Frontotemporal Dementias

A Complex Multi-Syndrome Family of Neurodegenerative Disorders:

Many Questions, Few Answers

Clinical Phenotypes, Neuropathology & Mechanisms for Our Largest Umbrella Concept in Neurodegenerative Disorders

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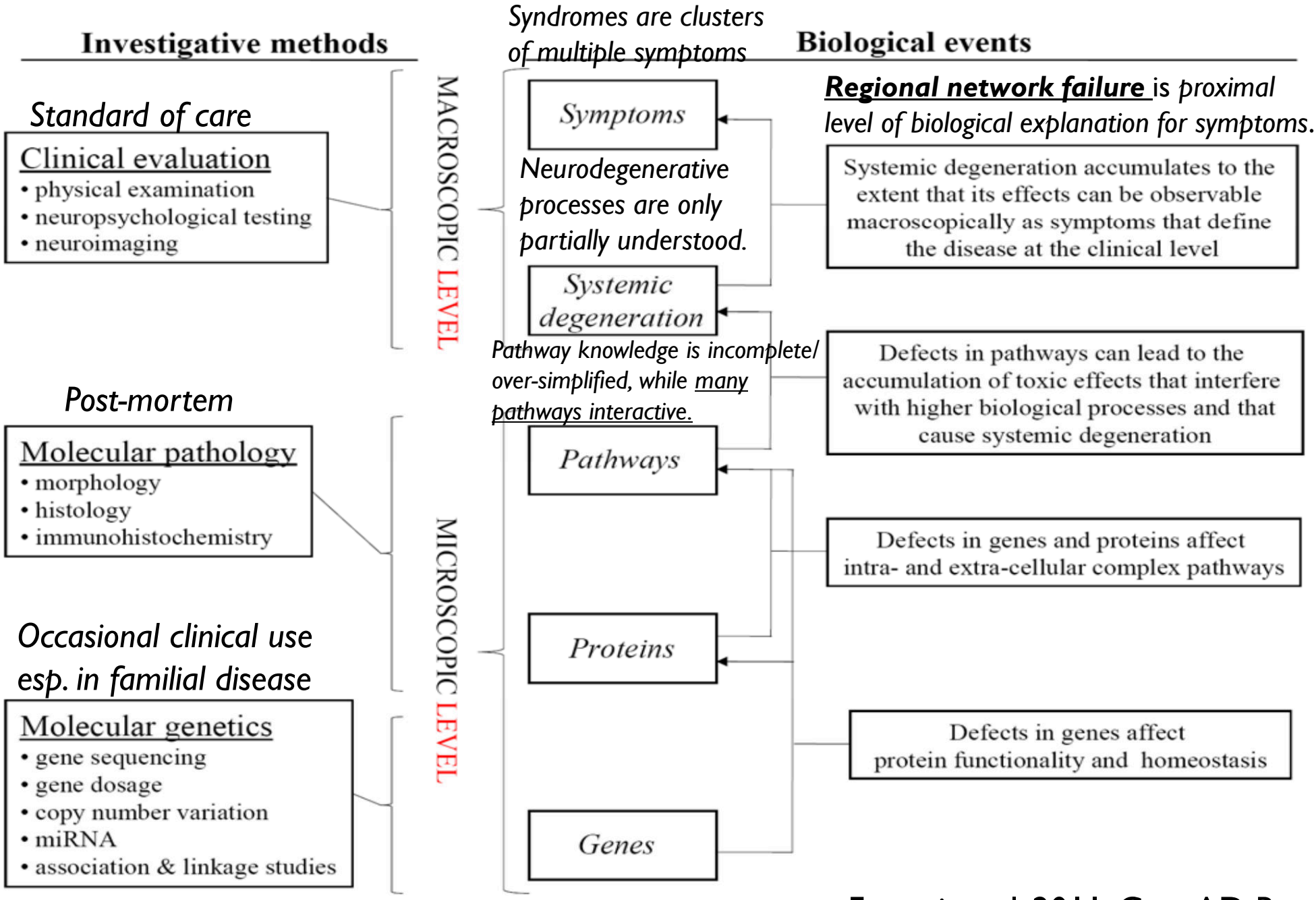
History and evolution of FTD/ FTLD-ALS categories

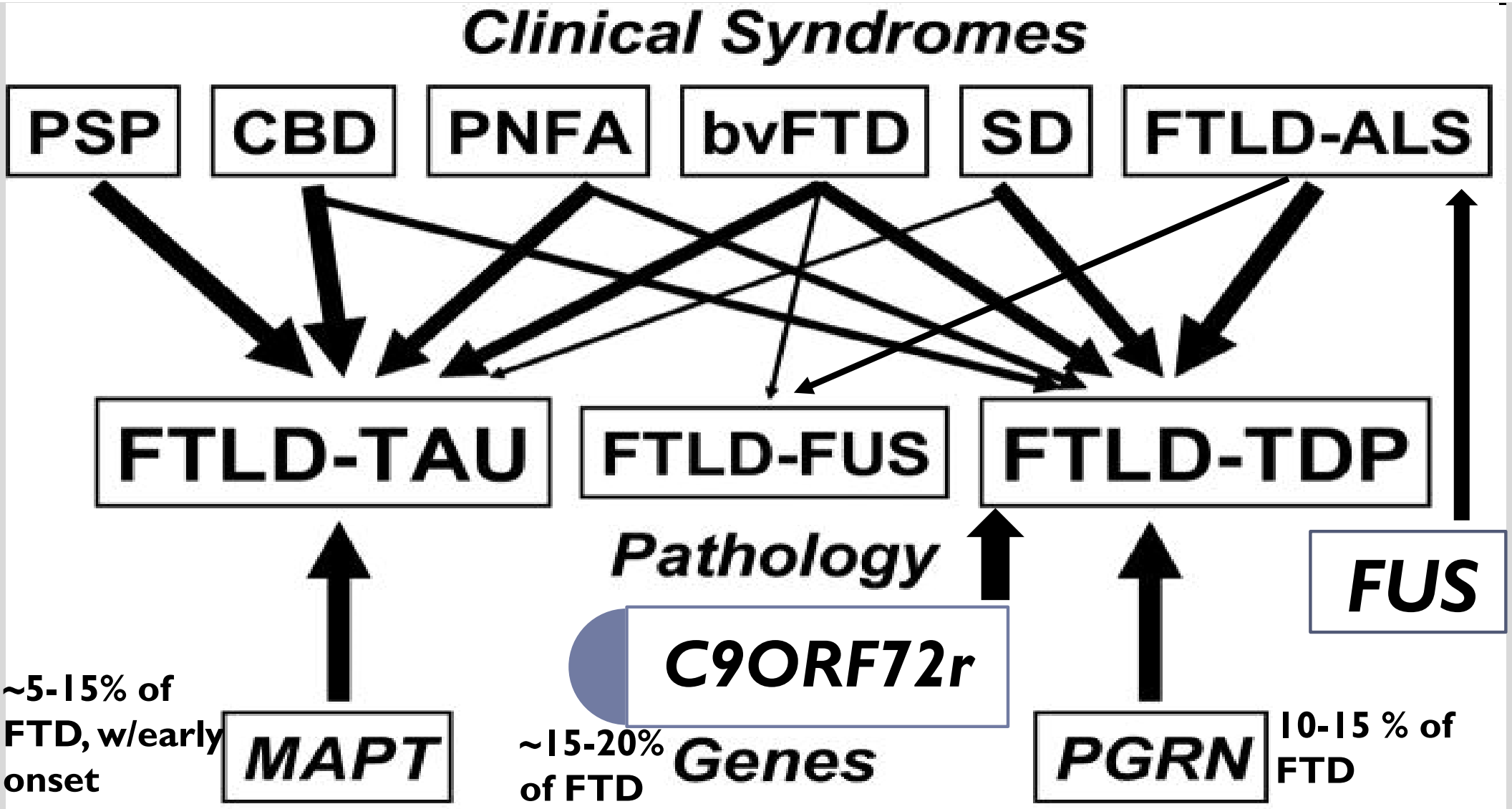
- 130 years ago (1892), Czech neuropsychiatrist Arnold Pick described a dementing disorder ***14 years before AD*** – both pathologically and clinically distinct, showing ***behavioral and language deficits not amnesia***, with balloon-like neuronal inclusions described by AloisAlz 1911 ('Pick's bodies').
- Pick's disease→Pick dementia complex→frontotemporal lobar degeneration.
- Imaging work confirmed frontotemporal versus classic medial temporal atrophy of AD. By 1990s, category of FTD included 2 basic histopathologies: *tau positive or ubiquitin-positive inclusions* (~10% cases WDH). Placeholders?
- In 2006, Newmann et al. described TAR DNA-binding protein-43 as primary ubiquitinated aggregate in FTD, also found in ***95% of ALS***. Huge finding!
- Additional finding of 'fused-in sarcoma' protein (~10% of cases) described in 2009 in cases previously WDH (w/out distinctive histopathology).
- ***FTD and ALS seen as pure subtypes on a complex continuum***, but with many questions about what might create such phenotypic complexity.

Levels of Analysis and Clinical Evaluation

(with clarifications and caveats in italics)

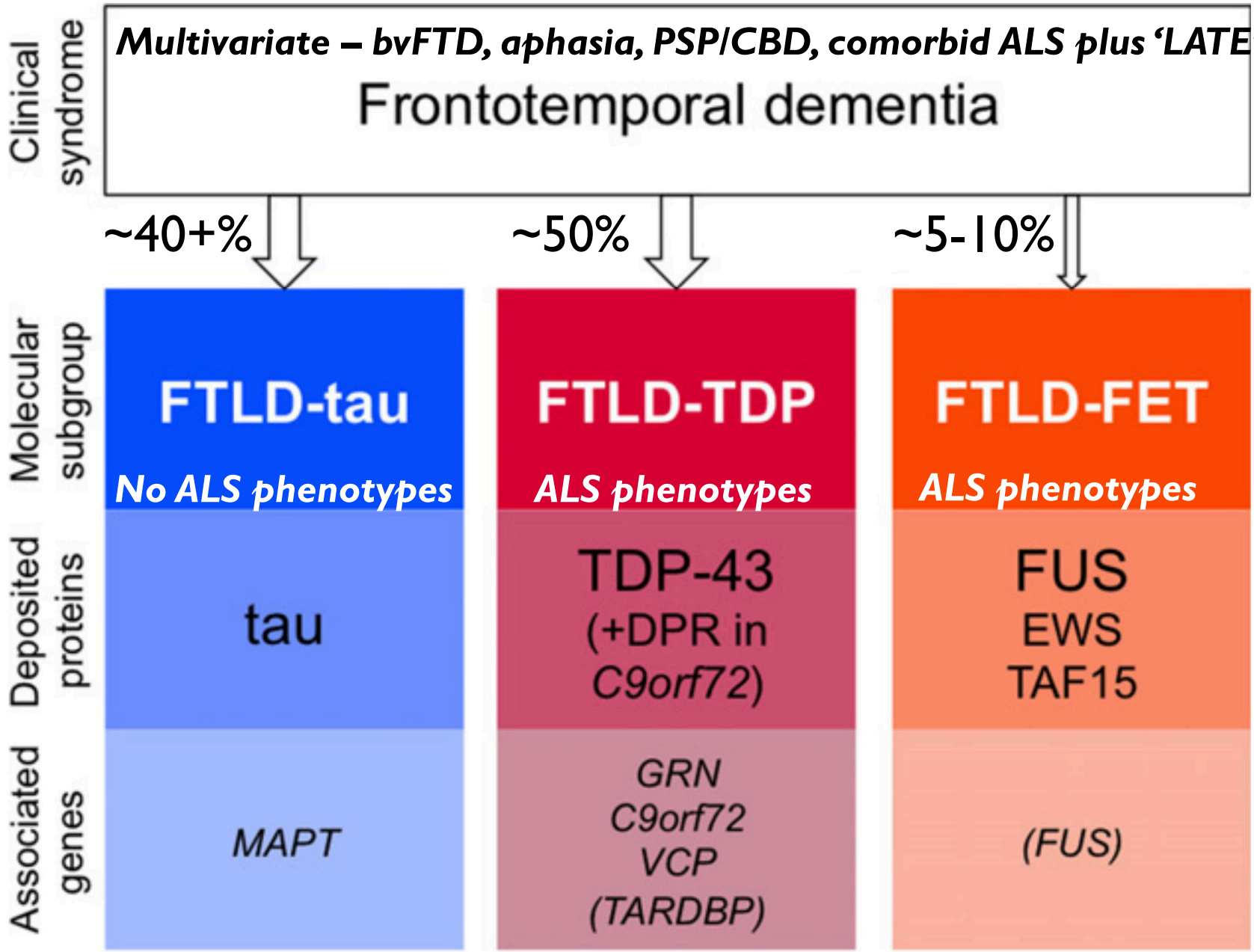


Ferrari et al, 2011, Curr AD Res



Clinical, pathologic & genetic spectrum of frontotemporal lobar degeneration (FTLD). Syndromes (top row), pathologic subtypes (middle) & genes (bottom row). **bvFTD** = behavioral-variant frontotemporal dementia; **CBD** = corticobasal degeneration; **FTLD-ALS** = FTLD w/amyotrophic lateral sclerosis; **FTLD-Tau** = FTLD with tau-positive inclusions; **FTLD-FUS** = FTLD w/fused in sarcoma (FUS)-positive inclusions; **FTLD-TDP** = FTLD w/TAR DNA-binding protein 43-positive inclusions; ***MAPT*** = microtubule-associated protein tau; ***PGRN*** = progranulin; **PNFA** = progressive non-fluent aphasia; **PSP** = progressive supranuclear palsy; **SD** = semantic dementia. **C9orf72** – chromosome 9 open reading frame repeats. ***Genetic mutations in ~35-50% of all FTD cases, making this most genetically loaded NDD.***

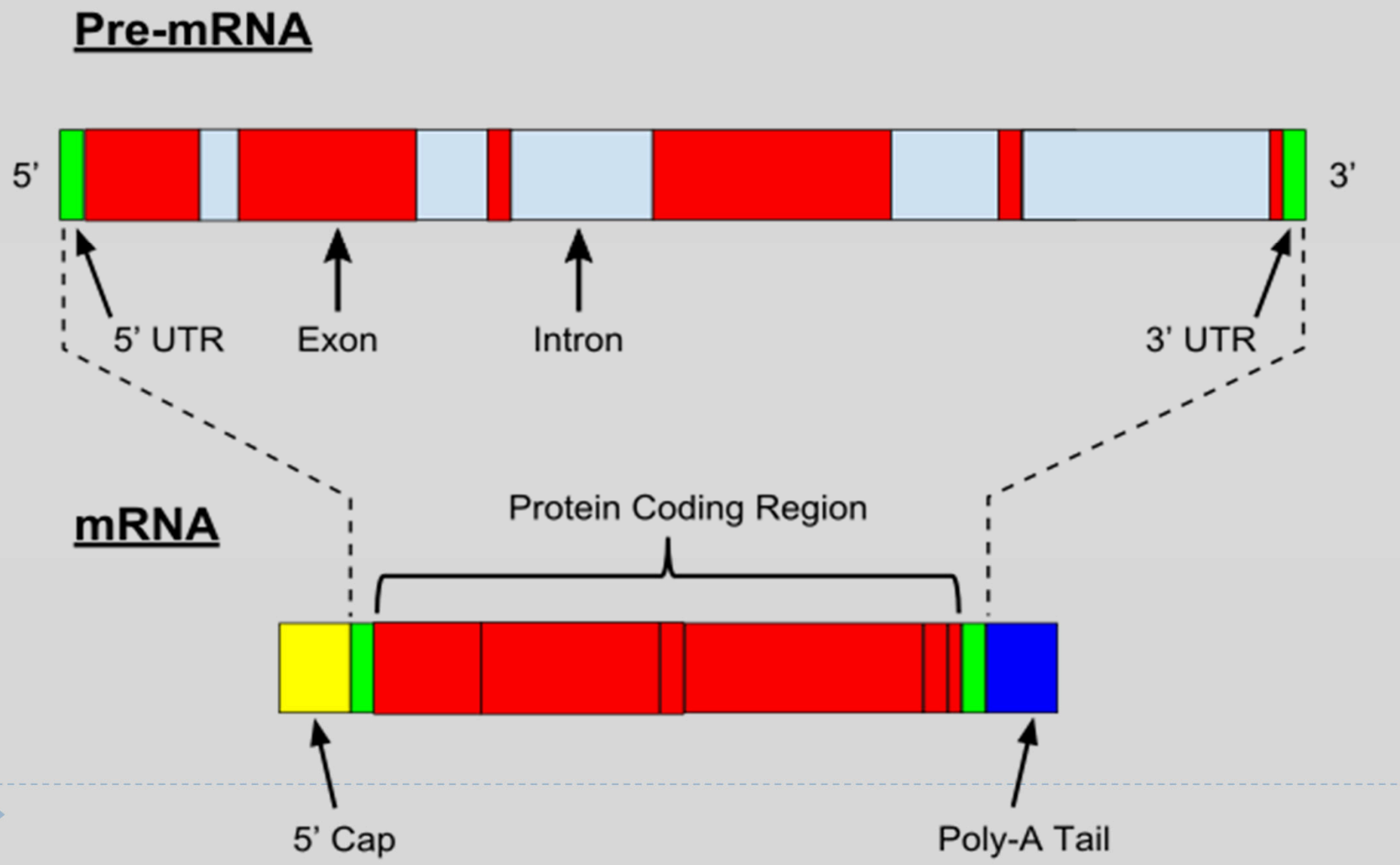
Updated typology with latest correlations



Haase & Neumann 2016

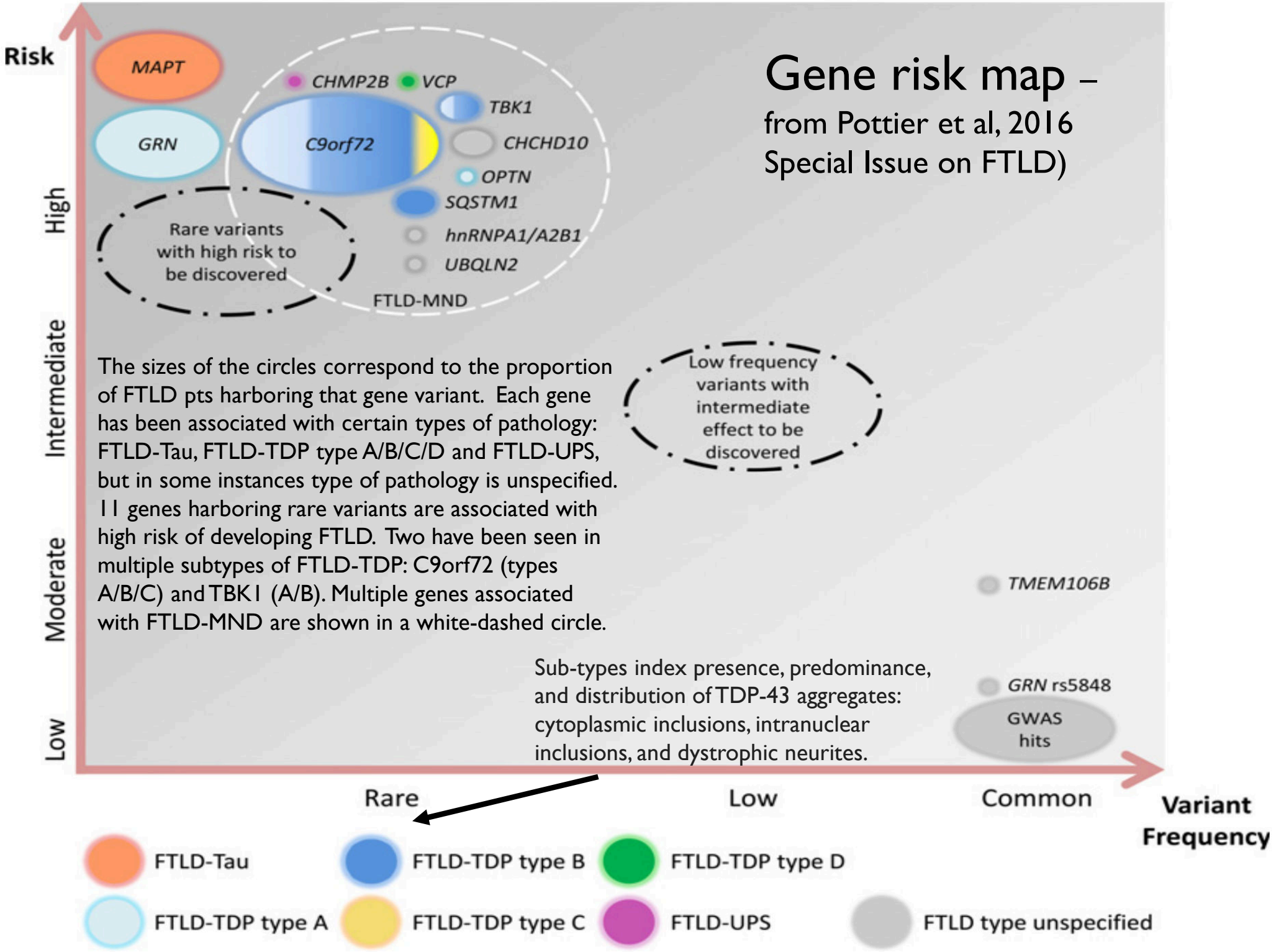
Maturation of RNA via binding protein effects – removes introns → different protein isoforms

Introns are not 'junk' but provide basis for alternative splicing and thus many isoforms of a particular protein from just one gene.

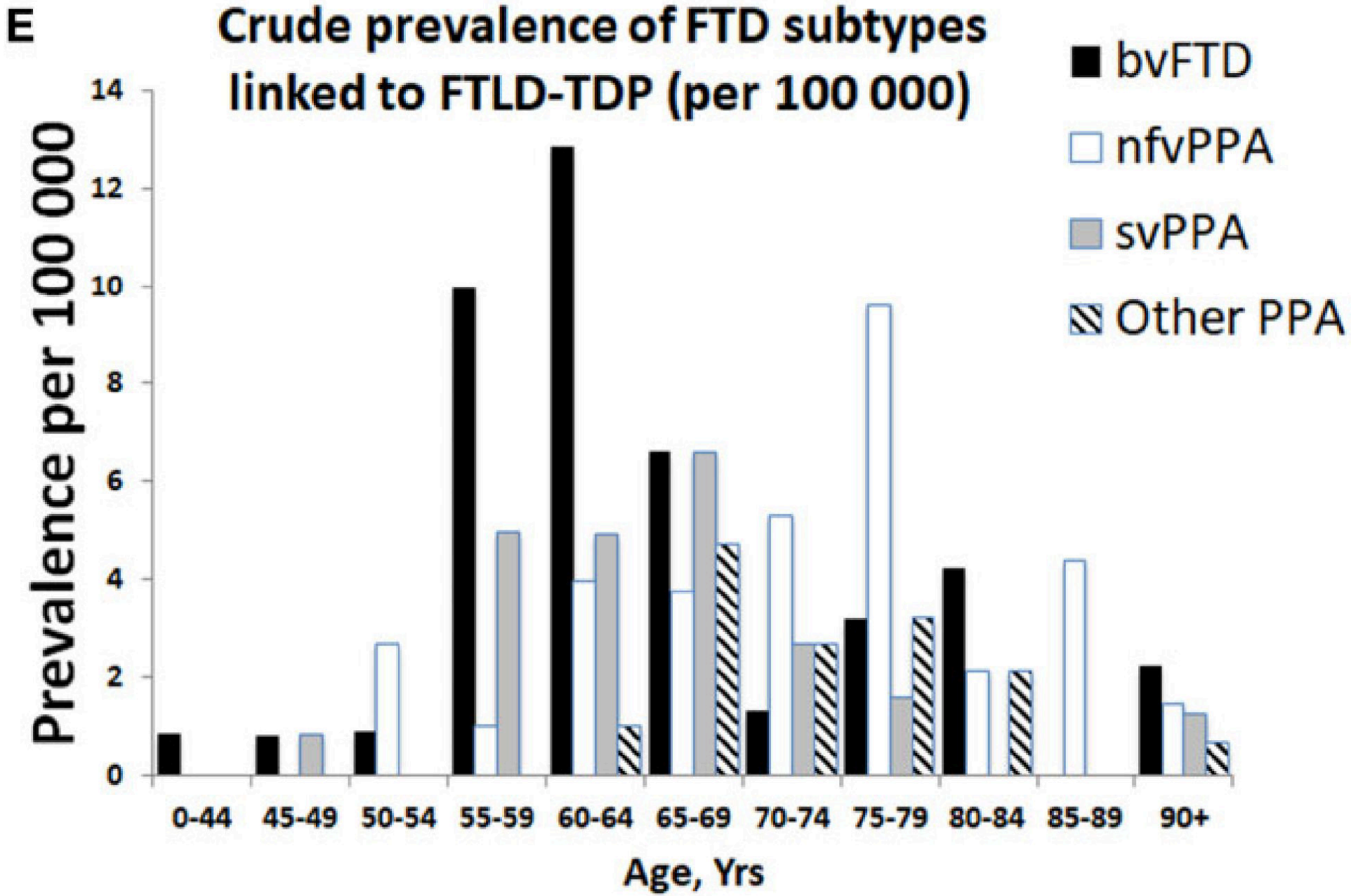


Challenging Heterogeneity of FTLDs: a confusing/frustrating wastebasket?

- From nosological standpoint, ***largest 'clumping' of neurodegenerative disorders ever***, uniting Pick's disease (behavioral variant), primary aphasias, & Parkinsonian syndromes (PSP/CBD), ***&*** ALS, under single umbrella. Clues:
  - 1) Discovery of ***common neuropathologies*** across phenotypes, w/shared mutations.
  - 2) '***Phenotypic dedifferentiation:*** ~10-20% of ALS cases → FTLD, but ~50% show ↓cognition. ~10-15% of patients w/FTLD eventually →ALS, but ~50+% w/subclinical pyramidal motor dysfunction (UMN and/or LMN); within FTLD, there is also 'phenotypic dedifferentiation' (initial PPA case over time develops ↑ sxns of bvFTD);
- Four common histopathologies (mutated gene): 1) ubiquitin w/ TAR-DNA binding inclusions (***progranulin/C9orf72R/VCP***); 2) tauopathy, but no plaque (***MAPT***); 3) Pick's bodies, also tauopathy; 4) fused-in sarcoma protein (***FUS***).
- Smattering of other rare mutations (VCP, FUS, TDP43, CHMP2B, SOD1, ANG).
- Each histopathological disease can present w/many clinical phenotypes, but some phenotypes are a 'more preferred' pathway for that proteinopathy.
- Most common 'bvFTD': apathy, disinhibition, ↓ insight, TOM & empathy, other personality changes, stereotypy/'hyperorality,' dysexecutive cognitive profile. Psychosis/showing a pre-existing psych dx is common, esp. in C9 mutations.
- Higher percentage than any other NND (35-45+%) show relevant mutation, either autosomal dominant/inherited or in sporadic disease (acquired).


Risk
High
Intermediate
Moderate
Low
MAPT
GRN
C9orf72
CHMP2B
VCP
TBK1
CHCHD10
OPTN
SQSTM1
hnRNPA1/A2B1
UBQLN2
FTLD-MND
Rare variants with high risk to be discovered
Gene risk map –
from Pottier et al, 2016
Special Issue on FTLD)
The sizes of the circles correspond to the proportion of FTLD pts harboring that gene variant. Each gene has been associated with certain types of pathology: FTLD-Tau, FTLD-TDP type A/B/C/D and FTLD-UPS, but in some instances type of pathology is unspecified. 11 genes harboring rare variants are associated with high risk of developing FTLD. Two have been seen in multiple subtypes of FTLD-TDP: C9orf72 (types A/B/C) and TBK1 (A/B). Multiple genes associated with FTLD-MND are shown in a white-dashed circle.
Low frequency variants with intermediate effect to be discovered
TMEM106B
GRN rs5848
GWAS hits
Sub-types index presence, predominance, and distribution of TDP-43 aggregates: cytoplasmic inclusions, intranuclear inclusions, and dystrophic neurites.
Rare
Low
Common
Variant Frequency
FTLD-Tau
FTLD-TDP type A
FTLD-TDP type B
FTLD-TDP type C
FTLD-TDP type D
FTLD-UPS
FTLD type unspecified

Behavioral variant common in early onset, later onset cases shift towards the aphasias



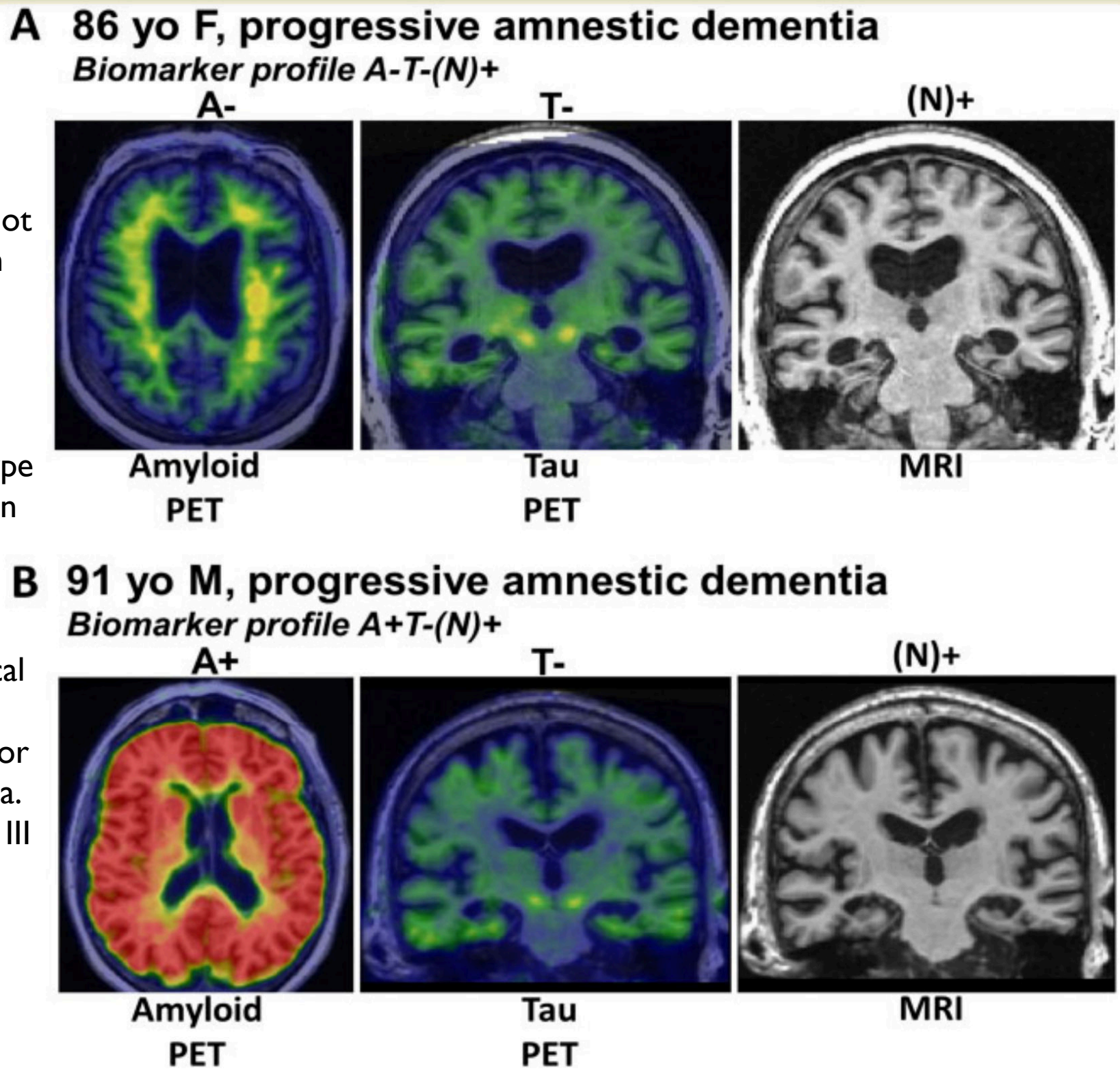
'LATE' – **L**imbic-predominant **A**ge-related **T**AR DNA-binding protein **E**ncephalopathy ***(Nelson et al, 2019)***

- 'LATE' is a common TDP-43 proteinopathy, assoc. w/amnestic dementia, thus mimicking AD. In retrospective autopsy studies, present in 25-50% of individuals > 80 years at autopsy, often comorbid w/other proteinopathies.
- Distinguishable from most FTLD w/ TDP-43 pathology, based on age of onset (@ older subjects) & limbic distribution of TDP-43 proteinopathy.
- ***Staging***: (1) amygdala; (2) entorhinal cortex & subiculum; (3) HC dentate & occipitotemporal cortex; (4) insula, V. striatum, BF & inf. temporal cortex; (5) SN, inferior olive & tectum; (6) BG & mid frontal cortex; (Josephs et al., 2016).
- Genetic studies: 5 risk genes: *PGRN, TMEM106B, ABCC9, KCNMB2, & APOE4* → LATE pathogenetic mechanisms overlap with both FTD & AD.
- Does not appear coincident with ALS/motor neuron disease syndromes.
- Many w/ LATE pts have comorbid pathologies, most often Aβ & tauopathy. Given that 'oldest-old' at greatest risk for 'LATE', & advanced ages form most rapidly growing demographic group, LATE has under-recognized impact on PH.
- Currently, there are no validated biomarkers, which are badly needed.

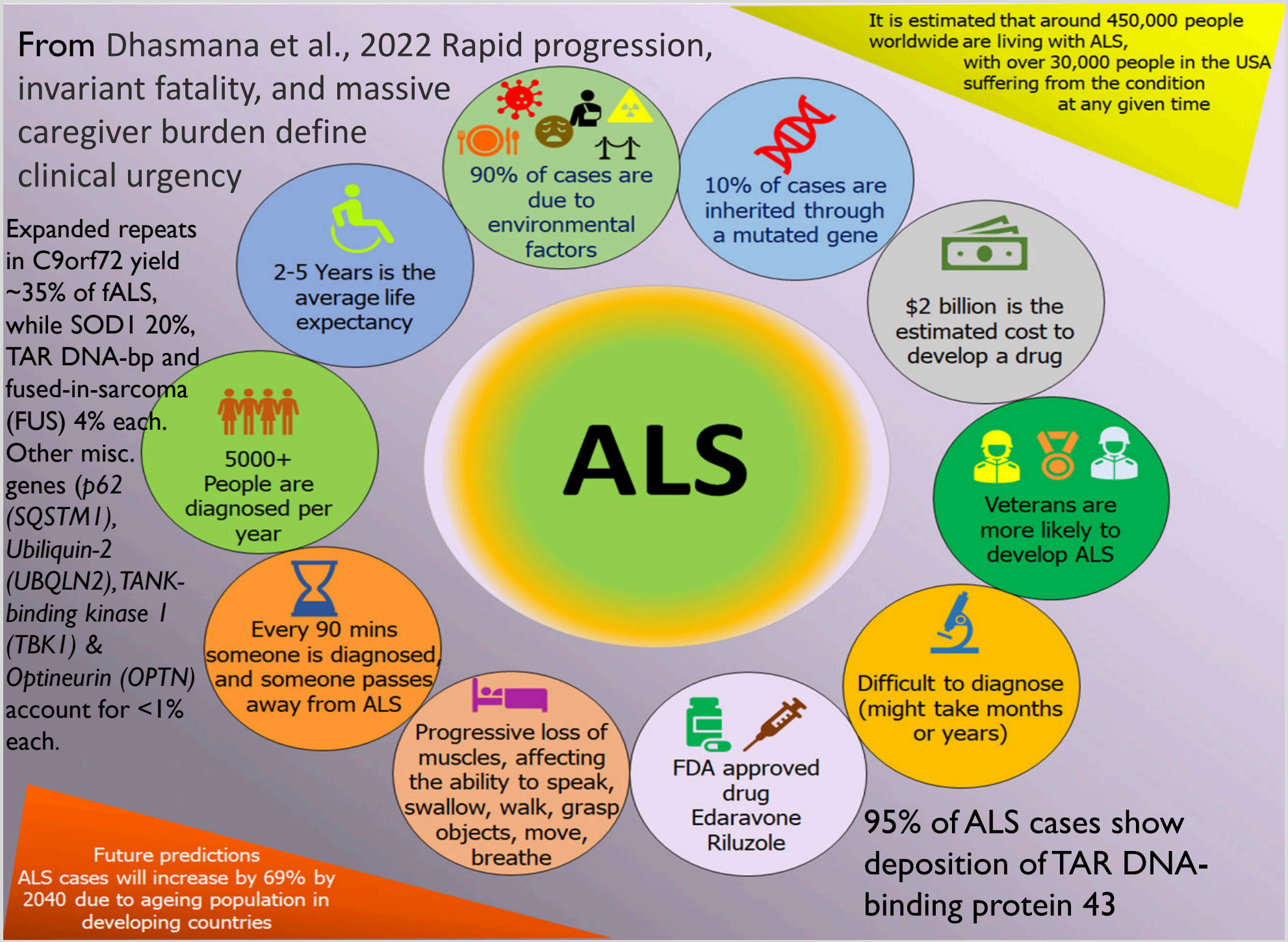
Neuroimaging results w/lack of tauopathy→AD not viable explanation for ↓ cognition.

Results like this, combined w/an amnestic phenotype argue presumption of 'LATE'.

Case B shows probable preclinical AD, not viable explanation also for amnestic dementia. Relevant to failed III trials in AD



Simple graphic summary of ALS



Clinical findings in ALS: Signs/symptoms by affected motor neuron. Both upper motor neurons (UMN) & lower motor neurons (LMN) have to be affected for the diagnosis of ALS, but different combinations of LMN & UMN signs can be observed. Limb onset is found in around 65% of patients but most patients will develop signs in both bulbar region & limbs within course of disease. ~50% have snxs of FTD.

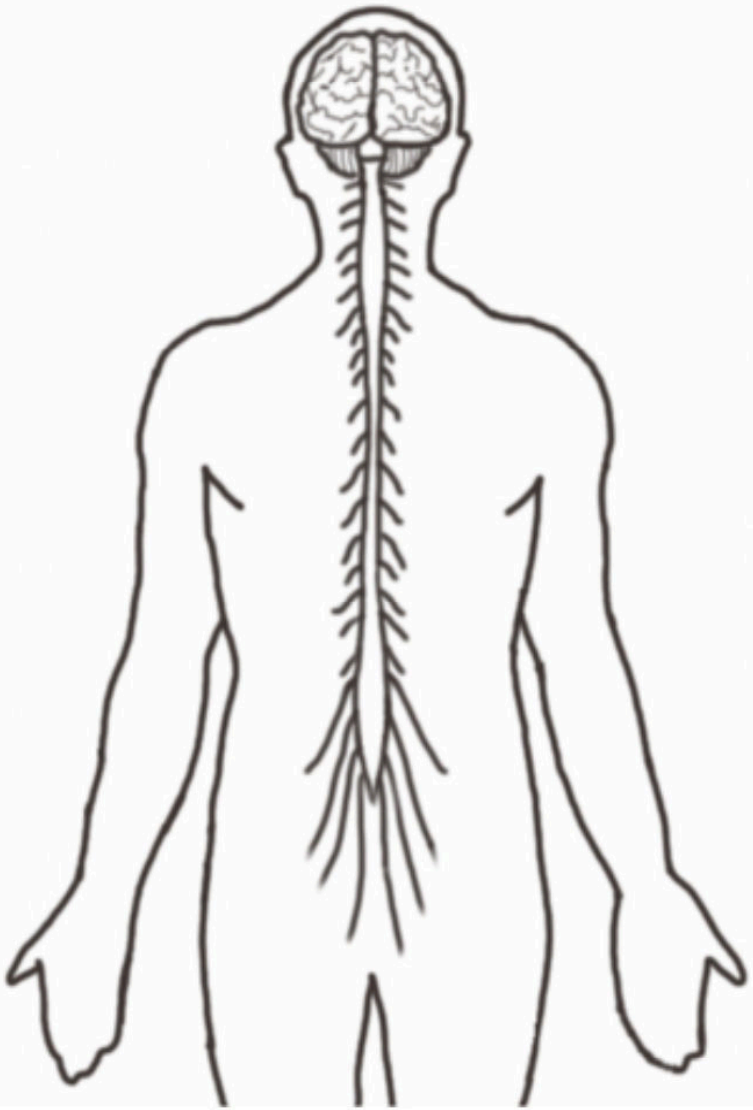
Fronto-Temporal Dementia
Personality change
Behavioural abnormalities
Language dysfunction
Memory impairment

Picher-Martel et al, 2016
Special Issue J of Neurochem

Limb onset

UMN signs
Weakness
Babinski's sign
Hoffman's sign
Spasticity

LMN signs
Weakness
Muscle atrophy
Fasciculations



Bulbar onset

UMN signs
Slow speech
Palmomental reflex
Jaw jerk reflex

LMN signs
Facial weakness
Low palatal elevation
Dysarthria
Tongue fasciculations
Tongue atrophy

Panel: Consensus guidelines for the clinical diagnosis of frontotemporal dementia

Clinical profile: character change and disordered social conduct are the dominant features initially and throughout the disease course.

Core diagnostic features
- Insidious onset and gradual progression
- Early decline in social interpersonal conduct
- Early impairment in regulation of personal conduct
- Early emotional blunting
- Early loss of insight

Note: this list applies mainly to executive variant of FTLD not PPA

Supportive diagnostic features

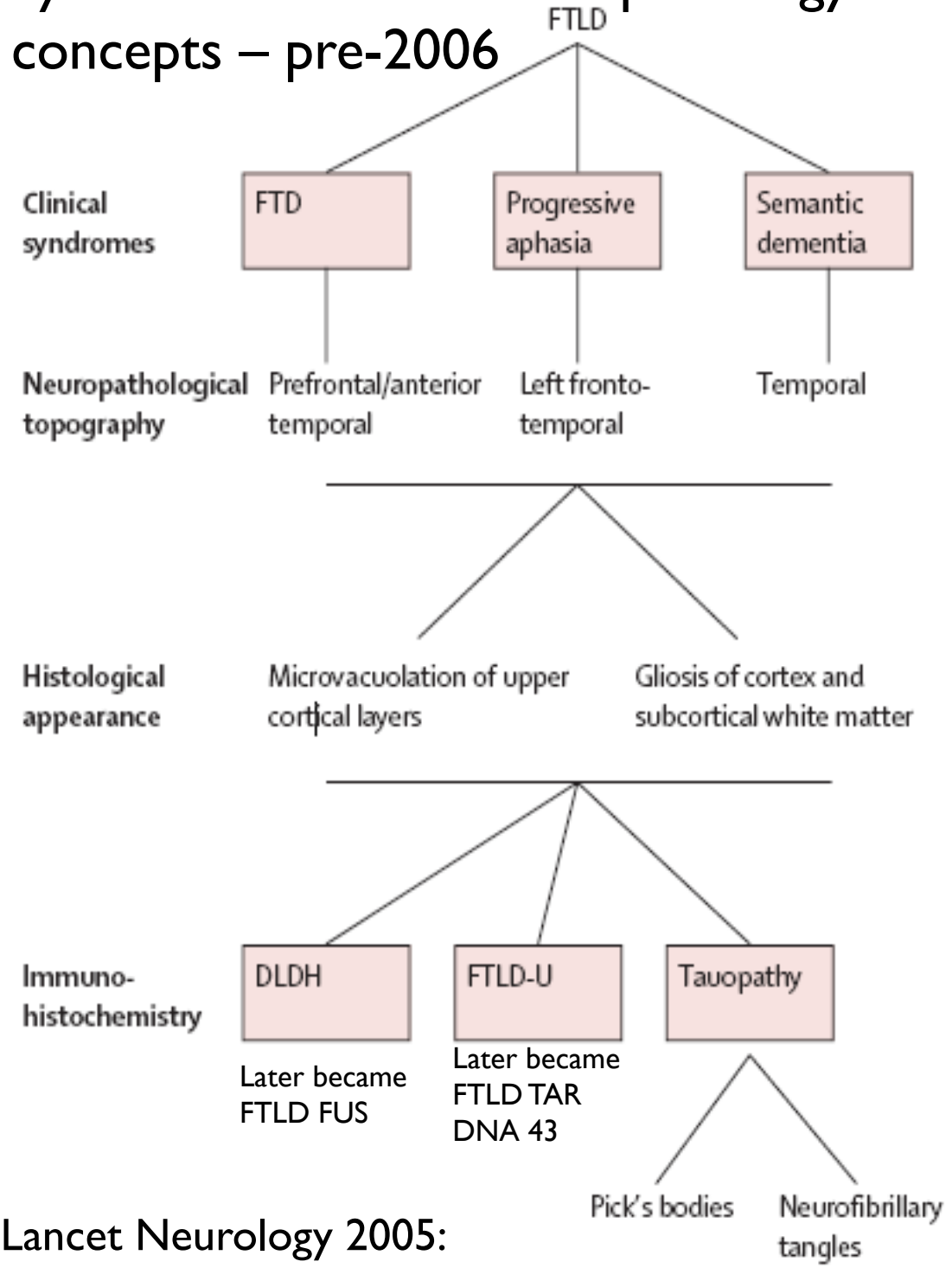
Behavioural disorder
- Decline in personal hygiene and grooming
- Mental rigidity and inflexibility
- Distractibility and impersistence
- Hyperorality and dietary changes
- Perseverative and stereotyped behaviour
- Utilisation behaviour

Speech and language
- Altered speech output: aspontaneity and economy of speech; press of speech
- Stereotypy of speech
- Echolalia
- Perseveration
- Mutism

Physical signs
- Primitive reflexes
- Incontinence
- Akinesia, rigidity and tremor
- Low and labile blood pressure

Investigations
- Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
- Electroencephalography: normal on conventional electroencephalogram despite clinically evident dementia
- Brain imaging (structural or functional): predominant frontal or anterior temporal abnormality

Syndromes & classic histopathology concepts – pre-2006



Lancet Neurology 2005:
Neary, Snowden, & Mann

Primary progressive aphasias – two FTD phenotypes, and a 3rd that implicates AD

Clinical features	svPPA	nfvPPA	lvPPA
Spontaneous speech (fluency, errors, grammar, prosody)	Fluent, garrulous and circumlocutory, semantic errors, intact grammar and prosody	Slow and hesitant, effortful ± apraxic, phonetic errors, may be agrammatic, aprosodic	Hesitant, not effortful or apraxic, frequent word-finding pauses and loss of train of sentence, intact grammar, intact prosody
Naming	Severe anomia with semantic paraphasias	Moderate anomia with phonetic errors and phonemic paraphasias	Mild to moderate anomia with occasional phonemic paraphasias
Single word comprehension	Poor	Intact early on, but affected later on	Intact early on, but affected later on
Sentence comprehension	Initially preserved, later on becomes impaired as word comprehension is impaired	Impaired if grammatically complex	Impaired, especially if long
Single word repetition	Relatively intact	Mild to moderately impaired if polysyllabic, otherwise intact	Relatively intact (compared with sentence repetition)
Sentence repetition	Relatively intact	Can be effortful, impaired if grammatically complex	Impaired, with length effect
Reading	Surface dyslexia	Phonological dyslexia ± phonetic errors on reading aloud	Phonological dyslexia
Writing	Surface dysgraphia	Phonological dysgraphia	Phonological dysgraphia

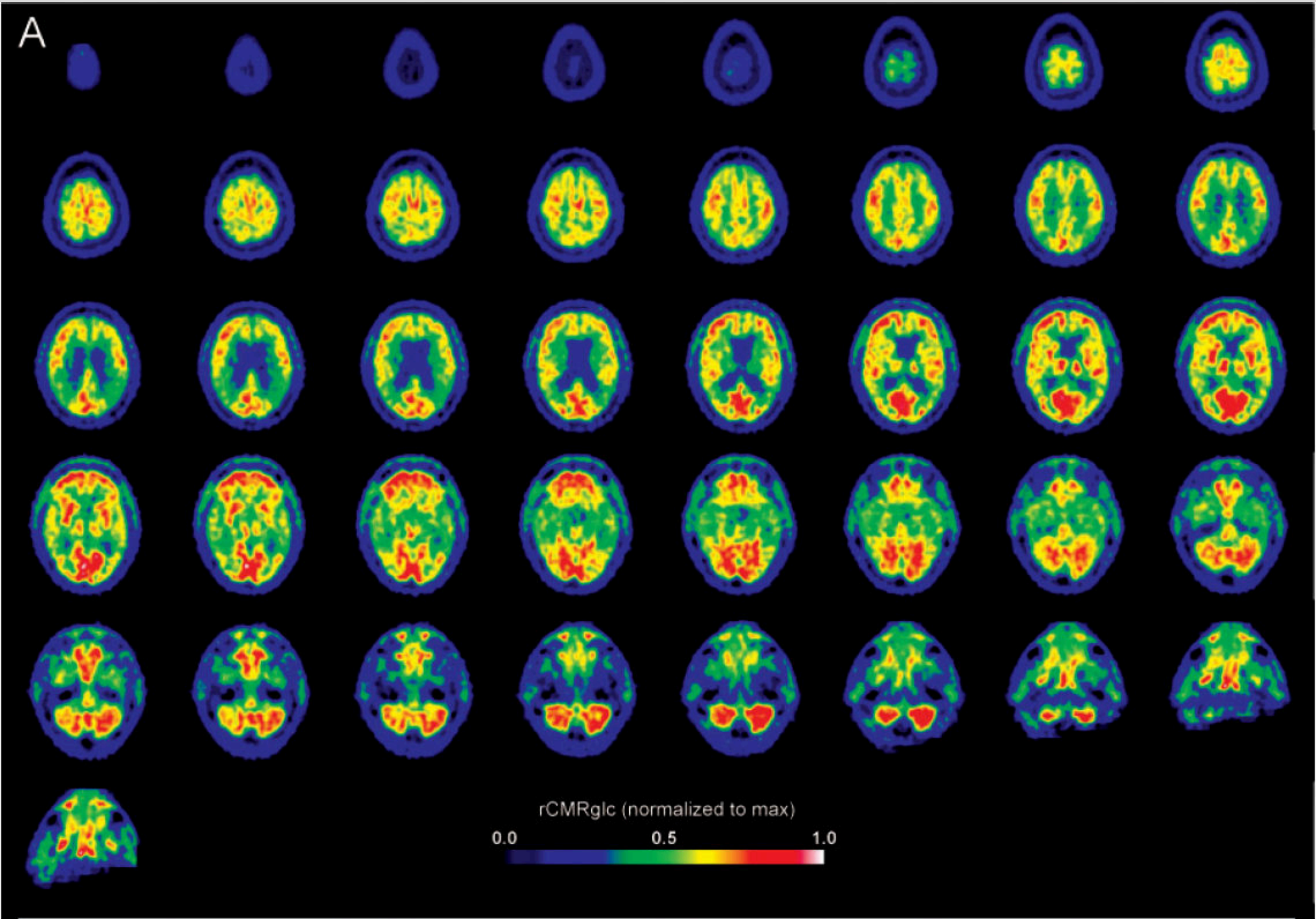
svPPA, semantic variant primary progressive aphasia; nfvPPA, non-fluent variant primary progressive aphasia; lvPPA, logopenic variant primary progressive aphasia. Clinical features are adapted from tables in Rohrer *et al.* (2008, 2010a), Seelaar *et al.* (2011) and Gorno-Tempini *et al.* (2011). (Wollacott and Rohrer, 2016, J of Neurochem, Special Issue)

Neuroimaging Results
Some Representative Cases

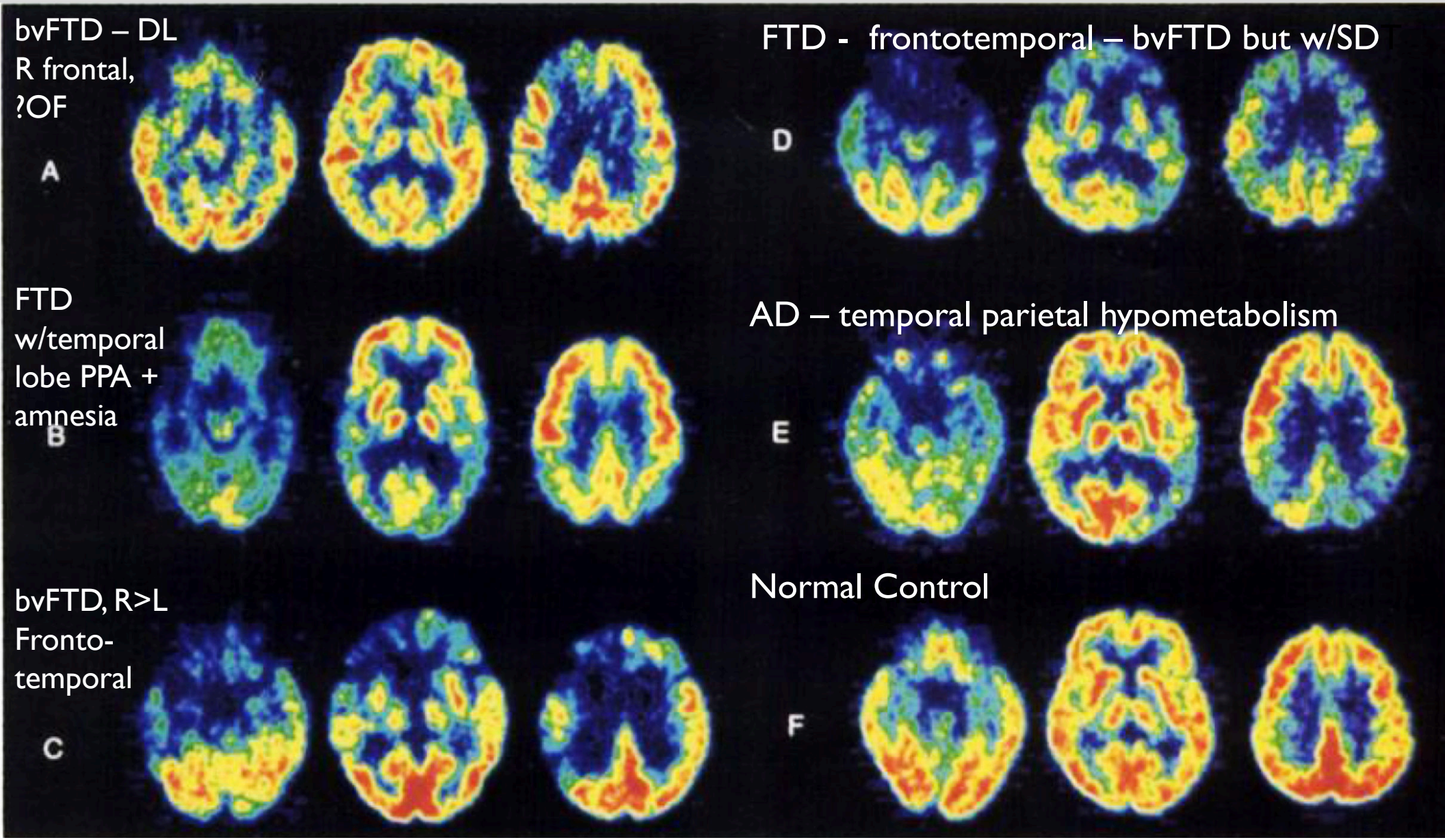
Networks and Regions Impacted in Metabolic and Structural Imaging Show Correlation with Cognitive and Behavioral Phenotypes

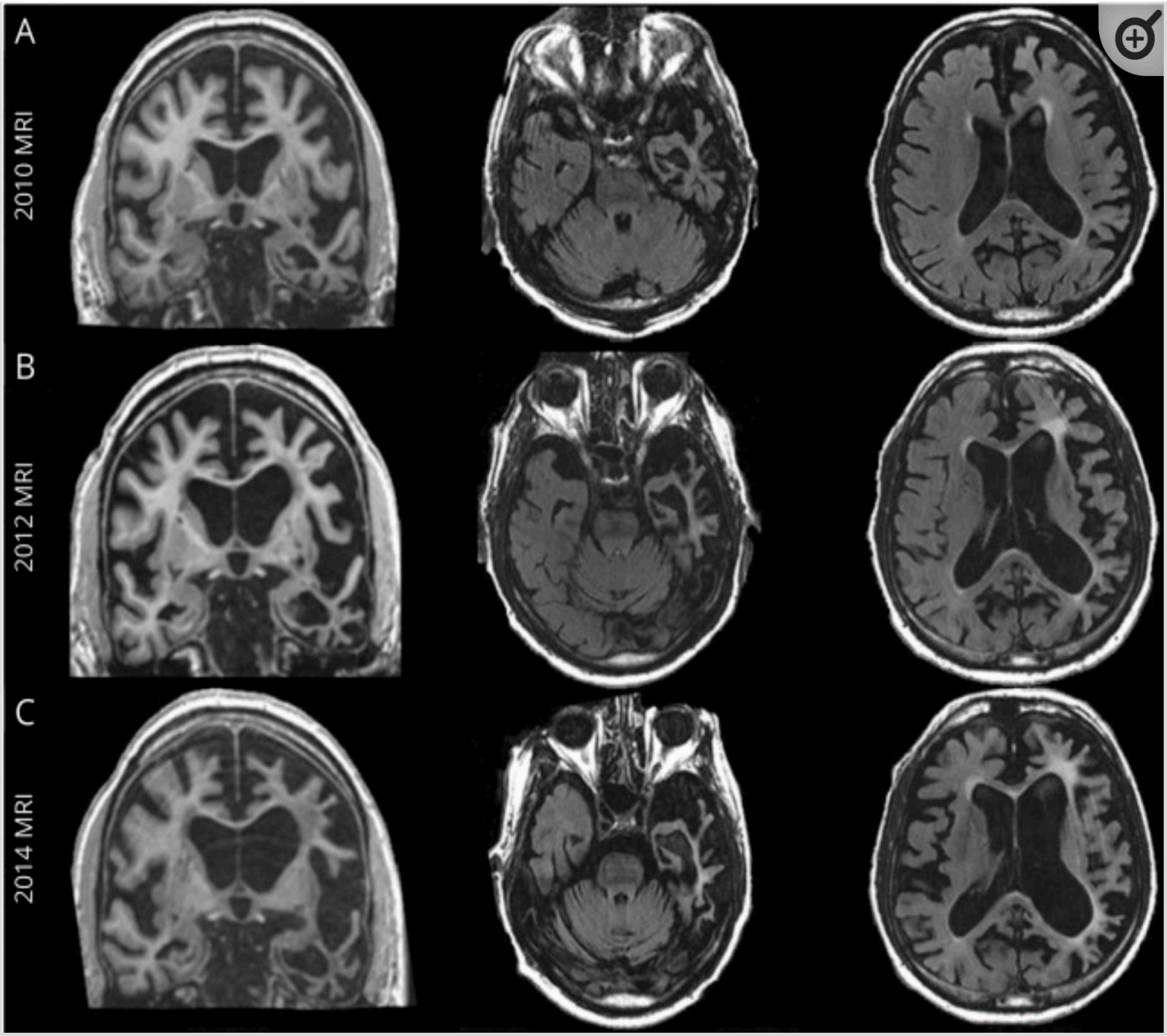
Neuroimaging thus remains the only currently available biomarker

Classic AD pattern with characteristic temporoparietal hypo-metabolism.



Cerebral metabolic rate for glucose imaging in FTD patients (w/AD & normal control subject).
(A) A 70-yr-old woman with FTD; **MMSE:21**. Reduced in R frontal lobe.
(B) 71-yr-old woman with FTD, PPA temporal type; **MMSE:17**. Severe bilateral temporal, ↓parietal-occipital activity also.
(C) A 62-yr-old man with FTD, **MMSE:24** severely reduced in frontal and temporal lobe, R>L, R BG and R parietal lobe.
(D) A 73-yr-old woman with FTD, diagnosed as frontotemporal type; **MMSE:5** CMR severely reduced in temporal & frontal lobe, L>R. Bilateral parietal metabolism also decreased.
(E) A 58-yr-old man with Alzheimer's disease; **MMSE:15** Bilateral temporoparietal-reduction – typical AD pattern.
(F) A 64-yr-old normal woman. No focal or global reduction of metabolism.





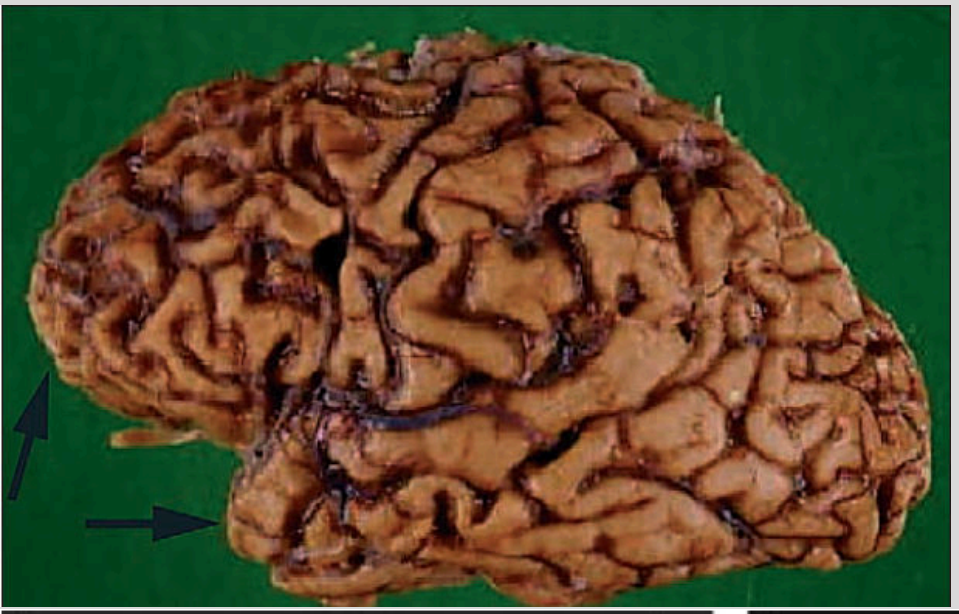
Progranulin mutation w/PNFA, executive & behavioral Δ (apathy/disorganization), onset in middle 60's. Noted ***marked*** laterality of atrophy

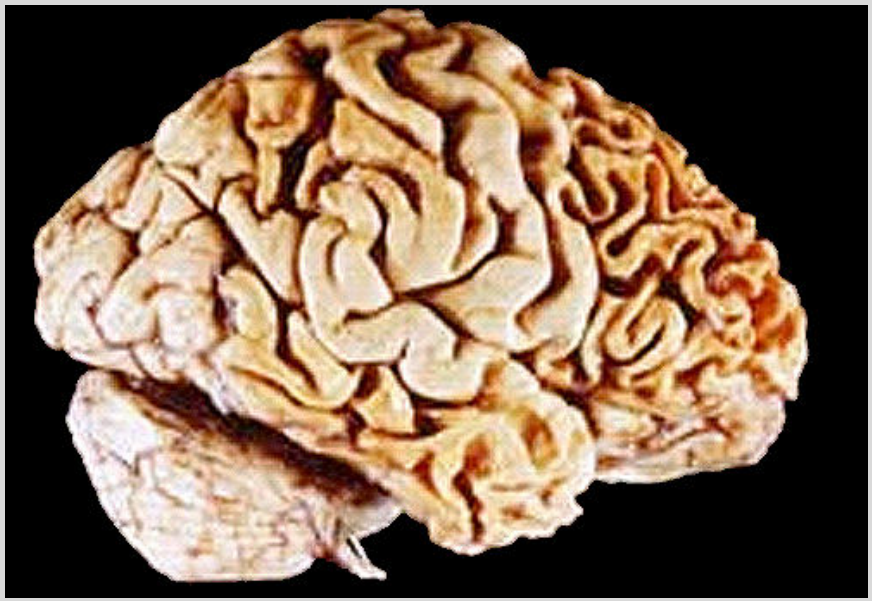
A 67-year-old R-handed man w/progressive forgetfulness, logopenia/dysnomia (esp.nouns) & ↑ mild apathy 3+ years. Difficulties w/ complex attention, calculations, & delayed recall. No parkinsonian or motor neuron findings. ↑Difficulties with problem-solving ~5 years after symptom onset, forcing retirement. Progression of aphasia symptoms predominated over next few years, w/episodic memory less affected. At his final evaluation, 6 months PTD, he showed → ↑global aphasia, was dependent on ADLs, and had switched to his L hand for tasks due to severe apraxia of his dominant hand. He had preserved social graces, humor, enjoyment for music.

He died at age 76 years, 12 years after initial symptom onset. Family history + for dementia and/or parkinsonism in an autosomal dominant pattern affecting >15 relatives. TDP-43-positive neuronal intranuclear inclusions in neocortex & striatum consistent w/FTLD-TDP. Genetic sequencing in progranulin (*GRN*) gene identified a heterozygous mutation in exon 3 of *GRN*.

Structural Atrophy and Imaging

VmPFC Atrophic Change in pts with poor behavioral controls





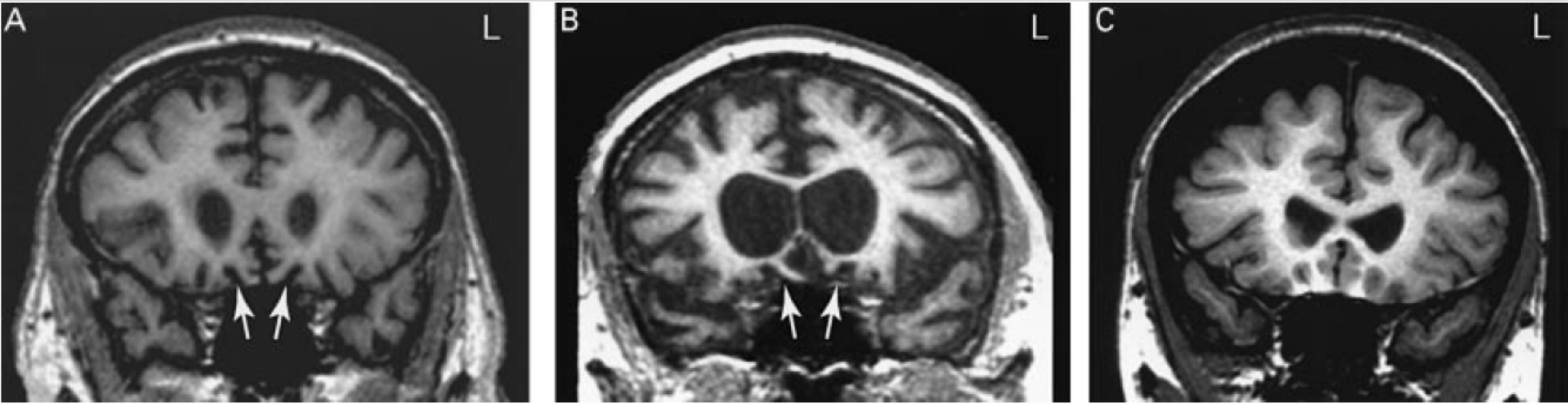
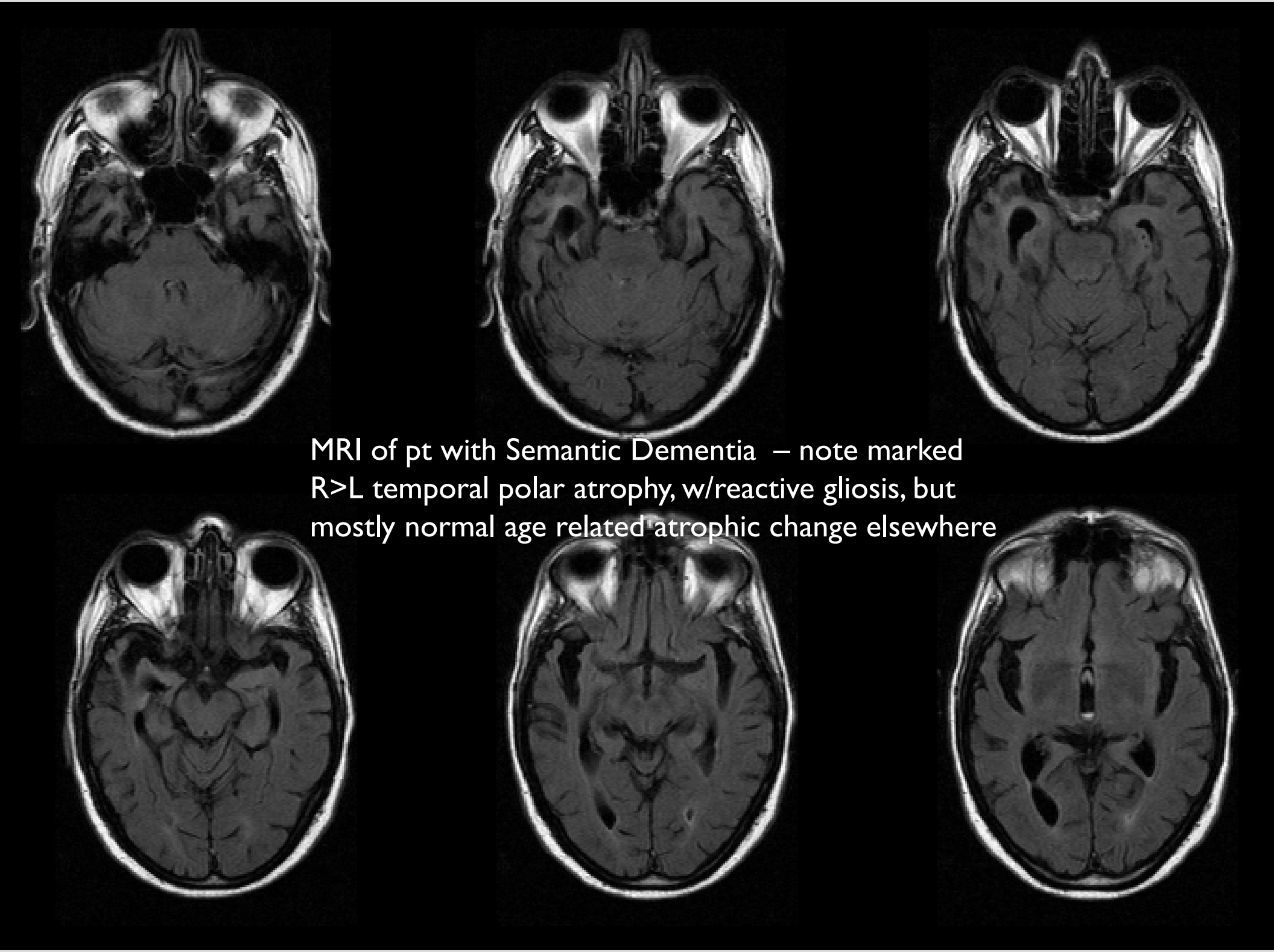
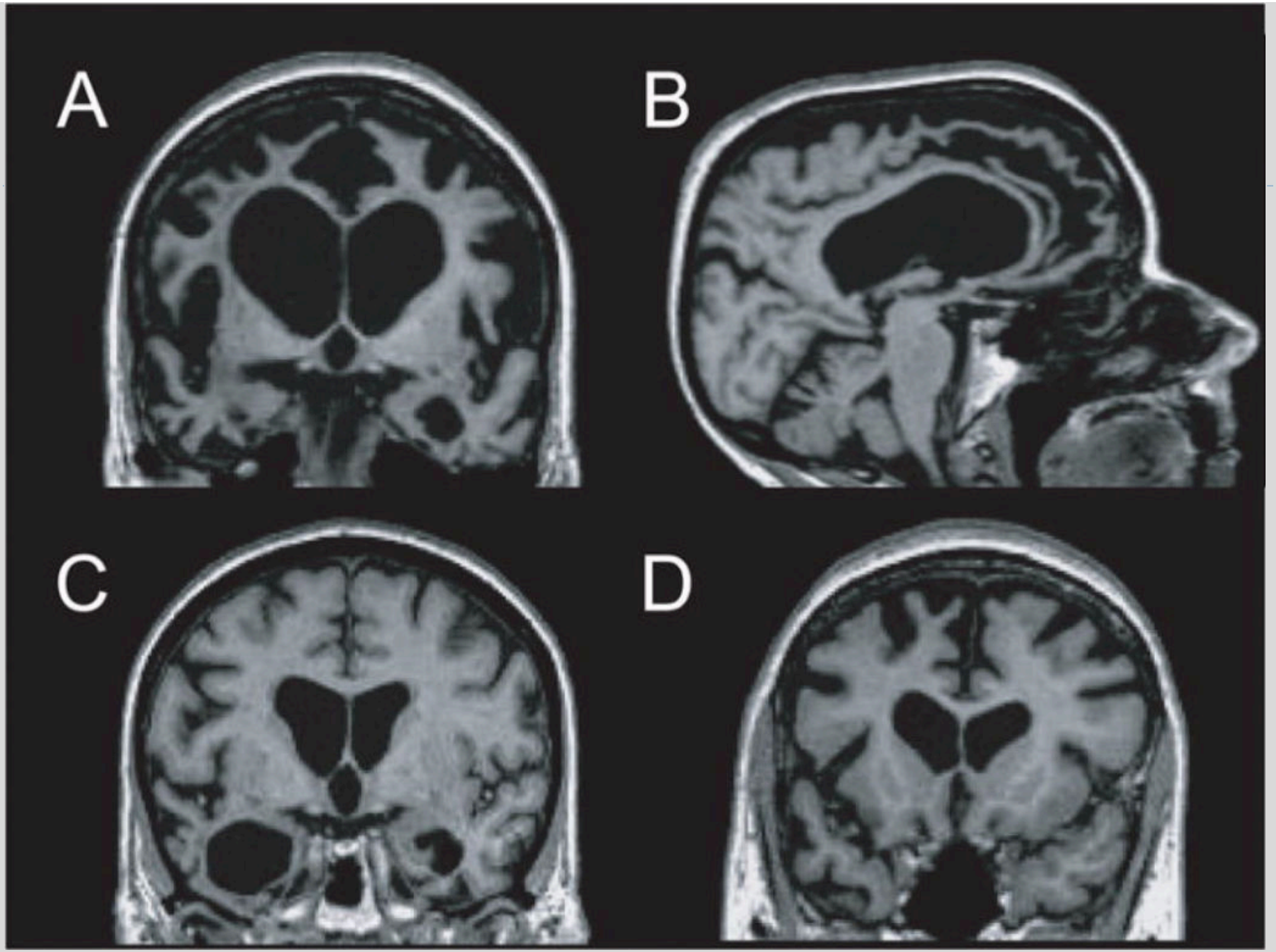


Fig. 1 Coronal MRI scans at the level used to rate degree of ventromedial and dorsolateral frontal atrophy. (**A**) Mild ventromedial atrophy (arrows). (**B**) Severe ventromedial (arrows) and moderate dorsolateral atrophy. (**C**) A comparable normal individual. L = left hemisphere.



MRI of pt with Semantic Dementia – note marked R>L temporal polar atrophy, w/reactive gliosis, but mostly normal age related atrophic change elsewhere



MRI findings in FTLD.T1 images from behavioural-variant frontotemporal dementia (bvFTD) [**a** and **b**], semantic dementia (SD) [**c**] and progressive nonfluent aphasia (PNFA) [**d**]. (**a** and **b**) bvFTD patient shows marked atrophy throughout the medial and lateral frontal cortex and the temporal poles, with striking relative preservation of the posterior brain regions on a sagittal view. (**c**) Patient with SD shows asymmetric degeneration of temporal poles (L > R). (**d**) PNFA patient shows atrophy in left inferolateral and dorsomedial frontal cortex and anterior insula.

Genes, Proteins, Pathways . . . and Neurodegeneration

How do such disparate gene mutations create such similar phenotypes but also how do the same mutations also create such disparate phenotypes?

And how are sporadic disease and familial disease so similar in phenotypes?

Despite highly disparate nature of FTD/ALS syndromes, 50% show TDP43 neuropathology and implicate new concepts ('RNA toxicity'/failure of RBP)

Appearance of TAR-DNA43 outside of FTLD challenges old boxology models, towards conceptualizing neurodegenerative commonalities

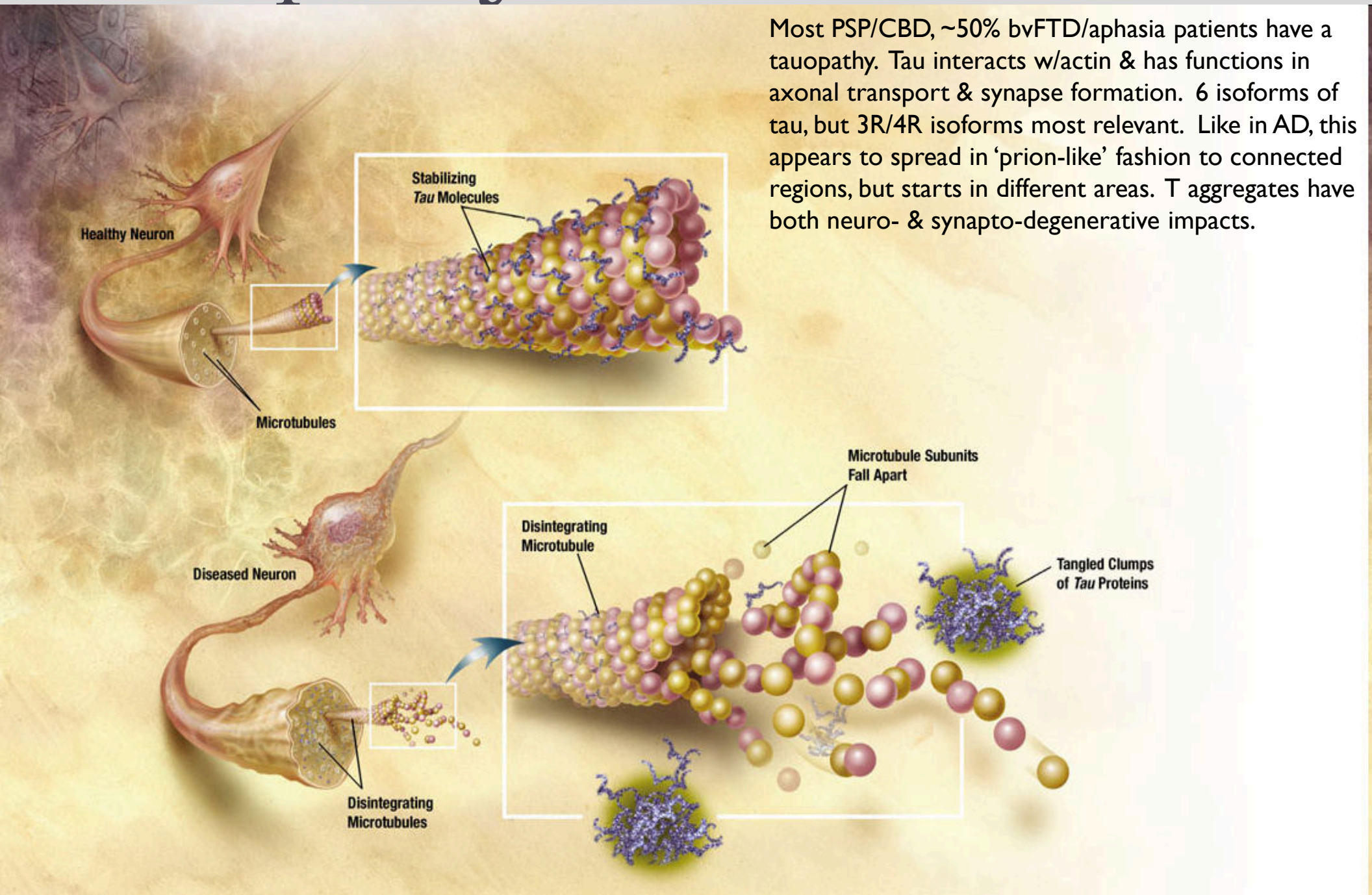
How far away is a 'general field theory' of neurodegeneration?!

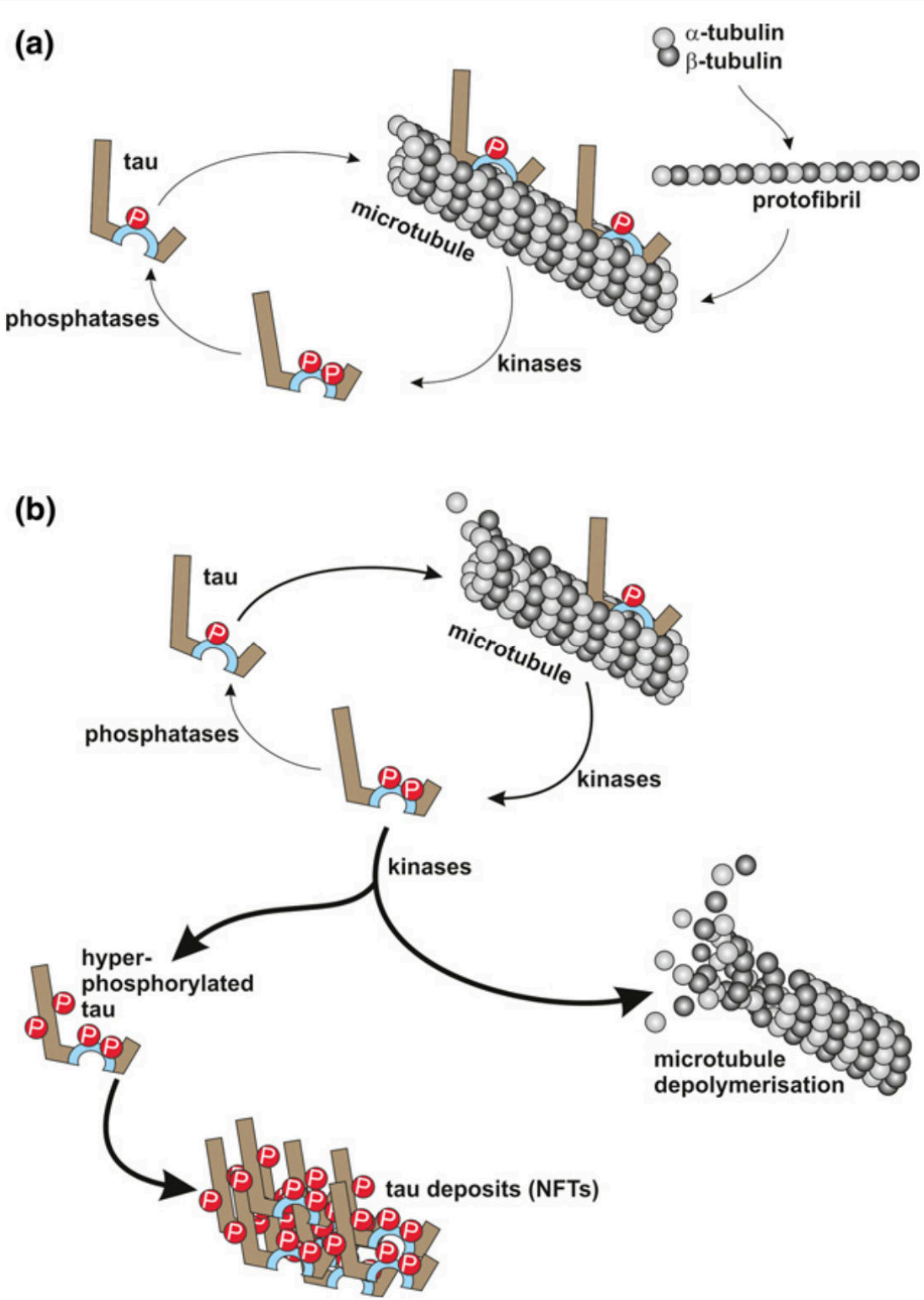
Tauopathy – first protein discovered in FTLD. MAPT – first associated mutation

- Study of tau began in 70s – Weingarten & colleagues described a protein essential for assembly of microtubules (polymers of tubulin), which they termed tau (tubulin-associated unit) or Greek letter τ.
- Located on chromosome 17 – 6 isoforms formed from variable splicing of 14 exons. Mutations of MAPT in FTLD (50+) all show reduced conformity/binding function to microtubules.
- Makes FTLD the 2nd most common tauopathy (tau not mutated in AD, but chemically altered). Both show → LOF/TGOF.
- Normally tau localized primarily to distal axons, but in FTLD forms phosphorylated aggregates in soma/dendrites, compromising axonal transport, clogging up synapses & endosomes/autophagy. Like AD.
- Frontotemporal/BG atrophy patterns with Parkinsonianism (CBD & PSP) common, especially later in disease course. ALS very, very rare.

Tauopathy in FLTD vs. AD

Most PSP/CBD, ~50% bvFTD/aphasia patients have a tauopathy. Tau interacts w/actin & has functions in axonal transport & synapse formation. 6 isoforms of tau, but 3R/4R isoforms most relevant. Like in AD, this appears to spread in 'prion-like' fashion to connected regions, but starts in different areas. T aggregates have both neuro- & synapto-degenerative impacts.





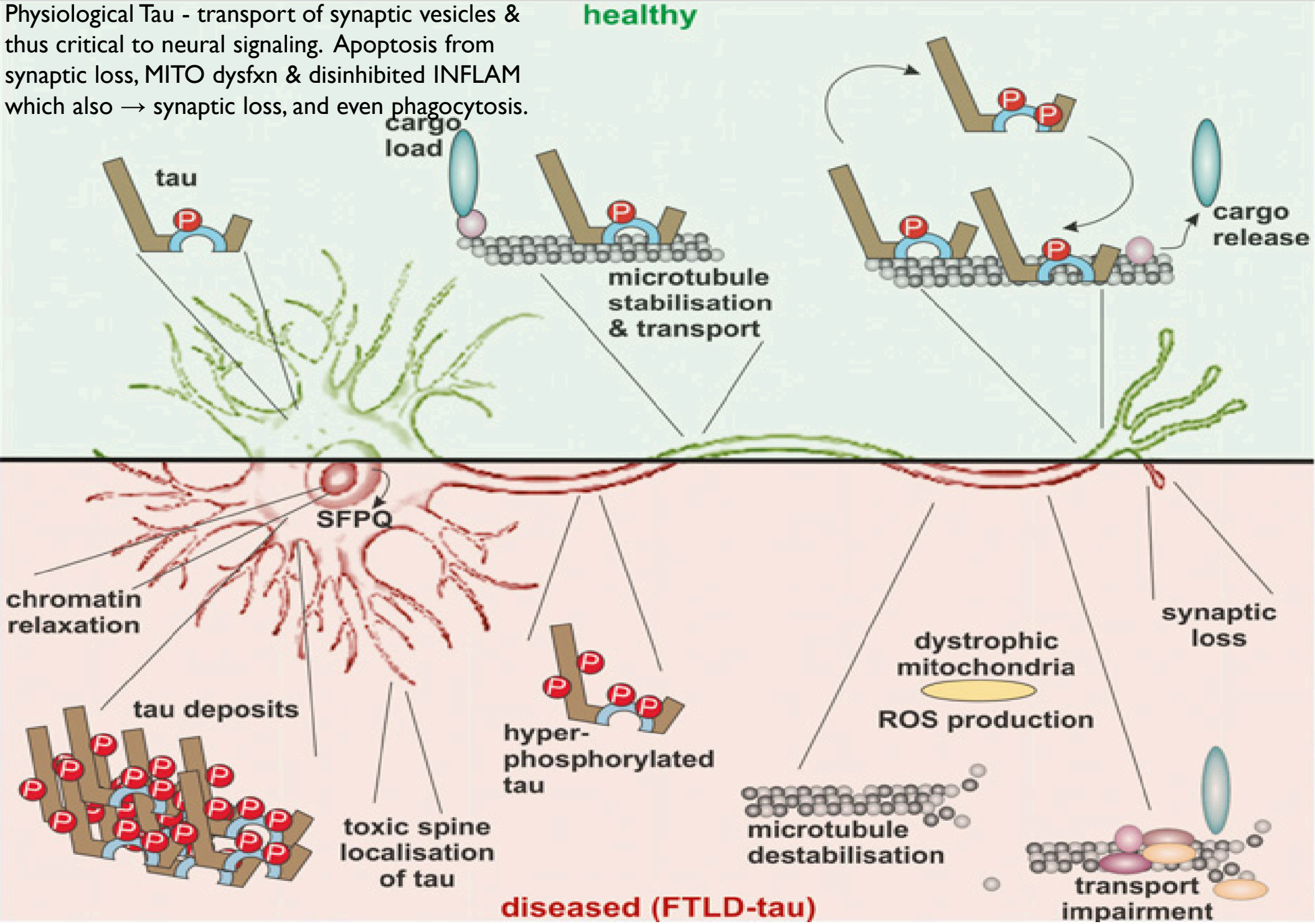
Normal balance between phosphatases & kinases disrupted → tau post-translational modification/ dysfunction → pathways into ↑PHF/NFTs. Better documented in AD vs FTD

This may emerge due to various cellular stresses (in AD appears driven by Aβ oligomers) but also in FTLD-tau. Still not clearly understood, and likely to be very multifactorial, with both genetic and environmental causes.

Tau aggregates cause a variety of problems with axonal transport, synaptic function, and can even induce apoptosis at higher levels.

Loss of healthy τ function w/toxic gain of function

Physiological Tau - transport of synaptic vesicles & thus critical to neural signaling. Apoptosis from synaptic loss, MITO dysfxn & disinhibited INFLAM which also → synaptic loss, and even phagocytosis.



Finer grained detail around synaptic dysfxn

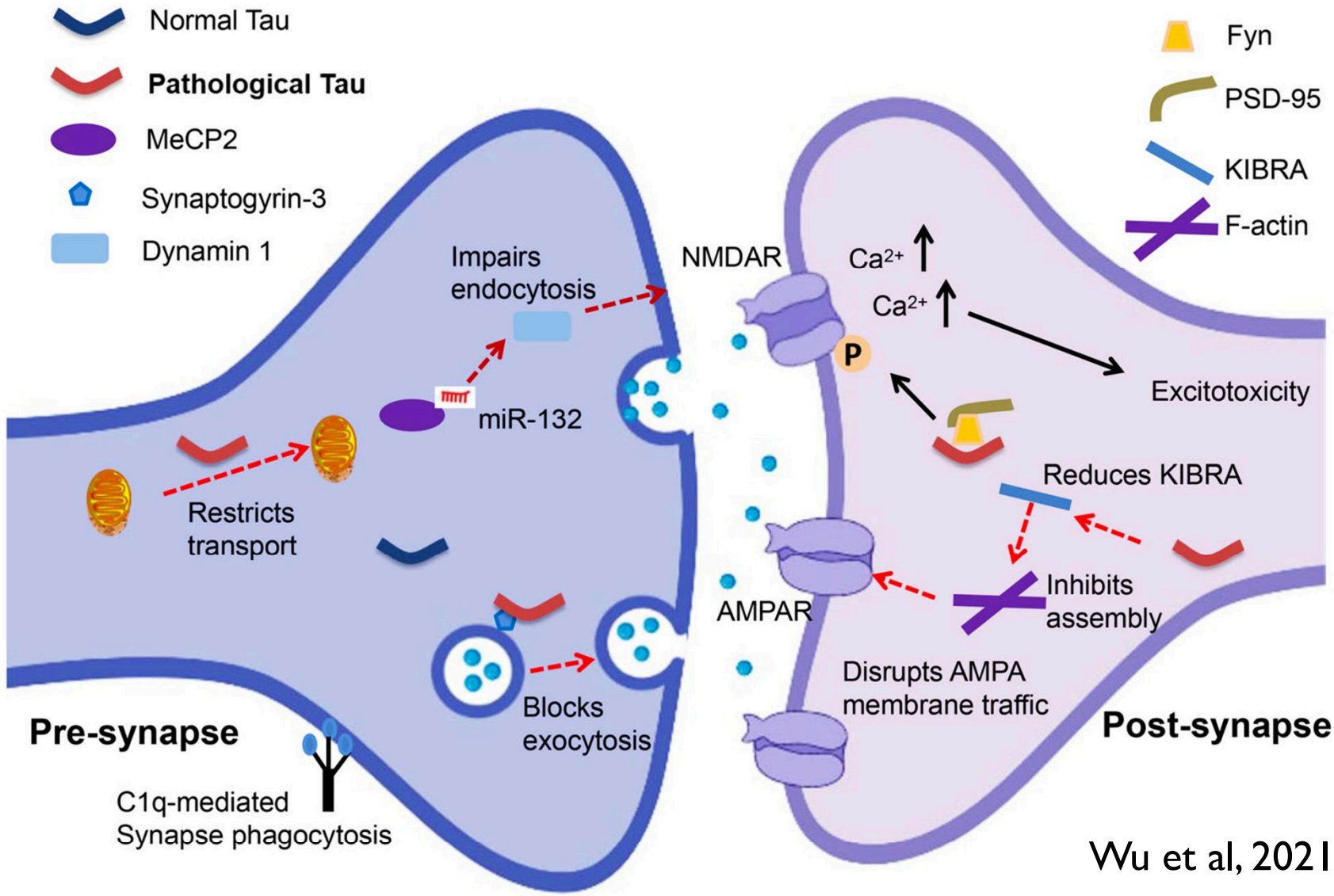


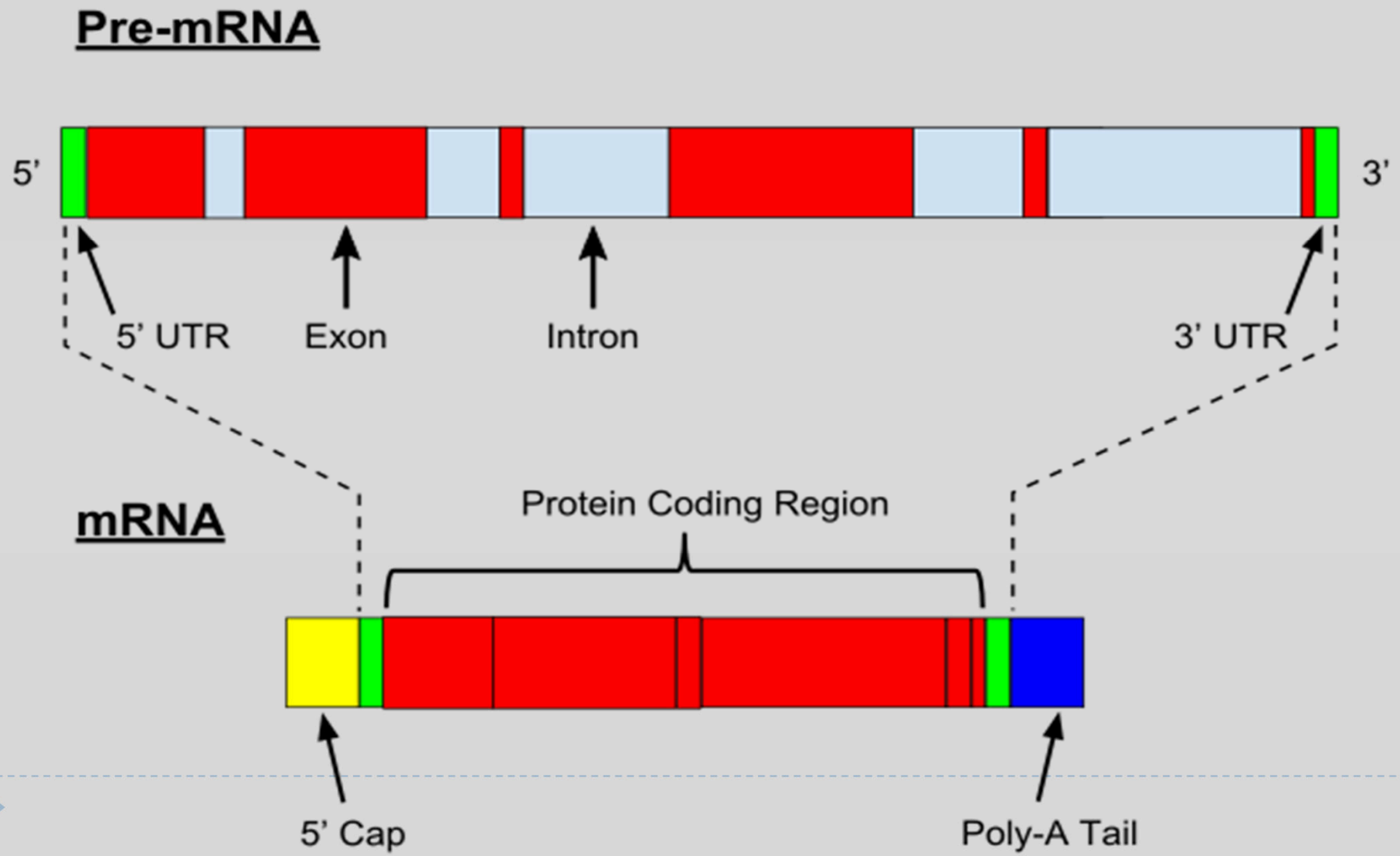
Fig. 1 Pathological tau induces synaptic dysfunction. At presynaptic terminals, the interaction of pathological tau with synaptogyrin-3 on synaptic vesicles hampers vesicle mobility and impairs presynaptic vesicle cycling. Pathological tau impairs neuronal endocytosis through the miR-132–meCP2–dynamin 1 pathway. Pathological tau induces tagging of synapses by complement initiation factor (C1q) and activates synapse phagocytosis by microglia. The infiltration of pathological tau into postsynapses recruits Fyn to NMDAR/PSD-95 complexes and causes excitotoxicity mediated by amyloid-β and excessive glutamate. Accumulation of acetylated tau contributes to KIBRA deficiency, which blocks the activity-dependent F-actin polymerization and disrupts AMPA receptor membrane anchoring at postsynapses

Second pathognomic protein discovered in FTDs – TAR DNA binding protein-43

- TAR DNA binding protein-43 – discovered as transcriptional repressor in HIV – a ribonucleoprotein supporting the RNA life cycle, shuttling nucleus ↔ cytoplasm, but mostly nuclear. Rare mutations in FTLD-ALS.
- Regulated by 'phase' transitions (dispersed↔liquid↔gel), but unknown stresses→ ↑fibrillar aggregates, w/↑nuclear depletion/cytosol aggregation.
- Roles in splicing, miRNA, lncRNA, stress granules, mRNA translation/ axonal transport & DNA repair, suggesting wide cellular disruptions.
- Core business of the cell: make proteins to support cell phenotypic fnxs (in neurons, many synaptic proteins/vesicles – disruption is *severe* threat).
- TDP-43 aggregation spreads from cell-to-cell in 'prion-like' manner.
- 45-50% of FTD show TAR DNA 43 deposition & ***almost all ALS*** excepting those with mutations in SOD1, or FUS (all C9orf72r).
- Connection to failing LAS/(PGRN) unclear, but it is the bp for PGRN.
- Appears in 30-40+% of pts w/histopathologically confirmed AD, and in some PD, CTE and HD cases → concomitant in other NDD.

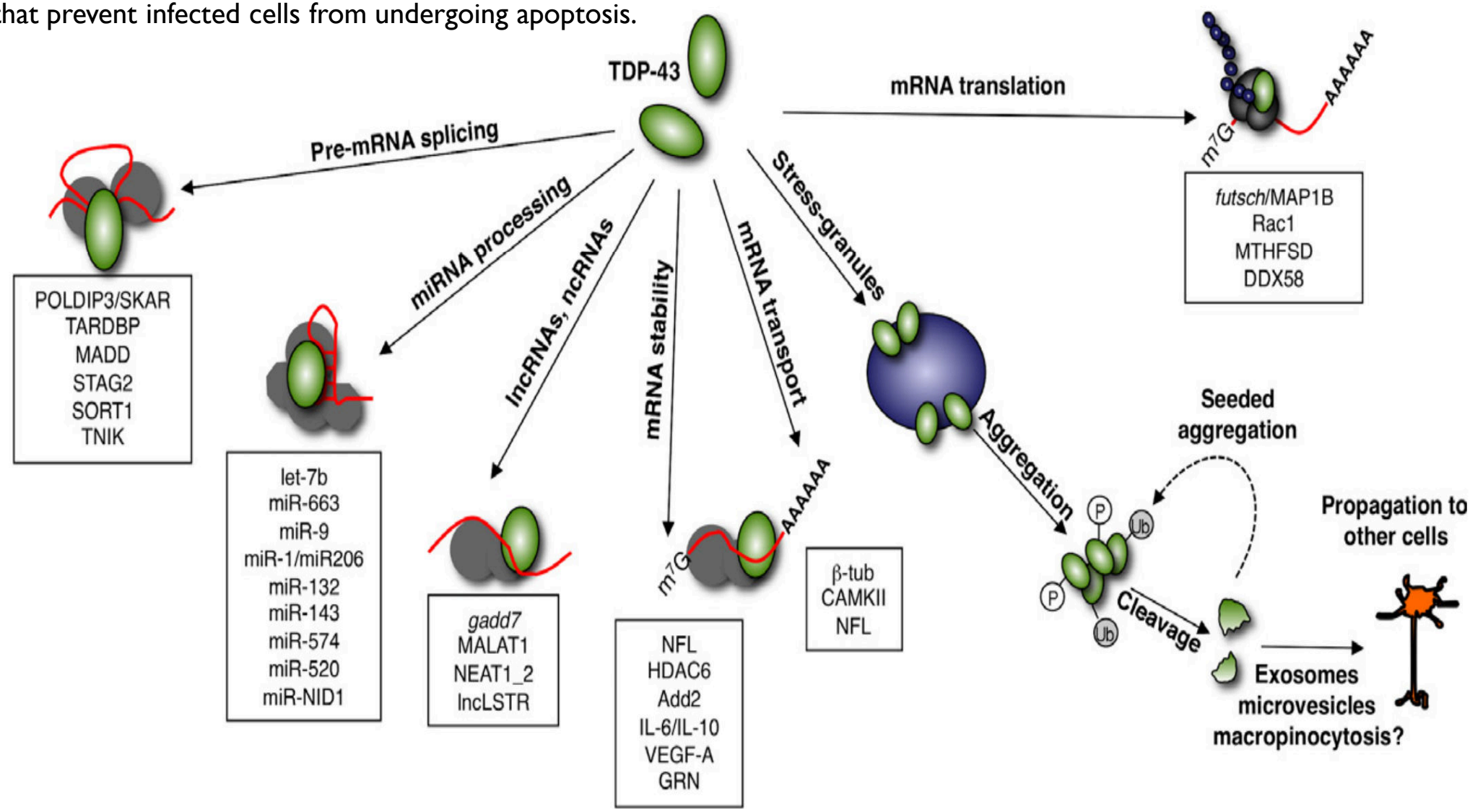
Maturation of RNA via binding protein effects – removes introns → different protein isoforms

Introns are not 'junk' but provide basis for alternative splicing and thus many isoforms of a particular protein within just one gene.

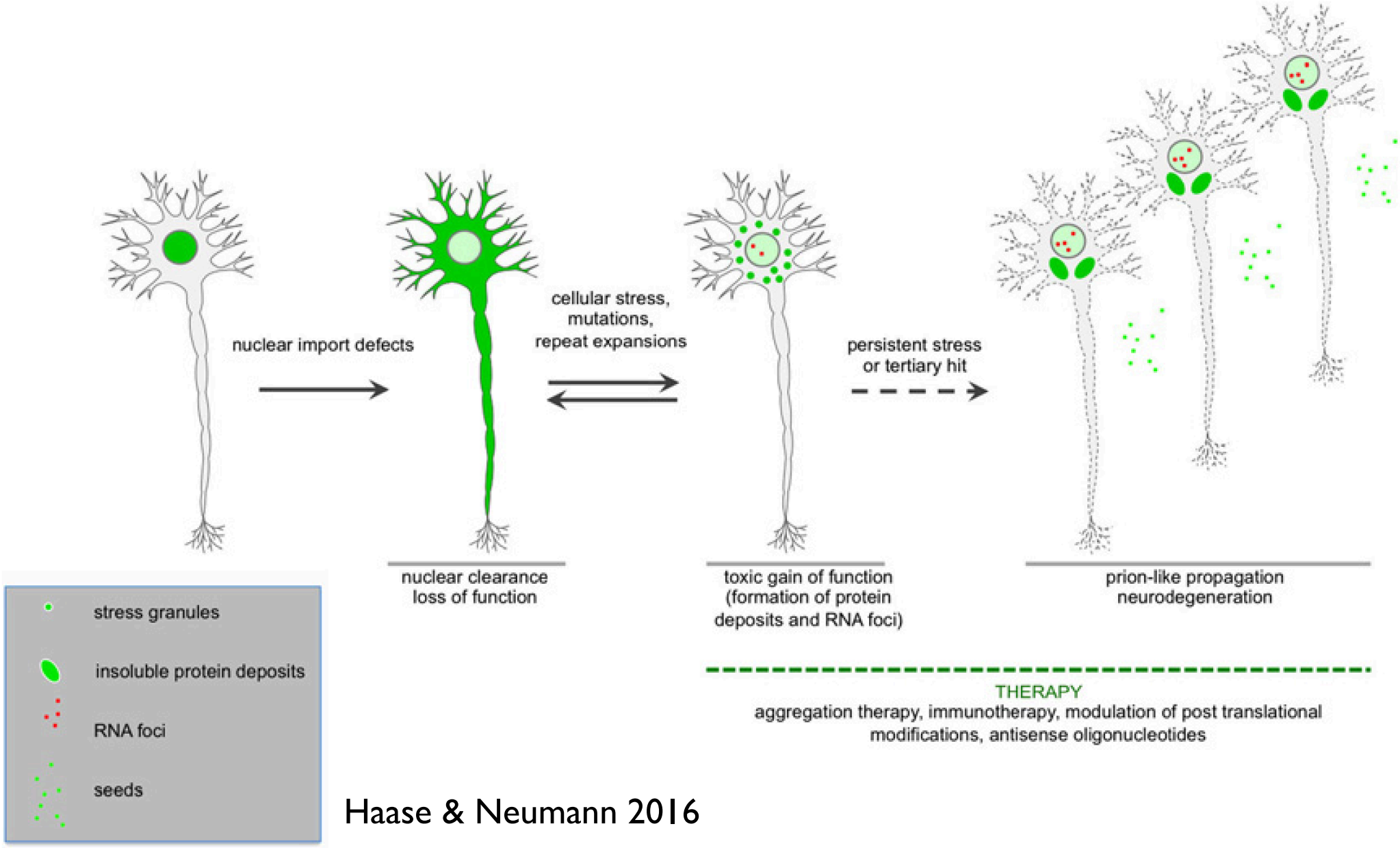


TAR ('transactive response element') DNA binding protein-43 functional chart

'TAR' is a portion of the HIV virus that appears to be a precursor to micro-RNA – it binds to RNAbp to produce miRNAs that prevent infected cells from undergoing apoptosis.



Sequence of failures (proteostatic⊣ nuclear import, ↑aggregates of DBP→ prion-like spread), but then?

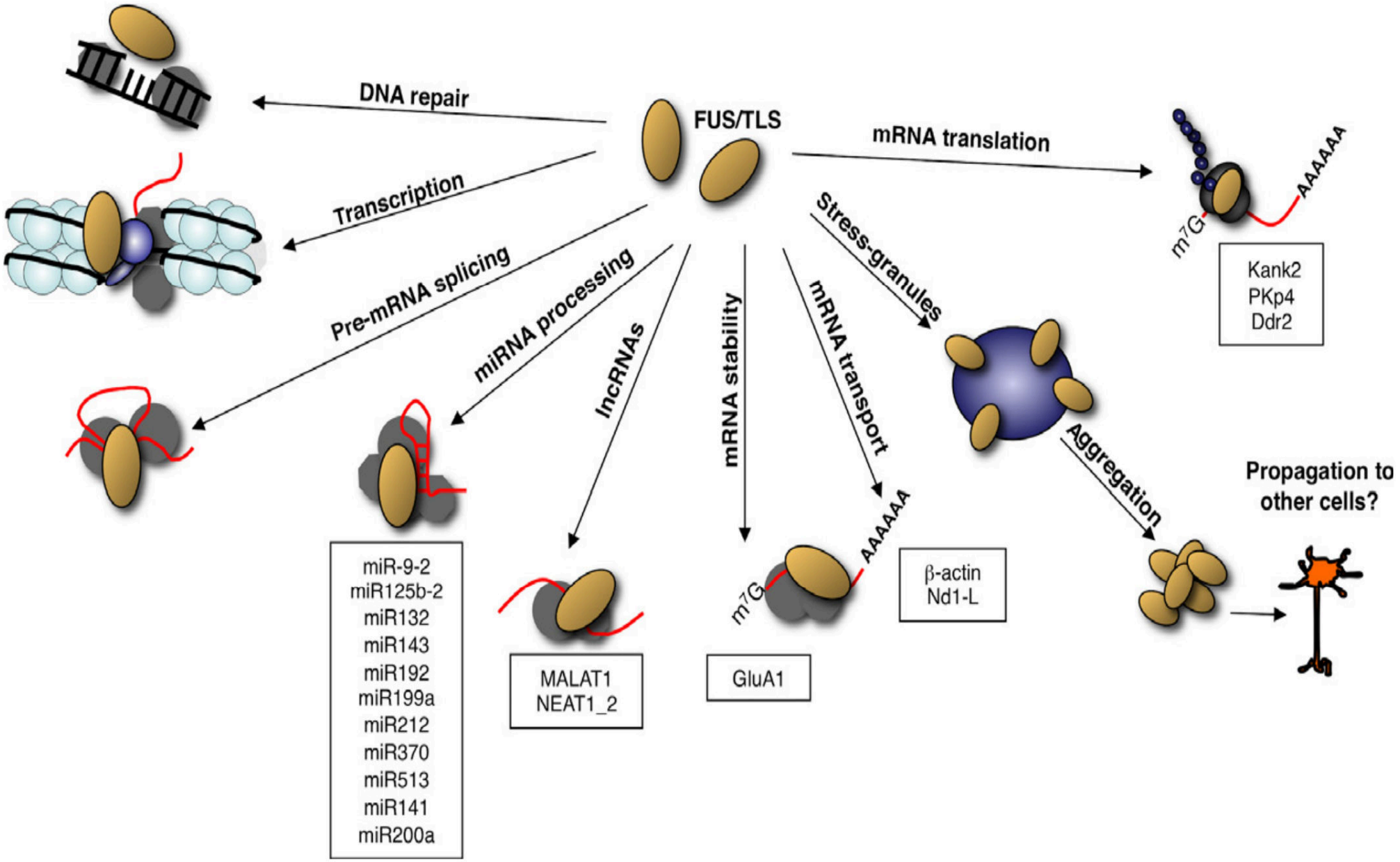


Haase & Neumann 2016

FUS – fused in sarcoma protein (FET)

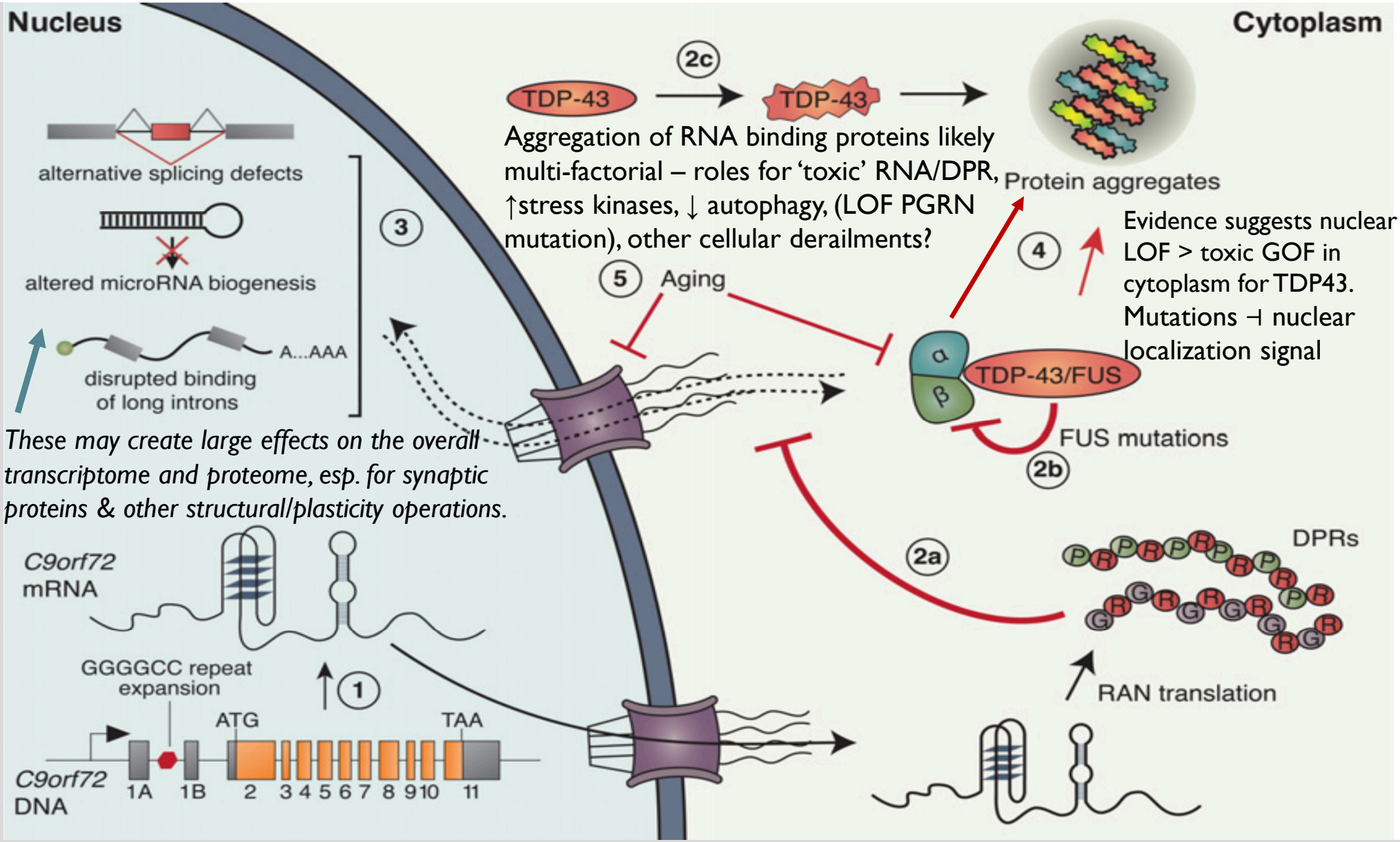
- In 2009, FUS protein ID'd in FTLD, in cells previously designated as 'w/out distinctive histopathology' – heavily associated with bvFTD.
- Rare mutations associated with ALS/FTD, but most cases with FUS deposition are not thought to be due to mutation.
- Discovered as chimeric protein in CA. Role in RNA life cycle/ splicing/maturation → ↑ plasticity, also binds with nuclear receptors → initiation/repression of transcription (from miRNA inhibition).
- Appears rapidly at sites of DNA damage w/HDAC → DNA repair; mutations in FUS nuclear localization sequence impairs poly ADP-ribose polymerase (PARP)-dependent DNA damage response.
- Suggests possible role in aging, in terms of preventing senescence?
- Like TDP-43, primary nuclear localization (NLS) appears to fail (rare mutations affect NLS) → pathological cytoplasmic aggregation.
- *Role of two DNA/RNA bp in FTLD suggests neurodegeneration may be initiated by failure of core nuclear RNA machinery?*

FUS/TLS protein functional chart – sizable functional overlap w/TDP-43



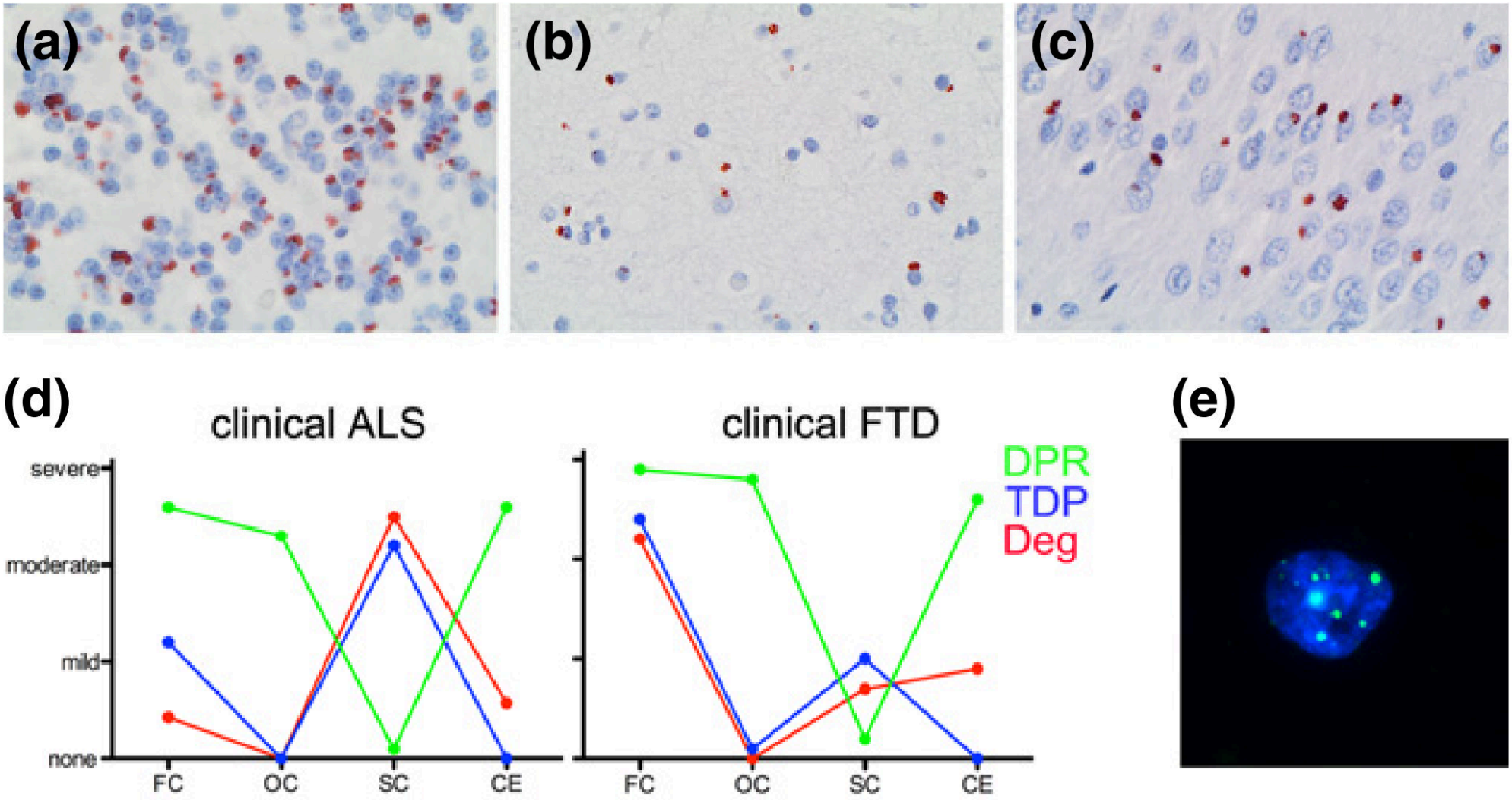
Abnormal expansion of a hexanucleotide repeat in noncoding region of chromosome 9 open reading frame 72 gene → RNA toxicity?

- Discovery in 2011, mutation in C9orf72 'expansion repeats'. ***Most common genetic cause of both ALS & FTD*** – basis by which ALS & FTD co-occur in families. Gene regulates RAB GTPase (membranes/vesicles fxn) → LOF? (N/A) RNA transcribed w/expanded GGGGCC repeats → 5 dipeptides (both 'junk').
- Toxic GOF: RNA accumulation in nucleus & cytoplasm: (1) Intranuclear G4C2exp RNA foci, (2) dysregulated gene expression, (3) sequestration of RNA bp, (4) susceptibility to excitotoxicity (GLUT). ***Toxicity via disrupted nucleocytoplasmic transport***. Dipeptides also → ER stress, OS, ⊣stress granules, deficits in translation, DNA repair but RNA appears more toxic.
- Drosophila cells w/expanded G4C2 repeat & also human in vitro (aged iPSC-derived neurons ← C9ORF72r) both show defect in RNA export, with clear 'dosage effect' around number of repeats. Yields RNA 'foci' in nucleus.
- These studies imply a novel mechanism of neurodegeneration: ***compromise of nucleocytoplasmic transport through the nuclear pore***.
- 'Genetic anticipation' (successive amplification) may exist for this mutation, as seen in Huntington's (CAG repeat expansion). Repeats variable CNS vs. serum.



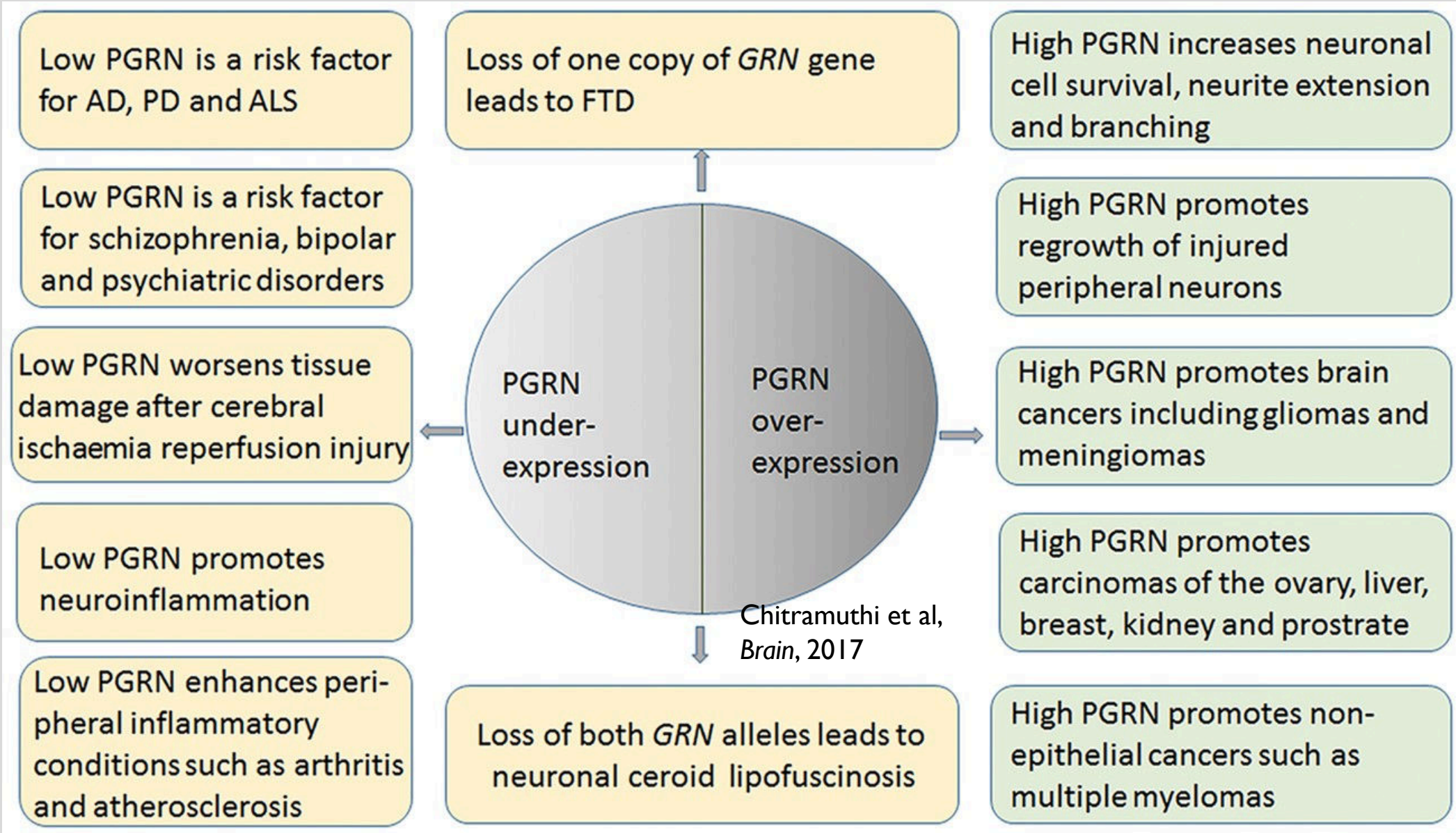
(1) C9orf72 hexanucleotide repeats transcribed→ toxic mRNA (G-quads/hairpins→ sequester DBPs). In cytoplasm C9orf72R is RAN-translated into dipeptide repeat proteins (DPRs). **(2a)** DPRs or **(2b)** FUS/TDP43muta –⊣ nucleo-cytoplasmic transport. **(2c)** Cell stress (or BP mutation) → cytoplasmic accumulation of TDP-43. **(3)** Altered RNA metabolism, as TDP-43/FUS not imported into nucleus → splicing defects, altered miRNA biogenesis, & disrupted mRNAs. **(4)** ALS/FTD mutations impair BP dynamics and nuclear re-import of these BPs → ↑ aberrant/ insoluble cytoplasmic aggregates. (5) Age-related oxidative damage of nuclear pore components w/↓importins could synergize w/genetic mutations and/or environmental factors to –⊣ ***nucleocytoplasmic transport*** → ***ALS/FTD***.

TDP43 agg but not dipeptide deposition correlated with ND



Dipeptide repeat pathology (DPR) in C9orf72 mutation. (a) TDP-43-negative neuronal cytoplasmic inclusions (NCI) in cerebellar granular layer, (b) NCI in frontal cortex, (c) NCI in hippocampal dentate granule cells, (d) anatomical distribution of DPR pathology in phenotypic subgroups with C9orf72 mutation, (e) RNA foci in neuronal nucleus. (a), p62 immunohistochemistry (IHC); (b), polyGA IHC; (c), poly-GP IHC; (e), RNA FISH with (GGGGCC)n probe. CE cerebellum; Deg, degeneration; FC, frontal cortex; OC, occipital cortex; SC, spinal cord. (Mackenzie and Neumann 2016)

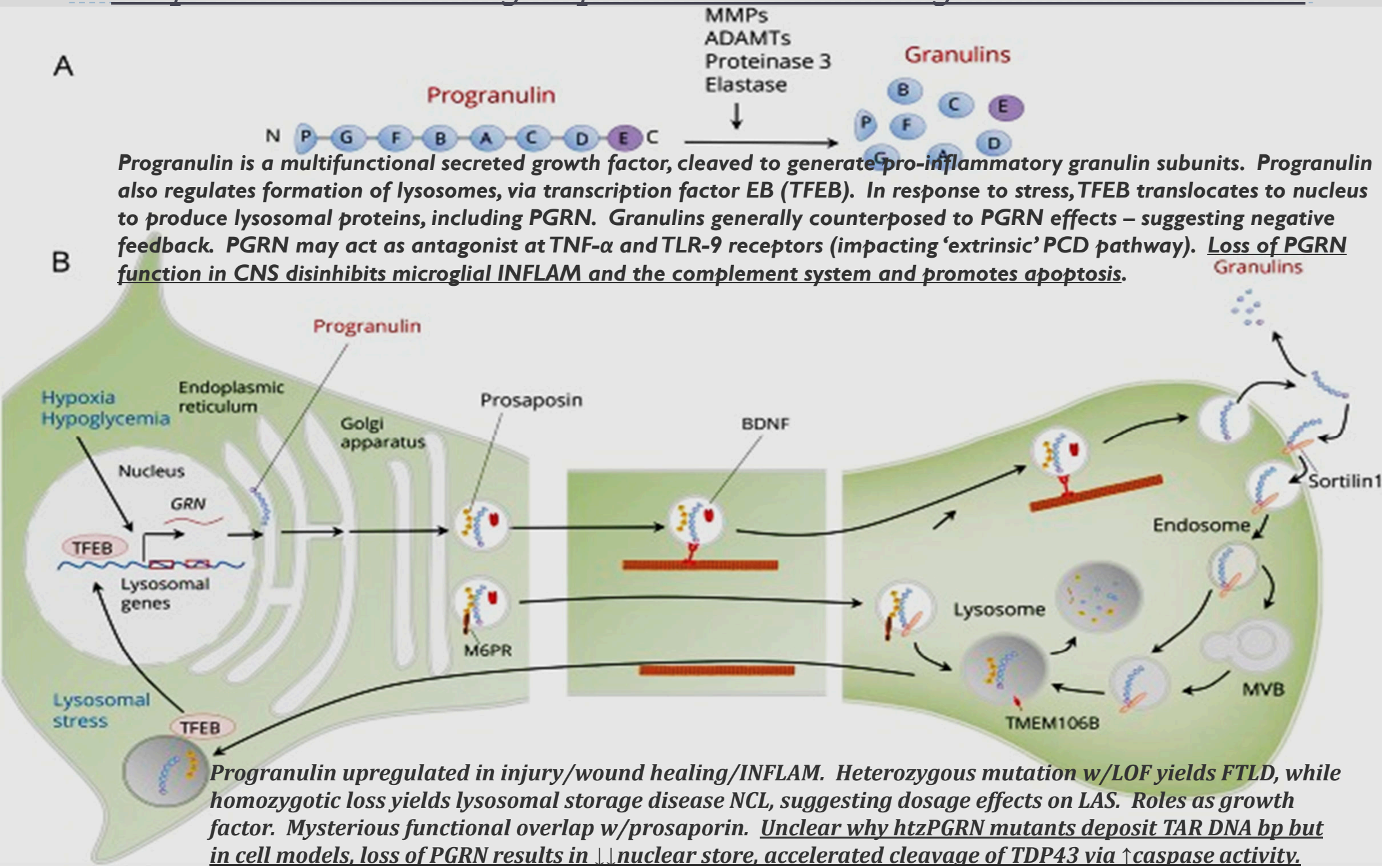
Dosage effects – low PGRN promotes INFLAM, ↓healing, FTLD & psych disorders, but high PGRN promotes cancers, suggesting strong apoptosis modulation by dose



Chitramuthi et al, *Brain*, 2017

Progranulin – roles in autophagy, neuroplasticity, control of apoptosis and INFLAM (Townley et al, 2018)

All processes centrally implicated in neurodegenerative disorders

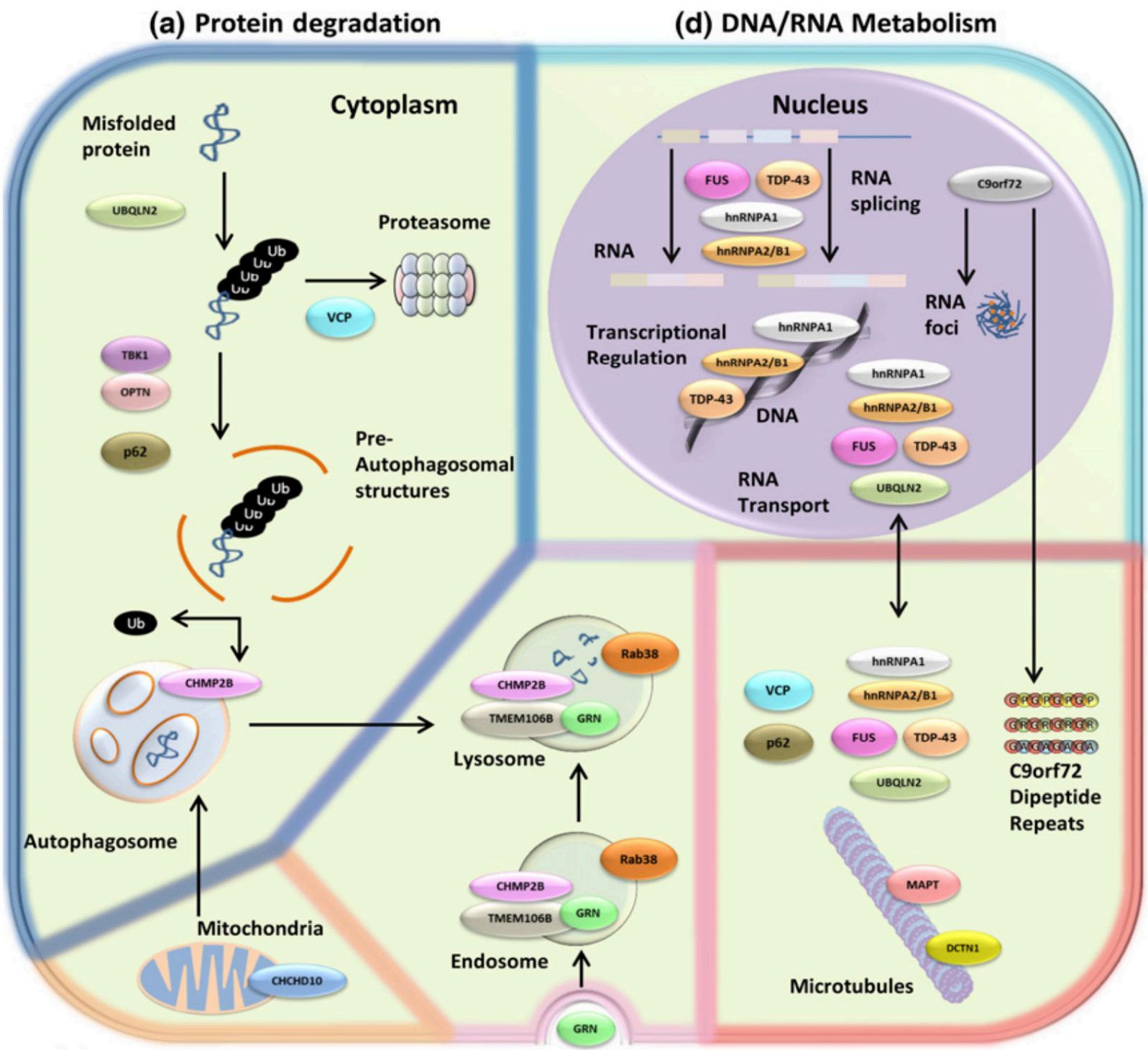


Progranulin is a multifunctional secreted growth factor, cleaved to generate pro-inflammatory granulin subunits. Progranulin also regulates formation of lysosomes, via transcription factor EB (TFEB). In response to stress, TFEB translocates to nucleus to produce lysosomal proteins, including PGRN. Granulins generally counterposed to PGRN effects – suggesting negative feedback. PGRN may act as antagonist at TNF-α and TLR-9 receptors (impacting 'extrinsic' PCD pathway). Loss of PGRN function in CNS disinhibits microglial INFLAM and the complement system and promotes apoptosis.

Progranulin upregulated in injury/wound healing/INFLAM. Heterozygous mutation w/LOF yields FTLD, while homozygotic loss yields lysosomal storage disease NCL, suggesting dosage effects on LAS. Roles as growth factor. Mysterious functional overlap w/prosaporin. Unclear why htzPGRN mutants deposit TAR DNA bp but in cell models, loss of PGRN results in ↓↓nuclear store, accelerated cleavage of TDP43 via ↑caspase activity.

A neglected part of the NDD storyline – primary loss of synapses/synaptopathy

- All neurodegenerative disorders are 'synaptopathies' – frequently neglected in focus on proteinopathy or even inflammation (known to impact synapses).
- ALS on autopsy: degradation of motor neuron terminals. In ALS/FTD, also of all classic corticostriatal pathways (↓glutamatergic & GABAergic synapses).
- Deletion of axon terminals appears correlated w/TDP 43 aggregation: many possible pathways but perhaps ↓ mRNA for synaptic proteins/vesicles?
- Suppression or knockout models of TDP 43 show abnormal synapses.
- Down regulation of similar RNAbp (FUS) → loss of dendritic spines & AMPA receptors, suggesting primary dependence of neuroplasticity on RNA BPs.
- Corticofugal (top-down) spread of TDP 43 aggregates suggests that synaptic loss may be heaviest in prefrontal and/or primary motor cortex areas and spread to lower motor neurons and basal ganglia from cortical neurons.
- Other data suggests dentate gyrus of the hippocampus is ND starting point, spreading to other classic limbic and paralimbic structures (esp. in LATE?).
- Some data suggests circadian dysfunction from early involvement of pineal body/suprachiasmatic nucleus in patients with chromosome 9orf72r forms.



(from Pottier et al, 2016 Special Issue on FTLD)

(a) Protein degradation: Ubiquitination tags proteins for degradation (UBQLN2) further transported either to proteasome (VCP) or pre-autophagosomal structures [OPTN/TBK1 complex, p62] which fuse to → autophagosomes (CHMP2B).

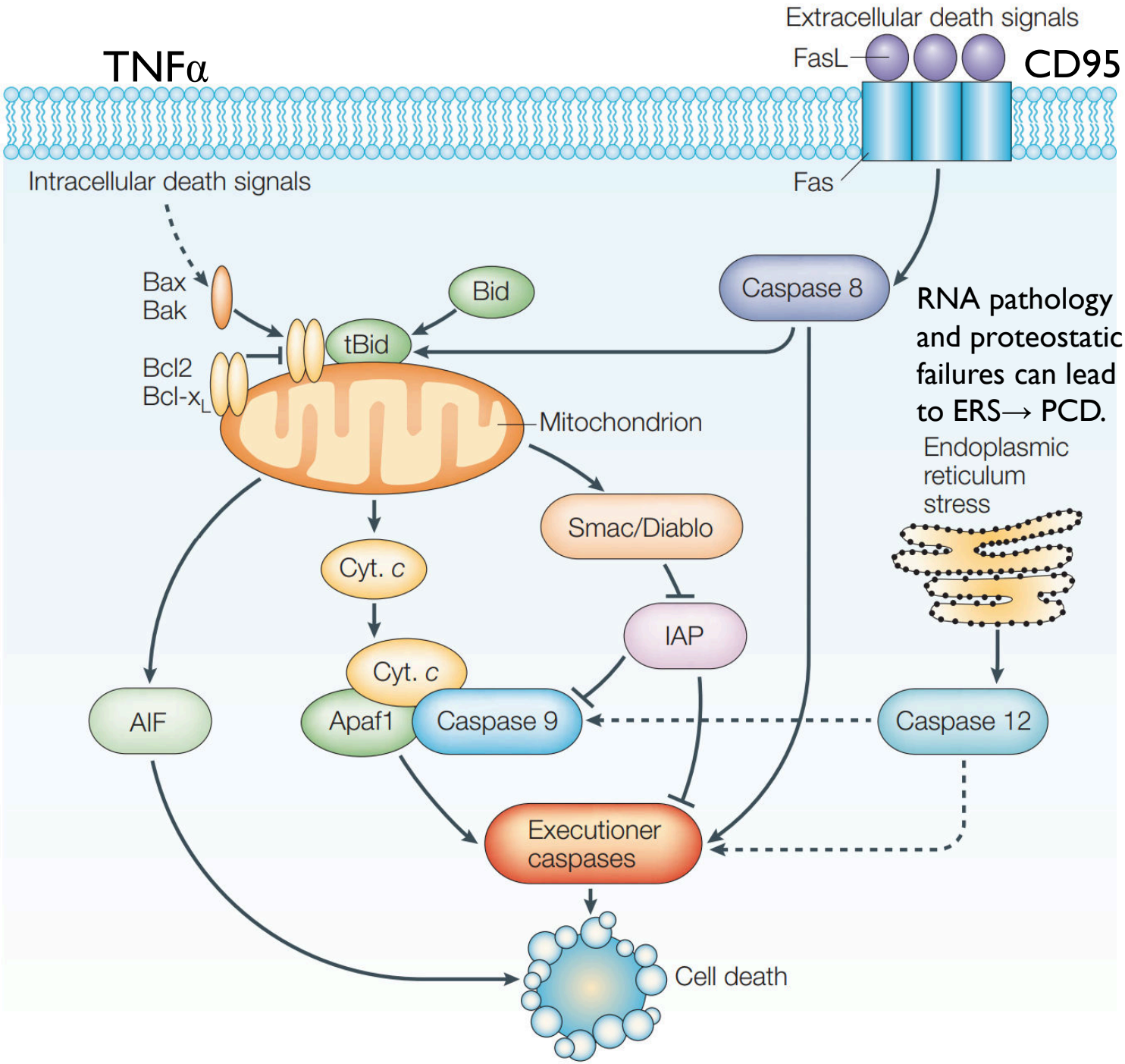
(b) Lysosomal trafficking - selective cargo recruitment [CHMP2B, Rab38, GRN TMEM106B,] & vesicle fusion (CHMP2B, Rab38).

(c) Mitochondrial dysfunction - (CHCHD10) leads to recycling of MITO into autophagosomes.

(d) DNA-RNA metabolism is disrupted via RNA aberrant splicing (TDP-43, FUS, hnRNPA1 hnRNPA2/B1), transcription regulation (TDP-43, hnRNPA1, hnRNPA2/B1), RNA transport (TDP-43, FUS, UBQLN2, hnRNPA1, hnRNPA2/B1) or by causing nuclear RNA foci (C9orf72).

(e) Protein aggregation: (VCP, p62, hnRNPA1, hnRNPA2/B1, TDP-43, FUS, UBQLN2, C9orf72 dipeptides, MAPT, and DCTN1) mutations → ↓ proteostasis.

Pathways into programmed cell death



Extracellular signals via cellular death receptors (Fas), and intracellular signals, including damage to subcellular constituents (esp. MITO) and/or endoplasmic reticulum stress, all trigger genetically conserved pathways for programmed cell death (PCD). The two main PCD pathways both drive activation of downstream executioner caspases →cell death. TNFα receptors can also provide extracellular death signaling. PSD part of ND continuum (w/pyroptosis and necrosis). All of these plus immune attack contribute to neurodegen,

AIF, apoptosis-inducing factor; Cyt., cytochrome; FasL, Fas ligand; IAP, inhibitor of apoptosis; tBid, truncated Bid.

Putting the pieces together – core frontotemporal–ALS disease pathways

- In common with all NDD, ***autophagy/lysosomal system heavily implicated***, in common PRGN mutations, & in rare mutations of other genes w/lysosome/endosome autophagy role (CHMP2B, VCP, UBQLN2, SQSTM1, TBK1, OPTN) which all tend to produce mixed FTLD-ALS.
- TMEM106B (dendrite morphogenesis/maintenance by regulating lysosomal trafficking) modulates LAS disruption from other genes, particularly PRGN and can be either protective or 'risky'.
- Disruption of axonal transport and integrity is implicated in FTLD w/tau mutations which disrupt microtubules –⊣ neural signaling/network function.
- A novel major pathway is disruption of RNA/DNA metabolism/lifecycle, by junk protein (dipeptides in C9orf72) and also by junk RNA – indexed by most common proteinopathy –TDP43 failure/deposition. Central to ALS?
- Roles for inflammation (big in AD), and mitochondrial dysfunction (big in PD) remain to be fully clarified, but evidence suggests gliosis tracks TDP43 but also tauopathy. Suggests inflammation critical in all NDD? Neglected?

Explanatory challenges in FTLD-ALS

- ***Diversity of clinical phenotypes, even in autosomal disease***: causal trajectories complex, from epigenetic, environmental & other genetic interactions? Differential vulnerability of neuronal populations in different regions? Roles of non-neuronal cells? Aging processes?
- What ties together PGRN, tau, & C9orf72R genes in terms of a degenerative pathway? What cellular processes tie together FUS, TDP-43, tau deposition as proteinopathies? How do very different mutations (***PGRN/C9orf72R***) create a shared proteinopathy (TAR DNA-43)?
- Partially mapped transactions between binding proteins/RNA, LAS (lysosome/autophagy), & nucleocytoplasmic 'shuttle'/ transport systems, as loci of proteostatic failure. Like other NDD, PS failure is precedent.
- What leads to gliosis? Why is this contribution to ND ignored? Relative roles of apoptosis, pyroptosis, & necrosis? mTOR disinhibition?
- What are logical approaches to therapeutics/target selection? Stage-specific? PGRN upregulation? In C9orf72e pts, blocking RAN translation to prevent toxic RNA/DPR with *antisense oligonucleotides*?

Treatments – both symptomatic and disease modifying – lack of good options!

- Classic symptomatically-focused psychopharm approaches in bvFTD show poor risk/benefit ratios. Neuroleptics → ↑ apathy in disinhibited patients, stimulants → ↑ disinhibition in apathetic patients. Classical antidepressants not shown effective.
- Parkinsonianism in PSP & CBD poorly responsive to classic levodopa Rx.
- Both cholinesterase inhibitors and Namenda ineffective in multiple trials.
- Disinhibition/apathy/personality change/lack of empathy all create *severe* caregiver stress. ***Behavioral care support***. Families need permission to hand off/limit care.
- Approaches to tauopathy (aggregation inhibitors like MB, tau antibodies, GSK-3 inhibitors) have all failed – echoing similar failure in Alzheimer's. TDP43?
- Absence of biomarkers (other than patterns of regional atrophy, and indexing progranulin in PGRN mutation patients) hampers designing clinical trials.
- ***Progranulin is attractive target***, especially for mutation carriers (Ca^{++} blockers, HDAC inhibitor, genticinG418), but also for other FTD. Approaches to ↓ inflammation? ***Adiponectin, other CR mimetics/autophagy promoters untested***. Why?
- Upregulating 'importins' ↑nucleocytoplasmic transport, antisense oligonucleotides to block toxic RNA and dipeptides in C9orf72r.

Challenges to a big picture view of NDD – some pieces of a massive puzzle not yet assembled

- Neurodegenerative disorders show multiple proteinopathies (PP), particularly as patients get older, suggesting PP pathways intersect, and arguing strongly against traditional 'boxology' models of NDD. *Sinking tides lower all boats?*
- Age-related vulnerabilities in proteostasis → ↑Aggregated proteins in NDD?
  - *Upregulated in aging, in compensatory neuroplasticity and/or immune challenge.*
  - *Challenging to autophagy systems or inhibiting of them – difficult to clear.*
  - *Prion-like properties when pathologically aggregated, phosphorylated, etc.*
  - *Therapeutic efforts targeting removal have been spectacular failures. Why? Too late? Wrong target altogether, or only helpful in combination with other targets?*
- Neurodegeneration must relate to cellular and biological phenotypes of aging. Interactive, and generally mutually promoting. Declining proteostasis is on the short list, but it's hardly alone. Disrupting 'amplifying recursions' may do more than any single target? Single factors memes are popular (AD)/easier to study.
- Whatever the complexities might be in protein aggregation & failed clearance, as NDDs advance, *atrophy and gliosis appear conjoined across many NDD*, suggesting that clinical stages = a destructive disinhibition of innate immunity, also seen in other DOA – ***we simply do not know how to inhibit this!***

Appendix

Histopathology, earlier classic papers, other misc.

Best comprehensive source for FTLD-ALS is ***https://onlinelibrary.wiley.com/toc/14714159/2016/138/S1*** *Journal of Neurochemistry (2016)*

Appendix – TDP 43 histopathological subtypes (Bigio J Mol Neurosci. 2011 Nov; 45(3): 390–401.

- The inclusions in FTLD-TDP type 1 (Cairns et al. 2007a; Sampathu et al. 2006; Mackenzie et al. 2006; Josephs et al. 2009; Armstrong et al. 2010) include neuronal cytoplasmic inclusions (NCIs), neuronal intranuclear inclusions (NIIs), and dystrophic neurites (DNs), predominantly in upper cortical layers. The dentate gyrus generally has few NCIs and occasional NIIs and few to absent DNs. Hippocampal sclerosis (HS) is uncommon, and subcortical gray matter and brainstem TDP pathology can be mild to severe. The clinical presentation can be that of either behavioral variant frontotemporal dementia (bvFTD) or primary progressive aphasia (PPA), and those with aphasia have either primary non-fluent aphasia or, less commonly, semantic dementia (SD). Clinical and pathologic ALS is sometimes present. A positive family history is common, present in up to 50% of cases, and mutations in progranulin (*GRN*) are most often found in familial cases. Males are affected slightly more frequently than females at an approximate ratio of 3:2, and the average duration of disease is 8.4 years.

Histopathological TDP 43 subtype 2

- In FTLD-TDP type 2 (Cairns et al. 2007a; Sampathu et al. 2006; Mackenzie et al. 2006; Josephs et al. 2009; Armstrong et al. 2010), DNs, sometimes described as “long,” predominate over NCIs and may be predominantly located in upper cortical layers. NIIs are infrequent to absent. The dentate gyrus may have few to moderate NCIs, but NIIs are absent and DNs are few to absent. HS can be prominent. Subcortical gray matter TDP pathology is generally moderate, and brainstem TDP pathology is rare. The clinical presentation can be bvFTD but is more commonly PPA, most often SD.you ALS is uncommon. Family history is positive in approximately 30% of cases, but there are as yet no known associated genetic mutations. Males and females are equally affected, and the average duration of disease is 8.1 years.

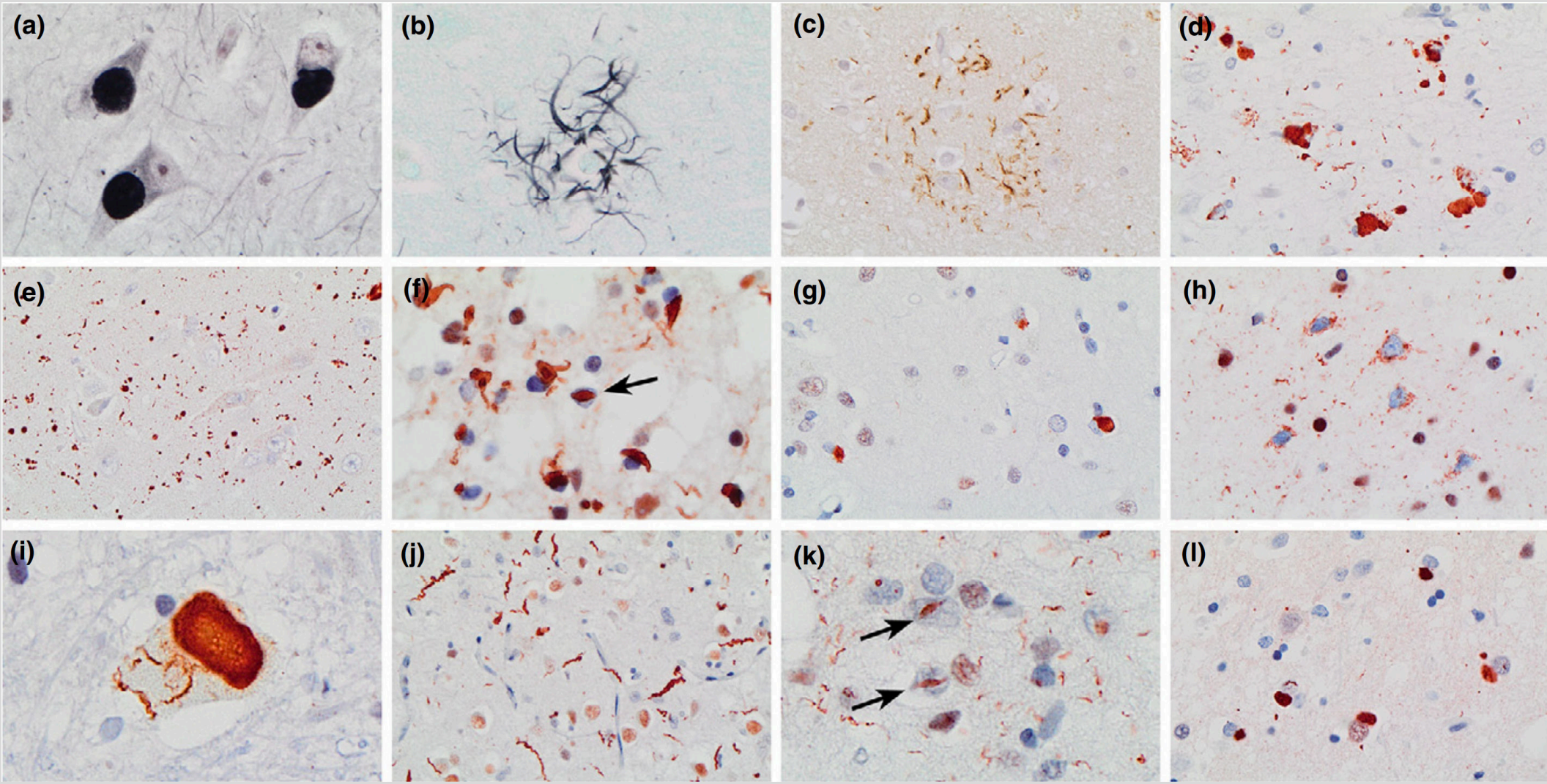
Histopathological TDP 43 subtype 3

- Type 3 FTLD-TDP (Cairns et al. 2007a; Sampathu et al. 2006; Mackenzie et al. 2006; Josephs et al. 2009; Armstrong et al. 2010; Brandmeir et al. 2008; Gitcho et al. 2009) pathology consists predominantly of NCIs, which may be present in lower as well as upper cortical layers. NIIs and DNs are rare. In many type 3 cases, NCIs are frequent in the dentate gyrus, and in some of these, the cortical DNs are few. In others, however, dentate gyrus NCIs are few. HS is often prominent, while subcortical gray and brainstem TDP pathology can be mild to severe. The clinical presentation is most often bvFTD and rarely PPA, and ALS is often present. About one-third of cases have a positive family history; some of these are due to mutations in *TARDBP*, and some of these are in families with linkage to chromosome 9p. Males are affected more often than females at a ratio of 3:1. The average duration of disease is shorter than in the other two groups at 5.4 years, likely because more of these cases have ALS.

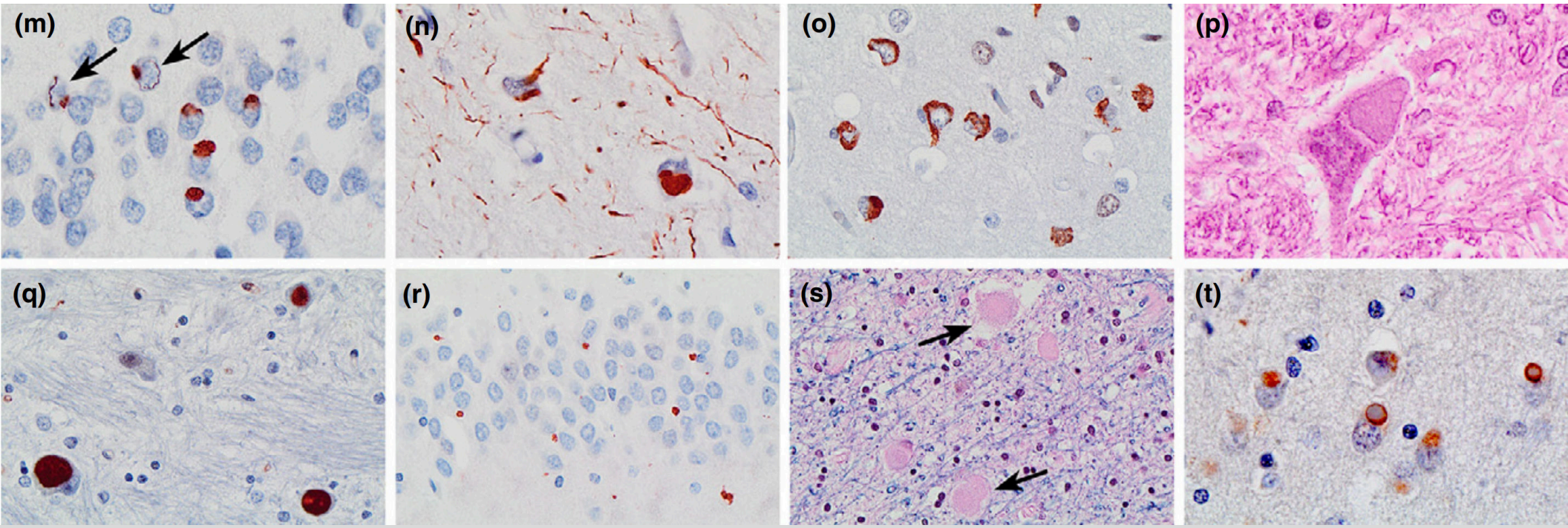
Histopathological TDP 43 subtypes 4

- FTLD-TDP Type 4 pathology (Cairns et al. 2007a; Mackenzie et al. 2010; Forman et al. 2006; Guinto et al. 2007) consists almost entirely of frequent NIIs and infrequent NCIs and DNs in upper layers with relative sparing of the dentate gyrus. HS is usually absent. Subcortical gray matter TDP pathology may be moderate, and brainstem TDP pathology is often mild. Patients are equally likely to present with bvFTD or PPA. ALS is not part of the disease, but inclusion body myositis may be present. The full clinical spectrum of the disease, not always present in each affected individual, includes inclusion body myositis, Paget's disease of the bone, and frontotemporal dementia (IBM-PFD). Family history is positive in virtually all cases, as all are related to mutations in the gene for valosin-containing protein (*VCP*). Males and females are equally affected, and the average duration of disease is 13.3 years.

- Neurogenetics. 2007 Nov;8(4):237-48. Epub 2007 Sep 6.
- **The molecular genetics and neuropathology of frontotemporal lobar degeneration: recent developments.**
- Mackenzie IR, Rademakers R.
- Department of Pathology, Vancouver General Hospital, 855 West 12th Avenue, Vancouver, BC, V5Z 1M9, Canada. ian.mackenzie@vch.ca
- Significant advances in past year in understanding of neuropathological and molecular genetic basis of frontotemporal lobar degeneration (FTLD).
- Whereas, in the past, most attention focused on FTLD associated with tau-based pathology and tau mutations, recently greater attention paid to non-tau FTLD.
- FTLD with tau-negative, ubiquitinated inclusions (FTLD-U) is now recognized as the most common pathology associated with clinical FTLD. Mutations in the progranulin gene (PGRN) have been identified as the cause of FTLD-U linked to chromosome 17. A rapidly growing number of PGRN mutations have been identified, and to date, all appear to cause FTLD by reducing the amount of functional PGRN protein (haploinsufficiency).
- The neuropathology associated with each of the non-MAPT FTLD genes and loci (PGRN, valosin-containing protein gene, CHMP2B and 9p), has been shown to be a specific subtype of FTLD-U. The ubiquitinated pathological protein in FTLD-U has been identified as TAR DNA-binding protein with M (r) 43 kDa (TDP-43).
- It is anticipated that these discoveries will facilitate the development of new diagnostic tests and therapeutics.



Neuropathological features of FTLD subtypes: (a) Pick bodies, (b) tufted astrocyte in PSP, (c) astrocytic plaque in corticobasal degeneration, (d) globular glial inclusions, (e) argyrophilic grains, (f) FTLD-TDP type A w/short neurites, neuronal cytoplasmic inclusions (NCI), lentiform neuronal intranuclear inclusions (NII, arrow) in layer II, (g) FTLD-TDP type B w/NCI in deep cortical laminae, (h) neuronal pre-inclusions, (i) amyotrophic lateral sclerosis (ALS) type NCI in lower motor neuron, (j) FTLD-TDP type C with long neurites, (k) FTLD-TDP type D with short neurites and NII (arrows), (l) oval NCI in neocortex of atypical frontotemporal lobar degeneration w/ubiquitin-positive inclusions (aFTLD-U)



Neuropathological features of FTLD subtypes continued: (m) vermiform NII (arrows) & oval NCI in hippocampal dentate granule cells of aFTLD-U, (n) intermediate filament-positive NCI in neuronal intermediate filament inclusion disease (NIFID), (o) NCI of varying morphology in NIFID, (p and q) basophilic inclusion bodies, (r) ubiquitin-positive NCI in hippocampus of frontotemporal dementia (FTD) with CHMP2B mutation, (s) axonal spheroids (arrows) in cerebral white matter in hereditary leukodystrophy with spheroids, (t) PRKAR1B-positive NCI in familial FTD with PRKAR1B mutation. (a), Bielschowsky silver stain; (b), Gallyas silver stain; (c–e), tau immunohistochemistry (IHC); (f–k), TDP-43 IHC; (l,m and q), fused in sarcoma (FUS) IHC; (n), a-internexin IHC; (o), TAF15 IHC: (p), hematoxylin and eosin (HE) stain; (r), ubiquitin IHC; (s), combined HE/Luxol fast blue stain; (t), PRKAR1B IHC

Table 1 Characteristic FDG PET findings in neurodegenerative diseases

Disease	Brain regions with reduced FDG uptake
Alzheimer disease (AD)	temporoparietal association cortex posterior cingulate cortex and precuneus variably also frontolateral association cortex
Dementia with Lewy bodies (LBD)	as in AD, plus primary visual cortex
Frontotemporal dementia (FTD)	predominantly frontomesial, also frontolateral and temporal
Parkinson disease	cortical impairment similar to LBD possible (high uptake preserved in striatum)
Multiple system atrophy*	putamen, brainstem, cerebellum, often also cerebral cortex
Progressive supranuclear palsy	frontal, basal ganglia and midbrain
Corticobasal degeneration	mainly parietal and central cortex, striatum and thalamus possibly also frontal cortex often very asymmetric
Spinocerebellar degeneration	variable, depending on subtype, may be similar to MSA
Chorea Huntington	caudate nuclei, putamen, with progression also thalamus and cortex

*: including sporadic olivopontocerebellar atrophy and striatonigral degeneration

FTD seen to have amnestic presentation, mimicking AD, as far back as 2005

- Early/severe memory impairment is generally held to be an exclusion criterion for the clinical diagnosis of frontotemporal dementia (FTD).
- The present study (Graham et al., 2005 *Brain*) examined records of all patients in Cambridge–Sydney neuropathological series of patients with dementia and a pathological diagnosis of FTD to identify those for whom STM complaints were dominant at presentation.
- 8/71 patients met criteria. For two patients, memory loss was only complaint; for one patient, memory loss accompanied by personality change; for two more patients, memory loss accompanied by prominent dysexecutive symptoms; and for three patients, memory loss found with apathy but no other behavioral changes.
- In 7/8 patients local teams initially diagnosed AD; treated with ACh Rx.
- All 8/71 later developed behavioral features: in 4/8, the diagnosis was revised to FTD, while in other 4/8, the diagnosis of FTD was made only on neuropathological examination after death.
- In conclusion, severe amnesia at presentation in FTD is more common than previously thought, suggesting clinical criteria for diagnosis of FTD may need revision. The underlying basis of memory impairments in FTD patients may be heterogeneous.

Table 2 *Clinical presentation, imaging results and pathological diagnosis for all patients*

	Patient							
	1	2	3	4	5	6	7	8
Pathological series	Cambridge	Cambridge	Cambridge	Sydney	Sydney	Sydney	Sydney	Sydney
Sex	M	F	M	F	M	F	M	F
Age at first presentation	62	53	50	62	77	63	55	44
Duration of symptoms before presentation	2 years	3 years	1.5 years	0.5 years	2 years	5 years	1 year	1 year
Age at death (yr)	69	55	52	70	89	70	56	62
Main initial complaint(s)	Memory loss	Memory loss, personality change, many fixed routines	Memory loss	Memory loss, apathy and neglect of personal hygiene	Memory loss and apathy	Memory loss and difficulties with any tasks involving judgement or decision-making	Memory loss and apathy	Memory loss and difficulties with any tasks involving judgement or decision-making
Past medical history	Depression, high cholesterol	Unremarkable	Unremarkable	Parkinson's disease	Unremarkable	Unremarkable	Unremarkable	Unremarkable
Family history of dementia	None	None	None	None	Patient's father, two paternal aunts and seven siblings all developed a dementia in later life	None	None	Mother developed dementia in later life
Examination	Unremarkable	Unremarkable	Unremarkable	Tremor, rigidity and bradykinesia of the limbs, R > L	Unremarkable	Unremarkable	Unremarkable	Unremarkable
Imaging	MRI: diffuse involutional changes with marked atrophy of both hippocampi. HMPAO-SPECT: biparietal and frontal hypoperfusion	MRI: moderate generalised atrophy, marked at the left temporal pole. HMPAO-SPECT: left temporal and parietal hypoperfusion	MRI: mild diffuse involutional changes. HMPAO-SPECT: left frontal hypoperfusion	None performed	CT: mild generalized atrophy and dilatation of both lateral ventricles	CT: moderate generalized atrophy and dilatation of both lateral ventricles	None performed	CT: mild generalized atrophy

Initial clinical diagnosis, clinical progression, and final histopathological diagnosis (Graham et al., 2005)

Initial clinical diagnosis	AD	FTD	AD	PD plus AD	AD (Familial)	AD	AD	AD
Neuropsychology: WMS-LM, VR[a]	3	3	3	2	3	2	–	4
Neuropsychology: RAVLT[b]	–	–	3	–	4	–	4	4
Clinical progression	Became mildly parkinsonian; two generalized seizures; later hyperorality, mute, difficulty in swallowing	Pronounced behavioural disturbance; arrested for assault and shoplifting. Died of bronchial carcinoma	Repetitive and obsessive behaviours; disinhibition; increase in preference for sweet foods	Increase in preference for sweet foods; later hyperorality and urinary incontinence without insight	Progressively apathetic; gross neglect of personal hygiene and housework without insight	Apathetic; marked echolalia; bruxism leading to recurrent dislocation of the jaw	Died soon after diagnosis due to a myocardial infarction	Very slow progression, became apathetic and incontinent of urine, lack of insight
Final clinical diagnosis	AD or DLB	FTD	FTD	PD plus dementia (unspecified)	AD (familial)	FTD	AD	FTD
Pathological diagnosis	FTD-MND	FTD with Pick bodies	CBD	FTD with Pick bodies	FTD with Pick bodies	FTD lacking distinctive histology	FTD lacking distinctive histology	FTD lacking distinctive histology
Global staging of severity of brain atrophy (0–4)[c]	2	3	1	3	3	3	1	3

AD = Alzheimer's disease; FTD = frontotemporal dementia; PD = Parkinson's disease; DLB = dementia with Lewy bodies; CBD = corticobasal degeneration; HMPAO-SPECT = [99mTc]-hexamethyl propyleneamine oxime single photon emission computed tomography. [a]Wechsler Memory Scale = Logical Memory and Visual Reproduction subscales (Wechsler, 1987); [b]Rey Auditory Verbal Learning Test (Schmidt, 1996). For both WMS-LM, VR and RAVLT, results are rated as follows: 0 = within normal range (within 1 standard deviation of control mean); 1 = below average (between 1 and 2 SD below control mean); 2 = impaired (more than 2 SD below control mean); 3 = very impaired but able to complete task; 4 = too impaired to complete task; – = task not performed/data not available. [c]Global staging of severity of brain atrophy: stage 0 = no atrophy; stage 1 = mild atrophy = confined to orbital and superior medial frontal cortex and hippocampus; stage 2 = moderate atrophy = confined to frontal cortex = temporal cortex and basal ganglia; stage 3 = severe atrophy of orbital and superior medial frontal cortex and hippocampus; stage 4 = severe global atrophy (Broe *et al.* = 2003).

Neurodegenerative Disorders as Proteinopathies

with both sporadic and familial subtypes

Table 1 Neurodegenerative diseases characterized by the deposition of aggregated proteins

Toxic protein	Protein deposit	Familial disease	Gene mutated	Sporadic disease	Risk factor
β-amyloid	Senile plaques	FAD	*APP* *PS1* *PS2*	Alzheimer disease	*Apoe4*
Tau	Neuronal and glial inclusions	FTDP-17 inclusions	*MAPT*	AD and tauopathies[a]	*MAPT* haplotype
α-synuclein	Lewy bodies Lewy neurites	Familial PD[b]	*SNCA* (α-synuclein)	Lewy body disease[c]	*SNCA* polymorphism *MAPT* haplotype
	Glial cytoplasmic inclusions	Not identified	Not applicable	Multiple system atrophy	Not identified
Polyglutamine repeat expansion	Nuclear and cytoplasmic inclusions	Huntington disease Kennedy disease DRPLA SCA1 SCA2 SCA3 SCA6 SCA7 SCA17	*HD* (huntingtin) *AR* (androgen receptor) *DRPLA* (atrophin-1) *ATXN1* (ataxin-1) *ATXN2* (ataxin-2) *ATXN3* (ataxin-3) *CACNA1A*[d] *ATXN7* (ataxin-7) *TBP* (TATA binding protein)	Not applicable	Not identified
PrP^{SC}	Protease-resistant PrP[e]	Familial prion protein disease[f]	*PRNP*	Sporadic prion protein disease[g]	*PRNP* polymorphism
SOD	Hyaline inclusions	Autosomal dominant familial ALS	*SOD1* (Cu/Zn SOD)	Sporadic ALS	Not identified
ABri/ADan	Amyloid plaques and angiopathy	Familial British/Danish dementia	*BRI*	Not identified	Not identified
Neuroserpin	Collins bodies	FENIB[h]	*SERPINI1* (neuroserpin)	Not identified	Not identified

- Frontal Dementias Etiological, Clinical, Therapeutical and Pathological Aspects 3rd International Conference, Lund, Sweden, August, 1998

- **Comparative Cognitive Neuropsychological Studies of Frontal Lobe Function: Implications for Therapeutic Strategies in Frontal Variant Frontotemporal Dementia**
  S. Rahman, T.W. Robbins, B.J. Sahakian

  Patients with mild frontal variant frontotemporal dementia (fvFTD) are usually unaware of pervasive changes in their personality and behavior, despite how these changes have prompted the referral from the patient's spouse or caregiver. *They may show marked deficits on tests sensitive to ventromedial prefrontal/orbitofrontal function, in relative absence of impairments on tests sensitive to dorsolateral prefrontal function.* The specific nature of these neuropsychological deficits, together with converging evidence from clinical and neuropathological studies, may provide useful clues about predominant locus of dysfunction in early stage fvFTD.

- NOTE: Studies have demonstrated early orbital hypoperfusion on SPECT and PET imaging in many FTD patients, also suggesting early orbital/ventral medial prefrontal involvement.

Behavioral Variant FTD
(Rabinovici and Miller)

- ***Marked changes in personality/behavior, often mixture of apathy and disinhibition***. Apathy is characterized by loss of interest in personal affairs and responsibilities, social withdrawal and, as disease advances, loss of awareness of personal hygiene and even sphincter control.
- ***Disinhibition is manifested by a multitude of socially inappropriate behaviors,*** including confrontation seeking, making hurtful or insensitive remarks, or engaging in frankly sociopathic behaviors (e.g. shoplifting, traffic violations) or (rarely) physical assault. Patients can appear cold, unempathetic, showing little concern for the effect of their behavior on loved ones.
- ***Insight is dramatically impaired,*** with either frank denial of illness or very shallow recognition of a cognitive problem (often described as mild memory problems or word-finding difficulties).
- ***Some patients develop dramatic changes in religious beliefs, political convictions, or dress and social style***, personality changes that are so profound they have been described as a "change in self".
- ***Repetitive motor behaviors*** (e.g. rubbing, picking, throat clearing, pacing and wandering), idiosyncratic hoarding and collecting, changes in eating behaviour (e.g. overeating and weight gain, loss of table manners) and hyperorality (including oral exploration of inedible objects) are also common.

- **Pick Complex: An integrative approach to frontotemporal dementia: primary progressive aphasia, corticobasal degeneration, progressive supranuclear palsy.**

- Kertesz A. Department of Clinical Neurological Sciences, St. Joseph's Hospital, University of Western Ontario, London, Ontario, Canada. andrew.kertesz@sjhc.london.on.ca (2003)
- BACKGROUND: Frontotemporal dementia (FTD) is a new label for clinical Pick's disease (PiD) because the eponymic term is increasingly restricted to pathologic finding of Pick bodies. This restriction created impression that PiD is rare and that is it difficult to diagnose. FTD is also a term most often used for behavioral and personality alterations. Primary progressive aphasia (PPA) and corticobasal degeneration (CBD), formerly the extrapyramidal variety of PiD, are also part of the syndrome. Recently, chromosome 17 localization and tau mutations were discovered in familial forms of the disease.
- REVIEW SUMMARY: FTD consists of behavioral and personality changes, often beginning with apathy and disinterest, which may be mistaken for depression. Disinhibition and perseverative, compulsive behavior often appear at the same time. A quantifiable frontal behavioral inventory is useful in the diagnosis beyond a checklist. The second type of presentation is progressive language loss (PPA). A less common variety is semantic dementia: the meaning of nouns and objects is lost. As the disease progresses, all components tend to overlap. CBD and progressive supranuclear palsy (PSP), although described as distinct entities, show great deal of clinical, pathologic, genetic, & biochemical overlap. The evidence suggests they also belong to the complex. The association of motor neuron disease (MND) with FTD complex is reviewed.
- CONCLUSIONS: Clinical Pick's disease or Pick Complex includes the overlapping syndromes of FTD, PPA, CBD, PSP, and FTD-MND. The neuropathological and genetic spectrum should be viewed with emphasis on the commonalities rather than the differences, allowing recognition of relatively high frequency of this presenile syndrome.