FRONTOTEMPORAL DEGENERATION

Murray Grossman[1], William W. Seeley[2†], Adam Boxer[2], Argye E. Hillis[3], David Knopman[4], Peter Ljubenov[2], Bruce Miller[2], Olivier Piguet[5], Rosa Rademakers[6], Jennifer Whitwell[7], Henrik Zetterberg[8], John C. van Swieten[9]

[1]Department of Neurology and Penn Frontotemporal Degeneration Center, University of Pennsylvania,

[2]Department of Neurology and Memory and Aging Center, University of California, San Francisco,

[3]Department of Neurology, Johns Hopkins University

[4]Department of Neurology, Mayo Clinic, Rochester MN

[5]School of Psychology and Brain and Mind Center, University of Sydney,

[6]VIB Center for Molecular Neurology, University of Antwerp,

[7]Department of Radiology, Mayo Clinic, Rochester MN

[8] Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK; UK Dementia Research Institute at UCL, London, UK; Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China; and Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA

[9]Department of Neurology, Erasmus University

[†]email: bill.seeley@ucsf.edu

Author contributions

Introduction (M.G. and B.L.M.); Epidemiology (D.K.); Mechanisms/pathophysiology (W.S. and R.R.); Diagnosis, screening and prevention (M.G., J.L.W. and H.Z.); Management (A.L.B., A.E.H. and P.L.); Quality of life (O.P.); Outlook (M.G. and J.C.VS.); Overview of Primer (M.G.).

Competing interests

HZ has served at 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 Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). There is NO Other Competing Interest.

Acknowledgements

MG is supported by AG066597. JW is supported by R01-DC12519, R01-DC14942, R01-NS89757 and RF1-NS112153; O.P. is supported by a National Health and Medical Research Council of Australia Leadership Fellowship (GNT2008020). HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2022-01018 and #2019-02397), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, and Swedish State Support for Clinical Research (#ALFGBG-71320).

Abstract

Frontotemporal degeneration (FTD) is one of the most common causes of early age-of-onset dementia and is characterized by early social-emotional-behavioral and/or language changes that can be accompanied by a pyramidal or extrapyramidal motor disorder. About 20%-25% of individuals with FTD are estimated to carry a mutation associated with a specific FTD 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 FTD, the most common underlying pathological diagnoses are frontotemporal lobar degeneration (FTLD) owing to a tauopathy (FTLD-tau) or a TDP-43 proteinopathy (FTLD-TDP), although a 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 FTD have been elusive, which has impeded development of disease-modifying treatments for sporadic FTD. 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 promising results.

[H1] Introduction

Frontotemporal dementia (FTD) is among the most common clinical forms of early-onset neurodegenerative disease, but it is substantially understudied. FTD clinical syndromes include a disorder of social behavior and personality known as behavioral variant FTD (bvFTD) and impairments of speech and language known as primary progressive aphasia (PPA; Figure 1). bvFTD and PPA can present with or without an accompanying motor disorder. The scope of FTD is now thought to include individuals with extrapyramidal disorders such as progressive

supranuclear palsy (PSP) and corticobasal syndrome (CBS), and pyramidal disorders such as amyotrophic lateral sclerosis (ALS)

. Whilst these motor conditions seem to present with relatively distinct phenotypes, the pathology responsible for these conditions overlaps with the pathology associated with FTD.

Two forms of neuropathology account for ~95% of individuals with clinical FTD: frontotemporal lobar degeneration related to misfolded tau (FTLD-tau) and FTLD associated with TAR DNA-binding protein of ~43kD (FTLD-TDP) pathobiology[1]. A less common pathology is 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. 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 (Figure 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, it around 20% to 25% of patients with FTD carry a genetic mutation[3–5], and are referred to as having familial frontotemporal lobar degeneration (fFTLD). Most cases of genetic FTLD are familial, but up to 10% of cases with a *C9orf72* repeat expansion are found in patients with seemingly sporadic disease[6–8]. fFTLD represents 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 participate in 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 anatomic distribution of misfolded proteins in the brain at autopsy corresponds reasonably well to 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 treatments administered to presymptomatic cases may someday delay disease onset. At the same time, advances in treatments of FTD can lead to important scientific discoveries that can 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.

[H1] Epidemiology

[H2] Problems with epidemiological studies

Determining accurate estimates of the prevalence and incidence of FTD is challenging. Data on FTLD epidemiology is almost entirely from patients obtaining neurological diagnosis 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-counting of cases of FTD is a major concern. Misdiagnoses of Alzheimer's disease or a psychiatric illness are common. Moreover, over-estimating the prevalence and incidence of FTD could occur if persons with dysexecutive dementia who lack substantial language or behavioral disturbances are diagnosed with FTD[11,12] when at autopsy most of these patients will prove to have 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 [13,14]. Another source of variability in epidemiological data is whether patients with FTD who simultaneously exhibit the features of

PSP syndrome, CBS or ALS are diagnosed with FTD or instead with one of the motor syndromes.

[H2] Prevalence and age at onset

The prevalence of FTD peaks around 60-70 years of age (Figure 2). The prevalence of clinically diagnosed FTD syndromes (excluding PSP syndrome and CBS) is ~10-15 cases per 100,000 in 45-64 year olds[15] 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 [16–19]. Including PSP syndrome in the definition of FTD leads to incidence estimates of ~16 cases per 100,000 person-years in 65-74 year olds[19]. The prevalence of bvFTD and some PPA syndromes such as semantic variant PPA declines before 65 years of age, whereas PSP syndrome, CBS and non-fluent PPA often do not become symptomatic until after 65 years of age[16]. By contrast, the prevalence of clinically diagnosed AD dementia in those over 65 years is ~2-3 times higher, with an incidence of ~100 cases per 100,000 person-years[20].

Up to 37% of patients with FTD have a dominantly inherited form[3–5], although the proportion of patients with dominantly inherited FTD is highly variable by clinical site, with a median of 20-25% for proven mutation carriers. Dominantly inherited FTLD tends to manifest at an earlier age than sporadic FTLD[21]. In the largest international fFTLD series to date, the mean age at symptom onset was 49.5 years (SD 10.0) in those with *MAPT* mutations, 58.2 years (SD 9.8) in those with *C9orf72* repeat expansion, and 61.3 years (SD 8.8) in those with *GRN* mutations[21]. 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[21]. The correlation between familial age of onset and individual age of onset was strongest in persons with *MAPT* mutations and was more variable in persons with *GRN* mutations or the repeat expansion of *C9orf72*.

[H2] Survival

Survival of patients with FTLD varies according to clinical phenotype. In one meta-analysis[22], 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), non-fluent PPA (naPPA) syndromes (7.7 years) and semantic variant PPA (svPPA, 12.2 years). Of note, age and sex did not affect survival and education levels had a negligible effect on survival. Survival varies by genotype in persons with dominantly inherited FTLD[21]; 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[21], and as phenotype is associated with survival, between-genotype differences in survival may mainly reflect the distribution of clinical syndromes caused by each genotype.

[H2] Risk factors

Aside from age and family history, no other established risk factors for FTLD have been identified. Men and women are equally affected. In autopsy studies in the US, FTLD is very rare in Black individuals, although pathologically-defined AD is more common in Black people than in white people [23]. fFTLD is rarer in Asia than in Europe[24]. The frequency of the genetic subtypes of FTLD varies geographically[21] (Figure 3). Of note, lack of access to skilled diagnosticians in some countries or regions and concerns about variations in social norms between cultures likely contribute to the racial and geographic variations in FTD diagnosis and, therefore, reported prevalence.

[H1] 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 level. 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.

[H2] Key pathological molecules

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 (Figure 2). 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 with TAR DNA-binding protein of 43 kDa (TDP-43; FTLD-TDP), or FTLD-FET (with inclusions composed of the FET family of proteins FUS, Ewing sarcoma protein and TAF-15). Each major molecular class comprises several specific histopathological subtypes that are based on the morphology and distribution of the inclusions (Figure 3). 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[25].

[H3] 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[26–28]. Pick's disease is a 3-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[29]. By contrast, the diverse and subtype-specific neuronal and glial inclusions that occur in PSP, CBD and globular glial tauopathy (GGT) are all composed predominantly of 4-repeat (4R) tau[29] . Chronic traumatic encephalopathy (CTE) is often considered an acquired form of FTLD that is related to repetitive head trauma (usually in the context of contact sports participation), in which the pathology includes perivascular neurofibrillary tangles composed of 3R and 4R tau, prominent neuropil threads and tau astrogliopathy.

[H3] 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, least often, the nucleus[28]. Although these features most often occur together, some neurons may show isolated nuclear TDP-43 depletion associated with neuronal degeneration [30]. TDP-43 aggregation in glia, most often oligodendrocytes, varies within and between subtypes but is less prominent than aggregation in neurons[31]. FTLD-TDP can be divided into 3 major subtypes (A, B, and C) based on the morphology, subcellular localization and laminar distribution of the inclusions[31]. 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 Type FTLD-TDP B; and long, swollen dystrophic neurites in FTLD-TDP Type C [31]. 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 characterized by abundant granulofilamentous inclusions and more prominent fine grains and threads than Type B[32]; however, whether type E is a distinctive subtype or lies on a continuum

with Type B is uncertain. Ultrastructural studies like those used to distinguish FTLD-tau subtypes may soon help better disambiguate FTLD-TDP subtypes. 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 distinctive mechanisms that are beginning to emerge.

[H3] FTLD-FET and FTLD-FUS. FTLD-FET is linked to the FET family of RNA-binding proteins (FUS, EWS and TAF15). These proteins are normally found in the nucleus[33] although nuclear depletion of the aggregating protein is a less reliable feature of FTLD-FET than FTLD-TDP. FTLD-FET is usually sporadic[34] and subtypes are defined by the morphology and distribution of the neuronal cytoplasmic and nuclear inclusions. Subtypes include atypical FTLD with ubiquitin-positive inclusions (aFTLD-U), basophilic inclusion body disease (BIBD), and neuronal intermediate filament inclusion disease (NIFID)[35,36]. Patients with these subtypes have inclusions composed of all 3 FET family proteins[37], whereas patients with familial ALS or FTD due to *FUS* mutations have neuronal inclusions containing only FUS.

[H2] Genetic mechanisms

FTD is estimated to be a familial disease in about 20%-25% of cases, 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)[38], *GRN* (encoding progranulin)[39,40], and *C9orf72* (encoding chromosome 9 open reading frame 72; Table 1)[41,42]. Each gene is associated with a specific 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[43–46]. (Table 1)

MAPT was the first FTD gene to be identified, proving that tau aggregation and dysfunction alone are sufficient to cause neurodegeneration[38]. 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[47]. Missense *MAPT* mutations mostly affect microtubule binding domains, whereas splicing mutations alter the 4R to 3R tau isoform ratio[48]. 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[49,50]. Common genetic variation in two major *MAPT* haplotypes (H1 and H2) is associated with a significantly increased risk of sporadic tauopathies[51].

Pathogenic 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*[41,42]*. C9orf72* encodes a protein involved in regulation of endosomal trafficking and autophagy[52], 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 proteins translated in an unconventional fashion from the repeat RNA[8,53]. 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[54]. Although this hexanucleotide expansion is most often inherited, a minority of FTD patients with C9orf72 repeat expansions lack a family history but present with a clinical syndrome indistinguishable from the inherited form[8,53].

Heterozygous loss-of-function mutations in *GRN* are the second most common cause of inherited FTLD-TDP[39,40]. 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[55] suggested that lysosomal homeostasis might be disrupted in FTD[56]. 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[45,57].

In rare cases, other genes are associated with FTLD-TDP (such as *VCP*, *SQSTM1*, *TBK1*, *TARDBP* and *OPTN*) and FTLD-UPS (*CHMP2B*) [5]. Although mutations in these genes only explains 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 signaling [5]. Importantly, genome-wide association studies (GWAS) in international cohorts of patients with clinical FTD or those with FTLD-TDP identified a number of common gene variants tagging FTD risk loci which support the same pathways[45,58] such as *RAB38* (encoding RAB38) and *CTSC* (encoding Cathepsin C) implicated in vesicle trafficking and lysosomal function[58], two independent hits at the HLA locus involved in immunity[45,58], and *DPP6* (encoding dipeptidyl peptidase like 6) and *UNC13A* (encoding unc-13 homolog A) involved in synaptic signaling and neuronal survival[45,59].

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[34]. 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)[60].

[H2] 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 epicenters[61], which show prominent atrophy at clinical presentation and have functional and anatomical connections to brain areas that degenerate in later stages of disease. These epicenters 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[62].

Each FTD syndrome is linked to a different set of epicenters: the anterior cingulate and frontoinsular cortices in bvFTD, the inferomesial temporal poles in svPPA, the inferior frontal gyrus in naPPA, the peri-rolandic cortex in CBS, and the dorsal midbrain tegmentum in PSP-Richardson's Syndrome (PSP-RS)[61,63,64]. Individual patients may also have a small number of additional less common epicenters, and identifying these epicenters can improve prediction of future regional degeneration[65].

Early targeted neuron types in the FTD epicenters are largely unknown, with the exception of von Economo neurons (VEN) and fork cells in bvFTD[66,67]. These morphologically specialized glutamatergic Layer 5b projection neurons are being studied to understand the early pathophysiology of FTLD[30,68,69], similar to the long-standing focus on upper and lower motor neurons in ALS research[70]. For other FTD syndromes, additional research is needed to identify the most vulnerable neuron types within each syndrome's epicenters. 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 epicenters 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 aging. Less autonomously, healthy neurons in the epicenter may take up toxic, misfolded disease proteins after these proteins are released into the extracellular space from dying neurons[71]. 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 epicenter may receive misfolded disease protein conformers via connectivity-dependent, trans-synaptic spreading[72–74]. 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[75]. This mechanism provides one plausible account for the network-based spatial progression observed in FTD, AD, and other neurodegenerative disorders[63,76,77]. Other, not mutually exclusive, contributors to network-based degeneration may include chronic metabolic demands related to network-level inhibition/excitation imbalance[78] or intrinsic vulnerability factors (such as cell types and expressed genes) held in common among networked brain regions[79].

[H1] Diagnosis, screening and prevention

Radiologic 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 FTLD pathology is useful as it can optimize the use of more expensive and invasive diagnostic tests. The most important and cost-effective tool is probably 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 for fFTLD often reveals a combination of language, behavioral and motor features that does not easily map onto clinical syndromes observed in sporadic FTD[8,80,81].

Results from genetic testing provide strong evidence for the underlying pathology. However, one important consideration is whether the patient and their 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 their family. This discussion 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 FTD patients 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. The next important step in clinical diagnosis thus is to distinguish between patients with a variant of PPA compared to patients with predominantly bvFTD.

[H2] Clinical syndromes associated with FTD

[H3] 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 centers[82–84].

Patients with semantic variant PPA (svPPA) have prominent difficulty with naming and comprehension of single words[85]. The use of content words (referring to an object or action) in speech is often substantially diminished at diagnosis[86] and use of content words in comprehension and expression continues to decline over time [87]. 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 like “dream” or “belief” relative to concrete words like “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[88,89]. Patients with svPPA also show increased use of pronouns like “he” and deictic words with vague reference like “this” that carry vague or partial meaning[86]. Of note, these language difficulties occur in oral and written communication, 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, which 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” or “yacht”[90]. svPPA is characteristically associated with left anterior temporal lobe atrophy. A related semantic behavioral variant of FTD, anchored in the right anterior temporal lobe, has recently been described in a large cohort[91]. 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 change in behavior and personality such as the development of complex rituals changes in religious and/or political beliefs, and compulsive behavior 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[92–95].

Patients with non-fluent/agrammatic PPA (naPPA or nfvPPA) have slowed, effortful speech, and fluency is substantially diminished[96]. 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 naPPA, often accompanied by

frank grammatical errors[97], and reduced fluency and grammatical difficulties progress over time [98]. Grammatical deficits are difficult to attribute to a sensory-motor abnormality, as patients with naPPA typically have similar deficits in comprehension, reading and writing[99]. Nevertheless, comprehension and expression of single words is largely preserved in those with naPPA.[100,101] 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[102,103]. 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. naPPA, including PPAOS, is often associated with FTLD-tau pathology[100,101].

[H3] bvFTD. The phenotype of bvFTD varies between patients, but there are core diagnostic features common to most presentations[9]. Consensus criteria for bvFTD can have early deficits in several domains of social functioning and personality: disinhibition and difficulty controlling their impulse to say or engage in socially inappropriate activities; apathy and reduced initiative; loss of sympathy and/or empathy; perseverative and compulsive or ritualistic behavior including development of unusual religious and political beliefs; and hyperoral behavior such as eating despite feeling sated and eating non-edibles. Clinical judgment 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[104,105]. Patients might show only a limited number of features or mild symptoms, and owing to their unusual appearance in the patient relative to their premorbid behavior, this may raise suspicion of a prodromal form of bvFTD[106]. Many patients with bvFTD also have deficits in executive function such as poor planning and organization, limited judgment, reduced insight, and impaired perspective-taking related to understanding the thoughts and beliefs of others[107–109]. There are reports of psychiatric

presentations of bvFTD such as psychosis and delusions in patients with an identified mutation associated with fFTLD[110,111]. Despite some important associations, a specific pattern of behavior and personality change in patients with bvFTD has not been strongly associated with a specific pathology[112].

[H3] Presentations related to motor impairments. In all patients with suspected FTD, performing a neurological exam is important to look for a motor disorder. PSP syndrome is characterized by frequent falls and problems with ocular motility, and is associated with extrapyramidal features such as axial rigidity, gait instability, involuntary tremor and dystonia. Patients with PSP can also have deficits in behavior and planning, with prominent impairment in impulse control. PSP can be heterogeneous in presentation and is a marker of FTLD-tau pathology in up to 90% of patients[115,116]. 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 [117,118]. Of note, naPPA and PPAOS can co-occur and may be an early marker of underlying PSP and CBD pathology [113,114].

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 amyotrophic lateral sclerosis (ALS) or motor neuron disease (MND), referred to as FTD-ALS or FTD-MND when patients also have features of FTD[119–122]. [104,105] naPPA and behavioral features can occur after the onset of ALS, but the severity may be attenuated, and in some cases PPA or bvFTD can precede ALS[119]. ALS-FTD is associated with FTLD-TDP pathology in >90% of patients[123,124].

[H2] 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 (**Figure 5**). These abnormalities can be seen as atrophy on MRI and hypometabolism on [^{18}F] fluorodeoxyglucose PET (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[121,125]. Findings from neuroimaging are heterogeneous between patients, although several brain regions seem to be almost universally involved, including anterior cingulate, anterior insula, orbital and medial frontal lobe and temporal pole, consistent with the concept of an epicenter. Degeneration of basal and limbic networks is a core feature of bvFTD[121]. Similar, although milder, degeneration and reduced connectivity, together with additional degeneration and reduced connectivity in the motor cortex are observed in patients with ALS-FTD[120,121,126]. 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 rate of progression in patients with bvFTD[127,128].

In contrast to bvFTD, degeneration and reduced connectivity in svPPA affects the left anteromedial temporal lobes (**Figure 5**), with degeneration gradually spreading posteriorly within the left anteromedial temporal regions[129] and to the right temporal lobes, insula and orbitofrontal cortex[130]. svPPA is associated with greater left temporal atrophy and a greater anterior-posterior gradient of hippocampal atrophy, compared with AD[129]. Patients with naPPA show most prominent atrophy and hypometabolism in left posterior-inferior frontal regions, including Broca's area (relating to agrammatism) and superior premotor cortex (relating to apraxia of speech; **Figure 5**), with degeneration spreading into the prefrontal cortex and basal ganglia and posteriorly into the motor cortex over time[130,131]. Disruption in brain connectivity is observed within the frontal lobes in naPPA[125]. Patients with PPAOS can also show accentuated

involvement of the superior premotor cortex (**Figure 5**), with reduced connectivity with the premotor cortex, and with degeneration typically spreading into Broca's area if agrammatism develops later in disease[132]. Patients with CBS show asymmetric atrophy and hypometabolism of the posterior frontal and anterior parietal (i.e. peri-Rolandic) lobes, in addition to involvement of the basal ganglia[133] (Figure 5). The frontal lobes can show mild atrophy and hypometabolism in PSP syndrome, although the dominant features include atrophy and disrupted connectivity between regions along the dentatorubrothalamic tract, including the midbrain and superior cerebellar peduncle[134] (Figure 5). Individuals with FTD-ALS can show some atrophy in the motor system extending into frontal cortex, but it is often difficult to capture because of the rapid rate of progression[135]. Converging evidence suggests that the patterns of regional spread in these FTD syndromes is related to brain functional connectivity whereby disease spreads from epicenters through highly connected brain regions[65,72,73].

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 occipital lobes, cerebellum, and thalamus. Hence, genetic mutations alter the patterns of neurodegeneration typically associated with sporadic bvFTD and ALS[136]. Grey matter atrophy and degeneration of specific white matter tracts can be observed many years before symptom onset in patients with fFTLD[137,138]. Presymptomatic changes in the temporal lobe and uncinate fasciculus are observed in *MAPT* carriers[139–141], changes in frontoparietal lobes and internal capsule are observed in *GRN* carriers[139,140], and changes in the cerebellum, thalamus and posteriorly located white matter tracts are observed in *C9orf72* carriers[139–141]. While matter degeneration seems to precede atrophy, at least in *GRN* carriers[142]. Moreover,

assessments of brain atrophy may have value in predicting the development of symptomatic illness in individuals with fFTLD [143,144]. Changes in functional connectivity in the brain have also been observed in presymptomatic fFTLD[145,146], 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 naPPA and PPAOS, rapid cortical degeneration is associated with CBD pathology, whereas midbrain atrophy is associated with PSP pathology[132]. In general, patients with FTLD 4R tauopathies show greater white matter degeneration compred with FTLD-TDPClick or tap here to enter text. [100]. 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 bysuch aggregates, even presymptomatically[147,148]. However, use 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.

[H2] FLUID-BASED BIOMARKERS

One challenge in clinical diagnostics and for clinical trial recruitment is to diagnose patients with FTD during life and to differentiate them from patients with other neurodegenerative diseases (such as sporadic AD) or psychiatric diseases.

Diagnostic biomarkers

Biomarkers for AD can be used to differentiate between AD and FTD. High CSF concentrations of total tau (T-tau) and phosphorylated tau (P-tau) are AD-specific, and tau-associated FTD subtypes do not show elevated CSF tau concentrations[149,150]. Moreover, amyloid pathology does not occur in most forms of FTD, therefore, CSF beta-amyloid 1-42

(Aβ42) concentrations and ratio of 42 to 40 amino acid long Aβ (CSF Aβ42/Aβ40) are typically normal in FTD[150,151]. Consequently, a high ratio of T-tau or P-tau to Aβ42 is an AD-specific finding that separates AD from FTD with high diagnostic accuracy[152]. Similarly, these biomarkers can be used to identify patients with frontal lobe dysfunction and AD pathology rather than FTD[152,153]. Moreover, the logopenic variant of PPA (that is usually associated with AD pathology) can be identified by elevated CSF tau levels and reduced CSF Aβ42/Aβ40[154].

Levels of several Aβ species including Aβ38, Aβ40, Aβ42 and soluble amyloid precursor protein fragments (sAPPβ and sAPPα) are lower in CSF from patients with FTD compared with cognitively normal controls[152,155,156]. The reason for this difference is unclear, but it is distinct from the selective reduction of Aβ42 seen in AD. However, the general reduction in concentrations of APP-derived proteins and peptides in CSF is not specific to FTD as it is also found in patients with normal pressure hydrocephalus[157] and neuroinflammatory conditions[158].

Several studies have demonstrated that CSF neurofilament light (NfL) concentration, a general marker of neurodegeneration, is high in patients with FTD[159], including those with autopsy-confirmed FTLD[153,160,161]. High CSF NfL levels combined with negative AD biomarkers is suggestive of a non-AD neurodegenerative disease (including FTLD) and a non-psychiatric disorder[162,163].

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 cognitively normal controls, with almost a 100% differentiation between those with AD and FTD[164–167]. Similar to findings in CSF, blood NfL concentrations are increased in patients with FTD compared with those with AD[155,168,169], although blood NfL levels have with limited performance for discriminating FTD from other neurodegenerative diseases[170,171]. Blood NfL levels discriminate FTD from primary psychiatric disorders with high diagnostic accuracy[172,173]. Moreover, blood NfL levels are a reliable biomarker of phenoconversion of presymptomatic to

symptomatic genetic FTD; blood NfL level is used regularly for this purpose in Sweden, Germany, and France, and increasingly in the US[174,175].

Biomarkers of specific FTD-related proteinopathies (TDP-43, tau, or FUS) are needed to enable the development of drugs targeting specific FTLD pathologies. One study suggested some important progress in discriminating between FTLD-tau and FTLD-TDP by plasma GFAP/NfL ratio [176]. Moreover, CSF and blood tau biomarkers seem to reflect an Aβ-driven increase in neuronal tau phosphorylation and secretion[177–179] 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[180]. 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 compared with controls[181]. No biomarkers of FTLD-FET pathology are available.

[H2] Prognostic biomarkers

Several studies have indicated that NfL concentrations in CSF and blood reflect disease intensity and predict clinical progression of FTD[155,168,174,182–185]. Longitudinal analysis of CSF NfL concentration demonstrated that NfL levels are stably increased in symptomatic FTD without clear longitudinal changes[183]. 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[175], and a large longitudinal study of genetic FTD showed that **[Au: increased?]** increasing NfL levels in blood can identify people with mutations approaching symptom onset and capture rates of brain atrophy[186]. 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.

[H2] Other biomarkers

Reduced CSF and blood progranulin concentrations have been found in *GRN* mutation carriers with almost 100% diagnostic accuracy[187–189]. 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 dipeptide repeat proteins produced by the expansion, is increased in carriers even at the presymptomatic stage[190–193]. This marker should be useful as a pharmacodynamic biomarker in gene-silencing studies.

As CSF and blood NfL levels are markers of the severity 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[194].

[H1] Management

[H2] Non-Medication treatments

The most used non-medical treatments for FTD are behavioral therapies, such as speech and language therapy for PPA[195] or cognitive rehabilitation for bvFTD[196,197]. In addition, family members and aides 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, and to provide alternatives to obsessive-compulsive behaviors (such as popping bubble wrap rather than pulling out hair)[198].

Studies have aimed to augment behavioral 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 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[199].

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 at least 1 to 2 months after treatment. The main effects were improved naming, largely driven by tDCS. However, larger, randomized, controlled trials (RCT) 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.

[H3] Repetitive Transcranial Magnetic Stimulation

Small (n = 6-20) cross-over RCTs have been carried out to determine the effects of high-frequency rTMS on spontaneous speech (word count)[200], object and action naming[197], and verbal fluency[201] 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[202].[201] ,[200]. Some trials determined the target for active rTMS during a pre-treatment phase (personalized approach)[200] whereas other trials evaluated the same target in all participants (such as right and left dorsolateral prefrontal cortices[202], or the left prefrontal cortex[201]). All have used high frequency rTMS which stimulates firing of neurons.

These studies have shown improvements in word count, patient and caregiver perception of change, mood, and regional brain metabolism on FDG-PET in the high frequency rTMS condition[200], action but not object naming[202] in participants with naPPA only, and verbal fluency in participants with naPPA and lvPPA[201]. The increased regional brain metabolism reported in one study[200] suggests enhancement of synaptic activity with high-frequency rTMS. Moreover, one open-label trial of 10 daily sessions of rTMS over bilateral dorsolateral prefrontal cortex in nine patients with bvFTD and two with PPA indicated gains in the Montreal Cognitive Assessment and other cognitive and behavioral assessments, with no improvements in mood, after treatment[203].

[H3] Trancranial 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[204]. 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[205].

Most studies of tDCS have used anodal (faciliatory) tDCS over the left hemisphere in combination with language intervention. One study of tDCS or sham over left dorsolateral frontal cortex for 25 minutes per day for two weeks (10 days), 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[205].

Another cross-over RCT reported greater gains in naming treated words in individuals with PPA who received 15 daily sessions of anodal tDCS accompanied by written naming therapy, with different benefits observed in patients with naPPA and lvPPA[206]. Moreover, this study also reported a generalization to untreated words that was maintained 2 months later only

in patients tDCS. However, there were no effects in svPPA. Follow-up studies demonstrated that volume of specific brain regions[207], white matter integrity[208] or baseline language and cognitive performance[207] could predict better response 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 fMRI[209] and reductions in GABA in targeted regions[210].

Another cross-over RCT compared three tDCS conditions in patients with svPPA: left temporal pole anodal tDCS, right temporal pole cathodal (inhibitory) tDCS, and sham stimulation. This study reported an improvement in semantic processing in patients that received left anodal and right cathodal tDCS compared with sham[211].

Although most stimulation studies have been aiming to improve language in patients with PPA, at least one trial aimed to enhance theory of mind using tDCS in 16 patients with bvFTD and 16 controls[212]. This study found improved accuracy in comprehension of communicative intentions in participants with bvFTD who received anodal tDCS over medial frontal cortex.

[H2] Pharmacological management

Approved symptomatic therapies for AD (memantine and cholinesterase inhibitors) are not efficacious for FTD[213–215], 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 [216–219]. In a placebo-controlled crossover trial in 10 patients with bvFTD, trazadone (a serotonin receptor antagonist and reuptake inhibitor) significantly improved multiple neuropsychiatric and behavioral symptoms but was not consistently well-tolerated.

More specific SSRIs that have favorable tolerability profiles (such as sertraline, citalopram and escitalopram) are typically preferred in clinical practice compared with medications with off-target effects, including anticholinergic effects[216,220].

Antipsychotics are occasionally used for treatment of severe agitation and disinhibition but are supported only by a small body of evidence from case studies and open label trials in patients with FTD[216,217]. Antipsychotics use is also limited by their black box warning for increased mortality and their extrapyramidal side effects (EPS), which is a particular risk in FTD[221]. 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. 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 3, randomized, placebo-controlled trial of patients with a range of dementia aetiologies[222]. However, this trial produced only limited long-term efficacy and safety data and only included seven patients with FTD (of which only three were enrolled in the randomized portion of the trial).

Anticonvulsants have also been evaluated for behavioral management in patients with FTD but, similarly to antipsychotics, use of anticonvulsants is limited by a paucity of data and often unfavorable tolerability profiles. Only a few case studies have described the use of valproate for management of agitation and hypersexuality[216,223], carbamazepine for management of hypersexuality[224], and topirimate for compulsive eating[225–228] in patients with FTD.

Other less commonly used pharmacological therapies for FTD include dextromethorphan (which improved apathy and disinhibition in one study)[229] and stimulants (of which methylphenidate reduced risk-taking in a novel testing paradigm)[230]. In the future, symptomatic therapies might also include oxytocin, which may improve social interest in FTD[231] although this drug is still being investigated in an RCT in patients with FTD (NCT01386333) and has yet to enter clinical use.

[H2] 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 3 trial of a methylthioninium chloride formulation) enrolled a pathologically heterogeneous cohort of patients with bvFTD (NCT03446001); however, most drug development programs 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[232]. However, trials of drugs intended to stabilize microtubules (davunetide[233] and abeotaxane[234]), limit tau phosphorylation via glycogen synthase kinases (tideglusib)[235], and limit pathogenic tau acetylation (salsalate)[236] have yielded negative results in PSP-RS.

A small trial of plasma infusions from young healthy donors also yielded negative results in PSP-RS[236]. Moreover, passive immunization against the N-terminal tau epitopes did not slow disease progression in patients with PSP-RS in well-powered phase 2 trials (NCT03413319, NCT03068468). However, 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), tau phosphorylated at ammino acid 217 (JNJ-63733657), and filamentous tau (BIIB076) are under investigation in AD (NCT03375697, NCT04185415 and NCT03056729) and may warrant future investigation in FTLD-tau. Results from a trial studying the use of a vaccine against the 294–305 region of 4-repeat tau (ADDvac1) in patients with naPPA are pending (NCT03174886).

Ongoing clinical development programs for FTLD-tau are harnessing other strategies, including suppression of tau expression via antisense oligonucleotides (ASOs) like NIO752 (NCT04539041) and alteration of tau autophagy and phosphorylation via rho-kinase inhibitors like fasudil (NCT04734379). Other trials are targeting the suppression of downstream

pathological dysregulation of retro-transposable elements via the reverse transcriptase inhibitor TPN-101 (NCT04993768), and augmentation of downstream lipid membrane injury via deuterated linoleic acid, RT001 (NCT04937530).

[H2] Clinical Trial Development in FTLD-TDP

Autosomal dominant mutations have been a primary focus for drug development 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. Previous trials of nimodipine and FRM-0334 (which upregulated progranulin in preclinical models) did not affect extracellular progranulin levels in clinical trials[237,238]; however, passive immunization with AL001 (a monoclonal antibody targeting the sortilin receptor, which shuttles progranulin to the lysome)[239], seemed to normalize plasma and CSF progranulin in patients with *GRN* haploinsufficiency. A phase 3 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)[240].

Much of drug development for pathogenetic *C9orf72* expansion has focused on intrathecal ASO strategies that are intended to decrease expanded transcripts and dipeptide repeat (DPR) proteins translated from the hexanucleotide expansion. Proof of concept for suppression of CSF DPRs has been observed in a single patient with C9orf72-ALS treated with afinersen[241].Mechanistically similar ASOs (BIIB078 and WVE-004) are also being investigated in patients with ALS (NCT03626012 and NCT04931862) and FTD (NCT04931862) due to *C9orf72* expansion. 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 oin 80% of patients,[93] this syndrome may be a growing focus in future trials. The first of such trials (NCT05184569) will investigate 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.

[H1] Quality of life

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, motor and social-emotional functioning, that vary in combination, severity and progression[242]. 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[243]

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. Other changes that directly or indirectly interfere with functional capacity include disturbances of socio-emotional engagement and regulation, which affect interpersonal relationships, decreased sleep quality, and disturbances in movement coordination and motor control. The latter is particularly relevant for individuals with co-existing

ALS exhibiting swallowing difficulty, or those with motor systems presentation of FTD (such as CBS or PSP). Finally, some patients have psychiatric symptoms, such as depression, anxiety and delusions, the latter of which is more frequently observed in individuals carrying a *C9orf72* hexanucleotide repeat expansion[244]. Apathy is also common across FTD syndromes and is characterized by a difficulty in engaging in, and sustaining, activities. 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[245–248].

The deteriorating QOL and associated burden of care remains one of the major predictors of transition to supported accommodation and nursing home placement for patients with dementia[249]. Few institutions are specialized in management of younger, physically healthy individuals with FTD who tend to present with marked behavioral 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 FTD in the absence of disease-modifying treatments or cure.

Of note, most knowledge of the changes in QOL in patients with FTD and their families is mostly from studies of Western populations. Whether such approaches are relevant and applicable to family units from non-Western populations are 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 supports is mostly lacking[250251]. 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. Increase 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. Moreover, increased stress and anxiety have also been reported in the primary informal carers[252]. 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 upcoming years [253].

[H1] 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[187–189]. Several targeted treatment trials for fFTLD are on-going and additional studies are planned. However, treatment approaches for sporadic FTD are less advanced and additional work is needed before a treatment program can be successfully 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[86,254], bvFTD without obvious PPA or the presence of an

obvious motor speech disorder[114,255,256], and the identification 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 in 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 centers are less like to emerge. Automated analysis of digitized speech also may 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 FTLD and could be useful for identification of changes and as outcome measures. Eye-tracking tasks digitized measures such as wearables, and collection of autonomic variables particularly during evaluation of individuals with bvFTD also have the potential to quantitatively detect earlier and more subtle social cognition and executive function deficits than traditional paper-and-pencil tasks. For example, an eye-tracking paradigm can consist of an anti-saccade task and oculomotor capture (i.e.to evaluate inhibition), predictive pursuit (i.e. prediction), a spatial anticipation task (i.e. rule shifting), self-paced eye movements (i.e. apathy), basic and complex emotion recognition tasks (i.e. Reading the Eyes in the Mind test), and a free viewing task for higher order social cognitive processes, and 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. 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 behavior 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[150,257–259], novel exosome analyses in CSF and blood[178,260–262], and evaluation of epigenetics[263–265] have allowed development of less invasive biomarkers in blood and novel markers of disease. New blood biomarkers based on the ratio of NfL to glial fibrillary acidic protein (GFAP) show some promise in distinguishing sporadic FTD due to FTLD-tau versus FTLD-TDP[176]. Innovative single-nucleus RNA (snRNA) expression studies of brains from patients with sporadic FTD or fFTLD will lead to more insight and the potentially the identification of new fluid biomarkers in CSF or blood. The value of such candidate biomarkers can be investigated in ongoing longitudinal and international studies of healthy and symptomatic carriers with FTD mutations and patients with sporadic FTD. Innovative techniques may also identify new insights in the disease mechanisms. For example, one study using single-nucleus RNA sequencing of FTD-GRN brain samples identified disease-associated subtypes of astrocytes and endothelial cells, with enrichment of fibroblasts and mesenchymal cell numbers. 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[266].

Available neuroimaging data collected in longitudinal studies of fFTLD and sporadic FTD will enable quantitative measurement of changes in grey matter volume. However, the harmonization of multi-site 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 (RISH) features, can be used to optimize and validate post-

processing harmonization strategy of multi-shell acquisitions, with one site selected as reference. Other MRI sequences such as arterial spin labeling[267–269] and spectroscopy[270–273], novel analyses encompassing data science network approaches[65,125,274,275], and MRI using more powerful 7 tesla magnets[276] will improve sensitivity to changes in brain anatomy. High-resolution MRI in *ex vivo* cases at 7 tesla are proving highly informative in FTD and ALS[276–278]. Moreover, molecular PET imaging has begun to target more specific pathological entities in the brains of patients with FTD[132,147,148], and novel radioligands will improve *in vivo* diagnosis and provide an important way to assess response during disease-modifying treatment trials. Finally, cross-sectional and longitudinal optical coherence tomography can be used to identify autopsy-confirmed thinning of the outer retinal layer in patients with FTLD-tau compared with controls and compared with their own inner retinal layer[279] .

Developments in artificial intelligence and machine learning, such as discriminative event-based model (DEBM)[142,280–282], allow the extraction of patterns from large-scale datasets of high-dimensional longitudinal measurements of multi-modal biomarkers. In addition to group-wise staging based on a composite of considered data, this method also estimates the probability the 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 multi-modal tools are likely to improve early detection of disease and improve stratification within treatment trials to optimize timing for effective therapeutic interventions.

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 sFTLD	Pathology	Most common clinical presentations	Genetic disease modifier(s) in human patients	Refs
MAPT	5-20%	0-2%	FTLD-tau	bvFTD, PSP-RS and CBS	None identified	
GRN	5-25%	5%	FTLD-TDP	bvFTD, naPPA and CBS	TMEM106B and GFRA2	
C9orf72	20-30%	6%	FTLD-TDP	bvFTD and FTD-ALS	TMEM106B, SLITRK2 and C6orf10/LOC101929163	

fFTLD: familial frontotemporal lobar degeneration; sFTLD: sporadic frontotemporal dementia; bvFTD: behavioral variant frontotemporal dementia; PSP-RS: progressive supranuclear palsy – Richardson's syndrome; CBS: corticobasal degeneration; naPPA: non-fluent/agrammatic variant of primary progressive aphasia; ALS: amyotrophic lateral sclerosis.

Figure 1. FTD syndromes and associated pathology

Clinical FTD syndromes color-coded according to the proportion associated with a specific pathology and subtypes of each pathology as well as the associated genetic mutation with each.

Figure 2: Prevalence of frontotemporal degeneration-associated syndromes[16]

(A) Prevalence of FTD-associated syndromes by age at onset (green bars) and by age at diagnosis. (B) Distribution of cases by clinical syndrome (n = 53). bvFTD, behavioral variant frontotemporal dementia (including FTD-MND/ ALS-FTD; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; nfvPPA, nonfluent agrammatic variant primary progressive aphasia; other PPA, other primary progressive aphasia logopenic variant and unclassifiable; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia. The inclusion of ALS-FTD or FTD-MND may vary from study to study depending on the focus of the work.

Figure 3: Geographic distribution of genetic subtypes of frontotemporal degeneration. Data from Ref[21]

Figure 4. FTLD pathologies.

Figure 5: Characteristic patterns of neurodegeneration in different FTD syndromes. Group-level differences in brain volume loss for each syndrome of FTD compared with healthy controls. naPPA 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. PPAOS is typically associated with abnormalities in the lateral superior premotor cortex and supplementary motor cortex, often bilaterally. 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. bvFTD is typically associated with bilateral abnormalities in the prefrontal cortex and anterior temporal lobes. 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. CBS is typically associated with asymmetric abnormalities in the frontoparietal lobes. ALS-FTD is typically associated with mild abnormalities in the frontal lobe.

Box 1. Cognitive examination for suspected FTD.

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

1. *Langua*ge: 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.

2. *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 (e.g. “F”), and digit-symbol substitution.

3. *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).

4. *Visual perceptual-spatial functioning:* such as copying a figure and judging the angle of a line.

5. *Episodic memory:* including measures of verbal and visual learning.

6. *Attention:* such as raising a hand every time the letter “A” is heard in a sequence of letters presented over 1-2 minutes.

References

1. Cairns, N. *et al.* Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol* **114**, 5–22 (2007).

2. Robinson, J. L. *et al.* Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain* **141**, 2181–2193 (2018).

3. Goldman, J. S. *et al.* Comparison of family histories in FTLD subtypes and related tauopathies. *Neurology* **65**, 1817–1819 (2005).

4. Wood, E. M. *et al.* Development and validation of pedigree classification criteria for frontotemporal lobar degeneration. *JAMA Neurol* **70**, 1411–1417 (2013).

5. Mol, M. O. *et al.* Underlying genetic variation in familial frontotemporal dementia: sequencing of 198 patients. *Neurobiol Aging* **97**, 148.e9-148.e16 (2021).

6. Al-Chalabi, A. & Lewis, C. M. Modelling the Effects of Penetrance and Family Size on Rates of Sporadic and Familial Disease. *Hum Hered* **71**, 281–288 (2011).

7. Blitterswijk, M. van *et al.* Evidence for an oligogenic basis of amyotrophic lateral sclerosis. *Hum Mol Genet* **21**, 3776–3784 (2012).

8. Boeve, B. F. *et al.* Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. *Brain* **135**, 765–783 (2012).

9. Rascovsky, K. *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**, 2456–2477 (2011).

10. Gorno-Tempini, M. L. *et al.* Classification of primary progressive aphasia and its variants. *Neurology* **76**, 1006–1014 (2011).

11. Townley, R. A. *et al.* Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. *Brain Commun* **2**, fcaa068- (2020).

12. Ossenkoppele, R. *et al.* The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. *Brain* **138**, 2732–2749 (2015).

13. Hornberger, M., Shelley, B. P., Kipps, C. M., Piguet, O. & Hodges, J. R. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? *Journal of Neurology, Neurosurgery & Psychiatry* **80**, 591–593 (2009).

14. Steketee, R. M. E. *et al.* Structural and functional brain abnormalities place phenocopy frontotemporal dementia (FTD) in the FTD spectrum. *YNICL* **11**, 595–605 (2016).

15. Kvello-Alme, M., Bråthen, G., White, L. R. & Sando, S. B. The Prevalence and Subtypes of Young Onset Dementia in Central Norway:\\ A Population-Based Study. *J Alzheimer's Dis* **Preprint**, 1–1 (2019).

16. Coyle-Gilchrist, I. T. S. *et al.* Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology* **86**, 1736–1743 (2016).

17. Knopman, D. & Roberts, R. Estimating the Number of Persons with Frontotemporal Lobar Degeneration in the US Population. *J Mol Neurosci* **45**, 330–335 (2011).

18. Turcano, P. *et al.* Incidence of frontotemporal disorders in Olmsted County: A population-based study. *Alzheimer's Dementia* **16**, 482–490 (2019).

19. Logroscino, G. *et al.* Incidence of frontotemporal lobar degeneration in Italy: The Salento-Brescia Registry study. *Neurology* **92**, e2355–e2363 (2019).

20. Niu, H., Álvarez-Álvarez, I., Guillén-Grima, F. & Aguinaga-Ontoso, I. Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurología Engl Ed* **32**, 523–532 (2017).

21. Moore, K. M. *et al.* Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurology* **19**, 145–156 (2020).

22. Kansal, K. *et al.* Survival in Frontotemporal Dementia Phenotypes: A Meta-Analysis. *Dement Geriatr Cogn* **41**, 109–122 (2016).

23. Graff-Radford, N. R., Besser, L. M., Crook, J. E., Kukull, W. A. & Dickson, D. W. Neuropathologic differences by race from the National Alzheimer's Coordinating Center. *Alzheimer's Dementia* **12**, 669–677 (2016).

24. Fukuhara, R. *et al.* Family history of frontotemporal lobar degeneration in Asia – an international multi-center research. *Int Psychogeriatr* **26**, 1967–1971 (2014).

25. Mackenzie, I. R. A. *et al.* Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. *Acta Neuropathol* **117**, 15–18 (2009).

26. Sanders, D. W. *et al.* Distinct Tau Prion Strains Propagate in Cells and Mice and Define Different Tauopathies. *Neuron* **82**, 1271–1288 (2014).

27. Shi, Y. *et al.* Structure-based classification of tauopathies. *Nature* **598**, 359–363 (2021).

28. Narasimhan, S. *et al.* Pathological Tau Strains from Human Brains Recapitulate the Diversity of Tauopathies in Nontransgenic Mouse Brain. *J. Neurosci.* **37**, 11406–11423 (2017).

29. Dickson, D. W., Kouri, N., Murray, M. E. & Josephs, K. A. Neuropathology of Frontotemporal Lobar Degeneration-Tau (FTLD-Tau). *J Mol Neurosci* **45**, 384–389 (2011).

30. Nana, A. L. *et al.* Neurons selectively targeted in frontotemporal dementia reveal early stage TDP-43 pathobiology. *Acta Neuropathol* **137**, 27–46 (2019).

31. Mackenzie, I. R. A. *et al.* A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol* **122**, 111–113 (2011).

32. Lee, E. B. *et al.* Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration. *Acta Neuropathol* **134**, 65–78 (2017).

33. Andersson, M. K. *et al.* The multifunctional FUS, EWS and TAF15 proto-oncoproteins show cell type-specific expression patterns and involvement in cell spreading and stress response. *Bmc Cell Biol* **9**, 37 (2008).

34. Neumann, M. *et al.* A new subtype of frontotemporal lobar degeneration with FUS pathology. *Brain* **132**, 2922–2931 (2009).

35. Lashley, T. *et al.* A comparative clinical, pathological, biochemical and genetic study of fused in sarcoma proteinopathies. *Brain* **134**, 2548–2564 (2011).

36. Mackenzie, I. R. A. *et al.* Distinct pathological subtypes of FTLD-FUS. *Acta Neuropathol* **121**, 207–218 (2011).

37. Neumann, M. *et al.* FET proteins TAF15 and EWS are selective markers that distinguish FTLD with FUS pathology from amyotrophic lateral sclerosis with FUS mutations. *Brain* **134**, 2595–2609 (2011).

38. Hutton, M. *et al.* Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**, 702–705 (1998).

39. Baker, M. *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* **442**, 916–919 (2006).

40. Cruts, M. *et al.* Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* **442**, 920–924 (2006).

41. DeJesus-Hernandez, M. *et al.* Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. *Neuron* **72**, 245–256 (2011).

42. Renton, A. E. *et al.* A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. *Neuron* **72**, 257–268 (2011).

43. Barbier, M. *et al.* SLITRK2 , an X-linked modifier of the age at onset in C9orf72 frontotemporal lobar degeneration. *Brain* **144**, 2798–2811 (2021).

44. Gallagher, M. D. *et al.* TMEM106B is a genetic modifier of frontotemporal lobar degeneration with C9orf72 hexanucleotide repeat expansions. *Acta Neuropathol* **127**, 407–418 (2014).

45. Pottier, C. *et al.* Genome-wide analyses as part of the international FTLD-TDP whole-genome sequencing consortium reveals novel disease risk factors and increases support for immune dysfunction in FTLD. *Acta Neuropathol* **137**, 879–899 (2019).

46. Zhang, M. *et al.* A C6orf10/LOC101929163 locus is associated with age of onset in C9orf72 carriers. *Brain* **141**, 2895–2907 (2018).

47. Forrest, S. L. *et al.* Retiring the term FTDP-17 as MAPT mutations are genetic forms of sporadic frontotemporal tauopathies. *Brain* **141**, 521–534 (2018).

48. Rademakers, R., Cruts, M. & Broeckhoven, C. van. The role of tau (MAPT) in frontotemporal dementia and related tauopathies. *Hum. Mutat.* **24**, 277–295 (2004).

49. Strang, K. H. *et al.* Distinct differences in prion-like seeding and aggregation between Tau protein variants provide mechanistic insights into tauopathies. *J Biol Chem* **293**, 2408–2421 (2018).

50. Strang, K. H., Golde, T. E. & Giasson, B. I. MAPT mutations, tauopathy, and mechanisms of neurodegeneration. *Lab Invest* **99**, 912–928 (2019).

51. Yokoyama, J. S. *et al.* Shared genetic risk between corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia. *Acta Neuropathol* **133**, 825–837 (2017).

52. Farg, M. A. *et al.* C9ORF72, implicated in amytrophic lateral sclerosis and frontotemporal dementia, regulates endosomal trafficking. *Hum Mol Genet* **26**, 4093–4094 (2017).

53. Blitterswijk, M. van, DeJesus-Hernandez, M. & Rademakers, R. How do C9ORF72 repeat expansions cause amyotrophic lateral sclerosis and frontotemporal dementia. *Curr Opin Neurol* **25**, 689–700 (2012).

54. Gendron, T. F. & Petrucelli, L. Disease Mechanisms of C9ORF72 Repeat Expansions. *Csh Perspect Med* **8**, a024224 (2018).

55. Smith, K. R. *et al.* Strikingly Different Clinicopathological Phenotypes Determined by Progranulin-Mutation Dosage. *Am J Hum Genetics* **90**, 1102–1107 (2012).

56. Zhou, X., Kukar, T. & Rademakers, R. Frontotemporal Dementias, Emerging Milestones of the 21st Century. *Adv Exp Med Biol* **1281**, 219–242 (2021).

57. Deerlin, V. M. V. *et al.* Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. *Nat Genet* **42**, 234–239 (2010).

58. Ferrari, R. *et al.* Assessment of common variability and expression quantitative trait loci for genome-wide associations for progressive supranuclear palsy. *Neurobiology of Aging* **35**, 1514.e1-1514.e12 (2014).

59. Ferrari, R., Manzoni, C. & Hardy, J. Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues. *Neurobiol Aging* **78**, 98–110 (2019).

60. Rooij, J. van *et al.* Somatic TARDBP variants as a cause of semantic dementia. *Brain* **143**, 3827–3841 (2020).

61. Zhou, J., Gennatas, E. D., Kramer, J. H., Miller, B. L. & Seeley, W. W. Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron* **73**, 1216–1227 (2012).

62. Ravits, J. M. & Spada, A. R. L. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* **73**, 805–811 (2009).

63. Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L. & Greicius, M. D. Neurodegenerative diseases target large-scale human brain networks. *Neuron* **62**, 42–52 (2009).

64. Gardner, R. C. *et al.* Intrinsic connectivity network disruption in progressive supranuclear palsy. *Ann Neurol* **73**, 603–616 (2013).

65. Brown, J. A. *et al.* Patient-Tailored, Connectivity-Based Forecasts of Spreading Brain Atrophy. *Neuron* **104**, 856-868.e5 (2019).

66. Kim, E.-J. *et al.* Selective Frontoinsular von Economo Neuron and Fork Cell Loss in Early Behavioral Variant Frontotemporal Dementia. *Cereb Cortex* **22**, 251–259 (2012).

67. Seeley, W. W. *et al.* Early frontotemporal dementia targets neurons unique to apes and humans. *Ann Neurol* **60**, 660–667 (2006).

68. Lin, L.-C. *et al.* Preferential tau aggregation in von Economo neurons and fork cells in frontotemporal lobar degeneration with specific MAPT variants. *Acta Neuropathologica Commun* **7**, 159 (2019).

69. Pineda, S. S. *et al.* Single-cell profiling of the human primary motor cortex in ALS and FTLD. *Biorxiv* 2021.07.07.451374 (2021) doi:10.1101/2021.07.07.451374.

70. Genç, B. & Özdinler, P. H. Moving forward in clinical trials for ALS: motor neurons lead the way please. *Drug Discov Today* **19**, 441–449 (2014).

71. Frost, B., Ollesch, J., Wille, H. & Diamond, M. I. Conformational Diversity of Wild-type Tau Fibrils Specified by Templated Conformation Change*. *J Biol Chem* **284**, 3546–3551 (2009).

72. Kim, E.-J. *et al.* Evidence of corticofugal tau spreading in patients with frontotemporal dementia. *Acta Neuropathol* **139**, 27–43 (2020).

73. Porta, S. *et al.* Patient-derived frontotemporal lobar degeneration brain extracts induce formation and spreading of TDP-43 pathology in vivo. *Nat Commun* **9**, 4220 (2018).

74. de Calignon, A. *et al.* Propagation of Tau Pathology in a Model of Early Alzheimer's Disease. *Neuron* **73**, 685–697 (2012).

75. Frost, B. & Diamond, M. I. Prion-like mechanisms in neurodegenerative diseases. *Nat Rev Neurosci* **11**, 155–159 (2010).

76. Greicius, M. D., Srivastava, G., Reiss, A. L. & Menon, V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proc National Acad Sci* **101**, 4637–4642 (2004).

77. Raj, A., Kuceyeski, A. & Weiner, M. A Network Diffusion Model of Disease Progression in Dementia. *Neuron* **73**, 1204–1215 (2012).

78. Palop, J. J., Chin, J. & Mucke, L. A network dysfunction perspective on neurodegenerative diseases. *Nature* **443**, 768–773 (2006).

79. Fu, H., Hardy, J. & Duff, K. E. Selective vulnerability in neurodegenerative diseases. *Nat Neurosci* **21**, 1350–1358 (2018).

80. Kelley, B. J. *et al.* Prominent phenotypic variability associated with mutations in Progranulin. *Neurobiol Aging* **30**, 739–751 (2009).

81. Chen-Plotkin, A. S. *et al.* Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. *Arch Neurol* **68**, 488–497 (2011).

82. Mesulam, M. M., Wieneke, C., Thompson, C., Rogalski, E. & Weintraub, S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain* **135**, 1537–1553 (2012).

83. Sajjadi, S. A., Patterson, K., Arnold, R., Watson, P. C. & Nestor, P. J. Primary progressive aphasia. *Neurology* **78**, 1670–1677 (2012).

84. Wicklund, M. R. *et al.* Quantitative application of the primary progressive aphasia consensus criteria. *Neurology* **82**, 1119–1126 (2014).

85. Hodges, J. R. & Patterson, K. Semantic dementia: a unique clinicopathological syndrome. *The Lancet Neurology* **6**, 1004–1014 (2007).

86. Cho, S. *et al.* Automated analysis of lexical features in frontotemporal degeneration. *Cortex* **137**, 215–231 (2021).

87. Cousins, K. A. Q., Ash, S., Olm, C. A. & Grossman, M. Longitudinal Changes in Semantic Concreteness in Semantic Variant Primary Progressive Aphasia (svPPA). *Eneuro* **5**, ENEURO.0197-18.2018 (2018).

88. Cousins, K. A. Q., Ash, S., Irwin, D. J. & Grossman, M. Dissociable substrates underlie the production of abstract and concrete nouns. *Brain Lang* **165**, 45–54 (2017).

89. Bonner, M. F., Price, A. R., Peelle, J. E. & Grossman, M. Semantics of the Visual Environment Encoded in Parahippocampal Cortex. *Journal of Cognitive Neuroscience* **28**, 361–378 (2016).

90. Hoffman, P., Jefferies, E., Ehsan, S., Jones, R. W. & Ralph, M. A. L. Semantic memory is key to binding phonology: Converging evidence from immediate serial recall in semantic dementia and healthy participants. *Neuropsychologia* **47**, 747–760 (2009).

91. Younes, K. *et al.* Right temporal degeneration and socioemotional semantics: semantic behavioural variant frontotemporal dementia. *Brain* (2022) doi:10.1093/brain/awac217.

92. Josephs, K. A. *et al.* Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol* **122**, 137–153 (2011).

93. Spinelli, E. G. *et al.* Typical and atypical pathology in primary progressive aphasia variants. *Ann Neurol.* **81**, 430–443 (2017).

94. Mesulam, M. M. *et al.* Primary progressive aphasia and the evolving neurology of the language network. *Nat Rev Neurol* **10**, 554–569 (2014).

95. Hodges, J. R. *et al.* Clinicopathological correlates in frontotemporal dementia. *Ann Neurol.* **56**, 399–406 (2004).

96. Gunawardena, D. *et al.* Why are patients with progressive nonfluent aphasia nonfluent? *Neurology* **75**, 588–594 (2010).

97. Wilson, S. M. *et al.* Neural correlates of syntactic processing in the nonfluent variant of primary progressive aphasia. *J. Neurosci.* **30**, 16845–16854 (2010).

98. Ash, S. *et al.* A longitudinal study of speech production in primary progressive aphasia and behavioral variant frontotemporal dementia. *Brain Lang* **194**, 46–57 (2019).

99. Grossman, M. Linguistic Aspects of Primary Progressive Aphasia. *Annu. Rev. Linguist.* **4**, 377–403 (2018).

100. Giannini, L. A. A. *et al.* Divergent patterns of TDP-43 and tau pathologies in primary progressive aphasia. *Ann Neurol* **85**, 630–643 (2019).

101. Josephs, K. A. *et al.* Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain* **129**, 1385–1398 (2006).

102. Botha, H. *et al.* Classification and clinicoradiologic features of primary progressive aphasia (PPA) and apraxia of speech. *Cortex* **69**, 220–236 (2015).

103. Josephs, K. A. *et al.* The evolution of primary progressive apraxia of speech. *Brain* **137**, 2783–2795 (2014).

104. Dodich, A., Crespi, C., Santi, G. C., Cappa, S. F. & Cerami, C. Evaluation of Discriminative Detection Abilities of Social Cognition Measures for the Diagnosis of the Behavioral Variant of Frontotemporal Dementia: a Systematic Review. *Neuropsychol Rev* **31**, 251–266 (2021).

105. Stock, J. V. den *et al.* Current Potential for Clinical Optimization of Social Cognition Assessment for Frontotemporal Dementia and Primary Psychiatric Disorders. *Neuropsychol Rev* 1–7 (2022) doi:10.1007/s11065-022-09554-3.

106. Barker, M. S. *et al.* Proposed research criteria for prodromal behavioural variant frontotemporal dementia. *Brain* **145**, awab365 (2022).

107. Healey, M. *et al.* More Than Words: Extra-Sylvian Neuroanatomic Networks Support Indirect Speech Act Comprehension and Discourse in Behavioral Variant Frontotemporal Dementia. *Front Hum Neurosci* **14**, 598131 (2021).

108. Rankin, K. P., Kramer, J. H. & Miller, B. L. Patterns of Cognitive and Emotional Empathy in Frontotemporal Lobar Degeneration. *Cognitive and Behavioral Neurology* **18**, 28–36 (2005).

109. Wittenberg, D. *et al.* The early neuropsychological and behavioral characteristics of frontotemporal dementia. *Neuropsychol Rev* **18**, 91–102 (2008).

110. Devenney, E. M. *et al.* The neural correlates and clinical characteristics of psychosis in the frontotemporal dementia continuum and the C9orf72 expansion. *Neuroimage Clin* **13**, 439–445 (2017).

111. Kumfor, F. *et al.* Examining the presence and nature of delusions in Alzheimer's disease and frontotemporal dementia syndromes. *Int. J. Geriat. Psychiatry* **37**, 10.1002/gps.5692 (2022).

112. Irwin, D. J. *et al.* Asymmetry of post-mortem neuropathology in behavioural-variant frontotemporal dementia. *Brain* **141**, 288–301 (2017).

113. Josephs, K. A. & Duffy, J. R. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. *Current Opinion in Neurology* **21**, 688-692 10.1097-WCO.0b013e3283168ddd (2008).

114. Parjane, N. *et al.* Digital Speech Analysis in Progressive Supranuclear Palsy and Corticobasal Syndromes. *J Alzheimer's Dis* **82**, 33–45 (2021).

115. Respondek, G. *et al.* The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. *Mov. Disord.* **29**, 1758–1766 (2014).

116. Respondek, G. *et al.* Validation of the Movement Disorder Society Criteria for the Diagnosis of 4-Repeat Tauopathies. *Movement Disord* **35**, 171–176 (2020).

117. Armstrong, M. J. *et al.* Criteria for the diagnosis of corticobasal degeneration. *Neurology* **80**, 496–503 (2013).

118. Lee, S. E. *et al.* Clinicopathological correlations in corticobasal degeneration. *Ann Neurol.* **70**, 327–340 (2011).

119. Strong, M. J. *et al.* Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. *Amyotroph Lateral Scler Frontotemporal Degener* **124**, 1–22 (2017).

120. Ahmed, R. M. *et al.* Tackling clinical heterogeneity across the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia spectrum using a transdiagnostic approach. *Brain Commun* **3**, fcab257- (2021).

121. Cividini, C. *et al.* Amyotrophic Lateral Sclerosis–Frontotemporal Dementia. *Neurology* **98**, e402–e415 (2022).

122. Abrahams, S., Newton, J., Niven, E., Foley, J. & Bak, T. H. Screening for cognition and behaviour changes in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* **15**, 1–6 (2013).

123. Neumann, M., Kwong, L. K., Sampathu, D. M., Trojanowski, J. Q. & Lee, V. M.-Y. TDP-43 Proteinopathy in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis: Protein Misfolding Diseases Without Amyloidosis. *Arch Neurol-chicago* **64**, 1388–1394 (2007).

124. Kawakami, I., Arai, T. & Hasegawa, M. The basis of clinicopathological heterogeneity in TDP-43 proteinopathy. *Acta Neuropathol* **138**, 751–770 (2019).

125. Nigro, S. *et al.* Altered structural brain networks in linguistic variants of frontotemporal dementia. *Brain Imaging Behav* **16**, 1113–1122 (2022).

126. Temp, A. G. M. *et al.* Cognitive Profiles of Amyotrophic Lateral Sclerosis Differ in Resting-State Functional Connectivity: An fMRI Study. *Front Neurosci-switz* **15**, 682100 (2021).

127. Illán-Gala, I. *et al.* Diagnostic Utility of Measuring Cerebral Atrophy in the Behavioral Variant of Frontotemporal Dementia and Association With Clinical Deterioration. *Jama Netw Open* **4**, e211290 (2021).

128. Anderl-Straub, S. *et al.* Predicting disease progression in behavioral variant frontotemporal dementia. *Alzheimer's Dementia Diagnosis Assess Dis Monit* **13**, e12262 (2021).

129. Wisse, L. E. M. *et al.* Cross-sectional and longitudinal medial temporal lobe subregional atrophy patterns in semantic variant primary progressive aphasia. *Neurobiol Aging* **98**, 231–241 (2021).

130. Bocchetta, M., Espinosa, M. del M. I., Lashley, T., Warren, J. D. & Rohrer, J. D. In vivo staging of frontotemporal lobar degeneration TDP-43 type C pathology. *Alzheimer's Res Ther* **12**, 34 (2020).

131. Tetzloff, K. A. *et al.* Progressive agrammatic aphasia without apraxia of speech as a distinct syndrome. *Brain* **142**, 2466–2482 (2019).

132. Josephs, K. A. *et al.* A molecular pathology, neurobiology, biochemical, genetic and neuroimaging study of progressive apraxia of speech. *Nat Commun* **12**, 3452 (2021).

133. Boxer, A. L. *et al.* Patterns of Brain Atrophy That Differentiate Corticobasal Degeneration Syndrome From Progressive Supranuclear Palsy. *Arch Neurol-chicago* **63**, 81–86 (2006).

134. Whitwell, J. L. *et al.* Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? *Mov. Disord.* **32**, 955–971 (2017).

135. Agosta, F. *et al.* The Cortical Signature of Amyotrophic Lateral Sclerosis. *Plos One* **7**, e42816 (2012).

136. Spinelli, E. G. *et al.* Structural MRI Signatures in Genetic Presentations of the Frontotemporal Dementia/Motor Neuron Disease Spectrum. *Neurology* **97**, e1594–e1607 (2021).

137. Rohrer, J. D. *et al.* C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. *Lancet neurology* **14**, 291–301 (2015).

138. Staffaroni, A. M. *et al.* Rates of Brain Atrophy Across Disease Stages in Familial Frontotemporal Dementia Associated With MAPT, GRN, and C9orf72 Pathogenic Variants. *Jama Netw Open* **3**, e2022847 (2020).

139. Cash, D. M. *et al.* Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. *Neurobiol Aging* **62**, 191–196 (2018).

140. Jiskoot, L. C. *et al.* Longitudinal cognitive biomarkers predicting symptom onset in presymptomatic frontotemporal dementia. *J Neurol* **129**, 3091 (2018).

141. Panman, J. L. *et al.* Gray and white matter changes in presymptomatic genetic frontotemporal dementia: a longitudinal MRI study. *Neurobiol Aging* **76**, 115–124 (2019).

142. Panman, J. L. *et al.* Modelling the cascade of biomarker changes in GRN-related frontotemporal dementia. *J Neurology Neurosurg Psychiatry* **92**, 494–501 (2021).

143. Feis, R. A. *et al.* A multimodal MRI-based classification signature emerges just prior to symptom onset in frontotemporal dementia mutation carriers. *J Neurology Neurosurg Psychiatry* **90**, 1207 (2019).

144. Staffaroni, A. M. *et al.* Individualized atrophy scores predict dementia onset in familial frontotemporal lobar degeneration. *Alzheimer's Dementia* **16**, 37–48 (2019).

145. Premi, E. *et al.* The inner fluctuations of the brain in presymptomatic Frontotemporal Dementia: The chronnectome fingerprint. *Neuroimage* **189**, 645–654 (2019).

146. Tsvetanov, K. A. *et al.* Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. *Alzheimer's Dementia* **17**, 500–514 (2021).

147. Levy, J. P. *et al.* 18F-MK-6240 tau-PET in genetic frontotemporal dementia. *Brain* **145**, awab392-(2021).

148. Wolters, E. E. *et al.* [18F]Flortaucipir PET Across Various MAPT Mutations in Presymptomatic and Symptomatic Carriers. *Neurology* **97**, e1017–e1030 (2021).

149. Irwin, D. J. *et al.* Ante mortem cerebrospinal fluid tau levels correlate with postmortem tau pathology in frontotemporal lobar degeneration. *Ann Neurol.* **82**, 247–258 (2017).

150. Swift, I. J. *et al.* Fluid biomarkers in frontotemporal dementia: past, present and future. *J Neurology Neurosurg Psychiatry* **92**, 204–215 (2021).

151. Cousins, K. A. Q. *et al.* ATN status in amnestic and non-amnestic Alzheimer's disease and frontotemporal lobar degeneration. *Brain* **143**, 2295–2311 (2020).

152. Paterson, R. W. *et al.* Cerebrospinal fluid in the differential diagnosis of Alzheimer's disease: clinical utility of an extended panel of biomarkers in a specialist cognitive clinic. *Alzheimer's Res Ther* **10**, 32 (2018).

153. Cousins, K. A. Q. *et al.* ATN incorporating cerebrospinal fluid neurofilament light chain detects frontotemporal lobar degeneration. *Alzheimer's Dementia* **17**, 822–830 (2021).

154. Norise, C. *et al.* Clinical Correlates of Alzheimer's Disease Cerebrospinal Fluid Analytes in Primary Progressive Aphasia. *Front Neurol* **10**, 485 (2019).

155. Illán-Gala, I. *et al.* Challenges associated with biomarker-based classification systems for Alzheimer's disease. *Alzheimer's Dementia Diagnosis Assess Dis Monit* **10**, 346–357 (2018).

156. Gabelle, A. *et al.* Decreased sAβPPβ, Aβ38, and Aβ40 Cerebrospinal Fluid Levels in Frontotemporal Dementia. *Journal of Alzheimer's Disease* **26**, 553–563 (2011).

157. Jeppsson, A. *et al.* CSF biomarkers distinguish idiopathic normal pressure hydrocephalus from its mimics. *J Neurology Neurosurg Psychiatry* **90**, 1117 (2019).

158. Augutis, K. *et al.* Cerebrospinal fluid biomarkers of β-amyloid metabolism in multiple sclerosis. *Mult Scler J* **19**, 543–552 (2012).

159. Verde, F., Otto, M. & Silani, V. Neurofilament Light Chain as Biomarker for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. *Front Neurosci-switz* **15**, 679199 (2021).

160. Mattsson-Carlgren, N. *et al.* Cerebrospinal Fluid Biomarkers in Autopsy-Confirmed Alzheimer Disease and Frontotemporal Lobar Degeneration. *Neurology* **98**, 10.1212/WNL.0000000000200040 (2022).

161. Zhang, J. V. *et al.* Neurofilament Light Chain Related to Longitudinal Decline in Frontotemporal Lobar Degeneration. *Neurology Clin Pract* **11**, 105–116 (2020).

162. Ducharme, S. *et al.* Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. *Brain* **143**, 1632–1650 (2020).

163. Vijverberg, E. G. B. *et al.* Cerebrospinal fluid biomarker examination as a tool to discriminate behavioral variant frontotemporal dementia from primary psychiatric disorders. *Alzheimer's Dementia Diagnosis Assess Dis Monit* **7**, 99–106 (2017).

164. Benussi, A. *et al.* Diagnostic and prognostic value of serum NfL and p-Tau181 in frontotemporal lobar degeneration. *J Neurology Neurosurg Psychiatry* **91**, 960–967 (2020).

165. Ashton, N. J. *et al.* Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol* **141**, 709–724 (2021).

166. Karikari, T. K. *et al.* Head-to-head comparison of clinical performance of CSF phospho-tau T181 and T217 biomarkers for Alzheimer's disease diagnosis. *Alzheimer's Dementia* **17**, 755–767 (2021).

167. Thijssen, E. H. *et al.* Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurology* **20**, 739–752 (2021).

168. Rohrer, J. D. *et al.* Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. *Neurology* **87**, 1329–1336 (2016).

169. Steinacker, P. *et al.* Serum neurofilament light chain in behavioral variant frontotemporal dementia. *Neurology* **91**, e1390–e1401 (2018).

170. Ashton, N. J. *et al.* A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun* **12**, 3400 (2021).

171. Forgrave, L. M., Ma, M., Best, J. R. & DeMarco, M. L. The diagnostic performance of neurofilament light chain in CSF and blood for Alzheimer's disease, frontotemporal dementia, and amyotrophic lateral sclerosis: A systematic review and meta-analysis. *Alzheimer's Dementia Diagnosis Assess Dis Monit* **11**, 730–743 (2019).

172. Katisko, K. *et al.* Serum neurofilament light chain is a discriminative biomarker between frontotemporal lobar degeneration and primary psychiatric disorders. *J Neurol* **267**, 162–167 (2020).

173. Shweiki, M. R. A. *et al.* Neurofilament light chain as a blood biomarker to differentiate psychiatric disorders from behavioural variant frontotemporal dementia. *J Psychiatr Res* **113**, 137–140 (2019).

174. Rojas, J. C. *et al.* Plasma Neurofilament Light for Prediction of Disease Progression in Familial Frontotemporal Lobar Degeneration. *Neurology* **96**, 10.1212/WNL.0000000000011848 (2021).

175. Wilke, C. *et al.* Stratifying the Presymptomatic Phase of Genetic Frontotemporal Dementia by Serum NfL and pNfH: A Longitudinal Multicentre Study. *Ann Neurol* **91**, 33–47 (2022).

176. Cousins, K. A. Q. *et al.* Distinguishing Frontotemporal Lobar Degeneration Tau From TDP-43 Using Plasma Biomarkers. *Jama Neurol* **79**, 1155–1164 (2022).

177. Sato, C. *et al.* Tau Kinetics in Neurons and the Human Central Nervous System. *Neuron* **98**, 861–864 (2018).

178. Kanmert, D. *et al.* C-Terminally Truncated Forms of Tau, But Not Full-Length Tau or Its C-Terminal Fragments, Are Released from Neurons Independently of Cell Death. *J Neurosci* **35**, 10851–10865 (2015).

179. Maia, L. F. *et al.* Changes in Amyloid-β and Tau in the Cerebrospinal Fluid of Transgenic Mice Overexpressing Amyloid Precursor Protein. *Sci Transl Med* **5**, 194re2 (2013).

180. Steinacker, P., Barschke, P. & Otto, M. Biomarkers for diseases with TDP-43 pathology. *Mol Cell Neurosci* **97**, 43–59 (2018).

181. Scialò, C. *et al.* TDP-43 real time quaking induced conversion reaction optimization and detection of seeding activity in CSF of amyotrophic lateral sclerosis and frontotemporal dementia patients. *Brain Commun* **2**, fcaa142- (2020).

182. Meeter, L. H. *et al.* Neurofilament light chain: a biomarker for genetic frontotemporal dementia. *Annals of Clinical and Translational Neurology* **3**, 623–636 (2016).

183. Ljubenkov, P. A. *et al.* Cerebrospinal fluid biomarkers predict frontotemporal dementia trajectory. *Ann Clin Transl Neur* **5**, 1250–1263 (2018).

184. Meeter, L. H. H. *et al.* Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum. *Neurology* **90**, e1231–e1239 (2018).

185. Scherling, C. S. *et al.* Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. *Ann Neurol.* **75**, 116–126 (2014).

186. Ende, E. L. van der *et al.* Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. *Lancet Neurology* **18**, 1103–1111 (2019).

187. Goossens, J. *et al.* Diagnostic value of cerebrospinal fluid tau, neurofilament, and progranulin in definite frontotemporal lobar degeneration. *Alzheimer's Res Ther* **10**, 31 (2018).

188. Huin, V. *et al.* Homozygous GRN mutations: new phenotypes and new insights into pathological and molecular mechanisms. *Brain* **143**, 303–319 (2019).

189. Meeter, L. H. H. *et al.* Progranulin Levels in Plasma and Cerebrospinal Fluid in Granulin Mutation Carriers. *Dementia Geriatric Cognitive Disord Extra* **6**, 330–340 (2016).

190. Lehmer, C. *et al.* Poly-GP in cerebrospinal fluid links C9orf72-associated dipeptide repeat expression to the asymptomatic phase of ALS/FTD. *Embo Mol Med* **9**, 859–868 (2017).

191. Meeter, L. H. H. *et al.* Poly(GP), neurofilament and grey matter deficits in C9orf72 expansion carriers. *Ann Clin Transl Neur* **5**, 583–597 (2018).

192. Gendron, T. F. *et al.* Poly(GP) proteins are a useful pharmacodynamic marker for C9ORF72-associated amyotrophic lateral sclerosis. *Science Translational Medicine* **9**, eaai7866 (2017).

193. Wilson, K. M. *et al.* Development of a sensitive trial-ready poly(GP) CSF biomarker assay for C9orf72-associated frontotemporal dementia and amyotrophic lateral sclerosis. *J Neurology Neurosurg Psychiatry* **93**, 761–771 (2022).

194. Khalil, M. *et al.* Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol* **14**, 577–589 (2018).

195. Robinaugh, G. & Henry, M. L. Chapter 14 Behavioral interventions for primary progressive aphasia. *Handb Clin Neurology* **185**, 221–240 (2022).

196. Lasaponara, S., Marson, F., Doricchi, F. & Cavallo, M. A Scoping Review of Cognitive Training in Neurodegenerative Diseases via Computerized and Virtual Reality Tools: What We Know So Far. *Brain Sci* **11**, 528 (2021).

197. Cotelli, M. *et al.* Cognitive telerehabilitation in mild cognitive impairment, Alzheimer's disease and frontotemporal dementia: A systematic review. *J Telemed Telecare* **25**, 67–79 (2017).

198. Manoochehri, M. & Huey, E. Diagnosis and Management of Behavioral Issues in Frontotemporal Dementia. *Curr Neurol Neurosci Rep* **12**, 528–536 (2012).

199. Sheppard, S. M. Chapter 16 Noninvasive brain stimulation to augment language therapy for primary progressive aphasia. *Handb Clin Neurology* **185**, 251–260 (2022).

200. Pytel, V. *et al.* Personalized Repetitive Transcranial Magnetic Stimulation for Primary Progressive Aphasia. *J Alzheimer's Dis* **84**, 151–167 (2021).

201. Hosseini, M. *et al.* Proceedings #10: Transcranial Direct Current Stimulation Mediates Improvements in Verbal Fluency for Patients with Primary Progressive Aphasia. *Brain Stimul* **12**, e69–e71 (2019).

202. Cotelli, M. *et al.* Prefrontal cortex rTMS enhances action naming in progressive non-fluent aphasia. *Eur J Neurol* **19**, 1404–1412 (2012).

203. Antczak, J. *et al.* Repetitive transcranial magnetic stimulation for the treatment of cognitive impairment in frontotemporal dementia: an open-label pilot study. *Neuropsych Dis Treat* **14**, 749–755 (2018).

204. Byeon, H. Meta-Analysis on the Effects of Transcranial Direct Current Stimulation on Naming of Elderly with Primary Progressive Aphasia. *Int J Environ Res Pu* **17**, 1095 (2020).

205. Cotelli, M. *et al.* Effectiveness of language training and non-invasive brain stimulation on oral and written naming performance in Primary Progressive Aphasia: A meta-analysis and systematic review. *Neurosci Biobehav Rev* **108**, 498–525 (2019).

206. Tsapkini, K. *et al.* Electrical brain stimulation in different variants of primary progressive aphasia: A randomized clinical trial. *Alzheimer's Dementia Transl Res Clin Interventions* **4**, 461–472 (2018).

207. Aguiar, V. de *et al.* Brain volumes as predictors of tDCS effects in primary progressive aphasia. *Brain Lang* **200**, 104707 (2020).

208. Zhao, Y. *et al.* White Matter Integrity Predicts Electrical Stimulation (tDCS) and Language Therapy Effects in Primary Progressive Aphasia. *Neurorehab Neural Re* **35**, 44–57 (2021).

209. Tao, Y., Ficek, B., Wang, Z., Rapp, B. & Tsapkini, K. Selective Functional Network Changes Following tDCS-Augmented Language Treatment in Primary Progressive Aphasia. *Front Aging Neurosci* **13**, 681043 (2021).

210. Harris, A. D. *et al.* Reductions in GABA following a tDCS-language intervention for primary progressive aphasia. *Neurobiol Aging* **79**, 75–82 (2019).

211. Teichmann, M. *et al.* Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia. *Ann Neurol.* **80**, 693–707 (2016).

212. Cotelli, M. *et al.* Enhancing theory of mind in behavioural variant frontotemporal dementia with transcranial direct current stimulation. *Cognitive Affect Behav Neurosci* **18**, 1065–1075 (2018).

213. Kimura, T. & Takamatsu, J. Pilot study of pharmacological treatment for frontotemporal dementia: Risk of donepezil treatment for behavioral and psychological symptoms. *Geriatr Gerontol Int* **13**, 506–507 (2013).

214. Boxer, A. L., Knopman, D. S., Kaufer, D. I. & Grossman, M. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology* **12**, 149–156 (2013).

215. Mendez, M. F., Shapira, J. S., McMurtray, A. & Licht, E. Preliminary Findings: Behavioral Worsening on Donepezil in Patients With Frontotemporal Dementia. *Am J Geriatric Psychiatry* **15**, 84–87 (2007).

216. Chow, T. W. & Mendez, M. F. Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration. *Am J Alzheimer's Dis Other Dementias* **17**, 267–272 (2002).

217. Moretti, R., Torre, P., Antonello, R. M., Cazzato, G. & Bava, A. Frontotemporal Dementia: Paroxetine as a Possible Treatment of Behavior Symptoms. *Eur Neurol* **49**, 13–19 (2003).

218. Prodan, C. I., Monnot, M. & Ross, E. D. Behavioural abnormalities associated with rapid deterioration of language functions in semantic dementia respond to sertraline. *J Neurology Neurosurg Psychiatry* **80**, 1416 (2009).

219. Herrmann, N. *et al.* Serotonergic Function and Treatment of Behavioral and Psychological Symptoms of Frontotemporal Dementia. *Am J Geriatric Psychiatry* **20**, 789–797 (2012).

220. Deakin, J. B., Rahman, S., Nestor, P. J., Hodges, J. R. & Sahakian, B. J. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. *Psychopharmacology* **172**, 400–408 (2004).

221. Kerssens, C. J., Kerrsens, C. J. & Pijnenburg, Y. A. L. Vulnerability to neuroleptic side effects in frontotemporal dementia. *Eur J Neurol* **15**, 111–112 (2008).

222. Tariot, P. N. *et al.* Trial of Pimavanserin in Dementia-Related Psychosis. *New Engl J Med* **385**, 309–319 (2021).

223. Gálvez-Andres, A. *et al.* Secondary Bipolar Disorder and Diogenes Syndrome in Frontotemporal Dementia. *J Clin Psychopharm* **27**, 722–723 (2007).

224. Poetter, C. E. & Stewart, J. T. Treatment of Indiscriminate, Inappropriate Sexual Behavior in Frontotemporal Dementia With Carbamazepine. *J Clin Psychopharm* **32**, 137–138 (2012).

225. Cruz, M., Marinho, V., Fontenelle, L. F., Engelhardt, E. & Laks, J. Topiramate may Modulate Alcohol Abuse But not Other Compulsive Behaviors in Frontotemporal Dementia. *Cogn Behav Neurol* **21**, 104–106 (2008).

226. Nestor, P. J. Reversal of abnormal eating and drinking behaviour in a frontotemporal lobar degeneration patient using low-dose topiramate. *J Neurology Neurosurg Psychiatry* **83**, 349 (2012).

227. Singam, C., Walterfang, M., Mocellin, R., Evans, A. & Velakoulis, D. Topiramate for Abnormal Eating Behaviour in Frontotemporal Dementia. *Behav Neurol* **27**, 285–286 (2020).

228. Shinagawa, S., Tsuno, N. & Nakayama, K. Managing abnormal eating behaviours in frontotemporal lobar degeneration patients with topiramate. *Psychogeriatrics* **13**, 58–61 (2013).

229. Huey, E. D., Garcia, C., Wassermann, E. M., Tierny, M. C. & Grafman, J. Stimulant Treatment of Frontotemporal Dementia in 8 Patients. *J Clin Psychiatry* **69**, 1981–1982 (2008).

230. Rahman, S. *et al.* Methylphenidate (‘Ritalin’) can Ameliorate Abnormal Risk-Taking Behavior in the Frontal Variant of Frontotemporal Dementia. *Neuropsychopharmacol* **31**, 651–658 (2006).

231. Finger, E. C. *et al.* Oxytocin for frontotemporal dementia: A randomized dose-finding study of safety and tolerability. *Neurology* **84**, 174–181 (2015).

232. Höglinger, G. U. *et al.* Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov. Disord.* **32**, 853–864 (2017).

233. Boxer, A. L. *et al.* Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. *The Lancet Neurology* **13**, 676–685 (2014).

234. Tsai, R. M. *et al.* Reactions to Multiple Ascending Doses of the Microtubule Stabilizer TPI-287 in Patients With Alzheimer Disease, Progressive Supranuclear Palsy, and Corticobasal Syndrome. *Jama Neurol* **77**, 215–224 (2020).

235. Tolosa, E. *et al.* A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. *Movement Disord* **29**, 470–478 (2014).

236. VandeVrede, L. *et al.* Open-Label Phase 1 Futility Studies of Salsalate and Young Plasma in Progressive Supranuclear Palsy. *Mov Disord Clin Pract* **7**, 440–447 (2020).

237. Ljubenkov, P. A. *et al.* Effect of the Histone Deacetylase Inhibitor FRM-0334 on Progranulin Levels in Patients With Progranulin Gene Haploinsufficiency. *Jama Netw Open* **4**, e2125584 (2021).

238. Sha, S. J. *et al.* An 8-week, open-label, dose-finding study of nimodipine for the treatment of progranulin insufficiency from GRN gene mutations. *Alzheimer's Dementia Transl Res Clin Interventions* **3**, 507–512 (2017).

239. Kao, A. W., McKay, A., Singh, P. P., Brunet, A. & Huang, E. J. Progranulin, lysosomal regulation and neurodegenerative disease. *Nat Rev Neurosci* **18**, 325–333 (2017).

240. Logan, T. *et al.* Rescue of a lysosomal storage disorder caused by Grn loss of function with a brain penetrant progranulin biologic. *Cell* **184**, 4651-4668.e25 (2021).

241. Tran, H. *et al.* Suppression of mutant C9orf72 expression by a potent mixed backbone antisense oligonucleotide. *Nat Med* **28**, 117–124 (2022).

242. Snowden, J. S. *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. *Brain* **135**, 693–708 (2012).

243. Logsdon, R. G., Gibbons, L. E., McCurry, S. M. & Teri, L. Quality of Life in Alzheimer's Disease Patient and Caregiver Reports.pdf. *Journal of Mental Health and Aging* **5**, 21–31 (1999).

244. Piguet, O. & Kumfor, F. Frontotemporal dementias: main syndromes and underlying brain changes. *Curr Opin Neurol* **33**, 215–221 (2020).

245. Gentry, M. T. *et al.* Quality of life and caregiver burden in familial frontotemporal lobar degeneration: Analyses of symptomatic and asymptomatic individuals within the LEFFTDS cohort. *Alzheimer's Dementia* **16**, 1115–1124 (2020).

246. Hvidsten, L. *et al.* Quality of Life in People with Young-Onset Dementia: A Nordic Two-Year Observational Multicenter Study. *J Alzheimer's Dis* **71**, 1381–1381 (2019).

247. Massimo, L. *et al.* Apathy in Frontotemporal Degeneration: Neuroanatomical Evidence of Impaired Goal-directed Behavior. *Front. Hum. Neurosci.* **9**, 611 (2015).

248. Wong, S. *et al.* Apathy and its impact on carer burden and psychological wellbeing in primary progressive aphasia. *J Neurol Sci* **416**, 117007 (2020).

249. Toot, S., Swinson, T., Devine, M., Challis, D. & Orrell, M. Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis. *Int Psychogeriatr* **29**, 195–208 (2017).

250. Karnatz, T. *et al.* Burden of caregivers of patients with frontotemporal lobar degeneration – a scoping review. *Int Psychogeriatr* **33**, 891–911 (2021).

251. Yassuda, M. S. *et al.* Apathy and functional disability in behavioral variant frontotemporal dementia. *Neurology: Clinical Practice* **8**, 120–128 (2018).

252. Rajagopalan, J. *et al.* Experiences of people with dementia and their caregivers during the COVID-19 pandemic in India: A mixed-methods study. *Dementia* **21**, 214–235 (2022).

253. Mok, V. C. T. *et al.* Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future. *Alzheimer's Dementia* **16**, 1571–1581 (2020).

254. García, A. M. *et al.* Automated Detection of Speech Timing Alterations in Autopsy-Confirmed Nonfluent/Agrammatic Variant Primary Progressive Aphasia. *Neurology* **99**, e500–e511 (2022).

255. Nevler, N. *et al.* Automatic measurement of prosody in behavioral variant FTD. *Neurology* **89**, 650–656 (2017).

256. Nevler, N. *et al.* Automated analysis of natural speech in amyotrophic lateral sclerosis spectrum disorders. *Neurology* **95**, e1629–e1639 (2020).

257. Ende, E. L. *et al.* Novel CSF biomarkers in genetic frontotemporal dementia identified by proteomics. *Ann Clin Transl Neur* **6**, 698–707 (2019).

258. Swarup, V. *et al.* Identification of evolutionarily conserved gene networks mediating neurodegenerative dementia. *Nat Med* **25**, 152–164 (2019).

259. Teunissen, C. E. *et al.* Novel diagnostic cerebrospinal fluid biomarkers for pathologic subtypes of frontotemporal dementia identified by proteomics. *Alzheimers Dement (Amst)* **2**, 86–94 (2016).

260. Iguchi, Y. *et al.* Exosome secretion is a key pathway for clearance of pathological TDP-43. *Brain* **139**, 3187–3201 (2016).

261. Schneider, R. *et al.* Downregulation of exosomal miR-204-5p and miR-632 as a biomarker for FTD: a GENFI study. *J Neurology Neurosurg Psychiatry* **89**, 851 (2018).

262. Sheinerman, K. S. *et al.* Circulating brain-enriched microRNAs as novel biomarkers for detection and differentiation of neurodegenerative diseases. *Alzheimer's Research & Therapy* **9**, 89 (2017).

263. McMillan, C. T. *et al.* C9orf72 promoter hypermethylation is neuroprotective: Neuroimaging and neuropathologic evidence. *Neurology* **84**, 1622–1630 (2015).

264. Allen, M. *et al.* Gene expression, methylation and neuropathology correlations at progressive supranuclear palsy risk loci. *Acta Neuropathol* **132**, 197–211 (2016).

265. Belzil, V. V., Katzman, R. B. & Petrucelli, L. ALS and FTD: an epigenetic perspective. *Acta Neuropathol* **132**, 487–502 (2016).

266. Gerrits, E. *et al.* Neurovascular dysfunction in GRN-associated frontotemporal dementia identified by single-nucleus RNA sequencing of human cerebral cortex. *Nat Neurosci* **25**, 1034–1048 (2022).

267. Tosun, D. *et al.* Diagnostic utility of ASL-MRI and FDG-PET in the behavioral variant of FTD and AD. *Annals of Clinical and Translational Neurology* **3**, 740–751 (2016).

268. Olm, C. A. *et al.* Arterial spin labeling perfusion predicts longitudinal decline in semantic variant primary progressive aphasia. *J Neurol* **263**, 1927–1938 (2016).

269. Meeter, L. H., Kaat, L. D., Rohrer, J. D. & Swieten, J. C. V. Imaging and fluid biomarkers in frontotemporal dementia. *Nat Rev Neurol* **19**, 109 (2017).

270. Chen, Q. *et al.* Frontal lobe 1 H MR spectroscopy in asymptomatic and symptomatic MAPT mutation carriers. *Neurology* **93**, e758–e765 (2019).

271. Quinn, C. *et al.* Frontal lobe abnormalities on MRS correlate with poor letter fluency in ALS. *Neurology* **79**, 583–588 (2012).

272. Cheong, I. *et al.* Ultra-High Field Proton MR Spectroscopy in Early-Stage Amyotrophic Lateral Sclerosis. *Neurochem Res* **42**, 1833–1844 (2017).

273. Coulthard, E. *et al.* Proton magnetic resonance spectroscopy in frontotemporal dementia. *J Neurol* **253**, 861–868 (2006).

274. Ranasinghe, K. G. *et al.* Distinct spatiotemporal patterns of neuronal functional connectivity in primary progressive aphasia variants. *Brain* **140**, 2737–2751 (2017).

275. Mandelli, M. L. *et al.* Healthy brain connectivity predicts atrophy progression in non-fluent variant of primary progressive aphasia. *Brain* **139**, 2778–2791 (2016).

276. Tisdall, M. D. *et al.* Ex vivo MRI and histopathology detect novel iron-rich cortical inflammation in frontotemporal lobar degeneration with tau versus TDP-43 pathology. *Neuroimage Clin* **33**, 102913 (2022).

277. Pallebage-Gamarallage, M. *et al.* Dissecting the pathobiology of altered MRI signal in amyotrophic lateral sclerosis: A post mortem whole brain sampling strategy for the integration of ultra-high-field MRI and quantitative neuropathology. *Bmc Neurosci* **19**, 11 (2018).

278. Meadowcroft, M. D. *et al.* Histological–MRI correlation in the primary motor cortex of patients with amyotrophic lateral sclerosis. *J Magn Reson Imaging* **41**, 665–675 (2015).

279. Kim, B. J. *et al.* Persistent and Progressive Outer Retina Thinning in Frontotemporal Degeneration. *Front Neurosci-switz* **13**, 298 (2019).

280. Fonteijn, H. M. *et al.* An event-based model for disease progression and its application in familial Alzheimer's disease and Huntington's disease. *NeuroImage* **60**, 1880–1889 (2012).

281. Young, A. L. *et al.* A data-driven model of biomarker changes in sporadic Alzheimer's disease. *Brain* **137**, 2564–2577 (2014).

282. Olm, C. A. *et al.* Event-based modeling of T1-weighted MRI is related to pathology in frontotemporal lobar degeneration due to tau and TDP. *Neuroimage Clin* **37**, 103285 (2023).