Clinicopathologic and genetic aspects of hippocampal sclerosis

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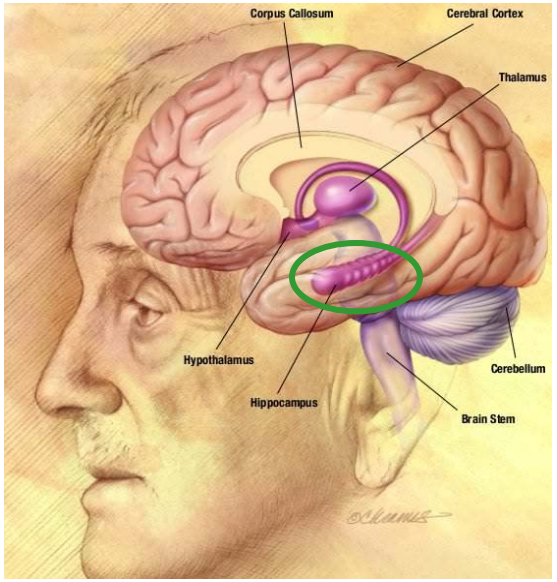
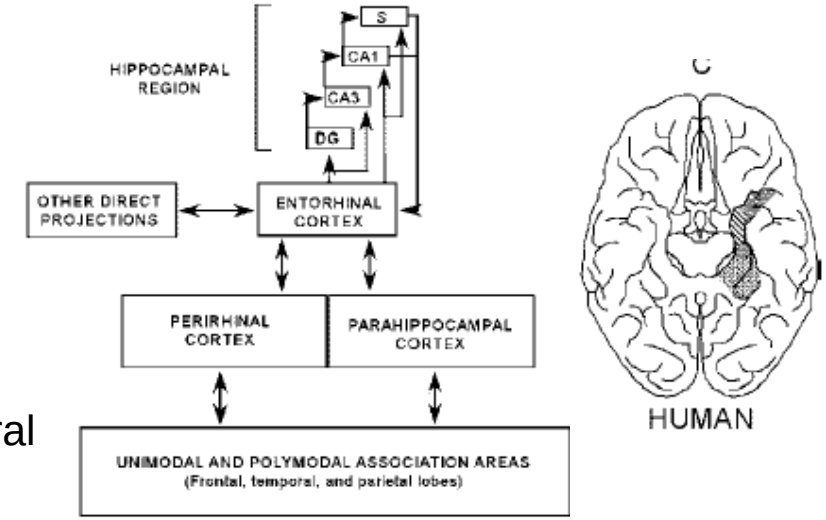
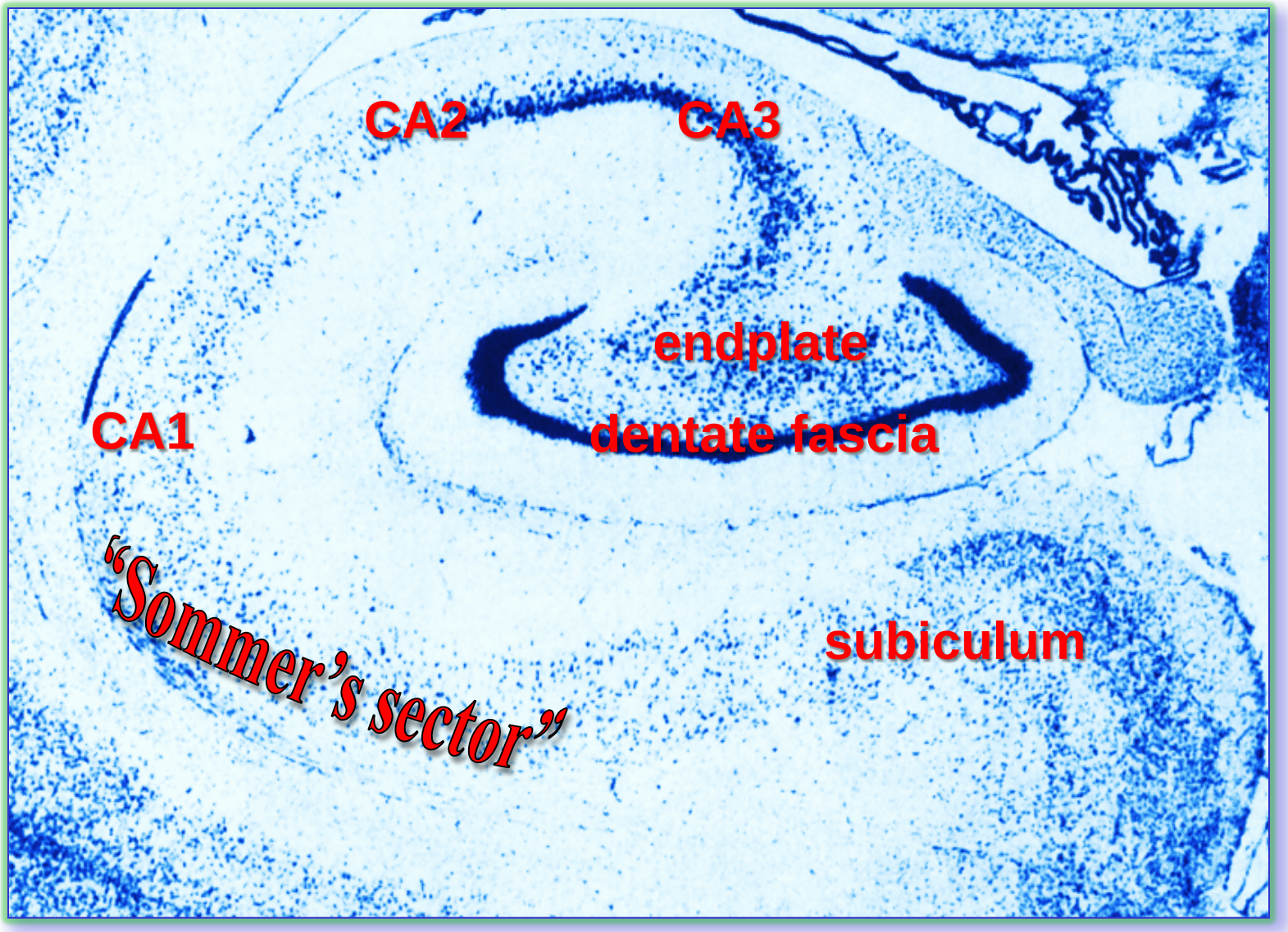
The hippocampus in health & disease

- **A major structure of the medial temporal lobe critical for learning and memory.**
- **Selective damage or dysfunction leads to amnestic syndrome**
- **Vulnerable to hypoxia, ischemia and a range of neurodegenerative disorders.**





Squire LR, Stark CEL, Clark RE. The medial temporal lobe. *Annu Rev Neurosci* 2004;27:279–306.



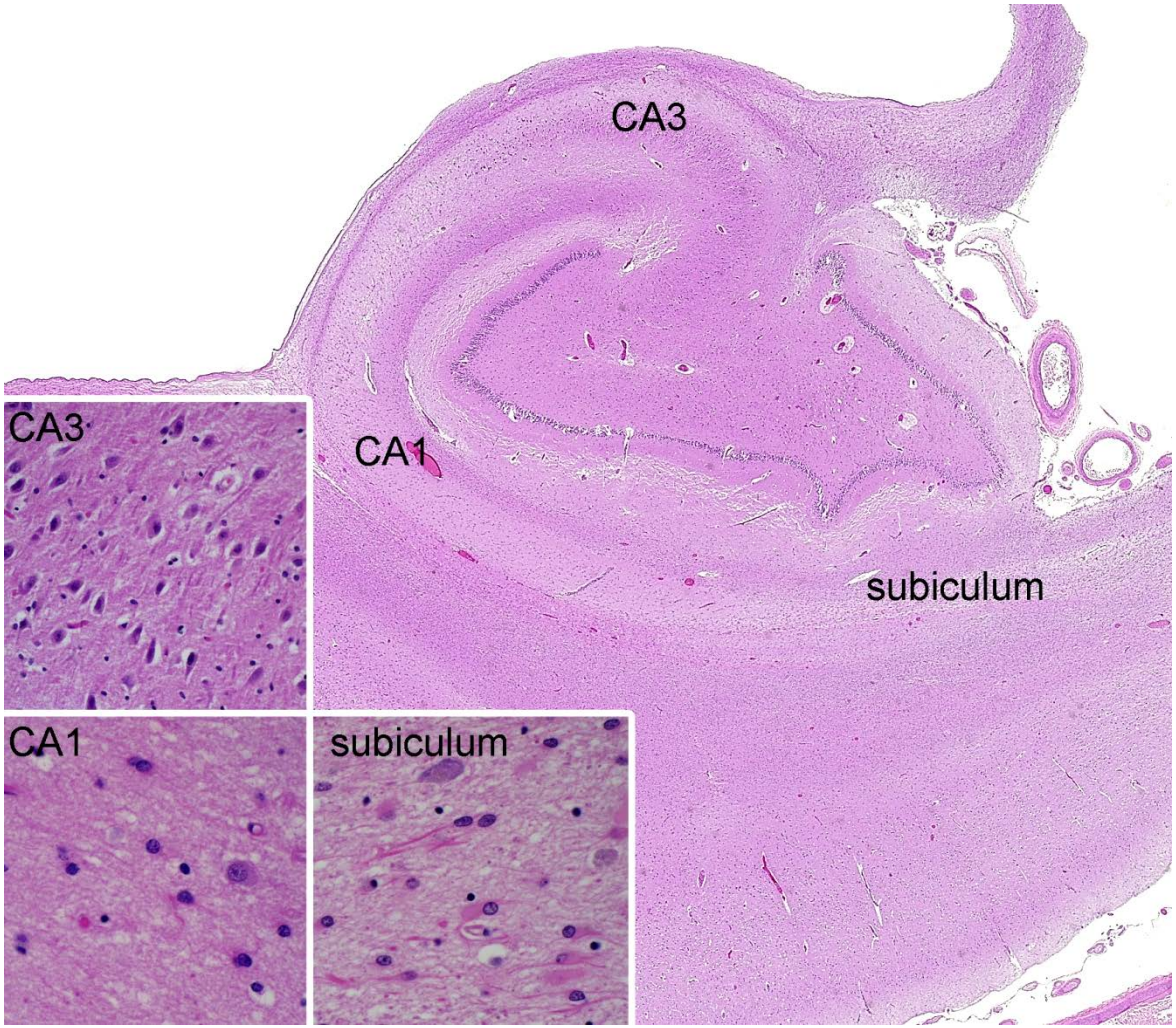
Nissl stained section of hippocampus (Hp) at level of lateral geniculate nucleus

Hippocampus & selective vulnerability

- **Alzheimer's disease**
  - CA1 & subiculum, early in disease process (Braak staging scheme)
  - Dentate fascia (Df) (Pick body like inclusions*) in advanced stages of AD
- **Tauopathies**
  - 3R tau – Pick's disease (CA1 & Df)
  - 4R tau – AGD, PSP, CBD (CA2 & Df)
- **Synucleinopathies**
  - Lewy body disease (CA2/3)

*Dickson DW, et al. Pick body-like inclusions in the dentate fascia of the hippocampus in Alzheimer's disease. *Acta Neuropathol* 71:38-45, 1986.

Hippocampal sclerosis in FTLD

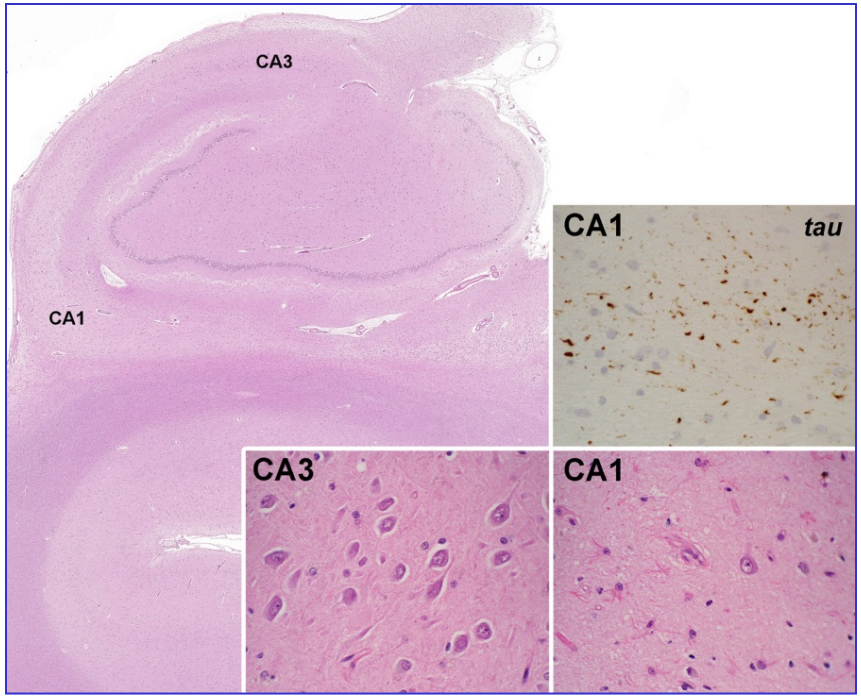


HpScl in 79% of FTLD-U and 26% FTLD-MND

Hippocampal sclerosis tauopathy

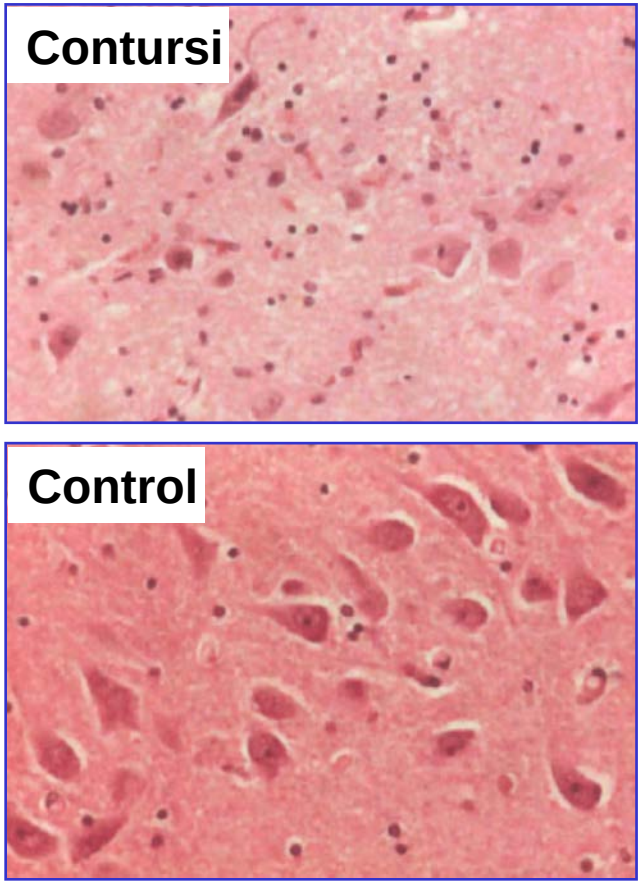
- **Some cases of argyrophilic grain disease, a medial temporal 4R-tauopathy that increases in frequency with age, have HpScl.**
  - Beach TG, et al. Hippocampal sclerosis dementia with tauopathy. *Brain Pathol* 2003;13: 263-278.
- **Mayo ADRC cases: MCI is common in HpScl with or without AGD.**

  Jicha GA, et al. Argyrophilic grain disease in demented subjects presenting initially with amnestic mild cognitive impairment, *J Neuropathol Exp Neurol* 2006;65:602-609.



Hippocampal sclerosis in familial DLBD

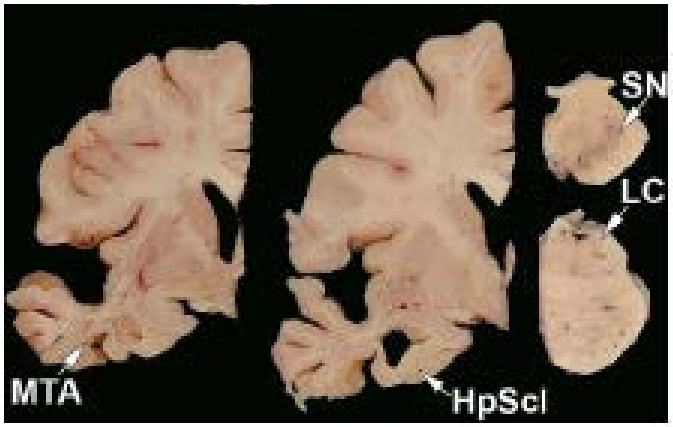
- **CA2/3 neuronal loss in cases with *SNCA* mutations**
  - A53T (Contursi kindred)
  - *SNCA* triplication (Iowa kindred)
  - *SNCA* duplication (Swedish American kindred)
  - Associated with Lewy neurites



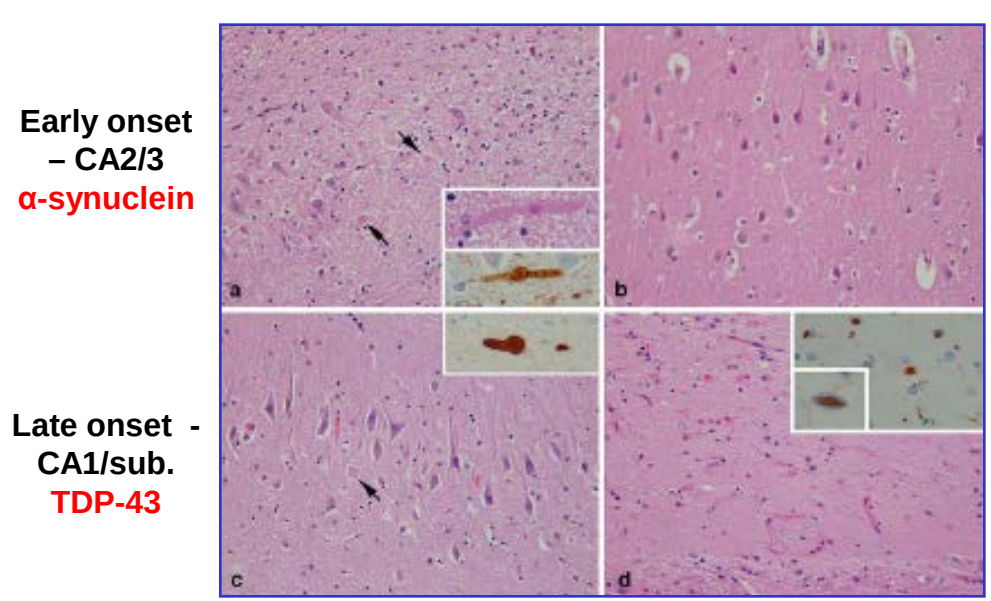
Farrer M, et al. Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. *Ann Neurol* 2004;55:174-179.

Hippocampal sclerosis in familial PD

- **Greek-American kindred with A53T mutation in *SNCA*.**
- **Two autopsies: early onset PD (onset at 31 & death at 39 years); late onset PD (onset at 59 & death at 71 years)**
- **Both had DLBD and HpScl.**

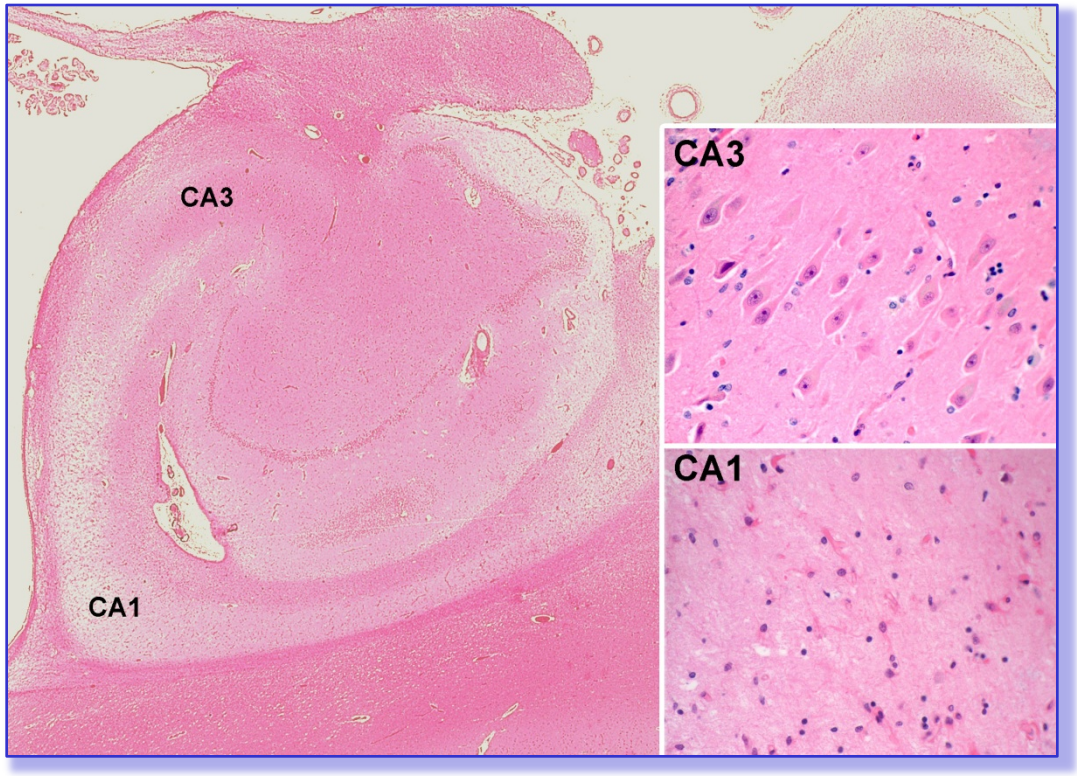


Markopoulou K, et al. Clinical, neuropathological and genotypic variability in SNCA A53T familial Parkinson's disease. Variability in familial Parkinson's disease. *Acta Neuropathol* 2008;116:25-35.



Hippocampal sclerosis (HpScl) in the elderly

- **HpScl detected in >20% of demented patients ≥80 years of age.**
- **Clinical syndrome: slowly progressive amnestic syndrome.**
- **Not associated with epilepsy.**
- **In some cases it was the only structural abnormality to explain dementia.**
- **Synaptophysin loss only in hippocampus, not cortex or basal ganglia.**



Dickson DW, et al. Hippocampal sclerosis: a common pathological features of dementia in very old (≥80 years of age) humans. Acta Neuropath 1994;88:212-221.

TDP-43 in HpScl

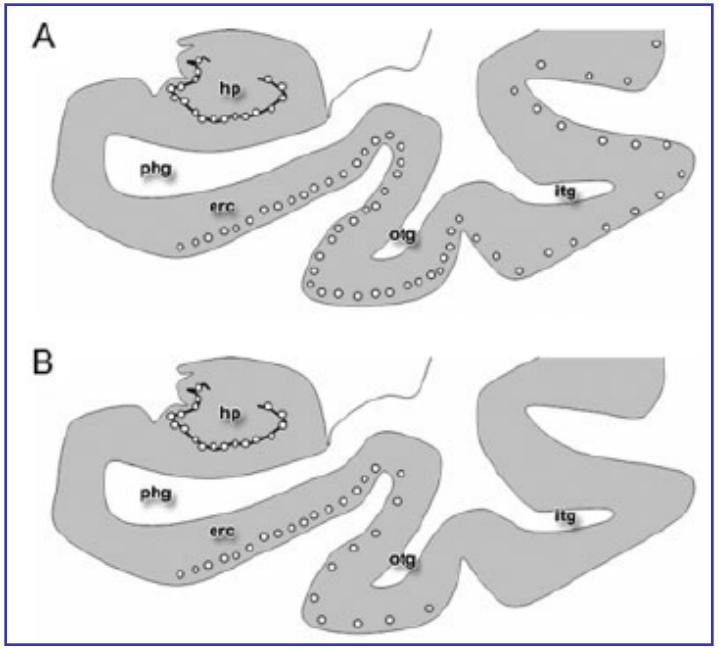
- **TAR DNA binding protein of 43-kDA**
- **Gene (*TARDBP*) on chromosome 1**
- **Nuclear DNA/RNA binding protein involved in transcriptional regulation**
- **Component of neuronal inclusions in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS)**
  - Neumann M, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314:130-133.

TDP43 immunoreactivity in AD with & without HpScl

	N	TDP-43
AD (with HpScl)	44	33 (75%)
AD (no HpScl)	30	9 (30%)
AD (all)	74	42 (57%)

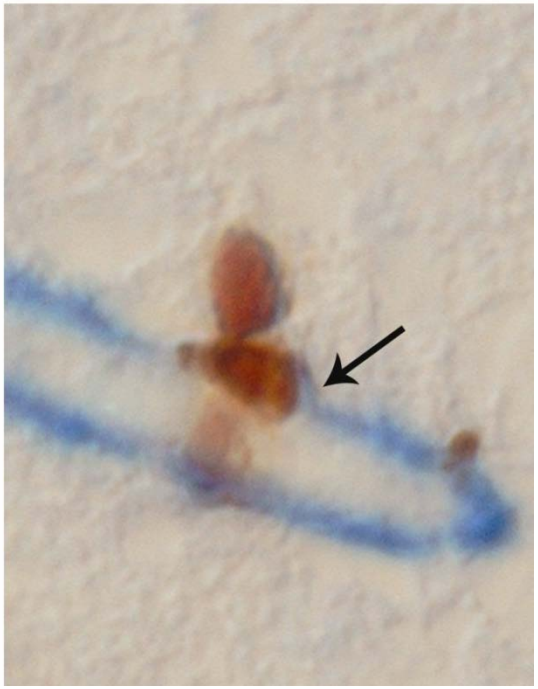
Most cases have TDP-43 pathology in limbic-predominant distribution, unlike FTLD, which is widespread.

diffuse vs. limbic types

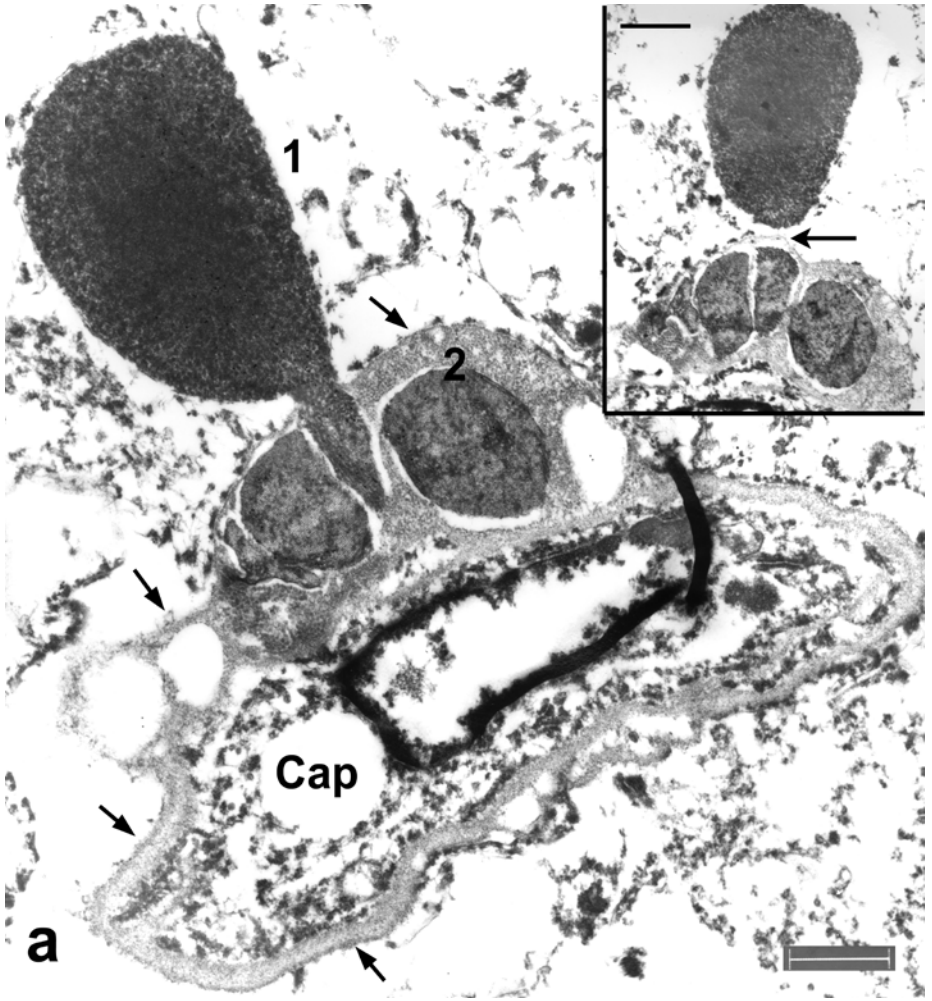


Amador-Ortiz C, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann Neurol* 2007;61:435-445.

TDP-43 microvasculopathy in HpScl

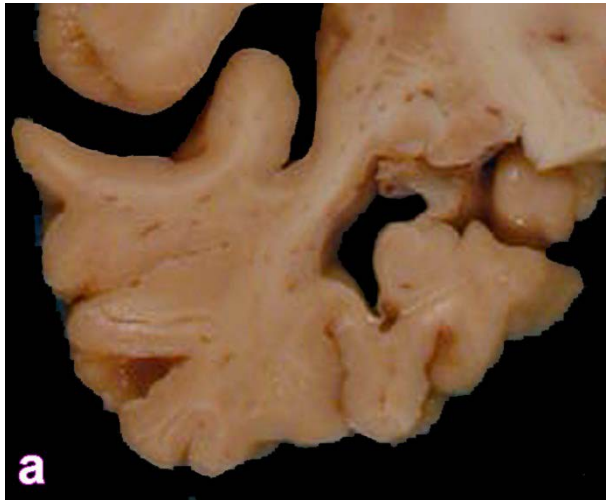


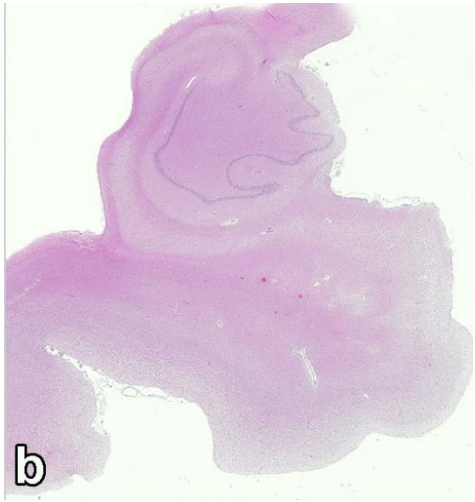
TDP-43 – brown
Collagen IV – blue



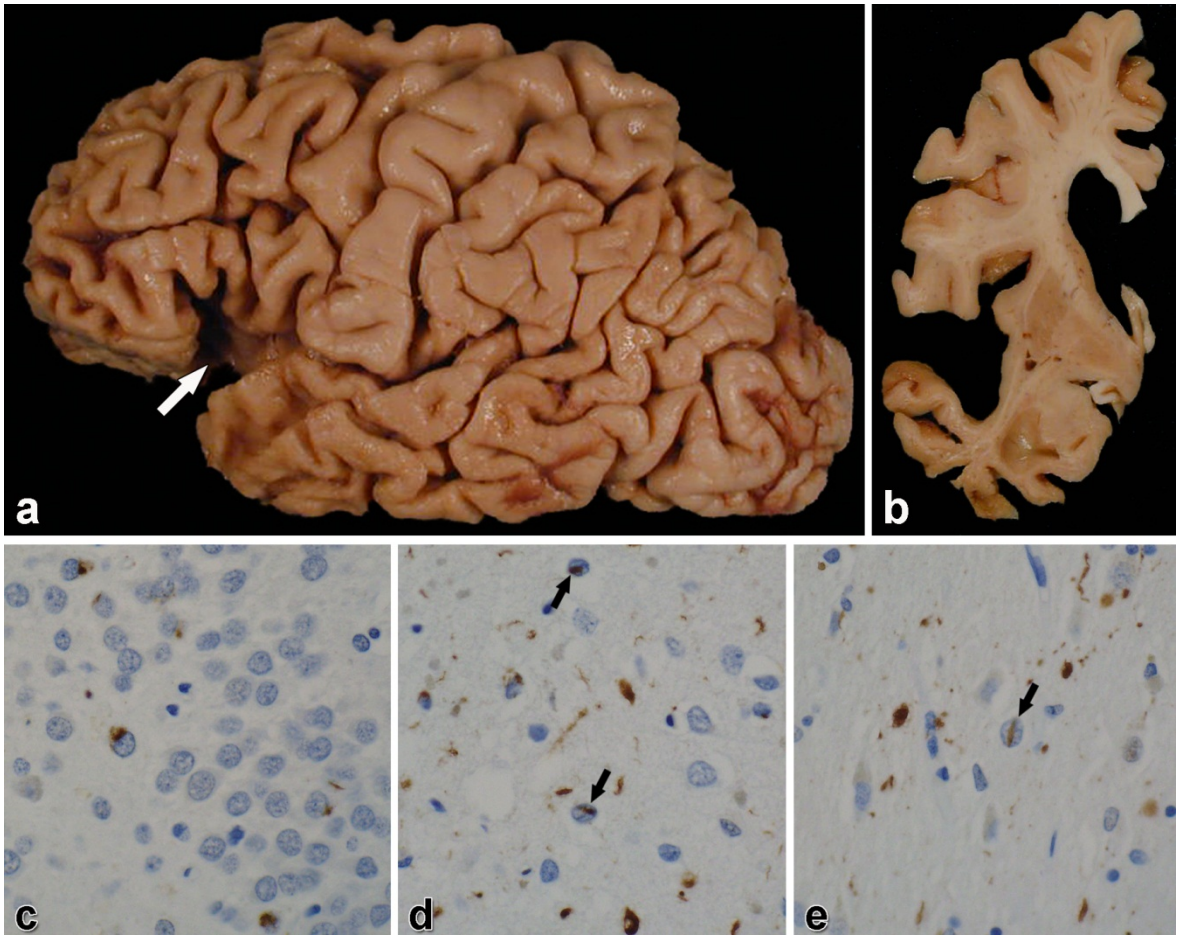
Lin WL, et al. Transactivation response DNA-binding protein 43 microvasculopathy in frontotemporal degeneration and familial Lewy body disease. *J Neuropathol Exp Neurol* 2009;68:1167-76.

HpScl in FTLD-TDP with *GRN* mutation





a & b = hippocampal atrophy (“sclerosis”)



a = peri-Sylvian atrophy (progressive aphasia), b = fronto- temporal atrophy; c dentate fascia inclusions; d = cortical neurites, cytoplasmic and intranuclear inclusions (arrows); e = striatal inclusions

3'UTR variant in *GRN* (rs5848) is a risk factor for FTLD-TDP and for HpScl

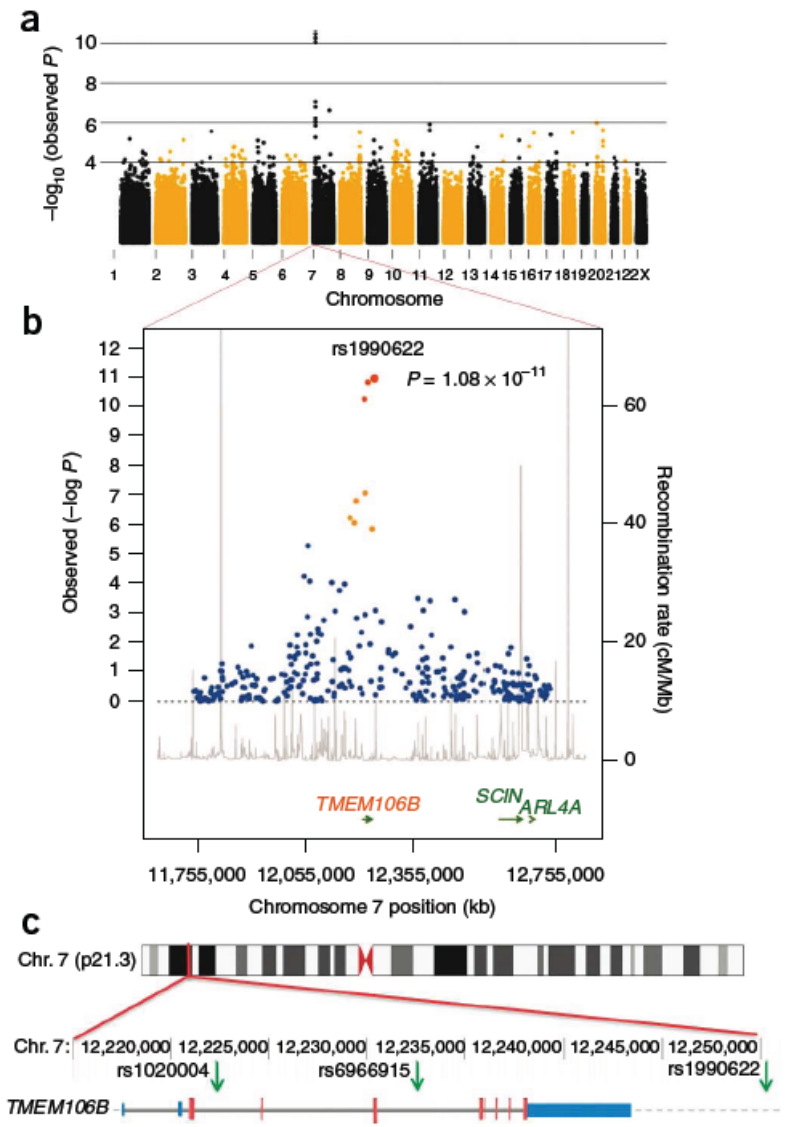
genotype	FTLD-TDP	Controls
CC	21 (36%)	199 (46%)
CT	23 (39%)	191 (44%)
TT	15 (25%)	43 (10%)
p=0.003		

Rademakers R, et al. Common variation in the miR-659 binding-site of *GRN* is a major risk factor for TDP43-positive frontotemporal dementia. *Hum Mol Genet* 2008;17:3631-42.

Dickson DW, et al. Common variant in *GRN* is a genetic risk factor for hippocampal sclerosis in the elderly. *Neurodegener Dis* 2010;7:170-174.

genotype	HpScl	No HpScl
CC	16 (28%)	286 (49%)
CT	33 (58%)	253 (43%)
TT	8 (14%)	48 (8%)
p=0.020		

TMEM106B in FTLD-TDP & HpScl



TMEM106B is an important risk factor for FTLD-TDP even in *GRN* mutation carriers.

A variant in TMEM106B, rs1990622, has a protective effect on risk for FTLD-TDP.

Progranulin acts upstream of TMEM106B

TMEM106B is localized in the late endosome/lysosome compartments and TMEM106B levels are regulated by lysosomal activities.

Van Deerlin VM, et al. Common variants at 7p21 are associated with fronto-temporal lobar degeneration with TDP-43 inclusions. *Nat Genet* 2010;42:234-239.

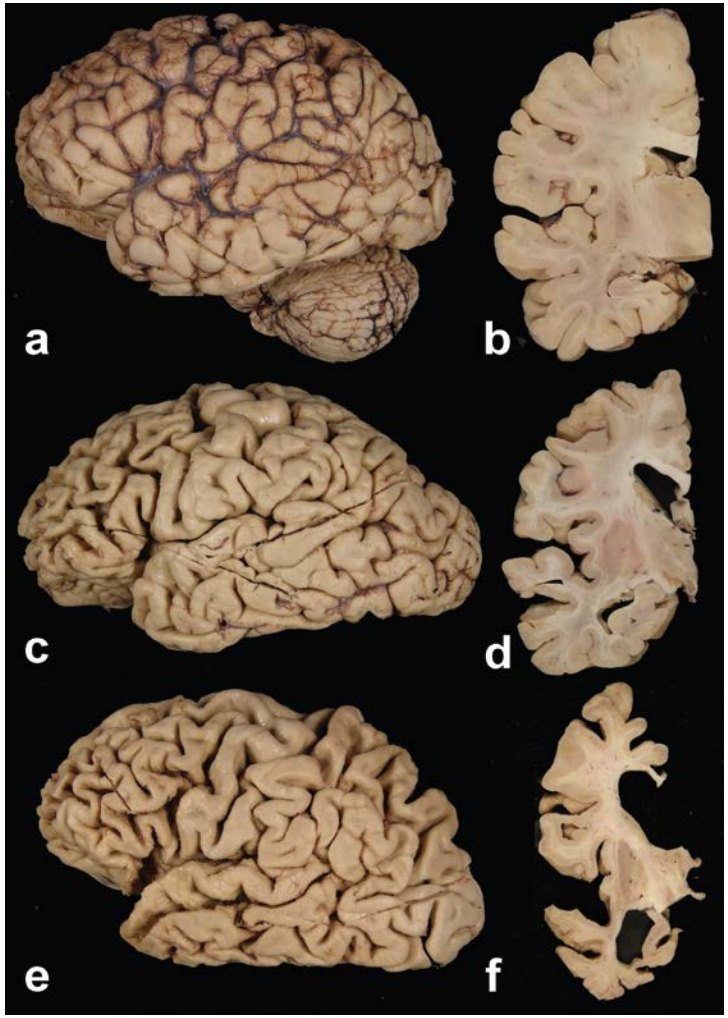
TMEM106B in HpScl

- **Genotyping *TMEM106B* rs1990622 and TDP-43 immunohistochemistry of 907 AD, including 88 with HpScl.**
  - AD with rs1990622 C-allele were significantly less likely to have TDP-43 pathology, but especially lee likely to have HpScl ($p<0.0001$).
  - These data suggest that increased levels of progranulin in the hippocampus may protect against insults that would otherwise lead to hippocampal damage.

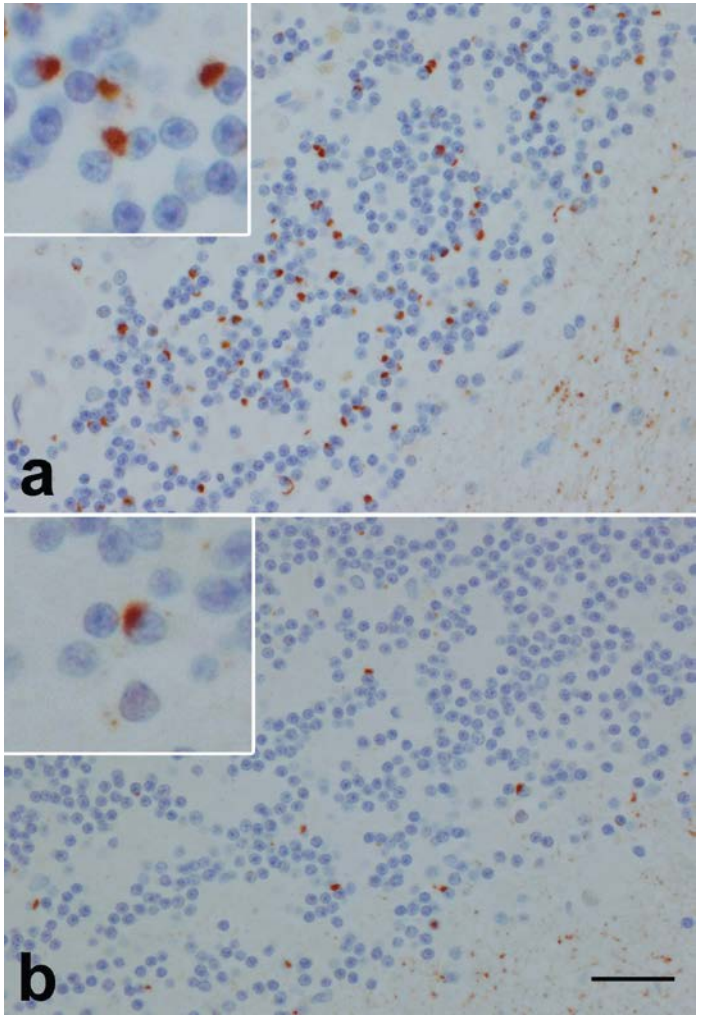
Rutherford NJ, et al. TMEM106B risk variant is implicated in the pathologic presentation of Alzheimer disease. Neurology 2012;79:717-718.

Chromosome 9 linked FTD/ALS

Variable brain atrophy



Constant cerebellar inclusions



HpScI in c9FTD/ALS

Table 3 Pathologic features

Case #	Path type	Braak NFT Stage	SN score	HpScI score
1	ALS	II	0–1	0
2	ALS	0–I	0–1	0
3	ALS	I	0	0
4	ALS	II	1	0
5	ALS	III	0–1	0
6	FTLD-MND	I–II	1	0
7	FTLD-MND	II	1	0
8	FTLD-MND	II	0–1	0–1
9	FTLD-MND	II	3	1
10	FTLD-MND	V–VI	2	3
11	FTLD-MND	II	2	3
12	FTLD-MND	0	2	1
13	FTLD-TDP	0–I	3	0
14	FTLD-TDP	IV	3	3
15	FTLD-TDP	II	1	0–1
16	FTLD-TDP	II–III	1	1
17	FTLD-TDP	II–III	0–1	2–3
18	FTLD-TDP	II	3	2
19	FTLD-TDP	III	1	2
20	FTLD-TDP	II–III	3	3

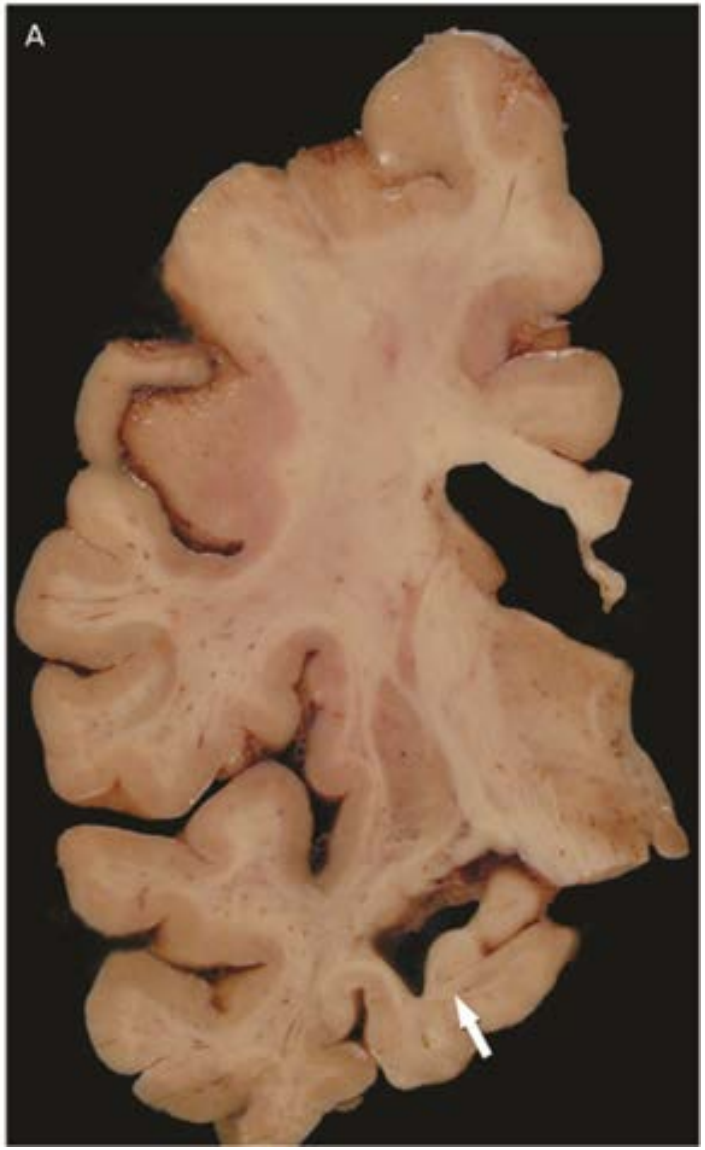
FTLD-TDP – 7/8
FTLD-MND – 4/7
ALS – 0/5

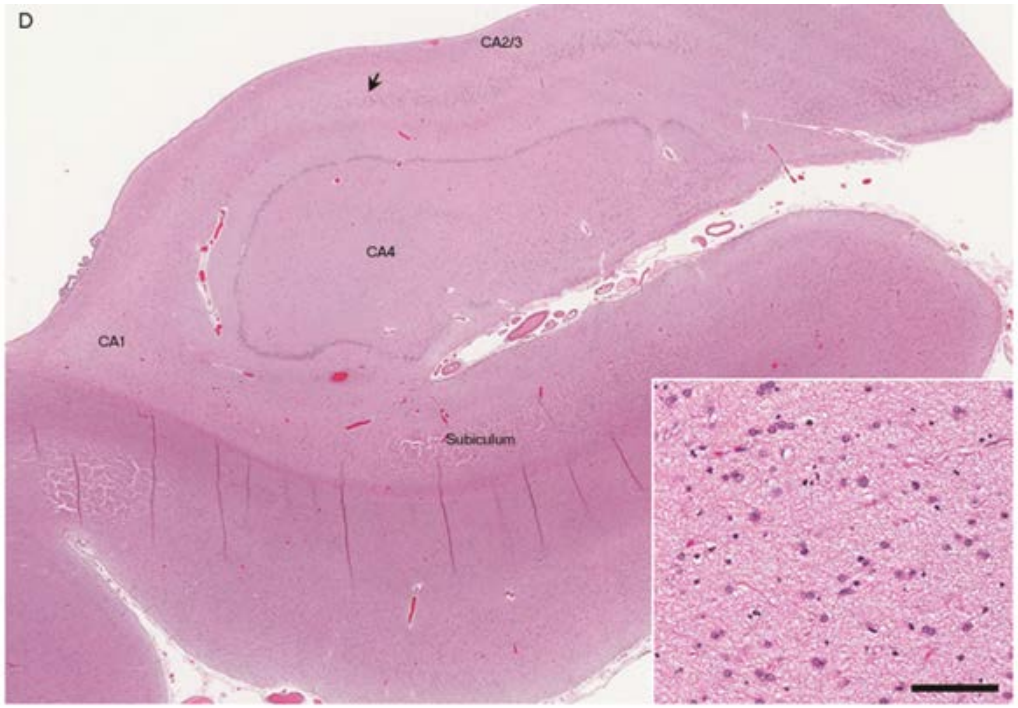
Murray ME, et al. Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in C9ORF72. Acta Neuropathol 2011;122:673-690.

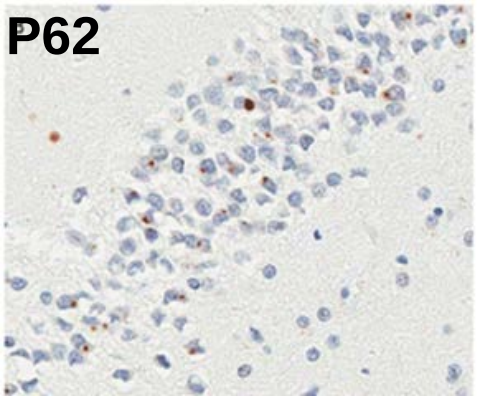
“Pure” HpScl with C9ORF72 mutation

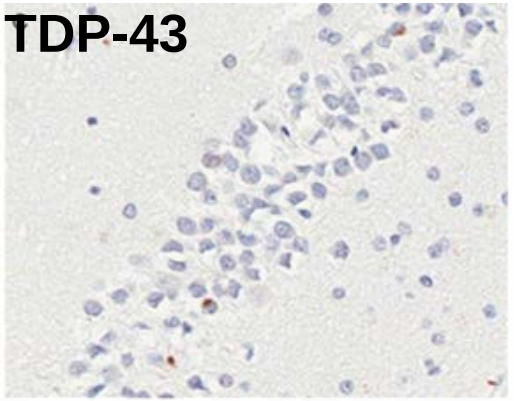
- This 76-year-old man presented at 72-years-of-age with a 10-year history of slowly progressive episodic memory impairment. Clinical diagnosis: Alzheimer’s disease
- He had no change in personality or behavior. He was socially active.
- His mother had slowly progressive amnestic dementia with onset in her 70’s and death at age 96.
- Neurological evaluation showed mild bradykinesia, paucity of spontaneous speech, and a mild tremor.
- He scored 24/30 on MMSE with points lost for orientation and recall.
- Neuropsychological evaluation showed severe impairment in memory, especially for delayed recall.

c9HpScl - Neuropathology









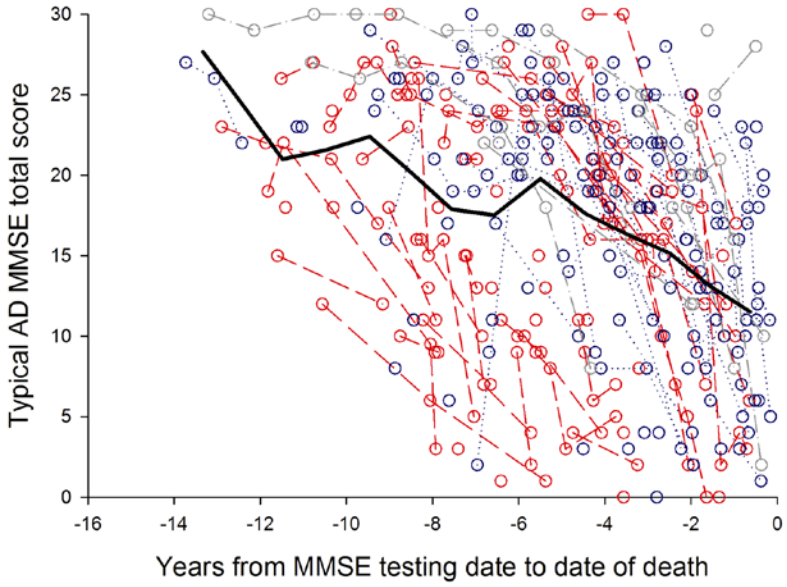
Comparison of HpScl to Limbic Predominant AD (LP-AD)

- AD cases with a Braak NFT stage of more than IV were identified from the Mayo Clinic Jacksonville brain bank database.
- Thioflavin S fluorescence microscopy, was used to assess density and distribution of neurofibrillary tangles in three cortical regions and two hippocampal sectors.
- Data were used to construct an algorithm to classify AD cases into typical, hippocampal sparing, or limbic predominant.
- Classified cases were compared for clinical, demographic, pathological, and genetic characteristics.

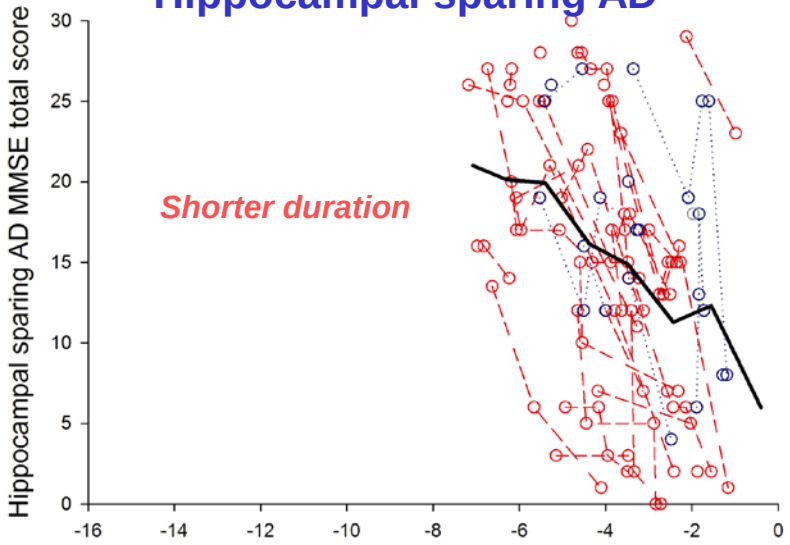
Murray et al. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 2011;10:785-96.

Rate of clinical decline – Mini-Mental State Exam

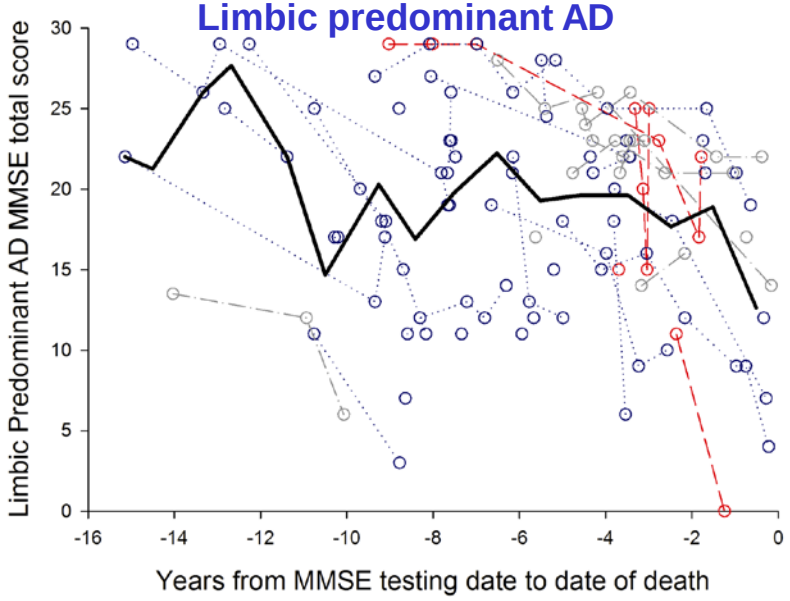
Typical AD



Hippocampal sparing AD



Limbic predominant AD



MMSE	AD subtypes			
	HpSp	Typical	LP	*p-value*
Initial score	**20 (15,25)**	**23 (15,26)**	**23 (18,28)**	**0.64**
Final score	**7 (2,13)**	**11 (6,16)**	**15 (8,19)**	**0.076**
Rate of decline	**4.8 (8.3,3.1)**	**2.8 (4.4,1.5)**	**1.4 (2.8,0.8)**	**0.009**

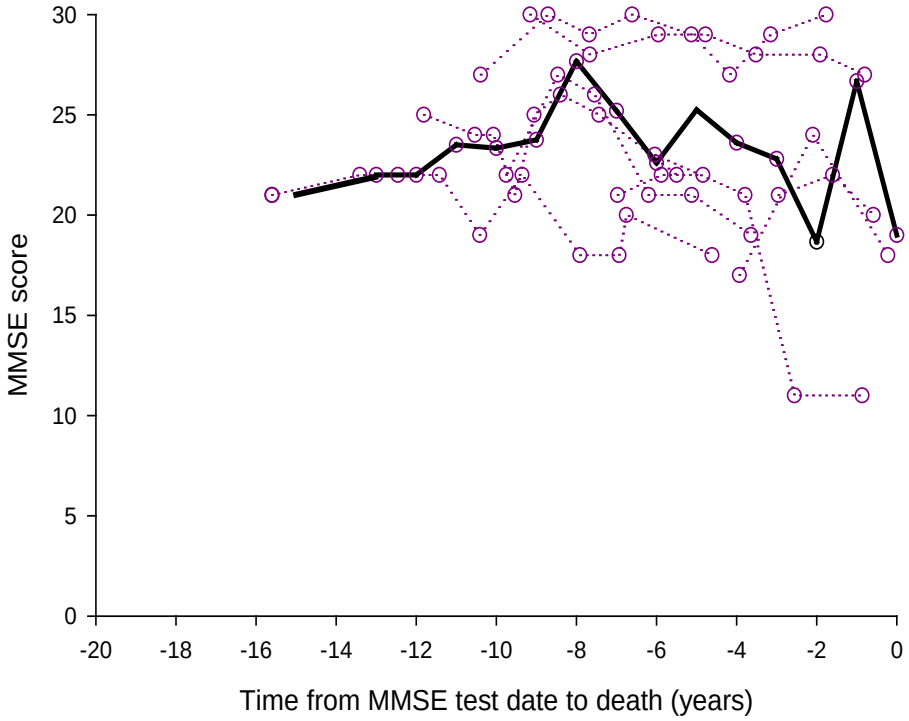
Shown for each measure is median and interquartile range.

Red symbols/lines age of onset <70 years.

Black line = moving average

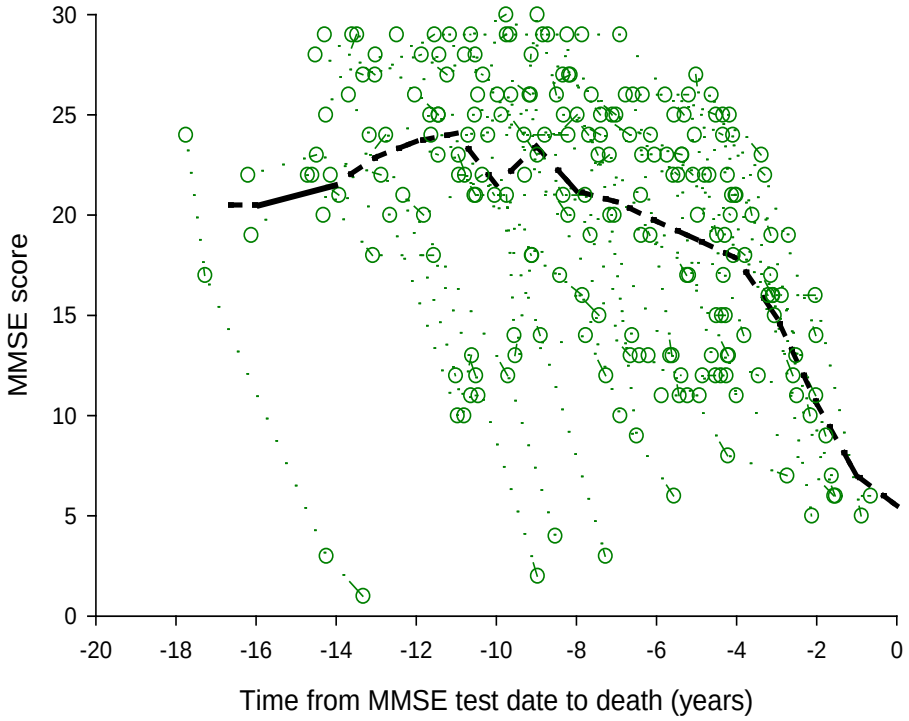
Comparison of HpScl to AD-HpScl

Pure HpScl



Median rate of decline: -0.3 (-2.2, 0.0)

AD-HpScl



Median rate of decline: -2.1 (-4.2, -1.1)

Comparison of LP-AD, HpScl-AD and HpScl

	LP-AD	HpScl-AD	HpScl	P-value
Number	151	154	35	
Age at death	86 (82-90)*	86 (82-91)*	90 (84-94)	ns
Women	70%	61%	58%	0.003
Brain weight (grams)	1040 (941-1120)**	1000 (900-1125)**	1160 (1030-1235)	<0.001
Braak NFT stage	6 (5-6)**	6 (5-6)**	2 (2-3)	<0.001
TDP-43, %positive	35%*	87%	90%	<0.001
Type 1, %positive	47%*	72%	80%	<0.001
Type 3, %positive	62%*	28%	20%	<0.001
APOE, ε4 allele	66%**	65%**	35%	0.007
GRN, T allele	49%	68%	63%	0.004
TMEM106B, C allele	74%*	51%	43%	<0.001

Pairwise tests: * different from AD-HpScl and HpScl; ** different from HpScl

Summary of HpScl and LP-AD

- **AD-HpScl has overlapping features with LP-AD and pure HpScl consistent with it being a mixed type of dementia.**
  - APOE ε4 is over-represented in both LP-AD and AD-HpScl
  - GRN and TMEM106B variants are similar in AD-HpScl and pure HpScl
- **HpScl has unique features that overlap with FTLD-TDP but pathology restricted to medial temporal lobe consistent with a *forme fruste* of FTLD-TDP.**