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Primer

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Frontotemporal lobar degeneration

Murray Grossman[1,17], William W. Seeley[2,3] ✉, Adam L. Boxer[2], Argye E. Hillis[4], David S. Knopman[5], Peter A. Ljubenov[2], Bruce Miller[2], Olivier Piguet[6], Rosa Rademakers[7], Jennifer L. Whitwell[8], Henrik Zetterberg[9,10,11,12,13,14,15] & John C. van Swieten[16]

Abstract

Frontotemporal lobar degeneration (FTLD) is one of the most common causes of early-onset dementia and presents with early social–emotional–behavioural and/or language changes that can be accompanied by a pyramidal or extrapyramidal motor disorder. About 20–25% of individuals with FTLD are estimated to carry a mutation associated with a specific FTLD pathology. The discovery of these mutations has led to important advances in potentially disease-modifying treatments that aim to slow progression or delay disease onset and has improved understanding of brain functioning. In both mutation carriers and those with sporadic disease, the most common underlying diagnoses are linked to neuronal and glial inclusions containing tau (FTLD-tau) or TDP-43 (FTLD-TDP), although 5–10% of patients may have inclusions containing proteins from the FUS–Ewing sarcoma–TAF15 family (FTLD-FET). Biomarkers definitively identifying specific pathological entities in sporadic disease have been elusive, which has impeded development of disease-modifying treatments. Nevertheless, disease-monitoring biofluid and imaging biomarkers are becoming increasingly sophisticated and are likely to serve as useful measures of treatment response during trials of disease-modifying treatments. Symptomatic trials using novel approaches such as transcranial direct current stimulation are also beginning to show promise.

Sections

A full list of affiliations appears at the end of the paper. ✉e-mail: bill.seeley@ucsf.edu

We dedicate this work to the late Murray Grossman, who passed away on 4 April 2023. Murray was a dear friend to us all and to a worldwide community of neurologists and neuroscientists. He combined an acute interest in cognitive neuroscience that began as a graduate student with his clinical acumen as a behavioural neurologist to advance our knowledge of the frontotemporal degenerations. We will remember Murray, who was the driving force behind this review, for his wisdom and grace.

Introduction

Frontotemporal dementia (FTD) is among the most common clinical forms of early-onset neurodegenerative disease, but it is substantially under studied. FTD clinical syndromes include a disorder of social behaviour and personality known as behavioural variant FTD (bvFTD) and impairments of speech and language known as primary progressive aphasia (PPA) (Fig. 1). bvFTD and PPA can present with or without an accompanying motor disorder. The scope of FTD is now thought to include extrapyramidal motor disorders such as progressive supranuclear palsy–Richardson syndrome (PSP-RS) and corticobasal syndrome (CBS), and pyramidal motor disorders such as amyotrophic lateral sclerosis (ALS). While these motor conditions seem to present with relatively distinct phenotypes, the pathology responsible for these conditions overlaps with the pathology associated with bvFTD and PPA, leading to a broadened concept of FTD as encompassing all of these diverse syndromes.

Frontotemporal lobar degeneration (FTLD) is an umbrella term used to refer to non-AD neuropathological entities that are commonly found at autopsy in patients with an FTD clinical syndrome. Two FTLD major molecular classes account for ~95% of individuals with clinical FTD: FTLD related to misfolded tau (FTLD-tau) and FTLD associated with TAR DNA-binding protein of ~43 kDa (FTLD-TDP) pathobiology[1]. A less common pathology is FTLD related to FUS–Ewing sarcoma–TAF15 (FTLD-FET). One reason why FTD provides such a valuable scientific platform is that each of these pathological entities tends to occur in isolation in early-onset dementia[2]. The neuropathological subtypes of FTLD can be further subdivided (Fig. 1). Of note, each FTLD neuropathology can be associated with more than one clinical syndrome, and each clinical syndrome may be associated with different FTLD subtypes in different individuals (Fig. 1).

Disease-modifying treatments depend on identifying the pathology underlying an FTD syndrome. Two broad methods can be used to determine the associated pathology: the identification of a specific genetic mutation or use of biomarkers. While there is some variance depending on the reporting site, around 20–25% of people with FTD carry a genetic mutation[3–5], and are referred to as having familial FTLD (fFTLD). Most people with genetic FTLD have fFTLD, but a *C9orf72* repeat expansion is found in up to 10% of people with seemingly sporadic disease[6–8]. Individuals with fFTLD are an important subset of patients to study as there is a reliable association between specific genetic mutations and the underlying pathology. This association allows patients with an identified mutation to receive disease-modifying treatments targeting a specific pathology. By comparison, associations between clinical phenotype and underlying pathology are more variable in sporadic disease. Thus, biomarkers are being investigated to help clarify our understanding of the cause of sporadic FTD. The anatomical distribution of misfolded proteins in the brain at autopsy corresponds reasonably well with changes in clinical manifestations and findings on MRI and molecular PET. The use of biofluid biomarkers to identify the cause of FTD is also promising.

Although FTD cannot be cured at this time, recent scientific advances may lead to treatments that slow disease progression, and

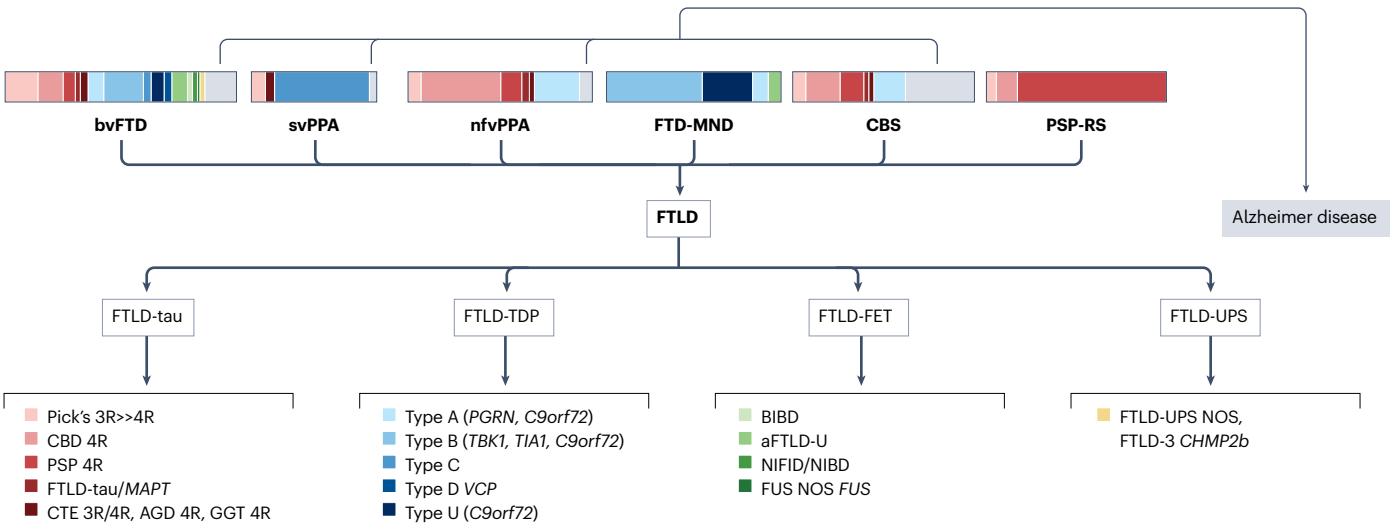

Fig. 1 | FTD syndromes and associated pathology. Clinical FTD syndromes colour-coded according to the proportion associated with a specific pathology and subtypes of each pathology as well as the associated genetic mutation with each. Genes shown without parentheses represent the only known causes of the associated neuropathological entity (for example, *VCP* in FTLD-TDP, type D), whereas genes shown in parentheses indicate that the pathology is also seen in patients with sporadic disease. 3R, three-repeat; 4R, four-repeat; AGD, argyrophilic grain disease; aFTLD-U, atypical FTLD; BIBD, basophilic inclusion body disease; bvFTD, behavioural variant FTD; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; FET, FUS–Ewing sarcoma–TAF15; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GGT, globular glial tauopathy; MND, motor neuron disease; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; NIBD, neurofilament inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; PSP, progressive supranuclear palsy; PSP-RS, PSP–Richardson syndrome; svPPA, semantic variant primary progressive aphasia; TDP, TAR DNA-binding protein; UPS, ubiquitin proteasome system.

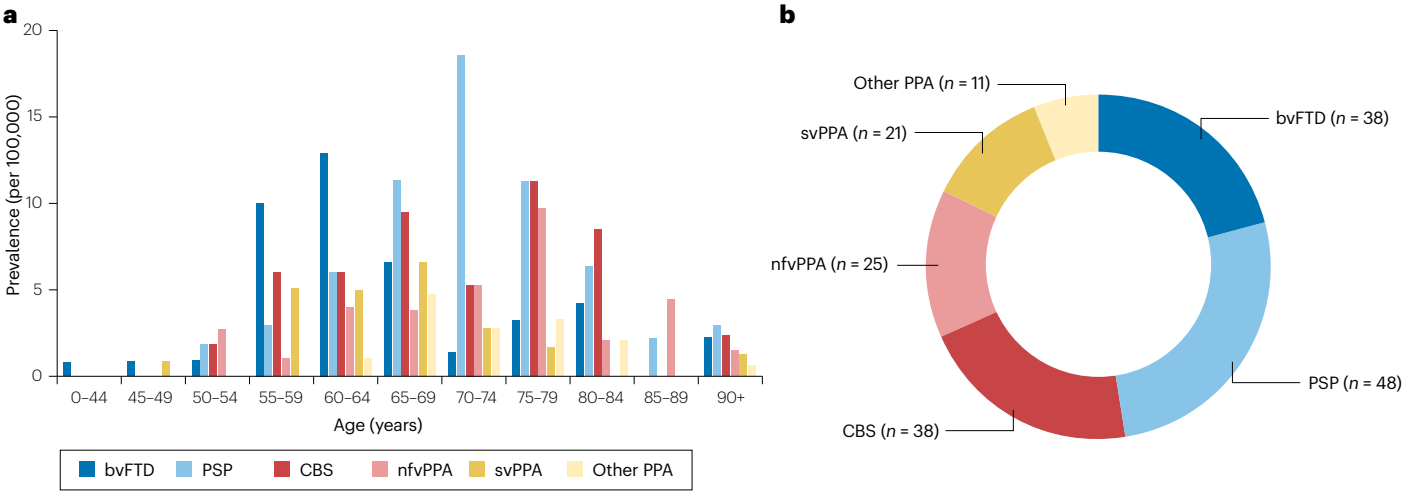

Fig. 2 | Prevalence of frontotemporal lobar degeneration-associated syndromes. a, Prevalence of FTD syndromes by age. **b**, Distribution of cases by clinical syndrome. The inclusion of frontotemporal dementia–amyotrophic lateral sclerosis (FTD-ALS) and FTD–motor neuron disease (FTD-MND) may vary from study to study depending on the focus of the work. bvFTD, behavioural variant frontotemporal dementia (including FTD-MND or FTD-ALS); CBS, corticobasal syndrome; nfvPPA, non-fluent/agrammatic variant PPA; other PPA, logopenic variant and unclassifiable PPA; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; svPPA, semantic variant PPA. Adapted with permission from ref. 18, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

treatments that delay disease onset may become available to treat FTD presymptomatically. At the same time, advances in treatments for FTD could lead to important scientific discoveries that could improve our understanding of brain functioning.

This Primer reviews the critical clinical and biological characteristics of FTD, highlighting the scientific importance of FTD research in expanding our understanding of neurogenetics and spreading of neuropathology, and discusses efforts leading to disease-modifying treatments for this disease.

Epidemiology

Problems with epidemiological studies

Determining accurate estimates of the prevalence and incidence of FTD is challenging. Data on FTD epidemiology are almost entirely from patients with a neurological diagnosis obtained in routine clinical practice. As diagnosis of the two main clinical syndromes of FTD – bvFTD[9] and PPA[10] – requires expertise and experience beyond primary care, under-diagnosis of patients with FTD is a major concern. Misdiagnosis of psychiatric illness is common[11]. Moreover, the prevalence and incidence of FTD could be over-estimated if people with dysexecutive dementia who lack substantial language and behavioural disturbances are diagnosed with FTD[12,13] when at autopsy most of these people will prove to have had Alzheimer disease (AD). A non-progressive psychiatric syndrome known as bvFTD phenocopy syndrome often mimics bvFTD in the absence of neurodegeneration, but this syndrome remains controversial and may have diverse underlying causes[14–16]. Another source of variability in epidemiological data is that patients with FTD who simultaneously exhibit the features of PSP-RS, CBS or ALS may be diagnosed with FTD or with one of the motor syndromes.

Prevalence and age at onset

The prevalence of FTD peaks around 60–70 years of age (Fig. 2). The prevalence of clinically diagnosed FTD syndromes (excluding PSP-RS and CBS) is ~10–15 cases per 100,000 among those aged 45–64 years[17] with an incidence of ~2.7 to 4.1 cases per 100,000 person-years in the same age range based on a relatively small number of reports from individual sites, mainly in the USA and Western Europe[18–21]. Including PSP-RS in the definition of FTD leads to incidence estimates of ~16 cases per 100,000 person-years in the age range 65–74 years[21]. The prevalence of bvFTD and some PPA syndromes such as semantic variant PPA (svPPA) declines before 65 years of age, whereas PSP-RS, CBS and non-fluent/agrammatic variant PPA (nfvPPA) often do not become symptomatic until after 65 years of age[18]. By contrast, the prevalence of clinically diagnosed AD dementia in those over 65 years of age is about two to three times higher, with an incidence of ~100 cases per 100,000 person-years[22].

Up to 37% of people with FTD have a dominantly inherited form[3–5], although the proportion of people with dominantly inherited FTD is highly variable by clinical site, with a median of 15–20% for proven mutation carriers. Dominantly inherited FTLD tends to manifest at an earlier age than sporadic FTLD[23]. In the largest international fFTLD series to date, the mean age at symptom onset was 49.5 years (s.d. 10.0 years) in those with *MAPT* mutations, 58.2 years (s.d. 9.8 years) in those with *C9orf72* repeat expansion, and 61.3 years (s.d. 8.8 years) in those with *GRN* mutations[23]. In those with dominantly inherited FTLD due to *MAPT*, *C9orf72* and *GRN* mutations, individual age at onset is significantly correlated with parental age at onset and mean family age at onset and death[23]. The correlation between familial age of onset and individual age at onset is strongest in people with *MAPT* mutations and is more variable in those with *GRN* mutations or the repeat expansion of *C9orf72*.

Survival

Survival of patients with FTLD varies according to clinical phenotype. In one meta-analysis[24], median survival was shortest in patients with bvFTD combined with ALS (2.8 years). Median survival was longer in those with bvFTD without an accompanying motor disorder (9.6 years), nfvPPA syndromes (7.7 years) and svPPA (12.2 years). Of note, age and

sex did not affect survival, and education level had a negligible effect on survival. Survival varies by genotype in people with dominantly inherited FTLD[23]; mean age at death was 59 years in *MAPT* mutation carriers, 65 years in *C9orf72* mutation carriers, and 69 years in *GRN* mutation carriers. Moreover, mean disease duration was 6.4 years in those with *C9orf72* mutations, 7.1 years in those with *GRN* mutations, and 9.3 years in individuals with *MAPT* mutations. As genotype determines phenotype in dominantly inherited FTLD[23], and as phenotype is associated with survival, between-genotype differences in survival may mainly reflect the distribution of clinical syndromes caused by each genotype.

Risk factors

Apart from age and family history, no other established risk factors for FTLD have been identified. Men and women are equally affected. Autopsy studies in the USA found that FTLD is very rare in Black people, although pathologically defined AD is more common in Black people than in white people[25]. fFTLD is rarer in Asia than in Europe[26]. The frequency of the genetic subtypes of FTLD varies geographically[23] (Fig. 3). Of note, lack of access to skilled diagnosticians in some countries or regions and concerns about variations in social norms between cultures are likely to contribute to the racial and geographic variations in FTD diagnosis and, therefore, reported prevalence.

Mechanisms/pathophysiology

Significant mechanistic insights into FTLD over the past two decades have been gained through the identification of new disease proteins, genes and targeted neural systems. These discoveries have highlighted the substantial heterogeneity of FTLD at the clinical, neuropathological and genetic levels. At the same time, new findings have revealed remarkable clinical–anatomical–genetic–pathological correlations and have helped identify early vulnerable neuron types and candidate mechanisms at the root of the network-based degeneration observed in FTLD.

Key pathological molecules

FTLD is divided into three major molecular classes based on the composition of disease protein inclusions that are found in neurons and glia: FTLD-tau, FTLD-TDP or FTLD-FET (with inclusions composed of the FET family of proteins: FUS, Ewing sarcoma protein and TAF15). Each major molecular class comprises several specific histopathological subtypes that are based on the morphology and distribution of the inclusions (Figs. 1 and 4). Rare FTLD cases in which inclusions contain only proteins of the ubiquitin proteasome system (UPS), perhaps in association with an as-yet unidentified disease protein, have also been described and classified as FTLD-UPS[27].

FTLD-tau. FTLD-tau subtypes are defined by the morphology and biochemistry of their tau inclusions, which contain specific tau isoforms based on alternative splicing of *MAPT* exon 10. Each FTLD-tau subtype is characterized by tau inclusions with distinctive seeding properties and ultrastructure, supporting the concept that the different entities may reflect specific pathogenic tau strains[28–30]. Pick disease is a three-repeat (3R) tau-predominant subtype of FTLD that is characterized by round, circumscribed, neuronal cytoplasmic inclusions, ballooned deep layer neurons, fine neuropil threads and ramified astrocytic inclusions[31]. By contrast, the diverse and subtype-specific neuronal and glial inclusions that occur in progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and globular glial tauopathy are all composed of four-repeat (4R) tau[31]. Chronic traumatic encephalopathy is often

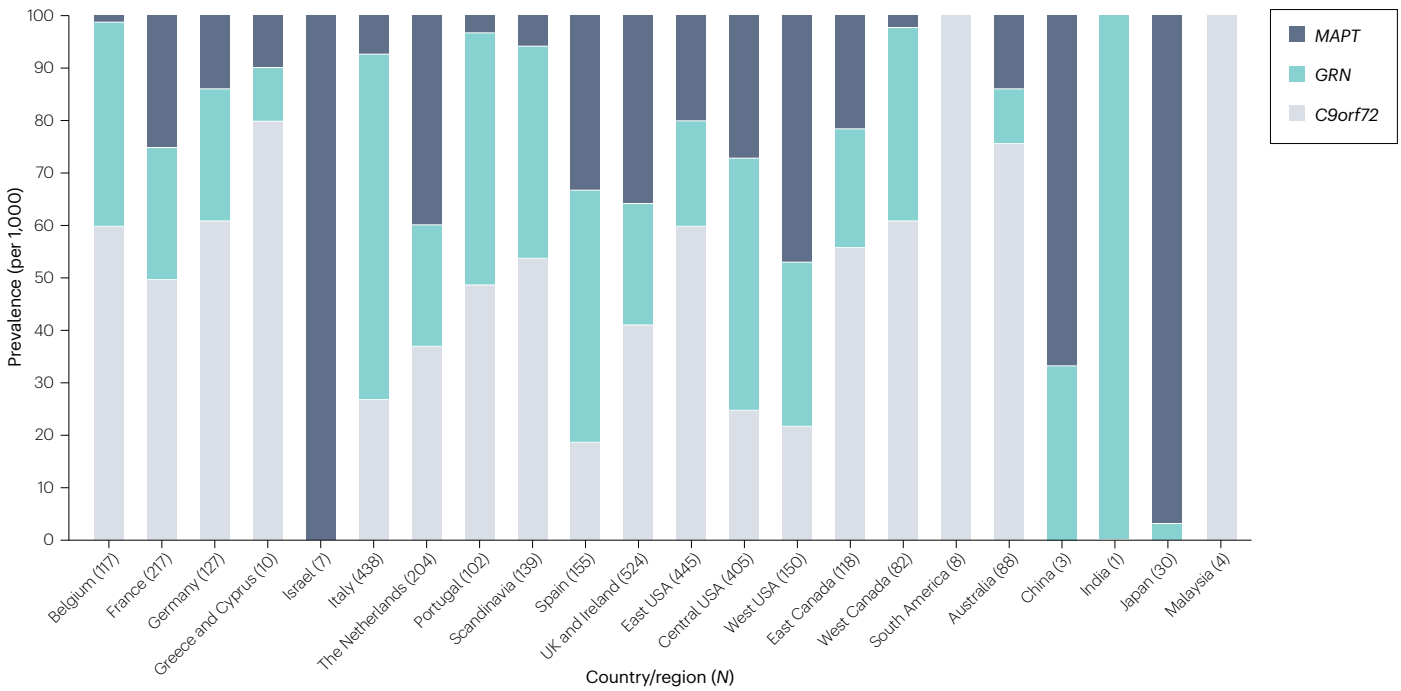

Fig. 3 | Geographic distribution of genetic subtypes of frontotemporal lobar degeneration. Bars show the relative frequency of the three most prevalent genetic forms of frontotemporal degeneration across 22 countries/regions. Numbers shown in parentheses for each country/region indicate the total number of reported cases. Data from ref. 23.

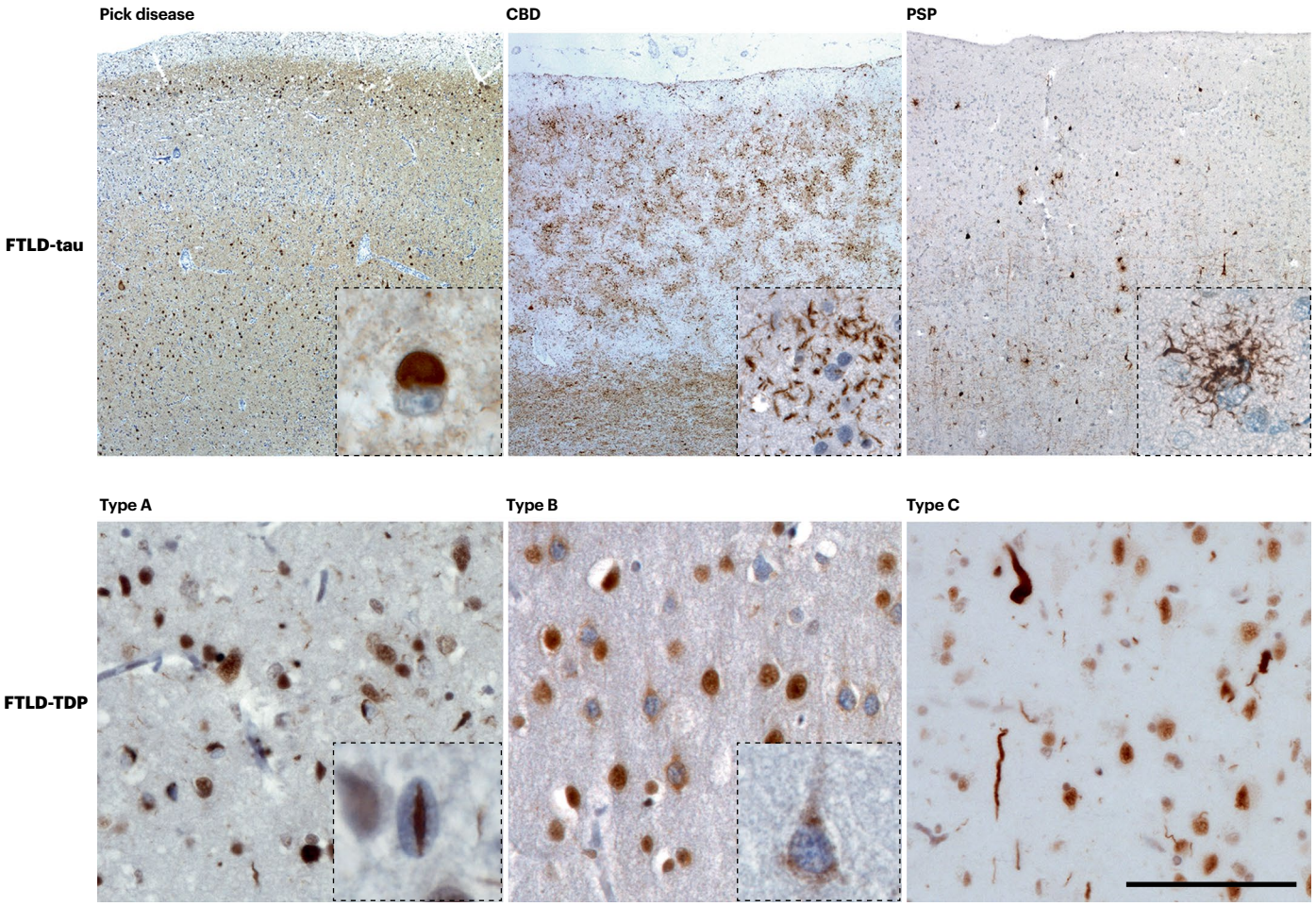

Fig. 4 | Frontotemporal lobar degeneration pathology. Photomicrographs show the characteristic features of the six most common frontotemporal lobar degeneration (FTLD) subtypes: FTLD-tau (top row, CP-13 antibody to P-tau at S202) includes Pick disease, characterized by Pick bodies (inset) most prominent in cortical layers two, five and six; corticobasal degeneration (CBD), characterized by astrocytic plaques (inset) and copious white matter axonal and oligodendroglial tauopathy; and progressive supranuclear palsy (PSP), characterized by prominent tufted astrocytes (inset), neuronal cytoplasmic inclusions and oligodendroglia coiled bodies. FTLD–TAR DNA-binding protein (FTLD-TDP; bottom row, pan-TDP antibody) includes: type A, with rare neuronal nuclear inclusions (inset) and frequent compact or crescentic neuronal cytoplasmic inclusions and short neuropil threads, all most prominent in upper cortical layers; type B, featuring granular/stippled neuronal cytoplasmic inclusions (inset) without substantial neuropil threads; and type C, characterized by long, swollen dystrophic neurites. Note that normal nuclear TDP-43 immunoreactivity is absent in inclusion-bearing neurons. Insets are cropped to highlight a single characteristic feature of each disorder. Scale bar, 1,000 μm in top row panels and 100 μm in bottom row panels. Adapted with permission from ref. 304, Annual Reviews.

considered an acquired form of FTLD-tau that is related to repetitive head trauma (usually in the context of participation in contact sports), in which the pathology includes perivascular neurofibrillary tangles composed of 3R and 4R tau, prominent neuropil threads and tau astrogliopathy[32].

FTLD-TDP. TDP-43 is a DNA/RNA-binding protein that is ubiquitously expressed in neuronal nuclei and is a master transcriptional regulator. FTLD-TDP is associated with loss of normal nuclear TDP-43 and aggregation of TDP-43 in the cytoplasm, dendrites, axons and, in some cases, the nucleus[30]. Although nuclear TDP-43 depletion and cytoplasmic aggregation most often occur together, some neurons may show isolated nuclear depletion associated with neuronal degeneration[33]. TDP-43 aggregation in glia, most often oligodendrocytes, varies within and between FTLD-TDP subtypes and occurs less frequently than in neurons[34]. FTLD-TDP can be divided into three major subtypes (A, B and C) based on the morphology, subcellular localization, and laminar distribution of the inclusions[34]. Distinguishing features have been proposed for each subtype: dense neuropil threads and compact round or crescent-shaped neuronal cytoplasmic inclusions in superficial cortical layers and rare neuronal intranuclear inclusions in FTLD-TDP type A; abundant superficial and deep layer granular or stippled neuronal cytoplasmic inclusions in FTLD-TDP type B; and long, swollen dystrophic neurites in FTLD-TDP type C[34]. A rare subtype of FTLD-TDP – type D – features abundant neuronal intranuclear inclusions and has been observed only in patients with mutations in *VCP*. Another subtype – type E – has been recently proposed and is described as showing abundant granulofilamentous inclusions and more prominent

Table 1 | Frequency, pathology, common clinical presentations, and genetic modifiers of the most common genetic mutations associated with FTLD

FTD gene	Frequency in fFTLD (%)	Frequency in sFTD (%)	Pathology	Most common clinical presentations	Genetic disease modifier(s) in humans	Refs.
MAPT	5–20	0–2	FTLD-tau	bvFTD, PSP-RS and CBS	None identified	44,298–300
GRN	5–25	5	FTLD-TDP	bvFTD, nfvPPA and CBS	*TMEM106B* and *GFRA2*	45,46,63,301,302
C9orf72	20–30	6	FTLD-TDP	bvFTD and FTD-ALS	*TMEM106B*, *SLITRK2* and *C6orf10/LOC101929163*	47–50,52,303

bvFTD, behavioural variant frontotemporal dementia; CBS, corticobasal syndrome; fFTLD, familial FTLD; FTD, frontotemporal dementia; FTD-ALS, frontotemporal dementia–amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; PSP-RS, progressive supranuclear palsy–Richardson syndrome; sFTD, sporadic frontotemporal dementia; TDP, TAR DNA-binding protein.

fine grains and threads than type B[35]; however, whether type E is a distinctive subtype or lies on a continuum with type B is uncertain[36]. Ultrastructural studies such as those used to distinguish FTLD-tau subtypes may soon help better disambiguate FTLD-TDP subtypes[37]. Moreover, the relative pathogenetic significance of nuclear TDP-43 depletion compared with TDP-43 aggregation remains unclear; most likely, both factors contribute to neuronal demise but through distinct mechanisms that are beginning to emerge.

FTLD-FET and FTLD-FUS. FTLD-FET is linked to the FET family of RNA-binding proteins. These proteins are normally found in the nucleus[38] although nuclear depletion of the aggregating protein is a less reliable feature of FTLD-FET than FTLD-TDP. FTLD-FET is usually sporadic[39] and subtypes are defined by the morphology and distribution of the neuronal cytoplasmic and nuclear inclusions. Subtypes include atypical FTLD with ubiquitin-positive inclusions, basophilic inclusion body disease and neuronal intermediate filament inclusion disease[40,41]. Patients with these subtypes have inclusions composed of all three FET family proteins[42], whereas patients with familial ALS or FTD due to *FUS* mutations have neuronal inclusions containing only FUS[43].

Genetic mechanisms

FTD is estimated to be a familial disease in about 20–25% of affected individuals, and is associated with autosomal dominant inheritance; however, a complex picture of heritability has emerged with varying degrees of familial aggregation between clinical FTD phenotypes[3,4]. Mutations in three genes account for most cases of fFTLD: *MAPT* (encoding microtubule-associated protein tau)[44], *GRN* (encoding progranulin)[45,46] and *C9orf72* (encoding chromosome 9 open reading frame 72)[47,48] (Table 1). Each gene is associated with a different spectrum of clinical presentations and one major molecular class; however, substantial variability exists in clinical presentation even within families carrying the same mutation, suggesting the involvement of genetic disease modifiers. Genetic modifiers might drive brain atrophy in specific networks leading to associated clinical phenotypes and might influence disease penetrance or age at onset[49–52] (Table 1).

MAPT was the first FTD gene to be identified, proving that tau aggregation and dysfunction alone are sufficient to cause neurodegeneration[44]. FTLD-tau owing to *MAPT* mutations can result in inclusions containing predominantly 3R, 4R or mixed 3R/4R tau, with the inclusion isoform composition, cell types affected and morphological patterns depending on the specific mutation[53]. Missense *MAPT* mutations mostly affect microtubule binding domains, whereas splicing mutations alter the 4R to 3R tau isoform ratio[54]. Mutations in *MAPT* have various effects on the function and properties of tau including loss of function owing to reduced microtubule binding and dysregulated microtubule dynamics, as well as aberrant tau aggregation and seeding[55,56]. Common genetic variation in two major *MAPT* haplotypes (H1 and H2) is associated with a significantly increased risk of sporadic tauopathies[57].

Pathogenetic variants in multiple genes can cause FTLD-TDP. The most common genetic cause of FTLD-TDP is a CCCCGG hexanucleotide expansion in the non-coding region of *C9orf72* (refs. 47,48). *C9orf72* encodes a protein involved in regulation of endosomal trafficking and autophagy[58], and the CCCCGG repeat expansion is thought to cause disease through loss of *C9orf72* expression and toxicity owing to repeat RNA aggregates and dipeptide repeat (DPR) proteins translated in an unconventional fashion from the repeat RNA[8,59]. Other consequences of the CCCCGG repeat expansion are nucleolar stress, RNA dysregulation, nucleocytoplasmic transport deficits and impaired protein degradation, and these changes have been suggested to contribute to disease[60]. Although this hexanucleotide expansion is most often inherited, a minority of patients with FTD with *C9orf72* repeat expansions lack a family history but present with a clinical syndrome indistinguishable from the inherited form[8,59].

Heterozygous loss-of-function mutations in *GRN* are the second most common cause of inherited FTLD-TDP[45,46]. While early studies focused on the neurotrophic properties of progranulin and its role in the inflammatory response, the discovery that homozygous loss-of-function mutations in *GRN* could cause the lysosomal storage disorder neuronal ceroid lipofuscinosis[61] suggested that lysosomal homeostasis might be disrupted in FTD[62]. Interestingly, genetic variants in *TMEM106B*, encoding another lysosomal protein, are a major modifier of penetrance of *GRN* mutations, providing further independent support for an important role for progranulin in lysosomes[51,63].

In rare cases, other genes are associated with FTLD-TDP (such as *VCP*, *SQSTM1*, *TBK1*, *TIA1*, *TARDBP* and *OPTN*) and FTLD-UPS (*CHMP2B*)[5]. Although mutations in these genes only explain disease in ~3–5% of patients[5], research into the role of these genes in FTD contributed to the identification of key overarching pathways, including autophagy and proteasomal degradation, endolysosomal function, inflammation and immune system signalling[5]. Importantly, genome-wide association studies in international cohorts of patients with clinical FTD or those with FTLD-TDP identified a number of risk loci for FTD which are involved in the same pathways[51,64] including *RAB38* (encoding RAB38) and *CTSC* (encoding cathepsin C) implicated in vesicle trafficking and lysosomal function[64], two independent hits at the HLA locus involved in immunity[51,64], and *DPP6* (encoding dipeptidyl peptidase-like 6) and *UNC13A* (encoding unc-13 homologue A) involved in synaptic signalling and neuronal survival[51,65].

The genetic contribution to FTLD-FET is unclear. Mutations in *FUS* cause ALS but rarely FTD, and the consistent absence of a family history in patients with FTLD-FET suggests that FTLD-FET is not a single-gene disorder[39]. However, a more complex oligogenic inheritance could mask familial aggregation, or other mechanisms such as somatic mutations in the brain could be involved. Supporting evidence for the latter is the identification of somatic *TARDBP* mutations in brain tissue samples from two patients with FTLD-TDP type C (which is regarded as a sporadic disease)[66].

Mapping disease onset and progression

For most neurodegenerative disorders, disease begins within one or a small number of brain regions, referred to by some as epicentres[67], which show prominent atrophy at clinical presentation and have functional and anatomical connections to brain areas that degenerate in later stages of disease. These epicentres often contain a specialized neuron type that has heightened vulnerability to the early pathological process; for example, in ALS, the primary motor cortex, bulbar motor nuclei and spinal cord anterior horns contain upper or lower motor neurons, which show early vulnerability to TDP-43 pathobiology[68].

Each FTD syndrome is linked to a different set of canonical epicentres: the anterior cingulate and frontoinsular cortices in bvFTD, the inferomesial temporal poles in svPPA, the inferior frontal gyrus in nfvPPA, the peri-rolandic cortex in CBS, and the dorsal midbrain tegmentum in PSP-RS[67,69,70]. Individual patients may also have a small number of additional less common epicentres, and identifying these epicentres can improve prediction of future regional degeneration[71].

Early targeted neuron types in the FTD epicentres are largely unknown, with the exception of von Economo neurons and fork cells in bvFTD[72,73]. These morphologically specialized glutamatergic layer 5b projection neurons are being studied to understand the early pathophysiology of FTLD[33,74,75], similar to the long-standing focus on upper and lower motor neurons in ALS research[76]. For other FTD syndromes, additional research is needed to identify the most vulnerable neuron types within each syndrome's epicentres. Moreover, as each pathological subtype of FTLD can present as several FTD syndromes, research should seek to clarify how the same disease, even when caused by the same genetic mutation, can target different cell types and epicentres across individuals.

Multiple mechanisms may contribute to FTLD progression. Progression may reflect staggered onset of FTLD pathological changes within anatomically distributed neurons that share some core cell autonomous vulnerability factor(s). Protein misfolding may begin independently within neurons of the same type in response to a common genetic or environmental trigger that emerges with ageing. Less autonomously, healthy neurons in the epicentre may take up toxic, misfolded disease proteins after these proteins are released into the extracellular space from dying neurons[77]. This cell-to-cell, connectivity-independent mechanism could contribute to the local amplification that often characterizes early disease. Moreover, healthy neurons within or well beyond the epicentre may receive misfolded disease protein conformers via connectivity-dependent, trans-synaptic spreading[78–80]. According to this hypothesis, disease proteins act in a prion-like manner to induce proteins to adopt the disease-specific conformation which subsequently propagates exponentially down axons, across synapses and into the next neurons in the network[81]. This mechanism provides one plausible account for the network-based spatial progression observed in FTD, AD and other neurodegenerative disorders[69,82,83]. Other, not mutually exclusive, contributors to network-based degeneration may include chronic metabolic demands related to network-level inhibition–excitation imbalance[84] or intrinsic vulnerability factors (such as cell types and expressed genes) held in common among networked brain regions[85].

Diagnosis, screening and prevention

Radiological and laboratory studies useful in diagnosing FTD are often invasive and costly. Accordingly, the availability of a battery of relatively inexpensive but informative tools that can screen for FTD is useful as it can optimize the use of more expensive and invasive diagnostic tests. The most important and cost-effective tool is clinical examination. Clinical examination for suspected FTD includes medical and family history, neurological examination with special attention to the cranial nerves and the motor system, and cognitive examination. Cognitive examination should assess several domains (Box 1).

One initial step in FTD diagnosis occurs after family history taking. Careful examination of patients with evidence of fFTLD often reveals a combination of language, behavioural and motor features that does not easily map onto clinical syndromes observed in sporadic FTD[8,86,87].

Results from genetic testing provide strong evidence for the underlying pathology. However, one important consideration is whether the patient and the patient's family want to know the results of genetic testing. If genetic testing has not been performed, the clinician and a genetic counsellor should discuss the benefits and risks of genetic testing with the patient and the patient's family. This discussion

Box 1

Cognitive examination for suspected FTD

A cognitive examination in patients with suspected frontotemporal dementia (FTD) should evaluate several aspects of cognition.

- Language: measures of object naming, conversational speech, single word and sentence comprehension, multi-syllable and sentence repetition, speech with attention to fluency and speech errors, reading site vocabulary words and writing
- Executive functioning: measures of planning, organization and working memory such as repeating lists of numbers in forward and reverse orders, naming as many words as possible in one minute beginning with a target letter (for example, 'F') and digit–symbol substitution
- Social cognition: including measures of Theory of Mind, empathy and perspective-taking, mental flexibility, apathy, insight, and emotional recognition and understanding (brief versions of most of these measures remain to be developed, and supplemental neuropsychological evaluation may be required)
- Visual perceptual–spatial functioning: such as copying a figure and judging the angle of a line
- Episodic memory: including measures of verbal and visual learning
- Attention: such as raising a hand every time the letter 'A' is heard in a sequence of letters presented over 1–2 min

should include consideration that a small percentage of patients with FTD may have a de novo repeat expansion of *C9orf72*, important to consider in patients without a family history since testing could therefore provide a more definitive diagnosis with implications for other living family members[7]. Continuing discovery of rare mutations implicated in a clinical diagnosis of FTD have prompted many clinicians to screen all patients with FTD for all mutations, but practice continues to evolve in this area.

In sporadic disease, some clinical syndromes are commonly associated with a specific form of pathology (Fig. 1). The next important step in clinical diagnosis is therefore to distinguish between patients with a variant of PPA compared and patients with predominantly bvFTD, CBS or PSP-RS.

Clinical syndromes associated with FTD

bvFTD. The phenotype of bvFTD varies between patients, but there are core diagnostic features common to most presentations[9]. Consensus criteria for bvFTD outline early deficits in several domains of social functioning and personality: disinhibition and difficulty controlling impulses to engage in socially inappropriate statements or actions; apathy and reduced initiative; loss of sympathy and/or empathy; perseverative and compulsive or ritualistic behaviour including development of unusual religious and political beliefs; and hyperoral behaviour such as eating despite feeling sated and eating non-edibles. Clinical judgement of these features is particularly important because most measures of social cognition, while targeting key clinical features and aiming to offer important insights, may yield inconsistent results from clinic to clinic or have not been well validated in autopsy studies[88,89]. Patients might show only a limited number of features or mild symptoms, but unusual behaviour relative to their baseline may raise suspicion of a prodromal form of bvFTD[90]. Many patients with bvFTD also have deficits in executive function such as poor planning and organization, difficulty multi-tasking, limited judgement, and reduced insight[91–93]. Psychiatric features, such as psychosis and delusions, have been reported in patients with an identified fFTLD mutation[94,95] but can also be seen in those with sporadic bvFTD. Despite some important associations, a specific pattern of behaviour and personality change in patients with bvFTD has not been strongly associated with a specific pathology[96].

PPA. The most prominent feature of PPA is language dysfunction. Recommended criteria for the diagnosis of each PPA variant are available[10] and have largely stood the test of time, although there are some ambiguities that can result in diagnostic differences between centres[97–99].

Patients with svPPA have prominent difficulty with naming and comprehension of single words[100]. The use of content words (referring to an object or action) in speech is often substantially diminished at diagnosis[101] and the use of content words in comprehension and expression continues to decline over time[102]. Some clinicians have argued that patients with svPPA have a "reversal of the concreteness effect" whereby they have superior comprehension and expression of abstract words such as 'dream' or 'belief' relative to concrete words such as 'tiger' or 'apple', which has been attributed to disease in the most anterior portions of the visual processing stream in the temporal lobe, which associates visual percepts with meaning[103,104]. Patients with svPPA also show increased use of pronouns such as 'he' and deictic words with a vague reference such as 'this' that carry vague or partial meaning[101]. Of note, these language difficulties occur in oral and written communication, and therefore they cannot be attributed to a limitation of a peripheral sensory–motor system. Speech is otherwise fluent and prosodically appropriate.

Patients with svPPA might also show impaired episodic memory owing to their difficulty processing single words during verbal memory testing, but svPPA can be differentiated from amnestic AD by the demonstration of relatively good visual episodic memory in patients with svPPA. Many patients with svPPA have difficulty reading and spelling sight vocabulary words such as 'once' and 'yacht'[105]. svPPA is characteristically associated with left anterior temporal lobe atrophy. A related semantic behavioural variant of FTD, anchored in the right anterior temporal lobe, has recently been described in a large cohort[106]. Core features include loss of empathy, loss of person-specific semantic memory, and non-verbal semantic impairments such as recognizing and interpreting facial expression. These patients also may demonstrate characteristic changes in behaviour and personality such as the development of complex rituals, changes in religious and/or political beliefs, and compulsive behaviour and reduced mental flexibility. Many of these features may also emerge as left anterior temporal svPPA progresses. Sporadic svPPA is frequently associated with FTLD-TDP type C pathology[107–109].

Patients with nfvPPA have slowed, effortful speech, and fluency is substantially diminished[110]. One potential cause of slowed, effortful speech is the degradation of the grammatical system that is used to relate series of words in a sentence. Sentential syntax is typically simplified in patients with nfvPPA, often accompanied by frank grammatical errors[111], and reduced fluency and grammatical difficulties progress over time[112]. Grammatical deficits are difficult to attribute to a sensory–motor abnormality, as patients with nfvPPA typically have similar deficits in comprehension, reading and writing[113]. Nevertheless, comprehension and expression of single words is largely preserved in those with nfvPPA[114,115]. Another cause of non-fluent speech is the production of speech errors known as apraxia of speech (AOS), and a disorder known as primary progressive AOS (PPAOS) has been described[116,117]. Clinical features of PPAOS include sounds substituted for target speech sounds and pauses in the speech stream in unexpected places in a sentence and even within a word. This has been attributed to degradation of the motor speech planning system. nfvPPA, including PPAOS, is often associated with FTLD-tau pathology[114,115].

Presentations related to motor impairment. In all patients with suspected FTD, performing a neurological examination is important to look for a motor disorder[118]. PSP-RS is characterized by frequent falls and problems with ocular motility, and it is associated with extrapyramidal features such as axial rigidity, gait instability, involuntary tremor and dystonia. Patients with PSP-RS can also have deficits in behaviour and planning, with prominent impairment in impulse control. PSP-RS can be heterogeneous in presentation and is a marker of FTLD-tau pathology in up to 90% of patients[119,120]. CBS typically presents as a lateralized extrapyramidal disorder involving limb rigidity, limb apraxia, dystonia, a coarse tremor and gait instability. Most patients with CBS have tau pathology although up to 30% of patients with CBS have underlying AD[121,122]. Of note, nfvPPA and PPAOS can co-occur with PSP-RS or CBS and may be an early marker of underlying PSP or CBD pathology[118,123].

Another motor presentation of FTD may feature bulbar and/or limb weakness with muscle atrophy and fasciculations. This presentation is consistent with a diagnosis of ALS or motor neuron disease (MND), referred to as FTD-ALS or FTD-MND when patients also have features of FTD[88,89,124–127]. bvFTD- or PPA-like features can occur after

the onset of ALS, but the severity may be attenuated, and in some cases bvFTD or PPA can precede ALS[124]. FTD-ALS is associated with FTLD-TDP pathology in >90% of patients[128,129].

Imaging biomarkers

Neuroimaging is a key component of the diagnostic work-up of patients with FTD, and each FTD syndrome is associated with abnormalities in specific brain regions, mostly found within the frontal, temporal and insular lobes (Fig. 5). These abnormalities can be seen as atrophy on MRI and hypometabolism on [^{18}F]fluorodeoxyglucose (FDG) PET.

Patients with bvFTD typically show bilateral atrophy and hypometabolism in the prefrontal and anterior temporal lobes on MRI and FDG PET, with reduced structural and functional connectivity observed within and between frontotemporal regions[126,130]. Findings from neuroimaging are heterogeneous between patients, although several brain regions seem to be almost universally involved, including the anterior cingulate, anterior insula, orbital and medial frontal lobe and temporal pole, consistent with the concept of an epicentre. Degeneration of basal and limbic networks is a core feature of bvFTD[126,131]. Similar, although milder, degeneration and reduced connectivity, together with additional degeneration and reduced connectivity in the motor cortex are observed in patients with FTD-ALS[125,126,132]. Of note, the presence of frontal and anterior temporal degeneration aids in the differential diagnosis of sporadic bvFTD from AD, as AD involves posterior regions of the brain, and has prognostic value in predicting the rate of progression in patients with bvFTD[133,134].

In contrast to bvFTD, degeneration and reduced connectivity in svPPA affects the left anteromedial temporal lobe (Fig. 5), with degeneration gradually spreading posteriorly within the left anteromedial temporal regions[135] and to the right temporal lobes, insula and orbitofrontal cortex[136]. svPPA is associated with greater left temporal atrophy and a greater anterior–posterior gradient of hippocampal atrophy than in AD[135]. Patients with nfvPPA show most prominent atrophy and hypometabolism in the left posterior–inferior frontal regions, including Broca's area (relating to agrammatism) and the superior premotor cortex (relating to AOS) (Fig. 5), with degeneration spreading into the prefrontal cortex and basal ganglia and posteriorly into the motor cortex over time[136,137]. Disruption in brain connectivity is observed within the frontal lobes in nfvPPA[130]. Patients with PPAOS can also show accentuated involvement of the superior premotor cortex (Fig. 5), with reduced connectivity and degeneration typically spreading into Broca's area if agrammatism develops later in the disease[138]. Patients with CBS show asymmetric atrophy and hypometabolism of the posterior frontal and anterior parietal (that is, the peri-Rolandic) lobes, in addition to involvement of the basal ganglia[139] (Fig. 5). The frontal lobes can show mild atrophy and hypometabolism in PSP-RS, although the dominant features include atrophy and disrupted connectivity between regions along the dentatorubrothalamic tract, including the midbrain and superior cerebellar peduncle[140] (Fig. 5). Individuals with FTD-ALS can show some atrophy in the motor system extending into the frontal cortex, but it is often difficult to capture because of the rapid rate of progression[141]. Converging evidence suggests that the patterns of regional spread in these FTD syndromes is related to brain functional connectivity whereby disease spreads from epicentres through highly connected brain regions[71,78,79].

Genetic mutations that cause FTD are associated with characteristic patterns of degeneration. People with *MAPT* mutations show predominant anterior temporal lobe degeneration, although this varies according to the specific mutation; those with *GRN* mutations show asymmetric temporoparietal and frontal degeneration with rapid rates of atrophy; and those with *C9orf72* mutations show widespread patterns of degeneration with unique involvement of the occipital lobes, cerebellum and thalamus[142]. Hence, genetic mutations

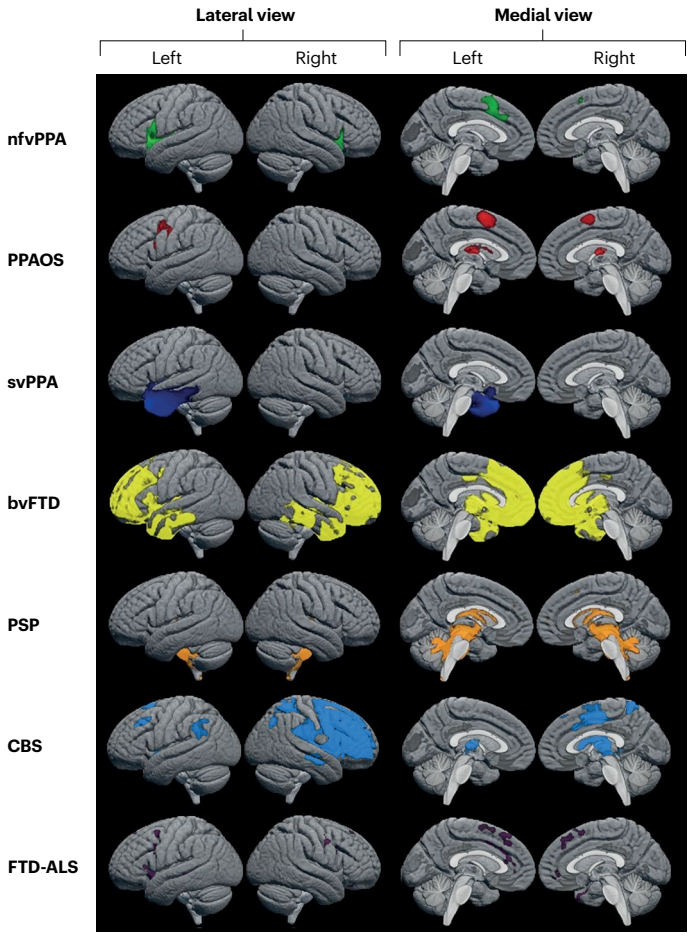

Fig. 5 | Characteristic patterns of neurodegeneration in different FTD syndromes. Group-level differences in brain volume loss for each syndrome of frontotemporal dementia (FTD) compared with healthy controls. Non-fluent/agrammatic variant primary progressive aphasia (nfvPPA) is typically associated with abnormalities in Broca's area in the left hemisphere, although left middle and superior premotor cortex and homologous regions in the right hemisphere can become involved with disease progression. Primary progressive apraxia of speech (PPAOS) is typically associated with abnormalities in the lateral superior premotor cortex and supplementary motor cortex, often bilaterally. Semantic variant PPA (svPPA) is typically associated with abnormalities in the left anteromedial temporal lobe, with spread into the right anteromedial temporal lobe and left orbitofrontal cortex with progression. Behavioural variant FTD (bvFTD) is typically associated with bilateral abnormalities in the prefrontal cortex, insula and anterior temporal lobes. Progressive supranuclear palsy (PSP) is typically associated with atrophy of regions along the dentatorubrothalamic white matter tract, running from the dentate nucleus of the cerebellum, through the superior cerebellar peduncle to the midbrain and then the thalamus. Mild involvement of the frontal lobe can be observed. Corticobasal syndrome (CBS) is typically associated with asymmetric abnormalities in the frontoparietal lobes. FTD–amyotrophic lateral sclerosis (FTD-ALS) is typically associated with mild abnormalities in the frontal lobe.

alter the patterns of neurodegeneration typically associated with sporadic bvFTD and ALS[143]. Grey matter atrophy and degeneration of specific white matter tracts can be observed many years before symptom onset in patients with fFTLD[144,145]. Presymptomatic changes in the temporal lobe and uncinate fasciculus are observed in *MAPT* carriers[146–148], changes in the frontoparietal lobes and internal capsule are observed in *GRN* carriers[146,147], and changes in the cerebellum, thalamus and posteriorly located white matter tracts are observed in *C9orf72* carriers[146–148]. White matter degeneration seems to precede atrophy, at least in *GRN* carriers[149]. Moreover, assessments of brain atrophy may have value in predicting the development of symptomatic illness in individuals with fFTLD[150,151]. Hypometabolism on FDG PET also offers a promising imaging marker to detect changes at the preclinical stage in fFTLD, with a suggestion that changes in metabolism precede atrophy in *GRN* carriers[152]. Changes in functional connectivity in the brain have also been observed in presymptomatic fFTLD[153,154], although more work is needed to determine the diagnostic use of these changes.

Predicting underlying pathology in patients with FTD is a key diagnostic issue and one in which neuroimaging is potentially informative. Patterns of degeneration differ across the common pathologies that underlie FTD. For example, in nfvPPA and PPAOS, rapid cortical degeneration is associated with CBD pathology, whereas midbrain atrophy is associated with PSP pathology[138]. In general, patients with FTLD 4R tauopathies show greater white matter degeneration than those with FTLD-TDP[4,114]. Molecular PET ligands that can detect tau proteins in the brain show excellent utility for detecting aggregates that contain both 3R and 4R tau, and strong uptake of these ligands is observed in patients with specific *MAPT* mutations that are characterized by such aggregates, even presymptomatically[155,156]. However, the value of the currently available tau PET ligands is less certain in FTLD-tau subtypes containing 3R or 4R tau (but not both); more work is needed to develop ligands that specifically bind to these tauopathies.

Fluid-based biomarkers

Diagnostic biomarkers. Biomarkers for AD can be used to differentiate between AD and FTD. High cerebrospinal fluid (CSF) concentrations of total tau (t-tau) and phosphorylated tau (P-tau) are generally associated with AD, and tau-associated FTD subtypes do not show elevated CSF tau concentrations[157,158]. Elevated CSF P-tau levels (at residues 181 or 217, the typical P-tau epitopes measured in AD) are probably a function of mixed 3R/4R tau accumulation typical of AD but are also seen in rare R406W *MAPT* mutations[159]. Elevated t-tau has also been variably identified in *GRN* mutation carriers[160,161]. Amyloid pathology does not occur in most forms of FTD; therefore, CSF β-amyloid 1–42 (Aβ42) concentrations and the ratio of 42 to 40 amino acid long Aβ in the CSF (CSF Aβ42/Aβ40) are typically normal in FTD[158,162]. Consequently, a high ratio of t-tau or P-tau 181 to Aβ42 is an AD-specific finding that separates AD from FTD with high diagnostic accuracy[163]. Similarly, these biomarkers can be used to identify patients with frontal lobe dysfunction due to AD pathology rather than FTLD[163,164]. Moreover, the logopenic variant of PPA (lvPPA, usually associated with AD pathology) is often associated with elevated CSF tau levels and reduced CSF Aβ42/Aβ40 (ref. 165).

Several studies have demonstrated that the CSF concentration of neurofilament light (NfL), a general marker of neurodegeneration, is high in patients with FTD[166], including those with autopsy-confirmed FTLD[164,167]. High CSF NfL levels combined with negative AD biomarkers is suggestive of a non-AD neurodegenerative disease (including FTLD) and a non-psychiatric disorder[168,169].

Blood-based ultrasensitive tests for AD-related pathologies and neurodegeneration have been rapidly developed over the past few years. Plasma concentrations of P-tau181, P-tau217 and P-tau231 are increased in patients with AD, but not in those with FTD, compared with the concentrations in cognitively normal controls, with almost a 100% differentiation between those with AD and FTLD[170–173]. Similar to the findings in CSF, blood NfL concentrations are increased in patients with FTD compared with those with AD[174–176], although blood NfL levels have limited performance for discriminating FTD from other neurodegenerative diseases[177,178]. Blood NfL levels discriminate FTD from primary psychiatric disorders with high diagnostic accuracy[179,180]. Moreover, blood NfL levels are a reliable biomarker of phenoconversion of presymptomatic to symptomatic genetic FTD; blood NfL levels are used regularly for this purpose in Sweden, Germany and France, and increasingly in the USA[181,182].

Biomarkers of specific FTD-related proteinopathies (TDP-43, tau and FET family proteins) are needed to enable the development of drugs targeting specific FTLD pathologies. One study suggested that FTLD-tau and FTLD-TDP can be discriminated using the ratio of plasma glial fibrillary acidic protein (GFAP) to NfL[183], a finding that requires replication in other samples. Moreover, CSF and blood tau biomarkers seem to reflect an Aβ-driven increase in neuronal tau phosphorylation and secretion[184–186] and are, therefore, normal in those with Aβ-negative FTD. Fluid biomarkers of FTLD-tau pathology are not available and are important future research avenues.

Although methods are emerging to measure TDP-43 in CSF and plasma, available assays cannot differentiate between normal and pathological TDP-43 or discriminate between patients with FTD and controls[187]. A pilot study using a real-time quaking-induced conversion assay to detect seeds of misfolded TDP-43 in lumbar CSF showed higher TDP-43 seed prevalence of positivity in patients with FTD or ALS than in controls[188]. No biomarkers of FTLD-FET pathology are available.

Prognostic biomarkers

Several studies have indicated that NfL concentrations in CSF and blood reflect disease intensity and predict clinical progression of FTD[174,175,181,189–192]. Longitudinal analysis of CSF NfL concentrations demonstrated that NfL levels are stably increased in symptomatic FTD without clear longitudinal changes[190]. One recent study suggested that increased serum NfL concentration and rate of change can identify people with presymptomatic FTD mutations who are close to converting to symptomatic disease[182], and a large longitudinal study of genetic FTD showed that increasing NfL levels in blood can identify people with mutations approaching symptom onset and capture rates of brain atrophy[193]. NfL levels might be an important inclusion criterion in clinical trials of novel disease-modifying drug candidates and might provide valuable information regarding treatment efficacy. However, the challenge with this potential use of blood NfL levels is to determine the underlying cause of the increase and exclude other potential causes, including head trauma, stroke and peripheral nerve injury, before diagnosing onset of neurodegeneration in presymptomatic mutation carriers.

Other biomarkers

Reduced CSF and blood progranulin concentrations have been found in *GRN* mutation carriers with almost 100% diagnostic accuracy[161,194,195]. Disease-modifying treatments aimed at restoring progranulin deficits in mutation carriers can be monitored using this marker. In individuals with the *C9orf72* expansion, poly(GP), one of the DPR proteins produced

by the expansion, is increased in carriers even at the presymptomatic stage[196–199]. This marker should be useful as a pharmacodynamic biomarker in gene silencing studies.

As CSF and blood NfL levels are markers of the intensity of neurodegeneration, a successful disease-modifying treatment for FTD should reduce the concentrations of these markers or flatten their increase over time. Indeed, successful treatment of spinal muscular atrophy and multiple sclerosis results in clear reductions in NfL levels within 6–12 months[200].

Management

Non-medication treatments

The most-used non-medical treatments for FTD are behavioural therapies, such as speech and language therapy for PPA[201] or cognitive rehabilitation for bvFTD[202,203]. In addition, family members and helpers can encourage activities, such as music, dancing, art and computer games, to reduce agitation and improve quality of life (QOL), reduce the rate of decline in cognition[204], and provide alternatives to obsessive–compulsive behaviours (such as popping bubble wrap rather than pulling out hair)[205].

Studies have aimed to augment behavioural rehabilitation with non-invasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both rTMS and tDCS involve invoking non-painful stimulation over the skull to reduce or enhance brain activity. The basis of these approaches is borrowed from post-stroke recovery, which involves reorganization of brain networks that underlie specific functions by recruiting healthy brain areas to 'take over' functions of the lesioned areas or to reduce suppression of preserved brain areas by diseased areas. Although FTD is progressive, brain dysfunction is focal initially, so that healthier areas might be recruited into damaged networks to restore function, at least temporarily[206].

Most trials of non-invasive stimulation in patients with FTD have been small, and results have not always been consistent. However, one meta-analysis of 22 studies revealed a significant, heterogeneous and moderate effect of tDCS and rTMS in language improvement in PPA at least 1 to 2 months after treatment[207]. The main effects were improved naming, largely driven by tDCS. However, larger randomized controlled trials (RCTs) are required to identify the optimal parameters (such as modality, frequency of rTMS and site of stimulation), duration of treatment and candidates most likely to benefit.

Repetitive transcranial magnetic stimulation. Small (n = 6–20) crossover RCTs have been carried out to determine the effects of high-frequency rTMS on spontaneous speech (word count)[208], object and action naming[203], and verbal fluency[209] in patients with FTD. Secondary outcomes of these trials include changes in other language tasks, global cognition, neuropsychiatric symptoms and brain metabolism using FDG PET[208–210]. Some trials determined the target for active rTMS during a pretreatment phase (personalized approach)[208], whereas other trials evaluated the same target in all participants (such as right and left dorsolateral prefrontal cortices[210], or the left prefrontal cortex[209]). All used high-frequency rTMS which stimulates firing of neurons.

Transcranial direct current stimulation. One recent meta-analysis of studies of tDCS for language improvement in patients with PPA reported an effect size of 0.82 (95% CI 0.16–1.47), which is considered a 'large effect' and was statistically significant[211]. Another meta-analysis revealed improvements in oral naming of untrained items and written naming for both trained and untrained items in patients with PPA who received tDCS combined with language therapy[212].

Most studies of tDCS have used anodal (facilitatory) tDCS over the left hemisphere in combination with language intervention. One study of tDCS or sham over the left dorsolateral frontal cortex for 25 min per work day for 2 weeks (ten sessions), combined with individualized speech and language therapy, showed significant improvement in naming accuracy and daily living language abilities in patients with PPA who received tDCS plus speech and language therapy[212].

Another crossover RCT found greater gains in naming treated words in individuals with PPA who received 15 daily sessions of anodal tDCS accompanied by written naming therapy designed to improve written naming of objects, with different benefits observed in patients with nfvPPA and lvPPA[213]. Moreover, this study also found a generalization to untreated words that was maintained 2 months later only in patients who had received tDCS. However, there were no effects of tDCS over sham in individuals with svPPA. Follow-up studies demonstrated that volume of specific brain regions[214], white matter integrity[215] and baseline language and cognitive performance[214] could predict better responses to anodal tDCS plus written naming therapy. Further studies showed that tDCS in combination with written naming therapy resulted in changes in the language network on resting state functional MRI[216] and reductions in GABA in targeted regions[217].

Pharmacological management

Approved symptomatic therapies for AD (memantine and cholinesterase inhibitors) are not efficacious in FTD[218–220], but several other pharmacological options can help manage FTD symptoms.

Selective serotonin reuptake inhibitors (SSRIs) are the most-used pharmacological therapies in patients with FTD and have been shown to curb depression, irritability, disinhibition, dietary changes and compulsiveness in case studies and small open label trials in patients with bvFTD and PPA[221–224]. In a placebo-controlled crossover trial in ten patients with bvFTD, trazodone (a serotonin receptor antagonist and SSRI) significantly improved multiple neuropsychiatric and behavioural symptoms but was not consistently well tolerated[225]. More specific SSRIs that have favourable tolerability profiles (such as sertraline, citalopram and escitalopram) are typically preferred in clinical practice compared with medications with off-target effects, including anticholinergic effects[221,226].

Antipsychotics are occasionally used for treatment of severe agitation and disinhibition but their use is supported only by a small body of evidence from case studies and open label trials in patients with FTD[221,222]. The use of antipsychotics is also limited by their black box warning for increased mortality and their extrapyramidal side effects (EPS), which is a particular risk in FTD[227]. Atypical antipsychotics with low dopamine D_2 receptor affinity (such as quetiapine) tend to be more commonly used owing to their lower rate of EPS[228]. One atypical antipsychotic with a very low risk of EPS, pimavanserin (a novel serotonin 5-HT_{2A} receptor inverse agonist and antagonist), seemed to have a high efficacy in managing psychosis in a phase III randomized placebo-controlled trial in patients with dementia with a range of aetiologies[229]. However, this trial produced only limited long-term efficacy and safety data and included only seven patients with FTD (of whom only three were enrolled in the randomized portion of the trial).

Anticonvulsants have also been evaluated for behavioural management in patients with FTD but, similar to antipsychotics, the use of anticonvulsants is limited by a paucity of data and often unfavourable

tolerability profiles. Only a few case studies have investigated the use of valproate for the management of agitation and hypersexuality[221,230], carbamazepine for the management of hypersexuality[231], and nimodipine for the management of compulsive eating[232–235] in patients with FTD.

Other less commonly used pharmacological therapies for FTD include dextromethorphan (which improved apathy and disinhibition in one study)[236] and stimulants (of which methylphenidate reduced risk-taking in a novel testing paradigm)[237]. In the future, symptomatic therapies might also include oxytocin, which may improve social interest in FTD[238] although this drug is still being investigated in an RCT in patients with FTD (NCT03260920) and has yet to enter clinical use.

Clinical trial development in FTLD-tau

No disease-modifying therapies for FTLD are available; however, several clinical trials on FTLD-tau have been carried out. The largest completed trial for FTLD-tau (a negative phase III trial of a methylthioninium chloride formulation) enrolled a pathologically heterogeneous cohort of patients with bvFTD (NCT03446001); however, most drug development programmes emphasize focus on specific groups of patients in whom the underlying FTLD pathology can be predicted during life. Specifically, many trials have targeted tauopathy in patients with PSP-RS, a syndrome that strongly predicts FTLD-tau at autopsy[239]. However, trials of drugs intended to stabilize microtubules (davunetide[240] and abeotaxane[241]), limit tau phosphorylation via glycogen synthase kinases (tideglusib)[242] and limit pathogenetic tau acetylation (salsalate)[243] have yielded negative results in patients with PSP-RS.

A small trial of plasma infusions from young healthy donors also yielded negative results in PSP-RS[243]. Moreover, passive immunization against the amino-terminal tau epitopes did not slow disease progression in patients with PSP-RS in well-powered phase II trials (NCT03413319, NCT03068468). Of note, some pathogenetic forms of tau may be truncated at the N terminus[244]. Additionally, subtypes of FTLD tau (3R and 4R tau-predominant subtypes) are defined by relative abundance of isoforms containing three or four microtubule binding domain repeats. Thus, future successful passive and active immunization strategies may target alternative tau species, including regions closer to the microtubule binding domain. For example, antibodies targeting the mid-domain of tau (JNJ-63733657) and tau phosphorylated at amino acid 217 (JNJ-63733657) are under investigation in AD (NCT04619420 and NCT04867616) and may warrant future investigation in FTLD-tau. Results from a trial studying the use of a vaccine against the 294–305 region of four-repeat tau (ADDvac1) in patients with nfvPPA are pending (NCT03174886).

Ongoing clinical development programmes for FTLD-tau are harnessing other strategies, including suppression of tau expression via antisense oligonucleotides (ASOs) such as NIO752 (NCT04539041) and alteration of tau autophagy and phosphorylation via rho-kinase inhibitors such as fasudil (NCT04734379). Other trials are targeting the suppression of downstream pathological dysregulation of retro-transposable elements via the reverse transcriptase inhibitor TPN-101 (NCT04993768).

Clinical trial development in FTLD-TDP

Autosomal dominant mutations have been a primary focus for the development of drugs for FTLD-TDP, largely owing to the homogeneity of pathophysiology within each fFTLD cohort. Several ongoing trials have enrolled individuals with pathogenetic *GRN* mutations, in whom CSF progranulin concentrations provide a rational pharmacodynamic measure for drugs that might rescue *GRN* haploinsufficiency. In previous clinical trials, nimodipine and FRM-0334 (which upregulated progranulin in preclinical models) did not affect extracellular progranulin levels[160,245]; however, passive immunization with AL001 (a monoclonal antibody targeting the sortilin receptor, which shuttles progranulin to the lysosome)[246] seemed to normalize plasma and CSF progranulin in patients with *GRN* haploinsufficiency. A phase III study of AL001 is ongoing in symptomatic and asymptomatic individuals with *GRN* haploinsufficiency (NCT04374136). Several other plausible mechanisms to increase CNS progranulin levels are also under investigation, including *GRN* gene therapy (PR006 and PBFT02) using adenovirus vectors (NCT04408625 and NCT04747431) and peripheral delivery of progranulin fused to a human transferrin receptor (DNL539)[247].

Much of the focus in the development of drugs for pathogenetic *C9orf72* expansion has been on intrathecal ASO strategies that are intended to decrease expanded transcripts and DPR proteins translated from the hexanucleotide expansion. Proof of concept for suppression of CSF DPRs has been observed in a single patient with *C9orf72* expansion-related ALS treated with afinersen[248]. A mechanistically similar ASO (BIIB078) is also being investigated in patients with ALS and FTD (NCT04931862) due to *C9orf72* expansion. A recent phase IIa pilot study of the PIKFYVE kinase inhibitor, AIT-101 (apilimod dimesylate), in *C9orf72* expansion-related ALS demonstrated reduction in CSF DPR concentrations[249]. Other diverse clinical trials in those with *C9orf72* expansions are investigating the use of metformin to reduce DPR expression (NCT04220021), AL001 to boost progranulin (NCT03987295) and a reverse transcriptase inhibitor to reduce downstream dysregulation of retro-transposable elements (NCT04993755).

Few trials have enrolled patients with sporadic FTLD-TDP owing to the challenge of antemortem diagnosis. However, as svPPA is due to FTLD-TDP pathology in 80% of patients[108], this syndrome may be a growing focus in future trials. The first of such trials (NCT05184569) is investigating verdiperstat, a myeloperoxidase inhibitor intended to limit glial-derived oxidative stress, in patients with svPPA, and may serve as a template for other trails in sporadic FTLD-TDP.

Quality of life

The QOL of individuals diagnosed with FTD and their immediate family members — most frequently the primary informal care providers — is commonly affected. Reduced QOL relates to deterioration in multiple domains, including behaviour, cognition, language, and motor and social–emotional functioning, that vary in combination, severity and progression[250]. Although an overall definition of what constitutes QOL varies, cognitive function, activities of daily living capacity, psychological wellbeing and social integration are domains that are generally taken into consideration when estimating QOL in dementia. The integrity of these dimensions can be captured by combining results from specific tests or using global instruments such as the QOL in AD[251].

Changes in cognition observed in the main subtypes of FTD, such as executive function, language and memory, are likely to affect the QOL of patients as they progressively interfere with many aspects of activities of daily living. Disturbances of socioemotional engagement and regulation, which affect interpersonal relationships, decreased sleep quality, and disturbances in movement coordination and motor control, may also directly or indirectly interfere with functional capacity[252,253]. Progressive reduction in motor control is particularly relevant in patients with FTD-ALS experiencing swallowing difficulty, or those with FTD presenting with motor disorders (such as CBS or PSP). Finally, some patients have psychiatric symptoms, such as depression, anxiety and delusions, the last of which is more frequently observed

in individuals carrying a *C9orf72* hexanucleotide repeat expansion[254]. Apathy is also common in patients with FTD but is most frequently observed in those with bvFTD and is characterized by difficulty in engaging in, and sustaining, activities[255]. Notably, changes in emotional disturbance and apathy in patients with FTD are the features that are most related to increased burden of care, increased depression, stress and anxiety, and reduced QOL in the carers of individuals with FTD[256–259].

Deteriorating QOL and associated burden of care remain major predictors of transition to supported accommodation and nursing home placement in patients with dementia[260]. Few institutions are specialized in management of younger, physically healthy individuals with FTD who tend to present with marked behavioural changes. However, the effects of many clinical symptoms can be mitigated by individualized targeted interventions and can enhance QOL by improving functional capacity and reducing the need for neuroleptic or antipsychotic medications, which should remain the option of last resort. These practical interventions are the best approach for the management of FTD in the absence of disease-modifying treatments or cure.

Of note, most of the knowledge of the changes in QOL in patients with FTD and their families has come from studies in Western populations. Whether such approaches are relevant and applicable to family units from non-Western populations is not known. Indeed, understanding the effect of FTD on wellbeing and QOL, and management strategies in other populations with different social structures and in some instances limited health service support, is mostly lacking[261,262]. This will be one of the major challenges facing clinicians and researchers in the next decade.

The effects of the COVID-19 pandemic on QOL of patients with FTD and their families is also unknown. Increases in psychiatric features (depression, agitation and apathy) has been reported in patients with dementia following the introduction of lockdown measures, regardless of the type of dementia[263]. Moreover, increased stress and anxiety have also been reported in primary informal carers[264]. As discussed above, these changes are associated with decreased QOL. Whether this increase is more pronounced in patients with FTD and the long-term consequences of lockdown and associated social isolation on disease progression will only be known in upcoming years[265].

Outlook

Although the outlook for improved FTD diagnosis and treatment is highly positive, there is much work to be done. The two major goals of FTD research programmes are to develop a treatment for FTD and use findings from FTD to enhance our scientific knowledge of brain functioning in general.

Genetic studies of FTD have identified disease-causing mutations, and individuals with these mutations represent an important population for a disease-modifying treatment that can delay onset and slow progression of disease. Meaningful biomarkers have been identified for some of these mutations, which can be followed during treatment to gauge biological response[161,194,195]. Several targeted treatment trials in fFTLD are ongoing and additional studies are planned. However, treatment approaches for sporadic FTD are less advanced and additional work is needed before a successful treatment programme can be developed for sporadic FTD.

Although clinical measures are useful diagnostic tools that can screen patients inexpensively, developing tools with improved reliability and pathological diagnostic specificity would be valuable to determine eligibility for clinical trials and as biomarkers of clinical response during trials. One approach focuses on automated analyses of digitized speech samples, which has been evaluated in those with PPA[101,266] and bvFTD without obvious PPA or the presence of an obvious motor speech disorder[118,267,268], and for the identification of speech disorders that can be confidently attributed only to a motor speech impairment. Speech samples for automated analysis can be collected face-to-face or remotely with equal meaningfulness from patients with mild to severe impairment. Moreover, as speech is collected during natural conversation, there is less concern for the confounding role of learning effects associated with repeated administration of standard neuropsychological tasks. Similarly, owing to the automated analysis, differences across centres are less likely to emerge. Automated analysis of digitized speech may also be useful in screening for presymptomatic mutation carriers and clinical prediction of phenoconversion owing to its sensitivity to subtle speech changes.

Computer-based batteries of cognitive assessments are also being developed for use in individuals with FTLD, and could be useful for identification of changes and as outcome measures. Eye-tracking tasks using digitized measures obtained from wearables, and collection of autonomic variables, particularly during evaluation of individuals with bvFTD, also have the potential to quantitatively detect subtle social cognition and executive function deficits earlier than traditional paper-and-pencil tasks. For example, an eye-tracking paradigm can consist of an anti-saccade task and oculomotor capture (that is, to evaluate inhibition), predictive pursuit (that is, prediction), a spatial anticipation task (that is, rule shifting), self-paced eye movements (that is, apathy), basic and complex emotion recognition tasks (that is, Reading the Eyes in the Mind test), and a free viewing task for higher order social cognitive processes, and can also include collection of autonomic features (such as heart rate) to capture and follow baseline autonomic changes and responses to stimuli. Like digitized speech analyses, novel eye-tracking paradigms may detect early changes in those with fFTLD mutations and those with sporadic FTD and can differentiate FTD from other types of dementia such as atypical presentations of AD[269,270]. Online monitoring platforms of daily life changes in patients with FTD such as these speech, cognitive and ocular motility patterns might allow clinicians to initiate personalized treatment strategies tackling specific changes in behaviour and communication. These novel strategies will hopefully lead to fewer doctor visits, reduced work drop-out among partners, less frequent use of psychopharmacological drugs, and fewer acute hospital admissions.

New biofluid biomarkers are also under development to improve pathological diagnosis during life and to better predict disease progression. Improved sensitivity of recent technological advances, such as blood-based single-molecule array (SIMOA), proteomics[158,271–273], novel exosome analyses in CSF and blood[185,274–276], and evaluation of epigenetics[277–279], have allowed development of less-invasive biomarkers in blood and novel markers of disease. New blood biomarkers based on the ratio of NfL to GFAP show some promise in distinguishing sporadic FTD due to FTLD-tau from FTLD-TDP[183]. Innovative single-nucleus RNA expression studies in brains from individuals with sporadic FTD or fFTLD will lead to more insights and potentially the identification of new fluid biomarkers in CSF or blood. The value of such candidate biomarkers is being investigated in ongoing longitudinal and international studies in healthy and symptomatic carriers with FTD mutations and patients with sporadic FTD. Innovative techniques may also identify new insights into disease mechanisms. For example, one study using single-nucleus RNA sequencing in brain samples from individuals with *GRN* mutation-associated FTD identified disease-associated subtypes of astrocytes and endothelial cells, with enrichment of fibroblasts

and mesenchymal cell numbers[280]. The enriched expression of gene modules associated with blood–brain barrier dysfunction found in endothelial cells indicates that dysfunction of the neurovasculature may be another underlying pathophysiological process[280].

Available neuroimaging data collected in longitudinal studies in individuals with fFTLD and sporadic FTD will enable quantitative measurement of changes in grey matter volume. However, the harmonization of multisite diffusion-weighted images to evaluate changes in white matter volume is extremely challenging. New techniques for diffusion MRI (for example, with rotational invariant spherical harmonics features) could be used to optimize and validate postprocessing harmonization strategy of multishell acquisitions, with one site selected as reference. Other MRI sequences, such as arterial spin labelling[281–283] and spectroscopy[284–287], novel analyses encompassing data science network approaches[71,130,288,289], and MRI using powerful 7 T magnets[290] will improve sensitivity to changes in brain anatomy. High-resolution MRI at 7 T performed ex vivo are proving highly informative in FTD and ALS[290–292]. Moreover, molecular PET imaging has begun to target more specific pathological entities in the brain of patients with FTD[138,155,156], and novel radioligands will improve in vivo diagnosis and provide an important way to assess response during trials of disease-modifying treatments. Finally, cross-sectional and longitudinal optical coherence tomography could be used to identify autopsy-confirmed thinning of the outer retinal layer in patients with FTLD-tau compared with its thickness in controls and compared with the thickness of the inner retinal layer[293,294].

Developments in artificial intelligence and machine learning, such as the discriminative event-based model[149,295–297], have led to the availability of tools that can extract patterns from large-scale datasets of high-dimensional longitudinal measurements of multimodal biomarkers. In addition to group-wise staging based on a composite of considered data, these methods also estimate the probability that a biomarker is abnormal in each individual. Accounting for the timing of these changes relative to one another and applying them on an individual level will permit the prediction of disease onset, supporting accurate diagnosis in individuals with fFTLD and those with sporadic disease. Such multimodal tools are likely to improve early detection of disease and improve stratification within treatment trials to optimize timing for effective therapeutic interventions.

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Author contributions

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Competing interests

H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet

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[1]Department of Neurology and Penn Frontotemporal Degeneration Center, University of Pennsylvania, Philadelphia, PA, USA. [2]Departments of Neurology and Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA. [3]Department of Pathology, University of California, San Francisco, San Francisco, CA, USA. [4]Department of Neurology, Johns Hopkins University, Baltimore, MD, USA. [5]Department of Neurology, Mayo Clinic, Rochester, MN, USA. [6]School of Psychology and Brain and Mind Center, University of Sydney, Sydney, New South Wales, Australia. [7]VIB Center for Molecular Neurology, University of Antwerp, Antwerp, Belgium. [8]Department of Radiology, Mayo Clinic, Rochester, MN, USA. [9]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The University of Gothenburg, Mölndal, Sweden. [10]Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden. [11]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. [12]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK. [13]UK Dementia Research Institute at UCL, London, UK. [14]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China. [15]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA. [16]Department of Neurology, Erasmus University, Rotterdam, Netherlands. [17]Deceased: Murray Grossman.