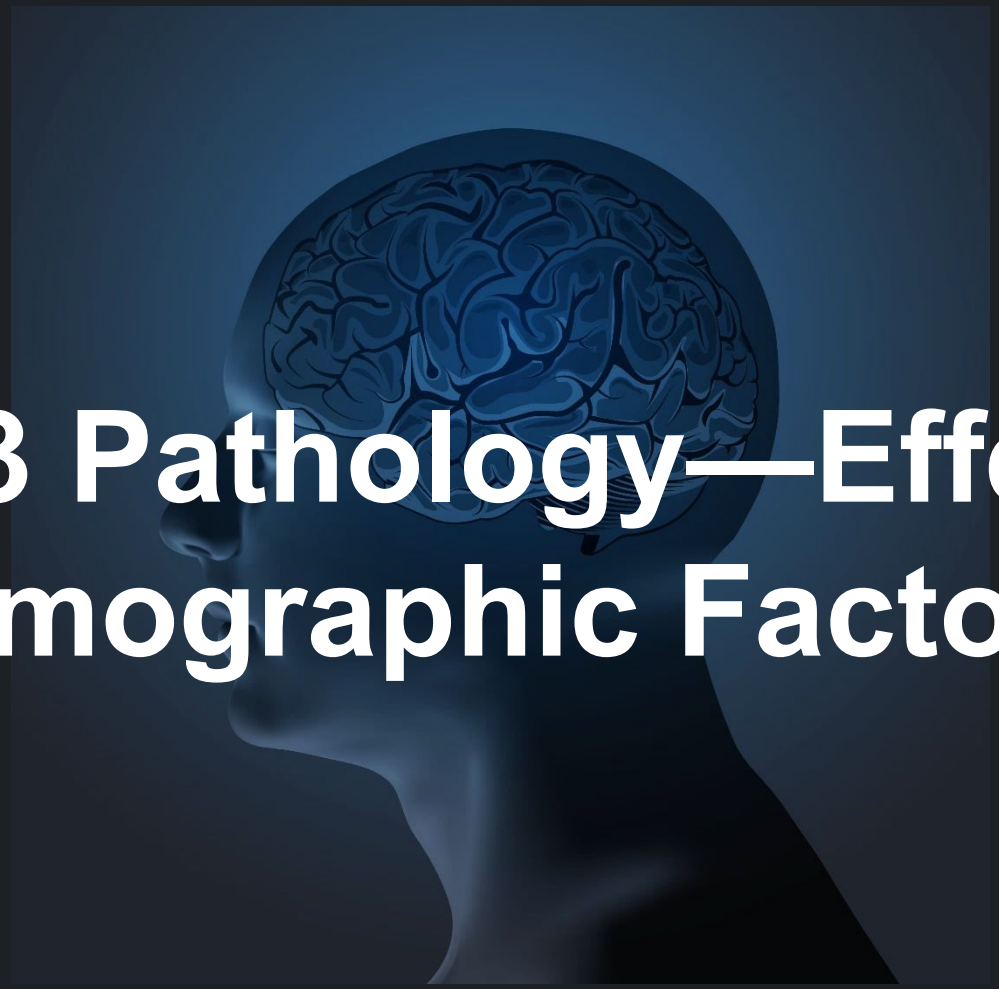

TDP43 Pathology—Effect of Demographic Factors

Gregory Jicha, MD, PhD
University of Kentucky

DISCLOSURES

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- **None of the above are related to the content of this presentation**
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Alzheimer's Public Educational Forum

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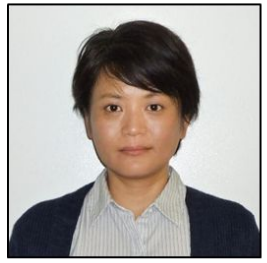

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University of Kentucky
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SANDERS-BROWN CENTER ON AGING
ALZHEIMER'S DISEASE CENTER
30 YEARS 1985-2015

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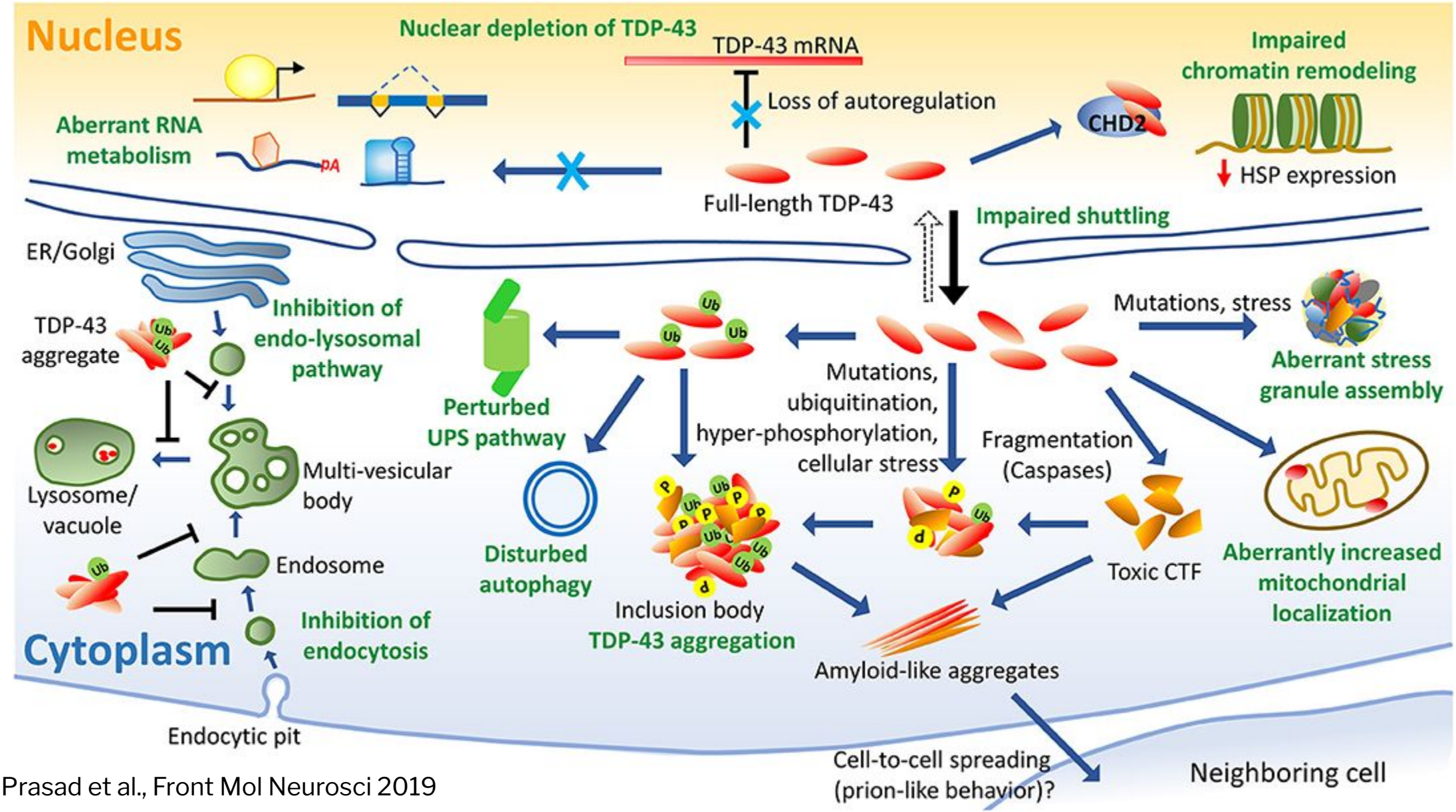
NACC
National Alzheimer's Coordinating Center

TDP43 relationships to dementia



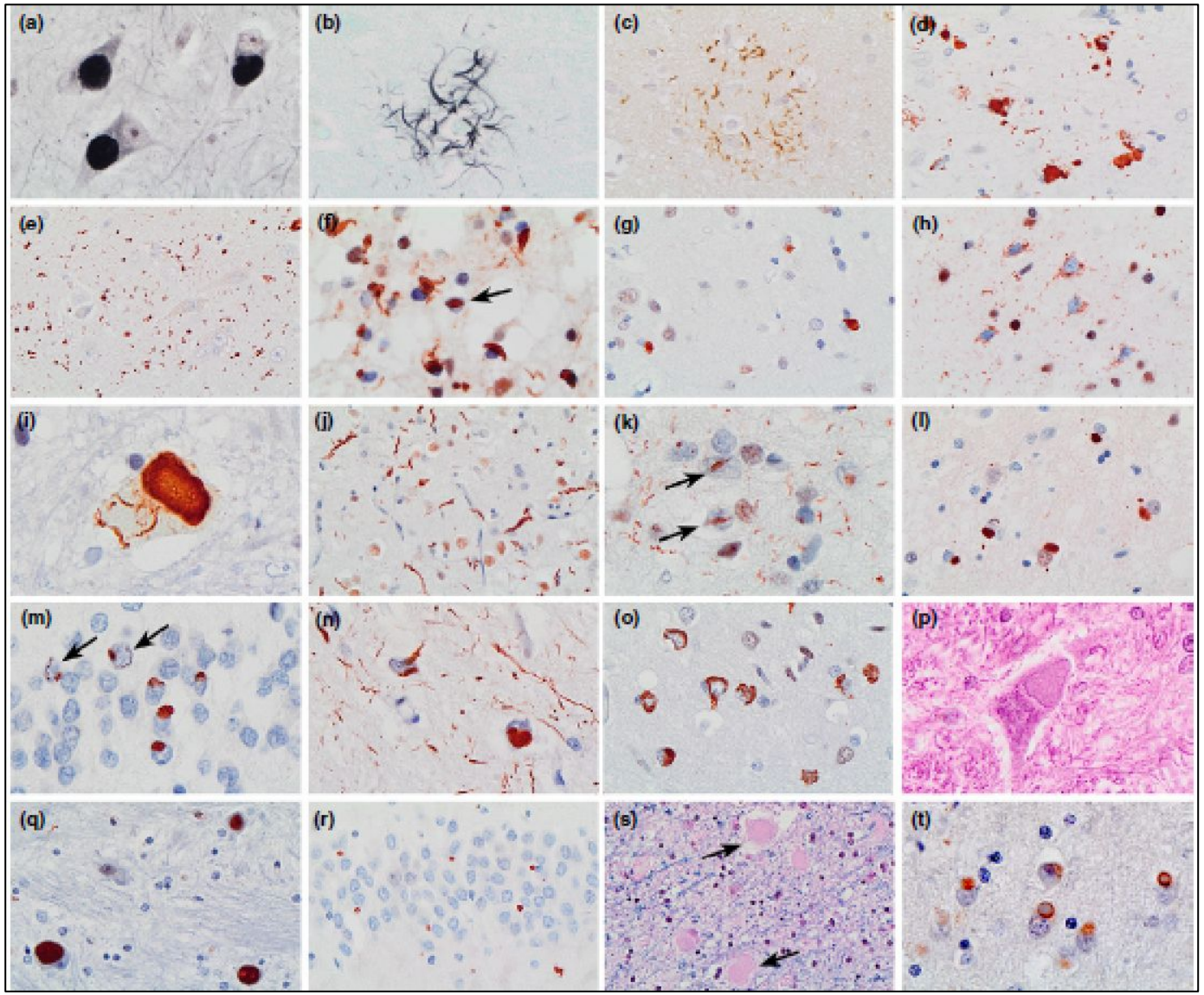
Prasad et al., Front Mol Neurosci 2019

TDP43 Pathology

TDP43 pathology is extremely heterogenous in its presentation

- Intranuclear
- Neuritic
- Cytoplasmic
- Axonal
- Neuronal
- Glial

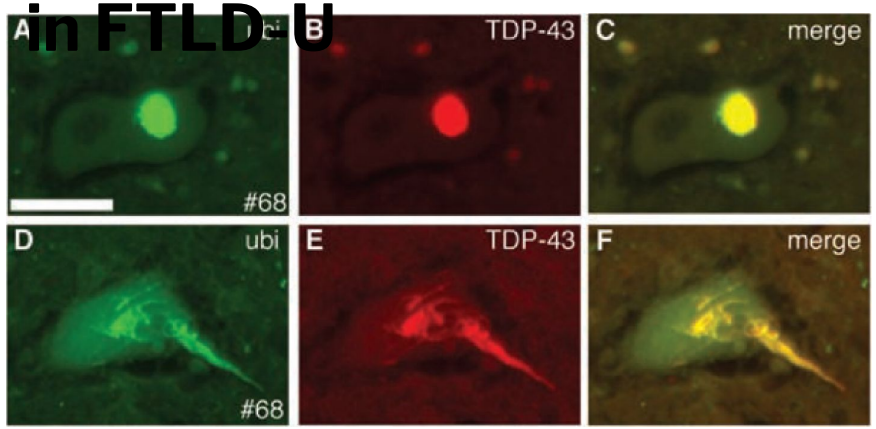
Irrespective of varied presentations (both clinically and pathologically, TDP43 is a major contributor to MCI and dementia states



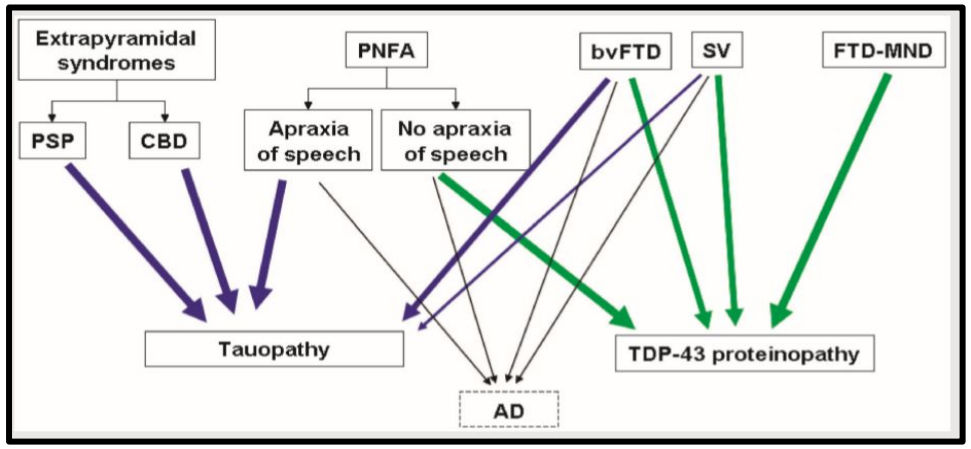
Mackenzie & Neumann, J Neurochem 2016

TDP43 in FTLD

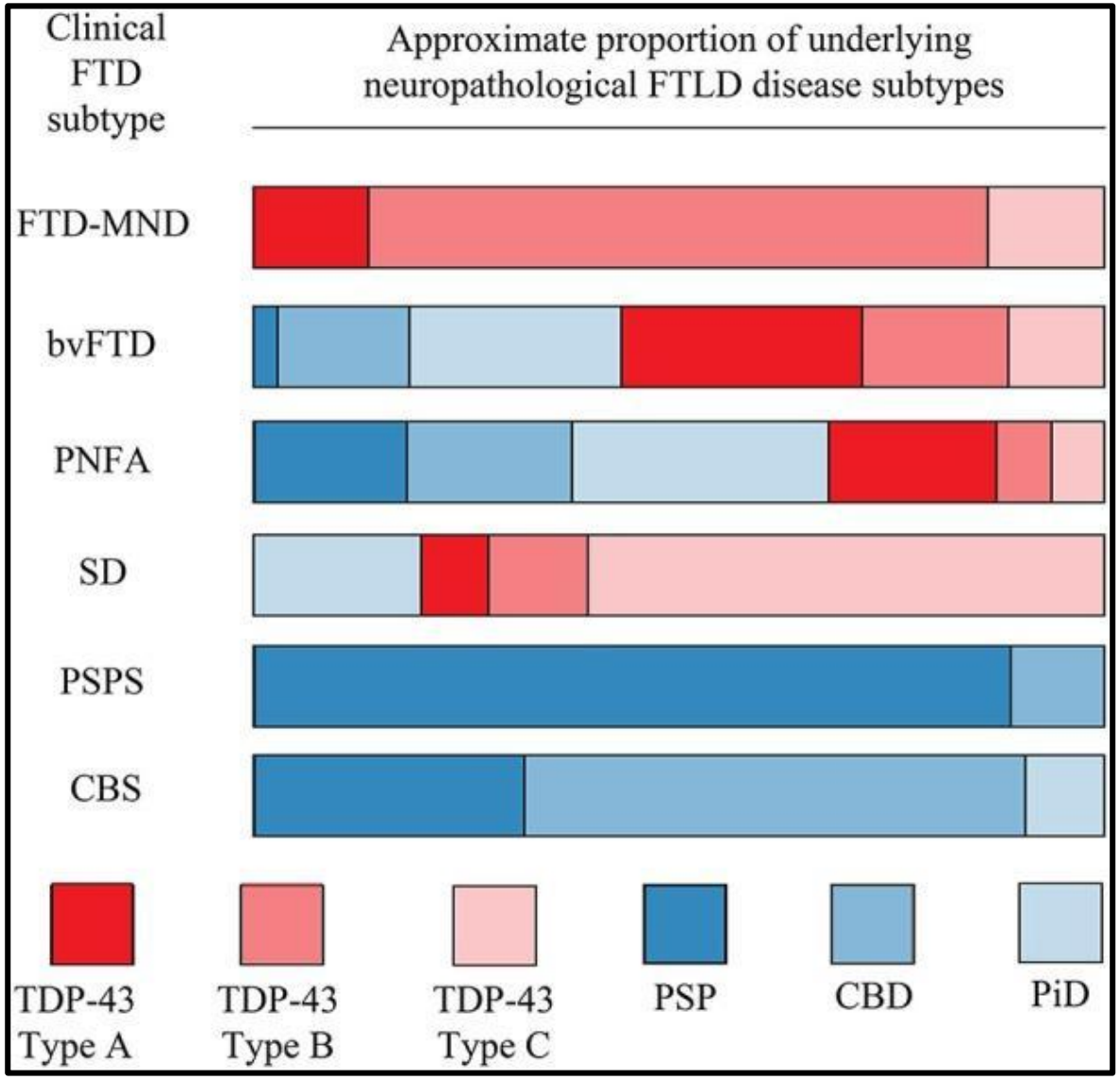
TDP43 identified as the major ubiquitinated protein in FTLD-U



Neumann et al., Science 2006

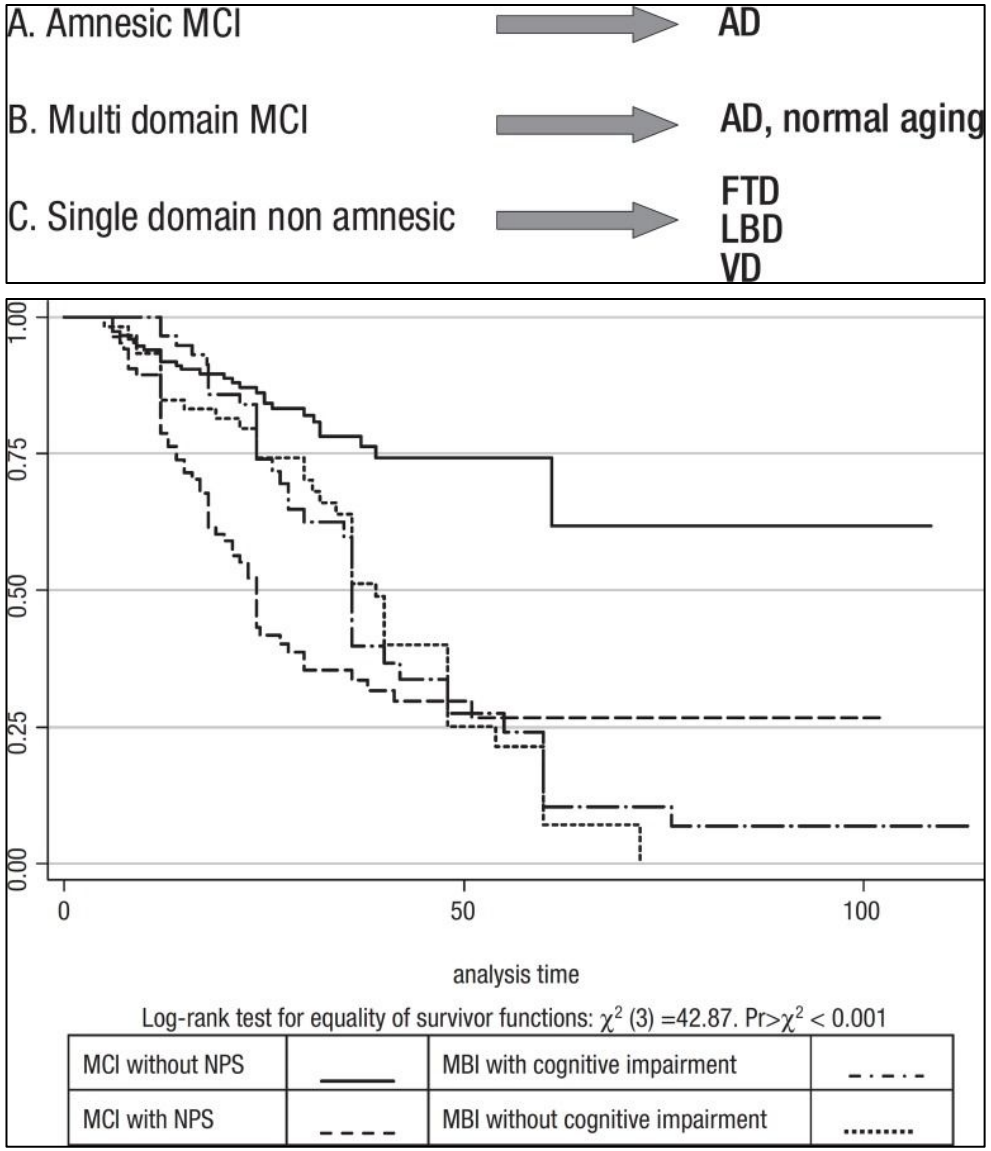


Gorsev et al., Continuum 2010

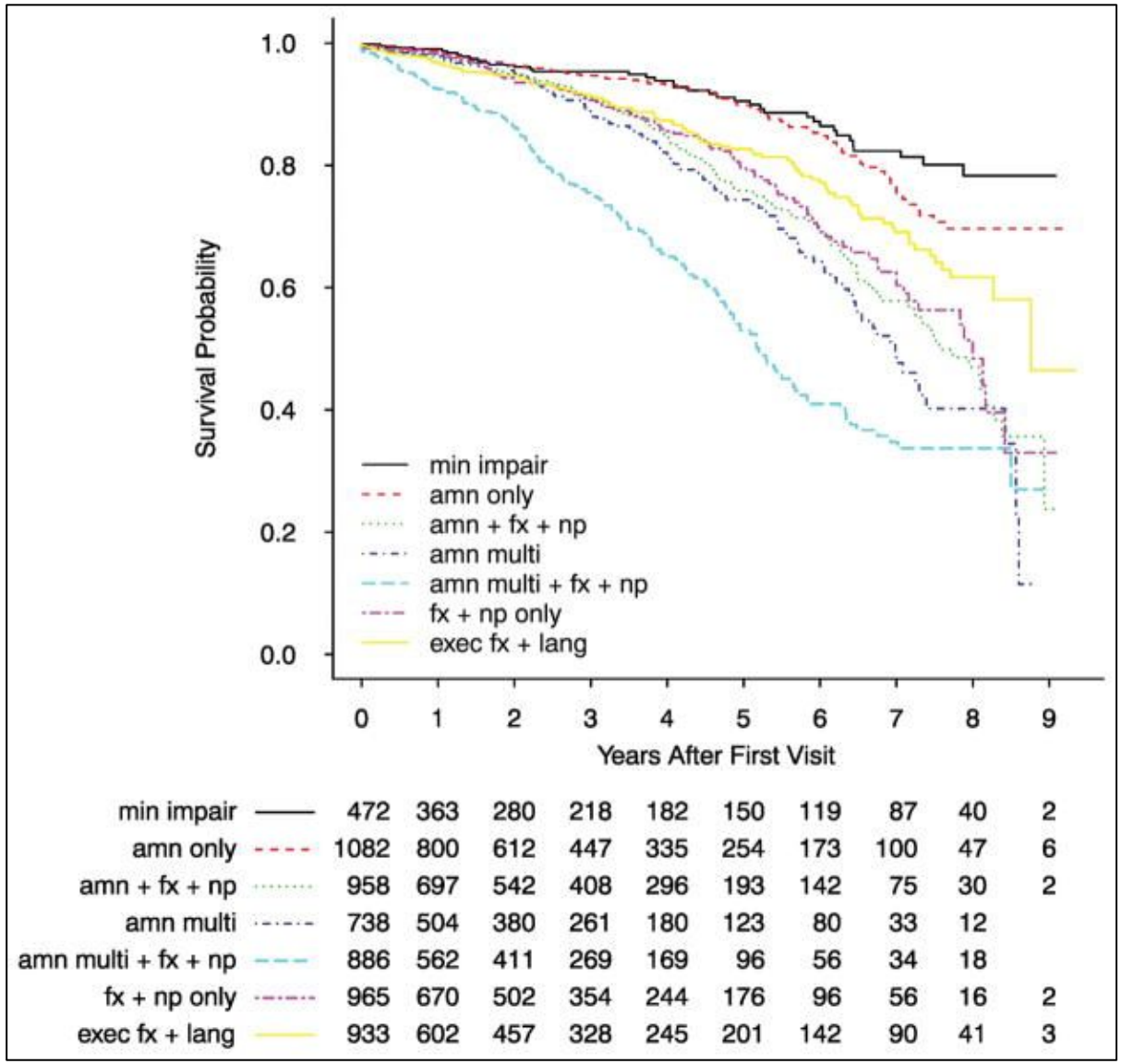


Alton & Lewis, Front Aging Neurosci 2014

MCI due to behavior/neuropsych symptoms?

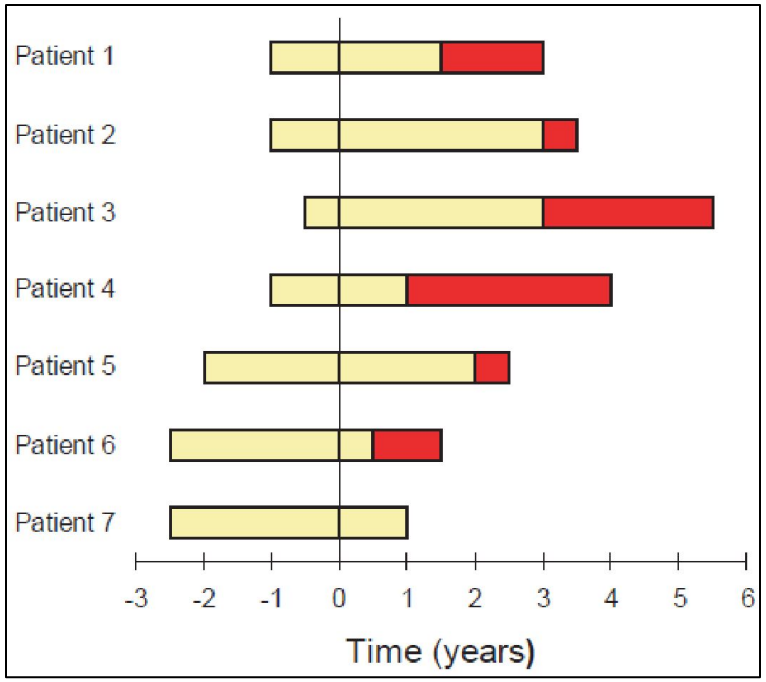


Taragano et al., Dement Neuropsychol 2008



Hanfelt et al., Neurobiol Dis 2019

MCI-FTLD?

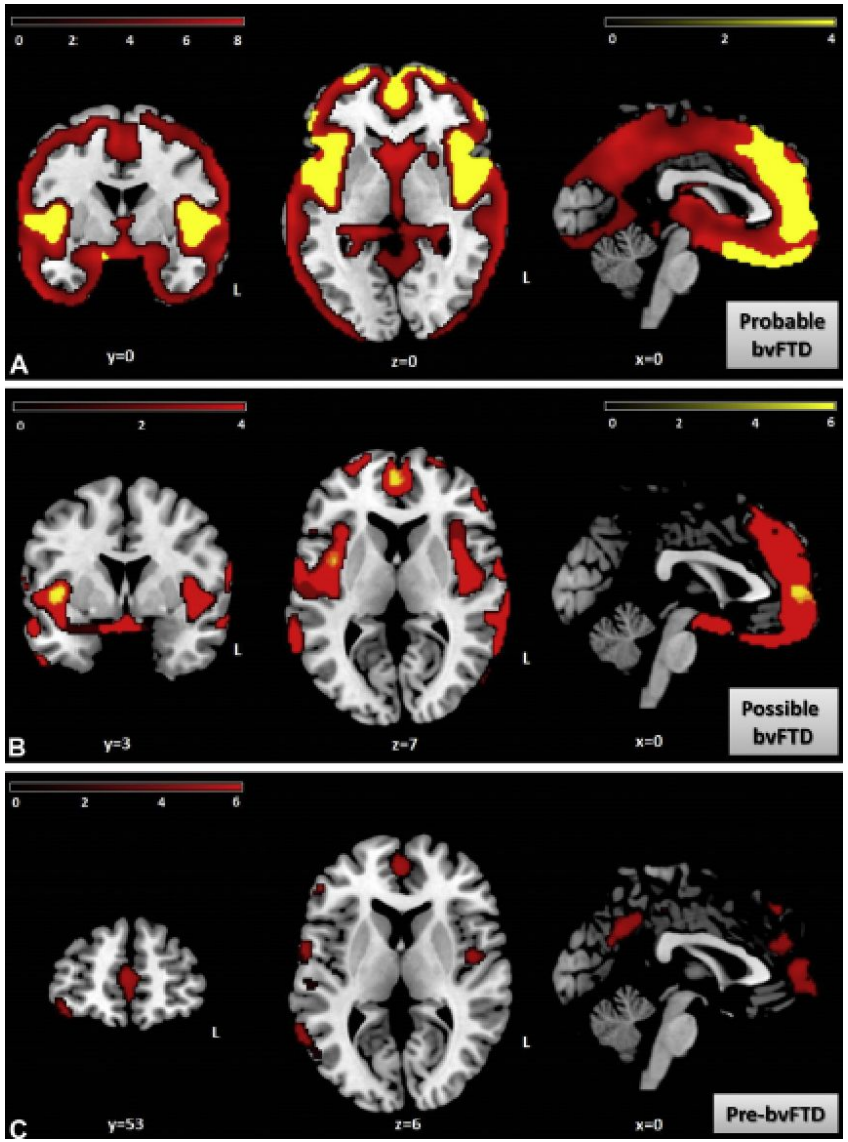


De Mendoca et al., JAD 2004

- **Short duration of MCI stage**
- **Cognition largely preserved**
- **Prominent frontal, behavioral, and neuropsychiatric signs**
- **FDG-PET abnormalities?**

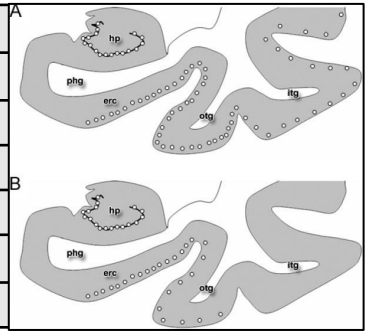
Variable	Pre-bvFTD (n = 23)
Behavioral abnormalities	
NPI total score	9.0 ± 7.4
FBI total score (AB)	6.4 ± 5.2
FBI A	4.6 ± 3.8
FBI B	2.0 ± 3.4
Screening for dementia	
MMSE	23.5 ± 6.3 (20)
Clock drawing	5.5 ± 3.1 (42)
Nonverbal reasoning	
Raven matrices	20.0 ± 7.7 (43)
Memory	
Short story	10.4 ± 6.4 (35)
Rey figure, recall	10.3 ± 8.3 (45)
Digit span, backward	5.1 ± 1.5 (14)
Visual-construction	
Rey figure, copy	**22.9 ± 9.6 (73)**
Language	
Phonological fluency	26.2 ± 10.6 (22)
Semantic fluency	25.5 ± 11.2 (26)[c]
Token test	29.3 ± 3.9 (19)[c]
Executive function	
Trail Making, A	153.5 ± 169.1 (44)
Trail Making, B	**307.1 ± 174.1 (70)**

Baroni et al., Neurobiol Aging 2015

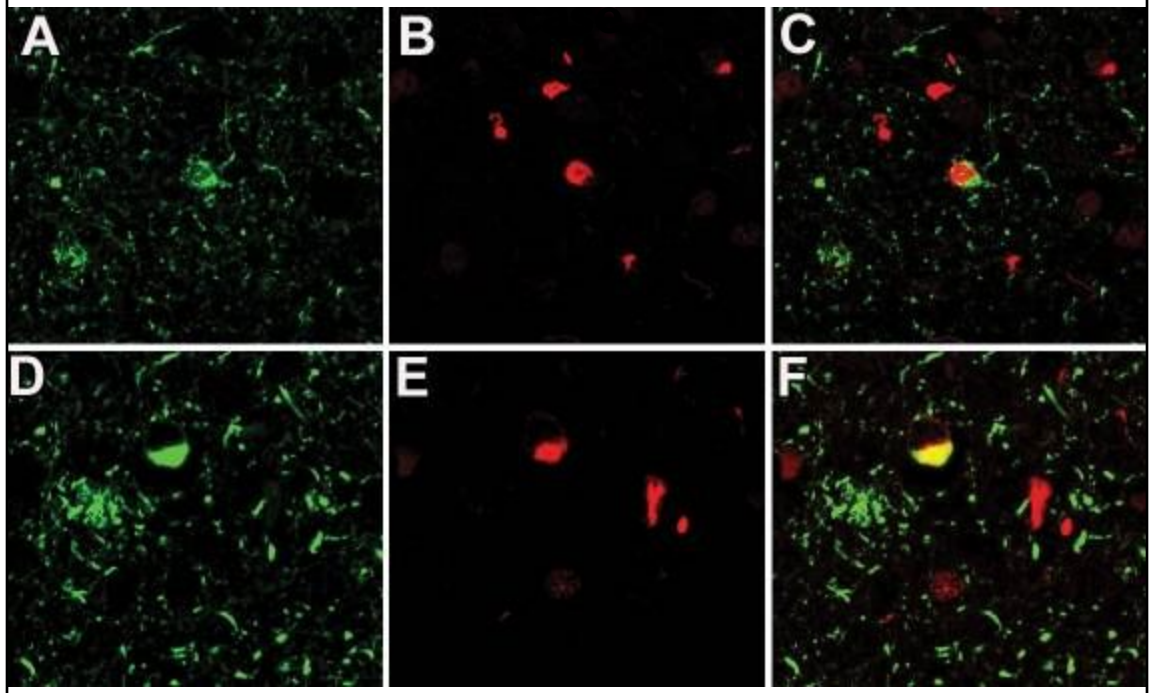


TDP43 implicated HS & AD

	Initial series				Confirmation Series
	HpScl/pure (n=11)	HpScl/other (n=10)	HpScl/AD (n=44)	AD (n=30)	AD (n=93)
Age at death, mean ± SD (y)	80 ± 17	78 ± 8	85 ± 6	85± 5	79 ± 9
Sex, M:F	7:4	6:4	22:22	9:21	46:47
Braak stage, median (25%-tile, 75%-tile)	2 (0.25, 2.9)	2 (1, 2.5)	5 (4.5, 6)	5.8 (5, 6)	5.5 (5, 6)
Brain weight, mean ± SD (g)	1170 ± 220	1120 ± 200	1020 ± 150	1000 ± 110	1040 ± 160
TDP-43 (%)	8 (73%)	5 (50%)	33 (75%)	9 (30%)	19 (20%)



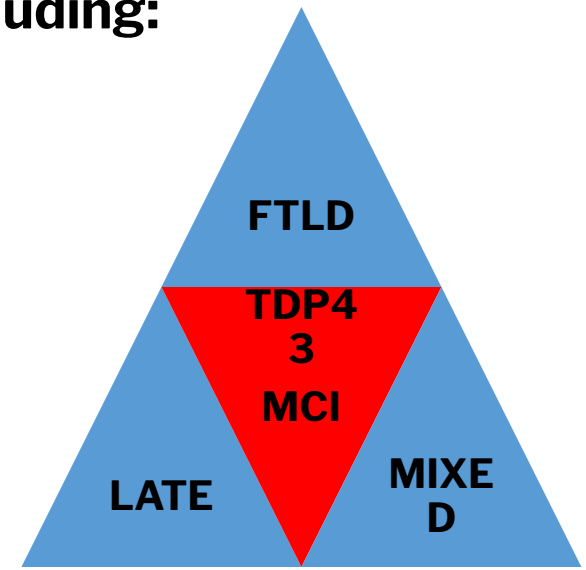
TDP43 & ptau IHC in an AD+HS representative



Amador-Ortiz et al., Ann Neurol 2007

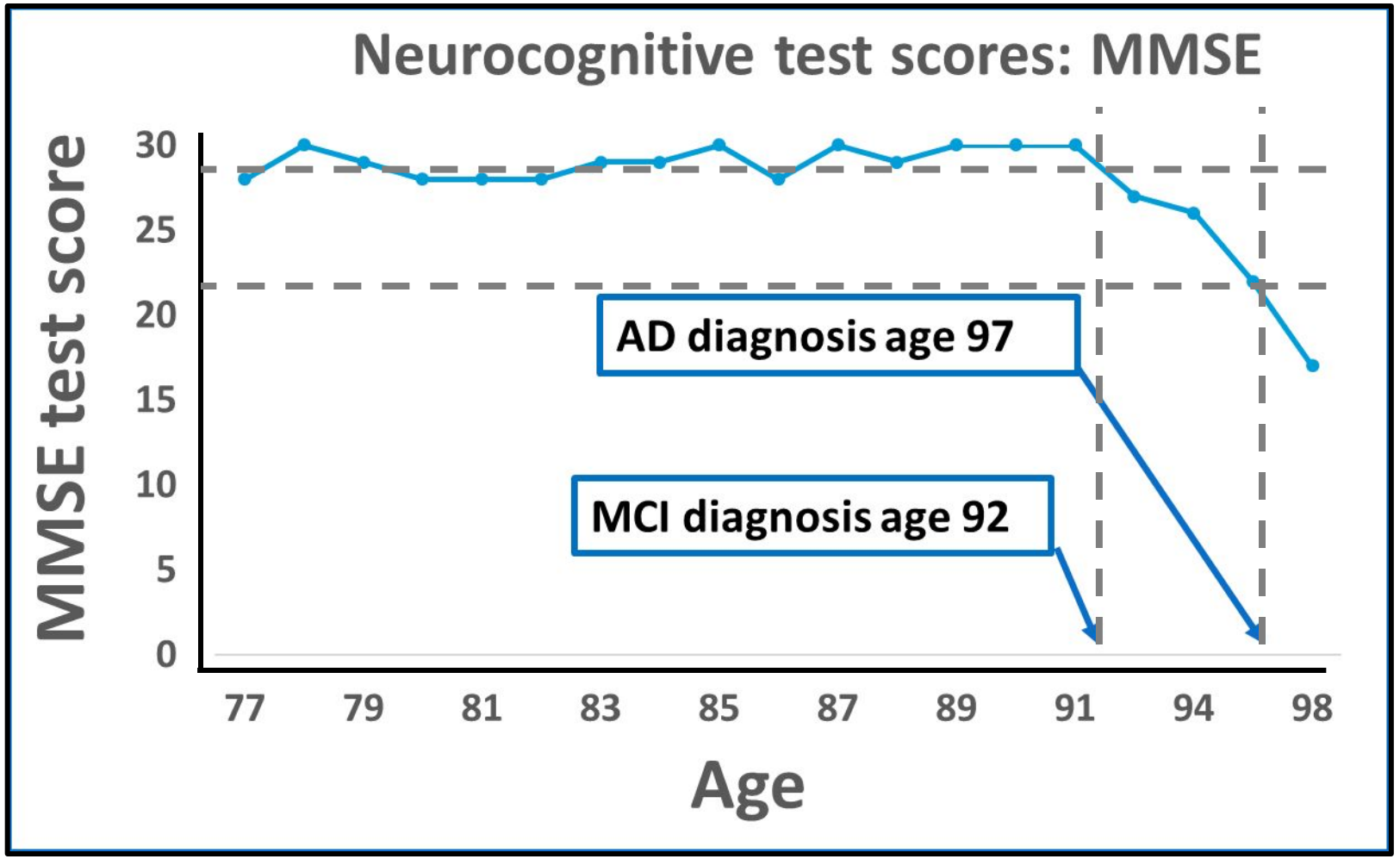
TDP43 appears to be a comorbid feature seen in conjunction with many other pathologies and clinical dementia syndromes including:

- FTD/FTLD
- AD
- LATE
- ALS
- PSP
- CBD
- LBD
- VaD
- CTE/TBI



Case #1: Clinical Hx

- Enrolled at age 77 in the longitudinal normal control program at UK
- PMHx: HTN (well controlled) only
- FHx: No dementia
- SocHx: lives independently, no Tob/EtOH
- Meds: lisinopril 20 mg qd
- PE/NE: essentially normal for age (mild length dependent peripheral neuropathy developed in later 80s
- Followed for 25 years, from normal, through MCI, dementia, and autopsy

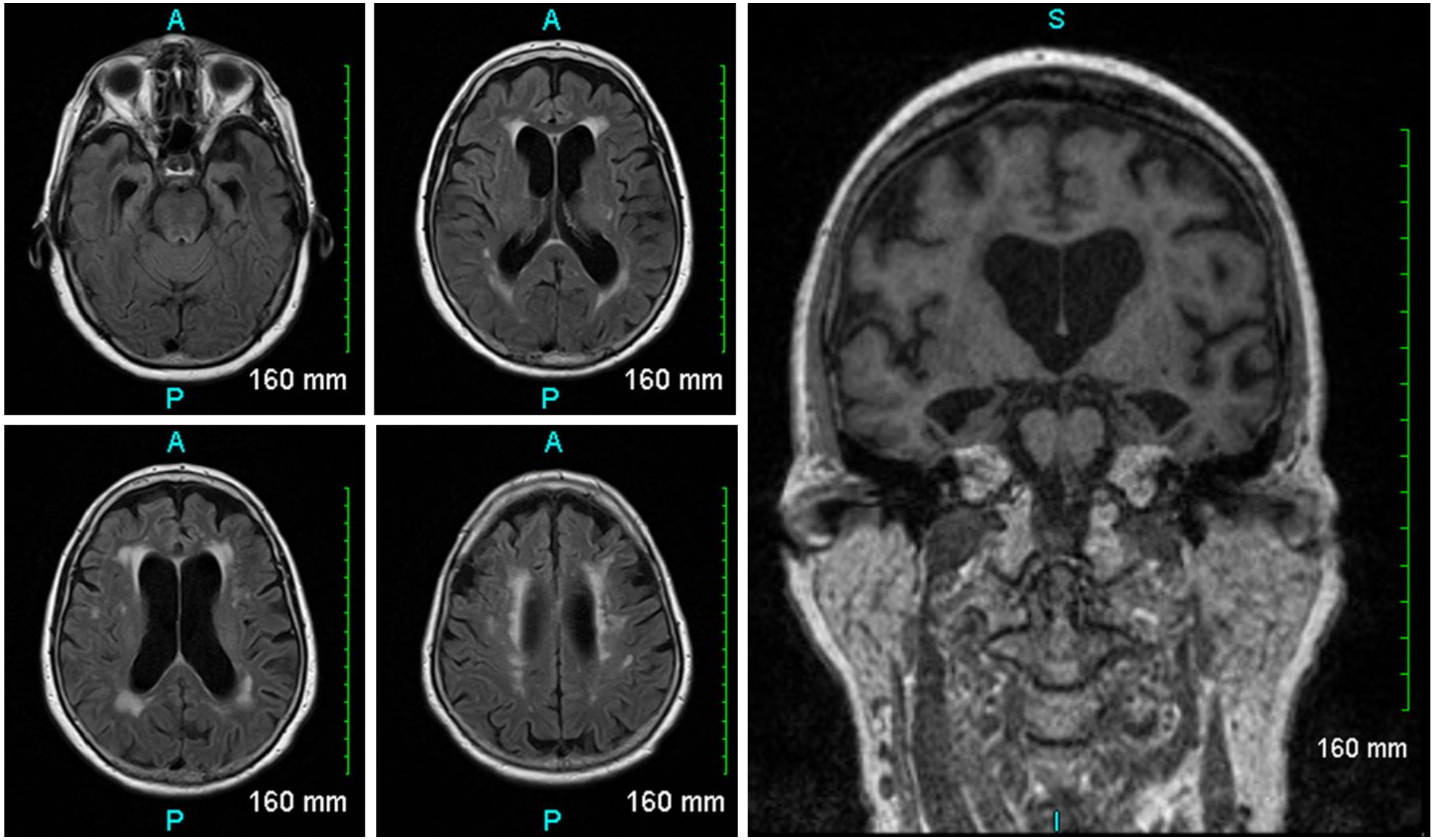


5 year period of progressive MCI

Case #1: MRI at MCI conversion

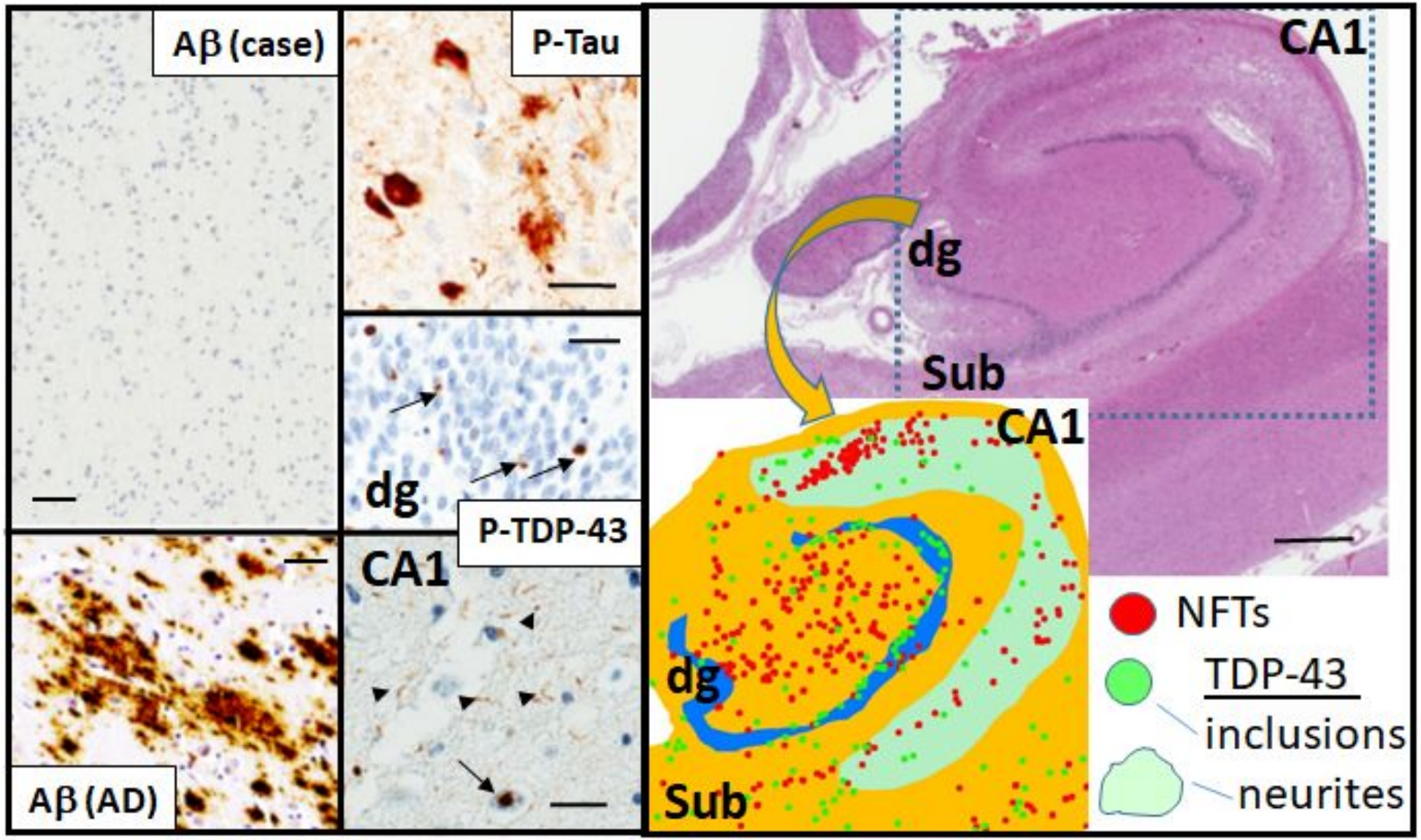
Transition from normal to MCI at age 92 years

Dx: MCI due to mixed AD & SVID

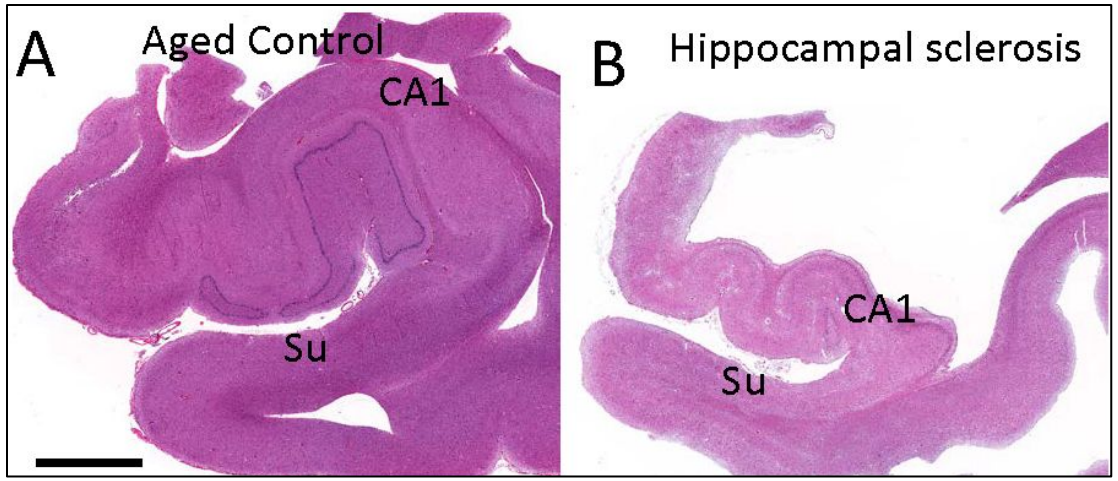


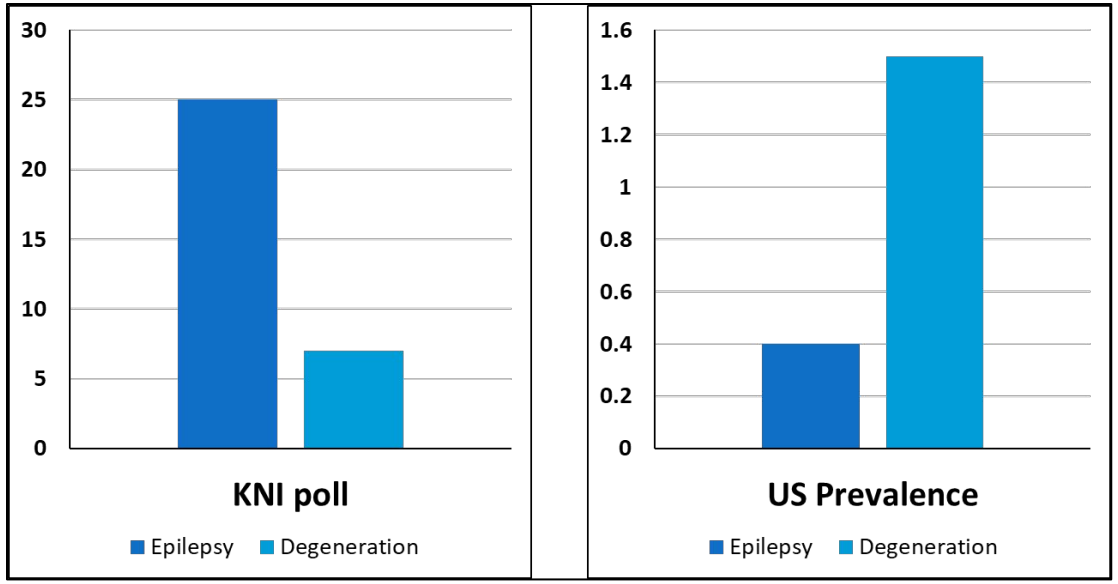
Case #1: Autopsy at age 102

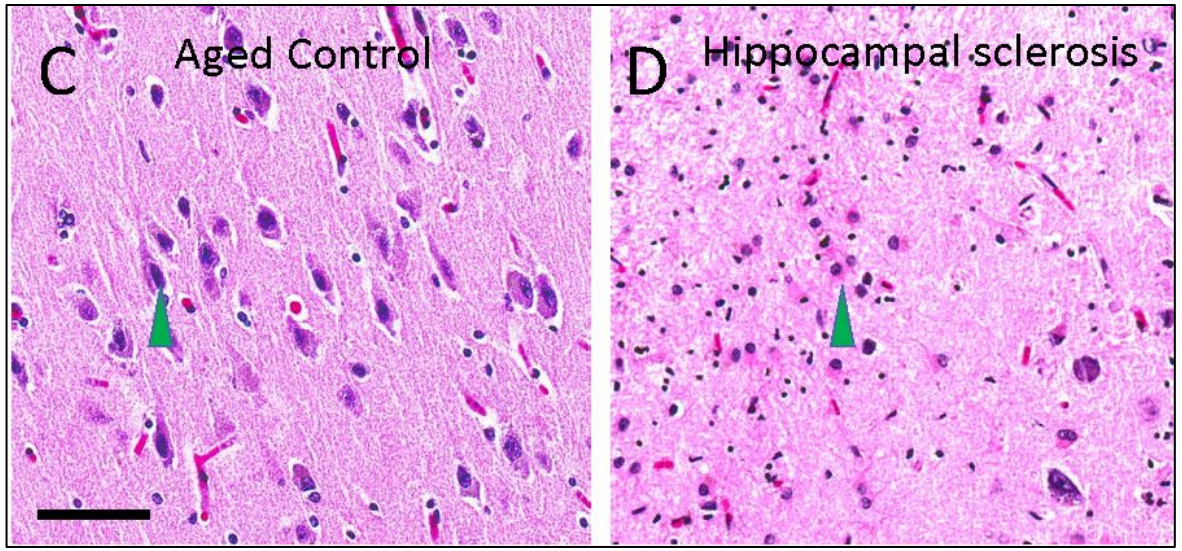
- No Aβ
- No Lewy bodies
- No infarcts
- PART+

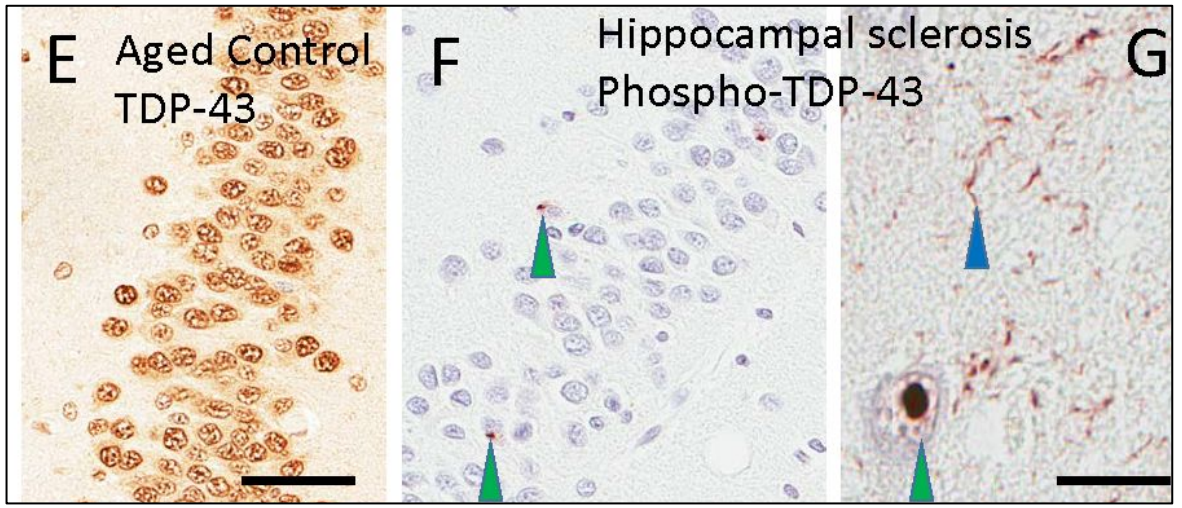


LATE/HS-Aging pathology







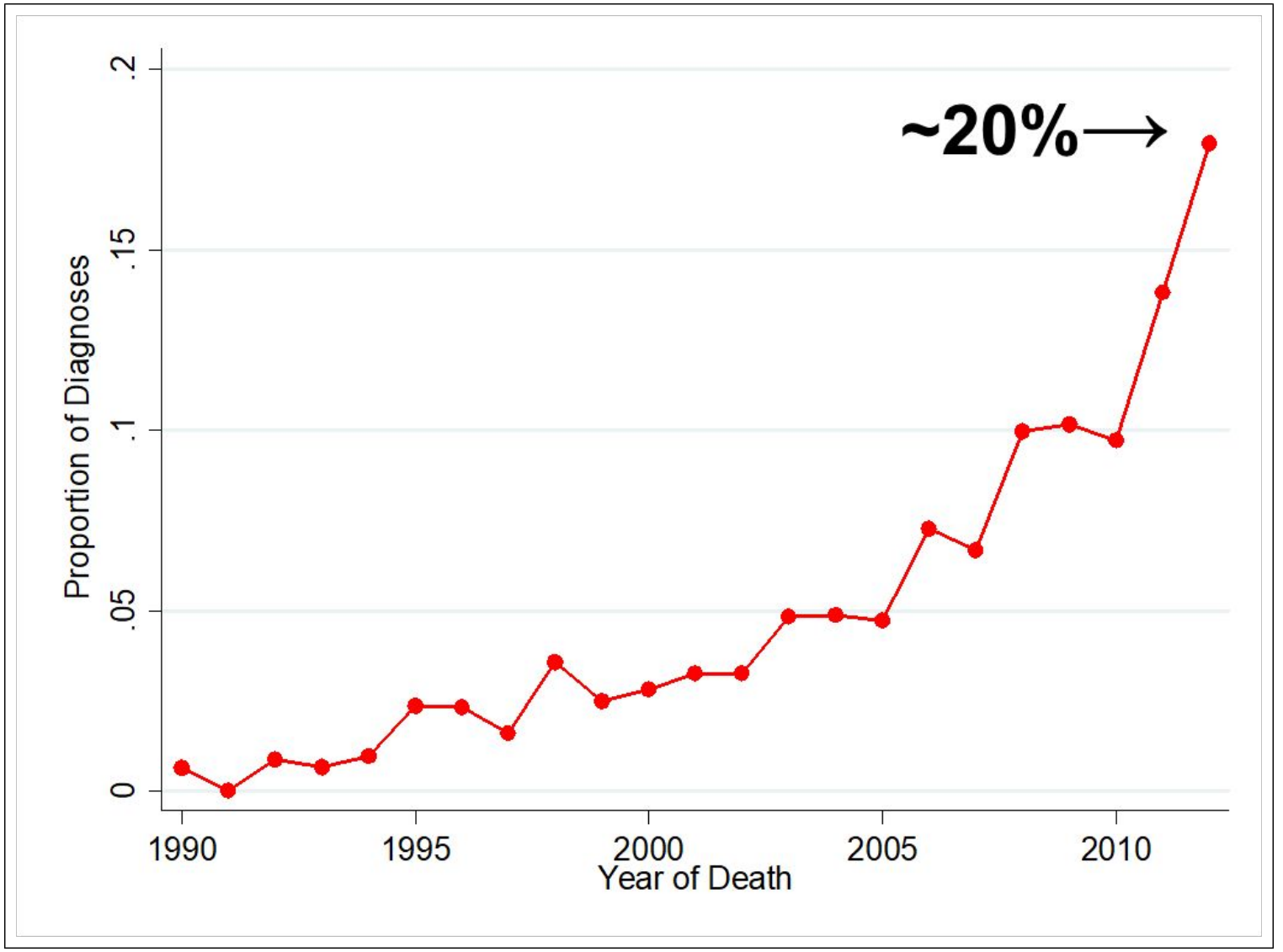


Jicha & Nelson, *Continuum, 2019*

HS epidemiology has changed?

Proportion of Hippocampal Sclerosis pathological diagnoses (primary and contributing) among autopsied participants in the NACC Neuropathology Data Set, by year of death, 1990-2012 (N=9,187).

- **Increasing awareness of HS in the 1990's**
- **Followed by the discovery of TDP43 and the increasing use of IHC staining at autopsy**

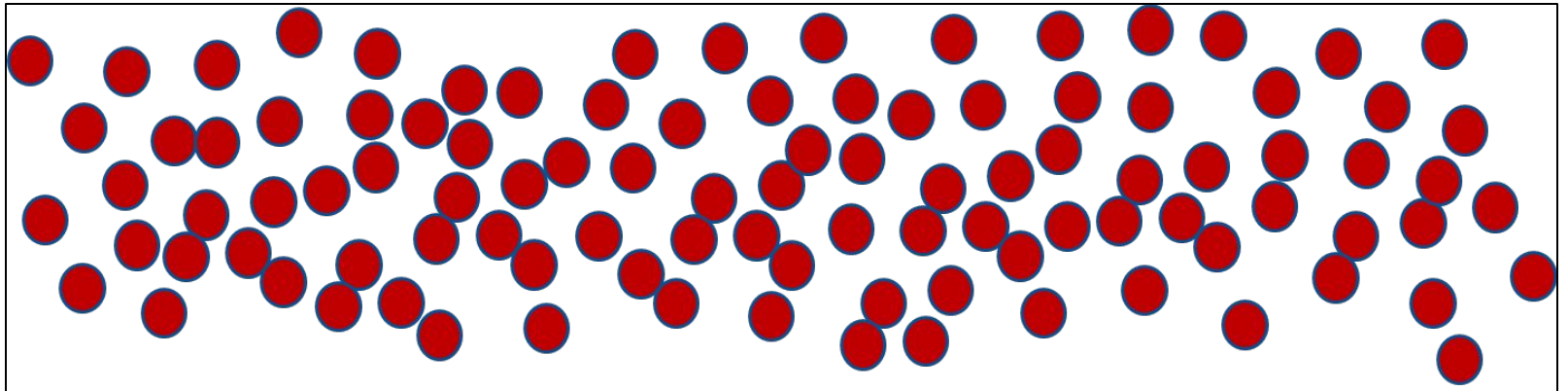


Brenowitz et al, *JAD, 2014*

FTLD-TDP43 vs. LATE

Have you ever diagnosed FTD?

FTD/FTLD

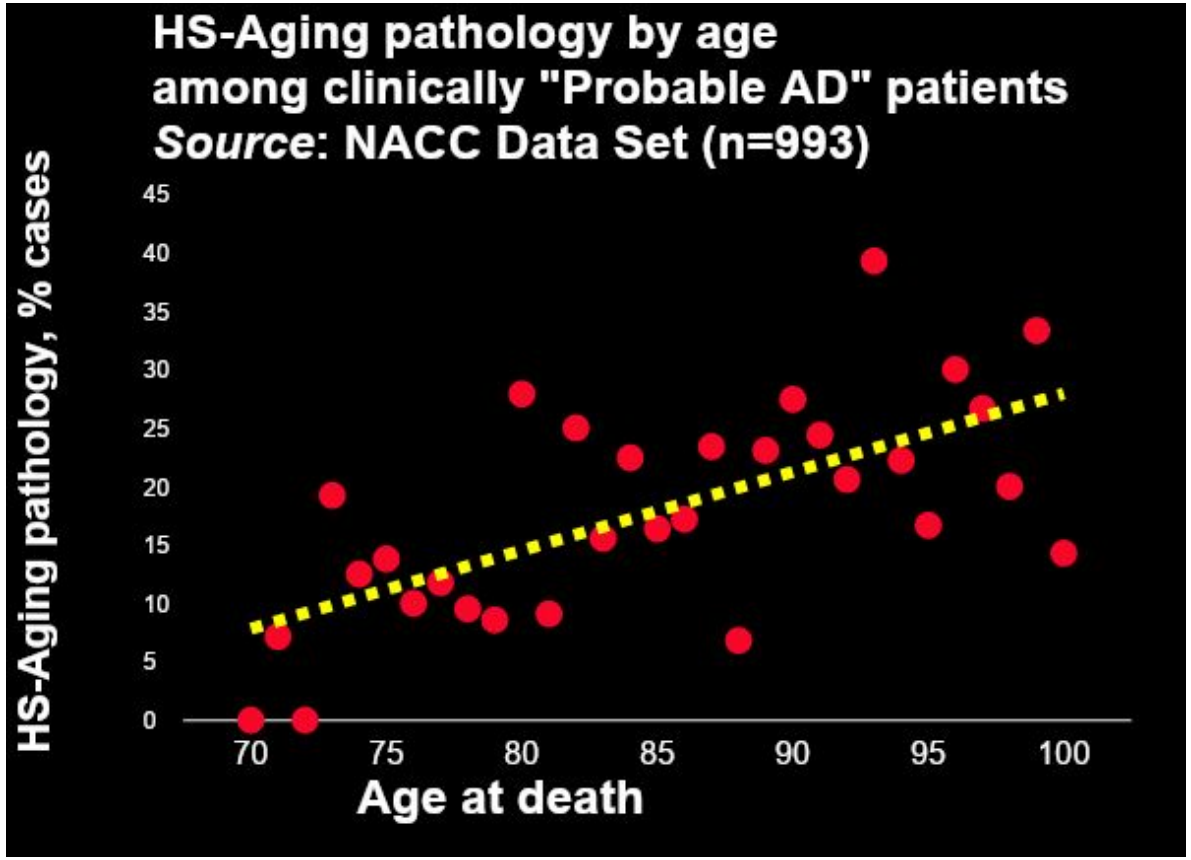


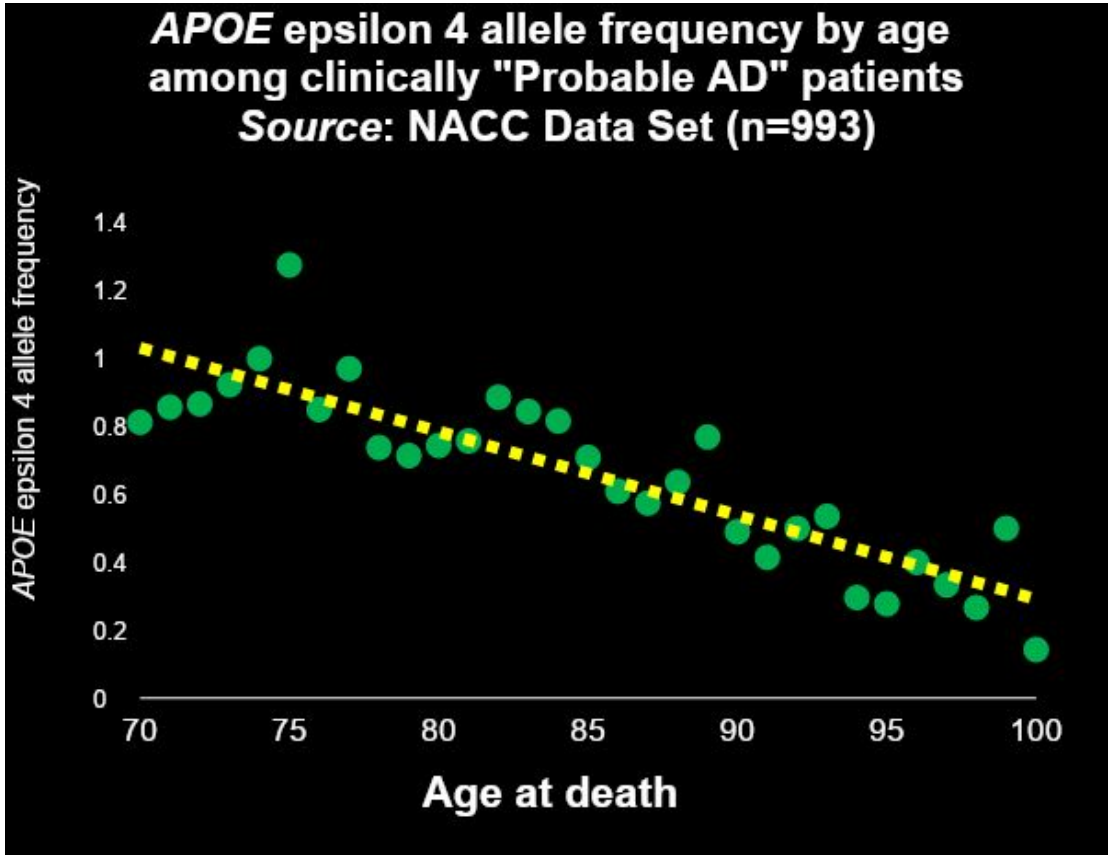
How many cases of LATE/HS-aging have you missed?

Hippocampal sclerosis of aging
(~100x higher risk than FTD/FTLD)

LATE: Age & ApoE associations

In advanced old age, persons with clinical "Probable AD" tend to lack the most common genetic feature of AD…





…and at autopsy tend to show HS-Aging pathology

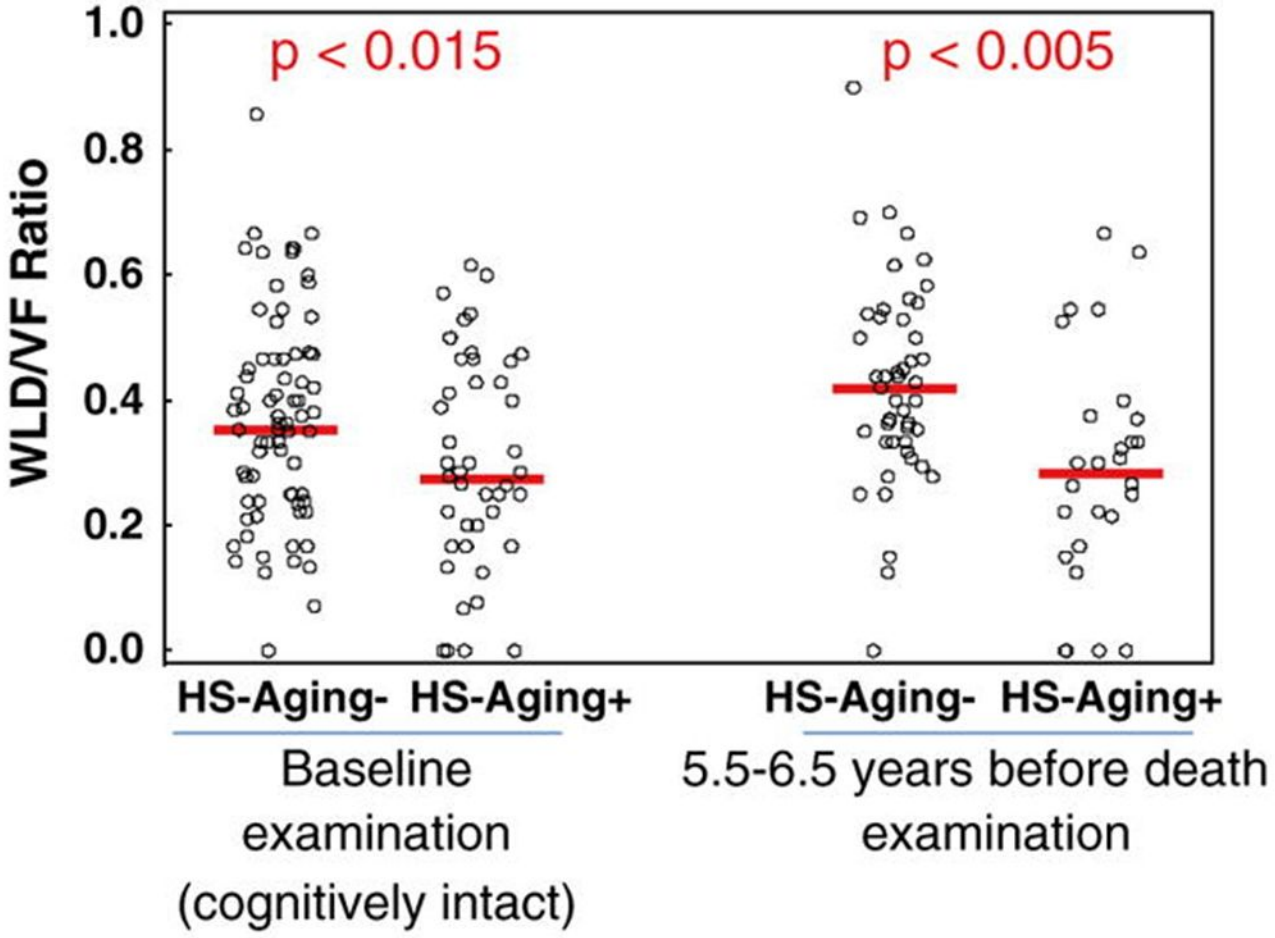
Nelson et al, JNEN, 2016

LATE: Neuropsych profile?

Neurocognitive test scores in HS-Aging:

Word list delayed recall (WLD)/Verbal fluency (VF) ratio

N= 43 cases with subsequent autopsy confirmed HS-Aging pathology, and N=75 controls



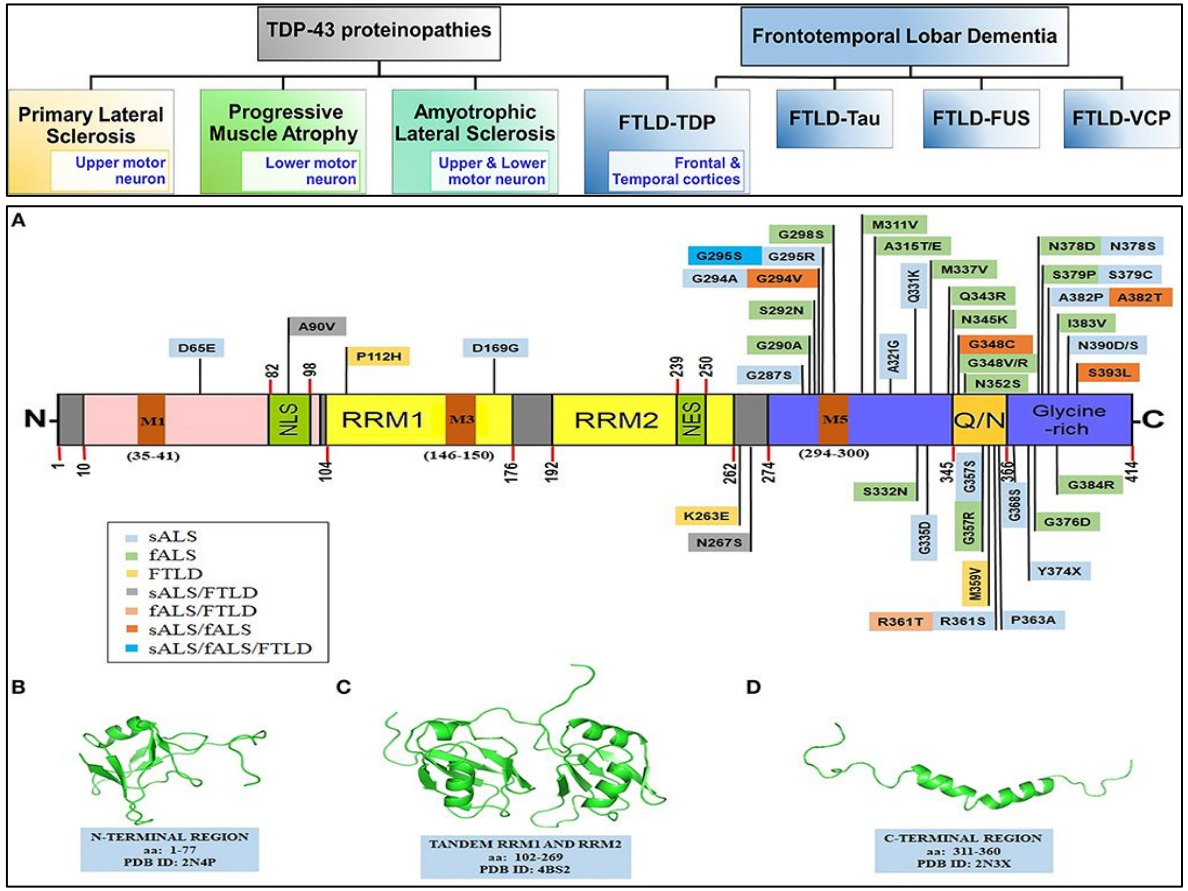
WLD/VF ratio is evident at baseline while cognitively intact and holds through the MCI stage!

Nelson et al., Acta Neuropathol. 2013

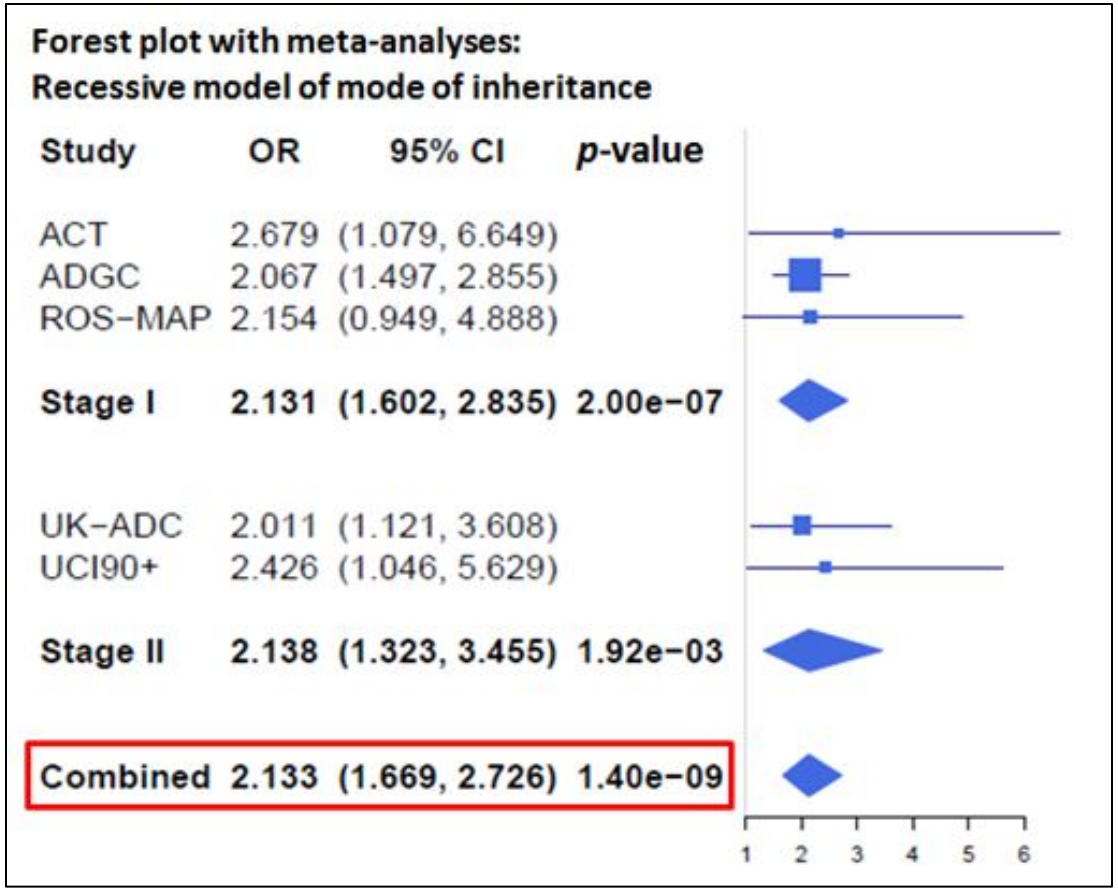
LATE: Unique genetic associations

Linked previously to FTLD-TDP
- *GRN*
- *TMEM106B*

Modulate K+ Channels, ID'd by GWAS
- *ABCC9*
- *KCNMB2*

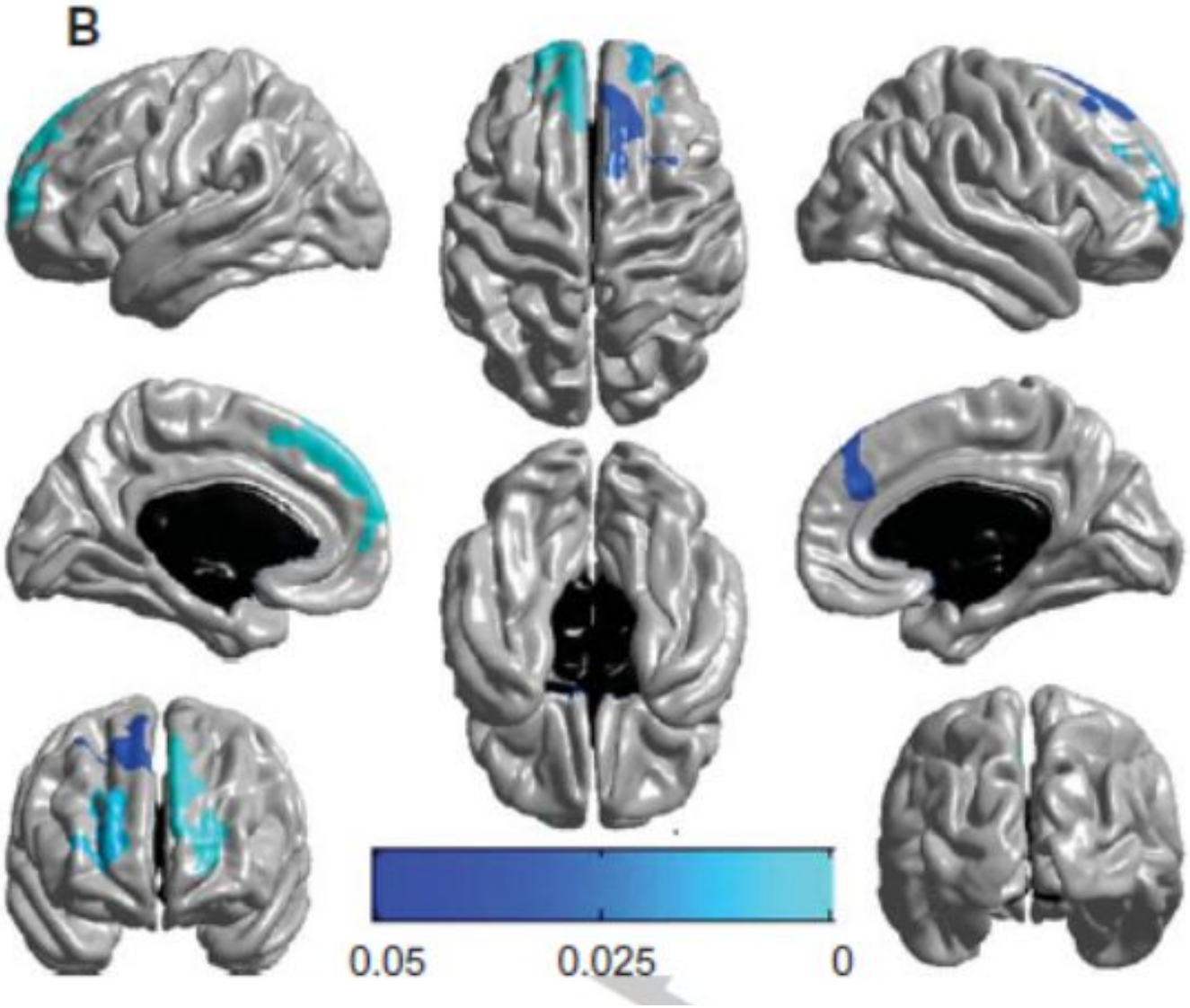


Prasad et al., Front. Mol. Neurosci., 14 February 2019



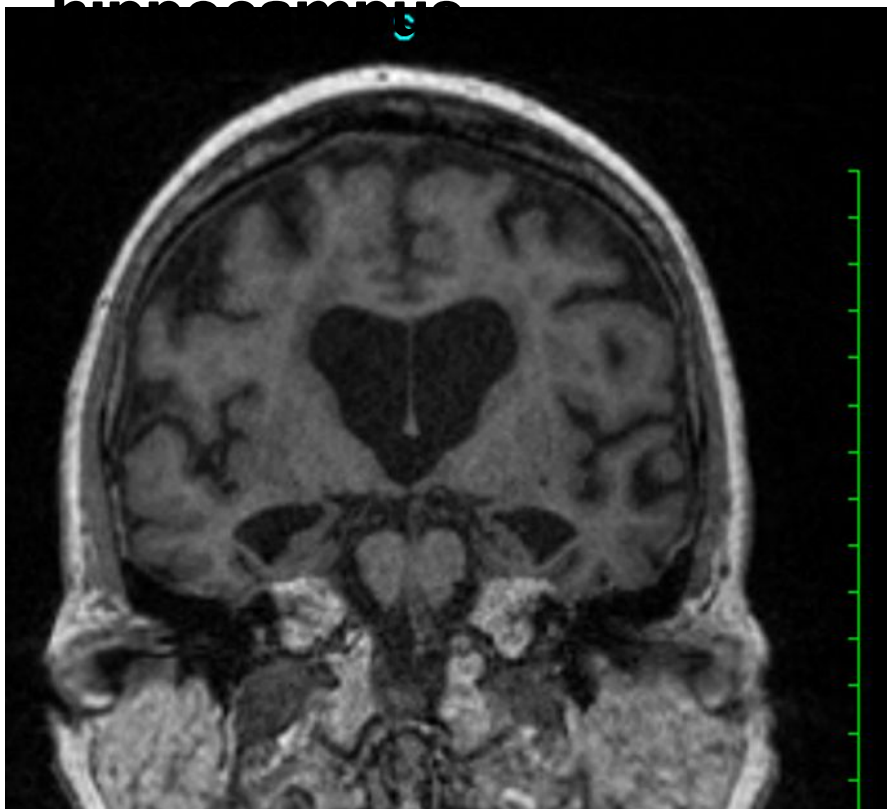
Nelson et al., Acta Neuropathol. 2014

LATE: Imaging profile?

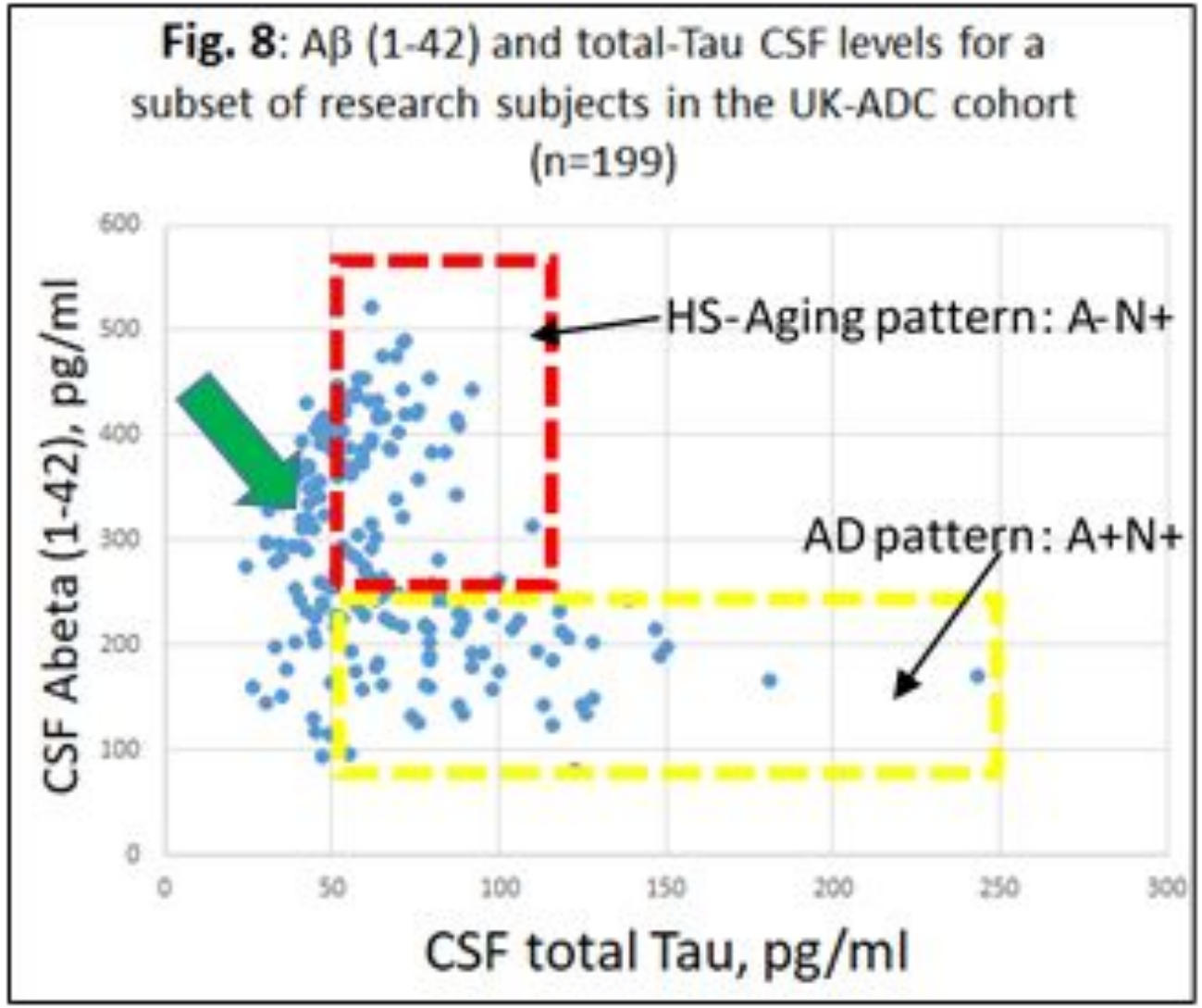


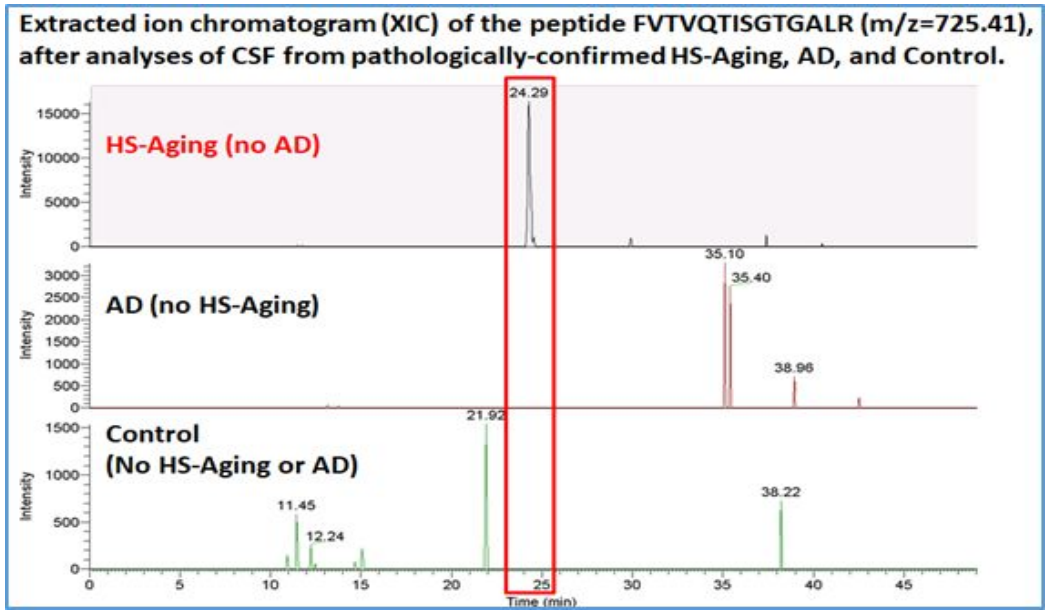
Nho et al., JAD 2016

- **HS-aging more severe atrophy**
- **Also extensive outside the hippocampus**



LATE: CSF profile?





- **Data for MCI & CI subjects only**
- **Traditional AD biomarkers may be used to rule out other pathologies**
- **New biomarkers may be discovered?**

Unpublished data

LATE: ATN framework?

Table 2. Features of HS-Aging that distinguish it from other common dementias

Underlying pathology →	Aβ plaques	Tau tangles	Neurodegeneration	MRI-detected infarcts and/or high Hachinski score
CSF findings →	Low CSF Aβ	High CSF phospho-tau	High CSF total tau	
Prevalent diseases ↓				
Alzheimer's disease	Y	Y	Y	N
PART/tauopathy	N	Y	+/-	N
Dementia with Lewy bodies	+/-	N	Y	N
Cerebrovascular disease	N	N	Y	Y
HS-Aging	N	N	Y	N

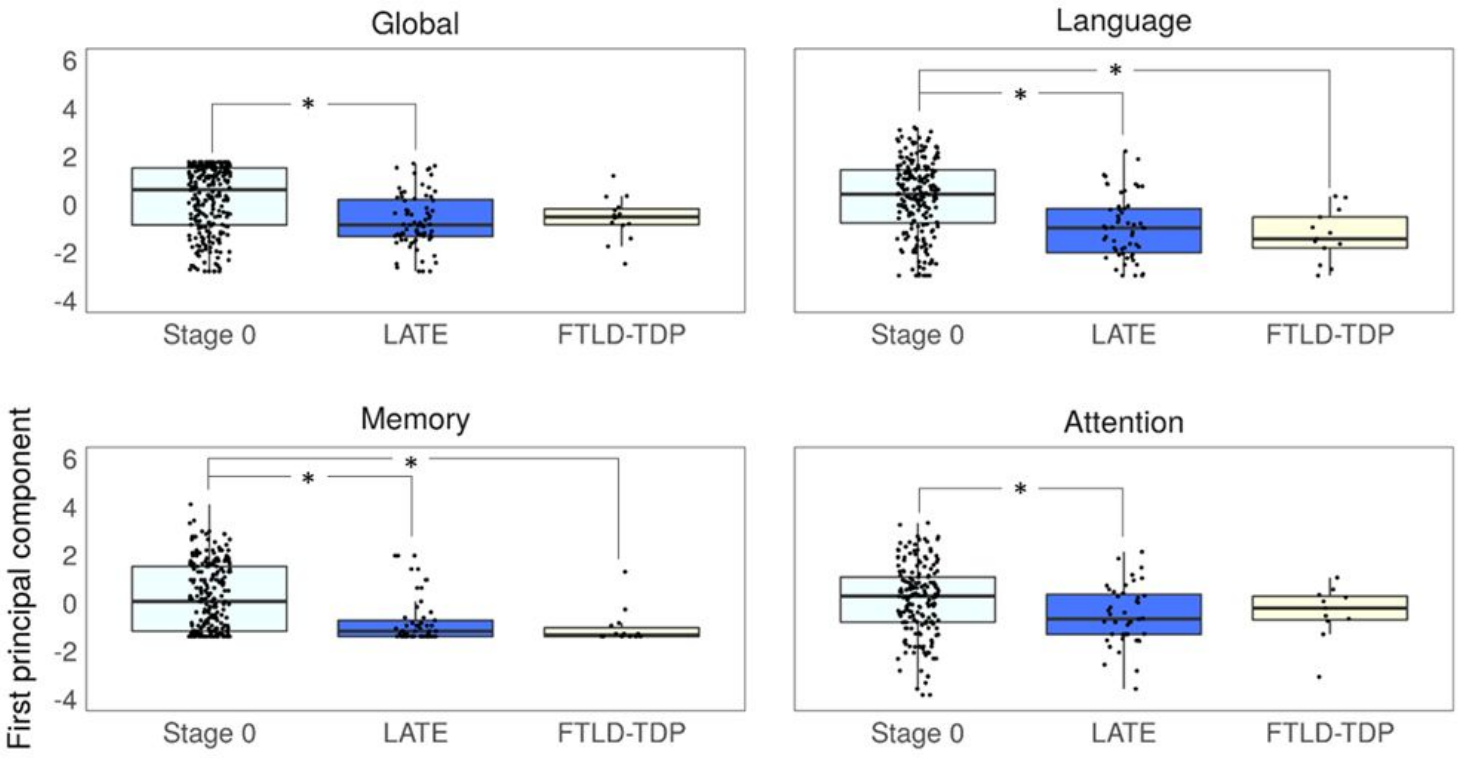
Unpublished data

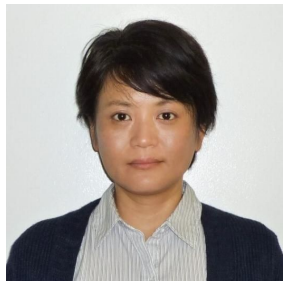
TDP43 demographic & clinical features

Variable		Non FTLD-TDP subjects			FTLD-TDP cases (n = 55)	P-value [a]
		Overall (n = 801)	Stage 0 None (n = 590)	LATE Stage 1 to 3 (n = 211)		
Age at death, mean ± SD		82.7 ± 8.7	82.2 ± 8.8	84.0 ± 8.5	76.6 ± 8.9	2.0×10^{-7}
Gender, n (%)						
	Men	440 (54.9)	326 (55.3)	114 (54.0)	32 (58.2)	0.85
	Women	361 (45.1)	264 (44.7)	97 (46.0)	23 (41.8)	
Years of education, mean ± SD		15.7 ± 3.1	15.6 ± 3.1	16.0 ± 3.0	16.2 ± 2.7	0.24
Difference in years between the last clinical visit and death, mean ± SD		1.1 ± 0.9	1.1 ± 0.9	1.1 ± 1.0	1.2 ± 1.1	0.62
APOE genotype, n (%)						
	-/-	354 (49.6)	276 (52.6)	78 (41.3)	31 (67.4)	0.0082 [b]
	-/ε4	289 (40.5)	203 (38.7)	86 (45.5)	13 (28.3)	
	ε4/ ε4	71 (9.9)	46 (8.8)	25 (13.2)	2 (4.3)	
Cognitive status at the last clinical visit, n (%)						
	Normal cognition	97 (12.1)	92 (15.6)	5 (2.4)	0 (0)	$< 1 \times 10^{-6}$ [b]
	Impaired-not-MCI	17 (2.1)	14 (2.4)	3 (1.4)	0 (0)	
	MCI	75 (9.4)	67 (11.4)	8 (3.8)	2 (3.6)	
	Dementia	612 (76.4)	417 (70.7)	195 (92.4)	53 (96.4)	

Unpublished data

TDP43 Cognitive performance?



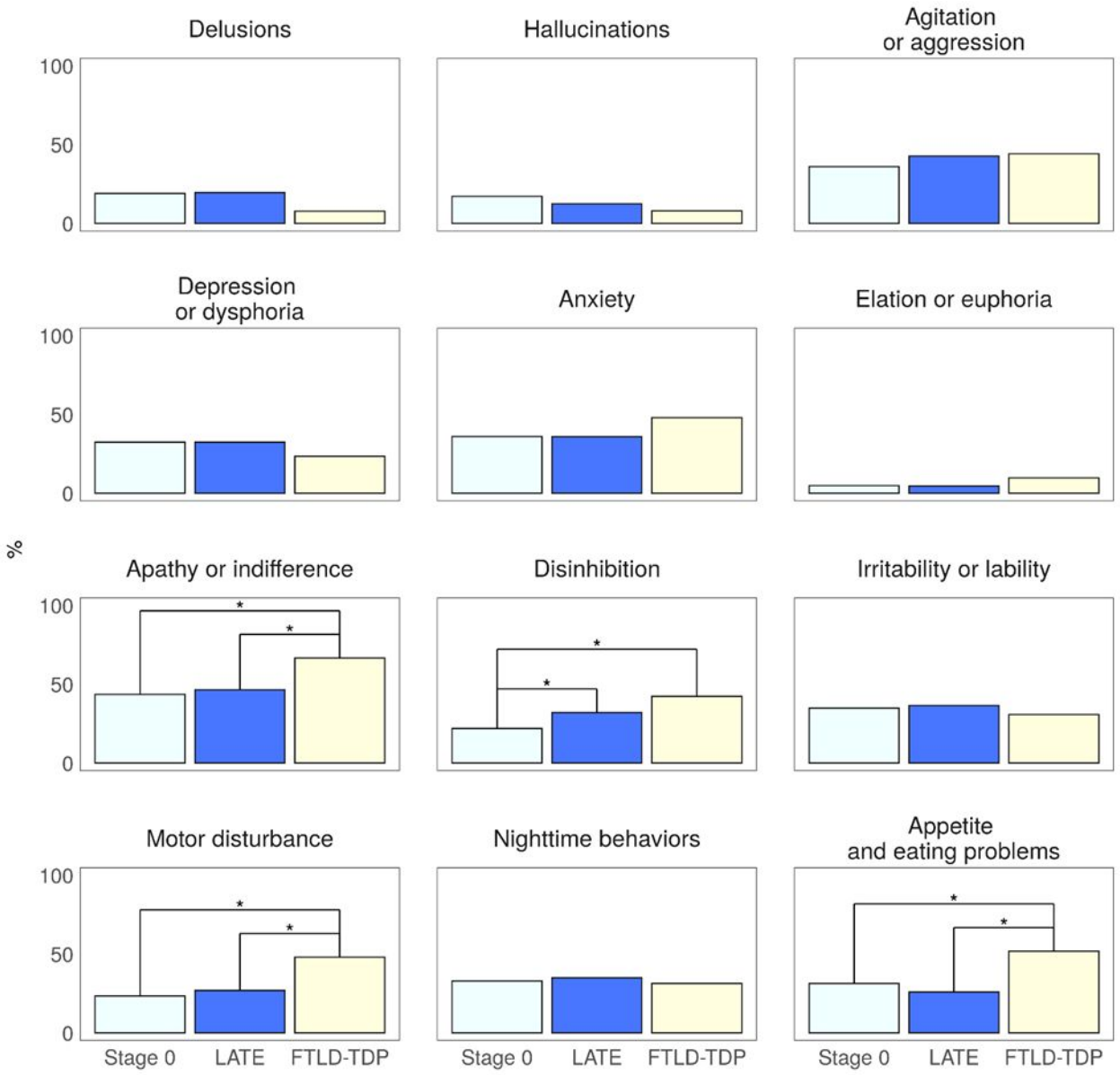


Yuriko Katsumata, PhD

- **NACC subjects included FTLD+/TDP+ (n=55), FTLD-/TDP+(n=211), and FTLD-/TDP- (n=590)**
- **NPI data was from the last visit proximate to death (< 3 years)**
- **LATE drives down cognitive performance compared to TDP- subjects in all domains except executive function**
- **FTLD+/TDP+ performed lower on language and memory tasks than TDP- subjects**
- **There were no observable differences on cognitive test scores between FTLD & LATE subjects**

Unpublished data

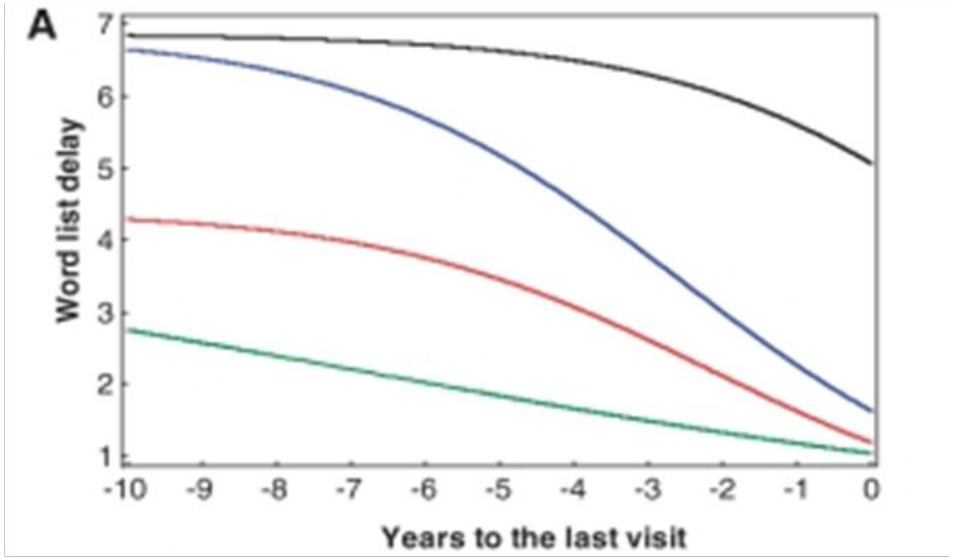
TDP43 BPSD?

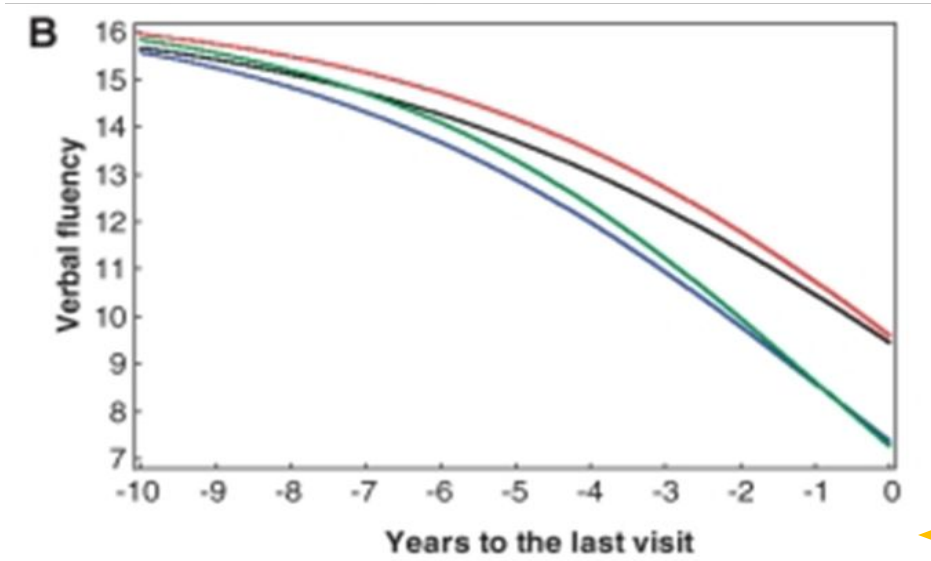


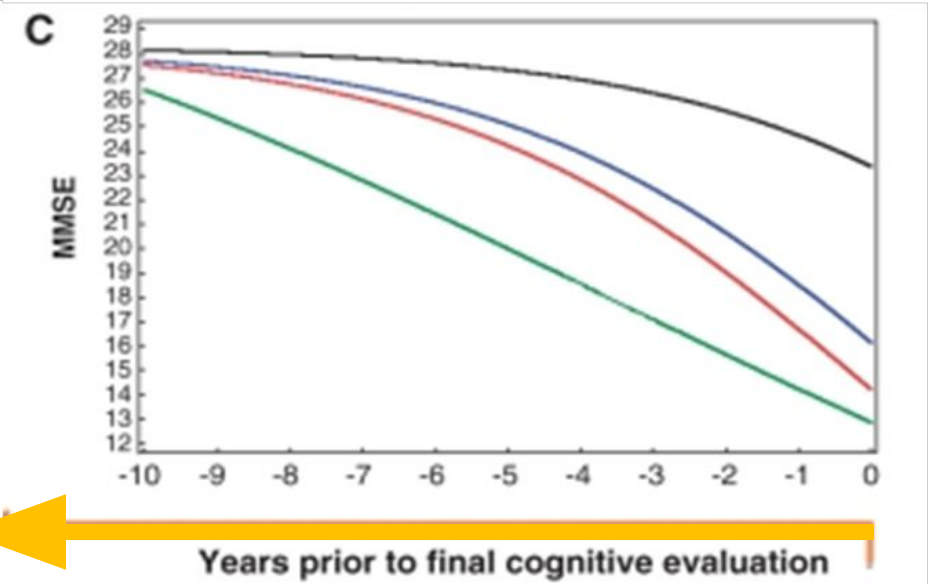
- **NACC subjects included FTLD+/TDP+ (n=55), FTLD-/TDP+(n=211), and FTLD-/TDP- (n=590)**
- **NPI data was from the last visit proximate to death (< 3 years)**
- **Overall, the LATE cases appeared more similar to the TDP- cases than to the FTLD+/TDP+ cases**
- **FTLD+/TDP+ cases demonstrated higher scores on apathy, disinhibition, aberrant motor activity, and eating problems than the other groups**
- **LATE cases demonstrated only increased disinhibition over TDP- cases in the unadjusted analysis**
- **The model (adjusted for age at death, gender, years of education, APOE**

Unpublished data

TDP43 & longitudinal decline?



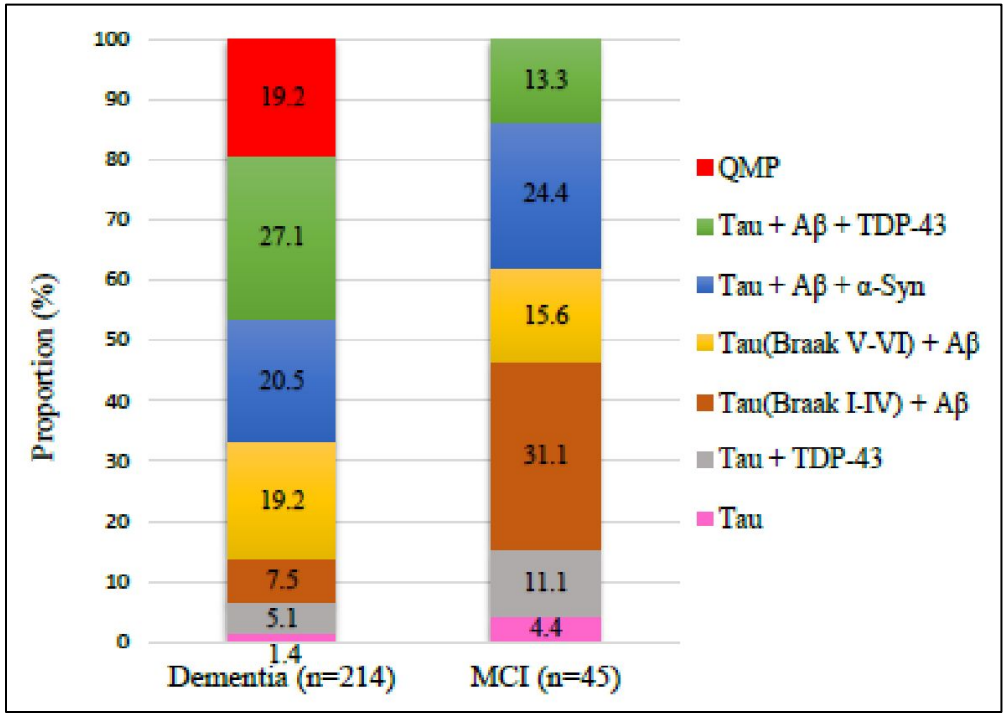




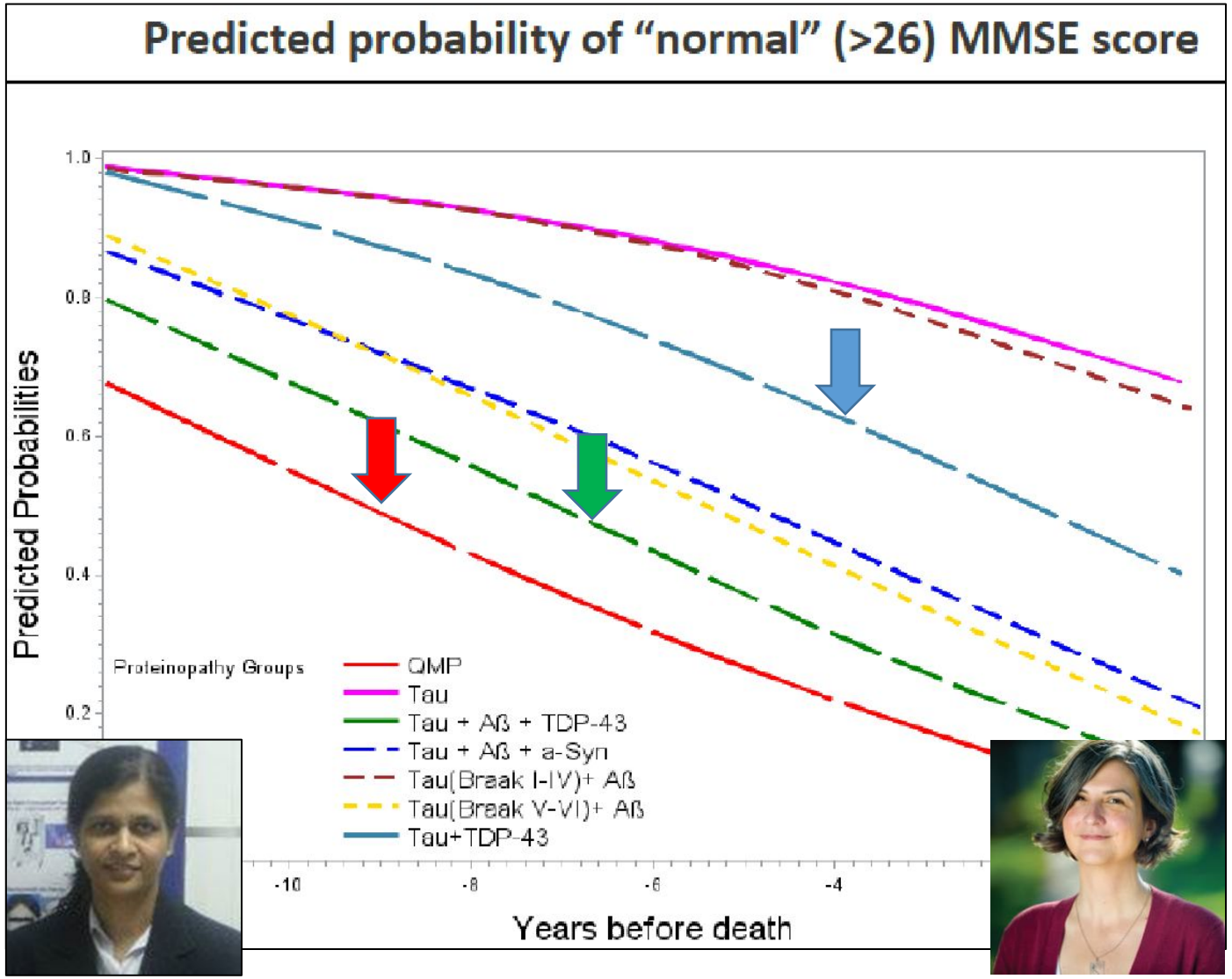
Nelson et al., Brain 2011

TDP43 in mixed disease states?

18th Annual MCI Symposium
Special Topic Workshop
Alzheimer's Public Educational Forum



- **Multiple pathologies contribute to MCI in the vast majority of cases**
- **The more pathologies accumulated, the greater the risk and severity of cognitive decline**
- **Quadruple misfolded proteins are not seen until the stage of dementia**

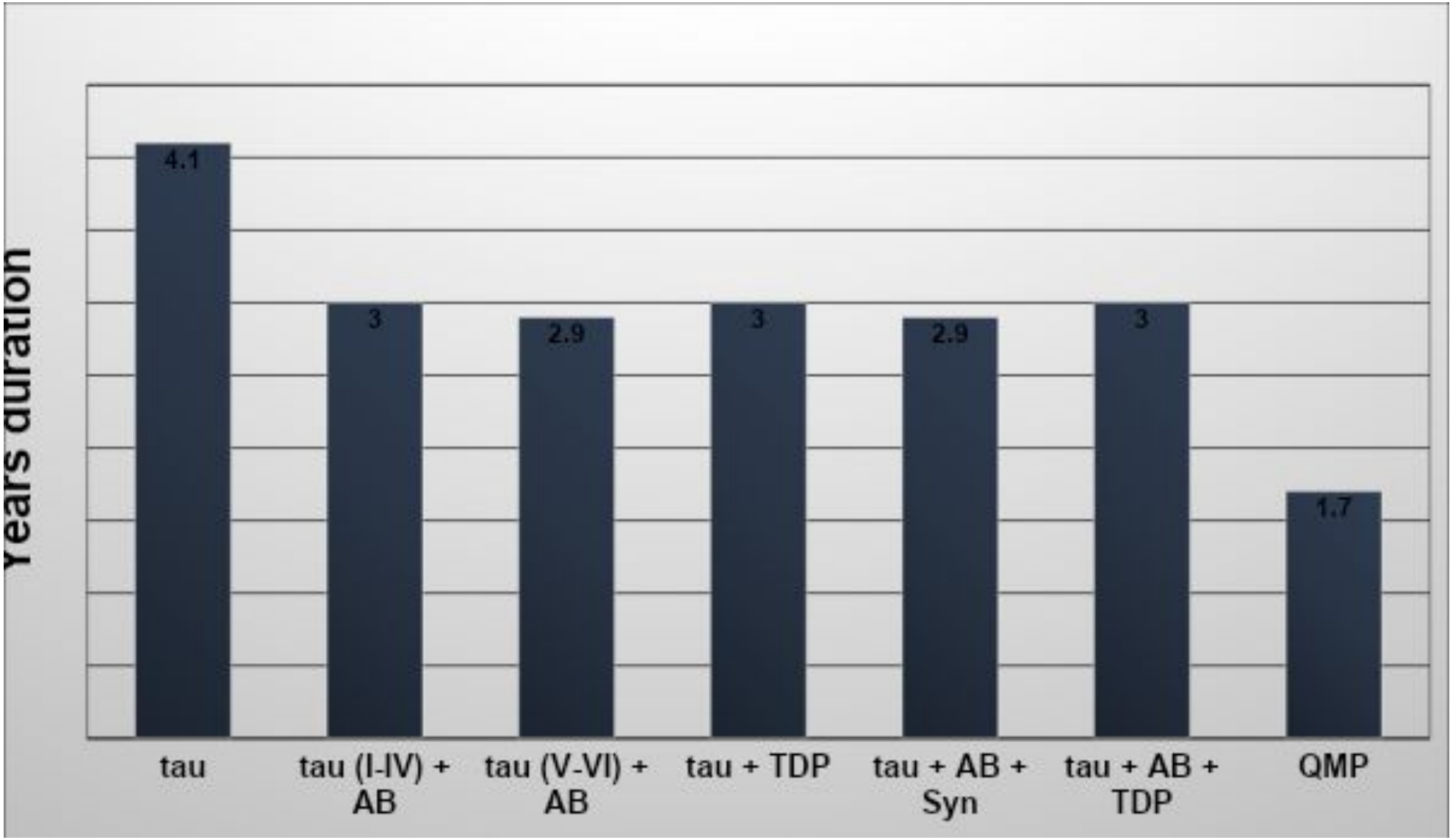


Shama Karanth

Erin Abner, PhD

Unpublished data

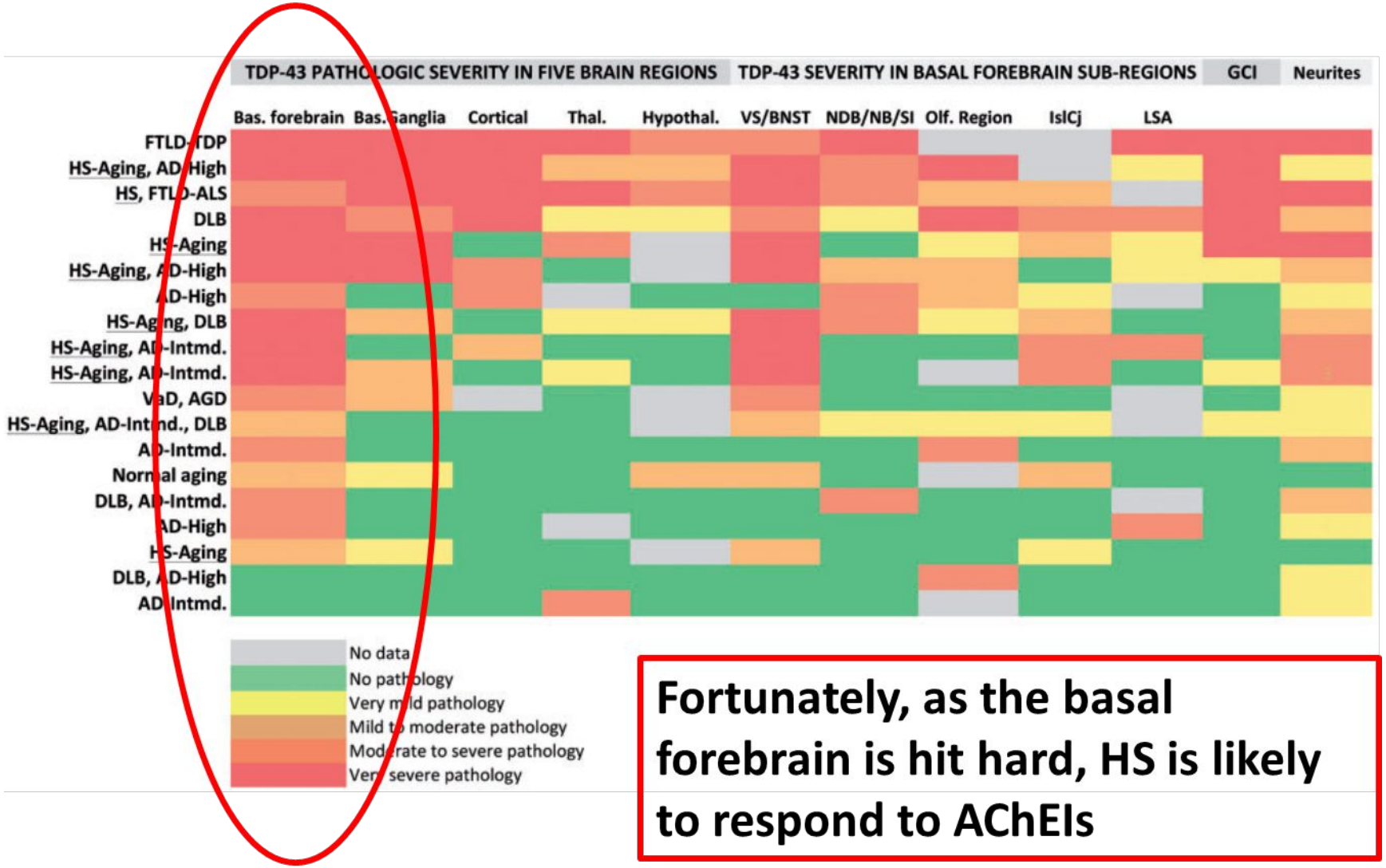
TDP43 in MCI



Shama Karanth

Erin Abner, PhD

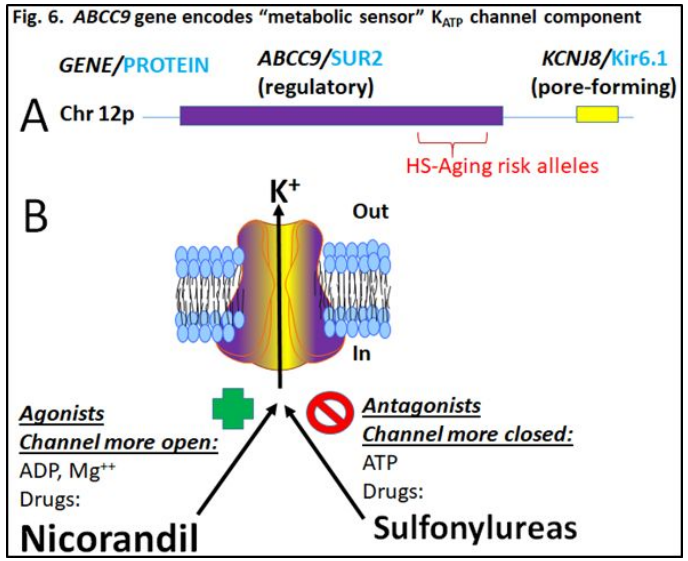
LATE: Treatment options?

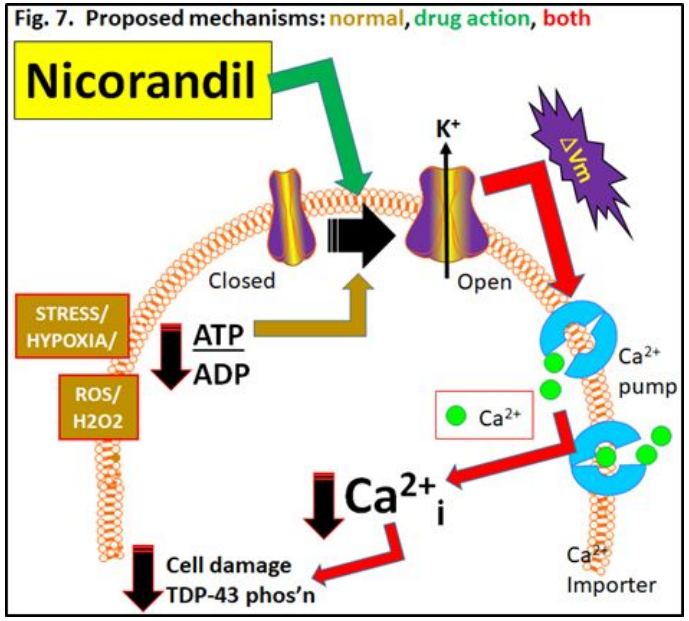


Fortunately, as the basal forebrain is hit hard, HS is likely to respond to AChEIs

Cykowski et al., J Neuropathol Exp Neurol. 2016

LATE: Emerging clinical trials?





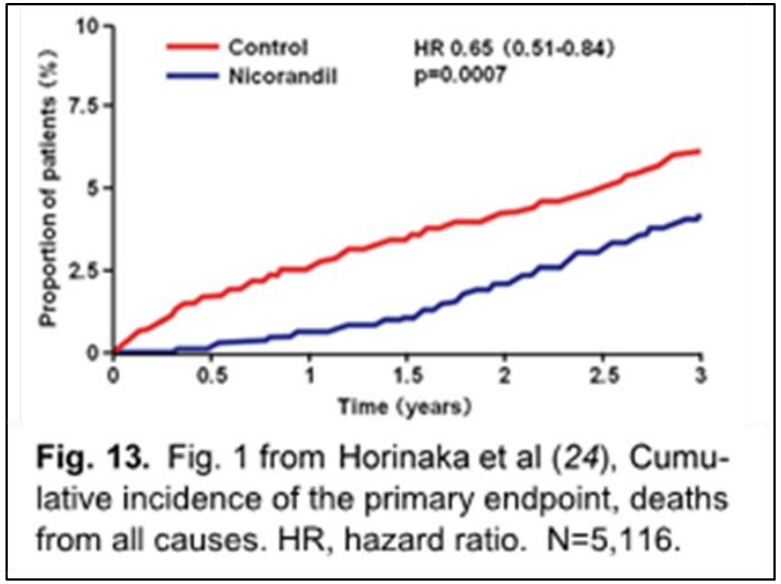


Fig. 13. Fig. 1 from Horinaka et al (*24*), Cumulative incidence of the primary endpoint, deaths from all causes. HR, hazard ratio. N=5,116.

Table 1. NACC cases (2010-2013) stratified by sulfonylurea drug use and eventual autopsy-proven HS-Aging pathology

	Sulfonylurea Use (N=36)		No Sulfonylurea Use (N=588)	
	HS-Aging Pathology (n=11)	No HS-Aging Pathology (n=25)	HS-Aging Pathology (n=97)	No HS-Aging Pathology (n=491)
Age at death, years	88.7±4.8	90.8±4.3	91.2±4.3	90.9±4.4
Number of longitudinal evaluations	4.5±1.1	4.4±1.7	3.9±1.8	3.9±1.7
Estimated sulfonylurea exposure, years	3.4 (Range 0.5-6.2)	3.5 (Range 0.5-6.8)	N/A	N/A
Taking sulfonylurea at final evaluation, %	81.80%	72.00%	N/A	N/A

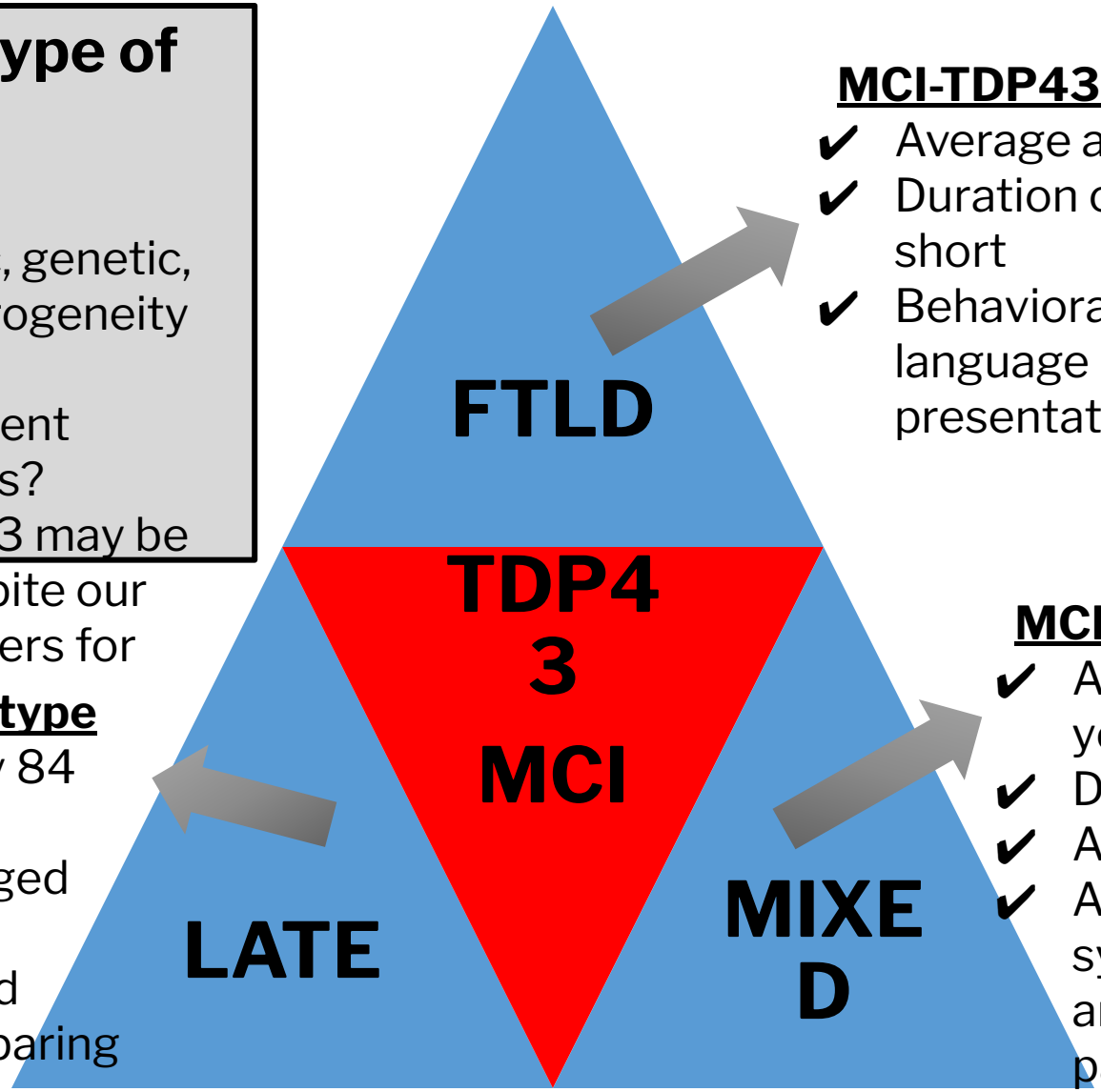
- **Nicorandil protects from death OR 0.65 [95% CI: 0.51-0.84]**
- **Sulfonylureas are linked to HS-aging OR 2.19 [95% CI: 1.04–4.63]**

Safety and Modulation of ABCC9 Pathways by Nicorandil for the Treatment of Hippocampal Sclerosis of Aging (SMArT-HS)
NIH R01AG061111 funded
ClinicalTrials.gov Identifier: NCT04120766

SUMMARY

The clinical phenotype of MCI-TDP43 is heterogenous

- Reflects the pathologic, genetic, and demographic heterogeneity of TDP43
- May represent convergent pathogenetic processes?
- Subtypes of MCI-TDP43 may be readily identifiable despite our current lack of biomarkers for TDP43



MCI-TDP43 of the FTLD-type

- ✔ Average age at autopsy 76 years
- ✔ Duration of MCI is variable but short
- ✔ Behavioral, psychiatric, or language predominant presentation

MCI-TDP43 of the LATE-type

- ✔ Average age at autopsy 84 years
- ✔ Duration of MCI prolonged
- ✔ Amnestic presentation
- ✔ Language, behavior, and psychiatric symptom sparing

MCI-TDP43 of the Mixed-type

- ✔ Average age at autopsy 84 years
- ✔ Duration of MCI shortest
- ✔ Amnestic component
- ✔ Associated signs & symptoms variable as they are often related to comorbid pathology