Frontotemporal Lobar Degeneration: A Clinical Approach

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Abstract

In this review, the authors outline a clinical approach to frontotemporal lobar degeneration (FTLD), a term coined to describe a pathology associated with atrophy of the frontal and temporal lobes commonly seen with abnormal protein aggregates. It accounts for ~10% of pathologically confirmed dementias. The three clinical syndromes associated with FTLD are jointly classified as frontotemporal dementia (FTD) and include behavioral variant frontotemporal dementia (bvFTD), nonfluent-agrammatic primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA; left: l-svPPA and right: r-svPPA). All syndromes have differential impairment in behavioral (bvFTD; r-svPPA), executive (bvFTD; nfvPPA), and language (nfvPPA; svPPA) functions early in the disease course. With all three there is relative sparing of short-term memory and visuospatial abilities early on, and with the two language syndromes, nfvPPA and svPPA, behavior is also intact. Symptoms are associated with specific atrophy patterns, lending unique imaging signatures to each syndrome (frontal: bvFTD and nfvPPA; temporal: svPPA). Common proteinopathies involve accumulation of tau, transactive response DNA binding protein 43, and fusion in sarcoma protein. Parkinsonism presents in all syndromes, especially cases with tau pathology and *MAPT* or *GRN* mutations. nfvPPA often has corticobasal degeneration or progressive supranuclear palsy as the underlying neuropathological substrate. bvFTD co-occurs with motor neuron disease in ~15% of cases, and many such cases are due to *C9Orf72* mutations. Other common genetic mutations in FTLD involve *GRN* and *MAPT*. Behavioral symptoms are best managed by selective serotonin reuptake inhibitors, while atypical antipsychotics should be used with caution given side effects. Promising etiologic treatments include anti-tau anti-bodies, antisense oligonucleotides, and progranulin enhancers.

Keywords

► frontotemporal dementia
► primary progressive aphasia
► behavior
► language
► parkinsonism
► diagnosis
► treatment

Frontotemporal lobar degeneration (FTLD) is defined as a pathologic endophenotype characterized by atrophy of the frontal and temporal lobes leading to three clinical syndromes with partially overlapping microscopic pathology. These are jointly called frontotemporal dementia (FTD) and include the behavioral variant frontotemporal dementia (bvFTD) and two types of the primary progressive aphasias (PPA),[1] the nonfluent-agrammatic (nfvPPA) and the semantic (svPPA). The three syndromes are associated with variable impairment in behavioral, executive, language, and even motor functions early in the disease course. Each has a unique atrophy pattern on neuroimaging. Commonly, there is accumulation of tau, transactive response DNA binding protein 43 (TDP-43), fusion in sarcoma protein (FUS), and p62 dipeptides.[2]

In 2011, revised consensus criteria were created for both bvFTD and PPA to incorporate advances in imaging, pathology, and genetics, aiming to improve early diagnostic accuracy.[3,4]
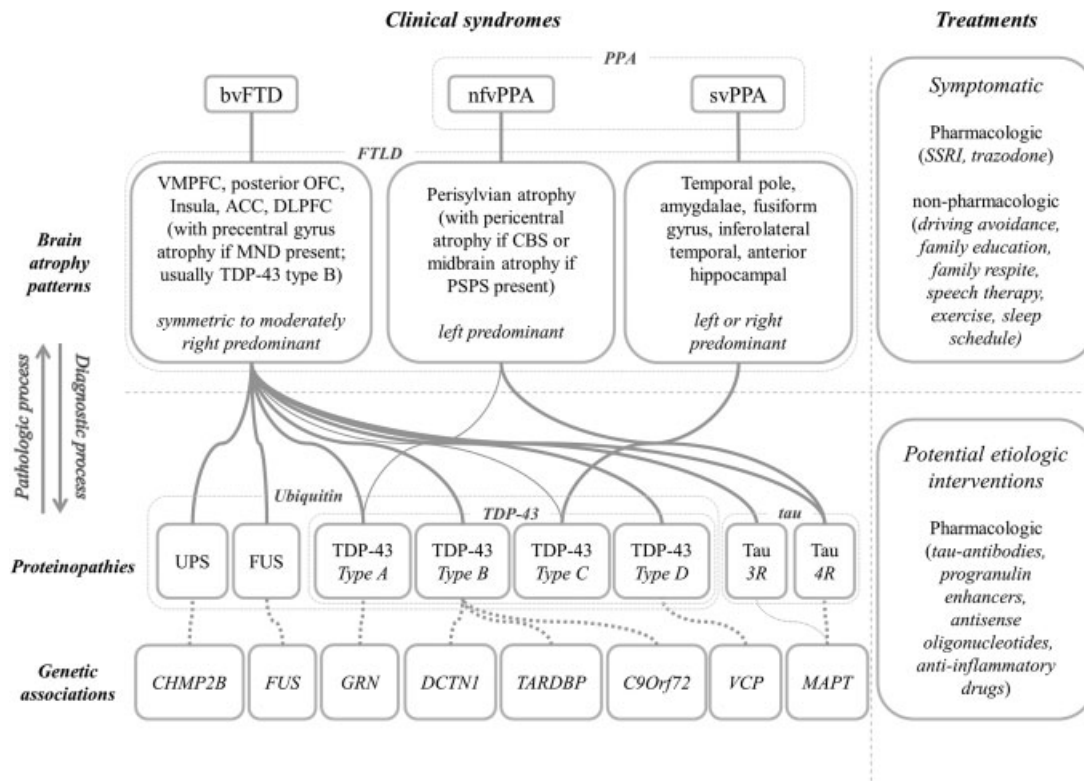
Fig. 1 Frontotemporal lobar degeneration (FTLD) phenotypes, endophenotypes, and therapeutic associations. Common atrophy patterns, pathologies, and genetic mutations are depicted. Syndromes correlate well to gross atrophy patterns; similarly, genetic mutations correlate to specific proteinopathies. Line weights represent relative associations. ACC, anterior cingulate cortex; bvFTD, behavioral variant frontotemporal dementia, CBS, corticobasal syndrome; *CHMP2B*, charged multivesicular body protein 2b; DCTN1, dynactin 1; DLPFC, dorsolateral prefrontal cortex; *FUS*, fusion in sarcoma; *GRN*, progranulin; *MAPT*, microtubule associated protein tau; MND, motor neuron disease; nfvPPA, nonfluent-agrammatic PPA; OFC, orbitofrontal cortex; PPA, primary progressive aphasia; PSPS, progressive supranuclear palsy syndrome; svPPA, sematic variant PPA; *TARDBP*, transactive response DNA binding protein gene; TDP-43, transactive response DNA binding protein 43; UPS, ubiquitin proteasome system; *VCP*, valosin containing protein; VMPFC, ventromedial prefrontal cortex.

Early and accurate diagnosis, however, is not straightforward in FTLD, given the pathological convergence associated with specific clinical syndromes and the syndromic divergence within pathologies (►**Fig. 1**). Even family members with a single genetic mutation are phenotypically heterogeneous.

Historical Perspective and Epidemiology

In 1892, Arnold Pick described patients with presenile dementia, aphasia, and lobar atrophy.[5] This entity was subsequently referred to as Pick disease, and the characteristic inclusion bodies associated with this condition, identified by Alois Alzheimer in 1911, were named Pick bodies in Pick's honor. In 1957, Delay, Brion, and Escourolle and in 1974 Constantinidis, Richard, and Tissot delineated the clinical and anatomical differences between Alzheimer disease (AD) and Pick disease, emphasizing that atrophy in Pick disease was frontally predominant, while in AD more posterior. Their classification schemas recognized that there were prominent extrapyramidal syndromes associated with Pick disease and that only a minority of cases had classic Pick bodies.[6,7] In 1982, Marsel Mesulam identified aphasia syndromes in patients with left-predominant hemispheric atrophy,[8] collectively termed PPA (now including nfvPPA, svPPA, and

logopenic variant PPA [lvPPA]).[1] Though Pick's first cases would currently be classified as svPPA of left-predominant atrophy (l-svPPA), in the past "Pick dementia" was considered synonymous to what is now called bvFTD. A right-predominant atrophy svPPA (r-svPPA) also exists and presents with early behavioral deficits, whereas its syndromic convergence and pathologic homology to l-svPPA allows both syndromes to be classified as svPPA (see below). Recent discoveries of specific proteinopathies (e.g., tau, TDP-43, FUS) as well as genetic mutations (e.g., *GRN*, *MAPT*, *C9Orf72*) has opened avenues for new therapeutic interventions.[9–16]

Epidemiologically, FTLD incidence is three to four cases per 100,000 person-years, with an estimated 20,000 to 30,000 cases in the United States at a given moment.[17] It is the third most common cause of degenerative dementia after AD and dementia with Lewy bodies, accounting for 5 to 10% of all pathologically confirmed cases.[18] Additionally, it is the second most common presenile dementia in patients younger than 65 years old after AD. Tau-positive cases tend to exhibit older disease onset and slower progression than TDP-43 and FUS FTLD subtypes.[19] ►**Table 1** contains epidemiologic features of FTLD subtypes, recognizing that diagnosis in most studies was based on pre-2011 diagnostic criteria.

Table 1 Epidemiology of frontotemporal lobar degeneration (FTLD)[19–22]

Clinical syndrome	Percentage of FTLD cases	Range of male percentage	Mean age of onset (range)[a]	Life expectancy in years from symptom onset (from diagnosis)[b]
bvFTD	54–69	53–70	58 (47–82)	with MND 6 (1) without MND 9 (5)
nfvPPA	14–35	14–63	63 (42–79)	9 (4)
r-svPPA	6–10	44–80	62 (52–85)	12 (5)
l-svPPA	9–12	52–80	59 (52–80)	12 (5)

[a]No statistical difference.
[b]Significantly shorter life expectancy only for bvFTD-MND cases.

Clinical Diagnosis

Frontotemporal lobar degeneration is caused by selective vulnerability of specific neuroanatomical networks. With bvFTD, nfvPPA, and svPPA degeneration starts within a specific hub and spreads across the respective network in a prion-like manner, conferring unique clinical characteristics at each stage of the disease.[23–25] As such, the most important clinical information lies in the temporal evolution of symptoms, and by extension, their neuroanatomical representation, allowing the physician to create a mental map of brain atrophy progression. The diagnostic process aims to identify the phenotypic syndrome (i.e., bvFTD vs. nfvPPA vs. svPPA vs. other dementia or nondementia syndromes), and then predict the most likely proteinopathy and possible genetic mutation (►**Figs. 1**,2, and ►**Tables 2**,3).[31] This approach can provide a more accurate prognosis, and as molecule-specific therapies develop, more tailored treatment.
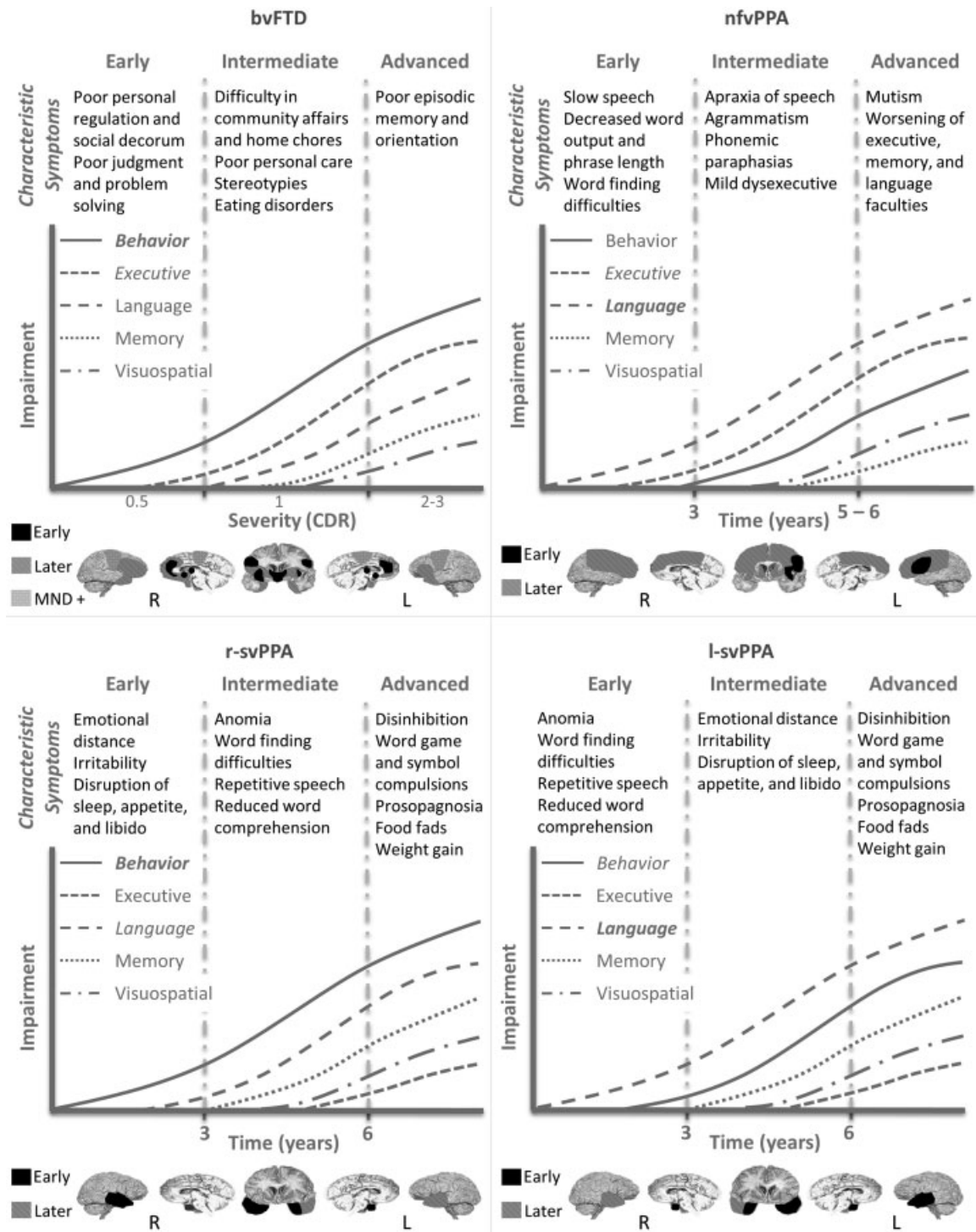
There are distinct differences between patients with right-versus left-sided disease. Right-predominant atrophy patients (bvFTD; r-svPPA) tend to be emotionally cold and distant, often disrupting family relationships, and present with behavioral disturbances that are often misinterpreted as psychiatric symptoms. Left-predominant atrophy patients mainly present with language impairments (►**Table 2**).

bvFTD is dominated by behavioral symptoms. Because early degeneration affects the paralimbic structures of the ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), and anterior insula, early symptoms involve social disinhibition, lack of motivation (apathy), and loss of empathy.[31,34] Often, family members believe the patient has lost interest in the family, is depressed, or suffers from a psychiatric disorder. Patients are often distractible and it is not uncommon for them to lose their jobs. Symptoms of disinhibition may range from inappropriate (e.g., hugging people in the street) to antisocial (e.g., commenting on peoples' weight). Lack of empathy is striking, and patients may ignore acute health issues of their spouses. As selective degeneration spreads to the temporal lobes, particularly the right, mental rigidity and unique eating habits start to emerge (e.g., eating only single-colored food). Some patients may develop cravings for carbohydrate-rich food such as sweets and chips. Compulsive behaviors can range from simple repetitive movements (e.g., tapping, coughing) to more complex compulsions (e.g., hoarding, collecting, cleaning, eating specific foods at specific times). As the dorsolateral prefrontal cortex (DLPFC) degenerates, executive abilities falter, with working memory impairment, difficulty with set-shifting and generation of ideas or alterations in attention.[36] Usually, patients have poor insight into their deficits, distort their history, and admit to having bvFTD as a matter-of-fact based on others' reports, rather than appreciating that something is amiss. This may relate to noso-adiaphoria (anosodiaphoria) rather than noso-agnosia (anosognosia).[37]

A slowly progressive bvFTD exists, termed "phenocopy" by Chris Kipps and John Hodges, which differs from the classic form due to decades-long progression and male predominance.[38] It is indistinguishable from the classic form based on simple diagnostic criteria, although measures of executive and functional impairment tend to be less severe in the phenocopy cases and atrophy may be mild, or even absent. Some of these patients are primarily psychiatric, although *C9Orf72* mutations may also be responsible for the syndrome.[39]

One in seven bvFTD patients develop *MND*,[22] which has a similar phenotype to sporadic MND, although often lower limb muscles seem to be spared early on. Because bv FTD-MND has strong pathological associations with TDP-43 type B and *C9Orf72* (and some other) mutations (►**Table 3**), it is often approached separately from bvFTD without MND. There is evidence of a *C9Orf72* mutation founder effect from 6,300 years ago in the Western world, making it the most common genetic cause of bvFTD-MND and accounting for about a third of familial cases, but these *C9Orf72* appear to be rare in south and eastern Asia.[13,14,44] *C9Orf72* mutations are large hexanucleotide repeat expansions (GGGGCC) in the intron region of chromosome 9, which leads to RNA nuclear accumulation and suppression of gene expression. The disease phenotype does not seem to depend on repeat length and there is only preliminary evidence that longer repeat sizes, specifically in the cerebellum, have a negative impact on survival.[45]

bvFTD

	Early	Intermediate	Advanced
Characteristic Symptoms	Poor personal regulation and social decorum Poor judgment and problem solving	Difficulty in community affairs and home chores Poor personal care Stereotypies Eating disorders	Poor episodic memory and orientation

Behavior
Executive
Language
Memory
Visuospatial

Impairment

0.5   1   2-3
Severity (CDR)

Early
Later
MND +
R   L

nfvPPA

	Early	Intermediate	Advanced
Characteristic Symptoms	Slow speech Decreased word output and phrase length Word finding difficulties	Apraxia of speech Agrammatism Phonemic paraphasias Mild dysexecutive	Mutism Worsening of executive, memory, and language faculties

Behavior
Executive
Language
Memory
Visuospatial

Impairment

3   5 – 6
Time (years)

Early
Later
R   L

r-svPPA

	Early	Intermediate	Advanced
Characteristic Symptoms	Emotional distance Irritability Disruption of sleep, appetite, and libido	Anomia Word finding difficulties Repetitive speech Reduced word comprehension	Disinhibition Word game and symbol compulsions Prosopagnosia Food fads Weight gain

Behavior
Executive
Language
Memory
Visuospatial

Impairment

3   6
Time (years)

Early
Later
R   L

l-svPPA

	Early	Intermediate	Advanced
Characteristic Symptoms	Anomia Word finding difficulties Repetitive speech Reduced word comprehension	Emotional distance Irritability Disruption of sleep, appetite, and libido	Disinhibition Word game and symbol compulsions Prosopagnosia Food fads Weight gain

Behavior
Executive
Language
Memory
Visuospatial

Impairment

3   6
Time (years)

Early
Later
R   L

Fig. 2 Syndrome natural history in frontotemporal lobar degeneration.[26–30] Common cognitive, behavioral, and atrophic patterns with disease progression; see text for details. Graphs depict relative qualitative symptom severity with disease progression. Speed of disease progression in bvFTD is more variable than other syndromes, with Clinical Dementia Rating (CDR) Scale scores ranging from 0.5 to 3 at 6 years from symptom onset.

nfvPPA is the prototypical syndrome with impairments in language structure and praxis. Characteristic deficits include nonfluent output, agrammatism, and apraxia of speech (AOS).[1,3] Patients understand the meaning of individual words or objects, but have trouble with more complex sentences. The neuroanatomical network affected by degeneration includes the dominant frontal operculum, its con-

nections to the supplementary motor area (SMA) through the frontal aslant tract, the premotor area, and the insular cortex.[28,46] Thus, early symptoms are slowness of speech, word-finding difficulties, and decreased word output and phrase length. Apraxia of speech (i.e., an articulation planning deficit) emerges as a disconnection between the frontal operculum and the SMA, associated with aslant tract

Table 2 Syndrome phenotypes and endophenotypes[4,32–35]

Clinical syndrome	Characteristic earliest symptoms	Early patient or family concerns	Behavioral features	Cognitive features	Motor features	Earliest atrophic areas	Common pathology
bvFTD	Apathy Disinhibition Loss of self and other awareness	Midlife crisis Mood disorder Psychosis	Apathy (54–96%) Disinhibition (73%) Lack of empathy (49–75%) Compulsions (67%) Loss of awareness (65%) Hyperorality (59%) Anxiety (56%)	Poor (lexical) generation Poor episodic memory Poor set-shifting	MND (~15%) Parkinsonism (~20%)	Anterior cingulate Frontoinsular (R > L)	most heterogeneous tau ≅ TDP-43 few FUS and UPS *tau: 3R or 4R* *TDP-43*: esp. Type A, B, or D
nfvPPA	Nonfluent speech AOS	Word-finding difficulties Slow or slurred speech	Later in course: Apathy and disinhibition Restlessness Aggression	Language impairment: nonfluent, aprosodic, agrammatic, AOS Executive impairment Poor episodic memory	Strong association with PSPS and CBS	Dominant FO Premotor SMA Anterodorsal insula	tau (esp. 4R) > TDP-43 AD pathology (30%)
r-svPPA	Emotional detachment Mental rigidity Atypical depression Irritability Bizarre dressing	"Cold and distant" Exaggeration of personality traits Mood disorder	Disinhibition (74%) Eating disorders (52%) Sleep disorders (52%) Loss of empathy (49%) Depression (44%)	Prosopagnosia Poor emotional recognition Word obsessions Poor semantic memory Increased visual alertness	Extremely rare Few cases of MND	Right anterior temporal Amygdala	TDP-43 (Type C) rare tau AD pathology (33%)
l-svPPA	Anomia Loss of word meaning	Word-finding difficulties	Eating disorders (52%) Sleep disorders (52%) Depression (44%)	Semantic anomia Surface dyslexia Verbal episodic memory loss	Extremely rare Few cases of MND	Left anterior temporal Amygdala	TDP-43 (Type C) rare tau AD pathology (33%)

Abbreviations: AOS, apraxia of speech; CBS, corticobasal syndrome; FO, frontal operculum; MND, motor neuron disease; PSPS, progressive supranuclear palsy syndrome; SMA, supplementary motor area.

Table 3 Clinicopathological associations[2,9–16,40–43]

Clinical syndrome	Characteristic clinicopathological associations

bvFTD	**tau**
	  Parkinsonism common (including CBS); "parietal" symptoms (e.g., acalculia) more common than in ubiquitin cases
	  Symmetric frontal atrophy involving temporal lobes; more prominent striatal atrophy and white matter abnormalities than ubiquitin cases
	  MAPT mutations (Chromosome 17)
	TDP-43 type A (see below)
	TDP-43 type B
	  Associated with bvFTD-MND; parkinsonism (rarely CBS)
	  Mildly asymmetric frontal atrophy and parietal, pulvinar and cerebellar atrophy
	  C9Orf72 mutations (Chromosome 9; Baltic ancestry; most common known genetic cause)
	  Less common genes: *TARDBP* (Italian/French ancestry; parkinsonism and MND), *DCTN1* (Perry syndrome)
	TDP-43 Type D
	  bvFTD (± MND), IBM and Paget disease of the bone; parkinsonism uncommon
	  VCP gene (Chromosome 9)
	FUS
	  Younger onset (30s to 40s); associated with bvFTD-MND; psychotic features (up to 36%)
	  FUS mutations (Chromosome 16)
	UPS
	  CHMP2B mutations (Chromosome 3; Denmark)
	Other genes related to TDP-43 pathology
	  UBQLN2 (MND, X-linked, mean onset 30s to 40s), *OPTN* (MND), *hnRNP A1,* and *A2/B1* (IBM and Paget disease)

nfvPPA	**TDP-43 type A**
	  Parkinsonism frequent (including CBS)
	  Asymmetric atrophy of dorsolateral frontoparietal lobes and basal ganglia
	  GRN mutations (Chromosome 17)
	tau
	  Strongly associated with AOS
	  Usually CBD or PSP

l-svPPA	**TDP-43 Type C**
	  Movement disorders uncommon; coexistence of autoimmune diseases and left-handedness
	  Left-predominant anterior temporal atrophy
	  Almost exclusive pathology; rarely genetic

r-svPPA	**TDP-43 Type C**
	  Movement disorders uncommon; coexistence of autoimmune diseases and left-handedness
	  Right-predominant anterior temporal atrophy
	  Almost exclusive pathology; rarely genetic

Abbreviations: AOS, apraxia of speech; CBD, corticobasal degeneration; CBS, corticobasal syndrome; *CHMP2B*, charged multivesicular body protein 2b; DCTN1, dynactin 1; *FUS*, fusion in sarcoma; *GRN*, progranulin; hnRNPA, heterogeneous nuclear ribonucleoprotein; IBM, inclusion body myositis; MND, motor neuron disease; *OPTN*, optineurin; PSP, progressive supranuclear palsy; *TARDBP*, TAR DNA-binding protein; *UBQLN2*, ubiquilin 2; UPS, ubiquitin proteasome system; *VCP*, valosin containing protein.

degeneration.[46] In contrast, agrammatism, which in addition to simplified phrases is defined by omission of function words and inflections, develops with progressive atrophy of the left frontal operculum and DLPFC, but also of the insula, anterosuperior temporal cortex, as well as white matter degeneration of the dominant cingulum and corpus callosum.[47] Emergence of phonemic paraphasias (e.g., phoneme transpositions, additions, omissions) relates to progressive atrophy of the insula, anterior cingulate, premotor cortex, and SMA.[47] In contrast to bvFTD, nfvPPA patients often become aware of their deficits prior to others and maintain a proper social decorum. As the disease moves into the contralateral frontal regions, some nfvPPA patients eventually develop

behavioral disturbances. Finally, nfvPPA often coincides with corticobasal syndrome (CBS) or progressive supranuclear palsy syndrome (PSPS), in which a 4-repeat tauopathy is probable, although CBS may also result from TDP-43 Type A pathology with or without *GRN* mutations (►**Table 3**).

Both svPPA syndromes have semantic knowledge deficits with intact speech fluency, but differ in that early symptoms in l-*svPPA* pertain to lexical meaning loss, whereas in r-svPPA to loss of emotional meaning and knowledge about faces.[48] Symptoms correlate to early atrophy of the anterior temporal pole, which serves as a hub for semantic knowledge and from which degeneration spreads.[25,26,28] Disease spreads to frontal areas once the uncinate fasciculus becomes affected, highlighting its

role in semantic processing,[46] while there is accompanying atrophy of the insula and anterior hippocampus.[26,28]

Early features of l-svPPA include word-finding difficulties, especially of nouns rather than verbs. Gradually, patients substitute specific words with superordinate categories (e.g., *animal* for *cat*), and eventually most nouns are called *things*. At later stages, loss of word meaning becomes very pronounced and patients have trouble recognizing what is shown to them and its general purpose. In contrast, early features of r-svPPA are behavioral, in keeping with an underlying right-predominant atrophy, while language problems present later in its course.[20,48] r-svPPA manifests with early emotional detachment, lack of empathy, and diagnosis is often delayed because symptoms are misinterpreted as psychiatric or worsening of chronic personality traits. Some patients' symptoms begin with impairment recognizing familiar faces, and evolve into a severe deficit in facial perception.

At intermediate svPPA stages, degeneration spreads to the opposite hemisphere and the two svPPA subtypes merge at the syndromic and atrophic level (►**Fig. 2**). In clinic, patients may show surface dyslexia, in which they incorrectly read irregularly-written low-frequency words (e.g., *yacht*). svPPA patients develop an interest for visually appealing objects, which may express itself as compulsions or artistic creativity. De novo creativity is a fascinating feature in FTLD, especially l-svPPA, which may emerge a few years prior to the onset of disabling symptoms, and is probably caused by abolishment of interhemispheric inhibition.

Parkinsonism in Frontotemporal Lobar Degeneration

Approximately one-fifth of bvFTD patients have parkinsonism on their first clinic visit.[35] Parkinsonian features are more common in bvFTD and nfvPPA patients, often those with tau pathology, *MAPT* and *GRN* mutations, and at later disease stages, whereas its presence does not affect survival (►**Tables 2** and **3**).[22,35] Most bvFTD cases have an akinetic-rigid form (60%) and the rest (40%) are tremor-predominant. Movement disorders rarely accompany svPPA.

Corticobasal syndrome and PSPS are often considered as clinical diagnoses when parkinsonism is present early in FTLD. Unlike classic Parkinson disease, where rigidity, tremor, and bradykinesia dominate the early phases, PSPS presents with axial rigidity, relative sparing of the arms, and lack of tremor. Presence of early falls and a supranuclear gaze palsy is typical for PSPS. Corticobasal syndrome is characterized by apraxia (especially of the feet), alien limb phenomenon, inattention, dystonia, and myoclonus. Cortical symptoms (e.g., aphasia) overlap with those observed in bvFTD and nfvPPA.[49,50] Corticobasal syndrome and PSPS are designed to predict 4-repeat tauopathies (i.e., corticobasal degeneration [CBD] and progressive supranuclear palsy [PSP], respectively). Although clinicopathological association is high for PSPS, CBS criteria have not been highly predictive and up to 50% of cases have alternative pathologies (e.g., AD [23%] and TDP-43 [13%]).[51] As a result, CBS criteria were recently revised, though their clinical utility and diagnostic accuracy remains to be seen.[49]

Parkinsonism in FTLD can also be due to specific genetic mutations. Two such genes are *MAPT* and *GRN*, which are 1.7 Mb apart on chromosome 17. *GRN* mutation deficits caused by progranulin haploinsufficiency have a mean age at onset of 59 years; MAPT mutations tend to present at an earlier age with a mean age at onset of 49 years. Life expectancy from the time of diagnosis is approximately 7 years for both. Shared signs of parkinsonism are rigidity and bradykinesia without a resting tremor. Furthermore, *GRN* mutation patients have asymmetric parkinsonism earlier in their course, and often display CBS, whereas *MAPT* mutation patients have a more symmetric akinetic-rigid parkinsonism and less typically exhibit CBS. On MRI, *GRN* mutation patients often show asymmetric atrophy that extends to the parietal lobes, and white matter signal abnormalities are common. In *MAPT* mutation cases, atrophy is more symmetric and parietal atrophy is not typically present.[52] Another gene associated with parkinsonism and often MND is *TARDBP*,[53] a rare mutation that has been reported in patients of Italian-French ancestry. In addition to rigidity and bradykinesia, rest tremor is more prevalent than in other FTLD-related mutations. *C9Orf72* and *FUS* mutations are also associated with parkinsonism, but, more typically, MND dominates their motor symptoms.

An interesting, yet unique, parkinsonism association in FTLD is the amyotrophic lateral sclerosis-Parkinson-dementia complex (ALS-PDC) of Guam[54] ALS-PDC is strongly familial, but no genetic or environmental cause has been verified, while its prevalence has gradually declined. Clinically, there is rigidity, bradykinesia, and a nondisabling action-induced tremor. Finally, linear pigment retinal epitheliopathy occurs in 56% of cases compared with 16% of controls.

Additional Studies

In addition to obtaining a history of present illness and performing a physical examination, which provide the most useful diagnostic information, workup for suspected FTLD should include neuropsychological testing and structural brain MRI. Neuropsychological testing allows confirmation of historically reported cognitive deficits. It may not be significantly abnormal in the early stages of bvFTD or r-svPPA because early symptoms are mostly behavioral. In nfvPPA and l-svPPA specific tests of language are required. Generally, bvFTD patients have deficits in executive control, svPPA patients have language difficulties, evident on confrontation naming, and nfvPPA patients perform poorly on fluent output, word generation, and understanding of complex syntax comprehension.[3,36] Tests of social cognition focused around social perception and behavior are helpful and may emerge in FTD prior to the onset of changes in executive control.[55]

One cornerstone of the FTLD workup is structural brain MRI. As reflected in ►**Fig. 2** and ►**Tables 2** and **3**, atrophy patterns vary between syndromes and even between genetic mutations within syndromes.[28,31,40] Clinicians should look for these changes in MRI sequences themselves and should not rely solely on the radiologist's impression, as radiologists often fail to comment on atrophy patterns. Additionally, MRI helps rule out other causes of cognitive and behavioral

Table 4 Criteria for the diagnosis of bvFTD, nfvPPA, and svPPA[1,3,4]

Syndrome	Possible/clinical diagnosis	Probable/imaging supported diagnosis[b]	Definite/pathologically or genetically proven diagnosis	Exclusionary criteria
bvFTD	At least 3 of the following: • Early[a] behavioral disinhibition • Early apathy or inertia • Early lack of empathy or sympathy • Early perseverations, stereotypies or compulsions • Dietary habit changes or hyperorality • Executive-predominant deficits on neuropsychological testing with relative sparing of memory and visuospatial skills	All of the following: • Meets possible criteria • Significant decline per informant, or CDR, or FAQ • Imaging consistent with bvFTD (frontal and/or anterotemporal)	All of the following: • Meets possible OR probable criteria • Histopathological evidence of FTLD and/or presence of known pathogenic mutation	• Deficits are not better explained by alternative diagnosis (degenerative, nondegenerative, or psychiatric)
nfvPPA[d]	At least one of the following: • Agrammatism Effortful, halting speech with inconsistent sound errors (AOS) At least two of the following: • Impaired comprehension of syntactically complex sentences • Spared single-word comprehension • Spared object knowledge	All of the following: • Meets possible/clinical criteria • Imaging consistent with nfvPPA (left posterior frontoinsular)	All of the following: • Meets possible OR probable criteria • Histopathological evidence of specific pathology[c] and/or presence of known pathogenic mutation	• Deficits are not better explained by alternative diagnosis (nondegenerative, or psychiatric) • Prominent initial deficits are not memory, visuospatial, or behavioral
svPPA[d]	All of the following: • Impaired confrontation naming • Impaired single-word comprehension At least 3 of the following: • Impaired object knowledge • Surface dyslexia or dysgraphia • Spared repetition • Spared grammar and motor speech production	All of the following: • Meets possible/clinical criteria • Imaging consistent with svPPA (anterior temporal lobe)	All of the following: • Meets possible OR probable criteria • Histopathological evidence of specific pathology[c] and/or presence of known pathogenic mutation	• Deficits are not better explained by alternative diagnosis (nondegenerative, or psychiatric) • Prominent initial deficits are not memory, visuospatial, or behavioral

Abbreviations: AOS, apraxia of speech; CDR, Clinical Dementia Rating Scale; FAQ, Functional Activities Questionnaire; FTLD, frontotemporal lobar degeneration; PET, positron emission tomography; SPECT, single-photon emission computed tomography.
[a]Approximately within the first 3 years from symptom onset.
[b]Imaging refers to structural magnetic resonance imaging atrophy, PET hypometabolism, or SPECT hypoperfusion.
[c]Specific pathology in 2011 PPA (primary progressive aphasia) criteria may be tau, TDP-43, Alzheimer disease, or other proteinopathy.
[d]Both nfvPPA and svPPA must satisfy PPA criteria by Mesulam[1] with language impairment being the most prominent, disabling, and earliest symptom.

impairment, such as tumors, vascular disease, prion, and paraneoplastic disorders; hence the need for sequences such as diffusion weighted imaging, fluid attenuated inversion recovery, and gradient echo.[28,31] In contrast to MRI, there are no characteristic changes on electroencephalography, other than mild frontal slowing.

Functional resting state imaging in FTLD, such as metabolism-associated positron emission tomography (PET), single-photon emission computed tomography, and functional MRI, highlights impairments to vulnerable brain networks associated with behavioral and cognitive deficits (i.e., frontal and anterior temporal lobes).[35] A conceptually similar approach

Table 5 Pharmacological treatments[64–82]

Medication	Dose	Population	Study designs	Combined study outcome	Side effects
Trazodone	Up to 300 mg daily	bvFTD	DB-CO-RCT	Improved behavior[a]	Fatigue, dizziness, hypotension
Fluvoxamine	50–150 mg daily	bvFTD, svPPA	OL	Improved stereotypies	Appetite loss
Paroxetine	Up to 40 mg daily	bvFTD	OL, OL-RCT, DB-CO-RCT	No definite behavioral benefit Improved mood, compulsions, and eating disorders	Well tolerated
Fluoxetine	20 mg daily	bvFTD	OL	Improved mood, compulsions, and eating disorders	Well tolerated
Sertraline	50–125 mg daily	bvFTD	OL-CT, OL	Improved stereotypies	Well tolerated
Citalopram	40 mg daily	bvFTD	OL	Improved behavior	Well tolerated
Donepezil	Up to 10 mg daily	bvFTD	OL, DC	No benefit	Worse behavioral symptoms
Galantamine	Up to 24 mg daily	bvFTD, PPA	OL to DB-RCT	No benefit	Mild GI symptoms
Rivastigmine	Up to 9 mg daily	bvFTD	OL-CT	Improved behavior	Well tolerated
Quetiapine	Up to 150 mg total daily dose	bvFTD, nfvPPA, svPPA	DB-CO-RCT	No definite benefit	Somnolence
Olanzapine	Up to 10 mg daily	bvFTD	OL	Improved agitation and anxiety	Somnolence, mild GI symptoms
Bromocriptine	Up to 7.5 mg 3 times daily	PPA	DB-CO-RCT	No benefit	Rare frustration intolerance
Methylphenidate	40 mg once	bvFTD	DB-CO-CT	Improved decision making within a few hours	Non-significant blood pressure increase
Dextroamphetamine	20 mg total daily dose	bvFTD, nfvPPA, svPPA	DB-CO-RCT	Improved behavior	Well tolerated
Memantine	Up to 20 mg daily	bvFTD, nfvPPA, svPPA	OL, DB-RC	No benefit	Well tolerated

Abbreviations: CO, crossover; CT, control trial; DB, double blind; DC, discontinuation of treatment; GI, gastrointestinal; OL, open-label; RCT, randomized control trial.
[a]Improved behavior usually corresponds to neuropsychiatric inventory scores or refers to irritability, agitation, depression, and eating disorders.

uses diffusion tensor imaging, which represents the structural integrity of white matter tracts connecting brain hubs. White matter tracts are affected early in the disease process, even in presymptomatic FTLD mutation carriers, and may provide even better diagnostic accuracy than volumetric MRI.[56,57]

Fluid biomarkers, such as blood and cerebrospinal fluid (CSF) have been extensively studied in FTLD. Testing for genetic mutations is useful if an autosomal dominant mutation is suspected (►Table 3). A risk factor for FTLD-tau, especially CBD and PSP, is histone 1 haplotype.[58] In contrast, minor *TMEM106B* allele homozygosity protects *GRN* and *C9Orf72* mutation carriers.[59,60] The best studied CSF biomarker is the tau: $A\beta_{1-42}$ ratio, which is significantly lower in FTLD than AD patients.[61]

Molecular PET is useful to test for the presence of amyloid pathology. Current guidelines recommend its use by a dementia expert (1) in patients younger than 65 years old, (2) in persistent or progressive unexplained mild cognitive impairment, and (3) in atypical or mixed-dementia presentations.[62] Thus, it is helpful in differentiating AD from bvFTD, or lvPPA from nfvPPA, or to identify dual pathology. Tau imaging will soon be available to search for tau-positive forms of FTLD.[63] Currently, there is no TDP-43 or FUS PET.

Diagnostic Criteria

Frontotemporal lobar degeneration diagnostic criteria were revised in 2011 for both bvFTD and PPA, aiming to improve diagnostic accuracy (►Table 4).[3,4] Nonetheless, there is still room for criteria improvement because diagnostic accuracy and interrater reliability is imperfect. In time, it is likely that criteria will incorporate molecular PET, improving direct syndrome-to-pathology diagnostic associations (►Fig. 1), while in parallel addressing multiple copathologies (e.g., AD and FTLD).

Treatment

►Table 5 lists symptomatic treatments tested in FTD trials. Prior etiologic treatments have either proven toxic or non-efficacious.[83] For more details on FTD therapies, see also the review in the current issue by Tsai and Boxer, Clinical Trials: Past, Current, and Future for Atypical Parkinsonian Syndromes. In general, selective serotonin reuptake inhibitors are mildly beneficial for compulsions and eating disorders. Dopaminergic medications have no definite behavioral benefit. Recent trials do not support the use of memantine, and cholinesterase inhibitors seem to worsen behavior. Atypical antipsychotics should be used with caution only in cases of severe agitation given their extrapyramidal side effects. Levodopa may be considered in parkinsonism, especially where tau pathology or *MAPT* mutations are suspected, but a sustained response is rarely present.

A promising etiologic therapy focuses on halting tau spread using anti-tau antibodies, which in animal models decrease protein accumulation and improve behavior.[84] Antisense oligonucleotides are being studied in *C9Orf72* mutations.[85] There is a single report of steroid treatment improving symptoms in svPPA, highlighting its association

Table 6 Foundations and Support Groups

Association for Frontotemporal Degeneration (AFTD) Radnor Station Building 2, Suite 320, 290 King of Prussia Road, Radnor, PA 19087, USA Telephone: +1–267–514–7221 or HelpLine: +1–866–507–7222 (toll free) http://www.theaftd.org
Consortium for Frontotemporal Dementia Research – The Bluefield Project to Cure Frontotemporal Dementia 1650 Owens Street, Room 205, San Francisco, CA 94158, USA http://www.bluefieldproject.org/contact-us
FRONTIER Frontotemporal Dementia Research Group NeuRA, PO Box 1165, Randwick NSW 2031, Australia Telephone: +61–2-9399–1000 https://www.neura.edu.au/contact-us
Tau Consortium http://tauconsortium.org
The Foundation for PSP | CBD and Related Brain Diseases (CurePSP) 30 E. Padonia Road, Suite 201, Timonium, MD 21093, USA Telephone: +1–410–785–7004 or +1–800–457–4777 (toll free) http://www.psp.org
National Institute of Neurological Disorders and Stroke (NINDS) Patient Recruitment and Public Liaison Office: +1–800–411–1222 (toll free) http://www.ninds.nih.gov/disorders/picks/picks.htm
The Frontotemporal Dementia Support Group (United Kingdom) The National Brain Appeal, Box 123, Queen Sq, London, WC1N 3BG, UK Regional contact information: http://www.ftdsg.org/Regional_contacts
Frontotemporal Dementia Caregiver Support Center http://ftdsupport.com
Family Caregiver Alliance 785 Market Street, Suite 750, San Francisco, CA 94103, USA Telephone: +1–415–434–3388 or +1–800–445–8106 http://www.caregiver.org
Neil L. Radin Caregivers Relief Foundation 4404 Aberdeen Lane Blackwood, Blackwood, NJ 08012, USA Telephone: +1–215–205–3162
FTD Support Forum http://ftdsupportforum.com

to autoimmunity.[86] Finally, treatments that raise progranulin levels are in development for *GRN* mutations.[83]

Nonpharmacological management of FTLD is as important as are pharmacological therapies. Family education and respite, a regular sleep schedule, social worker involvement, driving evaluation, exercise, and speech therapy can improve patients' and families' quality of life. Thus, a multidisciplinary dementia clinic is the optimal setting for management of FTLD. ►Table 6 contains information on foundations and support groups for FTLD.

Acknowledgments

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