2018 AANP Diagnostic Slide Session
Case 4a

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University of Pittsburgh Medical Center

Disclosures

- No relevant financial relationships to disclose

Clinical History

- 37 year old lawyer, no family history of dementia
  - At age 33, started to have performance issues at work
  - Progressively abulic and socially withdrawn
  - By age 34, he began to choke frequently on food and developed a nasal voice and bilateral ptosis
  - Unable to care for his children
- Physical exam:
  - No fasciculations, normal strength
  - Brisk reflexes, no Babinski sign or sustained clonus
  - Ptosis

Clinical History

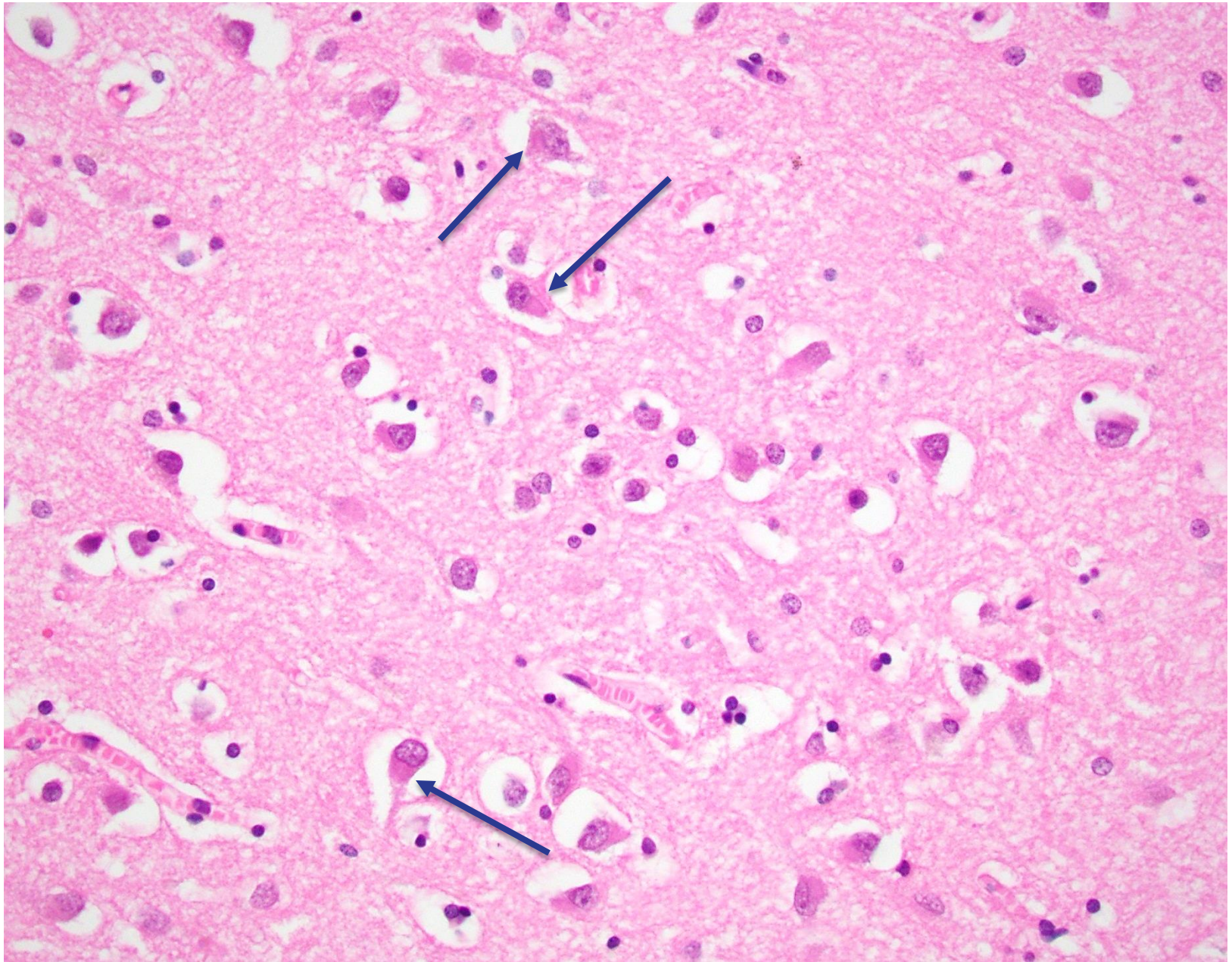
- Imaging studies:
  - Initial MRI and CT were normal
  - PET scan - bilateral frontal diminution of glucose utilization, worse on the right than the left, with extension to the right caudate

Gross Findings

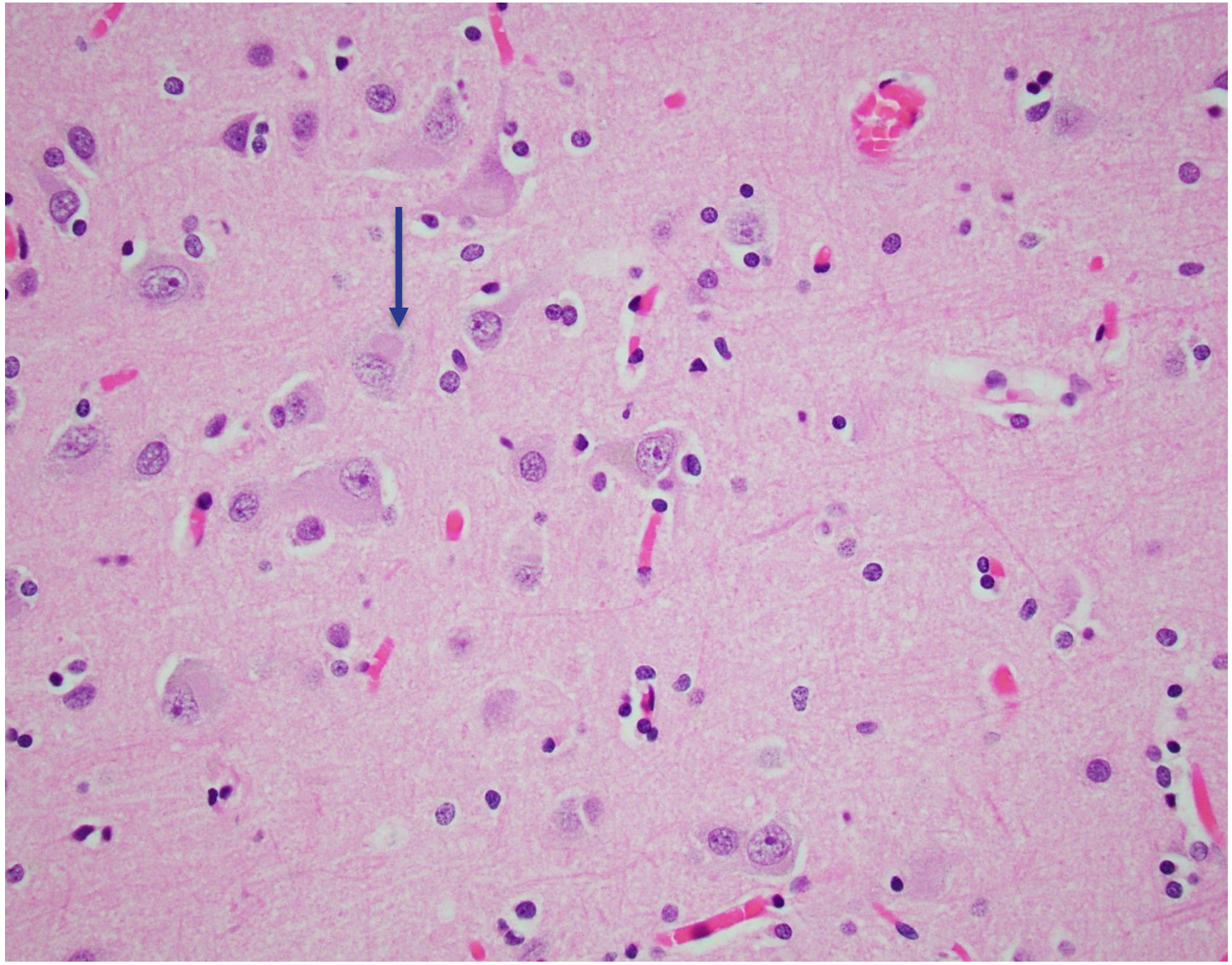
- Brain weight: 1160 grams (fresh)
- Moderate atrophy of the frontal lobe and caudate
- Mild atrophy of the temporal and parietal lobes

H&E: Frontal Cortex

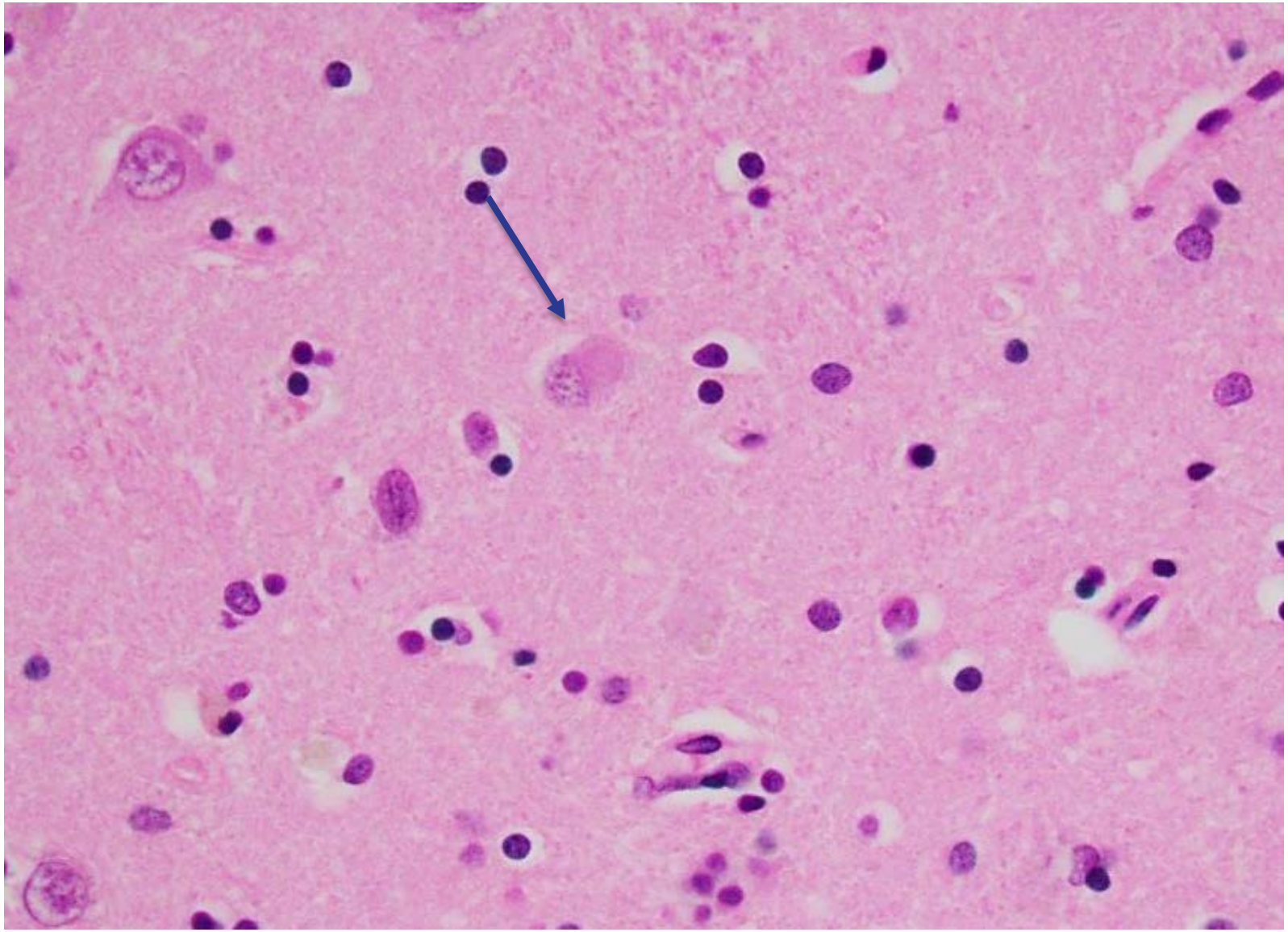
Case 4a



H&E: Pre-central Gyrus



H&E: Thalamus



2018 AANP DSS Case 4b

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June 9, 2018

DISCLOSURES: I have no relevant financial relationships to disclose

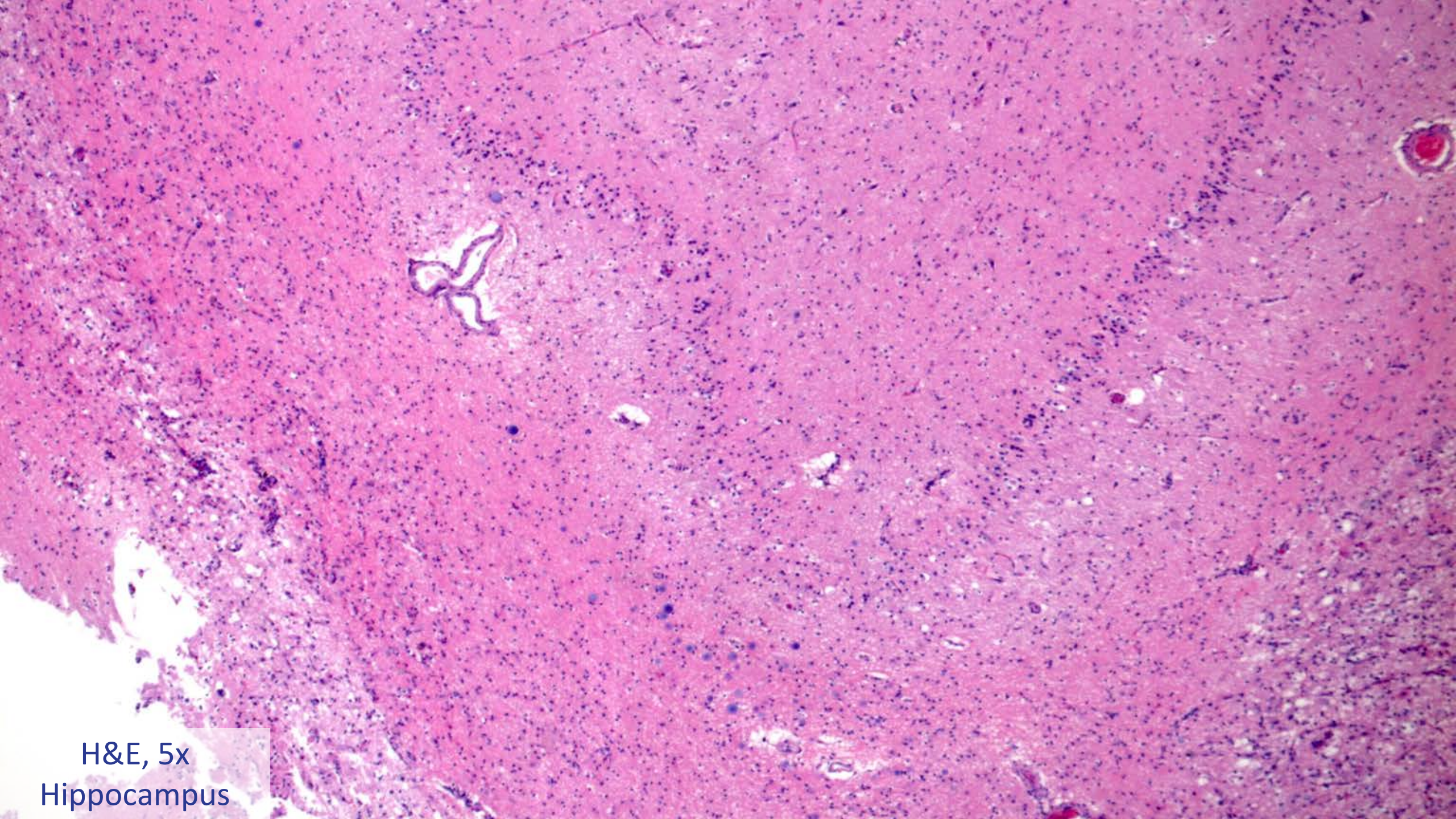
Clinical History

72-year-old RH female with incoordination and frequent falls

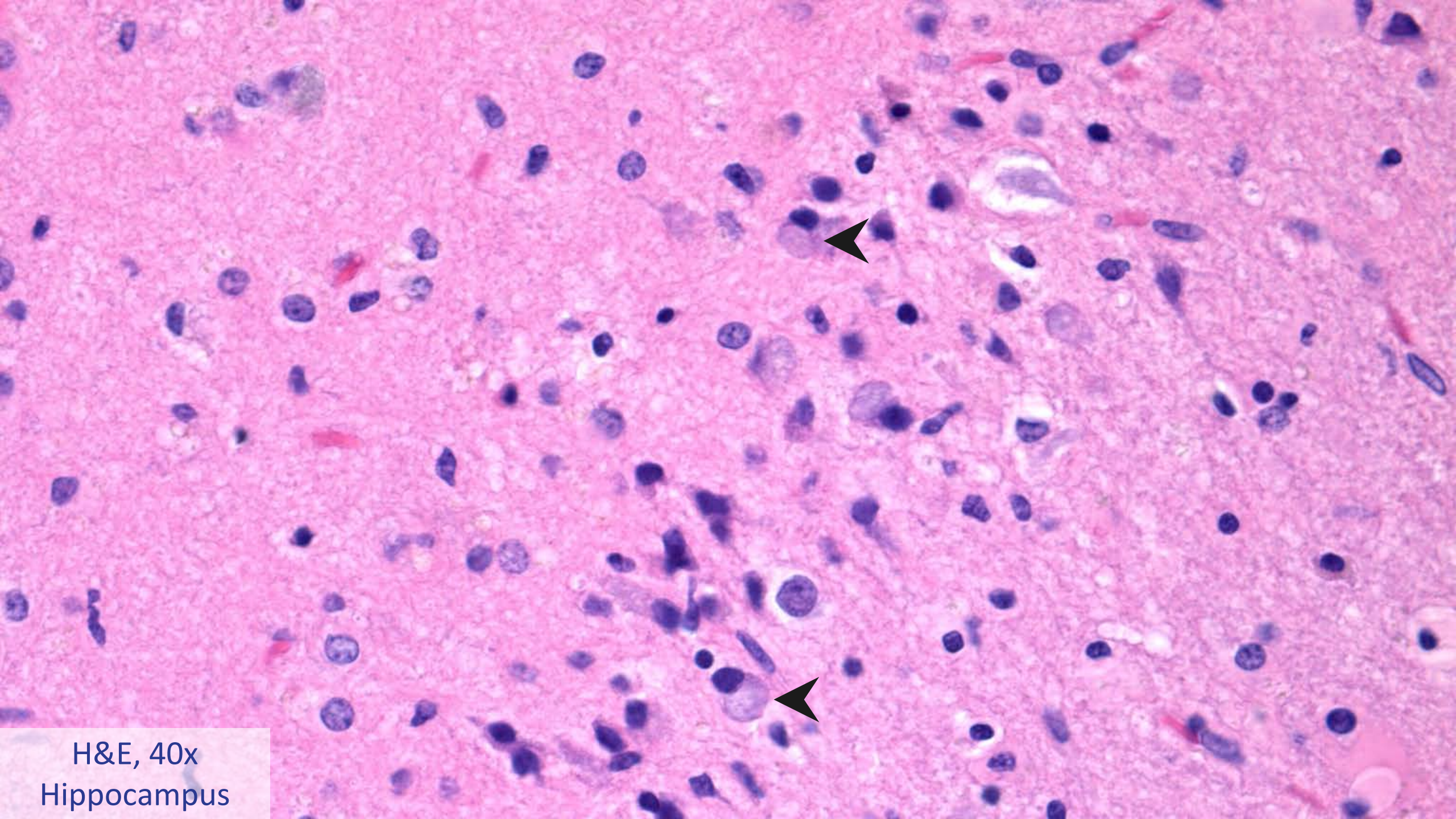
- Increasing forgetfulness, anosmia, micrographia
- Clinical diagnosis of possible Parkinson's disease
- Trial of carbidopa/levodopa → no improvement
- Died after 5 years of severe parkinsonism and dementia

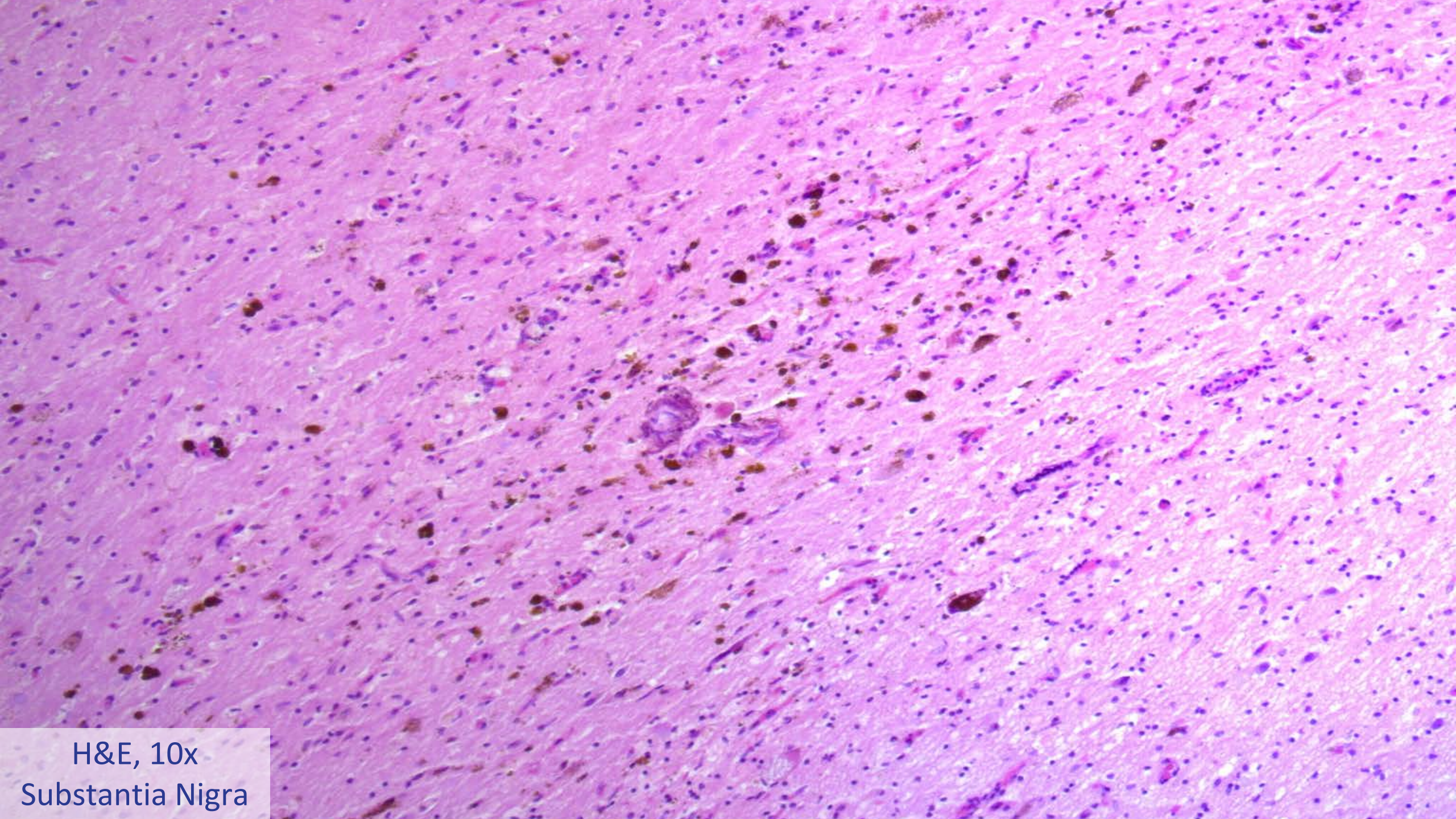
Autopsy Gross Findings

- Brain weight 1147 grams
- Diffuse cerebral atrophy
- Ex-vacuo hydrocephalus
- Depigmentation of substantia nigra



H&E, 5x
Hippocampus


H&E, 40x
Hippocampus



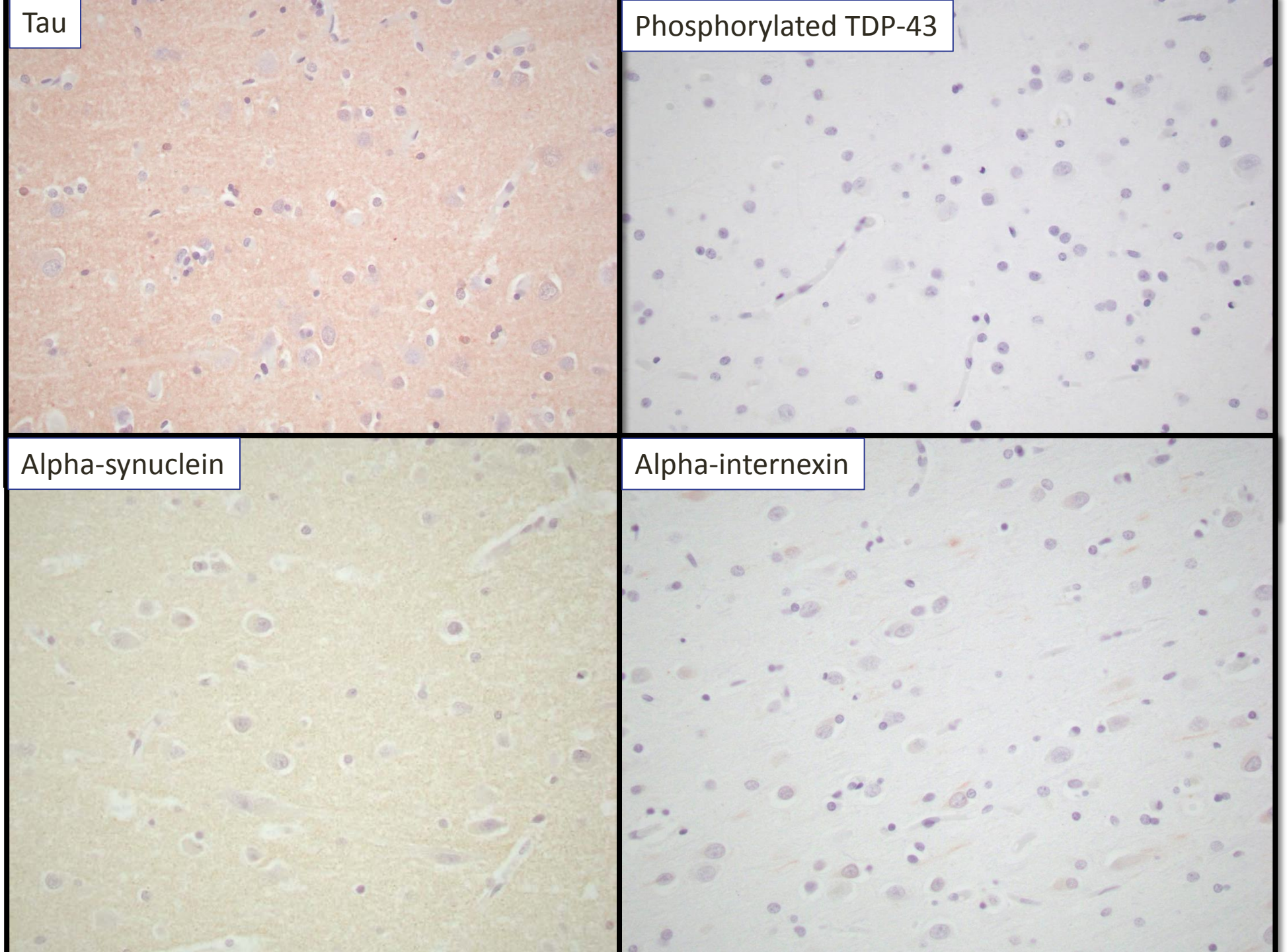
H&E, 10x
Substantia Nigra

Differential Diagnosis?

Frontotemporal Lobar Degeneration (FTLD)

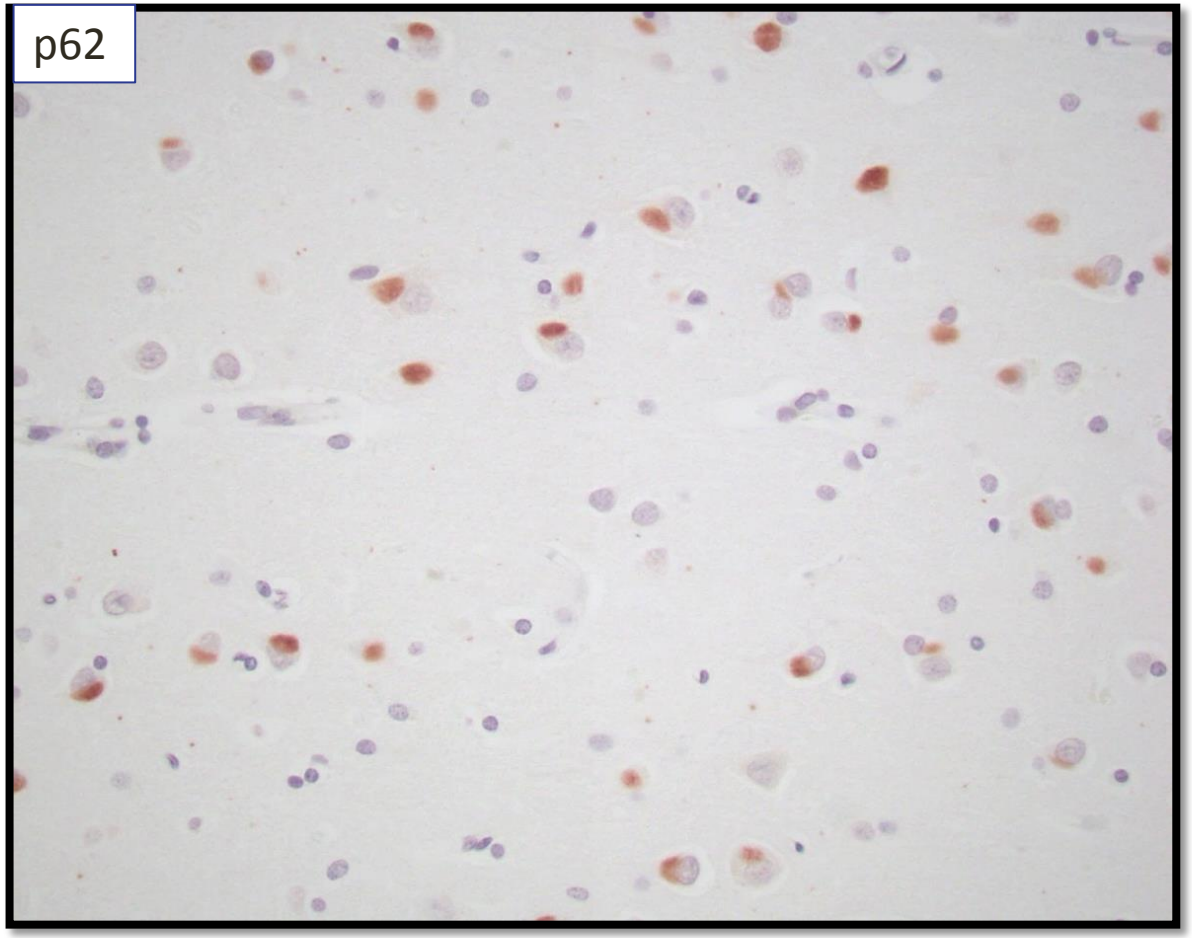
2010 recommendation		Associated genes
Major molecular class	**Recognized subtypes[a]**	
FTLD-tau	PiD	*MAPT*
	CBD	
	PSP	
	AGD	
	MSTD	
	NFT-dementia	
	WMT-GGI	
	Unclassifiable	
FTLD-TDP	Types 1–4	*GRN*
	Unclassifiable	*VCP*
		9p
		(*TARDBP*)[b]
FTLD-UPS	**FTD-3**	*CHMP2B*
FTLD-FUS	**aFTLD-U**	(*FUS*)[c]
	NIFID	
	BIBD	
FTLD-ni		

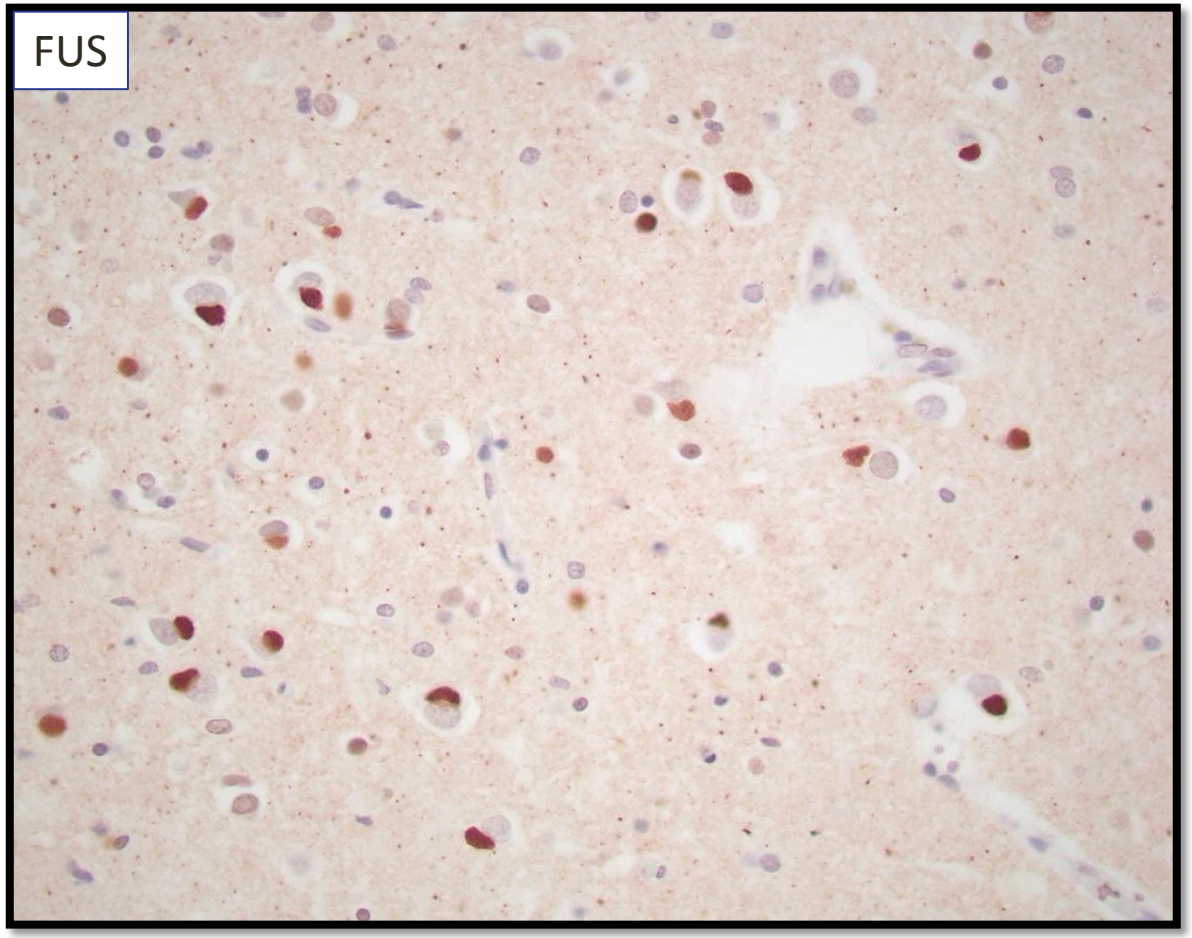
Mackenzie et al., *Acta Neuropathol* (2010) 119:1-4

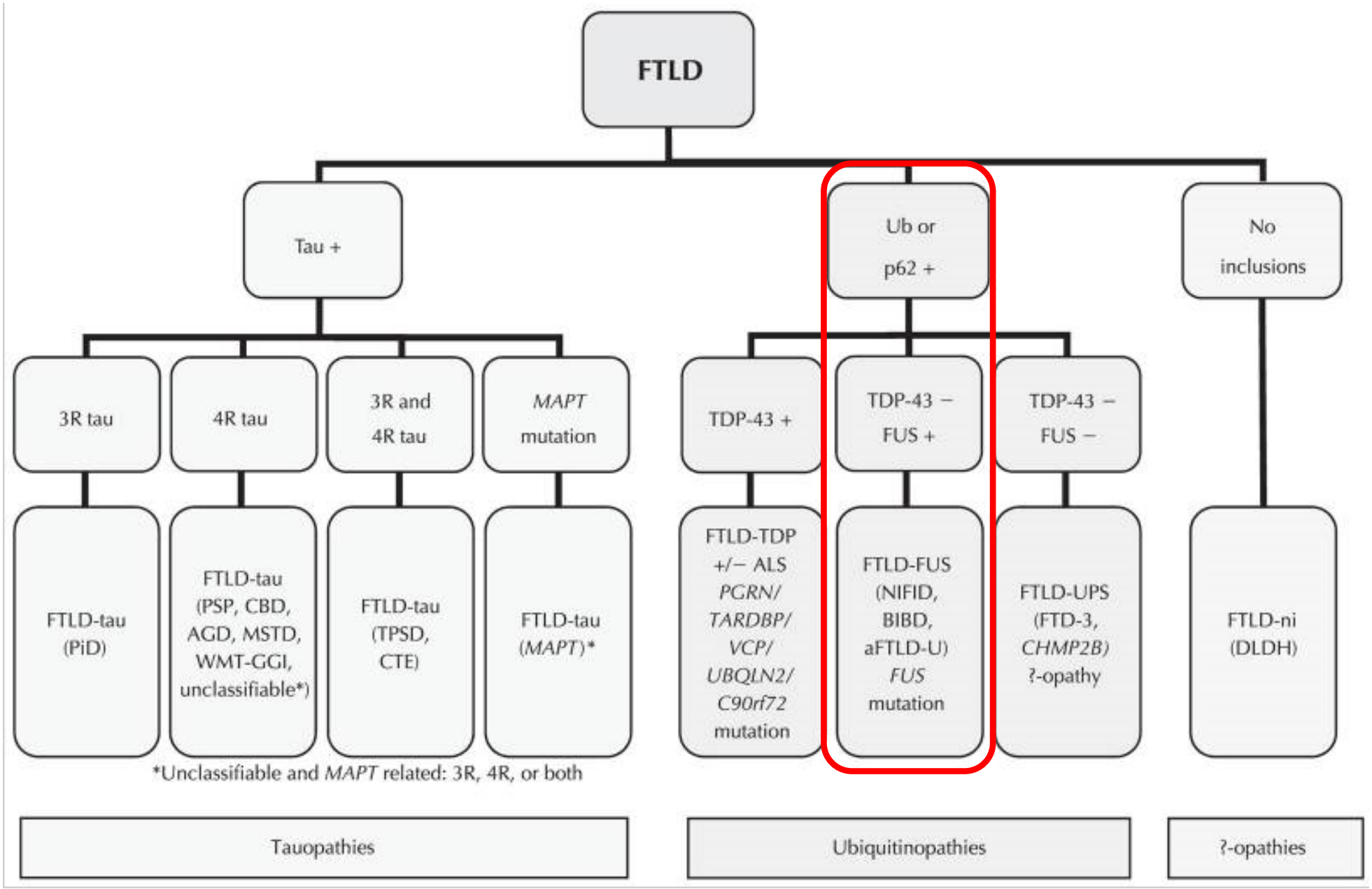

Tau
Phosphorylated TDP-43
Alpha-synuclein
Alpha-internexin

Case 4a

Case 4a







Bigio, *Arch Pathol Lab Med.* (2013) 137(3):314-325

FTLD-FUS (FET)

- FTLD subtypes that are immunoreactive for the *fused in sarcoma* protein (FUS)
  - Mostly sporadic without underlying FUS gene mutations
- 3 FTLD-FUS subtypes:
  - Basophilic Inclusion Body Disease (BIBD)
  - Neuronal Intermediate Filament Inclusion Disease (NIFID)
  - Atypical Frontotemporal Lobar Degeneration with Ubiquitinated Inclusions (aFTLD-U)

Pathologic Features of FTLD-FUS Subtypes

c

Diagnosis	Case	ub-ir NCI cerebral cortex	IF-ir NCI cerebral cortex	BI subcortical
aFTLD-U	1	++++	+	+
	2	++++	−	+
	3	++++	−	+
	4	++++	−	−
	5	++++	+	+
	6	++++	−	+
	7	++++	−	+
	8	++	−	−
	9	+++	−	+
	10	++++	−	+
NIFID	1	++++	+++	+
	2	++++	+++	++
	3	++++	+++	+
	4	++++	+++	++
	5	++++	++++	+
BIBD	1	++++	+	++++
	2	+++	+	++++
	3	++++	−	++++
	4	+++	++	++++
	5	++++	−	++++
	6	+++	+	++++
	7	+++	+	++++
	8	+++	+	++++

Semiquantitative grading: − none, + rare, ++ occasional, +++ moderate, ++++ numerous

aFTLD-U atypical frontotemporal lobar degeneration with ubiquitinated inclusions, *BI* basophilic inclusions, *BIBD* basophilic inclusion body disease, *IF-ir* intermediate filament immunoreactive, *NCI* neuronal cytoplasmic inclusions, *NIFID* neuronal intermediate filament inclusion disease, *ub-ir* ubiquitin immunoreactive

Mackenzie et al., Acta Neuropathol (2011) 121:207-218

Case 4a Final Diagnosis

Basophilic Inclusion Body Disease (BIBD)

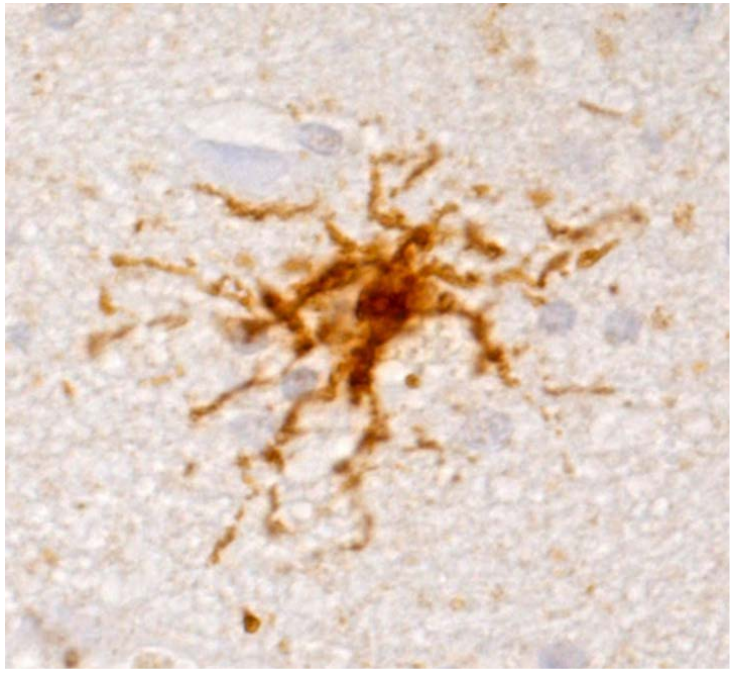
BIBD

- Histologic hallmark is the FUS-positive basophilic inclusion body
  - Mimics Pick bodies, but are tau-negative
- Basophilic inclusion bodies preferentially affect the superficial laminae of the neocortex and are also in the subcortical nuclei
- Clinically may present as behavioral-variant frontotemporal dementia or juvenile or adult-onset ALS
- Early age of onset, but no genetic cause identified

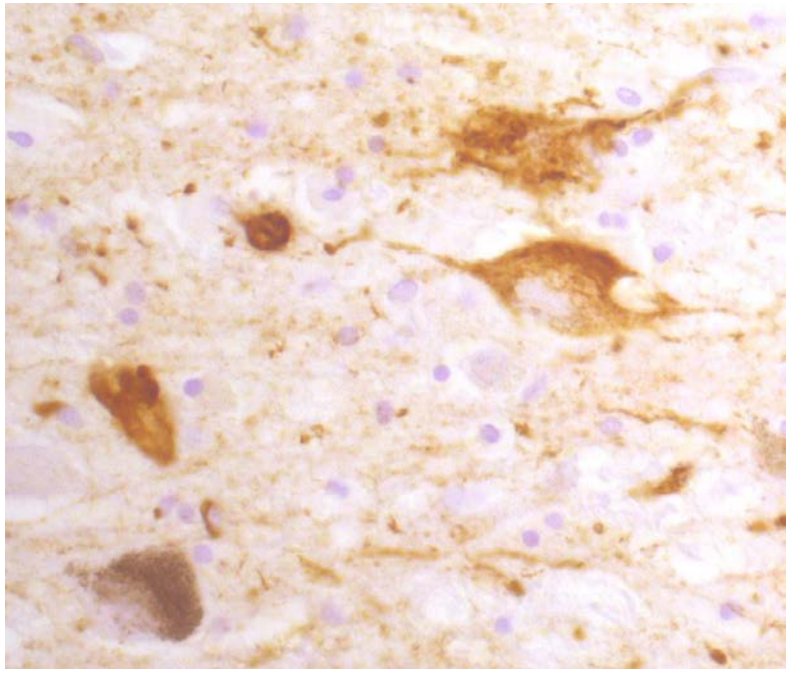
Additional stains for Case 4b

- Neocortical amyloid plaques (mild)
- Negative for TDP-43, FUS, α-synuclein

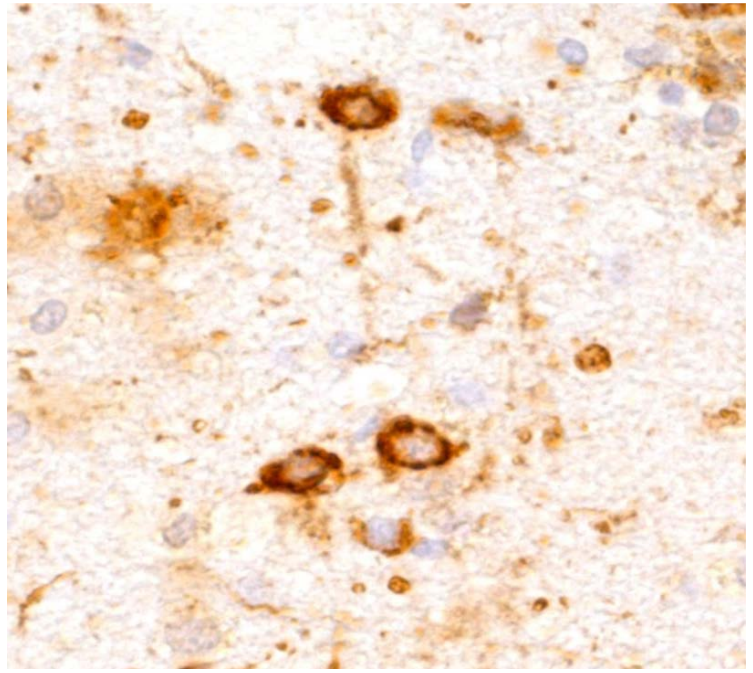
Case 4b



Frontal lobe

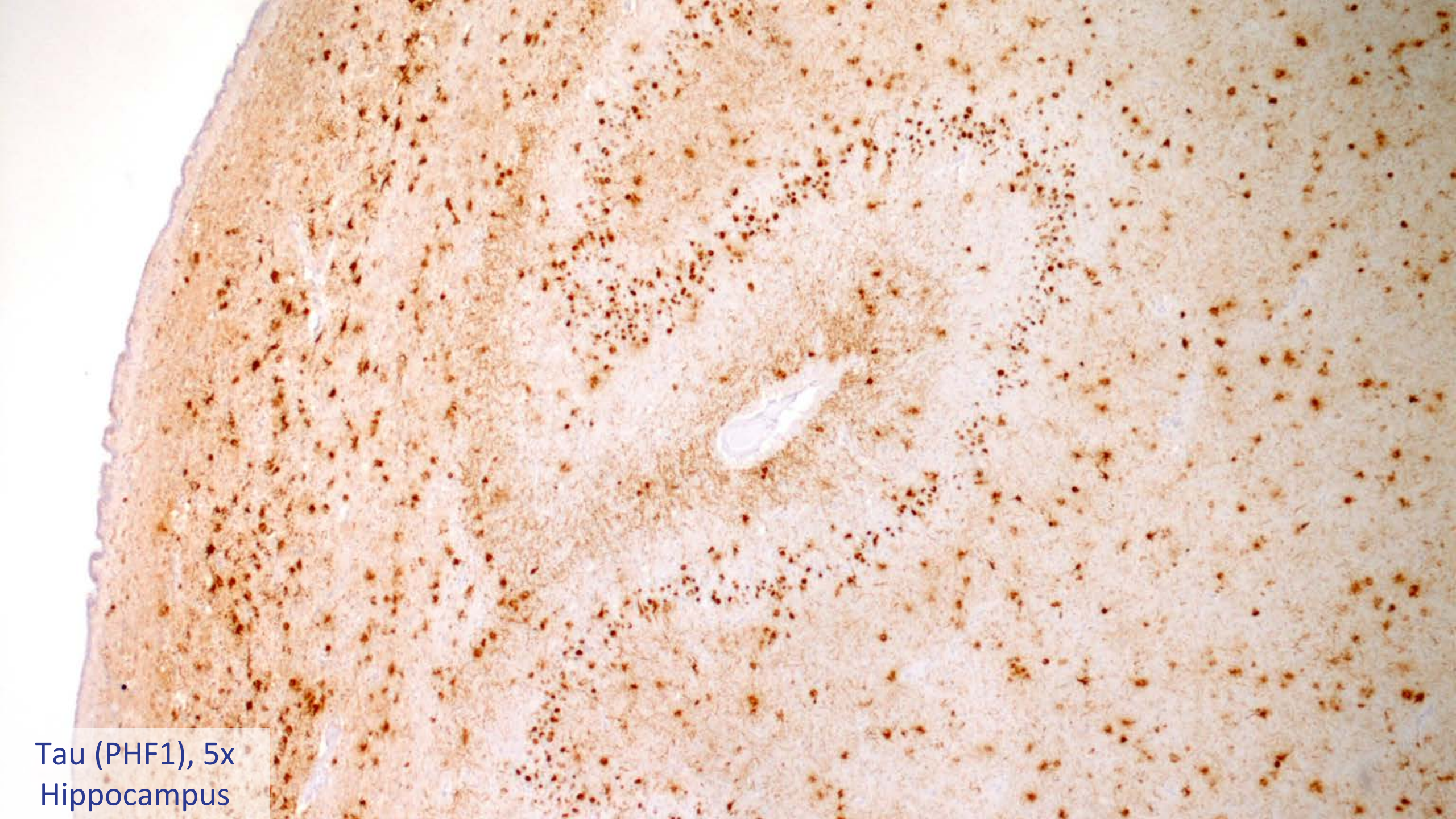


Substantia Nigra

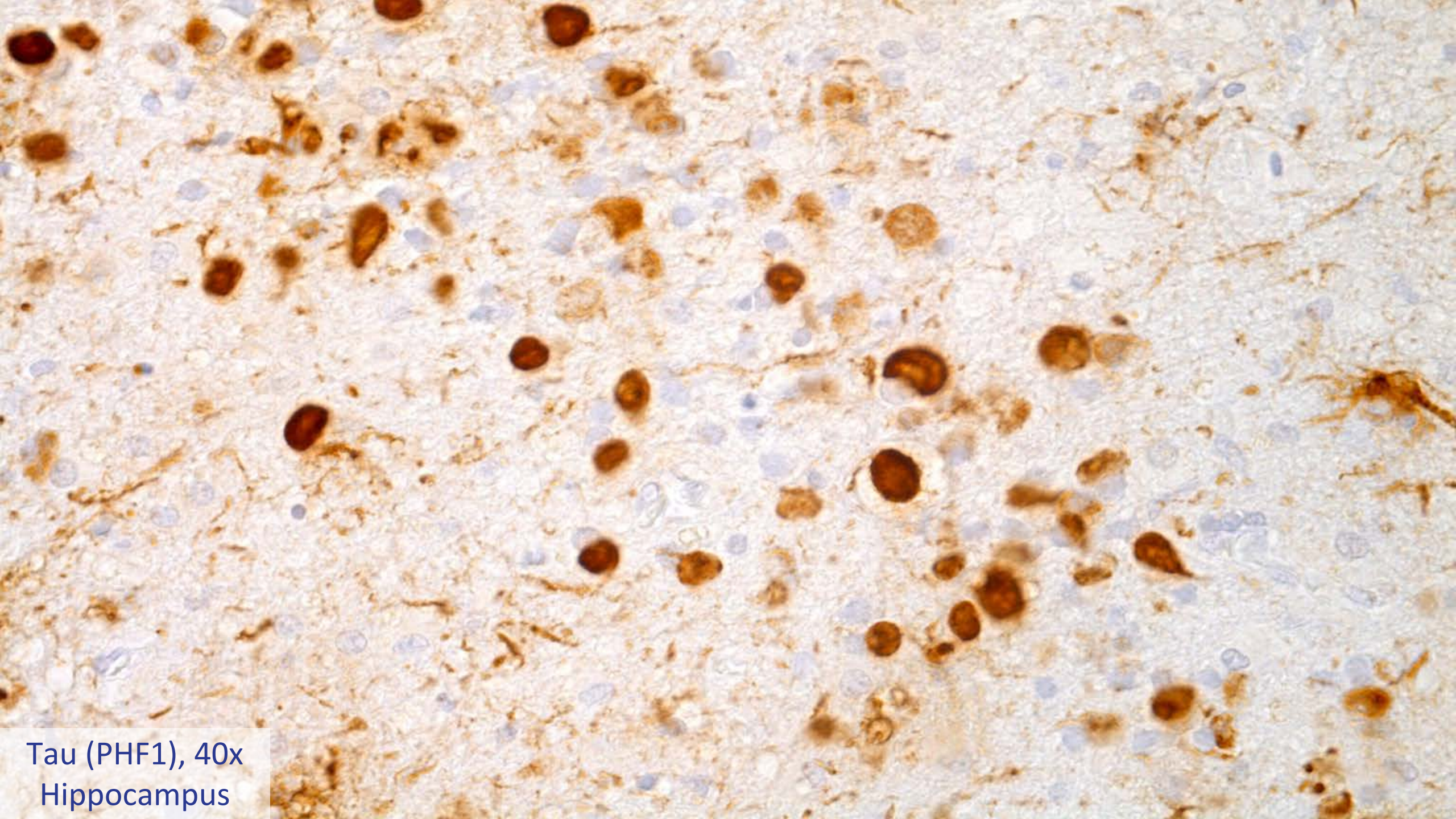


Cerebellar White matter

Tau (PHF1)

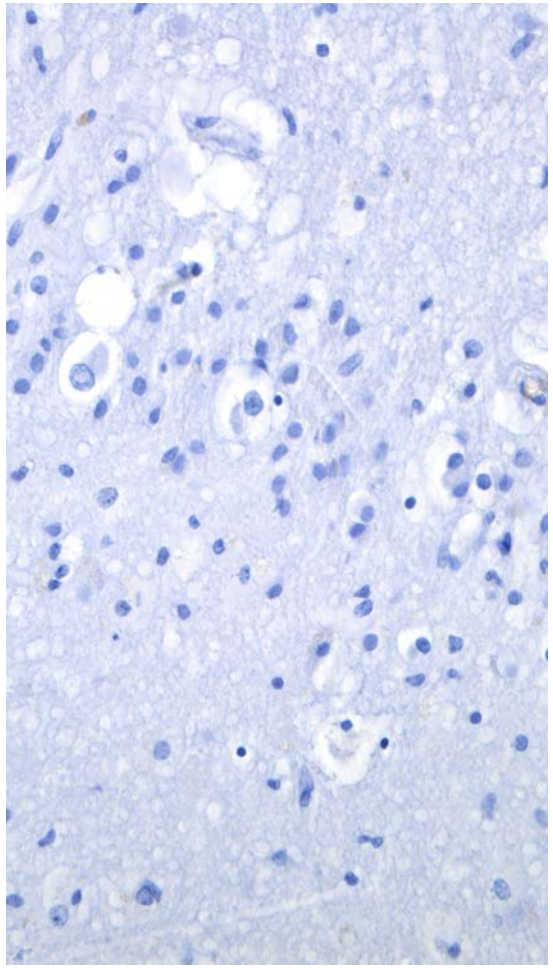


Tau (PHF1), 5x
Hippocampus

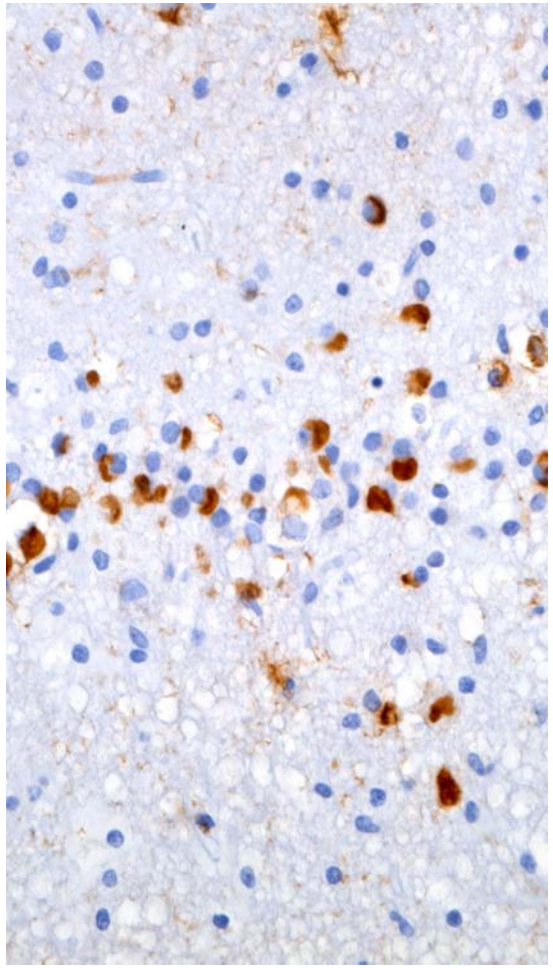


Tau (PHF1), 40x
Hippocampus

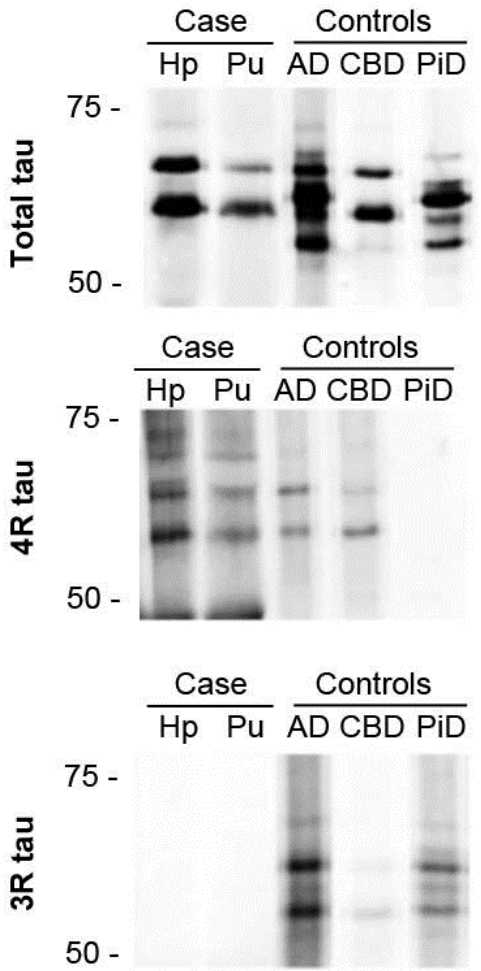
Case 4b



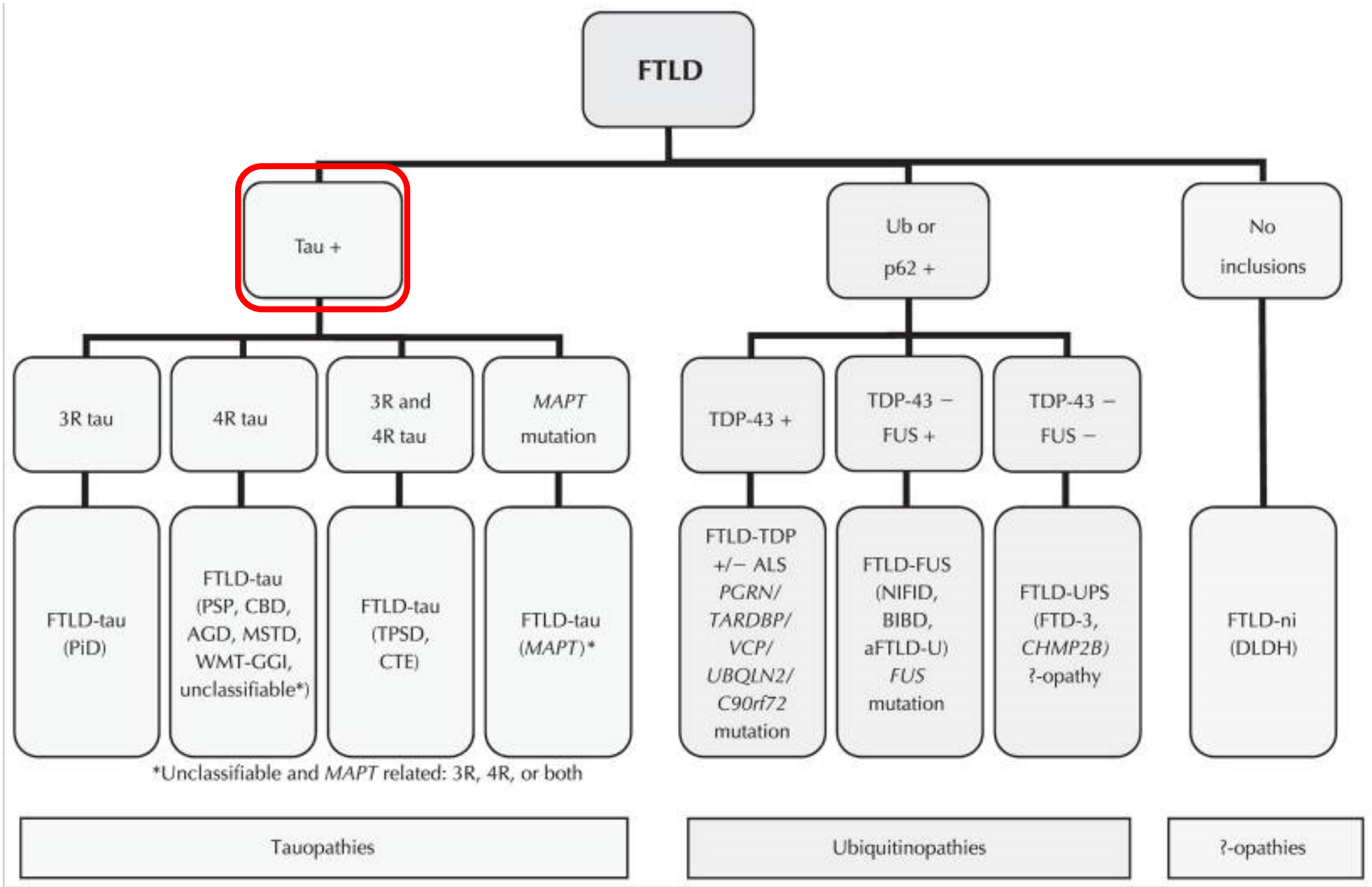
3R-Tau (RD3), 40x
Hippocampus



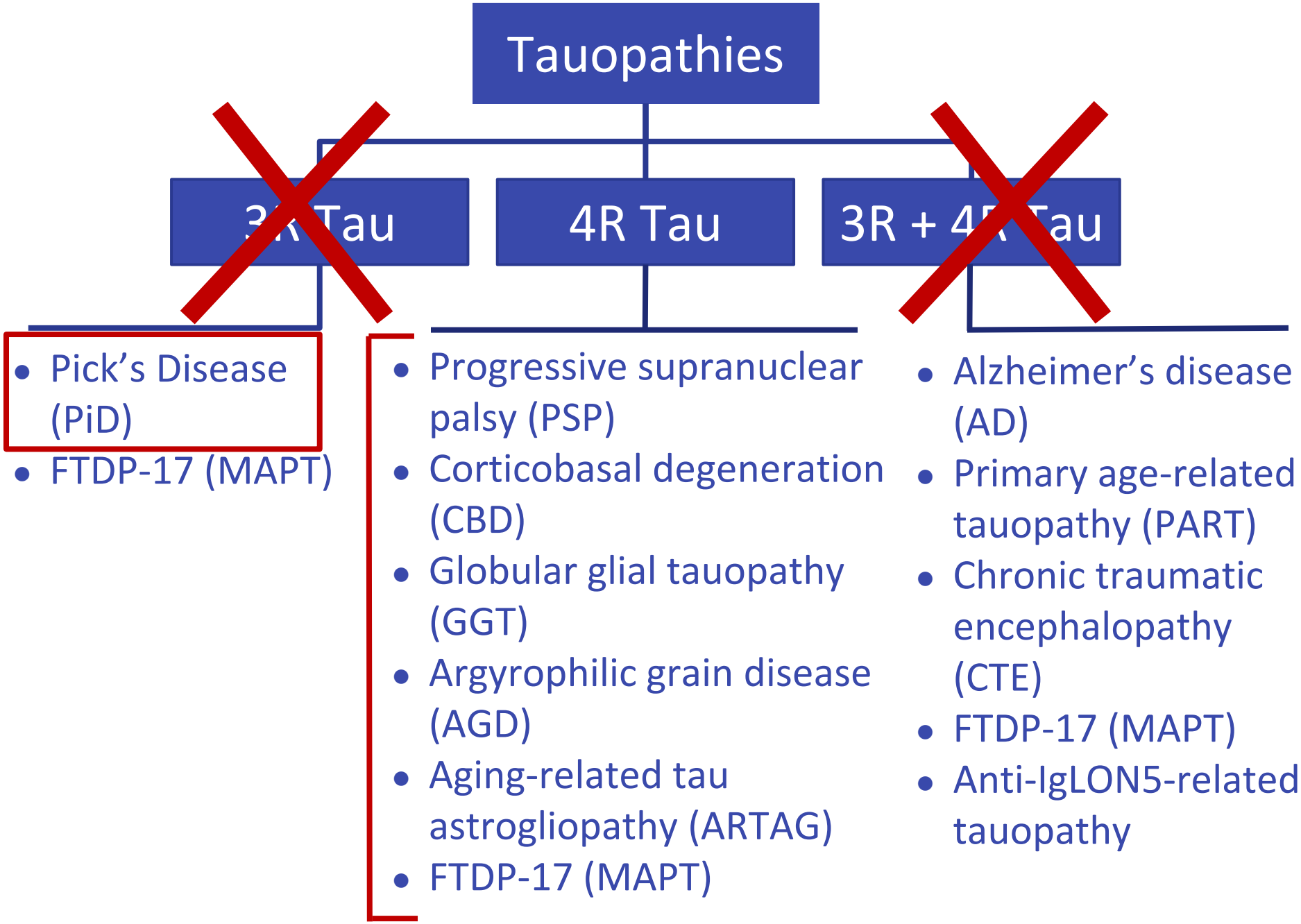
4R-Tau (RD4), 40x
Hippocampus



Biochemistry
(Immunoblot)



Bigio, *Arch Pathol Lab Med.* (2013) 137(3):314-325


Tauopathies
3R Tau
4R Tau
3R + 4R Tau
• Pick's Disease (PiD)
• FTDP-17 (MAPT)
• Progressive supranuclear palsy (PSP)
• Corticobasal degeneration (CBD)
• Globular glial tauopathy (GGT)
• Argyrophilic grain disease (AGD)
• Aging-related tau astrogliopathy (ARTAG)
• FTDP-17 (MAPT)
• Alzheimer's disease (AD)
• Primary age-related tauopathy (PART)
• Chronic traumatic encephalopathy (CTE)
• FTDP-17 (MAPT)
• Anti-IgLON5-related tauopathy

Case 4b Final Diagnosis

Progressive supranuclear palsy (PSP) with 4R-tau positive Pick body-like inclusions

Acknowledgements for Case 4b

Dr. Gabor G. Kovacs, MD PhD
Dr. John Q. Trojanowski, MD PhD

References (Case 4a)

- Mackenzie IRA, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathologica. 2010;119(1):1-4.
- Bigio EH. Making the Diagnosis of Frontotemporal Lobar Degeneration. Archives of pathology & laboratory medicine. 2013;137(3):314-325.
- Mackenzie, I.R.A., Munoz, D.G., Kusaka, H. et al. Distinct Pathological Subtypes of FTLD-FUS. Acta Neuropatholica. 2011; 121: 207.

References (Case 4b)

- **Kovacs GG, et al. (2017) Tauopathy with hippocampal 4-repeat tau immunoreactive spherical inclusions: a report of three cases. Brain Pathology doi:10.1111/bpa.12482**
  - ***This DSS case is one of the three cases described in this paper****
- Dickson DW, et al. (2007) Progressive Supranuclear Palsy: Pathology and Genetics. 17:74-82.
- Irwin DJ, et al. (2016) Deep clinical and neuropathological phenotyping of Pick disease. Ann Neurol 79(2):272-87.
- Kovacs GG (2015) Neuropathology of tauopathies: principles and practice. Neuropathology and Applied Neurobiology 41:3-23.
- Nelson PT, et al. (2016) “New Old Pathologies”: AD, PART, and Cerebral Age-related TDP-43 with Sclerosis (CARTS). J Neuropathol Exp Neurol 75(6); 482-98.