# FRONTOTEMPORAL DEMENTIA AND PRIMARY PROGRESSIVE APHASIA

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**Overview**

Frontotemporal dementia (FTD) is an umbrella term used to describe a family of neurological disorders that present with prominent changes in behavior or language, associated with degeneration of the frontal or anterior temporal lobes. First described by Arnold Pick and Alois Alzheimer at the turn of the 20th Century, FTD was "rediscovered" in the late 1980s - early 1990s, and has subsequently been shown to be as common as Alzheimer's disease (AD) in patients who develop an early-onset dementia (before age 65). The term primary progressive aphasia (PPA) was introduced by Marsel Mesulam in the 1980s to describe patients who present with early isolated loss of language abilities in the setting of focal atrophy in the left hemisphere language network. PPA patients with frontal or anterior temporal atrophy also fall under the FTD umbrella (Figure 1). More recent work has highlighted the clinical, genetic and neuropathological overlap between FTD/PPA and amyotrophic lateral sclerosis (ALS), as well as the atypical parkinsonian disorders corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). In this course we will review the clinical features of FTD and PPA, describe their genetic and neuropathological underpinnings, and demonstrate how these disorders have advanced our understanding of the neural networks involved in language and social/emotional cognition. We will conclude by describing currently available and experimental therapies.

**Demographics and Epidemiology**

FTD accounts for approximately 5% of all dementia, but is (along with AD) the most common cause of dementia in patients presenting before age 65. The prevalence of FTD has been estimated at 15-22/100,000, and incidence at 2.7-4.1/100,000 (Onyike and Diehl-Schmid 2013). Males and females are equally affected. The disease typically presents in the sixth decade, though the age of onset can vary widely from the third to the ninth decade, with 25% of patients developing symptoms after age 65. FTD is more rapidly progressive than AD and associated with shorter survival, particularly if accompanied by motor-neuron disease or extrapyramidal features. Overall median survival has been estimated at 6-11 years from symptom onset and 3-4 years from diagnosis.

**Clinical Syndromes**

Approximately half of all FTD patients present with prominent changes in behavior and personality (behavioral-variant FTD, bvFTD), while 50% present with either nonfluent-variant PPA (nfvPPA) or semantic-variant PPA (svPPA) (Bang et al. 2015, Rabinovici and Miller 2010). The logopenic-variant of PPA (lvPPA) is associated with posterior-predominant neurodegeneration and AD pathology, and is thus not included under the FTD umbrella (Figure 1). The key features of each syndrome are described below, and a summary of clinical, anatomical, genetic and histopathologic correlations is presented in Table 1. The closely associated disorders CBD and PSP will be covered in a separate lecture in this course.

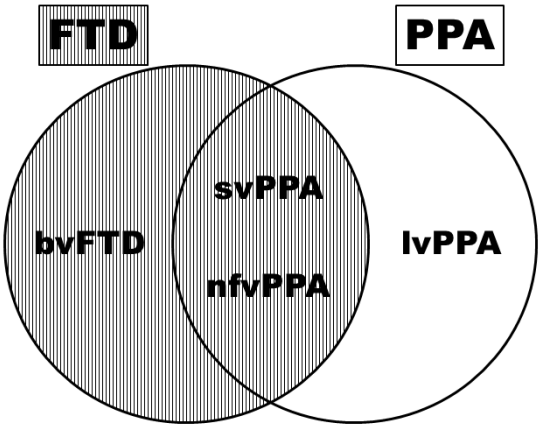


**Figure 1.** Overlap between FTD and PPA.

**Behavioral-variant FTD –** bvFTD presents with marked changes in personality and behavior (Rascovsky et al. 2011). Patients show marked apathy, characterized by loss of interest in personal affairs and responsibilities, social withdrawal, and, ultimately, loss of awareness of personal hygiene and sphincter control. Disinhibition is manifested by socially inappropriate behaviors, including confrontation seeking, hurtful or insensitive remarks to others, frankly sociopathic behaviors (e.g. shoplifting, traffic violations) or (rarely) physical assault. Patients appear cold and unempathetic. Insight is dramatically impaired. Repetitive motor behaviors (e.g. rubbing, picking, throat clearing, pacing and wandering), idiosyncratic hoarding and collecting, changes in eating behavior (e.g. overeating and weight gain, loss of table

| Syndrome | Clinical features | Anatomy | Genetic correlation | Neuropathology |
|---|---|---|---|---|
| bvFTD | Changes in behvaior and personality. Can be associated with ALS. | ACC, frontal insula, OFC, DLPFC, temporal poles | *MAPT, GRN, C9ORF72* | TDP >Tau >> FUS |
| svPPA | L: Loss of word and object meaning. R: Rigidity, coldness, loss of empathy. | Anterior temporal lobes | Usually sporadic | TDP >> Tau |
| nfvPPA | Nonfluent aphasia, motor speech deficits, agrammatism. | L peri-Sylvian | *GRN* | Tau > TDP |
| lvPPA | Anomia, impaired sentence repetition with spared grammar, motor speech, word comprehension | L tempoparietal | Usually sporadic | AD |

**Table 1. Summary of FTD syndromes.** Most common genetic and neuropathological correlations are included. Abbreviations: bvFTD – behavioral-variant FTD; svPPA – semantic-variant PPA; nfvPPA – nonfluent variant PPA; lvPPA – logopenic-variant PPA; ACC – anterior cingulate cortex; OFC – orbitofrontal cortex; DLPFC – dorsolateral prefrontal cortex.

manners) and hyper-orality (including oral exploration of inedible objects) are common. Many patients are initially misdiagnosed as having a primary psychiatric disorder. Cognitive decline is typically less dramatic than the behavioral disturbance. The most common cognitive symptoms are poor judgment, inattentiveness and distractibility, loss of planning ability and disorganization. On cognitive testing patients show deficits on frontal/executive tasks, with a proclivity for making perseverative errors and violating test rules. Visuospatial function and (less reliably) episodic memory are spared. ALS can co-occur with any of the FTD clinical variants, but is most commonly associated with bvFTD. Patients may present with upper or lower motor-neuron signs in any myotomal distribution, with bulbar-onset most common. On MRI, bvFTD patients show prominent atrophy in the frontal and anterior temporal lobes, with sparing of posterior brain regions (Rabinovici et al. 2007). The "salience network," consisting of frontal insula, anterior cingulate and orbitofrontal cortex is targeted early in FTD, and dysfunction of this network mediates the host of maladaptive social and emotional behaviors that characterize the disease (Seeley et al. 2008). In diagnostically uncertain cases, FDG-PET (Foster et al. 2007), amyloid PET (Rabinovici et al. 2011) or CSF $A\beta_{42}$ and Tau levels (Bian et al. 2008) may be considered to help distinguish between AD and FTD.

**Semantic-variant PPA** - svPPA, also referred to as the temporal-variant of FTD, is characterized by a fluent, anomic aphasia and behavioral changes in the setting of marked, often asymmetric degeneration of the anterior temporal lobes (Gorno-Tempini et al. 2011). Patients with primary left-sided atrophy present with progressive loss of "semantic" knowledge about words, objects and concepts. This is initially manifest as a fluent aphasia with impoverished speech content and semantic paraphasic errors, but intact syntax and motor speech. With time, patients develop features of a multimodal agnosia. Patients with predominant right-sided anterior temporal atrophy present with a behavioral syndrome characterized by emotional blunting with a flat, bizarre affect, marked loss of empathy, and awkward social behavior (Seeley et al. 2005). Rigidity is common and manifest by strict schedules and routines, clock watching and restrictive dieting or food fads. On cognitive testing, patients perform poorly on tests of confrontation naming, word-to-picture matching, and category fluency, while episodic memory (particularly visual memory), spatial abilities and executive functions are initially spared. Patients with right-sided temporal atrophy typically develop the semantic loss characteristic of the left temporal variant after a mean of three years, as the disease spreads to the contralateral temporal pole, while left temporal patients develop the behavioral changes associated with right temporal disease within a similar time frame (Seeley et al. 2005). MRI reveals striking, at times focal atrophy of the anterior temporal lobes. The unique clinical features of svPPA have advanced our understanding of the important role of the left temporal pole in language comprehension, and the right temporal pole in empathy and emotional cognition (Rankin et al. 2006).

**Nonfluent-variant PPA -** nfvPPA is a progressive disorder of language expression and motor speech associated with left peri-Sylvian atrophy (Gorno-Tempini et al. 2011, Mesulam et al. 2014). Patients present with slow, effortful speech, impaired production and comprehension of grammar (agrammatism) and motor speech deficits. Apraxia of speech, defined as difficulty initiating speech, a slow rate of speech, or incorrect sequencing or omission of phonemes, is highly characteristic and can occur in isolation of other language disturbances (Josephs et al. 2013). Additional language features include phonemic paraphasic errors and mild anomia (without associated semantic loss). Comprehension is spared for single words and for all but the most complex syntactic structures. The elemental neurological examination may reveal supranuclear gaze palsies, parkinsonism and limb apraxia, reflecting a frequent overlap with CBD and PSP. Neuropsychological testing typically shows (in addition

to the aphasia) deficits in working memory and executive function, with sparing of episodic memory and visuospatial function. MRI reveals atrophy of the left frontal operculum, premotor and supplementary motor areas and anterior insula.

**Logopenic-variant PPA –** lvPPA is characterized by hesitant speech with frequent word-finding pauses and spontaneous phonological errors (Gorno-Tempini et al. 2011). The main distinguishing clinical feature is profound impairment in sentence repetition, particularly for long sentences with unpredictable content. This deficit is akin to a conduction aphasia in classical aphasia terminology, and is caused by an underlying impairment in auditory working memory. lvPPA is distinguished from svPPA by intact single word comprehension, and from nfvPPA by preservation of motor speech and grammar. In addition to the language deficits, neuropsychological testing typically reveals impaired auditory working memory (e.g. difficulty repeating a series of digits) and acalculia with variable involvement of executive and visuospatial functions and initial sparing of episodic memory (particularly visual memory). The diagnosis is supported by predominant atrophy in the left temporoparietal junction on MRI. As described below, lvPPA is often caused by underlying AD pathology, as reflected by its inclusion as an AD variant in new diagnostic criteria. Amyloid PET or CSF AD biomarkers can be obtained to support the diagnosis of lvPPA due to AD, or to rule-out AD in other PPA presentations.

**Neuropathology and Genetics**

The term frontotemporal lobar degeneration (FTLD) is preferred to describe the neuropathological correlates of FTD and to distinguish the pathological entities from the clinical syndromes. The gross pathology of FTLD is characterized by marked and often circumscribed atrophy of the frontal and anterior temporal lobes. On microscopic examination, there is loss of pyramidal neurons and microvacuolar degeneration in cortical layers II and III of frontal and temporal cortex, with a variable degree of cortical gliosis. The histopathological inclusions in FTLD can be split into two main categories: (1) FTLD-Tau; and (2) FTLD-TDP (Mackenzie et al. 2010). FTLD-Tau is defined by tau-positive neuronal and glial inclusions. The tau protein in neurons binds to axonal microtubules, promotes microtubule assembly and stabilization and is also involved in signal transduction. In the pathologic state tau is hyper-phosphorylated, disassembles from microtubules and forms toxic aggregates. The most common subtypes of FTLD-Tau are Pick's disease, CBD and PSP. Less common FTLD-related tauopathies include: argyrophilic grain disease, sporadic multiple system tauopathy with dementia and ALS-parkinsonism-dementia complex of Guam. FTLD-TDP is distinguished by the presence of tau-negative ubiquitinated inclusions composed of aggregated TAR DNA-binding protein 43 (TDP-43). TDP-43 is a nuclear protein involved in DNA transcription and splicing. Under pathologic conditions, TDP-43 is displaced from the cell nucleus to the cytoplasm, hyperphosphorylated, ubiquitinated and cleaved to produce C-terminal fragments that aggregate and form neuronal inclusions. A third, and much less common pathological cause of FTD is FTLD-FUS, with inclusions consisting of aggregated fused in sarcoma (FUS) protein (FTLD-FUS).

Correlations between FTD/PPA clinical syndromes and neuropathology are shown in Table 1 (Josephs et al. 2011). FTD-ALS and svPPA are strongly correlated with FTLD-TDP, while nfvPPA is usually associated with FTLD-Tau. bvFTD is associated with FTLD-TDP more frequently than FTLD-Tau. Rare cases of FTLD-FUS can be identified by very early age-at-onset (early 40s or younger), absence of family history, marked obsessive-compulsive behaviors and caudate atrophy. Discriminating between FTLD-Tau and FTLD-TDP during life is a major challenge in bvFTD and to some degree in nfvPPA. Emerging Tau PET ligands and CSF biomarkers are promising developments in this regard. AD is the causative pathology in 60%-90% of cases of lvPPA and 10%-20% of other FTD phenotypes (Mesulam et al. 2014). Amyloid PET or CSF Tau/Aβ can be used to rule AD in or out, though the presence of AD does not exclude FTLD co-pathology that may be equally or more relevant to the clinical presentation.

Up to 40% of FTLD patients have a history suggestive of familial transmission, with roughly 10% of patients showing an autosomal dominant inheritance pattern (Goldman et al. 2007). When obtaining the family history, in addition to FTD and ALS clinicians should also inquire about mid or late-life psychiatric disease, AD and parkinsonian disorders, as FTLD is often mistaken for these conditions. There are three common genes that lead to autosomal dominant FTD (Rademakers et al. 2012). Mutations in the Microtubule Associate Protein Tau (*MAPT*) gene lead to familial FTLD-Tau. *MAPT* mutations are most commonly associated with bvFTD, but can present as svPPA, nfvPPA, corticobasal syndrome (CBS), PSP and even an amnestic disorder reminiscent of AD. Mutations in the granulin gene (*GRN*) are associated with FTLD-TDP. Associated clinical phenotypes include bvFTD, nfvPPA and CBS. Hexanucleotide expansions in Chromosome 9 Open Reading Frame 72 (*C9ORF72*) lead to FTLD-TDP with or without motor-neuron disease. There is a strong correlation with familial FTD-ALS, ALS

or bvFTD. For all three common genes, clinical phenotype can vary even within a pedigree. On MRI, *MAPT* mutations are associated with temporal atrophy, *GRN* mutations with a highly asymmetric frontotemporal pattern that extends into parietal cortex, and *C9ORF72* with more global atrophy that also involves the thalamus and cerebellum. Curiously, mutations in *TARDP* (the gene that encodes TDP-43) and *FUS* are associated with ALS but only rarely with clinical FTD. Other implicated genes include *VCP*, *CHMP2B* and *TREM2* among others. As in autosomal dominant AD, multi-site international studies are underway in familial FTD to characterize the earliest clinical changes and relate them to imaging and biological markers.

**Treatment**

The first-line therapies to mitigate abnormal behaviors in FTD are non-pharmacologic, and include caregiver and family education, and environmental, behavioral and physical interventions designed to minimize the occurrence and consequences of undesired behaviors (Merrilees 2007). First line pharmacotherapy consists of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRI) based on the association of FTD with a serotonergic deficit, clinical trials (albeit few, with generally small sample sizes), and efficacy of these drugs in managing similar behaviors in patients with primary psychiatric disease (Rabinovici and Miller 2010). Atypical neuroleptics should be used only as a last resort and a temporary measure given their association with increased morbidity and mortality in dementia patients. Disruptive behaviors often taper off as apathy predominates in late disease stages, and the need for psychotropics should be revisited on a continuous basis.

AD symptomatic therapies such as cholinesterase inhibitors and memantine can be tried in lvPPA due to AD, but *should not be used in FTD syndromes* given evidence that they may worsen behavior and cognitive outcomes. Riluzole can be considered in patients with ALS, and levodopa should be tried (though is not usually effective) in patients with parkinsonism. Speech therapy can be very helpful in PPA, particularly if tailored to the preserved elements of language in the individual patient, and augmentative communication devices can be useful in later disease stages (Beeson et al. 2011). Physical and occupational therapy and home safety evaluations should be ordered as appropriate. We universally recommend a structured exercise program for physically able patients and caregivers. A discussion about end-of-life decisions and goals of care should be pursued pre-emptively.

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