Non-Alzheimer's dementia 1:

Frontotemporal dementia

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Abstract

Frontotemporal dementia is an umbrella clinical term that encompasses a group of neurodegenerative diseases characterised by progressive deficits in behaviour, executive function, or language. Frontotemporal dementia is a common type of dementia, particularly in patients younger than 65 years. The disease can mimic many psychiatric disorders because of the prominent behavioural features. Various underlying neuropathological entities lead to the frontotemporal dementia clinical phenotype, all of which are characterised by the selective degeneration of the frontal and temporal cortices. Genetics is an important risk factor for frontotemporal dementia. Advances in clinical, imaging, and molecular characterisation have increased the accuracy of frontotemporal dementia diagnosis, thus allowing for the accurate differentiation of these syndromes from psychiatric disorders. As the understanding of the molecular basis for frontotemporal dementia improves, rational therapies are beginning to emerge.

Introduction

Frontotemporal dementia is an insidious neurodegenerative clinical syndrome characterised by progressive deficits in behaviour, executive function, and language. The disorder is the third most common form of dementia across all age groups, after Alzheimer's disease and dementia with Lewy bodies, and is a leading type of early-onset dementia.[1] The first description of a patient with frontotemporal dementia was made by Arnold Pick in 1892;[2] the patient had aphasia, lobar atrophy, and presenile dementia. In 1911, Alois Alzheimer recognised the characteristic association with Pick bodies and named the clinicopathological entity Pick's disease,[3] which led to the use of Pick's disease as a synonym for frontotemporal dementia. In 1982, Mesulam described a language subtype of the disorder, later defined as primary progressive aphasia.[4] Revised diagnostic criteria have recently been issued.[5,6]

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Because of the close similarity of behavioural changes in patients with frontotemporal dementia to those seen in patients with psychiatric disorders, diagnosis is challenging. Here we review the clinical and laboratory features, epidemiology, genetics, and neuropathology of frontotemporal dementia to provide a comprehensive insight into this disorder and help differentiate it from psychiatric disorders and other neurodegenerative diseases. We also discuss therapeutic strategies for symptom management, and the most promising areas of therapeutic development.

Epidemiology

WHO estimates that dementia rates will double every 20 years, reaching 115·4 million in 2050.[7] In a meta-analysis of 73 articles of early-onset dementia (patient age <65 years), frontotemporal dementia was the second or third most prevalent dementia subtype in most studies, with a prevalence ranging from 3% to 26%.[1] Table 1 summarises the epidemiology of frontotemporal dementia.[8–10] Because the disorder is still missed and misdiagnosed, most numbers probably underestimate its true prevalence.

Clinical features

Frontotemporal dementia is classified into three clinical variants: behavioural-variant frontotemporal dementia, which is associated with early behavioural and executive deficits; non-fluent variant primary progressive aphasia, with progressive deficits in speech, grammar, and word output; and semantic-variant primary progressive aphasia, which is a progressive disorder of semantic knowledge and naming. The diagnostic criteria outline features, (ie, clinical, imaging-supported, and genetically confirmed diagnosis), that increase the likelihood that frontotemporal dementia-related neuropathology will be identified[5,6] (figure 1). As frontotemporal dementia progresses, the symptoms of the three clinical variants can converge, as an initially focal degeneration becomes more diffuse and spreads to affect large regions in the frontal and temporal lobes. Over time, patients develop global cognitive impairment and motor deficits, including parkinsonism, and motor neuron disease in some patients. Patients with end-stage disease have difficulty eating, moving, and swallowing. Death usually happens about 8 years after symptom onset and is typically caused by pneumonia or other secondary infections.

Behavioural-variant frontotemporal dementia

The most pronounced early symptoms of behavioural-variant frontotemporal dementia include personality changes, disinhibition, and apathy (table 2). Behavioural disinhibition can result in tactless and socially inappropriate behaviour (eg, approaching strangers without respect for physical and social boundaries); impulsive or careless actions (such as reckless spending); new criminal behaviours (eg, theft, urination in public, sexual advances, or hit-and-run accidents); and embarrassing personal remarks. Reduced inhibition often results in bad fiscal decisions that can lead to financial ruin. Although patients might make inappropriate sexual comments, they usually have decreased libido. Apathy manifests as reduced interest in work, hobbies, social interaction, and hygiene, and can be mistaken for depression. Patients show a loss of sympathy and empathy towards their families and friends, and a decrease in social interest and responsiveness to the emotions and needs of

other people. One of our patients was more concerned about going to the grocery store than attending the funeral of his spouse's parent. As a result, family members and friends can often resent the patient. Patients show stereotyped behaviours, including simple repetitive movements, compulsive ritualistic behaviours, and repetitive use of verbal phrases. Binge eating, increased consumption of sweets or alcohol, and weight gain are different aspects of the hyperorality in behavioural-variant frontotemporal dementia. Patients with behavioural variant frontotemporal dementia often show deficits in various executive tasks, although their visuospatial skills are fairly normal at first. Patients have little insight into their own behaviour and might not recognise many of the changes that are reported by a knowledgeable informant. Some patients have decreased sensitivity to pain.[11]

Some individuals who meet diagnostic criteria for behavioural-variant frontotemporal dementia have a very slow disease course (over decades) with slow progression of cognitive impairment and often normal MRI and PET studies. Their disease is classified as frontotemporal dementia phenocopy. Some of these individuals have a primary psychiatric disturbance such as bipolar disorder, Asperger's syndrome, or factitious disease,[12,13] whereas others might have a slow sporadic or genetic form of frontotemporal dementia.[14]

Primary progressive aphasia

Patients with primary progressive aphasia have a progressive, insidious decline in linguistic skills during the initial phase of the disease. Language dysfunction is the main symptom for the first 2 years of the illness. Deficits include language production, object naming, syntax, or word comprehension, and are apparent during conversation or through speech and language assessment. Language deficit is the main cause of impaired activities of daily living. Although the underlying cause is more often frontotemporal dementia, primary progressive aphasia can be associated with Alzheimer's disease. If prominent visuospatial impairment or episodic or visual memory impairments are present, Alzheimer's disease should be considered. The patient should not show behavioural disturbances during the initial disease phase; such changes are indicative of behavioural-variant frontotemporal dementia.[4]

Semantic-variant primary progressive aphasia

The term semantic dementia was used to describe a syndrome characterised by semantic aphasia and associative agnosia.[15] Symptoms result from early asymmetrical degeneration of anterior temporal lobes and amygdala. Semantic loss causes anomia for people, places, and objects; word-finding difficulties; and impaired word comprehension. Left temporal lobe variant presents with mainly linguistic semantic loss (semantic-variant primary progressive aphasia), whereas the right temporal lobe variant presents with behaviour changes.[16] Left temporal lobe variant is roughly three times more common than right temporal lobe variant.[17] Comprehension of individual words is impaired, especially for words that are not routinely used by the patient. Anomia tends to be more pronounced for nouns than for verbs or pronouns. Patients have surface dyslexia and dysgraphia, impairments in which words with atypical spelling or pronunciation are regularised (eg, bouquet is read as bo-ket). Other language domains are spared, especially during the initial disease phase, and patients retain correct grammar and fluent speech. The deficits in

recognition of objects and people go beyond the visual domain and tactile, olfactory, or gustatory clues do not help. As the disease spreads from the temporal lobes into the orbitofrontal cortex, behavioural changes occur, such as irritability, emotional withdrawal, insomnia, and strict or selective eating, often focused around one particular type of food; sometimes depression emerges.[16] Although semantics are lost in left temporal lobe variant, functions pertaining to the right side, such as visual attention, are sometimes heightened. Therefore, patients with left temporal lobe variant tend to develop visual compulsions such as repetitive playing of puzzles, jewellery beading, collecting coins, gardening, painting, and collecting brightly coloured objects. By contrast, patients with right temporal lobe variant develop verbal compulsions involving words and symbols, such as writing notes, letters, and telephone numbers; making puns; or playing Solitaire.

Non-fluent variant primary progressive aphasia

Non-fluent variant primary progressive aphasia is characterised by slow, laboured, and halting speech production, and by omission or misuse of grammar (agrammatism). Patients often make inconsistent speech sound errors, including insertions, deletions, substitutions, transpositions, and distortions. Patients might have trouble understanding sentences with complex syntactic constructions (eg, "the girl that the boy likes stood up"), but retain the ability to understand simpler sentences with the same semantic content (eg, "the boy likes a girl; that girl stood up"). Early in the disease, written language production and syntactic comprehension tests reveal mild grammatical errors. Some patients maintain intact writing despite the presence of marked deficits in spoken language. Single-word comprehension and object knowledge are not affected, although patients can have a mild anomia that is usually more pronounced for verbs than for nouns.[6]

Motor symptoms

About 12·5% of patients with behavioural-variant frontotemporal dementia develop motor neuron disease, typically including upper motor neuron signs (hyper-reflexia, extensor plantar response, spasticity), lower motor neuron signs (weakness, muscle atrophy, fasciculations), dysarthria, dysphagia, and pseudobulbar affect. Mild features of motor neuron disease can occur in up to 40% of patients with frontotemporal dementia.[18] Among the frontotemporal dementia variants, motor neuron disease arises frequently in patients with behavioural-variant frontotemporal dementia and less often in patients with semantic-variant primary progressive aphasia or non-fluent variant primary progressive aphasia.

Early parkinsonism is present in up to 20% of patients with frontotemporal dementia and is most often seen in patients with behavioural-variant frontotemporal dementia, followed by those with non-fluent variant primary progressive aphasia.[19] Patients with frontotemporal dementia have features of corticobasal syndrome or progressive supranuclear palsy syndrome. Corticobasal syndrome is characterised by asymmetrical parkinsonism, sensory–motor cortical dysfunction, alien-limb syndrome, and dystonia. Progressive supranuclear palsy syndrome is characterised by vertical supranuclear palsy, decreased saccade velocity, and early postural instability with falls. Behavioural changes, including executive dysfunction, apathy, and impulsivity, are common.[20]

The panel shows a clinical vignette describing a typical patient with frontotemporal dementia.

Differential diagnosis

Differential diagnosis of frontotemporal dementia needs a careful history that examines the progression of behavioural changes, family history, behaviour in face-to-face interviews, performance on neuropsychological testing, laboratory studies, and neuroimaging. Blood work should include a comprehensive metabolic panel including liver and kidney function tests, complete blood count, vitamin B12 concentration, and thyroid studies. Cerebrospinal fluid assessment should be done in atypical cases. Toxic (heavy metals, illicit drugs), inflammatory (autoimmune, paraneoplastic), or infectious (syphilis, HIV) causes should be considered. Patients should be screened for obstructive sleep apnoea. Normal pressure hydrocephalus and low intracranial pressure syndromes might cause dementia that mimics behavioural-variant frontotemporal dementia. Low cerebrospinal fluid β-amyloid concentrations suggest Alzheimer's disease, whereas very high cerebrospinal tau concentrations could suggest rapidly progressive dementia. β-amyloid imaging is helpful, particularly in young patients, to rule out Alzheimer's disease, although Alzheimer's disease and frontotemporal lobar degeneration neuropathology can co-occur. Family history of dementia, movement disorders, or psychosis might warrant genetic counselling and search for genes that cause frontotemporal dementia.

Adult-onset psychiatric disorders

Psychiatric disorders can mimic frontotemporal dementia. The repetitive and compulsive behaviours noted in patients with behavioural-variant frontotemporal dementia might lead to a misdiagnosis of obsessive-compulsive disorder. Similarly, apathy and emotional withdrawal might lead to a misdiagnosis of depression, although patients with frontotemporal dementia do not usually have other symptoms typical of depression and often deny sadness. Frontotemporal dementia can cause delusions and euphoria, which are features of bipolar disorder and schizophrenia. Of the frontotemporal dementia variants, behavioural-variant is the most likely to be misdiagnosed as a psychiatric disorder (such as schizophrenia, bipolar disorder, or depression).[21] Personality disorders can be the heralding sign of the behavioural-variant and borderline, antisocial, schizoid, schizotypal personality changes, and addictive disorders are common features of patients in the early stages of behavioural-variant frontotemporal dementia. A high rate of late-onset psychosis is a characteristic feature of inherited frontotemporal dementia associated with *C9orf72* mutations, the most common genetic form of the disorder. Furthermore, *C9orf72* mutations have been associated with schizophrenia and bipolar disorder.[22–24]

Alzheimer's disease and other neurodegenerative diseases

There is a substantial overlap of symptoms between Alzheimer's disease and frontotemporal dementia. Alzheimer's pathology could be suggested by predominance of memory and visuospatial deficits, social appropriateness, normal neurological examination, and evidence of generalised brain atrophy on imaging. A form of progressive aphasia with prominent

anomia, acalculia, and word-finding pauses (logopenic-variant primary progressive aphasia) is usually caused by Alzheimer's neuropathology.[6]

The movement abnormalities in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration are typically less responsive to levodopa than those in classic Parkinson's disease. Executive dysfunction, parkinsonism, and hallucinations can be seen in both dementia with Lewy bodies and frontotemporal dementia; however, patients with dementia with Lewy bodies have more pronounced parkinsonism, visuospatial deficits, and cognitive fluctuations compared with patients with frontotemporal dementia.[25,26] A diagnosis of progressive supranuclear palsy is suggested with predominant postural imbalance, slowing of saccadic velocities, a history of early falls, dysphagia, and pseudobulbar affect. Progressive supranuclear palsy and corticobasal degeneration can initially present as either behavioural-variant frontotemporal dementia or non-fluent variant primary progressive aphasia syndrome.[20]

Imaging

With continuing advances in imaging techniques, several methods can be used to help in the diagnosis of frontotemporal dementia. Structural MRI and CT show patterns of atrophy: frontotemporal dementia is characterised by predominant frontal or temporal atrophy, and atrophy in the frontoinsular region is especially indicative of frontotemporal dementia.[27] Fluorodeoxyglucose PET, functional MRI, and single-photon-emission CT likewise show disproportionate hypoperfusion and hypometabolism in these regions.[19] Research in molecular PET imaging is very active, not only because of the specificity it allows for differentiation of frontotemporal dementia from Alzheimer's disease, but also because of its potential for further differentiating among frontotemporal lobar degeneration syndromes. Amyloid tracer imaging can distinguish frontotemporal dementia from Alzheimer's disease, because amyloid deposition is not a neuropathological feature of frontotemporal dementia; guidelines recommend amyloid imaging in patients younger than 65 years with persistent or progressive unexplained mild cognitive impairment or atypical or mixed dementia presentation. Diffusion tensor imaging can show widespread white-matter degeneration in frontotemporal dementia, exceeding that seen in Alzheimer's disease.[28]

Functional connectivity network mapping, pioneered by Raichle and colleagues[29] and Buckner and colleagues,[30] is a technique to identify specific brain circuits with MRI. Seeley and colleagues[31] have shown that the frontotemporal dementia variants, Alzheimer's disease, and corticobasal syndrome each selectively affect a distinct functional connectivity network. Decreased intrinsic connectivity within the salience network is reported in behavioural-variant frontotemporal dementia in association with increased activity in the default mode network of brain regions. This pattern is reversed in Alzheimer's disease. In both cases, increased activity of spared cortical areas might suggest a compensatory effect of unimpaired networks. By examining how functional networks are affected, connectivity maps can improve differential diagnosis and longitudinal tracking of disease progress. The next frontier in molecular PET imaging is tau imaging. Various forms of tau tracers are being tested in patients with dementia. Tau imaging can potentially differentiate between Alzheimer's disease, non-Alzheimer's tauopathies, and tau-negative dementias.[32]

Neuropathology

Frontotemporal lobar degeneration is characterised by neuronal loss, gliosis, and microvacuolar changes of frontal lobes, anterior temporal lobes, anterior cingulate cortex, and insular cortex. Subtypes are associated with characteristic patterns of abnormal protein deposition.[33] Initial changes occur in the anterior cingulate cortex, fronto-insular cortex, orbitofrontal cortex, and cingulate-frontal transitional zones.[34] These regions have von Economo neurons and fork cells in layer 5 of the cortex, which are thought to play a central part in the integration of cortical and subcortical networks, and degenerate very early in behavioural-variant frontotemporal dementia.[35] Either the microtubule-associated protein tau (MAPT), the TAR DNA-binding protein with molecular weight 43 kDa (TDP-43), or the fused-in-sarcoma (FUS) protein account for nearly all cases of frontotemporal lobar degeneration. The corresponding pathological subtypes of frontotemporal lobar degeneration are frontotemporal lobar degeneration-tau, frontotemporal lobar degeneration-TDP, and frontotemporal lobar degeneration-FUS. A few cases of frontotemporal lobar degeneration have ubiquitin-only or p62-only positive inclusions, or no inclusions at all.[33]

Frontotemporal lobar degeneration-tau

Frontotemporal lobar degeneration-tau accounts for 36–50% of all cases of frontotemporal lobar degeneration according to different pathological series.[36–38] The most common subtypes of frontotemporal lobar degeneration-tau are Pick's disease, corticobasal degeneration, and progressive supranuclear palsy. Pick's disease constitutes 5% of all dementia cases and up to 30% of frontotemporal lobar degeneration-tau cases in various autopsy series.[37,39] The disease is characterised by striking knife-edge atrophy of frontal, temporal, and cingulate gyri, whereas the parietal lobe is better preserved. Pick bodies are the pathological hallmark of Pick's disease (figure 2A).[40] Corticobasal degeneration accounts for about 35% of frontotemporal lobar degeneration-tau cases.[37] Corticobasal degeneration shows predominant involvement of dorsal prefrontal cortex, supplemental motor area, peri-Rolandic cortex, and subcortical nuclei.[40] Microscopically, corticobasal degeneration is characterised by pre-tangles, neuritic threads, ballooned neurons, astrocytic plaques (figure 2C), and oligodendroglial coiled bodies.[40,41] Progressive supranuclear palsy accounts for about 31% of all cases of frontotemporal lobar degeneration-tau.[37] Progressive supranuclear palsy is associated with atrophy of the frontal convexity, milder than in corticobasal degeneration.[42] Subcortical atrophy is severe at the level of the globus pallidus, subthalamic nucleus, and brainstem nuclei. Microscopically, neuronal granular inclusions, tufted astrocytes, and globose tangles are seen (figure 2B) .[40]

Frontotemporal lobar degeneration-TDP

Frontotemporal lobar degeneration-TDP accounts for about 50% of all cases of frontotemporal lobar degeneration.[37,38] Three major subtypes of frontotemporal lobar degeneration-TDP (types A, B, and C) are recognised on the basis of the patterns of cytoplasmic or intranuclear pathology, and cortical association (figure 2E–G and figure 3).[43,44] In our centre, frontotemporal lobar degeneration-TDP type A accounts for about 50% of all cases of non-fluent variant primary progressive aphasia, 25% of suspected corticobasal degeneration cases, and a small proportion of behavioural-variant frontotemporal dementia

cases with or without motor neuron disease, whereas frontotemporal lobar degeneration-TDP type B accounts for about two-thirds of frontotemporal dementia–motor neuron disease cases and 25% of behavioural-variant frontotemporal dementia cases. Frontotemporal lobar degeneration-TDP type C accounts for about 90% of all cases of semantic-variant primary progressive aphasia (left) or temporal-variant behavioural-variant frontotemporal dementia (right).

Frontotemporal lobar degeneration-FUS

Behavioural-variant frontotemporal dementia associated with frontotemporal lobar degeneration-FUS accounts for about 10% of all frontotemporal lobar degeneration cases.[45] This entity is characterised by sporadic, early-onset frontotemporal dementia with severe disinhibition, sometimes psychosis, and other psychiatric and behavioural abnormalities in the absence of motor or linguistic deficits. Patients show distinctive FUS-immunoreactive inclusions that are abundant in the dentate gyrus (figure 2D), and severe striatal atrophy.[46]

Genetics

A family history of dementia is reported in up to 40% of cases of frontotemporal lobar degeneration, although a clear autosomal dominant history accounts for only 10% of cases. [47] Mutations in *C9orf72, MAPT*, and *GRN* genes account for about 60% of all cases of inherited frontotemporal lobar degeneration.[48] Genetic testing should be considered in patients with frontotemporal dementia with a strong family history of autosomal dominant neurological disorders including frontotemporal dementia, Alzheimer's disease, parkinsonism, motor neuron disease, inclusion body myopathy, or late-onset psychosis.[48,49]

C9orf72 gene mutations account for about 25% of familial cases of frontotemporal lobar degeneration and are the most common genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis.[50] *MAPT* and *GRN* mutations each account for 5–20% of familial frontotemporal lobar degeneration cases.[51] The prevalence of mutation types varies from region to region and might reflect founder effects. The expansion of a non-coding GGGGCC hexanucleotide repeat in the *C9orf72* gene is the most common cause of inherited frontotemporal dementia and amyotrophic lateral sclerosis worldwide, and accounts for a smaller proportion of sporadic cases.[50,52] *C9orf72* mutations are most frequent in Scandinavia and northern Europe, and account for more than 50% of all frontotemporal lobar degeneration mutations at our centre in San Francisco, but are rare in Asia. *MAPT* mutations were the first identified monogenic cause of inherited frontotemporal dementia and lead to neurodegeneration through changed microtubule stabilisation and increased propensity of tau self-aggregation.[53] *GRN* mutations are associated with haploinsufficiency with loss of two-thirds of functional progranulin concentrations in the serum and cerebrospinal fluid.[54,55] Progranulin is a secreted protein involved in cell-cycle regulation, wound repair, axonal growth, and modulation of inflammation.[56] Progranulin binds to the tumour necrosis factor (TNF) receptor, therefore potentially exercising a competing role against TNFα-induced inflammation.[57] A higher prevalence of non-thyroid-related autoimmune disorder has been reported in carriers of *GRN* mutations.[58] These mutations are most common in southern Europe, particularly Spain and Italy (table 3). TDP-43 and FUS

are RNA-binding ribonucleoproteins associated with regulation of transcription and translation, alternative splicing, and RNA transport and stabilisation. Mutations in either *TARDBP*, the gene encoding TDP-43, or *FUS* are associated with familial amyotrophic lateral sclerosis with or without frontotemporal dementia.[59] Table 3 summarises patterns of brain atrophy and proposed mechanisms of neurodegeneration associated with *C9orf72*, *MAPT*, *GRN*, *TARDBP*, *FUS*, *VCP*, or *CHMP2B* gene mutations.[46,59–71]

Treatment

No approved disease-modifying drugs are available for the treatment of frontotemporal dementia. Treatment is focused on management of behavioural symptoms. Severity of compulsion, agitation, aggressiveness, impulsivity, and aberrant eating behaviour can improve with the use of selective serotonin reuptake inhibitors.[72] Behavioural abnormalities can be managed with low doses of atypical antipsychotics.[73] Caution should be used when treating elderly patients with dementia with atypical antipsychotics because of the heightened risk of mortality secondary to cardiac events, falls, and infections.[74] Cholinesterase inhibitors are not beneficial and can worsen behavioural abnormalities seen in patients with frontotemporal dementia.[75] Memantine does not improve or delay progression of frontotemporal dementia symptoms.[76]

Advances in the understanding of the pathobiology of frontotemporal dementia have identified new potential therapeutic targets for the development of effective disease-modifying drugs. The discovery that pathological tau protein spreads trans-synaptically in a prion-like manner to consecutive brain regions along anatomical pathways of intrinsic connectivity has increased interest in the possibility that antibodies could be used to prevent trans-neuronal spreading of pathological abnormalities, therefore hopefully preventing the disease from further spreading.[31,77,78] Other therapeutic approaches to tauopathies under investigation are based on testing the efficacy of inhibitors of tau aggregation with methylene blue derivatives and microtubule stabilising drugs (eg, TPI-287), and by development of tau vaccines.[79]

The discovery of the pathogenic expansion in *C9orf72* as the most common cause of inherited frontotemporal dementia has increased interest in the development of antisense oligonucleotides to reduce concentrations of potentially toxic mRNAs.[80] This approach is under investigation with the aim of reducing the total amount of pathological tau species.[81]

Because neurodegeneration in *PGRN* mutation carriers is associated with progranulin haploinsufficiency and diminished progranulin serum concentrations, studies are attempting to curtail the progression of neurodegeneration in *PGRN* mutation carriers with molecules such as the histone deacetylase inhibitor suberoylanilide hydroxamic acid, which enhances progranulin transcription; alkalising compounds (such as chloroquine, bepridil, and amiodarone) that stimulate progranulin production; and inhibitors of the vacuolar ATPase, which all increase intracellular and secreted progranulin concentrations.[82,83] A clinical trial testing the efficacy of nimodipine is in progress at our institution (NCT01835665).

Conclusion and future directions

Frontotemporal dementia is a common dementia, particularly in individuals younger than 65 years. The clinical presentation of behavioural-variant frontotemporal dementia is characterised by the predominance of behavioural symptoms. Differentiation of the initial changes of this devastating neurodegenerative disease from common psychiatric disorders, particularly schizophrenia, depression, bipolar disorder, delusional disorders, obsessive-compulsive behaviour, and borderline, schizoidal, and antisocial personality disorders can be difficult. Many novel biological mechanisms leading to frontotemporal lobar degeneration have been identified. Nevertheless, the cause remains elusive and many questions remain unanswered.

What is the reason for the selective vulnerability of the frontal and temporal lobes of the brain to frontotemporal dementia? Insights into this selective susceptibility have come from the identification of von Economo neurons and fork cells as the initial target of degeneration in frontotemporal dementia.[35] However, little is known about the biology of these cell types.

Who is at risk of developing frontotemporal dementia? Can preclinical disease detection of at-risk individuals lead to disease prevention? Development of neuroimaging and molecular biomarkers will lead to the early identification of disease changes and potentially prevent, halt, or even reverse the pathological process. Genetic efforts will allow the discovery of new pathogenic mutations and risk-associated polymorphisms in familial frontotemporal lobar degeneration. Frontotemporal dementia preclinical phenomenology needs to be better characterised. Current routine behavioural and emotional assessments are not sufficiently sensitive in prediction of disease onset.

International efforts are necessary to characterise patients affected with the inherited forms of frontotemporal dementia. The advantage of this approach relies on the theoretical possibility of predicting the natural history of disease in carriers of pathogenic mutations. Such studies will be fundamental in designing effective clinical trials of disease-modifying drugs, when potential molecular candidates become available. Molecular PET imaging promises to improve effectiveness and robustness of clinical trials through a better differentiation of frontotemporal lobar degeneration subtypes in vivo.

How does frontotemporal lobar degeneration spread in the brain? What is the role of selective neuronal vulnerability in view of the findings regarding prion-like spreading of proteinopathies? Various and often co-occurring mechanisms of neurodegeneration are emerging, suggesting that many targets of therapeutic intervention will be identified in the future. As a result, future therapeutic strategies will probably involve simultaneous use of various drugs, similar to the treatment of hypertension, cancer, or HIV/AIDS. On the other hand, improvement of biomarker characterisation will lead to the development of proteinopathy-specific therapies.

Finally, what can we learn from the study of frontotemporal lobar degeneration syndrome that can be applied to the management of psychiatric disorders? Reports of the high frequency of long-standing early psychiatric symptoms and late-onset psychosis in carriers of *C9orf72* pathological expansion have renewed attention towards the clinical overlap of so-

called pure psychiatric disorders and traditional forms of neurodegeneration. Increased knowledge of the pathophysiology of behavioural dysfunction in frontotemporal lobar degeneration will probably provide further insights into the neurobiology of psychiatric diseases. After several decades of segregation between behavioural neurology and psychiatry, we might be witnessing the rebirth of neuropsychiatry, as we enter one of the most exciting times for the understanding and hopefully the treatment of frontotemporal dementia.

Acknowledgments

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Panel: Clinical vignette

A 69-year-old right-handed man with a past medical history of complex partial seizures, hypertension, and hyperlipidaemia was referred because of a 5-year history of progressive behavioural changes. His initial symptoms consisted of apathy and diminished interest in household chores. He reported increasing frustration at work because of difficulties dealing with job duties and related paperwork. His ability to do manual work at home declined. He developed difficulties operating a microwave and began losing weight because he could not follow directions on how to process precooked meals. He became confused about credit card payments. 1 year later, he began making potentially hurtful remarks publicly towards strangers in a way that the random target would be able to hear ("Do you think she really wanted this hair colour?"; "Why does he need to have so many tattoos?"). He began engaging strangers in conversations and, on one occasion, addressed a security guard screaming "I need security" and proceeded to hug him. He started using sexually inappropriate language with his wife, although his interest in sex declined. He began repeating sentences in a stereotypical way, often out of context, and later started making faces or talking with a Donald Duck-like voice in public, irrespective of the circumstances. He shoplifted from a grocery store on one occasion. He became distant and less empathic towards his family members. At the same time, he became hyperemotional with regard to life events of strangers, such as when reminded of the assassination of John Lennon. His eating habits changed and he began eating large amounts of ice cream and smoothies, yoghurt, and milk. He also began reporting bizarre visual hallucinations, such as seeing a dinosaur in his neighbour's backyard, and began talking to stuffed animals in the house. Later in the disease course, he developed hand clumsiness and began losing muscle bulk in his chest, shoulders, and legs. He developed motor stereotypies such as tapping and hitting his chest as a sign of strength, and started to have difficulties with swallowing. His family history was remarkable for epilepsy in his father and younger brother. His maternal grandmother had been unable to raise her children as a result of what was described as a nervous breakdown. One of his paternal uncles was affected with parkinsonism. The patient's neurological examination was remarkable for poor orientation and inappropriate behaviour, mildly diminished muscle bulk in the left arm, and mild kinetic tremors. His neuropsychological assessment revealed predominant and severe executive impairment. His brain MRI showed severe volume loss at the level of the orbitofrontal cortex, insular cortex, dorsolateral and mesial frontal gyri, and anterior temporal lobes, which was more severe on the right cerebral hemisphere. There was atrophy of the caudate nuclei, hippocampi, and cerebellar hemispheres. He was diagnosed with probable behavioural-variant frontotemporal dementia, probably secondary to frontotemporal lobar degeneration, associated withTDP-43type-B pathology.[5]
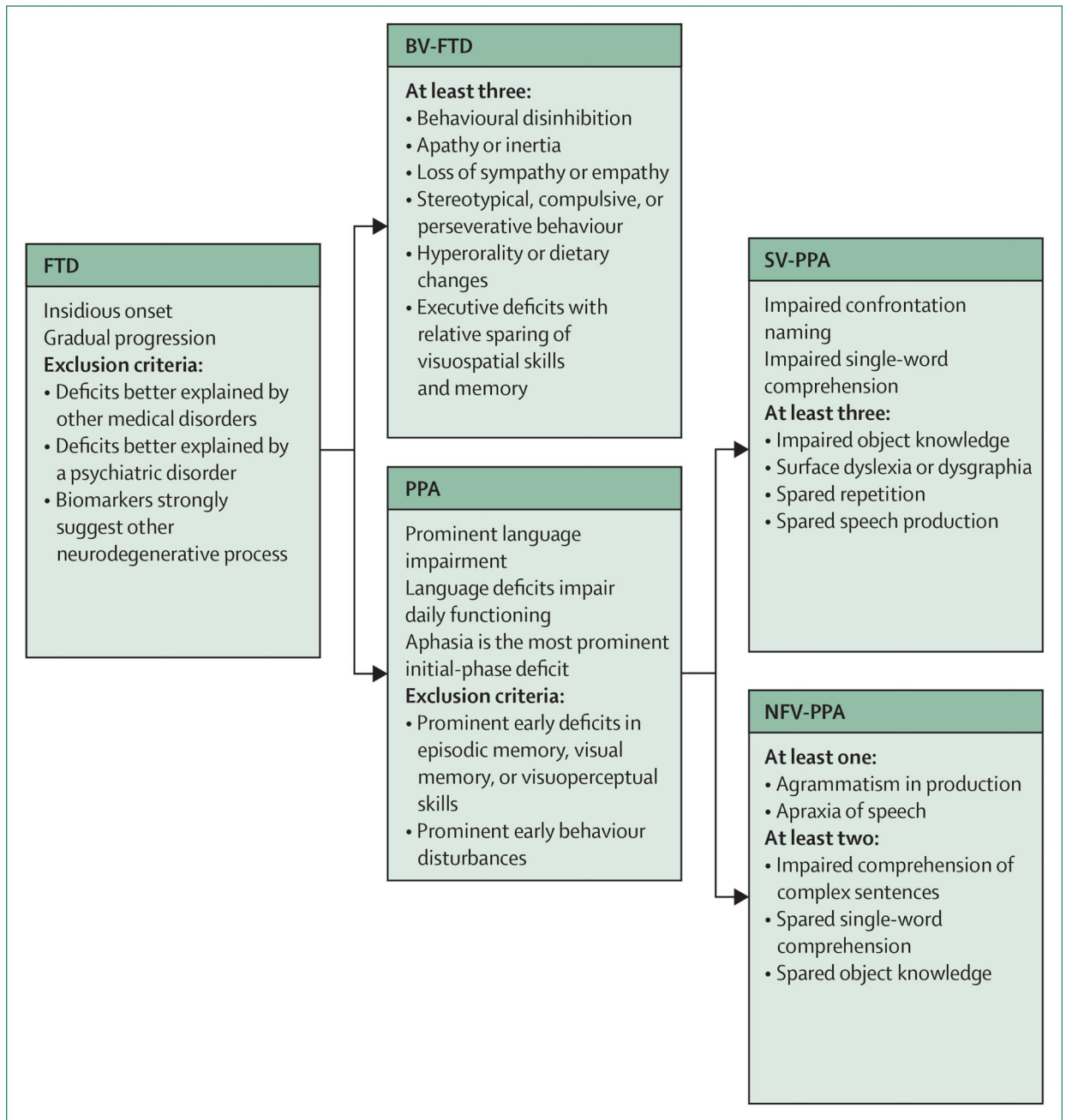
FTD

Insidious onset
Gradual progression
Exclusion criteria:
• Deficits better explained by other medical disorders
• Deficits better explained by a psychiatric disorder
• Biomarkers strongly suggest other neurodegenerative process

BV-FTD

At least three:
• Behavioural disinhibition
• Apathy or inertia
• Loss of sympathy or empathy
• Stereotypical, compulsive, or perseverative behaviour
• Hyperorality or dietary changes
• Executive deficits with relative sparing of visuospatial skills and memory

PPA

Prominent language impairment
Language deficits impair daily functioning
Aphasia is the most prominent initial-phase deficit
Exclusion criteria:
• Prominent early deficits in episodic memory, visual memory, or visuoperceptual skills
• Prominent early behaviour disturbances

SV-PPA

Impaired confrontation naming
Impaired single-word comprehension
At least three:
• Impaired object knowledge
• Surface dyslexia or dysgraphia
• Spared repetition
• Spared speech production

NFV-PPA

At least one:
• Agrammatism in production
• Apraxia of speech
At least two:
• Impaired comprehension of complex sentences
• Spared single-word comprehension
• Spared object knowledge

Figure 1. Diagnostic criteria for clinical diagnosis of FTD
These criteria focus mostly on symptoms that are present early in the illness, which tend to more clearly delineate the three variants of FTD. FTD=frontotemporal dementia. BV=behavioural variant. SV=semantic variant. NFV=non-fluent variant. PPA=primary progressive aphasia.
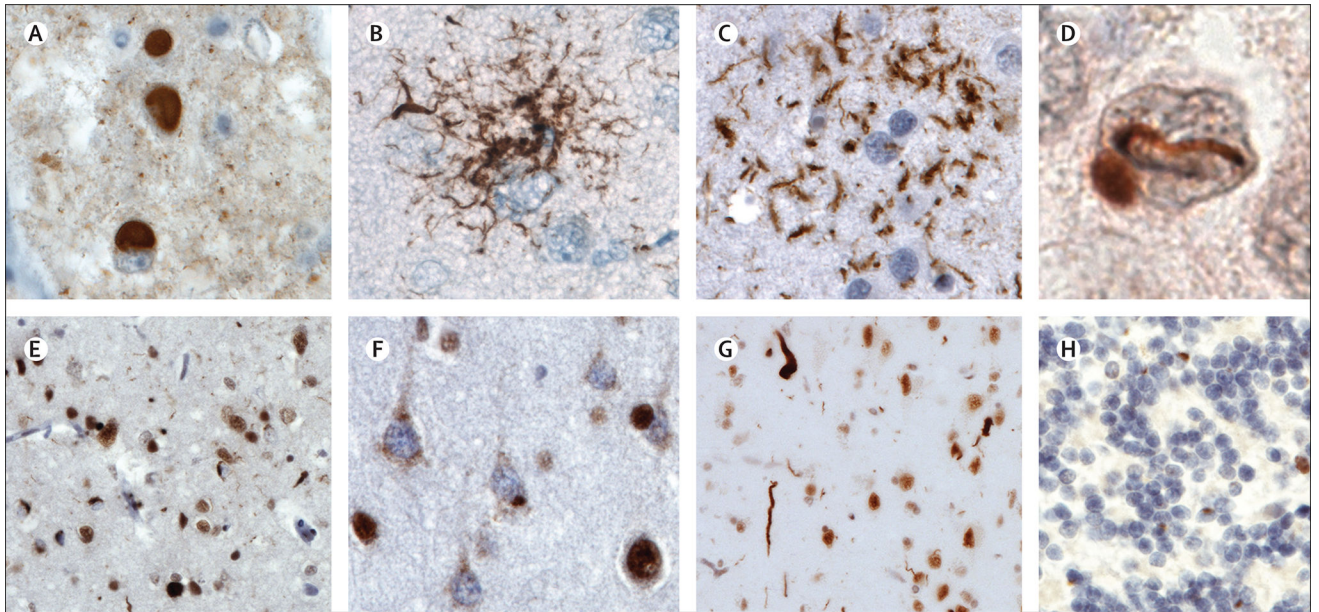
Figure 2. Neuropathology in FTLD-tau and FTLD-TDP

FTLD-tau (A) Pick bodies in Pick's disease; (B) a tufted astrocyte in progressive supranuclear palsy; (C) an astrocytic plaque in corticobasal degeneration; FTLD-TDP (E) small compact or crescentic neuronal cytoplasmic inclusions and short, then neuropil threads in FTLD-TDP type A; (F) diffuse or granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP type B; and (G) long, tortuous dystrophic neurites in FTLD-TDP type C.TDP can be seen within the nucleus in neurons lacking inclusions but mislocalises to the cytoplasm and forms inclusions in FTLD-TDP. The remaining FTLD cases are characterised by FUS-immunoreactive inclusions that stain negatively for tau and TDP-43; a vermiform neuronal nuclear inclusion in a dentate gyrus granule cell is shown (D); this neuron contains an ovoid cytoplasmic inclusion. In patients with hexanucleotide expansions in *C9orf72*, small juxtanuclear ubiquitin-positive, TDP-negative inclusions (H) are pathognomonic for the disorder. These inclusions contain dipeptide repeat proteins translated from the GGGGCC repeat in one of six reading frames. lmmunostains are 3-repeat tau (A), phospho-tau (B and C), FUS (D), TDP-43 (E–G) and ubiquitin (H). Sections are counterstained with haematoxylin. Scale bar applies to all panels and represents 50 μm in A, B, C, and H; 12 μm in D; and 100 μm in E and G. FTLD=frontotemporal lobar degeneration. TDP=TAR DNA-binding protein. FUS=fused-in-sarcoma.
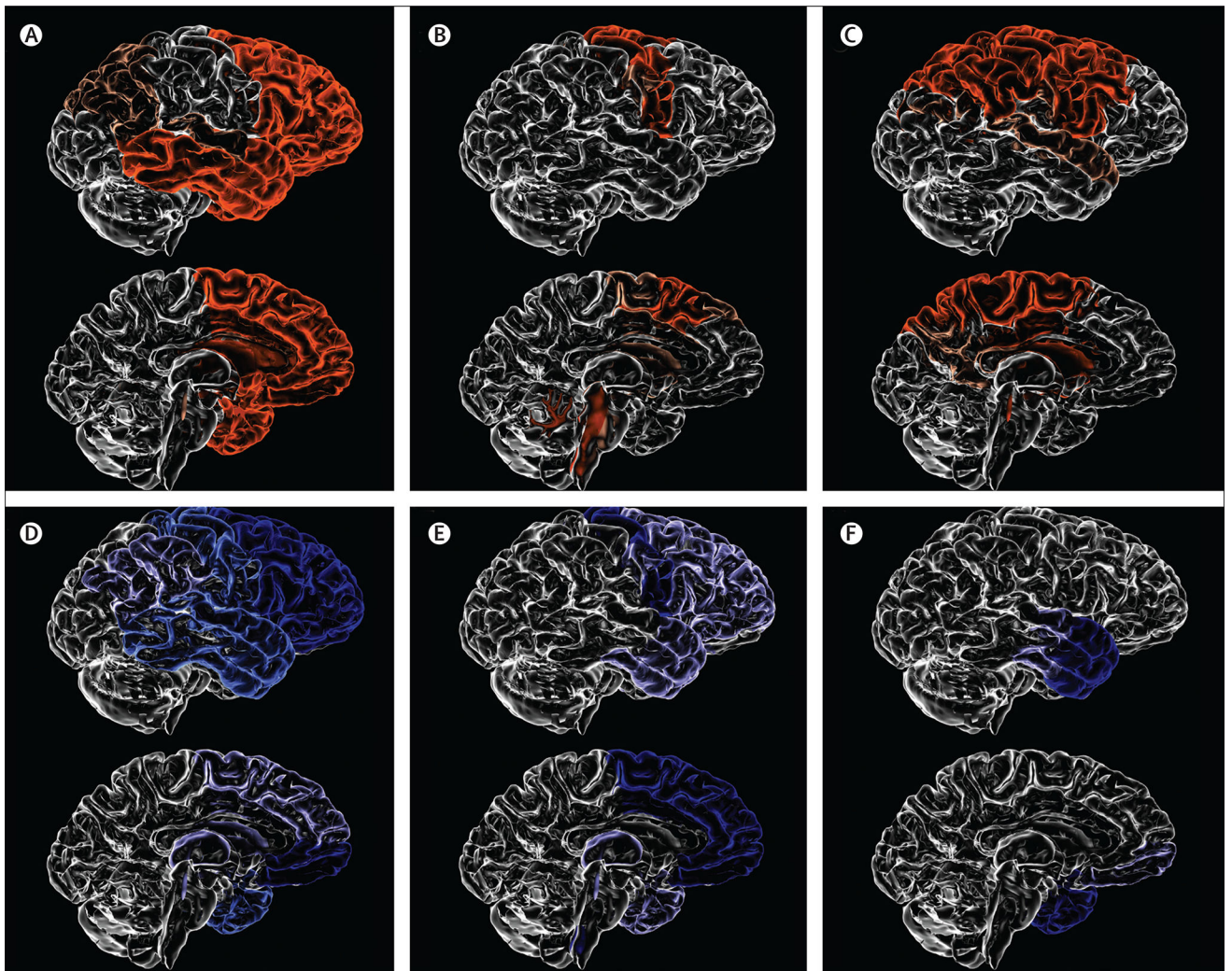
Figure 3. Patterns of brain atrophy in FTLD pathologies

(A) Pick's disease; (B) progressive supranuclear palsy; (C) corticobasal degeneration; (D) FTLD-TDP type A; (E) FTLD-TDP type B; (F) FTLD-TDP type C. FTLD-TDP type A is associated with an asymmetrical dorsal pattern of atrophy that includes the frontal lobe and temporal lobe (anterior, medial, and posterior regions), orbitofrontal cortex, anterior cingulate gyrus, inferior parietal lobe, striatum, and thalamus. FTLD-TDP type B is associated with a more medial pattern of atrophy mainly involving the medial and polar temporal lobe, anterior insular, cingulate and medial prefrontal cortices, and the orbitofrontal cortex. The frontal lobe is more severely affected in the posterior areas. FTLD-TDP type C is associated with either right-predominant or left-predominant anterior temporal lobe atrophy, with additional involvement of the amygdala, hippocampus, orbitofrontal cortex, and insular cortex. FTLD=frontotemporal lobar degeneration. TDP=TAR DN A-binding protein 43.

Table 1

Epidemiology of frontotemporal dementia[8–10]

	Age (years)	Prevalence
Patients with early-onset dementia	<65	3–26%
US general population	45–64	15–22 per 100 000
UK general population	45–64	3–26 per 100 000
Italy general population	45–64	22 per 100 000
Japan, UK, and Netherlands	30–64	1–16 per 100 000
Most common FTD variant		
USA and Europe	..	BV-FTD (50–70%)
Asia	..	SV-PPA or BV-FTD
Age at onset		
<45 years	..	10%
45–64 years	..	60%
>64 years	..	30%
Survival time		
From symptom onset	..	6–11 years
From clinical diagnosis		
FTD-MND	..	2 years
BV-FTD	..	3–4 years
NFV-PPA	..	5 years
SV-PPA	..	5+ years

FTD=frontotemporal dementia. BV=behavioural variant. MND=motor neuron disease. PPA=primary progressive aphasia. NFV=non-fluent variant. SV=semantic variant.

Table 2

Clinical symptoms characteristic of FTD

	BV-FTD	SV-PPA	NFV-PPA
Social symptoms			
Disinhibition, inappropriate or offensive behaviour, excessive jocularity, exaggerated emotional display, impulsivity, inappropriate sexual remarks, lack of embarrassment	73–98%	59%	18%
Loss of empathy, lack of emotional insight, social coldness	49–78%	28–49%	18%
Selfishness, disregard for others' feelings	83–89%	91%	No
Aggression	25–61%	28–64%	12%
Personal neglect, neglect of hygiene	83–92%	64%	No
Strange manner of dressing	Yes	Right-sided cases	No
Personality changes	Sometimes	Sometimes	Rarely
Emotional symptoms			
Apathy, low motivation, aspontaneity, decreased initiation of behaviour	54–96%	18–47%	41%
Depression, emotional detachment	Common	44%	Sometimes depression
Irritability	33%	50%	47%
Anxiety, social avoidance	No	Not usually	Yes
Exaggerated emotional display	33–39%	55%	Rarely
Eating and oral behaviours			
Overeating, gluttony	61–83%	36%	Rarely
Reduced selectivity, indiscriminate eating	41–55%	9%	Rarely
Increased selectivity, food fads	8–22%	55%	Rarely
Preference for sweet foods	25–56%	36%	Rarely
Preference for savoury foods	0%	9%	Rarely
Hyperorality	0–22%	18%	Rarely
Repetitive or compulsive behaviours			
Behavioural stereotypies	95%	72%	24%
Compulsive behaviours	5–15%	60–80%	Rarely
Word obsessions, repetitious use of verbal expressions	Sometimes	Often	Rarely
Sensory symptoms			
Reduced pain response	39–45%	27%	Rarely
Increased pain response, increased heat/cold response	0–33%	45–55%	Rarely
Incontinence	Sometimes	Sometimes	Rarely
Motor symptoms			
Motor neuron disease	15%	Rarely	Rarely
Parkinsonism	18–20%	3%	6%
Progressive supranuclear palsy syndrome	Rarely	Not known	Sometimes

	BV-FTD	SV-PPA	NFV-PPA
Corticobasal syndrome	Rarely	Not known	Sometimes
Executive symptoms			
Mental rigidity, inflexibility	41%	38%	12%
Inattention, disorganisation	Sometimes	Sometimes	Rarely
Loss of sensitivity to negative consequences, bad financial judgment	Sometimes	Sometimes	Rarely
Language symptoms			
Impaired word finding	45%	84%	71%
Apraxia of speech	5%	6%	94%
Agrammatism	0%	0%	53%
Impaired confrontation naming	30%	97%	71%
Impaired single-word comprehension	5%	84%	18%
Object agnosia	2%	34%	0%
Phonological errors	2%	9%	71%
Word repetition errors	0%	0%	53%
Sentence repetition errors	2%	6%	35%
Sentence comprehension errors	23%	72%	88%
Surface dyslexia	11%	81%	71%
Neuropsychiatric symptoms			
Delusions	14%	9%	6%
Hallucinations	20%	6%	6%
Other symptoms			
Sleep disorders	Sometimes	Rarely	Rarely
Restlessness	Sometimes	Sometimes	Rarely
Prosopagnosia	3%	47%	0%
Decreased libido	Sometimes	Sometimes	Rarely
Episodic memory deficits	Rarely	Rarely	Rarely

BV-FTD=behavioural-variant frontotemporal dementia. SV=semanticvariant. NFV= non-fluentvariant. PPA=primary progressive aphasia.

Table 3

Genetic and pathological correlation in FTLD

	Prevalence among familial FTD cases	Geographic prevalence of mutation carriers	Atrophy patterns	Common clinical presentations	FTLD proteinopathy	Mechanisms of neurodegeneration
C9orf72 (9p21.2)	13–50%	Scandinavia, west Europe, USA, Australia, rare in Asia	Symmetrical, orbitofrontal, medial and dorsolateral frontal, followed by temporal lobes, parietal and occipital lobes, cerebellum, posterior thalamus	BV-FTD FTD-MND ALS Parkinsonism Late-onset psychosis	TDP type B (less commonly type A) dipeptide repeat proteins in neocortex, thalamus, cerebellum, and hippocampus	Endosomal trafficking dysregulation; RNA-foci formation and impaired transcription processing; dipeptide repeat protein toxicity
MAPT (17q21.1)	5–20%	Northwest Europe, USA	Symmetric frontal, anterior cingulate cortex, insular, anterior, and medial temporal lobe	BV-FTD Parkinsonism	Tau (often unclassifiable, occasionally resembling Pick's disease), corticobasal degeneration or progressive supranuclear palsy	Altered microtubule stabilisation and/or increased propensity of tau self-aggregation
GRN (17q21.32)	5–20%	England, central and southern Europe, USA	Asymmetrical, anterior temporal, temporo-parietal, frontal (left > PPA; right > BV-FTD), anterior cingulate cortex, insular	BV-FTD NFV-PPA Parkinsonism CBS	TDP type A	Impaired neurotrophic function, promotion of inflammation, impaired lysosomal-mediated protein degradation
TARDBP (1p36.22)	Rare	Italy, France, North America, Japan, China, Australia	Symmetrical frontal (type A, DLPFC; type B, VMPFC), OFC, temporal atrophy	ALS FTD-MND	TDP type A or B	Impaired RNA-binding, transcription, translation, alternative splicing, RNA transport and stabilisation
FUS (16p11.2)	Rare	Worldwide	Frontal and temporal atrophy with striking striatal atrophy	ALS FTD-MND	FUS	Impaired RNA-binding, transcription, translation, alternative splicing, RNA transport and stabilisation
VCP (9p13.3)	Rare	West Europe, USA, Brazil, Korea, Australia	Frontal, temporal, and parietal lobes, especially prefrontal cortex and superior temporal gyrus; hippocampus, caudate nucleus, amygdala	BV-FTD FTD-MND Inclusion body myopathy Paget's disease of the bone	TDP type D	Impaired ubiquitin-proteasome mediated protein degradation and autophagy
CHMP2B (3p11.2)	Rare	Denmark	Generalised cortical atrophy, mostly severe in frontal and temporal cortices	BV-FTD FTD-MND	Ubiquitin proteasome system proteins	Impaired endosomal-lysosomal and autophagic protein degradation pathway

Pathology of frontotemporal lobar degeneration in patients with mutations in named genes, with chromosomal locations indicated in parentheses. FTD=frontotemporal dementia. FTLD=frontotemporal lobar degeneration. BV=behavioural variant. SV=semantic variant. NFV=non-fluent variant. PPA=primary progressive aphasia. MND=motor neuron disease. ALS=amyotrophic lateral sclerosis. TDP=TAR DNA-binding protein 43. FUS=fused-in-sarcoma. CBS=corticobasal syndrome. DLPFC=dorsolateral prefrontal cortex. VMPFC=ventromedial prefrontal cortex. OFC=orbitofrontal cortex.