# Frontotemporal Lobar Degeneration:

## Epidemiology, Pathophysiology, Diagnosis and Management

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## Abstract

Frontotemporal lobar degeneration (FTLD) is a clinically and pathologically heterogeneous syndrome, characterized by progressive decline in behaviour or language associated with degeneration of the frontal and anterior temporal lobes. While the seminal cases were described at the turn of the 20th century, FTLD has only recently been appreciated as a leading cause of dementia, particularly in patients presenting before the age of 65 years. Three distinct clinical variants of FTLD have been described: (i) behavioural-variant frontotemporal dementia, characterized by changes in behaviour and personality in association with frontal-predominant cortical degeneration; (ii) semantic dementia, a syndrome of progressive loss of knowledge about words and objects associated with anterior temporal neuronal loss; and (iii) progressive nonfluent aphasia, characterized by effortful language output, loss of grammar and motor speech deficits in the setting of left perisylvian cortical atrophy.

The majority of pathologies associated with FTLD clinical syndromes include either tau-positive (FTLD-TAU) or TAR DNA-binding protein 43 (TDP-43)-positive (FTLD-TDP) inclusion bodies. FTLD overlaps clinically and pathologically with the atypical parkinsonian disorders corticobasal degeneration and progressive supranuclear palsy, and with amyotrophic lateral sclerosis. The majority of familial FTLD cases are caused by mutations in the genes encoding microtubule-associated protein tau (leading to FTLD-TAU) or progranulin (leading to FTLD-TDP). The clinical and pathologic heterogeneity of FTLD poses a significant diagnostic challenge, and *in vivo* prediction of underlying histopathology can be significantly improved by supplementing the clinical evaluation with genetic tests and emerging biological markers. Current pharmacotherapy for FTLD focuses on manipulating serotonergic or dopaminergic neurotransmitter systems to ameliorate behavioural or motor symptoms. However, recent advances in FTLD genetics and molecular pathology make the prospect of biologically driven, disease-specific therapies for FTLD seem closer than ever.

Frontotemporal lobar degeneration (FTLD) is a clinically and pathologically heterogeneous syndrome, characterized by a progressive decline in behaviour or language associated with degeneration of the frontal and anterior temporal lobes. The original cases described by Arnold Pick and Alois Alzheimer (new references #1, #2)[84] demonstrated neuronal inclusions that were later shown to be tau-positive at histopathology. The link between tau and FTLD was further strengthened by the discovery that mutations in the microtubule-associated protein tau (*MAPT*) gene cause familial FTLD.[126−128] In 2006, the TAR

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DNA-binding protein 43 (TDP-43) was identified as the major ubiquitinated protein associated with tau-negative FTLD,[96] and mutations in the progranulin (*PGRN*) gene were shown to be responsible for the majority of familial tau-negative cases. [129⁻131] These recent discoveries coincide with the publication of autopsy series from multiple centres that have helped elucidate clinicopathologic correlations in FTLD, and with the development of biological markers that can further improve *in vivo* prediction of underlying histopathology. Together, these advances have created the opportunity to develop biologically driven, disease-specific therapies for FTLD.

In this article, we review the epidemiology, clinical presentations and pathophysiology of the FTLD-spectrum disorders. We also discuss current evidence for symptomatic treatment, and speculate on future therapeutic strategies.

## 1. Terminology

Nomenclature in FTLD can be confusing, with different terminologies applied throughout the literature. In this review, we adopt the terminology used in the 1998 Consensus Criteria published by Neary and colleagues.[1] FTLD is used as an umbrella term for three clinical variants that can be distinguished based on the early and predominant symptoms: behavioural-variant frontotemporal dementia (bvFTD); semantic dementia (SD); and progressive nonfluent aphasia (PNFA). FTLD-associated pathologies are subclassified into disorders with tau-inclusion bodies (FTLD-TAU) and those with TDP-43 inclusions (FTLD-TDP). FTLD shows significant clinical and pathologic overlap with the atypical parkinsonian disorders corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), and these are also considered in this review.

## 2. Epidemiology

The prevalence of FTLD in population-based studies has varied between 2.7/100,000 (with a peak of 9.4/100,000 in the 60- to 69-year age group) in the Zuid-Holland district in the Netherlands,[2] to 15.1/100,000 in adults aged <65 years in Cambridge, UK,[3] which is identical to the prevalence of Alzheimer's disease in the latter population. Two studies have reported a similar incidence of FTLD and Alzheimer's disease in adults with early age-of-onset dementia in Cambridge, UK (3.5/100,000 person-years for FTLD, 4.2/100,000 person-years for Alzheimer's disease in 45- to 64-year-olds)[4] and Rochester, Minnesota, USA (3.3/100,000 person-years for both diseases in the 50- to 59-year age group).[5] The disease typically presents in the sixth decade, although the age of onset can vary widely from the third to the ninth decade.[3,6,7] Although FTLD is generally considered a presenile dementia, individuals over the age of 65 years account for 20–25% of all cases.[3,6,7] Gislason and colleagues[8] found a surprisingly high (3%) prevalence of bvFTD when screening a cohort of 85-year-olds in Gothenburg, Sweden. Autopsy studies based on consecutive, unselected cases have demonstrated that FTLD accounts for roughly 5% of all pathologic diagnoses in patients with dementia.[9,10] However, this is likely to represent an underestimate of the true prevalence, since many of the autopsies reported in these series predated the modern molecular techniques currently used to diagnose FTLD (see section 4). Taken together, these epidemiologic data suggest that FTLD is a common cause of early-onset (age <65 years) dementia, with an incidence and prevalence similar to Alzheimer's disease, and is likely to be an underappreciated cause of dementia in older individuals.

Sex distribution in FTLD appears to vary by clinical syndrome, with most studies reporting a male preponderance in bvFTD, and a number of studies describing a male predominance in SD and a female predominance in PNFA.[3,6,7,11] Median survival in FTLD has been estimated at 6–11 years from symptom onset and 3–4 years from diagnosis.[7,11⁻13] In our centre, bvFTD is associated with the shortest survival (median 8.7 years from onset), SD

with the longest survival (11.9 years) and PNFA with intermediate survival (9.4 years),[11] while the Cambridge group has reported the longest survival in PNFA (mean 10.6 years from onset) followed by bvFTD (8.2 years) and SD (6.9 years).[7] Across centres, the presence of motor neuron disease is associated with early mortality (2.4–4.9 years from onset and 1.2–1.4 years from diagnosis).[7,11] Overall, survival is shorter and cognitive and functional decline are more rapid than in Alzheimer's disease.[11,12]

## 3. Clinical Syndromes

FTLD patients can be classified into three clinical syndromes depending on the early and predominant symptoms: a behavioural variant (bvFTD) and two language variants (SD and PNFA).[1] Each clinical variant is associated with a distinct regional pattern of brain atrophy and, to a varying degree, a characteristic histopathology (figure 1). Overlap between the syndromes can occur,[14] particularly later in the course as the disease spreads to involve the frontal and temporal lobes more diffusely.

### 3.1 Behavioural-Variant Frontotemporal Dementia

Patients with this clinical variant present with marked changes in personality and behaviour, and often display a mixture of apathy and disinhibition.[1,15⁻21] Apathy is characterized by loss of interest in personal affairs and responsibilities, social withdrawal and, as the disease advances, loss of awareness of personal hygiene and sphincter control. Disinhibition is manifested by a multitude of socially inappropriate behaviours, including confrontation seeking, making hurtful or insensitive remarks to others, engaging in frankly sociopathic behaviours (e.g. shoplifting, traffic violations) or (rarely in our experience) physical assault. [22,23] Patients appear cold and unempathetic, showing little concern for the effect of their behaviour on loved ones.[24] 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).[1] 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".[25] Repetitive motor behaviours (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. [26⁻32]

Cognitive decline is typically less dramatic than the behavioural disturbance, and patients may require institutionalization despite normal performance on neuropsychometric tests.[33] The most common cognitive symptoms are poor judgment, inattentiveness and distractibility, loss of planning ability and disorganization. On cognitive testing, patients often show deficits on frontal/executive tasks, such as tests of set shifting, mental flexibility, response inhibition and abstract reasoning.[18,34⁻36] Attention and working memory may be impaired, while episodic memory is variably spared.[35,37⁻39] Visuospatial function is almost always preserved early in the disease (in contrast to Alzheimer's disease).[40] The presence of rule violations, perseverative errors and confabulations during testing is highly characteristic, and can help differentiate bvFTD from other disorders.[35,41]

Amyotrophic lateral sclerosis (ALS) can co-occur with any of the FTLD clinical variants, but is most commonly associated with bvFTD.[42] When prospectively studied, approximately half of all bvFTD patients meet criteria for possible or probable ALS, while half of ALS patients show behavioural or cognitive deficits suggestive of bvFTD.[43,44] Patients with FTLD-ALS can present with either cognitive or motor dysfunction.[42] Bulbar-onset motor neuron disease is most common, although patients may present with either upper or lower motor neuron signs in any myotomal distribution.[44⁻46] Because of

the strong association between FTLD and ALS, all FTLD patients should undergo a careful neuromuscular evaluation (with consideration for electromyography), while all ALS patients should be screened for behavioural and cognitive changes.

Structural and functional neuroimaging studies have highlighted frontal atrophy, hypometabolism and hypoperfusion in patients with bvFTD (figure 2a and b).[47⁻49] While the dorsolateral prefrontal cortex is often involved, the earliest changes occur in a medial paralimbic network that includes anterior cingulate, orbital frontal and frontoinsular cortices, and atrophy in these regions best distinguishes FTLD from Alzheimer's disease.[47,50,51] The region of greatest atrophy within this network correlates with the clinical phenotype, with dorsomedial frontal atrophy associated with apathy and aberrant motor behaviour, and orbitofrontal atrophy associated with disinhibition.[52]

### 3.2 Semantic Dementia

SD, also referred to as the temporal-variant of FTLD, is characterized by a fluent, anomic aphasia and behavioural changes in the setting of marked, often asymmetric degeneration of the anterior temporal lobes (figure 2c).[1,53] Patients with primarily left-sided atrophy present initially with progressive loss of 'semantic' knowledge about words, objects and concepts.[1,54⁻56] This is manifest as a fluent aphasia with impoverished speech content and semantic paraphasic errors, but intact syntax, prosody and motor speech.[57,58] Loss of meaning follows a hierarchical pattern; for example, patients may first lose their ability to differentiate between types of dogs, and later become unable to distinguish dogs from other animals. Eventually, all animals may be referred to as 'things'. [57] With time, loss of knowledge extends beyond language, and patients develop features of a multimodal agnosia. [57,59] 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 spared.[56,57,60⁻62]

Patients with predominant right anterior temporal atrophy present with a behavioural syndrome that overlaps with bvFTD.[54,62] Patients develop emotional blunting with a flat, bizarre affect that has been described as 'alien'. There is a marked loss of empathy and interest in others, and social behaviour is described by informants as awkward, tactless and impervious to social cues.[56,63] Rigidity is common and manifests with strict schedules and routines, clock watching and restrictive dieting or food fads. Prosopagnosia and associative agnosia are emphasized in the current diagnostic criteria,[1] but behavioural changes often precede these findings by years.[54] Compared with patients with bvFTD, patients with right-predominant SD tend to be more rigid, have distinct types of compulsions and eating disorders, and have a higher rate of constitutional symptoms such as sleep disorders, weight loss and sexual dysfunction.[15,54,64⁻66]

Patients with right-sided SD typically develop the semantic-loss characteristic of the left temporal variant after a mean of 3 years, as the disease spreads to the contralateral temporal pole, while patients with left temporal SD develop the behavioural changes associated with right temporal disease within a similar timeframe.[54] Compulsions are common in both patient groups, with left temporal patients developing visually oriented compulsions (e.g. collecting bright objects), while right temporal patients develop verbally oriented compulsions (e.g. word jumbles, punning).[54] Disinhibition and apathy reminiscent of bvFTD develop 5–7 years after symptom onset, perhaps reflecting spread of the disease into the frontoinsular network.[47] Left-sided SD patients outnumber right-sided patients 3:1 in most series, although this may reflect a referral bias to behavioural neurology centres, since right-sided patients may be misdiagnosed as having a primary psychiatric disorder.[54,56]

### 3.3 Progressive Nonfluent Aphasia

PNFA is a progressive disorder of language expression and motor speech associated with left perisylvian atrophy.[1,58] 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 of PNFA, while dysarthria is more variably present.[58,67] 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. Reading is nonfluent and effortful, while writing is agrammatic and features phonemic paraphasias. The elemental neurologic examination may reveal supranuclear gaze palsies, parkinsonism and limb apraxia, reflecting a frequent association with CBD and PSP (see section 3.4**).** Neuropsychometric testing may show (in addition to the aphasia) mild deficits in working memory and executive function, with sparing of episodic memory and visuospatial function. [58] Behavioural disturbances can occur, but are less frequent and severe than in bvFTD and SD.[68] Anatomically, PNFA is associated with atrophy, hypometabolism and hypoperfusion of the left frontal operculum, premotor and supplementary motor areas and anterior insula (figure 2d).[58,69]

### 3.4 Frontotemporal Lobar Degeneration (FTLD) Overlap Syndromes: Corticobasal Degeneration and Progressive Supranuclear Palsy

FTLD clinical syndromes may show significant overlap with the atypical parkinsonian syndromes CBD and PSP, although both these syndromes were originally described as movement disorders.[14,70]

CBD was first described as a syndrome of asymmetric rigidity and apraxia.[71] Patients present with limb apraxia, axial and limb rigidity, dystonia, postural instability, myoclonus, supranuclear gaze palsies (primarily gaze apraxia and delayed saccades), the 'alien limb phenomenon' (spontaneous and at times antagonistic involuntary limb movements) and cortical sensory loss.[72] Cognitive features include executive and visuospatial dysfunction and, rarely, hemispatial neglect.[73,74] Although diagnostic criteria emphasize hemispheric asymmetry as a key feature, in our experience, symptoms and signs are often bilateral.

Patients with PSP show supranuclear gaze palsies (slowed and restricted saccades, with downgaze palsy being most specific), axial-predominant parkinsonism and profound retropulsion.[75] Pseudobulbar signs such as dysarthria, dysphagia and pseudobulbar affect often evolve. Cognitive dysfunction is referable to failure of frontal-subcortical circuits leading to executive dysfunction, psychomotor slowing and poor working memory.[76]

Patients with CBD and PSP may show behavioural changes similar to bvFTD or language changes reminiscent of PNFA.[70] Furthermore, patients who initially present with bvFTD or PNFA may, over time, evolve the movement disorders characteristic of CBD or PSP, with cognitive and behavioural changes preceding the movement disorder by years.[14,77,78]

## 4. Histopathology

On autopsy, FTLD patients show gross atrophy of the frontal and anterior temporal lobes. [79,80] Atrophy can be extreme and circumscribed, with marked sparing of posterior brain regions until the most advanced stages of disease (figures 2b and 3a).[81] On microscopic examination, there is loss of pyramidal neurons and microvacuolar degeneration in layers II and III of the frontal and temporal cortex, with a variable degree of cortical gliosis (figure 3b). Subjacent white matter shows both axonal and myelin loss and gliosis.[80,82,83] Patients with co-morbid motor neuron disease (FTLD-motor neuron disease) show further

upper and lower motor neuron loss, corticospinal tract degeneration and Bunina bodies on gross and microscopic evaluation.[80] Most cases of FTLD can be subclassified into the following two major categories, which are based on the presence or absence of specific inclusion bodies: (i) FTLD with tau inclusions (FTLD-TAU, figure 3c); and (ii) FTLD with tau-negative, ubiquitin and TDP-43-positive inclusions (FTLD-TDP, figure 3d).[83]

## 4.1 Tau-Positive FTLD (FTLD-TAU)

FTLD-related tauopathies are classified based on both the morphologic features and the biochemical composition of the tau-positive inclusions. Pick's disease, the prototypical tauopathy of FTLD, is characterized by the presence of Pick bodies, which are solitary, round or oval, argyrophilic inclusions found in the cytoplasm of neurons (figure 3c). These inclusions were first described by Alois Alzheimer,[84] but were later named after Arnold Pick by Onari and Spatz.[85] Pick bodies are most commonly found in the dentate gyrus of hippocampus, amygdala, and frontal and temporal neocortex.[82] They are stained by Bielschowsky but not Gallyas stains, and are most readily detected by tau immunohistochemistry.

CBD and PSP are at least as common as Pick's disease in patients presenting with FTLD clinical syndromes.[86] The characteristic microscopic features of CBD are astrocytic plaques composed of tau-immunoreactive processes, and tau-positive gray and white matter threads, whereas PSP is distinguished by globose neurofibrillary tangles and tufted astrocytes.[75,82,87,88] The distribution of pathology and pattern of atrophy further distinguish CBD and PSP from each other and from Pick's disease. CBD is characterized by frontal, parietal and striatal involvement, whereas in PSP the preponderance of pathology is in the brainstem (particularly midbrain), cerebellum and basal ganglia, with relative cortical sparing.[83,88−90]

Less common FTLD-related tauopathies include argyrophilic grain disease, sporadic multiple system tauopathy with dementia, neurofibrillary tangle dementia and ALS-parkinsonism-dementia complex of Guam.[83]

Patients with mutations in the *MAPT* gene (see section 5.1) may show the pathologic features of Pick's disease, CBD or PSP. Human *MAPT* can be alternatively spliced to include either three or four repeated amino-acid sequences that serve as microtubule-binding sites. The fourth repeat sequence is encoded on exon 10, such that inclusion of this exon leads to 4-repeat (4R) tau isoforms, while exclusion leads to 3-repeat (3R) isoforms.[91] Similar amounts of 3R and 4R tau are present in normal brain, whereas pathologic tau may be predominantly composed of 4R, 3R or a mix of the two isoforms, as is seen in Alzheimer's disease.[92] Tau inclusions in Pick's disease are predominantly 3R; inclusions in CBD, PSP, argyrophilic grain disease and multiple system tauopathy with dementia are composed of 4R tau; and tau inclusions in neurofibrillary tangle dementia and the Guam complex include a mix of 3R and 4R isoforms.[83] Either or both isoforms may predominate in FTLD with *MAPT* mutations.

## 4.2 TAR DNA-Binding Protein 43 (TDP-43)-Positive FTLD (FTLD-TDP)

Tau-negative FTLD pathology has been more elusive to define and, as a result, has been described in the literature using various terms. The initial impression was that many cases of tau-negative FTLD were not associated with distinguishing protein inclusions, and were thus described as dementia lacking distinctive histology (DLDH).[93] With advances in immunohistochemistry, it became apparent that a large majority of DLDH cases showed immunoreactivity to ubiquitin, leading to the term FTLD with ubiquitin-positive inclusions

(FTLD-U).[94,95] In 2006, the ubiquitinated protein in the vast majority of FTLD-U brains was found to be TDP-43.[96] Thus, the term FTLD-TDP is preferred in this review.

TDP-43 is a ubiquitously expressed, highly conserved nuclear protein involved in DNA transcription and splicing.[97] Under pathologic conditions, TDP-43 is displaced from the cell nucleus to the cytoplasm, hyperphosphorylated, ubiquitinated and cleaved to produce C-terminal fragments.[96,98,99] Neuronal and glial TDP-43 inclusions are found in the vast majority of cases previously classified as FTLD-U with and without motor neuron disease, and in familial cases associated with *PGRN* and valosin-containing protein (*VCP*) gene mutations (see section 5.3).[100⁻103] Inclusions are most abundant in the dentate gyrus of hippocampus (figure 3d) and in layer II neurons in the frontotemporal cortex, and may also be found in cranial nerve nuclei and in the anterior horn cells in the spinal cord.[83,96] TDP-43 inclusions are also found in patients with sporadic ALS, and mutations in TDP-43 have been linked to autosomal dominant ALS.[104,105] These observations support the concept of an FTLD-ALS clinical and pathologic continuum, and provide compelling evidence for a pathogenic role for TDP-43 in this disease spectrum. Nevertheless, there are a number of unresolved questions regarding the primary role of TDP-43 in FTLD pathogenesis. Mutations in TDP-43 have thus far been very rarely linked to FTLD clinical presentations,[106,107] [add new reference #3 Benajiba et al. Annals of Neurology 2009 and #4 Kovacs et al. Movement Disorders 2009) and the mechanisms by which TDP-43 accumulation leads to neurodegeneration have not been delineated. Furthermore, TDP-43 inclusions are not specific to FTLD, and can be been found in many other degenerative dementias, including Alzheimer's disease, dementia with Lewy bodies, Pick's disease, CBD and ALS-parkinsonism complex of Guam.[108⁻112] Whether the role of TDP-43 in these disorders differs from its role in FTLD remains to be determined.

### 4.3 Fused in Sarcoma (FUS)-Positive FTLD and other Rare Variants

A total of 5–20% of FTLD-U cases stain negative for TDP-43.[113⁻115] The inclusions in many of these cases were recently found to consist of the protein fused in sarcoma (FUS) (new references #5, #6). Like TDP-43, FUS is a ubiquitously expressed DNA/RNA binding protein that regulates gene expression, and chromosomal translocations of FUS lead to human sarcomas and hematological malignancies (new reference #7). As with TDP-43, mutations in the FUS gene are associated with familial ALS (new reference #8), while FTLD-FUS cases are nearly always sporadic. The clinical phenotype is distinct and characterized by very early age-at-onset (mean age 38 years in the largest series to date) (new reference #5), severely disturbed behaviour, and profound caudate atrophy on MRI (new references #5, #6). FTLD-FUS inclusions are similar in morphology and distribution to TDP-43 inclusions, though unlike TDP-43, some of the normal nuclear staining pattern is retained in affected neurons (new reference #5). FUS-positive inclusions have now been demonstrated in other rare pathologic variants of FTLD including basophilic inclusion body disease (new reference #9) and neuronal intermediate filament disease (new reference #10), [117,118] though not in the rare familial cases associated with chromatin-modifying protein 2B (*CHMP2B*) gene mutations (see section 5.3)[116] (new reference #11). Finally, even applying modern immunohistochemical techniques, a minority of FTLD patients fail to show discernable inclusions and thus continue to meet criteria for DLDH.[119,120]

## 5. Genetics

Up to 40% of FTLD patients have a history that is suggestive of familial transmission, with roughly 10% of patients showing an autosomal dominant inheritance pattern.[121⁻123] When obtaining the family history, in addition to FTLD and ALS, clinicians should also inquire about mid- or late-life psychiatric disease, Alzheimer's disease and parkinsonian disorders, since FTLD is often mistaken for these conditions. Familial FTLD is most

common in patients with bvFTD and FTLD-ALS and least common in patients with SD. FTLD was first linked to chromosome 17q21–22 in 1994, prompting the designation frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).[124,125] In 1998, *MAPT* was identified as the causal gene in FTDP-17 families with tau-positive histopathology[126−128] and, in 2006, mutations in the *PGRN* gene were found to account for FTDP-17 families with tau-negative histopathology.[129−131] Over 40 mutations in *MAPT* and nearly 70 mutations in *PGRN* have been linked to FTLD thus far.[234] Taken together, *MAPT* and *PGRN* mutations account for the majority of familial FTLD, although the frequency of mutations varies considerably depending on the population that is being studied.[122,123] In our centre, PGRN mutations are more common than *MAPT* mutations; however, in European cohorts, the frequency of *MAPT* and *PGRN* mutations appears to be similar.[123,129,132]

## 5.1 FTLD Associated with Microtubule-Associated Protein Tau Gene Mutations

The tau protein in neurons binds to axonal microtubules, promotes microtubule assembly and stabilization and is also involved in signal transduction. *MAPT* mutations lead to neurodegeneration via a variety of mechanisms.[133−138] Mutant protein may have a decreased binding affinity to microtubules, leading to impaired microtubule assembly, stability and, ultimately, disruption of axonal transport. Alternatively, mutant tau may have an increased affinity to self aggregate into filamentous, insoluble inclusions that are neurotoxic. These mechanisms are not mutually exclusive and often act synergistically. Many *MAPT* mutations are located in or adjacent to the alternatively spliced exon 10 (see section 4.3), altering the normal 1:1 ratio between 3R and 4R isoforms in favour of 4R, which binds poorly to microtubules and shows an increased affinity for self-aggregation. [127,128,139] Regardless of the mechanism, *MAPT* mutations are highly penetrant and lead to disease onset between the ages of 40 and 60 years (mean 55 years), with disease duration ranging from 8–10 years.[122,123,140] The clinical phenotype can be quite variable even within a single pedigree, and may include clinical features of bvFTD, SD, PNFA, CBD, PSP and even ALS.[141,142] Presymptomatic gene carriers may show cognitive deficits decades before the predicted onset of dementia, suggesting a possible neurodevelopmental component.[143] The pathologic features are also variable and can range the gamut of FTLD-TAU (see section 4.1).

In addition to causative mutations, normal genetic variation in *MAPT* can modify the risk for developing a tauopathy. *MAPT* has two extended haplotypes, H1 and H2, which are in complete disequilibrium with each other and show no recombination.[144] These two haplotypes were likely to have been created by an inversion event involving 200 noncoding polymorphisms. The H1/H1 genotype is consistently over-represented in CBD and PSP, [144,145] suggesting there is an increased vulnerability to developing 4R tauopathies in H1 homozygotes.

## 5.2 FTLD Associated with Progranulin Gene Mutations

Progranulin is a secreted growth factor that plays an important role in inflammation, wound healing and tumour growth in non-brain tissue.[146,147] In the brain, *PGRN* RNA is highly expressed in cortical and hippocampal pyramidal cells and cerebellar Purkinje cells.[148] Putative roles include regulation of sexual differentiation in the embryonic brain, promotion of neuronal survival and stimulation of neuritic outgrowth.[149,150] *PGRN* knockout mice show behavioural changes (increased anxiety and aggression), perhaps as a result of alterations in expression of the serotonin 5-HT$_{1A}$ receptor.[151] Interestingly, expression patterns of large numbers of genes in the frontal cortex are altered in patients with *PGRN* mutations compared with non-demented controls.[152] Nearly all mutations described thus far are nonsense or missense mutations that lead to absent or nonfunctional protein.

[129,153] (new reference #12) Thus, in contrast to *MAPT* mutations that lead to disease by toxic gain of function, *PGRN* mutations appear to lead to neurodegeneration via haploinsufficiency.[129] Putative mechanisms by which loss of *PGRN* function may lead to neurodegeneration include chronic depletion of neurotrophic support and inadequate response to neuronal injury. As in *MAPT*, a subtle developmental abnormality rendering the brain more vulnerable to neurodegeneration is also possible. Compared with *MAPT*, *PGRN* mutations are associated with more variable age of onset (range 35–89 years, mean 60 years) and penetrance (estimated at only 50% by age 60 years, but 90% by age 70 years).[123] *PGRN* mutations were found in 3.2% of sporadic FTLD cases in one study,[153] in contrast to *MAPT* mutations, which are exceedingly rare in sporadic FTLD.

Similar to *MAPT*, the clinical phenotype in patients with *PGRN* mutations can be variable even within a pedigree, and there are no clear genotype/phenotype relationships.[154,155] Hallucinations and delusions are more common than in sporadic or *MAPT*-related FTLD, occurring in up to 25% of patients.[154] A total of 20–25% of *PGRN* patients present with a progressive aphasia similar to PNFA, although apraxia of speech is often absent.[156] bvFTD and CBD clinical phenotypes are also common. Parietal involvement may be more frequent than in other FTLD types, and 10–30% may have an Alzheimer's disease-like amnestic presentation.[154,157,158] Parkinsonism is common and may be the predominant feature,[159] whereas motor neuron disease is rare.[129] The mechanistic link between *PGRN* and TDP-43 is under active investigation: one group has reported that *PGRN* suppression leads to caspase-dependant cleavage and translocation of TDP-43 from the nucleus to the cytoplasm,[160] but this has result has not been replicated in subsequent studies [new reference #13].

### 5.3 Additional Genes and Linkages

Although mutations in *MAPT* and *PGRN* account for the majority of cases of autosomal dominant FTLD, additional rare mutations have been described. A single Danish family with an FTLD phenotype has been found to have a mutation in the *CHMP2B* gene on chromosome 3p11.[161,162] *CHMP2B* is part of the endosomal sorting complex involved in cargo sorting into multivesicular bodies in the endosomal/lysosomal system. Interestingly, an additional *CHMP2B* mutation has recently been linked to ALS.[163] Mutations in the *VCP* gene at 9p13 are linked to an autosomal dominant FTLD syndrome associated with Paget's disease and inclusion body myositis.[164] VCP is an adenosine triphosphatase that is involved in protein degradation in the endoplasmic reticulum. *VCP* mutation carriers show variable penetrance and phenotypic variation, with myopathy developing in the majority of carriers, while FTLD and Paget's disease occur in fewer than 50%, sometimes decades after onset of the myopathy.[165] Despite the presence of TDP-43 or FUS-positive inclusions in FTLD, mutations in these genes are associated with familial ALS but so far only very rarely with clinical FTLD (new references #3, #4, #14). Up to 10% of autosomal dominant forms of FTLD are not accounted for by currently known genes. An important gene is likely to reside at 9p21.3–13.3, a linkage site found in a number of families with familial FTLD-ALS, although the associated gene has yet to be identified.[166,167] International genome-wide association studies are underway in an attempt to identify additional causative and risk-modifying genes.[168]

## 6. Differential Diagnosis

As in any case of progressive dementia, the clinician must first exclude treatable conditions that can mimic FTLD, such as metabolic disturbances, nutritional deficiencies, CNS infections, substance abuse, vascular disease, heavy metal toxicity, and primary neoplastic and paraneoplastic conditions. These can often be excluded by the combination of a careful medical history, laboratory testing and neuroimaging, preferably with magnetic resonance

imaging (MRI). A subset of patients presenting with bvFTD may have a primary psychiatric disorder, usually major depression or bipolar affective disorder.[169,170] These patients show little progression over time and do not have frontotemporal atrophy on MRI. However, in our experience, it is far more common for patients with degenerative FTLD to be misdiagnosed with a psychiatric disorder than vice versa.[171]

Once the FTLD syndrome is determined to be degenerative, the next challenge is to predict the underlying histopathology. Recent clinicopathologic studies have demonstrated consistent relationships between the FTLD syndrome and the most likely underlying pathology.[14,78,172−174] In patients with sporadic FTLD, SD is most often associated with TDP-43 inclusions, PNFA is frequently associated with one of the tau-inclusion disorders (in particular CBD), whereas patients with bvFTD are split between FTLD-TAU and FTLD-TDP (figure 1). Very early age of onset in a sporadic case of bvFTD suggests FTLD-FUS. The presence of motor neuron disease strongly predicts FTLD-TDP pathology, whereas parkinsonism is suggestive of FTLD-TAU. However, in familial cases, PNFA and parkinsonism are commonly found in patients with either *MAPT* or *PGRN* mutations. The PSP clinical syndrome is highly predictive of FTLD-TAU, while clinical CBD can be caused by either FTLD-TAU or FTLD-TDP, the latter usually in association with a *PGRN* mutation. Aside from the link between motor neuron disease and FTLD-TDP, which is nearly 100% specific, these clinicopathologic correlations are probabilistic: they are reproducible across centres at the group level, but do not always hold true for individual patients.

A total of 10–30% of patients presenting with an FTLD clinical syndrome are found to have Alzheimer's disease on autopsy.[172−174] Identifying these patients with high accuracy during life is of paramount importance because they may be candidates for emerging therapies directed against β-amyloid. Patients presenting with a progressive dysexecutive syndrome in the absence of behavioural changes or a movement disorder are more likely to have the frontal-variant of Alzheimer's disease[175] than FTLD. Patients with logopenic aphasia, a progressive aphasia characterized by slow, hesitant speech, frequent word-finding pauses and profound deficits in sentence repetition, are also more likely to have underlying Alzheimer's disease.[176,177] Even accounting for these clinical distinctions, a significant minority of patients with typical FTLD clinical presentations are ultimately found to have underlying Alzheimer's disease pathology.[172] Dementia with Lewy bodies can be ruled out clinically by the absence of visual hallucinations (which are uncommon in FTLD), fluctuations and rapid eye movement sleep behaviour.[178] Vascular dementia can be excluded by the absence of cortical and subcortical vascular lesions on MRI.

Neuroimaging studies can help improve diagnostic accuracy by identifying signature anatomic patterns that distinguish FTLD from Alzheimer's disease. The presence of posterior temporal and parietal brain atrophy on MRI, hypometabolism on fluoro-deoxy-glucose positron emission tomography (FDG-PET) or hypoperfusion on single proton emission computerized tomography are predictive of a pathologic diagnosis of Alzheimer's disease, whereas medial prefrontal lesions are specific for FTLD.[21,50,179−182] These characteristic anatomic patterns are again reproducible at the group level, but do not always hold true for individual patients.

Much effort in recent years has focused on developing and testing biological markers that directly measure the pathologic changes associated with each disease. CSF levels of the 42 amino acid β-amyloid polypeptide (Aβ$_{42}$) and tau are a sensitive and specific marker of Alzheimer's disease,[183,184] and the ratio of tau to Aβ$_{42}$ can help discriminate between pathologically confirmed cases of Alzheimer's disease and FTLD.[185] Amyloid PET imaging with the Aβ-specific ligand ^{11}C-labeled Pittsburgh Compound-B (PIB) can detect

the fibrillar Aβ plaques of Alzheimer's disease with high sensitivity and specificity and can help exclude the presence of Alzheimer's disease pathology in patients with FTLD clinical presentations.[177,186,187] Although these biomarkers are not yet available for clinical practice, they hold great promise as diagnostic tools that will improve *in vivo* diagnostic accuracy in the future. Accurately differentiating FTLD-TAU from FTLD-TDP in individual patients on clinical grounds can be challenging, particularly in patients with bvFTD, and the development of specific imaging and CSF markers for FTLD pathologic subtypes is an important area of active investigation.[188–190]

## 7. Treatment

### 7.1 Behavioural and Cognitive Symptoms

Current pharmacotherapy for FTLD focuses primarily on symptomatic, neurotransmitter-based treatments.[191] None of the drugs were developed specifically for FTLD, and the rationale for their use is their efficacy in treating similar symptoms in primary psychiatric conditions or in other neurodegenerative disorders.[27] Most reports of FTLD treatments in the literature are based on single cases or small case series, and the few clinical trials that have been published have largely been open-label studies with small sample sizes.[192] Two recent systematic literature reviews identified a total of six double-blind, placebo-controlled trials for FTLD, with sample sizes ranging from 8 to 36 participants.[192,193] Evaluating the efficacy of FTLD treatments is further complicated by the absence of standardized clinical scales. Clinical instruments used to measure efficacy in Alzheimer's disease, such as the Mini-Mental State Examination, Alzheimer Disease Assessment Scale-Cognitive, or Clinical Dementia Rating (CDR) scale, emphasize memory loss and do not adequately capture the executive and language deficits seen in FTLD.[194] Even instruments used to measure behavioural disturbances in Alzheimer's disease such as the Neuropsychiatric Inventory (NPI) may not be applicable to FTLD, since longitudinal improvement on the NPI in FTLD patients may reflect worsening apathy due to disease progression.

Of all neurotransmitter-based therapies for FTLD, drugs that modify serotonin have the strongest biological rationale, since there is strong evidence for a selective serotonergic deficit in this disorder.[191] Patients with FTLD show alterations in the levels of serotonin metabolites in the CSF,[195] and significant neuronal loss in the serotonergic dorsal raphe nuclei on autopsy.[196] A decrease in 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors in the frontal cortex has been demonstrated both in pathological specimens[196–199] and *in vivo* using PET.[200] Furthermore, many of the behavioural symptoms of FTLD, such as depression, compulsions, repetitive behaviours, disinhibition, stereotypical movements and dysregulated eating, respond to selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) in patients with primary psychiatric disease.

The efficacy of SSRIs in FTLD has been demonstrated in relatively small, often uncontrolled trials.[201] Open-label studies (n = 11–18; study duration = 12 weeks to 6 months) of fluoxetine,[202] fluvoxamine,[202,203] sertraline[28,202] and paroxetine,[202] and one randomized controlled trial (n = 16; duration = 14 months) of paroxetine,[204] have demonstrated efficacy in controlling behavioural disturbances and stereotypical movements in FTLD, whereas one very brief (n = 10; duration = 6 weeks) randomized study of paroxetine failed to show any benefit.[205] Trazodone, which has serotonin reuptake and mixed agonist/antagonist activity, lowered NPI scores in a 12-week, crossover, placebo-controlled study,[206] although fatigue, dizziness and hypotension were common and limiting adverse effects at the high dosages used in this study (up to 300 mg/day). A recent meta-analysis suggested that the use of serotonergic drugs in FTLD is associated with a mean reduction of 15.4 points on the NPI, although the absence of a placebo control in many of the included studies, the small sample sizes and publication bias limit the reliability of

this estimate.[191] In our practice, we prescribe SSRIs or SNRIs as first-line drug therapy for behavioural disturbances in FTLD. The preferred agents used in our clinic are listed in table I. When apathy is prominent, we may try venlafaxine for its activating properties; when parkinsonism is present, bupropion is considered because of its dopaminergic tone. It should be emphasized that our choices are based on adverse effect profiles and clinical experience and are not based on the (very limited) clinical trial data.

In patients with severe behavioural disturbances (agitation, psychosis) that are refractory to SSRIs, treatment with atypical antipsychotics may be considered. This practice is supported by a single open-label study of olanzapine (n = 17 ; duration = 24 months), which showed similar efficacy in lowering the NPI score to that reported with SSRIs.[207] Single cases reporting benefit for risperidone[208] and aripiprazole[209] have also been published. This class of medications should be used with great caution for two reasons. First, FTLD patients are particularly vulnerable to extrapyramidal adverse effects.[210] Second, atypical antipsychotics are associated with an increased (1.6- to 1.7-fold) mortality risk in elderly patients with dementia, prompting the US FDA to issue a 'black box warning' on their use. [235] Increased mortality appears to be related to an increase in cardiovascular events and infections, and may also reflect a nonspecific effect of sedation in this vulnerable population. Our clinical practice is to use atypical antipsychotics only as a last resort, after first trying behavioural modifications (see section 7.3) and SSRIs or SNRIs. We prefer quetiapine to other antipsychotic agents because of its relatively low dopamine $D_2$ receptor antagonism. The increased mortality risk and concerning potential adverse effects are discussed with patients and families, and the need for continued use is re-evaluated at every clinic visit. Often, atypical antipsychotics are necessary only as a temporizing measure, and can be tapered as patients become more apathetic (and thus less agitated and disinhibited) as the disease progresses.

Acetylcholinesterase inhibitors have an important role in treating cognitive and behavioural symptoms in Alzheimer's disease and dementia with Lewy bodies, and have thus generated interest as a potential treatment in FTLD. However, in contrast to Alzheimer's disease and dementia with Lewy bodies, there is no cholinergic deficit in FTLD.[211−213] Three studies have examined acetylcholinesterase inhibitor use in FTLD with mixed results. One open-label study (n = 20; duration = 12 months) found that rivastigmine improved neuropsychiatric symptoms and caregiver burden but did not halt cognitive decline.[214] A trial of galantamine in FTLD and primary progressive aphasia (PPA), which included an 18-week, open-label phase followed by an 8-week, randomized, double-blind, placebo-controlled withdrawal (n = 36), found a nonsignificant trend for benefit in language function and global severity in the PPA subgroup.[215] However, in retrospect, many of the patients in the PPA group may have had the logopenic variant of progressive aphasia that is associated with underlying Alzheimer's disease. In a third open-label trial (n = 24; duration = 6 months), donepezil was associated with a reversible worsening of behaviour and showed no benefit on cognitive measures.[216] Our clinical experience is more consistent with the latter study, and we do not prescribe acetylcholinesterase inhibitors for FTLD unless we have reason to suspect the patient truly has underlying Alzheimer's disease (e.g. positive PIB-PET study).

Memantine, a noncompetitive NMDA antagonist, effectively treats agitation in moderate-to-severe Alzheimer's disease, and may exert a neuroprotective effect by preventing chronic neuronal depolarization that can lead to excitotoxicity.[217] A case series reporting three FTLD patients treated with memantine showed improved NPI scores over 3 months of follow-up.[218] Two open label studies (n = 16 and 43, trial durations = 26 weeks) have demonstrated good tolerability,[219] [220] and larger randomized, placebo-controlled studies of memantine in FTLD are currently in progress.

### 7.2 Motor and Sphincter Symptoms

Patients with parkinsonism should receive a trial of levodopa/carbidopa, although the response to levodopa may be poor or transient, particularly in CBD and PSP.[221,222] Dopamine agonists such as pramipexole or ropinirole should be considered in patients who do not respond to levodopa. Unlike levodopa, these medications act at the postsynaptic terminal, and do not rely on the presynaptic conversion of levodopa to dopamine in the substantia nigra, which can suffer severe neuronal loss in CBD and PSP. Patients with FTLD-ALS are candidates for riluzole treatment,[223] and should be referred to a multidisciplinary ALS centre where their pulmonary and nutritional status can be closely monitored.[224]

Urinary incontinence is common in FTLD and may occur through a variety of mechanisms, including loss of voluntary sphincter control due to degeneration of medial frontal cortex, and both upper and lower motor neuron bladder dysfunction (particularly in CBD and PSP). Patients should be referred for urodynamic studies to determine the cause and optimal treatment of the bladder dysfunction. Upper motor neuron bladder dysfunction may respond to anticholinergic medications, although these should be used sparingly because they may exacerbate cognitive and neuropsychiatric deficits. When necessary, drugs with lower CNS penetration such as trospium chloride or darifenacin are preferred. Intermittent catheterization should be considered in patients with lower motor neuron bladder dysfunction, given the risk of infection associated with indwelling catheters (these are also poorly tolerated in FTLD patients). Constipation is common and responds in most cases to a daily bowel regimen.

### 7.3 Nonpharmacological Interventions

While this report focuses on pharmacological treatment, the first-line therapy for behavioural disturbances in FTLD should be nonpharmacological,[27,225,226] since current drug therapies for FTLD are modestly effective at best and have serious potential adverse effects. An FTLD treatment plan that does not include nonpharmacological interventions is unlikely to be successful. The cornerstones of nonpharmacological treatment in FTLD include caregiver and family education, and environmental, behavioural and physical interventions designed to minimize the occurrence and consequences of undesired behaviours.[225] Caregiver and patient support groups can be invaluable. Additional helpful interventions include physical, occupational and speech therapy, home safety evaluations and the implementation of augmentative communication devices. We universally suggest a structured exercise programme for physically able patients and caregivers because, in our anecdotal experience, regular physical activity may delay or slow the progression of motor symptoms. A frank and pre-emptive discussion about end-of-life decisions and goals of care is imperative.[226]

### 7.4 Future Directions

Efforts to develop specific, disease-modifying therapies for FTLD are focused on the critical proteins implicated in pathogenesis, namely tau, progranulin and TDP-43. Tau-directed therapies have a significant head start in terms of identifying pathogenic mutations, generating animal models and elucidating molecular mechanisms. Transgenic mice expressing human pathogenic *MAPT* mutations show behavioural and motor deficits, with an age- and gene dose-dependent accumulation of tau inclusions (reviewed by Rademakers and colleagues).[227] Mice expressing the human P301L mutation, the most studied transgenic model of FTLD-TAU, show impaired performance on memory tasks, increased docility, decreased weight, vocalization and grooming behaviours, and severe motor deficits leading to paralysis.[228] Pathologic inclusions of hyperphosphorylated 4R tau are found in neurons and glial cells (similar to those seen in human pathologic specimens), and motor

neuron loss is seen in the anterior horn of the spinal cord.[228,229] Mice expressing a variety of other pathogenic *MAPT* mutations all show a range of similar behavioural and pathologic changes, although the morphology of tau inclusions and the degree of neurodegeneration varies between models.[227] Expression of *MAPT* mutations in non-rodent models such as *Drosophila melanogaster*[230] and *Caenorhabditis elegans*[231] similarly leads to behavioural changes, tau accumulation and neurodegeneration.

Animal models of FTLD-TAU do not show the anatomic selectivity seen in human disease, and the human symptoms of impaired comportment and aphasia cannot be recapitulated in an animal model. Nevertheless, transgenic models have helped elucidate the molecular mechanisms involved in human tauopathies, and have identified a number of potential therapeutic strategies. These include inhibition of tau kinases (particularly the glycogen synthase kinase 3β [GSK3β] and cyclin-dependant kinase 5 pathways), inhibition of tau fibrillization, manipulation of tau-processing pathways (e.g. ubiquitination), inhibition of tau expression, tau-independent microtubule stabilization and immunosuppression.[193,232] Lithium and valproic acid are GSK3β inhibitors that are approved for other indications and are being considered for FTLD clinical trials. Tau drug discovery is also a major focus of the pharmaceutical industry given the apparent role of tau in the pathogenesis of Alzheimer's disease.

The roles of progranulin and TDP-43 in FTLD have only recently been described. The molecular mechanisms that surround their function in normal brain and disease are still being elucidated, and transgenic animals expressing disease-causing *PGRN* mutations are currently being developed.[123] The haploinsufficiency mechanism that appears to underlie *PGRN*-associated neurodegeneration is unique and will require novel strategies to increase expression of wild-type *PGRN*. The relevance of progranulin to sporadic FTLD with TDP-43 inclusions is still not clear, although a recent study suggests that *PGRN* haplotype can modify the risk for developing sporadic FTLD-TDP.[233] Based on the changes in TDP-43 localization and biochemistry seen in autopsy specimens, the steps involved in pathologic TDP-43 processing are hypothesized to include hyperphosphorylation, ubiquitination, cleavage and translocation from nucleus to cytoplasm,[96] suggesting a number of potential therapeutic targets. Although *CHMP2B* and *VCP* mutations are rare, the mechanisms by which these mutations lead to frontotemporal degeneration may also be relevant to sporadic disease and remain areas of active investigation.

The capacity to effectively test candidate disease-modifying drugs in FTLD will depend greatly on our ability to identify biologically homogeneous patient populations for clinical trials. Based on our current understanding of clinicopathologic correlations, patients with PNFA, CBD, PSP and *MAPT* mutations would be preferred candidates for a tau-specific drug, while patients with *PGRN* mutations, SD or FTLD-ALS would be the preferred population in which to test a progranulin/TDP-43-based therapy. The detection of Aβ pathology by CSF or imaging biomarkers should exclude patients from participation in FTLD clinical trials. The development of tau- and TDP-43-specific biomarkers will be necessary to further improve *in vivo* prediction of histopathology, particularly in patients with bvFTD who are equally likely to have FTLD-TAU or FTLD-TDP.

The efficacy of candidate drugs will need to be tested with clinical outcome measures that are sensitive to the changes seen with disease progression in FTLD. In a recently published 'virtual clinical trial', Knopman and colleagues[194] tested the utility of new cognitive and functional instruments to measure longitudinal change in FTLD. These included an FTLD-specific CDR scale that added 'behaviour, comportment and personality' and 'language' to the existing CDR domains, and a composite cognitive measure based on tests of executive function and language. These measures performed more favourably as prospective outcome

variables for FTLD clinical trials than the 'traditional' cognitive, behavioural and functional measures used to measure outcomes in Alzheimer's disease trials. In addition to piloting these new tools, the study by Knopman et al.[194] demonstrated the feasibility of conducting a collaborative, multicentre trial in FTLD. Such a collaborative effort will certainly be necessary to recruit the cohort of over 200 FTLD patients per trial that may be needed to demonstrate treatment effects in FTLD.[194]

## 8. Conclusions

FTLD is increasingly recognized as a leading cause of early-onset dementia. The proclivity of the disease for the social and language networks of the brain make it a particularly devastating illness, because it robs patients of these uniquely human functions, often during the prime of their lives. The past two decades of research have led to major advances in our understanding of the genetics and molecular mechanisms of FTLD. Nevertheless, the remarkable anatomic selectivity of the disease remains a mystery. As with other neurodegenerative disorders, a major goal of future FTLD research is to translate our increasing understanding of pathogenesis into effective treatments that will slow, halt or ultimately prevent this devastating disease.

## Acknowledgments

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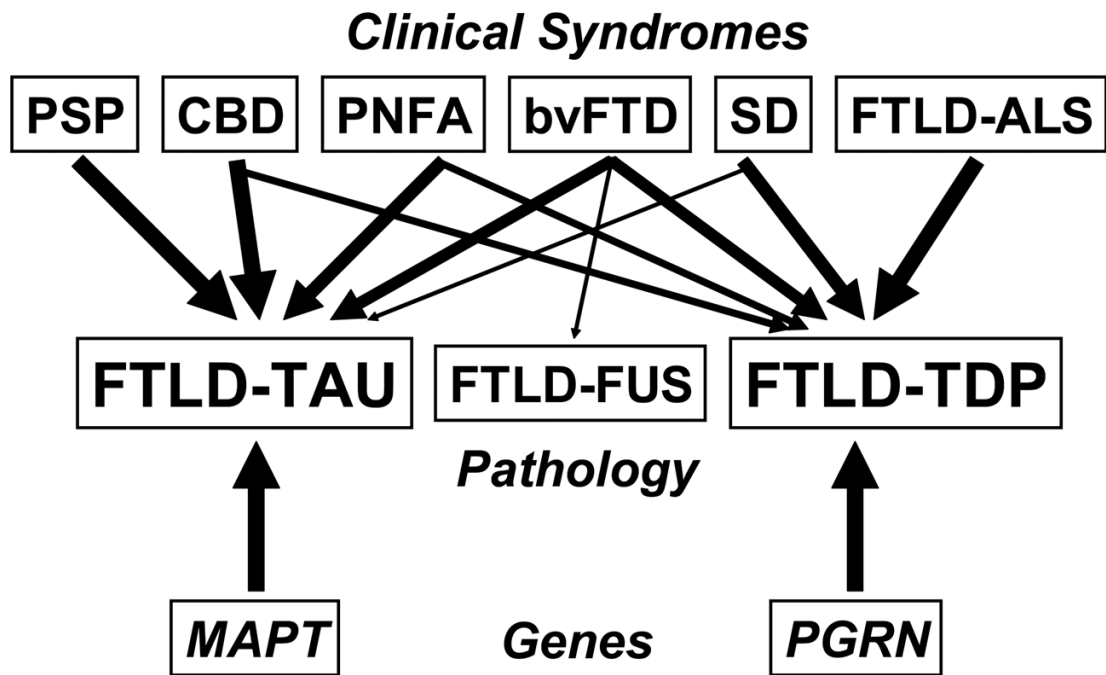
**Fig. 1.**
Clinical, pathologic and genetic spectrum of frontotemporal lobar degeneration (FTLD).
Clinical syndromes (top row), pathologic subtypes (middle row) and common gene
mutations (bottom row) in FTLD are shown. Arrows represent links between clinical
syndromes, genes and underlying histopathology, with thicker arrows corresponding to
stronger relationships. **bvFTD** = behavioural-variant frontotemporal dementia; **CBD** =
corticobasal degeneration; **FTLD-ALS** = FTLD with amyotrophic lateral sclerosis; **FTLD-
TAU** = FTLD with tau-positive inclusions; **FTLD-FUS** = FTLD with fused in sarcoma
(FUS)-positive inclusions; **FTLD-TDP** = FTLD with TAR DNA-binding protein 43
(TDP-43)-positive inclusions; *MAPT* = microtubule-associated protein tau; *PGRN* =
progranulin; **PNFA** = progressive nonfluent aphasia; **PSP** = progressive supranuclear palsy;
**SD** = semantic dementia.
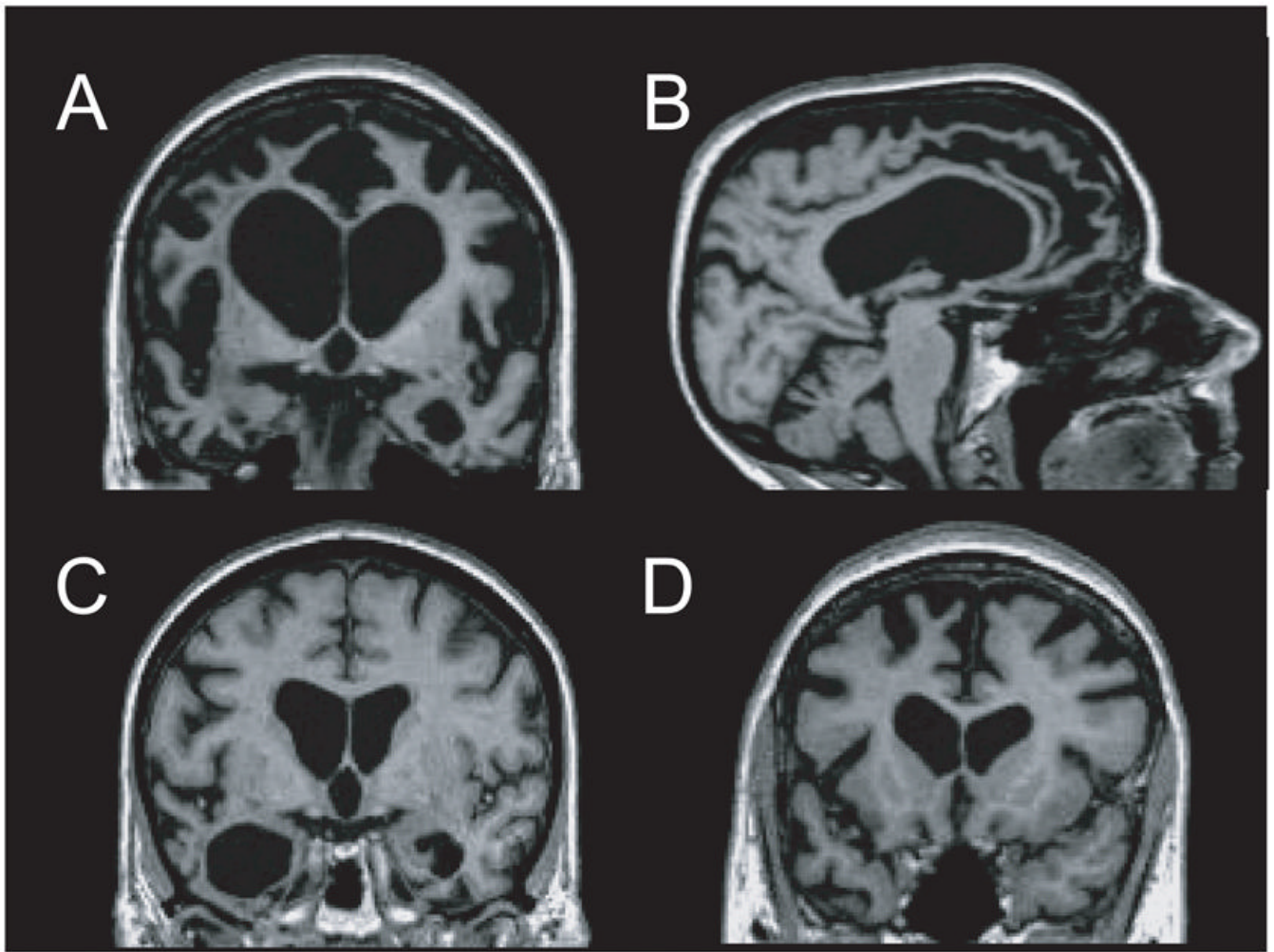
**Fig. 2.**
MRI findings in frontotemporal lobar degeneration (FTLD). T1-weighted images from representative patients with behavioural-variant frontotemporal dementia (bvFTD) [**a** and **b**], semantic dementia (SD) [**c**] and progressive nonfluent aphasia (PNFA) [**d**] are displayed in neurologic orientation. (**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 the temporal poles (left greater than right). (**d**) PNFA patient shows atrophy in the left inferolateral and dorsomedial frontal cortex and anterior insula.
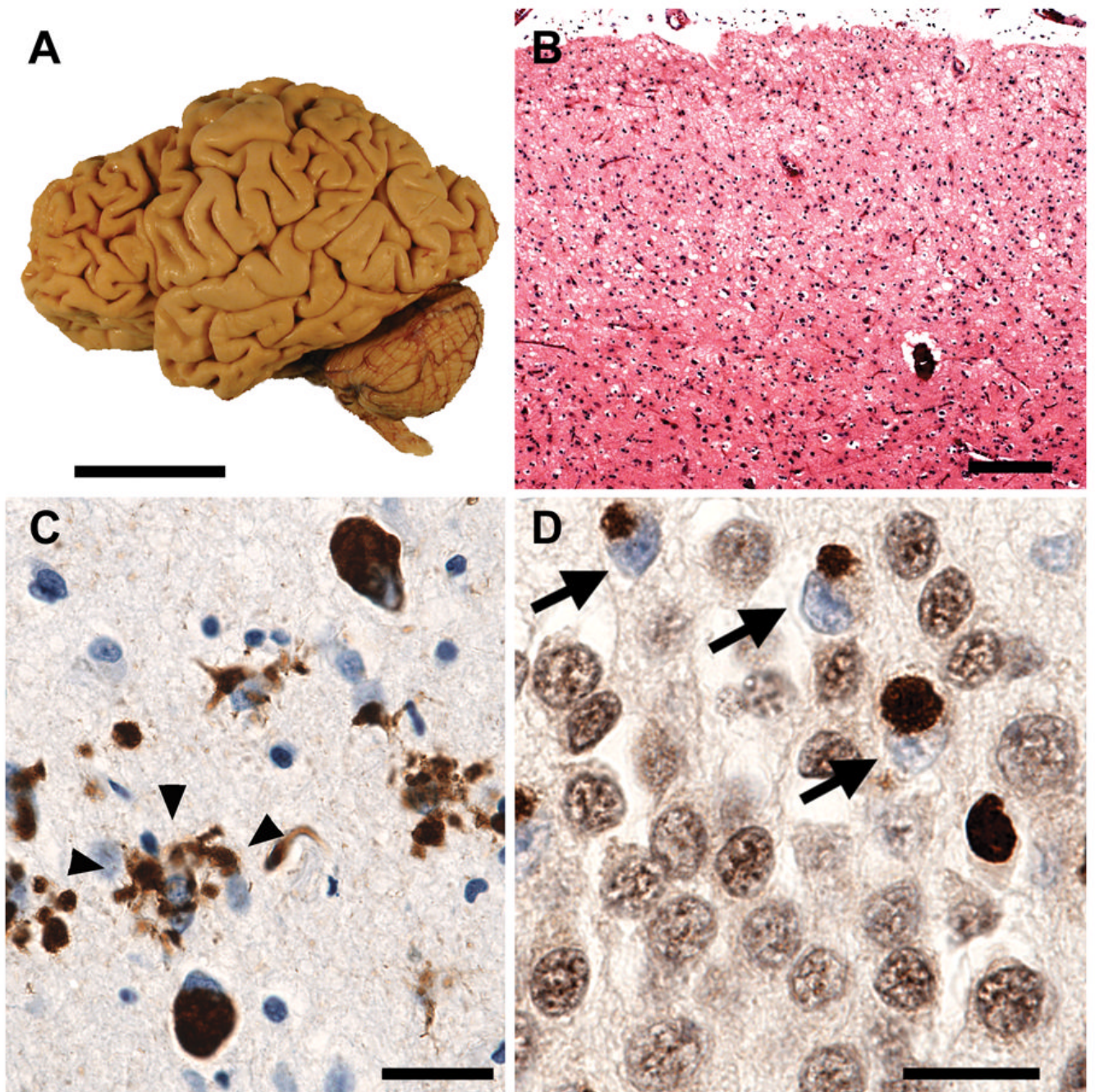
**Fig. 3.**
Frontotemporal lobar degeneration (FTLD) pathology. (**a**) Typical FTLD features circumscribed atrophy affecting anterior cortical and subcortical regions, as seen in this patient with progressive nonfluent aphasia due to underlying corticobasal degeneration. Scale bar = 5 cm. (**b**) Regardless of the associated disease protein, affected regions show neuronal loss, gliosis and microvacuolation, especially in superficial cortical layers. Hematoxylin and eosin stain. Scale bar = 200 microns. (**c**) Pick's disease, a tau-positive form of FTLD, shows cytoplasmic hyperphosphorylated tau inclusions within neurons (Pick bodies) and in ramified astroglial processes (arrowheads). CP-13 antibody, courtesy of P. Davies. (**d**) In FTLD due to TAR DNA-binding protein 43 (TDP-43) proteinopathy, affected

neurons like these dentate gyrus granule cells show cytoplasmic TDP-43 inclusions and clearing of TDP-43 from its normal nuclear location (arrows). TDP-43 antibody. Scale bars in **c** and **d** = 25 microns. Figure provided by W.W. Seeley, University of California, San Francisco.

**Table I**

Symptomatic therapy in frontotemporal lobar degeneration

| Symptom | Therapy |
| --- | --- |
| Behavioural disturbances | Caregiver education |
| | Environmental, physical and behavioural modifications |
| | Antidepressants |
| |    escitalopram, citalopram, sertraline |
| |    bupropion (with parkinsonism) |
| |    venlafaxine (with prominent apathy) |
| | Antipsychotics[b] |
| |    quetiapine |
| Aphasia | Speech therapy |
| | Augmentative communication devices |
| Parkinsonism | Physical, occupational and speech therapy |
| | Levodopa/carbidopa |
| | Pramipexole, ropinirole |
| Motor neuron disease | Multidisciplinary treatment |
| |    neurologic |
| |    nutritional |
| |    pulmonary |
| |    physical, occupational and speech therapy |
| | Riluzole[c] |
| Bladder dysfunction | |
|   upper motor neuron | Trospium chloride, darifenacin |
|   lower motor neuron | Intermittent catheterization |

[a]Nonpharmacological therapies are paramount, and drug therapy in isolation is unlikely to be successful. Listed pharmacological agents are based on the clinical experience of the authors, and all recommendations represent off-label use unless otherwise specified. Medications should always be started at low doses and titrated slowly.

[b]Should be used as last resort and with extreme caution because of increased mortality risk.

[c]US FDA-approved for the treatment of amyotrophic lateral sclerosis.