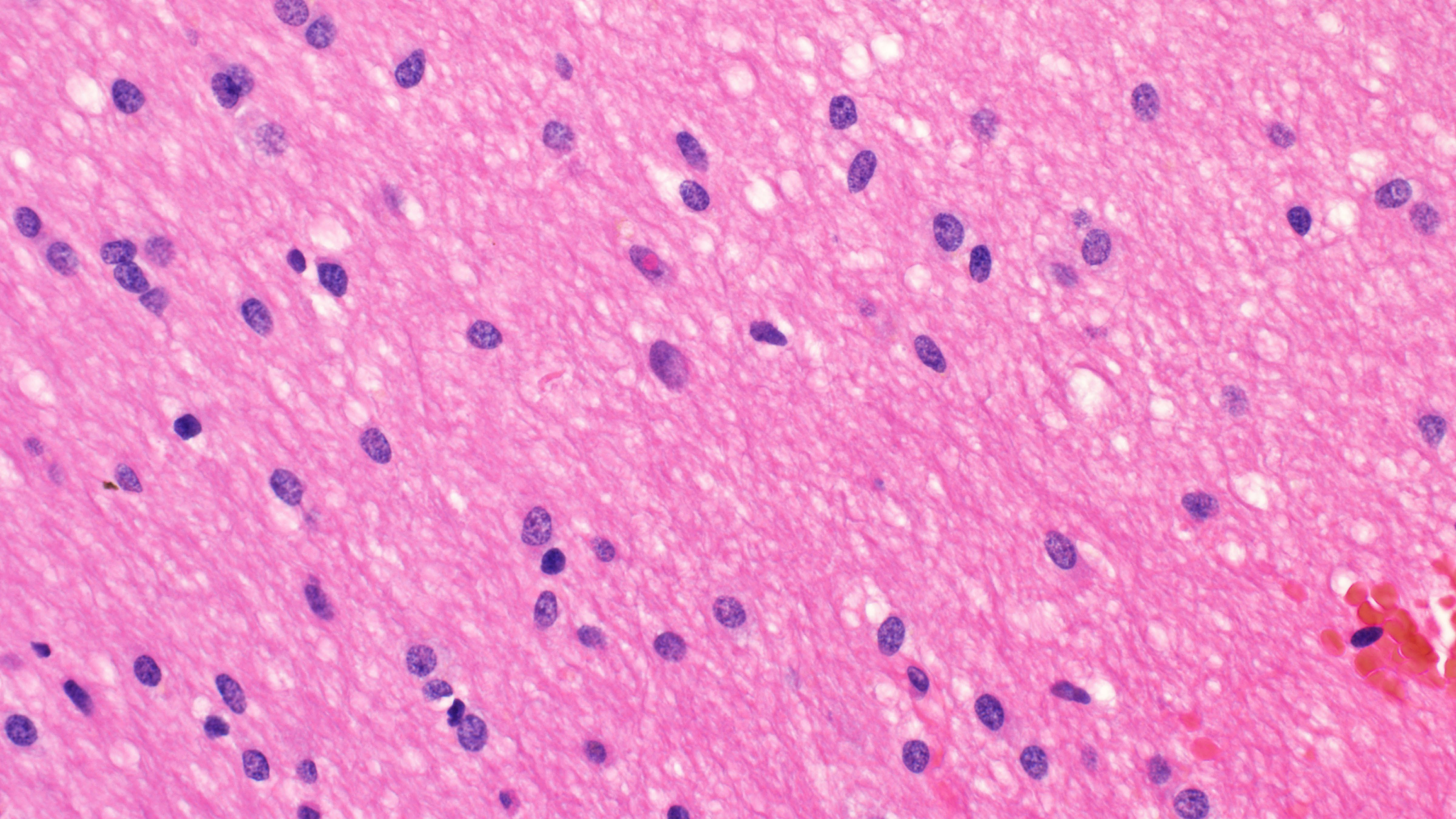


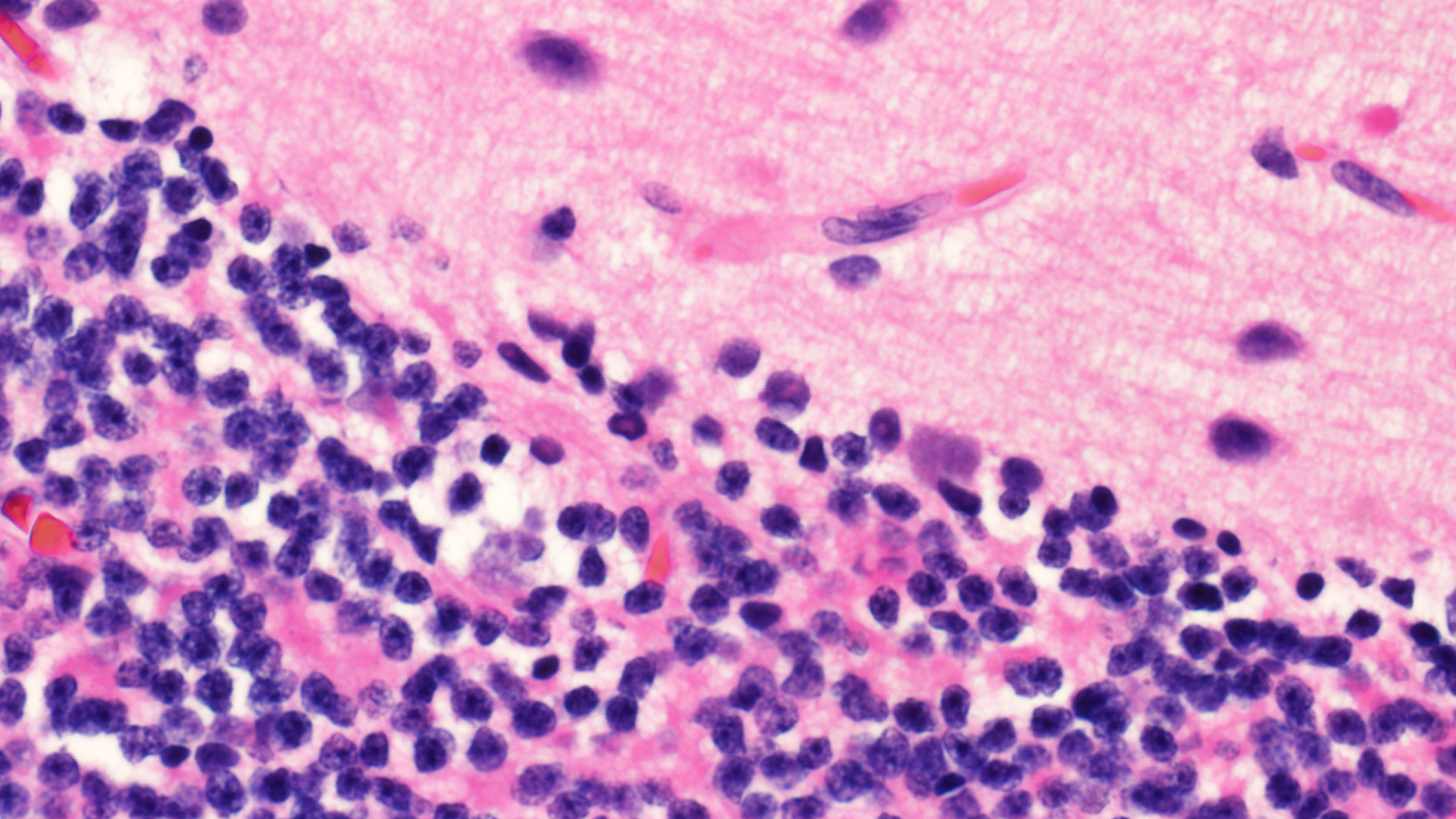


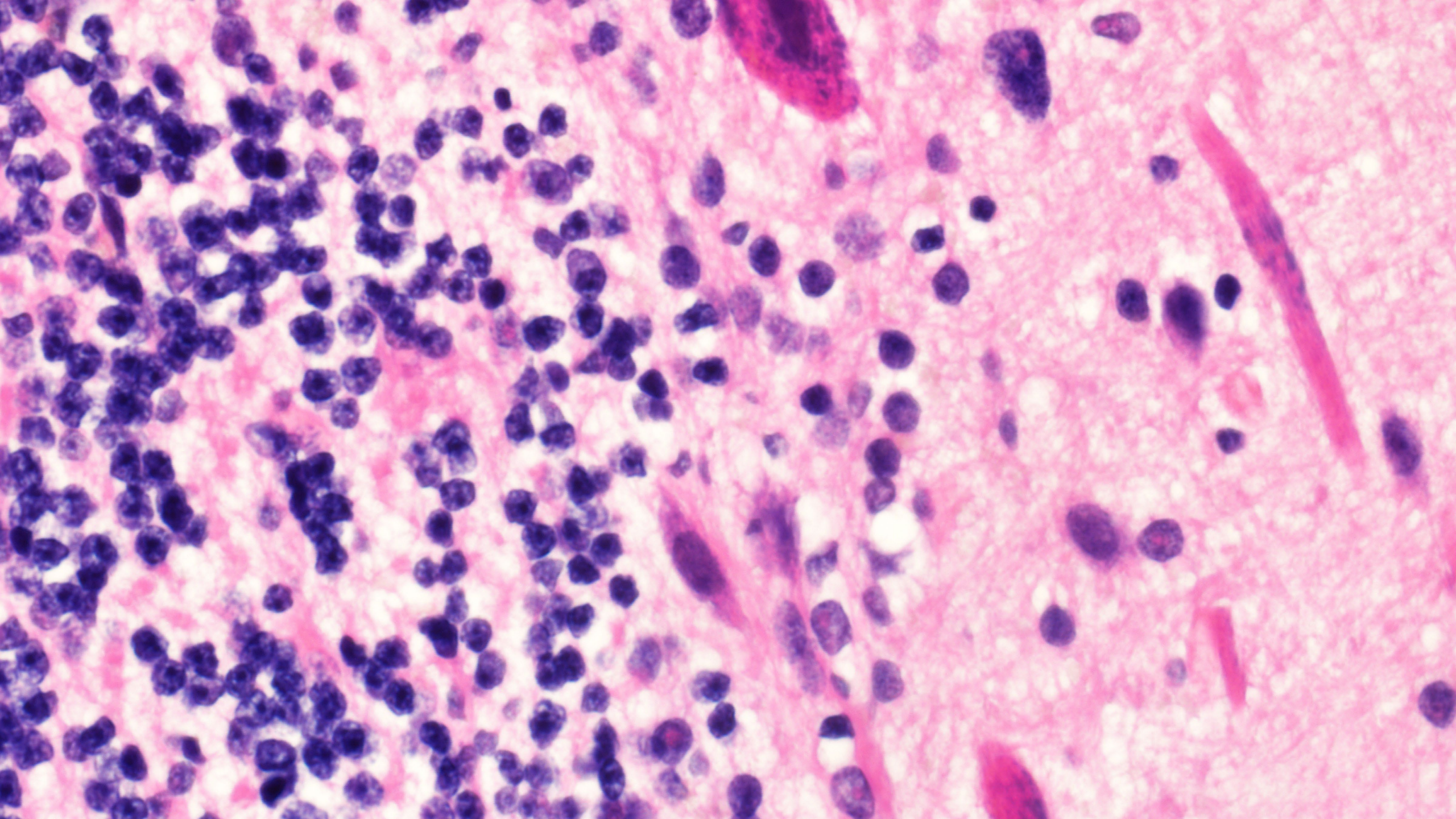


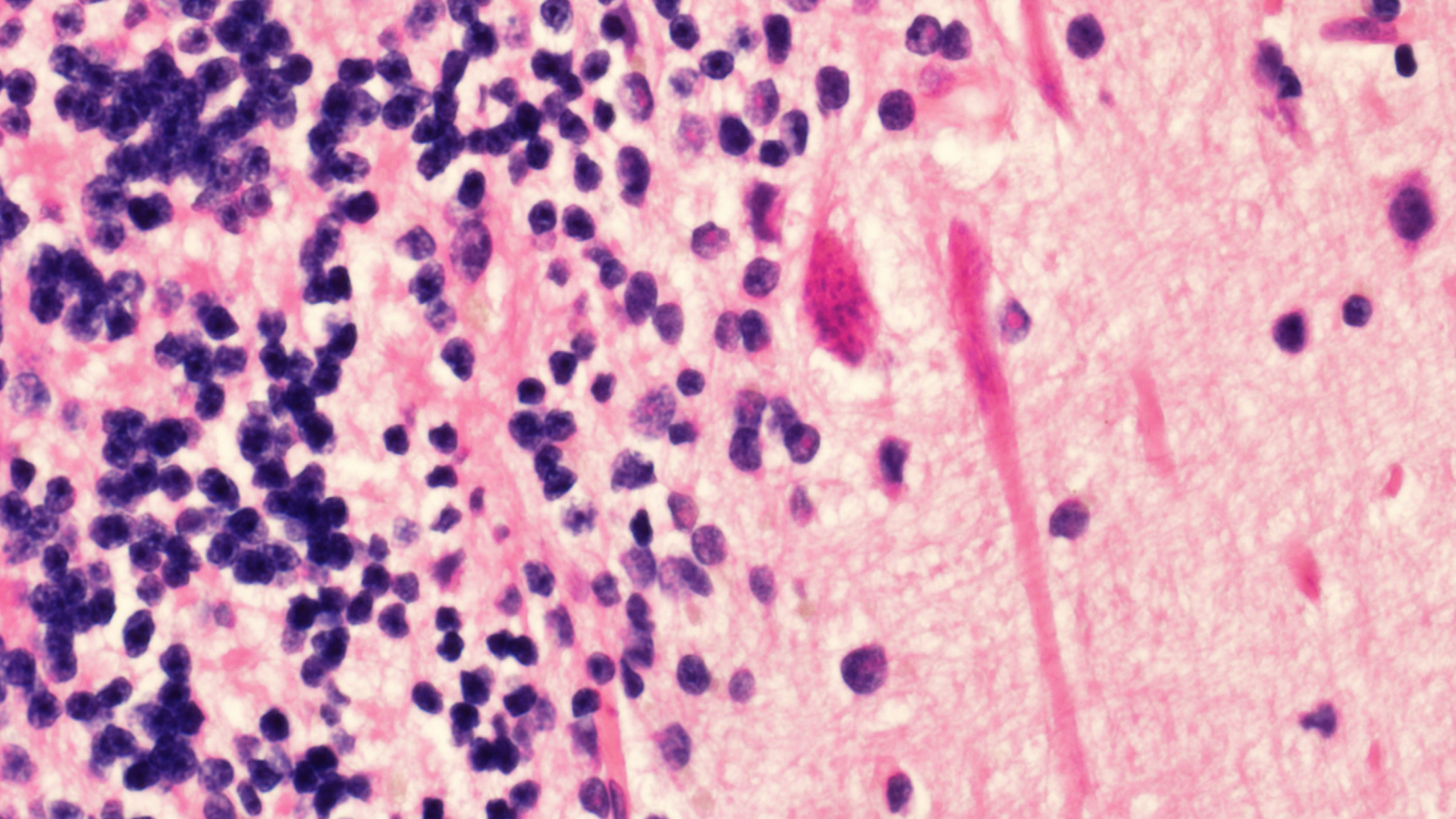






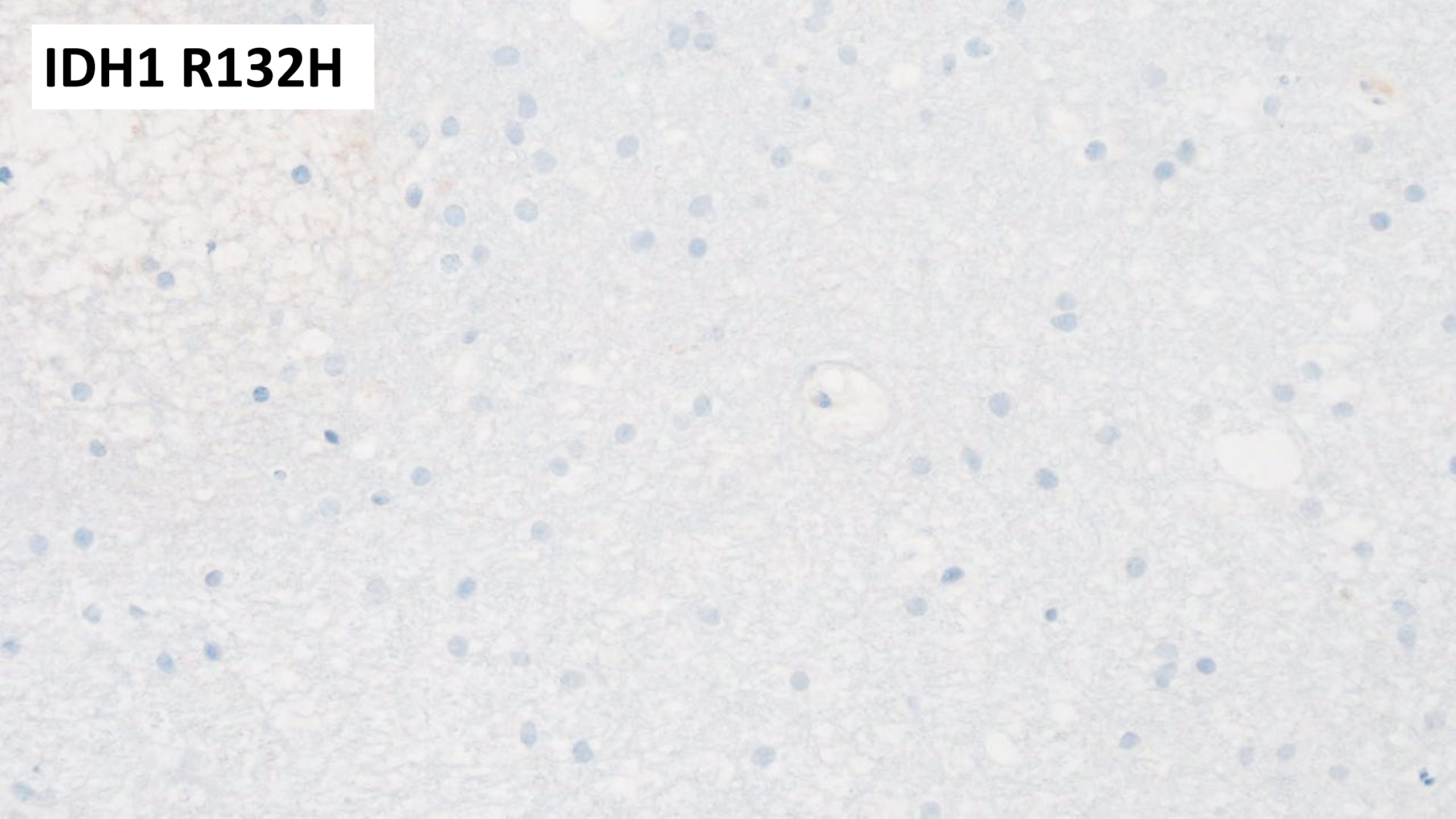






Discussion

- Differential diagnosis
- Ancillary studies?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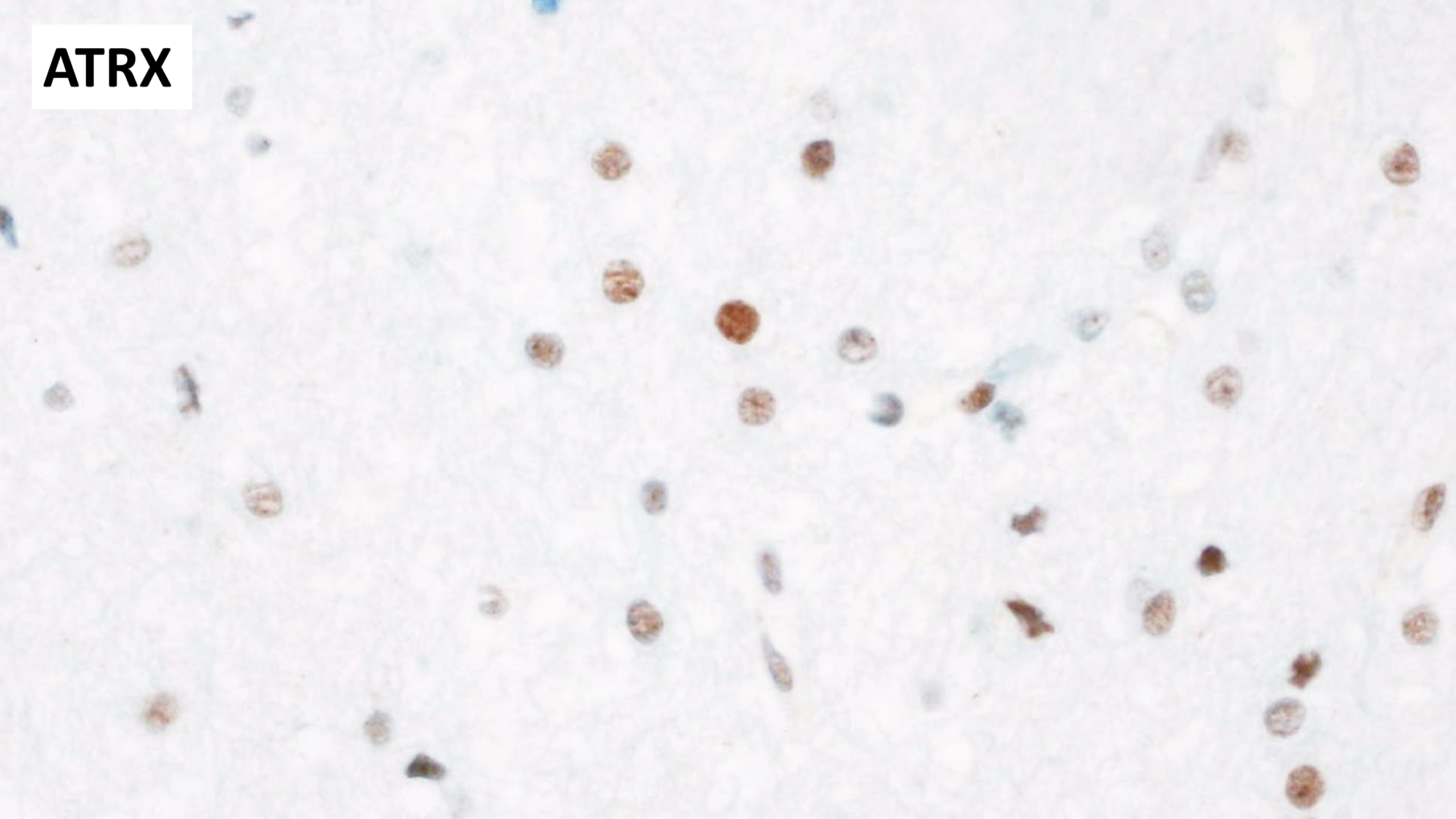
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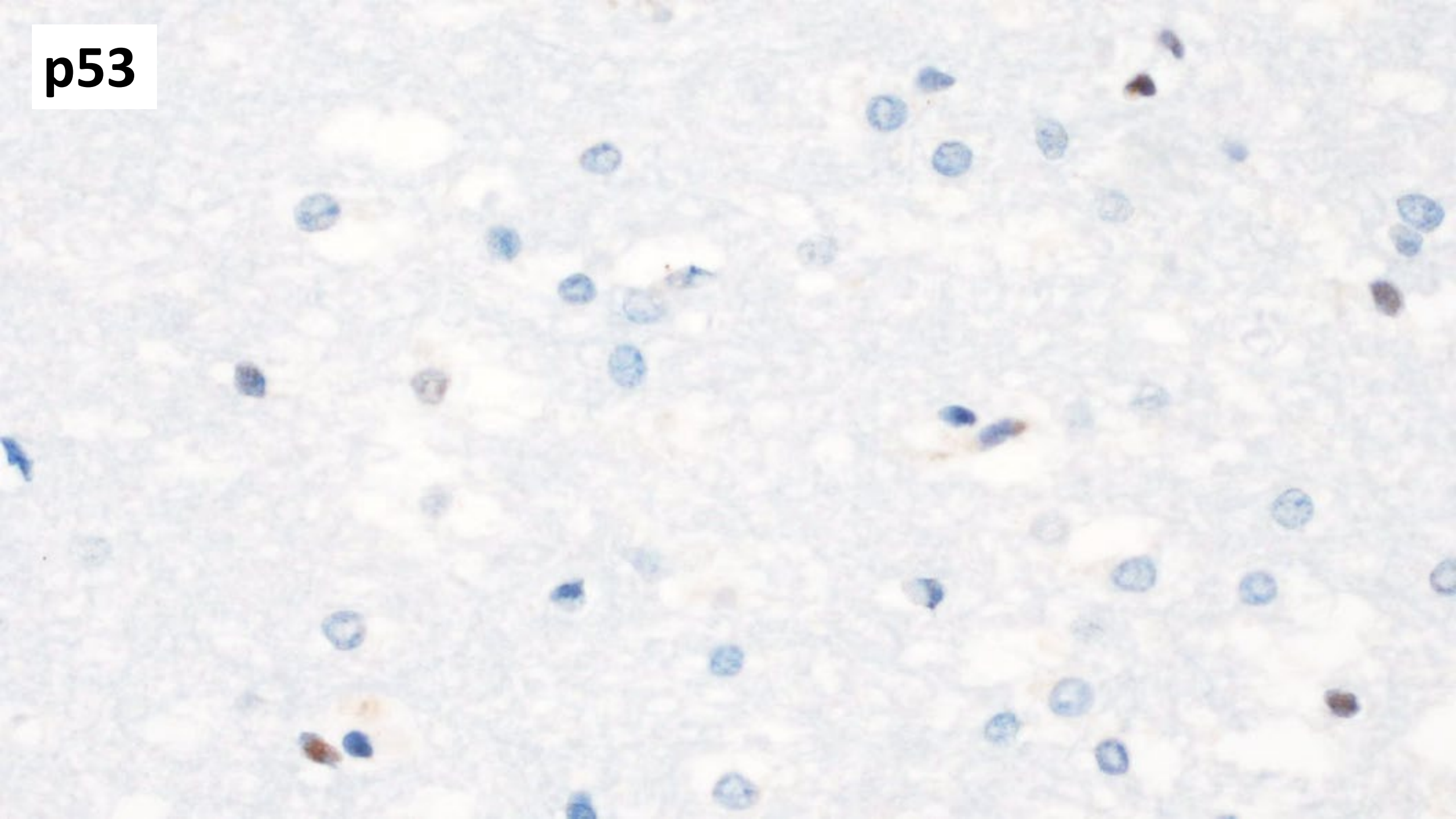
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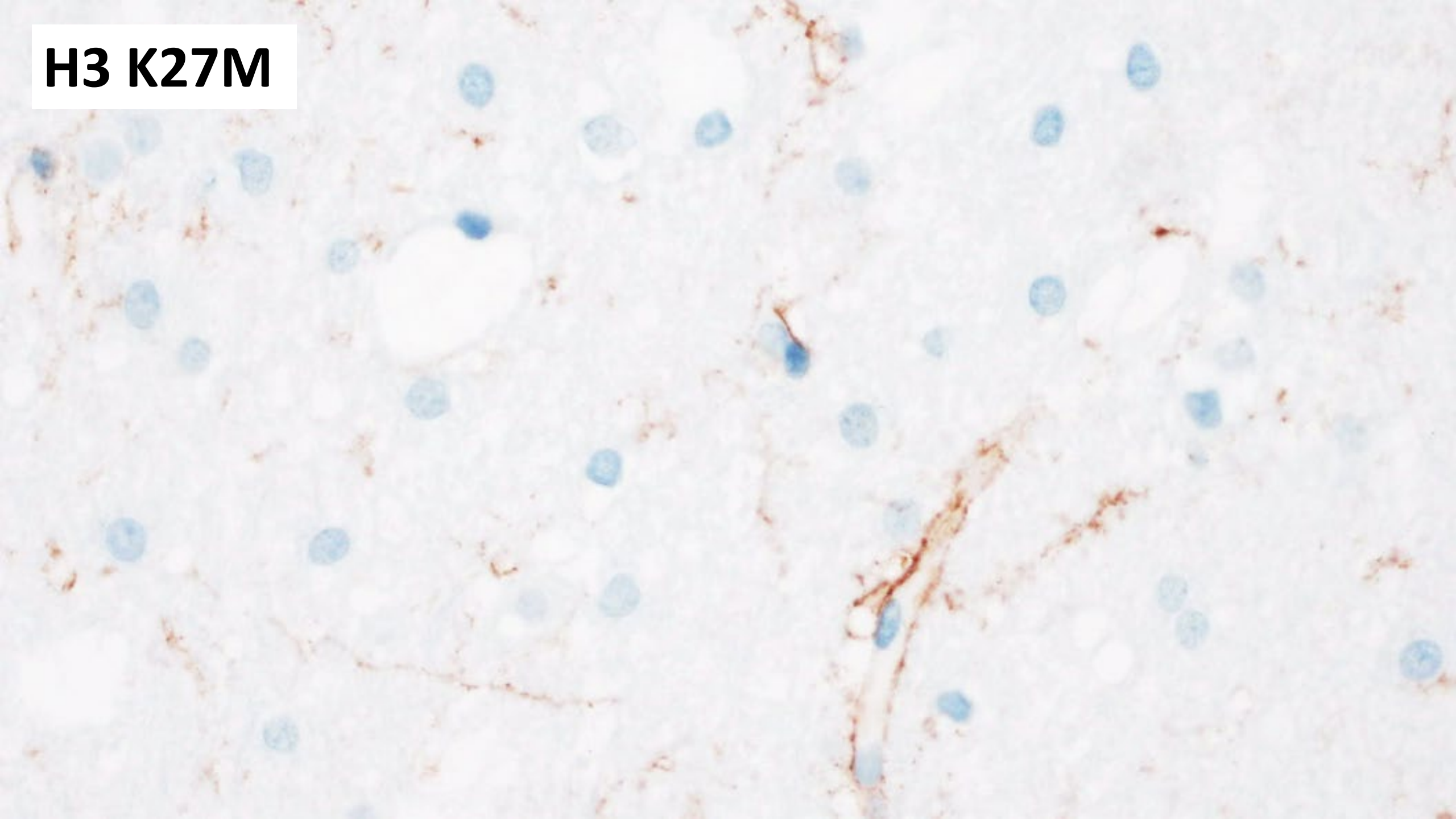
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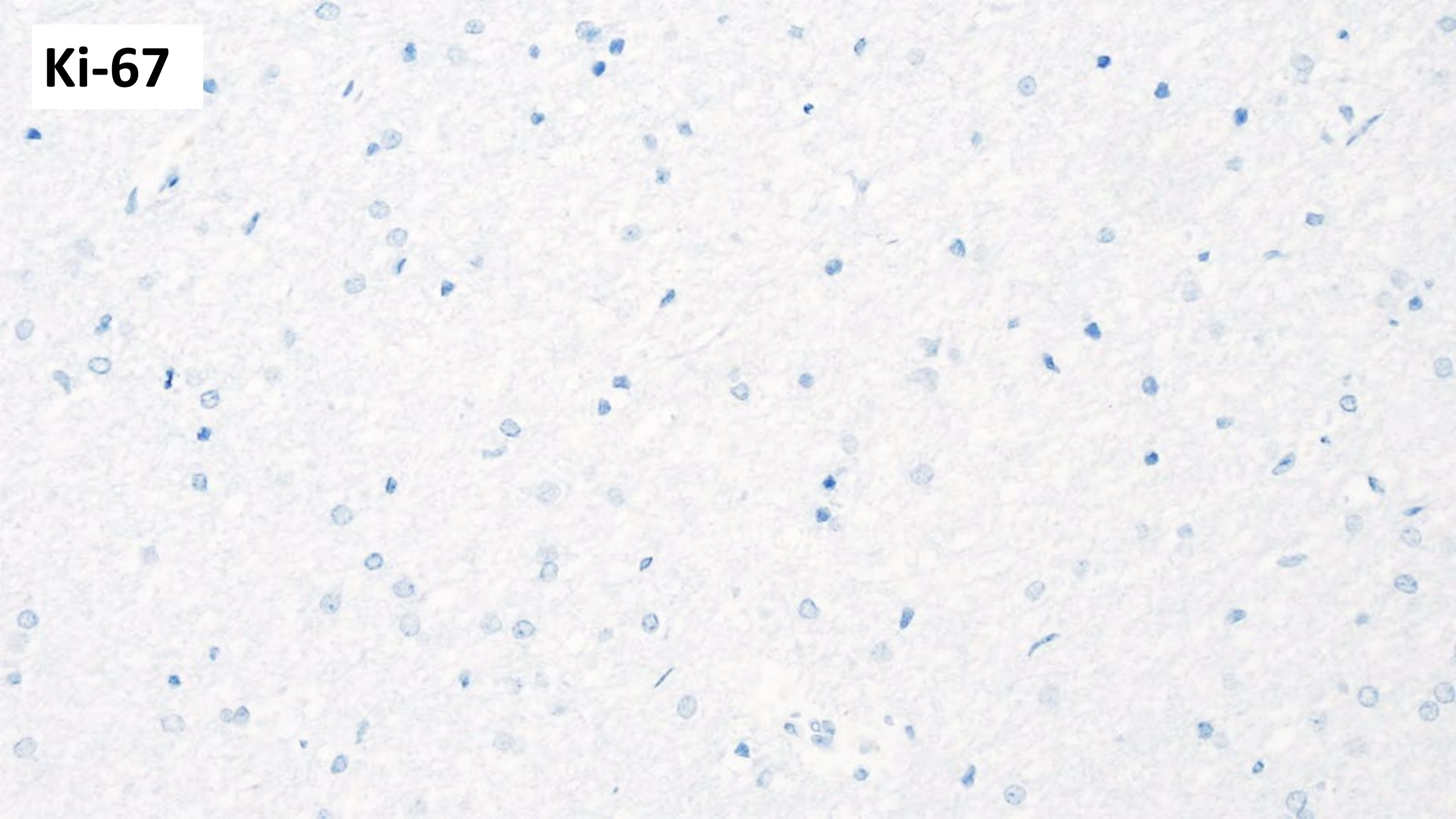
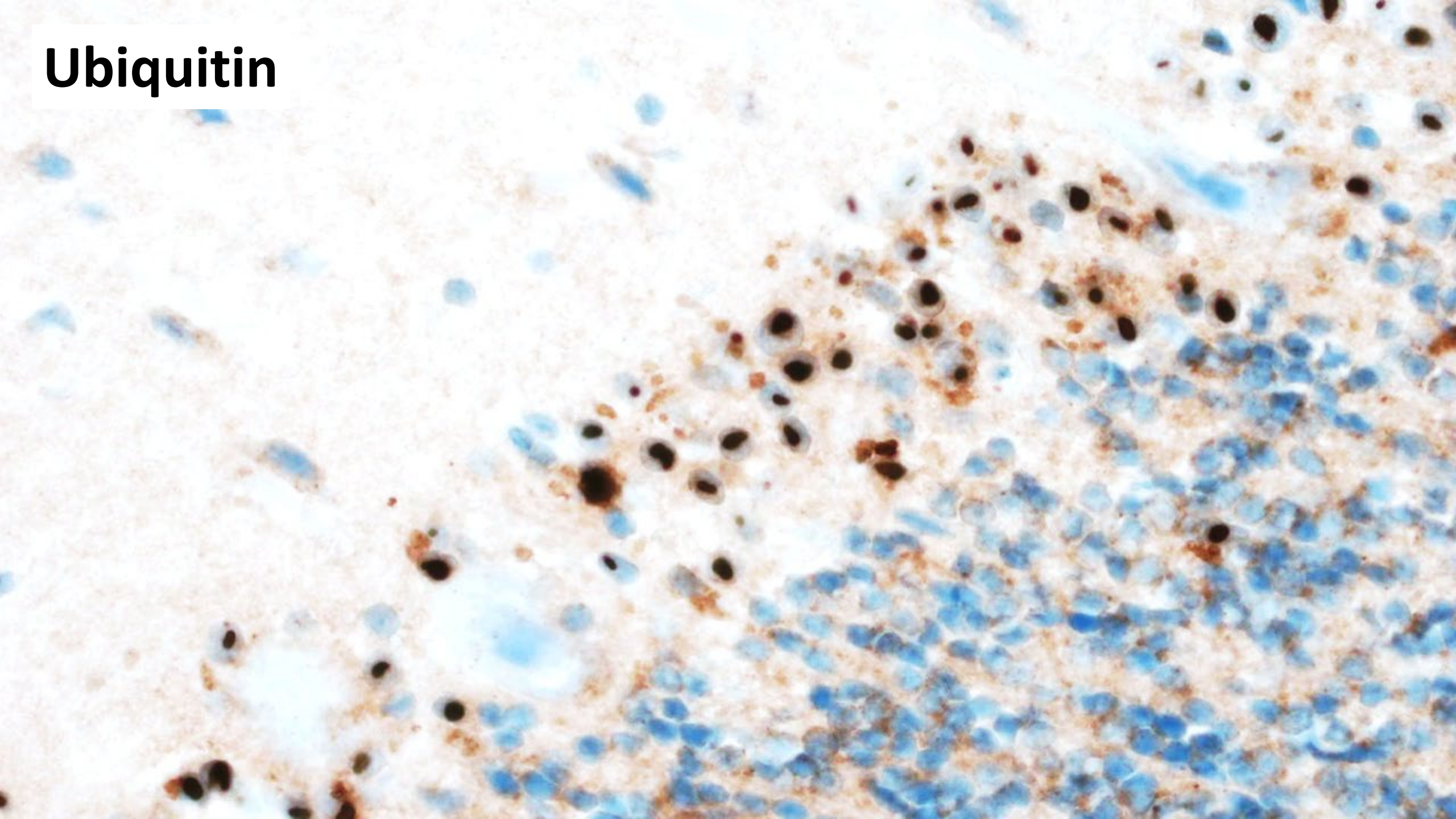
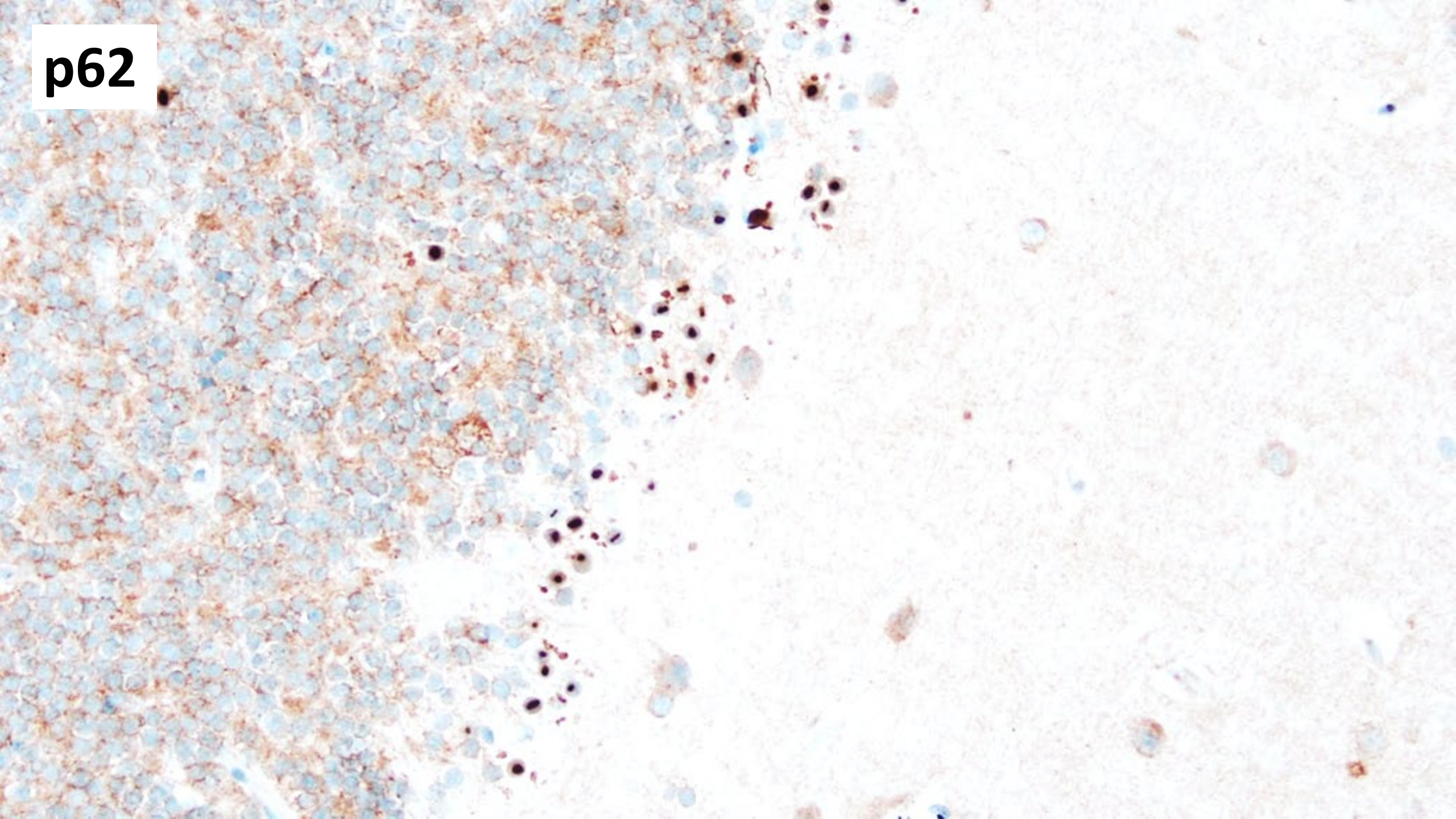

Ki-67

Ubiquitin

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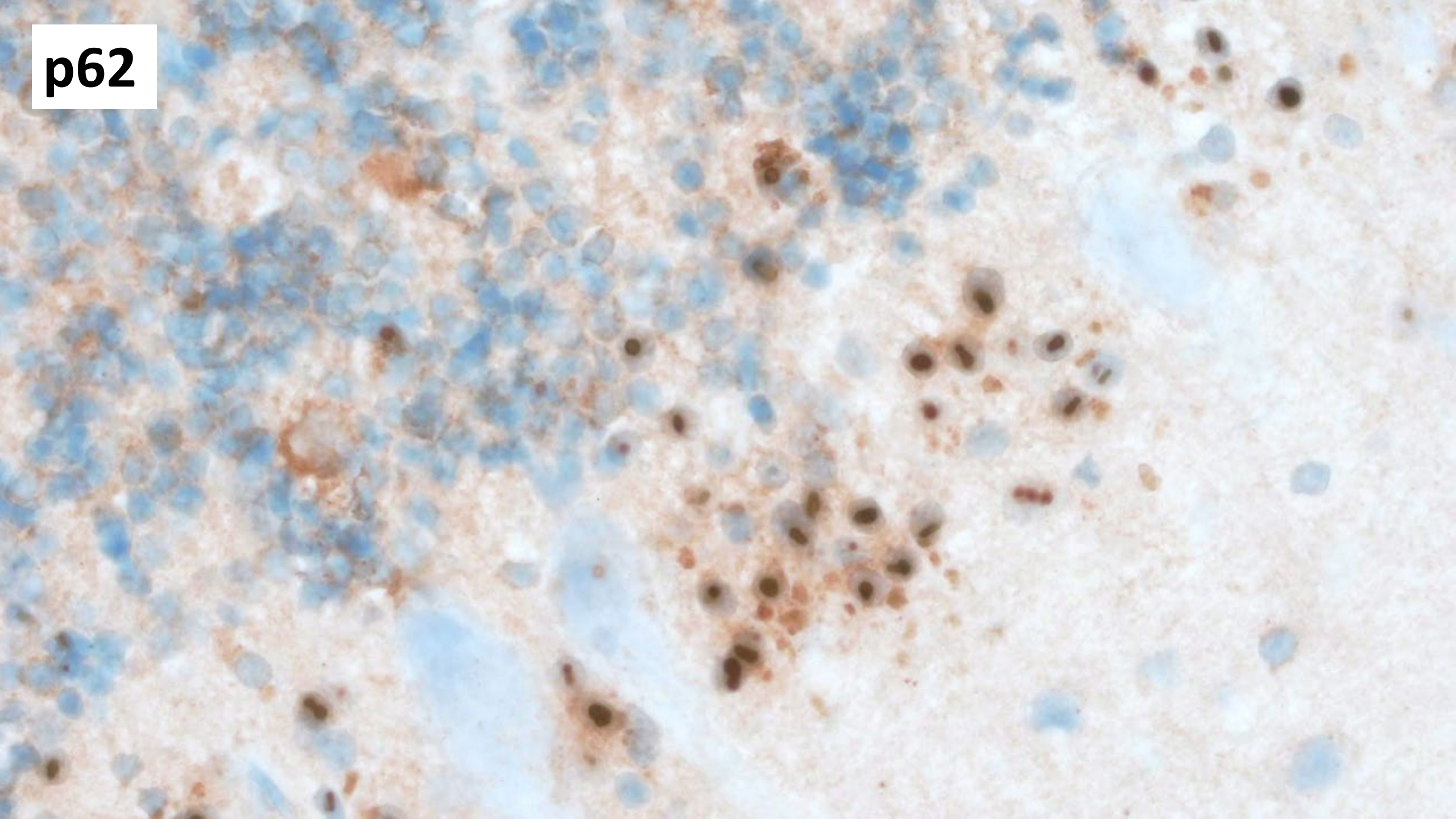
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Diagnosis:

- Findings suggestive of fragile X-associated tremor ataxia syndrome (FXTAS)

Tissue molecular testing

- SNP-copy number microarray and 500-gene NGS panel failed to detect any abnormalities in the biopsied tissue.

Clinical follow-up

- Based on the biopsy results, the patient was referred to medical genetics, where peripheral blood was drawn for germline testing.

Results: PREMUTATION ALLELE

GENE	MODE OF INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
FMR1	X-Linked	Repeat Number: 97,METHYL:NONE	Hemizygous	Premutation

97 CGG repeats in *FMR1* gene

Reference Range

Classification	CGG Repeat Size
Normal	less than 45
Intermediate ("gray zone")	45-54
Premutation	55-200
Full mutation	greater than 200

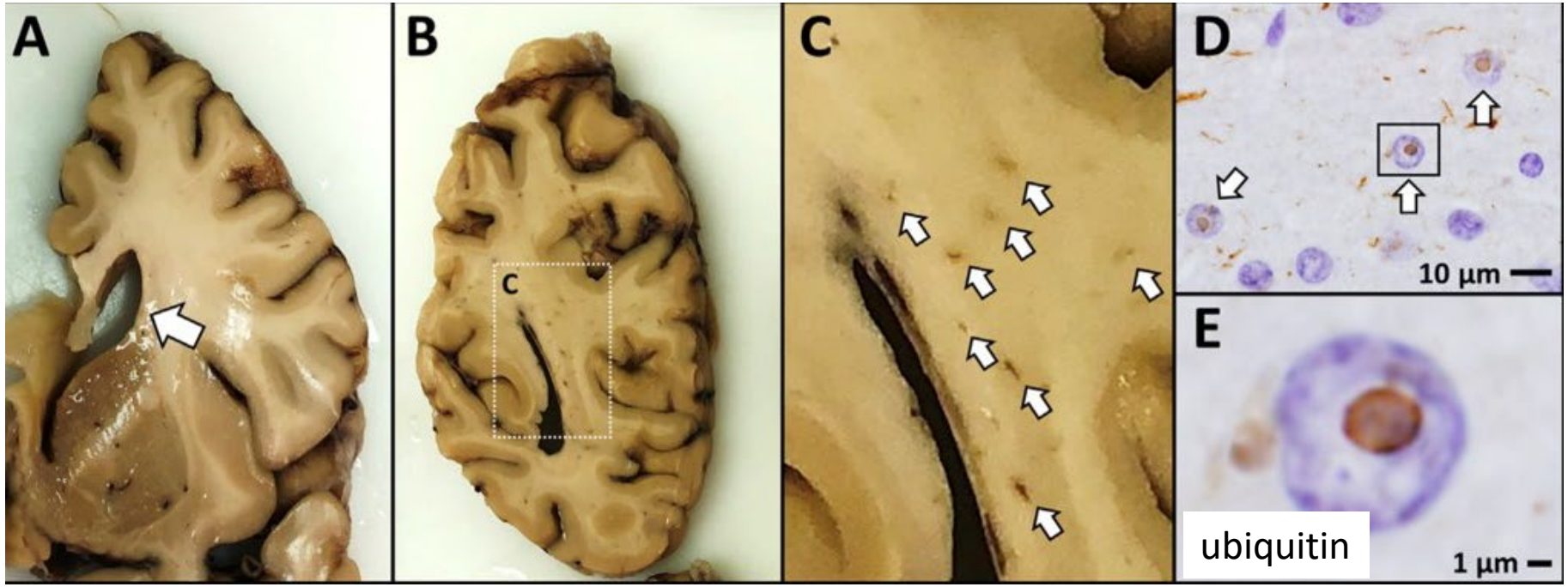
Fragile X-associated tremor ataxia syndrome (FXTAS)

- Trinucleotide **CGG** repeat expansion in *FMR1* gene on X chromosome
  - **Fragile X syndrome**: ≥200 repeats, diagnosed around age 3
  - **FXTAS**: 55-200 repeats (premutation carrier) onset in 50s or older
  - Primary ovarian insufficiency: female with premutation, < 40 years

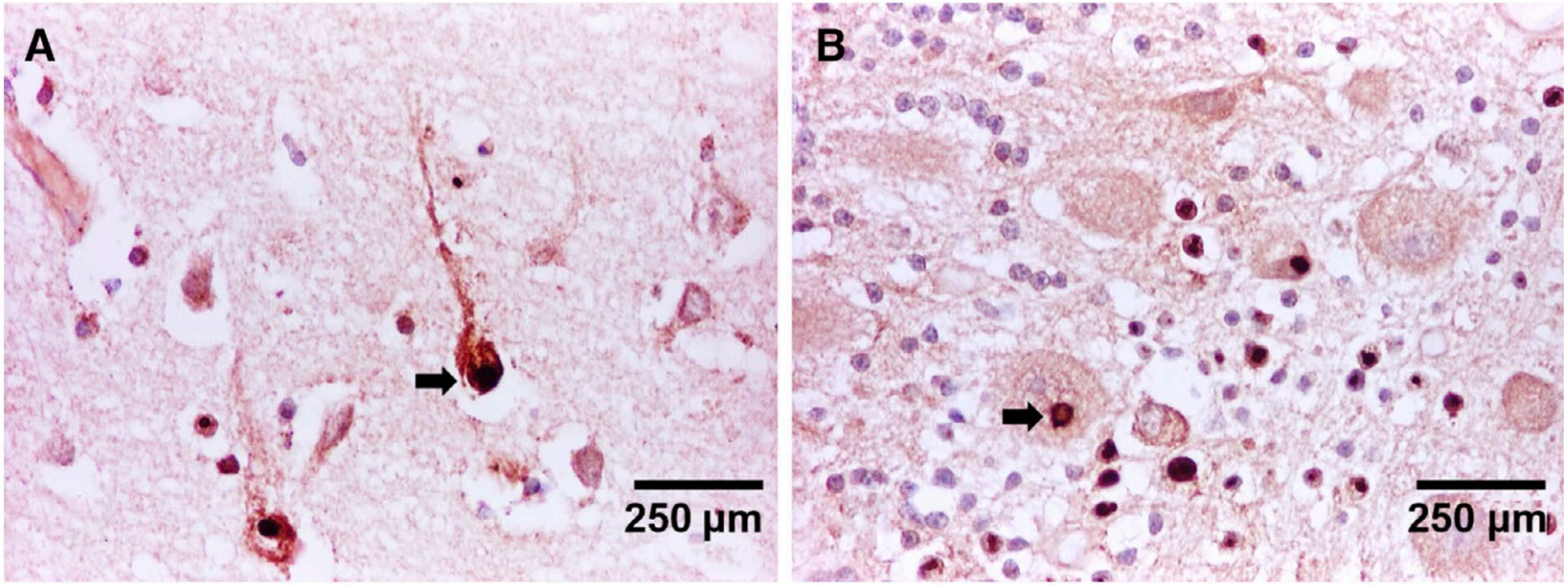
- Clinical features (major diagnostic criteria):
  - Essential tremor and/or ataxia. May show parkinsonism, neuropathies, executive function and memory deficits.
  - MRI: Increased **T2** FLAIR signal in middle cerebellar peduncle
    - Also cerebral white matter lesions and mild generalized atrophy
  - *FMR1* sequencing showing 55-200 repeats

Fragile X-associated tremor ataxia syndrome (FXTAS)

- Gross spongiosis and discoloration of cerebellar white matter is present in the vast majority of FXTAS cases
  - May also be focal cerebral WM lesions and subcortical WM discoloration
- Histopathology:
  - Presence of intranuclear inclusions in **astrocytes** and neurons positive for **ubiquitin**, **p62**, αB-crystallin and *FMR1* mRNA.
  - Inclusions are widespread: frontal cortex, cerebellum, hippocampus, basal ganglia, brainstem and PNS.
  - White matter lesions demonstrate a loss of myelin, as well as axonal degeneration and gliosis.
  - Perivascular iron deposition and patchy astrogliosis



Salcedo-Arellano MJ, et al. PMID: 31927143



Robinson AC, et al. PMID: 32830366.

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