UNIVERSITY of WASHINGTON

AANP DSS-2026-9

Joyce Opara, MD

Neuropathology Fellow – PGY 4

University of Washington

Authors:

- Caitlin Latimer MD PhD
- Amber Nolan MD PhD

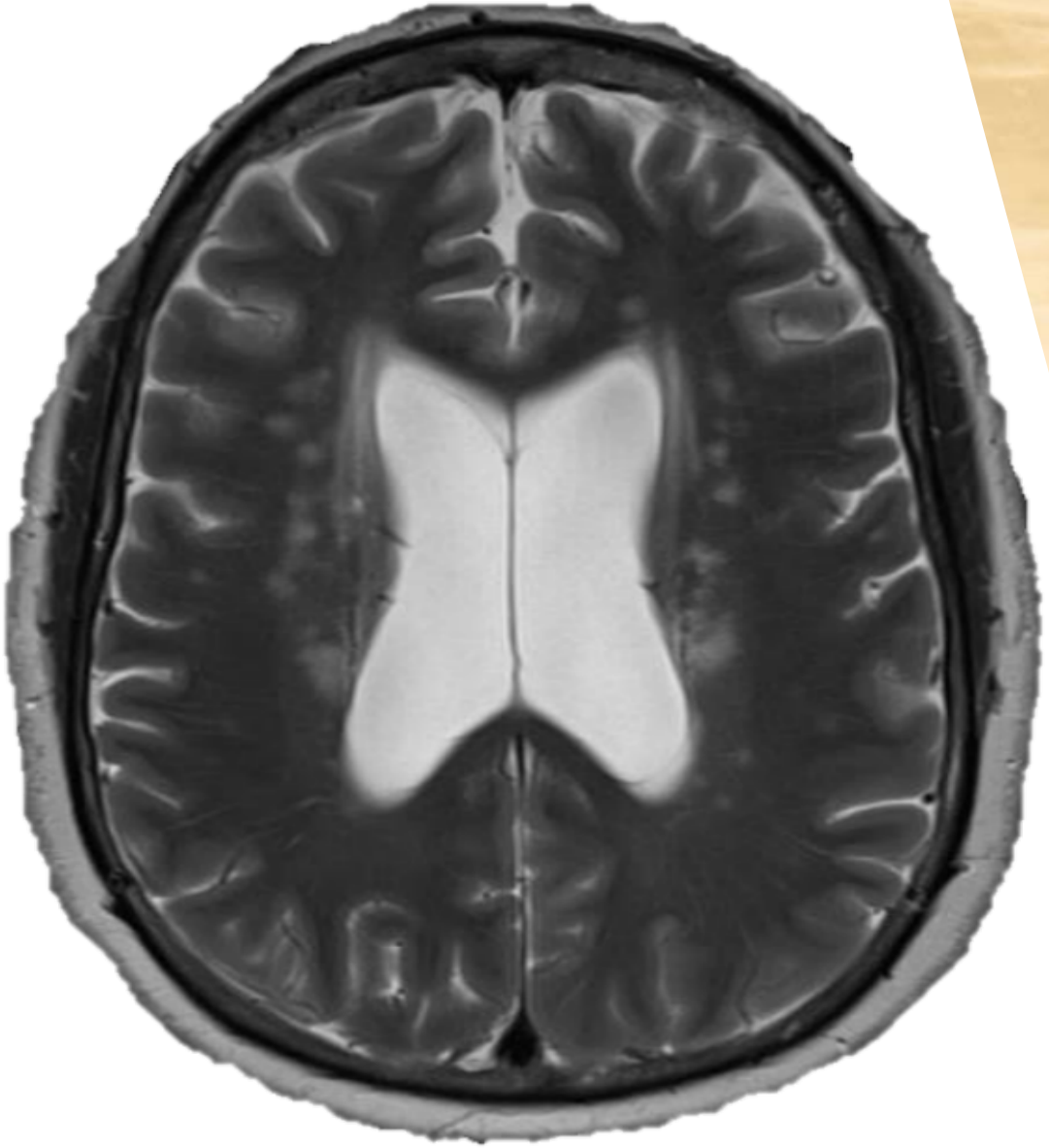
Clinical history:

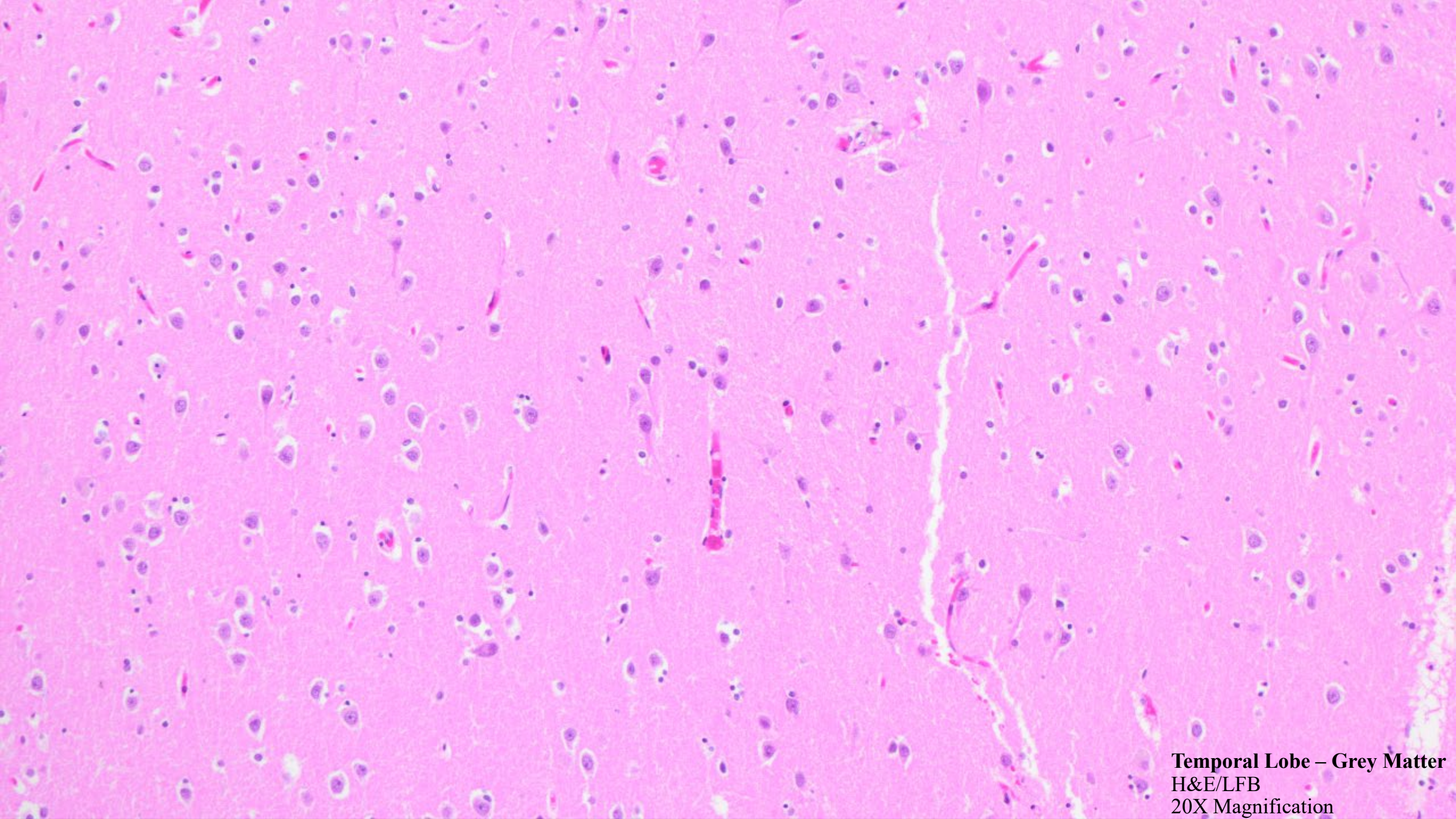
- 65-year-old with progressive neuropsychiatric symptoms for 10 years (age of onset 55 y/o)
  - > Mild cognitive impairment
    - Last MOCA, 3 months prior to death (25/30)
  - > Depression and behavioral changes
- PMH: TBI as a child

Family history:

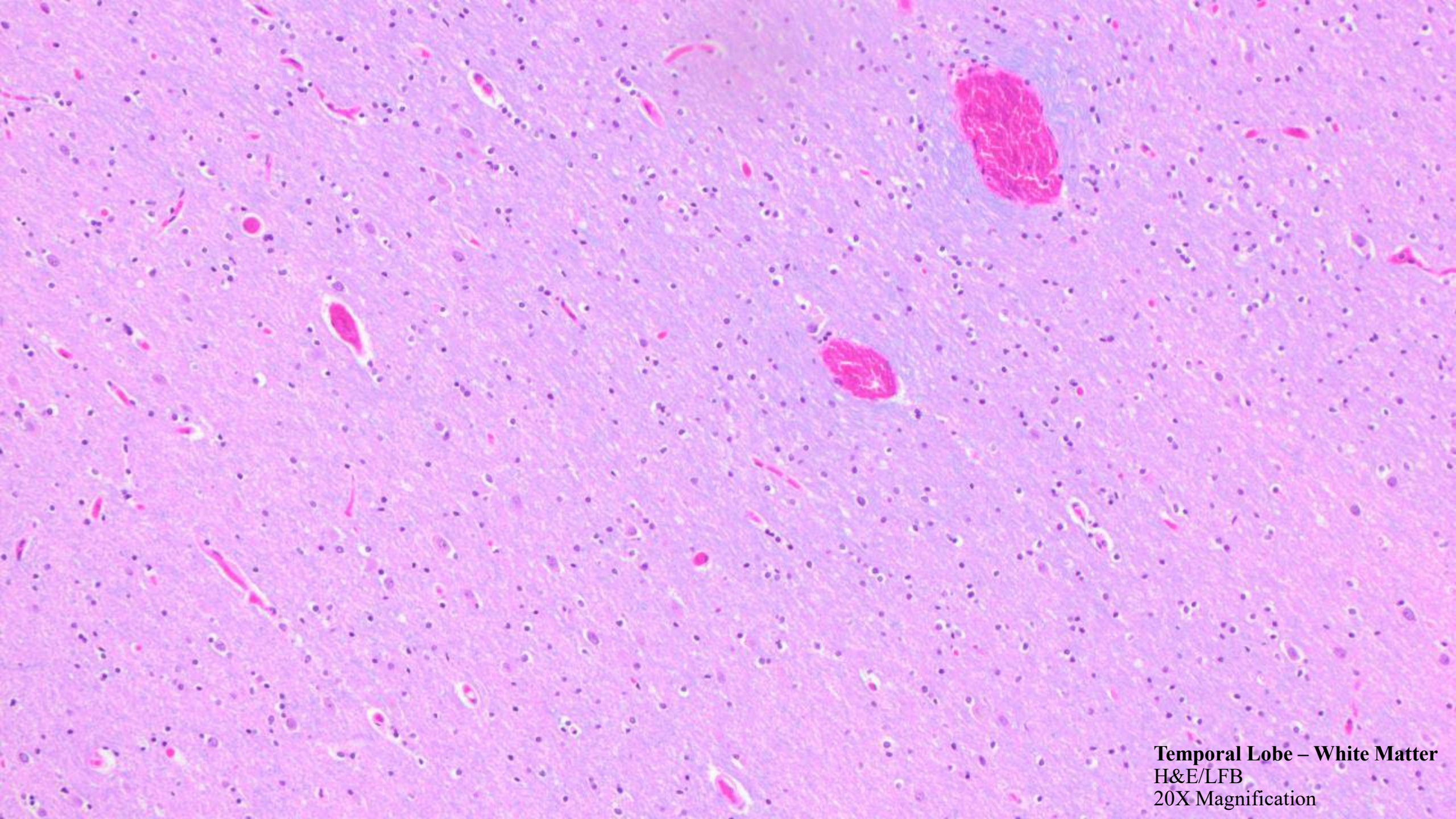
- Multiple affected first-degree relatives with:
  - > Motor neuron disease
  - > Parkinsonism
  - > Frontotemporal dementia

T2 Flair

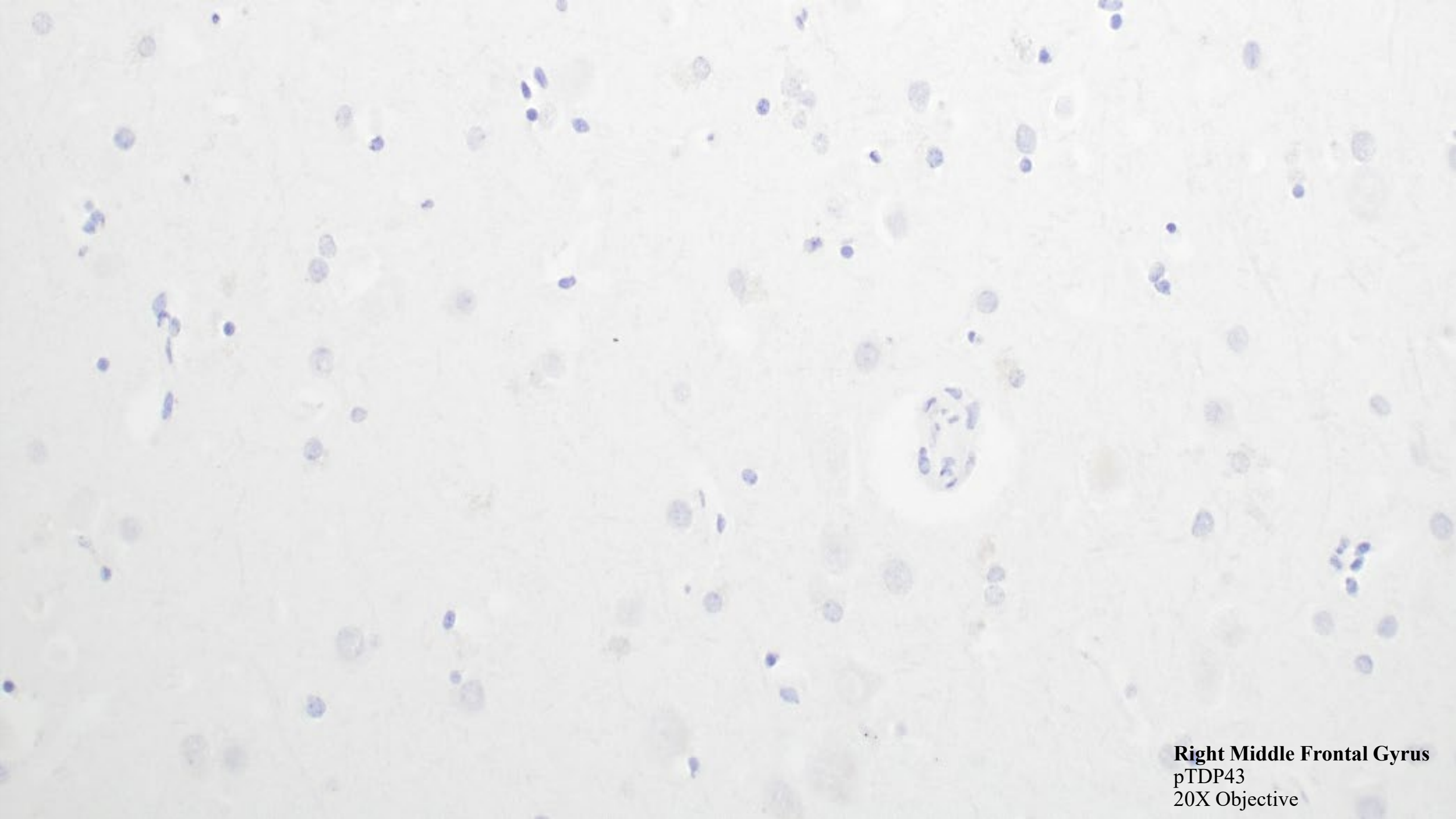




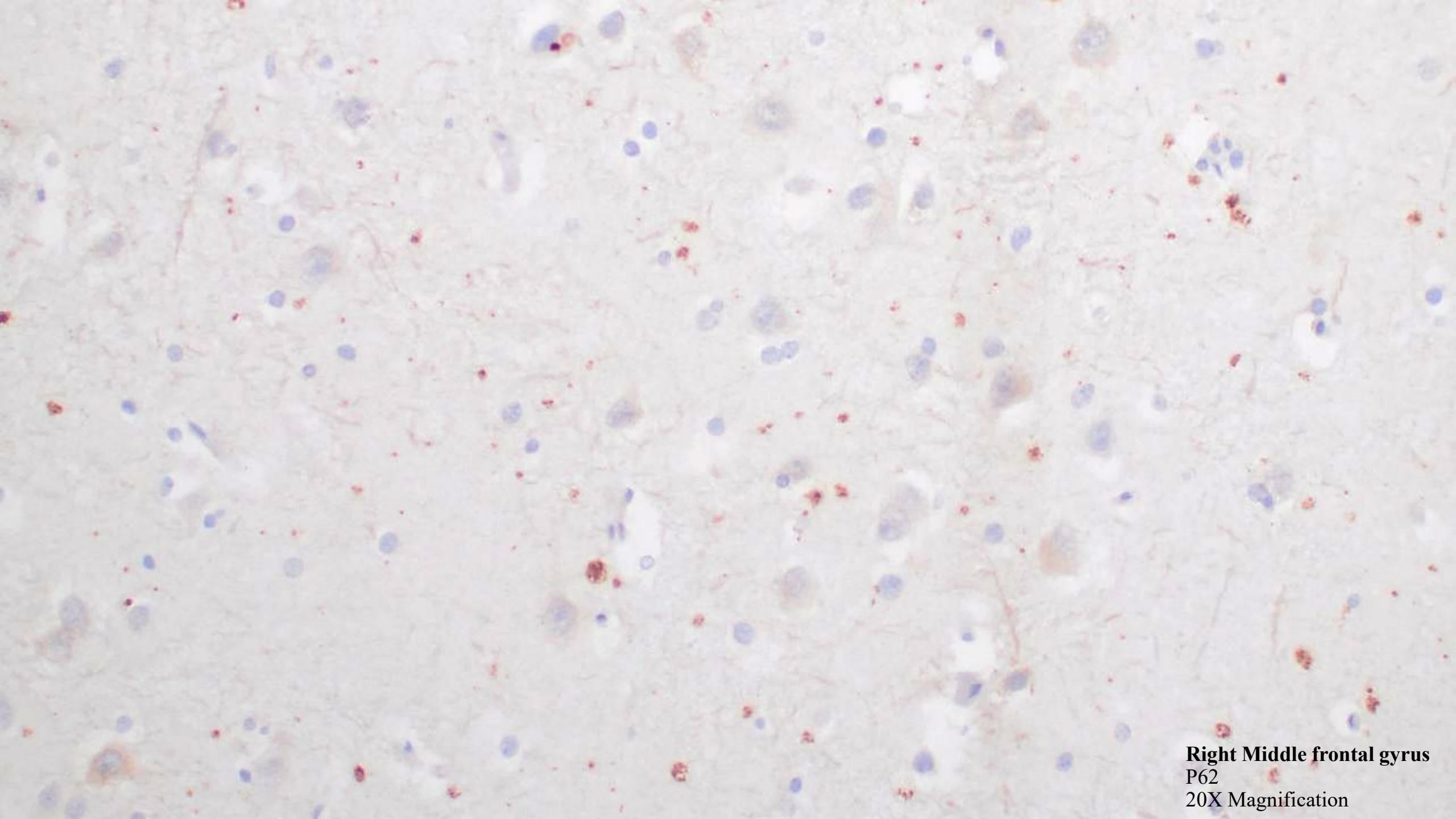
Temporal Lobe – Grey Matter
H&E/LFB
20X Magnification



Temporal Lobe – White Matter
H&E/LFB
20X Magnification



Right Middle Frontal Gyrus
pTDP43
20X Objective

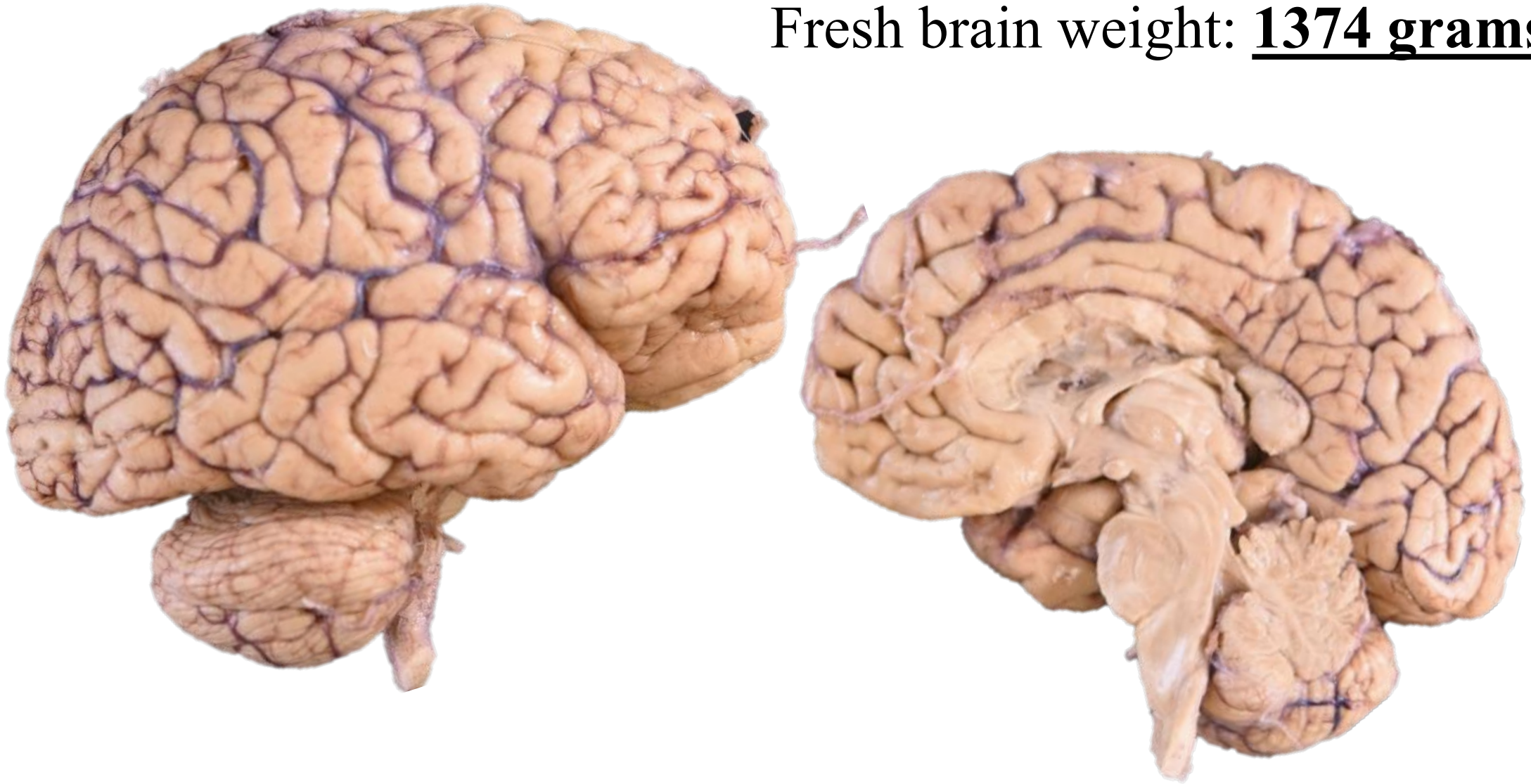


Right Middle frontal gyrus
P62
20X Magnification

The case is open for Discussion

Gross Examination of the Brain

Fresh brain weight: **1374 grams**



Gross examination of Spinal cord

Anterior View

Posterior View

Histologic review:

Histology (H&E)

- Minimal neurodegenerative changes
- No significant spongiosis
- No inflammatory or vascular pathology

Alzheimer Disease Neuropathologic Change

- Thal phase 1
- Braak stage II
- Absent CERAD neuritic plaques
- **Insufficient** to explain clinical syndrome

Family History:

- Father: Diagnosed with amyotrophic lateral sclerosis (ALS) at age 60, deceased at 74 years (Motor symptoms, no cognitive changes)
- Paternal uncle: ALS, 2-year disease course (Motor symptoms, no cognitive changes)
- Brother with Parkinson disease onset at 59
- Brother with Bell's palsy (+/- synkinesis) onset at age 45
- **Brother with behavioral variant of frontotemporal dementia onset at 52, deceased at 60 years**

Genetic Findings of Donor

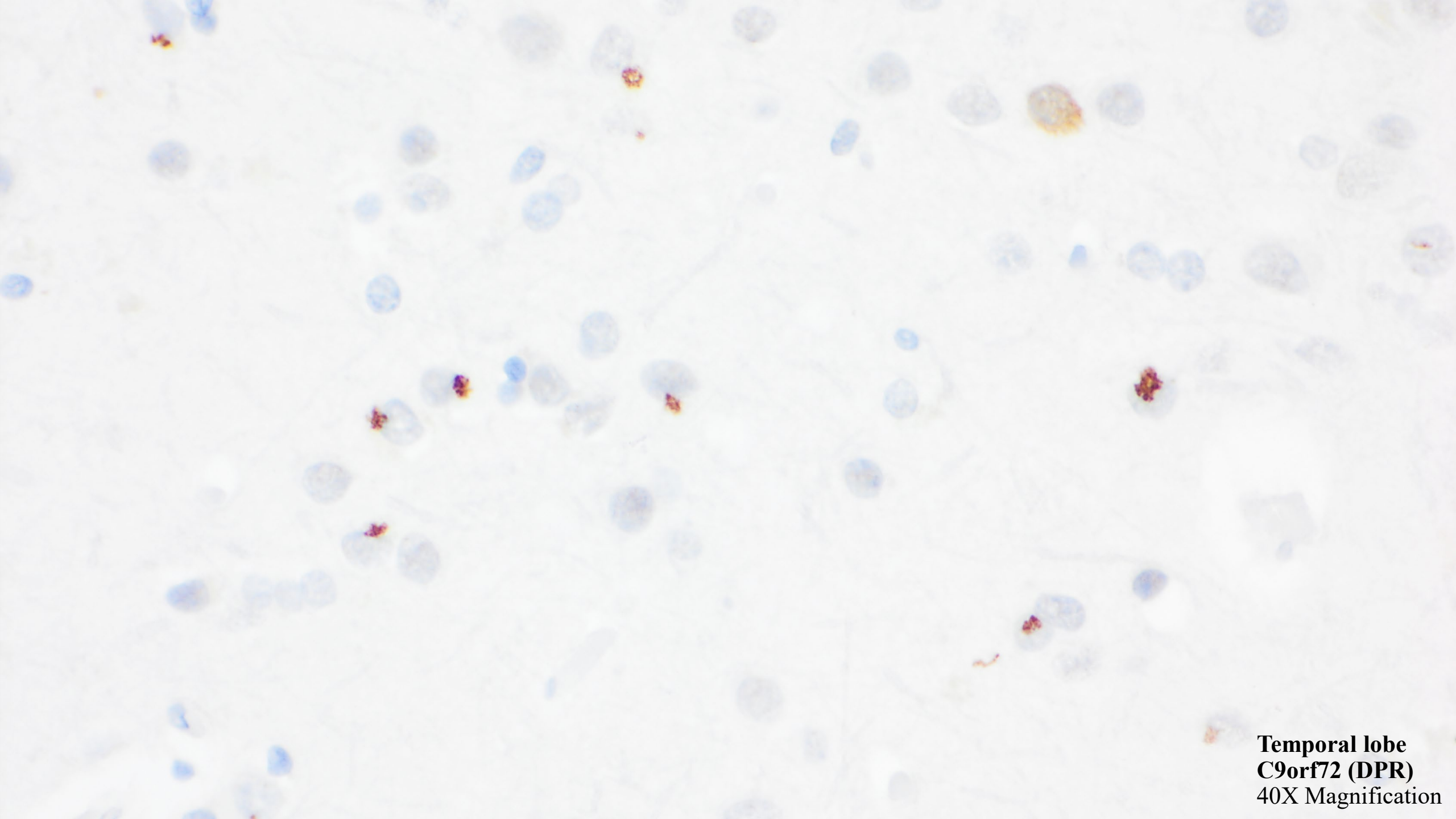
- (May 2018, UWMC Center for Precision Diagnostics): **Positive for a pathogenic C9orf72 GGGGCC repeat expansion** (10, >145 repeats).
  - **Same C9orf72 expansion as brother**, with histologically confirmed TDP-43 pathology
  - Meets criteria for genetically definite FTLD
- APOE Genotype: 3/4

Differential Diagnostic Considerations:

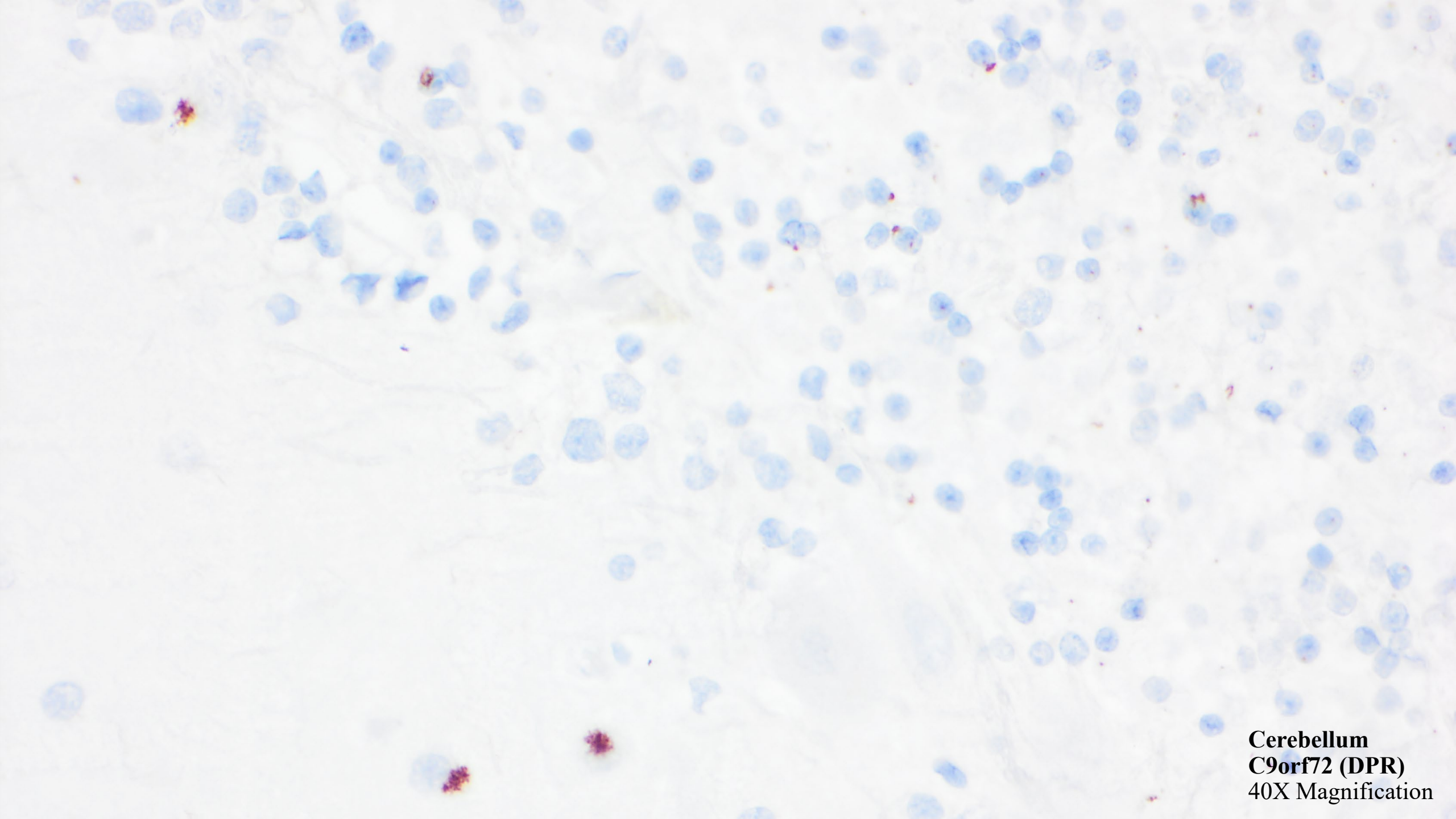
- Current FTLD Classification
  - FTLD-TDP, FTLD-FUS, FTLD-UPS
    - Does not accommodate this phenotype

- FTLD-FUS (excluded by IHC)
- FTLD-UPS (protein identified as DPR)

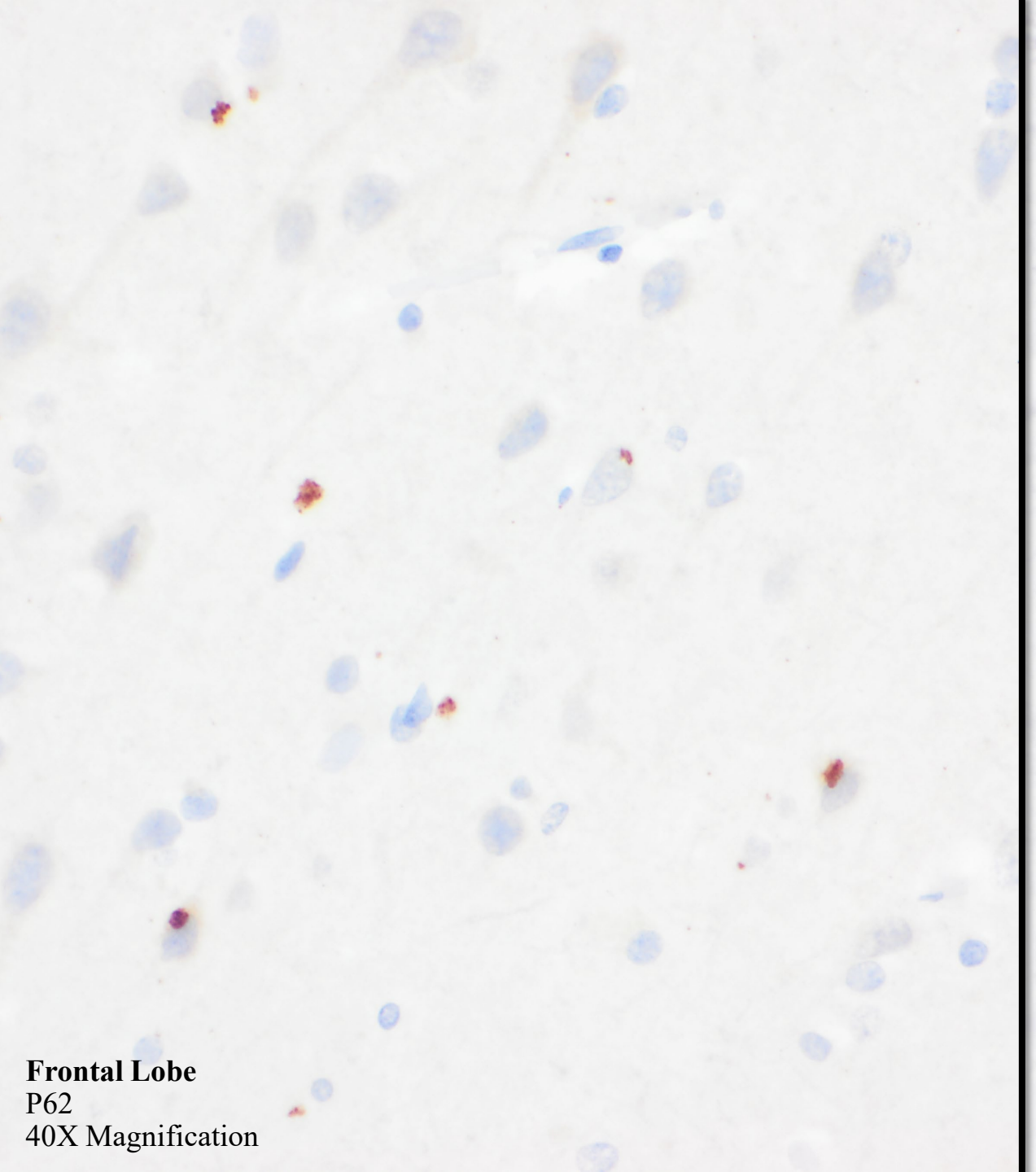
- **Preclinical or atypical C9orf72 neurodegeneration**



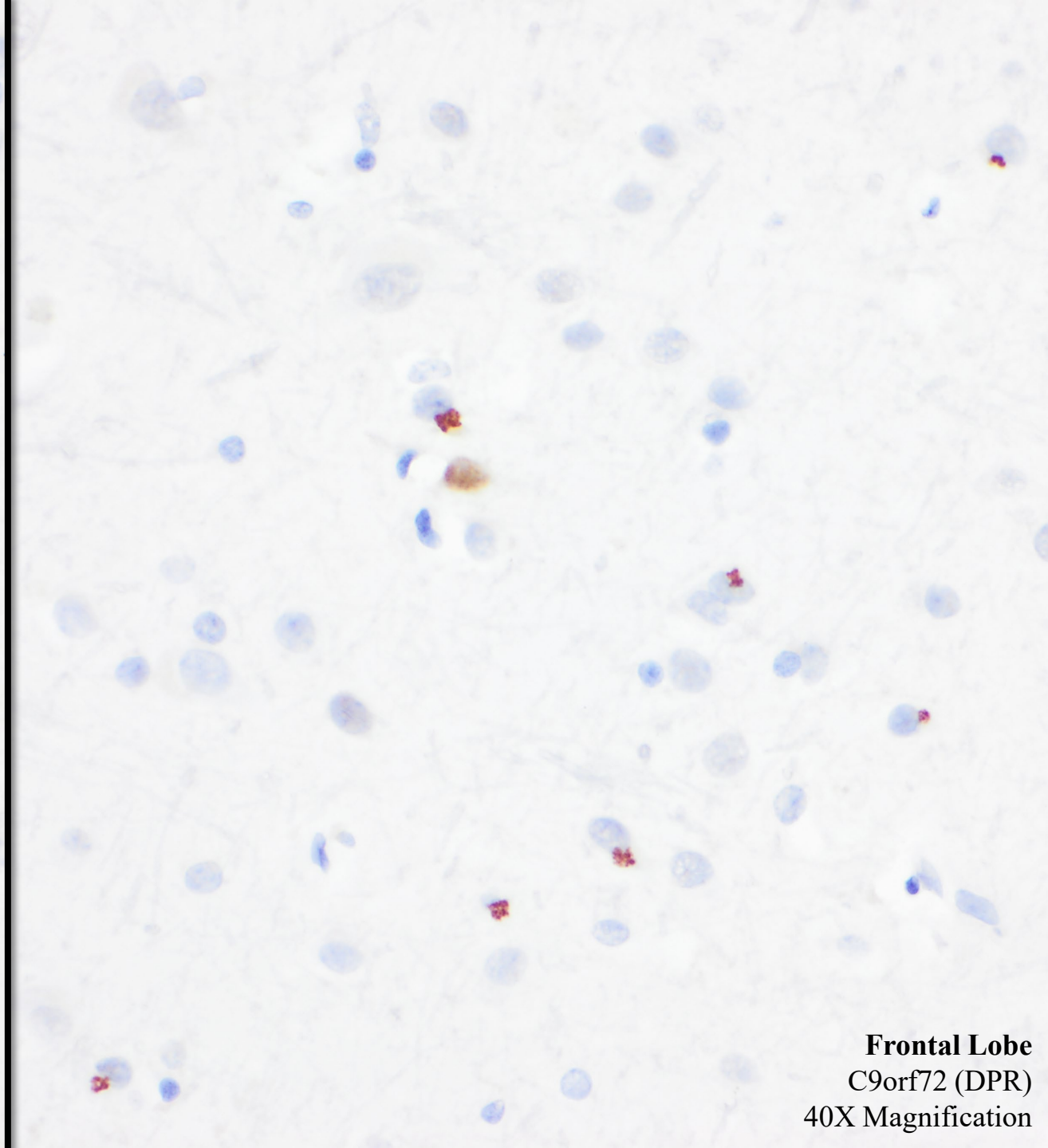
Temporal lobe
C9orf72 (DPR)
40X Magnification



Cerebellum
C9orf72 (DPR)
40X Magnification

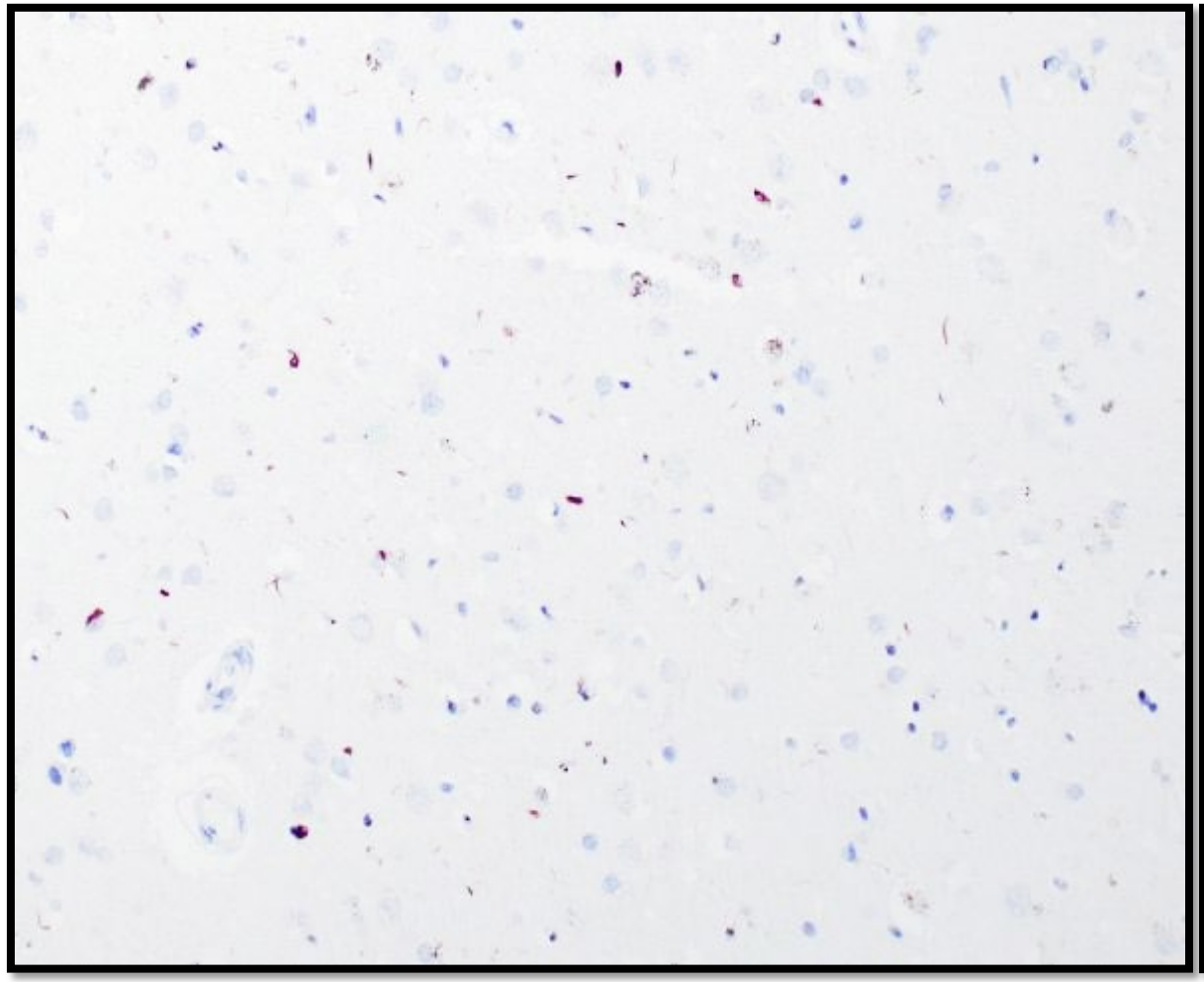


Frontal Lobe
P62
40X Magnification

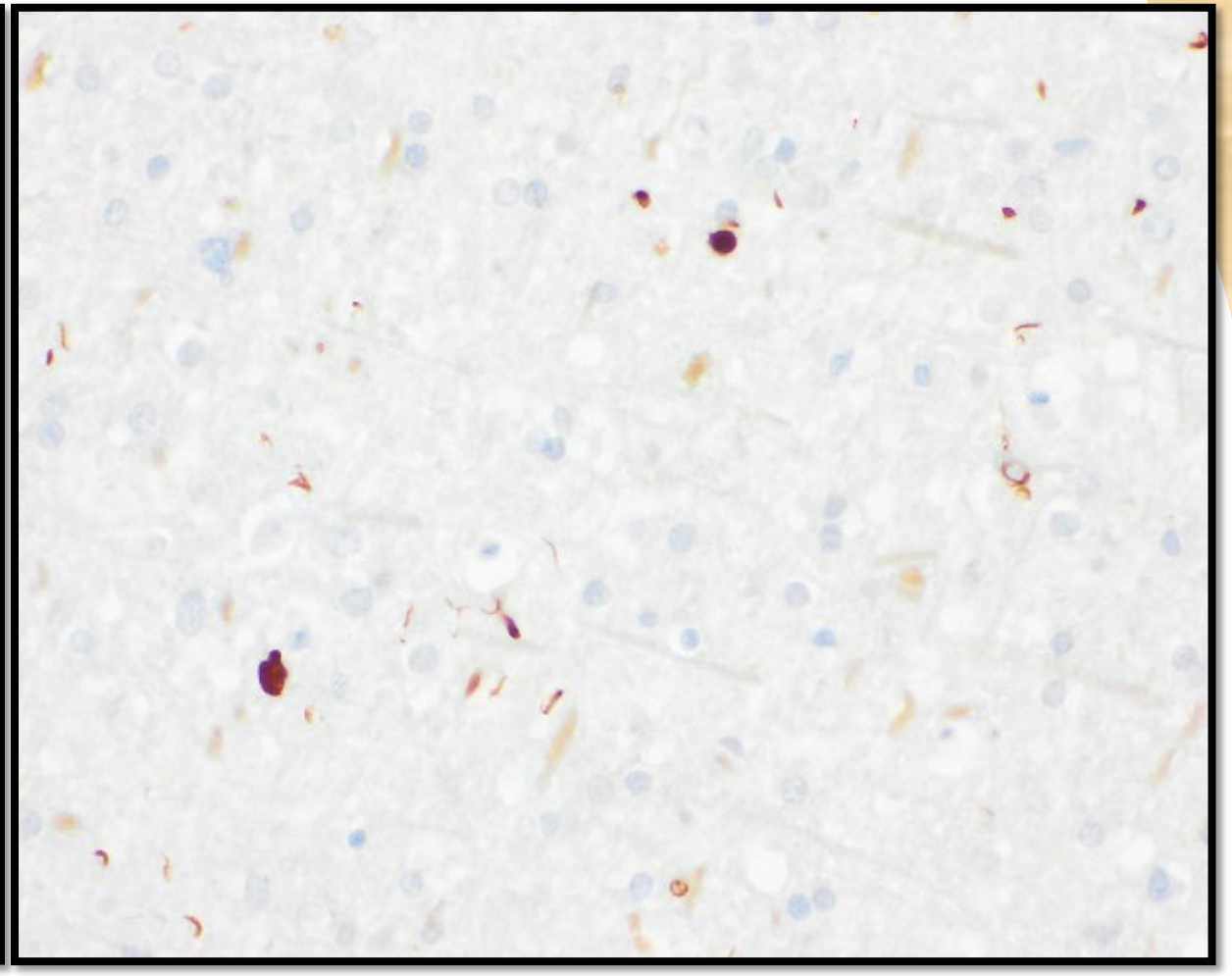


Frontal Lobe
C9orf72 (DPR)
40X Magnification

Brother's pTDP43 pathology:

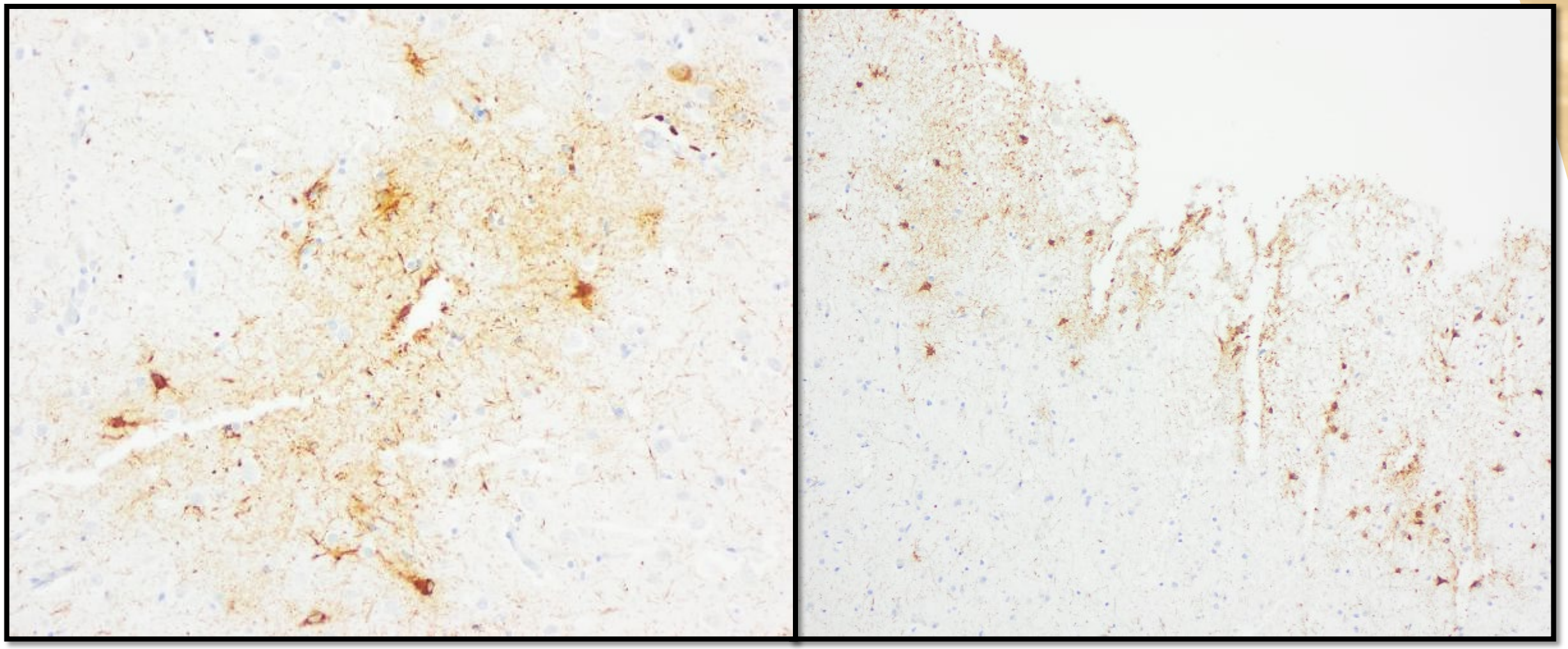


Temporal Lobe
pTDP43
20X Magnification



Temporal Lobe
pTDP43
40X Magnification

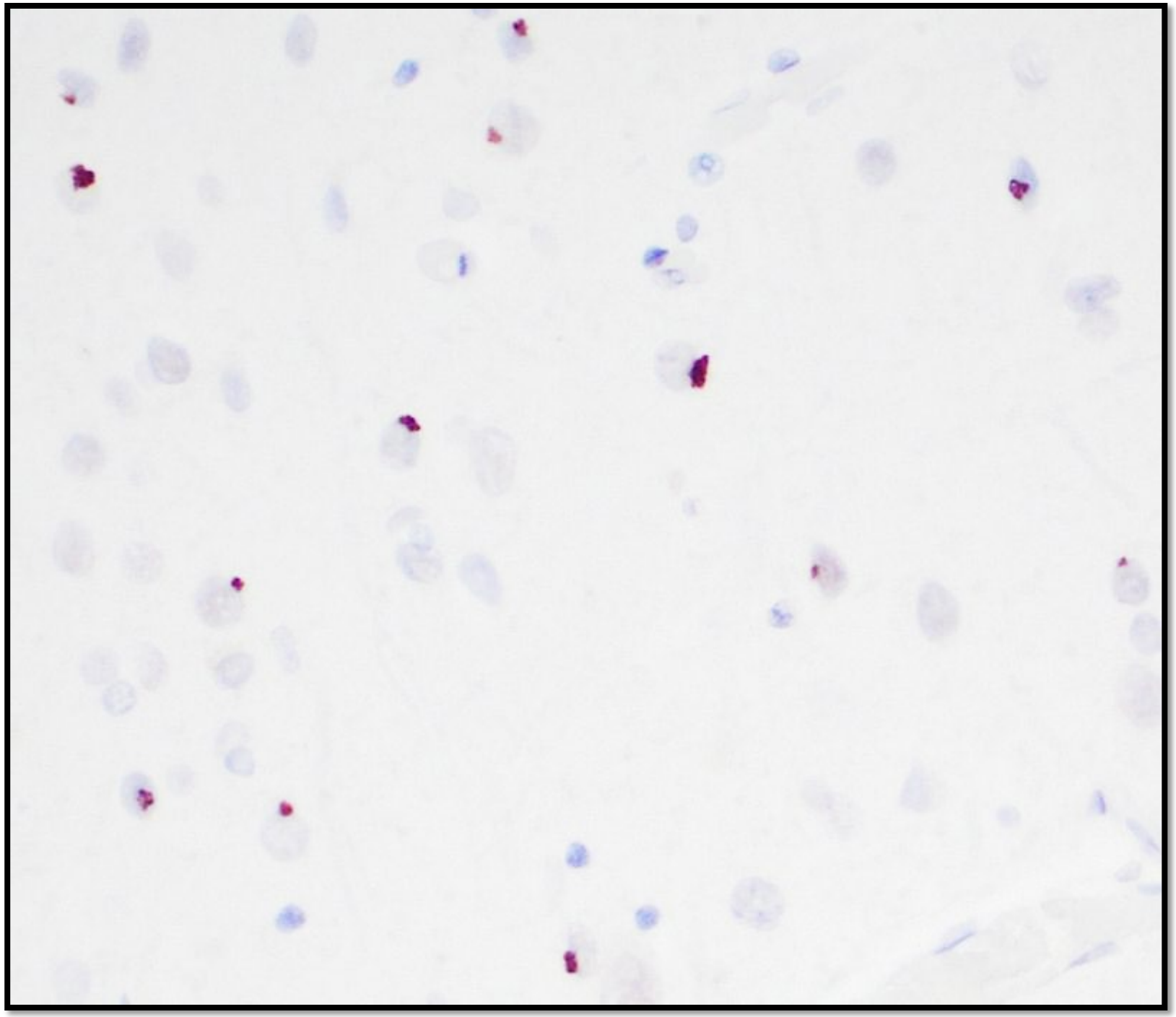
Brother's CTE pathology:



Prefrontal cortex
Tau
40X Magnification

Prefrontal Crotex
Tau
20X Magnification

Brother's pathology:



Temporal Lobe
C9orf72
40X Magnification

Final Neuropathologic Diagnosis:

Carrier of C9orf72 repeat expansion without pTDP-43 aggregation

Why This Is Unexpected:

- pTDP43 often considered the driving focus of disease
  - C9orf72 leads to abnormal TDP43 localization
  - Nearly all C9orf72-associated FTLD shows TDP-43 pathology
- Intrafamilial variability
  - Siblings with the same mutation, but different pathology
    - Brother shows pTDP43 and High-stage CTE
  - Highlights Modifying factors
- Pathogenic implications
  - Neurodegeneration may occur independent of pTDP43 aggregation

Supports RNA/DPR toxicity mechanisms:

- Specific phenomena such as dipeptide repeat (DPR) proteins and RNA foci can be observed in c9orf72 cases.
- Repeat-associated Non-ATG translation produces toxic dipeptide repeat proteins (DPRs)
  - From sense transcripts:
    - **poly(GA)**
    - poly(GP)
    - poly(GR)
  - From antisense transcripts:
    - poly(PR)
    - poly(PG)
    - poly(PA)

Supports Poly(GA) Toxicity mechanisms:

- poly(GA)
  - Forms aggregates → Impairs the ubiquitin-proteasome system → Induces ER stress → contributes to neuronal death.
- This case demonstrates a "pre-TDP43 deposition" C9orf72 case
    - DPR protein pathology in the absence of detectable TDP-43 pathology
    - Supporting the hypothesis that DPR accumulation not only represents an early upstream event in C9orf72-associated neurodegeneration, but is directly pathogenic.

References

- Gendron, T. F., & Petrucelli, L. (2018). Disease mechanisms of C9ORF72 repeat expansions. *Cold Spring Harbor perspectives in medicine*, *8*(4), a024224.

- Sampognaro, P. J., Vatsavayai, S. C., Cosme, C. G., Hwang, J. H. L., Nolan, A., Huang, E. J., ... & De May, M. G. (2019). C9orf72-specific phenomena associated with frontotemporal dementia and gastrointestinal symptoms in the absence of TDP-43 aggregation. Acta neuropathologica, 138(6), 1093-1097.

- Valente ES, Caramelli P, Gambogi LB, Mariano LI, Guimarães HC, Teixeira AL, de Souza LC. Phenocopy syndrome of behavioral variant frontotemporal dementia: a systematic review. Alzheimers Res Ther. 2019 Apr 1;11(1):30. doi: 10.1186/s13195-019-0483-2. PMID: 30935398; PMCID: PMC6444822.

THANK YOU!

Caitlin S. Latimer MD, PhD

Amber Nolan MD, PhD