MAYO CLINIC

Neurodegenerative tauopathies: clinicopathologic correlates

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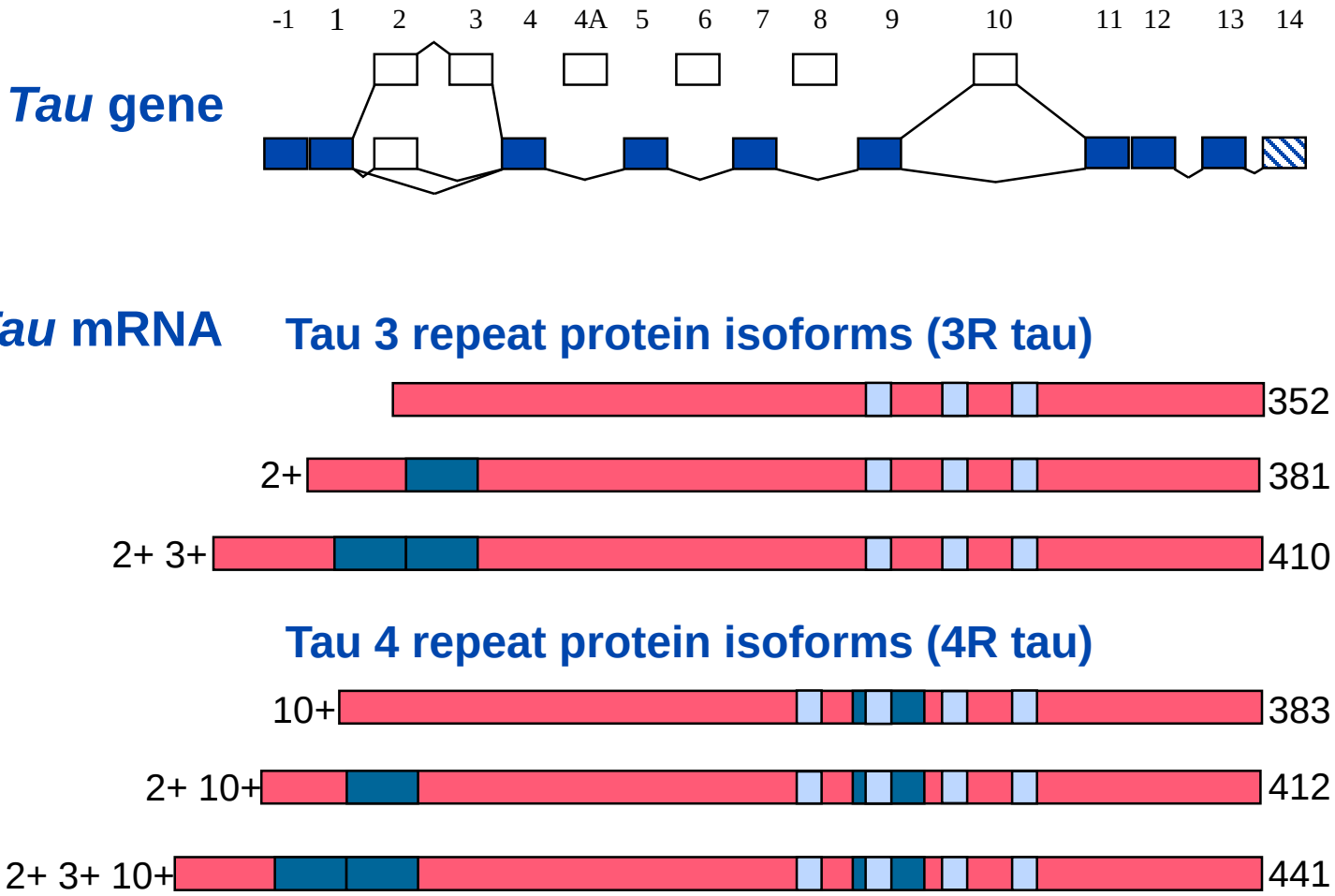
Tau abnormalities in neurodegenerative tauopathies

- Abnormally phosphorylated
  - More phosphorylation than normal.
  - Phosphorylation of abnormal sites (*e.g.,* microtubule binding domain)
- Altered conformation
  - Normally, tau is a natively unfolded (random structure) protein that is soluble.
  - In disease states, it forms highly ordered fibrils with beta sheet secondary structure.
- Ubiquitination
  - Multiple target lysines in tau
  - Several E3 ligases; CHIP is implicated in ubiquitination of phospho-tau species.
- Truncated – C' and N' termini in disease
  - Proteases – calpain, caspase 3

Alternative mRNA splicing of the tau gene generates 6 major isoforms



Molecular classification of neurodegenerative tauopathies

- 3R tauopathies
  - Pick disease (PiD)
- 4R tauopathies
  - Corticobasal degeneration (CBD)
  - Progressive supranuclear palsy (PSP)
  - Argyrophilic grain disease (AGD)
- 3R + 4R tauopathies
  - Neurofibrillary tangle dementia (NFTD)

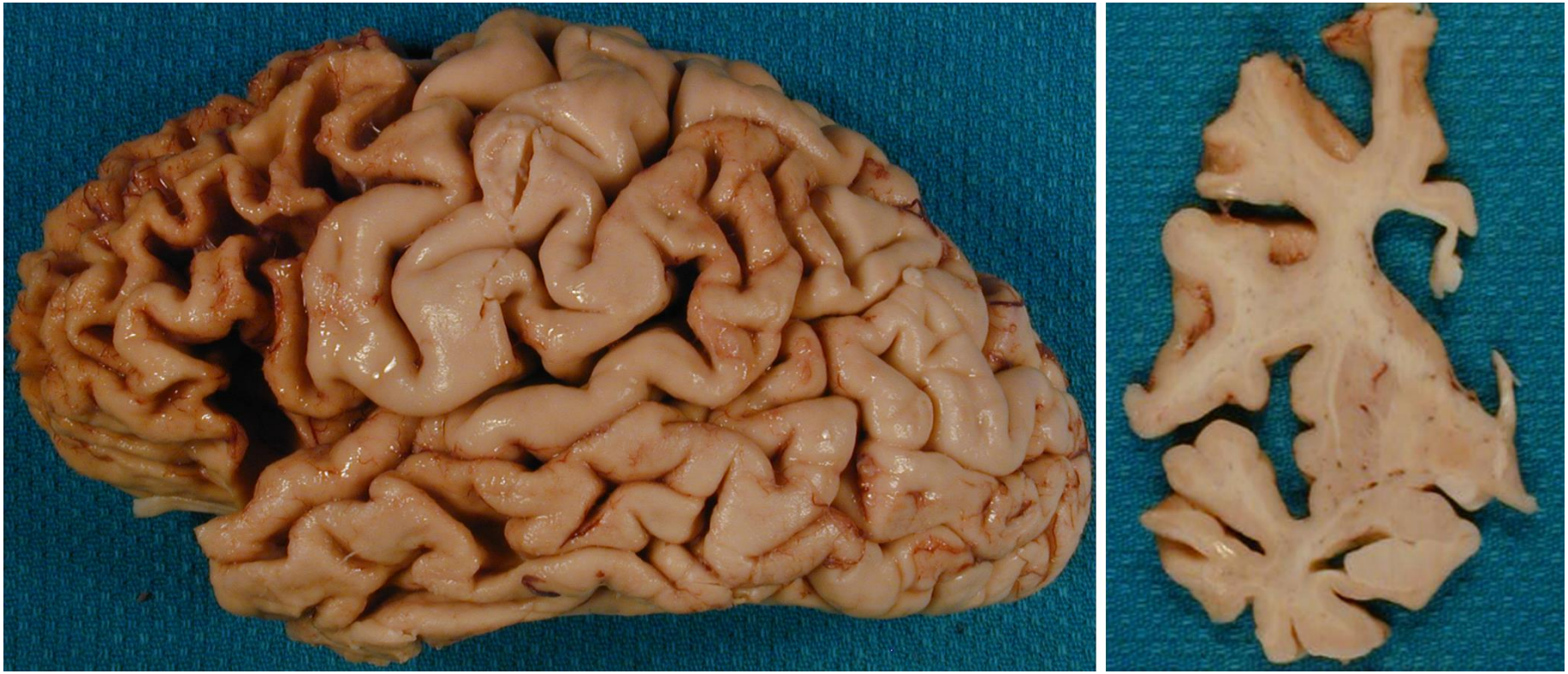
Clinical spectrum of neurodegenerative tauopathies

- Frontotemporal dementia spectrum
  - Behavioral variant frontotemporal dementia
  - Progressive aphasia
    - Progressive nonfluent aphasia
    - Semantic dementia (uncommon in tauopathies)
  - Progressive asymmetric apraxic syndrome (corticobasal syndrome)
  - Progressive amnestic syndrome
- Atypical parkinsonism
  - Richardson syndrome (PSP syndrome)
  - Pure akinesia with gait failure

Pick's disease

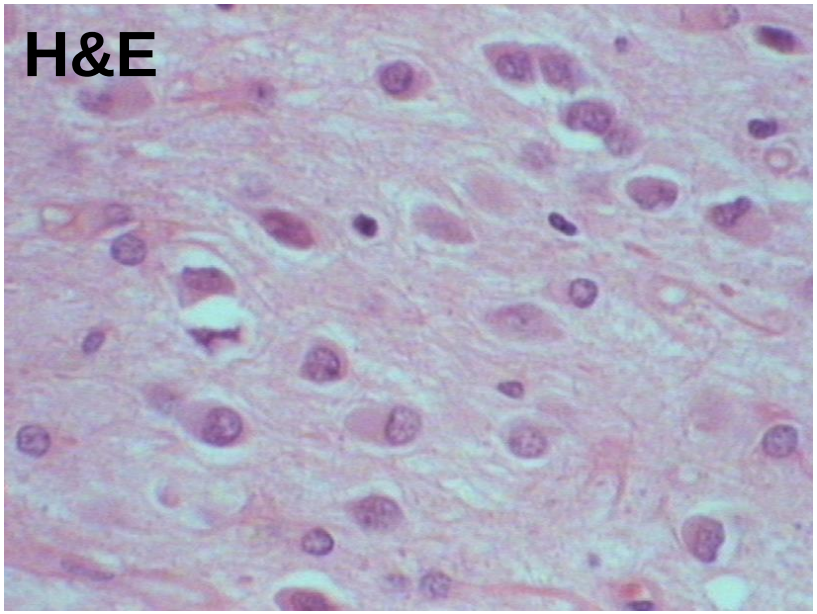
- Frontal lobe dementia syndrome
  - May present with progressive aphasia
  - May present with corticobasal syndrome (~25% of Pick's disease cases in Mayo Clinic Brain Bank)
- Sporadic disorder; familial cases may have mutations in tau gene
- Often presenile (before age 65 y/o)
- Rare (<5% of all frontotemporal degenerations)

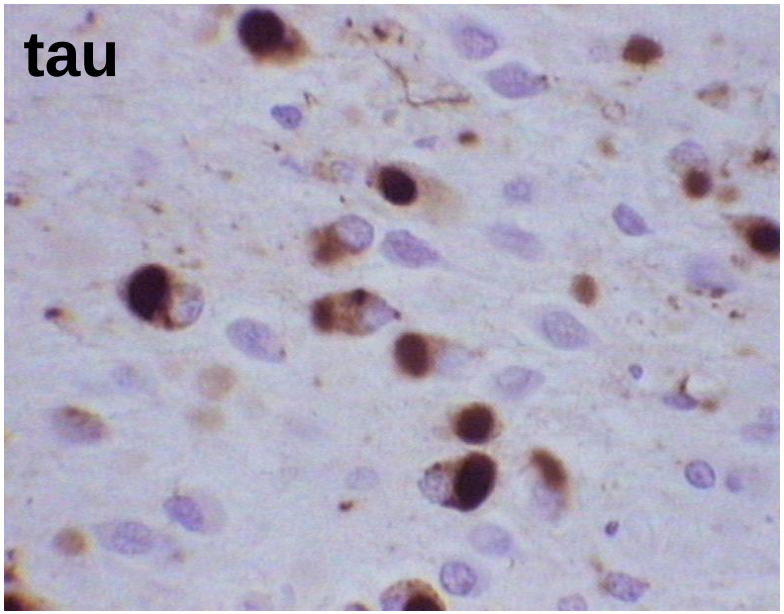
Pick's disease – lobar atrophy



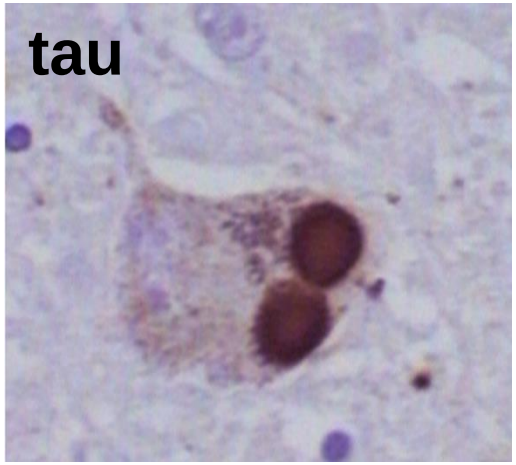
Circumscribed atrophy - frontotemporal

Pick bodies

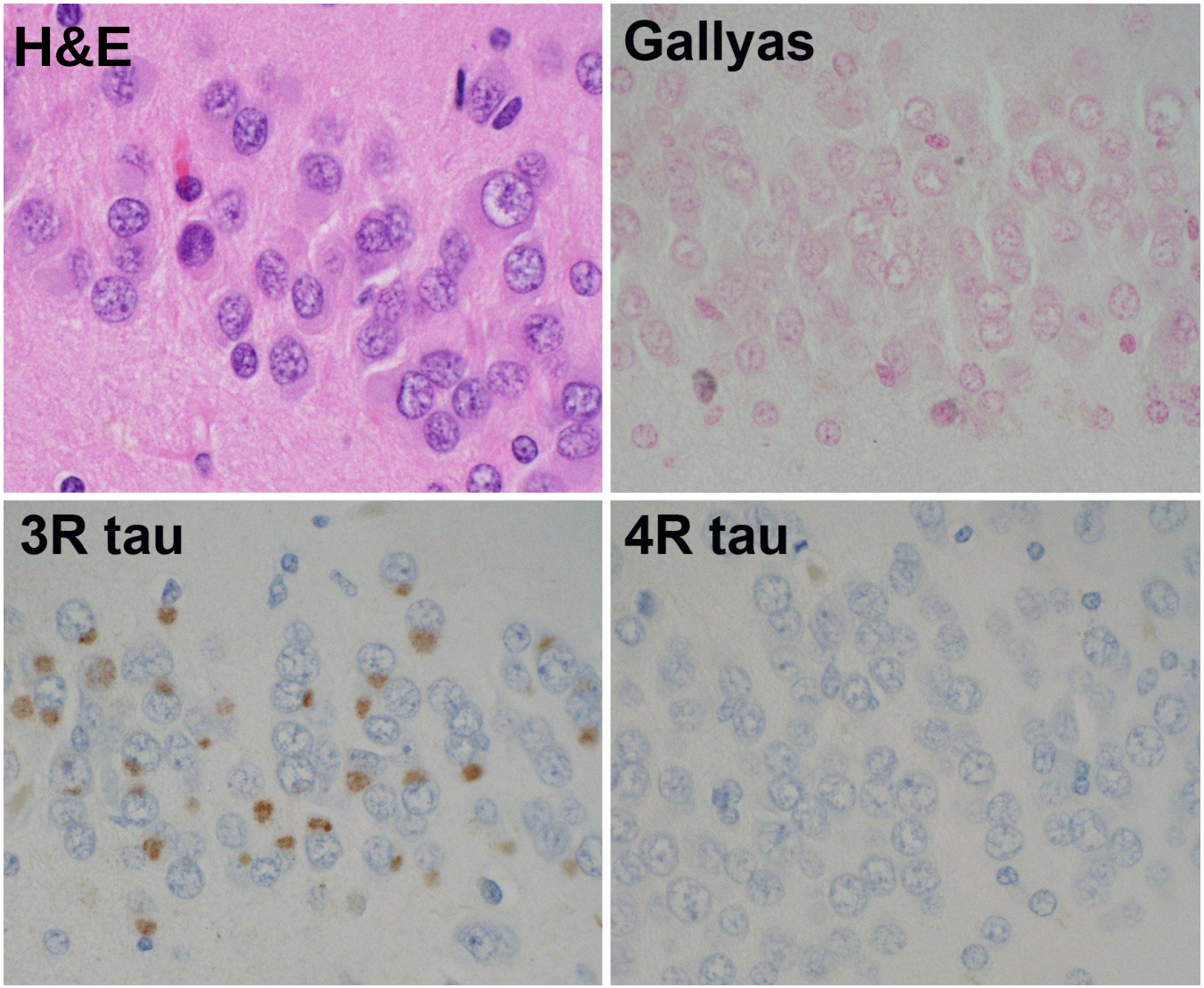




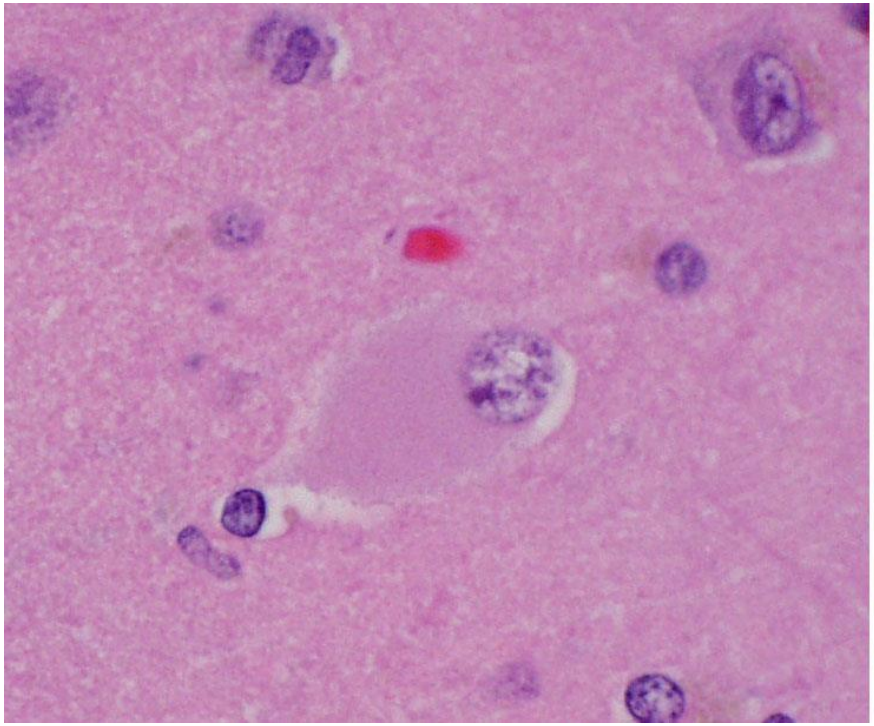
Pick bodies in hippocampus (above) and locus ceruleus

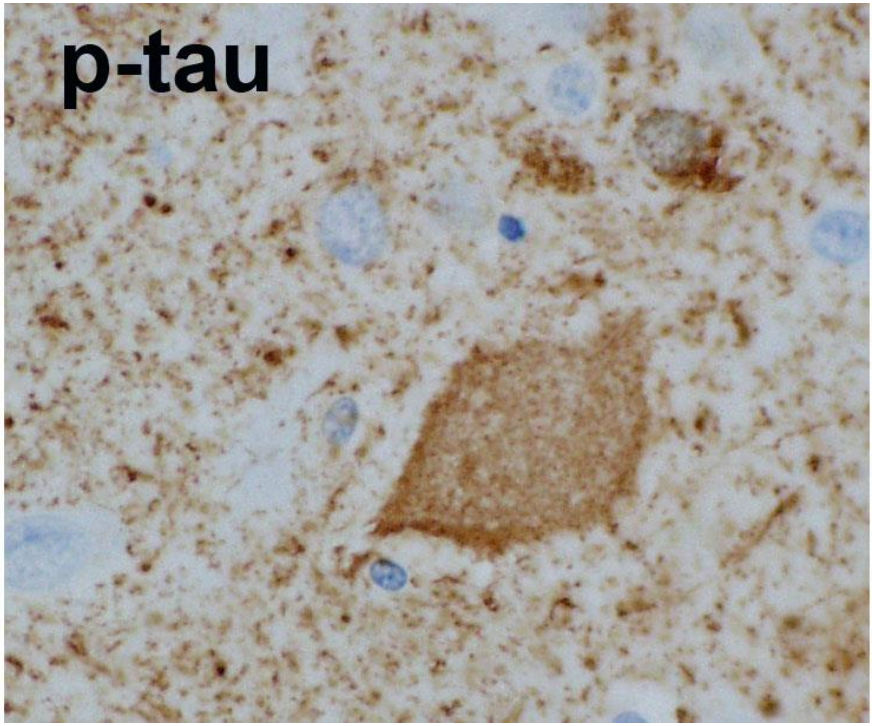


Pick bodies – 3R tau



Pick cells



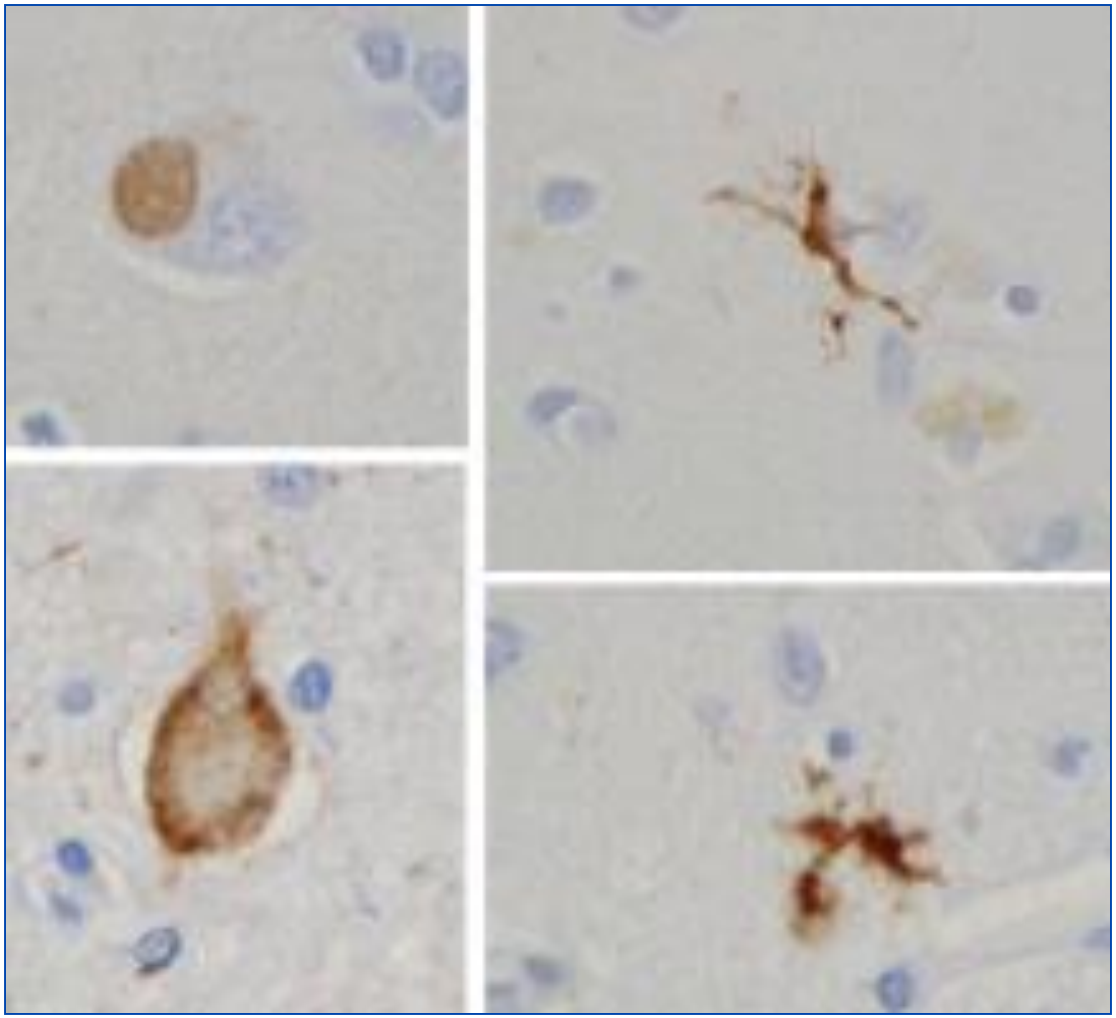


also known as “ballooned neurons”

Glial pathology in Pick's disease

neurons glia

3R tau



4R tau

Corticobasal degeneration (CBD)

- Usually sporadic, but some familial cases.
  - Pathology & some of the clinical features overlap with FTDP-17 (especially, multisystem tauopathy)
  - Novel *MAPT* mutation (N410H*)
- Progressive asymmetric rigidity & apraxia
- Nonfluent aphasia or frontal lobe dementia is common
- Imaging studies show atrophy and hypometabolism in superior frontal and parasagittal regions.

* Kouri N, Carlomagno Y, Baker M, Liesinger AM, Caselli RJ, Wszolek ZK, Petrucelli L, Boeve BF, Parisi JE, Josephs KA, Uitti RJ, Ross OA, Graff-Radford NR, DeTure MA, Dickson DW, Rademakers R. Novel mutation in MAPT exon 13 (p.N410H) causes corticobasal degeneration. *Acta Neuropathol* 2014;127:271-282.

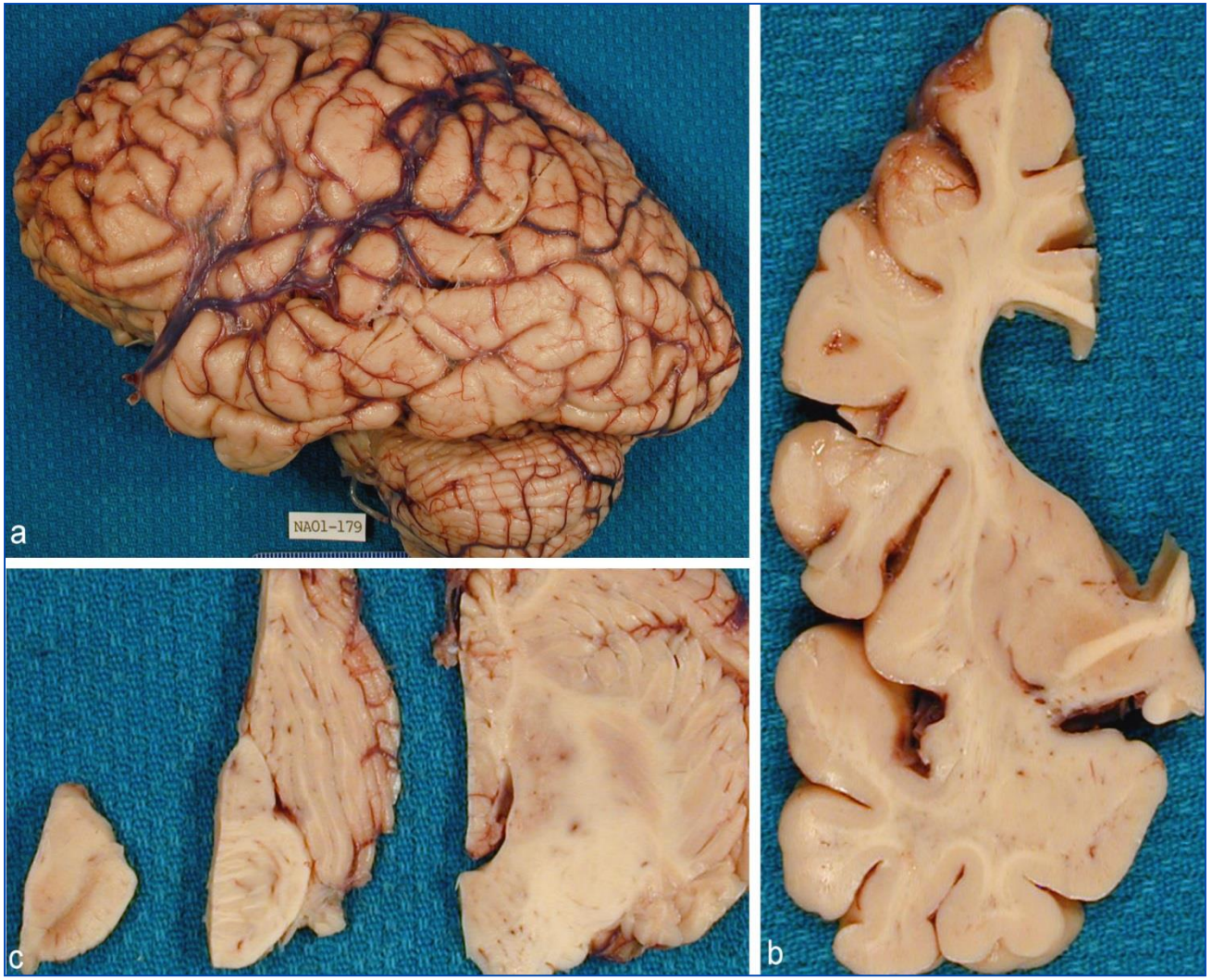
Terminology

- CBS – corticobasal syndrome
  - Asymmetrical, akinetic-rigid syndrome with apraxia, myoclonus and dystonia
    - Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. *Brain* 1989;112:1171-92.
- CBD – corticobasal degeneration
  - 4R tauopathy affecting cortical and subcortical gray and white matter with threads, ballooned neurons and astrocytic plaques
    - Dickson DW, Bergeron C, Chin SS, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol* 2002;61:935-46.

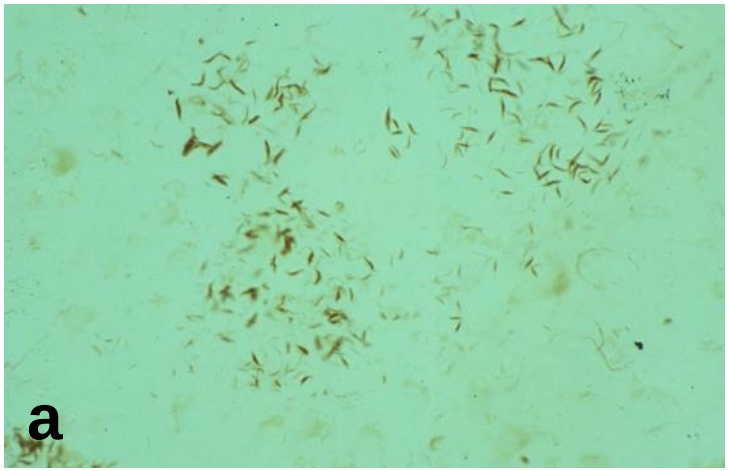
Neuropathology of CBD

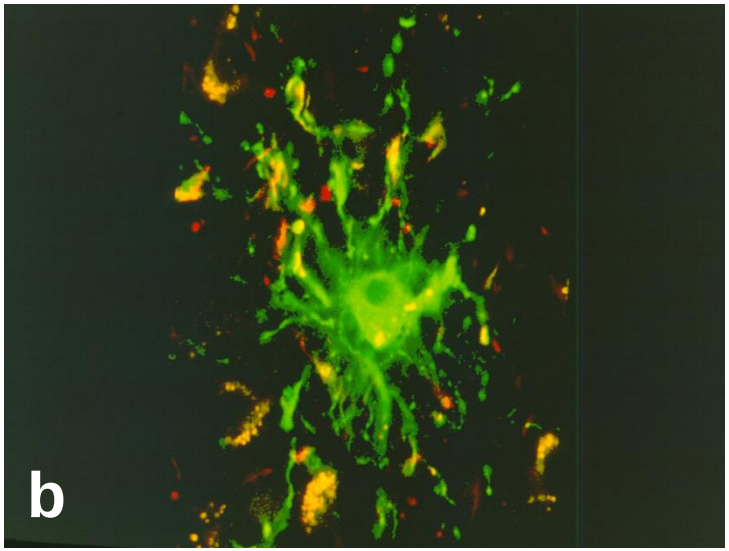
- Gross findings
  - Variable degree of cortical & basal ganglia atrophy, with loss of pigment in substantia nigra
- Microscopic findings
  - Ballooned neurons are usually numerous
  - Tau-immunoreactive neuronal lesions “NFT-like” pleomorphic neuronal inclusions
  - Glial lesions - astrocytic plaques & oligodendroglial coiled bodies
  - Numerous neuropil threads

Corticobasal degeneration

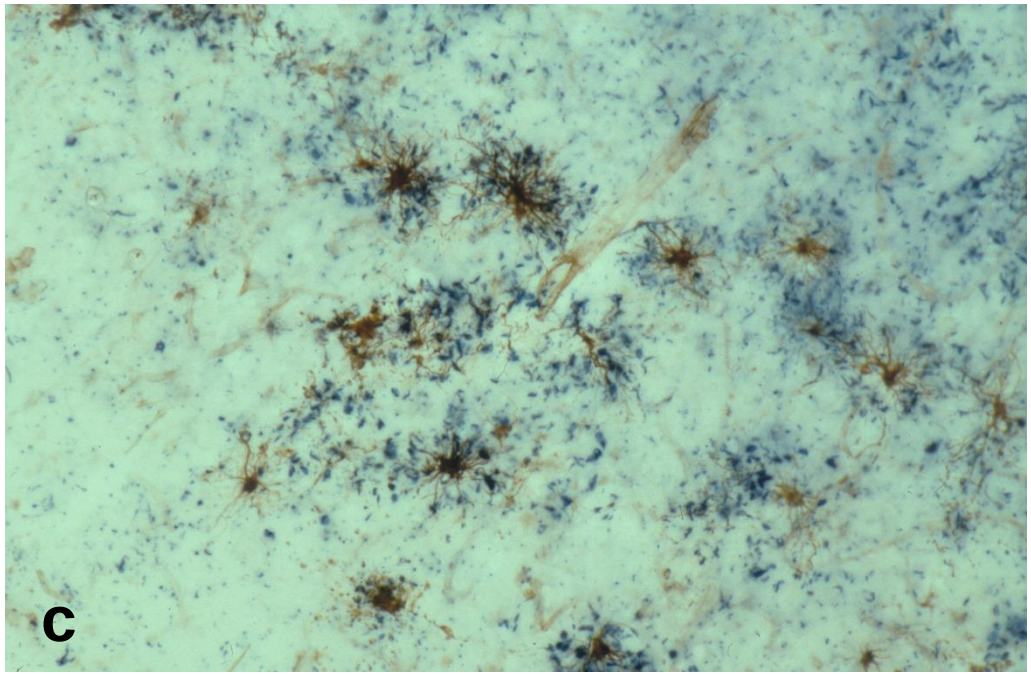


CBD – astrocytic plaques





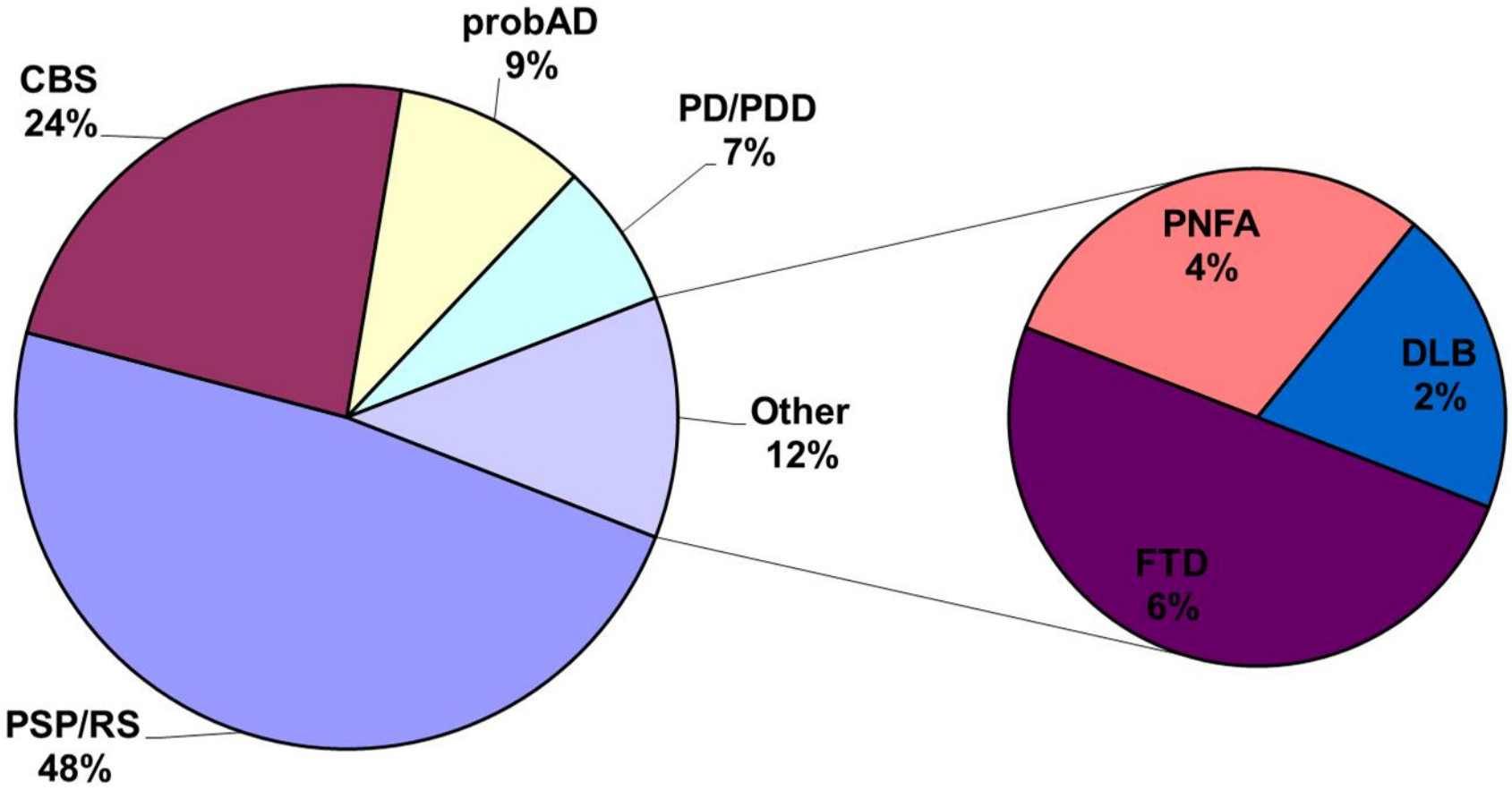
a – Ab39 (NFT-specific antibody)
b – Confocal: CD44 (green) & tau (red) – double stained (yellow)
c – GFAP (blue) & tau (blue)



CBD clinical presentations with respect to distribution of focal cortical pathology

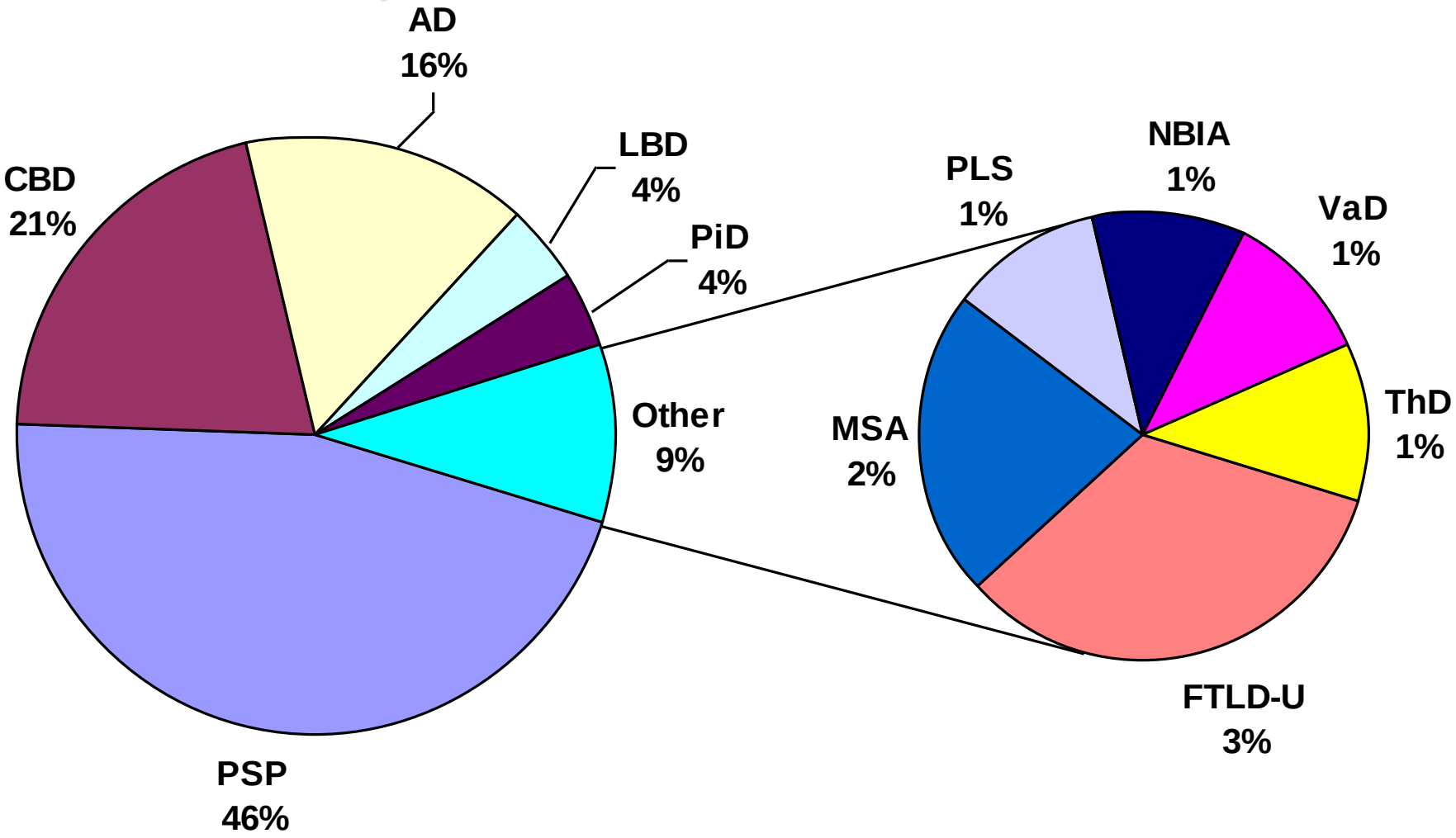
- Asymmetrical cortical pathology
  - Parasagittal – superior frontoparietal
    - Corticobasal syndrome
  - Peri-Sylvian (frontal operculum)
    - Progressive nonfluent aphasia (apraxia of speech)
  - Occipitotemporal
    - Posterior cortical syndrome
- Symmetrical cortical pathology
  - Frontal lobe
    - Frontal dementia
  - Peri-Rolandic (motor cortex)
    - PSP/Richardson syndrome

CBD – clinical presentations (Mayo Clinic brain bank)



PSP/Richardson syndrome is the most common clinical presentation of CBD.

CBS – underlying pathology (Mayo Clinic brain bank)



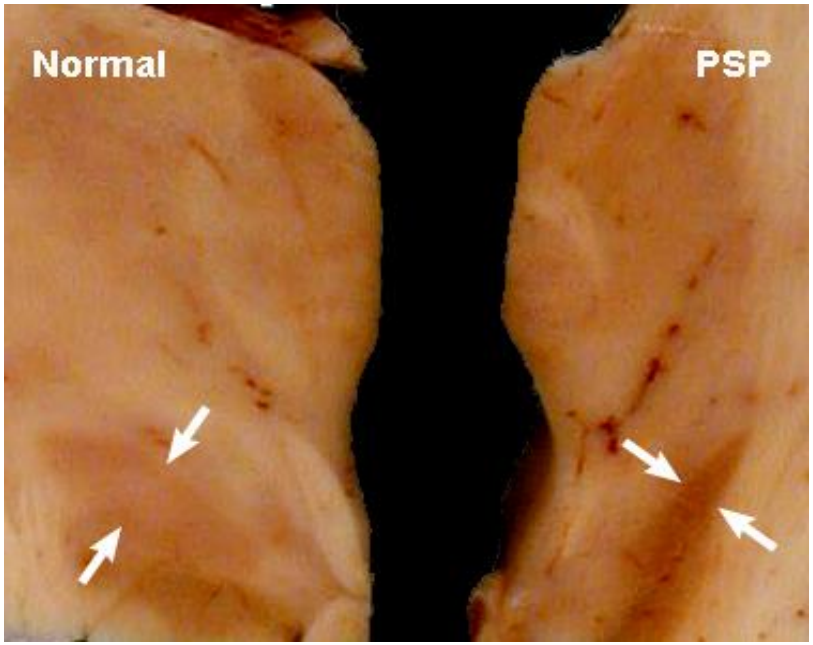
PSP is the most common pathologic substrate of CBS.

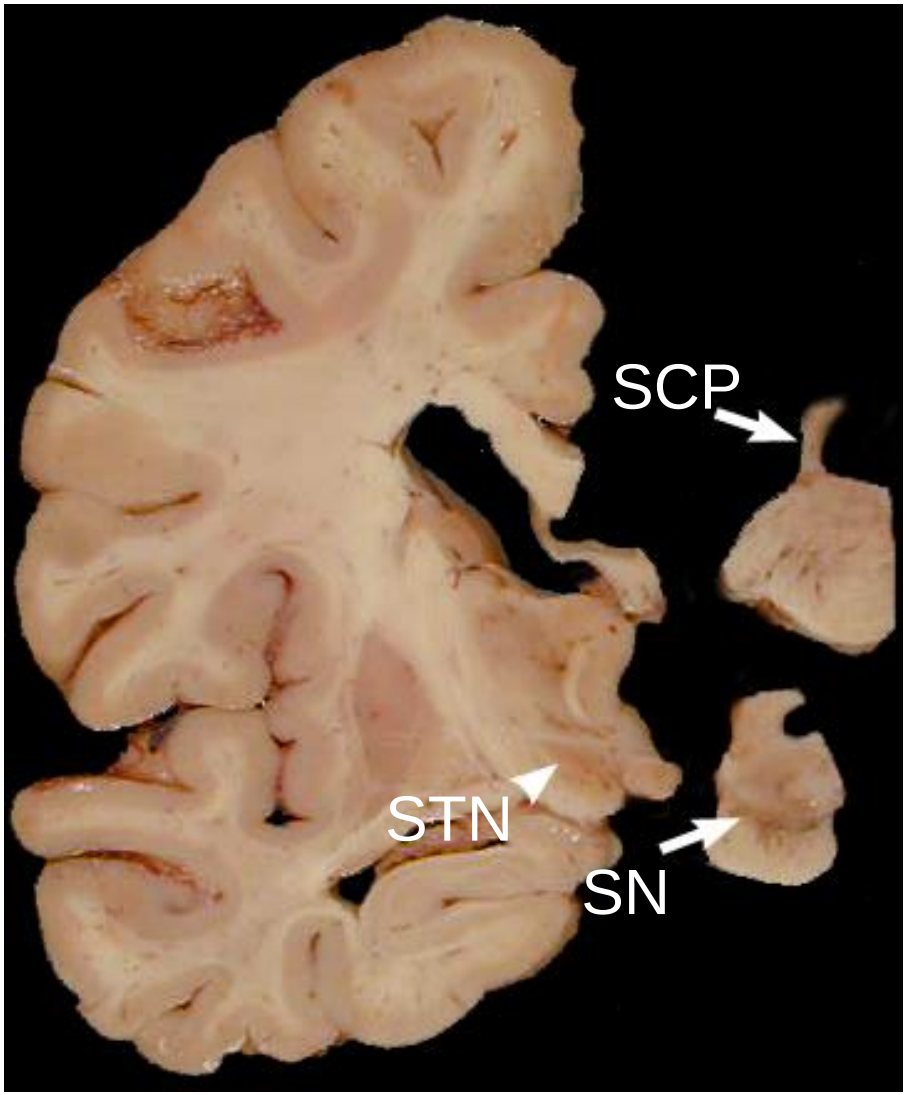
Progressive supranuclear palsy

- Clinical features of typical PSP
  - Presentation: unexplained falls
  - Neurological findings:
    - Symmetric truncal rigidity with nuchal dystonia
    - Bradykinesia
    - Slow and unsteady gait
    - Impaired eye movements, particularly downward gaze
    - Frontal lobe symptoms - subcortical dementia
  - Duration: 7 years
- Atypical presentations
  - Corticobasal syndrome, progressive nonfluent aphasia, frontal lobe dementia

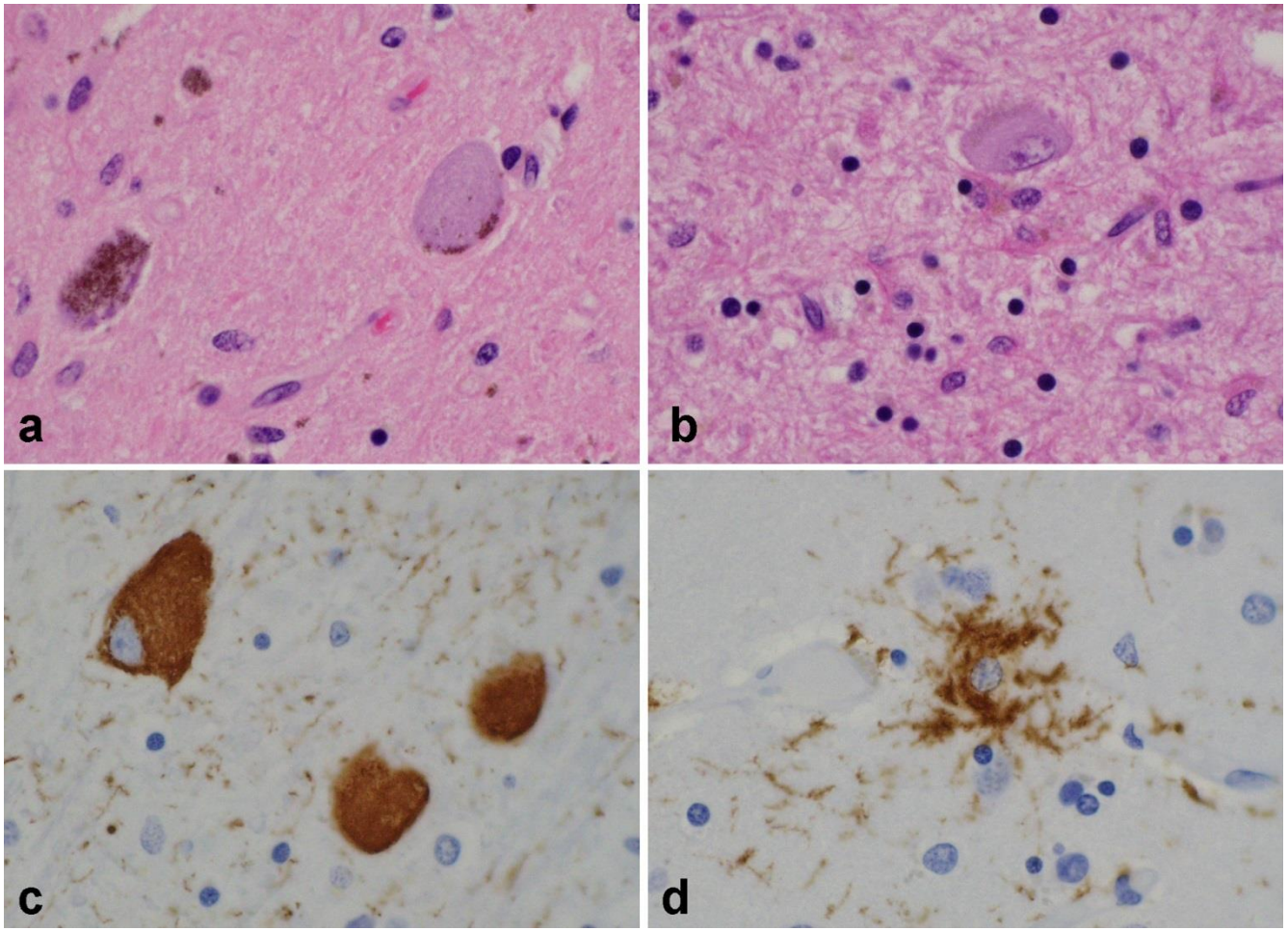
Progressive supranuclear palsy

Subthalamic nucleus





PSP – microscopic findings

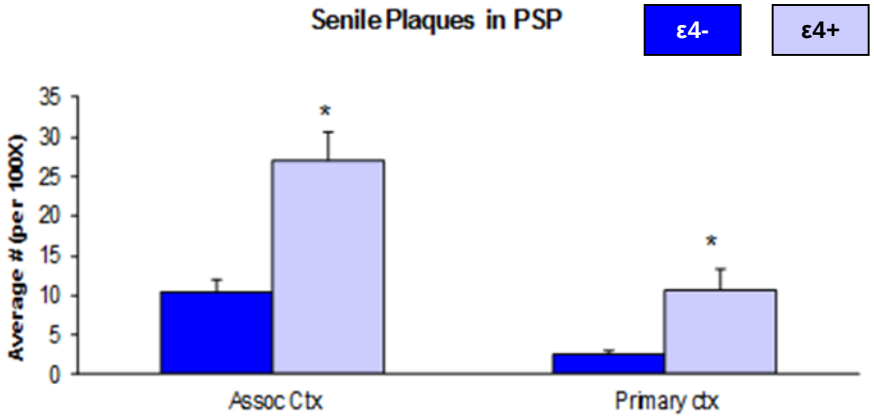


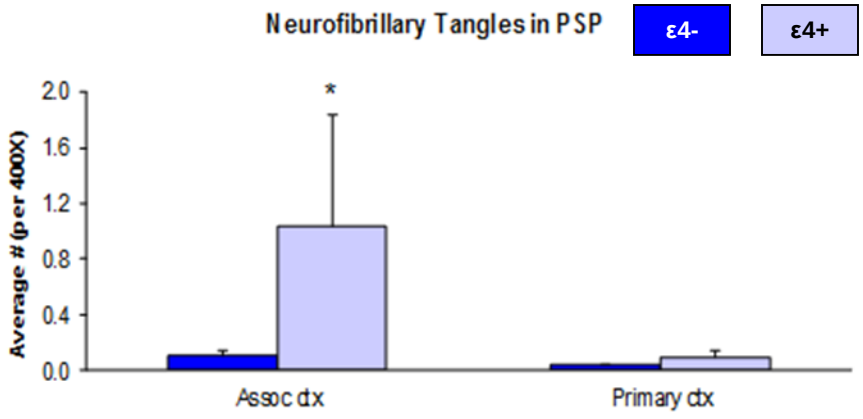
a – substantia nigra globose NFT; b – subthalamic nucleus gliosis;
c – tau-positive NFT; d - tau-positive astrocyte (“tufted astrocyte”)

Mixed PSP

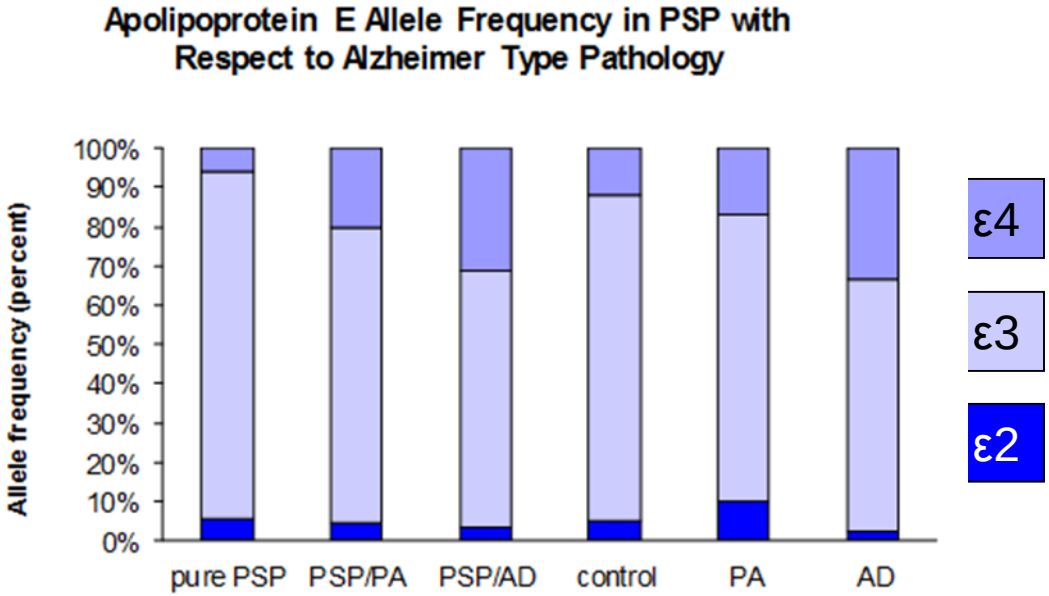
- PSP with concurrent degenerative changes (n=1095)
  - Alzheimer type pathology
    - Plaques & tangles = AD (8%)
    - Plaques, only = pathologic aging (PA) (16%)
  - Lewy body disease (7%)
  - Argyrophilic grains (25%)

Alzheimer pathology & apolipoprotein-E in PSP





AD-type pathology in PSP correlates with age, female sex and APOE ε4 carrier state, but not tau haplotype.



Atypical clinical presentations of PSP

- PSP presenting with frontotemporal dementia syndromes
  - Frontal lobe dementia
  - Progressive nonfluent aphasia
  - Corticobasal syndrome
- PSP presenting with atypical parkinsonism
  - Asymmetric L-DOPA responsive parkinsonism (PSP-P)
  - Pure akinesia/gait failure with freezing (PAGF)

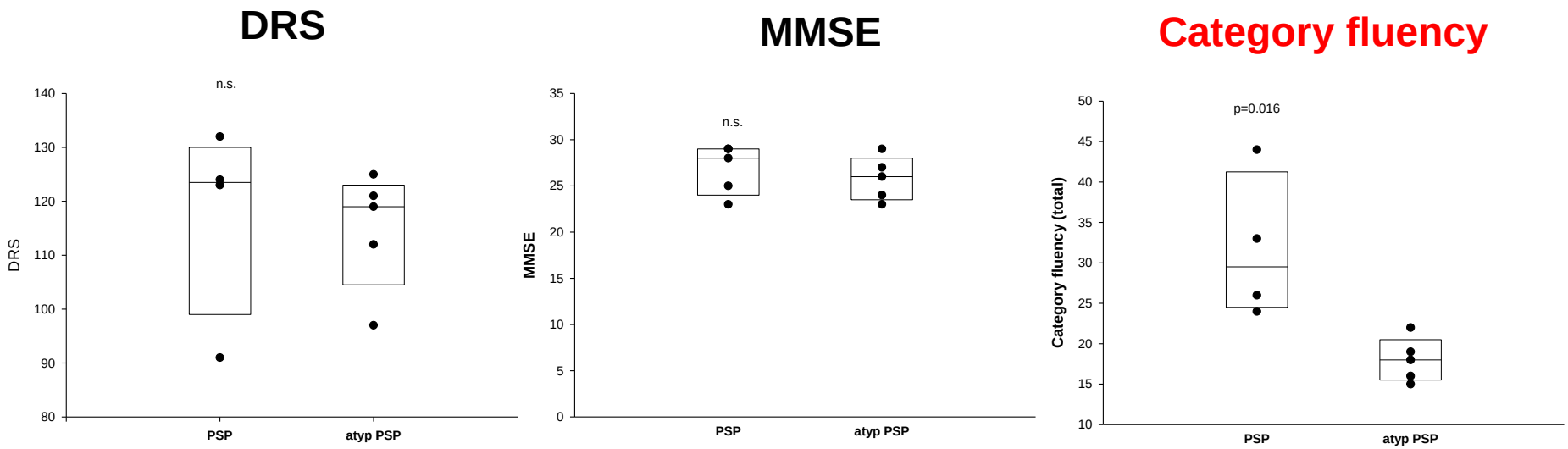
PSP with frontal type dementia

		AD Classification			Tau pathology			
Case	AD path.	CERAD	Khachaturian	Braak stage	Subcortical path.	GM	TA	WM
Frontal lobe dementia								
1	0	0	0	0	3–5+	3+	5+	5+
2	0	0	0	0	3+	1+	1+	3+
3	0	0	0	1	1–3+	1+	1+	1+
4	rare NP	0	0	1	3+	3+	3+	1+
5	0	0	0	2	1–3+	1+	5+	1+
6	mild NP	0	0	2	1–3+	3+	5+	1+
7	mild NP	0	0	2	3–5+	3+	5+	3+
Typical PSP								
8	0	0	0	0	3–5+	rare	rare	0
9	0	0	0	0	1–3+	0	0	0
10	0	0	0	0	3–5+	1+	0	0
11	0	0	0	0	1–3+	0	0	0

GM = gray matter neuronal tau
TA = tufted astrocytes
WM = white matter tau pathology

Bigio EH, Brown DF, White CL, 3rd. Progressive supranuclear palsy with dementia: cortical pathology. *J Neuropathol Exp Neurol* 1999;58:359-564.

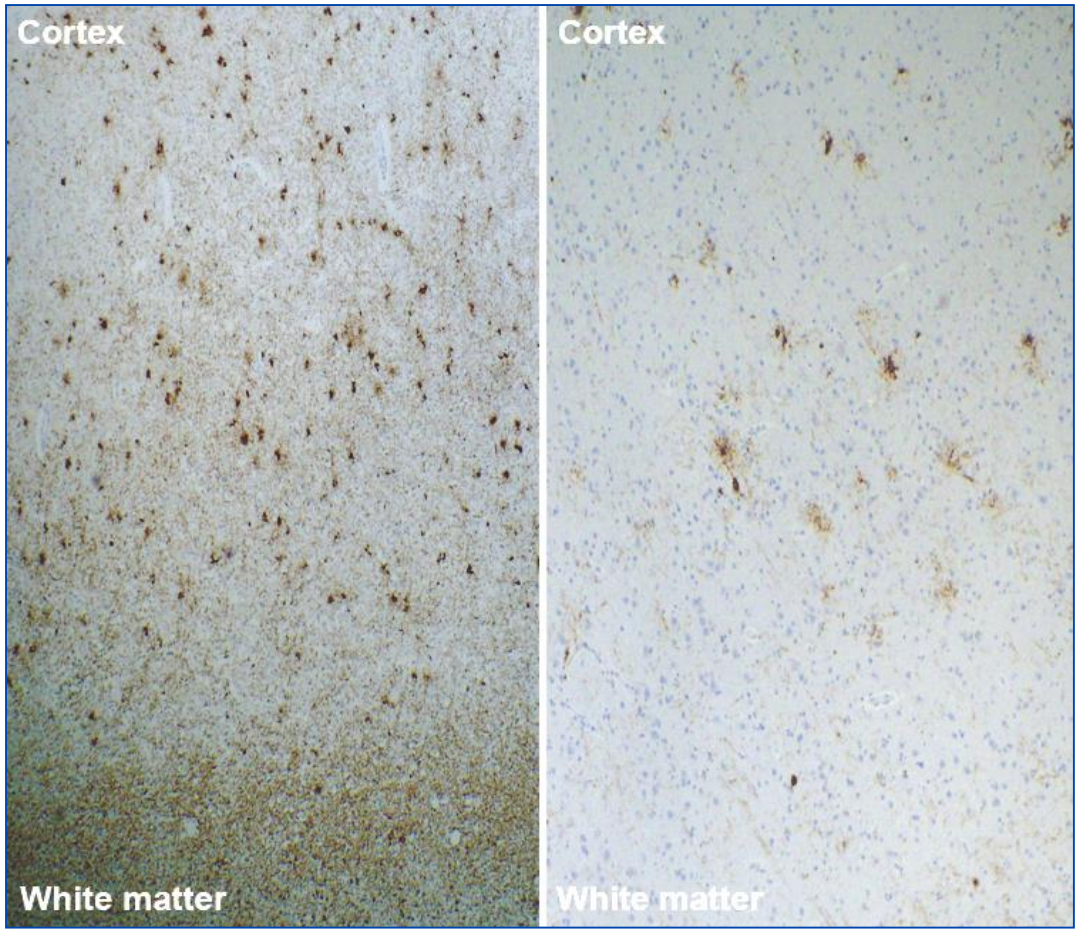
PSP presenting with progressive nonfluent aphasia (PSP-PNFA)



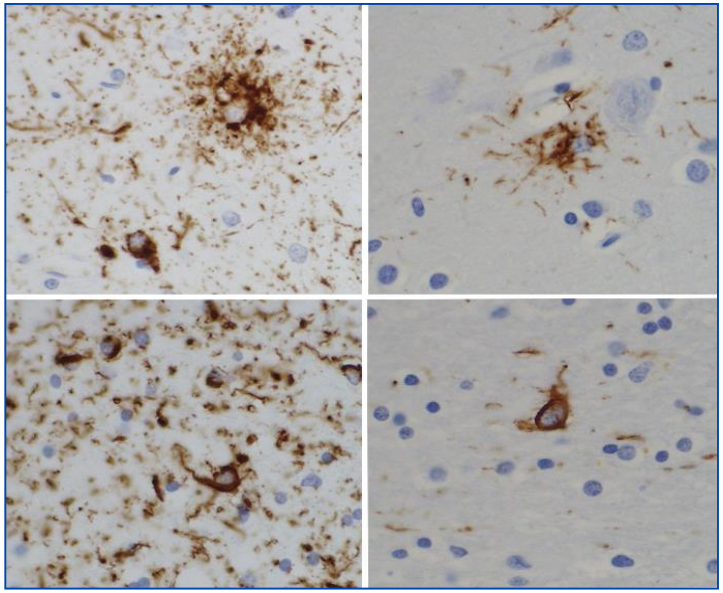
PSP-PNFA is similar to PSP on global cognitive measures, such as DRS and MMSE, but impaired on language tests, such as category fluency.

Josephs KA, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. *Neurocase* 2005;11:283-296.

PSP presenting with progressive nonfluent aphasia (PSP-PNFA)



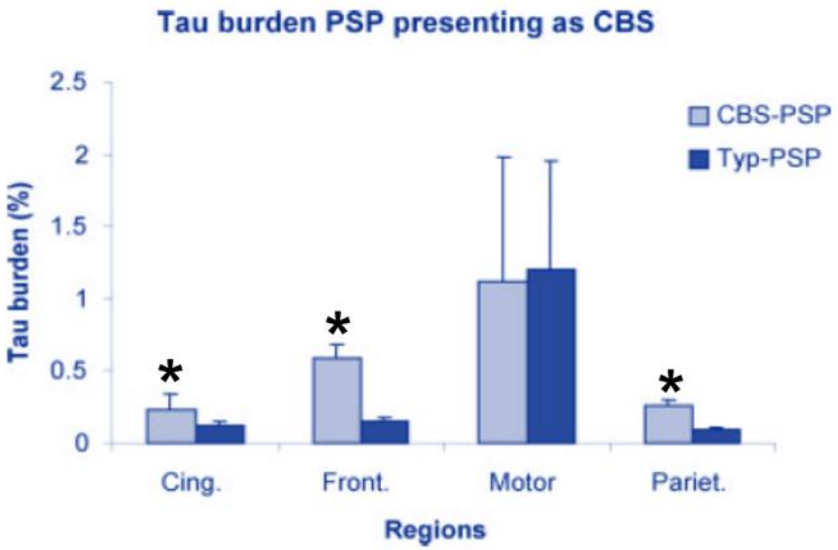
Similar morphologic lesions, but more severe cortical tau pathology.



Atypical **Typical** **Atypical** **Typical**

PSP presenting with corticobasal syndrome

- Progressive asymmetrical rigidity and apraxia
- Fisted hand in 4 of 5 cases
- Vertical gaze palsy in 4 of 5 cases
- None had falls within the first year
- Age at death: 82 ± 5 y; 4 of 5 were females
- Braak stage: IV (concurrent AD in 2 of 5 cases)



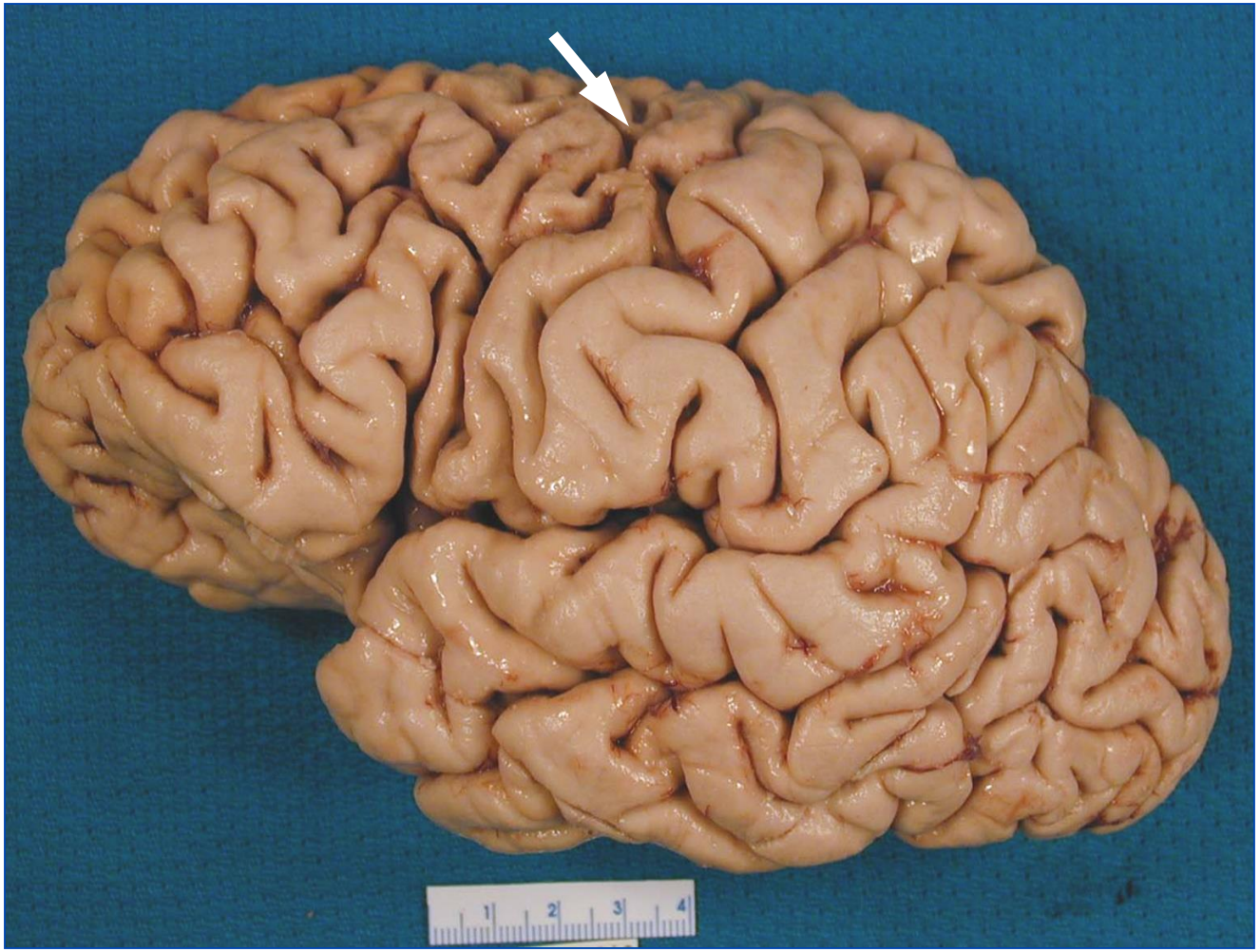
Tsuboi Y, et al. Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. *Mov Disord* 2005;20:982-988.

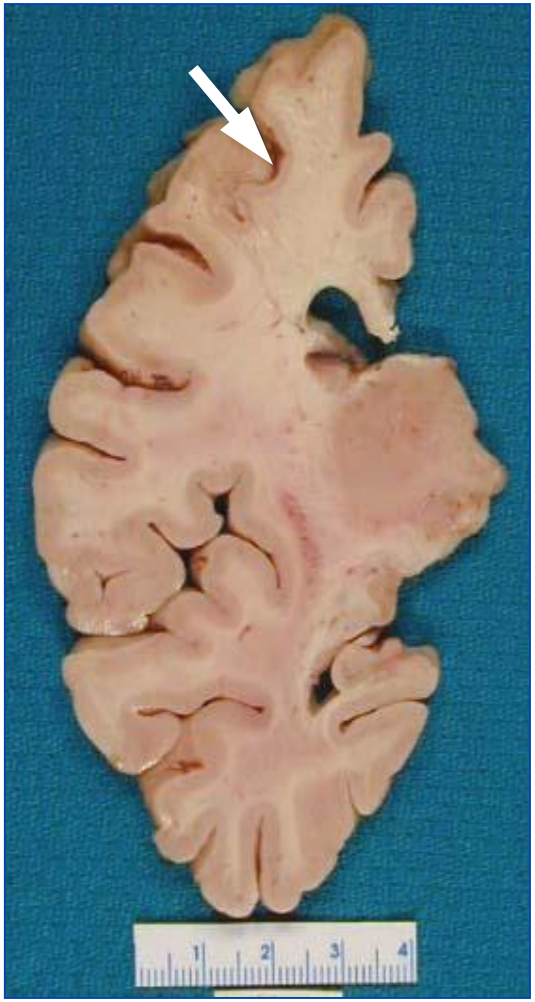
Atypical PSP with spastic paraparesis

- Prominent upper motor neuron signs, including spasticity, hyperreflexia, Babinski sign, upper motor neuron pattern of weakness
- Antemortem clinical diagnoses - primary lateral sclerosis (PLS) or corticobasal syndrome (CBS)
- Limb apraxia in some, often asymmetrical
- Other features include Parkinsonism, with bradykinesia, rigidity, and postural instability
- Vertical gaze palsy, uncommon

Josephs KA, et al. Atypical progressive supranuclear palsy with corticospinal tract degeneration. *J Neuropathol Exp Neurol* 2006; 65:396-405.

PSP with spastic paraparesis (PSP-PLS)

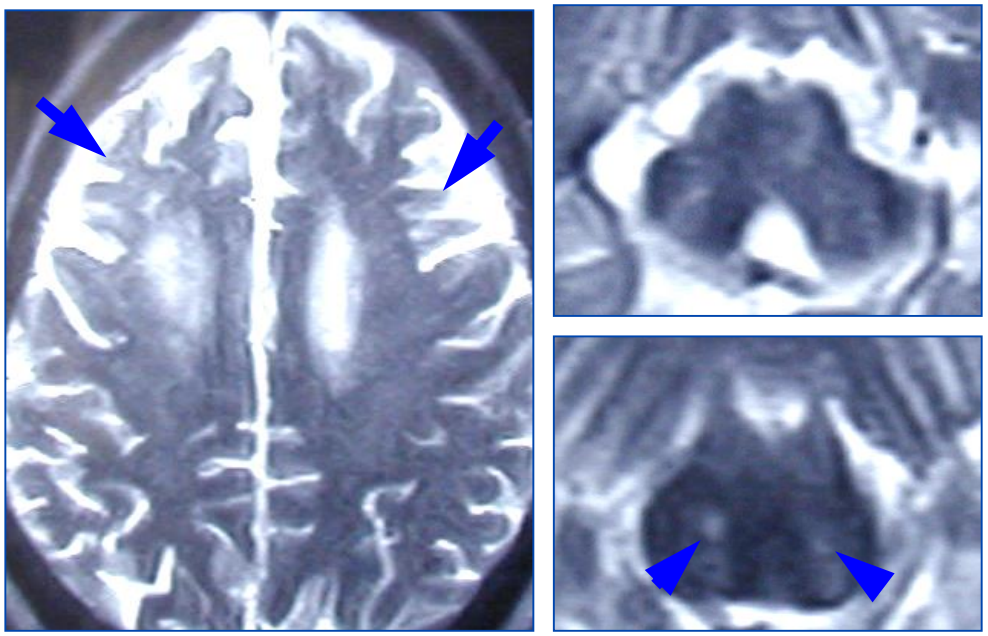




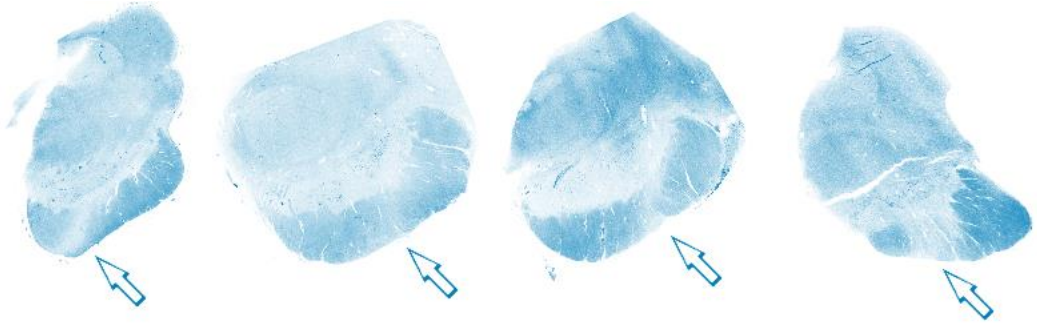
Clinical syndrome: dementia with asymmetrical apraxia & spasticity

Corticospinal tract degeneration in PSP-PLS

Increased T2 signal in corticospinal tract



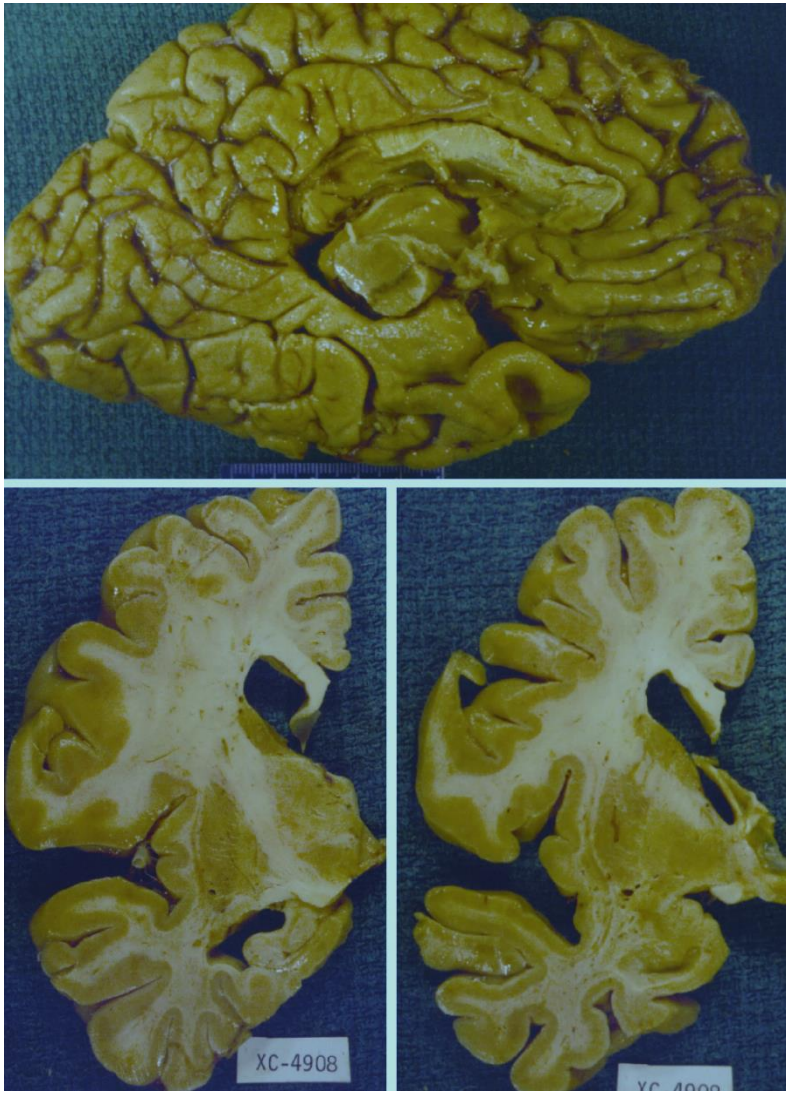
Luxol fast blue of midbrain of 4 cases of PSP-PLS shows corticospinal tract degeneration in cerebral peduncle.



Summary

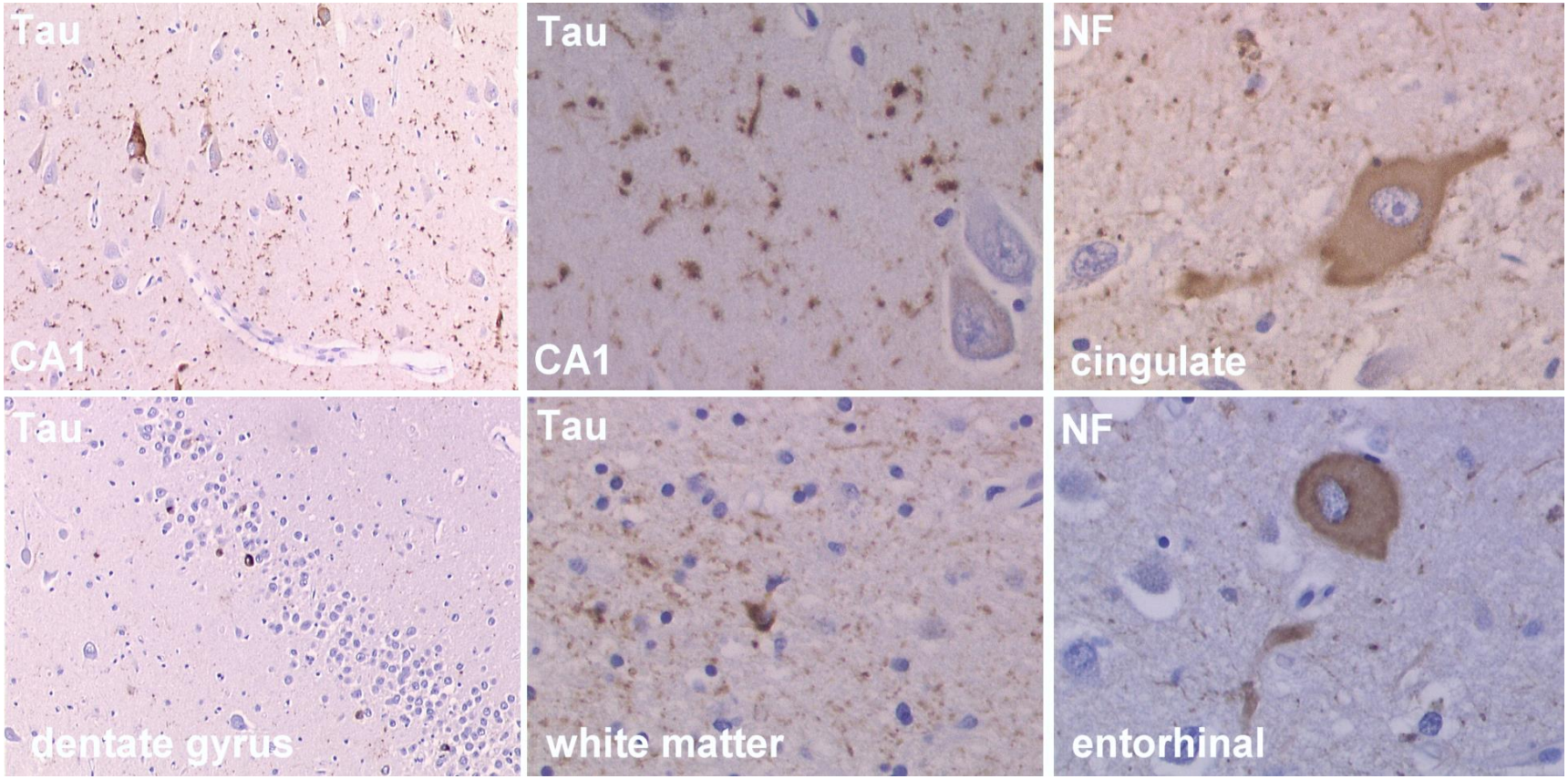
- Anatomy predicts the clinical syndrome, not the underlying pathology.
- PSP can be asymmetrical.
  - PSP-CBS
- PSP can have severe cortical pathology.
  - PSP-CST
- CBD can be symmetrical.
  - CBD-RS

Argyrophilic grain disease



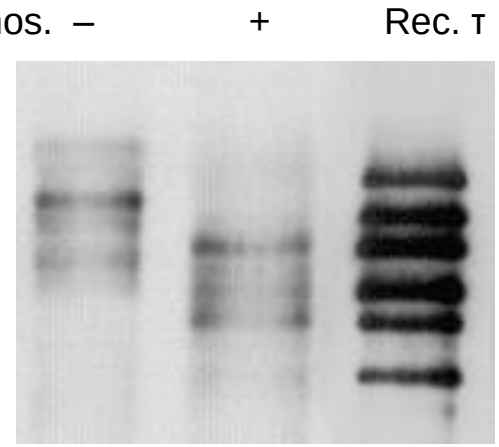
- Some patients with AGD had an amnestic syndrome
- Brain is often grossly normal, but rare cases may show medial temporal lobe atrophy (often associated with hippocampal sclerosis)
- Pathology limited to limbic lobe structures
  - Hippocampus
  - Amygdala
  - Hypothalamus
- “medial temporal tauopathy”

Argyrophilic grain disease

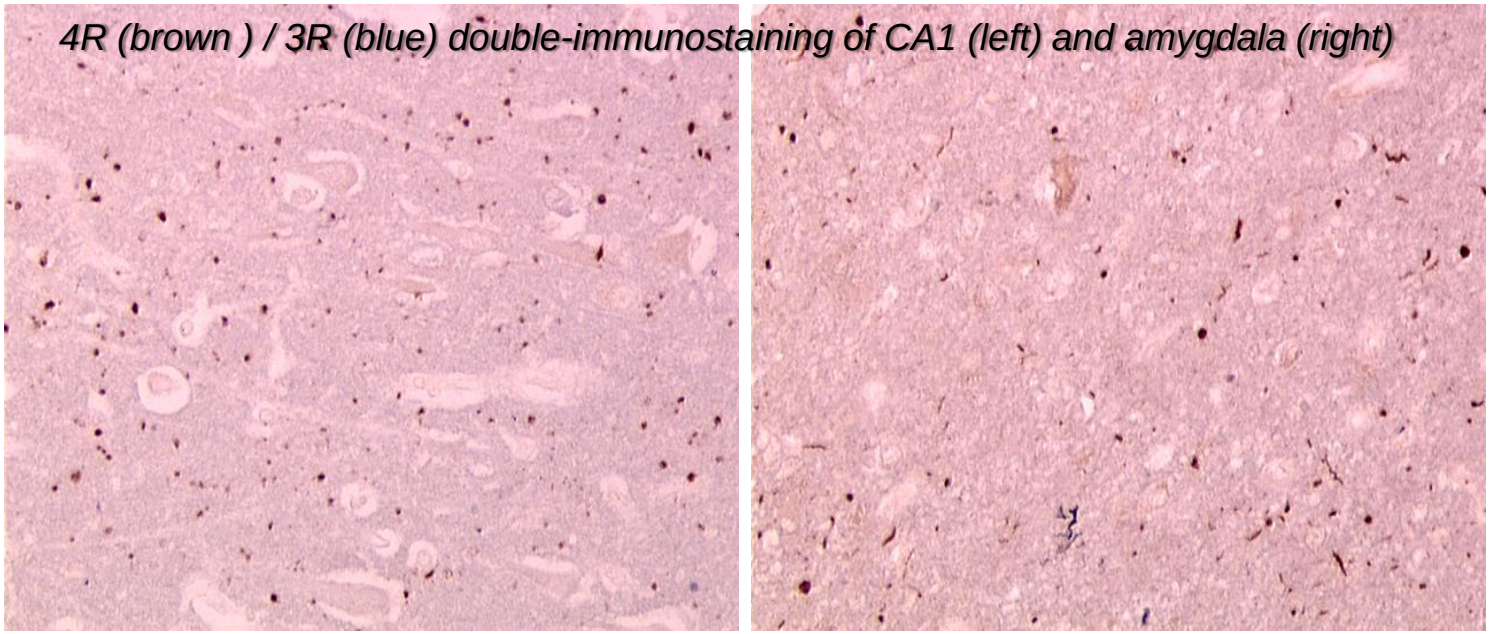


- Tau positive grains & “pre-tangles” in CA1 and dentate gyrus
- Tau positive glia (“coiled bodies”) in white matter
- Ballooned neurons in limbic lobe (neurofilament-positive)

AGD is a 4R tauopathy



4R:3R=2.2



Togo T, Sahara N, Yen S-H, Cookson N, Ishizawa T, Hutton M, de Silva R, Lees A, Dickson DW. Argyrophilic grain disease is a sporadic 4-repeat tauopathy. *J Neuropathol Exp Neurol* 61:547-556, 2002.

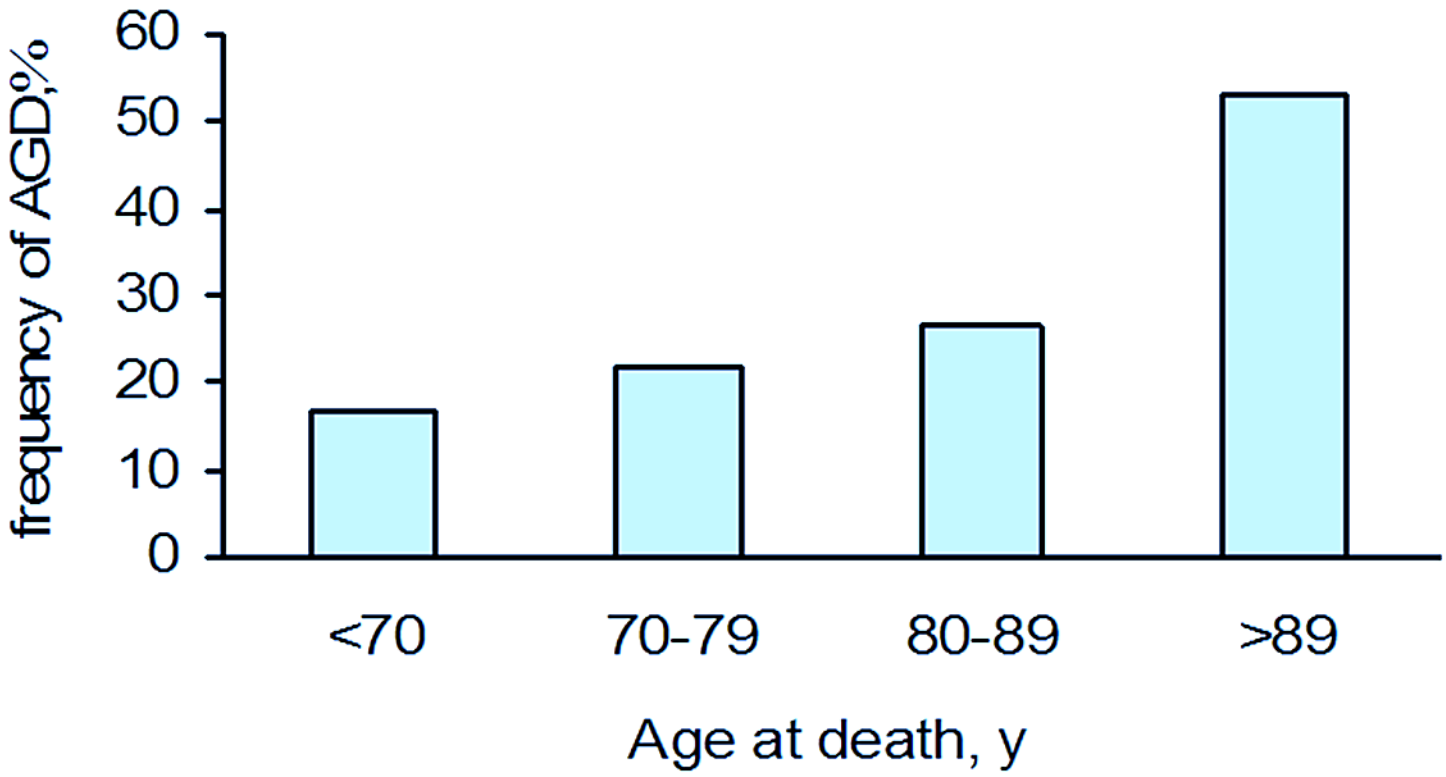
Clinical significance of AGD

- AGD in mild cognitive impairment
  - 34 patients with MCI studied at autopsy
  - AD – 24/34 (70%); AGD – 18/34 (53%) (all but one also had Alzheimer type pathology)
- Imaging correlates – voxel based morphometry
  - 22 patients with AGD (8 demented; 14 nondemented)
  - VBM demonstrated hippocampal atrophy in those with dementia (N=3), but not in those without (N=9).
  - There was no difference in whole brain volume between the groups.
  - Alone, AGD, is not associated with brain atrophy.

Josephs KA, Whitwell JL, Parisi JE, Knopman DS, Boeve BF, Geda YE, Jack CR Jr, Petersen RC, Dickson DW: Argyrophilic grains: A distinct disease or an additive pathology? *Neurobiol Aging* 29:566-73, 2008.

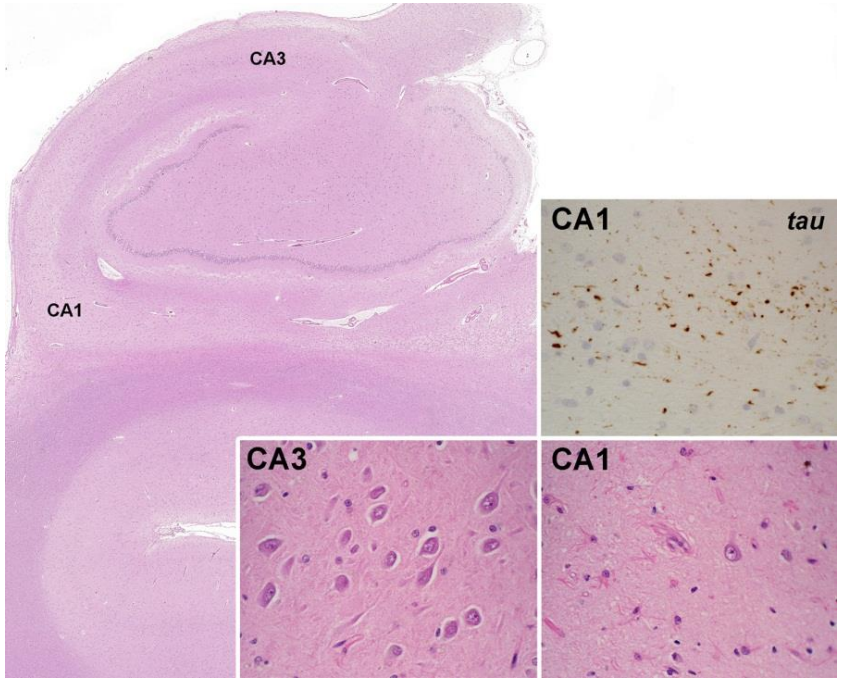
Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, Petersen RC: Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol* 63:674-681, 2006.

AGD increases with age



Hippocampal sclerosis tauopathy

- Some cases of argyrophilic grain disease (AGD) have hippocampal sclerosis (HpScl).
  - Beach TG, et al. Hippocampal sclerosis dementia with tauopathy. *Brain Pathol* 2003;13: 263-78.
- HpScl with or without AGD in patients with mild cognitive impairment



The spectrum of 4R tauopathies

- Sporadic 4R tauopathies are PSP, CBD and AGD
- Genetic, biochemical & pathologic overlap
  - The H1 tau haplotype is increased in PSP, CBD & AGD
  - Sarkosyl-insoluble tau is enriched in 4R tau
  - Neuronal & glial tau (+) lesions
    - CBD: concentrated in cortex & basal ganglia
    - AGD: concentrated in limbic lobe
    - PSP: concentrated in basal ganglia & brainstem
  - Ballooned neurons and differential diagnosis
    - CBD – many in convexity cortex
    - AGD – only in limbic lobe
    - PSP – rare

Neurodegenerative tauopathies

	Limbic lobe	Assoc-iation cortices	Motor cortex	Basal ganglia	Thalamus	Midbrain	Pons & medulla	Cere-bellum dentate
PiD (3R)	CA1, dentate & amyg-dala	Limbic & fronto-temp-oral						
CBD (4R)		Fronto-parietal				Sub-stantia nigra		
PSP (4R)					Sub-thalamic nucleus	Sub-stantia nigra		
AGD (4R)	CA2 & amyg-dala							

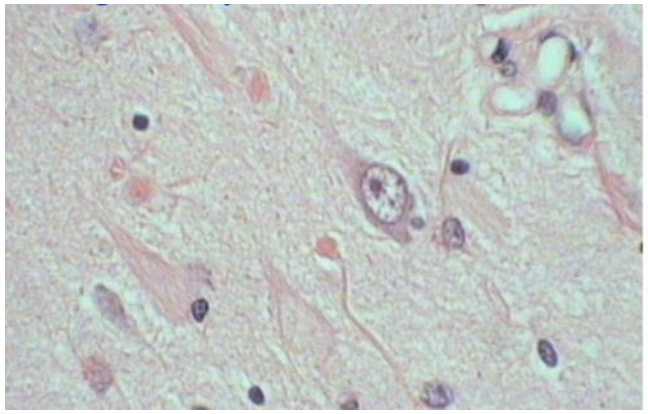
Shading indicates severity of pathology.

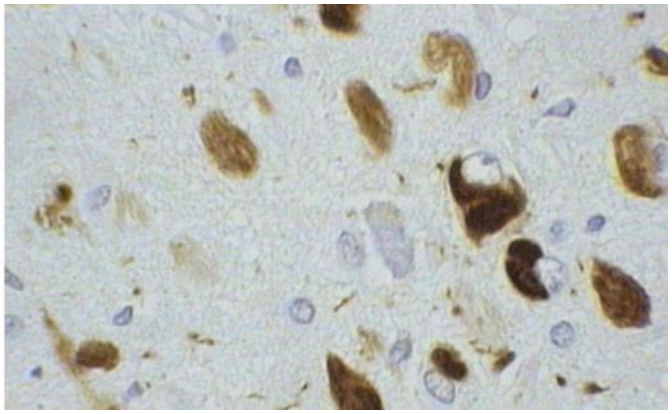
Tangle predominant dementia

- Late onset degenerative dementia
- Amnestic syndrome
- Possible increased frequency of APOE ε2 allele
- Medial temporal lobe atrophy
- NFT with atypical Braak staging
  - Severe limbic system neurofibrillary degeneration
  - No neuritic plaques
  - Few amyloid plaques

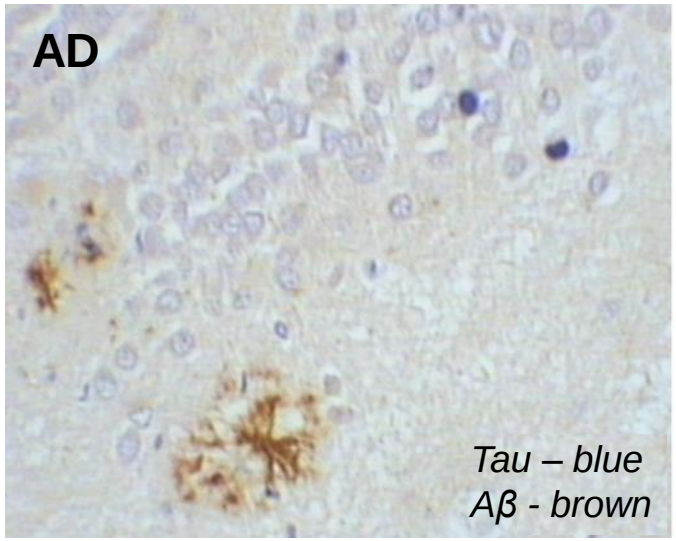
Tangle predominant dementia

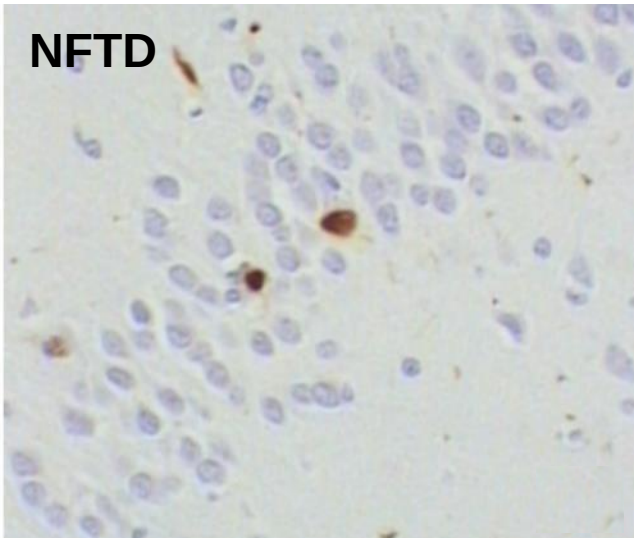
Hippocampal pyramidal layer





Hippocampal dentate fascia

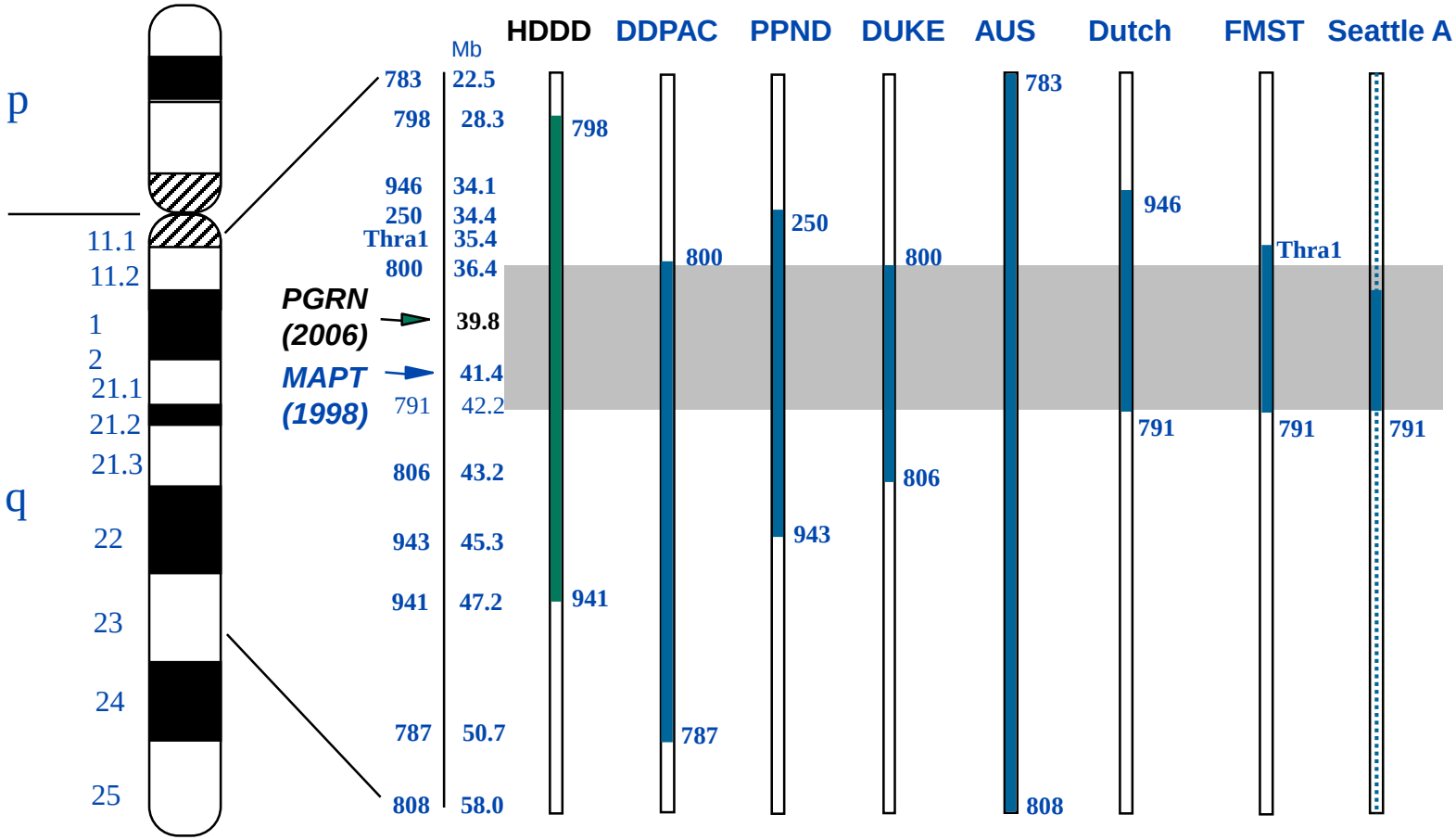




Molecular pathology of FTDP-17

- Tauopathies - FTDP-17t
  - 3R, 4R or 3R+4R tau
  - Tau-positive neuronal & glial inclusions
  - *MAPT* mutations
- Non-tauopathies - FTDP-17u
  - FTLD-U and FTLD-MND
  - TDP-43-positive neuronal inclusions
  - *PGRN* or *VCP* mutations

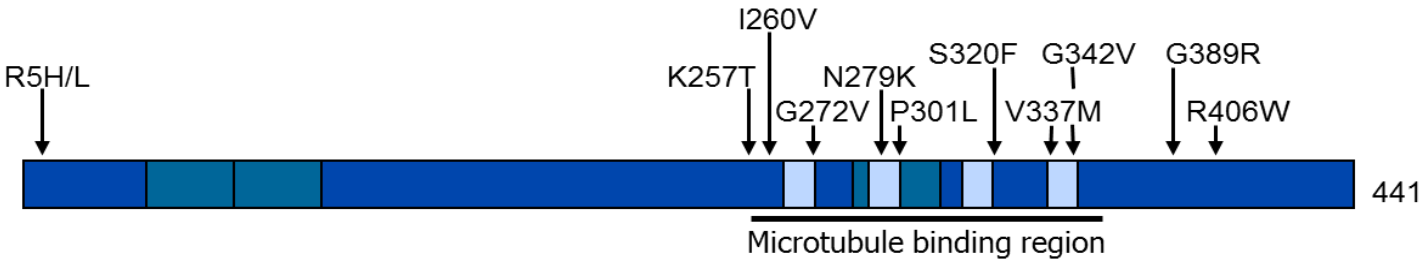
Frontotemporal dementia & Parkinsonism linked to chromosome 17 (FTDP-17)



Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. *Ann Neurol* 1997;41:706-715.

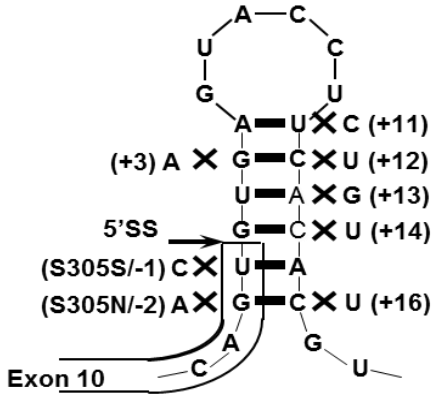
FTDP-17 - coding & splice site mutations in *MAPT*

1. Mutations that disrupt microtubule binding and enhance aggregation

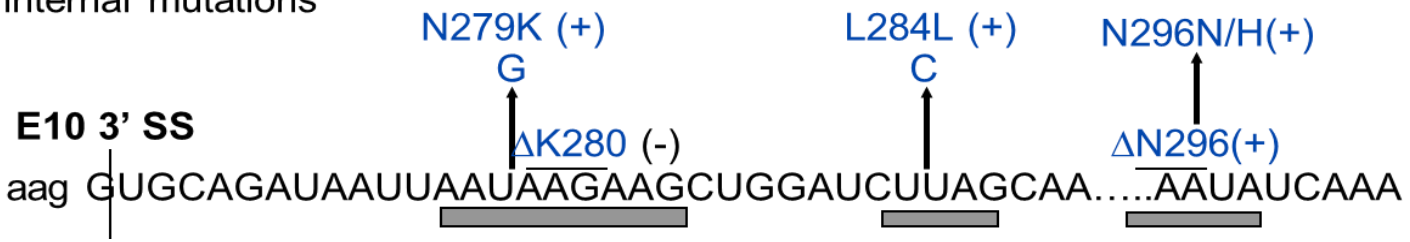


2. E10 tau RNA splicing mutations (increase 4R)

5' splice site

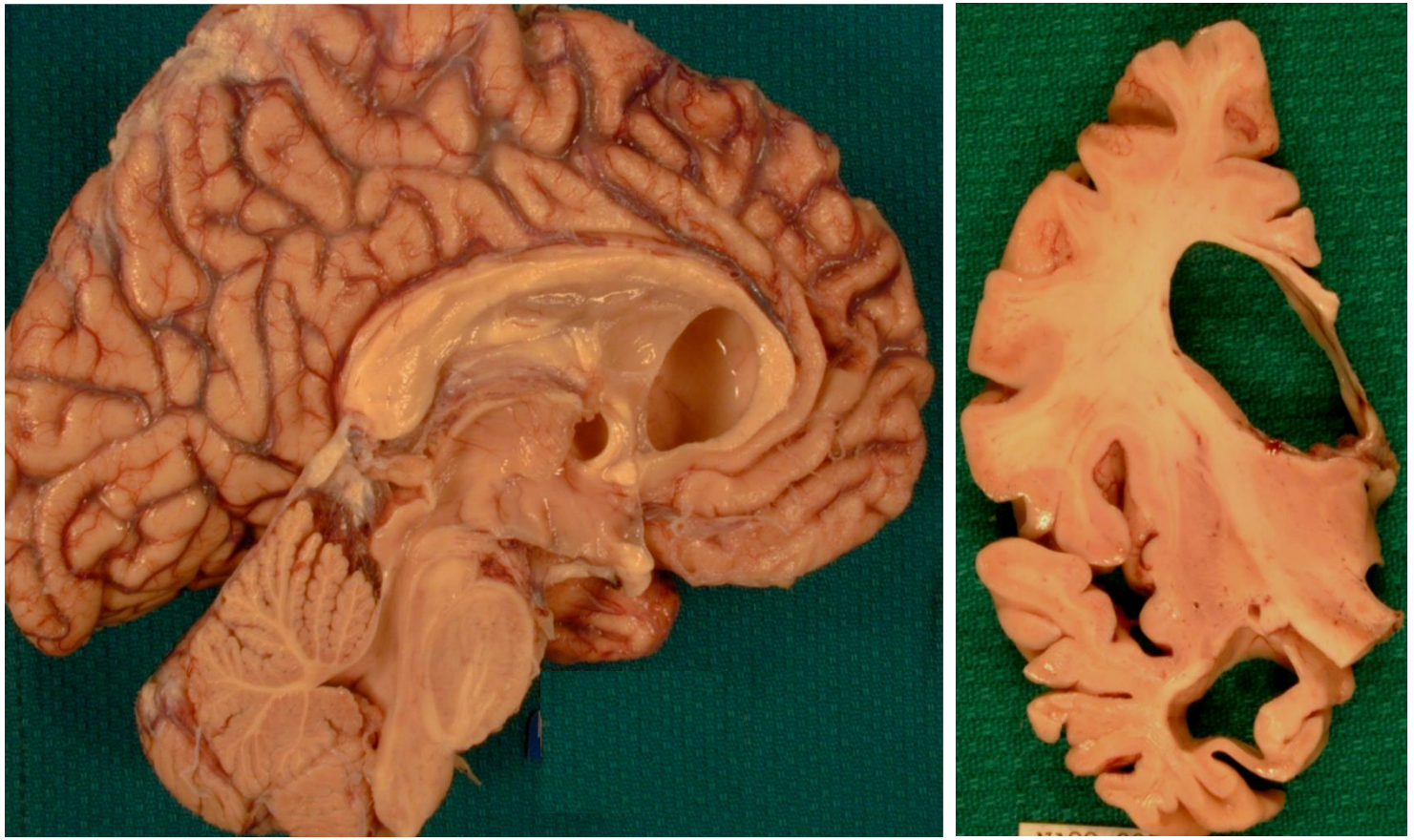


E10 internal mutations



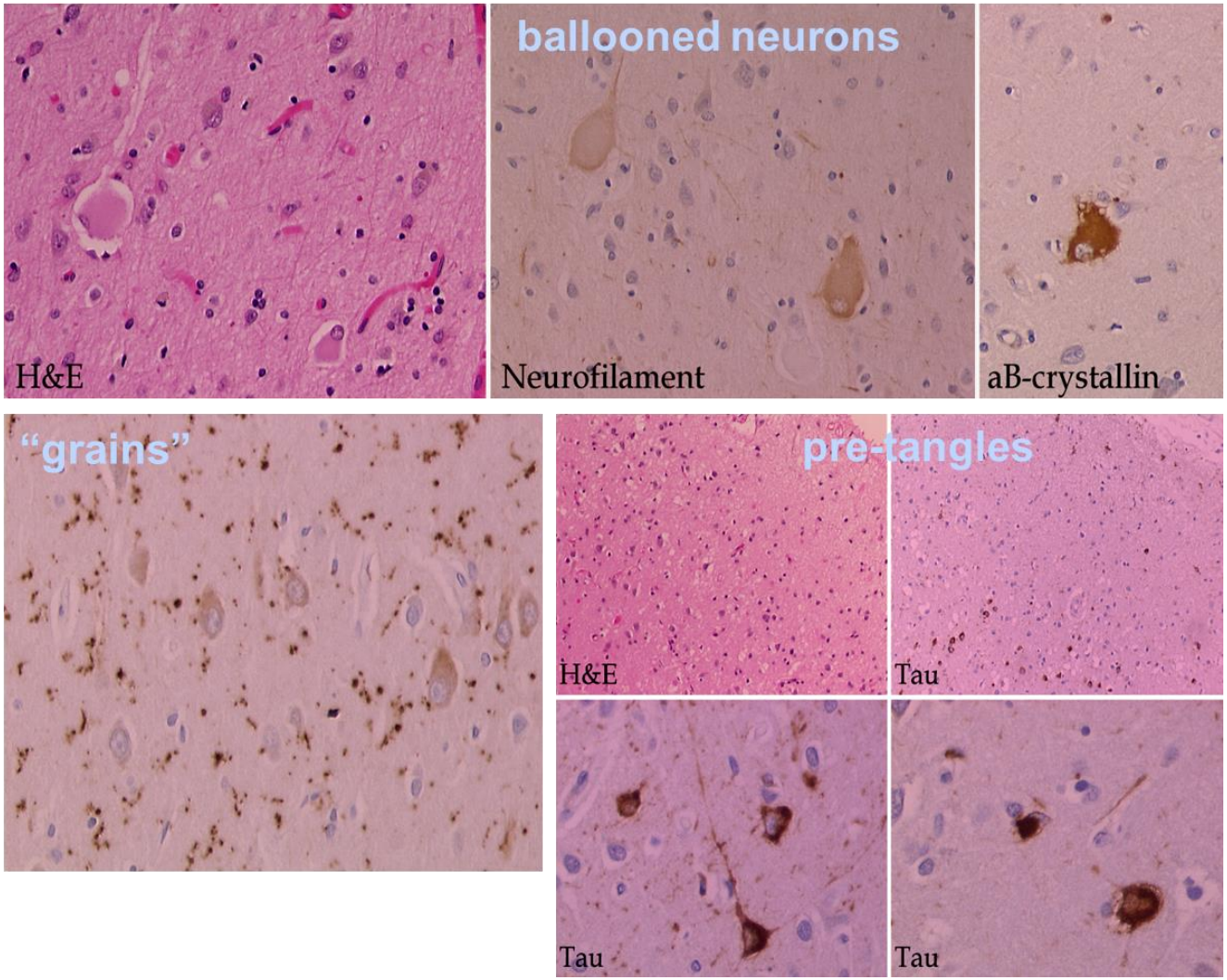
FTDP-17t

Presenile, frontal lobe dementia with disinhibition;
Parkinsonism occurred late in the disease course



E10 splice site mutation

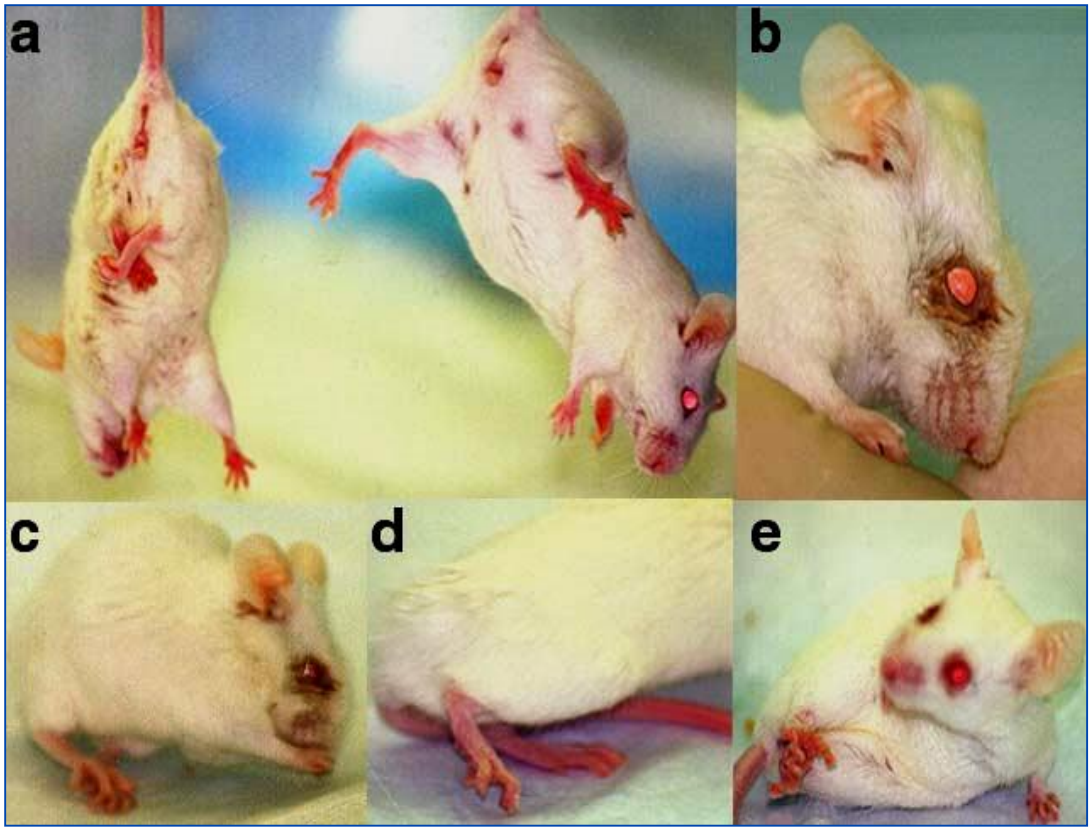
FTDP-17t


ballooned neurons
H&E
Neurofilament
aB-crystallin
"grains"
pre-tangles
H&E
Tau
Tau
Tau

Modeling tauopathies in transgenic mice

Mutant (P301L) tau transgenic mice

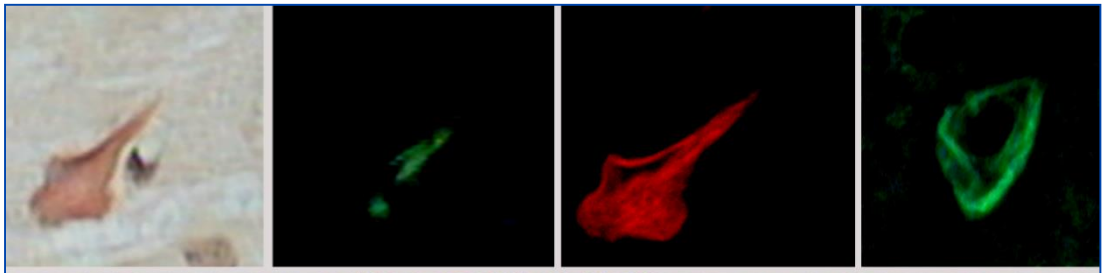
Progressive hind limb paralysis; dystonic posturing; poor righting reflex.



Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat Genet* 2000;25:402-405.

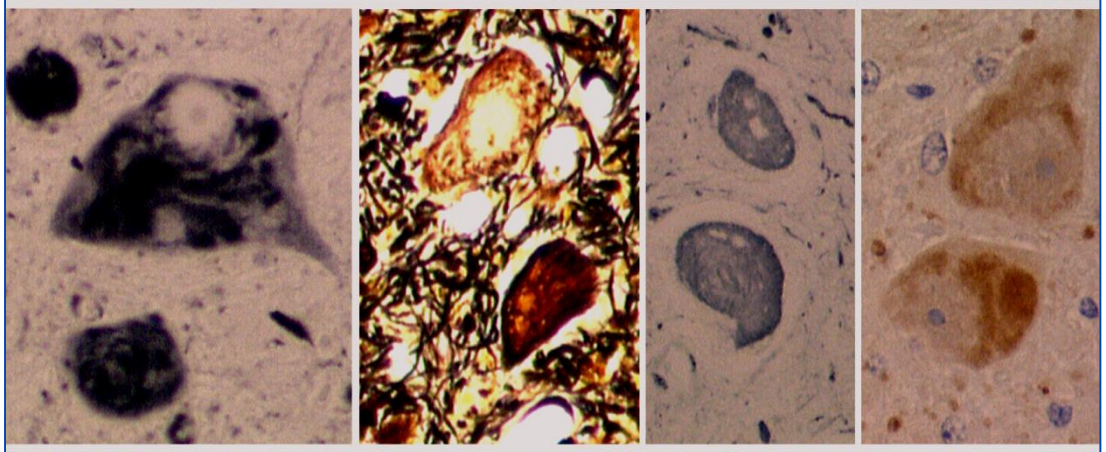
NFT in mutant tau transgenic mice

Congo red



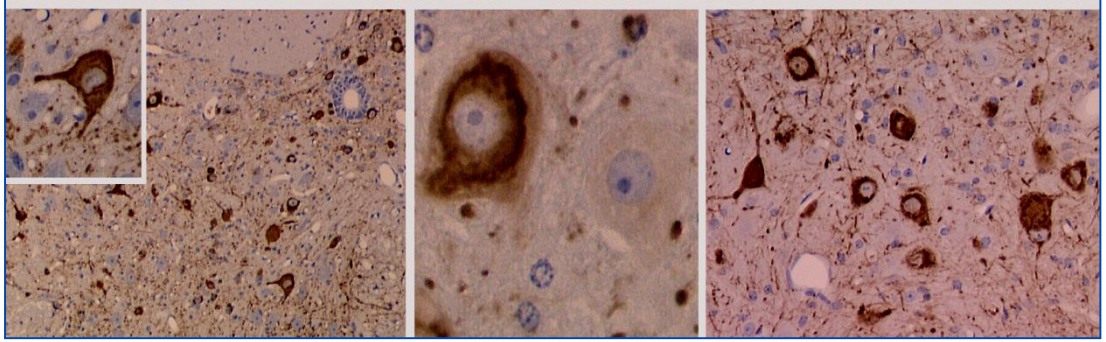
Thioflavin-S

Silver stains



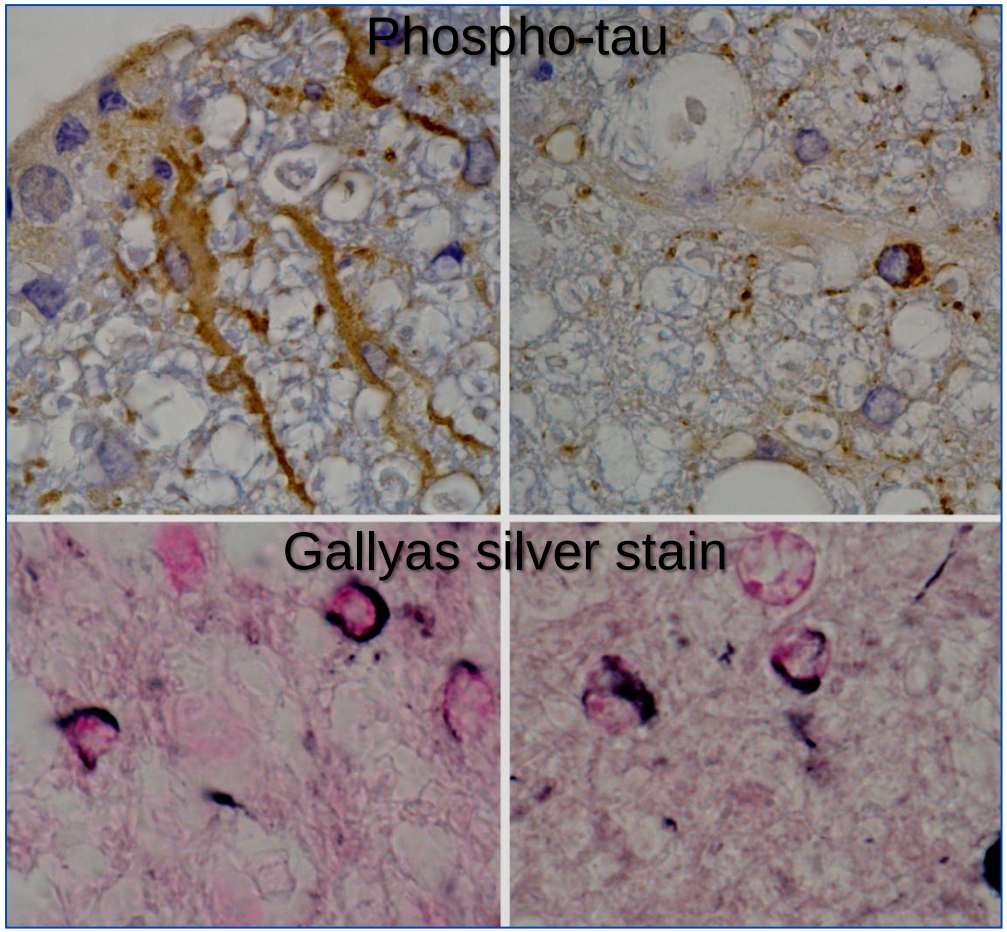
Ubiquitin immuno-stains

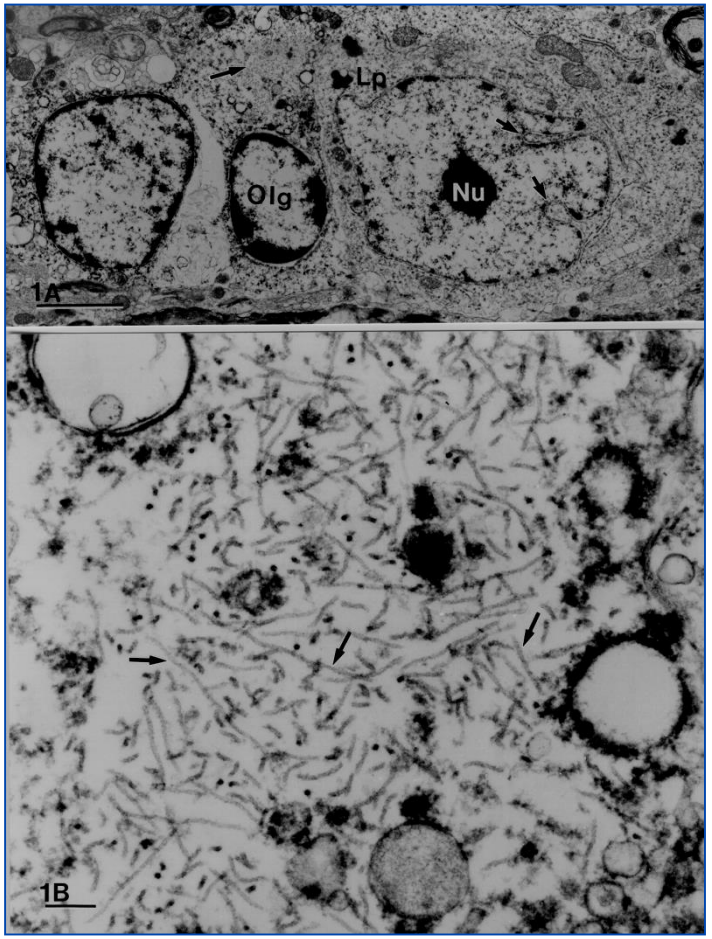
Phospho-tau immunostains



Conformational tau epitopes

Glial inclusions (astrocytic & oligodendroglial) in mutant tau mice





Summary

- Abnormal tau accumulates as fibrils within both neurons and glia.
- Neurofibrillary pathology is associated with neuronal loss and gliosis, which correlates with clinical deficits.
- Tauopathies can be classified based upon the predominant isoforms within pathologic structures.
- Tauopathies have a range of clinical phenotypes.
- Animal models of tauopathies have been created to study disease pathogenesis and to develop modifying treatments.

Acknowledgements

- Brain bank coordinators
  - Deann Gibson (formerly Beth Marten)
- Neuropathology – histology & immunohistochemistry
  - Monica Casey-Castanedes, Virginia Phillips, Linda Rousseau
- Database management & image analysis
  - Melissa E. Murray, PhD
- Electron microscopy; biochemistry
  - Wenlang Lin, PhD; Naruhiko Sahara, PhD & Shu-Hui Yen, PhD
- PSP clinicopathologic studies
  - Keith Josephs, MD, Yoshio Tsuboi, MD, Zeshan Ahmed, PhD
- CBD clinicopathologic & genetic studies
  - Naomi Kouri, PhD,
- AGD clinicopathologic studies
  - Takashi Togo, MD, PhD; Greg Jicha, Md, PhD
- Funding
  - CurePSP Foundation for PSP | CBD and Related Brain Diseases
  - P50 NS072187 – Udall Center for Excellence in Parkinson's Disease Research