Diagnosis of Fronto Temporal Lobar Degenerations (FTLD)

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Disclosure

None

Learning objectives

- Clarify the complex FTLD scenario
- Provide basic knowledge of these neurodegenerative disorders
- Present the current neuropathological and molecular data of FTLD
- Describe the clinical features of the different types of FTLD
- Give to the clinical neurologist a diagnostic approach in front of an clinical case evocative of FTLD spectrum

Key message

- FTLD : spectrum of neurodegenerative disorders characterized by a degeneration of the frontal and anterior temporal lobe; complex and heterogeneous diseases
- One of the most common forms of presenile dementia
- Several different proteins aggregates : tau, TDP-43, FUS…
- Many genes (MAPT, C9ORF72, GRN, VCP…), explaining 50-60% of familial FTLD
- Wide spectrum of disorders : bvFTD, nfvPPA, svPPA, PSP, CBDS, FTLD-ALS…
- Diagnostic approach : clinical phenotype, family history, location of atrophy on MRI, exclusion of treatable neurological and psychiatric conditions
- Consider genetic testing if family history or certain clinical features

OUTLINE

Introduction

FTLD proteotypes / Neuropathology

FTLD genotypes / Genetics

FTLD phenotypes / Clinical description:

- Major phenotypes
- Related phenotypes

Diagnostic approach of FTLD syndromes

Introduction (1)

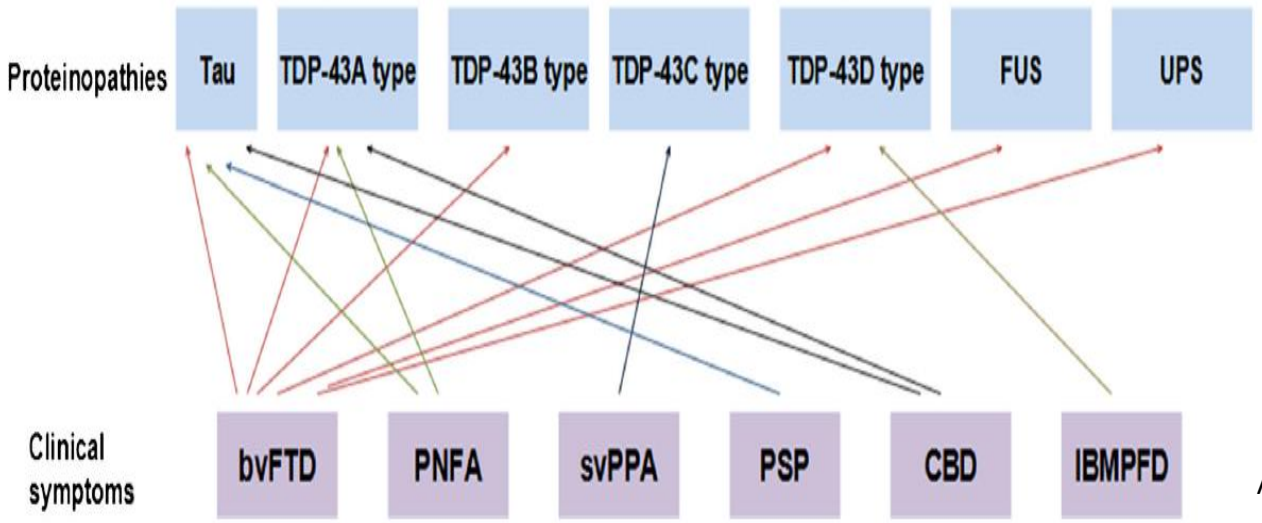
- FTLD : spectrum of neurodegenerative disorders characterized by a degeneration primarily located in the frontal and anterior temporal lobe
- One of the most common forms of presenile dementia
- Variability and overlapping in clinical, genetic and histopathologic features
- Symptoms ranging from behavioral and executive disturbances to different language disorders +/- motor neuron disorders or parkinsonism
- Different proteins detected in aggregates : Tau, TAR-DNA-Binding Protein-43 (TDP-43), Fused in Sarcoma (FUS) and other ubiquitin proteins (U)
- Many causative genes described, mostly MAPT, C9Orf72, GRN, VCP….

Introduction (2)

- FTLD : reserved for patients with clinical presentations of FTD and identification of an FTD-causing mutation or histopathologic evidence of FTD
- FrontoTemporal Dementia (FTD) : refers to one of several clinical subtypes, defined by the hallmark patterns of symptoms and signs observed
- Syndromes assigned to the FTLD spectrum (Seltman and Matthews 2012):
  - the 3 types FTD :
    - behavioral variant of frontotemporal dementia (bvFTD)
    - semantic and non-fluent variant of primary progressive aphasia (svPPA and nfvPPA)
  - FTD with motor neuron disease (FTD-MND), mainly ALS (FTD-ALS)
  - Progressive supranuclear palsy (PSP)
  - Corticobasal syndrome (CBS)

FTLD proteotypes / Neuropathology

- FTLD characterized by proteinaceous intracellular aggregates in the brain
- Two pathologic categories of FTLD according to the protein observed :
  - microtubule-associated protein Tau in about 40% of FTLD
  - ubiquitin proteins in about 60% of FTLD; among them :
    - transactive response (TAR) DNA binding protein 43 (TDP-43) in 80%
    - fused in sarcoma protein (FUS) in 10%
- Each FTLD pathological subtype can cause several FTD syndromes



Molecular and genetic classification of FTLD
Adapted from Li et al., 2015

FTLD-tau

- Tau protein stabilizes axonal microtubules by interacting with tubulin
- Encoded by the microtubule-associated protein tau (MAPT) gene → 6 tau isoforms produced by alternative splicing, different expressions
- MAPT mutations consistently associated with tau pathology
- Tau becomes aberrantly hyperphosphorylated, dissociates from microtubules, and forms aggregates within neurons and glia
- Among FTLD cases, different electrophoretic profiles (Noble et al., 2013) :
  - phosphorylated 3R isoforms (3R tauopathy) → Pick's disease (PiD)
  - phosphorylated 4R isoforms (4R tauopathy) → PSP, CBD

FTLD-TDP

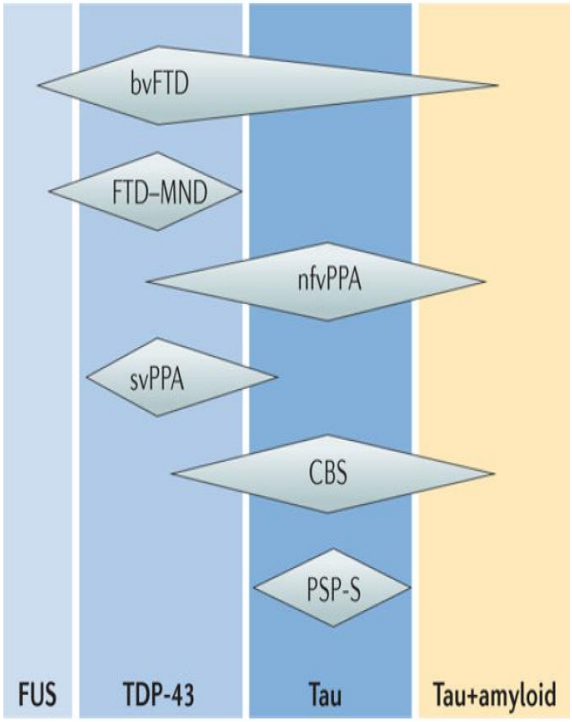
- TARDNA-binding protein 43 (TDP-43) : major ubiquitinated protein associated with tau-negative FTLD
- TDP-43 encoded by the TARDBP gene
- About 50% of FTLD patients have aggregates positive for TDP-43
- TDP-43 subclassified according to patterns of TDP-43-containing neuronal cytoplasmic inclusions and dystrophic neurites in diseased neurons
- 4 subtypes of FTLD-TDP, according to morphological appearance of inclusions and lesions distribution : types A to D (Mackenzie et al., 2010)

FTLD-FUS

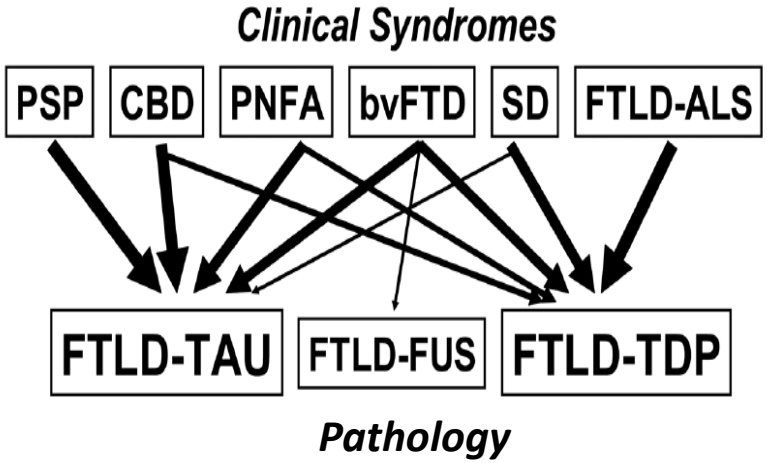
- Fused in sarcoma (FUS) : RNA-binding protein involved in splicing and nuclear export of mRNA
- FUS mutations mainly associated with bvFTD and FTD-MND (and ALS alone)
- Specific phenotype related to sporadic FTLD-FUS :
  - young onset (22–46 years)
  - prominent caudate atrophy
  - unique phenotypic features : marked obsessiveness, social withdrawal, hyperorality, stimulus-bound repetitive, ritualistic behaviours
  - cognitive profile : subcortical executive dysfunction in the absence of cortical language, perceptual and praxis impairments

Correlations phenotype/proteotype

- bv-FTD : all molecular subtypes
- nfv-PPA (PNFA) : around 85% show 4R or 3R tau pathology
- CBDS : mainly 4R tau pathology
- PSP : 4R tau pathology
- sv-PPA (SD) : 90% of TDP-43 (type C)
- FTD–ALS : almost always TDP-43 pathology (usually type B)



Clinico-pathological correlations for FTLD (FTLD pathologies in blue)
Elahi & Miller, 2017



Adapted from Rabinovici & Miller, 2010

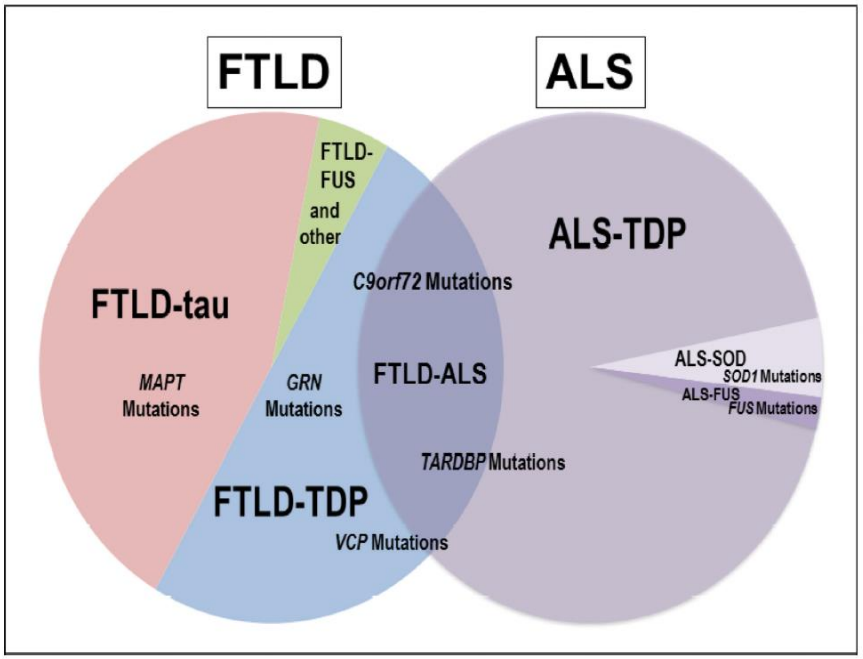
FTLD genotypes / Genetics

- Positive family history observed in 40–50 % of the FTLD
- About 10-15% show a clear autosomal dominant inheritance pattern
- In familial FTLD, genes associated with homogenous pathological signatures
- Many genes identified, currently explaining 50-60% of familial FTLD
- FTLD-tau : associated with MAPT mutations
- FTLD-TDP : very diverse mutations, 4 main molecular etiologies
  - Mutations in chromosome 9 open reading frame 72 gene (*C9orf72*)
  - Mutations in the progranulin gene (*GRN*)
  - Mutations in valosin-containing protein gene (*VCP)* and TAR DNA-binding protein gene (*TARDBP*)

Genetics of FTLD

- MAPT, GRN and C9ORF72 mutations : at least 17% of familial FTLD
  - MAPT → mainly bvFTD, PPA; parkinsonism; no ALS
  - C9ORF 72 → FTD, FTD-ALS and ALS
  - GRN → parkinsomism in 40%; bvFTD in 60% of cases; PPA, CBS; low plasma level
- TARDBP and FUS genes mutations: number of cases of bv-FTD, FTD-ALS, …
- Rare mutations in other genes encoding :
  - Valosin Containing Protein (VCP) → Inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD)
  - Charged Multivesicular Body Protein2B (CHMP2B) → Usually bvFTD, also more global loss of cognition, parkinsonism, dystonia, and myoclonus
  - Ubiquilin-2 (UBQLN2) → described in FTD-MND, dominant X-linked
  - Sequestosoma (SQSTM1) and other genes mutations

Genetic associations in FTLD and ALS



Irwin et al. 2015

- FTLD-Tau : 45% of all FTLD; mutations in *MAPT* (sole known cause of hereditary forms)
- FTLD-TDP : 50% of all FTLD; hereditary forms associated with pathogenic mutations in *GRN*, *C9orf72*, *TARDBP and VCP* and other genes
- FTLD-ALS/ALS cases more associated with *C9orf72 and TARDBP;* less commonly linked to *VCP* and rarely *GRN*
- *TARDBP* rarely associated with FTLD without co-morbid ALS
- Very rare cases of FTLD (other) associated with pathogenic mutations in *CHMP2B* and FTLD-U neuropathology

FTLD phenotypes / Clinical description

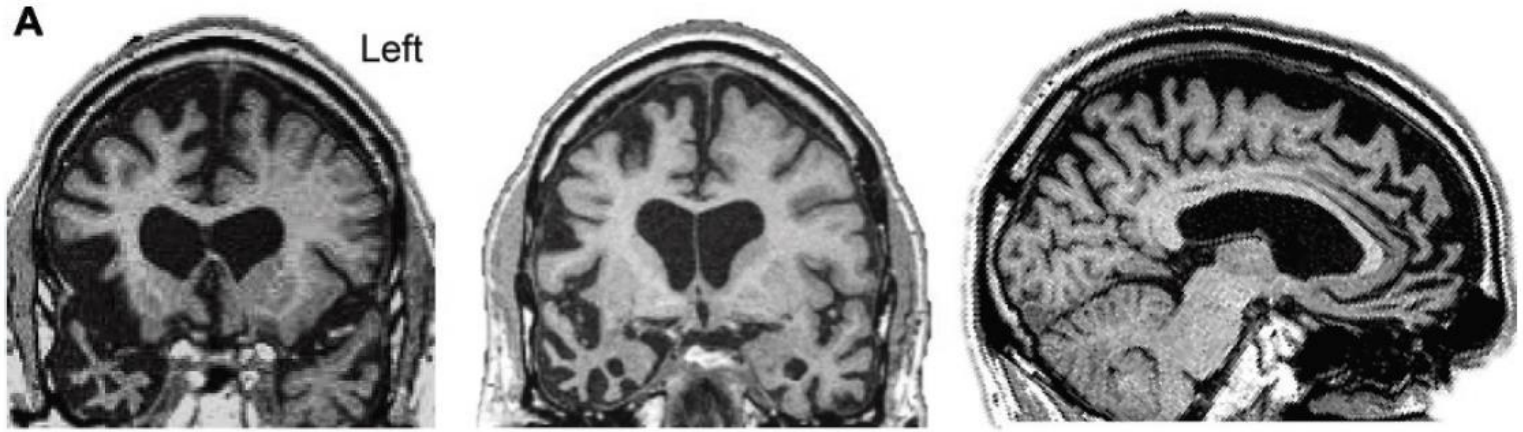
Major phenotypes

1 – behavioral variant FTD (bvFTD)

- Represents more than 50% of FTLD cases and the most heritable form
- Onset typically before the age of 65; male predominance
- Changes in personality and behavior, mixture of apathy and disinhibition
- Repetitive motor behaviors, changes in eating behavior, hyperorality
- Poor judgment, distractibility, loss of planning ability, perseverative errors
- Deficits on frontal/executive tasks (dorsolateral prefrontal cortex)
- Attention and working memory impaired; episodic memory relatively spared
- Semantic loss, aphasia (often adynamic)
- Parkinsonism, oculomotor control problems, or motor neuron disease

1 – bvFTD

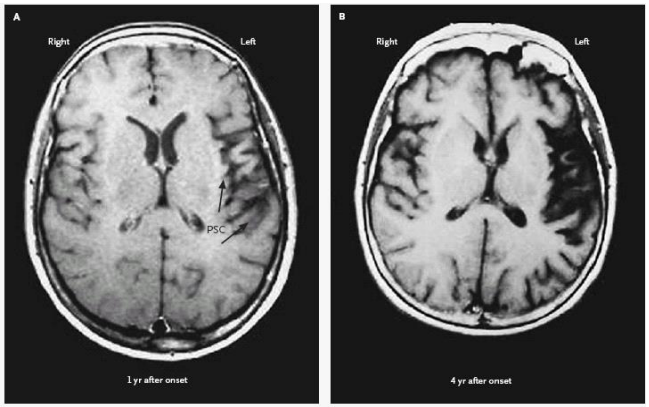
- Neuroimaging → frontal atrophy, hypometabolism and hypoperfusion
- Earliest changes : anterior cingulate, orbital frontal, frontoinsular cortices
- Dorsolateral prefrontal cortex often involved
- Region of greatest atrophy correlates with clinical phenotype :
  - dorsomedial frontal → apathy and aberrant motor behaviour
  - orbitofrontal → disinhibition

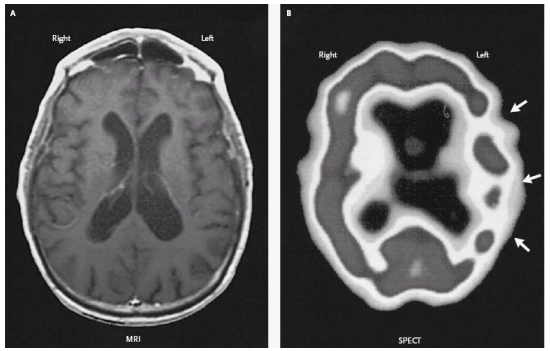


Seeley, 2019

2 – Non Fluent/agrammatic variant Primary Progressive Aphasia (nfvPPA)

- Agrammatism and motor speech deficits
- Apraxia of speech : difficulty initiating, slow rate of speech, incorrect sequencing of phonemes
- Phonemic paraphasic errors and mild anomia (without semantic loss)
- Comprehension : spared for single words and simple sentences, impaired for complex sentences
- Deficits in working memory and executive function; episodic memory, visuospatial function spared
- Supranuclear gaze palsy, parkinsonism and limb apraxia → frequent association with CBD and PSP
- Neuroimaging : dominant inferior frontal lobe (including Broca areas), left frontal operculum, premotor and supplementary motor areas and anterior insula, superior temporal gyrus

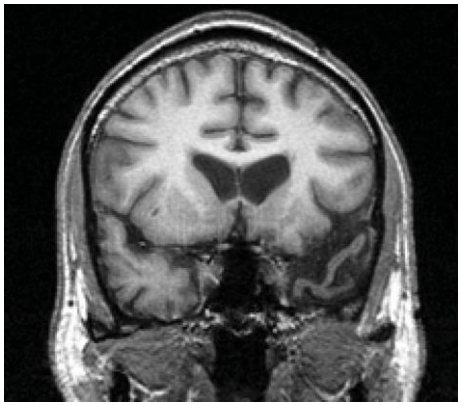




Mesulam, Ann Neurol, 2001

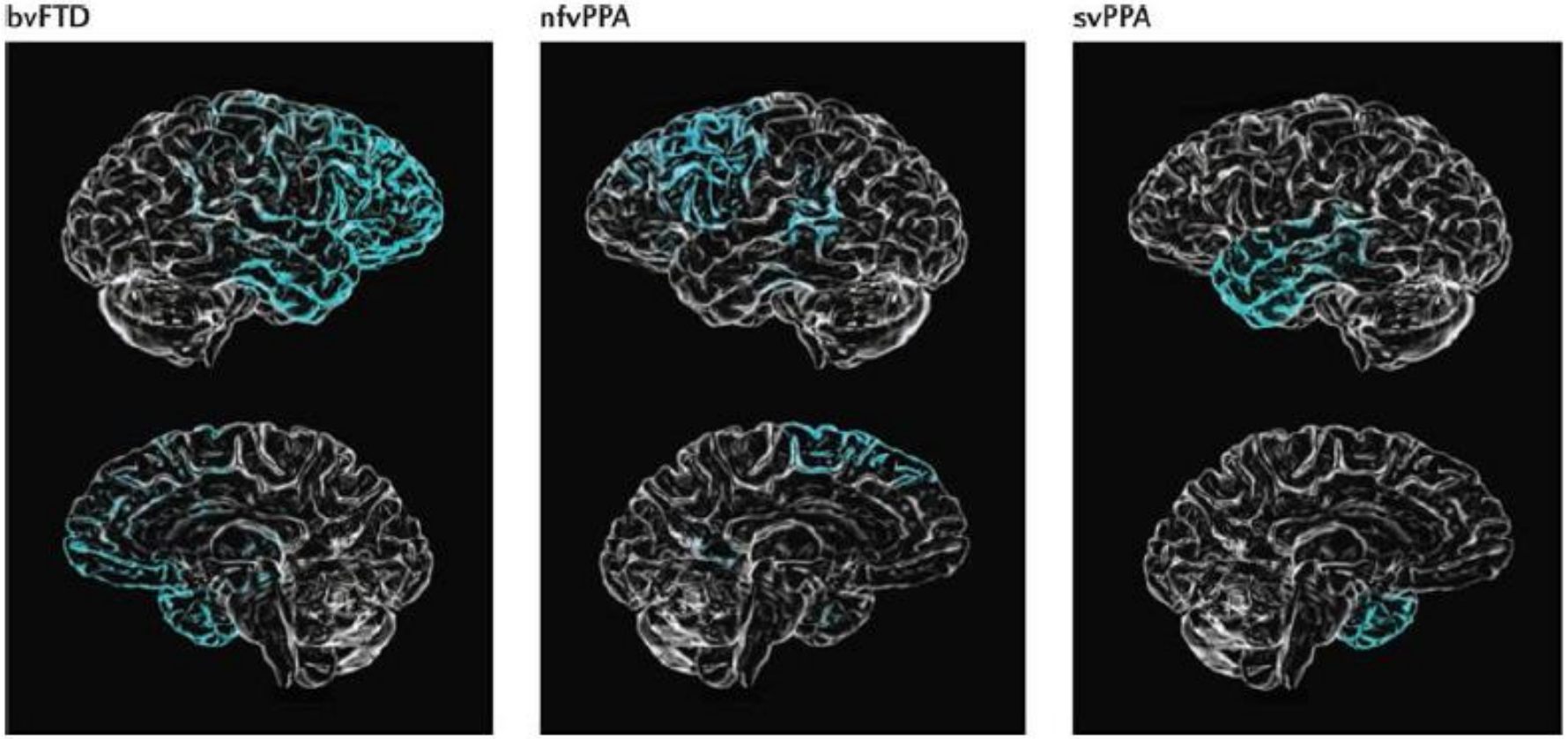
3 – Semantic variant PPA (svPPA)

- Atrophy of the medial and lateral portions of the anterior temporal lobes, usually more on the left
- Core features : Anomia and single-word comprehension deficits (Gorno-Tempini et al., 2011)



Hodges et al, Lancet Neurology, 2007

- Progressive loss of 'semantic' knowledge about words, loss of word meaning, objects and concepts → multimodal agnosia with time
- Fluent aphasia with impoverished speech content and semantic paraphasic errors
- Intact grammar, prosody and motor speech
- Impaired confrontation naming and category fluency, single-word comprehension
- Spared episodic memory, spatial abilities and executive functions
- Right temporal involvement → behavioral syndrome that overlaps with bvFTD



Patterns of brain atrophy in FTD syndromes

Elahi & Miller, 2017

FTLD phenotypes / Clinical description

Related phenotypes (Motor FTD syndromes)

1 – FTD with Motor Neuron Disease (MND)

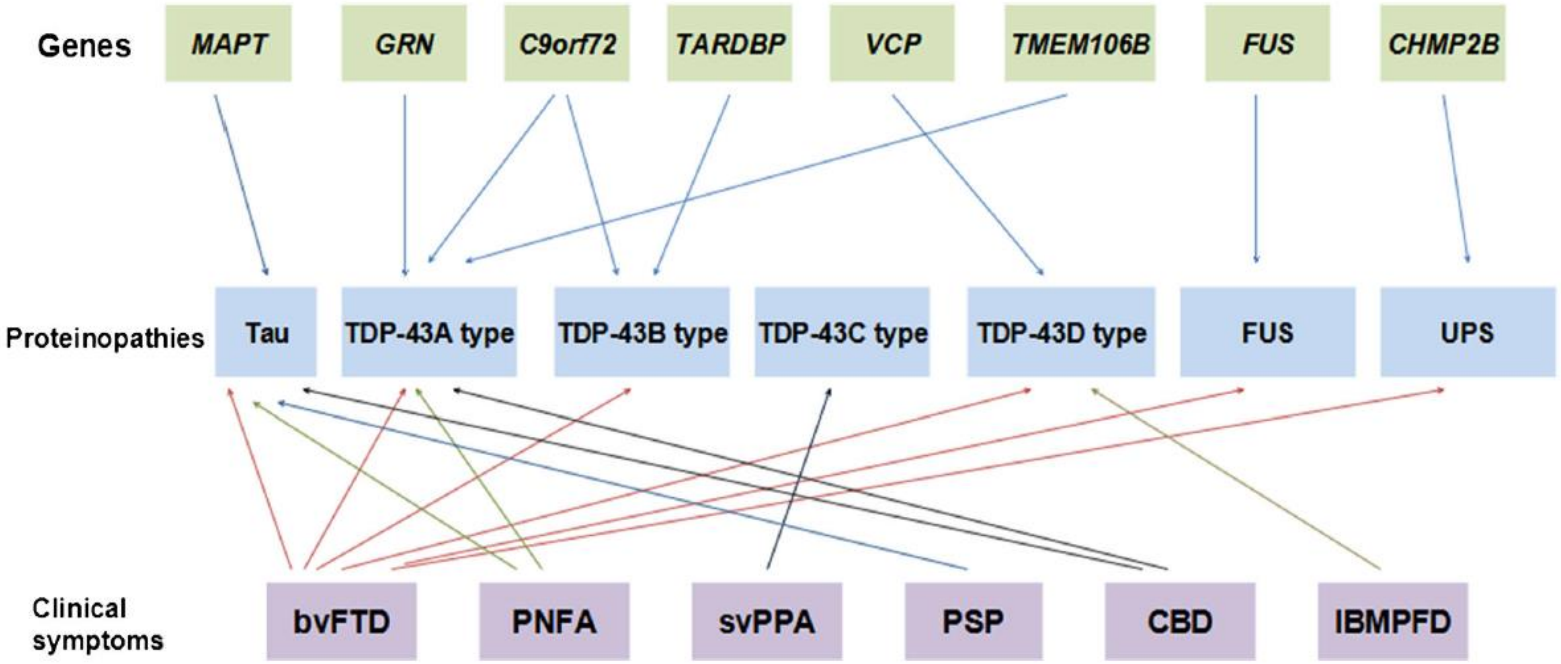
- ALS : most common form of presentation of MND
- Familiar and sporadic cases of ALS may have frontal lobe dysfunctions : personality and behavior changes, planning, organization and language dysfunction…
- About 40% of ALS patients show symptoms of FTD
- About 50% of FTD patients have ALS-like symptoms
- ALS symptoms may precede, occur simultaneously, or follow the signs and symptoms of FTD
- Most common symptomatology : cognitive change first, followed by weakness

2 – FTD overlap syndromes

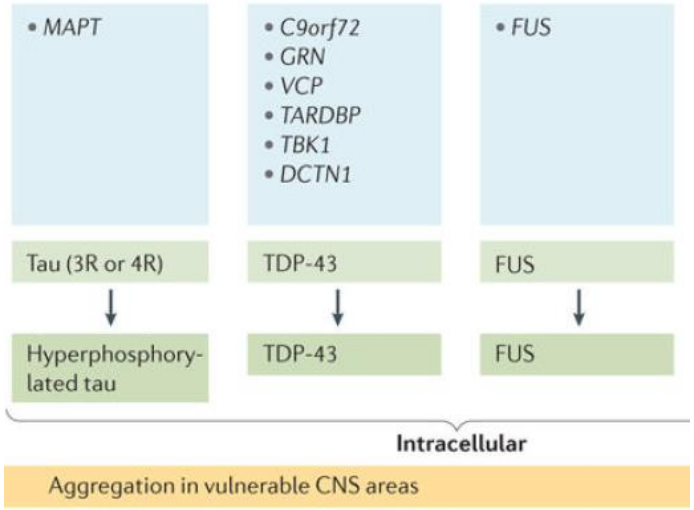
- Cortico basal degeneration syndrome : CBDS
  - extrapyramidal symptoms with progressive asymmetric rigidity and dystonia
  - limb apraxia, cortical sensory loss, alien limb syndrome, hemispatial neglect and myoclonus
  - executive and visuospatial dysfunction
  - frequent combined picture, often associated with nfvPPA and behavioral disorders in the last stages of the disease

- Progressive Supranuclear Palsy syndrome : PSPS
  - primarily postural instability, axial predominant parkinsonism, profound retropulsion
  - supranuclear gaze palsies
  - dysarthria, apraxia of speech, dysphagia and pseudobulbar affect
  - executive dysfunction, psychomotor slowing and poor working memory

Summary
Molecular, genetic anc clinical correlations in FTLD



From Li et al., 2015



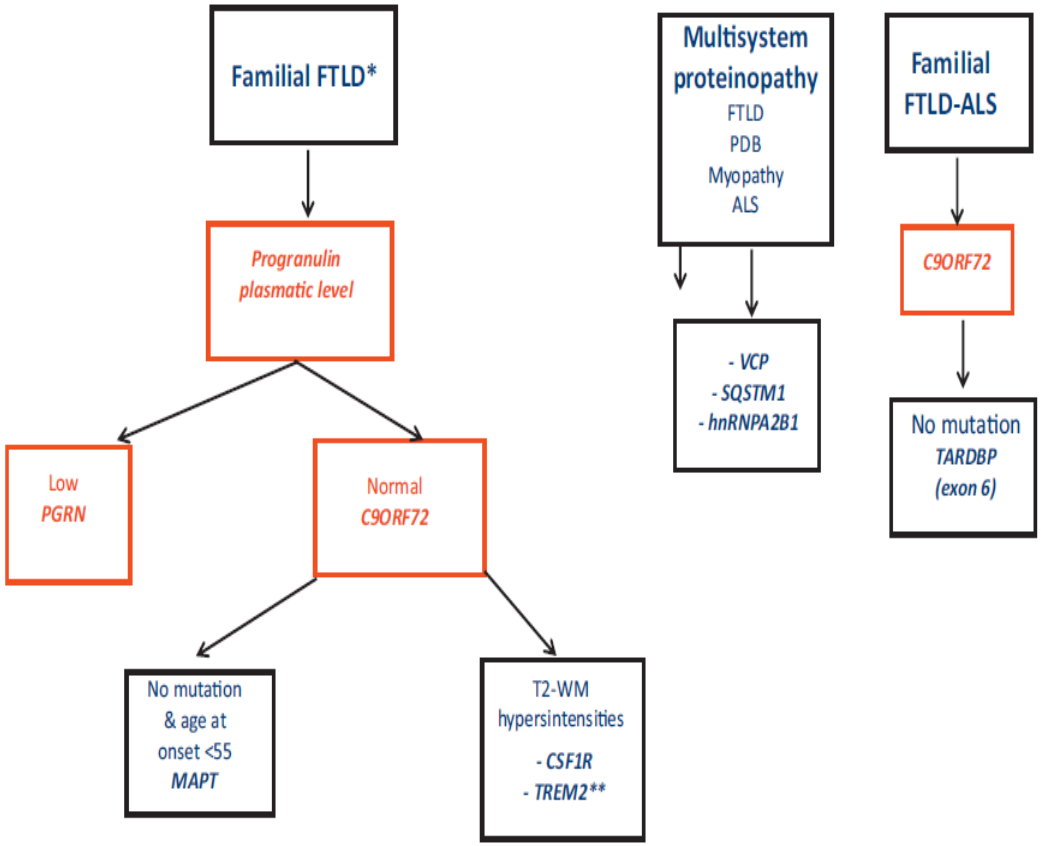
Adapted from Elahi & Miller, 2017

Diagnostic approach

- Based on clinical symptoms, family history (intrafamilial phenotype heterogeneity), location of atrophy
- MRI to evaluate pattern of atrophy and non degenerative lesions
- Exclude treatable conditions that can mimic FTLD : metabolic nutritional conditions, CNS infections, substance abuse, vascular disease, heavy metal toxicity, primary neoplastic and paraneoplastic conditions…
- Exclude primary psychiatric disorder (major depression or bipolar affective disorder) : little progression over time and no FT atrophy on MRI
- Amyloid biomarkers (CSF or PET) if AD is included in the differential diagnosis
- Next challenge : predict the underlying histopathology (probabilistic correlations)

Diagnosis algorythm for genetic testing for familial FTLD and FTLD-ALS patients (Leber, 2013)

- Consider genetic testing for bvFTD and FTLD-ALS patients
- Algorythm for genetic testing based on 4 criteria :
  - Presence of ALS in the patient himself or in one of his relatives
  - Age at onset of FTLD
  - Level of progranulin in plasma
  - Other disorders present in the patient or associated in his family



REFERENCES (1)

- Cruts M, Theuns J, Van Broeckhoven C, Locus-specific mutation databases for neurodegenerative brain diseases. Hum Mutat 33(9): 1340–4 (2012).
- Elahi FM and Miller BL (2017). A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol. August ; 13(8): 457–476.
- Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, Bisceglio G, Rovelet-Lecrux A, Boeve B, Petersen RC, et al. (2009). Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. Brain : a journal of neurology; 132:583–591.
- Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S (1997). Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference Conference Participants. Ann Neurol 41(6): 706–15
- Gorno-Tempini M.L., Hillis A.E., Weintraub S, Kertesz A., Mendez M., Cappa S.F., Ogar J.M., Rohrer J.D., et al. (2011). Classification of primary progressive aphasia and its variants. Neurology 76 March 15, 1006-1014
- Hernandez I, Fernandez MV, Tarraga L, Boada M, Ruiz A (2018). Frontotemporal Lobar Degeneration (FTLD): Review and Update for Clinical Neurologists. Curr Alzheimer Res.;15(6):511-533
- Hodges JR, Patterson K (2007). Semantic dementia : a unique clinicopathological syndrome. Lancet Neurol, Vol 6, Issue 11, 1004-1014
- Irwin DJ, Cairns NJ, Grossman M, McMillan CT, Lee EB, Van Deerlin VM, Lee VMY, and Trojanowski JQ (2015). Frontotemporal Lobar Degeneration: Defining Phenotypic Diversity Through Personalized Medicine. *Acta Neuropathol*; 129(4): 469–491
- Knopman DS, Roberts RO (2011). Estimating the number of persons with frontotemporal lobar degeneration in the US population. J Mol Neurosci;45(3):330–335
- Le Ber I. (2013). Genetics of frontotemporal lobar degeneration. An up-date and diagnostic algorythm. Rev Neurol (Paris), 169 ; 811-819
- Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, *et al.* (2008). Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain 131(3): 732–46
- Li YQ, Tan MS, Yu JTand Tan L (2016). Frontotemporal Lobar Degeneration: Mechanisms and Therapeutic Strategies. Molecular Neurobiology, Vol 53, Issue 9, 6091–6105

REFERENCES (2)

- Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I et al. (2010). Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol; 119:1–4.
- Mesulam MM (2001). Primary progressive aphasia. Ann Neurol. 2001 Apr;49(4):425-32.
- McKhann GM[1], Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ; Work Group on Frontotemporal Dementia and Pick's Disease (2001). Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol;58(11):1803-9.
- Noble W, Hanger DP, Miller CCJ, Lovestone S (2013). The importance of tau phosphorylation for neurodegenerative diseases. Front Neurol 4: 83
- Premi E, Padovani A, Borroni B (2012). FRONTOTEMPORAL LOBAR DEGENERATION. *Neurodegenerative Diseases, Shamim I. Ahmad ed,,* Landes Bioscience and Springer Science+Business Media, 114-127
- Rabinovici GD and Miller BL (2010). Frontotemporal Lobar Degeneration: Epidemiology, Pathophysiology, Diagnosis and Management. CNS Drugs, 24(5): 375–398
- Rascovsky K,Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134; 2456–2477
- Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, *et al.* (2009). The heritability and genetics of frontotemporal lobar degeneration. Neurology 73(18): 1451–6
- Rohrer JD, Ridgway GR, Modat M, Ourselin S, Mead S, Fox NC, *et al.* (2010). Distinct profiles of brain atrophy in frontotemporal lobar degeneratio caused by progranulin and tau mutations. Neuroimage, 53(3): 1070–6
- Seeley WW (2019). Behavioral Variant Frontotemporal Dementia. CONTINUUM (MINNEAP MINN) ; 25(1 , DEMENTIA):76–100.
- Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, Pestronk A, Whyte MP, Kimonis VE. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nature genetics. 2004; 36:377–381.
- Whitwell JL, Weigand SD, Boeve BF, Senjem ML, Gunter JL, Dejesus-Hernandez M, *et al.* (2012). Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. Brain 135(3): 794–806