Update on Frontotemporal Dementia (FTD)

Ging-Yuek Robin Hsiung, MD MHSc

Department of Medicine, Division of Neurology

University of British Columbia

Vancouver Coastal Health

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Clinic for Alzheimer Disease and Related Disorders

UBC Hospital

Disclosure

- Received Grants or contracts from CIHR, NIA/NIH, has been a clinical trials investigator supported by Anavex, Biogen, Cassava, and Lilly

- Participated in expert advisory committee supported by Biogen, Roche, and NovoNordisk.

- I am the current president of C5R (Consortium of Canadian Centres for Clinical Cognitive Research).

Learning Objectives

1. To appreciate the recent advances in genetics and pathology of FTD (FTLD)

2. To be able to recognize the different types of FTD

3. Updates on upcoming clinical trials on FTD

Epidemiology of FTD

- 2nd most common cause of degenerative dementia in those under age 70 (after Alzheimer-AD) (Feldman et al, 2003)
- Median age of onset ~58, but can range from 28-81 (Rosso, 2003)
- FTLD ~18-36/100000, ~12000-18000 new cases/yr (in US) (Knopman 2011)
- 20-40% have an autosomal dominant family history
- FTD refers to the clinical presentation vs. Frontotemporal Lobar Degeneration (FTLD) = the pathological diagnosis

Clinical presentation of FTD

FTD (FTLD – pathological Dx)

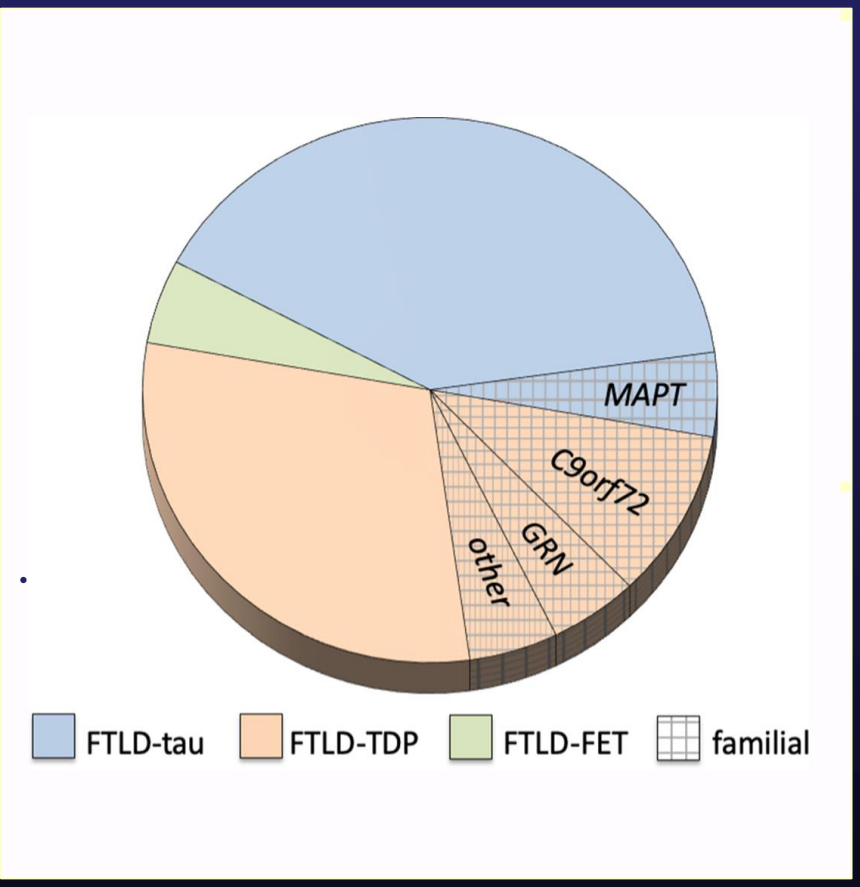
Usually younger than AD, very heterogeneous

3 main syndromes + ALS:

1. Behavioural Variant (bvFTD)
2. Primary Progressive Aphasia (PPA)
   a) Semantic Dementia
   b) Progressive Non-Fluent Aphasia
   & Logopenic Progressive Aphasia
   & Progressive apraxia of speech
3. FTD with movement disorders
   a) Progressive Supranuclear Palsy
   b) Corticobasal Degeneration (CBD)
   & Parkinsonism (FTDP-17)

& those associated with motor neuron disease (ALS-FTD)

Proportions of the different pathologies of FTLD



Around 20% of all FTD cases are caused by autosomal dominant mutations within:

- Progranulin (***GRN***)
- Chromosome 9 open reading frame 72 (***C9orf72***)
- Microtubule associated protein tau (***MAPT***)

Symptomatic FTD patients with different genetic mutations may present differently clinically due to:

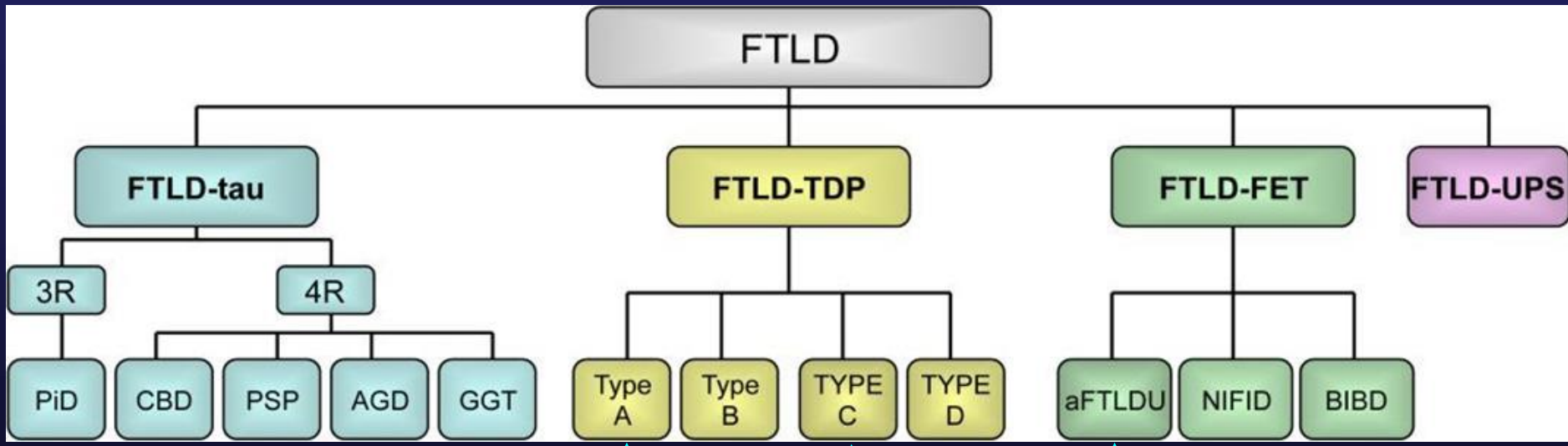
- Anatomical regions affected in Grey [1,2,3] & White Matters [4,5]
- Behavioral disturbances and neuropsychiatric symptoms [6,7]

1 Whitwell et al. Brain 2012
2 Cash et al. Neurobiol Aging 2018
3 Staffaroni et al. JAMA Netw Open 2020
4 Sudre et al. Neuroimage Clin 2019
5 Mahoney et al. Ann Neurol 2015
6 Benussi et al. JAMA Netw Open 2021
7 Sellami et al. J Alzheimers Dis 2018

Summary of Known Genes associated with FTD

Chromosome	Gene	Pathology	Clinical Phenotype	Pathogenesis
17q21.1	Tau (*MAPT*)	FTLD-tau (3R or 4I or mix)	bvFTD, nfvPPA, memory, Parkinson	Missense & splice site mutations, early onset FTD with variable degree of Parkinsonism & motor neuron disease
17q21.31	Progranulin (*GRN*)	FTLD-TDP type A	bvFTD, nfvPPA, Parkinson, CBS	Nonsense & deletions leads to haploinsufficiency, wide age of onset 39-85, with variable phenotype with frontal behaviour, PPA, Parkinsonism, & CBD
9p21	*C9orf72*	FTLD-TDP typa B >> A	bvFTD, nfvPPA, ALS, psychosis	Hexanucleotide repeat, ?altered TDP-43 aggregation by inhibiting transcription (loss of function) vs. generation of toxic RNA species (toxic gain of function)
2p13.3	*TIA1*	FTLD-TDP type B	myopathy, ALS, nfvPPA, bvFTD	Missense mutations promotes TIA1 to from stress granules with TDP-43 aggregation
12q14.2	*TBK1*	FTLD-TDP type A or B	ALS, bvFTD, nfvPPA	Missense,, loss of function
9p13.3	*VCP*	FTLD-TDP- type D	IBM, PDB, bvFTD, ALS	Missense mutations, rare
3p11.2	*CHMP2B*	FTLD_UPS		Missence mutations, rare, only reported in one family
5q35.3	*SQSTM1*	FTLD-TDP	PDB, ALS, FTD, myopathy	missense
16p11.2	*FUS*	FTLD-FET	Young onset psychosis, bvFTD	Mostly missense mutation, causes about 3% of familial ALS (no dementia); Young onset atypical FTLD has FUS pathology
2p13.1	*DCTN1*	unknown	Perry's syndrome, neuropathy	missense
10p13	*OPTN*	FTLD-TDP	ALS, glaucoma	Loss of function, missense
1p36.22	*TARDBP*	ALS-TDP	ALS	missense mutations causes ALS+/- dementia. Pathology in 50% of FTLD and >80% of ALS;

Molecular Pathological Classification of FTLD



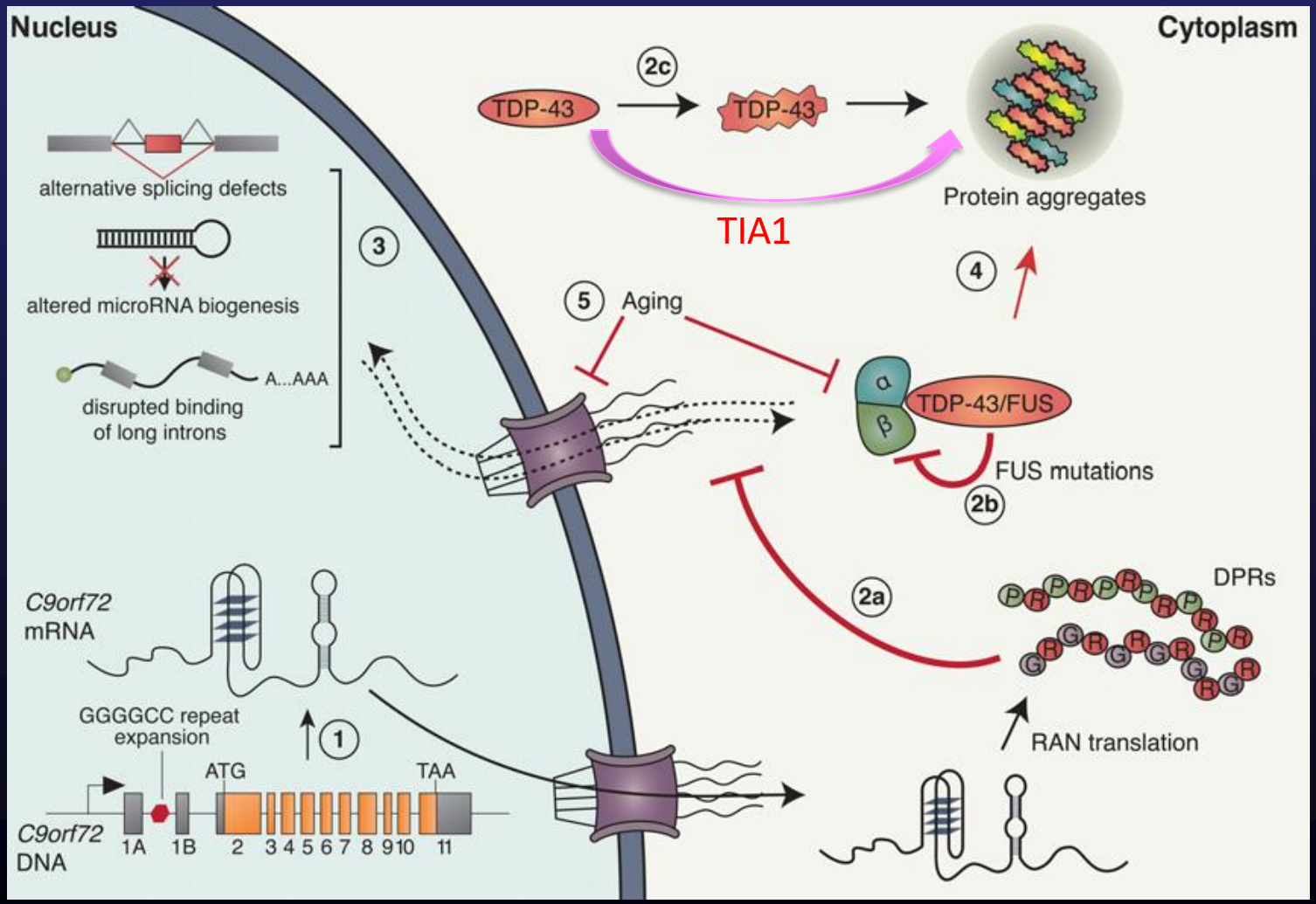
AD (mix 3R & 4R)
FTDP-17 (3R, 4R, or mix)

Modified from Mackenzie & Neumann, J Neurochem 2016: 138 Suppl:54-70

Nuclear transport dysfunction meditates abnormal protein aggregation in FTD and ALS

TDP-43
FUS
C9ORF72
HNRNPA1
HNRNPA2B1
VCP
ATXN2

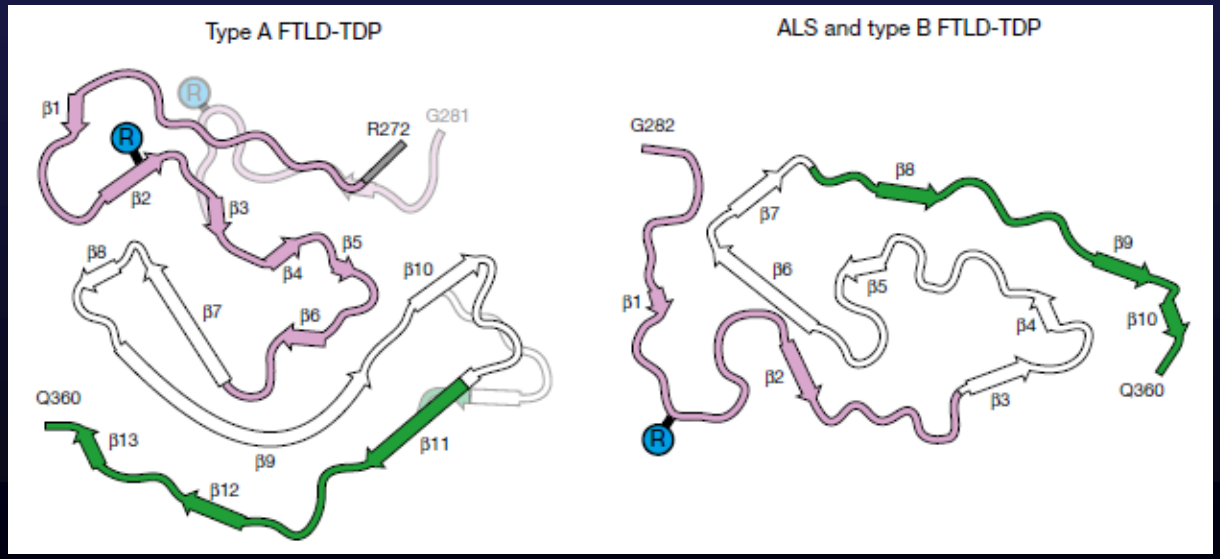
TIA1



From Jacocic et al, J Neurochem 2016

Amyloid filaments in FTLD & ALS

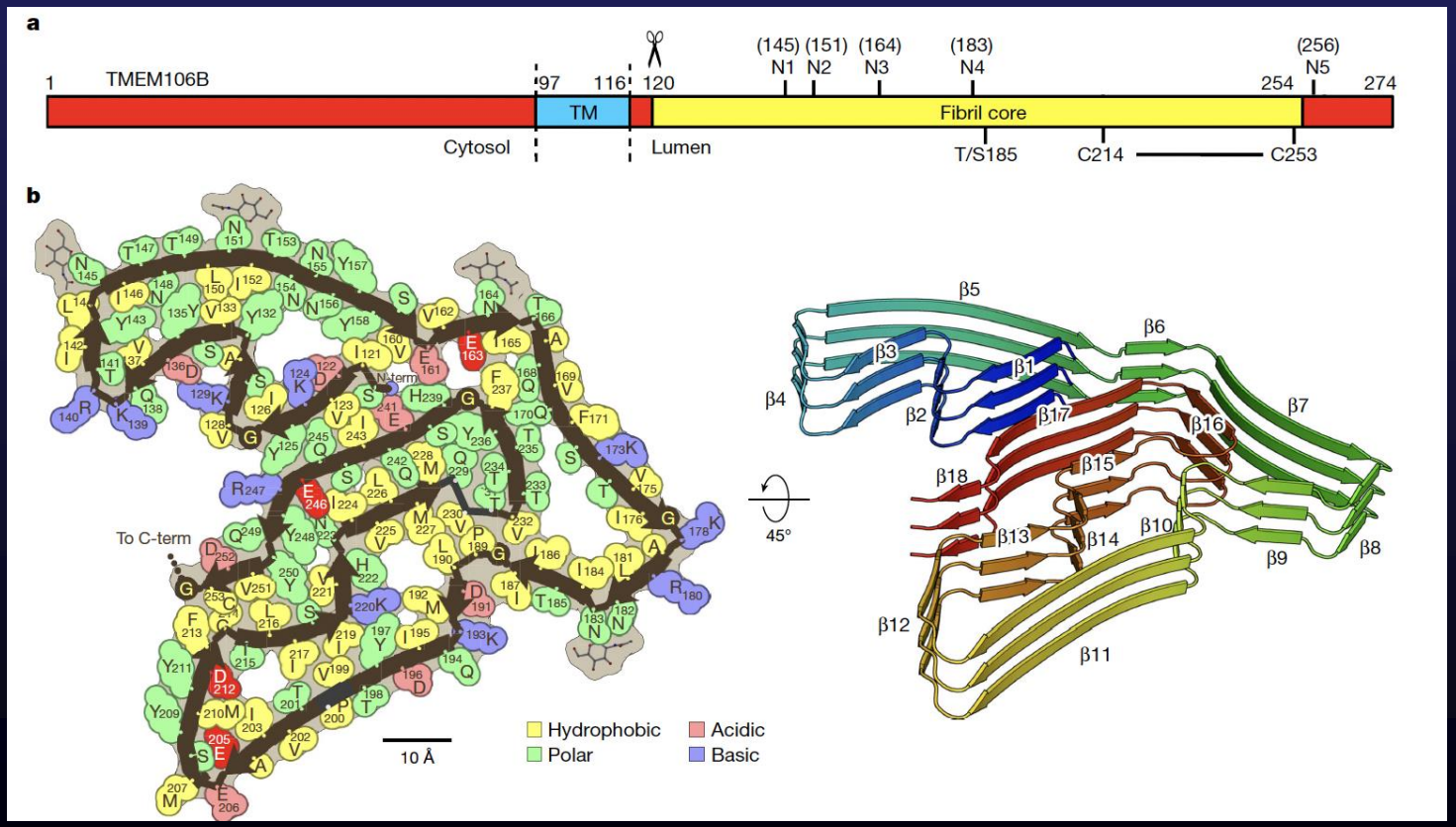
- TDP-43 pathology characterizes >90% of ALS and ~50% of FTLD
- Amyloid filaments are found in both FTLD-TDP type A and Type B with distinct fold patterns



From Arseni et al, Nature 2022; Arseni et al, Nature 2023

Amyloid fibrils in FTLD-TDP are composed of TMEM106B

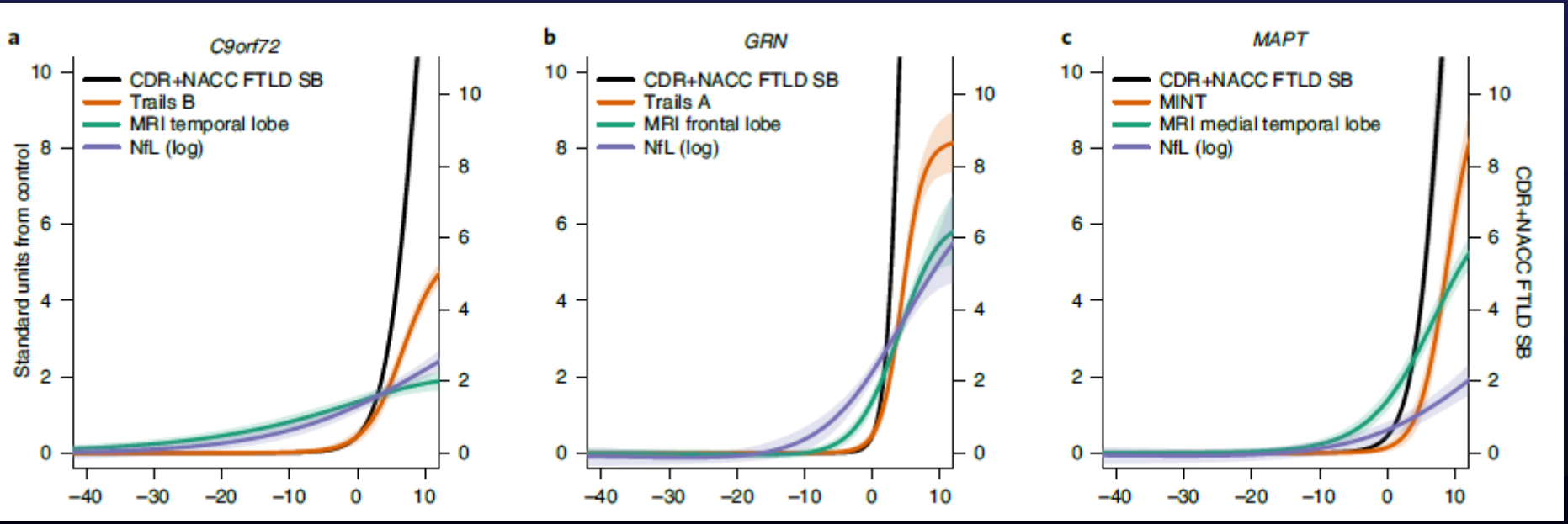
- Amyloid fibrils in FTLD-TDP are made up of a 135-residue carboxy-terminal fragment of transmembrane protein 106B (TMEM106B), a lysosomal membrane protein



From Jiang et al, Nature 2022

Fluid Biomarkers in FTD

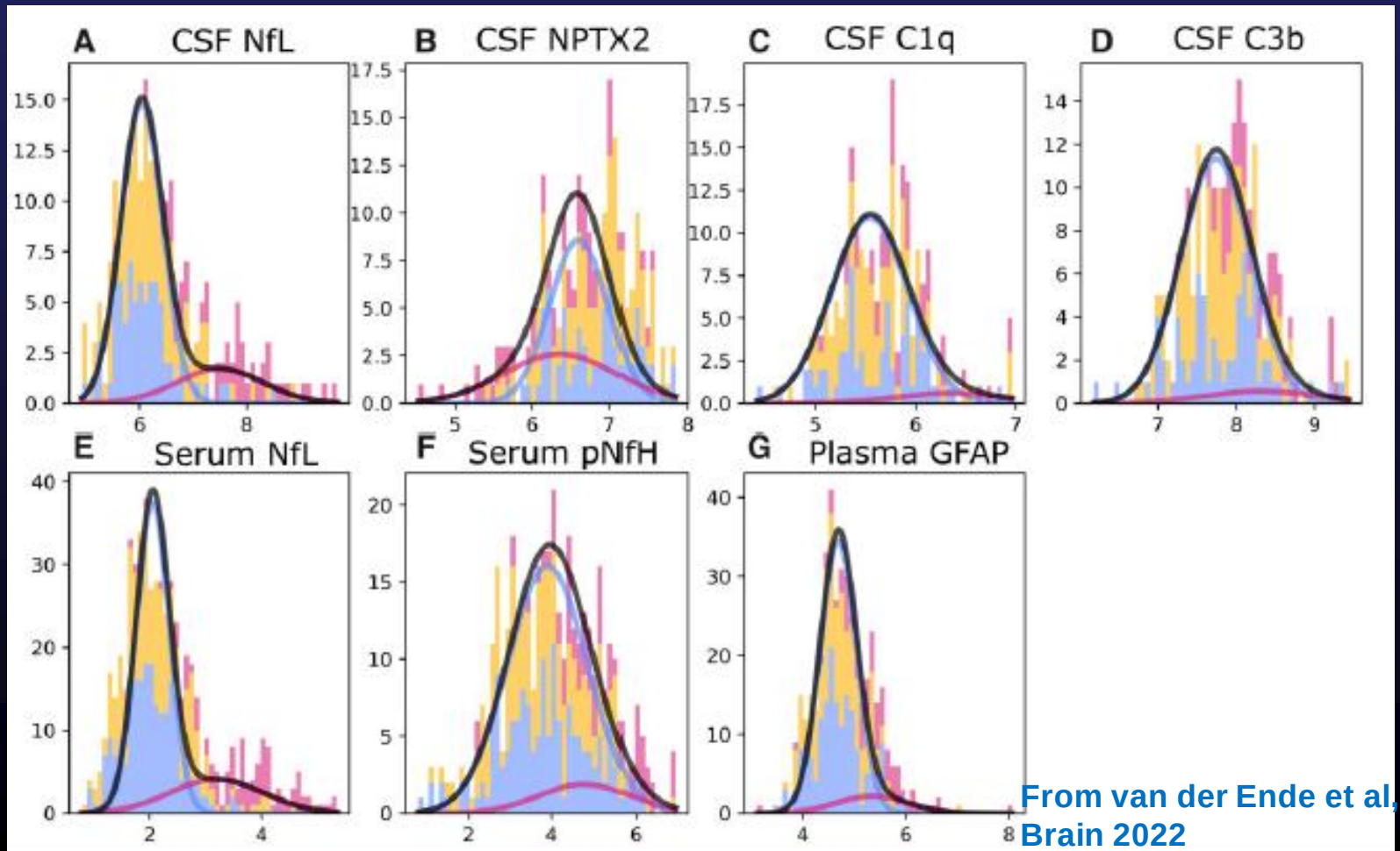
- CSF NfL rises 20 years before symptoms onset in *C9orf72* carriers, and 10-15 yrs in *GRN* & *MAPT* carriers
- Difference between different genes



From Staffaroni et al, Nat Med 2022

Fluid Biomarkers in FTD

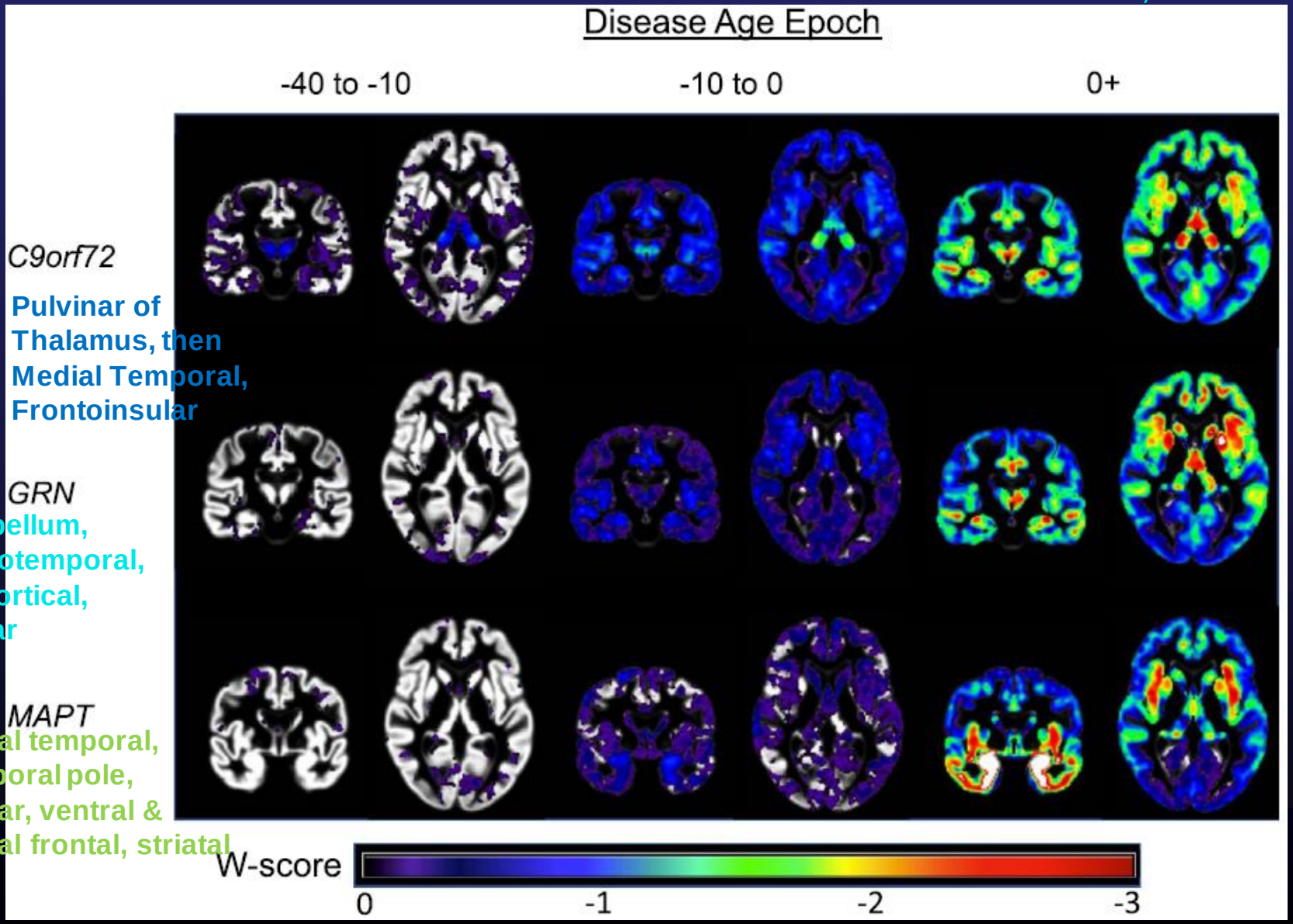
- CSF NPTX2 was the first detected to be abnormal in carriers, then NfL, then others



From van der Ende et al, Brain 2022

Brain Atrophy in FTD

From Staffaroni et al, Nat Med 2022



Clinical Presentations

Behavioural Variant FTD

- Present with early behavioural changes and Executive Deficits

Non-fluent Variant FTD (PPA)

- Progressive deficits in speech, grammar, and word output

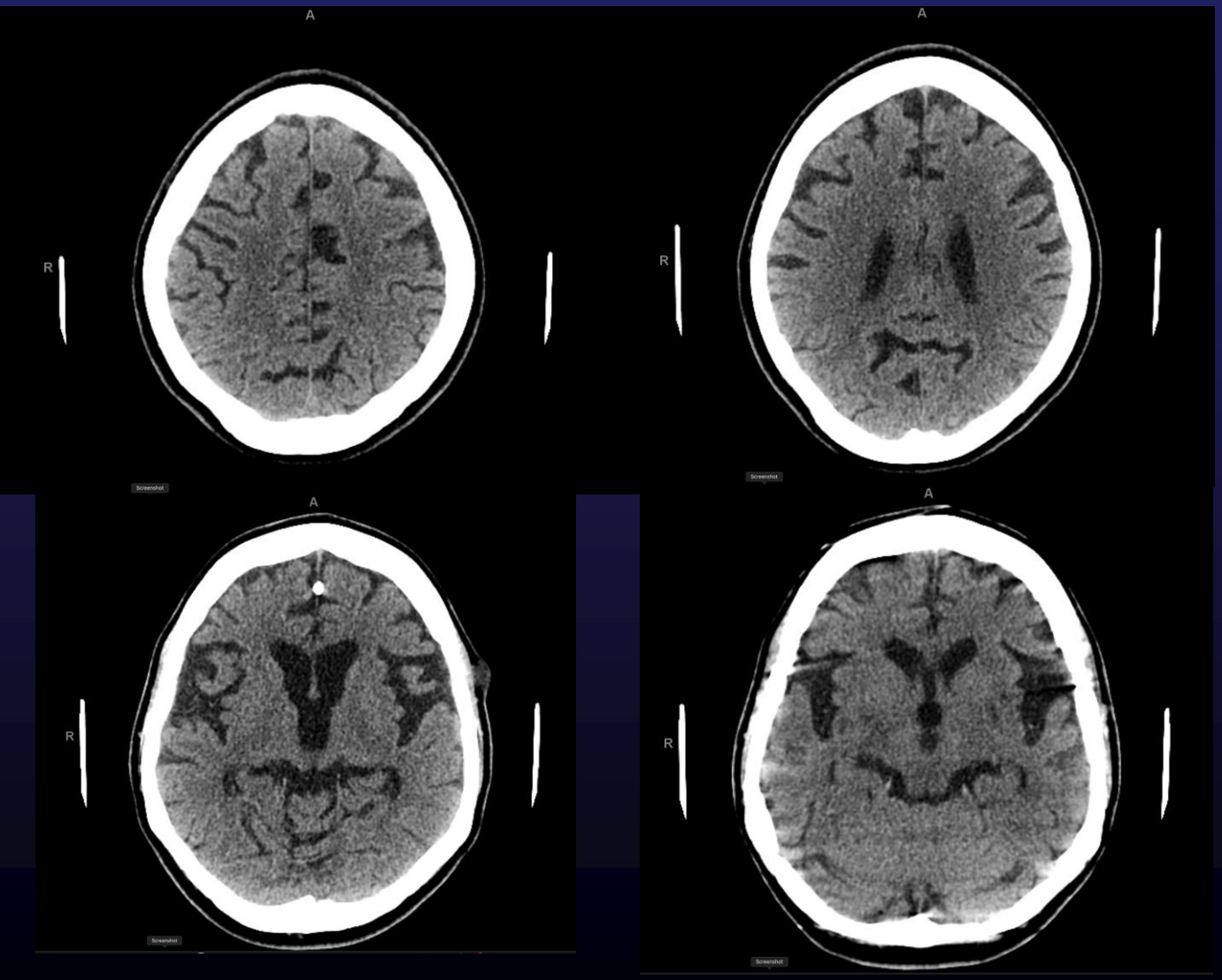
Semantic Variant FTD (PPA)

- Progressive loss of semantic knowledge, naming,

Case study 1

- 72 y.o. retired nurse with behavioural change X 2 years
- MOCA 24 (-1 trail, -1 digit span backward, -2 serial 7, -1 similarities, -1 recall)

Case study 1



- Subtle frontal sulci wider than parietal region

bvFTD Criteria (Rascovsky 2011)

Possible (3/6):

A. Behavioural Disturbance (social inappropriate, loss of manner/decorum, or impulsiveness/ rash/ careless actions)
B. Early Apathy or Inertia
C. Loss of Sympathy or Empathy
D. Early Perseverative, stereotyped, or compulsive/ritualistic behaviour
E. Dietary change (food fads, binging, or hyperorality)
F. Neuropsych profile (all 3 criteria in F must be fulfilled)
    1. Deficits in executive tasks
    2. Relative sparing of episodic memory
    3. Relative sparing of visuospatial skills

Probable: above + functional decline + Imaging (focal atrophy or hypometabolism)

Definite: Biopsy or Autopsy results (tauopathy, TDPopathy, FUSopathy)

DDx of bv-FTD

- Frontal Variant of AD
- Other diseases with frontal lobe lesions
- Psychiatric: Mood disorder, Delusional disorder, personality disorder, Asperger's syndrome, "FTD phenocopy", or slowly progressive form of FTD
- R/O others: B12, VDRL, HIV, TSH, LFT, renal, for atypical – CSF, autoimmune panel
- Brain scan: MRI, SPECT, FDG-PET

Treatment of bvFTD

Unfortunately only symptomatic

1. ChEIs do not work, and only borderline evidence for memantine
2. SSRI – weak RCT / open label studies
- Paroxetine, Sertraline, Trazodone, Fluvoxamine, Citalopram, moclobemide
3. Aggression – atypical antipsychotics, Beta-blockers
4. Dextroamphetamine – some improvements on NPI

Counselling for patients, caregivers, provide support:
http://lifeandminds.ca/whendementiaisinthehouse/index.html

Primary Progressive Aphasia

(Mesulam, Ann Neuro 2001)

- Main clinical feature is difficulty with language.
- Deficits are the principal cause of impaired daily living activities.
- Aphasia is the most prominent deficit at onset
- 3 Subtypes

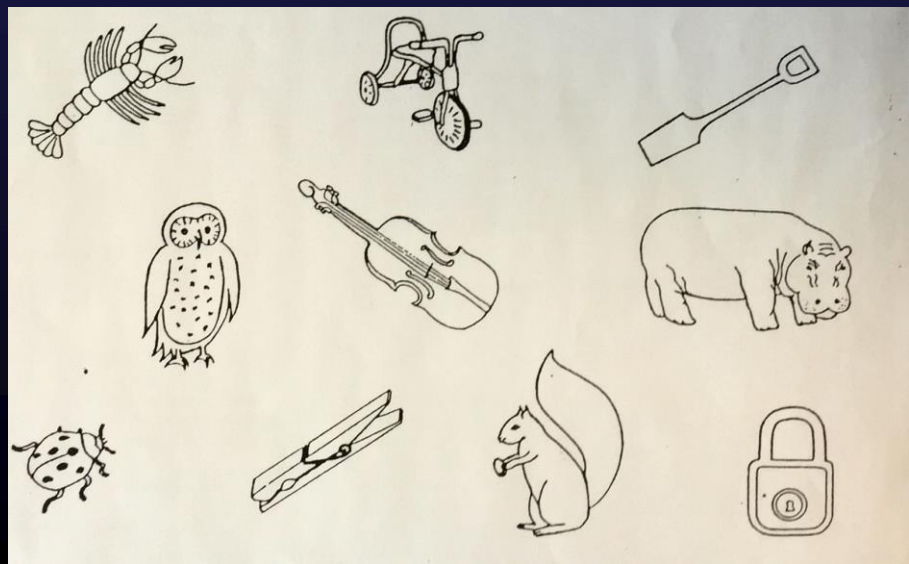
1. Progressive Non-Fluent Aphasia (PNFA), a.k.a. non-fluent, agrammatic or dysfluent variant of PPA (nfvPPA),
2. Semantic Dementia (SD), a.k.a. semantic variant of PPA (svPPA), or fluent variant of PPA
3. Logopenic Progressive Aphasia (LPA), a.k.a. Logopenic aphasia, or logopenic variant of PPA (lvPPA)
4. ? Progressive Apraxia of Speech

PPA – Summary of Features

	PNFA	SD	LPA
Fluency	Severely impaired, effortful, halting speech	Not impaired	Mildly impaired, slow but intact syntax
Grammar/Syntax	++ errors & simplification	Generally normal	OK for simple, impaired for complex sentences
Confrontational naming/word retrieval	Preserved in the early phase (verbs > nouns)	Severely impaired (nouns > verbs)	Impaired single word retrieval
Repetition	Impaired	Preserved	Single word OK, impaired phrase or sentences
Comprehension	Impaired syntactic comprehension, spared word comprehension	Severely impaired (nouns)	Spared single word comprehension, impaired sentence comprehension
Dyslexia	Phonological	Surface	Phonological

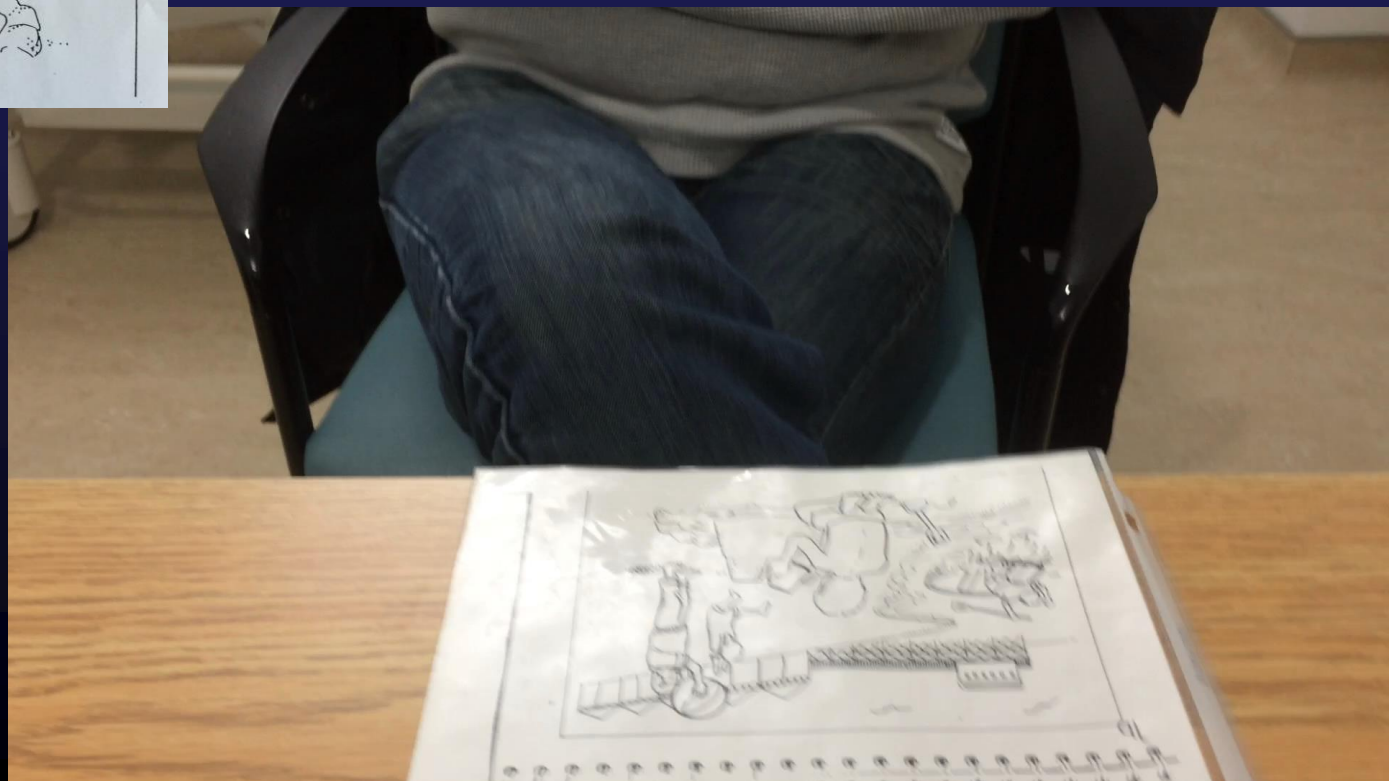
Case study 2

- 54 y.o. photographer with increasing difficulty getting sentences out, comprehension still quite normal
- MOCA 25 (-2 repeat sentences, -2 recall, -2 date)
- Speech quite hesitant
- Picture naming 9/10



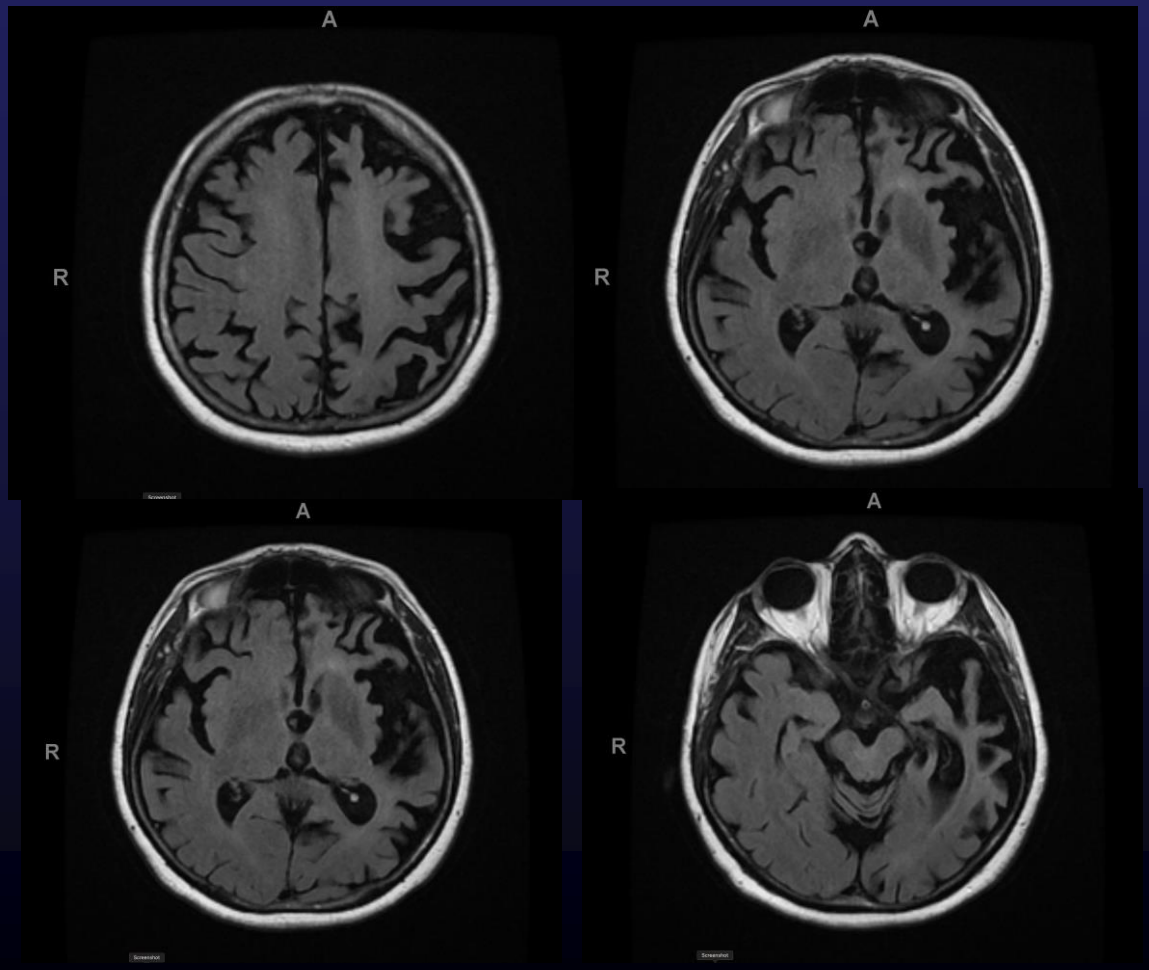
Case study 2

It's boat .. and um… yep…
And um… yep… yep… yep… yep
So it's … a… kids… ball…here
It's a… yep … yep … it's … a … sand



Case study 2

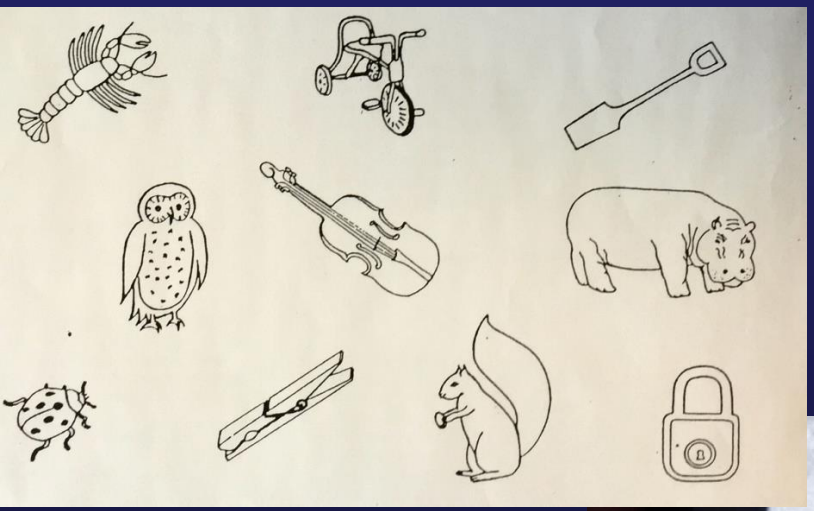
- Dominant frontal lobe atrophy (example not this case



Case study 3

- 71 y.o. realtor noticed difficulty remembering clients' names x 2 yrs, even though she recognizes them well
- Then started to have difficulty naming objects
- MOCA 24 (-3 naming animals, -3 delayed recall)
- Spontaneous speech is fluent

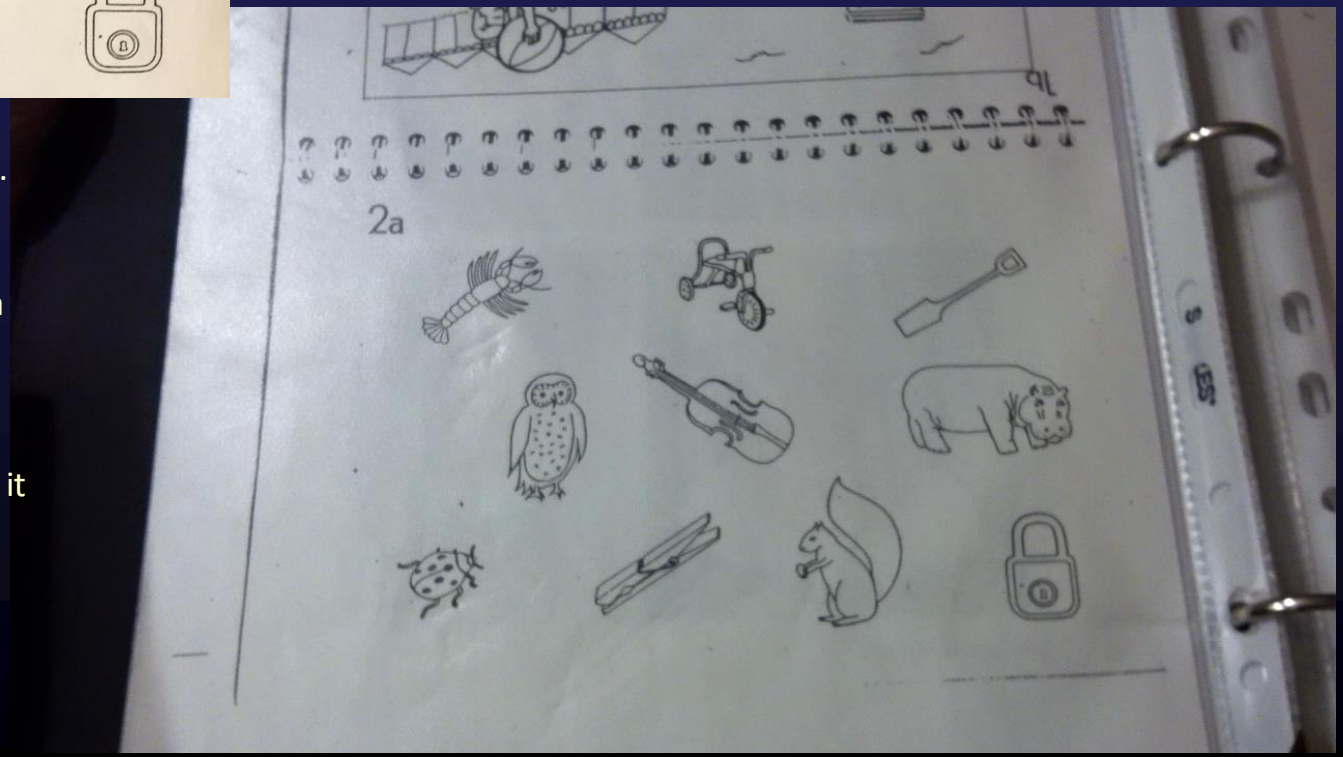
Case study 3



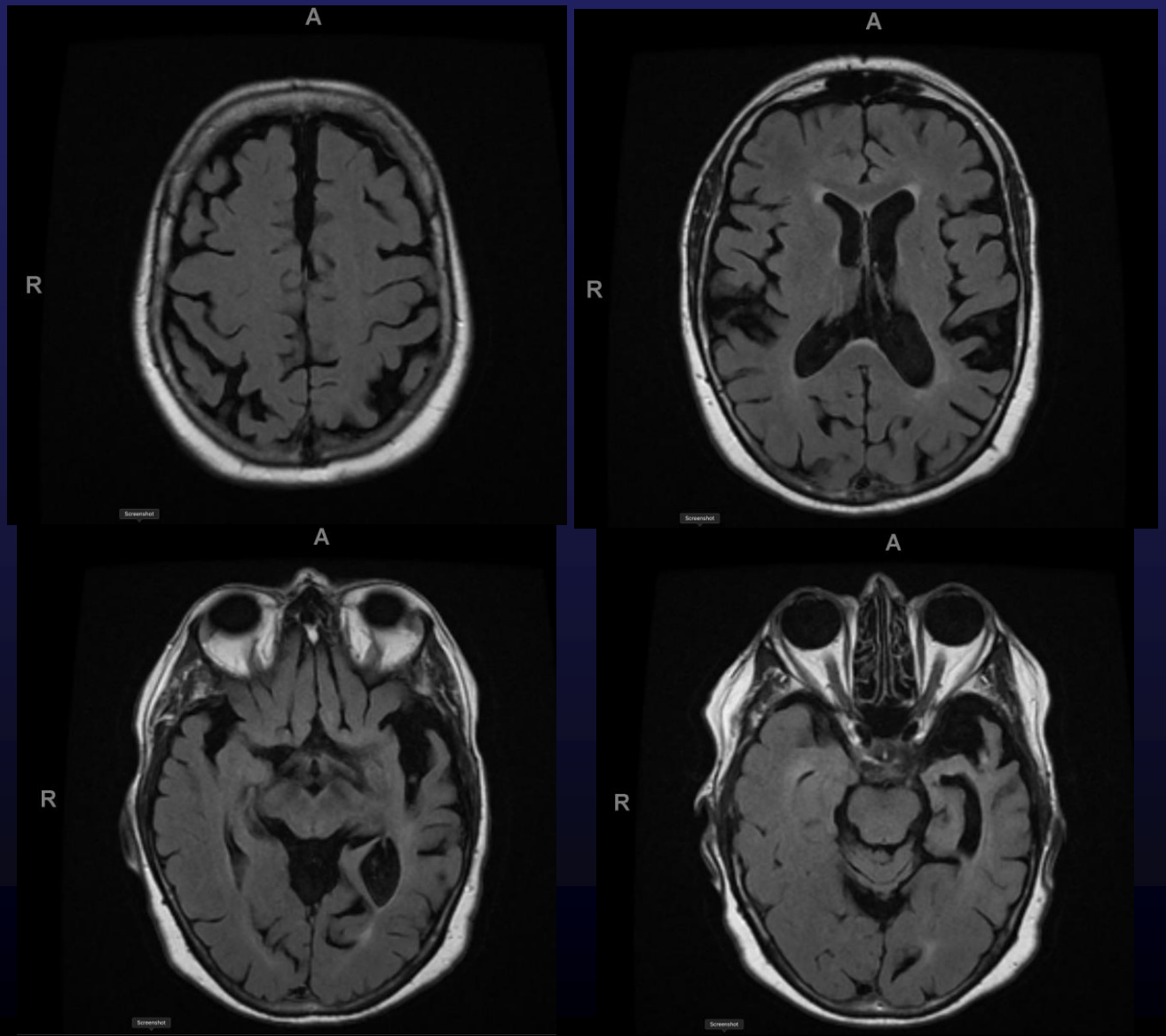
They are ones that are in the water, and I don't know what the names is, but they move around, and all that kind of stuff, and uh they eat stuff.
This one is something you go on when you're… you can drive by your foot …you move different places… and so on.
This one is where you dug, where you can dug into, like that guy did that … well … whatever. … er…oh…
This is an animal that also flies, and I don't know the name, but it's a very special system, and it's usually very pretty, something nice to see, and so on.

This is what you can make fantastic … um… what… how do you say it… noise… well that's not really what it is… but it's when you make "da da da da…"…
And all that kind of stuff… yeah…

And you can make music with it, and it has a name, but I don't know …



Case study 3



Surface Dyslexia

- Difficulty with whole word recognition and spelling, especially when the words have irregular spelling-sound correspondences

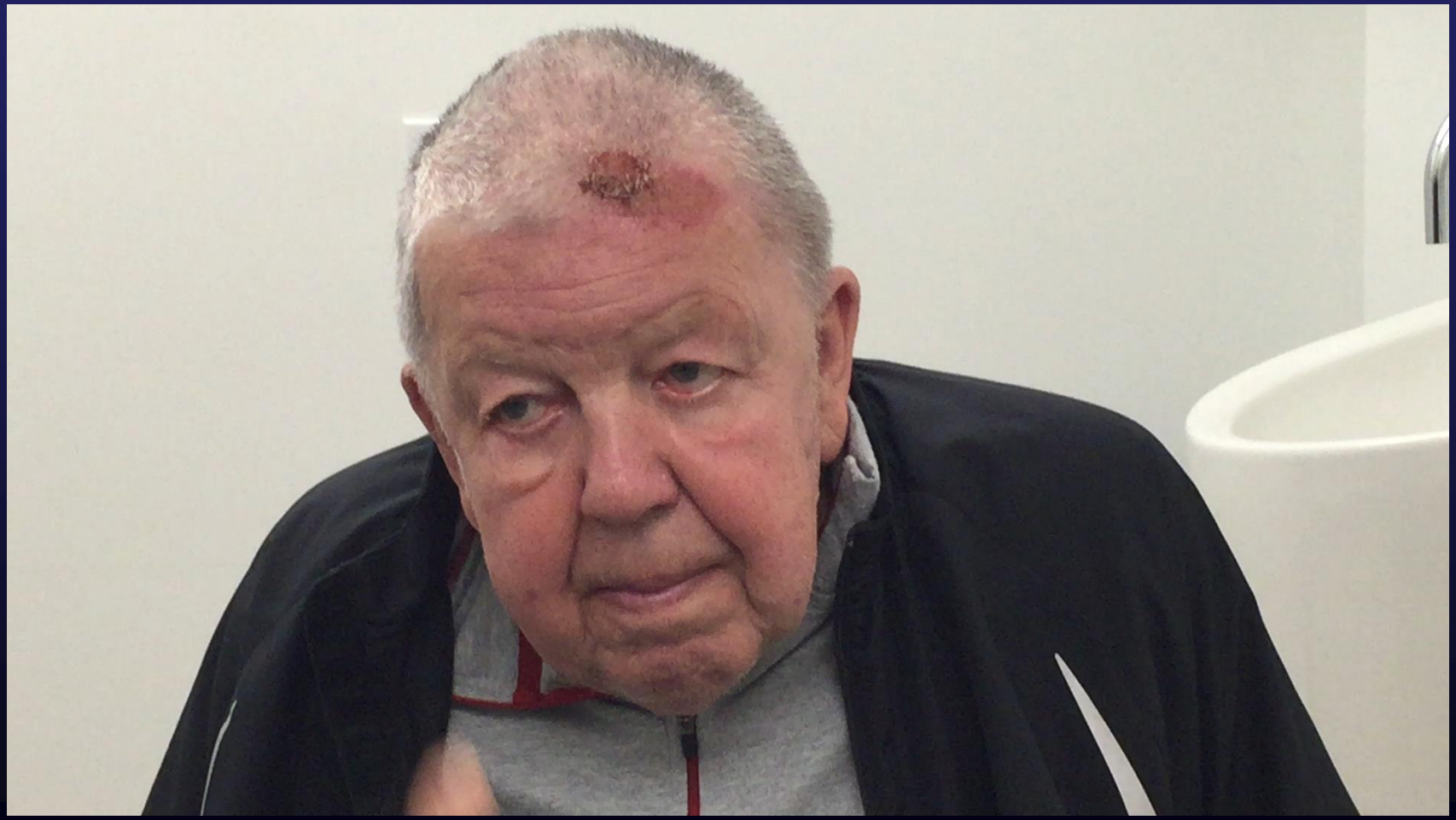
- Test: Read irregular words that do not sound like their phonological spelling

E.g. Island, yacht, chaos, colonel, sergeant

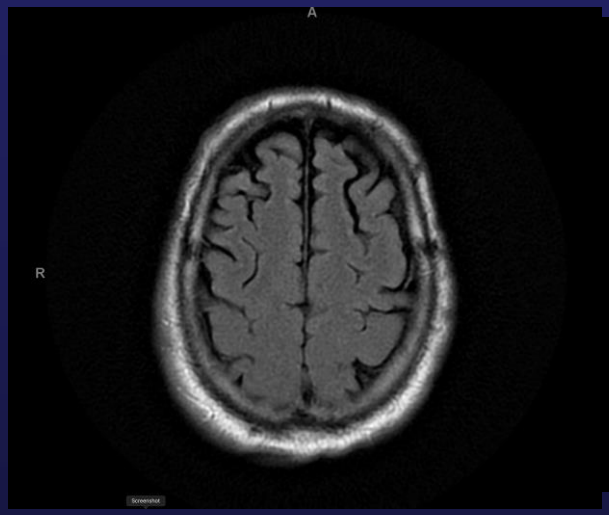
Case study 4

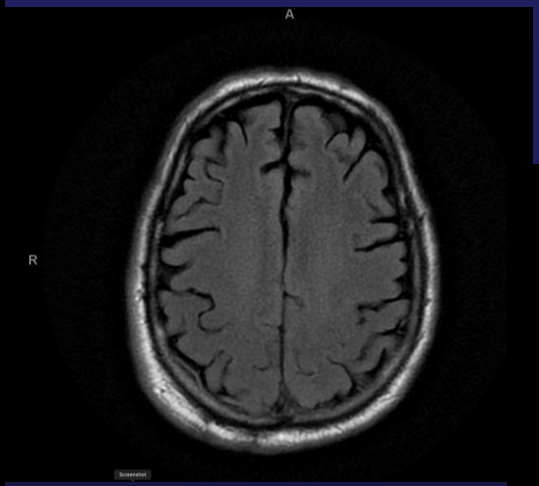
- 66 y.o. man with subtle memory difficulties, not getting his words out, and family noticed worsening temper, anger outbursts
- Speech ”stumbling”, sometimes stop in the middle of a sentence and cannot complete his thoughts
- MOCA 22 (-1 trail, -1 clock, -1 digit forward, -2 serial 7, -2 delayed recall, -1 date)
- P/E unsteady gait, fell 3X last 3 months

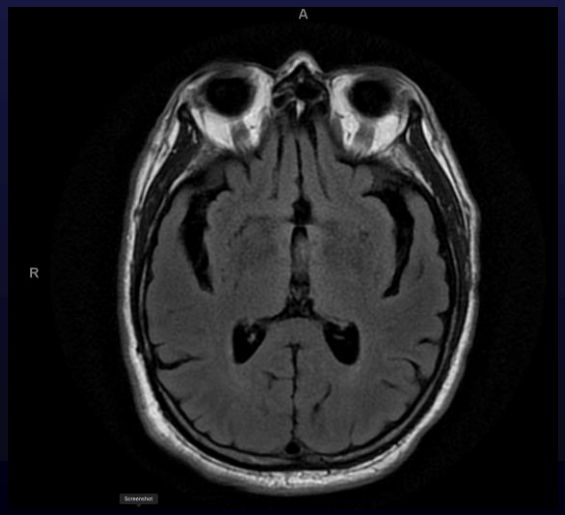
Case study 4

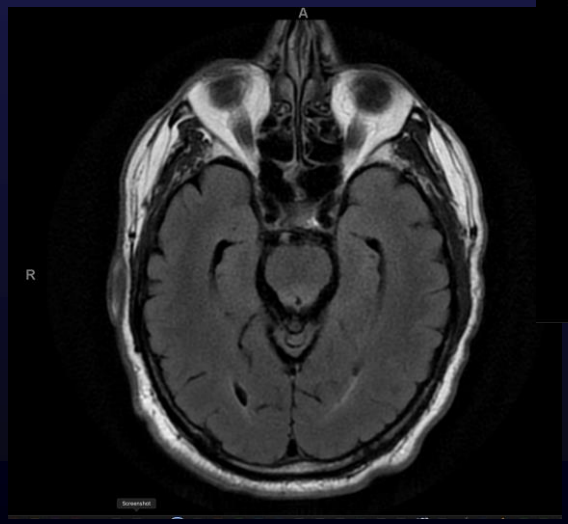


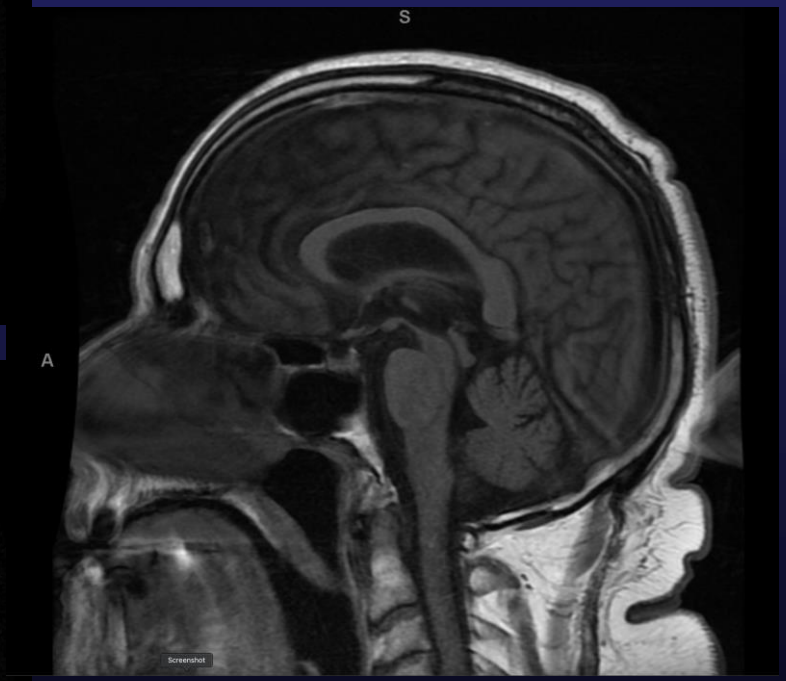
Case study 4











Progressive Supranuclear Palsy

Mandatory: sporadic, > 40, gradual progression

Exclusionary: any symptoms consistent with other disease (e.g. AD, MSA, DLB, encephalitis, ataxia, NPH, stroke, HD, NPC, PD, etc…)

4 functional domains:

1. Oculomotor Dysfucntion
2. Postural Instability
3. Akinesia
4. Cognitive Dysfunction

Updated criteria from Hoglinger et al, Mov Dis 2017

Progressive Supranuclear Palsy

TABLE 2. Core clinical features

	Functional Domain			
Levels of Certainty	Ocular Motor Dysfunction	Postural Instability	Akinesia	Cognitive Dysfunction
Level 1	**O1:** Vertical supranuclear gaze palsy	**P1:** Repeated unprovoked falls within 3 years	**A1:** Progressive gait freezing within 3 years	**C1:** Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	**O2:** Slow velocity of vertical saccades	**P2:** Tendency to fall on the pull-test within 3 years	**A2:** Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2:** Frontal cognitive/behavioral presentation
Level 3	**O3:** Frequent macro square wave jerks or "eyelid opening apraxia"	**P3:** More than two steps backward on the pull-test within 3 years	**A3:** Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	**C3:** Corticobasal syndrome

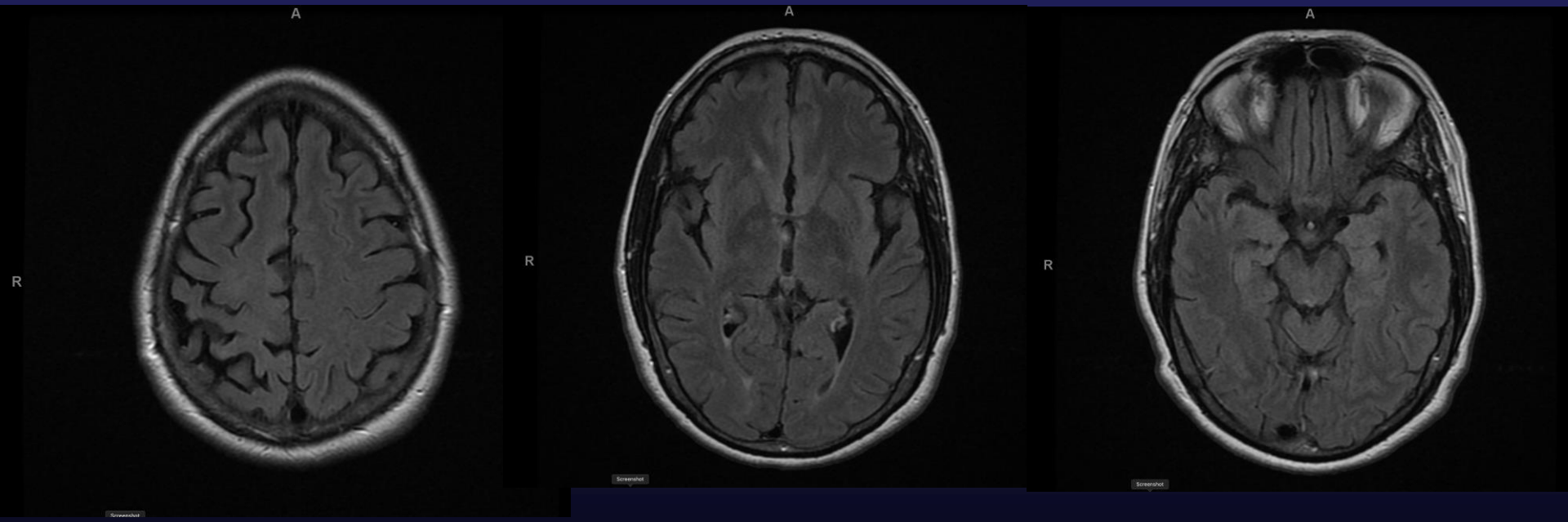
Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in Table 4.

Hoglinger et al, Mov Dis 2017

Case study 5

- 61 y.o. right handed lady developed “stiffness” and clumsiness in left hand X 1 yr
- Initial MOCA 26/30 (-1 cube, -1 clock, -2 serial 7)
- Exam: left hand rigidity/increase tone, dystonic posturing, decreased rapid alternating movement

Case study 5



Corticobasal Degeneration (CBD) (syndrome - CBS)

5 phenotypes	Features
Probable CBS	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible CBS	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal Behavioural-Spatial Syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
nfvPPA	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
PSP Syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Armstrong et al, Neurology 2013

New treatment being tested

- Monoclonal Ab against sortilin receptor (Alector)
- AAV9-based gene therapy to replace progranulin (Prevail)
- AAV1-vector delivery of GRN into brain (PassageBio)
- Orally available Progranulin (Denali)
- Orally active agent to increase progranulin (Arkuda)
- ASO against C9orf72 (Wave)
- ASO against tau (Eisai)

Summary

1. FTD syndromes are complex, but have recognizable phenotypes (although they may overlap)
2. Pathological causes of FTLD are heterogeneous
3. Genetic mutations predict underlying pathology
4. Imaging may help with diagnosis
5. Emerging fluid biomarkers may be helpful?
6. Current management is symptomatic
7. Disease modifying therapy are being tested