Innovations in Diagnostics for Alzheimer's Disease and Related Dementias

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Neurodegeneration

- Prevalence: Current estimates are that about 5.8 million people in the United States have Alzheimer's disease (AD) and related neurodegenerative diseases such as frontotemporal dementia, including 5.6 million aged 65 and older and about 200,000 under age 65 with younger-onset AD.

- Progressive loss of selective groups of neurons or "neuron systems" with associated secondary changes

Clinical Classification

- The major dementia syndromes can be classified depending upon the predominant cognitive deficit and the anatomical region affected, as follows:
  - Temporal-parietal syndrome is dominated by early memory disturbances; main example is AD.
  - Frontotemporal syndrome is dominated by a problem in executive functioning or language disturbances, with relative lack of memory disturbance early in the disease, e.g., FTD.
  - Subcortical dementia is dominated by reduced speed and efficiency of cognition and is associated with disease of deep grey matter structures, e.g., PSP.

- Clinical diagnosis does not predict pathology but rather indicates the neuroanatomical distribution. Only histopathological and biochemical studies provide a definitive diagnosis.

Proteinopathy

- Many neurodegenerative diseases are characterized by intracellular accumulation of abnormally configured proteins, with the formation of inclusion bodies.

- Classification of proteinopathy
  - TDP-43 proteinopathy: FTLD-TDP
  - Tauopathies: AD, PSP, CBD, FTLD linked to chromosome 17, and argyrophilic grain disease.
  - Alpha synucleinopathies: Parkinson disease, Lewy body diseases, multiple system atrophy
  - Polygluamine diseases: Huntington disease, spinocerebellar ataxias

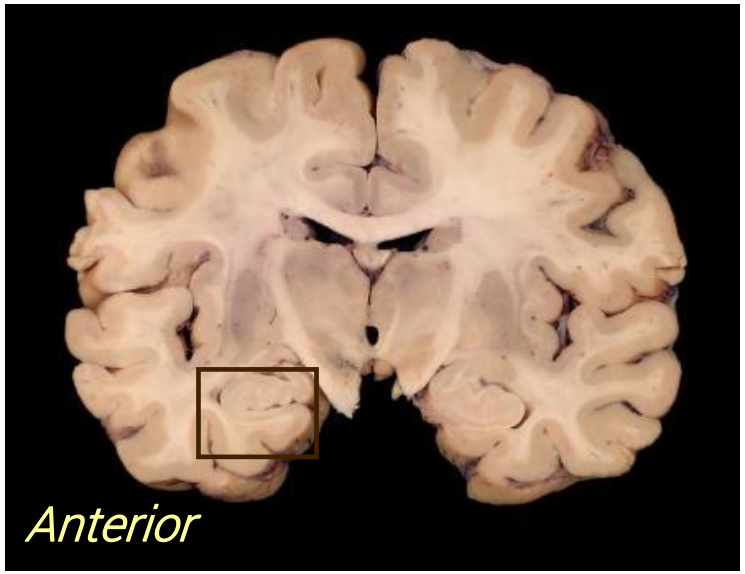
Pathology Classification

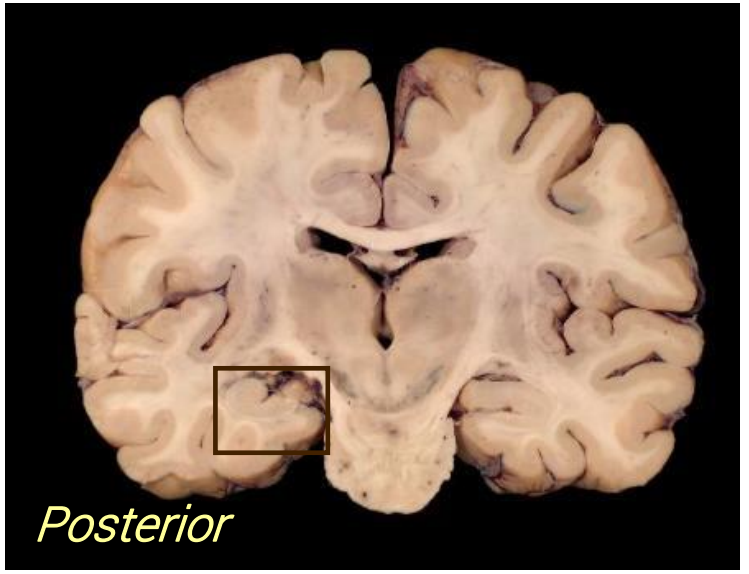
- Alzheimer's disease, most common
- Synucleinopathy
  - Parkinson disease, second most common
  - Dementia with Lewy bodies
  - Multiple system atrophy
- FTLD, second most common in people under age 65
  - FTLD-Tau
    - Pick disease
    - PSP
    - CBD
  - FTLD-TDP
    - ALS
- Trinucleotide repeat disorders (Huntington, DRPLA, SCA)

Alzheimer's Disease

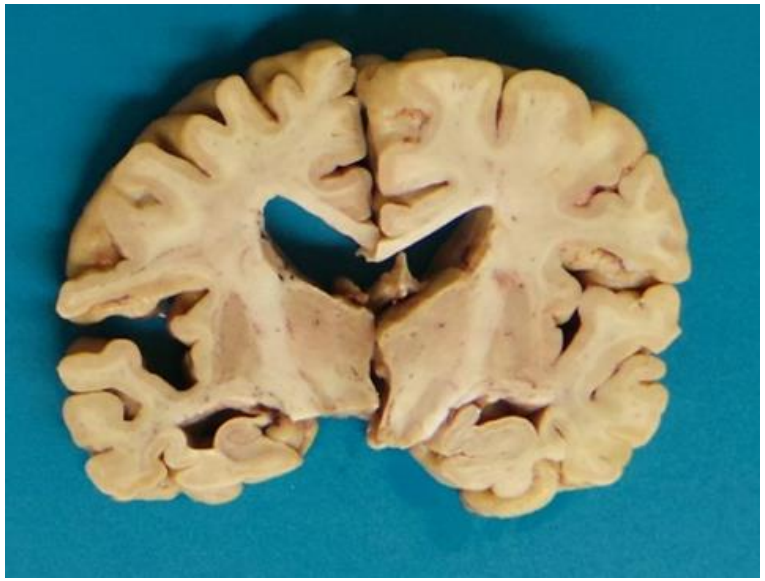
- Alois Alzheimer described what is now known as "Alzheimer's disease," 1907
  - Clinical: Primary memory disorder
  - Pathologic
    - Plaques: amyloid and beta amyloid peptide characterized in 1984
    - Tangles: tau identified as the major protein component in 1991

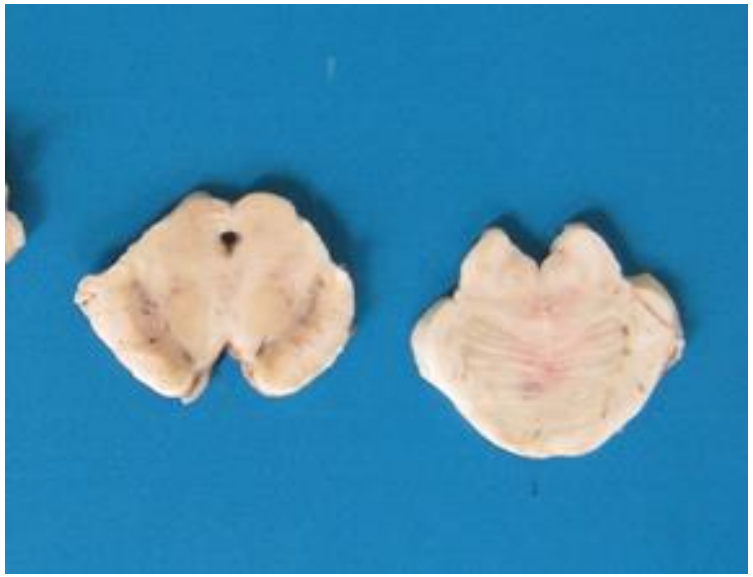
Hippocampus:
where new memories are formed

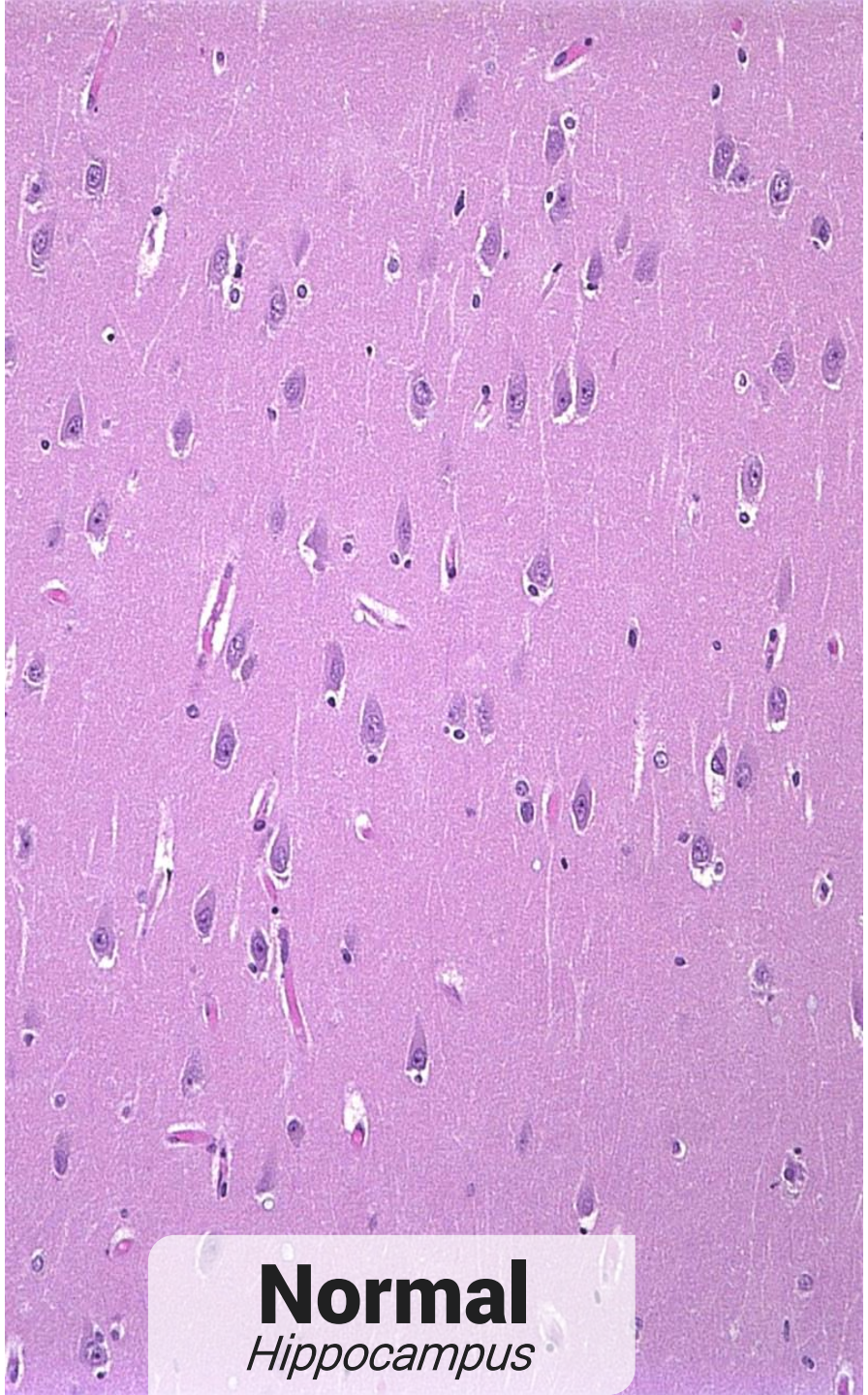




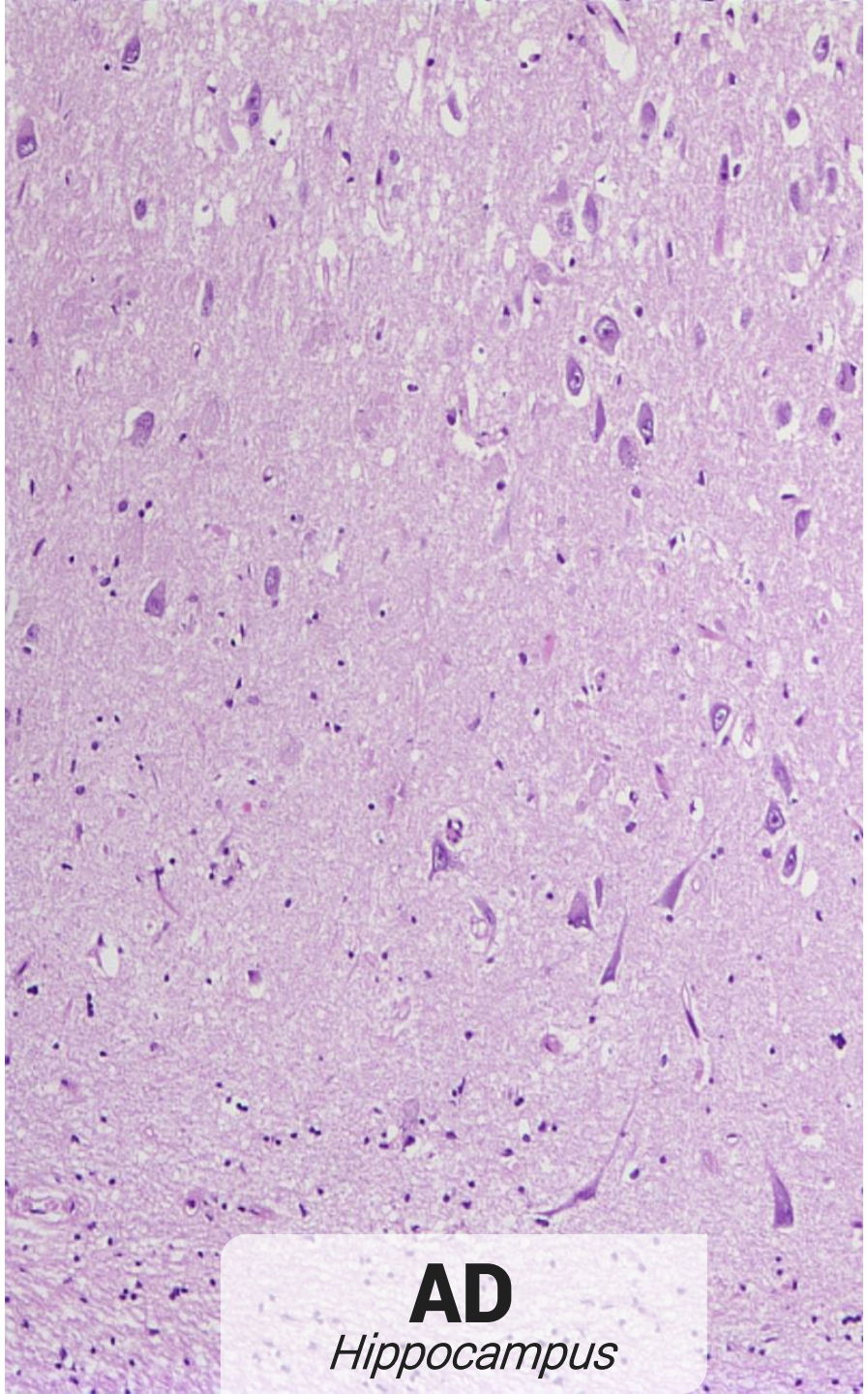
Gross Findings



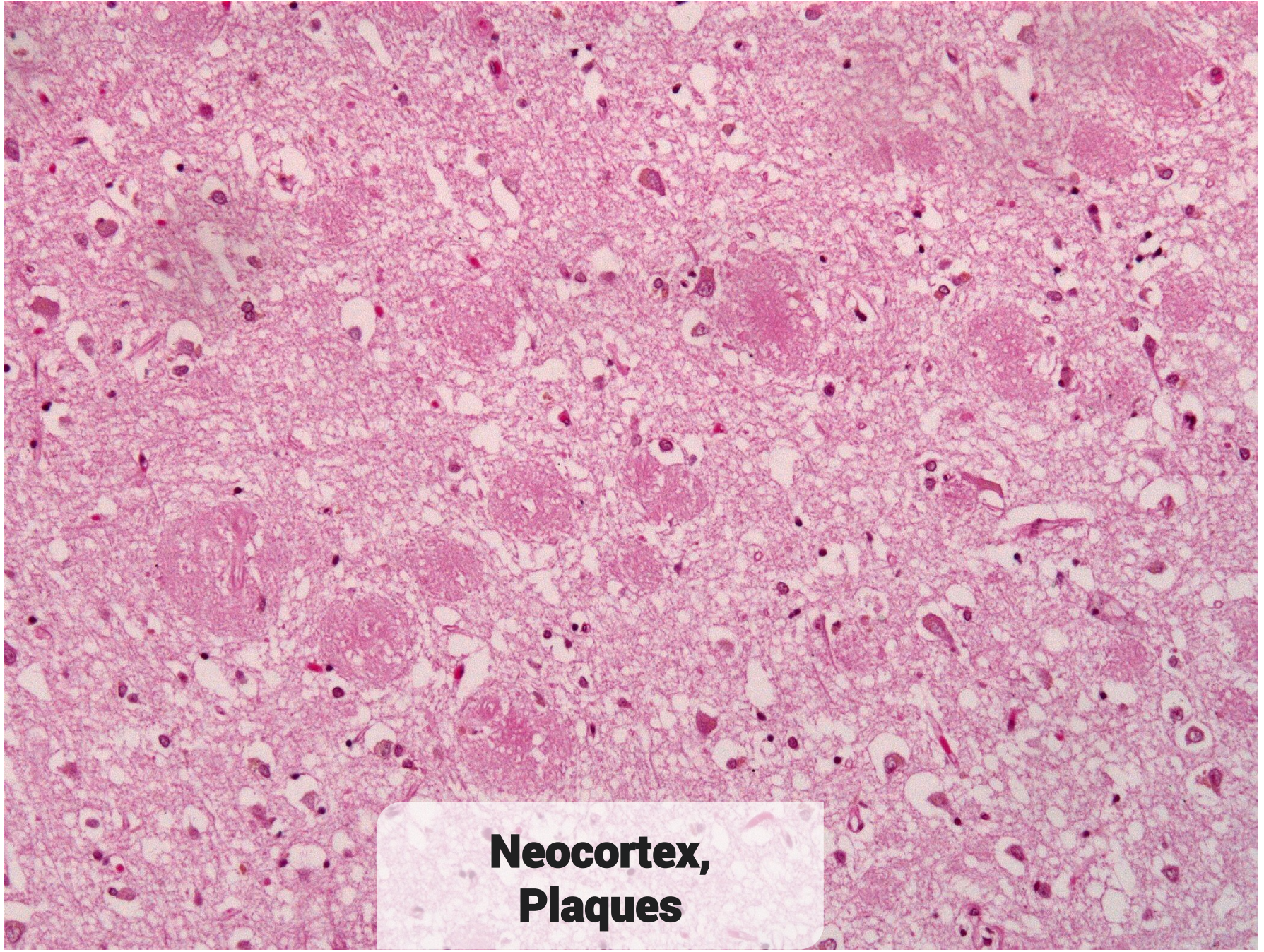




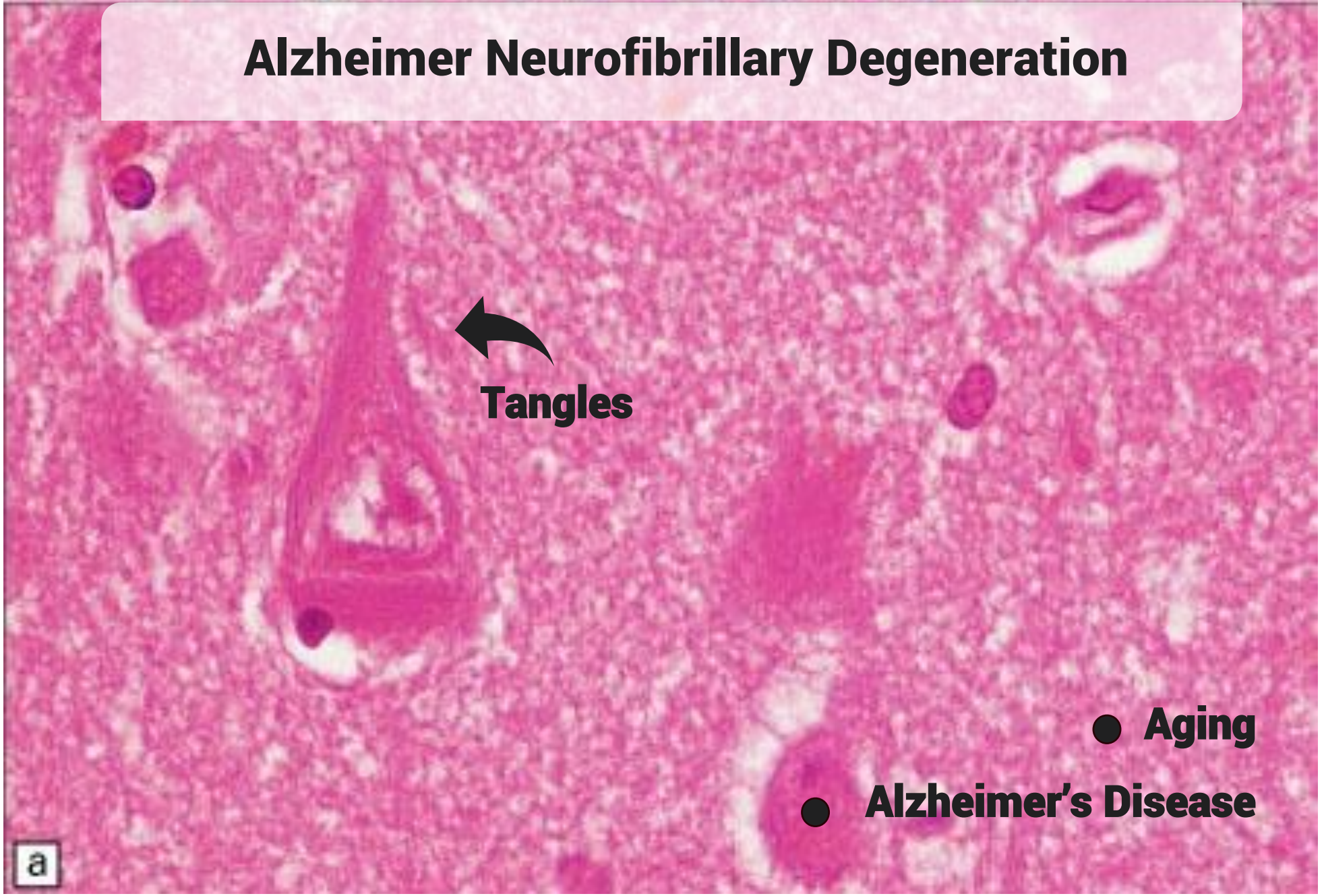
Normal
Hippocampus

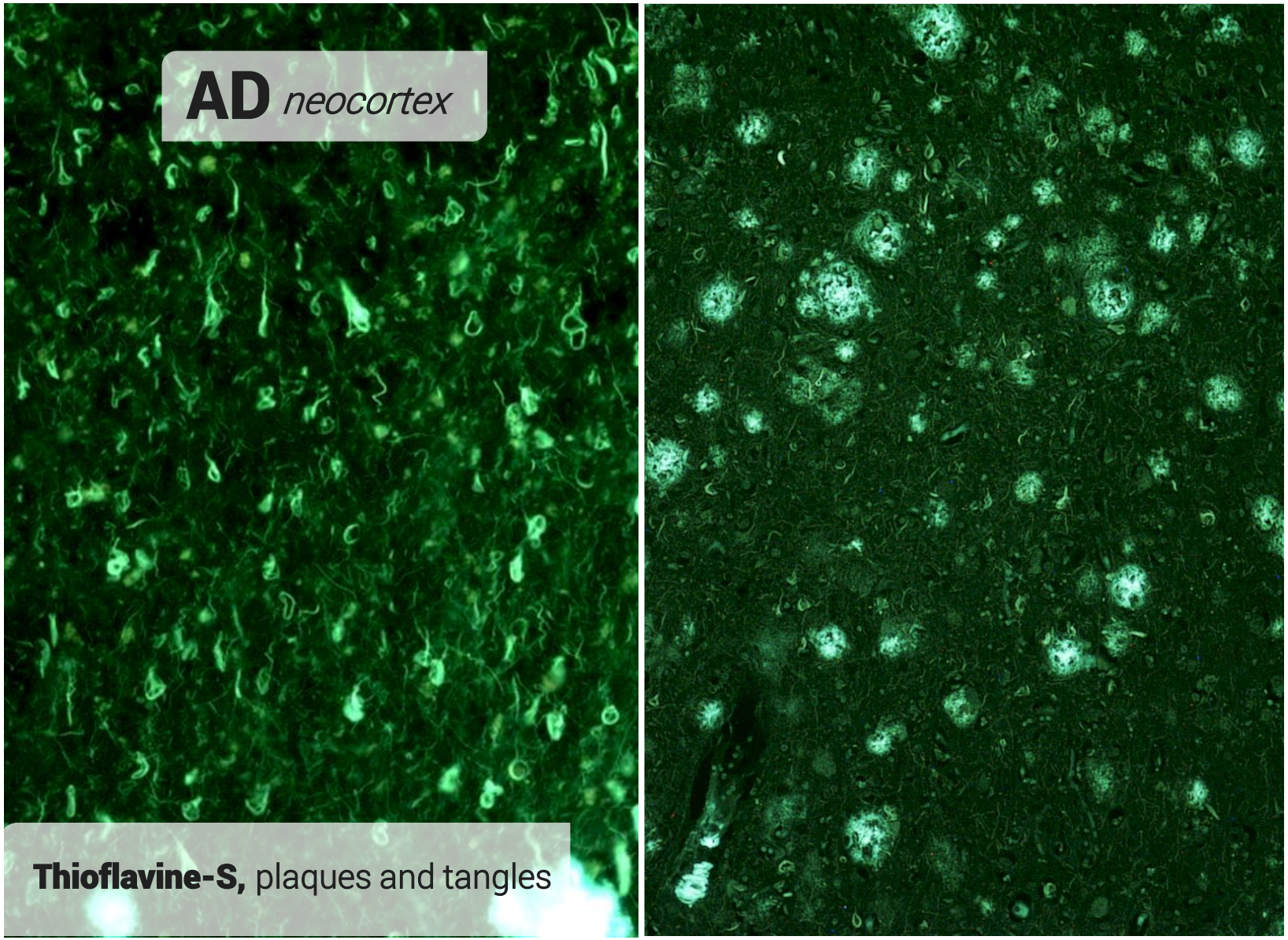


AD
Hippocampus


Neocortex,
Plaques

Alzheimer Neurofibrillary Degeneration




AD neocortex
Thioflavine-S, plaques and tangles

APP and Abeta

- Amyloid precursor protein: Membrane protein probably involved in regulation of synapse formation, plasticity, iron export
- Abnormal cleavage by β and γ secretase result in Abeta peptide

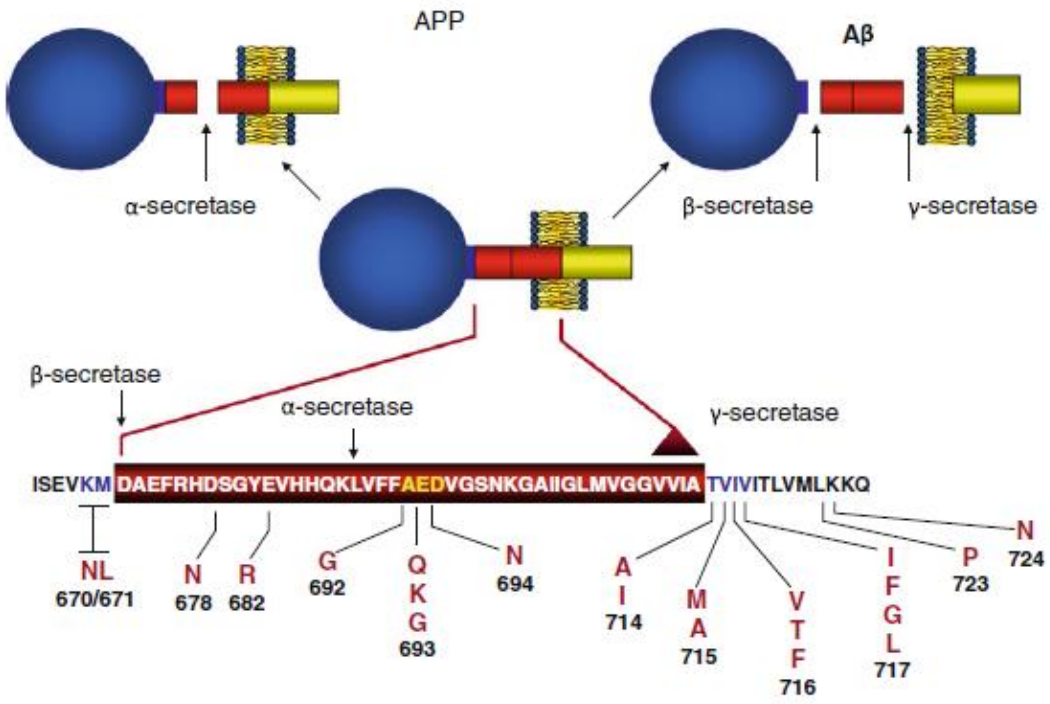
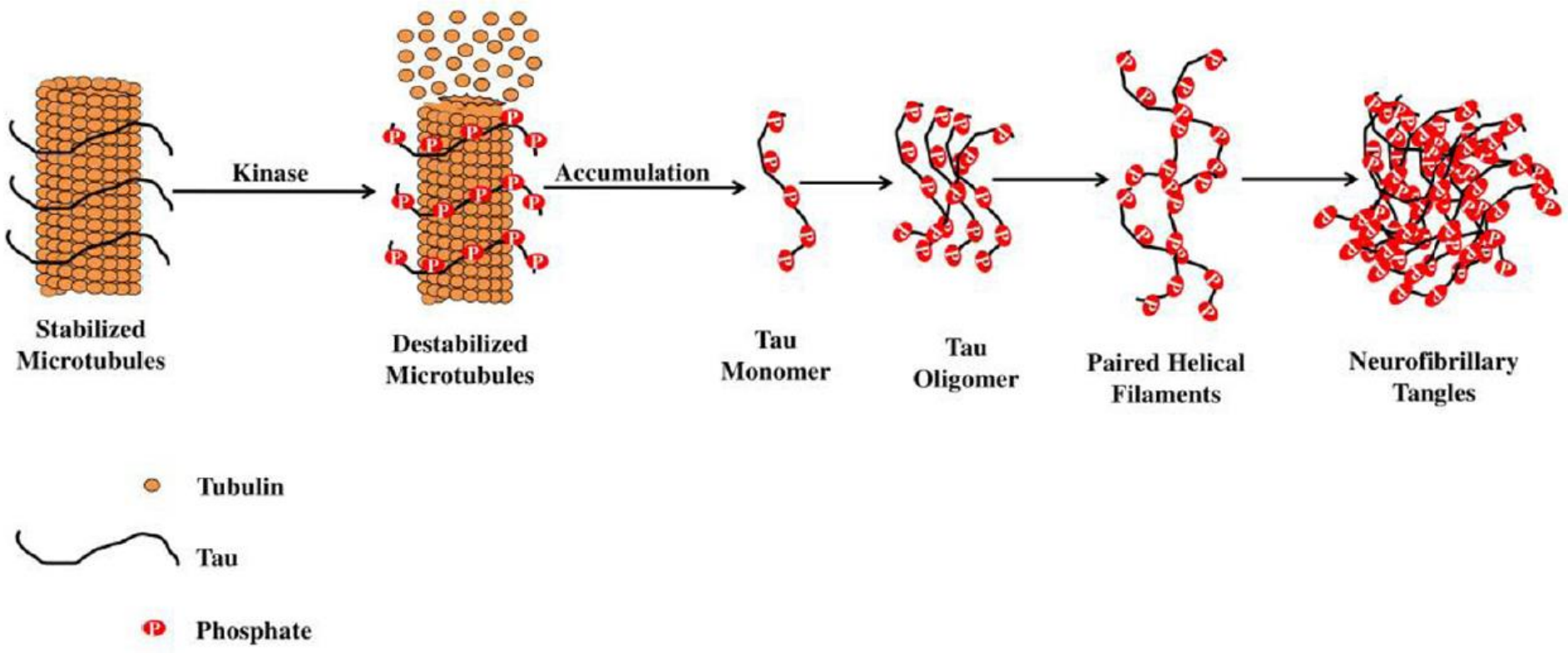


Fig. 2 APP protein structure and processing. The APP protein is a single-pass transmembrane protein with an extracellular globular domain (*top* of the figure). The extracellular segment is illustrated here in *blue*. The transmembrane segment is composed in part of sequence that makes up the Aβ peptide (*red*). The amino acid sequence of Aβ peptides and flanking regions are shown at the *bottom* along with the position and amino acid changes of different APP mutations. Locations of the α-, β-, and γ-secretase sites are shown. The γ-secretase site is shown with a *red triangle* because cleavage at this site can leave different C-terminal amino acids

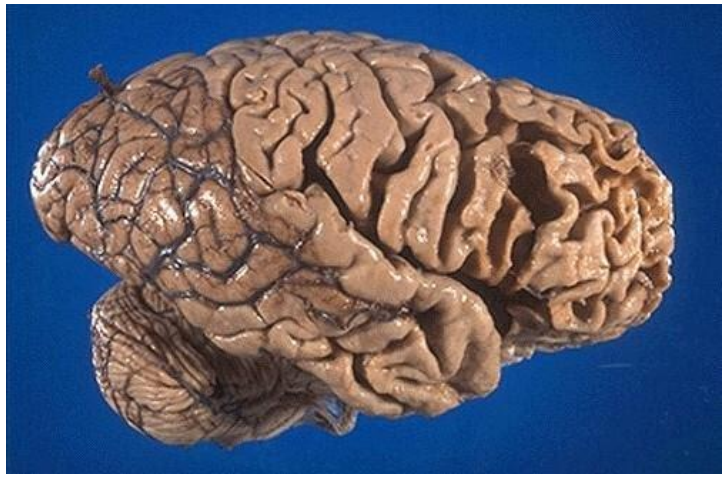
Schellenberg and Montine, Acta Neuropathologica, 2012..

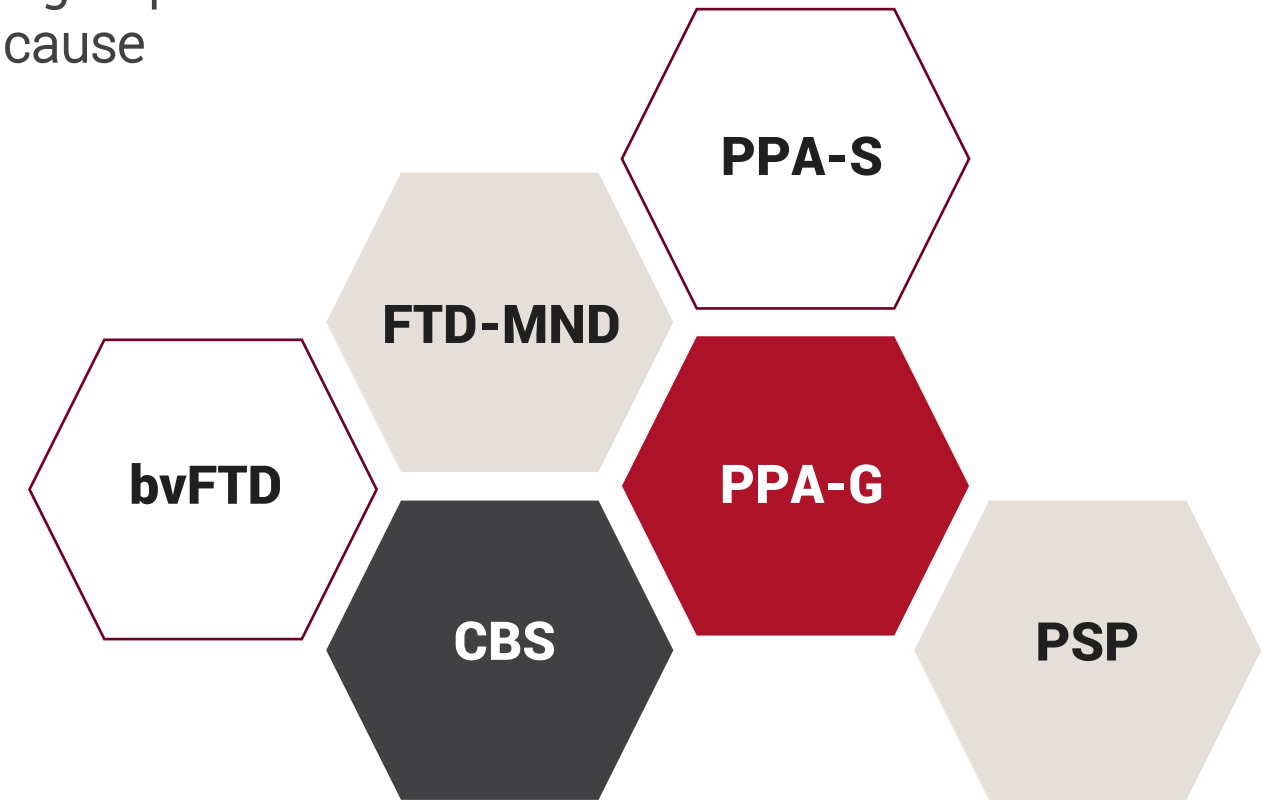
Formation of NFT



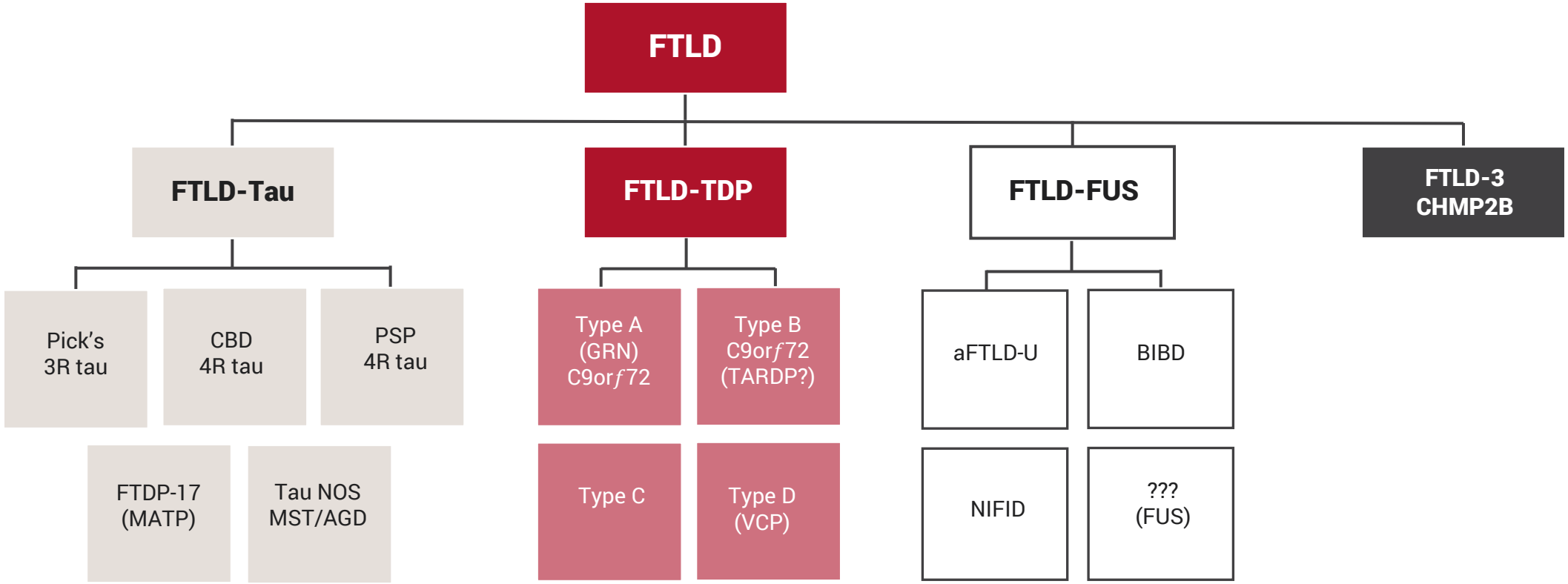
Frontotemporal Lobar Degeneration (FTLD)

- FTLD is a collective term describing a group of neurodegenerative disorders that cause selective atrophy of the frontal and temporal lobes
- Clinically referred to as FTD.





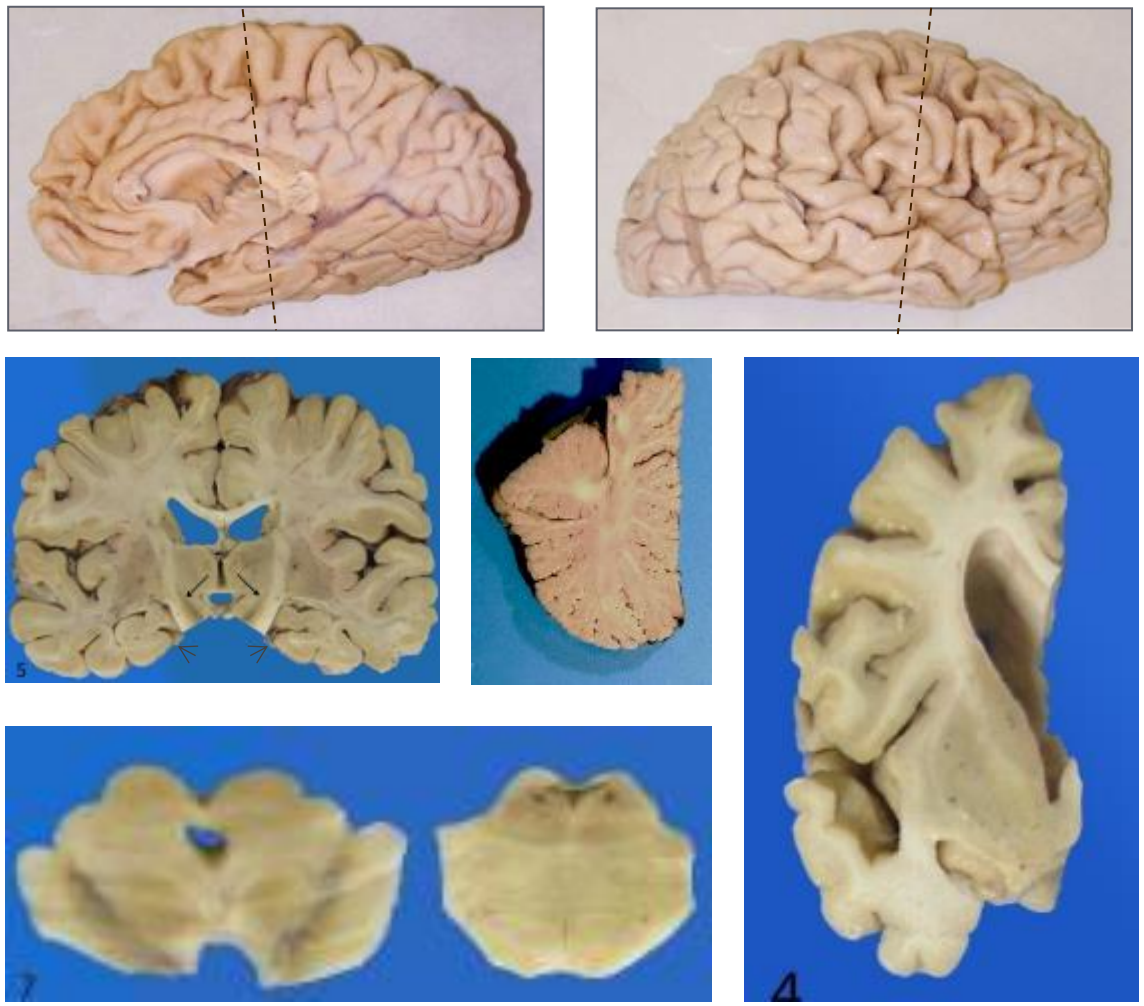
Frontotemporal Lobar Degeneration (FTLD)



Bigio. Arch Pathol Lab Med. 2013, 137(3): 314–325. Modified.

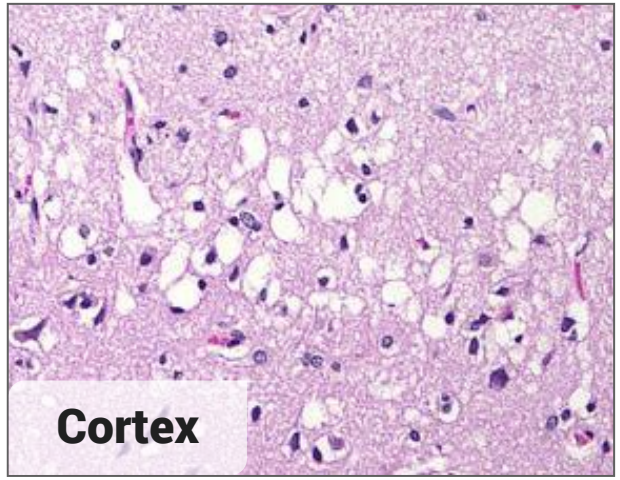
General Gross Findings

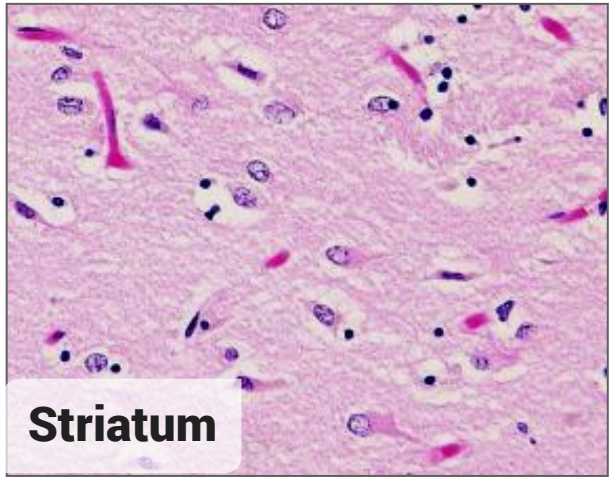
- Circumscribed lobar atrophy
- Ventricular dilatation (greater frontal poles)
- Variable caudate atrophy
- Variable nigral pallor
- Sometimes
  - Atrophy of subthalamic nucleus
  - Indistinct cerebellar dentate nucleus

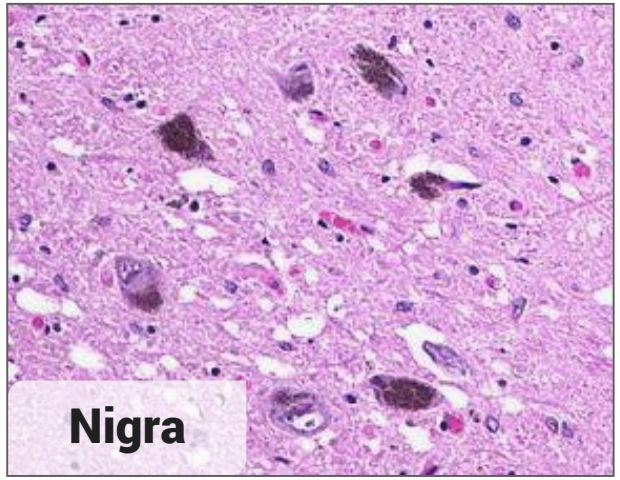


H and E Histology

- Microscopic pathology *variably shared by all FTLDs*
  - Superficial frontal/temporal (+/-other regions) microvacuolation and gliosis
  - Neuronal loss and gliosis in affected regions
- No abnormal protein inclusions

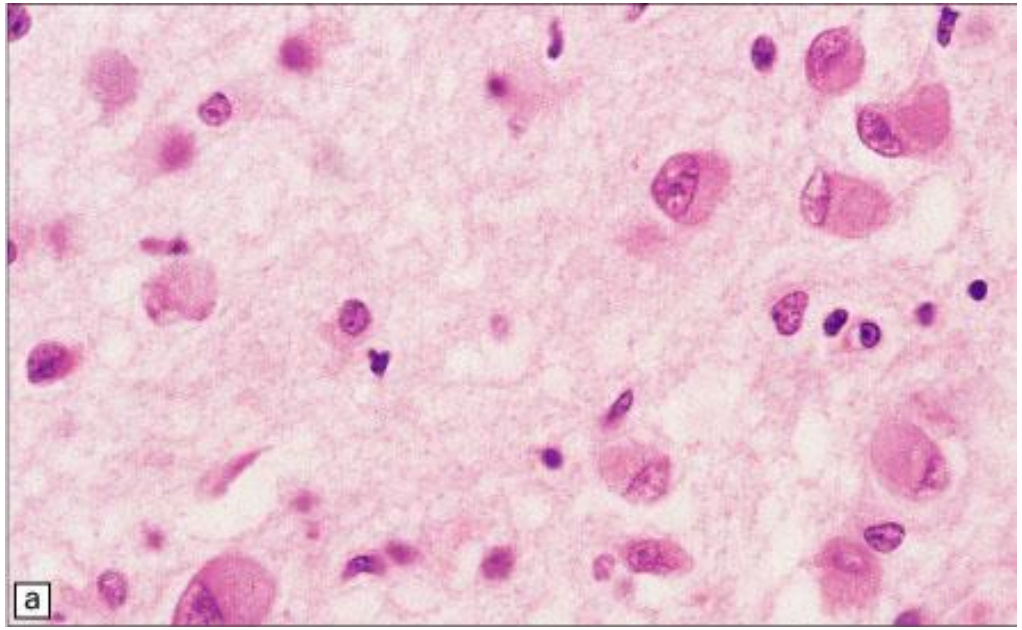


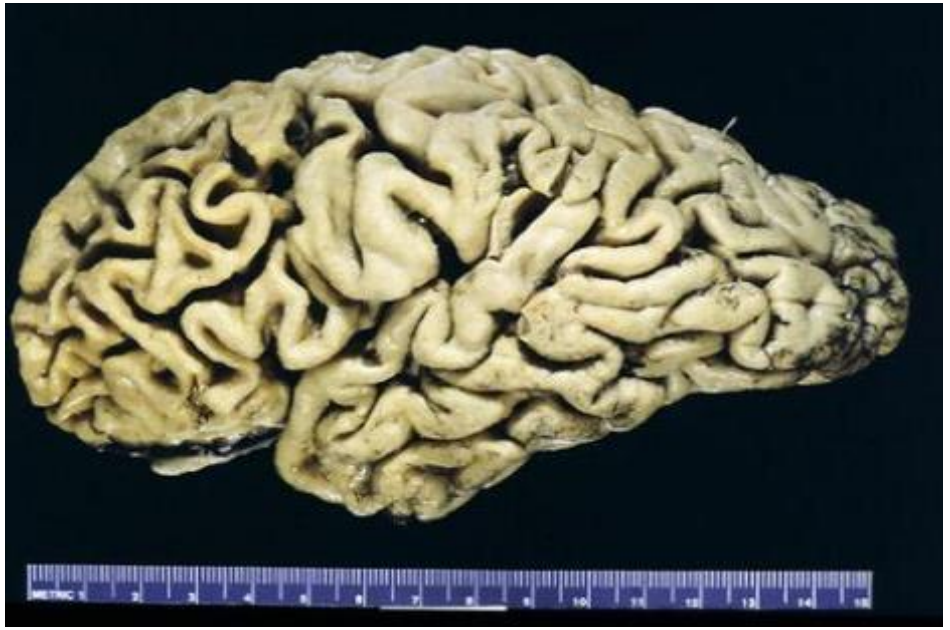




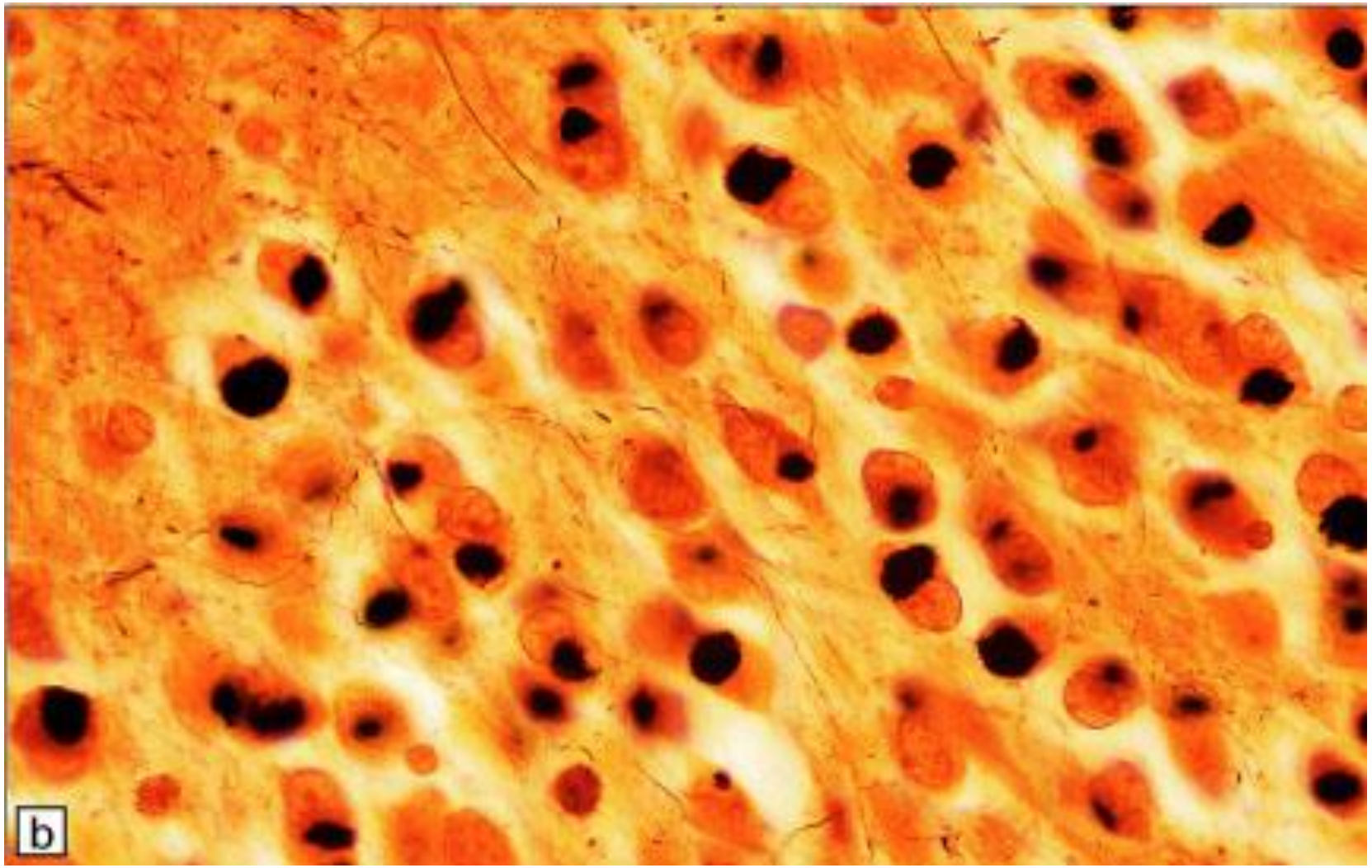
Pick Disease (FTLD-Tau [PiD]) Pathology

- Frontal temporal atrophy with sparing of posterior 2/3 of superior temporal gyrus ("knife edge" appearance)
- Pick bodies in hippocampal dentate and cortical neurons

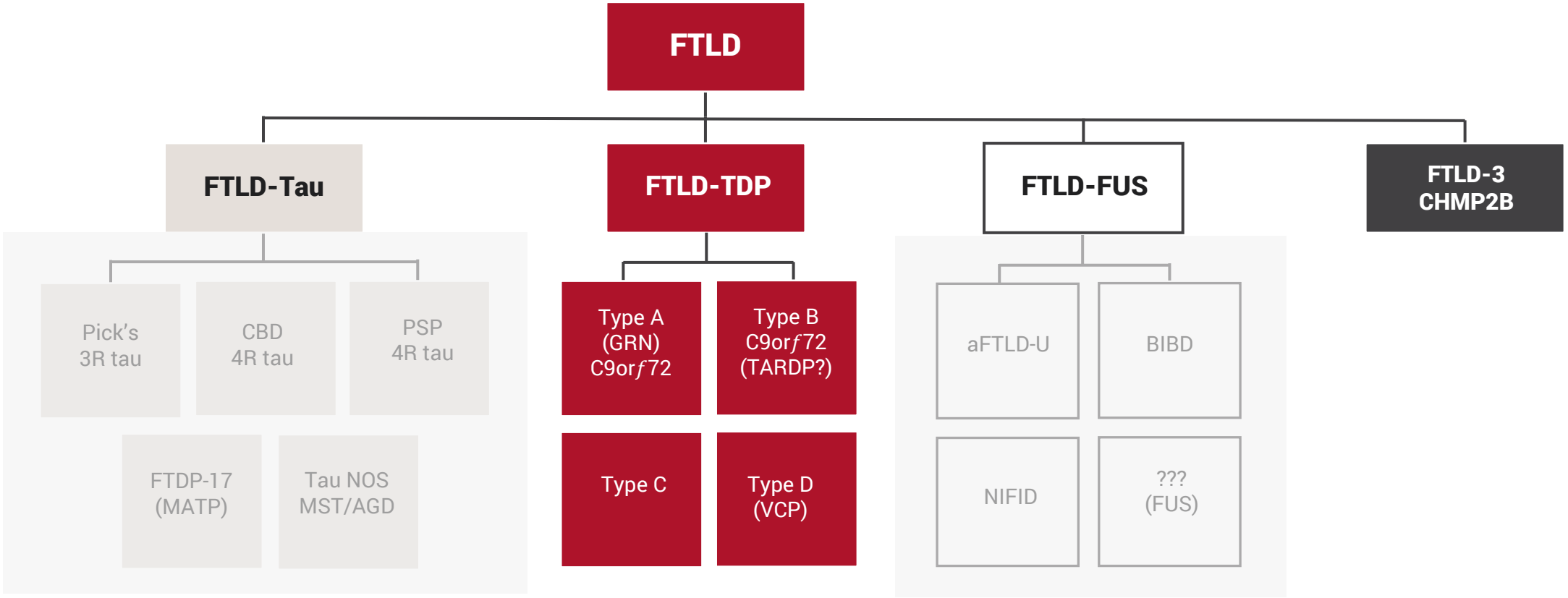




Pick Bodies

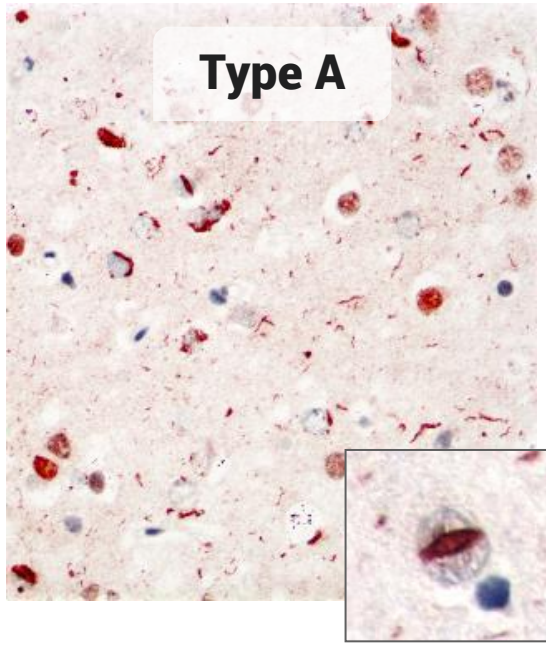


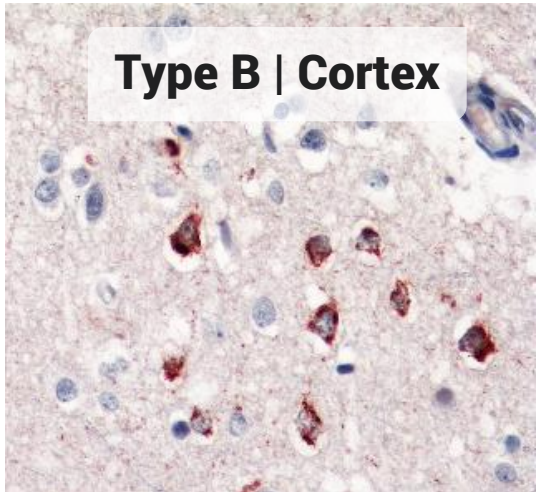
FTLD-TDP

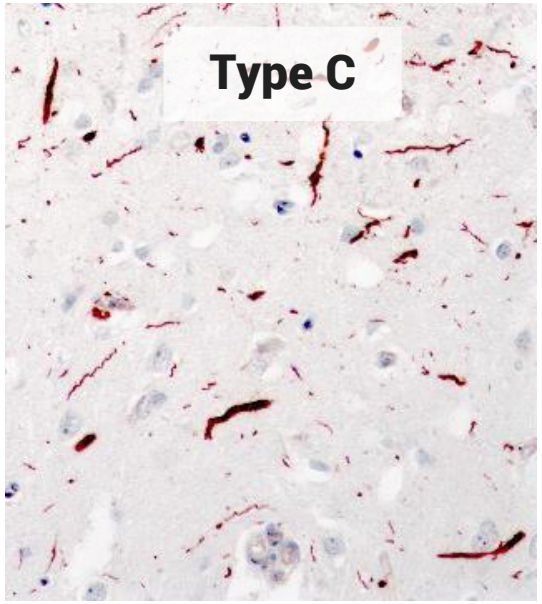


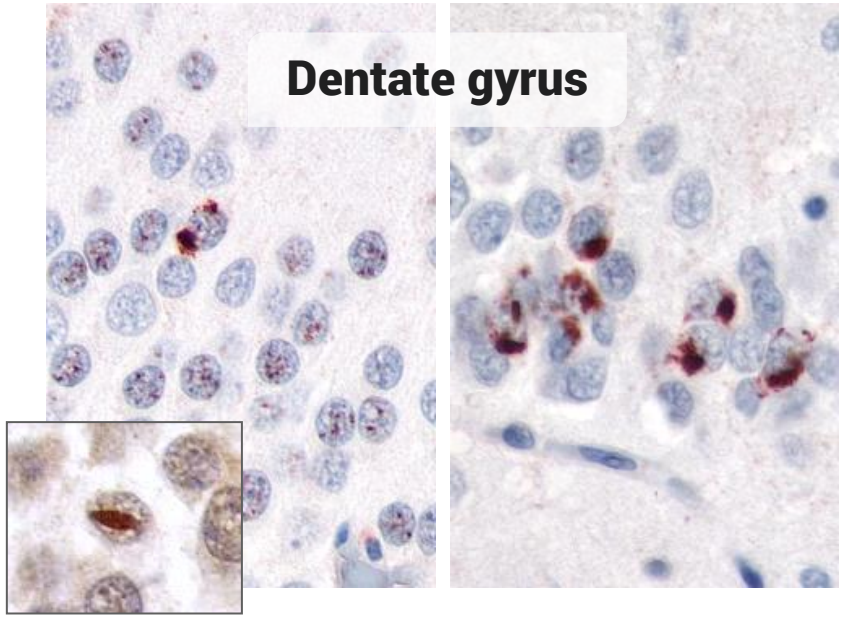
Bigio. Arch Pathol Lab Med. 2013, 137(3): 314–325. Modified.

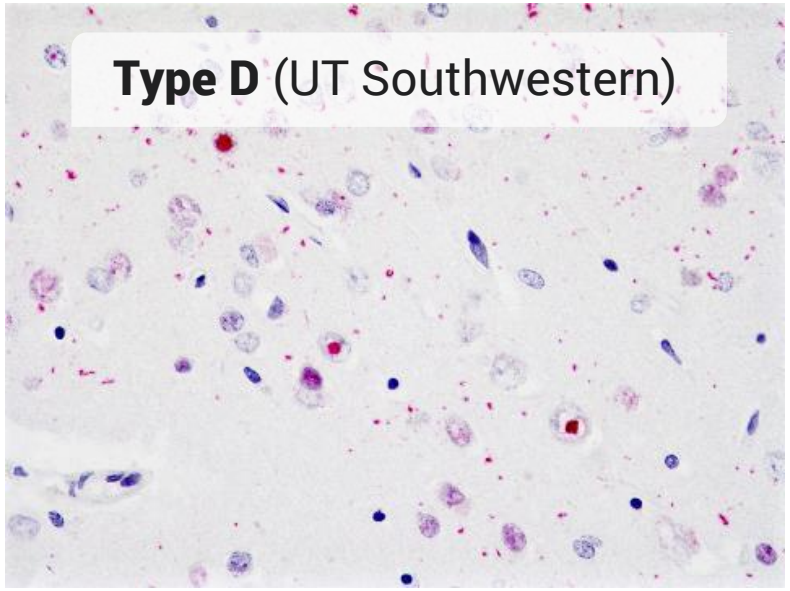
FTLD-TDP


Type A


Type B | Cortex

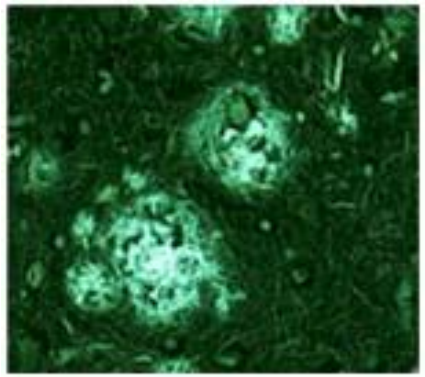
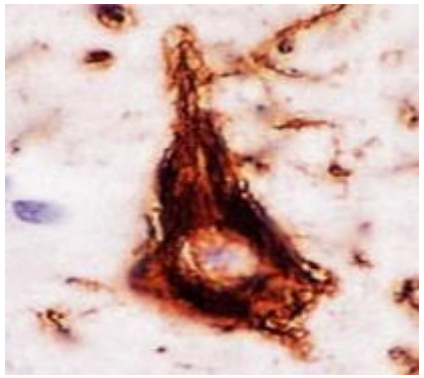
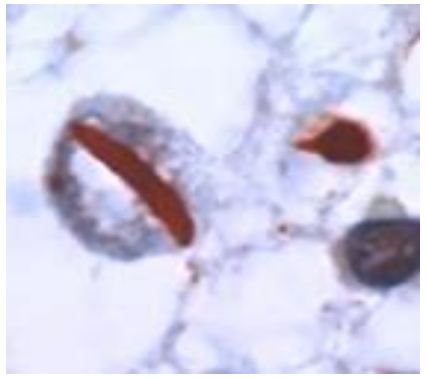
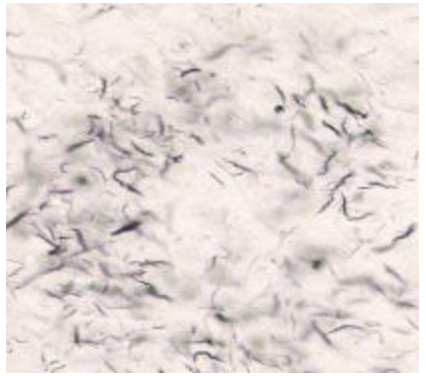
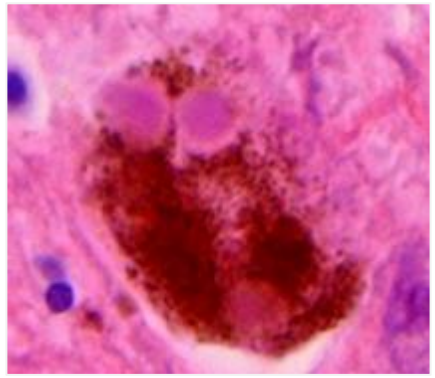

Type C


Dentate gyrus


Type D (UT Southwestern)

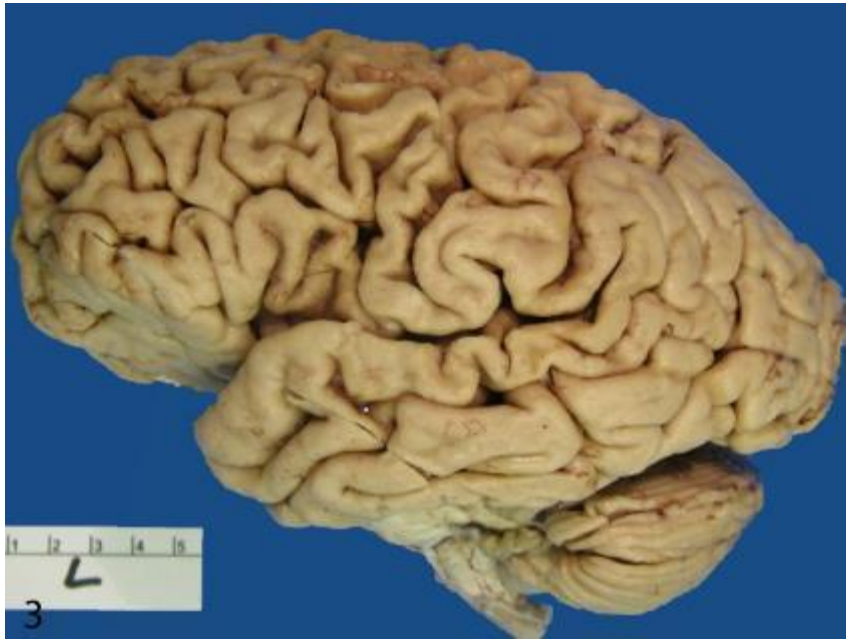
Autopsy Is the Gold Standard for Diagnosis

FTLD

AD		FTLD-TDP	FTLD-TAU	LBD
				
Beta-amyloid	P-Tau	TDP-43	P-TAU	Alpha-synuclein

Major Challenge

- Clinical phenotype: frontotemporal dementia
- Anatomic patterns: frontal and temporal involvement
- Pathology:
  - AD
  - FTLD-Tau
  - FTLD-TDP



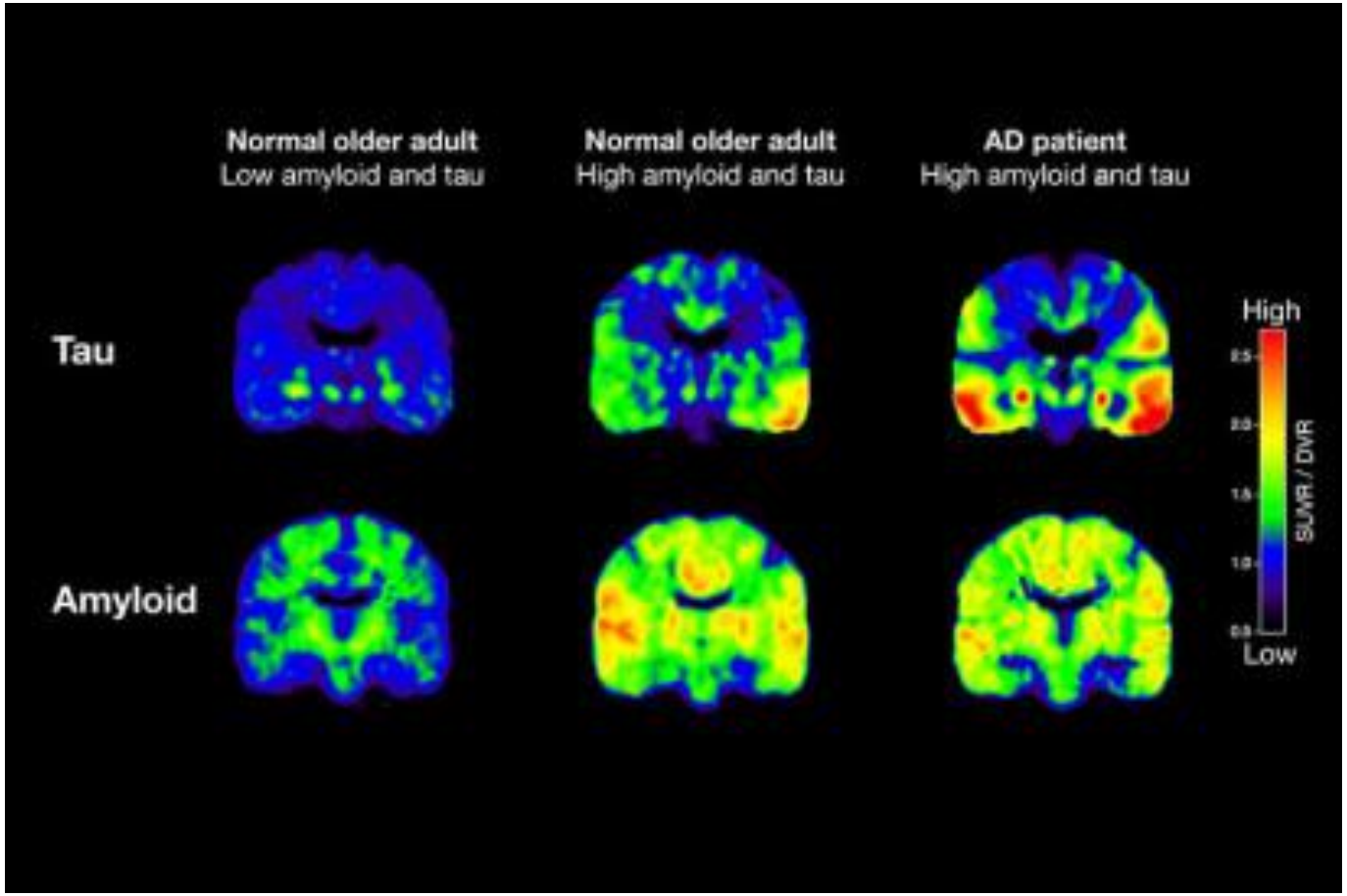
Major Challenge

Clinical diagnosis
Anatomic involvement

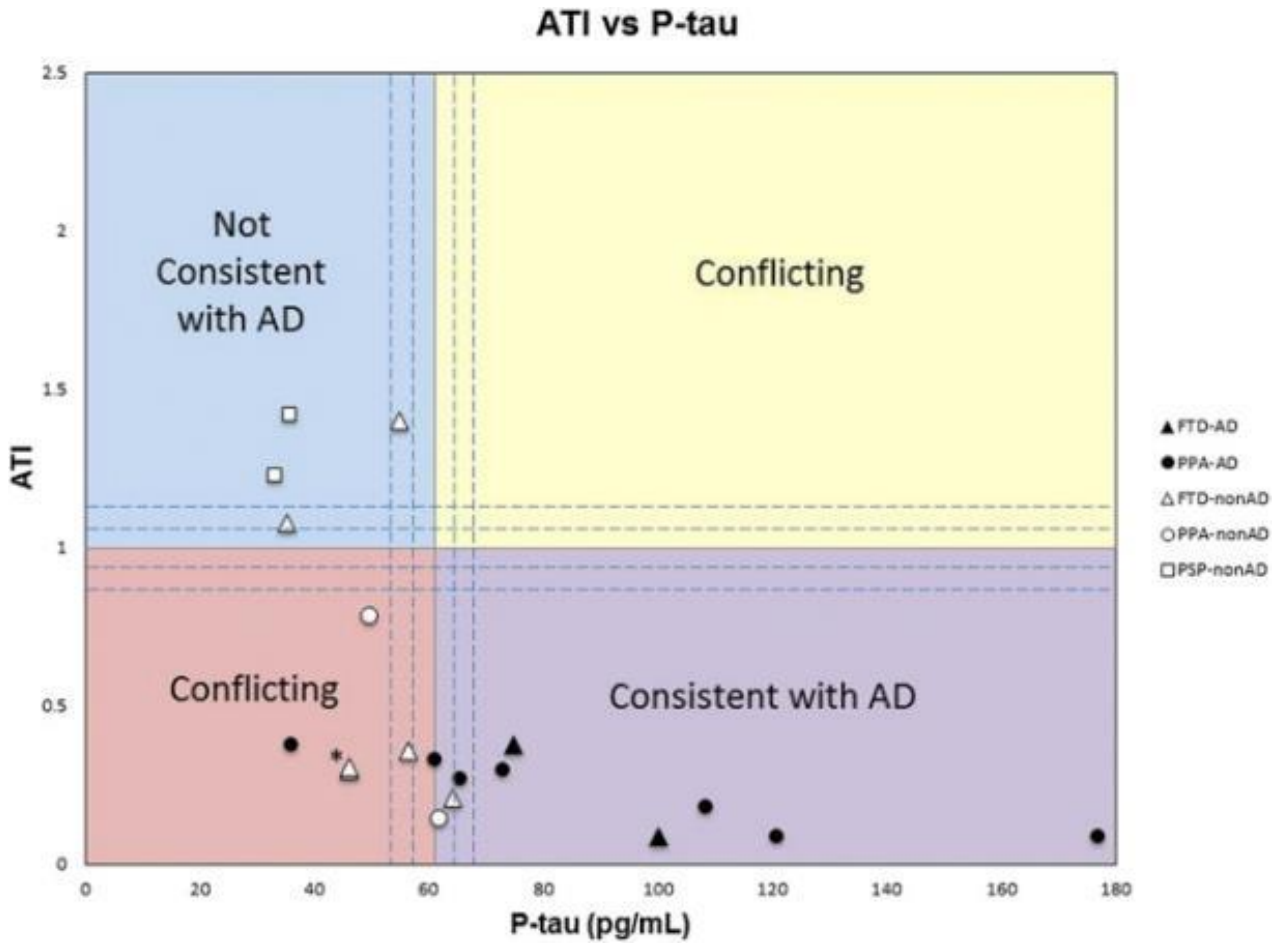
Autopsy diagnosis

Lack of biomarkers and disease-specific treatments

AD Biomarkers | PET Scans



Cerebrospinal Fluid Markers Detect Alzheimer's Disease



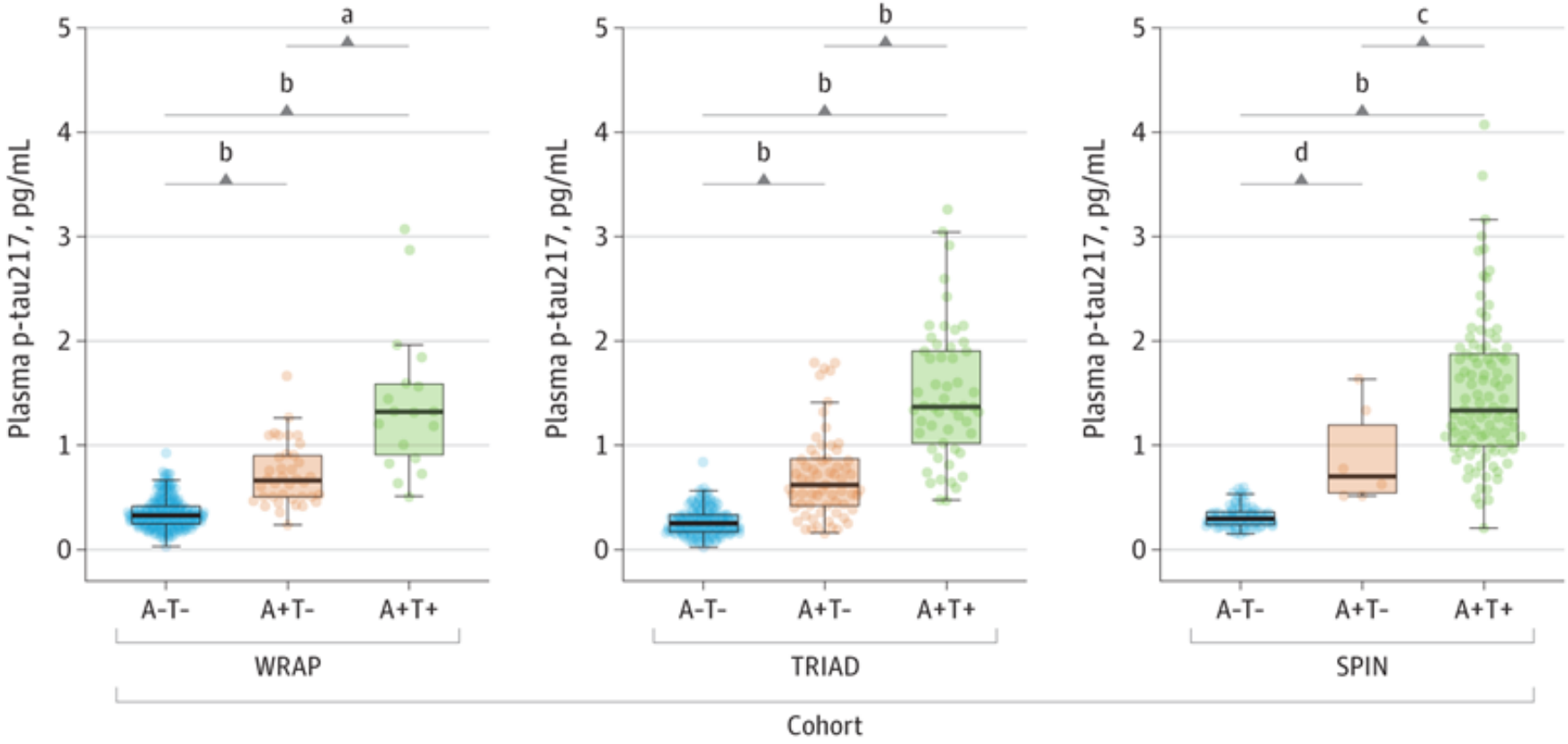
ATI (Aβ42/total tau index) and p-Tau, 0.88 sensitivity and 0.72 specificity

Oboudiyat, etal. Alzheimer's Dementa, 2017.

Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer's Disease Pathology

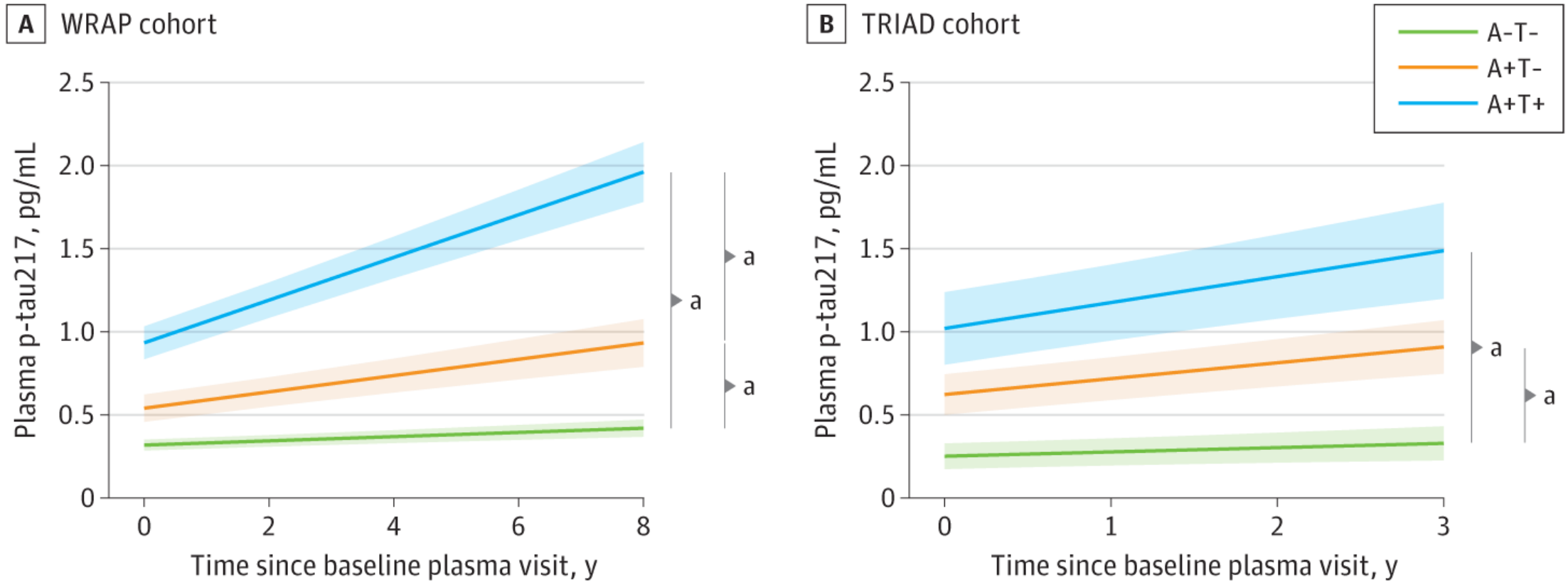
- The first blood test ever approved to help diagnose AD
- pTau 217 test proved to be as effective as PET scans and CSF tests for diagnosing AD
- Plasma pTau 217 is highly accurate for diagnosing AD at the MCI stage (~90% accuracy)
- Blood p-Tau biomarkers can detect AD pathology years before symptoms (~10–15 years)
- Plasma pTau 217 is a game-changer, making trials more accessible

Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer's Disease Pathology



Ashton NJ, et al. JAMA Neurology. 2024; 81(3):255-263.

Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer's Disease Pathology



Ashton NJ, et al. JAMA Neurology. 2024; 81(3):255-263.

Treatment: Anti-Aβ/Tau Monoclonal Antibody

- Anti-Aβ monoclonal antibody
  - Lecanemab
    - showed dose-dependent amyloid clearance and a reduction in clinical decline in Phase II trials.
    - Showed cognitive benefits observed alongside potential adverse events in Phase III trials.
    - Received **full FDA approval** based on its capacity to eliminate toxic brain amyloids.
  - Donanemab
    - Designated as **a breakthrough therapy**.
    - In clinical trials, donanemab was found to slow progression of AD by up to 60% in the earliest symptomatic stages.
- Anti-tau monoclonal antibodies

Major Challenges in Developing TDP-43 Biomarkers

Clinical diagnosis
Anatomic involvement

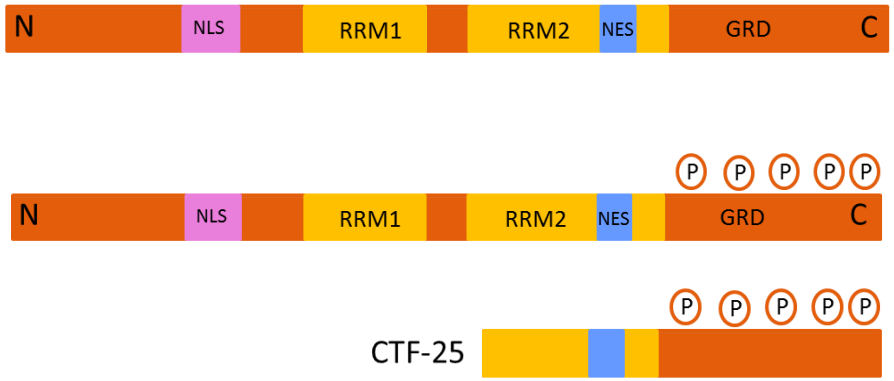
Autopsy diagnosis

Lack of biomarkers and disease-specific treatments

TDP-43 proteinopathy

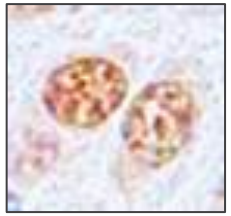
Heterogeneity in clinical manifestations and molecular pathology

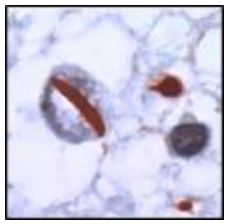
TDP-43

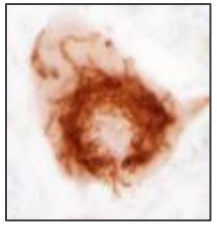


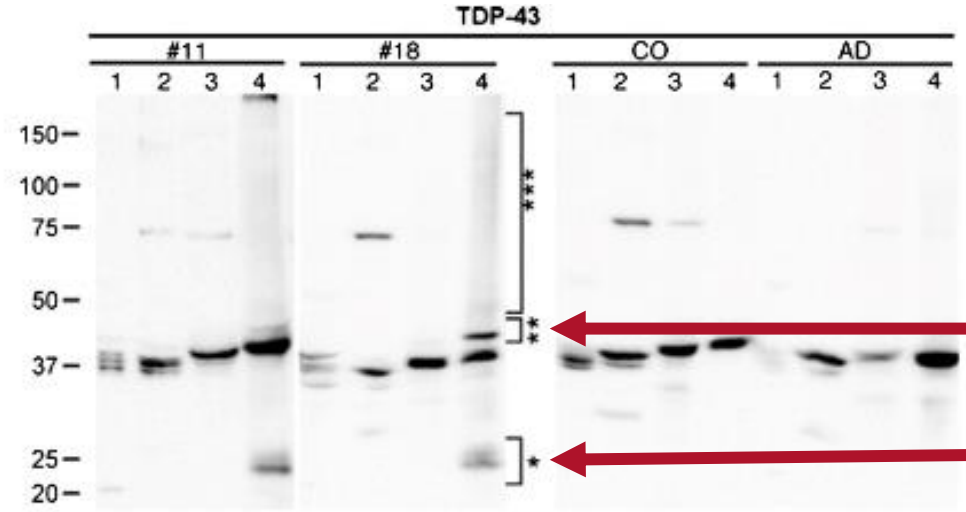
Normal

Pathologic







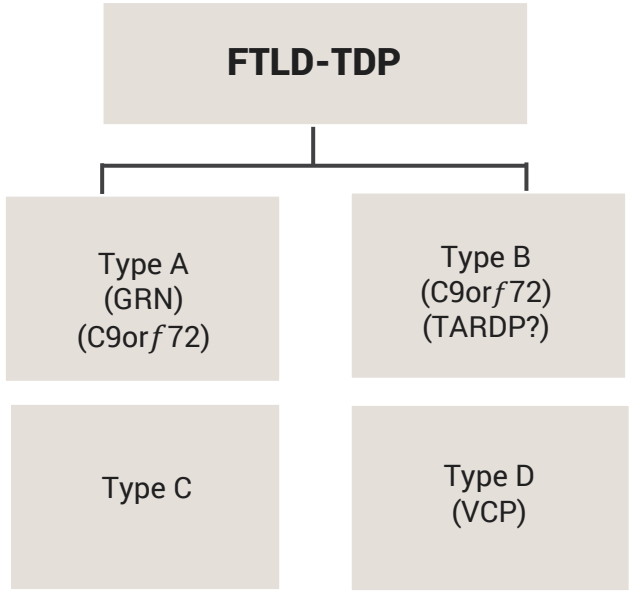


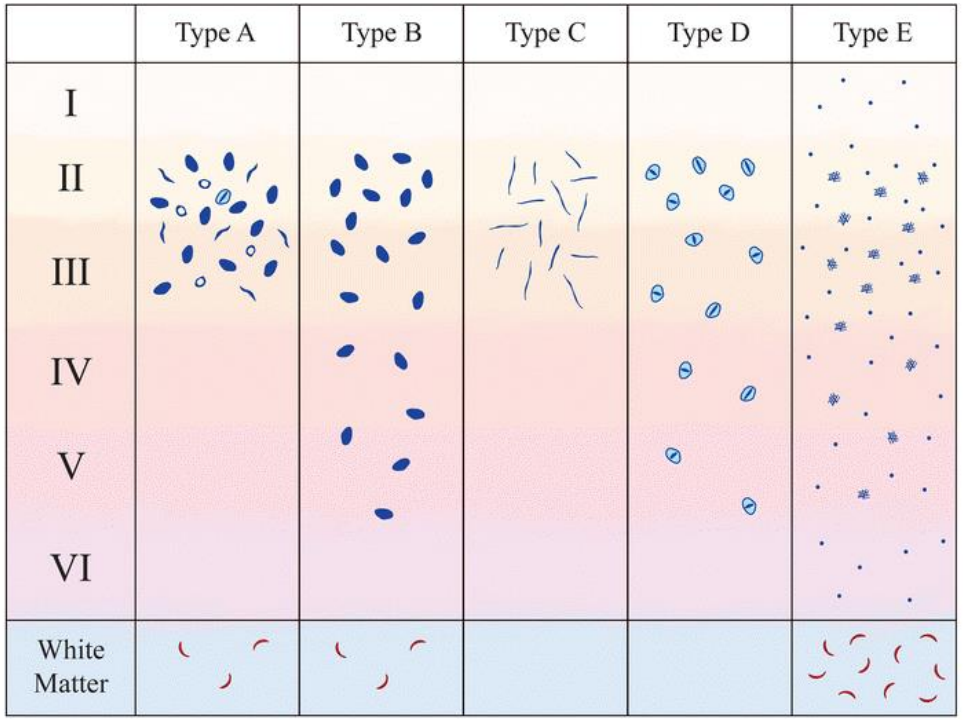
Phosphorylated TDP-43

C-terminal Fragment

Gold standard antibody, pp. 409-410

Clinicopathological and Genetic Heterogeneity in FTLD-TDP

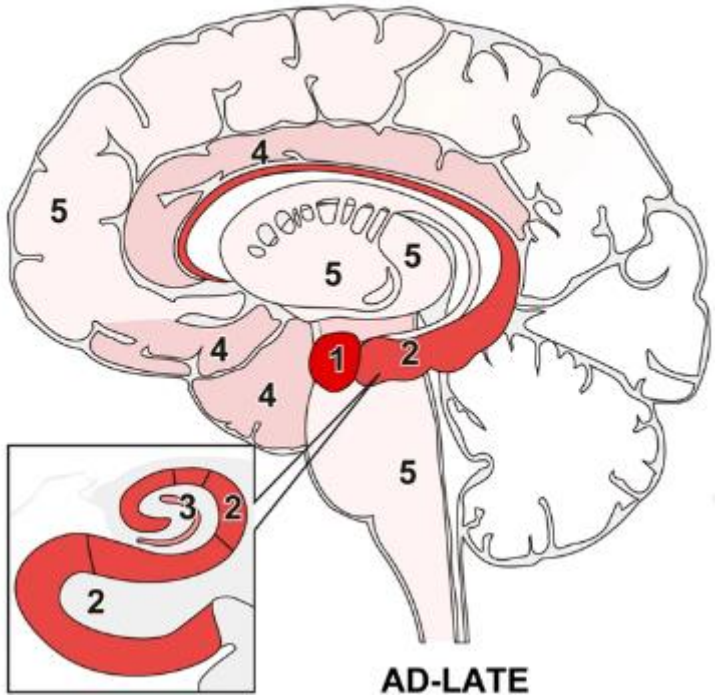




Lee, et al. Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration. Acta Neuropathol. 2017;134(1): 65-78.

TDP-43 Pathology in AD (LATE-NC)

- TDP-43 inclusions were also identified in 25–60% of pathologically confirmed AD cases, also called LATE neuropathological change (LATE-NC).
  - Stage 1: amygdala
  - Stage 2: + hippocampus
  - Stage 3: + frontal
- TDP-43 inclusions contribute independently to accelerated cognitive decline, a distinct loss of episodic and working memory, and faster rates of hippocampal atrophy.



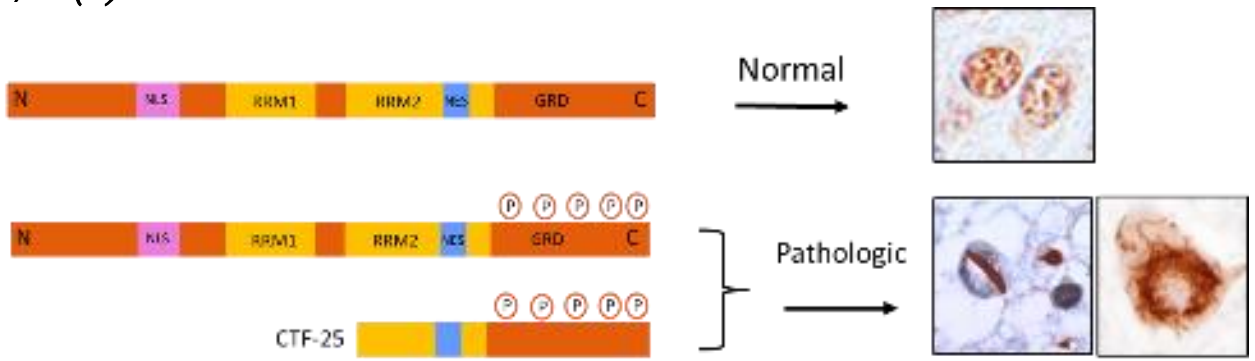
Josephs, et al. Updated TDP-43 in Alzheimer's disease staging scheme. Acta Neuropathol. 2016;131(4):571-85.
Meneses, et al. TDP-43 pathology in Alzheimer's disease. Mol Neurodegener. 2021;16(1):84
Nelson, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain 2019; 142: 1503–27.
Uemura, et al. Distinct characteristics of limbic-predominant age-related TDP-43 encephalopathy in Lewy body disease. Acta Neuropathol. 2022 Jan;143;1(1):15-31 (2022).

TDP-43 Molecular Heterogeneity

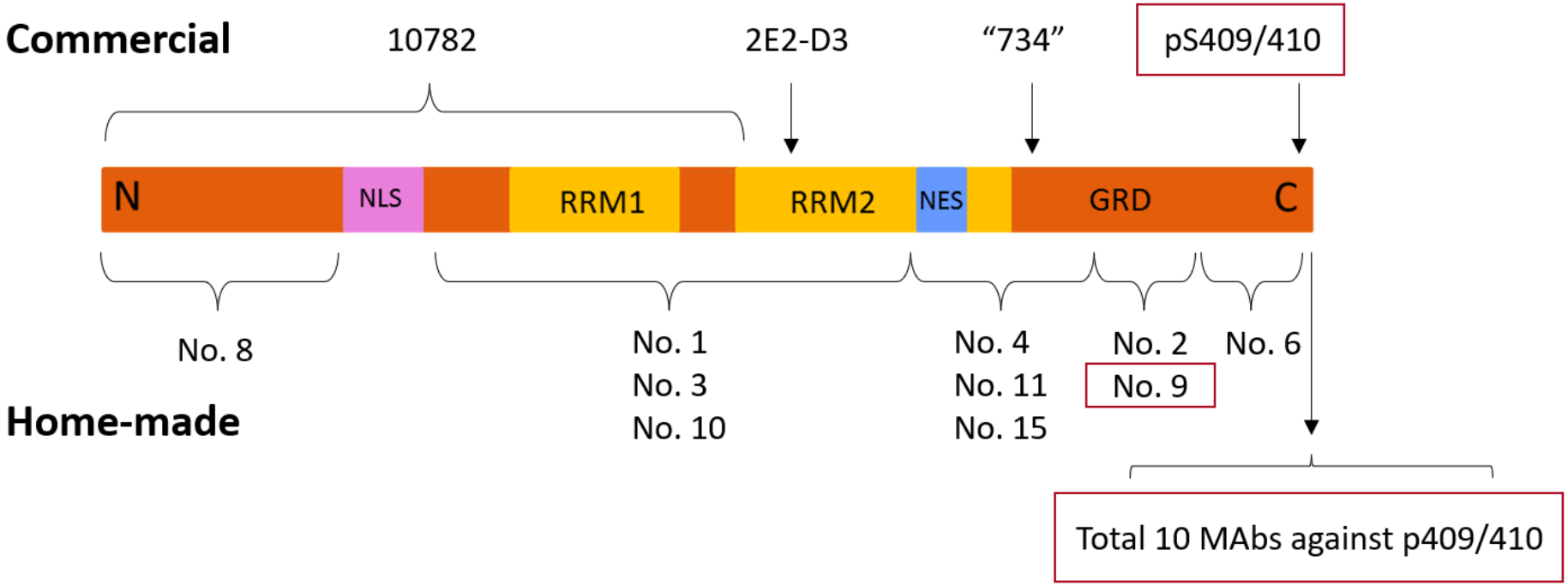
- TDP-43 inclusions represent a mixture of toxic and nontoxic TDP-43 species
  - Laferrière, et al., showed that the molecular properties of TDP-43 inclusions are correlated with specific neuropathological subtypes. Using SarkoSpin, a method for biochemically isolating pathologic TDP-43, they showed that the extracted TDP-43 assemblies exhibit cytotoxicity that reflects the disease duration of the respective subtype. These observations indicate that toxic TDP-43 species might be a link between a defined TDP-43 pathology and a specific clinical phenotype.

    Laferrière F, et al. Nat Neurosci. 2019;22(1):65-77.

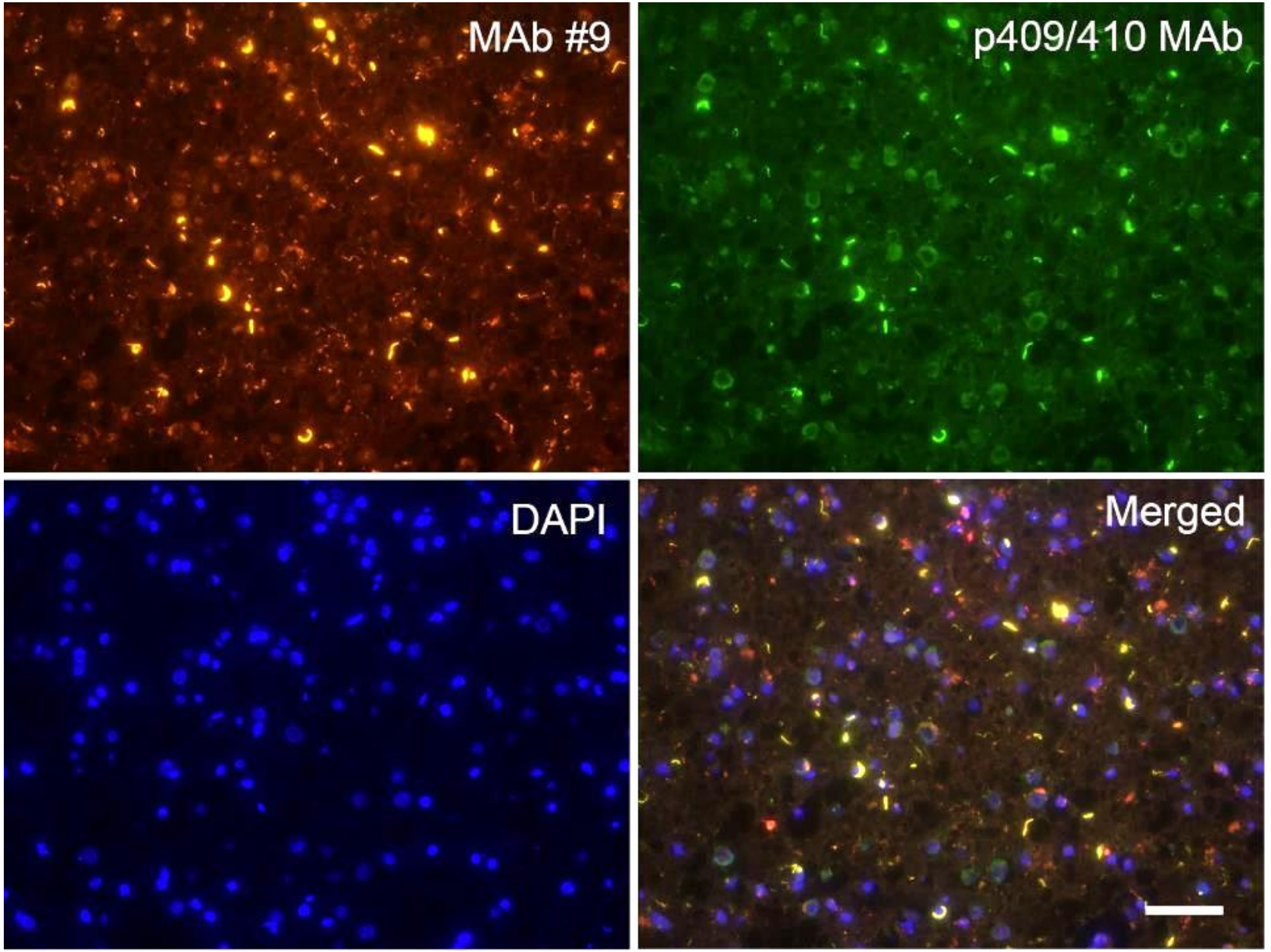
- Species-specific antibodies?



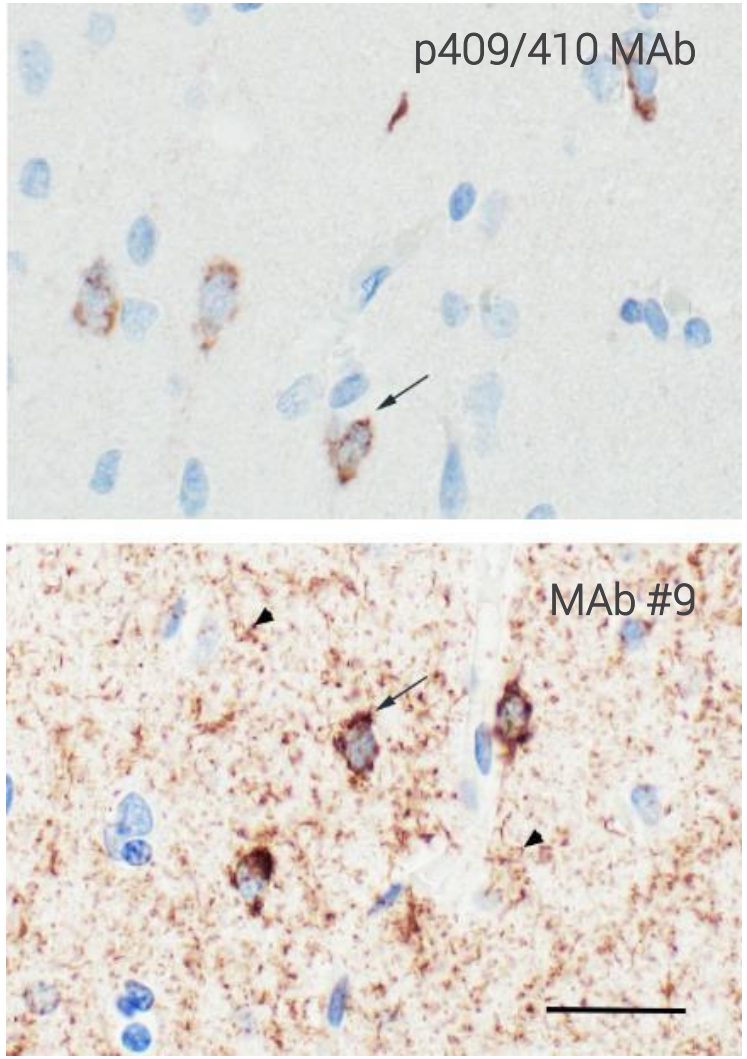
Preliminary and Published Studies



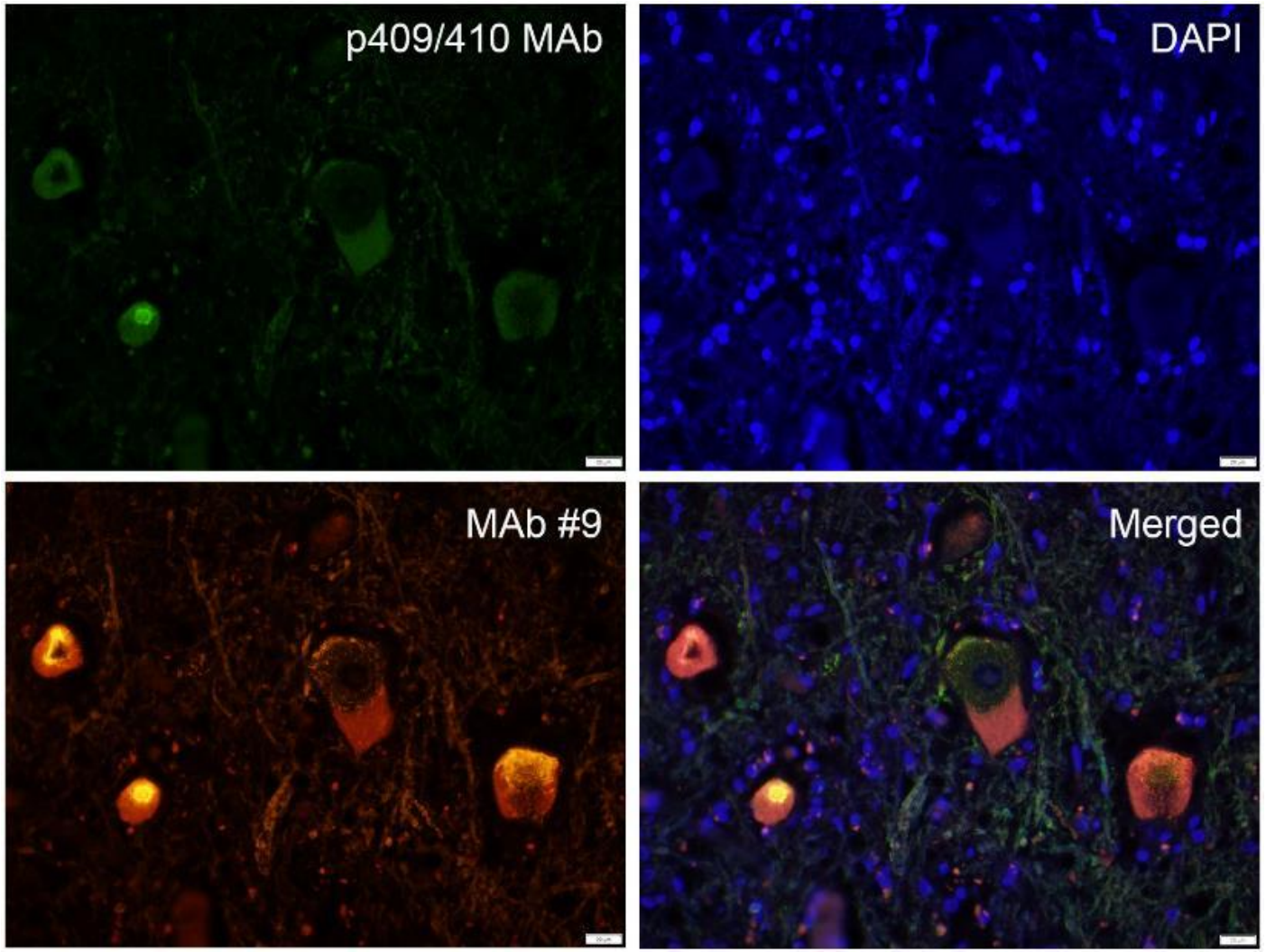
Mab #9 FTLD-TDP Type A



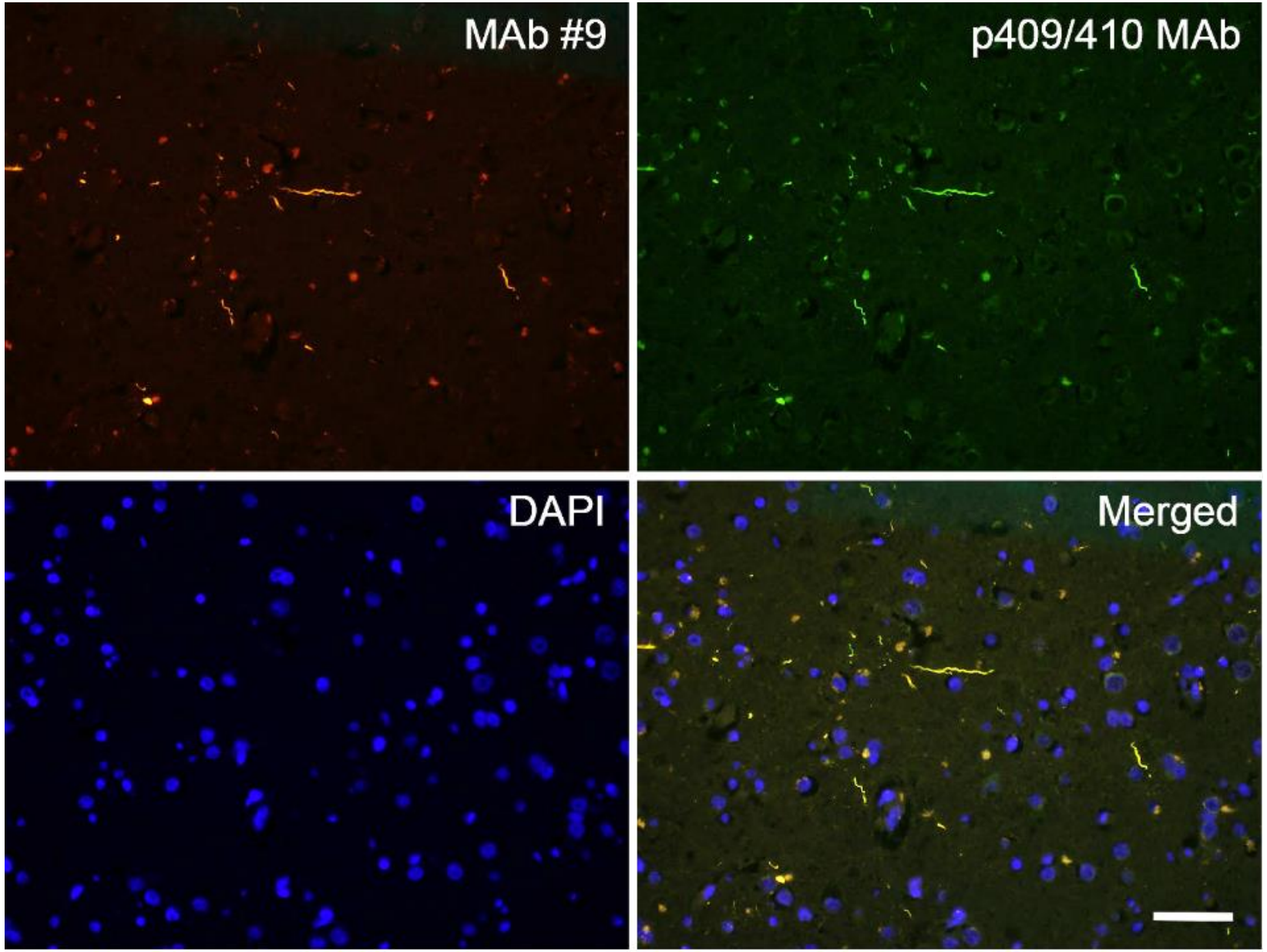
FTLD-TDP Type B Frontal Cortex



Anterior Horn of an ALS With C9 Mutation Patient

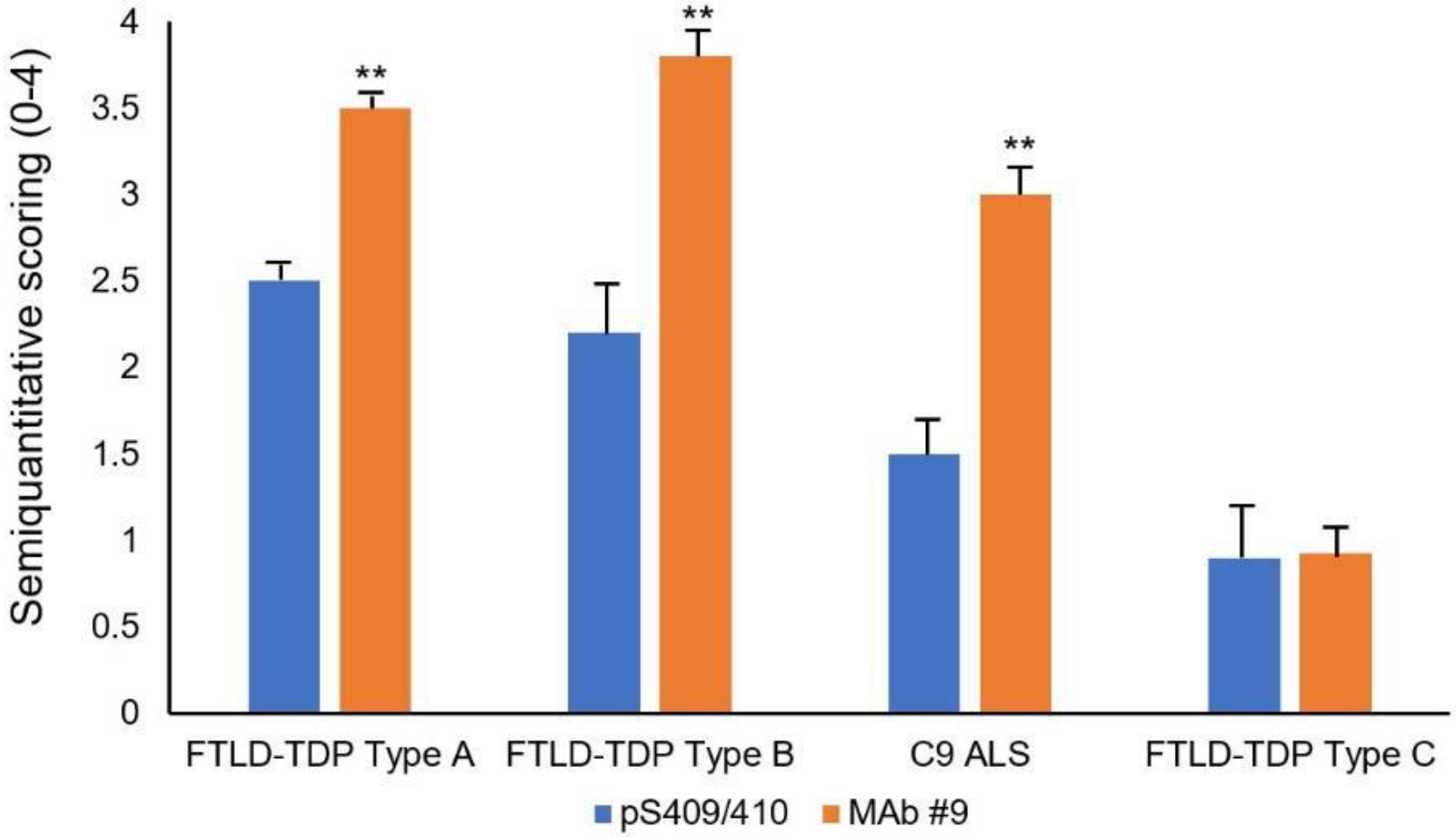


FTLD-TDP Type C

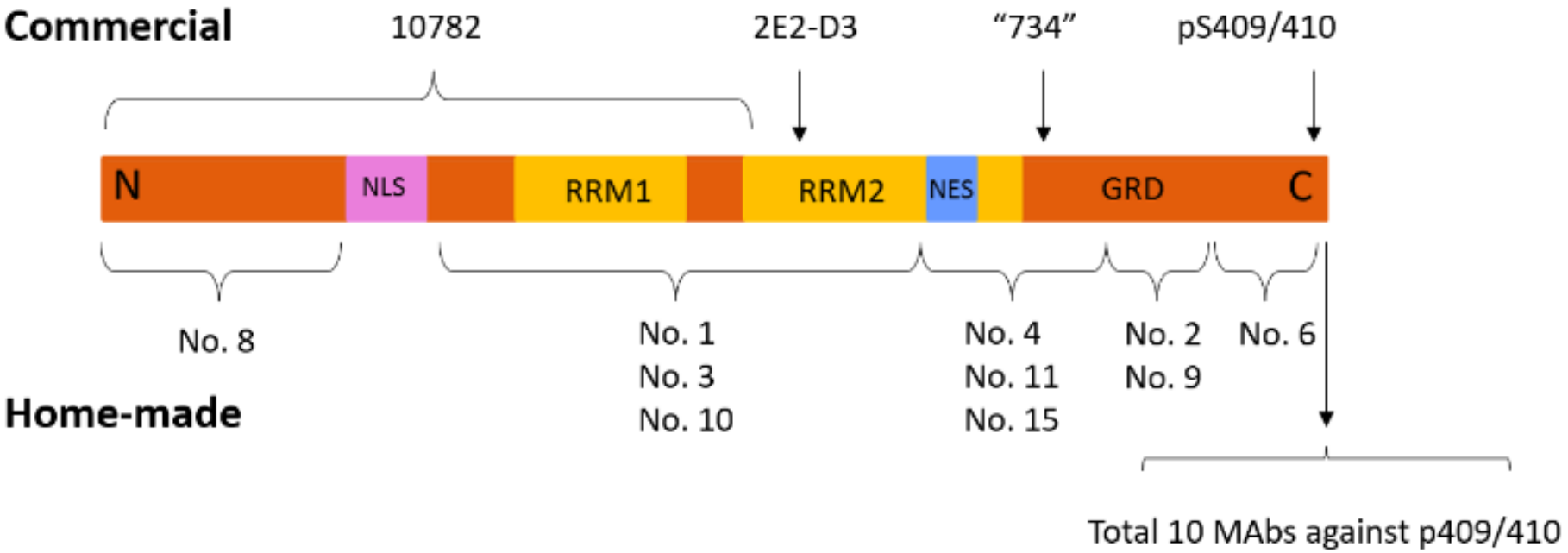


Kawles, et al. Brain. 2022; 145(3):1069-1078.

Density of TDP-43 Pathology

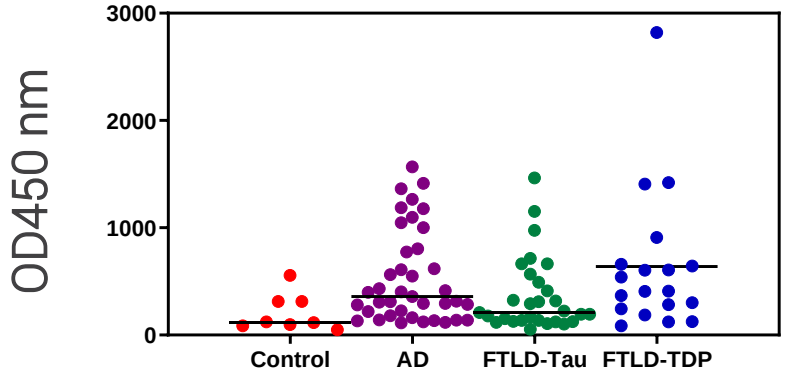


Antibody Pairs for ELISA

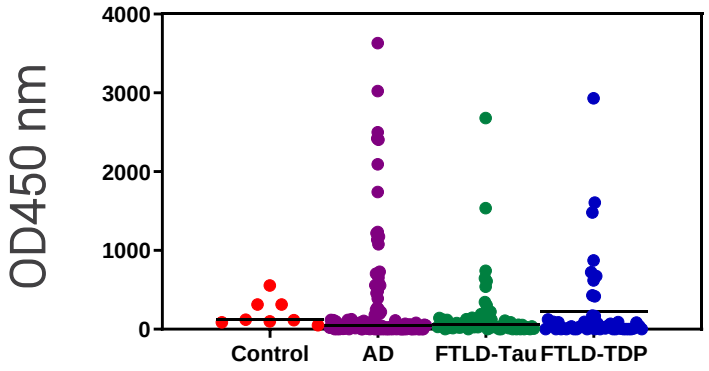


4 + 9: full length and CTF, pathologic
4 + 6: full length and CTF
9 + 5: phosphorylated, pathologic
4 + 14: full length and CFT, phosphorylated

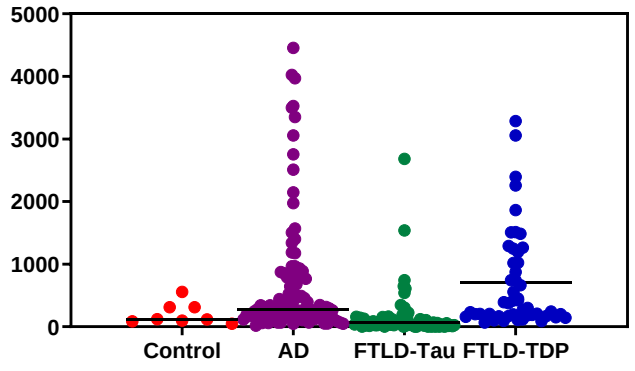
MSD With Different TDP-43 Antibody Pairs on Patient's Plasma Samples



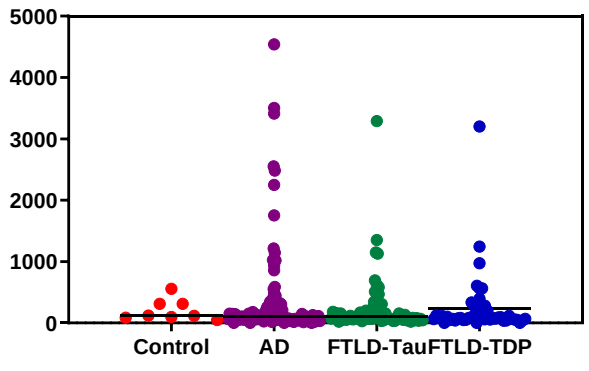
Antibody pair 9-5



Antibody pair 9-14

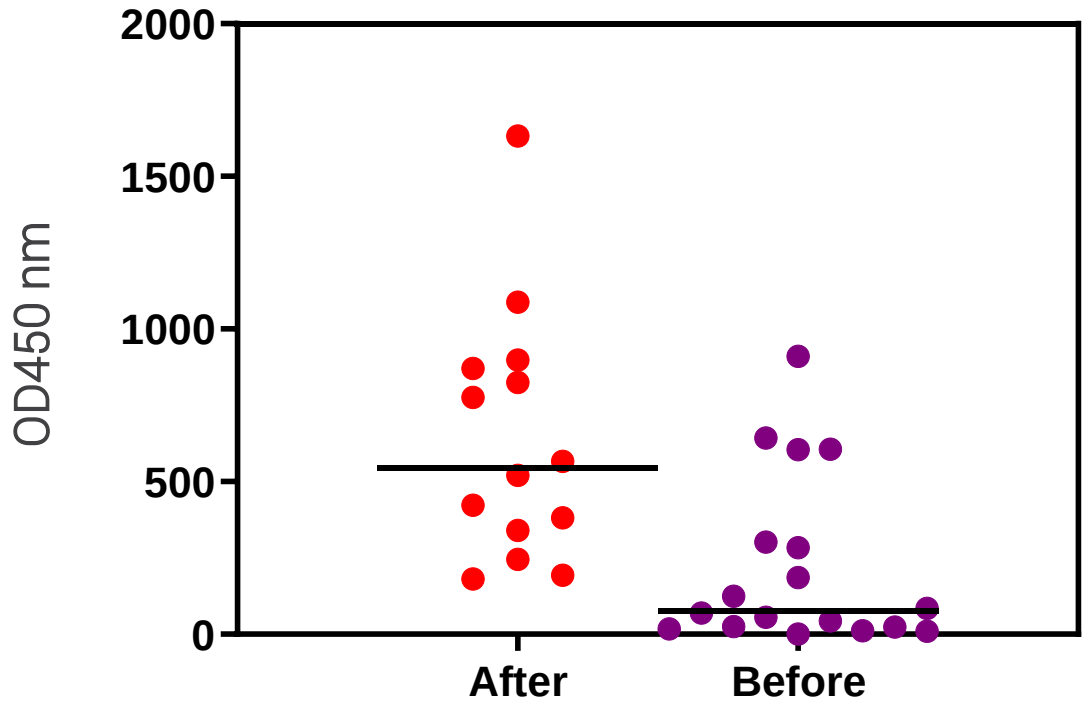


Antibody pair 9-4



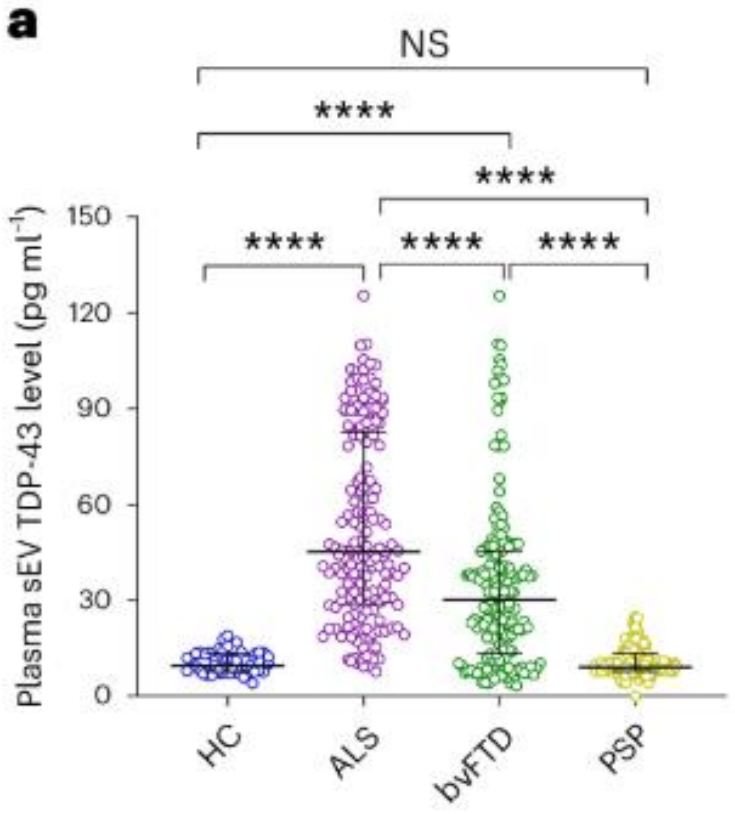
Antibody pair 4-6

Elevated TDP-43 Levels Following Freeze-Thaw



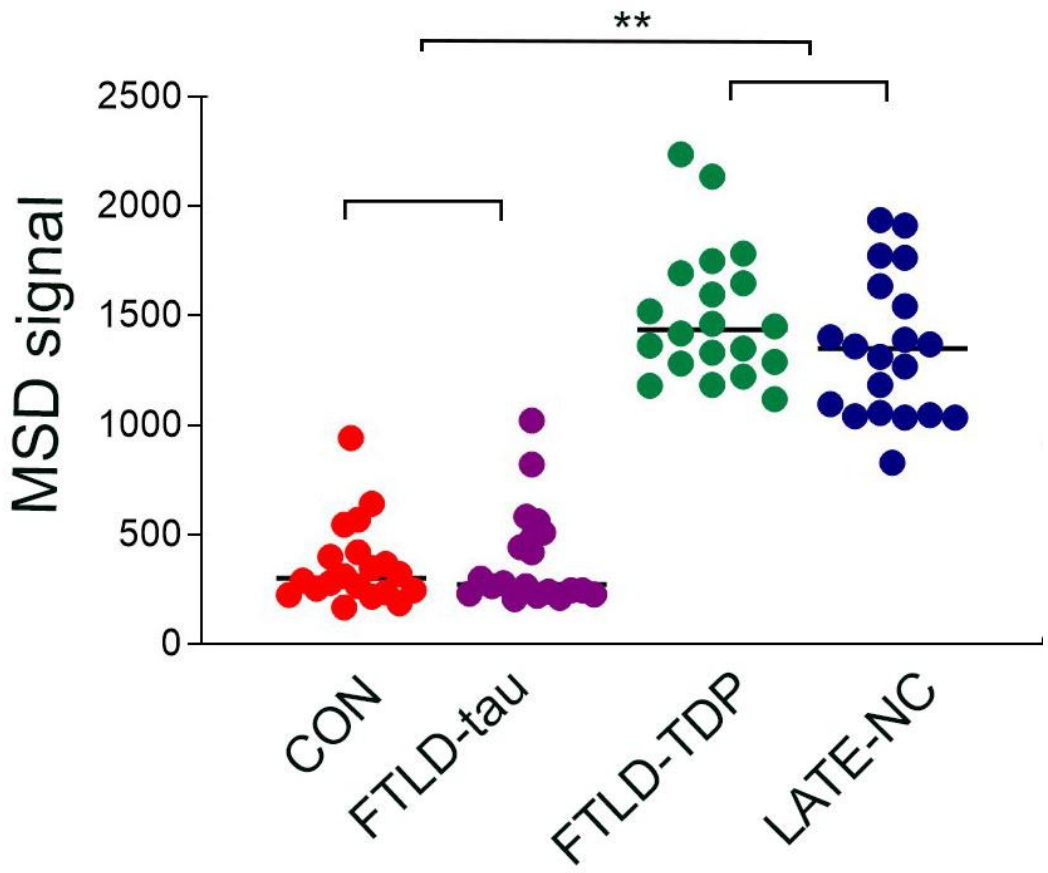
FTLD-TDP type A patient's plasma
Antibody pair 9-5

TDP-43 Levels in Plasma EV



Chatterjee, et al. Plasma extracellular vesicle tau and TDP-43 as diagnostic biomarkers in FTD and ALS. *Nature Medicine, 2024*

TDP-43 Levels in Plasma EV



Antibody pair 9-5

Summary

- Role of Biomarkers in Dementia
  - Biomarkers are essential for early diagnosis, disease staging, and monitoring treatment response in neurodegenerative diseases.
  - Shift from clinical symptom-based diagnosis to biomarker-driven precision medicine.
- Key Biomarkers and Their Clinical Applications
  - Amyloid-beta (Aβ) and Tau: Hallmarks of Alzheimer's disease (AD), detectable in CSF and blood.
  - TDP-43: Critical for diagnosing FTLD, ALS, and LATE, but lacks reliable blood-based detection.
- Advancements in Plasma and CSF Biomarker Technologies
  - Highly sensitive assays (Simoa, mass spectrometry, and immunoassays) enable blood-based detection of AD biomarkers.
  - Emerging technologies such as PET imaging tracers for TDP-43 and synaptic dysfunction.
- Future Directions in Biomarker Development
  - Development of novel blood-based biomarkers for TDP-43 pathology.
  - Integration of biomarkers into clinical trials for drug development and patient stratification.
  - Advancing personalized medicine by combining biomarker profiles with genetic and clinical data.

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